

**DESIGN, DEVELOPMENT AND CHARACTERIZATION
OF MOUTH DISSOLVING FILMS FOR THE
TREATMENT OF PSYCHOSIS**

A Thesis submitted to Gujarat Technological University

For the Award of

Doctor of Philosophy

In

PHARMACY

By

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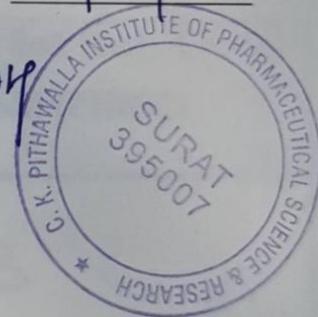
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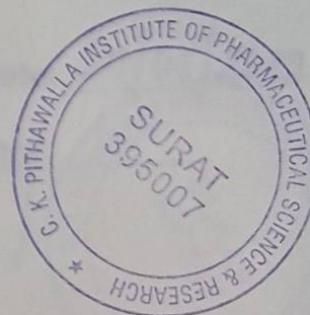
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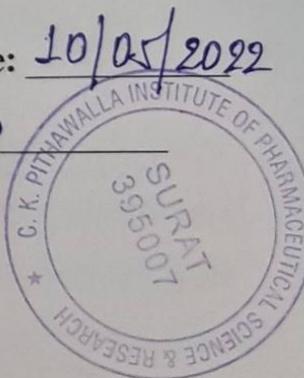
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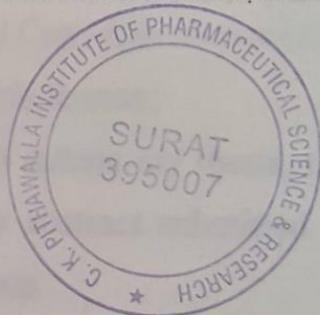
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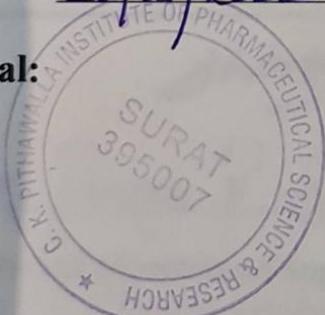
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ABSTRACT

Quetiapine fumarate and Ziprasidone Hydrochloride is a novel atypical antipsychotic that has been shown to be useful in treating schizophrenia. The aim of present study was to develop fast disintegrating Quetiapine fumarate and Ziprasidone Hydrochloride film by using various polymers with shorter disintegration time and greater drug release with a prospect of assisting various patients who have difficulty in swallowing conventional dosage forms & enhance bioavailability of drug and quick onset of action. MDFs also offer better convenience to patients with mental illness, as well as pediatrics, elderly, and developmentally disabled patients. MDFs were formulated using a solvent casting technique. A 3^2 full factorial design was applied to choose the optimized MDF, utilizing Design-Expert® software (Stat-Ease Inc., Minneapolis, MN, USA). The optimized MDF tensile strength, elongation, disintegration time, and dissolution rate was determined. This optimized MDF was subjected to in vitro dissolution, ex vivo permeation, stability studies. The % CDR of the optimized MDF in comparison with the market formulation was found to be 97% & 99% in 6 mins. These findings confirmed the success of the MDFs loaded with Quetiapine fumarate and Ziprasidone Hydrochloride.

Keywords: Mouth Dissolving Film, Quetiapine fumarate, Ziprasidone Hydrochloride, schizophrenia.

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Chapter-1

Introduction

CHAPTER 1

INTRODUCTION

1. INTRODUCTION

1.1 Introduction of Novel Drug Delivery^[1-5]

The manner in which a medication is administered can have a great effect on its efficacy. Some tablets have an best attention vary inside which they supply the most benefit, however quantities outdoor of this vary may additionally be poisonous or furnish no therapeutic benefit. Limited development in the efficacy of extreme sickness treatment, on the different hand, has highlighted the want for a multidisciplinary strategy to therapeutic shipping to tissue targets.

As a result, new techniques to pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, bio-recognition, and medicinal drug efficacy arose. Drug transport structures (DDS) are new multidisciplinary methodologies that mix polymer science, pharmaceutics, bio-conjugate chemistry, and molecular biology.

Various drug transport and drug focused on structures are now being developed in order to forestall drug degradation and loss, take away extreme negative effects, and expand drug bioavailability and the proportion of drug amassed in the required zone. Controlled and special drug delivery, beforehand basically a pipe dream or a possibility, is now a reality. During the preceding decade and a half, pharmaceutical and different scientists carried out considerable and intensive lookup in this subject of medicine research.

Examples of drug carriers encompass soluble polymers, insoluble or biodegradable microparticles, herbal and artificial polymers, microcapsules, cells, telephone ghosts, lipoproteins, liposomes, and micelles. The carriers can be designed to decay slowly, reply to stimuli (such as pH or temperature), and even be centered to particular humans (e.g., by using conjugating them with precise antibodies towards positive attribute elements of the vicinity of interest). Targeting refers to the potential to direct a drug-loaded gadget to a particular region. There are two integral methods for addressing the favored areas for drug release.

Targeting can be divided into two categories: passive and active.

1.1.1 Advantages Of Novel Drug Delivery System^[6-15]

1. Protection against chemical and physical deterioration.
2. Consistent delivery.
3. Better dispersion of tissue macrophages.
4. Stability is improved.
5. Improved pharmacological activity.
6. Toxic-free protection.
7. Increased bioavailability.
8. Increasing solubility

Any drug delivery system can be defined as one that includes:

- a) the drug formulation,
- b) the medical device or dosage form/technology used to transport the medication inside the body, and
- c) the mechanism used to release the drug.

The normal method of medication conveyance is to form the medication into a reasonable structure, like a squashed tablet for oral organization or an answer for intravenous infusion. Expanded measurements necessities, lower viability, poisonousness, and disagreeable aftereffects have all been exhibited to be significant inconveniences of these portion plans. New medication conveyance strategies have been made or are being created to tackle the restrictions of conventional medication organization frameworks to address the issues of the medical care calling. Two sorts of frameworks exist: controlled medication discharge frameworks and designated medicine conveyance frameworks.

1.1.2 The therapeutic benefits of these new systems include:^[15-20]

- Increased therapeutic efficacy Site-specific delivery Reduced toxicity/side effects
- Enhanced convenience
- Viable therapy for diseases that were previously incurable
- Possibility of using it as a preventative measure
- Patient compliance is improved.

1.1.3 Various Drug Delivery Systems: Carrier based Drug Delivery System^[21-25]

- A) Liposomes
- B) Nanoparticles
- C) Microspheres
- D) Monoclonal antibodies
- E) Niosomes
- F) Resealed erythrocytes as drug carriers

1.2 Introduction of Immediate Release Dosage Form^[26-29]

In this review and exploration, novel medication conveyance techniques are being created to extend markets/signs, protract item life cycles, and produce amazing open doors. Oral organization is the favored strategy for foundational impacts because of its usability, absence of agony, assortment, and, above all, patient consistence. These strong definitions are more affordable to make since they don't need sterile circumstances. As a result of patient consistence, high accuracy dose, and creation economy, tablets are the suggested strong portion structure. Excipients and hardware choices will be seriously impacted in the event that strong measurements structure advancements change in response to noteworthy enhancements in drug improvement, like genomics. The advancement of further developed oral protein conveyance innovation as moment discharge tablets that can deliver prescriptions all the more rapidly is particularly encouraging for ineffectively dissolvable medications like high atomic weight protein and peptide. The oral course stays the best course for directing helpful specialists because of its minimal expense of treatment, simplicity of assembling, and simplicity of organization. Therefore, patient consistence is very high. Numerous patients require a quick beginning of activity in a particular restorative condition, requiring prescription delivery at the earliest opportunity. About portion of the populace is impacted, bringing about a high pace of insufficient treatment.

1.2.1 Definition^[30-33]

Prompt delivery tablets are those that disintegrate and break up quick, delivering the medication. To empower prompt delivery, a satisfactory chemically OK diluent or transporter

might be used, the same length as the diluent or transporter doesn't significantly dial back drug discharge or potentially retention. Definitions that have been changed to give "adjusted," "controlled," "supported," "delayed," "expanded," or "postponed" drug discharge are excluded from this classification.

1.2.2 Pharmacokinetics^[34-35]

This field researches assimilation, conveyance, digestion, and discharge. The rate and measure of retention are significant on the grounds that medication focus arrives at restorative levels following assimilation and subsequently advances pharmacological movement. Customary portion definitions slow crumbling, bringing about quick disintegration. Tissue porousness, perfusion rate, drug restricting to tissue, disease status, drug cooperation, and different factors all impact medicine circulation.

The length and strength of a not entirely set in stone by the pace of medication leeway from the body or the site of activity, for example biotransformation. A lessening in liver volume and provincial blood stream to the liver eases back drug biotransformation through oxidation, decrease, and hydrolysis. The half-existence of medications released by the kidneys increments as renal freedom eases back.

1.2.3 Pharmacodynamic

Drug gathering communication is disabled in both the old and youthful grown-ups on the grounds that to atypical organ advancement. Antihypertensive drugs like prazosin can hinder the body's ability to react to reflexive boosts, lessen heart result, and produce orthostatic hypotension. The awareness of the cardiovascular framework to - adrenergic agonists and enemies has lessened. At the point when anti-microbials are given, resistance is brought down and considered. Theophylline bronchodilator activity is decreased in the older, and they are more powerless against barbiturates than more youthful people. In the older, associative illnesses are far reaching, and this is considered when a few pharmacological treatments are utilized.

1.2.4 Criteria for Immediate Release Drug Delivery System^[36-37]

- ✓ Immediate release dosage form should:
- ✓ In the case of solid dosage, it should dissolve or disintegrate quickly in the stomach.
- ✓ It should be compatible with taste masking in the case of liquid dose forms.

- ✓ Be portable without worrying about fragility.
- ✓ Have a pleasant taste in your tongue.
- ✓ After oral administration, it should leave little or no residue in the mouth.
- ✓ Low sensitivity to environmental factors such as humidity and temperature
- ✓ Be produced at a minimal cost utilising traditional processing and packaging equipment
- ✓ Rapid solubility and absorption of the drug, resulting in a quick commencement of effect.

1.2.5 Merits of Immediate Release Drug Delivery System^[38]

- ✓ Added convenience/improved compliance
- ✓ Stability and bioavailability have both improved.
- ✓ Allows for high drug loading and is suitable for controlled/sustained release actives.
- ✓ Ability to give liquid medicinal benefits in the form of a solid formulation.
- ✓ Adaptable and compatible with existing processing and packaging equipment

Economical

- ✓ Reduced disintegration and dissolving times for instant release oral dosage forms; improved solubility of medicinal content.

1.3 Other Excipients^[39-40]

Excipients balance the qualities of the actives in quick delivery dose structures. An exhaustive comprehension of the science of these excipients is fundamental to keep away from cooperations with the actives. One more test looked by formulators is laying out the expense of these synthetics. Excipients are fundamental in the advancement of quick softening tablets. These dormant food-grade synthetics give the appropriate organoleptic highlights and item execution when included the detailing. Excipients, except for certain actives that require veiling specialists, are general and can be utilized for a wide scope of actives.

1.3.1 Bulking Materials

Building materials are vital in the development of quick dissolving tablets. The substance can be utilized as a diluent, filler, or cost-cutting specialist. Building specialists further develop the arrangement's textural properties, bringing about better breakdown in the mouth. Building specialists likewise diminish the convergence of the dynamic fixing in the definition. For more noteworthy fluid dissolvability and tangible insight, sugar-based building specialists like

mannitol, polydextrose, lactitol, DCL (direct compressible lactose), and starch hydrolystate should be used in this conveyance framework. Mannitol, specifically, has a high water dissolvability and great tactile discernment. Building specialists are utilized in extents going from 10% to 90% of the complete load of the completed structure.

1.3.2 Emulsifying Agents

Emulsifying specialists are significant excipients in the definition of moment discharge tablets since they help in the crumbling and arrival of the medicine. Emulsifying substances are likewise valuable for balancing out immiscible combinations and upgrading bioavailability. For quick tablet definition, alkyl sulfates, propylene glycol esters, lecithin, sucrose esters, and different emulsifiers are completely suggested. These substances can be used in levels going from 0.05 percent to generally 15% of the absolute weight of the completed organization.

1.3.3 Lubricants

Lubricants, which aren't required excipients, can support the acceptability of these tablets after they've crumbled in the mouth. Ointments eliminate dirt from the medication transport system from the mouth to the stomach.

1.3.4 Sweeteners and Flavors

Patients will observe the merchandise more alluring due to the flavors and taste covering fixings. The consideration of these fixings assists with masking the brutality and obnoxious kinds of a portion of the dynamic synthetics. Regular and manufactured flavors can be utilized to work on the organoleptic nature of quick dissolving tablets. Formulators can utilize sugars like sugar, dextrose, and fructose, as well as non-nutritive sugars like aspartame, sodium saccharin, sugar alcohols, and sucralose. Sugars give mass to the blend while likewise giving it a charming flavor.

1.3.5 Super Disintegrants

A disintegrant is an excipient that is added to a tablet or container mix to help the compacted mass fall to pieces when it is put in a liquid climate.

1.3.5.1 Advantages:

- ✓ Can be used at low concentrations.
- ✓ Less impact on compressibility and flowability
- ✓ More intragranularly effective

1.3.5.2 Some super disintegrants are:

1. **Sodium Starch Glycolate** (Explotab, primogel) is utilised in concentrations ranging from 2 to 8%, with 4% being the best.

Rapid and widespread swelling with minimal gelling is the mechanism of action. Microcrystalline cellulose (Avicel, celex) is utilised at a concentration of 2-15 percent of the tablet's weight. Additionally, water wicking

2. **Cross-linked Povidone or crospovidone (Kollidone)** at a concentration of 2–5% of the tablet's weight. Water is completely insoluble in this substance.

Water wicking, enlarging, and perhaps some distortion recuperation are the systems of activity. In water, it rapidly scatters and grows, however it doesn't gel, even after expanded openness. When contrasted with other disintegrants, this one has the most elevated gamble of edema. Other disintegrants have a lower surface region to volume proportion.

3. Insoluble in water hydroxyl propyl cellulose with low substituents. In water, it grows rapidly. Enlarging is more perceptible in grades LH-11 and LH-21. Certain grades can likewise make them tie capacities while as yet having the option to break down. Fixation that is recommended 1% to 5%.

4. **Cross linked carboxy methyl cellulose sodium (Ac-Di-sol) Croscarmellose sodium:**

Mechanism of Action: Wicking due to fibrous structure, swelling with minimal gelling.

Effective Concentrations: 1-3% Direct Compression, 2-4% Wet Granulation

1.4 Introduction of Oral Cavity^[41]

The oral pit is underneath the nasal depressions on the face's front side. Its lines are characterized by a rooftop, a story, and parallel dividers. The front of the mouth opens to the face through the oral gap, while the rear of the mouth connects to the oropharynx by the oropharyngeal isthmus (likewise named the isthmus of the fauces). The oropharyngeal isthmus is encircled by the delicate sense of taste and palatoglossal curves.

The unpaired mandible, sphenoid, and hyoid bones, as well as the combined maxillae, palatine, and transient bones, all add to the mouth pit's construction.

The oral depression is partitioned into foremost and back districts by the dental curves (or teeth): the front oral vestibule is tracked down foremost to the teeth and behind the lips, while the oral hole legitimate is found behind the teeth. Salivary organs dampen within the mouth and

help in food absorption by emitting catalysts that assist carbs with separating quicker. The organs at concern are the parotid, submandibular, and sublingual organs.

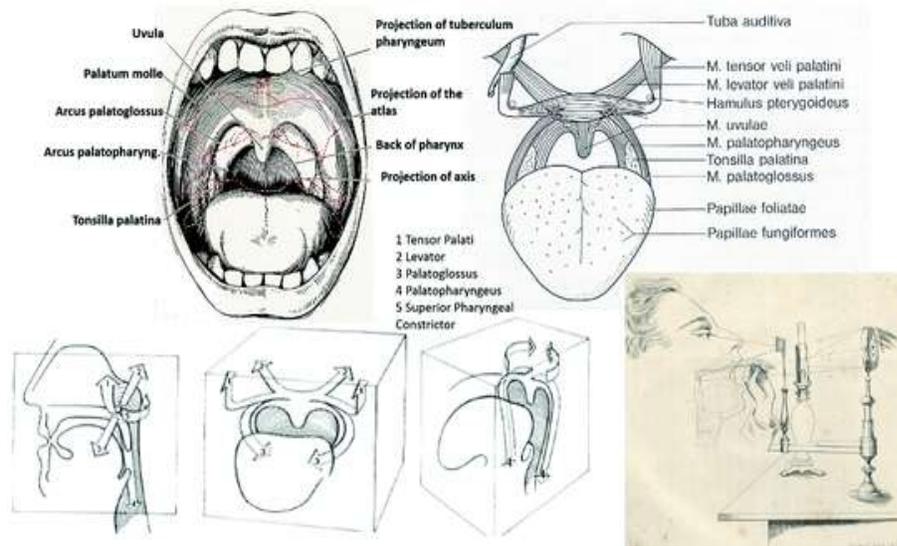


FIGURE 1. 1 Oral Cavity

TABLE 1. 1 Key facts about the oral cavity

| | |
|----------------------------------|--|
| Definition | The initial segment of the stomach related framework that contains the designs vital for rumination and discourse; teeth, tongue and salivary organs. |
| Tongue | A solid organ in the oral depression that empowers taste sensation, biting, gulping and talking. |
| Muscles of the tongue | <p>Intrinsic: Superior longitudinal, inferior longitudinal, transverse and vertical muscles</p> <p>Extrinsic: Genioglossus, hyoglossus, styloglossus and palatoglossus muscles</p> |
| Innervation of the tongue | <p>Motor: All muscles are innervated by hypoglossal nerve (CN XII), except for palatoglossus which is supplied by vagus nerve (CN X).</p> <p>Sensory:</p> <ul style="list-style-type: none"> ✓ General and taste sensation from the posterior third: glossopharyngeal nerve (CN IX); ✓ General sensation from the anterior two-thirds: lingual nerve |

| | |
|--|---|
| | (branch of the mandibular nerve - V3); ✓ Taste sensation from the posterior two-thirds: facial nerve (CN VII) |
|--|---|

1.4.1 Functions of the Oral Cavity Organs and Tissues ^[43-47]

1.4.1.1 lips and Cheeks

Lips, otherwise called labia, are plump strong folds verged within by mucosa and outwardly by skin. Between the two kinds of covering tissue on the lips lies a slim, straightforward epithelial covering tissue. Thus, the lips are less keratinized, permitting the ruddy pink shade of the blood in the fundamental vessels to appear on the other side. The cheeks are strong constructions with wet non-keratinized delineated squamous epithelium within and skin outwardly. Buccinator muscles, which level the cheeks against the teeth, and buccal fat, which shapes the profile on the face, both add to the prevalent and substandard lips' front end. Rumination happens when the lips and cheeks move the food around in the mouth and hold it set up while the teeth separate it. They additionally help in the advancement of words, which assists with the discourse interaction. Face appearance muscles are responsible for lip development. While the lips are shut, food and spit are held in the mouth.

1.4.1.2 Tongue

The tongue is a strong organ that makes the mouth's floor and is answerable for spit creation. Two various types of muscles support the tongue. The characteristic tongue muscles are answerable for changing the shape and size of the tongue during discourse and gulping. The tongue is moved from one side to another, forward and in reverse by extraneous muscles on the outside. Both muscle assembles work to drive food into the mouth and keep it there during rumination, teaming up with the lips and gums. Following that, the tongue controls nourishment for biting, shaping it into a round mass known as a bolus, and moving it to the rear of the mouth for gulping. The lingual frenulum is a mucous overlay that runs between the tongue and the sense of taste. The lingual frenulum is a minuscule overlay of mucous film that guides in the control of the tongue's back developments and legitimate articulation.

The tongue's upper surface and sides are canvassed in sodden, defined squamous epithelium. The terminal sulcus is a score that parts the dorsum of the tongue into two useful segments. The suku has papillae toward the front, some of which contain taste buds, and taste buds and little

organs toward the back, as well as lymphoid tissue. The pipes of minuscule salivary organs known as Von Ebner organs open into each of the circumvallate papillae on the back surface, which contain taste buds and are coordinated in a rearranged V and number 10-12. Filiform papillae are whitish tapered projections on the tongue's foremost 66% that don't contain taste buds and are organized in equal lines. Filiform papillae structure an unpleasant rough surface when the tongue is constrained against the hard sense of taste, which helps pack and break food. In this methodology, the dorsal mucosa of the tongue goes about as a masticatory mucosa. Fungiform papillae, which contain taste buds and are plentiful around the tip of the tongue, show up as mushroom-like red bits dispersed among the filiform papillae. Leaf-like foliate papillae can be seen on the parallel lines of the tongue's back segment. They simply have a couple of taste buds on their tongue.

1.4.1.3 Teeth and Gingiva

The four sorts of teeth are incisors, canines, premolars, and molars. Their shapes and positions let them play out their obligations. The incisor teeth are utilized to cleave food during rumination. Whenever food is devoured, the cuspids (canine teeth) shred it separated. To separate food, premolars (bicuspid) squashed it between their enormous, level surfaces. The tongue, cheeks, lips, and teeth join to shape a bolus before it is gulped.

Every tooth has three sections: a crown, a neck, and a base. The lacquer covered noticeable crown is ideally situated to endure the crushing that happens during the biting of hard and weak food varieties. In the crown, dentine lives behind the lacquer, though in the neck, cementum rests underneath the veneer. The tooth is kept up with set up in the jaw by projectional root divides that are embedded.

Rumination and talking both need the utilization of the teeth. The teeth are situated in alveoli along the alveolar edges of the mandible and maxilla. To frame the gingival sulcus, the gingivae, or gums, cover the alveolar cycles and broaden fairly into every attachment. The attachments are fixed with the periodontal tendon, which is comprised of solid sinewy connective tissue that associates the attachment dividers to the cemental surface of the roots. Thus, it keeps the teeth set up while likewise going about as a safeguard by retaining the tensions produced by biting.

1.4.1.4 Oral Mucosa

The wet coating of the mouth cavity is the oral bodily fluid film, frequently known as the oral mucosa. Oral mucosa has attributes of both skin and gastrointestinal mucosa, and is histologically of a momentary sort. The oral mucosa has various capacities. A portion of these capacities incorporate security, reasonableness, heat control, discharge, immunological action, and ingestion.

1.4.1.4.1 Protection

The significant capacity of the oral mucosa as a surface coating is to isolate and safeguard the oral pit's more profound tissues and organs from the climate. The oral delicate tissues are exposed to mechanical powers like pressure, extending, shearing, and surface scraped area because of seizing, gnawing, and biting food. The epithelium and connective tissue of the oral mucosa adjust to endure the conceivable pressure actuated by these exercises. A solid basal turnover of epithelial cells makes up for grinding misfortunes. Since microbial specialists don't stick to the surface cells of the mucosa because of fast surface reestablishment, microbial colonization is by implication restricted. Besides, on the grounds that to the quick basal turnover, twisted recuperating in the oral depression is quicker and more compelling. Accordingly, the oral mucosa epithelium goes about as the primary defensive boundary against hurtful synthetics.

1.4.1.4.2 Sensation

The mouth mucosa's tactile action gives data. The oral mucosa has receptors that recognize temperature, contact, agony, and taste. Sucking, choking, spewing, and salivation are totally set off by these receptors. In the cerebrum, there are additionally particular sensors that react to the flavor of water and produce thirst.

1.4.1.4.3 Thermal regulation

In contrasted with different well evolved creatures, for example, canines, who have broad mucosal temperature guideline, the human oral mucosa has a minor inclusion in internal heat level guideline. This is because of the shortfall of specific hotness shipping receptors in the veins.

1.4.1.4.4 Secretion

The oral mucosa's principle emission is salivation, which is delivered by the salivary organs and keeps up with the mouth mucosa wet. The three head salivary organs in people are the parotid, submandibular, and sublingual salivary organs. These organs are encased and situated external the mouth, with long channels bringing their emissions through the mucosa. The labial, lingual, palatal, buccal, glossopalatine, and retromolar organs are a gathering of little salivary organs in the mouth. These unencapsulated organs are arranged inside the mucosal films and have more limited channels.

1.4.1.4.5 Immune Mucosal Network

The oral cavity contains a few safe framework parts. Models incorporate gingival sulcus incendiary cells, epithelial Langerhans cells, and oral tonsillar tissues. Other invulnerable framework parts in typical oral tissues, like mucosal-related lymphoid tissue (Malt), assume a part in antigen handling and show, immune response arrangement and delivery, and cell-interceded effector pathways.

1.4.1.4.6 Absorption

In spite of the way that the oral epithelium has no absorptive capacity, porousness shifts in view of epithelial hindrance thickness, development design, and the shortfall of the layer corneum in various oral areas. The mouth's floor, which is one of the most slender epithelial areas, might be more permeable than different pieces of the body. This could clarify why a few medications can be ingested through the mouth (salicylic corrosive, dynamite, and so on) Blood seepage from the oral depression straightforwardly into the fundamental dissemination upgrades this drug conveyance pathway.

1.4.2 Physiological Processes in the Oral Cavity

1.4.2.1 Salivary Secretion

1.4.2.1.1 Control of Salivary Secretion

The cerebrum is accountable for salivary discharge. The salivary cores give parasympathetic nerve motivations to the salivary organs, which are essentially administered by them. At the medulla-pons intersection, salivatory cores are found. They are energized by taste and material signs from the tongue and different region of the mouth. A ton of spit is delivered because of these excitement. At the point when a smooth article is in the mouth, it animates significant

salivation, though harsh items diminish or even forestall salivation. The focal sensory system's higher focuses can manage salivation discharge. The craving region of the mind, which is situated close to the parasympathetic habitats of the foremost nerve center, is to some degree controlled by signals from the taste and smell portions of the cerebral cortex or the amygdala. Huge measures of watery, isotonic salivation with minimal natural material substance are delivered when parasympathetic cholinergic neurons are initiated. Celebrity (vasoactive digestive polypeptide) is delivered locally during this feeling, instigating vasodilation in the organ. The expanded blood stream to the organ additionally helps the organ's digestion and development. The thoughtful nerve supply is animated by transcendently - adrenergic receptors, which causes vasoconstriction and the development of less salivation wealthy in natural parts such ptyalin. The secretory reaction could be intervened to a limited extent by thoughtfully internal vated myoepithelial cell constrictions. Both adrenergic and cholinergic excitement cause salivary emission, and studies utilizing pharmacologic agonists and enemies uncover that the two frameworks cooperate. Reflexes in the stomach and upper digestive tract can likewise cause salivation. This procedure assists with weakening or kill aggravations found in the gastrointestinal lot.

The aroma, sight, contact, and sound of feast arrangement likewise advance salivary emission. These improvements involve mental actuation and learned conduct. In the cerebral cortex, the upgrades trigger recollections that interface the improvements to food. Whenever the cortex conveys messages to the cores in the cerebrum stem by means of extrapyramidal pathways, the salivary organs are initiated.

1.4.2.1.2 Saliva and Its Composition

The liquids discharged by the major and minor salivary organs make up salivation. The day by day volume of spit emitted by individuals is 1-1.5l. Salivary stream is diurnal, with the most reduced levels happening during rest and a fairly steady benchmark level all through waking hours, with set off stream intensifications. Basal rates in grown-ups range from 0.3 to 0.5 ml/min. Salivation is comprised of 99.5 percent water and 0.5 percent solutes artificially (electrolyte parts, catalyst and other salivary proteins) (electrolyte parts, chemical and other salivary proteins). The emissions of various organs contrasted enormously. The watery, amylase-rich serous salivation discharged by the parotid organs, the gooey spit emitted by the sublingual organ, and the mucinous spit emitted by the submandibular organ. Since numerous

proteins in salivation are quickly eliminated by appending to the hydroxyapatite of teeth and oral mucosal surfaces, blended spit isn't simply the amount of these releases. Spit's pH goes from 5.8 to 7.4, but it gets more isotonic and basic as it is discharged all the more rapidly. Salivary stream rate is impacted by the sort of taste boosts. By and large, citrus extracts or acrid food varieties cause the most noteworthy stream rate and Na^+ levels, while salt causes high protein and CaH levels.

Spit contains an assortment of salts, including chlorides, bicarbonates, sodium and potassium phosphates, and calcium phosphates. broken up gases and natural atoms, for example, urea, uric corrosive, serum egg whites, globulin, mucin, the bacteriolytic compound lysosyme, and the processing chemical salivary amylase are completely found in typical spit (ptyalin). Lactoperoxidase, blood bunch antigens, EGF, VIP, RNAase, DNAase, lingual lipase, kallikrein, and lactoferrin are among different compounds distinguished. Iodine, which is additionally contained in spit, is found in salivary organs.

1.4.2.1.3 Salivary Functions

Salivary emission is fundamental for the upkeep of solid oral tissues. Coming up next are the elements of this emission:

1. Spit saturates and greases up the mouth's tissues.
2. Spit helps discourse by dampening the lips and oral cavity.
3. It works with the biting and gulping of food.
4. It goes about as a dissolvable medium, passing synthetic mixtures on to taste buds, improving the impression of flavor and delight in food.
5. Its buffering limit, mineral substance, and antimicrobial qualities help to safeguard oral tissues.
6. Spit cleans the mouth and teeth by eliminating perilous microorganisms, food particles, and dead cells from the oral tissues.
7. The presence of spit makes wearing removable dental prostheses more agreeable..
8. The action of salivary amylase on starch is the essential processing capacity of spit. It produces disaccharides by separating the inside U1,4-glycosidic linkage in starch. The pH of salivation is great for the action of amylase. Lingual lipase is a fat-processing protein created by the Von Ebner organs on the tongue. It is answerable for the absorption of up to 30% of dietary fatty oils.

9. Spit contains cushions that help keep the mouth pH stable and kill disgorged stomach corrosive in the throat.

10. Anticandidal action has as of late been found in significant human salivary histatins, histatin-rich proteins found in human parotid and submandibular discharges.

11. Mercury, lead, sulfur, iodides, morphines, an assortment of medications, and infections like rabies, poliomyelitis, and HCV can be generally emptied from the body by spit emission.

1.4.2.2 Mastication (Chewing)

Rumination is the most common way of separating ingested food into small amounts, blending it in with spit, and shaping a bolus prior to gulping. Rumination is remembered to fill the accompanying roles:

1. It changes the dinner into a bolus that is promptly gulped.
2. It upgrades food edibility by diminishing molecule size precisely, expanding surface region for compound movement, and reflexively animating salivation and gastric juice emission for synthetic processing.
3. The salivary amylase action begins processing by consolidating the feast with salivation.
4. It safeguards the stomach related framework from being annoyed with a lot of food.
5. It empowers proper oral tissue improvement and extension.
6. It helps lymphatic and venous veins in the skin and muscles of the face to deplete.

Rumination is the result of an intricate arrangement of exercises that remember the opening and shutting of the jaws for a musical example, as well as broad tongue development.

1.4.2.3 Swallowing (Deglutition)

Food and salivation are moved from the mouth to the stomach through gulping, which is a directed strategy. A complicated reflex reaction called gulping is set off by afferent driving forces in the trigeminal, glossopharyngeal, and vagus nerves. These motivations are coordinated by the core of the tractus solitaries and the core questionable. The efferent filaments to the pharyngeal muscular structure and the tongue are conveyed by the trigeminal, facial, and hypoglossal nerves. Gulping starts when the substance of the mouth are deliberately assembled on the tongue and constrained in reverse into the throat. The gulping processes that follow are totally wild.

1.4.2.4 Speech

Maybe the most troublesome sensorimotor formative cycle in people is discourse improvement. The larynx produces sounds by the synchronized activities of the stomach, thoracic, and laryngeal muscles (phonation). The pharyngeal, oral, and nasal trenches all have an impact in the change of laryngeal sound into comprehensible discourse (enunciation). The laryngeal note has a reedy, breezy quality to it. Therefore, just a little measure of discourse data is contained in this sound, which is subsequently altered by thoughtful vibration in resounding chambers and the activity of organs such the lips, tongue, and delicate sense of taste. The resonators fill in as acoustic channels, improving a few frequencies while changing to other people. Discourse explanation engine upgrades are created by means of sensorimotor cycles like those utilized in oral taking care of and fine coordination somewhere else in the body. Discourse effectors, then again, are more assorted and physically circulated than some other sensorimotor coordination, working in a more extensive scope of examples and timetables with more significance to natural conditions or potentially setting. Without an inquiry, discourse is the most externalized human movement.

1.4.2.5 Sensation

The tangible capacity of the oral mucosa is significant in light of the fact that it gives an abundance of data regarding what's happening in the mouth, while the lips and tongue can identify upgrades from outside the mouth. The mouth has temperature, contact, and agony receptors, as well as taste buds not found wherever else in the body.

It's viewed as that a few receptors in the oral mucosa react to the flavor of water and sign thirst satiation. Gulping, choking, regurgitating, and salivation are totally set off by oral mucosa receptors. The feeling of taste in creatures is an oral compound sense that assists them with picking what to eat. Taste buds, which are found in four distinct areas of the mouth hole, are quick to communicate sentiments. Taste bud cell film particle diverts assume a part in upgrade transduction, and medications can influence taste buds. The view of taste progressively disintegrates with age because of a decrease in the quantity of taste buds, with severe flavor being the most impacted. In primates, neural circuits that intercede taste incorporate the cranial nerves VII, IX, X, the singular core in the mind stem, the ventroposteromedial core of the

thalamus, and the separate opercular cortex. The center taste circuits process sweet, pungent, harsh, and severe boosts sequentially and in equal.

1.4.2.6 Feeding Suckles

Nurse taking care of is a sensorimotor capacity that is created upon entering the world and turns out to be completely capable inside 2 hours of conveyance in an ordinary newborn child. Nursing is a newborn child's important conduct during the initial half a month following birth. As the baby becomes older, nursing turns out to be all the more impressive and cadenced, and hooking and establishing signals are at long last gained. Nurse is finished by moving the tongue, lower lip, and lower jaw corresponding to the sense of taste.

1.4.3 Some Other Functions and Activities of the Oral Cavity^[44-47]

The mouth has various capacities, the majority of which are imparted to the pharynx. The mouth and throat are continually functioning as a tactile source and in sensorimotor execution during rest and waking. The mouth is effectively stood firm on in a steady footing during rest, except for non-nourishing nursing in earliest stages, showing rehashed thalamic action. In the conscious express, the mouth and pharynx effectively partake in keeping up with the stance of the neck and the place of the designs around the pharyngeal aviation route. The mouth and pharynx's arrangement job is believed by certain scholars to be a critical action of the mouth and pharynx.

Engine adjustment of oral and pharyngeal stance endures during quiet flowing breathing; this situating around the pharynx is the essential system for keeping up with the pharyngeal aviation route during nasal gateway breath. The mouth depression is engaged with both nasal and oral respiratory tasks. The genioglossus muscle of the tongue, specifically, is locked in 100% of the time during motivation.

Oral and pharyngeal movements are synchronized while an individual is crying. During phonated lapse, the mouth opens by pushing the jaw descending and forward. The tip of the tongue is every now and again distended forward and up, while the body of the tongue is medially furrowed. These overall exercises of the mouth, pharynx, and larynx are performed by equal synchronization of constrained lapse and motivation. During motivations between shouts, the tongue turns out to be marginally smoothed and ascends toward the sense of taste, and motivations are somewhat done through the nose. As indicated by outer perception, hacking has

comparable mouth developments to wailing. Besides, the movements of emesis are strikingly like that of crying lapses. Since it makes mental and physiological reactions when animated during sexual contact, the mouth is a significant erogenous region. In response to sexual excitement in different areas, the mouth expands responsiveness, vascularity, and salivation.

1.5 Introduction of Mouth Dissolving Film ^[48-50]

The oral course of medication organization is the most liked because of its simplicity of organization, painlessness, versatility, patient consistence, and acknowledgment. Utilizing current novel advancements, numerous options in contrast to the oral course of medication conveyance have been proposed for pediatrics, geriatrics, sick, and rebelliousness patients. Bioadhesive mucosal measurements structures like cement tablets, gels, and fixes have been created because of innovative forward leaps. The utilization of polymeric movies to convey drug into the buccal pit has recently showed huge potential among the different portion structures. After deterioration as well as disintegration, orally breaking down films (ODFs) quickly hydrate by splashing salivation, letting the dynamic pharmacological part out of the measurements structure. ODFs are a kind of detailing that utilizes hydrophilic polymers to break up rapidly when presented to spit. Oral breaking down tablets (ODTs) and oral crumbling films are two sorts of orally deteriorating drug conveyance frameworks (ODFs). These frameworks were created in the last part of the 1970s as an option in contrast to standard dose structures such fast deteriorating tablets and containers for geriatric and pediatric patients who experienced issues gulping customary measurement structures. A standard ODF is about the size of a postage stamp. The appearance of ODT in the commercial center was intently attached to patient advising about right organization, with guidance like "don't bite/don't swallow." Despite these standards, biting and gulping occasions were ordinarily archived. Then again, ODFs freed the majority from these calamities.

1.5.1 The administration of ODFs has numerous advantages and some of them are as follows: ^[51-52]

- i. Reasonable transportation.
- ii. Geriatrics and youths make some simpler memories gulping.
- iii. Dosing that is both straightforward and precise.
- iv. There is no requirement for water during organization.

v. Advantageous for dysphasics who experience issues gulping tablets or cases.

Through keeping away from the hepatic first pass impact, expanded bioavailability and fast beginning of activity, as well as soundness No costly lyophilization, incredible mechanical strength, speedy crumbling, and diminished stifling worries are among the advantages of ODFs21a. As a result of its one of a kind elements and fast breaking down time traversing from seconds to one moment, ODFs21a has acquired critical footing in the drug business. The design of ODF takes into consideration the incorporation of an assortment of medications with different pharmacological impacts, like enemy of tussive, hostile to epileptic, against asthmatic, expectorant, etc. Temperatures are high, and there is a great deal of dampness in the air.

1.5.2 Disadvantages

1. The technological challenge of dose uniformity is difficult to address.
2. It is highly hygroscopic.
3. High doses (40 mg/4cm² piece) are ineffective.
4. For product stability and safety, special packaging is required.

1.5.3 Special Features of Mouth Dissolving Films ^[53-55]

1. A finely thin film
2. Negative in nature
3. Comes in a variety of sizes and forms
4. Rapid decomposition
5. Quick release
6. Make the mouth feel good.
7. Have a good sense of taste.
8. No residues should be left in the mouth.

1.5.4 Ideal Requirements ^[56-57]

The ideal requirements for ODF are summarized below:

- ✓ To ensure a strong production and packaging process as well as ease of handling and administration, ODF should be thin and flexible, but stable.
- ✓ The films must be transportable, non-sticky, and able to maintain a level shape without rolling up.
- ✓ Ease of administration for mentally ill, impaired, and uncooperative individuals.

- ✓ They should have a pleasing mouthfeel and a pleasant taste.
- ✓ There is no need for water.
- ✓ The time it takes for something to disintegrate should be as short as possible.
- ✓ They should be relatively unaffected by environmental factors such as temperature and humidity.
- ✓ They should be able to give liquid medicine benefits in the form of a solid preparation.
- ✓ The size of a unit FDF should not be so enormous that it interferes with the patient's ability to comply.
- ✓ The FDF's surface should be smooth and homogeneous.
- ✓ They should be physically and chemically stable for the duration of their shelf life.
- ✓ Cost-effective and simple to produce commercially.

1.5.5 Formulation Aspects For Mouth Dissolving Films^[58-62]

1.5.5.1 Active Pharmaceutical Ingredient

ODFs can contain allergy medicines, hostile to diarrheals, antidepressants, vasodilators, enemies of asthmatics, against emetic drugs, etc. ODFs' flavor can in like manner be masked with dimenhydrinate. ODFs regularly contain salbutamol sulfate, rizatriptan benzoate, verapamil ondansetron, dexamethasone, rofecoxib, cetirizine, pilocarpine, tianeptine sodium, indomethacin, and different meds.

1.5.5.2 Film Forming Polymer

Water-solvent polymers are utilized as film formers since they consider quick breaking down, a lovely mouth feel, and mechanical strength. The sort of polymer utilized and the sum used in the details decide the strip's strength. The most normally involved polymers for film creation are pullulan, gelatin, and hypromellose. Pullulan, gelatin, guar gum, thickener, HPMC, changed starches, PVPK30, PVA, and other water-solvent polymers are a couple of models.

1.5.5.2.1 Ideal properties of the polymers used in the oral film

1. Nontoxic, aggravation free, and boring polymers ought to be utilized.
2. It ought to be flavorless.
3. It ought to be without poisons that can be drained.
4. It should be modest and easy to get.
5. During the deterioration interaction, it ought not be a staggering impediment.

6. It should have extraordinary wetting and spreading properties.
7. It should be sufficiently able to strip, shear, and ductile.
8. It should have an extensive timeframe of realistic usability and not cause optional disease in the mouth.

1.5.5.3 Plastisizers

Plasticizers further develop mechanical properties like as rigidity and percent stretching in many details. Plasticizer fixations ordinarily range from 0% and 20% weighted normal. Plasticizers like PEG, glycerol, diethyl phthalate, triethyl citrate, tributyl citrate, and others are regularly utilized.

1.5.5.4 Sweetening Agent

Sugars have turned into a famous fixing in food sources and prescriptions intended to break up or deteriorate in the mouth. Normal and counterfeit sugars are utilized to build the attractiveness of oral dissolving details.

(1) A characteristic sugar that is water solvent, like xylose, ribose, glucose, sucrose, maltose, stevioside, and others.

(2) Water-solvent fake sugar: sodium or calcium saccharin salts, acesulfame-K, and so forth
Aspartame is a sugar comprised of dipeptides.

1.5.5.5 Saliva Stimulating Agent

Salivary energizers, which are by and large acidic in nature, help to separate ODFs by expanding spit creation in the buccal cavity. Probably the most regularly utilized salivation animating mixtures incorporate citrus extract, malic corrosive, tartaric corrosive, ascorbic corrosive, and lactic corrosive.

1.5.5.6 Surfactant

Surfactants are utilized as solubilizers, wetting specialists, and dispersants, making the film deteriorate like a flash and the dynamic fixing to be delivered right away. Surfactants likewise help the disintegration of ineffectively solvent medications in quick dissolving buccal movies. A few models are Polaxamer 407, sodium lauryl sulfate, benzalkonium chloride, benzthonium chloride, tweens and ranges, and others.

1.5.5.7 Flavor

Flavors are fundamental for veil the harsh or horrendous taste of the coordinated medication. How much still up in the air by the strength and nature of the flavor. Any flavor endorsed by the FDA in the United States, like sweet, sharp, or mint, can be utilized. As per one review, a flavor blend of mint, licorice, and sucralose successfully covers the harsh taste of diclofenac sodium. Electronic tongues are utilized to recognize the impacts of different taste concealing specialists (TMAs).

1.5.5.8 Colouring Agent

Whenever part of the plan fixings or medications are in insoluble or suspension structure, shades, for example, titanium dioxide or FD&C supported shading added substances are utilized in oral strips (at fixations not surpassing 1% w/w).

TABLE 1. 2 Percentage of various ingredients used in formulation of ODF

| Ingredients | Amount (w/w) |
|--------------------------|---------------------|
| Drug | 5-30 % |
| Water Soluble Polymer | 45 % |
| Plasticizer | 0-20 % |
| Saliva Stimulating Agent | 2-6 % |
| Surfactant | q.s |
| Sweeting Agent | 3-6 % |
| Flavor, Color, Filler | q.s |

1.6 Manufacturing Methods ^[63-67]

1.6.1 Solvent Casting Method

The most average methodology for assembling ODFs with water dissolvable excipients, polymers, and drugs broke up in de-ionized water is dissolvable projecting; as a result, a homogenous combination is accomplished by utilizing high shear powers produced by a shear processor. The pre-arranged arrangement is poured onto a petri plate and the dissolvable is permitted to dry by presenting it to high temperatures to create great quality movies. The dissolvable projecting strategy was utilized to make an orodispersible film of tianeptine sodium utilizing different grades of Lycoat and HPMC. In the dissolvable projecting procedure, the film

framing polymer is generally absorbed a reasonable dissolvable short-term. In view of basic physicochemical highlights of the API, like softening point, shear responsiveness, and polymorphic structure, the kind of API that should be remembered for ODF characterizes the ideal dissolvable. The medication's similarity with the dissolvable and other excipients is considered prior to finishing a detailing. The presence of caught air rises during the detailing system can affect the consistency of the completed film. With the assistance of a vacuum siphon, the blend is deaerated. The dissolvable projecting strategy was likewise utilized to make a mosapride orodispersible film definition. In the projecting system, the consistency of the answer for be poured is vital. Pullulan focuses going from 2% to 8% outcome in a low thickness arrangement that makes film projecting basic. Anastrozole quick dissolving films were additionally effectively made utilizing the dissolvable projecting strategy with HPMC (E5) and polyvinyl liquor (PVA).

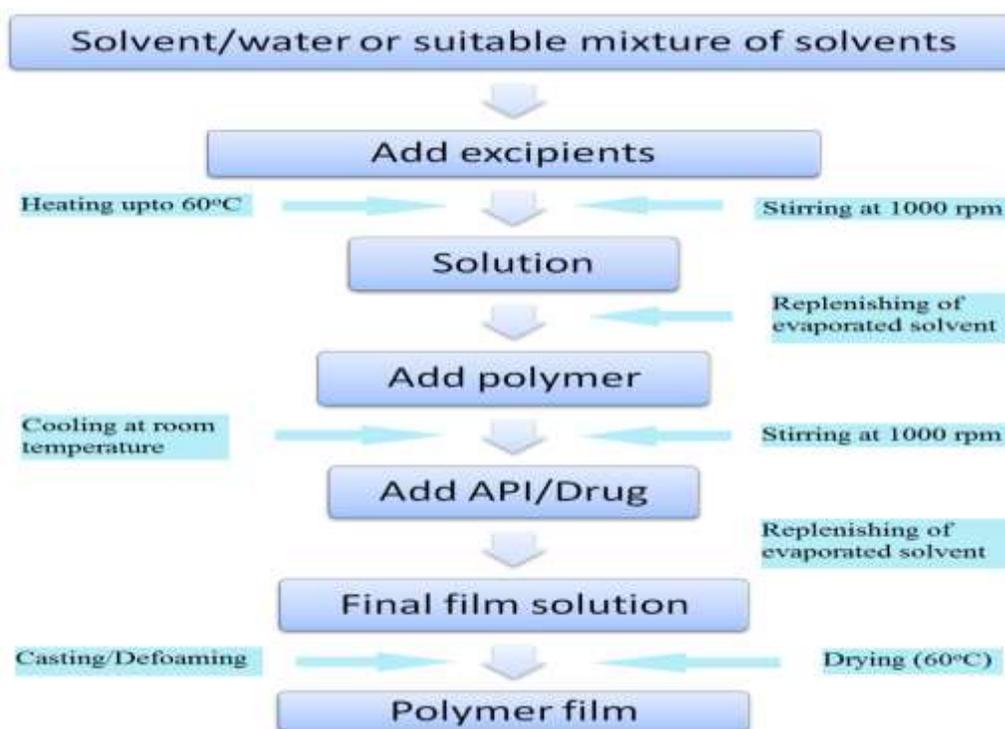


FIGURE 1. 2 Solvent Casting Method

1.6.2 Hot Melt Extrusion

In hot-liquefy expulsion, dry parts for the film are warmed and homogenized by an extruder screw until they are liquid and blended. The extrudate is driven into the fundamental film shape by a level expulsion kick the bucket. Lengthening rollers can influence the thickness and

strength of the film while it is as yet hot and adaptable. In the wake of cooling and cutting the expelled film, the hot soften expulsion procedure is talked about.

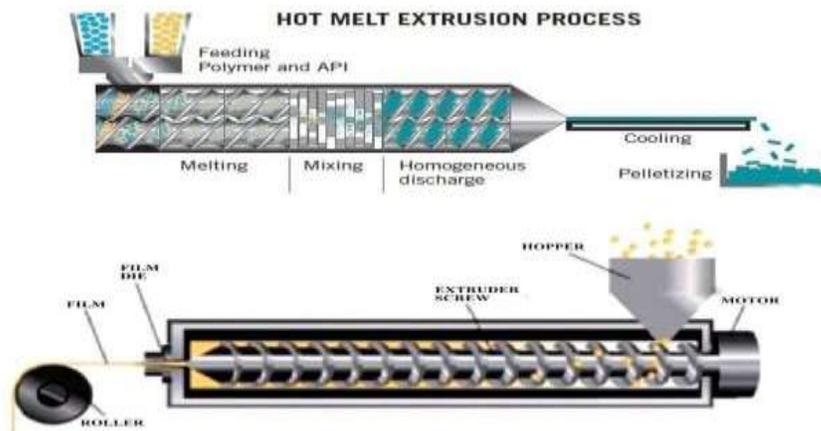


FIGURE 1.3 Hot melt extrusion technique

1.6.3 Semisolid Casting Method

A film-shaping polymer arrangement that is water solvent is made. The resultant arrangement is joined with a polymer arrangement that is corrosive insoluble (for example cellulose acetic acid derivation phthalate, cellulose acetic acid derivation butyrate). To acquire gel mass, an adequate measure of plasticizer is utilized. At last, the gel mass is shaped into the movies or strips utilizing heat-controlled drums. Somewhere in the range of 0.015 and 0.05 creeps of film thickness ought to be utilized. The corrosive insoluble polymer ought to be joined with the film framing polymer in a 1:413 proportion.

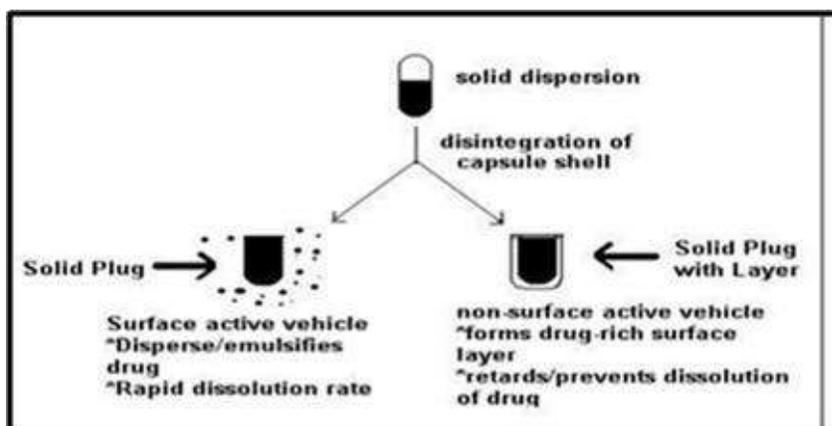


FIGURE 1.4 Solid Dispersion Extrusion Method

1.6.4 Rolling Method

This strategy includes making a pre-blend, adding a functioning, and afterward producing a film. Set up a pre-blend in with a film-framing polymer, a polar dissolvable, and different added substances (barring a medication) and add it to the expert clump feed tank. A first metering siphon and control valve ought to be utilized to take care of it to either of the first and second blenders. Add the required measure of medicine to the blender you've chosen. Consolidate the drug with the expert cluster pre-blend to get a uniform grid.. Second metering siphons convey a foreordained measure of uniform framework to the dish. At long last, the film is framed and shipped to the help roller on the substrate. The wet film is dried by means of controlled base drying. The most generally utilized solvents are water and a combination of water and liquor.

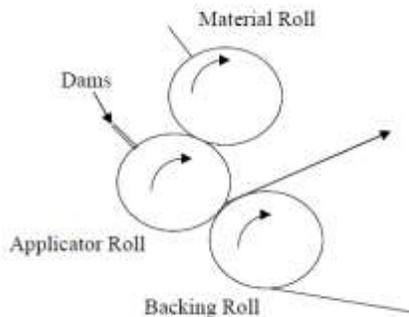


FIGURE 1.5 Rolling Method

1.7 Evaluation Parameters [68-69]

1. Thickness Test
2. Tack Test
3. Youngs Modulus
4. Tail flick Test
5. Thermodynamic Stability Study
6. Drug Content
7. Viscosity
8. Tensile Strength
9. Folding Endurance
10. Weight of films
11. % Elongation

12. Swelling Properties
13. Disintegration Time
14. Surface pH
15. Content Uniformity
16. Dissolution test

1.8 Marketed Product of Mouth Dissolving Film^[62-64]

TABLE 1. 3 Marketed Product of Mouth Dissolving Film

| Product | API | Manufacturer | Use |
|-----------------|--------------------------|---------------------------|-------------------|
| Listerine | Cool Mint | Prfizer | Mouth Ulcer |
| Benadryl | Diphenylhydramine HCL | Prfizer | Antiallergic |
| Suppress | Menthol | InnoZen, [®] Inc | Cough Suppressant |
| Klonopin wafers | Clonazepam | Solvay Pharmaceutical | Antianxiety |
| Theraflu | Dextromethorphan | Novartis | Antiallergic |
| Orajel | Menthol/Pectin | Del | Mouth Freshner |
| Gas-X | Simethicone | Novartis | Antiflatuating |

1.9 Introduction Of Design of Experiment (DoE)^[70-75]

Test configuration is anything but another idea. Sir Ronald Fisher, a splendid analyst, established the framework for present day measurable exploration during the 1920s with his "virtuoso" commitments to insights. The review took a proactive methodology, which is essential to the current administrative system that controls drug item improvement. Walter A. Shewhart, William E. Deming, and Joseph M. Juran explained on this idea by upholding for a cycle based culture for infusing quality into things. To stress the meaning of joining Quality into labor and products, Juran developed the five-venture technique "Quality by Design." This cycle involves getting to know the shopper, evaluating his needs, making an interpretation of them into item attributes, planning it, and carrying out it in tasks. W.E. Deming proposed his deliberate way to deal with shrewdness around 50 years before Juran, which joined framework thinking, fathoming variety, hypothesis of information, and brain science. He accepts that quality confirmation should focus on the cycle rather than the outcomes on the grounds that "on

the off chance that you can't characterize the interaction, you're not doing it right" and "quality is as of now in the item." Control graphs with measurable cycle control were important for Schewhart's quality improvement endeavors. The drug business is probably going to be quick to carry out these thoughts since it puts such a high significance on quality and interaction. Thus, right off the bat in the thousand years, administrative bodies discovered that quality couldn't be coordinated into items (that is, planned into them). A Design of Experiments (DoE) is utilized in exploration and industry to carry out Quality by Design (QbD). Since of Fisher's inheritance, it is known as the essential arrangement of drug improvement since it requires the use of factual thinking from the beginning. The turn of events and development of drug quality levels has become progressively popular. The greatest reason for quality worries, as per Juran, is the drug creation process. Review and testing can't demonstrate the security and adequacy of an ineffectively planned drug item. Subsequently, QbD accepts that expanding the quantity of examinations would not work on quality. To put it another way, to be implicit, the item's quality should be astounding. This way to deal with drug advancement begins with clear cut objectives and focuses on item and cycle ability. It is established on sound exploration and viable gamble the board. Information and comprehension are acquired when QbD is applied in drug creation.

a) Improving reason impact investigation and administrative adaptability; b) Stabilizing cycles and decreasing fluctuation; c) Increasing the productivity of drug improvement; d) Improving reason impact examination and administrative adaptability Most administrative bodies across the world have embraced hazard based strategies and severe quality affirmation in drug advancement.

The utilization of QbD strategies in the making of insightful systems has been archived in a few papers. Scientific quality administration is utilized to create and work on solid and practical logical techniques. Logical methodologies are utilized in QbD execution to create more exact outcomes while limiting the gamble of disappointment. For centuries, drug enterprises have zeroed in on improving each angle in turn (OFAT). All factors stay unaltered, except for one, which is modified inside a sensible reach (or level). Since the OFAT strategy doesn't consider factor associations, it might prompt deficient turn of events and streamlining. You might have the option to get prevalent outcomes in only a couple of tests assuming you construct preliminaries accurately. The Department of Energy utilizes measurable methodologies, for example, screening and advancement plans. In drug and scientific QbD, the DoE is the main

part. Thus, the current review looks at hypothetical and down to earth issues about DoE's application in drug and scientific QbD.

1.9.1 Definitions and Terminologies^[76-78]

Quality by Design (QbD) is an orderly way to deal with item and interaction advancement that underscores item and cycle comprehension and control while sticking to sound science and hazard the board. It's an information association and organizing approach for information about the connection among cycle and result factors. "Try Design" is one more name for it (DoE). Basically, deciding what data sources mean for results is the demonstration of making process information.

Treatment - Various treatment mixes are accessible.

Therapy levels - Treatment power during the investigations

Treatment (factors) - In a test, a controlled condition.

Exploratory unit - The individual to whom treatment will be regulated and a reaction will be estimated. Likewise alluded to as a response estimation.

Reactions - After medicines are applied to trial units, the outcomes are obtained.

Test plan - Treatment level task.

Examination of change (ANOVA) - Method for deciding the reasons for reaction changeability.

Replication - Observing the reactions of a few exploratory units under indistinguishable test conditions.

Randomization - The choice of test units was not done in a deliberate way.

Frustrating - An examination where one component or treatment's impact can't be isolated from the impact of another element or treatment.

Autonomous factors: Formulation researchers have direct impact over the interaction.

Subordinate factors: Result factors

Factors: Qualitative and quantitative variables.

Level: Value relegated to a variable

Reactions surface plot: A three-layered plot portraying the connection between the autonomous and ward factors.

Collaboration: It gives the net impact of at least two factors without requiring additivity of their belongings

Impact: Amount of the change

Form plot: A diagram of one autonomous variable plotted against one more while keeping the reaction consistent

Form lines: determined shape lines over a counterplot

Symmetry: When no connection happens because of the principle element of interest

Goal: Measuring frustrating

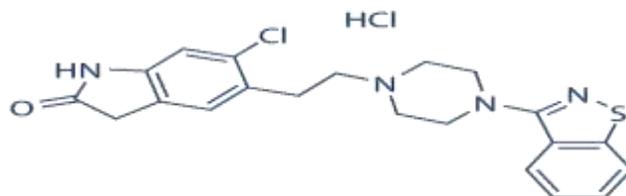
1.9.2 Advantages ^[78-80]

- ✓ DoE enjoys a great deal of benefits when contrasted with OFAT. The trial configuration approach is a system for making tests that amplify cycle information while consuming minimal measure of assets. However much right data as could reasonably be expected ought to be given. Analyze how factors interface with each other. Investigate every part independently to decide its relative significance. Inside a plan region, foreseeing the conduct of an interaction.
- ✓ On various fronts, OFAT outflanks DoE. Utilize the least assets attainable with trial plan systems. Information should be sent as definitively and proficiently as could really be expected. Investigate how they communicate. Decide every factor's relative significance. Take into account process conduct forecast inside the plan space. Basic Process Parameters (CPPs) and Critical Quality Attributes (CQAs) ought to be firmly connected. Drug things should be upgraded all the while since they contain countless CQAs. Work on the flexibility of the item or process, or its protection from wild components and outer occasions. Distinguish exceptions inside the laid out test lattices to guarantee that they are secured.
- ✓ By changing each component in turn, OFAT strategies, then again, distinguish nearby imperfect zones. Since this antiquated technique consumes a large chunk of the day, it can't investigate numerous elements on the double or take a gander at their associations. OFAT can't be utilized in QbD applications because of its blemishes. One of the benefits of the DoE strategy over OFAT tests is that it explains the exchange between input components. Association impacts are utilized to survey the effect of info things on yield.
- ✓ This technique can be utilized to work on a current plan by diminishing the quantity of trial preliminaries, dissecting and improving the troublesome association between autonomous factors, and decreasing the general measure of information. Accordingly, this factual technique is more functional than conventional exploratory work since it fuses variable

cooperations thus shows the factors' aggregate impacts. Besides, reaction surface plans like the Central Composite, Box-Behnken, and Hybrid can be valuable practically speaking.

1.10 DRUG PROFILE

1.10.1 ZPO HCL



Reason for Selection

It's an antipsychotic medication used to treat schizophrenia and bipolar disorder. Aside from film, the most widely used treatment, and a variety of other formulations have been developed so far.

Profile

Ziprasidone is an atypical antipsychotic used to treat schizophrenia, acute mania, and mixed states in bipolar disorder. Geodon and other trade names are used to market it.

Molar mass: 412.936 g/mol

Formula: C₂₁H₂₁ClN₄OS

Trade name: Geodon, Zeldox, Zipwell

Elimination half-life: 7 to 10 hours

Metabolism: Hepatic (aldehyde reductase)

Pharmacology

It's a benzothiazolylpiperazine derivative that's used to treat schizophrenia, acute mania, and mixed states in bipolar patients. At the dopamine D₂ and serotonin 5-HT_{2A} and 5-HT_{1D} receptors, it acts as both an antagonist and an agonist. It also reduces synaptic reuptake of serotonin and norepinephrine. The antischizophrenic effect of ziprasidone hydrochloride is unknown, however it could be mediated through a combination of dopamine D₂ and serotonin 5-HT₂ antagonism. Histamine H₁ and alpha-1 adrenergic receptors are also hostile to this drug.

Uses

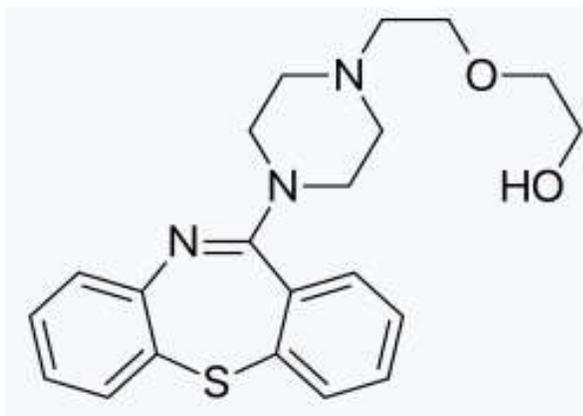
Treatment of schizophrenia as well as acute mania and mixed states associated with bipolar disorder.

Adverse effects

- Sleepiness and headache are very common adverse effects (>10%).

Producing too much saliva or having a dry mouth are common adverse effects (1–10 percent), as are runny nose, respiratory illnesses or coughing, nausea and vomiting, stomach aches, constipation or diarrhoea, loss of appetite, and weight gain (but the smallest risk for weight gain compared to other antipsychotics)

1.10.2 Quetiapine



Reason for Selection

Quetiapine, often known as Seroquel, is an atypical antipsychotic medication that is used to treat schizophrenia, bipolar disorder, and major depressive disorder. Because of its sedative effect, it is sometimes used as a sleep aid, however this is not recommended. It is taken orally.

Profile

Molar mass: 383.5099 g/mol

Formula: C₂₁H₂₅N₃O₂S

Trade name: Seroquel, Temprolide

Protein binding: 83%

Bioavailability: 100 %

Elimination half-life: 7 hours (parent compound); 9–12 hours (active metabolite, norquetiapine)

Pharmacology

- Quetiapine The fumarate salt form of quetiapine, a dibenzothiazepine derivative with antipsychotic properties, is known as fumarate. It's used to treat schizophrenia as well as acute manic episodes associated with bipolar I disorder. Some believe quetiapine's antipsychotic impact is mediated via antagonist activity at dopamine and serotonin receptors. The D1 and D2 dopamine receptors, the alpha 1 and alpha 2 adrenoreceptors, and the 5-HT1A and 5-HT2 serotonin receptor subtypes are all affected. Quetiapine also has an antihistamine H1 receptor antagonistic action.

Uses

- Primarily used to treat schizophrenia or bipolar disorder

Adverse effects

- Very common (>10% incidence) adverse effects Dry mouth, Dizziness, Headache;
- Common (1–10% incidence) adverse effects High blood pressure, Orthostatic hypotension, High pulse rate, Elevated serum triglycerides, Abdominal pain, Constipation, Vomiting, Increased liver enzymes, Fatigue, Pain

1.11 POLYMER PROFILE¹⁰⁴

1.11.1 HPMC E 5

- Hypromellose, short for hydroxypropyl methylcellulose, is a semisynthetic, inert, viscoelastic polymer used as eye drops, as well as an excipient and controlled-delivery component in oral medicaments, found in a variety of commercial products.

- **Formula:** $C_{56}H_{108}O_{30}$
- **Soluble in:** Insoluble in Water
- **Molar mass:** variable
- **Physical state:** Solid
- **Viscosity:** 4-6cps
- **Odor:** Odorless
- **Color:** White Powder

1.11.2 PEG-400

- It is a low-molecular-weight grade of polyethylene glycol. It is a clear, colorless, viscous liquid. Due in part to its low toxicity, PEG 400 is widely used in a variety of pharmaceutical formulations.

- **Density:** 1.13 g/cm³
- **Formula:** C_{2n}H_{4n+2}O_{n+1,n=8-2to9.1}
- **Viscosity:** 90.0 cSt at 25 °C, 7.3 cSt at 99 °C
- **Molar mass:** 380-420 g/mol
- **Melting point:** 4 to 8 °C (39 to 46 °F; 277 to 281 K)
- **LD₅₀ (median dose):** 30 mL/kg, orally in rats
- **Flash point:** 238 °C (460 °F; 511 K)

1.11.3 Citric acid

▪ Citric acid is a weak organic acid that has the chemical formula C₆H₈O₇. It occurs naturally in citrus fruits. In biochemistry, it is an intermediate in the citric acid cycle, which occurs in the metabolism of all aerobic organisms. More than a million tons of citric acid are manufactured every year.

- **Formula:** C₆H₈O₇
- **Molar mass:** 192.124 g/mol
- **Melting point:** 153 °C
- **Density:** 1.66 g/cm³
- **Boiling point:** 310 °C
- **Soluble in:** Water, Alcohol, Dimethyl sulfoxide, Ethyl acetate, Ether

1.11.4 Aspartame

▪ Aspartame is an artificial non-saccharide sweetener used as a sugar substitute in some foods and beverages. In the European Union, it is codified as E951. Aspartame is a methyl ester of the aspartic acid/phenylalanine dipeptide.

- **Formula:** C₁₄H₁₈N₂O₅
- **Molar mass:** 294.3 g/mol
- **Acidity (pK_a):** 4.5–6.0
- **Solubility in water:** Sparingly soluble
- **Solubility:** Slightly soluble in ethanol

1.11.5 Mannitol

▪ Mannitol is a type of sugar alcohol which is also used as a medication. As a sugar, it is often used as a sweetener in diabetic food, as it is poorly absorbed from the intestines. As a

medication, it is used to decrease pressure in the eyes, as in glaucoma, and to lower increased intracranial pressure.

- **Molar mass:** 182.172 g/mol
- **Formula:** $C_6H_{14}O_6$
- **CAS ID:** 69-65-8
- **Metabolism:** Liver, negligible
- **Elimination half-life:** 100 minutes
- **Trade name:** Osmitrol

1.11.6 Orange Flavor

- Oranges are a good source of folate, a source of vitamin A and B₁, and fiber
- Oranges are widely grown in warm climates worldwide, and the flavors of oranges vary from sweet to sour.
- The fruit is commonly peeled and eaten fresh, or squeezed for its juice

1.11.7 Methyl paraben

- Methylparaben, also methyl paraben, one of the parabens, is a preservative with the chemical formula CH_3 . It is the methyl ester of p-hydroxybenzoic acid.
- **Molar mass:** 152.15 g/mol
- **Formula:** $C_8H_8O_3$
- **point:** 275 °C
- **UV-vis (λ_{max}):** 255 nm (methanol)

1.11.8 Propyl paraben

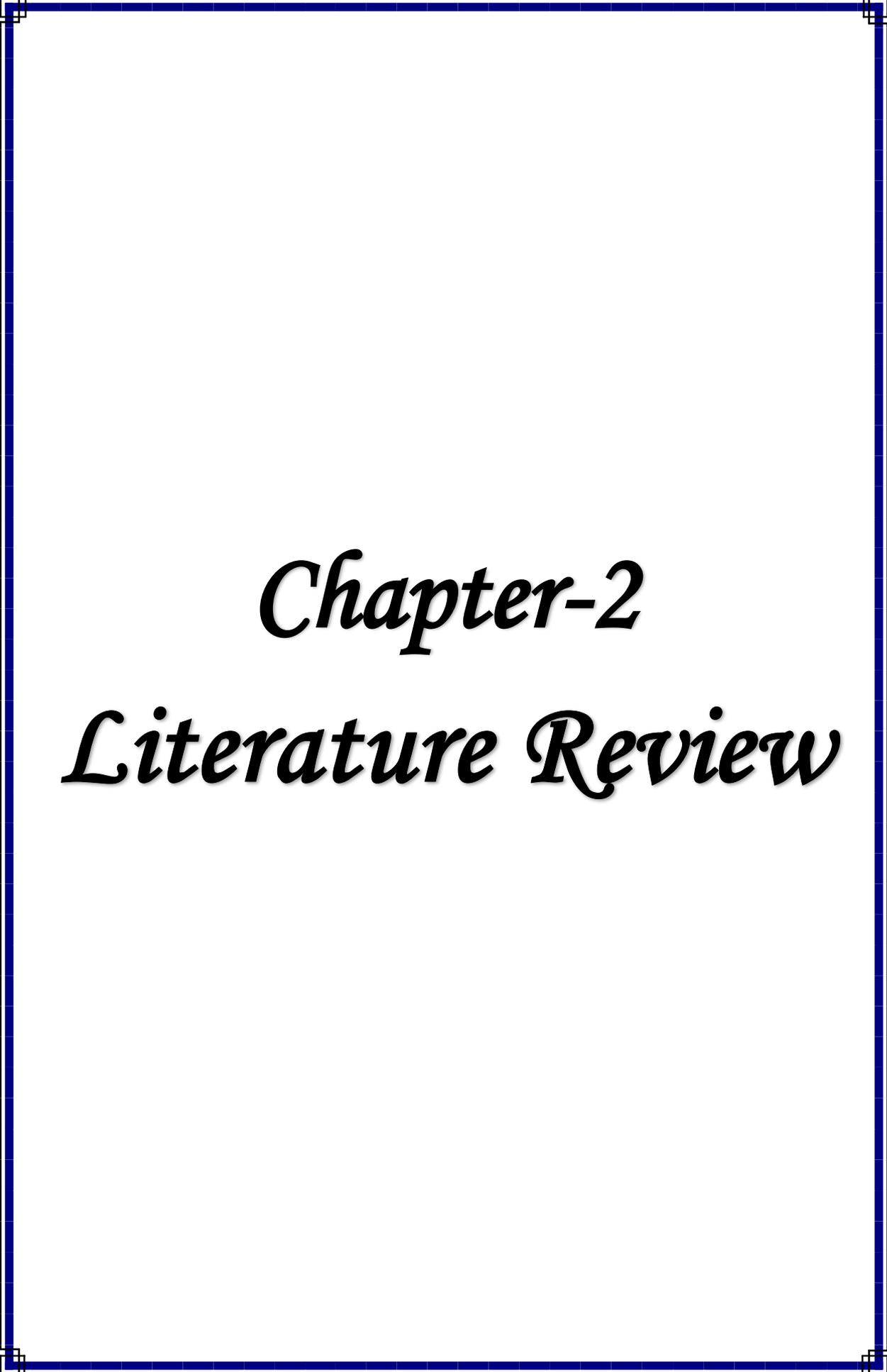
- Propylparaben, the n-propyl ester of p-hydroxybenzoic acid, occurs as a natural substance found in many plants and some insects, although it is manufactured synthetically for use in cosmetics, pharmaceuticals and foods.
- **Molar mass:** 180.2 g/mol
- **Formula:** $C_{10}H_{12}O_3$
- **Density:** 1.06 g/cm³
- **Melting point:** 96 to 99 °C (205 to 210 °F; 369 to 372 K)

1.11.9 Vanillin

Vanillin is an organic compound with the molecular formula $C_8H_8O_3$. It is a phenolic aldehyde. Its functional groups include aldehyde, hydroxyl, and ether. ... Synthetic vanillin is now used more often than natural vanilla extract as a flavoring agent in foods, beverages, and pharmaceuticals

1.11.10 Distilled water

Distilled water is water that has been boiled into vapor and condensed back into liquid in a separate container. Impurities in the original water that do not boil below or near the boiling point of water remain in the original container. Thus, distilled water is a type of purified water



Chapter-2
Literature Review

CHAPTER 2

LITERATURE REVIEW

2. LITERATURE REVIEW

2.1 Literature Review on Mouth Dissolving Film:

| Author Name & Publication Year | Title of Paper | Description | Journal Name | Reference No |
|--------------------------------|---|--|------------------------|--------------|
| Raza et al. (2019) | Effect of taste masking technology on fast dissolving oral film: dissolution rate and bioavailability | <p>Drug: Losartan potassium</p> <p>Polymer: HMCP, sodium carboxy methyl cellulose, sodium alginate</p> <p>Description: for the treatment of hypertension that had quick disintegration, optimal morphological qualities, and mechanical strength. Losartan is an antihypertensive medication that goes through a lot of first-pass metabolism, which means it has a low bioavailability. The medicine enters the bloodstream immediately through the buccal route, increasing its bioavailability.</p> | Nanotechnology | 81 |
| Bala et al. | Formulation | Drug: Aprepitant | Bulletin of Faculty of | 82 |

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|---------------------|---|--|--|----|
| (2018) | optimization and evaluation of fast dissolving film of aprepitant by using design of experiment | <p>Polymer: PEG 400</p> <p>Method : Solvent Casting Method</p> <p>Description: The aforesaid findings indicate that the created formulation has the potential to be a new dosage form for improving medication distribution, start of action, and patient compliance</p> | Pharmacy | |
| Linku et al. (2018) | Formulation and evaluation of fast dissolving oral film of anti-allergic drug | <p>Drug: Loratadine</p> <p>Polymer: HPMC, PEG 400, PG</p> <p>Method; solvent casting process</p> <p>Description: These findings imply that a Loratadine oral film that dissolves quickly could be effective for allergy treatment when a quick onset of action is required</p> | Asian Journal of Pharmaceutical Research and Development | 83 |
| Pooja et al (2018) | Design, Development and Evaluation of Oxcarbazepine Loaded Fast Dissolving Oral Film | <p>Drug: Oxcarbazepine</p> <p>Polymer: HPMC, PEG 400</p> <p>Method: Solvent Casting Method</p> <p>Description: The results obtained showed no physical chemical incompatibility between the drug and the polymers. The prepared films were clear,</p> | International Journal of Drug delivery | 84 |

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|-------------------|---|--|----------------|----|
| | | transparent and smooth surface. | | |
| Zhu et al. (2018) | Effect of taste masking technology on fast dissolving oral film: dissolution rate and bioavailability | <p>Drug: Loratadine</p> <p>Polymer: HPMC, PEG 400</p> <p>Description: The two films disintegrated more quickly than the commercial tablets. Rat pharmacokinetic tests revealed that the suspension film's oral bioavailability was substantially higher than that of commercial tablets, with a relative bioavailability of 175 percent. The bioavailability of the liposomal film was improved, but not as much as that of the suspension film.</p> | Nanotechnology | 85 |

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|-----------------------------|---|--|---|----|
| Pagilla et al. (2018) | Formulation and evaluation of lovastatin oral disintegration thin films | <p>Drug: Lovastatin</p> <p>Polymer: CCS,PVA, Gelatin</p> <p>Method: Solvent Casting Method</p> <p>Description: Film thickness, folding durability, in-vitro disintegration time, in-vitro drug release pattern, and drug content were all tested on the generated formulations. The interaction between drugs and polymers was studied using FTIR spectroscopy. Among all formulations, the formulation (F8) containing 4% crospovidone had the highest drug release (99.27%) and demonstrated good stability over a three-month period.</p> | GSC Biological and Pharmaceutical Sciences, | 86 |
| Karthikeyan D et al. (2013) | Development of fast dissolving oral film containing of rizatriptan benzoate as an antimigraine medication | <p>Drug: Rizatriptan benzoate</p> <p>Polymer: PG, Aspartame, Mannitol</p> <p>Description: In vitro evaluation investigations (30 ml of stimulated salivary fluid pH 6.8/ glass beaker/ 100 RPM) revealed the film composition of 200 mg polyvinyl alcohol and 200 mg Maltodextrin to be</p> | Indo American J Pharm Res | 87 |

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|---------------------------|---|---|-----------------------|----|
| | | appropriate. Ex vivo investigations revealed that 82.93 percent of the medication was absorbed through porcine oral mucosa. | | |
| Narayana PR et al. (2013) | Formulation and evaluation of fast dissolving films of loratidine by solvent casting method | Drug: Loratidine Polymer: HPMC, PG, PEG 400 Description: By adding loratidine into hypromellose films, fast-dissolving films can be created. The prepared optimum formulation disintegrated in less than 30 seconds. Within 4–6 minutes, the produced film formulation released 100 percent of the medication and exhibited good physicomechanical properties | The pharma innovation | 88 |
| Shaik MR et al. (2013) | Formulation and characterization of domperidone oral thin films | Drug: Domperidone Polymer: HPMC, PVA, Triethyl Citrate Description: Domperidone orodispersible film As a plasticizing agent and a film forming, triethyl citrate and polyvinyl alcohol were added to the film. In the film, Kollicoat IR was used as a superdisintegrant. In | Int J Pharm Sci. | 89 |

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|-------------------------|--|--|-----------|--|
| | | dissolution medium, the improved formulation released more than 95% domperidone in 3 minutes | | |
| Sayed S et al. (2013) | Fast-dissolving sublingual films of terbutaline sulfate: formulation and in vitro/in vivo evaluation | Drug: Terbutaline sulphate Polymer: maltodextrin, sodium alginate, carbopol 430, xanthan gum, hypromellose E5, PVP K25 Description: Crossover research in human volunteers was used to conduct a bioequivalence study against typical loral tablets. With a relative bioavailability of 204.08 percent, the improved film formulation resulted in much faster drug absorption. | Mol Pharm | |
| Londhe VY et al. (2012) | Formulation development and evaluation of fast dissolving film of telmisartan | Drug: Telmisartan Polymer: PVP,PVA Description: Lutrol E400 was employed as a plasticizer, and sodium and potassium hydroxide were added to increase the solubility of the active at alkaline pH. Alkalinizing chemicals in the dissolution medium caused 100 percent drug release within 5 minutes from the optimised | IJPS | |

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|--------------------------|---|--|-------------------------|----|
| | | formulation | | |
| Nagaraju R et al. (2012) | Design and evaluation of fast dissolving film containing nizatidine | <p>Drug: Nizatidine</p> <p>Polymer: Maltodextrin</p> <p>Description: Nizatidine is a fast-disintegrating film formulation used to treat acid reflux and ulcers. Films using 82 percent maltodextrin as a polymer, 16 percent glycerin, and 2% sorbitan monooleate as a plasticizer were deemed optimal. In pH 6.8 simulated saliva, more than 90% of the medication was released.</p> | Indian J Pharm Edu Res. | 90 |
| Desu P et al. (2012) | Formulation and evaluation of fast dissolving films of zolmitriptan | <p>Drug: Zolmitriptan</p> <p>Polymer: HPMC, Hypromellose E5</p> <p>Description: Anti-migraine zolmitriptan film that dissolves quickly to avoid hepatic first-pass metabolism. In this study, hypromellose E5 was used as the primary film forming. As a plasticizer, propylene glycol was utilised, along with acesulfame potassium and xylitol as a sweetener. In an in vitro dissolution test (6.8 pH phosphate buffer/Basket/100 RPM),</p> | Int Res J Pharm | 91 |

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|-----------------------|--|--|--------------------|----|
| | | the developed formulation showed the highest drug release | | |
| Bhyan B et al. (2012) | Formulation and evaluation of fast dissolving sublingual films of rizatriptan Benzoate | <p>Drug: Rizatriptan Benzoate, te</p> <p>Polymer: HPMC E15, Maltodextrin</p> <p>Description: The primary film former was HPMC E15, while the secondary film former was maltodextrin. As a plasticizer, glycerol was added to the mix. As a water soluble secondary sweetener, sugar alcohols like mannitol were used. Sweetener and surfactant were aspartame and sodium lauryl sulphate, respectively. In dissolution media comprising 900 ml pH 6.8 phosphate buffer in basket apparatus at 50 RPM, formulations containing hypromellose E15 (15 mg/ film) showed 90 percent in-vitro drug release in less than 10 minutes</p> | Int J Drug Dev Res | 92 |
| Mahajan A (2012) | Formulation & evaluation of fast dissolving buccal films of | <p>Drug: Sertraline</p> <p>Polymer: Povidone, Carbopol 934P</p> <p>Description: As the</p> | Int J Drug Dev Res | 93 |

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|---------------------------|--|--|--|----|
| | sertraline. | principal film forming agent, a mixture of povidone and carbopol 934P was used. As a plasticizer, polyethylene glycol 400 and propylene glycol were used. As a sweetening agent, saccharine sodium was used. In vitro release experiments revealed that in dissolving medium, 90–95 percent of the medication was released within 1 hour. | | |
| Murata Y et al. (2012) | Development of film dosage form containing allopurinol for prevention and treatment of oralmucositis | Drug: Allopurinol Polymer: Sodium Alginate Description: Allopurinol, a xanthine oxidase inhibitor, is available in film dosage forms. Without the addition of plasticizer, sodium alginate with different viscosity grades such as 300 cP, 500 cP, and 1000 cP, low molecular weight alginate, Gularonic acid-rich alginate, and pullulan were assessed as film forming polymers | International scholarly research network | 94 |
| Vijayasri K et al. (2012) | Montelukast sodium oral thin films: formulation and | Drug: Montelukast Polymer: Hypromellose E15, hypromellose E50, PVP | Asian J Pharm Clin Res. | 95 |

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|----------------------------|--|---|-----------------------|----|
| | invitro evaluation. | Description: Montelukast sodium orodispersible film formulation for asthma. Hypromellose E15, hypromellose E50, and polyvinylpyrrolidone were used to make oral thin films. Glycerol and mannitol were used as fillers and plasticizers, respectively. In a pH 6.8 phosphate buffer containing 0.5 percent SLS/ basket / 50 RPM, the optimised formulation released 93.49 percent during 20 minutes | | |
| Choudhary DR et al. (2012) | Development and characterization of pharmacokinetic parameters of fast-dissolving films containing levocetirizine. | Drug: levocetirizine Polymer: Pullulan Description: To hide the bitterness of levocetirizine, it was combined with - cyclodextrin. The primary film former was Pullulan. In dissolution media 93.54 3.9 percent levocetirizine was dissolved in 90 seconds. In rats, the pharmacokinetics of medication solution and film formulation were not significantly different. | ScientiaPharmaceutica | 96 |
| Panchal MS et al. (2012) | Formulation and evaluation of mouth | Drug: Ropinirole hydrochloride Polymer: PEG 400 and | IJPRAS | 97 |

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|------------------------|---|--|-------------------------------------|----|
| | dissolving film of ropinirole hydrochloride by using pullulan polymers. | pullulan Description: Ropinirole hydrochloride in an orodispersible film formulation. As a plasticizing agent and a film forming agent, PEG 400 and pullulan were added to the film. In simulated salivary fluid, the improved formulation released 90% of the medication in 1 minute. | | |
| Dixit AS et al. (2012) | Fast disintegrating films containing anastrozole as a dosage form for dysphagia patients. | Drug: Anastrozole Polymer: HPMC, Hypeomellose E5,PVA Description: Among all film formers, hypromellose E5 disintegrated the fastest, with a time of 15 seconds and a breakdown rate of over 90% in 240 seconds. There was no statistical difference in pharmacokinetic characteristics between the film formulation and the anastrozole solution, indicating a similar plasma level time profile | Archives of pharmaceutical research | 98 |
| Nagar M et al. (2012) | Formulation and evaluation of mouth dissolving film | Drug: Aripiprazole Polymer: PEG 1000 Description: To speed up the disintegration of | Der Pharmacia Lettre | 99 |

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| | of antipsychotic drug aripiprazole | hypromellos E3 films, maltodextrin and rice starch were added. As a plasticizer, PEG 1000 was employed. To improve the film's taste acceptability, sodium chloride and sucralose were added. As a preservative, thymol and potassium sorbate were added. 100 percent of the medication In 15 minutes, release was demonstrated in dissolving media | | |
| Joshi P et al. (2012) | Formulation development and evaluation of mouth dissolving film of domperidone. | Drug: Domperidone Polymer: Tween 80, Description: Domperidone and -cyclodextrin were dispersed in half the amount of water and methanol with tween 80 in an improved formulation and heated at 60°C. PEG 400 was used as a plasticizer and the main film former was hypromellose. In dissolution, the improved formulation including domperidone and -cyclodextrin in a 1:3 ratio demonstrated more than 75 percent drug release within 15 minutes. | J Pharm Bioall Sci | 100 |

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|------------------------|--|---|---------------------|-----|
| Tomar A et al. (2012) | Formulation and evaluation of fast dissolving oral film of dicyclomine as potential route of buccal delivery | <p>Drug: Dicyclomine</p> <p>Polymer: hypromellose, polyvinylalcohol, and eudragit RL-100</p> <p>Description: Dicyclomine, an anticholinergic medication, is available in an orodispersible film formulation. Oral films were made with the polymers hypromellose, polyvinylalcohol, and eudragit RL-100, as well as the plasticizer polyethylene glycol 400. In dissolution medium 300 ml pH 6.8 deionized simulated saliva in USP apparatus II (paddle) at 100 RPM, a formulation comprising polyvinyl alcohol as the principal film former demonstrated minimum disintegration and 94.14 percent drug release within 5 minutes.</p> | Int J drug Dev Res. | 101 |
| Qadir KA et al. (2012) | Formulation and evaluation of fast dissolving films of loratidine for sublingual use. | <p>Drug: Loratidine</p> <p>Polymer: Hypromellose, Polyvinyl pyrrolidone, and HPMC</p> <p>Description: Anti-histaminic medication loratidine in a fast-</p> | Int Res J Pharm. | 102 |

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| | | <p>dissolving film. As a major film forming agent, hypromellose, polyvinyl pyrrolidone, and hydroxypropyl cellulose were tested. As a plasticizer and sweetener, propylene glycol and aspartame were utilised. In vitro dissolution showed 70–92 percent release within 4 minutes for all formulations, and ex vivo drug release studies showed 64–86 percent release within 4 minutes for all formulations</p> | | |
| Saini S et al. (2011) | <p>Formulation, development and evaluation of oral fast dissolving anti-allergic film of levocetirizine dihydrochloride</p> | <p>Drug: Levocetirizine dihydrochloride Polymer: Maltodextrin, Hypromellose E15, Neotame, and Glycerin Description: Levocetirizine dihydrochloride as an orally consumable flash release film composition. Maltodextrin, hypromellose E15, neotame, and glycerin were used as film-formers, sweeteners, and plasticizing agents, respectively, in the film. In pH 6.8 simulated saliva, 90% of the medication from the</p> | J Pharm Sci Res. | 103 |

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| | | improved formulation was released within 5 minutes | | |
| Gupta MM et al. (2011) | Enhancement of dissolution rate of rapidly dissolving oral film of meclizine hydrochloride by complexation of meclizine hydrochloride with β -cyclodextrine. | Drug: Meclizine hydrochloride Polymer: hypromellose E5 and Polyethylene oxide Polyox N80 Description: Meclizine hydrochloride oral film that dissolves quickly. The principal film formers were hypromellose E5 and polyethylene oxide Polyox N80. In the formulation, disintegrating agents such as Kollidon CL, sodium starch glycollate, and croscarmellose sodium were used. To increase solubility and flavour masking of the bitter tasting medicine, meclizine hydrochloride was complexed with β -cyclodextrine. | JAPS | 104 |
| Ghorwade V et al. (2011) | Formulation and evaluation of montelukast sodium fast dissolving films by using gelatin as a film base. | Drug: Montelukast sodium Polymer: Gelatin, PEG Description: Montelukast sodium orodispersible film formulation with gelatin as the principal film-former and polyethylene glycol as the plasticizer. As a | Res J Pharm, Biol Chem Sci. | 105 |

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| | | dissolving agent, crospovidone and microcrystalline cellulose were used in the film. Quick disintegration was seen in the formulation comprising 10% MCC and 4% crospovidone. | | |
| Saini S et al. (2011) | Optimization of formulation of fast dissolving films made of pullulan polymer | <p>Polymer: Pullulan</p> <p>Description: The PEG films were translucent and white opaque in appearance. PEG produced translucent white films. Films containing glycerin took longer to dry than films containing PG. Polymer and plasticizer were present in the optimum film composition at low concentrations.</p> | Int J Pharm Sci Rev Res. | 106 |
| Kulkarni PK et al. (2011) | Formulation and evaluation of fast dissolving film containing rofecoxib. | <p>Drug: Rofecoxib</p> <p>Polymer: Hypromellose and Polyvinyl alcohol</p> <p>Description: For osteoarthritis and dental pain, rofecoxib is the medication of choice. Glycerin, polysorbate 80, and aspartame were utilised as plasticizers, solubilizers, and sweeteners, respectively, with hypromellose and polyvinyl</p> | Int Res J Pharm. | 107 |

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| | | alcohol as the major film forming polymers. Menthol was employed to disguise the flavour of the active ingredient. In vitro dissolving was performed in 500 mL of pH 1.2 hydrochloric acid in Paddle at 100 RPM with 0.5 percent w/w SLS | | |
| Prasanthi NL et al. (2011) | Design and development of sublingual fast dissolving films for an antiasthmatic drug. | Drug: Salbutamol sulphate Polymer: Hypromellose Description: The optimised batch contained hypromellose as a film former (2 percent w/w), tween 80 as a wetting agent (0.5 percent w/w), and aspartame as a sweetener (0.5 percent w/w). In a paddle assembly at 50 RPM, the improved formulation had adequate drug release in 300 ml pH 6.8-simulated saliva | Scholars Research Library | 108 |
| Mishra R et al. (2011) | Design and development of rapidly dissolving films using ion exchange resin for taste masking. | Drug: Cetirizine hydrochloride Polymer: Hypromellose E3 and Hydroxypropyl cellulose LF Description: They found that increasing the amount of polymers hypromellose | IJDFR | 109 |

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| | | E3 and hydroxypropyl cellulose LF enhanced the disintegration time, and that dissolving the produced films in 900 ml 0.1N HCl in USP dissolution equipment XXIV at 50 RPM increased the disintegration time | | |
| Raju S et al. (2011) | Flash release oral films of metoclopramide hydrochloride for pediatric use: formulation and in-vitro evaluation. | Drug: Metoclopramide Polymer: Hypromellose, CMC Description: A formulation containing hypromellose released 99.40 percent of the medication within 30 seconds. | J Chem Pharm Res. | 110 |
| Prabhu P et al. (2011) | Formulation and evaluation of fast dissolving film of levocetirizine dihydrochloride. | Drug: Levocetirizine dihydrochloride Polymer: hypromellose E50, Hypromellose E15, and PVA Description: The dissolution investigation was carried out in a glass beaker filled with 30 mL of pH 6.8 simulated saliva and spun at 100 RPM. | Int J Pharma Investig. | 111 |
| Sumitha C et al. (2011) | Development of taste masked fast dissolving orally consumable films of | Drug: Sildenafil citrate Polymer: Hypromellose E5 Description: Sildenafil citrate oral films made with hypromellose E5 as a film former. As a plasticizer, a | Journal of Pharmaceutics and Cosmetology | 112 |

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| | sildenafil citrate. | cooling agent, and a sweetener, glycerol, menthol, and sucralose were used. Menthol was utilised as a powerful flavouring and cooling ingredient, although ion-exchanging agents like polacriline potassium were used to disguise the taste. | | |
| Mishra R et al. (2011) | Formulation and characterization of rapidly dissolving films of cetirizine hydrochloride using pullulan as a film forming agent. | Drug: Cetirizine Polymer: Pullulan, PG Description: The enhanced film formulation disintegrated in less than 30 seconds. In 500 mL distilled water, 900 mL 0.1N hydrochloric acid, and 500 mL simulated salivary fluid, a multimedia dissolving profile of the optimised formulation was created | Ind J Pharm Edu Res | 113 |
| Kunte S et al. (2010) | Fast dissolving strips: A Novel Approach for the Delivery of Verapamil. | Drug: Verapamil Polymer: HPMC E6 Method: Solvent Casting Method Description: The film formulation with 2% hypromellose (HPMC E6) and 3.5 percent maltodextrin was deemed optimal since it showed the highest release in a | . J Pharm Bioallied Sci. | 114 |

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| | | dissolution test (900ml pH 6.6 phosphate buffer/ basket/ 50 RPM) when compared to other formulations | | |
| Cilurzo F et al. (2010) | Diclofenac fast-dissolving film: suppression of bitterness by a taste-sensing system | Drug: Maltodextrin Polymer: HPMC Description: In the film's formulation, nicotine was used as a tartrate salt. Maltodextrin films with a dextrose equivalent value of 6 were stiffer and less brittle than maltodextrin films with a dextrose equivalent value of 12. The time it took for the prepared films to disintegrate was about 10 seconds. The inclusion of mint and milk flavour masks the harsh taste of nicotine | Drug Dev Ind Pharm. | 115 |
| El-Setouhy DA et al. (2010) | Formulation of a novel tianeptine sodium orodispersible film | Drug: Sodium Tianeptine Polymer: Lycoat NG73 Description: The orodispersible film made from lycoat NG73 and propylene glycol had the best drug solubility in dissolution media (400 ml freshly distilled water / basket/ 100 RPM), physicomechanical | AAPS PharmSciTech | 116 |

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|------------------------|---|--|----------------------|-----|
| | | characteristics, and in vitro disintegration time. The pharmacokinetic properties of the film containing lycoat NG73 were assessed compared with a reference marketed product (Stablon® tablets) in rabbits | | |
| Murata Y et al. (2010) | Preparation of fast dissolving films for oral dosage from natural polysaccharides | Drug: Dexamethasone, Pilocarpine, and Lidocaine Polymer: Pullulan Description: Dexamethasone was completely released from the films after 15 minutes, albeit at a slower rate than pilocarpine or lidocaine in a pH 7.4 phosphate buffer solution poured in a petriplate with 300 RPM shaking. | Materials | 117 |
| Singh S et al. (2010) | Formulation and evaluation of rapidly disintegrating film of levocetizine hydrochloride | Drug: Levocetizine Hydrochloride Polymer: Sodium alginate Description: Within 6 minutes, 70–85 percent of the medication was released in dissolving medium | Der Pharmacia Lettre | 118 |
| Koland M et al. (2010) | Fast dissolving sublingual films of ondansetron hydrochloride: Effect of | Drug: Ondansetron hydrochloride Polymer: polyvinyl alcohol, polyvinyl pyrrolidone, and carbopol 934P | J Young Pharm | 119 |

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| | additives on in vitro drug release and mucosal permeation | Description: In vitro dissolving studies showed that roughly 81 to 96 percent of the drug was released in simulated salivary fluid within 7 minutes and that approximately 66 to 80 percent of the drug was diffused from a porcine membrane model. | | |
| Sumitha C et al. (2009) | Taste masking of ondansetron hydrochloride by polymer carrier system and formulation of rapid disintegrating films | Drug: Ondansetron hydrochloride Polymer: Hypromellose E15 and Polyethylene oxide N-10 Description: Due to no release in simulated salivary fluid, the formulation comprising 7% w/w polyethylene oxide N-10 and a 2:1 drug-polymer ratio was chosen as the flavour masked formulation. Dissolution tests were performed using a paddle at 50 RPM in 500 mL of simulated stomach juice without enzymes. | Int J Chem Res. | 120 |
| Shimoda H et al. (2009) | Preparation of a fast dissolving oral thin film containing | Drug: Dexamethasone Polymer: Hypromellose Description: In a dissolution medium of 900ml pH 1.2 | Eur J Pharm Biopharm | 121 |

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| | dexamethasone: A possible application to antiemesis during cancer | phosphate buffer in a paddle system at 50 RPM, approximately 90% of the active was released from the formulation within 5 minutes. | | |
| Cilurzo F et al. (2008) | Fast dissolving films made of maltodextrins. | Drug: Maltodextrins Polymer: Polyethylene glycol 400, Sorbitan oleate Description: Orally consumable orodispersible film using maltodextrin as the main water-soluble polymer, but with glycerin added up to 16–20 percent w/w to increase flexibility and tensile strength. Plasticizers such as polyethylene glycol 400, sorbitan oleate, glycerin, and propylene glycol were tested. Piroxicam was included as an active ingredient in an improved placebo formulation | Eur J Pharm Biopharm. | 122 |
| Dinge A et al. (2008) | Formulation and evaluation of fast dissolving films for delivery of triclosan to the oral cavity | Drug: Triclosan Polymer: Hypromellose Description: When compared to films containing Triclosan-HPBCD complex, films containing Triclosan-Poloxamer 407 with | AAPS PharmSciTech | 123 |

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| | | eugenol as a mouth freshener demonstrated enhanced in vitro dissolving properties, improved taste masking, and antibacterial activity | | |
| Sharma R et al. (2007) | Development of taste masked film of valdecoxib for oral use | Drug: Valdecoxib Polymer: Eudragit EPO and Hypromellose Description: In an in vitro dissolution test, the film with a higher glycerol concentration released the medication faster. As a taste-masked valdecoxib film, a fast-dissolving film comprising eudragit EPO, aspartame, and menthol was regarded optimal. | Indian J Pharm Sci | 124 |
| Mashru R. et al. (2005) | Development and evaluation of fast-dissolving film of salbutamol sulphate | Drug: Salbutamol sulphate Polymer: Polyvinyl alcohol Description: The best answers for prepared film formulation were found at medium polymer and plasticizer concentration levels, as well as a high sugar alcohol concentration level, according to the data. Drug release properties were shown to be similar in pure water, simulated salivary fluid, and pH 1.2 | Drug Dev Ind Pharm. | 125 |

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| | | simulated stomach acid for optimized film formulation | | |
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2.2 Literature Review on ZPO HCL:

| Author Name & Publication Year | Title of Paper | Description | Journal Name | Reference No |
|----------------------------------|--|--|-------------------------|--------------|
| Vaishali L & Sreevidya K. (2021) | Formulation, Evaluation, and Pharmacodynamic Investigation of Ziprasidone- β -cyclodextrin In-Situ Nasal Gel | Drug: Ziprasidone hydrochloride Polymer: β cyclodextrin (β CD) and Polaxomer 407 Description: The solubility of ziprasidone was efficaciously enhanced by its inclusion complex with β -cyclodextrin and was formulated as in-situ nasal gel. The optimized formulation comprising drug with β -cyclodextrin showed significant release and mucoadhesive strength to confirm suitable residence time at the site of action. | Proceedings | 126 |
| Anup Kumar.et al (2021) | Formulation and Evaluation of Nasal Mucoadhesive Microspheres of Atypical Antipsychotic | Drug; Ziprasidone hydrochloride Polymer: Chitosan Description: In conclusion, the present study showed that Ziprasidone chitosan microspheres can deliver | IAR Journal of Pharmacy | 127 |

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| | Agent | intanasally which can improve the therapeutic outcome for the Epileptic seizure. | | |
| Muhammad M. et (2020) | Formulation And Evaluation Of ZPO HCL Oral Controlled Release Matrix Tablets | Drug; Ziprasidone hydrochloride Polymer:HPMC K13 Description: it can be concluded that controlled release Ziprasidone hydrochloride matrix tablets can be efficiently prepared by using HPMC through a cost-effective and simple direct compression method. | Pharmacophore | 128 |
| Kailash S. et al (2018) | Formulation and Evaluation of Gastro Retentive Sustained Release Tablets of Ziprasidone Hydrochloride | Drug; Ziprasidone hydrochloride Polymer: Mg sterate, HPMC K4M, Description: In the present study gastro relative floating matrix tablet of ziprasidoneHClwere successfully prepared by direct compression method. The study showed that ratio of polymer agent can be used as matrix forming agent to sustain release of the drug to the concentration of polymers increased drug release rate | Research J. Pharm. and Tech. | 129 |

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| | | decreased among all there formulation F6 was found to be the best formulation. | | |
| Saish R. et al (2018) | Solubility Enhancement and Formulation Development of Ziprasidone Immediate Release Oral Drug Delivery | Drug: Ziprasidone Polymer: β -cyclodextrin Description: The optimized pellet formulation prepared using extrusion spheronization technique consisting drug: β -CD inclusion complex showed rough surface of pellets with more than 80% drug release within 60 minutes which was comparative to marketed tablet formulation. | Pharmaceutical Resonance | 130 |
| Kajal S. & Kiran B. (2016) | Solubility Enhancement And Formulation Of Fast Dissolving Tablet Of Ziprasidone Hydrochloride | Drug: Ziprasidone Hydrochloride Polymer: Sulfobutylether- β -cyclodextrin Description: The effect of types and concentrations of superdisintegrant on the disintegration time and dissolution profile of Ziprasidone Hydrochloride fast dissolving tablets were studied. The % drug release of Fast Dissolving tablet F7 shows 98.25 % drug release after 20 minutes. However further | International Journal Of Research In Pharmacy And Chemistry | 131 |

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| | | in vivo studies are needed to justify the effect of increasing solubility of Ziprasidone Hydrochloride on its bioavailability. | | |
| Y. Miao, et al. (2016) | Characterization and evaluation of self-nanoemulsifying sustained-release pellet formulation of ziprasidone with enhanced bioavailability and no food effect | Drug: Ziprasidone Hydrochloride Polymer: PEG 400 Description: The extrusion-spheronization method was utilised to create ziprasidone-SNEDDS sustained-release pellets using the improved ziprasidone-SNEDDS. SEM, particle size, droplet size distribution, and zeta potential were all measured on the pellets. In vitro drug release experiments revealed that the ziprasidone-SNEDDS sustained-release pellets had a sustained release profile, with 90% of the pellets being released within 10 hours | Informa Healthcare USA | 132 |
| A. Gauniya (2015) | | Drug: Ziprasidone Hydrochloride Polymer: Kollidone and Tween 80 Description: ZIP and ZIP nanocrystals were | | 133 |

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| | | subjected to differential scanning calorimetry, which revealed that there was no interaction between ZIP and stabilisers. The solubility of ZIP nanocrystals increased substantially as compared to ZIP | | |
| D. Zakowiecki (2015) | Formulation, Optimization And Characterization Of Ziprasidone Nanocrystals Prepared By Media Milling Technique | Drug: Ziprasidone Hydrochloride Polymer: Gelatin Description: The dissolution rate of the produced ziprasidone free base preparations was found to be equivalent to or even higher than that of the reference formulation including ziprasidone hydrochloride, which has a 400-fold higher water solubility than the free base | International Journal of Pharmacy and Pharmaceutical Sciences | 134 |
| Vasanth P. M et al (2013) | Development of gastroretentive drug delivery system of ziprasidone hydrochloride | Drug: Ziprasidone Hydrochloride Description: A psychotropic agent is ziprasidone hydrochloride. A sustained-release formulation of Ziprasidone hydrochloride is desirable to reduce the frequency of administration and enhance | Scholars Research Library | 135 |

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| | | patient compliance. | | |
| Koteswari Poluri.et al (2013) | Formulation Development And Evaluation Of Novel Oral Soluble Films Of Ziprasidone Hydrochloride In The Treatment Of Schizophrenia | Drug; ZPO HCL Polymer: HPMC. Description: Overall findings suggested that ZPO HCL oral soluble films of HPMC E5 exhibited a desired disintegration time ≤ 50 seconds, good drug loading efficiency and stability. | International Journal of Pharmacy and Pharmaceutical Sciences | 136 |
| A. J., et al (2012) | Natural gums as sustained release carriers: development of gastroretentive drug delivery system of ZPO HCL | Drug: Ziprasidone Hydrochloride Polymer:HPMC K4 Description: As a result, the objective has been set to assess the potential of Okra gum and LBG in combination with HPMC K4 for a gastro-retentive drug delivery system of ZPO HCL utilising a simplex lattice design (SLD). | DARU Journal of Pharmaceutical Sciences | 137 |
| S. Kumar (2011) | Formulation and evaluation of bi-layer floating tablets of ZPO HCL and trihexyphenidyl HCl | Drug: Ziprasidone Hydrochloride Polymer: HPMC Description: The drug release involved non-diffusional methods, according to the n values of the Korsmeyer equation. | Brazilian Journal of Pharmaceutical Sciences | 138 |

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| | | According to the results of this investigation, bi-layer tablets containing ZPO HCL and trihexyphenidyl HCl will be a useful technique for extending the metabolism and increasing the bioavailability of ZPO HCL and Trihexyphenidyl HCl. | | |
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2.3 Literature Review on Quetiapine Fumarate:

| Author Name & Publication Year | Title of Paper | Description | Journal Name | Reference No |
|--------------------------------|---|---|---|--------------|
| Keyur S. et al (2021) | Formulation and Evaluation of Gastroretentive Floating Tablets of Quetiapine Fumarate | Drug: Quetiapine Fumarate Polymer: Description: From the factorial design batches it was found that floating lag time was decreased with increasing the amount of sodium bicarbonate and decreasing the amount of natrosol 250 HHX. Here % release of drug was decreased with increase the extent of natrosol 250 HHX. The in-vitro release kinetics revealed Korsmeyer-Peppas model is followed and drug | Journal of Drug Delivery and Therapeutics | 139 |

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| | | release is by anomalous diffusion. | | |
| Mehetre G. et al (2020) | Quetiapine Fumarate Buccoadhesive Tablet-Formulation and In Vitro Evaluation | Drug: Quetiapine Fumarate Polymer: HPMC, Carbopol, Description: Study and test results as FTIR analysis proved compatibility of polymers with the drug; the blend of polymers help control the drug release over an extended time period. Bioadhesive studies revealed promising adherence to buccal mucosa helping for controlled drug release and thereby enhanced bioavailability. The release analysis revealed erosion mediated drug release. | Research J. Pharm. and Tech. | 140 |
| Asha R., et al. (2017) | Formulation And Evaluation Of Albumin Nanoparticles Of Anti-Psychotic Drugs | Drug: Quetiapine Fumarate Polymer: HPMC Description: Simple coacervation was used to make AI-NPs from Quetiapine fumarate (QA), ZPO HCL (ZA), and Paliperidone (PA). On a magnetic stirrer, aqueous solutions of albumin in | Journal of science research in pharmacy | 142 |

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| | | <p>various concentrations were churned, and a precisely weighed amount of medication was added under constant swirling. Acetone was added drop by drop to the albumin drug solution (desolvating agent) until the solution became barely turbid.</p> | | |
| A. Gavan, et al. (2017) | <p>Formulation and pharmaceutical development of quetiapine fumarate sustained release matrix tablets using a QbD approach</p> | <p>Drug: Quetiapine Fumarate Polymer: HPMC Description: The influence of matrix-forming polymer (HPMC) % and filler type on the cumulative ratio of medication released at different time intervals for a period of 24 hours was evaluated using a quadratic D-optimal experimental design, and the optimal formulations were defined.</p> | Acta Pharm. | 143 |
| H. Baishya (2016) | <p>EFFECT OF COMPACTION PROCESS IN GRANULOMETRY;</p> | <p>Drug: Quetiapine Fumarate Description: the goal of this study is to develop a long-acting pharmaceutical composition having Quetiapine fumarate in a sustained-release matrix formulation 7, with one of the compacted ingredients within a specified particle</p> | International Journal of Pharmaceutical Sciences and Research | 144 |

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| | | size, in order to maintain blood levels of the active ingredient. | | |
| Lakshmi P. et al (2016) | Formulation development, In-vitro and In-vivo evaluation of novel solid oral dosage form containing Quetiapine nanoparticles. | Drug: Quetiapine Fumarate Polymer: PVP, Mannitol Description: The enhancement of the oral bioavailability of the nanoparticle formulation can be attributed to increase in the surface area obtained by particle size reduction. This enhancement in the oral bioavailability can be explored on the strong possibility of the dose reduction of quetiapine fumarate so that dose related side effects of this drug can be minimized. | International Journal of Drug Delivery | 145 |
| A. Bharathi et al (2014) | Formulation development and evaluation of sustained release matrix tablets of quetiapine fumarate; | Drug: Quetiapine Fumarate Polymer: Guar gum, Tara gum, Microcrystalline cellulose, Description: Quetiapine is well tolerated and effective in patients who are particularly vulnerable to these severe side effects, such as the elderly and adolescents, as well as those who have pre- | Journal of Chemical and Pharmaceutical Research | 146 |

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| | | existing dopaminergic pathologies like Alzheimer's disease and Parkinson's disease | | |
| G. Garbacz (2014) | Release Characteristics of Quetiapine Fumarate Extended Release Tablets Under Biorelevant Stress Test Conditions; | Drug: Quetiapine Fumarate Description: Quetiapine is designated as a BCS class II medicine because of its low solubility over the physiological pH range but high permeability. Dissolving tests of tablets containing 50 and 400 mg quetiapine were carried out using a 0.1 mol/L HCl (pH 1.0) solution as an artificial medium to simulate fasting stomach circumstances and phosphate buffer pH 6.8 (USP) as a dissolution medium to simulate fasting intestinal conditions. | AAPS PharmSciTech | 147 |
| R Mohapatra. Et al (2013) | Formulation and Development of pH Independent Once Daily Matrix Tablet of Quetiapine Fumarate | Drug: Quetiapine Fumarate Polymer: udragit NE 30D and Polyethylene oxide Description: It was thus concluded that the desired drug dissolution profile could be achieved by formulating Quetiapine Fumarate as matrix SR tablets using polyox WSR 303 & polyox WSR 205 | Research Journal of Pharmaceutical, Biological and Chemical | 148 |

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|--|--|---|---------------------------------|------------|
| | | <p>combinations. During course of study various sustained released tablet formulations (T1-T16) of QF were formulated by using eudragit NE 30D as matrix forming agent. Different percentages of polyox WSR 303 & polyox WSR 205 were used and the amount of drug was 300 mg in all batches.</p> | | |
| <p>Arjun N. & Kishan V. (2013)</p> | <p>Preparation, Characterization and Evaluation of Quetiapine Fumarate Solid Lipid Nanoparticles to Improve the Oral Bioavailability</p> | <p>Drug: Quetiapine Fumarate Polymer: Sodium carboxymethyl cellulose Description: SLN using three different lipids after checking the compatibility by DSC studies. The SLN preparation with Dynasan 118 was optimized based on the particle size, PDI, zeta potential, entrapment efficiency, and drug release characteristics. During <i>in vivo</i> bioavailability studies 3.71 times of relative bioavailability improvement was found when compared to reference suspension. Thus, quetiapine fumarate when formulated as</p> | <p>Journal of Pharmaceutics</p> | <p>149</p> |

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| | | SLN could improve the oral bioavailability. | | |
| Arun K. et al (2013) | Formulation And Evaluation Of Quetiapine Immediate Release Film Coated Tablets | Drug: Quetiapine Fumarate Polymer: HPMC Description: The results indicate that there were insignificant changes during studies. Hence, the results suggest the feasibility of developing immediate release tablets consisting of Quetiapine, which has an excellent tolerability profile offering high patient acceptability that may promote patient adherence to medication and an improved quality of life. | Asian Journal of Pharmaceutical and Clinical Research | |
| Appa R. et al (2012) | Formulation and evaluation of buccoadhesive quetiapine fumarate tablets | Drug: Quetiapine Fumarate Polymer: HPMC Description: The present work was aimed at developing a buccoadhesive Quetiapine Fumarate tablets. Progressive hydration technology was employed by using various grades of HPMC in combination with carbopol and HPC for their reported buccoadhesive and release | Brazilian Journal of Pharmaceutical Sciences | 150 |

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| | | rate controlling abilities. | | |
| Deepak S. & Rana A. (2010) | Development and in vitro evaluation of Quetiapine Fumarate Sustain release tablets | Drug: Quetiapine Fumarate Polymer: HPMC, PVP K30 Description: In conclusion, PVP K30 and HPMC K15M can be used as rate controlling polymers by appropriate selection of the level of polymers in the matrix. | International Journal of PharmTech Research | 151 |

2.4 Patent Summary:

TABLE 2. 1 Patent Summary

| Sr. No | Patent No | Title |
|--------|-----------------|---|
| 1 | US20060198873A1 | Orally dissolving films |
| 2 | US9694008B2 | Fast-dissolving oral film preparation comprising aripiprazole |
| 3 | WO2016190714A1 | Orally fast dissolving film formulation including aripiprazole and method for producing the same |
| 4 | EP2883540A1 | Fast-dissolving oral film preparation comprising aripiprazole |
| 5 | US5948430A | Water soluble film for oral administration with instant wettability |
| 6 | US8178674B2 | Process for the preparation of ziprasidone |
| 7 | US6150366A | Ziprasidone formulations |
| 8 | CN104744454A | Production method of ziprasidone |
| 9 | US20070265447A1 | Process for the Preparation of Ziprasidone (5-[2-[4-(1,2-Benzisothiazol-3-Y1)-1-Piperazinyl]Ethyl]-6-Chloro-1,3-Dihydro-2H-Indol-2- One |
| 10 | EP1975169A1 | Process for the preparation of ziprasidone |
| 11 | US7687622B2 | Process for preparing quetiapine fumarate |

| | | |
|----|--------------|--|
| 12 | US7238686B2 | Polymorphs of quetiapine fumarate |
| 13 | US8048876B2 | Process for preparing quetiapine and quetiapine fumarate |
| 14 | CN102552128A | Quetiapine fumarate injection and preparation method thereof |
| 15 | CN101991555A | Quetiapine fumarate tablet and preparation method thereof |

Chapter-3
Need & Objective
(ZPO HCL)

CHAPTER 3

NEED & OBJECTIVE

3. FORMULATION & DEVELOPMENT OF ZIPRASIDONE HYDROCHLORIDE MOUTH DISSOLVING FILM FOR PSYCHOSIS TREATMENT

3.1. RATIONAL OF RESEARCH WORK:

3.1.1. RATIONAL OF MOUTH DISSOLVING FILM FORMULATION (MDF)

The oral route is one of the most commonly utilised medicine delivery modalities due to its safety, ease of administration, and patient acceptability. Around 60% of conventional dosage forms are available in oral solid dose forms. Orally dissolving strips and films aid patients such as paediatrics, geriatrics, bedridden, and emetic patients, as well as difficulties like acute allergy responses or coughing. They can be employed on a local as well as a national level. Orally dissolving film and strips are becoming more popular as an alternative to fast dissolving tablets due to their faster dissolve rate, greater flexibility, and improved patient compliance. Currently, studies are being conducted on the use of orally dissolving films as prospective carriers for a variety of active therapeutic ingredients. Orally dissolving film items such as Listerine, Chloraseptic, Triaminic, and multivitamins are commercially marketed. The backbone of an orally dissolving film is made up of a plasticizer and a film forming polymer, or a mixture of polymers, which provides it elasticity and shape.

Fast disintegrating films are the most sophisticated form of solid dosage form due to their flexibility. It improves the efficacy of active medicinal compounds when compared to dissolving tablets since they break down in the oral cavity in a short amount of time after contact with less saliva. This method of distribution involves placing a thin film on the tongue or mucosal tissue that is instantly wet by saliva. When the film is moist, it quickly disintegrates, allowing the medicine to be absorbed through the oral mucosa. A fast disintegrating film made of hydrophilic polymer that rapidly disintegrates for the buccal cavity delivers the medicine to the systemic circulation via buccal mucosa. Fast dissolving drug delivery systems are specifically intended for medicines with significant first pass metabolism and low dosage to maximise bioavailability.

3.1.2 RATIONAL OF FORMULATION & DEVELOPMENT OF MOUTH DISSOLVING FILM FOR PSYCHOSIS TREATMENT:

Hallucinations, dementia, and convulsions are all symptoms of psychosis. It must be treated early in order to limit the risk of long-term brain damage. Pharmacotherapy with antipsychotic medications is still the most prevalent treatment for psychosis. The treatment of psychosis differs from that of other illnesses. A newer antipsychotic in an orally dissolving film format is an appropriate pharmaceutical candidate. Antipsychotics designed as an orally dissolving strip that must be placed on the patient's tongue without being swallowed to deliver the dose would substantially simplify dose administration and improve patient compliance. The goal of this study was to design, develop, and characterise antipsychotic medication mouth dissolving films.

3.1.3. RATIONAL OF FORMULATION & DEVELOPMENT OF ZIPRASIDONE HYDROCHLORIDE MOUTH DISSOLVING FILM FOR PSYCHOSIS TREATMENT

Ziprasidone Hydrochloride is a new atypical antipsychotic drug that has demonstrated to be effective in the treatment of schizophrenia. Atypical antipsychotic drug ziprasidone hydrochloride is used to treat schizophrenia and mania. It's considered a BCS class II medicament. It has a solubility problem. Ziprasidone Hydrochloride is rapidly absorbed and extensively metabolised through N-dealkylation, oxidation, reductive cleavage, hydration, and N-dearylation. It binds to adrenergic, histamine, serotonin, and dopamine receptors. Ziprasidone Hydrochloride is a difficult-to-dissolve drug. The goal of this research is to develop an oral mouth dissolving film that will improve the medicine's solubility. Fast dissolving film provides several benefits, particularly for paediatric and geriatric patients who have difficulty swallowing regular pills and capsules, and it increases patient compliance.

3.2. OBJECTIVES OF RESEARCH WORK

The prime objectives were to develop MDF drug delivery system that:

1. To make release of drug at oral mouth cavity and hence dose and dose frequency can be decreased thereby obtaining greater therapeutic efficacy.
2. To Show better in-vitro release/diffusion performance than conventional dosage forms.

3.3. PLAN OF RESEARCH WORK:

3.3.1. Literature survey and Patent Search related to Drug, Polymer & MDF Technology.

3.3.2. Selection of Drug, Polymer and Methodology for formulation & development of MDF drug delivery system

3.3.3. Pre-formulation study of Drug

- ✓ Organoleptic characteristics of drug
- ✓ Melting Point
- ✓ Solubility
- ✓ Partition Co-efficient
- ✓ Identification of drug by λ_{max} , FT-IR study.
- ✓ Preparation of Calibration Curve of Drug
- ✓ Drug- polymer Compatibility study FT-IR study

3.3.4. Preparation of MDF.

3.3.5. Preliminary Trial Batches for selection of materials

3.3.6. Formulation of Drug loaded MDF Using Factorial Design (DoE) approach

3.3.7. Characterization of Drug loaded MDF

- ✓ Thickness
- ✓ Weight variation
- ✓ Drug Content
- ✓ Measurement of mechanical property
- ✓ Folding endurance
- ✓ Physical appearance and texture analysis of the films
- ✓ In vitro disintegration
- ✓ In vitro dissolution
- ✓ Flux and Permeability Co-efficient Study
- ✓ Kinetics of drug release
- ✓ Statistical analysis
- ✓ Validation batches (Check Point Analysis) and its characterization of drug loaded

MDF

- ✓ FT-IR Study of Optimized MDF Formulation
- ✓ Comparison of optimized MDF with conventional marketed formulation.
- ✓ Ex- vivo study subjected to IAEC approval and permission
- ✓ Accelerated stability study

3.3.8. Thesis writing and paper publication in esteem journal.

3.4. EXPECTED OUTCOME

The foundation of a successful pharmaceutical formulation is the conveyance of the medicament to the target site at a therapeutically relevant level, with little or no discomfort and unwanted effects on the patient. In this sense, the route of drug delivery plays a vital role. Because it is the easiest to administer, oral medicine administration is the most common method of drug delivery. However, it has drawbacks, such as reduced bioavailability due to the first-pass effect and a predisposition for producing high and low plasma concentrations of drug quickly, resulting in poor patient compliance. Continuous intravenous infusion has been discovered to overcome the drawbacks of the oral route by maintaining a steady and sustained medicine concentration within therapeutic range for a long time. However, there are significant drawbacks to this type of drug delivery, including as needle pain and unintended needle sticks, which necessitate periodic hospitalisation and medical care during therapy.

Mouth dissolving film is now a day's preferred route of drug administration due to patient compliance. The main expected outcome of present work will be:

- ✓ Development of Mouth Dissolving Film (MDF)
- ✓ Formulation of effective formulation for the treatment of psychosis patients
- ✓ Patient's compliance due to development of MDF.

Chapter-4
Materials &
Methodology
(ZPO HCL)

CHAPTER 4

MATERIALS & METHODOLOGY

4. MATERIALS & EQUIPMENTS USED

The following materials, chemical substances and devices might also be used for Ziprasidone Mouth Dissolving Film for Psychosis Treatment as per following Table.

4.1 List of Materials

TABLE 4. 1 List of Materials

| MATERIALS | SOURCE |
|----------------|-----------------------------|
| ZPO HCL | Zota Healthcare LTD, Surat. |
| HPMC E5 | Zota Healthcare LTD, Surat. |
| PEG 400 | Zota Healthcare LTD, Surat. |
| Citric Acid | Zota Healthcare LTD, Surat. |
| Aspartame | Zota Healthcare LTD, Surat. |
| Mannitol | Zota Healthcare LTD, Surat. |
| Orange Flavour | Zota Healthcare LTD, Surat. |
| Methyl Paraben | Zota Healthcare LTD, Surat. |
| Propyl Paraben | Zota Healthcare LTD, Surat. |
| Vanillin | Zota Healthcare LTD, Surat. |

4.2 List of Equipments

TABLE 4. 2 List of Equipments

| EQUIPMENTS | MODEL AND SOURCE |
|------------------------------|--|
| UV – Visible Spectrometer | UV-1700, Shimadzu Corporation. |
| Mechanical Stirrer | Remi instrument division |
| Electronic Balance | Ohaus corporation NJ, USA |
| Humidity Cabinet | Analytical Technologies, Bangalore. |
| Scanning Electron Microscope | JEOL JSM-6380KVM Oxford Instruments, England |
| FT-IR Spectrophotometer | Shimadzu Corporation |
| Compound Microscope | Acculab |

| | |
|---------------------------------------|--|
| Dissolution Apparatus I, USP I | Macro scientific works private limited, Delhi. |
| Malvern | Malvern Instruments LTD. |

4.3 Methodology

4.3.1 Preformulation of ZPO HCL

The Preformulation find out about is often generate facts beneficial to improve secure dosage varieties that can be heavily produced for manufacturer.

4.3.1.1 Organoleptic Characteristics of ZPO HCL

Physical look at was done to check Organoleptic Qualities of ZPO HCL like Tone and Smell.

4.3.1.2 Taste Evaluation Study by Spitting

Eight sound grown-up male volunteers between the ages of 24 and 42 participated in a solitary measurement, single visually impaired preliminary. Preceding the preliminary, all subjects gave composed informed assent and were instructed with regards to the review's motivation, dangers, and length.

ZPO HCL was given to each chip in at irregular. Before the review, the volunteers were encouraged to flush their mouths with 200 cc of refined water. The volunteers were told to place the medication in their mouth for 30 seconds, record the breaking down span of the film test, and rate the plan in view of the elements showed in Table 3, in particular mouth feel, flavor or harshness, film trailing sensation, simplicity of taking care of, and in general acknowledgment. The volunteers were told to let out the example with spit and wash their mouths with 200 cc refined water following 3 minutes. Following 2 hours, the indistinguishable methodology was finished the subsequent example. To stay away from drug openness, subjects were encouraged to throw up the definition and salivation.

TABLE 4.3 Parameters, Score and Results of Taste Evaluation Study

| Parameters | 1 | 2 | 3 | 4 | 5 |
|---------------------|--------------------|---------|-------------------------------|-----------------------------|--|
| Mouth feel | Gritty /Irritating | Gritty | Slightly Gritty | Smooth | Very smooth |
| Taste (Bitterness) | Very bitter | Bitter | Slightly bitter | Slightly sweet/ Acceptable | Very sweet |
| After taste | Very Bitter | Bitter | Slightly bitter | Slightly sweet/ Acceptable | Very sweet |
| Ease of handling | Very brittle | Brittle | Acceptable and does not break | Flexible and easy to handle | Patient friendly and very easy to handle |
| Acceptance | Very poor | Poor | Acceptable | Good | Excellent |

4.3.1.3 Determination of Melting Point of ZPO HCL

Melting point of ZPO HCL was evaluated by the capillary method.

4.3.1.4 Identification and Determination of Wavelength max (λ_{max}) of ZPO HCL

The 10 mg of drug was disintegrated in DMSO and the volume was raised up to 100 ml involving methanol in a 100 ml volumetric flask to make a stock arrangement of 100 mcg/ml. Pipetting 1 ml of this stock arrangement into a 10 ml volumetric flask and filling it to the imprint yielded a centralization of 10 mcg/ml. An UV- spectrophotometer was utilized to check the resultant arrangement in the range of 200 and 400 nm (Model-1700, Shimadzu, Japan). The most extreme worth got from the UV range of the example was contrasted with the UV range provided in the authority monograph.

4.3.1.5 Solubility study of ZPO HCL

Overabundance drug was taken in glass vials containing 20mL of the suitable dissolvable solvent and the supernatant arrangement was shifted following 24 hours at room temperature utilizing a 0.45 m pore size channel. The initial 10 mL of the filtrate were disposed of and the rest was weakened with water and investigated spectroscopically at 317nm. Different solvents were used all through the procedure, including water, (CH₃)₂CO, ethanol, chloroform, ether and pH 7.4 Phosphate buffer.

4.3.1.6 Determination of Partition Co-efficient:

It was once decided via soaking 10mL of n-octanol in 10mL of phosphate buffer pH 7.4 for 24 hours in a isolating funnel. The isolating funnel will be stuffed with 10mg of medicine, observed through four hours of intermediate shaking. The quantity of medicinal drug dissolved in every section was once measured at 317 nm towards a clean after the layers of solvent have been separated the use of a funnel.

4.3.1.7 Preparation of Calibration Curve for ZPO HCL

4.3.1.7.1 Calibration Curve for ZPO HCL IN 0.1N HCL solution

Preparation of Stock solution

100 mg of drug was used to be exactly weighed in 100 mL volumetric flask. To create 100 mcg/ml solution, the quantity was once extended to 100 ml via including 0.1N HCL solution. 1 ml of the solution (100 mcg/ml) was pipetted into volumetric flasks and diluted to 10 ml with 0.1N HCL to get concentrations ranging from 1.0 to 5.0 mcg/ml.

Preparation of standard working solution

1ml of the stock arrangement (100g/ml) was taken and weakened with 0.1N HCL answer for make 10ml. To create a convergence of 1.0 to 5.0 mcg/ml, proper aliquots of the arrangement were taken into different volumetric flasks and made up to 10ml with 0.1N HCL. A drug adjustment blend in 0.1 N HCl was created by dissolving definitively gauged 100 mg of medication in a 100 ml volumetric flask. The volume was then raised to 100 ml utilizing 0.1N HCL answer for produce a 100 mcg/ml solution, which was then examined in an UV spectrophotometer.

4.3.1.8 Calibration Curve for ZPO HCL in Saline buffer pH 7.4

Preparation of Stock solution

A 100 mg/ml stock arrangement of ZPO HCL was created in saline buffer pH 7.4 by dissolving 10 mg of the medication in 10 ml of methanol and afterward filling the rest of saline buffer pH 7.4. The most noteworthy grouping of ZPO HCL was found by checking reasonable weakenings with a decent relationship coefficient. Different standard weakenings of the stock arrangement were made to acquire arrangements of 2,4,6,8, and 10 mcg/ml, and their absorbance values were estimated at fixed wavelength.

Preparation of Standard working solution

The subsequent solutions was sequentially made with saline buffer pH 7.4 to get solutions of 10, 20, 40, 50, and 100 mc g/ml. The convergence of ZPO HCL was tried further by estimating the absorbance at 317nm.

4.3.1.9 Identification of ZPO HCL by FT-IR Spectroscopy

*The potassium bromide IR disc will be made utilizing a water powered pellet press with 1mg of ZPO HCL, checked at 4000-400 cm⁻¹ in FTIR, and the IR spectra contrasted with the ZPO HCL reference range.

4.3.1.10 Drug- Excipients Compatibility Studies by FT-IR

A potassium bromide IR circle will be produced using a combination of ZPO HCL, HPMC E5, Stake 400, Citrus extract, Aspartame, and Mannitol, which will be examined in the 4000-400 cm⁻¹ region in FTIR and contrasted with a reference spectra of ZPO HCL.

4.3.1.11 Particle Size Study:

Unadulterated Medication Molecule size examination had done utilizing Optical Magnifying lens and Malvern Instrument.

4.4 Formulation and Development of ZPO HCL MDF ²²⁻⁵⁴

4.4.1 Preliminary Trial Batches of ZPO HCL MDF:

In early preliminaries, the impacts of polymer type and focus, plasticizer type and fixation, breaking down specialists, and other excipients on MDF will be analyzed. These fundamental clusters of quick deteriorating films were tried utilizing morphological examination, weight variety, crumbling time, surface pH, collapsing perseverance, thickness, drug content consistency, percent uniform medication conveyance, and an in-vitro drug discharge study to foster the QbD Approach.

4.4.2 Dose calculation of ZPO HCL for mould

Dose of drug = ORAL DOSE * ORAL BIOAVAILABILITY/ BODY SURFACE AREA

- Area of mould is 24 cm² (12 cm × 2 cm).
- Area of film is 6 cm² (3 cm × 2 cm).
- Total number of films in each mould 24/6 = 4
- One film contains 25 mg of drug than 4 films containing 100 mg drug
- So, one mould containing 100 mg drug

4.4.3 Solvent casting method

Oral fast deteriorating films are made by dissolving the film forming materials (polymers) and plasticizer in refined water, blending continually on an attractive stirrer for 4

hours, and afterward keeping the arrangement short-term in refined water for expanding. In the mean time, in a different holder, the excess excipients, including spit invigorating specialist, Super dissolving specialist, improving specialist, surfactant, flavor, and medicine, are broken up in water for 45 minutes with steady mixing. After the twirling is finished, the two solutions are blended and whirled on an attractive stirrer for one more hour. Then, at that point, for 60 minutes, let the solution be permit the froths to settle. Sonicate the solution in a sonicator to remove any air bubbles. The completed combination is filled a shape and dried to make a film. The film ought to be air-dried prior to being painstakingly eliminated and cut into a 62 centimeter size.

TABLE 4. 4 Materials and their concentration used for Preliminary trial Batches of ZPO HCL MDF

| SL. NO | ROLE OF MATERIAL | MATERIALS TO BE USED | CONCENTRATION |
|--------|----------------------|---|-------------------|
| 1 | Drug | <i>ZPO HCL</i> | 100 mg |
| 2 | Polymers | HPMC E5, HPMC K4M, Acacia, Tragacanth, Gelatin, Xanthum Gum, PVA, PVP and Pullnan | 0.1 gm to 0.5 gm |
| 3 | Plasticizers | PEG 200, PEG 400, PEF 800, PG, IPA | 0.1 gm to 0.5 gm |
| 4 | Disintegrating Agent | Cross Providone, Kryon T-314, Banana Powder | 0.05 gm to 0.1 gm |
| 5 | Solvent | Distilled water | Q.S. |
| 6 | Sweeting Agent | Aspartame, Mannitol | Q.S. |
| 7 | Flavouring Agent | Vanillin | Q.S. |
| 8 | Preservative | Citric acid, Methyl paraben, Propyl paraben | Q.S. |

4.4.4 Preliminary Trial Batches of ZPO HCL MDF

4.4.4.1 Selection of Polymer and concentration for ZPO HCL MDF:

The various polymers and their fixations were utilized to plan ZPO HCL MDF to fix the polymer type and focus. The subtleties are as per the following:

TABLE 4.5 Polymer and concentration for ZPO HCL MDF

| | | | | | |
|--|-----------------|-------------------|--------------------|------------|----------------|
| POLYMER TYPE USED | HPMC E5 | Acacia | Gelatin | PVA | PULLNAN |
| | HPMC K4M | Tragacanth | Xanthum gum | PVP | |
| POLYMER CONCENTRATION USED (mg) | 100 | 300 | 500 | | |

4.4.4.2 Selection of plasticizer for ZPO HCL MDF

The different plasticizer and their fixations were utilized to get ready ZPO HCL MDF to fix the plasticizer type and focus. The different plasticizer utilized were as per the following:

TABLE 4.6 Plasticizer type and concentration for ZPO HCL MDF

| | | | | |
|--|----------------|----------------|------------|------------|
| PLASTICIZER TYPE USED | PEG 200 | PEG 400 | PG | IPA |
| PLASTICIZER CONCENTRATION USED (ml) | 1 to 2 | | 0.5 to 1.0 | |

4.4.4.3 Selection of disintegrating agent for ZPO HCL MDF

The various disintegrating agents and their concentrations were utilized to make ZPO HCL MDF to fix the disintegration type and concentration. The subtleties are as follows: The different polymer utilized were as:

TABLE 4.7 Disintegrating agent type and concentration for ZPO HCL MDF

| | | | |
|--|---------------------------|------------------------|--------------------------|
| DISINTEGRATING AGENT TYPE USED | Cross Povidone (g) | Kyron T-314 (g) | Banana Powder (g) |
| DISINTEGRATING AGENT CONCENTRATION (mg) | 50 to 100 mg | | |

4.5 Formulation and Development of ZPO HCL MDF by Design of Experiment (DoE) Using QbD Approach

A plan space could address detailing and cycle information, like properties of medication fixings, materials, gear, protected innovation, and completed item quality. For this point, a danger appraisal of MDF quality can be performed in view of a comprehension of the interaction and its related parts. Fundamental review and later Plan of Trial and error (DoE) would be finished high-hazard boundaries. In light of the impact of basic quality models of the expected item profile, we will give a plan space to creating powerful definition. MDF will be evaluated in view of various elements.

4.6 Characterization of ZPO HCL MDF

4.6.1 Weight variation

Mouths dissolving oral movies were burdened a logical equilibrium, and the normal load for each film was processed. It is liked for motion pictures to have a weight that is almost consistent. It's basic to guarantee that a film contains the suitable measure of excipients and Programming interface.

4.6.2 Thickness of Films

A micrometer screw check was utilized to gauge the thickness of the film at five unique places, and a normal of three estimations was determined. This is expected to give consistency in the film thickness, which is connected to portion precision in the film.

4.6.3 Folding endurance

Collapsing perseverance is estimated by collapsing a similar piece of film again and over until it breaks. The collapsing perseverance esteem is the times a film can be collapsed in a similar spot without breaking.

4.6.4 Weight Uniformity

A foreordained fix region should be fragmented and shown up an advanced equilibrium. The normal weight and standard deviation will be determined utilizing individual loads.

4.6.5 Surface pH

The film to be tried was splashed with 0.5 cc of refined water and put away for 30 seconds in a Petri dish. In the wake of bringing the anode of the pH meter in contact with the outer layer of the plan and permitting 1 moment for equilibration, the pH was recorded. For every plan, a normal of three judgments was made.

4.6.6 *In vitro* disintegration test

At the point when an oral film comes into contact with water or salivation, it starts to crumble quicker. A quick dissolving film's breaking down time ought to be between 5 to 30 seconds. One more technique was to plunge the film in 25 mL water in a measuring utensil to outwardly decide the deterioration time. The second the film started to break or crumble was caught when the container was delicately shaken.

4.6.7 Drug content Determination

After a precisely gauged amount of film (over 100 mg) is broken down in 100 mL of Phosphate support pH 7.4 in which medicine is solvent, the arrangement is shaken constantly for 24 hours in a shaker hatchery. The arrangement is then sonicated completely. After sonication and sifting, how much medication in arrangement is resolved spectrophotometrically.

4.6.8 Tensile Strength

$$\text{Tensile strength} = F/a \times b (1+L/l)$$

4.6.9 Flux and Permeability coefficient

$$K_p = J/C$$

4.6.10 In-vitro Permeation study

An in-vitro pervasion study can be completed utilizing a dissemination cell receptor compartment with a limit of 12 ml. Extracted cellophane paper was put between the contributor and receptor offices of the dispersion cell. Arranged patches were put on top of paraffin film. The receptor compartment of the dissemination cell was loaded up with phosphate support pH 7.4. The entire thing was mounted on an attractive stirrer, and the arrangement in the receptor compartment was continually whirled with attractive dots at 50 rpm while keeping the temperature at 32 0.5 °C. Drug still up in the air by spectrophotometric examination of tests taken at different stretches. The receptor stage was topped off with new information.

4.6.11 Kinetic Analysis of Release Data:

4.6.11.1 Zero Order Release

$$Q_t = Q_0 + K_0t$$

4.6.11.2 First Order Release Equation

$$\text{Log } C = \text{Log } C_0 - Kt / 2.303$$

4.6.11.3 Higuchi Square Root of Time Equation:

$$Q = KH \times t^{1/2}$$

4.6.11.4 Validation or check point analysis of ZPO HCL MDF

Plan and portrayal of expected bunches from Overlay plots proposed by StatEase programming will be utilized for approval or designated spot examination. The consequences of the normal and noticed bunches will be looked at.

4.6.11.5 Taste Evaluation Study by Spitting

Eight sound grown-up male volunteers between the ages of 24 and 42 participated in a solitary dose and single visually impaired preliminary. Preceding the preliminary, all subjects gave composed informed assent and were instructed with regards to the review's motivation, dangers, and term.

ZPO HCL advanced MDF will be given to every member at arbitrary. Before the review, the volunteers were encouraged to flush their mouths with 200 cc of refined water. The volunteers were told to place the medication in their mouth for 30 seconds, record the deterioration span of the film test, and rate the detailing in view of the variables demonstrated in Table, in particular mouth feel, flavor or harshness, film trailing sensation, simplicity of dealing with, and generally acknowledgment. The volunteers were told to let out the example with salivation and wash their mouths with 200 cc refined water following 3 minutes. The subsequent example was treated similarly following 2 hours (either the test or the reference test).

4.6.11.6 Scanning electron microscope

The surface morphology of the better definition was analyzed utilizing filtering electron microscopy. A falter coater (JSM 6390, Make - JEOL) was utilized to cover a 150A gold layer on a checking electron magnifying instrument test holder with a twofold sided tap for 2 minutes in a vaccum of 310-1atm organ gas. The examples were therefore inspected utilizing a checking electron magnifying instrument.

4.6.11.7 Skin Permeation Study (*Ex- vivo* Study)

The skin penetration examination will require IAEC freedom and assent (*ex-vivo* study). The skin of pale skinned person rodents will be eliminated with care. After the hypodermal fat tissue has been taken out, the skin will be utilized as an obstruction film for the examinations. The best definition from *in vitro* tests will be utilized in this review, with rodent skin going about as a boundary between the giver and receptor compartments. An attractive stirrer will be utilized to disturb the receptor compartment, which will be loaded up with phosphate support pH 7.4 and warmed to 37.1 °C. The examples will be contrasted with a clear utilizing an UV spectrophotometer set to 317 nm.

4.6.11.8 Comparison of optimized ZPO HCL MDF with Marketed ZPO HCL formulation

The upgraded plan ZPO HCL MDF will be contrasted and Advertised regular ZPO HCL.

4.6.11.9 Stability Studies

The picked combination was put in golden shaded containers that were painstakingly fixed and cotton-stopped up. They were then kept at 40°C/75% RH for a month and assessed at predefined spans for actual appearance, *in vitro* breaking down time, drug content homogeneity, and medication discharge tests.

Chapter-5
Results &
Discussion
(ZPO HCL)

CHAPTER 5

RESULTS & DISCUSSION

5. RESULTS & DISCUSSION

5.1 PREFORMULATION STUDY OF ZPO HCL

5.1.1 ORGANOLEPTIC PROPERTIES

TABLE 5. 1 Organoleptic characteristics of Drugs

| S.No. | Parameters |
|-------|-------------------------|
| 1. | White in color |
| 2. | Characteristics in odor |
| 3. | Bitter in taste |

The actual appearance of unadulterated medication was analyzed outwardly as per Indian Pharmacopeia. Our faculties, including the eye, tongue, and nose, were utilized to evaluate shading, scent, and taste in this examination.

5.1.2 MELTING POINT

Utilizing an advanced dissolving point instrument and the slim combination strategy, the liquefying point of the picked prescription was processed. One finish of a fine was fixed with the assistance of a burner. The open finish of the slim cylinder was delicately tapped to settle the amassed material after it was placed into a little piece of powder. The technique was rehashed a couple of times more. The narrow cylinder was then positioned utilizing the liquefying point gadget. The temperature at which the medication starts to break down not set in stone.

TABLE 5. 2 Determination of melting point of drugs

| S.No. | Ziprasidone HCL Melting Point | |
|-------|-------------------------------|----------------|
| | Observed value (n =3) | Standard value |
| 1. | 272-276 °C | 274-276 °C |

The liquefying point was utilized to decide the example's virtue. The dissolving point of the prescription example was $272-276 \pm 2^{\circ}\text{C}$, which was inside the reach and shown that the example was unadulterated ZPO HCL.

5.1.3 DETERMINATION OF WAVELENGTH OF ZPO HCL

The fittingly gauged amount of 100 mg of medication test was broken up in DMSO and volume moved toward 100 ml involving methanol in a 100 ml volumetric flask to frame a stock arrangement of 100 mcg/ml. The stock arrangement was then pipetted into a 10 ml volumetric flask, and the volume was raised to the imprint to accomplish a convergence of 10 mcg/ml. The subsequent solution was then examined in the range of 200 and 400 nm with an UV-spectrophotometer (Model-1700, Shimadzu, Japan). The UV range was recorded and the most elevated worth acquired was contrasted with the authority monograph's UV range.

TABLE 5. 3 Wavelength maximum (λ max) of ZPO HCL

| Drug | λ max | |
|---------|----------------------|------------------------|
| | Actual λ max | Observed λ max |
| ZPO HCL | 317 | 317.47 |

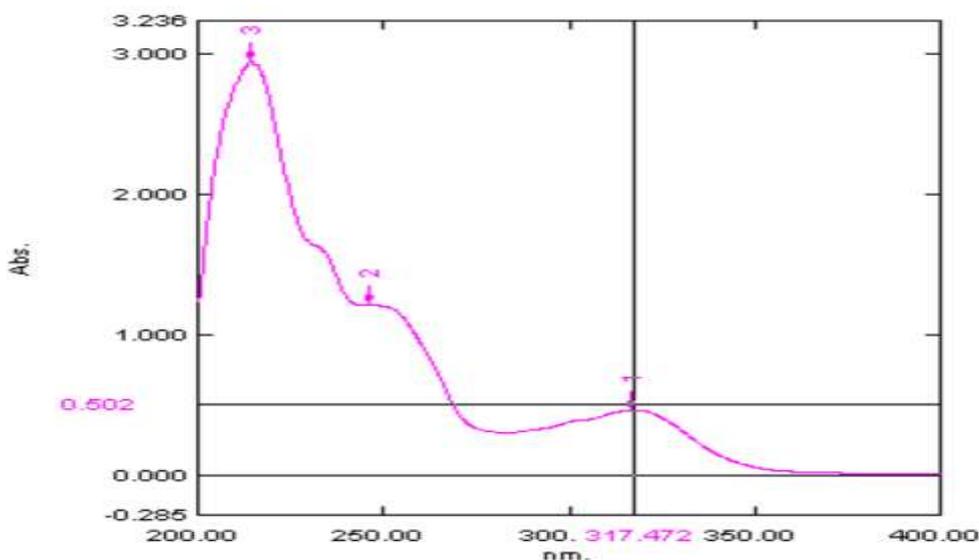


FIGURE 5. 1 UV Spectrum of ZPO HCL

5.1.4 SOLUBILITY STUDIES

The dissolving and dispersion liquids for drug delivery and pervasion studies were picked in view of Ziprasidone solvency information in different liquids. A medication test's not set in stone by dissolving 100 mg of the example in expanding volumes of different liquids. How much dissolvable expected to break down the medication was determined, and the medication's still up in the air.

TABLE 5. 4 Solubility profile of ZPO HCL

| S.No. | Solvent | Solubility | |
|-------|----------|-------------------------------------|-----------|
| | | ZPO HCL | |
| | | Conc. (mg/ml) Mean \pm SD, n=3 | Inference |
| 1. | HCl | 12.1 | Soluble |
| 2. | NaOH | 10.63 | Soluble |
| 3. | Ethanol | 11.59 | Soluble |
| 4. | Methanol | 11.15 | Soluble |
| 5. | Water | 0.0069 | Insoluble |
| 6. | DMSO | 1.13 | Soluble |

From experiment, it was found that ZPO HCL was soluble in HCl, NaOH, Ethanol, Methanol and DMSO.

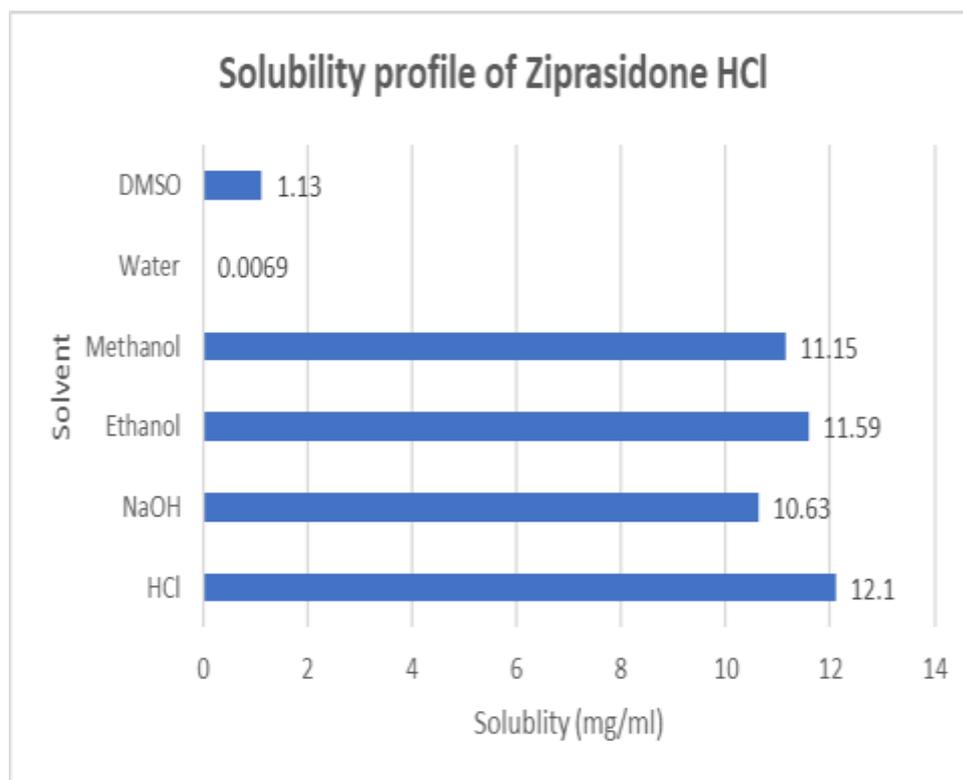


FIGURE 5. 2 Solubility of profile of ZPO HCL

5.1.5 PARTITION COEFFICIENT

The partition coefficient was resolved utilizing n-octanol as a non-aqueous stage and phosphate buffer pH 7.4 (PBS pH 7.4) as an aqueous stage. These two phases were joined in equivalent parts and kept in independent channels until they were soaked. Permit 30 minutes for the framework to settle subsequent to blending. In isolating channels, 10 mg of medication was isolated into 10 ml areas of n-octanol and PBS pH 7.4 to compute the segment coefficient. A mechanical shaker was utilized to shake the isolating pipes for 24 hours. Following fitting weakening, two stages were isolated, with the aqueous stage separated utilizing Whatman filter paper and how much drug in the aqueous stage decided spectrophotometrically at wavelength 318 nm, utilizing phosphate buffer solution pH 7.4 as a clear.

TABLE 5. 5 Determination of Partition Coefficient of selected Drugs

| S.No. | Sample | Partition Coefficient (Mean \pm SD, n=3) |
|-------|---------|--|
| 1. | ZPO HCL | 4.61 \pm 0.43 |

5.1.6 Calibration Curve

5.1.6.1 ZPO HCL Calibration Curve in 0.1N HCL

Preparation of standard stock solution (100µg/ml) in 0.1N HCL

10 mg of drug was accurately taken in a 100 mL volumetric flask. To make a 100 mcg/ml solution, the volume was expanded to 100 ml by adding 0.1N HCL. In isolated volumetric flask, 1 ml of the stock solution (100 mcg/ml) was weakened to 10 ml with 0.1N HCL solution, making solution of 1.0 to 5.0 mcg/ml.

Preparation of standard working solution

1ml was pipetted from the stock solution (100 mcg/ml) and weakened to 10ml with 0.1N HCL solution. Proper aliquots of the solution were taken into different volumetric flask and made up to 10ml with 0.1N HCL solution for accomplish a centralization of 1.0 to 5.0 mcg/ml. By dissolving exactly gauged 100 mg of prescription in a 100 ml volumetric flask, a drug alignment blend in 0.1 N HCl was made. The volume was therefore expanded to 100 ml utilizing 0.1N HCL solution to get solution of 100 mcg/ml, which was then checked in an UV spectrophotometer.

TABLE 5. 6 Calibration Curve of ZPO HCL in 0.1 N HCl

| Conc. (µg/ml) | Absorbance (nm) Mean ±SD; n=3 |
|---------------|----------------------------------|
| 0 | 0±0.00 |
| 1 | 0.106±0.032 |
| 2 | 0.214±0.021 |
| 3 | 0.318±0.101 |
| 4 | 0.421±0.002 |
| 5 | 0.512±0.028 |
| 6 | 0.644±0.091 |
| 7 | 0.750±0.022 |
| 8 | 0.844±0.108 |
| 9 | 0.941±0.002 |
| 10 | 0.999±0.091 |

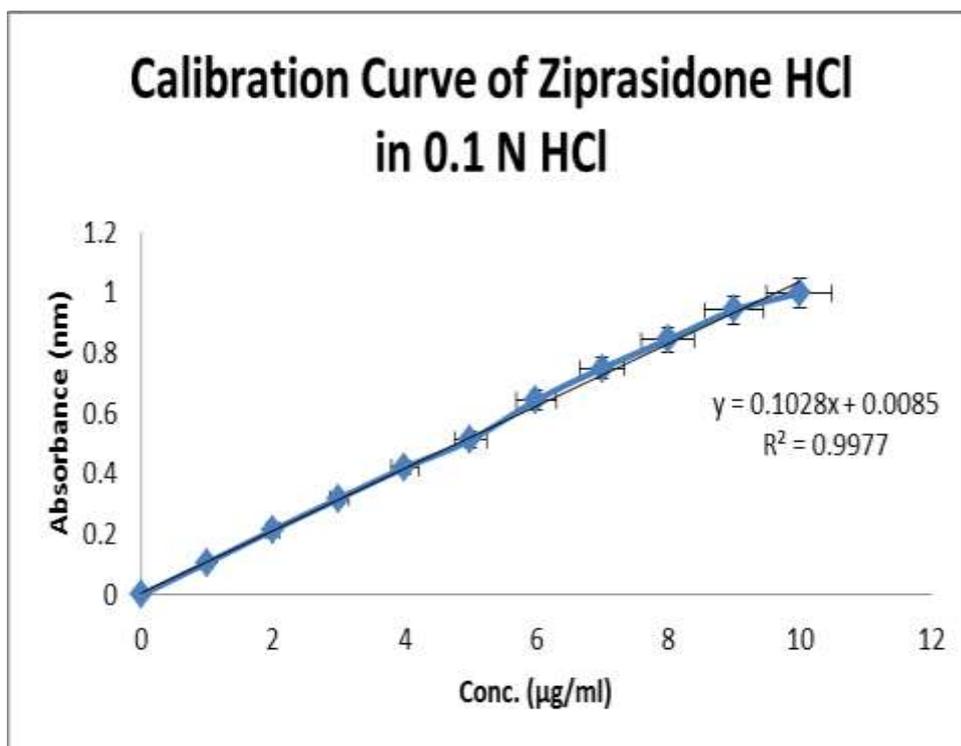


FIGURE 5.3 Standard Curve of ZPO HCL in 0.1 N HCl at 317 nm

TABLE 5.7 Summary Report of calibration curve for ZPO HCL

| Parameters | ZPO HCL |
|---|---------------|
| Wavelength (λ_{max}) | 317 |
| Beer's limit ($\mu\text{g/ml}$) | 0-10 |
| Corrélation coefficient (R^2) | 0.9977 |
| Slope | 0.1028 |
| Obeys Beer law in conc. range of 0-20 mcg/ml | |
| R^2 value shows linearity | |

5.1.7 ZPO HCL Calibration Curve in Phosphate buffer pH 7.4 (pH of Salivary stimulating fluid)

Preparation of standard stock solution (100 µg/ml) in Phosphate buffer pH 7.4 (pH of Salivary stimulating fluid)

Weigh 100 mg of drug accurately in a 10 mL volumetric flask to make 100 mcg/ml solution, the volume was raised to 100 ml by adding Phosphate buffer pH 7.4 to the blend.

To deliver a convergence of 1 to 10 mcg/ml, 1 ml of the stock solution (100 mcg/ml) was pipetted and weakened to 10 ml in isolated volumetric flask with Phosphate buffer pH 7.4.

Preparation of standard working solution

1 ml of the stock solution (100 mcg/ml) was pipetted and weakened with Phosphate buffer pH 7.4 to make 10 ml. To get groupings of 1 to 10 g/ml, suitable aliquots of the solution were filled in different volumetric flask and made up to 10 ml with Phosphate buffer pH 7.4 to acquire convergences of 1 to 10 mcg/ml.

The alignment blend for drug in Phosphate buffer pH 7.4 was made by dissolving 100 mg of drug in a 100 ml volumetric flask that was unequivocally gauged. The volume was then expanded to 100 ml utilizing Phosphate buffer pH 7.4 to produce solution of 100 mcg/ml, which was then observed in an UV spectrophotometer.

TABLE 5. 8 Calibration Curve of ZPO HCL in Phosphate buffer pH 7.4

| Conc. (µg/ml) | Absorbance (nm) Mean ±SD; n=3 |
|---------------|----------------------------------|
| 0 | 0±0.00 |
| 1 | 0.024±0.021 |
| 2 | 0.031±0.022 |
| 3 | 0.042±0.039 |
| 4 | 0.055±0.012 |
| 5 | 0.071±0.002 |
| 6 | 0.080±0.005 |

| | |
|----|-------------|
| 7 | 0.086±0.010 |
| 8 | 0.103±0.029 |
| 9 | 0.107±0.017 |
| 10 | 0.115±0.008 |

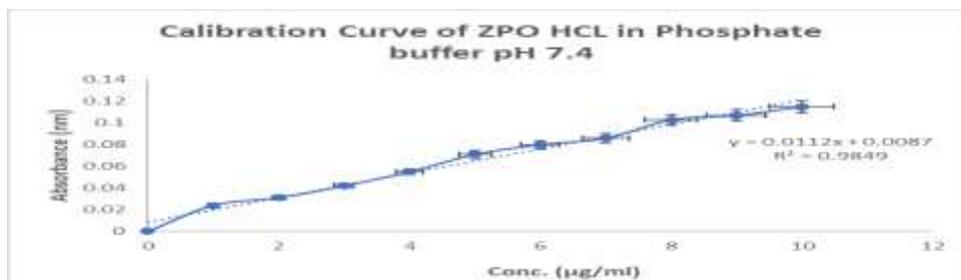


FIGURE 5.4 Standard Curve of ZPO HCL in Phosphate buffer pH 7.4

TABLE 5.9 Summary Report of calibration curve for ZPO HCL in Phosphate buffer pH 7.4

| Parameters | ZPO HCL |
|---|---------|
| Wavelength (λ_{max}) | 317 |
| Beer's limit ($\mu\text{g/ml}$) | 0-10 |
| Corrélation coefficient (R^2) | 0.9849 |
| Slope | 0.0112 |
| Obeys Beer law in conc. range of 0-10 mcg/ml | |
| R^2 value shows linearity | |

5.1.8 Identification of ZPO HCL by FTIR Spectra

On an unadulterated medication test, infrared spectroscopy was used to recognize the substance. The medication was compacted utilizing IR grade potassium bromide in a KBr press at 5.5 metric huge loads of strain to make a medication pellet. The pellet was embedded in an IR compartment and filtered between wave numbers 4000-450 cm^{-1} with a FTIR spectrophotometer (Model-8400 S, Shimadzu, Japan).

TABLE 5. 10 Interpretation of FTIR Spectra of ZPO HCL

| S.No. | Inference | Standard wave no.(cm ⁻¹) | Observed wave no.(cm ⁻¹) | Interpretation |
|-------|----------------|--------------------------------------|--------------------------------------|----------------------|
| 1. | C-H bending | 735-755 | 736 | 1,2 disubstituted |
| 2. | C-O stretching | 1200-1275 | 1246 | Alkyl aryl ether |
| 3. | C=C stretching | 1626-1662 | 1627 | Alkane disubstituted |
| 4. | C-H stretching | 2695-2830 | 2808 | Aldehyde |
| 5. | C-H stretching | 3000-3100 | 3070 | Alkane |
| 6. | O-H stretching | 2700-3200 | 3190 | Alcohol |

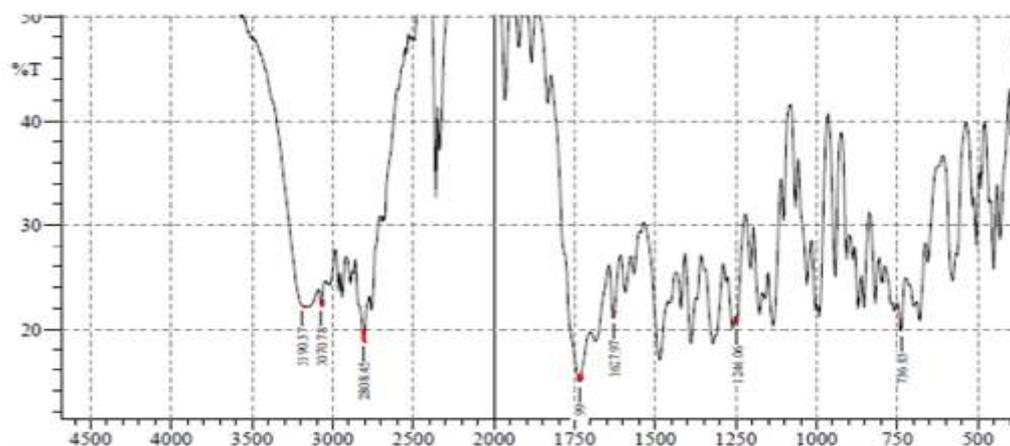


FIGURE 5. 5 FTIR Spectra of Pure Drug

5.1.9 Compatibility study of ZPO HCL with excipients by FTIR Spectra

TABLE 5. 11 Interpretation of FTIR Spectra of ZPO HCL

| S.No. | Inference | Standard wave no.(cm ⁻¹) | Observed wave no.(cm ⁻¹) | Interpretation |
|-------|----------------|--------------------------------------|--------------------------------------|----------------------|
| 1. | C-H bending | 735-755 | 736 | 1,2 disubstituted |
| 2. | C-O stretching | 1200-1275 | 1246 | Alkyl aryl ether |
| 3. | C=C stretching | 1626-1662 | 1627 | Alkane disubstituted |
| 4. | C-H stretching | 2695-2830 | 2808 | Aldehyde |
| 5. | C-H stretching | 3000-3100 | 3070 | Alkane |
| 6. | O-H stretching | 2700-3200 | 3190 | Alcohol |

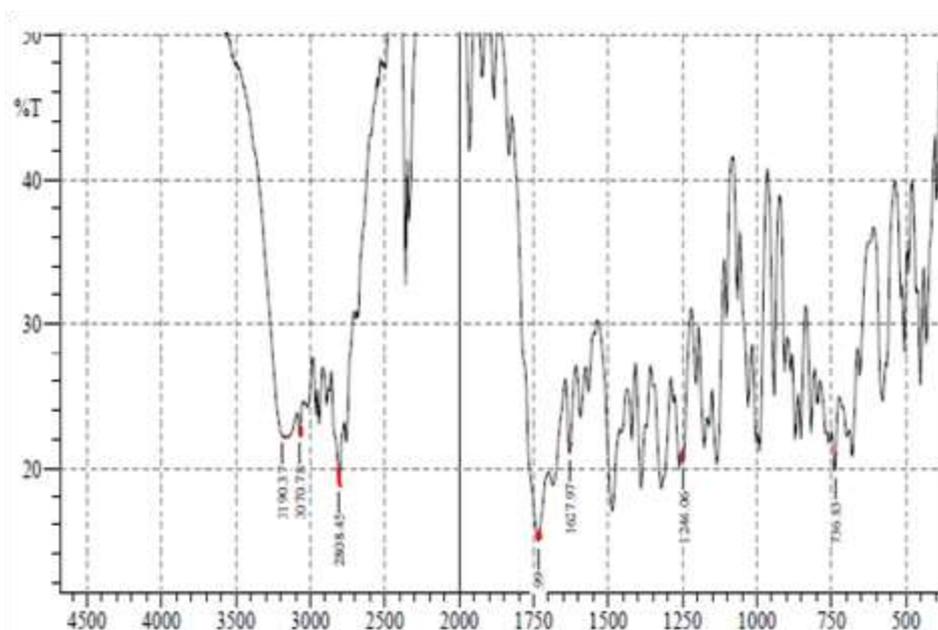


FIGURE 5.6 FTIR Spectra of Pure Drug with excipients

A combination of ZPO HCL, HPMC E5, Stake 400, Citrus extract, Aspartame, and Mannitol will be utilized to make a potassium bromide IR circle, which will be examined in the 4000-400 cm^{-1} region in FTIR and contrasted with a reference spectra of ZPO HCL. Whenever ZPO HCL was joined with polymers, no progressions in the IR tops were noticed. These discoveries highlight polymers' similarity with ZPO HCL.

5.2 Preparation of ZPO HCL Mouth Dissolving Film

5.2.1 Trial batches for ZPO HCL Mouth Dissolving Film

TABLE 5. 12 Selection of polymers type and concentration

| Ingredients | ZPOD T1 | ZPOD T2 | ZPOD T3 | ZPOD T4 | ZPOD T5 | ZPOD T6 | ZPOD T7 | ZPOD T8 | ZPOD T9 | ZPODT 10 | ZPODT 11 | ZPODT 12 |
|-----------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|-------------|-------------|-------------|
| Drug (gm) | 0.1 | | | | | | | | | | | |
| HPMC E5 LV (gm) | 0.1 | 0.3 | 0.5 | - | - | - | - | - | - | - | - | - |
| HPMCK4M (gm) | - | - | - | 0.1 | 0.3 | 0.5 | - | - | - | - | - | - |
| PVA (gm) | - | - | - | - | - | - | 0.1 | 0.3 | 0.5 | - | - | - |
| PVP (gm) | - | - | - | - | - | - | - | - | - | 0.1 | 0.3 | 0.5 |
| PEG 400 (ml) | 01 | | | | | | | | | | | |
| DW (mL) | Q.S | | | | | | | | | | | |
| Strip Form | Yes | | | | | | | | | | | |
| Stickiness | - | | | | | | | | | | | |
| Appearance | * | | | | | | # | | | | | |

DISCUSSION:

BATCH (ZPODT1- ZPODT3): In the scope of 0.1-0.5 gm, the strip framing polymer HPMC E5 LV was utilized. The strips were decided on their actual allure as well as their tenacity. From petridish, it was found that the strips arranged were non-tacky, straightforward, and had satisfactory stripping properties.

BATCH (ZPODT4-ZPODT6): HPMC K4M, a strip framing polymer, was utilized in fixations going from 0.1-0.5 gm. The strips were decided on their actual appeal as well as their tenacity. From petridish, it was found that the strips were non-tacky, clear, and had OK strip capacity.

BATCH (ZPODT7-ZPODT9): PVA, a strip framing polymer, was utilized in sums going from 0.1-0.5 gm. The strip with a centralization of 100mg was straightforward and non-tacky. At the point when the fixation was expanded to 1.0 gm, in any case, the strip became hazy because of air ensnarement. Also, the strip was hard to recognize from petridish.

BATCH (ZDT10-ZPODT12): PVP, a strip shaping polymer, was used in fixations going from 0.1-0.5 gm. Because of the production of knocks in the strips, the strips were non-tacky yet appeared to be hazy.

TABLE 5.13 Results of ZPODT1-ZPODT7

| Batch | Surface Texture | Weight uniformity (mg) (Mean \pm SD) n=3 | Avg. uniform Drug Distribution (%) \pm SD, n = 3 | Avg. Drug Content uniformity (%) \pm SD, n = 3 |
|--------|-----------------|--|--|--|
| ZPODT1 | Smooth | 100.3 \pm 0.2 | 98.72 \pm 0.21 | 99.36 \pm 0.37 |
| ZPODT2 | Smooth | 99.94 \pm 0.21 | 98.02 \pm 0.35 | 99.47 \pm 0.15 |
| ZPODT3 | Smooth | 100.26 \pm 0.39 | 99.6 \pm 0.2 | 99.92 \pm 0.41 |
| ZPODT4 | Smooth | 100.2 \pm 0.5 | 99.32 \pm 0.23 | 99.34 \pm 0.18 |
| ZPODT5 | Smooth | 100.18 \pm 0.57 | 98.36 \pm 0.15 | 99.46 \pm 0.35 |
| ZPODT6 | Smooth | 100.22 \pm 0.76 | 99.16 \pm 0.33 | 99.2 \pm 0.13 |
| ZPODT7 | Smooth | 99.9 \pm 0.32 | 98.62 \pm 0.25 | 100.02 \pm 0.62 |

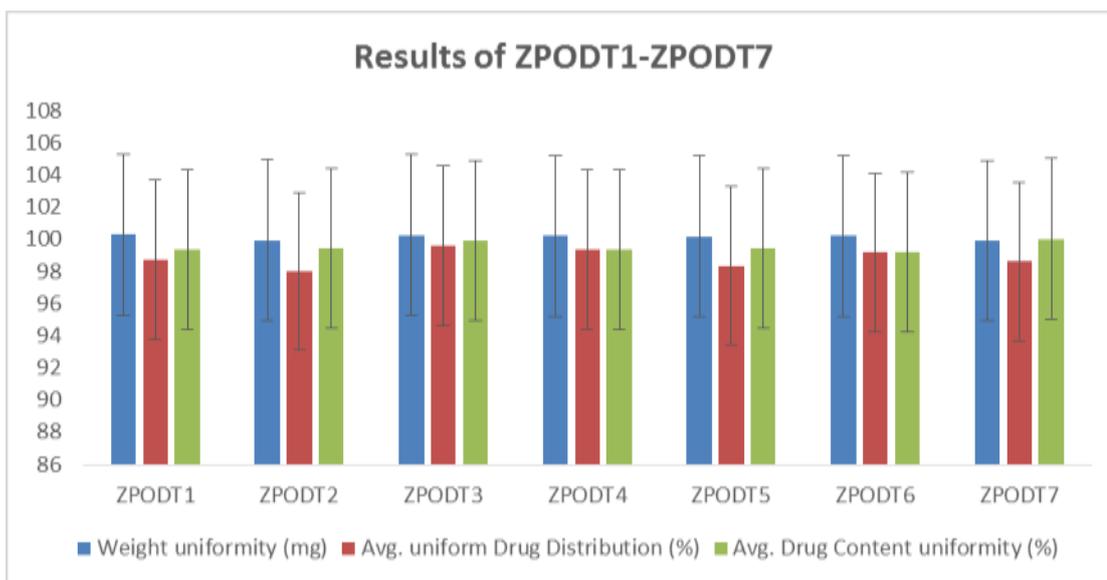


FIGURE 5.7 Results of ZPODT1-ZPODT7

TABLE 5. 14 Results of ZPODT1-ZPODT7

| Batch | Surface pH (Mean \pm SD) n=3 | Thickness (mm) (Mean \pm SD) n=3 | Avg. Tensile strength (N/cm ²) \pm SD, n = 3 |
|--------|-----------------------------------|---|--|
| ZPODT1 | 6.54 \pm 0.03 | 0.14 \pm 0.02 | 2.12 \pm 0.02 |
| ZPODT2 | 6.65 \pm 0.04 | 0.14 \pm 0.01 | 2.11 \pm 0.04 |
| ZPODT3 | 6.66 \pm 0.05 | 0.15 \pm 0.01 | 2.14 \pm 0.03 |
| ZPODT4 | 6.53 \pm 0.04 | 0.14 \pm 0.02 | 1.77 \pm 0.02 |
| ZPODT5 | 6.62 \pm 0.05 | 0.15 \pm 0.02 | 1.43 \pm 0.01 |
| ZPODT6 | 6.68 \pm 0.07 | 0.16 \pm 0.01 | 1.32 \pm 0.15 |
| ZPODT7 | 6.57 \pm 0.08 | 0.17 \pm 0.02 | 1.06 \pm 0.02 |

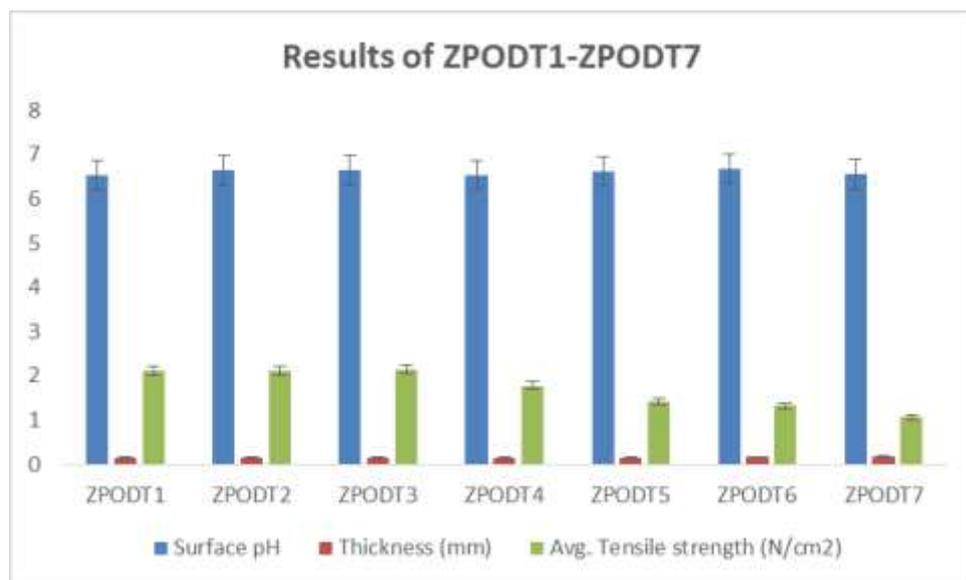


FIGURE 5.8 Results of ZPODT1-ZPODT7

TABLE 5. 15 Results of ZPODT1-ZPODT7

| Batch | Avg. Folding Endurance \pm SD, n = 3 | Avg. In Vitro Disintegration Time (sec) \pm SD, n = 3 |
|--------|---|---|
| ZPODT1 | 149.46 \pm 1.33 | 127.26 \pm 0.28 |
| ZPODT2 | 163.36 \pm 1.4 | 133.1 \pm 1.44 |
| ZPODT3 | 181.72 \pm 1.14 | 138.62 \pm 0.38 |
| ZPODT4 | 93.56 \pm 1.33 | 159.36 \pm 1.02 |
| ZPODT5 | 84.12 \pm 1.13 | 179.12 \pm 1.37 |
| ZPODT6 | 98.16 \pm 1.26 | 184.14 \pm 1.41 |
| ZPODT7 | 36.36 \pm 1.17 | 166.14 \pm 1.15 |

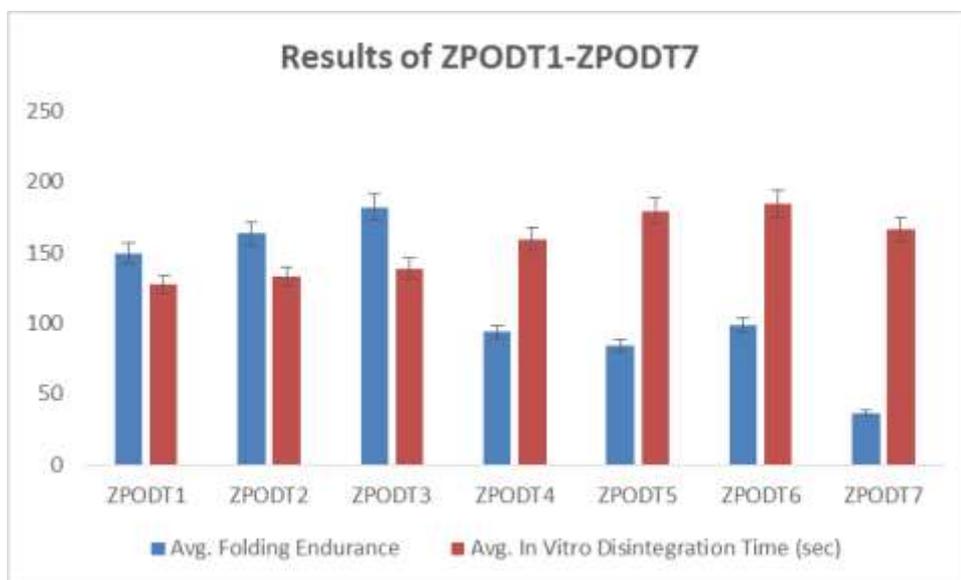


FIGURE 5. 9 Results of ZPODT1-ZPODT7

Inference

In view of the discoveries of the starter preliminary batches for polymer choice showed above, it was laid out that polymers HPMC E5 LV and HPMC K4M produced the best outcomes in the focus scopes of 0.1, 0.3, and 0.5 gm and subsequently these two polymers were picked for the plan of last MDFs.

TABLE 5. 16 Trial batch for selection of Polymer type and concentration

| Ingredients | ZPODT 13 | ZPODT 14 | ZPODT 15 | ZPODT 16 | ZPODT 17 | ZPODT 18 | ZPODT 19 | ZPODT 20 | ZPODT 21 | ZPODT 22 | ZPODT 23 | ZPODT 24 | ZPODT 25 | ZPODT 26 | ZPODT 27 |
|---------------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Drug (gm) | 0.1 | | | | | | | | | | | | | | |
| Acacia (gm) | 0.1 | 0.3 | 0.5 | - | - | - | - | - | - | - | - | - | - | - | - |
| Tragacanth (gm) | - | - | - | 0.1 | 0.3 | 0.5 | - | - | - | - | - | - | - | - | - |
| Gelatin (gm) | - | - | - | - | - | - | 0.1 | 0.3 | 0.5 | - | - | - | - | - | - |
| Xanthum gum (gm) | - | - | - | - | - | - | - | - | - | 0.1 | 0.3 | 0.5 | - | - | - |
| Pullulan (gm) | - | - | - | - | - | - | - | - | - | - | - | - | 0.1 | 0.3 | 0.5 |
| PEG 400 (ml) | 01 | | | | | | | | | | | | | | |
| DW (mL) | Q.S | | | | | | | | | | | | | | |
| Strip Form | Yes | | | No | | | Yes | | | | | | No | | |
| Stickiness | + | | | | | | | | | | | | | | |
| Appearance | # | | | | | @ | | | | | # | | @ | | |

BATCH (ZPODT13-ZPODT15): Acacia, a strip-framing polymer, was used in sums going from 0.1-0.5 gm. The pre-arranged strips were inspected, and it was found that they were tacky and hazy by all accounts, and that they were hard to eliminate from the petridish.

BATCH (ZPODT16-ZPODT18): Tragacanth, a strip-shaping polymer, was used in sums going from 0.1-0.5 gm. There was no strip delivered, as indicated by the discoveries.

BATCH (ZPODT19-ZPODT21): Gelatin, a strip-framing polymer, was used in sums going from 0.1-0.5 gm. The strips that came about were viewed as tacky and dark. It is extremely challenging to eliminate from the petridish.

BATCH (ZPODT22-ZPODT24): Thickener, a strip-shaping polymer, was used in sums going from 0.1-0.5 gm. The strips that shaped were tacky, misty, and hard to eliminate from the petridish.

BATCH (ZPODT25-ZPODT27): PULLNAN, a strip-shaping polymer, was utilized in focuses going from 0.1-0.5 gm. The strips that shaped were tacky, dark, and hard to eliminate from the petridish.

In view of the aftereffects of all of the above strip framing polymers, it was resolved that HPMC E5 LV and HPMC K4M strips were non-tacky, straightforward, and effectively removable from the petridish, showing great strip shaping limit. Thus, these polymers can be consolidated in details.

TABLE 5. 17 Trial batch for selection of Plasticizer type and concentration

| Ingredients | ZPLDT 1 | ZPLDT 2 | ZPLDT 3 | ZPLDT 4 | ZPLDT 5 | ZPLDT 6 | ZPLDT 7 | ZPLDT 8 | ZPLDT 9 | ZPLDT 10 | ZPLDT 11 | ZPLDT 12 | ZPLDT 13 | ZPLDT 14 | ZPLDT 15 |
|--------------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|-------------|-------------|-------------|-------------|-------------|-------------|
| HPMC E5 LV (mg) | 300 | | | | | | | | | | | | | | |
| Drug (mg) | 100 | | | | | | | | | | | | | | |
| PEG 200 (ml) | 1 | 1.5 | 2 | - | - | - | - | - | - | - | - | - | - | - | - |
| PEG 400 (ml) | - | - | - | 1 | 1.5 | 2 | - | - | - | - | - | - | - | - | - |
| PEG 800 (ml) | - | - | - | - | - | - | 1 | 1.5 | 2 | - | - | - | - | - | - |
| PG (ml) | - | - | - | - | - | - | - | - | - | 0.5 | 0.75 | 1.0 | - | - | - |
| IPA (ml) | - | - | - | - | - | - | - | - | - | - | - | - | 0.5 | 0.75 | 1.0 |
| DW (ml) | Q.S | | | | | | | | | | | | | | |
| Strip Form | Yes | | | | | | | | | | | | | | |
| Stickiness | - | | | | | | | + | | | | | | | |
| Appearance | * | | | | | | | @ | | | | # | | | |

The strips were made with Stake 200 and Stake 400 in focuses going from 1 to 2 mL. The subsequent strips were assessed for their actual appearance and tenacity. Stake 200 and Stake 400 strips were viewed as non-tacky, non-slick, straightforward for all intents and purposes, and easy to project. Stake 800, PG, and IPA strips, then again, were tacky, sleek, obscure and hard to project.

TABLE 5.18 Results of ZPLDT1-ZPLDT6

| Batch | Surface Texture | Weight uniformity (mg) (Mean \pm SD) n=3 | Avg. uniform Drug Distribution (%) \pm SD, n = 3 | Avg. Drug Content uniformity (%) \pm SD, n = 3 |
|---------------|-----------------|--|---|---|
| ZPLDT1 | Smooth | 98.06 \pm 0.05 | 96.417 \pm 0.35 | 97.46 \pm 0.11 |
| ZPLDT2 | Smooth | 101.02 \pm 0.15 | 98.22 \pm 0.15 | 98.66 \pm 0.15 |
| ZPLDT3 | Smooth | 99.6 \pm 0.02 | 95.02 \pm 0.1 | 99.20 \pm 0.05 |
| ZPLDT4 | Smooth | 99.05 \pm 0.16 | 99.40 \pm 0.13 | 99.61 \pm 0.18 |
| ZPLDT5 | Smooth | 99.07 \pm 0.32 | 99.22 \pm 0.14 | 100.60 \pm 0.05 |
| ZPLDT6 | Smooth | 99.06 \pm 0.31 | 99.26 \pm 0.10 | 99.51 \pm 0.24 |

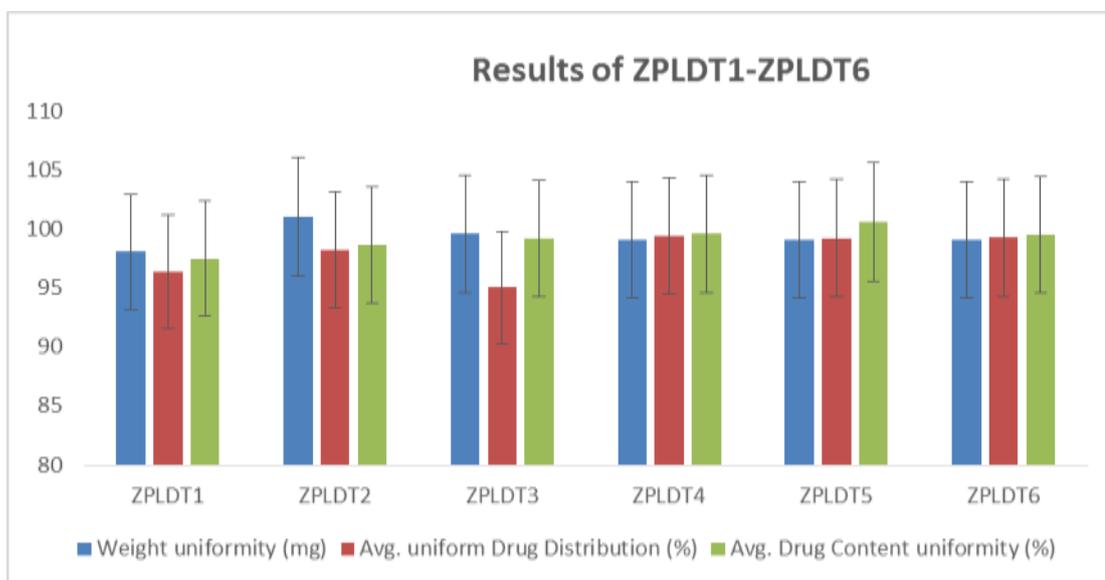


FIGURE 5.10 Results of ZPLDT1-ZPLDT6

TABLE 5. 19 Results of ZPLDT1-ZPLDT6

| Batch | Surface pH (Mean \pm SD) n=3 | Thickness (mm) (Mean \pm SD) n=3 | Avg. Tensile strength (N/cm ²) \pm SD, n = 3 |
|---------------|--------------------------------------|---|---|
| ZPLDT1 | 6.2 \pm 0.24 | 0.15 \pm 0.01 | 1.61 \pm 0.03 |
| ZPLDT2 | 7.00 \pm 0.19 | 0.11 \pm 0.01 | 1.9 \pm 0.02 |
| ZPLDT3 | 7.11 \pm 0.27 | 0.11 \pm 0.03 | 2.13 \pm 0.02 |
| ZPLDT4 | 7.12 \pm 0.25 | 0.14 \pm 0.02 | 2.68 \pm 0.15 |
| ZPLDT5 | 7.5 \pm 0.16 | 0.13 \pm 0.03 | 2.56 \pm 0.01 |
| ZPLDT6 | 7.32 \pm 0.11 | 0.15 \pm 0.01 | 2.26 \pm 0.12 |

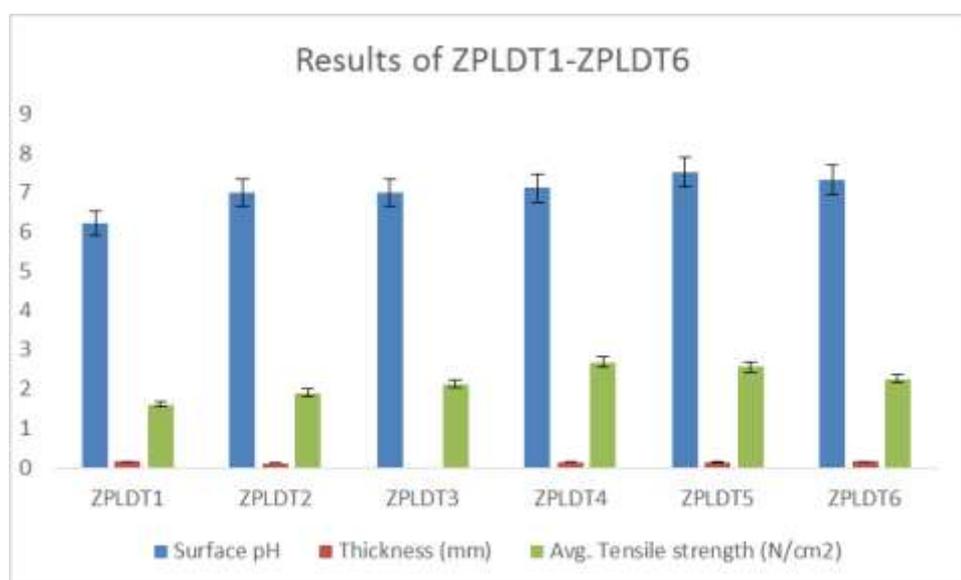


FIGURE 5. 11 Results of ZPLDT1-ZPLDT6

TABLE 5. 20 Results of ZPLDT1-ZPLDT6

| Batch | Avg. Folding Endurance ± SD, n = 3 | Avg. In Vitro Disintegration Time (sec) ± SD, n = 3 |
|---------------|---------------------------------------|--|
| ZPLDT1 | 121.45 ± 1.23 | 173.45 ± 1.33 |
| ZPLDT2 | 136.35 ± 2.18 | 167.25 ± 2.80 |
| ZPLDT3 | 155.45 ± 2.80 | 185.04 ± 2.14 |
| ZPLDT4 | 195.11 ± 0.28 | 113.15 ± 2.18 |
| ZPLDT5 | 205.05 ± 1.47 | 124.65 ± 2.07 |
| ZPLDT6 | 219.42 ± 1.30 | 129.11 ± 1.33 |

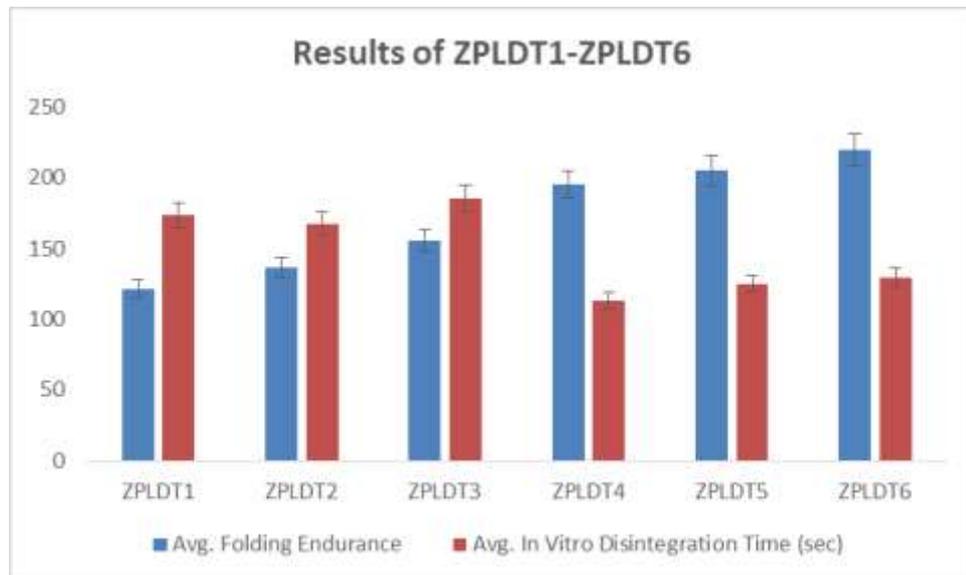


FIGURE 5. 12 Results of ZPLDT1-ZPLDT6

Inference

As per the outcomes got in the above expressed starter preliminary clusters for plasticizer determination, the best outcomes were acquired in Stake 400 in the focus scope of 1-2 ml.

TABLE 5. 21 Selection of disintegrating agent type and concentration

| Ingredients | ZPDT1 | ZPDT2 | ZPDT3 | ZPDT4 | ZPDT5 | ZPDT6 | ZPDT7 | ZPDT8 | ZPDT9 |
|---------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Drug (gm) | 0.1 | | | | | | | | |
| HPMC E5 LV(gm) | 0.3 | | | | | | | | |
| PEG 400 (ml) | 01 | | | | | | | | |
| Cross Povidone (gm) | 0.05 | 0.075 | 0.1 | - | - | - | - | - | - |
| Kyron T-314 (gm) | - | - | - | 0.05 | 0.075 | 0.1 | - | - | - |
| Banana Powder (gm) | - | - | - | - | - | - | 0.05 | 0.075 | 0.1 |
| DW (mL) | Q.S | | | | | | | | |
| Strip form | Yes | | | | | | | | |
| Stickiness | - | + | | | | | - | | |
| Appearance | # | | | * | | | | | |

DISCUSSION: The crumbling specialists Cross Povidone, Kyron T-314, and banana powder were utilized at groupings of 0.05, 0.075, and 0.1 gm in the strips. The created strips were assessed for their actual appearance, tenacity, and breaking down characteristics. The banana powder-containing strips were viewed as non-tacky, straightforward, and broke up. Notwithstanding deterioration, the strips holding back cross povidone and Kryon T-314 were tacky and obscure, while the strips holding back cross povidone and Kryon T-314 were tacky and dark.

TABLE 5.22 Results of ZPDT7-ZPDT9

| Batch | Surface Texture | Weight uniformity (mg) (Mean \pm SD) n=3 | Avg. uniform Drug Distribution (%) \pm SD, n = 3 | Avg. Drug Content uniformity (%) \pm SD, n = 3 |
|--------------|-----------------|--|--|--|
| ZPDT7 | Flexible | 107.13 \pm 1.33 | 101.45 \pm 0.38 | 99.30 \pm 0.14 |
| ZPDT8 | Flexible | 99.1 \pm 0.24 | 99.35 \pm 0.25 | 99.61 \pm 0.11 |
| ZPDT9 | Flexible | 99.10 \pm 0.15 | 99.15 \pm 0.13 | 99.18 \pm 0.37 |

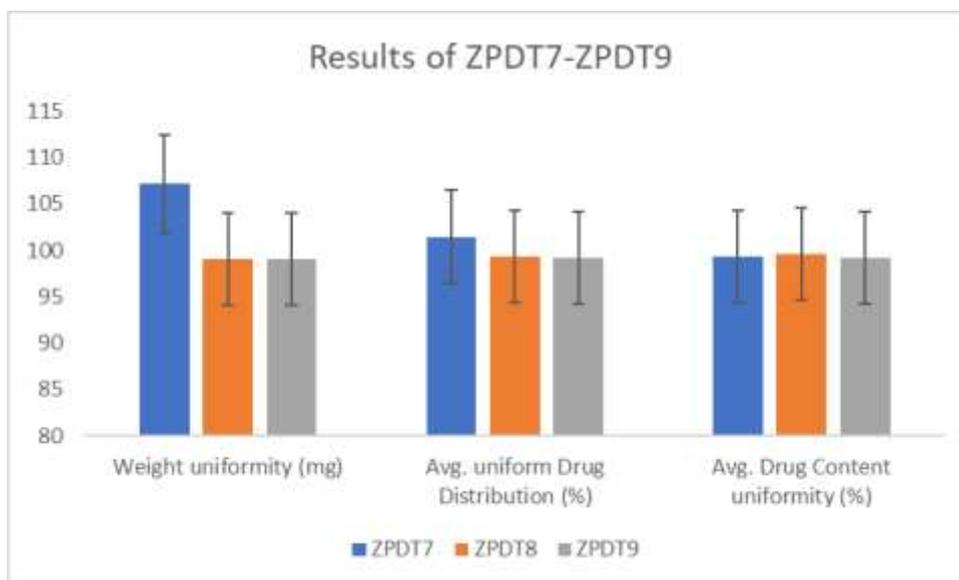


FIGURE 5.13 Results of ZPDT7-ZPDT9

TABLE 5. 23 Results of ZPDT7-ZPDT9

| Batch | Surface Texture | Surface pH (Mean \pm SD) n=3 | Thickness (mm) (Mean \pm SD) n=3 | Avg. Tensile strength (N/cm ²) \pm SD, n = 3 |
|--------------|-----------------|-----------------------------------|---------------------------------------|--|
| ZPDT7 | Flexible | 7.1 \pm 0.1 | 0.22 \pm 0.06 | 2.47 \pm 0.35 |
| ZPDT8 | Flexible | 7.03 \pm 0.06 | 0.17 \pm 0.02 | 2.73 \pm 0.15 |
| ZPDT9 | Flexible | 7.23 \pm 0.15 | 0.21 \pm 0.04 | 1.73 \pm 0.21 |

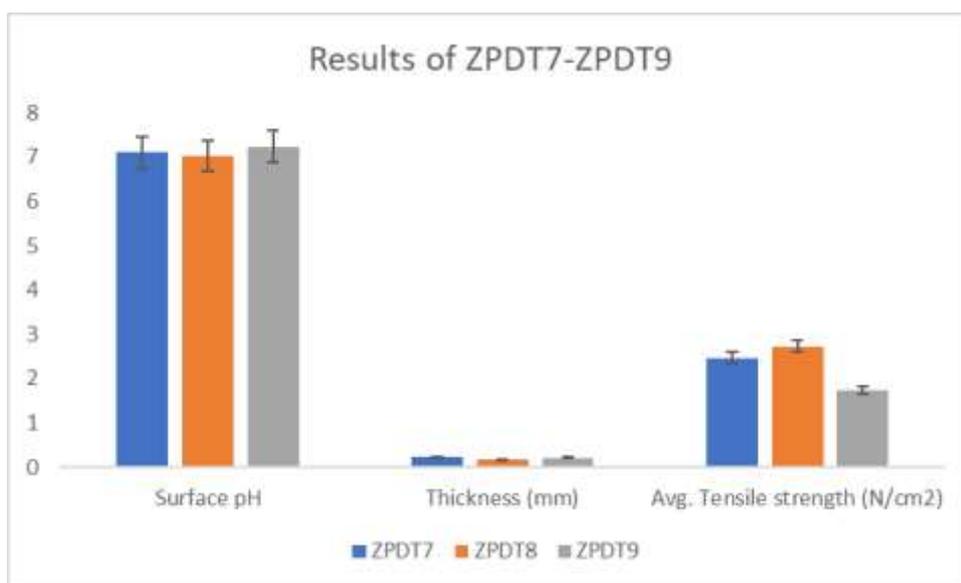


FIGURE 5. 14 Results of ZPDT7-ZPDT9

TABLE 5. 24 Results of ZPDT7-ZPDT9L

| Batch | Surface Texture | Avg. Folding Endurance ± SD, n = 3 | Avg. In Vitro Disintegration Time (sec) ± SD, n = 3 |
|--------------|-----------------|---------------------------------------|--|
| ZPDT7 | Flexible | 185.10 ± 1.23 | 23.05 ± 0.56 |
| ZPDT8 | Flexible | 198.35 ± 0.56 | 16.32 ± 0.46 |
| ZPDT9 | Flexible | 203.19 ± 2.23 | 23.43 ± 1.23 |

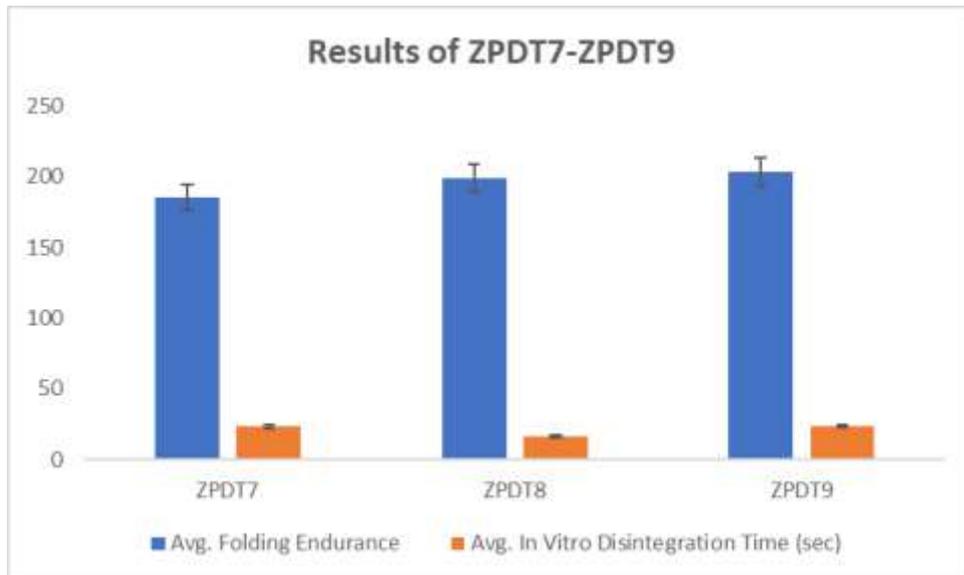


FIGURE 5. 15 Results of ZPDT7-ZPDT9

Inference

The 75 mg fixation was picked for the last MDF detailing since banana powder had the best deterioration season of the analyses.

5.3 Preparation of ZPO HCL Mouth Dissolving Film using Design of Experiment

5.3.1 PREPARATION OF MOUTH DISSOLVING FILM OF ZPO HCL USING 3² FACTORIAL DESIGN

As displayed in the plan format Tables, a 3² full factorial plan was utilized to examine the impact of autonomous factors X1 (Stake) and X2 (HPMC E5 LV) on subordinate factors like weight consistency (mg), crumbling time (sec), and thickness (mm), collapsing perseverance, and in-vitro drug discharge. Two variables were tried at three levels (1, 0, +1) in this plan, and each of the nine potential trial bunches were created. Table shows the creation of every one of the nine expected blends of MDF of ZPO HCL utilizing 3² full factorial plans.

TABLE 5. 25 Independent variable and their levels

| Independent Variables | Low level (-1) | Medium level (0) | High level (+1) |
|--------------------------------|----------------|------------------|-----------------|
| X1=amount of PEG (ml) | 1 | 1.5 | 2 |
| X2=amount of HPMC E5 LV (gm) | 0.250 | 0.300 | 0.350 |
| Dependent Variables | | | |
| Y1= Folding endurance | | | |
| Y2 = Disintegration Time (sec) | | | |
| Y3= % CDR (%) | | | |

5.3.2 Validation Analysis of Predicted and Actual Batches ZPO HCL MDF:

The 3² full factorial plan is broadly used to work on the detailing. In this review, two elements were investigated at three levels each, and test preliminaries were embraced on every one of the nine potential mixes. The groupings of Stake 400 (X1) and HPMC E5 LV (X2) were picked as free factors. Collapsing perseverance (Y1), crumbling term (Y2), and in-vitro drug discharge (Y3) were picked as reliant factors. Polynomial conditions can be

utilized to construe ends. The results of the trial configuration clusters are displayed in the table.

TABLE 5. 26 Batches codes of fast disintegrating films of ZPO HCL

| Ingredients | ZMDO F1 | ZMDO F2 | ZMDO F3 | ZMDO F4 | ZMDO F5 | ZMDO F6 | ZMDO F7 | ZMDO F8 | ZMDO F9 |
|---------------------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| PEG 400 (ml)-X1 | -1 | 0 | 1 | -1 | 0 | 1 | -1 | 0 | 1 |
| HPMC E5 LV (mg)- X2 | -1 | -1 | -1 | 0 | 0 | 0 | 1 | 1 | 1 |

TABLE 5. 27 Batches concentrations of fast disintegrating films of ZPO HCL

| Ingredients | ZMDO F1 | ZMDO F2 | ZMDO F3 | ZMDO F4 | ZMDO F5 | ZMDO F6 | ZMDO F7 | ZMDO F8 | ZMDO F9 |
|-----------------------------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| Drug (gm) | 0.1 | | | | | | | | |
| PEG 400 (ml) | 1.0 | 1.5 | 2.0 | 1.0 | 1.5 | 2.0 | 1.0 | 1.5 | 2.0 |
| HPMC E5 LV (gm) | 0.25 | | | 0.30 | | | 0.35 | | |
| Banana Powder (gm) | 0.075 | | | | | | | | |
| Aspartame (gm) | 0.040 | | | | | | | | |
| Citric acid (gm) | 0.070 | | | | | | | | |
| Tween 20 (gm) | 0.050 | | | | | | | | |
| Vanillin (gm) | 0.050 | | | | | | | | |
| Distilled water (ml) | 10 | | | | | | | | |

TABLE 5. 28 Evaluation parameters of factorial design batches

| Formulation Code | Avg. Weight (mg) ± SD, n=3 | Avg. uniform Drug Distribution (%) ± SD, n = 3 | Avg. Drug Content uniformity (%) ± SD, n = 3 |
|------------------|-------------------------------|---|---|
| ZMDOF1 | 110.81 ± 0.56 | 97.33 ± 1.05 | 98.30 ± 0.26 |
| ZMDOF2 | 107.65 ± 1.33 | 98.40 ± 0.11 | 99.25 ± 0.11 |
| ZMDOF3 | 108.81 ± 0.19 | 98.90 ± 0.59 | 98.65 ± 0.56 |
| ZMDOF4 | 116.15 ± 1.14 | 97.00 ± 0.47 | 99.3 ± 0.33 |
| ZMDOF5 | 118.00 ± 0.15 | 99.73 ± 0.13 | 99.95 ± 0.51 |
| ZMDOF6 | 115.60 ± 0.71 | 99.4 ± 0.28 | 98.92 ± 0.45 |
| ZMDOF7 | 109.31 ± 1.23 | 99.00 ± 0.15 | 99.86 ± 0.41 |
| ZMDOF8 | 126.31 ± 1.14 | 97.00 ± 0.65 | 98.65 ± 0.16 |
| ZMDOF9 | 127.15 ± 0.56 | 96.4 ± 0.36 | 102.80 ± 1.06 |

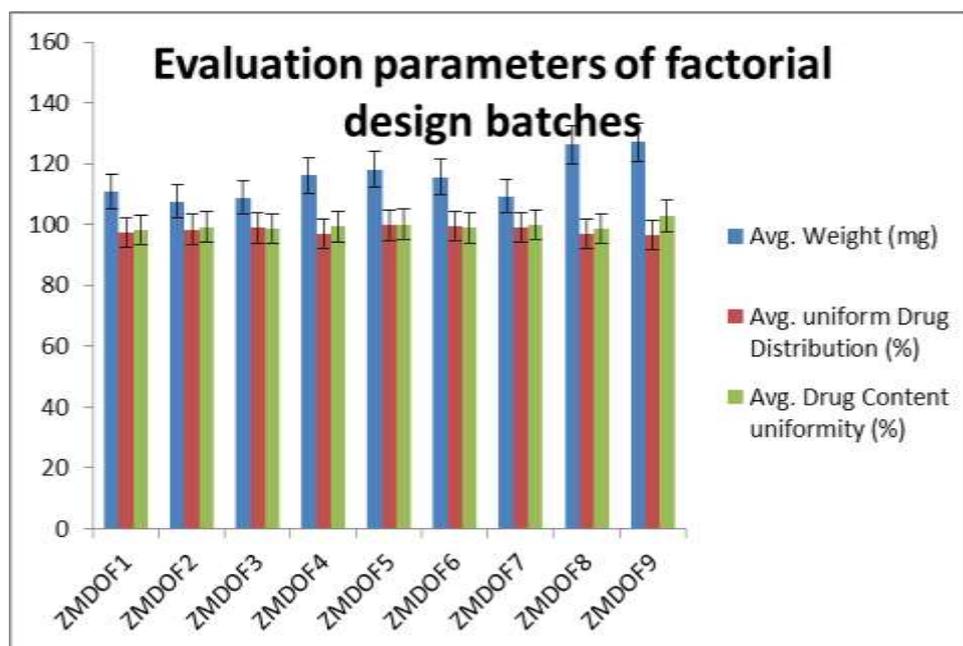


FIGURE 5. 16 Evaluation parameters of factorial design batches

TABLE 5. 29 Evaluation parameters of factorial design batches

| Formulation Code | Avg. Surface pH ± SD, n = 3 | Avg. Thickness (mm) ± SD, n = 3 | Avg. Tensile strength (N/cm2) ± SD, n = 3 |
|------------------|--------------------------------|------------------------------------|--|
| ZMDOF1 | 6.3 ± 0.13 | 0.14 ± 0.02 | 1.17 ± 0.21 |
| ZMDOF2 | 6.43 ± 0.03 | 0.18 ± 0.02 | 1.58 ± 0.13 |
| ZMDOF3 | 6.35 ± 0.14 | 0.19 ± 0.02 | 2.00 ± 0.27 |
| ZMDOF4 | 6.5 ± 0.15 | 0.16 ± 0.02 | 2.45 ± 0.16 |
| ZMDOF5 | 6.4 ± 0.25 | 0.18 ± 0.01 | 2.76 ± 0.16 |
| ZMDOF6 | 7.26 ± 0.10 | 0.19 ± 0.01 | 2.94 ± 0.26 |
| ZMDOF7 | 7.00 ± 0.24 | 0.20 ± 0.01 | 2.75 ± 0.16 |
| ZMDOF8 | 6.86 ± 0.17 | 0.19 ± 0.01 | 3.06 ± 0.22 |
| ZMDOF9 | 7.15 ± 0.18 | 0.24 ± 0.01 | 4.12 ± 0.12 |

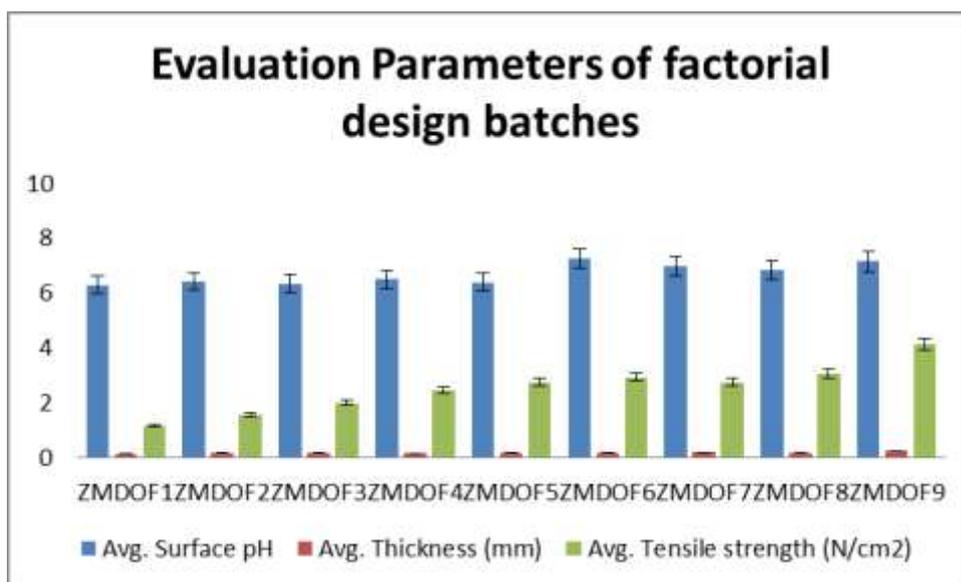


FIGURE 5. 17 Evaluation parameters of factorial design batches

TABLE 5. 30 Results of ZMDOF1- ZMDOF9

| Formulation Code | Avg. Folding Endurance \pm SD, n = 3 (Y ₁) | Avg. Disintegrating time (second) \pm SD, n = 3 (Y ₂) | % Drug release (In 6 min.) (Y ₃) |
|------------------|---|---|---|
| ZMDOF1 | 196.72 \pm 1.42 | 24.95 \pm 0.71 | 98.825 \pm 0.35 |
| ZMDOF2 | 202.15 \pm 1.16 | 26.60 \pm 1.37 | 99.06 \pm 0.21 |
| ZMDOF3 | 255.00 \pm 1.02 | 20.85 \pm 0.25 | 98.34 \pm 0.11 |
| ZMDOF4 | 265.25 \pm 0.05 | 22.75 \pm 0.11 | 97.90 \pm 0.41 |
| ZMDOF5 | 299.45 \pm 1.15 | 15.76 \pm 0.05 | 98.0 \pm 0.24 |
| ZMDOF6 | 321.25 \pm 1.15 | 24.34 \pm 0.62 | 96.00 \pm 0.15 |
| ZMDOF7 | 346.45 \pm 1.47 | 28.40 \pm 0.16 | 95.60 \pm 0.67 |
| ZMDOF8 | 375.81 \pm 0.73 | 27.64 \pm 0.11 | 94.42 \pm 0.06 |
| ZMDOF9 | 394.54 \pm 0.36 | 31.63 \pm 0.21 | 92.63 \pm 0.65 |

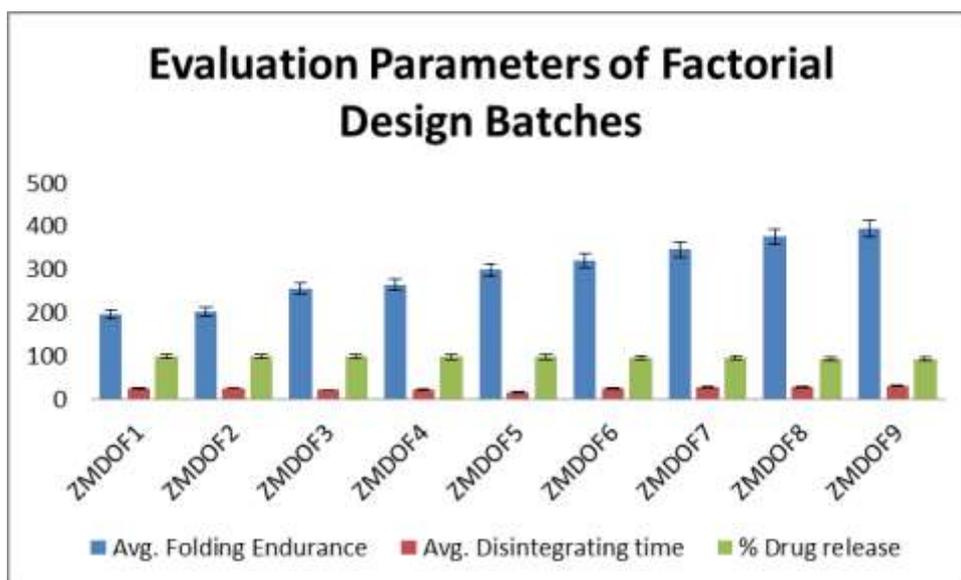


FIGURE 5. 18 Results of ZMDOF1- ZMDOF9

TABLE 5.31 *In-vitro* drug release (% drug release) of ZMDOF1- ZMDOF9

| Time (min) | ZMDO F1 | ZMDO F2 | ZMDO F3 | ZMDO F4 | ZMDO F5 | ZMDO F6 | ZMDO F7 | ZMDO F8 | ZMDO F9 |
|------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 18.21 ± 2.06 | 15.12 ± 1.23 | 15.12 ± 0.22 | 16.17 ± 1.05 | 15.09 ± 1.05 | 15.05 ± 0.57 | 14.04 ± 0.48 | 13.54 ± 1.25 | 10.13 ± 2.04 |
| 2 | 37.05 ± 3.15 | 34.54 ± 1.65 | 35.06 ± 1.15 | 36.16 ± 1.55 | 36.52 ± 1.66 | 34.9 ± 2.08 | 36.01 ± 0.07 | 33.44 ± 1.08 | 25.24 ± 1.01 |
| 3 | 48.54 ± 1.07 | 46.54 ± 1.23 | 50.42 ± 1.18 | 49.20 ± 1.11 | 47.21 ± 0.43 | 44.01 ± 2.04 | 45.5 ± 1.04 | 46.53 ± 0.21 | 38.50 ± 1.01 |
| 4 | 68.08 ± 1.19 | 67.68 ± 1.98 | 66.30 ± 2.01 | 65.80 ± 2.01 | 63.91 ± 1.05 | 63.90 ± 1.08 | 65.21 ± 1.40 | 61.20 ± 1.04 | 52.34 ± 2.07 |
| 5 | 94.2 ± 1.22 | 93.24 ± 2.15 | 92.07 ± 2.06 | 90.67 ± 1.01 | 85.56 ± 2.64 | 85.15 ± 1.03 | 84.04 ± 3.47 | 85.08 ± 0.68 | 78.04 ± 1.01 |
| 6 | 99.4 ± 0.23 | 99.04 ± 1.05 | 98.10 ± 1.95 | 98.97 ± 1.0 | 98.06 ± 0.96 | 97.25 ± 1.58 | 96.06 ± 1.55 | 95.02 ± 2.05 | 92.34 ± 1.21 |

Response 1: Folding endurance (Y₁)

Polynomial conditions can be utilized to make determinations in the wake of dissecting the quantity of coefficients and the numerical sign they impart (positive or negative). With p esteems under 0.05, the two boundaries X₁ (convergence of Stake 400) and X₂ (centralization of HPMC E5 LV) were demonstrated to be huge for collapsing perseverance (Y₁).

Polynomial equation:

$$Y_1 = 298.33 + 32.67 X_1 + 83.00 X_2 - 9.25 X_1 X_2 + 1.00 X_2^2 - 10.00 X_2^2$$

Table 5.32 ANOVA for Y₁

| | DF* | SS* | MS* | F | p value |
|------------|-----|----------|----------|--------|----------|
| Regression | 2 | 47257.23 | 23756.23 | 235.15 | < 0.0001 |
| Residual | 6 | 612.25 | 102.52 | - | - |
| Total | 8 | 47869.48 | - | - | - |

*DF: degree of freedom, SS: sum of squares, MS: means of squares

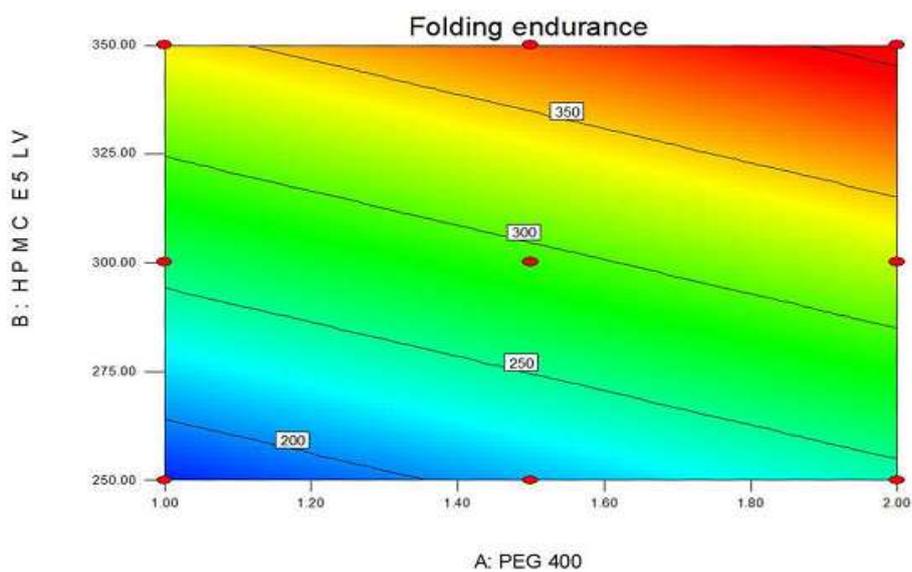


FIGURE 5.19 Contour plot for Y1 (folding endurance)

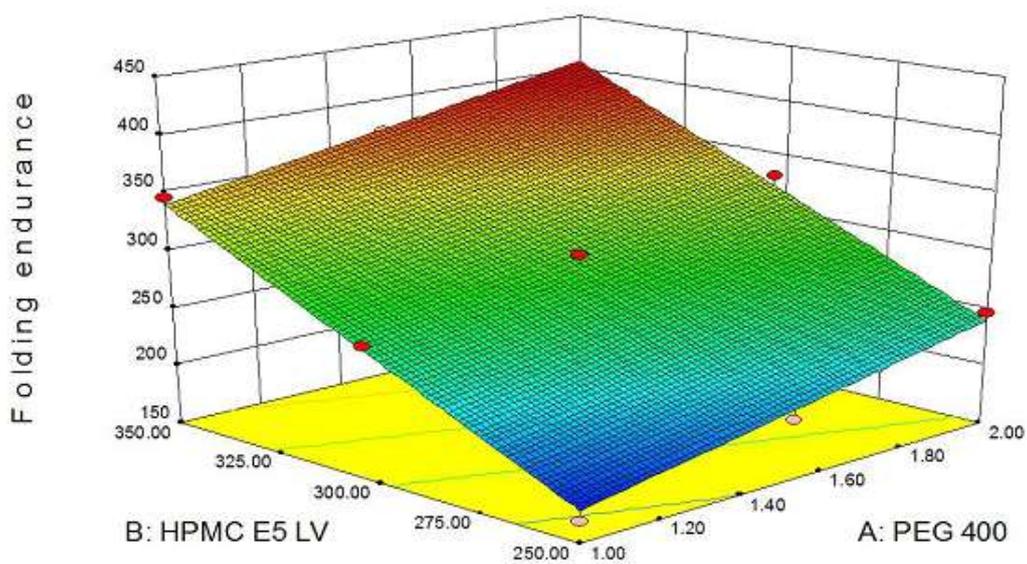


FIGURE 5.20 Surface plot for Y1 (folding endurance)

Response 2: Disintegrating time (Y₂)

Polynomial equations can be used to draw conclusions after analysing the number of coefficients and the mathematical sign they communicate (positive or negative). With p values less than 0.05, both factors X1 (concentration of PEG 400) (p= 0.0044) and X2 (concentration of HPMC E5 LV) (p= 0.0002) were found to be significant for disintegration time (Y₂).

Polynomial equation:

$$Y_2 = 37.68 + 7.00 X_1 + 20.12 X_2 + 4.08 X_1 X_2 + 0.98 X_1^2 + 10.35 X_2^2$$

TABLE 5. 33 ANOVA for Y₂

| | DF* | SS* | MS* | F | p value |
|------------|-----|---------|--------|--------|---------|
| Regression | 5 | 3005.91 | 601.18 | 124.15 | 0.0011 |
| Residual | 3 | 14.53 | 4.84 | - | - |
| Total | 8 | 3020.44 | - | - | - |

*DF: degree of freedom, SS: sum of squares, MS: means of squares

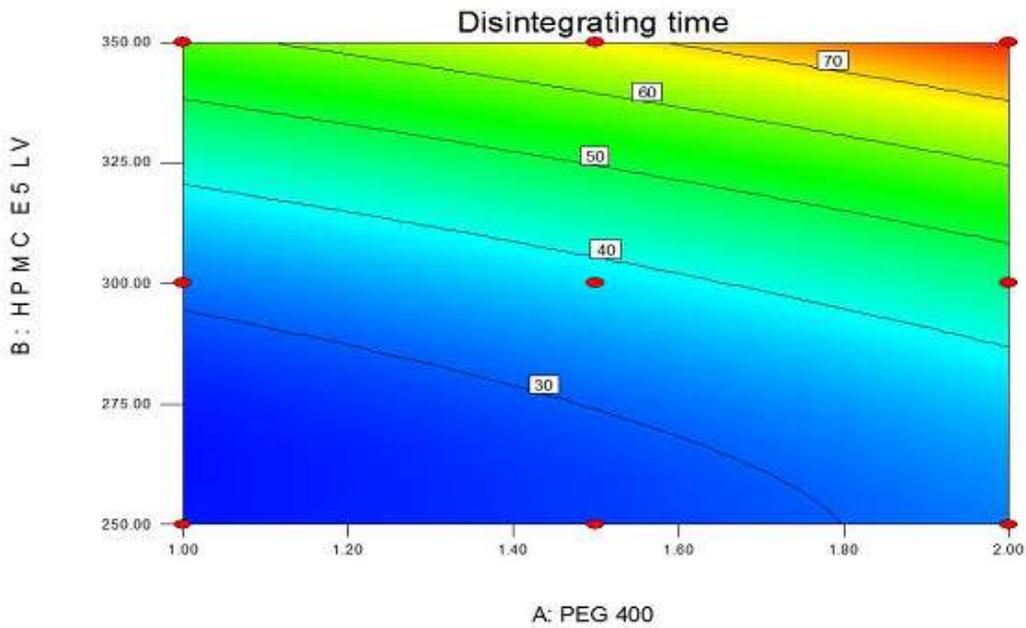


FIGURE 5. 21 Contour plot for Y₂ (disintegrating time)

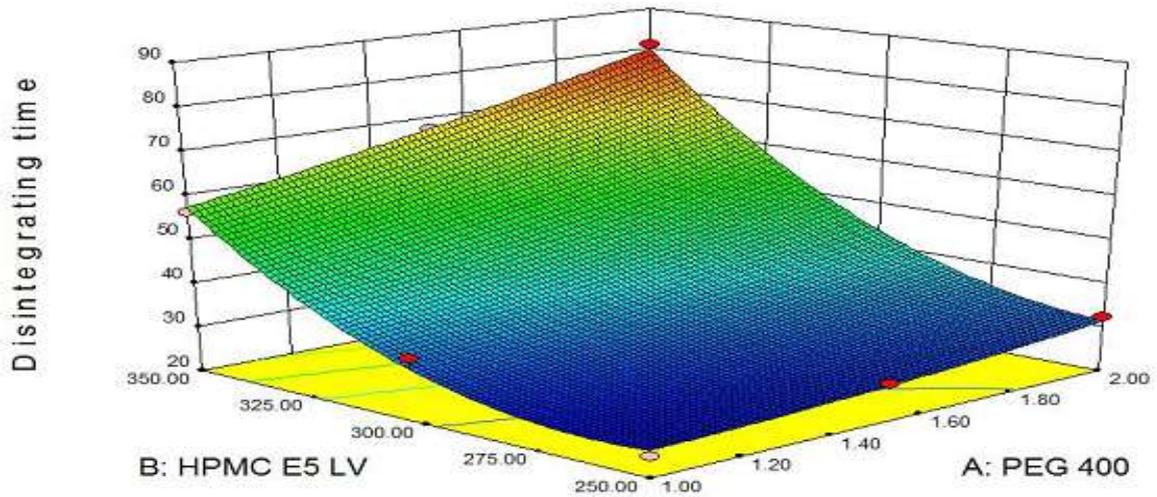


FIGURE 5.22 Surface plot for Y2 (disintegrating time)

For the breaking down time, the ANOVA results, form plot, and 3d surface plot uncovered a solid impact on the two autonomous parts (convergence of Stake 400, X1 and grouping of HPMC E5 LV, X2). As per the polynomial condition of crumbling time, both how much plasticizer and how much polymer positively affect deteriorating time. How much Stake 400 in the movies, as well as the convergence of HPMC E5 LV, were seen to expand the crumbling time. For all plans, the breaking down time goes from 24.67 2.516 to 81.33 3.215 minutes. The crumbling season of ZMDF9 was the speediest of the multitude of plans. Since ZMDF9 contains the most plasticizer Stake 400 and polymer HPMC E5 LV, it might have the best collapsing strength.

Response 3: % Drug release (Y₃)

Polynomial conditions can be utilized to reach inferences in the wake of investigating the quantity of coefficients and the numerical sign they convey (positive or negative). With p esteems under 0.05, the two factors X1 (convergence of Stake 400) (p= 0.0147) and X2 (grouping of HPMC E5 LV) (p= 0.0001) were demonstrated to be huge for percent drug discharge in a short time (Y3).

Polynomial equation:

$$Y_3 = 97.54 - 0.75 X_1 - 2.05 X_2 - 0.12 X_1 X_2 - 0.25 X_1^2 - 0.78 X_2^2$$

1

2

TABLE 5. 34 ANOVA for Y₃

| | DF | SS | MS | F | p value |
|------------|----|-------|-------|-------|---------|
| Regression | 2 | 28.55 | 14.27 | 49.26 | 0.0002 |
| Residual | 6 | 1.74 | 0.29 | - | - |
| Total | 8 | 30.28 | - | - | - |

DF: degree of freedom, SS: sum of squares, MS: means of squares

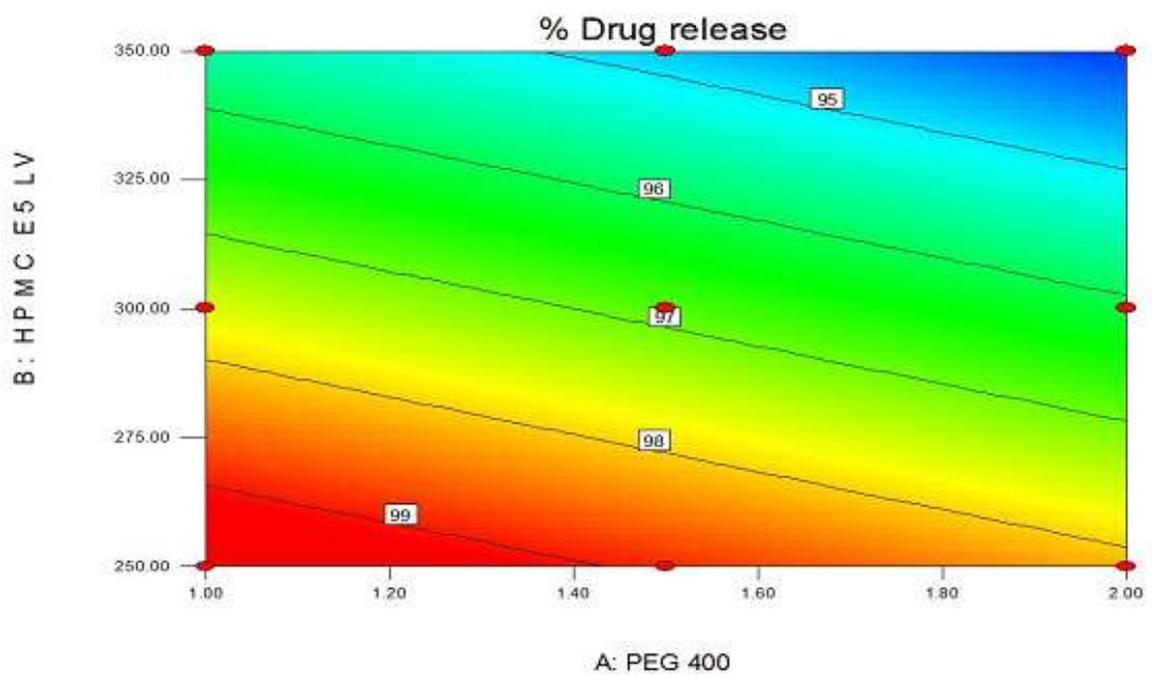


FIGURE 5. 23 Contour plot for Y₃ (% drug release in 6 minute)

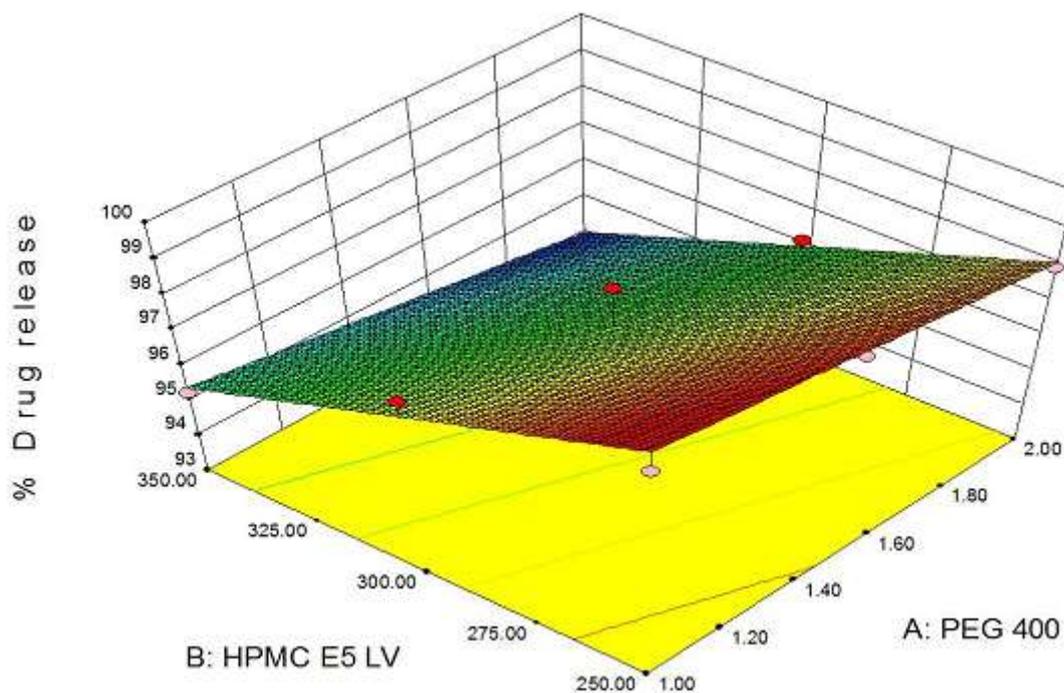


FIGURE 5. 24 Surface plot for Y3 (% drug release in 6 minute)

The ANOVA results, shape plot, and 3d surface plot uncovered that the two free factors essentially affected the percent drug discharge (shortly) (convergence of Stake 400, X1 and centralization of HPMC E5 LV, X2). As per the polynomial condition of percent drug discharge, both how much plasticizer and how much polymer negatively affect percent drug discharge. As how much Stake 400 and the grouping of HPMC E5 LV were raised, the percent drug arrival of the movies diminished. For all details, the percent drug discharge differs between 99.14 1.74 and 93.79 1.86. ZMDF1 showed the most elevated percent drug discharge when contrasted with different plans. The most elevated percent drug delivery could be because of the base measure of plasticizer Stake 400 and polymer HPMC E5 LV in ZMDF1.

5.4 EVALUATION OF FACTORIAL DESIGN BATCHES

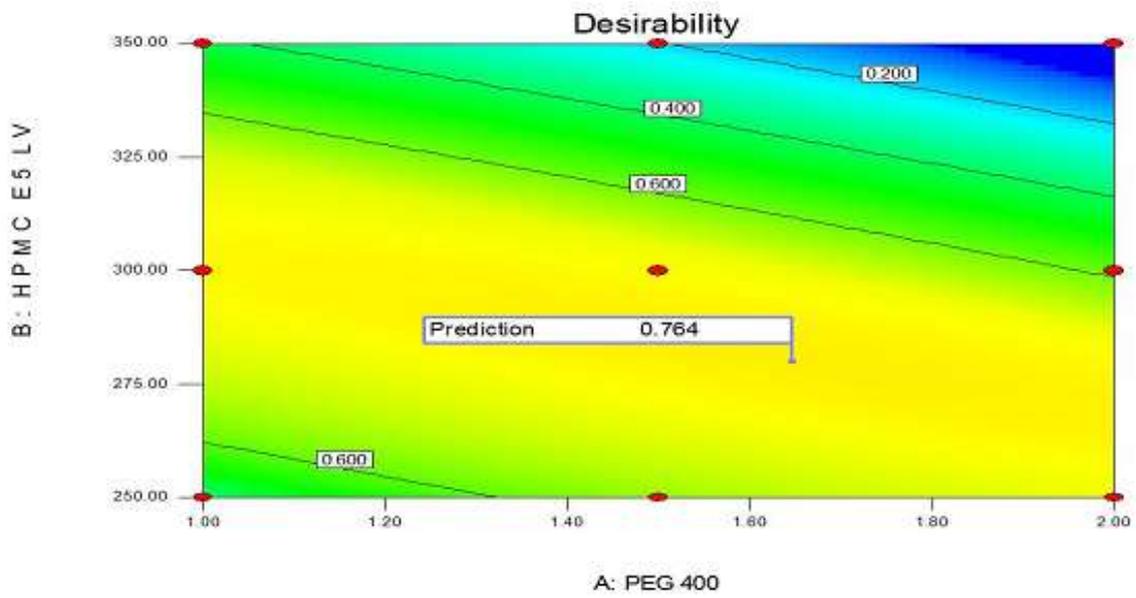


FIGURE 5.25 Desirability plot

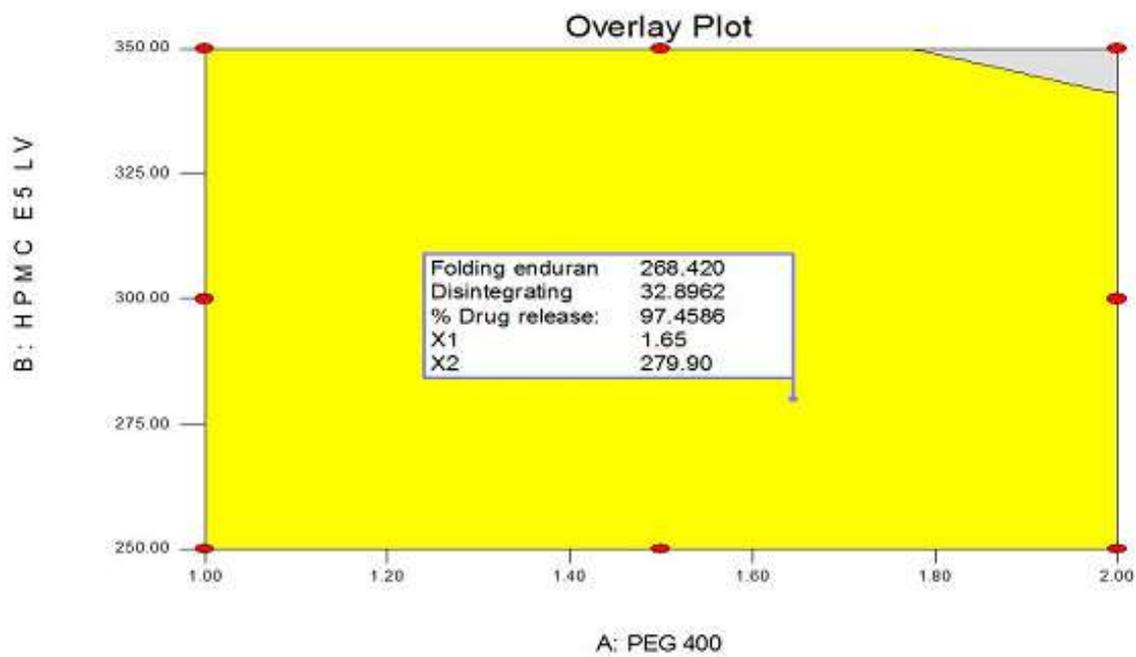


FIGURE 5.26 Overlay plot

According to the attractiveness research and overlay study, the prediction is 0.764 when 1.65 ml PEG 400 plasticizer and 279.90 mg HPMC E5 LV polymer are used.

Batch Selection: The detailing F5, which contains 1.5 ml Stake 400 plasticizer and 300 mg HPMC E5 LV polymer, was picked as the improved cluster in view of collapsing perseverance, drug dissolving time, percent drug discharge, rigidity, and medication content consistency results from the attractiveness study, overlay study, and other assessment of factorial plan clumps perception.

The region that met the ideal particulars was accomplished in this plot. The fundamental response shapes were superimposed over a structure plot to make this overlay plot. The zone of alluring response regards in the variable space is portrayed graphically. Regions that didn't meet the improving measures were covered up. A yellow zone signified land that met the models' prerequisites, while a dark tone indicated locale that didn't.

TABLE 5.35 Checkpoint batch

| Compositions (mg) | | Folding Endurance | | Disintegration Time (Sec) | | % CDR | |
|-------------------|------------|-------------------|----------|---------------------------|----------|-----------|----------|
| PEG 400 | HPMC E5 LV | Predicted | Observed | Predicted | Observed | Predicted | Observed |
| 1.65 | 279.90 | 268.420 | 266.530 | 32.8962 | 34.7834 | 97.4585 | 95.7569 |

A projected worth and noticed worth are essentially indistinguishable because of the designated spot group. Collapsing Perseverance (266.530), Crumbling time (34.7834 sec.), and percent CDR of the designated spot clump (95.75 percent). Thus, it is viewed as a bunch that has been enhanced. This clump was picked to make mouth dissolving film.

TABLE 5.36 Evaluation of mouth dissolving film ZMDOF10

| Sr. No | Evaluation parameter | Results |
|--------|--|-------------|
| 1. | Weight variation(mg) | 118.07±0.01 |
| 2. | Thickness (mm) | 0.15±0.02 |
| 4. | Surface pH | 6.7±0.04 |
| 5. | Tensile strength (kg/cm ²) | 2.55±0.011 |
| 6. | Drug content (%) | 99.10±0.10 |

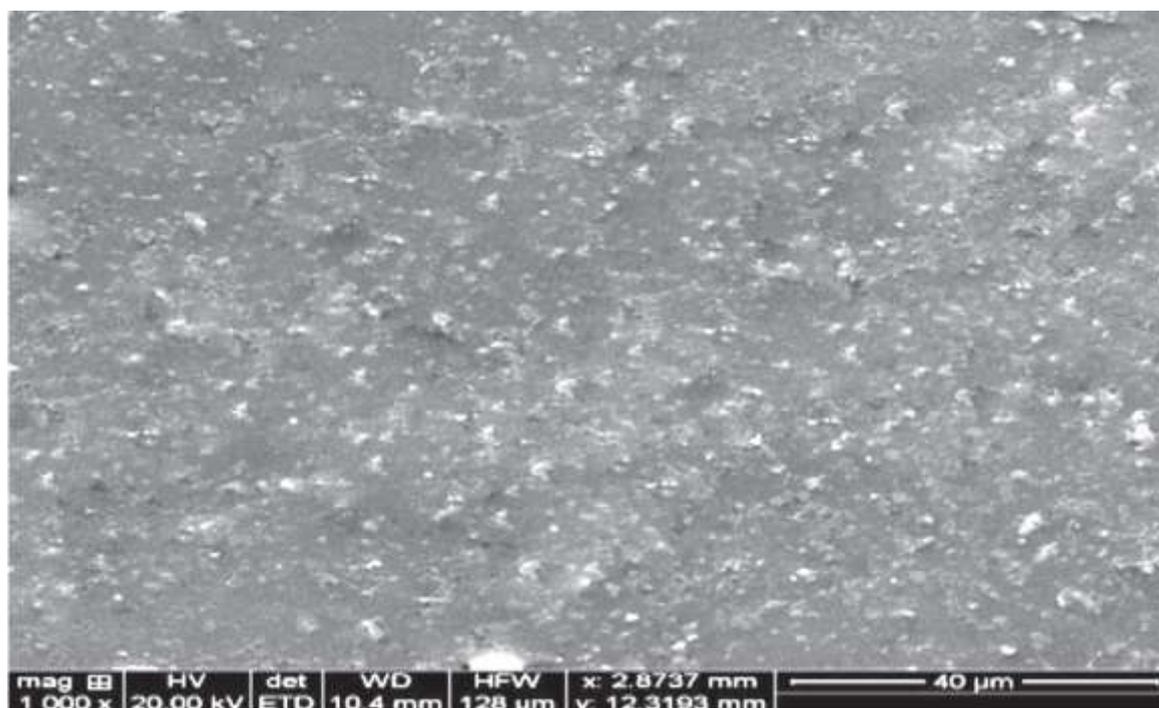


FIGURE 5.27 SEM OF ZMDOF10

TABLE 5. 37 Flux and permeability co-efficient of ZMDOF10

| Time (Mins) | Batch ZMDOF10 | |
|-------------|-----------------------------------|--------------------------------|
| | Flux J (mg/cm ² /hr) | Permeability co-efficient (kP) |
| 0 | 0.000 | 0 |
| 1 | 0.793 | 0.037393 |
| 2 | 0.014 | 0.000654 |
| 3 | 0.006 | 0.00028 |
| 4 | 0.010 | 0.000472 |
| 5 | 0.013 | 0.00059 |
| 6 | 0.217 | 0.010254 |
| 7 | 0.083 | 0.003931 |

Because of the discoveries, it was resolved that ZMDOF10 had a superior managed delivery somewhat. It supports accomplishing the highest level of viable focus. Motor investigation of ZMDOF10 discharge information.

TABLE 5. 38 Kinetic analysis of release data of ZMDOF10

| Model | Zero-Order | First-Order | Higuchi |
|----------------------------|---------------|--------------|--------------|
| R² value | 0.992 | 0.874 | 0.965 |
| Slope | 5.415 | 0.113 | 0.568 |
| Intercept | -0.321 | 0.675 | 1.784 |

The total amount of drug penetrated was calculated using the Higuchi and Zero order models, i.e. diffusion mechanisms.

5.4.1 FT-IR Study of Optimized MDF Formulation

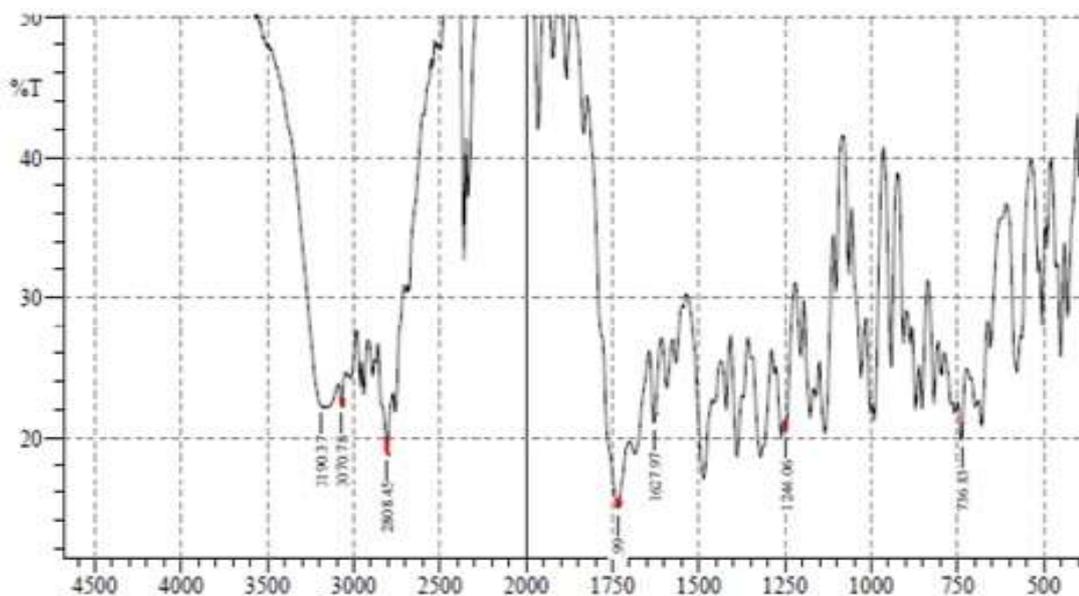


FIGURE 5. 28 FT-IR Study of Optimized MDF Formulation

5.4.2 Taste Evaluation Study by Spitting

Table shows the aftereffects of the taste assessment examination. The lumpiness and crabbiness of the detailing in the mouth were utilized to rate mouth feel in this review.

In all plans, the normal mouth feel recommended a smooth to exceptionally smooth sensation. Not entirely set in stone by the capacity to eliminate the film from the Alu pocket and spit it in the mouth without the utilization of water, which was considered patient-accommodating and magnificent.

5.4.3 Results of Taste and Palatability Evaluation

TABLE 5. 39 Results of Taste and Palatability Evaluation

| Sample Type | Mouth feel | Taste (Bitterness) | After Taste | Ease of handling | Acceptance |
|--------------------------|------------|--------------------|-------------|------------------|-------------|
| Test (Batch No. ZMDOF10) | 4.5± 0.46 | 4.50 ± 0.00 | 4.48 ± 0.35 | 5.00 ± 0.00 | 4.19 ± 0.52 |

5.4.4 Comparison of optimized MDF with conventional marketed formulation

TABLE 5. 40 Comparison of optimized MDF with conventional marketed formulation

| Time | % Drug release (ZMDOF10) | % Drug release of marketed Product (Zipwell-20) |
|------|--------------------------|---|
| 0 | 0.0 | 0.0 |
| 1 | 14.75± 0.13 | 0.264±2.12 |
| 2 | 34.3± 1.78 | 6.274±0.17 |
| 3 | 46.22±1.68 | 10.31±0.12 |
| 4 | 62.9± 1.26 | 43.22±1.21 |
| 5 | 87.95± 1.59 | 56.18±1.31 |
| 6 | 97.86±0.15 | 67.46±1.12 |

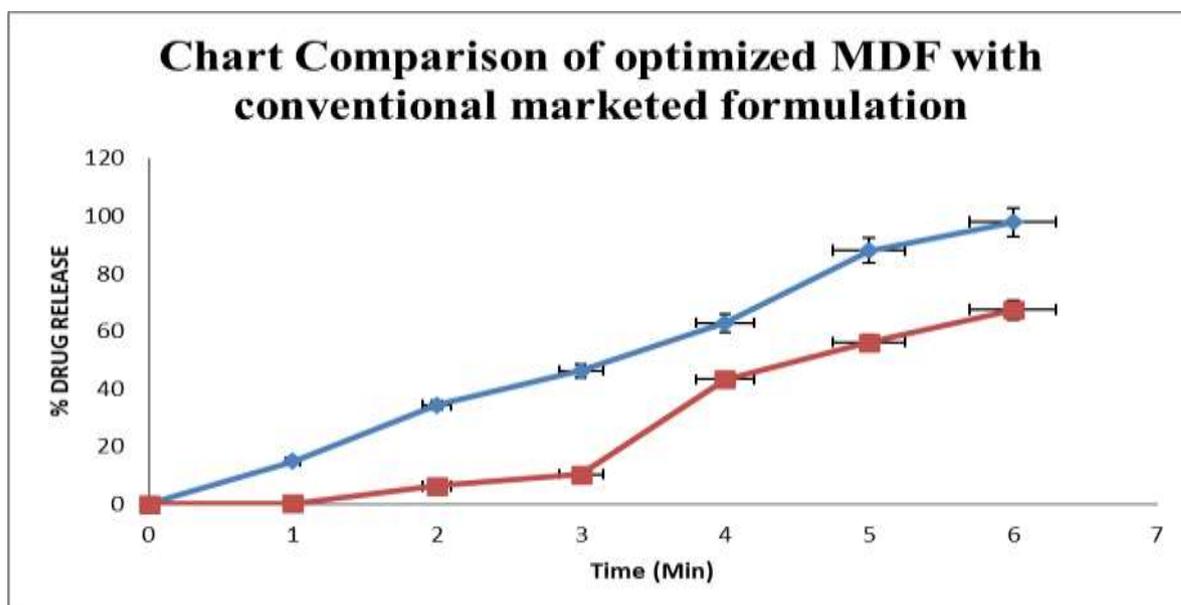


FIGURE 5. 29 Comparison of optimized MDF with conventional marketed formulation

5.4.5 Evaluation of optimized batch under stability study

TABLE 5. 41 Evaluation of optimized batch under stability study

| Stability Conditions | Sampling Time | Disintegration Time (sec \pm SD) | Drug Content (% \pm SD) | Tensile Strength (kg/cm ² \pm SD) | Visual Appearance |
|-------------------------|---------------|------------------------------------|---------------------------|--|-------------------|
| 40° C \pm 02° (Temp.) | Initial | 34.56 \pm 00.51 | 99.15 \pm 00.10 | 02.30 \pm 0.01 | Clear appearance |
| 75% \pm 05% RH | 03 months | 34.37 \pm 02.73 | 99.52 \pm 00.29 | 02.63 \pm 0.01 | Clear appearance |

Chapter-6
Need & Objective
(QIP FMT)

CHAPTER 6

NEED & OBJECTIVE

6. FORMULATION & DEVELOPMENT OF QUETIAPINE FUMARATE MOUTH DISSOLVING FILM FOR PSYCHOSIS TREATMENT

6.1 RATIONAL OF RESEARCH WORK:

6.1.1 RATIONAL OF MOUTH DISSOLVING FILM FORMULATION (MDF)

Because of its safety, convenience of administration, and patient acceptability, the oral route is one of the most used medication delivery methods. Oral solid dose forms are available in around 60% of conventional dosage forms. Patients such as paediatrics, geriatrics, bedridden, and emetic patients, as well as problems such as acute allergy responses or coughing, benefit from orally dissolving strips and films. They can be used both locally and nationally. Because of their faster dissolution rate, higher flexibility, and better patient compliance, orally dissolving film and strips are becoming more popular as an alternative to fast dissolving tablets. Currently, research is being done on the utilisation of orally dissolving films as potential carriers for several active medicinal components. Listerine, Chloraseptic, Triaminic, and multivitamins are among the commercially available orally dissolving film products. A plasticizer and film forming polymer, or a mixture of polymers, constitute the backbone of an orally dissolving film, which gives it the appropriate elasticity and shape.

Due to their flexibility, fast disintegrating films are the most advanced form of solid dosage form. When compared to dissolving tablets, it improves the efficacy of active pharmaceutical substances since they breakdown in the oral cavity in a short period of time following contact with less saliva. This delivery technique consists of a thin film that is placed on the tongue or mucosal tissue and is instantaneously wet by saliva. Once wet, the film quickly disintegrates, releasing the drug for oral mucosal absorption. The medicine is delivered to the systemic circulation via buccal mucosa using a fast disintegrating film made of hydrophilic polymer that rapidly disintegrates for the buccal cavity. For the increase of

bioavailability, fast disintegrating drug delivery systems are specifically designed for medicines with significant first pass metabolism and low dosage.

6.1.2 RATIONAL OF FORMULATION & DEVELOPMENT OF MOUTH DISSOLVING FILM FOR PSYCHOSIS TREATMENT:

Psychosis is a mental illness marked by hallucinations, dementia, and seizures. In order to reduce the possibility of lasting brain damage, it must be treated quickly. Antipsychotic medication pharmacotherapy is still the most common treatment for psychosis. The therapy of psychosis is different from the treatment of other diseases. An orally dissolving film formulation of a newer antipsychotic is an ideal medication candidate. Antipsychotics formulated as an orally dissolving strip, which must be placed on the patient's tongue without swallowing for dose delivery, would greatly simplify dose administration and enhance patient compliance. The goal of this study was to design, develop, and characterise antipsychotic medication mouth dissolving films..

6.1.3 RATIONAL OF FORMULATION & DEVELOPMENT OF QUETIAPINE FUMARATE MOUTH DISSOLVING FILM FOR PSYCHOSIS TREATMENT

The prevalence of psychotic disorders has risen dramatically. Furthermore, schizophrenia and bipolar disorder afflict between 2.4 and 5.7 million American adults, or around 1.1 and 2.6 percent of the population aged 18 and older, respectively. ODT is the most popular dosage form in tablet form, however film has greater advantages than tablet because to the bigger surface area, which allows for faster disintegration and hence dissolution in the oral cavity. The preparation of a fast dissolving film is a novel approach for the rapid and rapid release of a medicine for the treatment of psychotic disorder. Patients who have a rapid psychotic crisis and need to calm down will benefit from the proposed drug delivery.

Quetiapine fumarate is used to treat schizophrenia and bipolar disorder. However, because the medicine is substantially metabolised by the liver, its oral bioavailability is limited, making it a good option. With a half-life of 6 hours, quetiapine (QTP) is used to treat schizophrenic attacks and bipolar disorder. QTP is a medication that is quickly absorbed and well tolerated. QTP has a low risk of extrapyramidal symptoms. Within 1.5 hours, the peak plasma concentration of quetiapine fumarate is reached. Quetiapine fumarate has a bioavailability of roughly 9%, a half-life of 6 hours, and is broadly dispersed throughout the

body. The drug binds to plasma proteins in about 83 percent of cases. Because it is extensively metabolised in the liver to the sulfoxide metabolite and parent acid metabolite by sulfoxidation and oxidation, both of which are pharmacologically inactive and have low bioavailability, quetiapine fumarate was chosen as a model drug for fast disintegrating drug delivery to avoid extensive firstpass metabolism. This implies that the QTP quick dissolving film, which gives speedy relief from psychotic symptoms while minimising side effects, is required.

The goal of this study was to create a rapid disintegrating quetiapine fumarate film by combining several polymers with a shorter disintegration time and increased drug release, with the goal of benefiting patients who have trouble swallowing traditional dose forms. improve drug bioavailability and fast onset of action.

6.2 OBJECTIVES OF RESEARCH WORK

The prime objectives were to develop MDF drug delivery system that:

1. To make release of drug at oral mouth cavity and hence dose and dose frequency can be decreased thereby obtaining greater therapeutic efficacy.
2. To Show better in-vitro release/diffusion performance than conventional dosage forms.

6.3 PLAN OF RESEARCH WORK:

6.3.1. Literature survey and Patent Search related to Drug, Polymer & MDF Technology.

6.3.2. Selection of Drug, Polymer and Methodology for formulation & development of MDF drug delivery system

6.3.3. Preformulation study of Drug

- ✓ Organoleptic characteristics of drug
- ✓ Melting Point
- ✓ Solubility
- ✓ Partition Co-efficient
- ✓ Identification of drug by λ_{max} , FT-IR study.
- ✓ Preparation of Calibration Curve of Drug
- ✓ Drug- polymer Compatibility study FT-IR study

6.3.4. Preparation of MDF.

6.3.5. Preliminary Trial Batches for selection of materials

6.3.6. Formulation of Drug loaded MDF Using Factorial Design (DoE) approach

6.3.7. Characterization of Drug loaded MDF

- ✓ Thickness
- ✓ Weight variation
- ✓ Drug Content
- ✓ Measurement of mechanical property
- ✓ Folding endurance
- ✓ Physical appearance and texture analysis of the films
- ✓ In vitro disintegration
- ✓ In vitro dissolution
- ✓ Flux and Permeability Co-efficient Study
- ✓ Kinetics of drug release
- ✓ Stastical analysis
- ✓ Validation batches (Check Point Analysis) and its characterization of drug loaded MDF

- ✓ FT-IR Study of Optimized MDF Formulation
- ✓ Comparison of optimized MDF with conventional marketed formulation.
- ✓ Ex- vivo study subjected to IAEC approval and permission
- ✓ Accelerated stability study

6.3.8. Thesis writing and paper publication in esteem journal.

6.4. EXPECTED OUTCOME

The distribution of the medicament to the target site at a therapeutically relevant level, with negligible or little discomfort and adverse effects to the patient, are the cornerstones of a good pharmaceutical formulation. The route of drug delivery plays a significant role in this regard. The oral route is the most popular method of drug delivery due to its ease of usage. However, there are some possible downsides, such as poor bioavailability due to the first pass effect and a proclivity for producing abrupt high and low plasma concentrations of medication, which can lead to poor patient compliance. To overcome the disadvantages of the oral route, continuous intravenous infusion has been discovered to maintain a consistent and sustained medication concentration within therapeutic range for a long time. However, this method of drug delivery has several disadvantages, including as needle pain and unintentional needle sticks, necessitating recurrent hospitalisation and medical care during treatment.

Due to patient compliance, mouth dissolving film is now the recommended route of medication delivery. The following are the key predicted outcomes of this research:

- ✓ Development of Mouth Dissolving Film (MDF)
- ✓ Formulation of effective formulation for the treatment of psychosis patients
- ✓ Patient's compliance due to development of MDF.

Chapter-7
Materials &
Methodology
(QIP FMT)

CHAPTER 7

MATERIALS & METHODOLOGY

7. MATERIALS & EQUIPMENTS USED

The accompanying materials, synthetics and instruments might be utilized for Quetiapine Fumarate Mouth Dissolving Film for Psychosis Treatment according to following Table.

7.1. List of Materials

TABLE 7. 1 List of Materials

| MATERIALS | SOURCE |
|---------------------|-----------------------------|
| Quetiapine Fumarate | Zota Healthcare LTD, Surat. |
| HPMC E5 | Zota Healthcare LTD, Surat. |
| PEG 400 | Zota Healthcare LTD, Surat. |
| Citric Acid | Zota Healthcare LTD, Surat. |
| Aspartame | Zota Healthcare LTD, Surat. |
| Mannitol | Zota Healthcare LTD, Surat. |
| Orange Flavour | Zota Healthcare LTD, Surat. |
| Methyl Paraben | Zota Healthcare LTD, Surat. |
| Propyl Paraben | Zota Healthcare LTD, Surat. |
| Vanillin | Zota Healthcare LTD, Surat. |

7.2. List of Equipments

TABLE 7. 2 List of Equipments

| EQUIPMENTS | MODEL AND SOURCE |
|-----------------------------------|--|
| UV – Visible Spectrometer | UV-1700, Shimadzu Corporation. |
| Mechanical Stirrer | Remi instrument division |
| Electronic Balance | Ohaus corporation NJ, USA |
| Scanning Electron Microscope | JEOL JSM-6380KVM Oxford Instruments, England |
| FT-IR Spectrophotometer | Shimadzu Corporation |
| Dissolution Apparatus I, USP I | Macro scientific works private limited, Delhi. |
| Malvern | Malvern Instruments LTD. |

7.3. Methodology

7.3.1. Preformulation of Quetiapine Fumarate

The reason for the preformulation study is to assemble data that will assist makers with building stable measurements shapes that can be efficiently manufactured.

7.3.1.1. Organoleptic Characteristics of QTP FMT

The organoleptic attributes of QTP FMT, like tone and scent, were inspected truly.

7.3.1.1.1. Taste Evaluation Study by Spitting

In a solitary measurements and single visually impaired review, 8 solid grown-up male volunteers between the ages of 24 and 42 were selected. All subjects gave composed informed agree before the review and they were told with regards to the review's objective, dangers and term.

Each volunteer got QTP FMT at irregular. The volunteers were told to clean their mouths with 200 cc of distilled water before to the preliminary. The volunteers were approached to place the strip in their mouth for 30 seconds, record the deterioration time of the test film and give a score in light of the boundaries recorded in Table 3, in particular mouth feel, taste or sharpness, film delayed flavor impression, simplicity of dealing with, and by and large acknowledgment of the detailing. Following 3 minutes, the volunteers were told to let out the example with salivation and flush their mouths with 200 ml distilled water. Following 2 hours, the indistinguishable system was completed with subsequent sample (either test or reference test). Thus, spitting of detailing and salivation was told to volunteers to forestall openness of medication.

TABLE 7. 3 Parameters, Score and Results of Taste Evaluation Study

| Parameters | 1 | 2 | 3 | 4 | 5 |
|---------------------|--------------------|---------|-------------------------------|-----------------------------|--|
| Mouth feel | Gritty /Irritating | Gritty | Slightly Gritty | Smooth | Very smooth |
| Taste (Bitterness) | Very bitter | Bitter | Slightly bitter | Slightly sweet/ Acceptable | Very sweet |
| After taste | Very Bitter | Bitter | Slightly bitter | Slightly sweet/ Acceptable | Very sweet |
| Ease of handling | Very brittle | Brittle | Acceptable and does not break | Flexible and easy to handle | Patient friendly and very easy to handle |
| Acceptance | Very poor | Poor | Acceptable | Good | Excellent |

7.3.1.2. Determination of Melting Point of QTP FMT

Melting point of QTP FMT was evaluated by the capillary method.

7.3.1.3 Identification and Determination of Wavelength max (λ_{max}) of QTP FMT

To prepare a stock solution of 100 mcg/ml, the appropriately weighed amount of 100 mg of medication test was broken down in a combination of water and acetonitrile (1:1) (3 of every 200,000) and volume moved toward 100 ml utilizing water and acetonitrile in a 100 ml volumetric flask. Then, at that point, 1 ml of the stock solution was pipetted into a 10 ml volumetric flask and the volume was expanded to the imprint to get a convergence of 10 mcg/ml. The resultant solution was then observed in an UV- spectrophotometer (Model-1700, Shimadzu, Japan) in the range of 200 and 400 nm. The UV range test was recorded, and the most extreme worth got was contrasted with the UV range expressed in the authority monograph. The greatest frequency of Quetiapine fumarate was found to be 248 nm.

7.3.1.4. Solubility study of QTP FMT

Preformulation dissolvability testing was performed, which involved dissolving abundance drug in glass vials containing 20mL suitable dissolvable solvent and shifting the supernatant liquid following 24 hours at room temperature utilizing a 0.45 μ m pore size channel. The initial 10 mL of the filtrate was disposed of and the rest diluted with water and spectroscopically estimated at 248 nm. Different solvents like water, (CH₃)₂CO, ethanol, chloroform, ether and pH 7.4 Phosphate buffer, will be utilized all through the method.

7.3.1.5. Determination of Partition Co-efficient:

Not entirely set in stone by immersing 10mL of n-octanol in an isolating channel with 10mL phosphate cradle pH 7.4 for 24 hours. 10mg of drug will be put to the isolating pipe, trailed by 4 hours of moderate shaking. The layers of dissolvable were isolated utilizing a channel and how much drug broke up in each stage was estimated at 248 nm against a clear.

7.3.1.6. Preparation of Calibration Curve for QTP FMT

7.3.1.6.1. Calibration Curve for QTP FMT IN 0.1N HCL solution

Preparation of Stock solution

In a 100 mL volumetric flask, 100 mg of drug was precisely weighed. The volume was then expanded to 100 ml by adding 0.1N HCL solution to accomplish a 100 mcg/ml solution.

1 ml of the stock solution (100 mcg/ml) was pipetted and diluted to 10 ml with 0.1N HCL solution into different volumetric flasks and made up to 10 ml with 0.1N HCL solution to get solutions of 1.0 to 5.0 mcg/ml.

Preparation of standard working solution

1ml was taken from the stock solution (100 mcg/ml) and diluted to 10ml with 0.1N HCL solution. Proper aliquots of the solutions were taken into different volumetric flasks and made up to 10ml with 0.1N HCL solution to get the solutions of 1.0 to 5.0 mcg/ml.

By dissolving exactly weighed 100 mg of drug in a 100 ml volumetric flask, a medication alignment blend in 0.1 N HCl was made. The volume was consequently expanded to 100ml utilizing 0.1N HCL solution to get solution of 100 mcg/ml, which was then examined in an UV spectrophotometer.

7.3.1.6.2. Calibration Curve for QTP FMT in Saline buffer pH 7.4

Preparation of Stock solution

In saline support pH 7.4, a 100g/ml stock arrangement of QTP FMT was produced by dissolving 10 mg of the medication in 10 ml of methanol and afterward filling the leftover volume with saline cradle pH 7.4. By examining appropriate weakenings with a high relationship coefficient, the limit of QTP FMT was distinguished. Different standard weakenings were ready from the stock answer for get arrangements of 2,4,6,8, and 10 g/ml, and their absorbance values were estimated at fixed wavelength.

Preparation of Standard working solution

The previously mentioned arrangement was sequentially weakened with saline buffer pH 7.4 solution to get solutions of 10, 20, 40, 50, and 100 mcg/ml. The absorbance at 248 nm was utilized to assess how much QTP FMT is present.

7.3.1.7. Identification of QTP FMT by FT-IR Spectroscopy

Potassium bromide IR discs will be made utilizing 1mg of QTP FMT on a water powered pellet press and checked at 4000-400 cm⁻¹ in FTIR. The IR spectra acquired will be contrasted with the reference range of QTP FMT.

7.3.1.8. Drug- Excipients Compatibility Studies by FT-IR

A combination of QTP FMT, HPMC E5, Stake 400, Citrus extract, Aspatame, and Mannitol will be utilized to make a potassium bromide IR disc, which will be filtered in the 4000-400 cm⁻¹ region in FTIR and contrasted with a reference range of QTP FMT.

7.3.1.9. Particle Size Study:

Unadulterated drug Molecular size examination has been done utilizing Optical Magnifying lens and Malvern Instrument.

7.3.2. Formulation and Development of QTP FMT MDF by using QbD Approach

7.3.2.1. Setting up Quality Target Product Profile (QTPP) and Selection of Formulation and Process Variables by Preliminary Trial Batches of QTP FMT MDF:

The impact of polymer type and its concentration, plasticizer type and concentration, disintegrating agents and other excipients on MDF will be researched in primer preliminaries. To foster the QbD Approach, these starter clumps of quick deteriorating films were assessed utilizing different boundaries, for example, morphological review, weight variation, disintegration time, surface pH, collapsing perseverance, thickness, drug content consistency, percent uniform medication dissemination and in-vitro drug discharge study.

7.3.2.2. Dose calculation of QTP FMT for mould

Dose of drug = ORAL DOSE * ORAL BIOAVAILABILITY/ BODY SURFACE AREA

7.3.2.3. Solvent casting method

Same as Above

TABLE 7.4 Materials and their concentration used for Preliminary trial Batches of QTP FMT MDF

| SL. NO | ROLE OF MATERIAL | MATERIALS TO BE USED | CONCENTRATION |
|--------|------------------|---|------------------|
| 1 | Drug | <i>QTP FMT</i> | 100 mg |
| 2 | Polymers | HPMC E5, HPMC E50, Acacia, Tragacanth, Gelatin, Xanthum Gum, PVA, PVP and | 0.5 gm to 1.0 gm |

| | | | |
|---|----------------------|---|------------------|
| | | Pullnan | |
| 3 | Plasticizers | PEG 200, PEG 400, Poloxamer 407, PG, IPA | 0.5 gm to 1.0 gm |
| 4 | Disintegrating Agent | Cross Providone, Kryon T-314, Banana Powder | 0.5 gm to 1.0 gm |
| 5 | Solvent | Distilled water | Q.S. |
| 6 | Sweeting Agent | Aspartame, Mannitol | Q.S. |
| 7 | Flavouring Agent | Vanillin | Q.S. |
| 8 | Preservative | Citric acid, Methyl paraben, Propyl paraben | Q.S. |

7.3.2.4. Preliminary Trial Batches of QTP FMT MDF

7.3.2.4.1. Selection of Polymer and concentration for QTP FMT MDF:

The different polymers & their concentrations were used to prepare *QTP FMT MDF* to fix the polymer type and concentration. The details are as follows:

TABLE 7.5 Polymer and concentration for QTP FMT MDF

| POLYMER TYPE USED | HPMC E5 | Acacia | PVP | PULLNAN |
|---------------------------------|----------|------------|-------------|---------|
| | HPMC E50 | Tragacanth | Xanthum gum | |
| POLYMER CONCENTRATION USED (gm) | 0.5-1.0 | | | |

7.3.2.4.2. Selection of plasticizer for QTP FMT MDF

To fix the plasticizer type and concentration, QTP FMT MDF was arranged utilizing a few plasticizers with varying concentrations. Coming up next are the various plasticizers that were utilized:

TABLE 7. 6 Plasticizer type and concentration for QTP FMT MDF

| PLASTICIZER TYPE USED | PEG 200 | Poloxamer 407 | PG | IPA | PVA |
|--------------------------------|-----------|---------------|--------|-----------|----------|
| PLASTICIZER CONCENTRATION USED | 0.5-1.0ml | 10-20 mg | 1-2 ml | 0.5-1.0ml | 10-20 mg |

7.3.2.4.3. Selection of disintegrating agent for QTP FMT MDF

To fix the disintegrating agent type and concentration, numerous disintegrating agents and concentrations were used to make QTP FMT MDF. Coming up next are the different disintegrants that were utilized:

TABLE 7. 7 Disintegrating agent type and concentration for QTP FMT MDF

| DISINTEGRATING AGENT TYPE USED | Cross Povidone (g) | Kyron T-314 (g) | Banana Powder (g) |
|---|--------------------|-----------------|-------------------|
| DISINTEGRATING AGENT CONCENTRATION (gm) | 0.5 - 1.0 | | |

7.3.2.5. Risk Assessment of Critical Quality Attributes (CQAs) from Preliminary trial Batches to Develop QbD Approach

Process portrayal will recognize acceptable alterations in material and cycle boundaries, and hazard evaluation will be utilized to choose plan and interaction factors that might influence item quality for CQAs. At last, Interaction Configuration Space might have the option to give quality affirmation by understanding and fostering a control plan. In view of information space, basic quality characteristics are named high, medium, or generally safe. High danger boundaries are generally respected significant for Plan of Analyses since they have a more prominent impact than others and should be in multivariate reaches that can be acknowledged.

7.3.2.6. Formulation and Development of QTP FMT MDF by Design of Experiment (DoE) Using QbD Approach

A plan space could address detailing and interaction information, for example, characteristics connecting with drug fixing, materials, gear, protected innovation, and

finished item quality. Hazard evaluation on MDF quality should be possible for this reason in light of a comprehension of the interaction and definition related components. For high-hazard boundaries, fundamental exploration and later Plan of Trial and error (DoE) would be led. We will propose configuration space for creating strong definition in light of the impact of significant quality highlights of the objective item profile. MDF will be portrayed for an assortment of boundaries.

7.3.2.7. Characterization of QTP FMT MDF

7.3.2.7.1. Weight variation

On a scientific equilibrium, mouths dissolving oral movies were gauged, and the normal load for each film was determined. It is best for movies to have a weight that is basically steady. It's vital to ensure a film has the perfect proportion of excipients and Programming interface.

7.3.2.7.2. Thickness of Films

The thickness of the film was estimated at five separate areas utilizing a micrometer screw measure, and a normal of three readings was inferred. This is important to give consistency in the thickness of the film, which is connected to the portion precision in the film.

7.3.2.7.3. Folding endurance

Collapsing perseverance is estimated by collapsing a similar piece of film again and over until it breaks. The collapsing perseverance esteem is the times a film can be collapsed in a similar spot without breaking.

7.3.2.7.4. Thickness:

The thickness of a medication arranged fix is estimated with a computerized micrometer at different focuses on the fix, and the normal thickness and standard deviation are determined to ensure that the thickness of the fix is kept up with.

7.3.2.7.5. Weight Uniformity:

A characterized fix region should be parted into particular areas and made an appearance an advanced equilibrium. Individual loads will be utilized to lay out the normal weight and

standard deviation.

7.3.2.7.6. Surface pH

The film to be tried was drenched with 0.5 cc of refined water and put away for 30 seconds in a Petri dish. Subsequent to bringing the terminal of the pH meter in contact with the outer layer of the definition and permitting 1 moment for equilibration, the pH was recorded. For every detailing, a normal of three conclusions was made.

7.3.2.7.7. In vitro disintegration test

Whenever an oral film comes into contact with water or spit, the deterioration time starts to abbreviate. The breaking down an ideal opportunity for a quick dissolving film ought to be somewhere in the range of 5 and 30 seconds. One more way was to outwardly decide the breaking down time by plunging the film in 25 mL water in a measuring utencil. The container was delicately shaken, and the second when the film started to part or deteriorate was recorded.

7.3.2.7.8. Drug content Determination:

The arrangement is shaken ceaselessly for 24 hours in a shaker hatchery after a precisely gauged amount of film (over 100 mg) is broken up in 100 mL of Phosphate cradle pH 7.4 in which drug is solvent. After then, at that point, the whole arrangement is sonicated. How much medicine in arrangement is estimated spectrophotometrically after sonication and resulting sifting.

7.3.2.7.9. Tensile Strength:

Tensile strength = $F/a \times b (1+L/l)$

7.3.2.7.10. Flux and Permeability coefficient:

$K_p = J/C$

7.3.2.7.11. In-vitro Permeation study

A dispersion cell receptor compartment limit of 12 ml can be utilized to direct an in-vitro saturation research. Between the contributor and receptor compartments of the dispersion

cell, extracted cellophane paper was mounted. Over paraffin film, arranged patches were put. The dispersion cell's receptor compartment was loaded up with phosphate cushion pH 7.4. The whole gathering was mounted on an attractive stirrer, and the arrangement in the receptor compartment was continually and consistently whirled with attractive dots at 50 rpm while keeping a temperature of 32.0 ± 0.5 °C. Tests were taken at different times and spectrophotometrically assessed for drug focus. With an indistinguishable volume of phosphate support, the receptor stage was recharged.

7.3.2.7.12. Kinetic Analysis of Release Data:

7.3.2.7.12.1. Zero Order Release

$$Q_t = Q_0 + K_0t$$

7.3.2.7.12.2. First Order Release Equation

$$\text{Log } C = \text{Log } C_0 - Kt / 2.303$$

Plot: log cumulative percentage of drug remaining vs. time.

7.3.2.7.12.3. Higuchi Square Root of Time Equation:

$$Q = KH \times t^{1/2}$$

7.3.2.7.12.4. Hixson-Crowell Model

$$W_0^{1/3} - W_t^{1/3} = \kappa t$$

7.3.2.7.12.5. Korsmeyer- Peppas Release Mechanism

$$M_t / M_\infty = k t^n$$

7.3.2.7.13. Validation or check point analysis of QTP FMT MDF

Plan and portrayal of expected bunches from Overlay plots proposed by StatEase programming will be utilized for approval or designated spot examination. The aftereffects of the normal and noticed clumps will be analyzed.

7.3.2.7.14. Taste Evaluation Study by Spitting

In a solitary measurements and single visually impaired review, 8 sound grown-up male volunteers between the ages of 24 and 42 partook. All subjects gave composed informed

agree preceding the review, and they were told with regards to the review's objective, dangers, and span.

Each volunteer got an irregular portion of QTP FMT advanced MDF. The volunteers were told to clean their mouths with 200 cc of refined water before to the preliminary. The volunteers were approached to place the medication in their mouth for 30 seconds, record the deterioration season of the film test, and give a score in view of the boundaries recorded in Table 3, in particular mouth feel, taste or harshness, film lingering flavor, simplicity of taking care of, and generally acknowledgment of the detailing. Following 3 minutes, the volunteers were told to let out the example with spit and wash their mouths with 200 ml refined water. Following 2 hours, the indistinguishable method was finished the subsequent example (either test or reference sample). So, spitting of definition and salivation was told to volunteers to forestall openness of medication.

TABLE 7.8 Parameters, Score and Results of Taste Evaluation Study

| Parameters | 1 | 2 | 3 | 4 | 5 |
|---------------------|--------------------|----------|-------------------------------|-----------------------------|--|
| Mouth feel | Gritty /Irritating | Gritty | Slightly Gritty | Smooth | Very smooth |
| Taste (Bitterness) | Very bitter | Bitter | Slightly bitter | Slightly sweet/ Acceptable | Very sweet |
| After taste | Very Bitter | Bitter | Slightly bitter | Slightly sweet/ Acceptable | Very sweet |
| Ease of handling | Very brittle | Brittle | Acceptable and does not break | Flexible and easy to handle | Patient friendly and very easy to handle |
| Acceptance | Very poor | Poor | Acceptable | Good | Excellent |

7.3.2.7.15. Scanning electron microscope

Checking electron microscopy was utilized to analyze the surface morphology of the better definition. A filtering electron infinitesimal example holder with twofold sided taps was covered with a 150A gold layer for 2 minutes in a vaccum of 310-1atm organ gas utilizing a falter coater (JSM 6390, Make - JEOL). A filtering electron magnifying instrument was then used to examine the examples.

7.3.2.7.16. Skin Permeation Study (*Ex- vivo* Study)

IAEC endorsement and assent will be expected for the skin penetration examination (*ex- vivo* study). Skin from pale skinned person rodents will be painstakingly taken out. The skin

will be utilized as a hindrance layer for the examinations once the hypodermal fat tissue has been taken out. For this examination, the ideal plan from in vitro analyses will be utilized, with rodent skin filling in as a film between the contributor and receptor compartments. The receptor compartment will be loaded up with phosphate cradle pH 7.4 and unsettled at 37 1 °C utilizing an attractive stirrer. The examples will be contrasted with a clear utilizing an UV spectrophotometer set to 248 nm.

7.3.2.7.17. Comparison of optimized QTP FMT MDF with Marketed QTP FMT formulation:

The optimized formulation QTP FMT MDF will be compared with Marketed conventional QTP FMT.

7.3.2.7.18. Stability Studies

The picked organization was put in golden shaded jugs that were firmly shut and stopped up with cotton. They were hence kept up with for one month at 40°C/75% RH and surveyed for actual appearance, in vitro deterioration time, drug content homogeneity, and medication discharge learns at foreordained stretches.

Chapter-8
Results &
Discussion
(QIP FMT)

CHAPTER 8

RESULTS & DISCUSSION

8. Results & Discussion

8.1 PREFORMULATION STUDY OF QTP FMT

8.1.1. ORGANOLEPTIC PROPERTIES

TABLE 8.1 Organoleptic characteristics of Drugs

| S.No. | Parameters |
|-------|-------------------------|
| 1. | White in color |
| 2. | Characteristics in odor |
| 3. | Bitter in taste |

The actual appearance of unadulterated medication was inspected outwardly as per Indian Pharmacopeia. Shading, scent, and taste were assessed by our faculties (eye, tongue, and nose) in this examination.

8.1.2. MELTING POINT

The chose medication's dissolving point was determined utilizing an advanced liquefying point instrument and the hairlike combination technique. With the utilization of a burner, one finish of a fine was fixed. The narrow cylinder's open end was embedded into a little piece of powder, and the cylinder was delicately tapped to settle the accumulated material. The method was completed a few times more. The dissolving point gadget was then used to situate the slender cylinder. Not entirely settled at what temperature the medicine starts to liquefy.

TABLE 8.2 Determination of melting point of drugs

| S.No. | Quetiapine FMT Melting Point | |
|-------|------------------------------|------------------------|
| | Observed value (n =3) | Standard value |
| 1. | 172-176 ⁰ C | 170-175 ⁰ C |

The dissolving point was utilized to decide the example's virtue. The softening place of the drug test was 170-1750C, which was inside the reach and shown that the example was unadulterated QTP FMT.

8.1.3. DETERMINATION OF WAVELENGTH OF QTP FMT

To create a stock arrangement of 100 g/ml, the appropriately gauged amount of 100 mg of medication test was disintegrated in a combination of water and acetonitrile (1:1) (3 of every 200,000) and volume moved toward 100 ml utilizing water and acetonitrile in a 100 ml volumetric jar. Then, at that point, 1 ml of the stock arrangement was pipetted into a 10 ml volumetric cup, and the volume was expanded to the imprint to get a convergence of 10 g/ml. The resultant arrangement was then examined with an UV-noticeable spectrophotometer (Mdel-1700, Shimadzu, Japan) somewhere in the range of 200 and 400 nm. The UV range test was recorded, and the greatest worth got was contrasted with the UV range expressed in the authority monograph.

The λ max of QTP FMT and Quetiapine fumarate was viewed as 318 nm and 248 nm separately.

TABLE 8. 3 Wavelength maximum (λ max) of QTP FMT

| Drug | λ max | |
|---------|----------------------|------------------------|
| | Actual λ max | Observed λ max |
| QTP FMT | 250 | 248.5 |

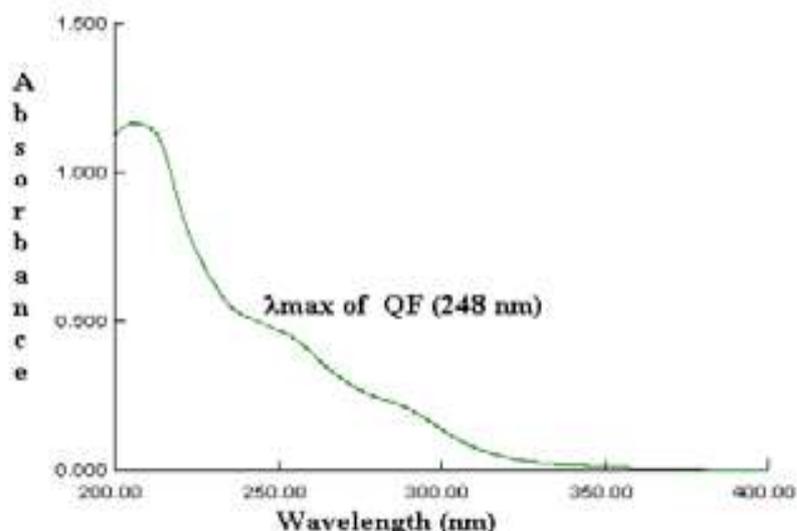


FIGURE 8. 1 UV Spectrum of QTP FMT

8.1.4. SOLUBILITY STUDIES

The dissolving and dissemination liquids for the medication delivery and pervasion examinations were picked in light of QTP FMT dissolvability information in different liquids. The solvency of the medication test was tried by dissolving 100 mg of the medication test in different liquids in expanding sums. Dissolvability was estimated by recording how much dissolvable important to disintegrate the medicine.

TABLE 8. 4 Solubility profile of QTP FMT

| S.No. | Solvent | Solubility | |
|-------|----------|-------------------------------------|----------------------|
| | | QTP FMT | |
| | | Conc. (mg/ml) Mean \pm SD, n=3 | Inference |
| 1. | HCl | 11.67 \pm 0.21 | Soluble |
| 2. | NaOH | 11.07 \pm 0.15 | Soluble |
| 3. | Ethanol | 0.07 \pm 0.02 | Slightly Soluble |
| 4. | Methanol | 0.86 \pm 0.03 | Sparingly Soluble |
| 5. | Water | 0.66 \pm 0.04 | Slightly Soluble |
| 6. | DMSO | 0.95 \pm 0.05 | Slightly Soluble |

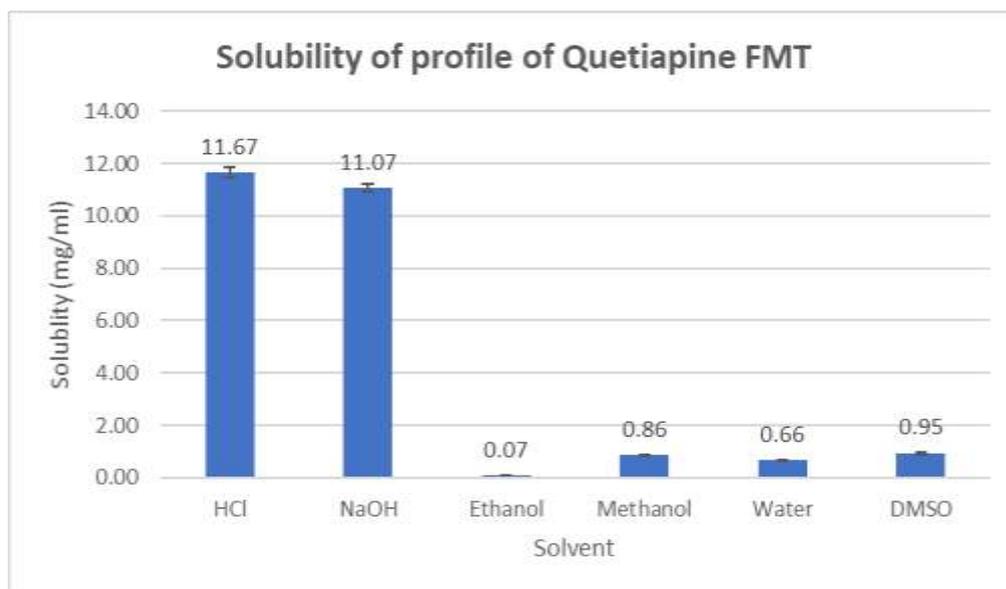


FIGURE 8. 2 Solubility profile of QTP FMT

8.1.5. PARTITION COEFFICIENT

In n-octanol as a non-aqueous stage and phosphate buffer solution pH 7.4 (PBS pH 7.4) as a aqueous stage, the medication partition coefficient was estimated. These two stages were blended in equivalent parts and held in isolated pipes until they were soaked with one another. In the wake of blending, let the framework be for 30 minutes. The partition coefficient was determined by isolating 10 mg of prescription into 10 ml parts of n-octanol and PBS pH 7.4 in isolating channels. The isolating channels were shaken for 24 hours on a mechanical shaker. Two stages were isolated, and the aqueous stage was shifted through Whatman filter paper, and how much drug in the aqueous stage was evaluated spectrophotometrically at max 248 nm utilizing phosphate buffer solution pH 7.4.

TABLE 8. 5 Determination of Partition Coefficient of selected Drugs

| S.No. | Sample | Partition Coefficient (Mean \pm SD, n=3) |
|-------|---------|--|
| 1. | QTP FMT | 3.35 \pm 0.53 |

8.1.6. Calibration Curve:

8.1.6.1. QTP FMT Calibration Curve in 0.1N HCL

Preparation of standard stock solution (100 μ g/ml) in 0.1N HCL

In a 100 mL volumetric flask, 100 mg of medicine was precisely weighed. The volume was then expanded to 100 ml by adding 0.1N HCL solution for accomplish a 100 mcg/ml solution. 1 ml of the stock solution (100 mcg/ml) was taken and diluted to 10 ml with 0.1N HCL solution in independent volumetric flask, bringing about a centralization of 1.0 to 5.0 mcg/ml.

Preparation of standard working solution

1ml was taken from the stock solution (100 mcg/ml) and diluted to 10ml with 0.1N HCL solution. Fitting aliquots of the solution were taken into different volumetric flasks and made up to 10ml with 0.1N HCL solution to accomplish a centralization of 1.0 to 5.0 mcg/ml. By dissolving definitively weighed 100 mg of drug in a 100 ml volumetric flask, a medication adjustment bend in 0.1 N HCl was made. The volume was thus expanded to 100ml utilizing 0.1N HCL solution to acquire solution of 10 mcg/ml, which was then examined in an UV spectrophotometer.

TABLE 8. 6 Calibration Curve of QTP FMT in 0.1 N HCl

| Conc. ($\mu\text{g/ml}$) | Absorbance (nm) Mean \pm SD; n=3 |
|----------------------------|---------------------------------------|
| 0 | 0 \pm 0.00 |
| 1 | 0.102 \pm 0.001 |
| 2 | 0.118 \pm 0.020 |
| 3 | 0.202 \pm 0.013 |
| 4 | 0.223 \pm 0.012 |
| 5 | 0.313 \pm 0.090 |
| 6 | 0.34/ \pm 0.021 |
| 7 | 0.388 \pm 0.027 |
| 8 | 0.417 \pm 0.023 |
| 9 | 0.489 \pm 0.011 |
| 10 | 0.513 \pm 0.003 |

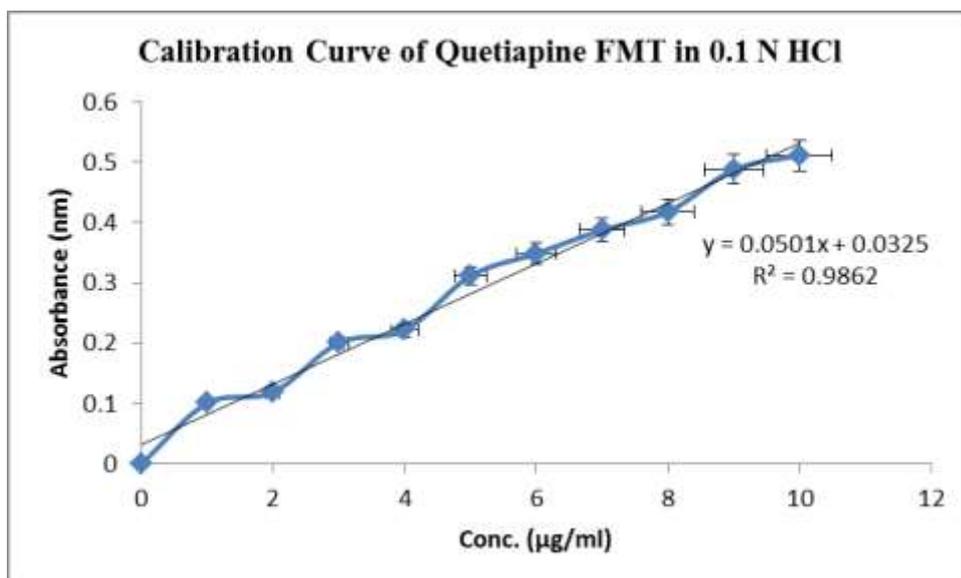


FIGURE 8.3 Standard Curve of QTP FMT in 0.1 N HCl at 248 nm

TABLE 8.7 Summary Report of calibration curve for QTP FMT

| Parameters | QTP FMT |
|---|--------------|
| Wavelength (λ_{max}) | 248 |
| Beer's limit ($\mu\text{g/ml}$) | 0-10 |
| Corrélation coefficient (R^2) | 0.986 |
| Slope | 0.050 |
| Obeys Beer law in conc. range of 0-10 mcg/ml | |
| R^2 value shows linearity | |

8.1.6.2. QTP FMT Calibration Curve in Phosphate buffer pH 7.4 (pH of Salivary stimulating fluid)

Preparation of standard stock solution (100 $\mu\text{g/ml}$) in Phosphate buffer pH 7.4 (pH of Salivary stimulating fluid)

In a 10 mL volumetric flask, precisely weighed 100 mg of drug. The volume was then expanded to 100 ml by adding Phosphate buffer pH 7.4 to accomplish a 100 mcg/ml solution. 1 ml of the stock solution (100 mcg/ml) was pipetted and diluted to 10 ml

in discrete volumetric flask with Phosphate buffer pH 7.4 to get a centralization of 1 to 10 mcg/ml.

Preparation of standard working solution

1 ml was pipetted from the stock solution (100 mcg/ml) and diluted to 10 ml with Phosphate buffer pH 7.4. Suitable aliquots of the solution were put into different volumetric flask and made up to 10 ml with Phosphate buffer pH 7.4 to get centralizations of 1 to 10 mcg/ml.

The alignment bend for drug in Phosphate buffer pH 7.4 was made by dissolving 100 mg of medication in a 100 ml volumetric flask that was exactly weighed. The volume was then expanded to 100 ml utilizing Phosphate buffer pH 7.4 to prepare a solution of 100 mcg/ml, which was then observed in an UV spectrophotometer.

TABLE 8. 8 Calibration Curve of QTP FMT in Phosphate buffer pH 7.4

| Conc. ($\mu\text{g/ml}$) | Absorbance (nm) Mean \pmSD; n=3 |
|--|---|
| 0 | 0 \pm 0.00 |
| 1 | 0.015 \pm 0.051 |
| 2 | 0.015 \pm 0.120 |
| 3 | 0.033 \pm 0.003 |
| 4 | 0.03 \pm 0.041 |
| 5 | 0.053 \pm 0.028 |
| 6 | 0.062 \pm 0.110 |
| 7 | 0.067 \pm 0.003 |
| 8 | 0.070 \pm 0.004 |
| 9 | 0.083 \pm 0.017 |
| 10 | 0.089 \pm 0.023 |

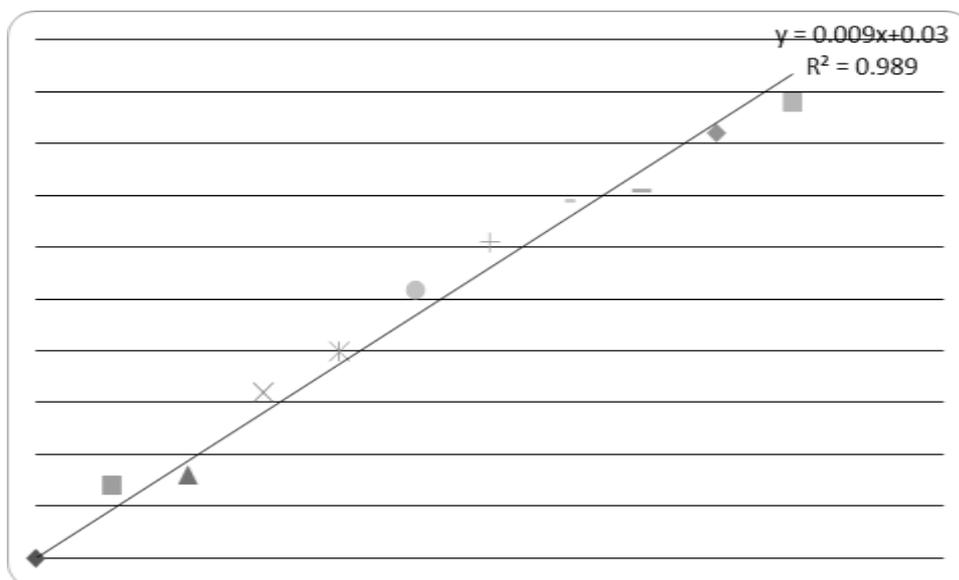


FIGURE 8.4 Standard Curve of QTP FMT in Phosphate buffer pH 7.4

TABLE 8.9 Standard Curve of QTP FMT in Phosphate buffer pH 7.4

| Parameters | QTP FMT |
|---|--------------|
| Wavelength (λ_{max}) | 248 |
| Beer's limit ($\mu\text{g/ml}$) | 0-10 |
| Corrélation coefficient (R^2) | 0.989 |
| Slope | 0.009 |
| Obeys Beer law in conc. range of 0-10 mcg/ml | |
| R^2 value shows linearity | |

8.1.7. Identification of QTP FMT by FTIR Spectra

To distinguish the substance, infrared spectroscopy was utilized on an unadulterated medication test. A medication pellet was made by compacting the medication with IR grade potassium bromide in a KBr press at 5.5 metric huge loads of tension. The pellet was put in an IR compartment and checked with a FTIR spectrophotometer (Model-8400 S, Shimadzu, Japan) between wave numbers 4000-450 cm^{-1} .

TABLE 8.10 Interpretation of FTIR Spectra of QTP FMT

| S.No. | Inference | Standard wave no.(cm ⁻¹) | Observed wave no.(cm ⁻¹) | Interpretation |
|-------|--------------------------|--------------------------------------|--------------------------------------|------------------------|
| 1. | O-H stretching | 3584-3700 | 3751 | Alcohol |
| 2. | C-H stretching | 3000-3100 | 3080 | Alkene |
| 3. | C-H stretching | 2840-3000 | 2881 | Alkane |
| 4. | C=C stretching | 1600-1650 | 1600 | Conjugated alkene |
| 5. | C-H bending | 1372-1290 | 1344 | Alkane methylene group |
| 6. | C-N stretching | 1020-1250 | 1032 | Amine |
| 7. | Substituted benzene ring | 780-800 | 795 | 1,3 di substituted |

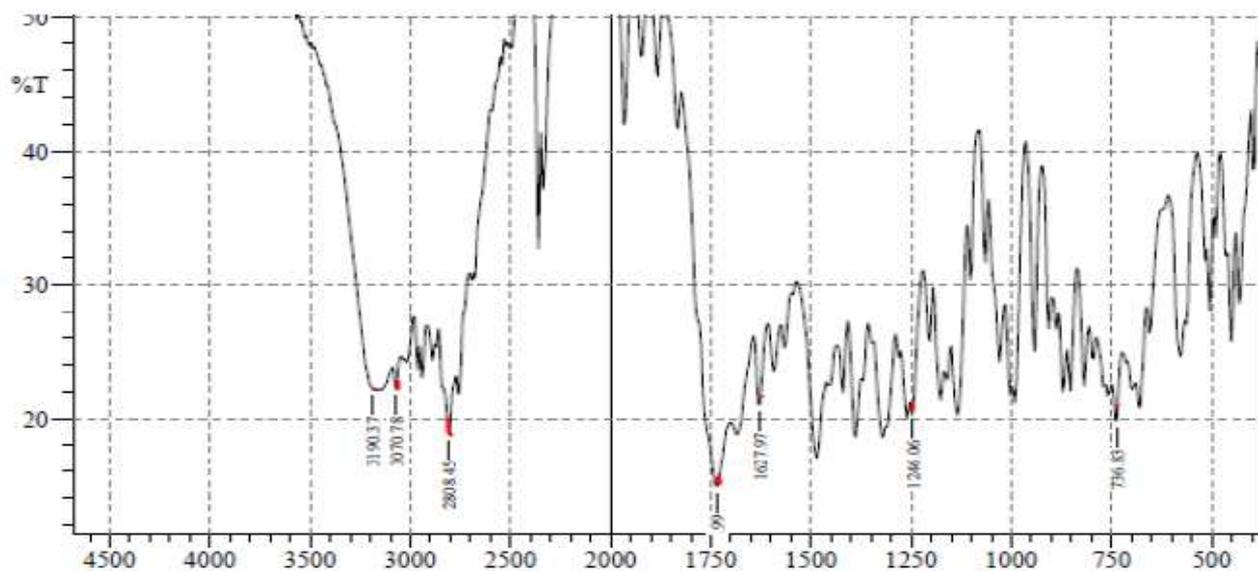


FIGURE 8.5 FTIR Spectra of Pure Drug

8.1.8. Compatibility study of QTP FMT with excipients by FTIR Spectra

TABLE 8. 11 Interpretation of FTIR Spectra of QTP FMT

| S.No. | Inference | Standard wave no.(cm^{-1}) | Observed wave no.(cm^{-1}) | Interpretation |
|-------|--------------------------|---------------------------------------|---------------------------------------|------------------------|
| 1. | O-H stretching | 3584-3700 | 3751 | Alcohol |
| 2. | C-H stretching | 3000-3100 | 3079 | Alkene |
| 3. | C-H stretching | 2840-3000 | 2882 | Alkane |
| 4. | C=C stretching | 1600-1650 | 1602 | Conjugated alkene |
| 5. | C-H bending | 1372-1290 | 1343 | Alkane methylene group |
| 6. | C-N stretching | 1020/1250 | 1033 | Amine |
| 7. | Substituted benzene ring | 780-800 | 794 | 1,3 di substituted |

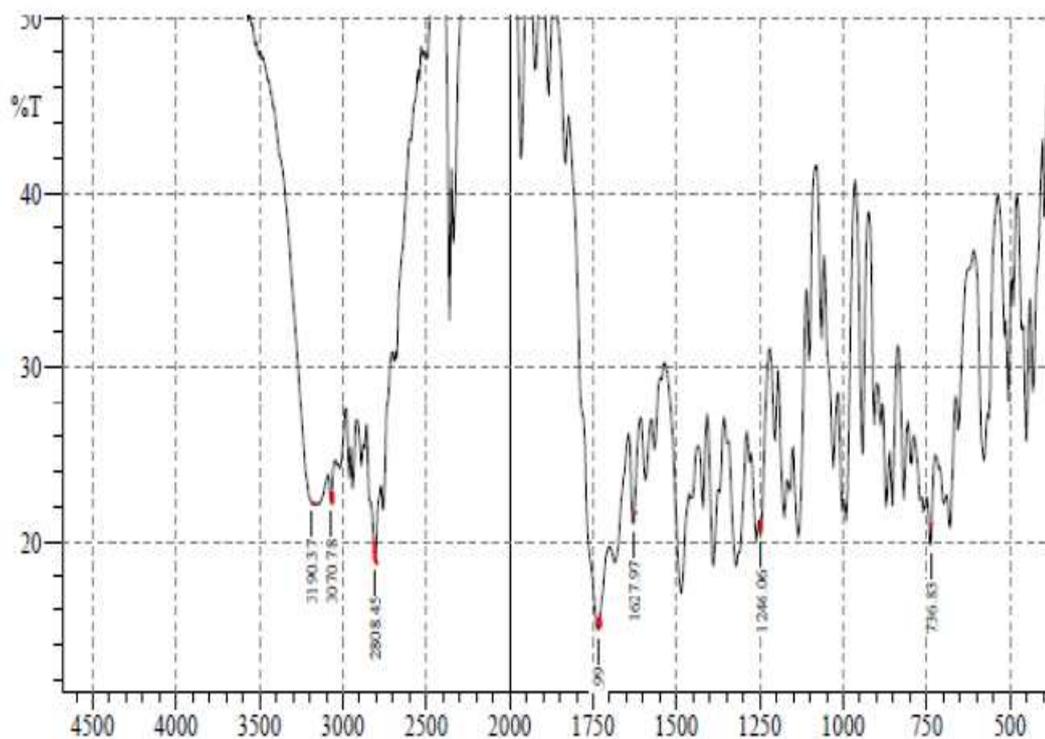


FIGURE 8. 6 FTIR Spectra of Pure Drug with excipients

A combination of QTP FMT, HPMC E5, Stake 400, Citrus extract, Aspartame, and Mannitol will be utilized to make a potassium bromide IR disc, which will be checked in the 4000-400 cm^{-1} region in FTIR and contrasted with a reference range of QTP FMT. At the point when QTP FMT was joined with polymers, no adjustments in the IR tops were noticed. These discoveries highlight polymers' similarity with QTP FMT

8.2.2. Trial batches for QTP FMT MDF for CQAs for QTP FMT MDF

TABLE 8. 12 selection of polymers type and concentration for QTP FMT MDF

| Ingredients | QTPODT 1 | QTPODT 2 | QTPODT 3 | QTPODT 4 | QTPODT 5 | QTPODT 6 | QTPODT 7 | QTPODT 8 | QTPODT 9 | QTPODT 10 | QTPODT 11 | QTPODT 12 |
|------------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|--------------|--------------|--------------|
| Drug | 0.184 gm | | | | | | | | | | | |
| PVP (gm) | 0.1 | 0.3 | 0.5 | - | - | - | - | - | - | - | - | - |
| EC (gm) | - | - | - | 0.1 | 0.3 | 0.5 | - | - | - | - | - | - |
| HPMC E5 (gm) | - | - | - | - | - | - | 0.1 | 0.3 | 0.5 | - | - | - |
| HPMC E50 (gm) | - | - | - | - | - | - | - | - | - | 0.1 | 0.3 | 0.5 |
| PEG 200 | 01 ml | | | | | | | | | | | |
| DW | Q.S | | | | | | | | | | | |
| Strip Form | Yes | | | | | | | | | | | |
| Stickiness | - | | | | | | | | | | | |
| Appearance | # | | | * | | | # | | | * | | |

DISCUSSION:

BATCH (QTPODT1-QTPODT3): PVP, a strip framing polymer, was utilized in sums going from 100 to 500 mg. The strip, which had a 300mg focus, was tacky and clear. The strip showed air entanglement as the fixation was expanded to 1.0gm, giving it a cloudy appearance. Likewise, the strip struggled separating itself from petridish.

BATCH (QTPODT4-QTPODT6): Strip shaping polymer EC at fixations going from 100 to 500 mg was used. The strip was tacky and clear with a grouping of up to 300mg. Because of the production of knots in the strips at 500 mg fixation, the strips were non-tacky yet cloudy by all accounts.

BATCH (QTPODT7- QTPODT9): The strip framing polymer HPMC E5 was used in focuses going from 100 to 500 mg. The strips were decided on their actual appeal as well as their tenacity. From petridish, it was found that the strips were non-tacky, clear, and had adequate peelability.

BATCH (QTPODT10-QTPO11): HPMC E50, a strip framing polymer, was utilized in fixations going from 100 to 500 mg. The strips were decided on their actual appeal as well as their tenacity. From petridish, it was found that the strips were non-tacky, clear, and had OK peelability.

TABLE 8.13 Results of QTPODT4- QTPODT12

| Batch | Surface Texture | Weight uniformity (mg) (Mean \pm SD) n=3 | Avg. uniform Drug Distribution (%) (\pm SD, n = 3) | Avg. Drug Content uniformity (%) (\pm SD, n = 3) |
|-----------------|-----------------|--|---|---|
| QTPODT4 | Smooth | 98.00 \pm 0.14 | 98.32 \pm 0.191 | 99.32 \pm 0.72 |
| QTPODT5 | Smooth | 98.00 \pm 0.57 | 98.65 \pm 0.221 | 99.16 \pm 0.53 |
| QTPODT7 | Smooth | 96.00 \pm 0.35 | 98.24 \pm 0.389 | 98.76 \pm 0.19 |
| QTPODT8 | Smooth | 97.00 \pm 1.13 | 98.46 \pm 0.244 | 99.65 \pm 0.08 |
| QTPODT9 | Smooth | 98.00 \pm 0.56 | 98.30 \pm 0.44 | 99.84 \pm 0.02 |
| QTPODT10 | Smooth | 99.00\pm0.48 | 99.45 \pm 0.189 | 99.40 \pm 0.43 |
| QTPODT11 | Smooth | 100.00\pm0.34 | 99.54 \pm 0.129 | 99.76 \pm 0.67 |
| QTPODT12 | Smooth | 101.00\pm0.35 | 99.12 \pm 0.131 | 99.50 \pm 0.19 |

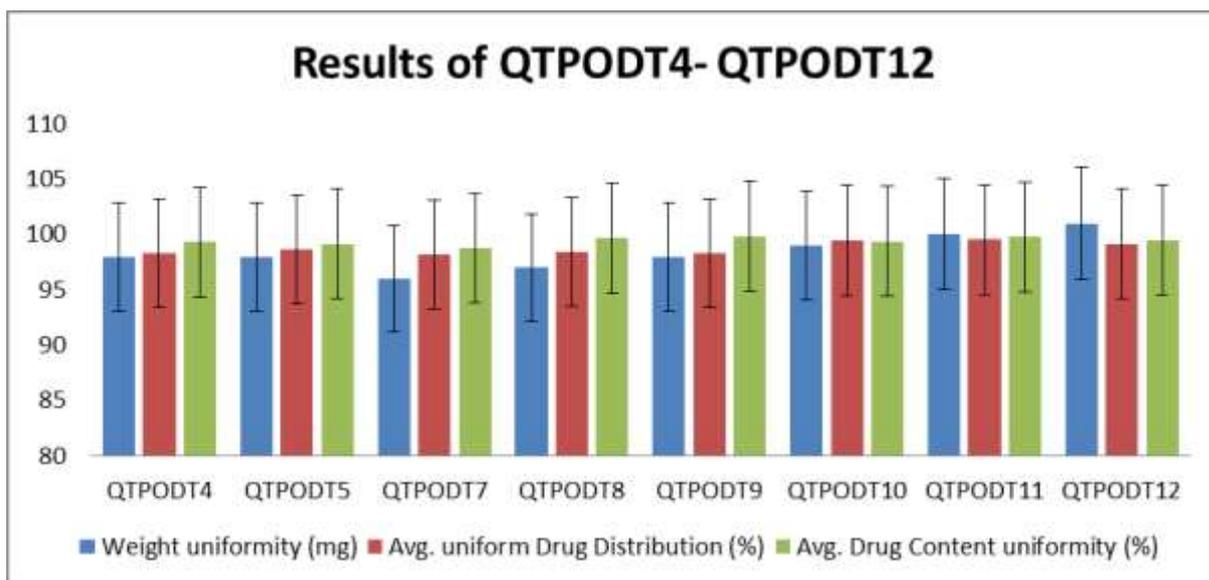


FIGURE 8.7 Results of QTPODT4- QTPODT12

TABLE 8. 14 Results of QTPODT4- QTPODT12

| Batch | Surface Texture | Surface pH (Mean \pm SD) n=3 | Thickness (mm) (Mean \pm SD) n=3 | Avg. Tensile strength (N/cm ²) \pm SD, n = 3 |
|-----------------|-----------------|-----------------------------------|---|--|
| QTPODT4 | Smooth | 6.98 \pm 0.05 | 0.14 \pm 0.01 | 1.02 \pm 0.01 |
| QTPODT5 | Smooth | 7.05 \pm 0.24 | 0.14 \pm 0.01 | 1.03 \pm 0.05 |
| QTPODT7 | Smooth | 6.80 \pm 0.18 | 0.17 \pm 0.02 | 1.64 \pm 0.01 |
| QTPODT8 | Smooth | 6.66 \pm 0.06 | 0.16 \pm 0.02 | 1.53 \pm 0.02 |
| QTPODT9 | Smooth | 6.36 \pm 0.13 | 0.15 \pm 0.01 | 1.06 \pm 0.03 |
| QTPODT10 | Smooth | 6.96 \pm 0.02 | 0.16 \pm 0.01 | 2.22 \pm 0.02 |
| QTPODT11 | Smooth | 6.84 \pm 0.28 | 0.17 \pm 0.01 | 2.38 \pm 0.01 |
| QTPODT12 | Smooth | 6.74 \pm 0.05 | 0.17 \pm 0.01 | 2.86 \pm 0.03 |

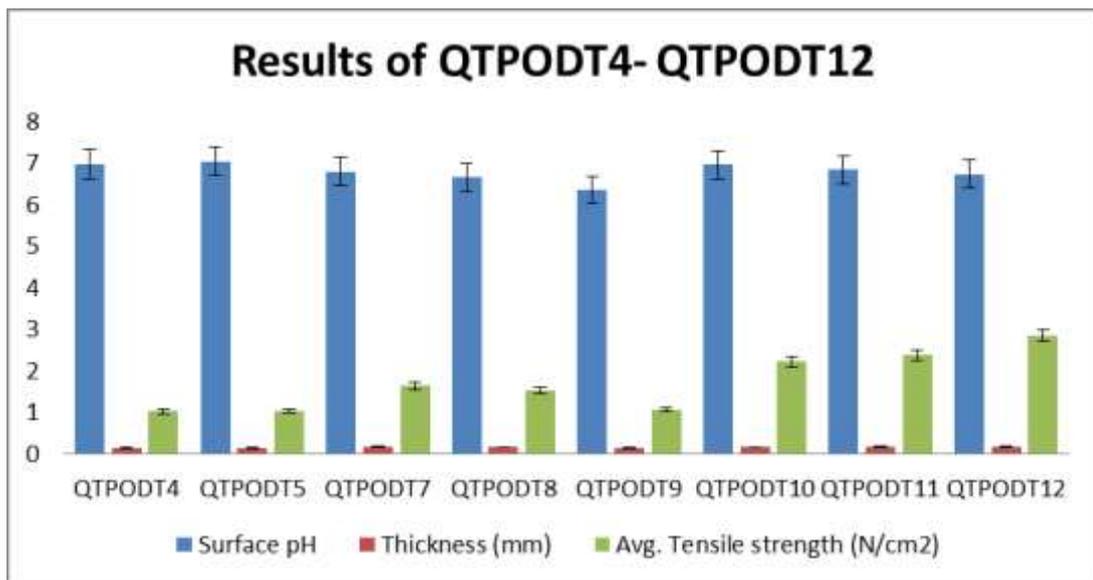


FIGURE 8. 8 Results of QTPODT4- QTPODT12

TABLE 8. 15 Results of QTPODT4- QTPODT12

| Batch | Surface Texture | Avg. In Vitro Disintegration Time (sec) \pm SD, n = 3 | Avg. Folding Endurance \pm SD, n = 3 |
|-----------------|-----------------|---|--|
| QTPODT4 | Smooth | 161.35 \pm 4.245 | 90.00 \pm 5 |
| QTPODT5 | Smooth | 169.5 \pm 3.375 | 97.00 \pm 4 |
| QTPODT7 | Smooth | 167.26 \pm 1.156 | 90.00 \pm 1 |
| QTPODT8 | Smooth | 180.27 \pm 1.271 | 101.00 \pm 5 |
| QTPODT9 | Smooth | 189.01 \pm 2.576 | 109.00 \pm 4 |
| QTPODT10 | Smooth | 121.68 \pm 1.936 | 148.00\pm3 |
| QTPODT11 | Smooth | 135.76 \pm 2.127 | 162.00\pm1 |
| QTPODT12 | Smooth | 141.65 \pm 1.377 | 173.00\pm2 |

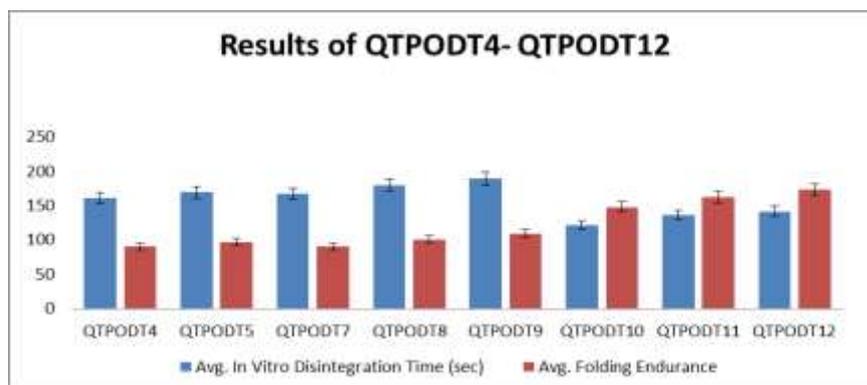


FIGURE 8. 9 Results of QTPODT4- QTPODT12

Inference

From the discoveries of the previously mentioned fundamental preliminary clusters for polymer choice, it was found that polymer HPMC E50 created the best outcomes in the focus scopes of 100, 300, and 500 mg. Therefore, HPMC E50 was picked for the last MDF synthesis.

TABLE 8. 16 Selection of Polymer type and concentration for QTP FMT MDF

| Ingredients | QTPODT 13 | QTPODT 14 | QTPODT 15 | QTPODT 16 | QTPODT 17 | QTPODT 18 | QTPODT 19 | QTPODT 20 | QTPODT 21 | QTPODT 22 | QTPODT 23 | QTPODT 24 | |
|-------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|---|
| Drug | 0.184 gm | | | | | | | | | | | | |
| Xanthum gum | 0.1 gm | 0.3 gm | 0.5 gm | - | - | - | - | - | - | - | - | - | |
| PULLNAN | - | - | - | 0.1 gm | 0.3 gm | 0.5 gm | - | - | - | - | - | - | |
| Acacia | - | - | - | - | - | - | 0.1 gm | 0.3 gm | 0.5 gm | - | - | - | |
| Tragacanth | - | - | - | - | - | - | - | - | - | 0.1 gm | 0.3 gm | 0.5 gm | |
| PEG 200 | 01 ml | | | | | | | | | | | | |
| DW | Q.S | | | | | | | | | | | | |
| Strip Form | Yes | | | No | | | Yes | | | No | | | |
| Stickiness | + | | | | | | | | | | | | |
| Appearance | # | | | | | @ | | | | | # | | @ |

BATCH (QTPODT13-QTPODT15): Xanthum gum, a strip-framing polymer, was used in focuses going from 100 to 500 mg. The pre-arranged strips were inspected, and it was found that they were tacky and cloudy for all intents and purposes, and that they were hard to eliminate from the petridish.

BATCH (QTPODT16-QTPODT18): PULLNAN, a strip-shaping polymer, was utilized in focuses going from 100 to 500 mg. It was found that no strip had been shaped.

BATCH (QTPODT19-QTPODT21): Acacia gum, a strip-shaping polymer, was used in sums going from 100 to 500 mg. The strips that shaped were tacky, dark, and hard to eliminate from the petridish.

BATCH (QTPODT22-QTPODT24): Strip-framing polymer acacia gum was utilized in dosages going from 100 to 500 mg. The tacky, hazy strips that framed were hard to eliminate from the petridish.

TABLE 8.17 Selection of Plasticizer type and concentration for QTP FMT MDF

| Ingredients | Q TPLDT 1 | Q TPLDT 2 | Q TPLDT 3 | Q TPLDT 4 | Q TPLDT 5 | Q TPLDT 6 | Q TPLDT 7 | Q TPLDT 8 | Q TPLDT 9 | Q TPLDT 10 | Q TPLDT 11 | Q TPLDT 12 | Q TPLDT 13 | Q TPLDT 14 | Q TPLDT 15 |
|-----------------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|---------------|---------------|---------------|---------------|---------------|---------------|
| HPMC E50 | 0.3 gm | | | | | | | | | | | | | | |
| Drug (gm) | 0.184 gm | | | | | | | | | | | | | | |
| PG (ml) | 0.5 | 0.75 | 1.0 | - | - | - | - | - | - | - | - | - | - | - | - |
| IPA (ml) | - | - | - | 0.5 | 0.75 | 1.0 | - | - | - | - | - | - | - | - | - |
| PVA (gm) | - | - | - | - | - | - | 0.01 | 0.015 | 0.020 | - | - | - | - | - | - |
| Poloxamer 407 (gm) | - | - | - | - | - | - | - | - | - | 0.01 | 0.015 | 0.020 | - | - | - |
| PEG 200 (ml) | - | - | - | - | - | - | - | - | - | - | - | - | 0.01 | 0.015 | 0.020 |
| DW (ml) | Q.S | | | | | | | | | | | | | | |
| Strip Form | Yes | | | | | | | | | | | | | | |
| Stickiness | + | | | | | | - | | | | | | + | | |
| Appearance | # | | | | | | * | | | | | | @ | | |

Strip-shaping polymer acacia gum was utilized in dosages going from 100 to 500 mg. The tacky, obscure strips that framed were difPEG 200 (1-2 ml), PVA and Poloxamer 407 (10-20 mg), and PG and IPA (0.5-1.0 ml) were utilized to make the strips. Actual appearance and tenacity of the created strips were analyzed. The strips holding back PVA and Poloxamer 407 were found to be non-tacky, non-slick, straightforward, and simple to project. Stake 200, PG, and IPA strips, then again, were tacky, sleek, misty, and hard to cast. Difficult to eliminate from the petridish.

TABLE 8.18 Results of QTPLDT7- QTPLDT12

| Batch | Surface Texture | Weight uniformity (mg) (Mean \pm SD) n=3 | Surface pH (Mean \pm SD) n=3 | Thickness (mm) (Mean \pm SD) n=3 | Avg. Tensile strength (N/cm ²) (Mean \pm SD), n = 3 | Avg. Drug Content uniformity (%) (Mean \pm SD), n = 3 | Avg. uniform Drug Distribution (%) (Mean \pm SD), n = 3 | Avg. In Vitro Disintegration Time (sec) (Mean \pm SD), n = 3 | Avg. Folding Endurance (Mean \pm SD), n = 3 |
|-----------------|-----------------|--|-----------------------------------|------------------------------------|---|---|---|--|---|
| QTPLDT7 | Smooth | 99.96 \pm 0.34 | 6.40 \pm 0.0.10 | 0.16 \pm 0.032 | 1.73 \pm 0.145 | 98.40 \pm 0.289 | 97.44 \pm 0.289 | 168.36 \pm 1.527 | 114.00 \pm 1.732 |
| QTPLDT8 | Smooth | 98.00 \pm 0.01 | 7.01 \pm 0.29 | 0.23 \pm 0.056 | 1.98 \pm 0.172 | 99.32 \pm 0.382 | 98.55 \pm 0.289 | 176.47 \pm 0.577 | 136.00 \pm 2.645 |
| QTPLDT9 | Smooth | 101.00 \pm 0.03 | 7.10 \pm 0.39 | 0.32 \pm 0.098 | 2.18 \pm 0.065 | 99.32 \pm 0.289 | 96.35 \pm 0.382 | 187.02 \pm 2.00 | 154.00 \pm 2.00 |
| QTPLDT10 | Smooth | 99.74\pm0.18 | 7.02 \pm 0.00 | 0.18\pm0.013 | 2.25 \pm 0.058 | 99.74 \pm 0.50 | 99.36 \pm 0.289 | 118.87 \pm 0.577 | 193.00 \pm 3.46 |
| QTPLDT11 | Smooth | 99.65 \pm 0.34 | 7.35 \pm 0.577 | 0.26 \pm 0.034 | 2.63 \pm 0.307 | 99.43 \pm 0.29 | 99.69 \pm 0.289 | 127.56 \pm 0.577 | 203.65 \pm 1.53 |
| QTPLDT12 | Smooth | 99.46 \pm 0.14 | 7.69 \pm 0.577 | 0.31 \pm 0.028 | 2.89 \pm 0.177 | 99.90 \pm 0.29 | 99.83 \pm 0.144 | 132.29 \pm 1.528 | 219.65 \pm 0.58 |

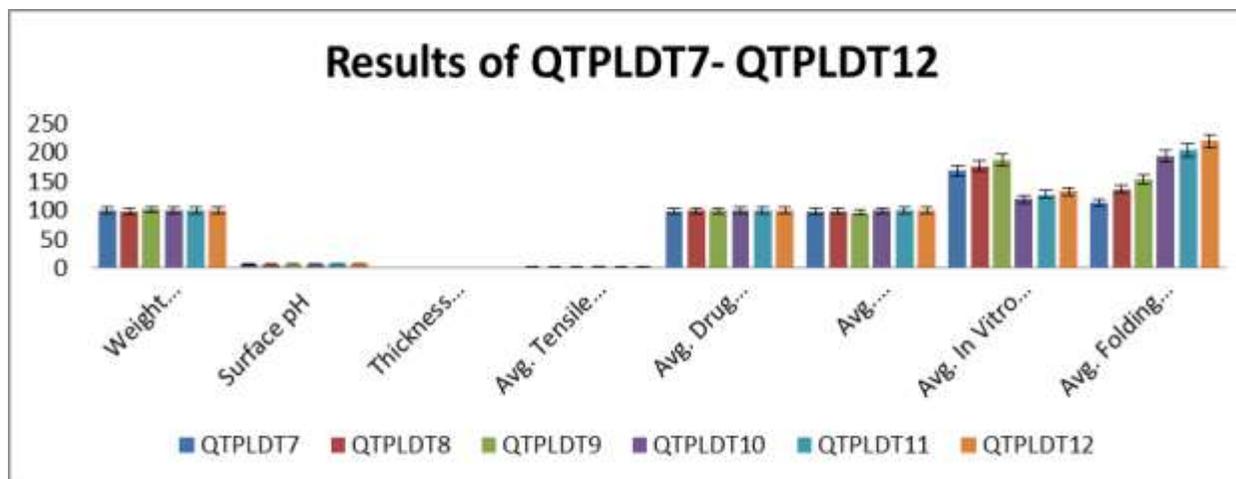


FIGURE 8.10 Results of QTPLDT7-QTPLDT12

Inference

In light of the after effects of the previously mentioned primer preliminary groups for plasticizer determination, it was found that Poloxamer 407 in the focus scope of 10-15 mg created the best outcomes.

TABLE 8. 19 Selection of disintegrating agent type and concentration for QTP FMT MDF

| Ingredients | QTPDT1 | QTPDT2 | QTPDT3 | QTPDT4 | QTPDT5 | QTPDT6 | QTPDT7 | QTPDT8 | QTPDT9 | |
|---------------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--|
| Drug (gm) | 0.184 | | | | | | | | | |
| HPMC E5 (gm) | 0.3 | | | | | | | | | |
| PEG 400 (ml) | 01 | | | | | | | | | |
| Cross Povidone (gm) | 0.050 | 0.075 | 0.1 | - | - | - | - | - | - | |
| Banana Powder (gm) | - | - | - | 0.050 | 0.075 | 0.1 | - | - | - | |
| Kyron T-314 (gm) | - | - | - | - | - | - | 0.050 | 0.075 | 0.1 | |
| DW | Q.S | | | | | | | | | |
| Strip form | Yes | | | | | | | | | |
| Stickiness | - | + | | | | | - | | | |
| Appearance | # | | | * | | | | | | |

DISCUSSION: The strips were made with 0.05, 0.075, and 0.1 gm convergences of the disintegrating agents Cross Povidone, Banana powder and Kyron T-314. The actual appearance and tenacity of the prepared strips were evaluated. The strips holding back banana powder and cross povidone were tacky and seemed hazy or non-straightforward. The strips holding back Kryon T-314, then again, were non-tacky and clear.

TABLE 8. 20 Results of QTPDT7- QTPDT9

| Batch | Surface Texture | Weight uniformity (mg) (Mean \pm SD) n=3 | Surface pH (Mean \pm SD) n=3 | Thickness (mm) (Mean \pm SD) n=3 | Avg. Tensile strength (N/cm ²) \pm SD, n = 3 | Avg. Drug Content uniformity (%) \pm SD, n = 3 | Avg. uniform Drug Distribution (%) \pm SD, n = 3 | Avg. In Vitro Disintegration Time (sec) \pm SD, n = 3 | Avg. Folding Endurance \pm SD, n = 3 |
|--------|-----------------|--|--------------------------------|------------------------------------|--|--|--|---|--|
| QTPDT7 | Smooth | 98.00 \pm 0.88 | 6.4 \pm 0.27 | 0.15 \pm 0.003 | 1.18 \pm 0.065 | 99.32 \pm 0.289 | 96.32 \pm 0.382 | 72.17 \pm 0.22 | 193.00 \pm 3.46 |
| QTPDT8 | Flexible | 104.00 \pm 0.29 | 7.02 \pm 0.28 | 0.20 \pm 0.003 | 1.092 \pm 0.152 | 99.90 \pm 0.29 | 99.24 \pm 0.144 | 66.32 \pm 0.23 | 197.65 \pm 0.58 |
| QTPDT9 | Flexible | 110.00 \pm 0.53 | 7.01 \pm 0.87 | 0.22 \pm 0.003 | 2.638 \pm 0.058 | 99.73 \pm 0.50 | 99.24 \pm 0.289 | 26.20 \pm 0.10 | 198.00 \pm 3.63 |

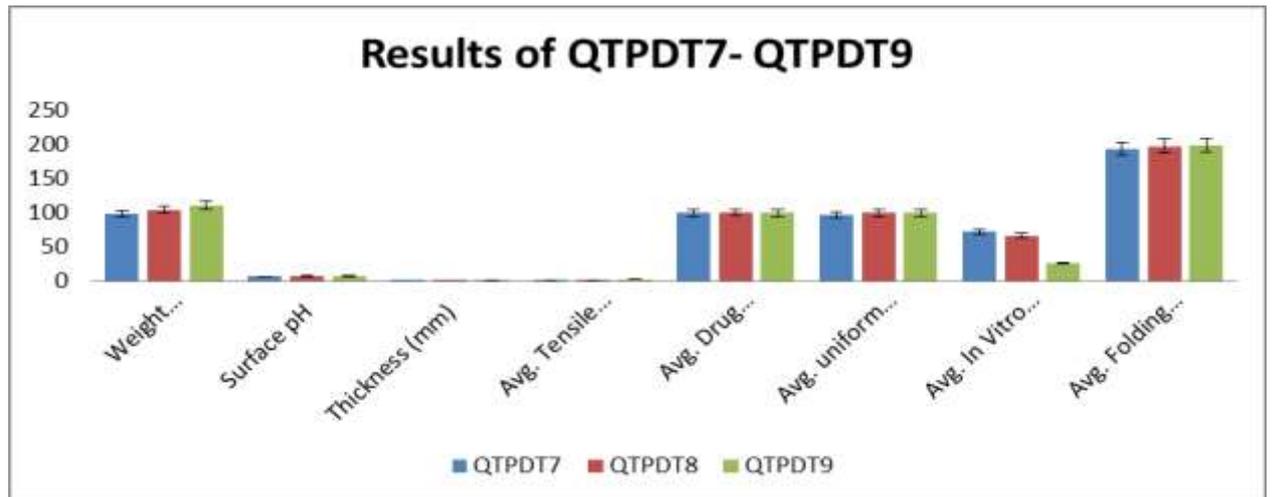


FIGURE 8.11 Results of QTPDT7- QTPDT9

Inference

The disintegration time for the clumps was best achieved with Kyron T-314 (mg), hence, 100mg was picked for the last MDF formation.

8.2.3. Preparation of QTP FMT Mouth Dissolving Film using Design of Experiment

PREPARATION OF MOUTH DISSOLVING FILM OF QTP FMT USING 3² FACTORIAL DESIGN

As expressed in the plan course of action Tables, a 3² complete factorial plan was utilized to explore the impact of free factors X1 (Poloxamer 407) and X2 (HPMC E50) on subordinate factors Y1 Elasticity (N/cm²), Y2 Breaking down Time (sec), and Y3 percent CDR (in 6 min). Two elements were evaluated at three levels (-1, 0, +1) in this plan, and each of the nine potential test clumps were figured out. Table shows the arrangement of each nine expected mixes of MDF of QTP FMT utilizing 3² full factorial designs.

TABLE 8. 21 Independent variable and their levels

| Factor code | Factor Name | Low (-1) | High (+1) |
|------------------------------|---------------------------------------|----------|-----------|
| Independent Variables | | | |
| X1 | Amount of P-407 (gm) | 0.01 | 0.020 |
| X2 | Amount of HPMC E50 (gm) | 0.250 | 0.350 |
| Dependent Variables | | | |
| Y1 | Tensile Strength (N/cm ²) | | |
| Y2 | Disintegration Time (sec) | | |
| Y3 | % CDR (in min) | | |

8.2.4. Validation Analysis of Predicted and Actual Batches QTP FMT MDF:

To improve the formulation, 3² complete factorial design is frequently used. Two factors were investigated in this design, each at three levels, and experimental trials were conducted on all nine conceivable combinations. Poloxamer 407 concentration (X1) and HPMC E50 concentration (X2) were chosen as independent variables. The dependent variables were Tensile Strength (Y1), Disintegrating Time (Y2), and In-vitro drug release (Y3). Conclusions can be drawn using polynomial equations. Table shows the results of the experimental design batches.

TABLE 8. 22 Batches Code of fast disintegrating films of QTP FMT

| Ingredients | QTPOF1 | QTPOF2 | QTPOF3 | QTPOF4 | QTPOF5 | QTPOF6 | QTPOF7 | QTPOF8 | QTPOF9 |
|-------------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| Poloxamer (mg)-X1 | +1 | -1 | 0 | 0 | +1 | -1 | -1 | 0 | +1 |
| HPMC E50 (mg)-X2 | -1 | -1 | -1 | 0 | 0 | 0 | +1 | +1 | +1 |

TABLE 8. 23 Batches concentrations of fast disintegrating films of QTP FMT

| Ingredients | QTPOF 1 | QTPOF 2 | QTPOF 3 | QTPOF 4 | QTPOF 5 | QTPOF 6 | QTPOF 7 | QTPOF 8 | QTPOF 9 |
|-----------------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| Drug (gm) | 0.184 | | | | | | | | |
| Poloxamer 407 (gm) | 0.020 | 0.010 | 0.015 | 0.015 | 0.020 | 0.010 | 0.010 | 0.015 | 0.020 |
| HPMC E50 (gm) | 0.250 | | | 0.300 | | | 0.350 | | |
| Kyron T-314 (gm) | 0.1 | | | | | | | | |
| Aspartame (gm) | 0.040 | | | | | | | | |
| Citric acid (gm) | 0.070 | | | | | | | | |
| Tween 20 (gm) | 0.050 | | | | | | | | |
| Vanillin (gm) | 0.050 | | | | | | | | |
| Distilled water (ml) | 10 | | | | | | | | |

8.2.5.3 Optimization of the Formulation

8.2.5.3.1 Formulation optimization by 3² factorial designs

Master Planning Programming The product variant 8.0.7.1 was utilized, and the outcomes from the underlying clumps yielded an aggregate of nine mouth dissolving film types. Table shows the outcomes. The wide reach showed the mouth dissolving film's veritable characteristics.

TABLE 8. 24 Evaluation parameters of factorial design batches QTPOF1- QTPOF9

| Formulation Code | Avg. Weight (mg) (Mean \pm SD), n=3 | Avg. uniform Drug Distribution (%) (Mean \pm SD), n = 3 | Avg. Drug Content uniformity (%) (Mean \pm SD), n = 3 |
|------------------|---------------------------------------|---|---|
| QTPOF1 | 105.83 \pm 0.236 | 96.33 \pm 1.22 | 97.30 \pm 0.16 |
| QTPOF2 | 103.65 \pm 1.13 | 97.42 \pm 0.01 | 98.25 \pm 0.31 |
| QTPOF3 | 105.82 \pm 0.19 | 96.90 \pm 0.19 | 99.65 \pm 0.16 |
| QTPOF4 | 102.15 \pm 0.40 | 95.00 \pm 0.15 | 98.9 \pm 0.24 |
| QTPOF5 | 98.00 \pm 0.02 | 97.73 \pm 0.38 | 97.97 \pm 0.11 |
| QTPOF6 | 101.61 \pm 0.24 | 96.40 \pm 0.48 | 97.97 \pm 0.55 |
| QTPOF7 | 102.31 \pm 0.14 | 96.00 \pm 0.06 | 99.09 \pm 0.01 |
| QTPOF8 | 99.35 \pm 1.04 | 98.00 \pm 0.46 | 97.65 \pm 0.76 |
| QTPOF9 | 106.15 \pm 0.16 | 96.62 \pm 0.06 | 97.21 \pm 0.36 |

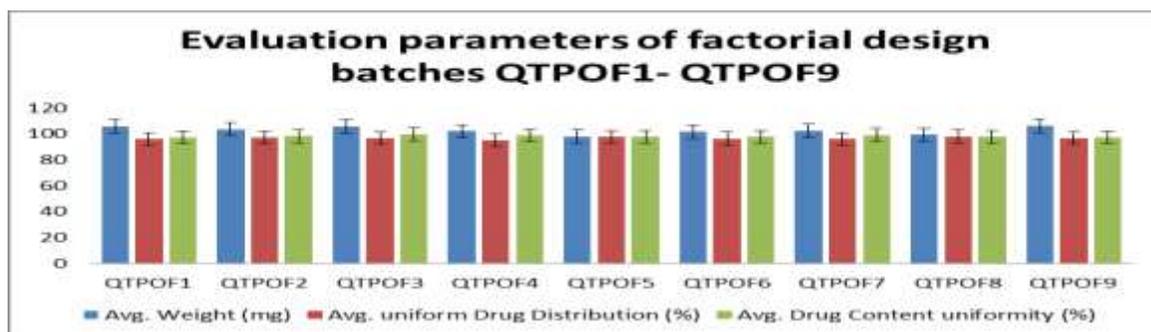


FIGURE 8. 12 Evaluation parameters of factorial design batches QTPOF1- QTPOF9

TABLE 8. 25 Evaluation parameters of factorial design batches QTPOF1- QTPOF9

| Formulation Code | Avg. Surface pH (Mean \pm SD), n = 3 | Avg. Thickness (mm) (Mean \pm SD), n = 3 | Avg. Folding Endurance (Mean \pm SD), n = 3 (Y ₁) |
|------------------|--|--|---|
| QTPOF1 | 6.70 \pm 0.26 | 0.15 \pm 0.01 | 144.00 \pm 1 |
| QTPOF2 | 6.74 \pm 0.13 | 0.16 \pm 0.02 | 146.00 \pm 2 |
| QTPOF3 | 6.82 \pm 0.05 | 0.17 \pm 0.03 | 149.00 \pm 5 |
| QTPOF4 | 6.7 \pm 0.19 | 0.21 \pm 0.01 | 155.00 \pm 4 |
| QTPOF5 | 6.72 \pm 0.02 | 0.22 \pm 0.02 | 158.00 \pm 1 |
| QTPOF6 | 6.81 \pm 0.25 | 0.24 \pm 0.01 | 159.00 \pm 1 |
| QTPOF7 | 6.74 \pm 0.15 | 0.28 \pm 0.02 | 164.00 \pm 3 |
| QTPOF8 | 6.71 \pm 0.08 | 0.31 \pm 0.3 | 167.00 \pm 5 |
| QTPOF9 | 6.70 \pm 0.26 | 0.33 \pm 0.04 | 169.00 \pm 2 |

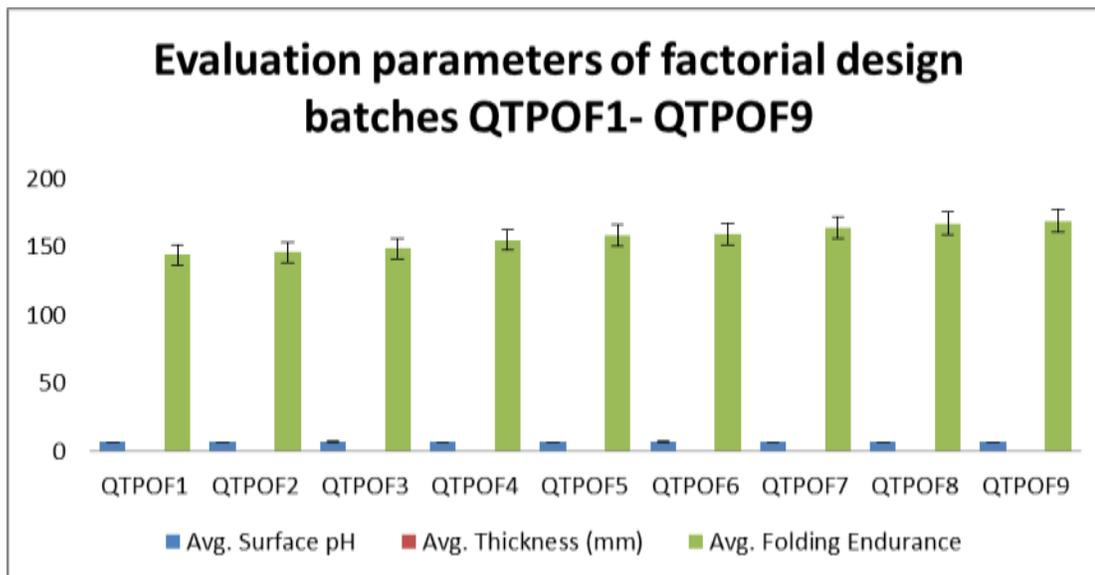


FIGURE 8. 13 Evaluation parameters of factorial design batches QTPOF1- QTPOF9

TABLE 8.26 Optimization of fast disintegrating films of QTP FMT using 3² Full factorial design QTPOF1-QTPOF9

| Formulation Code | Y1: Tensile strength (N/cm ²) | Y2: Disintegration Time (sec) | Y3: %CDR (In 6 min) |
|------------------|---|----------------------------------|---------------------------|
| QTPOF1 | 1.092±1.14 | 23.47±0.3 | 98.34±1.0 |
| QTPOF2 | 1.230±0.16 | 27.90±1.4 | 98.82±0.14 |
| QTPOF3 | 1.582±1.47 | 24.15±1.6 | 99.06±1.25 |
| QTPOF4 | 1.091±1.59 | 20.55±1.14 | 98.06±1.15 |
| QTPOF5 | 1.091±1.15 | 22.51±1.67 | 96.30±1.26 |
| QTPOF6 | 1.16±0.47 | 21.23±0.15 | 97.90±0.16 |
| QTPOF7 | 2.637±1.26 | 28.20±1.05 | 95.61±1.16 |
| QTPOF8 | 2.46±0.68 | 29.32±0.74 | 94.40±0.16 |
| QTPOF9 | 2.230±1.16 | 32.31±1.59 | 92.61±1.37 |

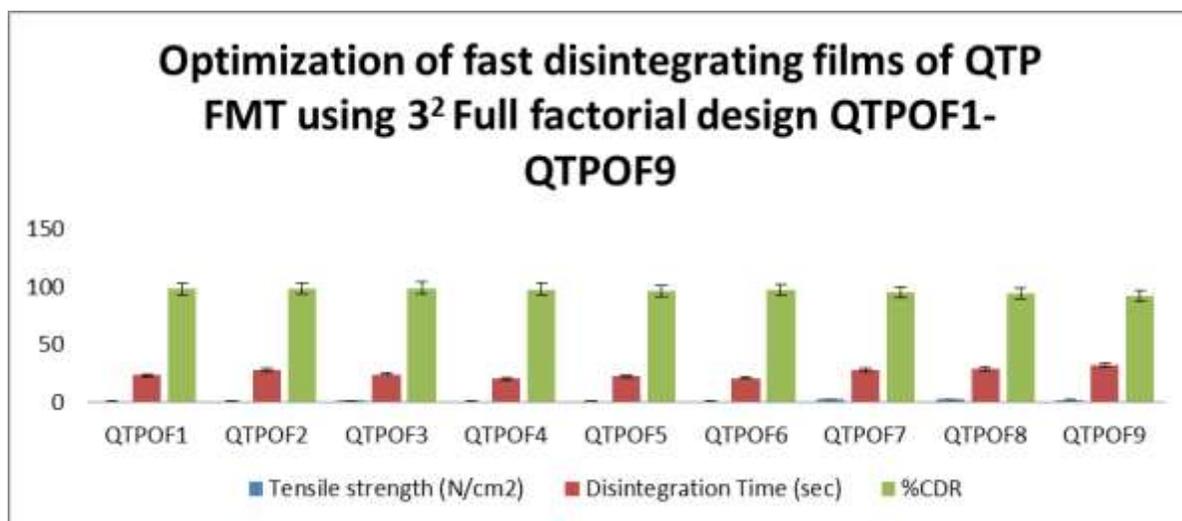


FIGURE 8.14 Optimization of fast disintegrating films of QTP FMT using 3² Full factorial design QTPOF1-QTPOF9

Statistical Analysis:

TABLE 8. 27 Model Selection

| Responses | Source | SD | R ² | Adj. R ² | Pred. R ² | PRESS | Suggested Model |
|-----------|-----------|-------|----------------|---------------------|----------------------|--------|-----------------|
| Y1: TS | Linear | 0.46 | 0.613 | 0.484 | 0.250 | 2.5 | |
| | 2FI | 0.50 | 0.618 | 0.389 | -0.047 | 3.5 | |
| | Quadratic | 0.18 | 0.972 | 0.926 | 0.708 | 1.0 | Suggested |
| | Cubic | 0.18 | 0.990 | 0.918 | -0.862 | 6.2 | Aliased |
| Y2: DT | Linear | 4.035 | 0.2596 | 0.013 | -0.726 | 227.73 | |
| | 2FI | 3.985 | 0.3982 | 0.037 | -1.661 | 351.10 | |
| | Quadratic | 0.532 | 0.9936 | 0.983 | 0.922 | 10.34 | Suggested |
| | Cubic | 0.045 | 1.0000 | 1.000 | 0.9972 | 0.369 | Aliased |
| Y3: %CDR | Linear | 0.835 | 0.8934 | 0.858 | 0.743 | 10.09 | |
| | 2FI | 0.721 | 0.9339 | 0.894 | 0.727 | 10.73 | |
| | Quadratic | 0.244 | 0.9955 | 0.988 | 0.964 | 1.43 | Suggested |
| | Cubic | 0.397 | 0.9960 | 0.968 | 0.2697 | 28.676 | Aliased |

TABLE 8. 28 Model coefficients and respective P-value

| Model term | Y1: TS | | Y2: DT | | | Y3: %CDR | | | |
|------------|-------------|---------------|---------------|-------------|-----------------|---------------|-------------|---------|---------------|
| | Full model | | Reduced Model | Full model | | Reduced Model | Full model | | Reduced Model |
| | coefficient | p-value | Coefficient | Coefficient | p-value | Coefficient | Coefficient | p-value | Coefficient |
| C | 1.216 | 0.015 | 1.122 | 20.60 | 0.0017 | - | 97.806 | 0.001 | - |
| X1 | -0.105 | 0.239* | - | 0.17 | 0.4948*# | - | -0.847 | 0.0034 | - |
| X2 | 0.574 | 0.004 | 0.5738 | 2.38 | 0.0016 | - | -2.265 | 0.0002 | - |
| X1X2 | -0.067 | 0.501* | - | 2.14 | 0.0040 | - | -0.630 | 0.0141 | - |
| X11 | -0.141 | 0.340* | - | 1.26 | 0.0445 | - | -0.573 | 0.0449 | - |
| X22 | 0.755 | 0.009 | 0.7545 | 6.14 | 0.0005 | - | -0.938 | 0.0122 | - |

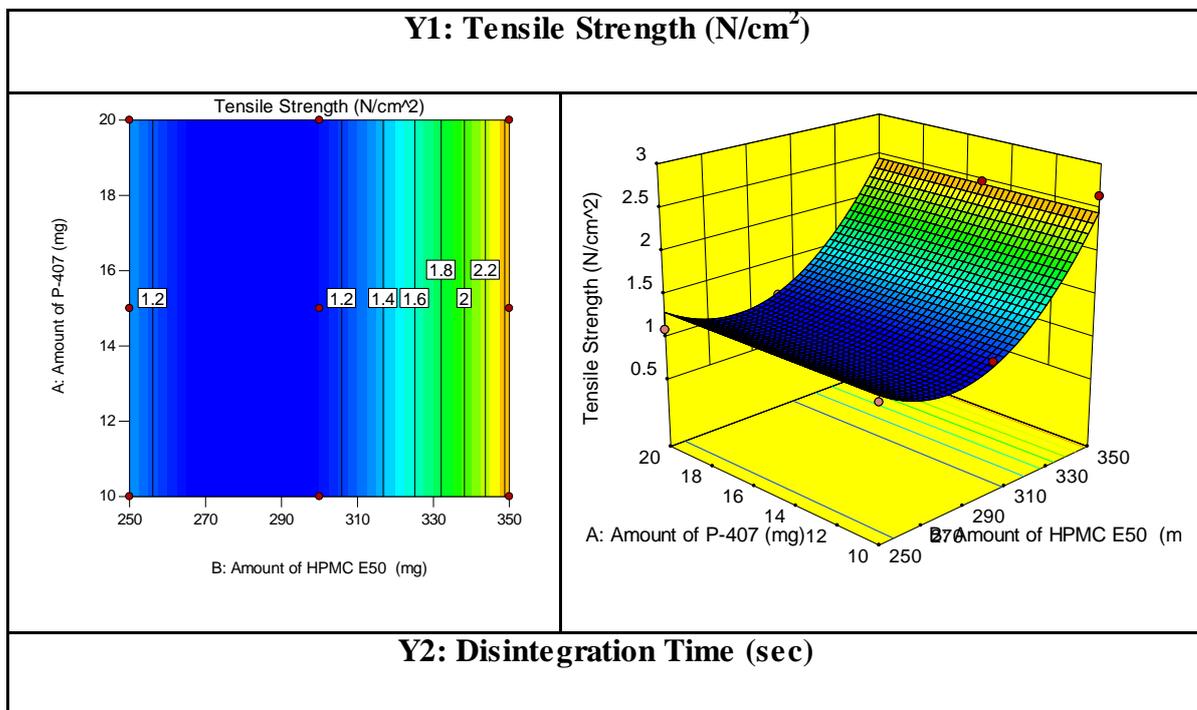
*Not significant ($p > 0.05$),

*# not significant but retained in model to maintain hierarchy

TABLE 8. 29 Regression analysis

| Model parameters | Y1: PS | | Y2: PDI | | Y3: EE | |
|---------------------|------------|---------------|------------|---------------|------------|---------------|
| | Full model | Reduced Model | Full model | Reduced Model | Full model | Reduced Model |
| df | 5 | 2 | 5 | 5 | 5 | 5 |
| F-value | 20.89 | 42.97 | 92.61 | 92.61 | 131.33 | 131.33 |
| P-value (model) | 0.0154 | 0.0003 | 0.0017 | 0.0017 | 0.0010 | 0.0010 |
| R ² | 0.9721 | 0.9347 | 0.9936 | 0.9936 | 0.9955 | 0.9955 |
| SSE | 0.0930 | 0.2174 | 0.8492 | 0.8492 | 0.1786 | 0.1786 |
| MSE | 0.0310 | 0.0362 | 0.2831 | 0.2831 | 0.0595 | 0.0595 |
| No. of term omitted | 3 | | 0 | | 0 | |

8.2.5.3.2 Effect on Responses Y1, Y2 & Y3



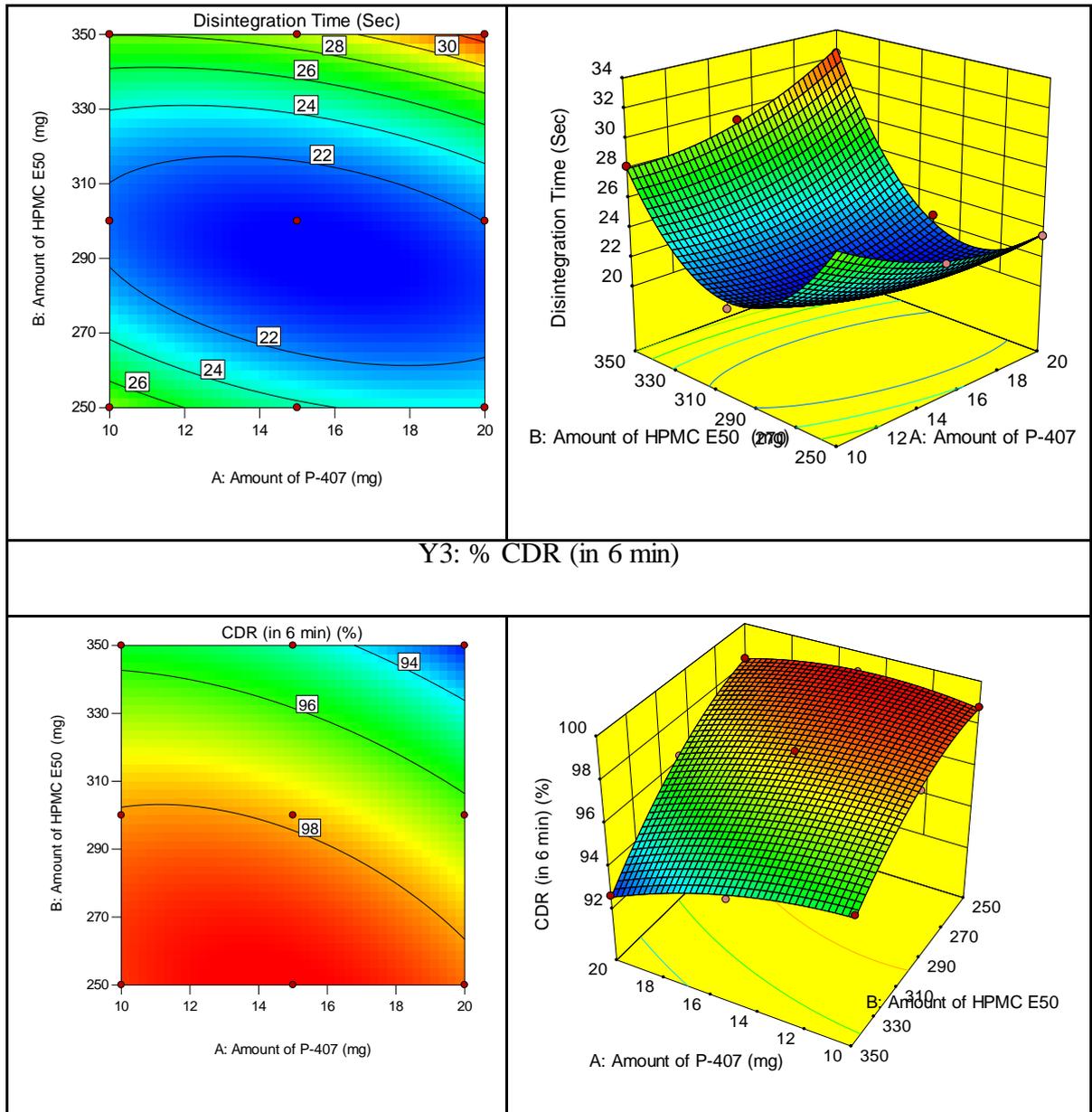


FIGURE 8.15 Surface Response Plot & 3D Surface Plot

The information showed was produced utilizing programming, and the surface plot and reaction surface plot were made utilizing a factorial plan. Fig. 8.15 shows the Surface plot of the variable's effect on responses Y1, Y2, and Y3, as well as the Reaction surface plot of the variable's effect on responses Y1, Y2, and Y3.

TABLE 8. 30 Optimization Target

| Responses | Target given for optimization |
|-----------|-------------------------------|
| Y1: TS | Maximize |
| Y2: DT | Minimize |
| Y3: %CDR | Maximize |

TABLE 8. 31 Checkpoint analysis

| Response | Type of Value | QTPOF10 | QTPOF11 |
|----------|---------------|--------------------|--------------------|
| | | Desirability= 1 | Desirability= 1 |
| | | X1= 10.58 | X1= 17.07 |
| | | X2= 335.32 | X2= 250 |
| Y1: TS | Predicted | 1.9 | 1.3 |
| | Observed | 2.01 | 1.21 |
| | % Error | -5.79 | 6.92 |
| Y2: DT | Predicted | 24.85 | 23.76 |
| | Observed | 25.35 | 22.78 |
| | % Error | -2.01 | 4.12 |
| Y3: %CDR | Predicted | 96.43 | 98.94 |
| | Observed | 98.81 | 99.92 |
| | % Error | -2.47 | -0.99 |

An anticipated worth and noticed worth are essentially indistinguishable because of the designated spot clump. QTPOF11 is the designated spot group with the best. Accordingly, it is viewed as a cluster that has been improved. The mouth dissolving film was made with this group.

TABLE 8. 32 Evaluation of mouth dissolving film

| Sr. No | Evaluation parameter | Results |
|--------|----------------------|-------------|
| 1. | Weight variation(mg) | 105.24±0.01 |
| 2. | Thickness (mm) | 0.20±0.02 |
| 3. | Folding endurance | 160±2.00 |
| 4. | Surface pH | 6.7±0.04 |
| 5. | Drug content (%) | 99.12±0.10 |



FIGURE 8. 16 SEM OF QTPOF11

TABLE 8. 33 Flux and permeability co-efficient of QTPOF11

| Time (Mins) | Batch QTOPF11 | |
|-------------|-----------------------------------|--------------------------------|
| | Flux J (mg/cm ² /hr) | Permeability co-efficient (kP) |
| 0 | 0.000 | 0 |
| 1 | 0.773 | 0.035393 |
| 2 | 0.034 | 0.000454 |
| 3 | 0.008 | 0.000428 |
| 4 | 0.012 | 0.000672 |
| 5 | 0.023 | 0.00069 |
| 6 | 0.317 | 0.010454 |
| 7 | 0.053 | 0.002931 |

TABLE 8. 34 Kinetic analysis of release data of QTPOF11

| Model | Zero-Order | First-Order | Higuchi |
|----------------------------|------------|-------------|---------|
| R² value | 0.982 | 0.864 | 0.985 |
| Slope | 5.315 | 0.153 | 0.668 |
| Intercept | -0.221 | 0.575 | 1.884 |

The cumulative amount of drug permeated was fitted to Zero order and Higuchi model i.e. diffusion mechanism.

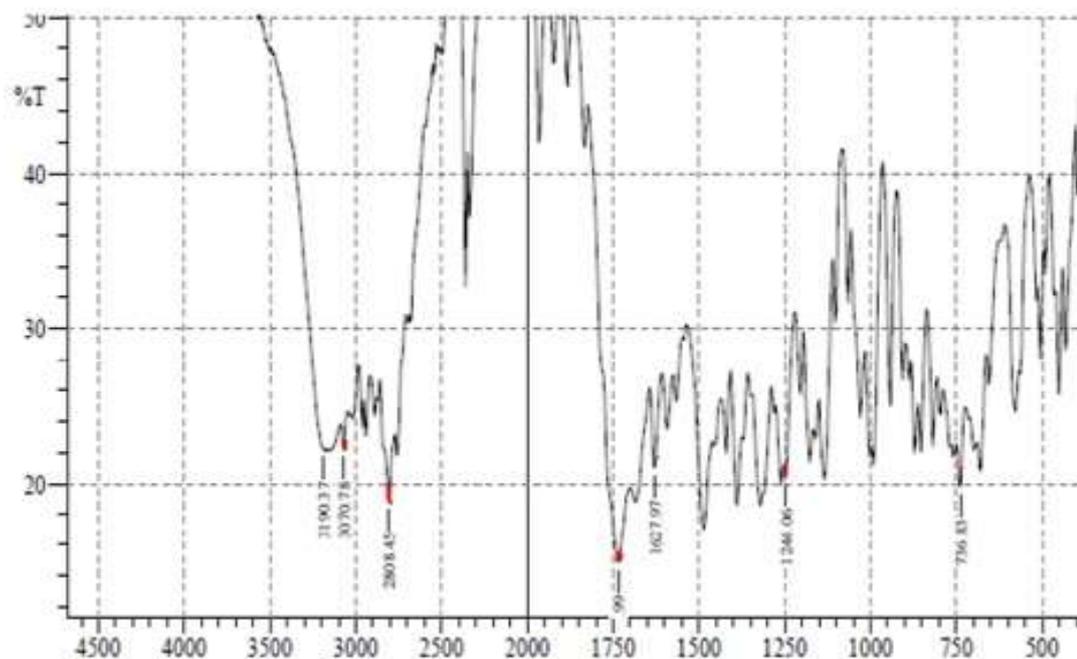


FIGURE 8. 17 FT-IR Study of Optimized MDF Formulation

8.6.2 Taste Evaluation Study by Spitting

Table sums up the discoveries of the taste assessment examination. The dirt and peevishness of the definition in the mouth were utilized to rate mouth feel in this review.

In all details, the normal mouth feel recommended a smooth to exceptionally smooth sensation. Still up in the air by the capacity to eliminate the film from the Alu pocket and spot it in the mouth without the utilization of water, which was considered patient-accommodating and phenomenal.

TABLE 8. 35 Results of Taste and Palatability Evaluation

| Sample Type | Mouth feel | Taste (Bitterness) | After taste | Ease of handling | Acceptance |
|--------------------------|----------------|--------------------|----------------|------------------|----------------|
| Test (Batch No. QTPOF11) | 4.36 ± 0.56 | 5.00 ± 0.00 | 4.68 ± 0.45 | 5.00 ± 0.00 | 5.00 ± 0.00 |

TABLE 8. 36 Comparison of optimized MDF with conventional marketed formulation

| Time (in mins) | % Drug release (QTPOF11) | % Drug release of Marketed Product (Qticare-25) |
|----------------|--------------------------|---|
| 0 | 0.0 | 0.0 |
| 1 | 0.477 ± 0.10 | 0.163 ± 0.11 |
| 2 | 8.924 ± 0.11 | 4.273 ± 0.07 |
| 3 | 16.75 ± 1.21 | 8.31 ± 0.22 |
| 4 | 55.51 ± 1.16 | 33.21 ± 1.31 |
| 5 | 84.35 ± 1.11 | 56.15 ± 1.11 |
| 6 | 99.25±0.16 | 61.00±0.33 |

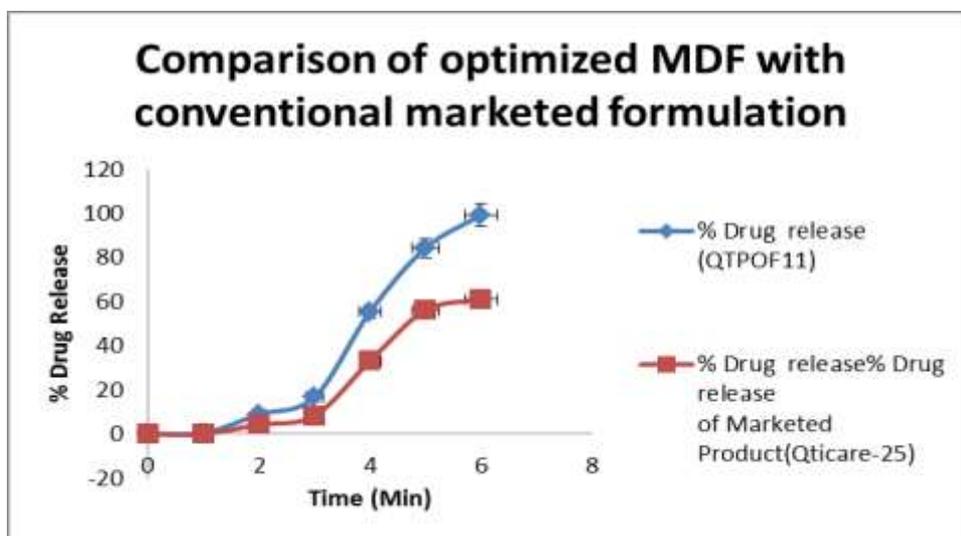
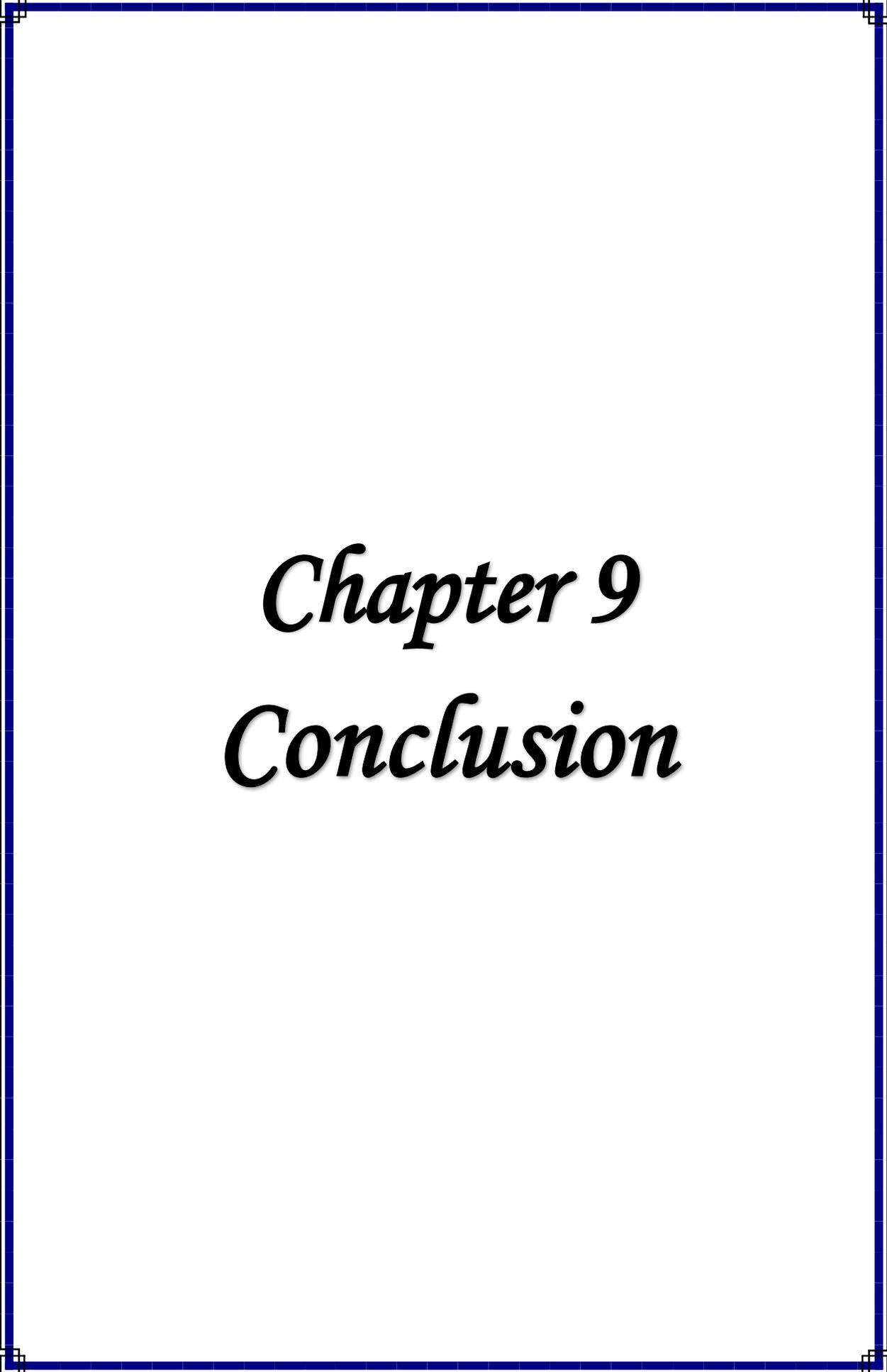


FIGURE 8. 18 Comparison of optimized MDF with conventional marketed formulation

8.6.3 Evaluation of optimized batch under stability study

TABLE 8. 37 Evaluation of optimized batch under stability study

| Stability Conditions | Sampling Time | Disintegration Time (sec \pm SD) | Drug Content (% \pm SD) | Tensile Strength (kg/cm ² \pm SD) | Visual Appearance |
|----------------------------|---------------|------------------------------------|---------------------------|--|-------------------|
| 40° C \pm 02° (Temp.) | Initial | 34.56 \pm 00.51 | 99.12 \pm 00.10 | 02.34 \pm 0.01 | Clear appearance |
| 75% \pm 05% RH | 03 months | 34.37 \pm 02.73 | 99.53 \pm 00.29 | 02.61 \pm 0.01 | Clear appearance |



Chapter 9
Conclusion

CHAPTER 9

CONCLUSION

9. Conclusion

To observe the best polymer for making quick dissolving strips of ZPO HCL and QTP FMT, various clusters of strips were made with various concentrations of polymer, disintegrating agents and plasticizer. These quick breaking down films were read up for their shape, weight variance, thickness, surface pH, elasticity, collapsing strength, percent drug content consistency, percent uniform medication dissemination and in-vitro drug release examinations. The plans of HPMC E5 and HPMC E50 0.1-0.5 gm polymer were browsed among 21 clusters of ZPO HCL and QTP FMT MDF in light of the assessed boundary. To observe the best plasticizer for making ZPO HCL and QTP FMT quick dissolving film, many groups of movies were made with various measures of plasticizer. Clumps of polyethylene glycol 400 (Stake 400) and Poloxamer 407 in the range of 1-2 ml were picked in view of the appraisal models. Besides, banana powder was picked as a fast disintegrating agent at a dose of 0.075 gm. These quick dissolving films were evaluated for their shape, weight variation, thickness, surface pH, elasticity, collapsing sturdiness, percent drug content consistency, percent uniform medication circulation and in-vitro drug release examinations. ZPO HCL and QTP FMT fast dissolving film were effectively made utilizing a 32 full factorial design with various definition mixes and was found to have great collapsing perseverance, breaking down time, percent drug discharge and other inspected measurements. The upgraded plan ZMDOF10 and QTPOF11 was shown to be steady for multi month under sped up strength conditions.

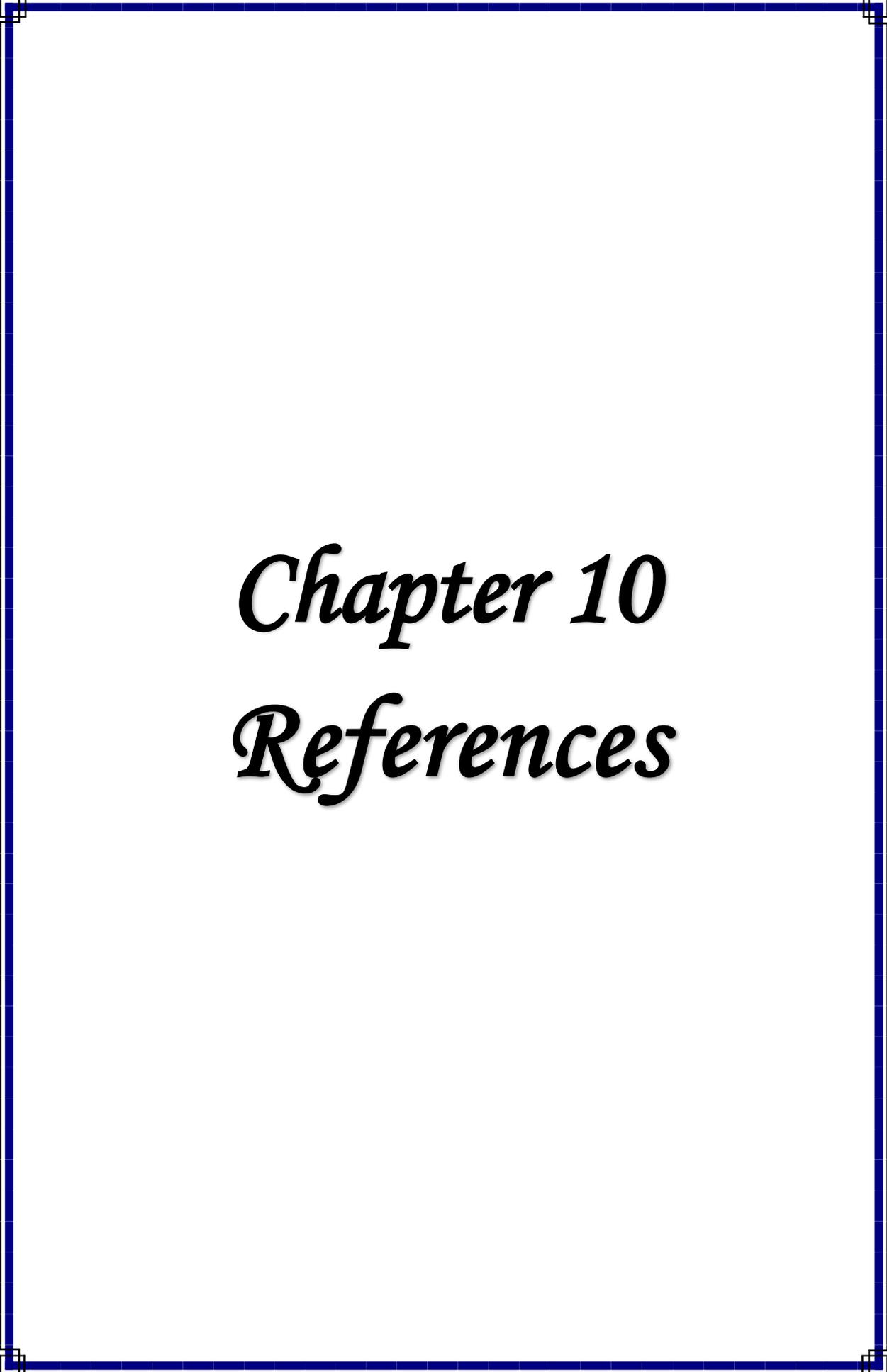
In the two details, every one of the measurements for taste assessment yielded positive discoveries. The subsequent film was meager and clear, with a smooth sensation and a decent sweet to severe taste. A 25-minute ex-vivo saturation investigation of the streamlined group was directed using the Franz Diffusion Cell.

Toward the finish of 15 minutes, over 80% of the drug had been delivered.

The consequences of the medication polymer communication uncovered that there was no interaction between the drugs and polymers. During a 90-day steadiness testing, the created definitions showed no change in percent drug content or actual qualities.

In view of the in-vitro characterization and ex-vivo permeation examination, it was resolved that Ziprasidone and Quetiapine Fumerate had a 80 % release rate and could be provided orally as a mouth dissolving film.

Therefore, the drug is delivered at the oral mouth cavity with a lower portion recurrence, bringing about better remedial adequacy.



Chapter 10
References

CHAPTER 10

REFERENCES

10. REFERENCES

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ABBREVIATION

| | |
|---|------------------|
| + | Sticky |
| - | Non-sticky |
| * | transparent |
| # | Semi-transparent |
| @ | non-transparent |

Appendix–A
List of
Publications

APPENDIX-A**LIST OF PUBLICATION**

| Sr. No | Title | Journal Name | Volumr & Issue | Year of Publication |
|---------------|--|---|---------------------------|----------------------------|
| 1 | Mouth Dissolving Film: A Comprehensive Review | International Journal of Pharmaceutical Research | 12(2) | 2020 |
| 2 | Critical Quality Attributes Analysis Study For Formulation of Quetiapine Mouth Dissolving Film | International Journal of Pharmaceutical Research | 12(3) | 2020 |
| 3 | Formulation and Development of Quetiapine Mouth Dissolving Films Using DoE Approach | International Journal of Pharmaceutical Research | 12(4) | 2020 |
| 4 | Formulation and Development of Ziprasidone Mouth Dissolving Films using DoE approach | World Journal of Pharmacy and Pharmaceutical Sciences | Article Accepted | |

Mouth Dissolving Film: A Comprehensive Review

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ABSTRACT

Oral administration of numerous medicinal dosage forms such as tablet, pill, syrup, solution, and emulsion is regarded one of the more convenient routes. Various rapid dissolving preparations, such as mouth dissolving film and MDT, have been created by Fast Dissolving Drug Delivery systems. Oral fast-dissolving film is a cutting-edge, patient-friendly, and innovative delivery technique. Due to its various comparative benefits of being cost-benefit, rapid dissolving without water aid, and substantially compliant to both geriatric and paediatric patients in emergency conditions and specialised diseases, the acceptance of this creative dosage form is growing day by day. Furthermore, it is a useful dosage form for drugs with pre-systemic metabolism and low bioavailability. The history, benefits, drawbacks, limitations, ideal qualities, classification, formulation considerations, manufacturing technique, assessment parameter, and commercial trends for oral fast dissolving films are all covered in this review article. Due to its unique properties, novel attributes, competitive position, and cost adequacy, it can be inferred that it is one of the fastest-growing dosage forms with a lot of potential, particularly for commercial application.

Keywords: Mouth Dissolving Film, Oral Administration, Bioavailability and Potential

INTRODUCTION

The oral route is the most acceptable in terms of patient compliance among the delivery methods. Many pharmaceutical companies have focused their research efforts on repurposing current medications in new dosage formulations. The oral film, a thin film made of hydrophilic polymers that dissolves quickly on the tongue or in the buccal cavity, is one such relatively recent dosage form. Formulating for youngsters has proven to be a difficult task. One of the most important elements impacting therapeutic regimen compliance is the palatability of paediatric oral drug formulations, among other things. (1,2) Systemic drug delivery can be as simple as using mouth dissolving films. The bypassing of the first pass effect and enhanced permeability due to well-supplied arterial and lymphatic drainage result in improved systemic bioavailability. The oral mucosa is also a very appealing and selective target for systemic drug delivery due to its huge surface areas of absorption, ease of ingesting and swallowing, and pain avoidance. For a wide range of patients, recent technological advancements have provided viable dose choices via the oral route. Buccal medication administration has recently become a popular method of drug administration. Bioadhesive mucosal dosage forms have been developed in a variety of ways. In the late 1970s, fast-dissolving

medication delivery systems were created as an alternative to tablets, capsules, and syrups for juvenile and geriatric patients who had difficulty ingesting typical oral solid-dosage forms. Fast dissolve, rapid dissolve, rapid melt, or quick disintegration are all terms used to describe the revolutionary technology of oral fast-dispersing dosage forms. All of these dose forms, however, serve the same purpose and have the same philosophy. An oral fast-dispersing or fast-dissolving dosage form is defined as a solid dosage form that dissolves or disintegrates quickly in the oral cavity, resulting in solution or suspension without the requirement for water administration. (3)

Advantages: (4-7)

- There's no danger of choking.
- Films for the mouth Give the mouth a wonderful feeling.
- Oral films are less fragile and more flexible, making them easier to travel, store, and handle.
- Because oral films do not require water to swallow, they are more widely accepted.
- Because the oral cavity has a wide surface area, the oral dose form disintegrates and dissolves quickly.
- Improve the dose form's stability.

Research Article

Critical Quality Attributes Analysis Study For Formulation Of Quetiapine Mouth Dissolving Film

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ABSTRACT:

The objective of the current work is to evaluate critical quality attributes (CQAs) of the mouth dissolving film of Quetiapine. It is ideally suitable for the treatment of emesis. Mouth dissolving dosage forms are gaining popularity in recent times, as these dosage forms requires no water for administration. To develop mouth dissolving films (MDF) of Quetiapine with aim of fast disintegration, dissolution and mechanical strength. Various types and concentration of Polymers, Plasticizers and disintegrating agent were used to check their effect on MDF. Films were prepared by solvent casting technique. Parameters like in-vitro disintegration time, tensile strength, content uniformity, folding endurance, swelling index, and in-vitro drug release were evaluated. The optimized film containing HPMC E5 & PEG- 400 was taken for further evaluation. In-vitro dissolution studies showed that of 96.37 ± 1.21 of Quetiapine was released within 5 min with an average disintegration time of 25 sec. FTIR spectrophotometry were used to identify drug-excipient interactions.

Keywords: Quetiapine, Mouth Dissolving Films (MDF), Critical Quality Attributes (CQAs), In-vitro dissolution studies

INTRODUCTION

Oral route is one of the most preferred routes of drug administration due to its safety, ease of administration, and acceptability by patients. About 60% of conventional dosage forms are available as the oral solid dosage forms.(1) Orally dissolving strips and films are useful in patients such as paediatrics, geriatrics, bedridden, and emetic patients and conditions such as sudden episodes of allergic attacks or coughing. They can be used for local and systemic delivery. (2,3) There is an increasing interest in the development of orally dissolving film and strips as an alternative to fast dissolving tablets, due to their faster dissolution rate, higher flexibility, and better patient compliance. Presently research work on the use of orally dissolving films as promising carriers for the delivery of multiple active pharmaceutical ingredients has emerged.(4-6) Marketed orally dissolving films products have also become available including Listerine, Chloraseptic, Triaminic, and multivitamins. The backbone of an orally dissolving film is generally formed of a plasticizer and film forming polymer or a mixture of polymers that provide the necessary elasticity and shape to the film. (7)

Fast disintegrating films are most advance form of solid dosage form due to its flexibility. It improves efficacy of active pharmaceutical

ingredients disintegrate in the short duration oral cavity after the contact with less amount of saliva as compared to dissolving tablets. (8,9) This delivery system consists of the thin film which is kept on tongue or mucosal tissue, which instantly wet by saliva, the film rapidly disintegrates to release the medication for oral mucosal absorption. (10) Fast disintegrating film is prepared using hydrophilic polymer that rapidly disintegrates for buccal cavity, delivering the drug to the systemic circulation via buccal mucosa. The fast disintegrating drug delivery system are specially designed for the drugs which have extensive first pass metabolism and have low dose, for the enhancement of bioavailability.(11-14)

Psychosis is a condition characterized by the hallucination, dementia etc. seizures. It requires quick management of in order to avoid the risk of permanent brain damage. Pharmacotherapy with anti-psychotic drugs remains the major treatment modality for psychosis. Management of Psychosis differs from the treatment of other diseased conditions. Newer Anti-psychotic is an ideal drug candidate for an orally dissolving film formulation.(15) The formulation of anti-psychotic as an orally dissolving strip, required to be placed on the patient's tongue without swallowing for dose administration, would significantly facilitate

Formulation And Development Of Quetiapine Mouth Dissolving Films Using Doe Approach

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ABSTRACT:

The objective of the current work is to formulate and evaluate the mouth dissolving film of Quetiapine. It is ideally suitable for the treatment of emesis. Mouth dissolving dosage forms are gaining popularity in recent times, as these dosage forms requires no water for administration. develop mouth dissolving films (MDF) of Quetiapine for the treatment of hypertension, with fast disintegration, optimum morphological properties, and mechanical strength. HPMC E5, PEG- 400 were used as the hydrophilic film-forming polymeric bases. Films were prepared by solvent casting technique. Parameters like in-vitro disintegration time, tensile strength, content uniformity, folding endurance, swelling index, and in-vitro drug release were evaluated. 3² factorial design was used to optimize the amounts of the polymer and the plasticizer. In-vitro dissolution studies showed that 96.37±1.21 of Quetiapine was released within 5 min with an average disintegration time of 25 sec. FTIR spectrophotometry were used to identify drug-excipient interactions.

Keywords: Quetiapine, Mouth Dissolving Films (MDF), 3² factorial design, In-vitro dissolution studies

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Appendix-B
List of Conference
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APPENDIX-B

LIST OF CONFERENCES ATTENDED

| Sr. No | Conference | Duration | Organized By |
|--------|---|-----------------------------------|---|
| 1 | Nanotechnology and its Application to Ocular Drug Delivery Systems | 28-30 th January, 2019 | Maliba Pharmacy College, UKA Tarsadia University, Gujarat. |
| 2 | Nanotechnology in the Pharmaceutical Sphere: Contemporary Approaches and Therapeutic Applications | 30 th January 2021 | Shree Naranjibhai Lalbhai Patel College of Pharmacy, UmraKh |

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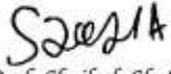
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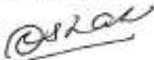
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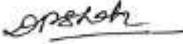
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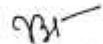
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on the 30th day of January 2021.


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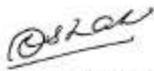
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Appendix-C
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APPENDIX-C

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2 Research is no longer game of chance or just limited to availability of new technology. It is never outcome of single individual's talent or efforts but it is one-of-a-kind process of meditation. I firstly thank Goddess XYZ to give me this opportunity to show my intellect and wisdom toward study and give me capacity to fulfil this project work. I have seen and experienced countless blessing showered on me by my parents, my guide, all other teachers, friends and all my well-wishers knowing that God's hand is there, always guiding me and leading me to greater heights. It provides me pleasure to convey my gratitude to all those who have directly or indirectly contributed to make this work success. I must make special mention of some of personalities and acknowledge my sincere indebtedness to them. With great sense of gratitude, I take this opportunity to thank my guide, XYZ. I want to thank my guide for his timely suggestions, generous and friendly nature, persistent encouragement, critical remarks and counsel during whole course of this work. Apart from guidance about research work, he also gave his personalized guidance and hearty support in matter of living happy and trustworthy life. His trust and scientific excitement towards me in most important moments of making right decisions and I am glad to work with him. I express my sincere gratitude to him who has enlightened my ideas and Resolved doubt regarding my dissertation. I was fortunate to have opportunity to work under his guidance. I would like to express my sincere thanks to all office bearer of XYZ for providing facility for my research work. My immediate and present attempt here is to acknowledge each one of them individually and institutionally. I heartily thanks peon of our college for their involvement and friendly attitude with instance support during my entire project work. I bow down with reverence to my parents, who always provided me with moral and they were actual driving force that enabled me to reach this stage. Parents are always perpetual source of inspiration and encouragement. No words can ever express what their constant undemanding love, sacrifice, dedication and prayers have done to help me achieve whatever I am today. I am thankful for their selfless love, good wishes, prayers and great sacrifices towards pursuit of my education.

3 I am very much thankful to XYZ. I am very Thankful to Director of XYZ for providing API. Thank you all once again!!! Mrs. Megha Gupta Date:

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23 Abstract: Quetiapine fumarate and Ziprasidone Hydrochloride is novel abnormal antipsychotic that has been proven to be beneficial in treating schizophrenia. intention of current learn about used to be to enhance quick disintegrating Quetiapine fumarate and Ziprasidone Hydrochloride movie by means of usage of quite number polymers with shorter disintegration time and larger drug launch with prospect of supporting number sufferers who have subject in swallowing traditional dosage varieties & decorate bioavailability of drug and rapid onset of action. MDFs additionally provide higher comfort to sufferers with intellectual illness, as properly as paediatric, elderly, and developmentally disabled patients. MDFs had been formulated usage of solvent casting technique. 32 full factorial layout used to be utilized to pick optimized MDF, utilising Design-Expert® software program (Stat-Ease Inc., Minneapolis, MN, USA). optimized MDF tensile strength, elongation, disintegration time, and three dissolved after 6 min. This optimized MDF was once subjected to in vitro dissolution, ex vivo permeation, stability. p.c CDR of optimized MDF in assessment with market method used to be found 97% & 99% in 6 mins. These findings proven success of MDFs loaded with Quetiapine fumarate and Ziprasidone Hydrochloride. Keywords: Mouth Dissolving Film, Quetiapine fumarate, Ziprasidone Hydrochloride, schizophrenia.

1

2.1. Introduction 1.1. Introduction of Novel Drug Delivery [1-5] The manner in which medication is administered can have giant effect on on its efficacy. Some tablets have best attention vary inside which they supply most benefit, however quantities outdoor of this vary may additionally be poisonous or furnish no therapeutic benefit. Limited development in efficacy of extreme sickness treatment, on different hand, has highlighted want for multidisciplinary strategy to therapeutic shipping to tissue targets. As result, new techniques to pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, bio-recognition, and medicinal drug efficacy arose. Drug transport structures (DDS) are new multidisciplinary methodologies that mix polymer science, pharmaceuticals, bio-conjugate chemistry, and molecular biology. Various drug transport and drug focused on structures are now being developed in order to forestall drug degradation and loss, take away extreme negative effects, and expand drug bioavailability and proportion of drug amassed in required zone. Controlled and special drug delivery, beforehand basically pipe dream or possibility, is now reality. During preceding decade and half, pharmaceutical and different scientists carried out considerable and intensive lookup in this subject of medicine research. Examples of drug carriers encompass soluble polymers, insoluble or biodegradable microparticles, herbal and artificial polymers, microcapsules, cells, telephone ghosts, lipoproteins, liposomes, and micelles. carriers can be designed to decay slowly, reply to stimuli (such as pH or temperature), and even be centered to particular humans (e.g., by using conjugating them with precise antibodies towards positive attribute elements of vicinity of interest). Targeting refers to potential to direct drug-loaded gadget to particular region. There are two integral methods for addressing favored areas for drug release. Targeting can be divided into two categories: passive and active. 1.1.1 Advantages Of Novel Drug Delivery System [6-15] 1. Protection against chemical and physical deterioration. 2. Consistent delivery. 3. Better dispersion of tissue macrophages.

3 4. Stability is improved. 5. Improved pharmacological activity. 6. Toxic-free protection. 7. Increased bioavailability. 8. Increasing solubility Any drug delivery system can be defined as one that includes: a) drug formulation, b) medical device or dosage form/technology used to transport medication inside body, and c) mechanism used to release drug. The normal method of medication conveyance is to form medication into reasonable structure, like squashed tablet for oral organization or answer for intravenous infusion. Expanded measurements necessities, lower viability, poisonousness, and disagreeable aftereffects have all been exhibited to be significant inconveniences of these portion plans. New medication conveyance strategies have been made or are being created to tackle restrictions of conventional medication organization frameworks to address issues of medical care calling. Two sorts of frameworks exist: controlled medication discharge frameworks and designated medicine conveyance frameworks. 1.1.2 therapeutic benefits of these new systems include: [15-20] • Increased therapeutic efficacy Site-specific delivery Reduced toxicity/side effects • Enhanced convenience • Viable therapy for diseases that were previously incurable • Possibility of using it as preventative measure • Patient compliance is improved. 1.1.3 Various Drug Delivery Systems: Carrier based Drug Delivery System [21-25] A) Liposomes B) Nanoparticles C) Microspheres D) Monoclonal antibodies E) Niosomes

4 F) Resealed erythrocytes as drug carriers 1.2 Introduction of Immediate Release Dosage Form [26-29] In this review and exploration, novel medication conveyance techniques are being created to extend markets/signs, protract item life cycles, and produce amazing open doors. Oral organization is favored strategy for foundational impacts because of its usability, absence of agony, assortment, and, above all, patient consistence. These strong definitions are more affordable to make since they don't need sterile circumstances. As result of patient consistence, high accuracy dose, and creation economy, tablets are suggested strong portion structure. Excipients and hardware choices will be seriously impacted in event that strong measurements structure advancements change in response to noteworthy enhancements in drug improvement, like genomics. advancement of further developed oral protein conveyance innovation as moment discharge tablets that can deliver prescriptions all more rapidly is particularly encouraging for ineffectively dissolvable medications like high atomic weight protein and peptide. oral course stays best course for directing helpful specialists because of its minimal expense of treatment, simplicity of assembling, and simplicity of organization. Therefore, patient consistence is very high. Numerous patients require quick beginning of activity in particular restorative condition, requiring prescription delivery at earliest opportunity. About portion of populace is impacted, bringing about high pace of insufficient treatment. 1.2.1 Definition [30-33] Prompt delivery tablets are those that disintegrate and break up quick, delivering medication. To empower prompt delivery, satisfactory chemically OK diluent or transporter might be used, same length as diluent or transporter doesn't significantly dial back drug discharge or potentially retention. Definitions that have been changed to give "adjusted," "controlled," "supported," "delayed," "expanded," or "postponed" drug discharge, are excluded from this classification. 1.2.2 Pharmacokinetics [34-35] This field researches assimilation, conveyance, digestion, and discharge. rate and measure of retention are significant on grounds that medication focus arrives at restorative levels following assimilation and subsequently advances pharmacological movement. Customary portion definitions slow crumbling, bringing about quick

5 disintegration. Tissue porousness, perfusion rate, drug restricting to tissue, disease status, drug cooperation, and different factors all impact medicine circulation. The length and strength of not entirely set in stone by pace of medication leeway from body or site of activity, for example biotransformation. lessening in liver volume and provincial blood stream to liver eases back drug biotransformation through oxidation, decrease, and hydrolysis. half-existence of medications released by kidneys increments as renal freedom eases back. 1.2.3 Pharmacodynamic Drug gathering communication is disabled in both old and youthful grown-ups on grounds that to atypical organ advancement. Antihypertensive drugs like prazosin can hinder body's ability to react to reflexive boosts, lessen heart result, and produce orthostatic hypotension. awareness of cardiovascular framework to - adrenergic agonists and enemies has lessened. At point when anti-microbials are given, resistance is brought down and considered. Theophylline bronchodilator activity is decreased in older, and they are more powerless against barbiturates than more youthful people. In older, associative illnesses are far reaching, and this is considered when few pharmacological treatments are utilized. 1.2.4 Criteria for Immediate Release Drug Delivery System [36-37] ✓ Immediate release dosage form should: ✓ In case of solid dosage, it should dissolve or disintegrate quickly in stomach. ✓ It should be compatible with taste masking in case of liquid dose forms. ✓ Be portable without worrying about fragility. ✓ Have pleasant taste in your tongue. ✓ After oral administration, it should leave little or no residue in mouth. ✓ Low sensitivity to environmental factors such as humidity and temperature ✓ Be produced at minimal cost utilising traditional processing and packaging equipment ✓ Rapid solubility and absorption of drug, resulting in quick commencement of effect. 1.2.5 Merits of Immediate Release Drug Delivery System [38] ✓ Added convenience/improved compliance

6 ✓ Stability and bioavailability have both improved. ✓ Allows for high drug loading and is suitable for controlled/sustained release actives. ✓ Ability to give liquid medicinal benefits in form of solid formulation. ✓ Adaptable and compatible with existing processing and packaging equipment Economical ✓ Reduced disintegration and dissolving times for instant release oral dosage forms; improved solubility of medicinal content. 1.3 Other Excipients [39-40] Excipients balance qualities of actives in quick delivery dose structures. exhaustive comprehension of science of these excipients is fundamental to keep away from cooperations with actives. One more test looked by formulators is laying out expense of these synthetics. Excipients are fundamental in advancement of quick softening tablets. These dormant food-grade synthetics give appropriate organoleptic highlights and item execution when included detailing. Excipients, except for certain actives that require veiling specialists, are general and can be utilized for wide scope of actives. 1.3.1 Bulking Materials Building materials are vital in development of quick dissolving tablets. substance can be utilized as diluent, filler, or cost-cutting specialist. Building specialists further develop arrangement's textural properties, bringing about better breakdown in mouth. Building specialists likewise diminish convergence of dynamic fixing in definition. For more noteworthy fluid dissolvability and tangible insight, sugar-based building specialists like mannitol, polydextrose, lactitol, DCL (direct compressible lactose), and starch hydrolystate should be used in this conveyance framework. Mannitol, specifically, has high water dissolvability and great tactile discernment. Building specialists are utilized in extents going from 10% to 90% of complete load of completed structure. 1.3.2 Emulsifying Agents Emulsifying specialists are significant excipients in definition of moment discharge tablets since they help in crumbling and arrival of medicine. Emulsifying substances are likewise valuable for balancing out immiscible combinations and upgrading bioavailability. For quick tablet definition, alkyl sulfates, propylene glycol esters,

7 lecithin, sucrose esters, and different emulsifiers are completely suggested. These substances can be used in levels going from 0.05 percent to generally 15% of absolute weight of completed organization. 1.3.3 Lubricants Lubricants, which aren't required excipients, can support acceptability of these tablets after they've crumbled in mouth. Ointments eliminate dirt from medication transport system from mouth to stomach. 1.3.4 Sweeteners and Flavors Patients will observe merchandise more alluring due to flavors and taste covering fixings. consideration of these fixings assists with masking brutality and obnoxious kinds of portion of dynamic synthetics. Regular and manufactured flavors can be utilized to work on organoleptic nature of quick dissolving tablets. Formulators can utilize sugars like sugar, dextrose, and fructose, as well as non-nutritive sugars like aspartame, sodium saccharin, sugar alcohols, and sucralose. Sugars give mass to blend while likewise giving it charming flavor. 1.3.5 Super Disintegrants A disintegrant is excipient that is added to tablet or container mix to help compacted mass fall to pieces when it is put in liquid climate. 1.3.5.1 Advantages: ✓ Can be used at low concentrations. ✓ Less impact on compressibility and flowability ✓ More intragranularly effective 1.3.5.2 Some super disintegrants are: 1. Sodium Starch Glycolate (Explotab, primogel) is utilised in concentrations ranging from 2 to 8%, with 4% being best. Rapid and widespread swelling with minimal gelling is mechanism of action. Microcrystalline cellulose (Avicel, celex) is utilised at concentration of 2-15 percent of tablet's weight. Additionally, water wicking 2. Cross-linked Povidone or crospovidone (Kollidone) at concentration of 2-5% of tablet's weight. Water is completely insoluble in this substance.

8 Water wicking, enlarging, and perhaps some distortion recuperation are systems of activity. In water, it rapidly scatters and grows, however it doesn't gel, even after expanded openness. When contrasted with other disintegrants, this one has most elevated gamble of edema. Other disintegrants have lower surface region to volume proportion. 3. Insoluble in water hydroxyl propyl cellulose with low substituents. In water, it grows rapidly. Enlarging is more perceptible in grades LH-11 and LH-21. Certain grades can likewise make them tie capacities while as yet having option to break down. Fixation that is recommended 1% to 5%. 4. Cross linked carboxy methyl cellulose sodium (Ac-Di-sol) Croscarmellose sodium:

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[https://www.slideshare.net/ijrpb/ijrpb-12-for- ...](https://www.slideshare.net/ijrpb/ijrpb-12-for-...)

Mechanism of Action: Wicking due to fibrous structure, swelling with minimal gelling. Effective Concentrations: 1-3% Direct Compression, 2-4% Wet Granulation 1.4

Introduction of Oral Cavity [41] The oral pit is underneath nasal depressions on face's front side. Its lines are characterized by rooftop, story, and parallel dividers. front of mouth opens to face through oral gap, while rear of mouth connects to oropharynx by oropharyngeal isthmus (likewise named isthmus of fauces). oropharyngeal isthmus is encircled by delicate sense of taste and palatoglossal curves. The unpaired mandible, sphenoid, and hyoid bones, as well as combined maxillae, palatine, and transient bones, all add to mouth pit's construction. The oral depression is partitioned into foremost and back districts by dental curves (or teeth): front oral vestibule is tracked down foremost to teeth and behind lips, while oral

hole legitimate is found behind teeth. Salivary organs dampen within mouth and help in food absorption by emitting catalysts that assist carbs with separating quicker. organs at concern are parotid, submandibular, and sublingual organs.

9 Figure 1. 1 Oral Cavity Table 1. 1 Key facts about oral cavity Definition The initial segment of stomach related framework that contains designs vital for rumination and discourse; teeth, tongue and salivary organs. Tongue A solid organ in oral depression that empowers taste sensation, biting, gulping and talking. Muscles of tongue Intrinsic: Superior longitudinal, inferior longitudinal, transverse and vertical muscles Extrinsic: Genioglossus, hyoglossus, styloglossus and palatoglossus muscles Innervation of tongue Motor: All muscles are innervated by hypoglossal nerve (CN XII), except for palatoglossus which is supplied by vagus nerve (CN X). Sensory: ✓ General and taste sensation from posterior third: glossopharyngeal nerve (CN IX); ✓ General sensation from anterior two-thirds: lingual nerve (branch of mandibular nerve - V3); ✓ Taste sensation from posterior two-thirds: facial nerve (CN VII)

10 1.4.1 Functions of Oral Cavity Organs and Tissues [43-47] 1.4.1.1 lips and Cheeks Lips, otherwise called labia, are plump strong folds verged within by mucosa and outwardly by skin. Between two kinds of covering tissue on lips lies slim, straightforward epithelial covering tissue. Thus, lips are less keratinized, permitting ruddy pink shade of blood in fundamental vessels to appear on other side. cheeks are strong constructions with wet non-keratinized delineated squamous epithelium within and skin outwardly. Buccinator muscles, which level cheeks against teeth, and buccal fat, which shapes profile on face, both add to prevalent and substandard lips' front end. Rumination happens when lips and cheeks move food around in mouth and hold it set up while teeth separate it. They additionally help in advancement of words, which assists with discourse interaction. Face appearance muscles are responsible for lip development. While lips are shut, food and spit are held in mouth. 1.4.1.2 Tongue The tongue is strong organ that makes mouth's floor and is answerable for spit creation. Two various types of muscles support tongue. characteristic tongue muscles are answerable for changing shape and size of tongue during discourse and gulping. tongue is moved from one side to another, forward and in reverse by extraneous muscles on outside. Both muscle assembles work to drive food into mouth and keep it there during rumination, teaming up with lips and gums. Following that, tongue controls nourishment for biting, shaping it into round mass known as bolus, and moving it to rear of mouth for gulping. lingual frenulum is mucous overlay that runs between tongue and sense of taste. lingual frenulum is minuscule overlay of mucous film that guides in control of tongue's back developments and legitimate articulation. The tongue's upper surface and sides are canvassed in sodden, defined squamous epithelium. terminal sulcus is score that parts dorsum of tongue into two useful segments. suku has papillae toward front, some of which contain taste buds, and taste buds and little organs toward back, as well as lymphoid tissue. pipes of minuscule salivary organs known as Von Ebner organs open into each of circumvallate papillae on back surface, which contain taste buds and are coordinated in rearranged V and number 10-12. Filiform papillae are whitish tapered projections on tongue's foremost 66% that don't contain taste

11 buds and are organized in equal lines. Filiform papillae structure unpleasant rough surface when tongue is constrained against hard sense of taste, which helps pack and break food. In this methodology, dorsal mucosa of tongue goes about as masticatory mucosa. Fungiform papillae, which contain taste buds and are plentiful around tip of tongue, show up as mushroom-like red bits dispersed among filiform papillae. Leaf-like foliate papillae can be seen on parallel lines of tongue's back segment. They simply have couple of taste buds on their tongue. 1.4.1.3 Teeth and Gingiva The four sorts of teeth are incisors, canines, premolars, and molars. Their shapes and positions let them play out their obligations. incisor teeth are utilized to cleave food during rumination. Whenever food is devoured, cuspids (canine teeth) shred it separated. To separate food, premolars (bicuspid) squashed it between their enormous, level surfaces. tongue, cheeks, lips, and teeth join to shape bolus before it is gulped. Every tooth has three sections: crown, neck, and base. lacquer covered noticeable crown is ideally situated to endure crushing that happens during biting of hard and weak food varieties. In crown, dentine lives behind lacquer, though in neck, cementum rests underneath veneer. tooth is kept up with set up in jaw by projectional root divides that are embedded. Rumination and talking both need utilization of teeth. teeth are situated in alveoli along alveolar edges of mandible and maxilla. To frame gingival sulcus, gingivae, or gums, cover alveolar cycles and broaden fairly into every attachment. attachments are fixed with periodontal tendon, which is comprised of solid sinewy connective tissue that associates attachment dividers to cemental surface of roots. Thus, it keeps teeth set up while likewise going about as safeguard by retaining tensions produced by biting. 1.4.1.4 Oral Mucosa The wet coating of mouth cavity is oral bodily fluid film, frequently known as oral mucosa. Oral mucosa has attributes of both skin and gastrointestinal mucosa, and is histologically of momentary sort. oral mucosa has various capacities. portion of these capacities incorporate security, reasonableness, heat control, discharge, immunological action, and ingestion.

12 1.4.1.4.1 Protection The significant capacity of oral mucosa as surface coating is to isolate and safeguard oral pit's more profound tissues and organs from climate. oral delicate tissues are exposed to mechanical powers like pressure, extending, shearing, and surface scraped area because of seizing, gnawing, and biting food. epithelium and connective

tissue of oral mucosa adjust to endure conceivable pressure actuated by these exercises. solid basal turnover of epithelial cells makes up for grinding misfortunes. Since microbial specialists don't stick to surface cells of mucosa because of fast surface reestablishment, microbial colonization is by implication restricted. Besides, on grounds that to quick basal turnover, twisted recuperating in oral depression is quicker and more compelling. Accordingly, oral mucosa epithelium goes about as primary defensive boundary against hurtful synthetics. 1.4.1.4.2 Sensation The mouth mucosa's tactile action gives data. oral mucosa has receptors that recognize temperature, contact, agony, and taste. Sucking, choking, spewing, and salivation are totally set off by these receptors. In cerebrum, there are additionally particular sensors that react to flavor of water and produce thirst. 1.4.1.4.3 Thermal regulation In contrasted with different well evolved creatures, for example, canines, who have broad mucosal temperature guideline, human oral mucosa has minor inclusion in internal heat level guideline. This is because of shortfall of specific hotness shipping receptors in veins. 1.4.1.4.4 Secretion The oral mucosa's principle emission is salivation, which is delivered by salivary organs and keeps up with mouth mucosa wet. three head salivary organs in people are parotid, submandibular, and sublingual salivary organs. These organs are encased and situated external mouth, with long channels bringing their emissions through mucosa. labial, lingual, palatal, buccal, glossopalatine, and retromolar organs are gathering of little salivary organs in mouth. These unencapsulated organs are arranged inside mucosal films and have more limited channels.

13 1.4.1.4.5 Immune Mucosal Network The oral cavity contains few safe framework parts. Models incorporate gingival sulcus incendiary cells, epithelial Langerhans cells, and oral tonsillar tissues. Other invulnerable framework parts in typical oral tissues, like mucosal-related lymphoid tissue (Malt), assume part in antigen handling and show, immune response arrangement and delivery, and cell-interceded effector pathways. 1.4.1.4.6 Absorption In spite of way that oral epithelium has no absorptive capacity, porousness shifts in view of epithelial hindrance thickness, development design, and shortfall of layer corneum in various oral areas. mouth's floor, which is one of most slender epithelial areas, might be more permeable than different pieces of body. This could clarify why few medications can be ingested through mouth (salicylic corrosive, dynamite, and so on) Blood seepage from oral depression straightforwardly into fundamental dissemination upgrades this drug conveyance pathway. 1.4.2 Physiological Processes in Oral Cavity 1.4.2.1 Salivary Secretion 1.4.2.1.1 Control of Salivary Secretion The cerebrum is accountable for salivary discharge. salivary cores give parasympathetic nerve motivations to salivary organs, which are essentially administered by them. At medulla-pons intersection, salivatory cores are found. They are energized by taste and material signs from tongue and different region of mouth. ton of spit is delivered because of these excitement. At point when smooth article is in mouth, it animates significant salivation, though harsh items diminish or even forestall salivation. focal sensory system's higher focuses can manage salivation discharge. craving region of mind, which is situated close to parasympathetic habitats of foremost nerve center, is to some degree controlled by signals from taste and smell portions of cerebral cortex or amygdala. Huge measures of watery, isotonic salivation with minimal natural material substance are delivered when parasympathetic cholinergic neurons are initiated. Celebrity (vasoactive digestive polypeptide) is delivered locally during this feeling, instigating vasodilation in organ. expanded blood stream to organ additionally helps organ's digestion and development. thoughtful nerve supply is animated by transcendently - adrenergic

14 receptors, which causes vasoconstriction and development of less salivation wealthy in natural parts such ptyalin. secretory reaction could be intervened to limited extent by thoughtfully internal vated myoepithelial cell constrictions. Both adrenergic and cholinergic excitement cause salivary emission, and studies utilizing pharmacologic agonists and enemies uncover that two frameworks cooperate. Reflexes in stomach and upper digestive tract can likewise cause salivation. This procedure assists with weakening or kill aggravations found in gastrointestinal lot. The aroma, sight, contact, and sound of feast arrangement likewise advance salivary emission. These improvements involve mental actuation and learned conduct. In cerebral cortex, upgrades trigger recollections that interface improvements to food. Whenever cortex conveys messages to cores in cerebrum stem by means of extrapyramidal pathways, salivary organs are initiated. 1.4.2.1.2 Saliva and Its Composition The liquids discharged by major and minor salivary organs make up salivation. day by day volume of spit emitted by individuals is 1-1.5l. Salivary stream is diurnal, with most reduced levels happening during rest and fairly steady benchmark level all through waking hours, with set off stream intensifications. Basal rates in grown-ups range from 0.3 to 0.5 ml/min. Salivation is comprised of 99.5 percent water and 0.5 percent solutes artificially (electrolyte parts, catalyst and other salivary proteins) (electrolyte parts, chemical and other salivary proteins). emissions of various organs contrasted enormously. watery, amylase-rich serous salivation discharged by parotid organs, gooey spit emitted by sublingual organ, and mucinous spit emitted by submandibular organ. Since numerous proteins in salivation are quickly eliminated by appending to hydroxyapatite of teeth and oral mucosal surfaces, blended spit isn't simply amount of these releases. Spit's pH goes from 5.8 to 7.4, but it gets more isotonic and basic as it is discharged all more rapidly. Salivary stream rate is impacted by sort of taste boosts. By and large, citrus extracts or acrid food varieties cause most noteworthy stream rate and Na⁺ levels, while salt causes high protein and CaH levels. Spit contains assortment of

salts, including chlorides, bicarbonates, sodium and potassium phosphates, and calcium phosphates. broken up gases and natural atoms, for example, urea, uric corrosive, serum egg whites, globulin, mucin, bacteriolytic compound

15 lysosyme, and processing chemical salivary amylase are completely found in typical spit (ptyalin). Lactoperoxidase, blood bunch antigens, EGF, VIP, RNAase, DNAase, lingual lipase, kallikrein, and lactoferrin are among different compounds distinguished. Iodine, which is additionally contained in spit, is found in salivary organs. 1.4.2.1.3 Salivary Functions Salivary emission is fundamental for upkeep of solid oral tissues. Coming up next are elements of this emission: 1. Spit saturates and greases up mouth's tissues. 2. Spit helps discourse by dampening lips and oral cavity. 3. It works with biting and gulping of food. 4. It goes about as dissolvable medium, passing synthetic mixtures on to taste buds, improving impression of flavor and delight in food. 5. Its buffering limit, mineral substance, and antimicrobial qualities help to safeguard oral tissues. 6. Spit cleans mouth and teeth by eliminating perilous microorganisms, food particles, and dead cells from oral tissues. 7. presence of spit makes wearing removable dental prostheses more agreeable.. 8. action of salivary amylase on starch is essential processing capacity of spit. It produces disaccharides by separating inside U1,4-glycosidic linkage in starch. pH of salivation is great for action of amylase. Lingual lipase is fat-processing protein created by Von Ebner organs on tongue. It is answerable for absorption of up to 30% of dietary fatty oils. 9. Spit contains cushions that help keep mouth pH stable and kill disgorged stomach corrosive in throat. 10. Anticandidal action has as of late been found in significant human salivary histatins, histatin-rich proteins found in human parotid and submandibular discharges. 11. Mercury, lead, sulfur, iodides, morphines, assortment of medications, and infections like rabies, poliomyelitis, and HCV can be generally emptied from body by spit emission. 1.4.2.2 Mastication (Chewing) Rumination is most common way of separating ingested food into small amounts, blending it in with spit, and shaping bolus prior to gulping. Rumination is remembered to fill accompanying roles:

16 1. It changes dinner into bolus that is promptly gulped. 2. It upgrades food edibility by diminishing molecule size precisely, expanding surface region for compound movement, and reflexively animating salivation and gastric juice emission for synthetic processing. 3. salivary amylase action begins processing by consolidating feast with salivation. 4. It safeguards stomach related framework from being annoyed with lot of food. 5. It empowers proper oral tissue improvement and extension. 6. It helps lymphatic and venous veins in skin and muscles of face to deplete. Rumination is result of intricate arrangement of exercises that remember opening and shutting of jaws for musical example, as well as broad tongue development. 1.4.2.3 Swallowing (Deglutition) Food and salivation are moved from mouth to stomach through gulping, which is directed strategy. complicated reflex reaction called gulping is set off by afferent driving forces in trigeminal, glossopharyngeal, and vagus nerves. These motivations are coordinated by core of tractus solitaries and core questionable. efferent filaments to pharyngeal muscular structure and tongue are conveyed by trigeminal, facial, and hypoglossal nerves. Gulping starts when substance of mouth are deliberately assembled on tongue and constrained in reverse into throat. gulping processes that follow are totally wild. 1.4.2.4 Speech Maybe most troublesome sensorimotor formative cycle in people is discourse improvement. larynx produces sounds by synchronized activities of stomach, thoracic, and laryngeal muscles (phonation). pharyngeal, oral, and nasal trenches all have impact in change of laryngeal sound into comprehensible discourse (enunciation). laryngeal note has reedy, breezy quality to it. Therefore, just little measure of discourse data is contained in this sound, which is subsequently altered by thoughtful vibration in resounding chambers and activity of organs such lips, tongue, and delicate sense of taste. resonators fill in as acoustic channels, improving few frequencies while changing to other people. Discourse explanation engine upgrades are created by means of sensorimotor cycles like those utilized in oral taking care of and fme coordination somewhere else in body. Discourse effectors, then again, are more assorted and physically circulated than some other sensorimotor coordination, working in more extensive scope of examples and

17 timetables with more significance to natural conditions or potentially setting. Without inquiry, discourse is most externalized human movement. 1.4.2.5 Sensation The tangible capacity of oral mucosa is significant in light of fact that it gives abundance of data regarding what's happening in mouth, while lips and tongue can identify upgrades from outside mouth. mouth has temperature, contact, and agony receptors, as well as taste buds not found wherever else in body. It's viewed as that few receptors in oral mucosa react to flavor of water and sign thirst satiation. Gulping, choking, regurgitating, and salivation are totally set off by oral mucosa receptors. feeling of taste in creatures is oral compound sense that assists them with picking what to eat. Taste buds, which are found in four distinct areas of mouth hole, are quick to communicate sentiments. Taste bud cell film particle diverts assume part in upgrade transduction, and medications can influence taste buds. view of taste progressively disintegrates with age because of decrease in quantity of taste buds, with severe flavor being most impacted. In primates, neural circuits that intercede taste incorporate cranial nerves VII, IX, X, singular core in mind stem, ventroposteromedial core of thalamus, and separate opercular cortex. center taste circuits process sweet, pungent, harsh, and severe boosts sequentially and in equal. 1.4.2.6 Feeding Suckles Nurse

taking care of is sensorimotor capacity that is created upon entering world and turns out to be completely capable inside 2 hours of conveyance in ordinary newborn child. Nursing is newborn child's important conduct during initial half month following birth. As baby becomes older, nursing turns out to be all more impressive and cadenced, and hooking and establishing signals are at long last gained. Nurse is finished by moving tongue, lower lip, and lower jaw corresponding to sense of taste. 1.4.3 Some Other Functions and Activities of Oral Cavity [44-47] The mouth has various capacities, majority of which are imparted to pharynx. mouth and throat are continually functioning as tactile source and in sensorimotor execution during rest and waking. mouth is effectively stood firm on in steady footing during rest, except for non-nourishing nursing in earliest stages, showing rehashed thalamic action. In conscious express, mouth and pharynx effectively partake in keeping up with stance of

18 neck and place of designs around pharyngeal aviation route. mouth and pharynx's arrangement job is believed by certain scholars to be critical action of mouth and pharynx. Engine adjustment of oral and pharyngeal stance endures during quiet flowing breathing; this situating around pharynx is essential system for keeping up with pharyngeal aviation route during nasal gateway breath. mouth depression is engaged with both nasal and oral respiratory tasks. genioglossus muscle of tongue, specifically, is locked in 100% of time during motivation. Oral and pharyngeal movements are synchronized while individual is crying. During phonated lapse, mouth opens by pushing jaw descending and forward. tip of tongue is every now and again distended forward and up, while body of tongue is medially furrowed. These overall exercises of mouth, pharynx, and larynx are performed by equal synchronization of constrained lapse and motivation. During motivations between shouts, tongue turns out to be marginally smoothed and ascends toward sense of taste, and motivations are somewhat done through nose. As indicated by outer perception, hacking has comparable mouth developments to wailing. Besides, movements of emesis are strikingly like that of crying lapses. Since it makes mental and physiological reactions when animated during sexual contact, mouth is significant erogenous region. In response to sexual excitement in different areas, mouth expands responsiveness, vascularity, and salivation. 1.5 Introduction of Mouth Dissolving Film [48-50] The oral course of medication organization is most liked because of its simplicity of organization, painlessness, versatility, patient consistence, and acknowledgment. Utilizing current novel advancements, numerous options in contrast to oral course of medication conveyance have been proposed for pediatrics, geriatrics, sick, and rebelliousness patients. Bioadhesive mucosal measurements structures like cement tablets, gels, and fixes have been created because of innovative forward leaps. utilization of polymeric movies to convey drug into buccal pit has recently showed huge potential among different portion structures. After deterioration as well as disintegration, orally breaking down films (ODFs) quickly hydrate by splashing salivation, letting dynamic pharmacological part out of measurements structure. ODFs are kind of detailing that

19 utilizes hydrophilic polymers to break up rapidly when presented to spit. Oral breaking down tablets (ODTs) and oral crumbling films are two sorts of orally deteriorating drug conveyance frameworks (ODFs). These frameworks were created in last part of 1970s as option in contrast to standard dose structures such fast deteriorating tablets and containers for geriatric and pediatric patients who experienced issues gulping customary measurement structures. standard ODF is about size of postage stamp. appearance of ODT in commercial center was intently attached to patient advising about right organization, with guidance like "don't bite/don't swallow." Despite these standards, biting and gulping occasions were ordinarily archived. Then again, ODFs freed majority from these calamities. 1.5.1 administration of ODFs has numerous advantages and some of them are as follows: [51-52] i. Reasonable transportation. ii. Geriatrics and youths make some simpler memories gulping. iii. Dosing that is both straightforward and precise. iv. There is no requirement for water during organization. v. Advantageous for dysphasics who experience issues gulping tablets or cases. Through keeping away from hepatic first pass impact, expanded bioavailability and fast beginning of activity, as well as soundness No costly lyophilization, incredible mechanical strength, speedy crumbling, and diminished stifling worries are among advantages of ODFs21a. As result of its one of kind elements and fast breaking down time traversing from seconds to one moment, ODFs21a has acquired critical footing in drug business. design of ODF takes into consideration incorporation of assortment of medications with different pharmacological impacts, like enemy of tussive, hostile to epileptic, against asthmatic, expectorant, etc. Temperatures are high, and there is great deal of dampness in air. 1.5.2 Disadvantages 1. technological challenge of dose uniformity is difficult to address. 2. It is highly hygroscopic. 3. High doses (40 mg/4cm² piece) are ineffective. 4. For product stability and safety, special packaging is required.

20 1.5.3 Special Features of Mouth Dissolving Films [53-55] 1. finely thin film 2. Negative in nature 3. Comes in variety of sizes and forms 4. Rapid decomposition 5. Quick release 6. Make mouth feel good. 7. Have good sense of taste. 8. No residues should be left in mouth. 1.5.4 Ideal Requirements [56-57] The ideal requirements for ODF are summarized below: ✓ To ensure strong production and packaging process as well as ease of handling and administration, ODF should be thin and flexible, but stable. ✓ The films must be transportable, non-sticky, and able to maintain level shape without rolling up.

✓ Ease of administration for mentally ill, impaired, and uncooperative individuals. ✓ They should have pleasing mouthfeel and pleasant taste. ✓ There is no need for water. ✓ The time it takes for something to disintegrate should be as short as possible. ✓ They should be relatively unaffected by environmental factors such as temperature and humidity. ✓ They should be able to give liquid medicine benefits in form of solid preparation. ✓ The size of unit FDF should not be so enormous that it interferes with patient's ability to comply. ✓ The FDF's surface should be smooth and homogeneous. ✓ They should be physically and chemically stable for duration of their shelf life. ✓ Cost-effective and simple to produce commercially. 1.5.5 Formulation Aspects For Mouth Dissolving Films [58-62] 1.5.5.1 Active Pharmaceutical Ingredient ODFs can contain allergy medicines, hostile to diarrheals, antidepressants, vasodilators, enemies of asthmatics, against emetic drugs, etc. ODFs' flavor can in like manner be

21 masked with dimenhydrinate. ODFs regularly contain salbutamol sulfate, rizatriptan benzoate, verapamil ondansetron, dexamethasone, rofecoxib, cetirizine, pilocarpine, tianeptine sodium, indomethacin, and different meds. 1.5.5.2 Film Forming Polymer Water-solvent polymers are utilized as film formers since they consider quick breaking down, lovely mouth feel, and mechanical strength. sort of polymer utilized and sum used in details decide strip's strength. most normally involved polymers for film creation are pullulan, gelatin, and hypromellose. Pullulan, gelatin, guar gum, thickener, HPMC, changed starches, PVPK30, PVA, and other water-solvent polymers are couple of models. 1.5.5.2.1 Ideal properties of polymers used in oral film 1. Nontoxic, aggravation free, and boring polymers ought to be utilized. 2. It ought to be flavorless. 3. It ought to be without poisons that can be drained. 4. It should be modest and easy to get. 5. During deterioration interaction, it ought not be staggering impediment. 6. It should have extraordinary wetting and spreading properties. 7. It should be sufficiently able to strip, shear, and ductile. 8. It should have extensive timeframe of realistic usability and not cause optional disease in mouth. 1.5.5.3 Plasticizers Plasticizers further develop mechanical properties like as rigidity and percent stretching in many details. Plasticizer fixations ordinarily range from 0% and 20% weighted normal. Plasticizers like PEG, glycerol, diethyl phthalate, triethyl citrate, tributyl citrate, and others are regularly utilized. 1.5.5.4 Sweetening Agent Sugars have turned into famous fixing in food sources and prescriptions intended to break up or deteriorate in mouth. Normal and counterfeit sugars are utilized to build attractiveness of oral dissolving details. (1) characteristic sugar that is water solvent, like xylose, ribose, glucose, sucrose, maltose, stevioside, and others.

22 (2) Water-solvent fake sugar: sodium or calcium saccharin salts, acesulfame-K, and so forth Aspartame is sugar comprised of dipeptides. 1.5.5.5 Saliva Stimulating Agent Salivary energizers, which are by and large acidic in nature, help to separate ODFs by expanding spit creation in buccal cavity. Probably most regularly utilized salivation animating mixtures incorporate citrus extract, malic corrosive, tartaric corrosive, ascorbic corrosive, and lactic corrosive. 1.5.5.6 Surfactant Surfactants are utilized as solubilizers, wetting specialists, and dispersants, making film deteriorate like flash and dynamic fixing to be delivered right away. Surfactants likewise help disintegration of ineffectively solvent medications in quick dissolving buccal movies. few models are Polaxamer 407, sodium lauryl sulfate, benzalkonium chloride, benzthonium chloride, tweens and ranges, and others. 1.5.5.7 Flavor Flavors are fundamental for veil harsh or horrendous taste of coordinated medication. How much still up in air by strength and nature of flavor. Any flavor endorsed by FDA in United States, like sweet, sharp, or mint, can be utilized. As per one review, flavor blend of mint, licorice, and sucralose successfully covers harsh taste of diclofenac sodium. Electronic tongues are utilized to recognize impacts of different taste concealing specialists (TMAs). 1.5.5.8 Colouring Agent Whenever part of plan fixings or medications are in insoluble or suspension structure, shades, for example, titanium dioxide or FD&C supported shading added substances are utilized in oral strips (at fixations not surpassing 1% w/w). Table 1. 2 Percentage of various ingredients used in formulation of ODF

| Ingredients | Amount (w/w) |
|-----------------------|--------------|
| Drug | 5-30 % |
| Water Soluble Polymer | 45 % |
| Plasticizer | 0-20 % |

23 Saliva Stimulating Agent 2-6 % Surfactant q.s Sweetening Agent 3-6 % Flavor, Color, Filler q.s 1.6 Manufacturing Methods [63-67] 1.6.1 Solvent Casting Method The most average methodology for assembling ODFs with water dissolvable excipients, polymers, and drugs broke up in de-ionized water is dissolvable projecting; as result, homogenous combination is accomplished by utilizing high shear powers produced by shear processor. pre-arranged arrangement is poured onto petri plate and dissolvable is permitted to dry by presenting it to high temperatures to create great quality movies. dissolvable projecting strategy was utilized to make orodispersible film of tianeptine sodium utilizing different grades of Lycoat and HPMC. In dissolvable projecting procedure, film framing polymer is generally absorbed reasonable dissolvable short-term. In view of basic physicochemical highlights of API, like softening point, shear responsiveness, and polymorphic structure, kind of API that should be remembered for ODF characterizes ideal dissolvable. medication's similarity with dissolvable and other excipients is considered prior to finishing detailing. presence of caught air rises during detailing system can affect consistency of completed film. With assistance of vacuum siphon, blend is deaerated. dissolvable projecting strategy was likewise utilized to make mosapride orodispersible film definition. In projecting system, consistency of answer for be poured is vital. Pullulan focuses going from 2% to 8% outcome in low thickness arrangement

that makes film projecting basic. Anastrozole quick dissolving films were additionally effectively made utilizing dissolvable projecting strategy with HPMC (E5) and polyvinyl liquor (PVA).

24 Figure 1. 2 Solvent Casting Method 1.6.2 Hot Melt Extrusion In hot-liquefy expulsion, dry parts for film are warmed and homogenized by extruder screw until they are liquid and blended. extrudate is driven into fundamental film shape by level expulsion kick bucket. Lengthening rollers can influence thickness and strength of film while it is as yet hot and adaptable. In wake of cooling and cutting expelled film, hot soften expulsion procedure is talked about. Figure 1. 3 Hot melt extrusion technique

25 1.6.3 Semisolid Casting Method A film-shaping polymer arrangement that is water solvent is made. resultant arrangement is joined with polymer arrangement that is corrosive insoluble (for example cellulose acetic acid derivation phthalate, cellulose acetic acid derivation butyrate). To acquire gel mass, adequate measure of plasticizer is utilized. At last, gel mass is shaped into movies or strips utilizing heat-controlled drums. Somewhere in range of 0.015 and 0.05 creeps of film thickness ought to be utilized. corrosive insoluble polymer ought to be joined with film framing polymer in 1:413 proportion. Figure 1. 4 Solid Dispersion Extrusion Method 1.6.4 Rolling Method This strategy includes making pre-blend, adding functioning, and afterward producing film. Set up pre-blend in with film-framing polymer, polar dissolvable, and different added substances (barring medication) and add it to expert clump feed tank. first metering siphon and control valve ought to be utilized to take care of it to either of first and second blenders. Add required measure of medicine to blender you've chosen. Consolidate drug with expert cluster pre-blend to get uniform grid.. Second metering siphons convey foreordained measure of uniform framework to dish. At long last, film is framed and shipped to help roller on substrate. wet film is dried by means of controlled base drying. most generally utilized solvents are water and combination of water and liquor.

26 Figure 1. 5 Rolling Method 1.7 Evaluation Parameters [68-69] 1. Thickness Test 2. Tack Test 3. Youngs Modulus 4. Tail flick Test 5. Thermodynamic Stability Study 6. Drug Content 7. Viscosity 8. Tensile Strength 9. Folding Endurance 10. Weight of films 11. % Elongation 12. Swelling Properties 13. Disintegration Time 14. Surface pH 15. Content Uniformity 16. Dissolution test 1.8 Marketed Product of Mouth Dissolving Film [62-64] Table 1. 3 Marketed Product of Mouth Dissolving Film Product API Manufacturer Use Listerine Cool Mint Prfizer Mouth Ulcer Benadryl Diphenylhydramine Prfizer Antiallergic

27 HCL Suppress Menthol InnoZen,® Inc Cough Suppressant Klonopin wafers Clonazepam Solvay Pharmaceutical Antianxiety Theraflu Dextromethorphan Novartis Antiallergic Orajel Menthol/Pectin Del Mouth Freshner Gas-X Simethicone Novartis Antiflatuating 1.9 Introduction Of Design of Experiment (DoE) [70-75] Test configuration is anything but another idea. Sir Ronald Fisher, splendid analyst, established framework for present day measurable exploration during 1920s with his "virtuoso" commitments to insights. review took proactive methodology, which is essential to current administrative system that controls drug item improvement. Walter A. Shewhart, William E. Deming, and Joseph M. Juran explained on this idea by upholding for cycle based culture for infusing quality into things. To stress meaning of joining Quality into labor and products, Juran developed five-venture technique "Quality by Design." This cycle involves getting to know shopper, evaluating his needs, making interpretation of them into item attributes, planning it, and carrying out it in tasks. W.E. Deming proposed his deliberate way to deal with shrewdness around 50 years before Juran, which joined framework thinking, fathoming variety, hypothesis of information, and brain science. He accepts that quality confirmation should focus on cycle rather than outcomes on grounds that "on off chance that you can't characterize interaction, you're not doing it right" and "quality is as of now in item." Control graphs with measurable cycle control were important for Schewhart's quality improvement endeavors. drug business is probably going to be quick to carry out these thoughts since it puts such high significance on quality and interaction. Thus, right off bat in thousand years, administrative bodies discovered that quality couldn't be coordinated into items (that is, planned into them). Design of Experiments (DoE) is utilized in exploration and industry to carry out Quality by Design (QBD). Since of Fisher's inheritance, it is known as essential arrangement of drug improvement since it requires use of factual thinking from beginning. turn of events and development of drug quality levels has become progressively popular. greatest reason for quality worries, as per Juran, is drug creation process. Review and testing can't demonstrate security and adequacy of ineffectively

28 planned drug item. Subsequently, QbD accepts that expanding quantity of examinations would not work on quality. To put it another way, to be implicit, item's quality should be astounding. This way to deal with drug advancement begins with clear cut objectives and focuses on item and cycle ability. It is established on sound exploration and viable gamble board. Information and comprehension are acquired when QbD is applied in drug creation. a) Improving reason impact investigation and administrative adaptability; b) Stabilizing cycles and decreasing fluctuation; c) Increasing productivity of drug improvement; d) Improving reason impact examination and administrative adaptability Most administrative bodies

across world have embraced hazard based strategies and severe quality affirmation in drug advancement. The utilization of QbD strategies in making of insightful systems has been archived in few papers. Scientific quality administration is utilized to create and work on solid and practical logical techniques. Logical methodologies are utilized in QbD execution to create more exact outcomes while limiting gamble of disappointment. For centuries, drug enterprises have zeroed in on improving each angle in turn (OFAT). All factors stay unaltered, except for one, which is modified inside sensible reach (or level). Since OFAT strategy doesn't consider factor associations, it might prompt deficient turn of events and streamlining. You might have option to get prevalent outcomes in only couple of tests assuming you construct preliminaries accurately. Department of Energy utilizes measurable methodologies, for example, screening and advancement plans. In drug and scientific QbD, DoE is main part. Thus, current review looks at hypothetical and down to earth issues about DoE's application in drug and scientific QbD. 1.9.1 Definitions and Terminologies [76-78] Quality by Design (QbD) is orderly way to deal with item and interaction advancement that underscores item and cycle comprehension and control while sticking to sound science and hazard board. It's information association and organizing approach for information about connection among cycle and result factors. "Try Design" is one more name for it (DoE). Basically, deciding what data sources mean for results is demonstration of making process information. Treatment - Various treatment mixes are accessible.

29 Therapy levels - Treatment power during investigations Treatment (factors) - In test, controlled condition. Exploratory unit - individual to whom treatment will be regulated and reaction will be estimated. Likewise alluded to as response estimation. Reactions - After medicines are applied to trial units, outcomes are obtained. Test plan - Treatment level task. Examination of change (ANOVA) - Method for deciding reasons for reaction changeability. Replication - Observing reactions of few exploratory units under indistinguishable test conditions. Randomization - choice of test units was not done in deliberate way. Frustrating - examination where one component or treatment's impact can't be isolated from impact of another element or treatment. Autonomous factors: Formulation researchers have direct impact over interaction. Subordinate factors: Result factors Factors: Qualitative and quantitative variables. Level: Value relegated to variable Reactions surface plot: three-layered plot portraying connection between autonomous and ward factors. Collaboration: It gives net impact of at least two factors without requiring additivity of their belongings Impact: Amount of change Form plot: diagram of one autonomous variable plotted against one more while keeping reaction consistent Form lines: determined shape lines over counterplot Symmetry: When no connection happens because of principle element of interest Goal: Measuring frustrating 1.9.2 Advantages [78-80] ✓ DoE enjoys great deal of benefits when contrasted with OFAT. trial configuration approach is system for making tests that amplify cycle information while consuming minimal measure of assets. However much right data as could reasonably be expected

30 ought to be given. Analyze how factors interface with each other. Investigate every part independently to decide its relative significance. Inside plan region, foreseeing conduct of interaction. ✓ On various fronts, OFAT outflanks DoE. Utilize least assets attainable with trial plan systems. Information should be sent as definitively and proficiently as could really be expected. Investigate how they communicate. Decide every factor's relative significance. Take into account process conduct forecast inside plan space. Basic Process Parameters (CPPs) and Critical Quality Attributes (CQAs) ought to be firmly connected. Drug things should be upgraded all while since they contain countless CQAs. Work on flexibility of item or process, or its protection from wild components and outer occasions. Distinguish exceptions inside laid out test lattices to guarantee that they are secured. ✓ By changing each component in turn, OFAT strategies, then again, distinguish nearby imperfect zones. Since this antiquated technique consumes large chunk of day, it can't investigate numerous elements on double or take gander at their associations. OFAT can't be utilized in QbD applications because of its blemishes. One of benefits of DoE strategy over OFAT tests is that it explains exchange between input components. Association impacts are utilized to survey effect of info things on yield. ✓ This technique can be utilized to work on current plan by diminishing quantity of trial preliminaries, dissecting and improving troublesome association between autonomous factors, and decreasing general measure of information. Accordingly, this factual technique is more functional than conventional exploratory work since it fuses variable cooperations thus shows factors' aggregate impacts. Besides, reaction surface plans like Central Composite, Box-Behnken, and Hybrid can be valuable practically speaking.

31 1.10 DRUG PROFILE 1.10.1 ZPO HCL Reason for Selection It's antipsychotic medication used to treat schizophrenia and bipolar disorder. Aside from film, most widely used treatment, and variety of other formulations have been developed so far. Profile Ziprasidone is atypical antipsychotic used to treat schizophrenia, acute mania, and mixed states in bipolar disorder. Geodon and other trade names are used to market it. Molar mass: 412.936 g/mol Formula: C 21 H 21 CIN 4 OS Trade name: Geodon, Zeldox, Zipwell Elimination half-life: 7 to 10 hours Metabolism: Hepatic (aldehyde reductase) Pharmacology It's benzothiazolylpiperazine derivative that's used to treat schizophrenia, acute mania, and mixed states in bipolar patients. At dopamine D2 and serotonin 5-HT2A and 5-HT1D receptors, it acts as both antagonist and agonist. It

also reduces synaptic reuptake of serotonin and norepinephrine. antischizophrenic effect of ziprasidone hydrochloride is unknown, however it could be mediated through combination of dopamine D2 and serotonin 5-HT2 antagonism. Histamine H1 and alpha-1 adrenergic receptors are also hostile to this drug. Uses Treatment of schizophrenia as well as acute mania and mixed states associated with bipolar disorder.

32 Adverse effects ▪ Sleepiness and headache are very common adverse effects (<10%). Producing too much saliva or having dry mouth are common adverse effects (1–10 percent), as are runny nose, respiratory illnesses or coughing, nausea and vomiting, stomach aches, constipation or diarrhoea, loss of appetite, and weight gain (but smallest risk for weight gain compared to other antipsychotics) 1.10.2 Quetiapine Reason for Selection Quetiapine, often known as Seroquel, is atypical antipsychotic medication that is used to treat schizophrenia, bipolar disorder, and major depressive disorder. Because of its sedative effect, it is sometimes used as sleep aid, however this is not recommended. It is taken orally. Profile Molar mass: 383.5099 g/mol Formula: C₂₁ H₂₅ N₃ O₂ S Trade name: Seroquel, Temprolide Protein binding: 83% Bioavailability: 100 % Elimination half-life: 7 hours (parent compound); 9–12 hours (active metabolite, norquetiapine) Pharmacology ▪ Quetiapine fumarate salt form of quetiapine, dibenzothiazepine derivative with antipsychotic properties, is known as fumarate. It's used to treat schizophrenia as well as

33 acute manic episodes associated with bipolar I disorder. Some believe quetiapine's antipsychotic impact is mediated via antagonist activity at dopamine and serotonin receptors. D1 and D2 dopamine receptors, alpha 1 and alpha 2 adrenoreceptors, and 5-HT1A and 5-HT2 serotonin receptor subtypes are all affected. Quetiapine also has antihistamine H1 receptor antagonistic action. Uses ▪ Primarily used to treat schizophrenia or bipolar disorder Adverse effects ▪ Very common (<10% incidence) adverse effects Dry mouth, Dizziness, Headache; Common (1–10% incidence) adverse effects High blood pressure, Orthostatic hypotension, High pulse rate, Elevated serum triglycerides, Abdominal pain, Constipation, Vomiting, Increased liver enzymes, Fatigue, Pain 1.11 POLYMER PROFILE 104 1.11.1 HPMC E 5 ▪ Hypromellose, short for hydroxypropyl methylcellulose, is semisynthetic, inert, viscoelastic polymer used as eye drops, as well as excipient and controlled-delivery component in oral medicaments, found in variety of commercial products. ▪ Formula: C₅₆ H₁₀₈ O₃₀ ▪ Soluble in: Insoluble in Water ▪ Molar mass: variable ▪ Physical state: Solid ▪ Viscosity: 4–6cps ▪ Odor: Odorless ▪ Color: White Powder 1.11.2 PEG-400 ▪ It is low-molecular-weight grade of polyethylene glycol. It is clear, colorless, viscous liquid. Due in part to its low toxicity, PEG 400 is widely used in variety of pharmaceutical formulations. ▪ Density: 1.13 g/cm³ ▪ Formula: C_{2n} H_{4n+2} O_{n+1}, n = 8 . 2 to 9 . 1 ▪ Viscosity: 90.0 cSt at 25 °C, 7.3 cSt at 99 °C

34 ▪ Molar mass: 380–420 g/mol ▪ Melting point: 4 to 8 °C (39 to 46 °F; 277 to 281 K) ▪ LD 50 (median dose): 30 mL/kg, orally in rats ▪ Flash point: 238 °C (460 °F; 511 K) 1.11.3 Citric acid ▪ Citric acid is weak organic acid that has chemical formula C₆H₈O₇. It occurs naturally in citrus fruits. In biochemistry, it is intermediate in citric acid cycle, which occurs in metabolism of all aerobic organisms. More than million tons of citric acid are manufactured every year. ▪ Formula: C₆ H₈ O₇ ▪ Molar mass: 192.124 g/mol ▪ Melting point: 153 °C ▪ Density: 1.66 g/cm³ ▪ Boiling point: 310 °C ▪ Soluble in: Water, Alcohol, Dimethyl sulfoxide, Ethyl acetate, Ether 1.11.4 Aspartame ▪ Aspartame is artificial non-saccharide sweetener used as sugar substitute in some foods and beverages. In European Union, it is codified as E951. Aspartame is methyl ester of aspartic acid/phenylalanine dipeptide. ▪ Formula: C₁₄ H₁₈ N₂ O₅ ▪ Molar mass: 294.3 g/mol ▪ Acidity (pK_a): 4.5–6.0 ▪ Solubility in water: Sparingly soluble ▪ Solubility: Slightly soluble in ethanol 1.11.5 Mannitol ▪ Mannitol is type of sugar alcohol which is also used as medication. As sugar, it is often used as sweetener in diabetic food, as it is poorly absorbed from intestines. As medication, it is used to decrease pressure in eyes, as in glaucoma, and to lower increased intracranial pressure. ▪ Molar mass: 182.172 g/mol ▪ Formula: C₆ H₁₄ O₆

35 ▪ CAS ID: 69-65-8 ▪ Metabolism: Liver, negligible ▪ Elimination half-life: 100 minutes ▪ Trade name: Osmitol 1.11.6 Orange Flavor ▪ Oranges are good source of folate, source of vitamin and B₁, and fiber ▪ Oranges are widely grown in warm climates worldwide, and flavors of oranges vary from sweet to sour. ▪ The fruit is commonly peeled and eaten fresh, or squeezed for its juice 1.11.7 Methyl paraben ▪ Methylparaben, also methyl paraben, one of parabens, is preservative with chemical formula CH₃. It is methyl ester of p-hydroxybenzoic acid. ▪ Molar mass: 152.15 g/mol ▪ Formula: C₈ H₈ O₃ ▪ point: 275 °C ▪ UV-vis (λ_{max}): 255 nm (methanol) 1.11.8 Propyl paraben ▪ Propylparaben, n-propyl ester of p-hydroxybenzoic acid, occurs as natural substance found in many plants and some insects, although it is manufactured synthetically for use in cosmetics, pharmaceuticals and foods. ▪ Molar mass: 180.2 g/mol ▪ Formula: C₁₀ H₁₂ O₃ ▪ Density: 1.06 g/cm³ ▪ Melting point: 96 to 99 °C (205 to 210 °F; 369 to 372 K) Vanillin Distilled water.

1.2. Literature Review: 2.1 Literature Review on Mouth Dissolving Film: Author Name & Publication Year Title of Paper Description Journal Name Reference No Raza et al. (2019)

100%

MATCHING BLOCK 30/131

W [https://docplayer.net/amp/213630941-Design-dev ...](https://docplayer.net/amp/213630941-Design-dev...)

Effect of taste masking technology on fast dissolving oral film: dissolution rate and bioavailability

Drug: Losartan potassium Polymer: HMCP, sodium carboxy methyl cellulose, sodium alginate Description: for treatment of hypertension that had quick disintegration, optimal morphological qualities, and mechanical strength. Losartan is antihypertensive medication that goes through lot of first-pass metabolism, which means it has low bioavailability. medicine enters bloodstream immediately through buccal route, increasing its bioavailability. Nanotechnology 81 Bala et al. (2018) Formulation optimization and evaluation of fast dissolving film of aprepitant by using design Drug: Aprepitant Polymer: PEG 400 Method : Solvent Casting Method Description: aforesaid findings indicate that Bulletin of Faculty of Pharmacy 82

2 of experiment created formulation has potential to be new dosage form for improving medication distribution, start of action, and patient compliance Linku et al. (2018) Formulation and evaluation of fast dissolving oral film of anti-allergic drug Drug: Loratadine Polymer: HPMC, PEG 400, PG Method; solvent casting process Description: These findings imply that Loratadine oral film that dissolves quickly could be effective for allergy treatment when quick onset of action is required Asian Journal of Pharmaceutical Research and Development 83 Pooja et al (2018) Design, Development and Evaluation of Oxcarbazepine Loaded Fast Dissolving Oral Film Drug: Oxcarbazepine Polymer: HPMC, PEG 400 Method: Solvent Casting Method Description: results obtained showed no physical chemical incompatibility between drug and polymers. prepared films were clear, transparent and smooth surface. International Journal of Drug delivery 84 Zhu et al. (2018)

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Effect of taste masking technology on fast dissolving oral film:

Drug: Loratadine Polymer: HPMC, PEG 400 Description: two films disintegrated more Nanotechnology 85

3 dissolution rate and bioavailability quickly than commercial tablets. Rat pharmacokinetic tests revealed that suspension film's oral bioavailability was substantially higher than that of commercial tablets, with relative bioavailability of 175 percent. bioavailability of liposomal film was improved, but not as much as that of suspension film. Pagilla et al. (2018) Formulation and evaluation of lovastatin oral disintegration thin films Drug: Lovastatin Polymer: CCS,PVA, Gelatin Method: Solvent Casting Method Description: Film thickness, folding durability, in-vitro disintegration time, in-vitro drug release pattern, and drug content were all tested on generated formulations. interaction between drugs and polymers was studied using FTIR spectroscopy. Among all formulations, formulation (F8) containing 4% crospovidone had highest drug release (99.27%) and demonstrated good stability over three-month period. GSC Biological and Pharmaceutical Sciences, 86 Karthikeyan D Development of fast Drug: Rizatriptan benzoate Indo American J Pharm 87

4 et al. (2013) dissolving oral film containing of rizatriptan benzoate as antimigraine medication Polymer: PG, Aspartame, Mannitol Description: In vitro evaluation investigations (30 ml of stimulated salivary fluid pH 6.8/ glass beaker/ 100 RPM) revealed film composition of 200 mg polyvinyl alcohol and 200 mg Maltodextrin to be appropriate. Ex vivo investigations revealed that 82.93 percent of medication was absorbed through porcine oral mucosa. Res Narayana PR et al. (2013) Formulation and evaluation of fast dissolving films of loratidine by solvent casting method Drug: Loratidine Polymer:HPMC, PG, PEG 400 Description: By adding loratidine into hypromellose films, fast-dissolving films can be created. prepared optimum formulation disintegrated in less than 30 seconds. Within 4– 6 minutes, produced film formulation released 100 percent of medication and exhibited good physicommechanical properties The pharma innovation 88 Shaik MR et al. (2013) Formulation and characterization of domperidone oral thin Drug: Domperidone Polymer: HPMC, PVA, Triethyl Citrate Description: Domperidone orodispersible film Int J Pharm Sci. 89

5 films As plasticizing agent and film forming, triethyl citrate and polyvinyl alcohol were added to film. In film, Kollicoat IR was used as superdisintegrant. In dissolution medium, improved formulation released more than 95% domperidone in 3 minutes Sayed S et al. (2013) Fast-dissolving sublingual films of terbutaline sulfate: formulation and in vitro/in vivo evaluation Drug: Terbutaline sulphate Polymer: maltodextrin, sodium alginate, carbopol 430, xanthan gum, hypromellose E5, PVP K25 Description: Crossover research in human volunteers was used to conduct bioequivalence study against typical 1oral tablets. With relative bioavailability of 204.08 percent, improved film formulation resulted in much faster drug absorption. Mol Pharm Londhe VY et al. (2012) Formulation development and evaluation of fast dissolving film of

telmisartan Drug: Telmisartan Polymer: PVP,PVA Description: Lutrol E400 was employed as plasticizer, and sodium and potassium hydroxide were added to increase solubility of IJPS

6 active at alkaline pH. Alkalizing chemicals in dissolution medium caused 100 percent drug release within 5 minutes from optimised formulation Nagaraju R et al. (2012) Design and evaluation of fast dissolving film containing nizatidine Drug: Nizatidine Polymer: Maltodextrin Description: Nizatidine is fast-disintegrating film formulation used to treat acid reflux and ulcers. Films using 82 percent maltodextrin as polymer, 16 percent glycerin, and 2% sorbitan monooleate as plasticizer were deemed optimal. In pH 6.8 simulated saliva, more than 90% of medication was released. Indian J Pharm Edu Res. 90

76%

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Desu P et al. (2012) Formulation and evaluation of fast dissolving films of zolmitriptan

Drug: Zolmitriptan Polymer: HPMC, Hypromellose E5 Description: Anti-migraine zolmitriptan film that dissolves quickly to avoid hepatic first-pass metabolism. In this study, hypromellose E5 was used as primary film forming. As plasticizer, propylene glycol was utilised, along with acesulfame potassium and xylitol as sweetener. Int Res J Pharm 91

7 In in vitro dissolution test (6.8 pH phosphate buffer/Basket/100 RPM), developed formulation showed highest drug release

80%

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Bhyan B et al. (2012) Formulation and evaluation of fast dissolving sublingual films of rizatriptan Benzoate

Drug: Rizatriptan Benzoate Polymer: HPMC E15, Maltodextrin Description: primary film former was HPMC E15, while secondary film former was maltodextrin. As plasticizer, glycerol was added to mix. As water soluble secondary sweetener, sugar alcohols like mannitol were used. Sweetener and surfactant were aspartame and sodium lauryl sulphate, respectively. In dissolution media comprising 900 ml pH 6.8 phosphate buffer in basket apparatus at 50 RPM, formulations containing hypromellose E15 (15 mg/ film) showed 90 percent in-vitro drug release in less than 10 minutes Int J Drug Dev Res 92 Mahajan (2012) Formulation & evaluation of fast dissolving buccal films of sertraline. Drug: Sertraline Polymer: Povidone, Carbopol 934P Description: As principal film forming agent, mixture of povidone and carbopol 934P was Int J Drug Dev Res 93

8 used. As plasticizer, polyethylene glycol 400 and propylene glycol were used. As sweetening agent, saccharine sodium was used. In vitro release experiments revealed that in dissolving medium, 90–95 percent of medication was released within 1 hour. Murata Y et al. (2012) Development of film dosage form containing allopurinol for prevention and treatment of oral mucositis Drug: Allopurinol Polymer: Sodium Alginate Description: Allopurinol, xanthine oxidase inhibitor, is available in film dosage forms. Without addition of plasticizer, sodium alginate with different viscosity grades such as 300 cP, 500 cP, and 1000 cP, low molecular weight alginate, Gularonic acid-rich alginate, and pullulan were assessed as film forming polymers International scholarly research network 94 Vijayasri K et al. (2012) Montelukast sodium oral thin films: formulation and invitro evaluation. Drug: Montelukast Polymer: Hypromellose E15, hypromellose E50, PVP Description: Montelukast sodium orodispersible film formulation for asthma. Hypromellose Asian J Pharm Clin Res. 95

9 E15, hypromellose E50, and polyvinylpyrrolidone were used to make oral thin films. Glycerol and mannitol were used as fillers and plasticizers, respectively. In pH 6.8 phosphate buffer containing 0.5 percent SLS/ basket / 50 RPM, optimised formulation released 93.49 percent during 20 minutes Choudhary DR

100%

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et al. (2012) Development and characterization of pharmacokinetic parameters of fast- dissolving films containing levocetirizine.

Drug: levocetirizine Polymer: Pullulan Description: To hide bitterness of levocetirizine, it was combined with - cyclodextrin. primary film former was Pullulan. In dissolution media 93.54 3.9 percent levocetirizine was dissolved in 90 seconds. In rats, pharmacokinetics of medication solution and film formulation were not significantly different.

86%

MATCHING BLOCK 35/131

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ScientiaPharmaceutica 96 Panchal MS et al. (2012) Formulation and evaluation of mouth dissolving film of ropinirole hydrochloride

Drug: Ropinirole hydrochloride Polymer: PEG 400 and pullulan Description: Ropinirole hydrochloride in orodispersible film formulation. As plasticizing agent and film IJPRAS 97

10 by using pullulan polymers. forming agent, PEG 400 and pullulan were added to film. In simulated salivary fluid, improved formulation released 90% of medication in 1 minute. Dixit AS et al. (2012)

95%

MATCHING BLOCK 36/131

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Fast disintegrating films containing anastrozole as dosage form for dysphagia patients.

Drug: Anastrozole Polymer: HPMC, Hypeomellose E5,PVA Description: Among all film formers, hypromellose E5 disintegrated fastest, with time of 15 seconds and breakdown rate of over 90% in 240 seconds. There was no statistical difference in pharmacokinetic characteristics between film formulation and anastrozole solution, indicating similar plasma level time profile

78%

MATCHING BLOCK 37/131

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Archives of pharmaceutical research 98 Nagar M et al. (2012) Formulation and evaluation of mouth dissolving film of antipsychotic drug aripiprazole

Drug: Aripiprazole Polymer: PEG 1000 Description: To speed up disintegration of hypromellos E3 films, maltodextrin and rice starch were added. As plasticizer, PEG 1000 was employed. To improve film's taste acceptability, sodium chloride and sucralose Der Pharmacia Lettre 99

11 were added. As preservative, thymol and potassium sorbate were added. 100 percent of medication In 15 minutes, release was demonstrated in dissolving media Joshi P et al. (2012) Formulation development and evaluation of mouth dissolving film of domperidone. Drug: Domperidone Polymer: Tween 80, Description: Domperidone and -cyclodextrin were dispersed in half amount of water and methanol with tween 80 in improved formulation and heated at 60°C. PEG 400 was used as plasticizer and main film former was hypromellose. In dissolution, improved formulation including domperidone and - cyclodextrin in 1:3 ratio demonstrated more than 75 percent drug release within 15 minutes. J Pharm Bioall Sci 100 Tomar et al. (2012) Formulation and evaluation of fast dissolving oral film of dicyclomine as potential route of buccal delivery Drug: Dicyclomine Polymer: hypromellose, polyvinylalcohol, and eudragit RL-100 Description: Dicyclomine, anticholinergic medication, is available in orodispersible film formulation. Oral films were made with Int J drug Dev Res. 101

12 polymers hypromellose, polyvinylalcohol, and eudragit RL-100, as well as plasticizer polyethylene glycol 400. In dissolution medium 300 ml pH 6.8 deionized simulated saliva in USP apparatus II (paddle) at 100 RPM, formulation comprising polyvinyl alcohol as principal film former demonstrated minimum disintegration and 94.14 percent drug release within 5 minutes. Qadir KA et al. (2012) Formulation and evaluation of fast dissolving films of loratidine for sublingual use. Drug: Loratidine Polymer: Hypromellose, Polyvinyl pyrrolidone, and HPMC Description: Anti-histaminic medication loratidine in fast-dissolving film. As major film forming agent, hypromellose, polyvinyl pyrrolidone, and hydroxypropyl cellulose were tested. As plasticizer and sweetener, propylene glycol and aspartame were utilised. In vitro dissolution showed 70–92 percent release within 4 minutes for all formulations, and ex vivo drug release studies showed 64–86 percent Int Res J Pharm. 102

13 release within 4 minutes for all formulations Saini S et al. (2011) Formulation, development and evaluation of oral fast dissolving anti-allergic film of levocetizine dihydrochloride Drug: Levocetizine dihydrochloride Polymer: Maltodextrin, Hypromellose E15, Neotame, and Glycerin Description: Levocetizine dihydrochloride as orally consumable flash release film composition. Maltodextrin, hypromellose E15, neotame, and glycerin were used as film- formers, sweeteners, and plasticizing agents, respectively, in film. In pH 6.8 simulated saliva, 90% of medication from improved formulation was released within 5 minutes J Pharm Sci Res. 103 Gupta MM et al. (2011) Enhancement of dissolution rate of rapidly

dissolving oral film of meclizine hydrochloride by complexation of meclizine hydrochloride with β -cyclodextrine. Drug: Meclizine hydrochloride Polymer: were hypromellose E5 and Polyethylene oxide Polyox N80 Description: Meclizine hydrochloride oral film that dissolves quickly. principal film formers were hypromellose E5 and polyethylene oxide Polyox N80. In formulation, disintegrating agents such as Kollidon CL, sodium starch glycollate, and croscarmellose sodium were JAPS 104

14 used. To increase solubility and flavour masking of bitter tasting medicine, meclizine hydrochloride was complexed with - cyclodextrine. Ghorwade V et al. (2011) Formulation and evaluation of montelukast sodium fast dissolving films by using gelatin as film base. Drug: Montelukast sodium Polymer: Gelatin, PEG Description: Montelukast sodium orodispersible film formulation with gelatin as principal film- former and polyethylene glycol as plasticizer. As dissolving agent, crospovidone and microcrystalline cellulose were used in film. Quick disintegration was seen in formulation comprising 10% MCC and 4% crospovidone. Res J Pharm, Biol Chem Sci. 105 Saini S et al. (2011) Optimization of formulation of fast dissolving films made of pullulan polymer Polymer: Pullulan Description: PEG films were translucent and white opaque in appearance. PEG produced translucent white films. Films containing glycerin took longer to dry than films containing PG. Polymer and plasticizer were present in optimum film composition at low concentrations. Int J Pharm Sci Rev Res. 106

15 Kulkarni PK et al. (2011) Formulation and evaluation of fast dissolving film containing rofecoxib. Drug: Rofecoxib Polymer: Hypromellose and Polyvinyl alcohol Description: For osteoarthritis and dental pain, rofecoxib is medication of choice. Glycerin, polysorbate 80, and aspartame were utilised as plasticizers, solubilizers, and sweeteners, respectively, with hypromellose and polyvinyl alcohol as major film forming polymers. Menthol was employed to disguise flavour of active ingredient. In vitro dissolving was performed in 500 mL of pH 1.2 hydrochloric acid in Paddle at 100 RPM with 0.5 percent w/w SLS Int Res J Pharm. 107 Prasanthi NL et al. (2011) Design and development of sublingual fast dissolving films for antiasthmatic drug. Drug: Salbutamol sulphate Polymer: Hypromellose Description: optimised batch contained hypromellose as film former (2 percent w/w), tween 80 as wetting agent (0.5 percent w/w), and aspartame as sweetener (0.5 percent w/w). In paddle assembly at 50 RPM, improved formulation had adequate drug release in 300 Scholars Research Library 108

16 ml pH 6.8-simulated saliva Mishra R et al. (2011) Design and development of rapidly dissolving films using ion exchange resin for taste masking. Drug: Cetirizine hydrochloride Polymer: Hypromellose E3 and Hydroxypropyl cellulose LF Description: They found that increasing amount of polymers hypromellose E3 and hydroxypropyl cellulose LF enhanced disintegration time, and that dissolving produced films in 900 ml 0.1N HCl in USP dissolution equipment XXIV at 50 RPM increased disintegration time IJDFR 109 Raju S et al. (2011) Flash release oral films of metoclopramide hydrochloride for pediatric use: formulation and in- vitro evaluation. Drug: Metoclopramide Polymer: Hypromellose, CMC Description: formulation containing hypromellose released 99.40 percent of medication within 30 seconds. J Chem Pharm Res. 110 Prabhu P

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et al. (2011) Formulation and evaluation of fast dissolving film of levocetirizine dihydrochloride.

Drug: Levocetirizine dihydrochloride Polymer: hypromellose E50, Hypromellose E15, and PVA Description: dissolution investigation was carried out in glass beaker filled with 30 mL of Int J Pharma Investig. 111

17 pH 6.8 simulated saliva and spun at 100 RPM. Sumitha C et al. (2011) Development of taste masked fast dissolving orally consumable films of sildenafil citrate. Drug: Sildenafil citrate Polymer: Hypromellose E5 Description: Sildenafil citrate oral films made with hypromellose E5 as film former. As plasticizer, cooling agent, and sweetener, glycerol, menthol, and sucralose were used. Menthol was utilised as powerful flavouring and cooling ingredient, although ion- exchanging agents like polacriline potassium were used to disguise taste. Journal of Pharmaceutics and Cosmetology 112 Mishra R et al. (2011) Formulation and characterization of rapidly dissolving films of cetirizine hydrochloride using pullulan as film forming agent. Drug: Cetirizine Polymer: Pullulan, PG Description: enhanced film formulation disintegrated in less than 30 seconds. In 500 mL distilled water, 900 mL 0.1N hydrochloric acid, and 500 mL simulated salivary fluid, multimedia dissolving profile of optimised formulation was created Ind J Pharm Edu Res 113 Kunte S et al. (2010) Fast dissolving strips: Novel Approach for Drug: Verapamil Polymer: HPMC E6 . J Pharm Bioallied Sci. 114

18 Delivery of Verapamil. Method: Solvent Casting Method Description: film formulation with 2% hypromellose (HPMC E6) and 3.5 percent maltodextrin was deemed optimal since it showed highest release in dissolution test (900ml pH 6.6

phosphate buffer/ basket/ 50 RPM) when compared to other formulations Cilurzo F et al. (2010) Diclofenac fast-dissolving film: suppression of bitterness by taste-sensing system Drug: Maltodextrin Polymer: HPMC Description: In film's formulation, nicotine was used as tartrate salt. Maltodextrin films with dextrose equivalent value of 6 were stiffer and less brittle than maltodextrin films with dextrose equivalent value of 12. time it took for prepared films to disintegrate was about 10 seconds. inclusion of mint and milk flavour masks harsh taste of nicotine Drug Dev Ind Pharm. 115 El-Setouhy DA et al. (2010) Formulation of novel tianeptine sodium orodispersible film Drug: Sodium Tianeptine Polymer: Lycoat NG73 Description: orodispersible film made from lycoat NG73 and propylene glycol had best AAPS PharmSciTech 116

19 drug solubility in dissolution media (400 ml freshly distilled water / basket/ 100 RPM), physicochemical characteristics, and in vitro disintegration time. pharmacokinetic properties of film containing lycoat NG73 were assessed compared with reference marketed product (Stablon® tablets) in rabbits Murata Y et al. (2010) Preparation of fast dissolving films for oral dosage from natural polysaccharides Drug: Dexamethasone, Pilocarpine, and Lidocaine Polymer: Pullulan Description: Dexamethasone was completely released from films after 15 minutes, albeit at slower rate than pilocarpine or lidocaine in pH 7.4 phosphate buffer solution poured in petriplate with 300 RPM shaking. Materials 117 Singh S et al. (2010) Formulation and evaluation of rapidly disintegrating film of levocetizine hydrochloride Drug: Levocetizine Hydrochloride Polymer: Sodium alginate Description: Within 6 minutes, 70–85 percent of medication was released in dissolving medium Der Pharmacia Lettre 118 Koland M et al. Fast dissolving sublingual Drug: Ondansetron hydrochloride J Young Pharm 119

20 al. (2010) films of ondansetron hydrochloride: Effect of additives on in vitro drug release and mucosal permeation Polymer: polyvinyl alcohol, polyvinyl pyrrolidone, and carbopol 934P Description: In vitro dissolving studies showed that roughly 81 to 96 percent of drug was released in simulated salivary fluid within 7 minutes and that approximately 66 to 80 percent of drug was diffused from porcine membrane model. Sumitha C et al. (2009) Taste masking of

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ondansetron hydrochloride by polymer carrier system and formulation of rapid disintegrating

films Drug: Ondansetron hydrochloride Polymer: Hypromellose E15 and Polyethylene oxide N-10 Description: Due to no release in simulated salivary fluid, formulation comprising 7% w/w polyethylene oxide N-10 and 2:1 drug-polymer ratio was chosen as flavour masked formulation. Dissolution tests were performed using paddle at 50 RPM in 500 mL of simulated stomach juice without enzymes. Int J Chem Res. 120 Shimoda H et al. (2009) Preparation of fast dissolving oral thin film containing dexamethasone: Drug: Dexamethasone Polymer: Hypromellose Description: In dissolution medium of 900ml Eur J Pharm Biopharm 121

21 possible application to antiemesis during cancer pH 1.2 phosphate buffer in paddle system at 50 RPM, approximately 90% of active was released from formulation within 5 minutes. Cilurzo F et al. (2008) Fast dissolving films made of maltodextrins. Drug: Maltodextrins Polymer: Polyethylene glycol 400, Sorbitan oleate Description: Orally consumable orodispersible film using maltodextrin as main water-soluble polymer, but with glycerin added up to 16–20 percent w/w to increase flexibility and tensile strength. Plasticizers such as polyethylene glycol 400, sorbitan oleate, glycerin, and propylene glycol were tested. Piroxicam was included as active ingredient in improved placebo formulation Eur J Pharm Biopharm. 122 Dinge et al. (2008) Formulation and evaluation of fast dissolving films for delivery of triclosan to oral cavity Drug: Triclosan Polymer: Hypromellose Description: When compared to films containing Triclosan-HPBCD complex, films containing Triclosan-Poloxamer 407 with eugenol as mouth freshener demonstrated AAPS PharmSciTech 123

22 enhanced in vitro dissolving properties, improved taste masking, and antibacterial activity Sharma R et al. (2007) Development of taste masked film of valdecoxib for oral use Drug: Valdecoxib Polymer: Eudragit EPO and Hypromellose Description: In in vitro dissolution test, film with higher glycerol concentration released medication faster. As taste-masked valdecoxib film, fast-dissolving film comprising eudragit EPO, aspartame, and menthol was regarded optimal. Indian J Pharm Sci 124 Mashru R. et al. (2005) Development and evaluation of fast- dissolving film of salbutamol sulphate Drug: Salbutamol sulphate Polymer: Polyvinyl alcohol Description: best answers for prepared film formulation were found at medium polymer and plasticizer concentration levels, as well as high sugar alcohol concentration level, according to data. Drug release properties were shown to be similar in pure water, simulated salivary fluid, and pH 1.2 simulated stomach acid for optimized film formulation Drug Dev Ind Pharm. 125

23 2.2 Literature Review on ZPO HCL: Author Name & Publication Year Title of Paper Description Journal Name Reference No Vaishali L & Sreevidya K. (2021) Formulation, Evaluation, and Pharmacodynamic Investigation of

Ziprasidone- β cyclodextrin In-Situ Nasal Gel Drug; Ziprasidone hydrochloride Polymer: β cyclodextrin (β CD) and Polaxomer 407 Description: solubility of ziprasidone was efficaciously enhanced by its inclusion complex with β -cyclodextrin and was formulated as in- situ nasal gel. optimized formulation comprising drug with β -cyclodextrin showed significant release and mucoadhesive strength to confirm suitable residence time at site of action. Proceedings 126 Anup Kumar.et al (2021) Formulation and Evaluation of Nasal Mucoadhesive Microspheres of Drug; Ziprasidone hydrochloride Polymer: Chitosan Description: In conclusion, present study showed that Ziprasidone chitosan microspheres IAR Journal of Pharmacy 127

24 Atypical Antipsychotic Agent can deliver intanasally which can improve therapeutic outcome for Epileptic seizure. Muhammad M. et (2020) Formulation And Evaluation Of ZPO HCL Oral Controlled Release Matrix Tablets Drug; Ziprasidone hydrochloride Polymer:HPMC K13 Description: it can be concluded that controlled release Ziprasidone hydrochloride matrix tablets can be efficiently prepared by using HPMC through cost-effective and simple direct compression method. Pharmacophore 128 Kailash S. et al (2018) Formulation and Evaluation of Gastro Retentive Sustained Release Tablets of Ziprasidone Hydrochloride Drug; Ziprasidone hydrochloride Polymer: Mg sterate, HPMC K4M, Description: In present study gastro relative floating matrix tablet of ziprasidoneHCLwere successfully prepared by direct compression method. study showed that ratio of polymer agent can be used as matrix forming agent to sustain release of drug to concentration of polymers increased drug release rate decreased among all there formulation F6 was found to be best formulation. Research J. Pharm. and Tech. 129 Solubility Enhancement Drug: Ziprasidone Pharmaceutical 130

25 Saish R. et al (2018) and Formulation Development of Ziprasidone Immediate Release Oral Drug Delivery Polymer: β -cyclodextrin Description: optimized pellet formulation prepared using extrusion spheronization technique consisting drug: β -CD inclusion complex showed rough surface of pellets with more than 80% drug release within 60 minutes which was comparative to marketed tablet formulation. Resonance Kajal S. & Kiran B. (2016) Solubility Enhancement And Formulation Of Fast Dissolving Tablet Of Ziprasidone Hydrochloride Drug; Ziprasidone Hydrochloride Polymer: Sulfobutylether- β -cyclodextrin Description: effect of types and concentrations of superdisintegrant on disintegration time and dissolution profile of Ziprasidone Hydrochloride fast dissolving tablets were studied. % drug release of Fast Dissolving tablet F7 shows 98.25 % drug release after 20 minutes. However further in vivo studies are needed to justify effect of increasing solubility of Ziprasidone Hydrochloride on its bioavailability. International Journal Of Research In Pharmacy And Chemistry 131

26 Y. Miao, et al. (2016) Characterization and evaluation of self- nanoemulsifying sustained- release pellet formulation of ziprasidone with enhanced bioavailability and no food effect Drug: Ziprasidone Hydrochloride Polymer: PEG 400 Description: extrusion-spheronization method was utilised to create ziprasidone-SNEDDS sustained-release pellets using improved ziprasidone-SNEDDS. SEM, particle size, droplet size distribution, and zeta potential were all measured on pellets. In vitro drug release experiments revealed that ziprasidone-SNEDDS sustained-release pellets had sustained release profile, with 90% of pellets being released within 10 hours Informa Healthcare USA 132 A. Gauniya (2015) Drug: Ziprasidone Hydrochloride Polymer: Kollidone and Tween 80 Description: ZIP and ZIP nanocrystals were subjected to differential scanning calorimetry, which revealed that there was no interaction between ZIP and stabilisers. solubility of ZIP nanocrystals increased substantially as compared to ZIP 133 D. Formulation, Optimization Drug: Ziprasidone Hydrochloride International Journal of 134

27 Zakowiecki (2015)

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And Characterization Of Ziprasidone Nanocrystals Prepared By Media Milling Technique

Polymer:Gelatin Description: dissolution rate of produced ziprasidone free base preparations was found to be equivalent to or even higher than that of reference formulation including ziprasidone hydrochloride, which has 400-fold higher water solubility than free base Pharmacy and Pharmaceutical Sciences Vasanth P. M et al (2013) Development of gastroretentive drug delivery system of ziprasaidone hydrochloride Drug: Ziprasidone Hydrochloride Description: psychotropic agent is ziprasidone hydrochloride. sustained-release formulation of Ziprasidone hydrochloride is desirable to reduce frequency of administration and enhance patient compliance. Scholars Research Library 135 Koteswari Poluri.et al (2013) Formulation Development And Evaluation Of Novel Oral Soluble Films Of Ziprasidone Hydrochloride In Treatment Of Schizophrenia Drug; ZPO HCL Polymer: HPMC. Description: Overall findings suggested that ZPO HCL oral soluble films of HPMC E5 exhibited desired disintegration time \leq 50 seconds, good drug loading efficiency and stability.

International Journal of Pharmacy and Pharmaceutical Sciences 136 A. J., et al. Natural gums as sustained Drug: Ziprasidone Hydrochloride DARU Journal of 137

28 (2012) release carriers: development of gastroretentive drug delivery system of ZPO HCL Polymer:HPMC K4
 Description: As result, objective has been set to assess potential of Okra gum and LBG in combination with HPMC K4 for gastro- retentive drug delivery system of ZPO HCL utilising simplex lattice design (SLD). Pharmaceutical Sciences S. Kumar (2011) Formulation and evaluation of bi-layer floating tablets of ZPO HCL and trihexyphenidyl HCl Drug: Ziprasidone Hydrochloride Polymer: HPMC Description: drug release involved non- diffusional methods, according to n values of Korsmeyer equation. According to results of this investigation, bi-layer tablets containing ZPO HCL and trihexyphenidyl HCl will be useful technique for extending metabolism and increasing bioavailability of ZPO HCL and Trihexyphenidyl HCl. Brazilian Journal of Pharmaceutical Sciences 138

29 2.3 Literature Review on Quetiapine Fumarate: Author Name & Publication Year Title of Paper Description Journal Name Reference No
 Keyur S. et al (2021) Formulation and Evaluation of Gastroretentive Floating Tablets of Quetiapine Fumarate Drug: Quetiapine Fumarate Polymer: Description: From factorial design batches it was found that floating lag time was decreased with increasing amount of sodium bicarbonate and decreasing amount of natrosol 250 HHX. Here % release of drug was decreased with increase extent of natrosol 250 HHX. in-vitro release kinetics revealed Korsmeyer-Peppas model is followed and drug release is by anomalous diffusion. Journal of Drug Delivery and Therapeutics 139
 Mehetre G. et al (2020) Quetiapine Fumarate Buccoadhesive Tablet- Formulation and In Vitro Evaluation Drug: Quetiapine Fumarate Polymer: HPMC, Carbopol, Description: Study and test results as FTIR analysis proved compatibility of polymers with drug; blend of Research J. Pharm. and Tech. 140

30 polymers help control drug release over extended time period. Bioadhesive studies revealed promising adherence to buccal mucosa helping for controlled drug release and thereby enhanced bioavailability. release 141analysis revealed erosion mediated drug release. Asha R., et al. (2017) Formulation And Evaluation Of Albumin Nanoparticles Of Anti-Psychotic Drugs Drug: Quetiapine Fumarate Polymer: HPMC Description: Simple coacervation was used to make AL-NPs from Quetiapine fumarate (QA), ZPO HCL (ZA), and Paliperidone (PA). On magnetic stirrer, aqueous solutions of albumin in various concentrations were churned, and precisely weighed amount of medication was added under constant swirling. Acetone was added drop by drop to albumin drug solution (desolvating agent) until solution became barely turbid. Journal of science research in pharmacy 142 A. Gavan, et al. (2017) Formulation and pharmaceutical development of quetiapine Drug: Quetiapine Fumarate Polymer: HPMC Description: influence of matrix-forming Acta Pharm. 143

31 fumarate sustained release matrix tablets using QbD approach polymer (HPMC) % and filler type on cumulative ratio of medication released at different time intervals for period of 24 hours was evaluated using quadratic D-optimal experimental design, and optimal formulations were defined. H. Baishya (2016) EFFECT OF COMPACTION PROCESS IN GRANULOMETRY; Drug: Quetiapine Fumarate Description: goal of this study is to develop long-acting pharmaceutical composition having Quetiapine fumarate in sustained-release matrix formulation 7, with one of compacted ingredients within specified particle size, in order to maintain blood levels of active ingredient. International Journal of Pharmaceutical Sciences and Research 144 Lakshmi P. et al (2016) Formulation development, In-vitro and In-vivo evaluation of novel solid oral dosage form containing Quetiapine nanoparticles. Drug: Quetiapine Fumarate Polymer: PVP, Mannitol Description: enhancement of oral bioavailability of nanoparticle formulation can be attributed to increase in surface area obtained by particle size reduction. This enhancement in oral bioavailability can be International Journal of Drug Delivery 145

32 explored on strong possibility of dose reduction of quetiapine fumarate so that dose related side effects of this drug can be minimized. A. Bharathi et al (2014) Formulation development and evaluation of sustained release matrix tablets of quetiapine fumarate; Drug: Quetiapine Fumarate Polymer: Guar gum, Tara gum, Microcrystalline cellulose, Description: Quetiapine is well tolerated and effective in patients who are particularly vulnerable to these severe side effects, such as elderly and adolescents, as well as those who have pre-existing dopaminergic pathologies like Alzheimer's disease and Parkinson's disease Journal of Chemical and Pharmaceutical Research 146 G. Garbacz (2014)

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Release Characteristics of Quetiapine Fumarate Extended Release Tablets Under Biorelevant Stress Test Conditions;

Drug: Quetiapine Fumarate Description: Quetiapine is designated as BCS class II medicine because of its low solubility over physiological pH range but high permeability. Dissolving tests of tablets containing 50 and 400 mg quetiapine were

carried out using 0.1 mol/L HCl (pH 1.0) solution as artificial medium to simulate fasting stomach circumstances and phosphate buffer AAPS PharmSciTech 147

33 pH 6.8 (USP) as dissolution medium to simulate fasting intestinal conditions. R Mohapatra. Et al (2013) Formulation and Development of pH Independent Once Daily Matrix Tablet of Quetiapine Fumarate Drug: Quetiapine Fumarate Polymer: udragit NE 30D and Polyethylene oxide Description: It was thus concluded that desired drug dissolution profile could be achieved by formulating Quetiapine Fumarate as matrix SR tablets using polyox WSR 303 & polyox WSR 205 combinations. During course of study various sustained released tablet formulations (T1-T16) of QF were formulated by using eudragit NE 30D as matrix forming agent. Different percentages of polyox WSR 303 & polyox WSR 205 were used and amount of drug was 300 mg in all batches. Research Journal of Pharmaceutical, Biological and Chemical 148 Arjun N. & Kishan V. (2013) Preparation, Characterization and Evaluation of Quetiapine Fumarate Solid Lipid Nanoparticles Drug: Quetiapine Fumarate Polymer: Sodium carboxymethyl cellulose Description: SLN using three different lipids after checking compatibility by DSC studies. Journal of Pharmaceutics 149

34 to Improve Oral Bioavailability SLN preparation with Dynasan 118 was optimized based on particle size, PDI, zeta potential, entrapment efficiency, and drug release characteristics. During in vivo bioavailability studies 3.71 times of relative bioavailability improvement was found when compared to reference suspension. Thus, quetiapine fumarate when formulated as SLN could improve oral bioavailability. Arun K. et al (2013) Formulation And Evaluation Of Quetiapine Immediate Release Film Coated Tablets Drug: Quetiapine Fumarate Polymer: HPMC Description: results indicate that there were insignificant changes during studies. Hence, results suggest feasibility of developing immediate release tablets consisting of Quetiapine, which has excellent tolerability profile offering high patient acceptability that may promote patient adherence to medication and improved quality of life. Asian Journal of Pharmaceutical and Clinical Research Appa R. et al Formulation and evaluation of buccoadhesive Drug: Quetiapine Fumarate Polymer: HPMC Brazilian Journal of Pharmaceutical 150

35 (2012) quetiapine fumarate tablets Description: present work was aimed at developing buccoadhesive Quetiapine Fumarate tablets. Progressive hydration technology was employed by using various grades of HPMC in combination with carbopol and HPC for their reported buccoadhesive and release rate controlling abilities. Sciences Deepak S. & Rana A. (2010) Development and in vitro evaluation of Quetiapine Fumarate Sustain release tablets Drug: Quetiapine Fumarate Polymer: HPMC, PVP K30 Description: In conclusion, PVP K30 and HPMC K 15M can be used as rate controlling polymers by appropriate selection of level of polymers in matrix. International Journal of PharmTech Research 151 2.5 Patent Summary: Table 2. 1 Patent Summary Sr. No Patent No Title 1 US20060198873A1 Orally dissolving films 2 US9694008B2 Fast-dissolving oral film preparation comprising aripiprazole 3 WO2016190714A1 Orally fast dissolving film formulation including

36 aripiprazole and method for producing same 4 EP2883540A1 Fast-dissolving oral film preparation comprising aripiprazole 5 US5948430A

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Water soluble film for oral administration with instant wettability 6 US8178674

B2 Process for preparation of ziprasidone 7 US6150366A Ziprasidone formulations 8 CN104744454A Production method of ziprasidone 9 US20070265447A1 Process for Preparation of Ziprasidone (5-[2-[4-(1,2-Benzisothiazol-3-Y1)-1-Piperaziny]Ethyl]-6-Chloro- 1,3-Dihydro-2H-Indol-2- One 10 EP1975169A1 Process for preparation of ziprasidone 11 US7687622B2 Process for preparing quetiapine fumarate 12 US7238686B2 Polymorphs of quetiapine fumarate 13 US8048876B2 Process for preparing quetiapine and quetiapine fumarate 14 CN102552128A Quetiapine fumarate injection and preparation method thereof 15 CN101991555A Quetiapine fumarate tablet and preparation method thereof

37 3. FORMULATION & DEVELOPMENT OF ZIPRASIDONE HYDROCHLORIDE MOUTH DISSOLVING FILM FOR PSYCHOSIS TREATMENT 3.1. RATIONAL OF RESEARCH WORK: 3.1.1. RATIONAL OF MOUTH DISSOLVING FILM FORMULATION (MDF) The oral route is one of most commonly utilised medicine delivery modalities due to its safety, ease of administration, and patient acceptability. Around 60% of conventional dosage forms are available in oral solid dose forms. Orally dissolving strips and films aid patients such as paediatrics, geriatrics, bedridden, and emetic patients, as well as difficulties like acute allergy responses or coughing. They can be employed on local as well as national level. Orally dissolving film and strips are becoming more popular as alternative to fast dissolving tablets due to their faster dissolve rate, greater flexibility, and improved patient compliance. Currently, studies are being conducted on use of orally dissolving films as prospective

carriers for variety of active therapeutic ingredients. Orally dissolving film items such as Listerine, Chloraseptic, Triaminic, and multivitamins are commercially marketed. backbone of orally dissolving film is made up of plasticizer and film forming polymer, or mixture of polymers, which provides it elasticity and shape. Fast disintegrating films are most sophisticated form of solid dosage form due to their flexibility. It improves efficacy of active medicinal compounds when compared to dissolving tablets since they break down in oral cavity in short amount of time after contact with less saliva. This method of distribution involves placing thin film on tongue or mucosal tissue that is instantly wet by saliva. When film is moist, it quickly disintegrates, allowing medicine to be absorbed through oral mucosa. fast disintegrating film made of hydrophilic polymer that rapidly disintegrates for buccal cavity delivers medicine to systemic circulation via buccal mucosa. Fast dissolving drug delivery systems are specifically intended for medicines with significant first pass metabolism and low dosage to maximise bioavailability.

38 3.1.2. RATIONAL OF FORMULATION & DEVELOPMENT OF MOUTH DISSOLVING FILM FOR PSYCHOSIS TREATMENT: Hallucinations, dementia, and convulsions are all symptoms of psychosis. It must be treated early in order to limit risk of long-term brain damage. Pharmacotherapy with antipsychotic medications is still most prevalent treatment for psychosis. treatment of psychosis differs from that of other illnesses. newer antipsychotic in orally dissolving film format is appropriate pharmaceutical candidate. Antipsychotics designed as orally dissolving strip that must be placed on patient's tongue without being swallowed to deliver dose would substantially simplify dose administration and improve patient compliance. goal of this study was to design, develop, and characterise antipsychotic medication mouth dissolving films.

39 3.1.3. RATIONAL OF FORMULATION & DEVELOPMENT OF ZIPRASIDONE HYDROCHLORIDE MOUTH DISSOLVING FILM FOR PSYCHOSIS TREATMENT: Ziprasidone Hydrochloride is new atypical antipsychotic drug that has demonstrated to be effective in treatment of schizophrenia. Atypical antipsychotic drug ziprasidone hydrochloride is used to treat schizophrenia and mania. It's considered BCS class II medicament. It has solubility problem. Ziprasidone Hydrochloride is rapidly absorbed and extensively metabolised through N-dealkylation, oxidation, reductive cleavage, hydration, and N-dearylation. It binds to adrenergic, histamine, serotonin, and dopamine receptors. Ziprasidone Hydrochloride is difficult-to-dissolve drug. goal of this research is to develop oral mouth dissolving film that will improve medicine's solubility. Fast dissolving film provides several benefits, particularly for paediatric and geriatric patients who have difficulty swallowing regular pills and capsules, and it increases patient compliance. 3.2. OBJECTIVES OF RESEARCH WORK: The prime objectives were to develop MDF drug delivery system that: 1. To make release of drug at oral mouth cavity and hence dose and dose frequency can be decreased thereby obtaining greater therapeutic efficacy. 2. To Show better in-vitro release/diffusion performance than conventional dosage forms.

40 3.3. PLAN OF RESEARCH WORK: 3.3.1. Literature survey and Patent Search related to Drug, Polymer & MDF Technology. 3.3.2. Selection of Drug, Polymer and Methodology for formulation & development of MDF drug delivery system 3.3.3. Pre-formulation study of Drug ✓ Organoleptic characteristics of drug ✓ Melting Point ✓ Solubility ✓ Partition Co-efficient ✓ Identification of drug by λ_{max} , FT-IR study. ✓ Preparation of Calibration Curve of Drug ✓ Drug- polymer Compatibility study FT-IR study 3.3.4. Preparation of MDF. 3.3.5. Preliminary Trial Batches for selection of materials 3.3.6. Formulation of Drug loaded MDF Using Factorial Design (DoE) approach 3.3.7. Characterization of Drug loaded MDF ✓ Thickness ✓ Weight variation ✓ Drug Content ✓ Measurement of mechanical property ✓ Folding endurance ✓ Physical appearance and texture analysis of films ✓ In vitro disintegration ✓ In vitro dissolution ✓ Flux and Permeability Co-efficient Study ✓ Kinetics of drug release ✓ Statistical analysis ✓ Validation batches (Check Point Analysis) and its characterization of drug loaded MDF ✓ FT-IR Study of Optimized MDF Formulation ✓ Comparison of optimized MDF with conventional marketed formulation. ✓ Ex- vivo study subjected to IAEC approval and permission

41 ✓ Accelerated stability study 3.3.8. Thesis writing and paper publication in esteem journal. 3.4. EXPECTED OUTCOME The foundation of successful pharmaceutical formulation is conveyance of medicament to target site at therapeutically relevant level, with little or no discomfort and unwanted effects on patient. In this sense, route of drug delivery plays vital role. Because it is easiest to administer, oral medicine administration is most common method of drug delivery. However, it has drawbacks, such as reduced bioavailability due to first-pass effect and predisposition for producing high and low plasma concentrations of drug quickly, resulting in poor patient compliance. Continuous intravenous infusion has been discovered to overcome drawbacks of oral route by maintaining steady and sustained medicine concentration within therapeutic range for long time. However, there are significant drawbacks to this type of drug delivery, including as needle pain and unintended needle sticks, which necessitate periodic hospitalisation and medical care during therapy. Mouth dissolving film is now day's preferred route of drug administration due to patient compliance. main expected outcome of present work will be: ✓ Development of Mouth Dissolving Film (MDF) ✓ Formulation of effective formulation for treatment of psychosis patients ✓ Patient's compliance due to development of MDF.

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The following materials, chemical substances and devices might also be used for Ziprasidone Mouth Dissolving Film for Psychosis Treatment as per

following Table. 4.1 List of Materials Table 4. 1 List of Materials MATERIALS SOURCE ZPO HCL Zota Healthcare LTD, Surat. HPMC E5 Zota Healthcare LTD, Surat. PEG 400 Zota Healthcare LTD, Surat. Citric Acid Zota Healthcare LTD, Surat. Aspartame Zota Healthcare LTD, Surat. Mannitol Zota Healthcare LTD, Surat. Orange Flavour Zota Healthcare LTD, Surat. Methyl Paraben Zota Healthcare LTD, Surat. Propyl Paraben Zota Healthcare LTD, Surat. Vanillin Zota Healthcare LTD, Surat. 4.2 List of Equipments Table 4. 2 List of Equipments EQUIPMENTS MODEL AND SOURCE UV – Visible Spectrometer UV-1700, Shimadzu Corporation. Mechanical Stirrer Remi instrument division Electronic Balance Ohaus corporation NJ, USA Humidity Cabinet Analytical Technologies, Bangalore. Scanning Electron Microscope JEOL JSM-6380KVM Oxford Instruments, England FT-IR Spectrophotometer Shimadzu Corporation Compound Microscope Acculab Dissolution Apparatus I, USP I Macro scientific works private limited, Delhi. Malvern Malvern Instruments LTD.

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Methodology 4.3.1 Preformulation of ZPO HCL The Preformulation find out about is often generate facts beneficial to improve secure dosage varieties that can be heavily produced for manufacturer. 4.3.1.1 Organoleptic Characteristics of ZPO HCL Physical look at was done to check Organoleptic Qualities of ZPO HCL like Tone and Smell. 4.3.1.2 Taste Evaluation Study by Spitting

Eight sound grown-up male volunteers between ages of 24 and 42 participated in solitary measurement, single visually impaired preliminary. Preceding preliminary, all subjects gave composed informed assent and were instructed with regards to review's motivation, dangers, and length. ZPO HCL was given to each chip in at irregular. Before review, volunteers were encouraged to flush their mouths with 200 cc of refined water. volunteers were told to place medication in their mouth for 30 seconds, record breaking down span of film test, and rate plan in view of elements showed in Table 3, in particular mouth feel, flavor or harshness, film trailing sensation, simplicity of taking care of, and in general acknowledgment. volunteers were told to let out example with spit and wash their mouths with 200 cc refined water following 3 minutes. Following 2 hours, indistinguishable methodology was finished subsequent example. To stay away from drug openness, subjects were encouraged to throw up definition and salivation. Table 4. 3

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Parameters, Score and Results of Taste Evaluation Study 44 4.3.1.3 Determination of Melting Point of ZPO HCL Melting point of ZPO HCL was evaluated by capillary method. 4.3.1.4 Identification and Determination of Wavelength max (λ_{max}) of

ZPO HCL The fittingly gauged amount of 10 mg of medication test was disintegrated in DMSO and volume was raised up to 100 ml involving methanol in 100 ml volumetric carafe to make stock arrangement of 100 g/ml. Pipetting 1 ml of this stock arrangement into 10 ml volumetric carafe and filling it to imprint yielded centralization of 10 g/ml. UV- noticeable spectrophotometer was utilized to check resultant arrangement somewhere in range of 200 and 400 nm (Model-1700, Shimadzu, Japan). most extreme worth got from UV range of example was contrasted with UV range provided in authority monograph. 4.3.1.5 Solubility study of ZPO HCL Overabundance medicine was broken up in glass vials containing 20mL of suitable dissolvable framework, and supernatant arrangement was sifted following 24 hours at room temperature utilizing 0.45 m pore size channel. initial 10 mL of filtrate were disposed of, and rest was weakened with water and investigated spectroscopically at 317nm. Different solvents will be used all through procedure, including water, CH₃CO,

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ethanol, chloroform, ether, and pH 7.4 Phosphate cushion. 4.3.1.6 Determination of Partition Co-efficient: It was once decided via soaking 10mL of n-octanol in 10mL

of phosphate buffer pH 7.4 for 24 hours in isolating funnel. isolating funnel will be stuffed with 10mg of medicine, observed through four hours of intermediate shaking. quantity of medicinal drug dissolved in every section was once measured at 317 nm towards clean after layers of solvent have been separated use of funnel. 4.3.1.7 Preparation of Calibration Curve for ZPO HCL 4.3.1.7.1 Calibration Curve for ZPO HCL IN 0.1N HCL solution Preparation of Stock solution 100 milligrammes of medication used to be exactly weighed in one hundred mL volumetric flask. To create one hundred g/ml solution, quantity was once extended to hundred ml via including 0.1N HCL solution. 1 ml of inventory answer (100 g/ml) used to be pipetted into various volumetric flasks and diluted to 10 ml with 0.1N HCL answer to get concentrations ranging from 1.0 to 5.0 g/ml.

45 Preparation of standard working solution 1ml of stock arrangement (100g/ml) was taken and weakened with 0.1N HCL answer for make 10ml. To create convergence of 1.0 to 5.0g/ml, proper aliquots of arrangement were taken into different volumetric jars and made up to 10ml with 0.1N HCL arrangement. A medication adjustment bend in 0.1 N HCL was created by dissolving definitively gauged 100 mg of medication in 100 ml volumetric cup. volume was then raised to 100ml utilizing 0.1N HCL answer for produce 100g/ml arrangement, which was then examined in UV spectrophotometer to approve that example observed Lager's Regulation. 4.3.1.8

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Calibration Curve for ZPO HCL in Saline buffer pH 7.4 Preparation of Stock solution A 100g/ml stock arrangement of ZPO HCL was created in saline cushion pH 7.4 by dissolving 10 mg of medication in 10 ml of methanol and

afterward filling rest of saline support pH 7.4. most noteworthy grouping of ZPO HCL was found by checking reasonable weakenings with decent relationship coefficient. Different standard weakenings of stock arrangement

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were made to acquire arrangements of 2,4,6,8, and 10 g/ml, and their absorbance values were estimated at fixed max with

transmission capacity and information pitch boundaries set at 0.5nm. Preparation of Standard working solution The subsequent arrangement was sequentially weakened with saline cushion pH 7.4 answer for get arrangements of 10, 20, 40, 50, and 100 g/ml. convergence of ZPO HCL was tried further by estimating absorbance at 317nm. 4.3.1.9 Identification of ZPO HCL by FT-IR Spectroscopy The potassium bromide IR circle will be made utilizing water powered pellet press with 1mg of ZPO HCL, checked at 4000-400 cm⁻¹ in FTIR, and IR spectra contrasted with ZPO HCL reference range. 4.3.1.10 Drug- Excipients Compatibility Studies by FT-IR A

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potassium bromide IR circle will be produced using combination of ZPO HCL, HPMC E5, Stake 400, Citrus extract, Aspartame, and Mannitol, which will be examined in 4000-400 cm⁻¹ region in FTIR and contrasted with reference spectra of ZPO HCL. 46 4.3.1.11 Particle Size Study: Unadulterated Medication Molecule size examination had done utilizing Optical Magnifying lens and Malvern Instrument. 4.4

Formulation and Development of ZPO HCL MDF 22-54 4.4.1 Preliminary Trial Batches of ZPO HCL MDF: In early preliminaries, impacts of polymer type and focus, plasticizer type and fixation, breaking down specialists, and other excipients on MDF will be analyzed. These fundamental clusters of quick deteriorating films were tried utilizing

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morphological examination, weight variety, crumbling time, surface pH, collapsing perseverance, thickness, drug content consistency, percent uniform medication conveyance, and in-vitro drug discharge study to foster QbD Approach. 4.4.2 Dose calculation of ZPO HCL for mould Dose of drug = ORAL DOSE * ORAL BIOAVAILABILITY/ BODY SURFACE AREA > Area of mould is 24 cm² (12 cm x 2 cm). > Area of film is 6 cm² (3 cm x 2 cm). > Total number of films in each mould 24/6 = 4 > One film contains 25 mg of drug than 4 films containing 100 mg drug > So, one mould containing 100 mg drug 4.4.3 Solvent casting method Oral fast deteriorating films are ready by dissolving film arrangement materials (polymers) and plasticizer in

refined water, blending continually on attractive stirrer for 4 hours, and afterward keeping arrangement short-term in refined water for expanding. In mean time, in different holder, excess excipients, including spit invigorating specialist, Super dissolving specialist, improving specialist, surfactant, flavor, and medicine, are broken up in water for 45 minutes with steady mixing. After twirling is finished, two arrangements are blended and whirled on attractive stirrer for one more hour. Then, at that point, for 60 minutes, let arrangement be to permit froths to settle. Sonicate arrangement in sonicator to kill any air bubbles. completed combination is filled shape and dried to make film. film ought to be air-dried prior to being painstakingly eliminated and cut into 62 centimeter size. Table 4. 4 Materials and their concentration used for Preliminary trial Batches of ZPO HCL MDF

47 SL. NO ROLE OF MATERIAL MATERIALS TO BE USED CONCENTRATION 1 Drug ZPO HCL 100 mg 2 Polymers HPMC E5, HPMC K4M, Acacia, Tragacanth, Gelatin, Xanthum Gum, PVA, PVP and Pullnan 0.1 gm to 0.5 gm 3 Plasticizers PEG 200, PEG 400, PEF 800, PG, IPA 0.1 gm to 0.5 gm 4 Disintegrating Agent Cross Providone, Kryon T-314, Banana Powder 0.05 gm to 0.1 gm 5 Solvent Distilled water Q.S. 6 Sweeting Agent Aspartame, Mannitol Q.S. 7 Flavouring Agent Vanillin Q.S. 8 Preservative Citric acid, Methyl paraben, Propyl paraben Q.S. 4.4.4

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Preliminary Trial Batches of ZPO HCL MDF 4.4.4.1 Selection of Polymer and concentration for ZPO HCL MDF: The various polymers

and their fixations were utilized to plan ZPO HCL MDF to fix polymer type and focus. subtleties are as per following: Table 4. 5 Polymer and concentration for ZPO HCL MDF 4.4.4.2 Selection of plasticizer for ZPO HCL MDF The different plasticizer and their fixations were utilized to get ready ZPO HCL MDF to fix plasticizer type and focus. different plasticizer utilized were as per following: POLYMER TYPE USED HPMC E5 Acacia Gelatin PVA PULLNAN HPMC K4M Tragacanth Xanthum gum PVP POLYMER CONCENTRATION USED (mg) 100 300 500

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Table 4. 6 Plasticizer type and concentration for ZPO HCL MDF PLASTICIZER TYPE USED PEG 200 PEG 400 PG IPA

PLASTICIZER CONCENTRATION USED (ml) 1 to 2 0.5 to 1.0 4.4.4.3 Selection of disintegrating agent for ZPO HCL MDF The various polymers and their focuses were utilized to get ready ZPO HCL MDF to fix polymer type and fixation. subtleties are as follows:

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The different polymer utilized were as per following: Table 4. 7 Disintegrating agent type and concentration for

ZPO HCL MDF 4.5

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Formulation and Development of ZPO HCL MDF by Design of Experiment (DoE) Using QbD Approach A plan space

could address detailing and cycle information, like properties of medication fixings, materials, gear, protected innovation, and completed item quality. For this point, danger appraisal of MDF quality can be performed in view of comprehension of interaction and its related parts. Fundamental review and later Plan of Trial and error (DoE) would be finished high-hazard boundaries. In light of impact of basic quality models of expected item profile, we will give plan space to creating powerful definition. MDF will be evaluated in view of various elements.

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DISINTEGRATING AGENT TYPE USED Cross Povidone (g) Kyron T-314 (g) Banana Powder (g)

DISINTEGRATING AGENT CONCENTRATION (mg) 50 to 100 mg

49 4.6 Characterization of ZPO HCL MDF 4.6.1 Weight variation Mouths dissolving oral movies were burdened logical equilibrium, and normal load for each film was processed. It is liked for motion pictures to have weight that is almost consistent. It's basic to guarantee that film contains suitable measure of excipients and Programming interface. 4.6.2 Thickness of Films A micrometer screw check was utilized to gauge thickness of film at five unique places, and normal of three estimations was determined. This is expected to give consistency in film thickness, which is connected to portion precision in film. 4.6.3 Folding endurance Collapsing perseverance is estimated by collapsing similar piece of film again and over until it breaks. collapsing perseverance esteem is times film can be collapsed in similar spot without breaking. 4.6.4 Thickness: A computerized micrometer is utilized to gauge thickness of medication arranged fix at different spots on fix, and normal thickness and standard not entirely set in stone to guarantee that fix's thickness is kept up with. 4.6.5 Weight Uniformity: A foreordained fix region should be fragmented and shown up advanced equilibrium. normal weight and standard deviation will be determined utilizing individual loads. 4.6.6 Surface pH The film to be tried was splashed with 0.5 cc of refined water and put away for 30 seconds in Petri dish. In wake of bringing anode of pH meter in contact with outer layer of plan and permitting 1 moment for equilibration, pH was recorded. For every plan, normal of three judgments was made. 4.6.7 In vitro disintegration test At point when oral film comes into contact with water or salivation, it starts to crumble quicker. quick dissolving film's breaking down time ought to be between 5 to 30 seconds. One more technique was to plunge film in 25 mL water in measuring utencil to outwardly decide deterioration time. second film started to break or crumble was caught when container was delicately shaken.

50 4.6.8

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Drug content Determination: After precisely gauged amount of film (over 100 mg) is broken down in 100 mL of Phosphate support pH 7.4 in which medicine is solvent, arrangement is shaken constantly for 24 hours in shaker

hatchery. arrangement is then sonicated completely. After sonication and sifting, how much medication in arrangement is resolved spectrophotometrically. 4.6.9 Tensile Strength: Tensile strength= $F/a \times b (1+L/l)$ 4.6.10 Flux and Permeability coefficient: $K_p = J/C$ 4.6.11

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In-vitro Permeation study An in-vitro pervasion study can be completed utilizing dissemination cell receptor compartment

with limit of 12 ml. Extracted cellophane paper was put between contributor and receptor offices of dispersion cell. Arranged patches were put on top of

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paraffin film. receptor compartment of dissemination cell was loaded up with phosphate support pH 7.4. entire thing was mounted on attractive stirrer, and arrangement in receptor compartment was

continually whirled with attractive dots at 50 rpm while keeping temperature at 32 0.5 °C. Drug still up in air by spectrophotometric examination of tests taken at different stretches. receptor stage was topped off with new information. 4.6.12

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Kinetic Analysis of Release Data: 4.6.12.1 Zero Order Release $Q_t = Q_0 + K_0t$ 4.6.12.2

First Order Release Equation $\log C = \log C_0 - Kt / 2.303$ 4.6.12.3 Higuchi Square Root of Time Equation: $Q = KH \times t^{1/2}$ 4.6.12.4 Validation or check point analysis of ZPO HCL MDF Plan and portrayal of expected bunches from Overlay plots proposed by StatEase programming will be utilized for approval or designated spot examination. consequences of normal and noticed bunches will be looked at.

51 4.6.12.5 Taste Evaluation Study by Spitting Eight sound grown-up male volunteers between ages of 24 and 42 participated in solitary dose and single visually impaired preliminary. Preceding preliminary, all subjects gave composed informed assent and were instructed with regards to review's motivation, dangers, and term. ZPO HCL advanced MDF will be given to every member at arbitrary. Before review, volunteers were encouraged to flush their mouths with 200 cc of refined water. volunteers were told to place medication in their mouth for 30 seconds, record deterioration span of film test, and rate detailing in view of variables demonstrated in Table, in particular mouth feel, flavor or harshness, film trailing sensation, simplicity of dealing with, and generally acknowledgment. volunteers were told to let out example with salivation and wash their mouths with 200 cc refined water following 3 minutes. subsequent example was treated similarly following 2 hours (either test or reference test). 4.6.12.6 Scanning electron microscope The surface morphology of better definition was analyzed utilizing filtering electron microscopy. falter coater (JSM 6390, Make - JEOL) was utilized to cover 150A gold layer on checking electron magnifying instrument test holder with twofold sided tap for 2 minutes in vaccum of 310-1atm organ gas. examples were therefore inspected utilizing checking electron magnifying instrument. 4.6.12.7 Skin Permeation Study (Ex- vivo Study) The skin penetration examination will require IAEC freedom and assent (ex-vivo study). skin of pale skinned person rodents will be eliminated with care. After hypodermal fat tissue has been taken out, skin will be utilized as obstruction film for examinations. best definition from in vitro tests will be utilized in this review, with rodent skin going about as boundary between giver and receptor compartments. attractive stirrer will be utilized to disturb receptor compartment, which will be loaded up with phosphate support pH 7.4 and warmed to 37 1 °C. examples will be contrasted with clear utilizing UV spectrophotometer set to 317 nm. 4.6.12.8 Comparison of optimized ZPO HCL MDF with Marketed ZPO HCL formulation: The upgraded plan ZPO HCL MDF will be contrasted and Advertised regular ZPO HCL.

52 4.6.12.9 Stability Studies The picked combination was put in golden shaded containers that were painstakingly fixed and cotton-stopped up. They were then kept at 40°C/75% RH for month and assessed at predefined spans for actual appearance, in vitro breaking down time, drug content homogeneity, and medication discharge tests.

53 5. RESULTS & DISCUSSION 5.1 PREFORMULATION STUDY OF ZPO HCL 5.1.1 ORGANOLEPTIC PROPERTIES Table 5. 1 Organoleptic characteristics of Drugs S.No. Parameters 1. White in color 2. Characteristics in odor 3. Bitter in taste The actual appearance of unadulterated medication was analyzed outwardly as per Indian Pharmacopeia. Our faculties, including eye, tongue, and nose, were utilized to evaluate shading, scent, and taste in this examination. 5.1.2 MELTING POINT Utilizing advanced dissolving point instrument and slim combination strategy, liquefying point of picked prescription was processed. One finish of fine was fixed with assistance of burner. open finish of slim cylinder was delicately tapped to settle amassed material after it was placed into little piece of powder. technique was rehashed couple of times more. narrow cylinder was then positioned utilizing liquefying point gadget. temperature at which medication starts to break down not set in stone. Table 5. 2 Determination of melting point of drugs S.No. Ziprasidone HCL Melting Point Observed value (n =3) Standard value 1. 272-276 ± 1 0 C 274-276 0 C The liquefying point was utilized to decide example's virtue. dissolving point of prescription example was 272-276 ± 2 0 C, which was inside reach and shown that example was unadulterated ZPO HCL. 5.1.3 DETERMINATION OF WAVELENGTH OF ZPO HCL The fittingly gauged

amount of 100 mg of medication test was broken up in DMSO and volume moved toward 100 ml involving methanol in 100 ml volumetric cup to frame stock arrangement of 100 g/ml. stock arrangement was then pipetted into 10 ml volumetric cup, and volume was raised to imprint to accomplish convergence of 10 g/ml. subsequent arrangement was then examined somewhere in range of 200 and 400

54 nm with UV-noticeable spectrophotometer (Mdel-1700, Shimadzu, Japan). example's UV range was recorded, and most elevated worth acquired was contrasted with authority monograph's UV range. Table 5. 3

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Wavelength maximum (λ max) of ZPO HCL Drug λ max Actual λ max Observed λ max ZPO HCL 317 317.47 Figure 5. 1 UV Spectrum of ZPO HCL 5.1.4 SOLUBILITY STUDIES

The dissolving and dispersion liquids for drug delivery and pervasion studies were picked in view of Ziprasidone solvency information in different liquids. medication test's not set in stone by dissolving 100 mg of example in expanding volumes of different liquids. How much dissolvable expected to break down medication was determined, and medication's still up in air. Table 5. 4 Solubility profile of ZPO HCL S.No. Solvent Solubility ZPO HCL Conc. (mg/ml) Mean \pm SD, n=3 Inference

1. HCl 12.1 Soluble
 2. NaOH 10.63 Soluble
 3. Ethanol 11.59 Soluble
 4. Methanol 11.15 Soluble
 5. Water 0.0069 Insoluble
 6. DMSO 1.13 Soluble

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From experiment, it was found that ZPO HCL was soluble in HCl, NaOH, Ethanol, Methanol and DMSO.

Figure 5. 2 Solubility of profile of ZPO HCL 5.1.5 PARTITION COEFFICIENT The medication segment coefficient was resolved utilizing n-ctanol as nn-watery stage and phosphate cradle arrangement pH 7.4 (PBS pH 7.4) as fluid stage. These two phases were joined in equivalent parts and kept in independent channels until they were soaked. Permit 30 minutes for framework to settle subsequent to blending. In isolating channels, 10 mg of medication was isolated into 10 ml areas of n-ctanol and PBS pH 7.4 to compute segment coefficient. mechanical shaker was utilized to shake isolating pipes for 24 hours. Following fitting weakening, two stages were isolated, with watery stage separated utilizing Whatman channel paper and how much

56 medication in fluid stage decided spectrophotometrically at max 318 and 248 nm, utilizing phosphate cradle arrangement pH 7.4 as clear. Table 5. 5

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Determination of Partition Coefficient of selected Drugs S.No. Sample Partition Coefficient (Mean \pm SD, n=3) 1. ZPO HCL 4.61 \pm 0.43 5.1.6 Calibration Curve: 5.1.6.1

ZPO HCL Calibration Curve in 0.1N HCL Preparation of standard stock solution (100 μ g/ml) in 0.1N HCL 10 milligrams of prescription was accurately shown up 100 mL volumetric flagon. To make 100 g/ml arrangement, volume was expanded to 100 ml by adding 0.1N HCL arrangement. In isolated volumetric carafes, 1 ml of stock arrangement (100 g/ml) was weakened to 10 ml with 0.1N HCL arrangement, bringing about centralization of 1.0 to 5.0 g/l. Preparation of standard working solution 1ml was pipetted from stock arrangement (100g/ml) and weakened to 10ml with 0.1N HCL arrangement. Proper aliquots of arrangement were taken into different volumetric carafes and made up to 10ml with 0.1N HCL answer for accomplish centralization of 1.0 to 5.0g/ml. By dissolving exactly gauged 100 mg of prescription in 100 ml volumetric flagon, medication alignment bend in 0.1 N HCl was made. volume was therefore expanded to 100ml utilizing 0.1N HCL answer for get answer of 100g/ml, which was then checked in UV spectrophotometer, affirming that example complied to Lager's Regulation. Table 5. 6 Calibration Curve of ZPO HCL in 0.1 N HCl Conc. (μ g/ml) Absorbance (nm) Mean \pm SD; n=3

0 0 \pm 0.00 1 0.106 \pm 0.032 2 0.214 \pm 0.021 3 0.318 \pm 0.101 4 0.421 \pm 0.002
 5 0.512 \pm 0.028 6 0.644 \pm 0.091 7 0.750 \pm 0.022 8 0.844 \pm 0.108 9 0.941 \pm 0.002 10 0.999 \pm 0.091 Figure 5. 3 Standard Curve of ZPO HCL in 0.1 N HCl at 318 nm Table 5. 7 Summery Report of calibration curve for ZPO HCL Parameters ZPO HCL

Wavelength (λ_{max}) 317 Beer's limit ($\mu\text{g/ml}$) 0-10 Corrélation coefficient (R²) 0.9977 Slope 0.1028 Obeys Beer law in conc. range of 0-20 mcg/ml R² value shows linearity 58 5.1.7 ZPO HCL Calibration Curve

in Phosphate buffer pH 7.4 (pH of Salivary stimulating fluid): Preparation of standard stock solution (100 $\mu\text{g/ml}$) in Phosphate buffer pH 7.4 (pH of Salivary stimulating fluid) Gauge 100 mg of medicine accurately in 10 mL volumetric flagon. To make 100 g/ml arrangement, volume was raised to 100 ml by adding Phosphate cushion pH 7.4 to blend. To deliver convergence of 1 to 10 g/ml, 1 ml of stock arrangement (100 g/ml) was pipetted and weakened to 10 ml in isolated volumetric carafes with Phosphate cradle pH 7.4. Preparation of standard working solution 1 ml of stock arrangement (100 g/ml) was pipetted and weakened with Phosphate support pH 7.4 to make 10 ml. To get groupings of 1 to 10 g/ml, suitable aliquots of arrangement were filled different volumetric carafes and made up to 10 ml with Phosphate support pH 7.4 to acquire convergences of 1 to 10 g/ml. The alignment bend for drug in Phosphate cushion pH 7.4 was made by dissolving 100 mg of medication in 100 ml volumetric flagon that was unequivocally gauged. volume was then expanded to 100 ml utilizing Phosphate cradle pH 7.4 to produce answer of 100 g/ml, which was then filtered in UV spectrophotometer to affirm that example submitted to Lager's regulation. Table 5. 8 Calibration Curve of ZPO HCL in Phosphate buffer pH 7.4

| Conc. ($\mu\text{g/ml}$) | Absorbance (nm) | Mean \pm SD; |
|----------------------------|-----------------|----------------|
| n=3 0 | 0.024 | ± 0.021 |
| 1 | 0.031 | ± 0.022 |
| 2 | 0.042 | ± 0.039 |
| 3 | 0.055 | ± 0.012 |
| 4 | 0.071 | ± 0.002 |
| 5 | 0.080 | ± 0.005 |
| 6 | 0.086 | ± 0.010 |
| 7 | 0.103 | ± 0.029 |
| 8 | 0.107 | ± 0.017 |
| 9 | 0.115 | ± 0.008 |

Figure 5. 4 Standard Curve of ZPO HCL in Phosphate buffer pH 7.4 Table 5. 9 Summery Report of calibration curve for ZPO HCL in Phosphate buffer pH 7.4 Parameters ZPO HCL

Wavelength (λ_{max}) 317 Beer's limit ($\mu\text{g/ml}$) 0-10 Corrélation coefficient (R²) 0.9956 Slope 0.0117 Obeys Beer law in conc. range of 0-10 mcg/ml R² value shows linearity 5.1.8

Identification of ZPO HCL by FTIR Spectra On unadulterated medication test, infrared spectroscopy was used to recognize substance. medication was compacted utilizing IR grade potassium bromide in KBr press at 5.5 metric huge loads of strain to make medication pellet. pellet was embedded in IR compartment and filtered between wave numbers 4000-450 cm^{-1} with FTIR specttrophptmeter (Mdel-8400 S, Shimadzu, Japan). Table 5. 10 Interpretation of FTIR Spectra of ZPO HCL S.No. Inference Standard wave no.(cm^{-1}) Observed wave no.(cm^{-1}) Interpretation

| S.No. | Inference | Standard wave no.(cm^{-1}) | Observed wave no.(cm^{-1}) | Interpretation |
|-------|----------------|---------------------------------------|---------------------------------------|----------------------|
| 1. | C-H bending | 735-755 | 736 | 1,2 disubstituted |
| 2. | C-O stretching | 1200-1275 | 1246 | Alkyl aryl ether |
| 3. | C=C stretching | 1626-1662 | 1627 | Alkane disubstituted |
| 4. | C-H stretching | 2695-2830 | 2808 | Aldehyde |
| 5. | C-H stretching | 3000-3100 | 3070 | Alkane |
| 6. | O-H stretching | 2700-3200 | 3190 | Alcohol |

Figure 5. 5 FTIR Spectra of Pure Drug 5.1.9 Compatibility study of ZPO HCL with excipients by FTIR Spectra Table 5. 11 Interpretation of FTIR Spectra of ZPO HCL S.No. Inference Standard wave no.(cm^{-1}) Observed wave no.(cm^{-1}) Interpretation

| S.No. | Inference | Standard wave no.(cm^{-1}) | Observed wave no.(cm^{-1}) | Interpretation |
|-------|----------------|---------------------------------------|---------------------------------------|----------------------|
| 1. | C-H bending | 735-755 | 736 | 1,2 disubstituted |
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| 3. | C=C stretching | 1626-1662 | 1627 | Alkane disubstituted |
| 4. | C-H stretching | 2695-2830 | 2808 | Aldehyde |
| 5. | C-H stretching | 3000-3100 | 3070 | Alkane |
| 6. | O-H stretching | 2700-3200 | 3190 | Alcohol |

61 Figure 5. 6 FTIR Spectra of Pure Drug with excipients A combination of ZPO HCL, HPMC E5, Stake 400, Citrus extract, Aspatame, and Mannitol will be utilized to make potassium bromide IR circle, which will be examined in 4000-400 cm^{-1} region in FTIR and contrasted with reference spectra of ZPO HCL. Whenever ZPO HCL was joined with polymers, no progressions in IR tops were noticed. These discoveries highlight polymers' similarity with ZPO HCL.

62 5.2 Preparation of ZPO HCL Mouth Dissolving Film 5.2.1 Trial batches for ZPO HCL Mouth Dissolving Film Table 5. 12 Selection of polymers type and concentration Ingredients ZPDT 1 ZPDT 2 ZPDT 3 ZPDT 4 ZPDT 5 ZPDT 6 ZPDT 7 ZPDT 8 ZPDT 9 ZPDT1 0 ZPDT1 1 ZPDT1 2 Drug (gm) 0.1 HPMC E5 LV (gm) 0.1 0.3 0.5 - - - - - HPMCK4 M (gm) - - - 0.1 0.3 0.5 - - - - - PVA (gm) - - - - - 0.1 0.3 0.5 - PVP (gm) - - - - - 0.1 0.3 0.5 PEG 400 (ml) 01 DW (mL) Q.S Strip Form Yes Stickiness - Appearance * #

63 DISCUSSION: BATCH (ZPDT1- ZPDT3): In scope of 0.1-0.5 gm, strip framing polymer HPMC E5 LV was utilized. strips were decided on their actual allure as well as their tenacity. From petridish, it was found that strips arranged were non-tacky, straightforward, and had satisfactory stripping properties. BATCH (ZPDT4-ZPDT6): HPMC K4M, strip framing polymer, was utilized in fixations going from 0.1-0.5 gm. strips were decided on their actual appeal as well as their

tenacity. From petridish, it was found that strips were non-tacky, clear, and had OK strip capacity. BATCH (ZPDT7-ZPDT9): PVA, strip framing polymer, was utilized in sums going from 0.1-0.5 gm. strip with centralization of 100mg was straightforward and non-tacky. At point when fixation was expanded to 1.0 gm, in any case, strip became hazy because of air ensnarement. Also, strip was hard to recognize from petridish. BATCH (ZDT10-ZPDT12): PVP, strip shaping polymer, was used in fixations going from 0.1-0.5 gm. Because of production of knocks in strips, strips were non-tacky yet appeared to be hazy.

64 Table 5. 13 Results of ZPDT1-ZPDT7 Batch Surface Texture Weight uniformity (mg) (Mean \pm SD) n=3 Avg. uniform Drug Distribution (%) \pm SD, n = 3 Avg. Drug Content uniformity (%) \pm SD, n = 3 ZPDT1 Smooth 100.3 \pm 0.2 98.72 \pm 0.21 99.36 \pm 0.37 ZPDT2 Smooth 99.94 \pm 0.21 98.02 \pm 0.35 99.47 \pm 0.15 ZPDT3 Smooth 100.26 \pm 0.39 99.6 \pm 0.2 99.92 \pm 0.41 ZPDT4 Smooth 100.2 \pm 0.5 99.32 \pm 0.23 99.34 \pm 0.18 ZPDT5 Smooth 100.18 \pm 0.57 98.36 \pm 0.15 99.46 \pm 0.35 ZPDT6 Smooth 100.22 \pm 0.76 99.16 \pm 0.33 99.2 \pm 0.13 ZPDT7 Smooth 99.9 \pm 0.32 98.62 \pm 0.25 100.02 \pm 0.62

65 Figure 5. 7 Results of ZPDT1-ZPDT7 Table 5. 14 Results of ZPDT1-ZPDT7 Batch

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Surface pH (Mean \pm SD) n=3 Thickness (mm) (Mean \pm SD) n=3 Avg. Tensile strength (N/cm²) \pm SD, n = 3

ZPO1 6.54 \pm 0.03 0.14 \pm 0.02 2.12 \pm 0.02 ZPO2 6.65 \pm 0.04 0.14 \pm 0.01 2.11 \pm 0.04 ZPO3 6.66 \pm 0.05 0.15 \pm 0.01 2.14 \pm 0.03

66 ZPO4 6.53 \pm 0.04 0.14 \pm 0.02 1.77 \pm 0.02 ZPO5 6.62 \pm 0.05 0.15 \pm 0.02 1.43 \pm 0.01 ZPO6 6.68 \pm 0.07 0.16 \pm 0.01 1.32 \pm 0.15 ZPO7 6.57 \pm 0.08 0.17 \pm 0.02 1.06 \pm 0.02 Figure 5. 8 Results of ZPDT1-ZPDT7

67 Table 5. 15 Results of ZPDT1-ZPDT7 Batch Avg. Folding Endurance \pm

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SD, n = 3 Avg. In Vitro Disintegration Time (sec) \pm SD, n = 3

ZPDT1 149.46 \pm 1.33 127.26 \pm 0.28 ZPDT2 163.36 \pm 1.4 133.1 \pm 1.44 ZPDT3 181.72 \pm 1.14 138.62 \pm 0.38 ZPDT4 93.56 \pm 1.33 159.36 \pm 1.02 ZPDT5 84.12 \pm 1.13 179.12 \pm 1.37 ZPDT6 98.16 \pm 1.26 184.14 \pm 1.41 ZPDT7 36.36 \pm 1.17 166.14 \pm 1.15

68 Figure 5. 9 Results of ZPDT1-ZPDT7 Inference In view of discoveries of starter preliminary bunches for polymer choice showed above, it was laid out that polymers HPMC E5 LV and HPMC K4M produced best outcomes in focus scopes of 100, 300, and 500, and subsequently these two polymers were picked for plan of last MDFs.

69 Table 5. 16 Trial batch for selection of Polymer type and concentration Ingredients ZPDT 13 ZPDT 14 ZPDT 15 ZPDT 16 ZPDT 17 ZPDT 18 ZPDT 19 ZPDT 20 ZPDT 21 ZPDT 22 ZPDT 23 ZPDT 24 ZPDT 25 ZPDT 26 ZPDT 27 Drug (gm) 0.1 Acacia (gm) 0.1 0.3 0.5 - - - - - Tragacanth (gm) - - - 0.1 0.3 0.5 - - - - - Gelatin (gm) - - - - - 0.1 0.3 0.5 - - - - - Xanthum gum (gm) - - - - - 0.1 0.3 0.5 - - - PULLNAN (gm) - - - - - 0.1 0.3 0.5 PEG 400 (ml) 01 DW (mL) Q.S Strip Form Yes No Yes No Stickiness + Appearance # @ # @

70 BATCH (ZPDT13-ZPDT15): Acacia, strip-framing polymer, was used in sums going from 0.1-0.5 gm. pre-arranged strips were inspected, and it was found that they were tacky and hazy by all accounts, and that they were hard to eliminate from petridish. BATCH (ZPDT16-ZPDT18): Tragacanth, strip-shaping polymer, was used in sums going from 0.1-0.5 gm. There was no strip delivered, as indicated by discoveries. BATCH (ZPDT19-ZPDT21): Gelatin, strip-framing polymer, was used in sums going from 0.1-0.5 gm. strips that came about were viewed as tacky and dark. It is extremely challenging to eliminate from petridish. BATCH (ZPDT22-ZPDT24): Thickener, strip-shaping polymer, was used in sums going from 0.1-0.5 gm. strips that shaped were tacky, misty, and hard to eliminate from petridish. BATCH (ZPDT25-ZPDT27): PULLNAN, strip-shaping polymer, was utilized in focuses going from 0.1-0.5 gm. strips that shaped were tacky, dark, and hard to eliminate from petridish. In view of aftereffects of all of above strip framing polymers, it was resolved that HPMC E5 LV and HPMC K4M strips were non-tacky, straightforward, and effectively removable from petridish, showing great strip shaping limit. Thus, these polymers can be consolidated in details.

71 Table 5. 17 Trial batch for selection of Plasticizer type and concentration Ingredient s ZPLD T 1 ZPLD T 2 ZPLD T 3 ZPLD T 4 ZPLD T 5 ZPLD T 6 ZPLD T 7 ZPLD T 8 ZPLD T 9 ZPLD T 10 ZPLD T 11 ZPL DT1 2 ZPLD T 13 ZPLD T 14 ZPLD T 15

HPMC E5 LV (mg) 300 Drug (mg) 100 PEG 200 (ml) 1 1.5 2 - - - - - PEG 400 (ml) - - - 1 1.5 2 - - - - -
 PEG 800 (ml) - - - - - 1 1.5 2 - - - - - PG (ml) - - - - - 0.5 0.75 1.0 - - - IPA (ml) - - - - - 0.5 0.75 1.0
 DW (ml) Q.S Strip Form Yes Stickiness - + Appearance * @ #

72 The strips were made with Stake 200 and Stake 400 in focuses going from 1 to 2 mL. subsequent strips were assessed for their actual appearance and tenacity. Stake 200 and Stake 400 strips were viewed as non-tacky, non-slick, straightforward for all intents and purposes, and easy to project. Stake 800, PG, and IPA strips, then again, were tacky, sleek, obscure, and hard to project. Table 5. 18 Results of ZPDT1-ZPDT6 Batch Surface Texture Weight uniformity (mg) (Mean ± SD) n=3 Avg. uniform Drug Distribution (%) ± SD, n = 3 Avg. Drug Content uniformity (%) ± SD, n = 3 ZPLDT1 Smooth 98.06 ± 0.05 96.417 ± 0.35 97.46 ± 0.11 ZPLDT2 Smooth 101.02 ± 0.15 98.22 ± 0.15 98.66 ± 0.15 ZPLDT3 Smooth 99.6 ± 0.02 95.02 ± 0.1 99.20 ± 0.05 ZPLDT4 Smooth 99.05 ± 0.16 99.40 ± 0.13 99.61 ± 0.18 ZPLDT5 Smooth 99.07 ± 0.32 99.22 ± 0.14 100.60 ± 0.05 ZPLDT6 Smooth 99.06 ± 0.31 99.26 ± 0.10 99.51 ± 0.24

73 Figure 5. 10 Results of ZPDT1-ZPDT6 Table 5. 19 Results of ZPDT1-ZPDT6 Batch

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Surface pH (Mean ± SD) n=3 Thickness (mm) (Mean ± SD) n=3 Avg. Tensile strength (N/cm²) ± SD, n = 3

ZPLDT1 6.2 ± 0.24 0.15 ± 0.01 1.61 ± 0.03 ZPLDT2 7.00 ± 0.19 0.11 ± 0.01 1.9 ± 0.02 ZPLDT3 7.11 ± 0.27 0.11 ± 0.03 2.13 ± 0.02

74 ZPLDT4 7.12 ± 0.25 0.14 ± 0.02 2.68 ± 0.15 ZPLDT5 7.5 ± 0.16 0.13 ± 0.03 2.56 ± 0.01 ZPLDT6 7.32 ± 0.11 0.15 ± 0.01 2.26 ± 0.12 Figure 5. 11 Results of ZPDT1-ZPDT6

75 Table 5. 20 Results of ZPDT1-ZPDT6 Batch Avg. Folding Endurance ±

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SD, n = 3 Avg. In Vitro Disintegration Time (sec) ± SD, n = 3

ZPLDT1 121.45 ± 1.23 173.45 ± 1.33 ZPLDT2 136.35 ± 2.18 167.25 ± 2.80 ZPLDT3 155.45 ± 2.80 185.04 ± 2.14 ZPLDT4 195.11 ± 0.28 113.15 ± 2.18 ZPLDT5 205.05 ± 1.47 124.65 ± 2.07 ZPLDT6 219.42 ± 1.30 129.11 ± 1.33

76 Figure 5. 12 Results of ZPDT1-ZPDT6 Inference As per outcomes got in above expressed starter preliminary clusters for plasticizer determination, best outcomes were acquired in Stake 400 in focus scope of 1-2 ml.

77 Table 5. 21 Selection of disintegrating agent type and concentration Ingredients ZDT1 ZDT2 ZDT3 ZDT4 ZDT5 ZDT6 ZDT7 ZDT8 ZDT9 Drug (gm) 0.1 HPMC E5 LV(gm) 0.3 PEG 400 (ml) 01 Cross Povidone (gm) 0.05 0.075 0.1 - - - - - Kyron T-314 (gm) - - - 0.05 0.075 0.1 - - - Banana Powder (gm) - - - - - 0.05 0.075 0.1 DW (mL) Q.S Strip form Yes Stickiness - + _ Appearance # * Disintegration Yes DISCUSSION: crumbling specialists Cross Povidone, Kyron T-314, and banana powder were utilized at groupings of 0.05, 0.075, and 0.1 gm in strips. created strips were assessed for their actual appearance, tenacity, and breaking down characteristics. banana powder- containing strips were viewed as non-tacky, straightforward, and broke up. Notwithstanding deterioration, strips holding back cross povidone and Kryon T-314 were tacky and obscure, while strips holding back cross povidone and Kryon T-314 were tacky and dark.

78 Table 5. 22 Results of ZPDT7-ZPDT9

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Batch Surface Texture Weight uniformity (mg) (Mean ± SD) n=3 Avg. uniform Drug Distribution (%) ± SD, n = 3 Avg. Drug Content uniformity (%) ± SD, n = 3 ZDT7 Flexible 107.13 ± 1.33 101.45 ± 0.38 99.30 ± 0.14 ZDT8 Flexible 99.1 ± 0.24 99.35 ± 0.25 99.61 ± 0.11 ZDT9 Flexible 99.10 ± 0.15 99.15 ± 0.13 99.18 ± 0.37

Figure 5. 13 Results of ZPDT7-ZPDT9

79 Table 5. 23 Results of ZPDT7-ZPDT9 Batch Surface Texture

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Surface pH (Mean \pm SD) n=3 Thickness (mm) (Mean \pm SD) n=3 Avg. Tensile strength (N/cm²) \pm SD, n = 3

ZDT7 Flexible 7.1 \pm 0.1 0.22 \pm 0.06 2.47 \pm 0.35 ZDT8 Flexible 7.03 \pm 0.06 0.17 \pm 0.02 2.73 \pm 0.15 ZDT9 Flexible 7.23 \pm 0.15 0.21 \pm 0.04 1.73 \pm 0.21 Figure 5. 14 Results of ZPDT7-ZPDT9

80 Table 5. 24 Results of ZPDT7-ZPDT9L Batch Surface Texture Avg. Folding Endurance \pm

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SD, n = 3 Avg. In Vitro Disintegration Time (sec) \pm SD, n = 3

ZDT7 Flexible 185.10 \pm 1.23 23.05 \pm 0.56 ZDT8 Flexible 198.35 \pm 0.56 16.32 \pm 0.46 ZDT9 Flexible 203.19 \pm 2.23 23.43 \pm 1.23 Figure 5. 15 Results of ZPDT7-ZPDT9 Inference The 75 mg fixation was picked for last MDF detailing since banana powder had best deterioration season of analyses.

81 5.3 Preparation of ZPO HCL Mouth Dissolving Film using Design of Experiment 5.3.1 PREPARATION OF MOUTH DISSOLVING FILM OF ZPO HCL USING 3 2 FACTORIAL DESIGN As displayed in plan format Tables, 3 2 full factorial plan was utilized to examine impact of autonomous factors X1 (Stake) and X2 (HPMC E5 LV) on subordinate factors like weight consistency (mg), crumbling time (sec), and thickness (mm), collapsing perseverance, and in-vitro drug discharge. Two variables were tried at three levels (1, 0, +1) in this plan, and each of nine potential trial bunches were created. Table shows creation of every one of nine expected blends

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of MDF of ZPO HCL utilizing 3 2 full factorial plans. Table 5. 25 Independent variable and their levels Independent Variables Low level (-1) Medium level (0) High level (+1) X1=amount of PEG (ml) 1 1.5 2 X2=amount of HPMC E5 LV (gm) 0.250 0.300 0.350 Dependent Variables Y1= Folding endurance Y2 = Disintegration Time (sec) Y3= % CDR (%) 5.3.2 Validation Analysis of Predicted and Actual Batches

ZPO HCL MDF: The 3 2 full factorial plan is broadly used to work on detailing. In this review, two elements were investigated at three levels each, and test preliminaries were embraced on every one of nine potential mixes. groupings

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of Stake 400 (X1) and HPMC E5 LV (X2) were picked as free factors. Collapsing perseverance (Y1), crumbling term (Y2), and in-vitro drug discharge (Y3) were picked as reliant factors. Polynomial conditions can be utilized to

construe ends. results of trial configuration clusters are displayed in table.

82 Table 5. 26 Batches codes of fast disintegrating films of ZPO HCL Ingredients ZMDOF 1 ZMDOF 2 ZMDOF 3 ZMDOF 4 ZMDOF 5 ZMDOF 6 ZMDOF 7 ZMDOF 8 ZMDOF 9 PEG 400 (ml)-X1 -1 0 1 -1 0 1 -1 0 1 HPMC E5 LV (mg)-X2 -1 -1 -1 0 0 0 0 0 0 Table 5. 27 Batches concentrations of fast disintegrating films of ZPO HCL Ingredients ZMDOF 1 ZMDOF 2 ZMDOF 3 ZMDOF 4 ZMDOF 5 ZMDOF 6 ZMDOF 7 ZMDOF 8 ZMDOF 9 Drug (gm) 0.1 PEG 400 (ml) 1.0 1.5 2.0 1.0 1.5 2.0 1.0 1.5 2.0 HPMC E5 LV (gm) 0.25 0.30 0.35 Banana Powder (gm) 0.075 Aspartame (gm) 0.040 Citric acid (gm) 0.070 Tween 20 (gm) 0.050 Vanillin (gm) 0.050 Distilled water (ml) 10 Table 5. 28 Evaluation parameters of factorial design batches Formulation Code Avg. Weight (mg) \pm SD, n=3 Avg. uniform Drug Distribution (%) \pm SD, n = 3 Avg. Drug Content uniformity (%) \pm SD, n = 3 ZMDOF1 110.81 \pm 0.56 97.33 \pm 1.05 98.30 \pm 0.26 ZMDOF2 107.65 \pm 1.33 98.40 \pm 0.11 99.25 \pm 0.11 ZMDOF3 108.81 \pm 0.19 98.90 \pm 0.59 98.65 \pm 0.56 ZMDOF4 116.15 \pm 1.14 97.00 \pm 0.47 99.3 \pm 0.33 ZMDOF5 118.00 \pm 0.15 99.73 \pm 0.13 99.95 \pm 0.51 ZMDOF6 115.60 \pm 0.71 99.4 \pm 0.28 98.92 \pm 0.45

83 ZMDOF7 109.31 \pm 1.23 99.00 \pm 0.15 99.86 \pm 0.41 ZMDOF8 126.31 \pm 1.14 97.00 \pm 0.65 98.65 \pm 0.16 ZMDOF9 127.15 \pm 0.56 96.4 \pm 0.36 102.80 \pm 1.06 Figure 5. 16 Evaluation parameters of factorial design batches Table 5. 29 Evaluation parameters of factorial design batches Formulation Code Avg.

Surface pH \pm SD, n = 3 Avg. Thickness (mm) \pm SD, n = 3 Avg. Tensile strength (N/cm²) \pm SD, n = 3

ZMDOF1 6.3 \pm 0.13 0.14 \pm 0.02 1.17 \pm 0.21 ZMDOF2 6.43 \pm 0.03 0.18 \pm 0.02 1.58 \pm 0.13 ZMDOF3 6.35 \pm 0.14 0.19 \pm 0.02 2.00 \pm 0.27 ZMDOF4 6.5 \pm 0.15 0.16 \pm 0.02 2.45 \pm 0.16 ZMDOF5 6.4 \pm 0.25 0.18 \pm 0.01 2.76 \pm 0.16 ZMDOF6 7.26 \pm 0.10 0.19 \pm 0.01 2.94 \pm 0.26 ZMDOF7 7.00 \pm 0.24 0.20 \pm 0.01 2.75 \pm 0.16 ZMDOF8 6.86 \pm 0.17 0.19 \pm 0.01 3.06 \pm 0.22 ZMDOF9 7.15 \pm 0.18 0.24 \pm 0.01 4.12 \pm 0.12

84 Figure 5. 17 Evaluation parameters of factorial design batches Table 5. 30 Results of ZMDOF1- ZMDOF9 Formulation Code Avg. Folding Endurance \pm SD, n = 3 (Y 1) Avg. Disintegrating time (second) \pm SD, n = 3 (Y 2) % Drug release (ln 6 min.) (Y 3) ZMDOF1 196.72 \pm 1.42 24.95 \pm 0.71 98.825 \pm 0.35 ZMDOF2 202.15 \pm 1.16 26.60 \pm 1.37 99.06 \pm 0.21 ZMDOF3 255.00 \pm 1.02 20.85 \pm 0.25 98.34 \pm 0.11 ZMDOF4 265.25 \pm 0.05 22.75 \pm 0.11 97.90 \pm 0.41 ZMDOF5 299.45 \pm 1.15 15.76 \pm 0.05 98.0 \pm 0.24 ZMDOF6 321.25 \pm 1.15 24.34 \pm 0.62 96.00 \pm 0.15 ZMDOF7 346.45 \pm 1.47 28.40 \pm 0.16 95.60 \pm 0.67 ZMDOF8 375.81 \pm 0.73 27.64 \pm 0.11 94.42 \pm 0.06 ZMDOF9 394.54 \pm 0.36 31.63 \pm 0.21 92.63 \pm 0.65

85 Figure 5. 18 Results of ZMDOF1- ZMDOF9 Table 5. 31 In-vitro drug release (% drug release) of ZMDOF1- ZMDOF9 Time (min) ZMDOF1 ZMDOF2 ZMDOF3 ZMDOF4 ZMDOF5 ZMDOF6 ZMDOF7 ZMDOF8 ZMDOF9 0 0 0 0 0 0 0 0 0 1 18.21 \pm 2.06 15.12 \pm 1.23 15.12 \pm 0.22 16.17 \pm 1.05 15.09 \pm 1.05 15.05 \pm 0.57 14.04 \pm 0.48 13.54 \pm 1.25 10.13 \pm 2.04 2 37.05 \pm 3.15 34.54 \pm 1.65 35.062 \pm 1.15 36.16 \pm 1.55 36.52 \pm 1.66 34.9 \pm 2.08 36.01 \pm 0.07 33.44 \pm 1.08 25.24 \pm 1.01 3 48.54 \pm 1.07 46.54 \pm 1.23 50.42 \pm 1.18 49.20 \pm 1.11 47.21 \pm 0.43 44.01 \pm 2.04 45.5 \pm 1.04 46.53 \pm 0.21 38.50 \pm 1.01 4 68.08 \pm 1.19 67.68 \pm 1.98 66.30 \pm 2.01 65.80 \pm 2.01 63.91 \pm 1.05 63.90 \pm 1.08 65.21 \pm 1.40 61.20 \pm 1.04 52.34 \pm 2.07 5 94.2 \pm 1.22 93.24 \pm 2.15 92.07 \pm 2.06 90.67 \pm 1.01 85.56 \pm 2.64 85.15 \pm 1.03 84.04 \pm 3.47 85.08 \pm 0.68 78.04 \pm 1.01 6 99.4 \pm 0.23 99.04 \pm 1.05 98.10 \pm 1.95 98.97 \pm 1.0 98.06 \pm 0.96 97.25 \pm 1.58 96.06 \pm 1.55 95.02 \pm 2.05 92.34 \pm 1.21

86 Response 1: Folding endurance (Y1) Polynomial conditions can be utilized to make determinations in wake of dissecting quantity of coefficients and numerical sign they impart (positive or negative). With p esteems under 0.05, two boundaries X1 (convergence of Stake 400) and X2 (centralization of HPMC E5 LV) were demonstrated to be huge for collapsing perseverance (Y1). Polynomial equation: $Y1 = 298.33 + 32.67 X1 + 83.00 X2 - 9.25 X1 X2 + 1.00 X2 - 10.00 X2^2$ Table 5. 32 ANOVA for Y1 DF* SS* MS* F p value Regression 2 47257.23 23756.23 235.15 > 0.0001 Residual 6 612.25 102.52 - - Total 8 47869.48 - - *DF: degree of freedom, SS: sum of squares, MS: means of squares Figure 5. 19 Contour plot for Y1 (folding endurance)

87 Figure 5. 20 Surface plot for Y1 (folding endurance)

88 1 2 Response 1: Folding endurance (Y 1) Polynomial conditions can be utilized to reach inferences in wake of examining quantity of coefficients and numerical sign they impart (positive or negative). With p esteems under 0.05, two boundaries X1 (convergence of Stake 400) (p=0.0002) and X2 (grouping of HPMC E5 LV) (p=0.0001) were demonstrated to be critical for collapsing perseverance (Y1). Polynomial equation: $Y 1 = 298.33 + 32.67 X 1 + 83.00 X 2 - 9.25 X 1 X 2 + 1.00 X 2 - 10.00 X$ Table 5. 33 ANOVA for Y1 DF* SS* MS* F p value Regression 2 47736.67 23868.33 234.26 > 0.0001 Residual 6 611.33 101.89 - - Total 8 48348.00 - - *DF: degree of freedom, SS: sum of squares, MS: means of squares For collapsing perseverance, ANOVA results, shape plot, and 3d surface plot uncovered critical impact of two autonomous parts (convergence of Stake 400, X1 and grouping of HPMC E5 LV, X2). As indicated by collapsing perseverance polynomial condition, both how much plasticizer and how much polymer positively affect collapsing perseverance. How much Stake 400 and centralization of HPMC E5 LV in movies were found to support collapsing perseverance of movies. Collapsing perseverance was found to run between 168 1.0 and 393 3.0 for all details. ZMDF9 plan has best collapsing perseverance when contrasted with different definitions. most elevated measure of plasticizer and polymer HPMC E5 LV that can be used in ZMDF9 might be justification behind greatest collapsing perseverance. Response 2: Disintegrating time (Y 2) Polynomial equations can be used to draw conclusions after analysing number of coefficients and mathematical sign they communicate (positive or negative). With p values less than 0.05, both factors X1 (concentration of PEG 400) (p= 0.0044) and X2 (concentration of HPMC E5 LV) (p= 0.0002) were found to be significant for disintegration time (Y2). Polynomial equation:

89 $Y2 = 37.68 + 7.00 X1 + 20.12 X2 + 4.08 X1 X2 + 0.98 X1^2 + 10.35 X2^2$ Table 5. 34 ANOVA for Y 2 DF* SS* MS* F p value Regression 5 3005.91 601.18 124.15 0.0011 Residual 3 14.53 4.84 - - Total 8 3020.44 - - *DF: degree of freedom, SS: sum of squares, MS: means of squares Figure 5. 21 Contour plot for Y2 (disintegrating time) Figure 5. 22 Surface plot for Y2

(disintegrating time) For breaking down time, ANOVA results, form plot, and 3d surface plot uncovered solid impact on two autonomous parts (convergence of Stake 400, X1 and grouping of

90 1 2 HPMC E5 LV, X2). As per polynomial condition of crumbling time, both how much plasticizer and how much polymer positively affect deteriorating time. How much Stake 400 in movies, as well as convergence of HPMC E5 LV, were seen to expand crumbling time. For all plans, breaking down time goes from 24.67 2.516 to 81.33 3.215 minutes. crumbling season of ZMDF9 was speediest of multitude of plans. Since ZMDF9 contains most plasticizer Stake 400 and polymer HPMC E5 LV, it might have best collapsing strength. Response 3: % Drug release (Y 3) Polynomial conditions can be utilized to reach inferences in wake of investigating quantity of coefficients and numerical sign they convey (positive or negative). With p esteems under 0.05, two factors X1 (convergence of Stake 400) (p= 0.0147) and X2 (grouping of HPMC E5 LV) (p= 0.0001) were demonstrated to be huge for percent drug discharge in short time (Y3). Polynomial equation: $Y_3 = 97.54 - 0.75 X_1 - 2.05 X_2 - 0.12 X_1 X_2 - 0.25 X_2^2 - 0.78 X_2^3$ Table 5. 35 ANOVA for Y 3 DF SS MS F p value Regression 2 28.55 14.27 49.26 0.0002 Residual 6 1.74 0.29 - - Total 8 30.28 - - - DF: degree of freedom, SS: sum of squares, MS: means of squares

91 Figure 5. 23 Contour plot for Y3 (% drug release in 6 minute) Figure 5. 24 Surface plot for Y3 (% drug release in 6 minute) The ANOVA results, shape plot, and 3d surface plot uncovered that two free factors essentially affected percent drug discharge (shortly) (convergence of Stake 400, X1 and centralization of HPMC E5 LV, X2). As per polynomial condition of percent drug discharge, both how much plasticizer and how much polymer negatively affect percent drug discharge. As how much Stake 400 and grouping of HPMC E5 LV were

92 raised, percent drug arrival of movies diminished. For all details, percent drug discharge differs between 99.14 1.74 and 93.79 1.86. ZMDF1 showed most elevated percent drug discharge when contrasted with different plans. most elevated percent drug delivery could be because of base measure of plasticizer Stake 400 and polymer HPMC E5 LV in ZMDF1. 5.4 EVALUATION OF FACTORIAL DESIGN BACHES Figure 5. 25 Desirability plot Figure 5. 26 Overlay plot According to attractiveness research and overlay study, prediction is 0.764 when 1.65

93 ml PEG 400 plasticizer and 279.90 mg HPMC E5 LV polymer are used. Batch Selection: detailing F5, which contains 1.5 ml Stake 400 plasticizer and 300 mg HPMC E5 LV polymer, was picked as improved cluster in view of collapsing perseverance, drug dissolving time, percent drug discharge, rigidity, and medication content consistency results from attractiveness study, overlay study, and other assessment of factorial plan clumps perception. The region that met ideal particulars was accomplished in this plot. fundamental response shapes were superimposed over structure plot to make this overlay plot. zone of alluring response regards in variable space is portrayed graphically. Regions that didn't meet improving measures were covered up. yellow zone signified land that met models' prerequisites, while dark tone indicated locale that didn't. Table 5. 36 Checkpoint batch Compositions (mg) Folding Endurance Disintegration Time (Sec) % CDR

| PEG 400 | HPMC E5 LV | Predicted | Observed | Predicted | Observed | Predicted | Observed |
|---------|------------|-----------|----------|-----------|----------|-----------|----------|
| 1.65 | 279.90 | 268.420 | 266.530 | 32.8962 | 34.7834 | 97.4585 | 95.7569 |

94 A projected worth and noticed worth are essentially indistinguishable because of designated spot group. Collapsing Perseverance (266.530), Crumbling time (34.7834 sec.), and percent CDR of designated spot clump (95.75 percent). Thus, it is viewed as bunch that has been enhanced. This clump was picked to make mouth dissolving film. Table 5. 37 Evaluation of mouth dissolving film ZMDOF10 Sr. No Evaluation parameter Results 1. Weight variation(mg) 118.07 ± 0.01 2. Thickness (mm) 0.15 ± 0.02 4. Surface Ph 6.7 ± 0.04 5. Tensile strength (kg/cm²) 2.55 ± 0.011 6. Drug content (%) 99.10 ± 0.10 Figure 5. 27 SEM OF ZMDOF10

95 Table 5. 38 Flux and permeability co-efficient of ZMDOF10 Time (Mins) Batch ZMDF10 Flux J (mg/cm²/hr) Permeability co-efficient (kP) 0 0.000 0 1 0.793 0.037393 2 0.014 0.000654 3 0.006 0.00028 4 0.010 0.000472 5 0.013 0.00059 6 0.217 0.010254 7 0.083 0.003931 Because of discoveries, it was resolved that ZMDOF10 had superior managed delivery somewhat. It supports accomplishing highest level of viable focus. Motor investigation of ZMDF10 discharge information. Table 5. 39 Kinetic analysis of release data of ZMDOF10 Model Zero-Order First-Order Higuchi R² value 0.992 0.874 0.965 Slope 5.415 0.113 0.568 Intercept -0.321 0.675 1.784 The total amount of drug penetrated was calculated using Higuchi and Zero order models, i.e. diffusion mechanisms.

96 FT-IR Study of Optimized MDF Formulation Figure 5. 28 FT-IR Study of Optimized MDF Formulation 5.4.2 Taste Evaluation Study by Spitting Table shows aftereffects of taste assessment examination. lumpiness and crabbiness of detailing in mouth were utilized to rate mouth feel in this review. In all plans, normal mouth feel recommended smooth to exceptionally smooth sensation. Not entirely set in stone by capacity to eliminate

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film from Alu pocket and spot it in mouth without utilization of water, which was considered patient- accommodating and

magnificent. 5.4.3 Results of Taste and Palatability Evaluation Table 5. 40

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Results of Taste and Palatability Evaluation Sample Type Mouth feel Taste (Bitterness) After Taste Ease of handling Acceptance

Test (Batch No. ZMDOF10) 4.5 ± 0.46 4.50 ± 0.00 4.48 ± 0.35 5.00 ± 0.00 4.19 ± 0.52

97 5.4.5 Comparison of optimized MDF with conventional marketed formulation Table 5. 41 Comparison of optimized MDF with conventional marketed formulation Time % Drug release (ZMDOF10) % Drug release of marketed Product (Zipwell-20) 0.0 ± 0.0 14.75 ± 0.13 0.264 ± 2.12 34.3 ± 1.78 6.274 ± 0.17 46.22 ± 1.68 10.31 ± 0.12 62.9 ± 1.26 43.22 ± 1.21 58.795 ± 1.59 56.18 ± 1.31 97.86 ± 0.15 67.46 ± 1.12 Figure 5. 29 Comparison of optimized MDF with conventional marketed formulation

98 5.4.5 Evaluation of optimized batch under stability study Table 5. 42 Evaluation of optimized batch under stability study Stability Conditions Sampling Time Disintegration Time (sec \pm SD) Drug Content (% \pm SD) Tensile Strength (kg/cm² \pm SD) Visual Appearance 40° C \pm 02° (Temp.) Initial 34.56 ± 00.51 99.15 ± 00.10 02.30 ± 0.01 Clear appearance 75% \pm 05% RH 03 months 34.37 ± 02.73 99.52 ± 00.29 02.63 ± 0.01 Clear appearance

99 6. FORMULATION & DEVELOPMENT OF QUETIAPINE FUMARATE MOUTH DISSOLVING FILM FOR PSYCHOSIS TREATMENT 6.1 RATIONAL OF RESEARCH WORK: 6.1.1 RATIONAL OF MOUTH DISSOLVING FILM FORMULATION (MDF) Because of its safety, convenience of administration, and patient acceptability, oral route is one of most used medication delivery methods. Oral solid dose forms are available in around 60% of conventional dosage forms. Patients such as paediatrics, geriatrics, bedridden, and emetic patients, as well as problems such as acute allergy responses or coughing, benefit from orally dissolving strips and films. They can be used both locally and nationally. Because of their faster dissolution rate, higher flexibility, and better patient compliance, orally dissolving film and strips are becoming more popular as alternative to fast dissolving tablets. Currently, research is being done on utilisation of orally dissolving films as potential carriers for several active medicinal components. Listerine, Chloraseptic, Triaminic, and multivitamins are among commercially available orally dissolving film products. plasticizer and film forming polymer, or mixture of polymers, constitute backbone of orally dissolving film, which gives it appropriate elasticity and shape. Due to their flexibility, fast disintegrating films are most advanced form of solid dosage form. When compared to dissolving tablets, it improves efficacy of active pharmaceutical substances since they breakdown in oral cavity in short period of time following contact with less saliva. This delivery technique consists of thin film that is placed on tongue or mucosal tissue and is instantaneously wet by saliva. Once wet, film quickly disintegrates, releasing drug for oral mucosal absorption. medicine is delivered to systemic circulation via buccal mucosa using fast disintegrating film made of hydrophilic polymer that rapidly disintegrates for buccal cavity. For increase of bioavailability, fast disintegrating drug delivery systems are specifically designed for medicines with significant first pass metabolism and low dosage. 6.1.2 RATIONAL OF FORMULATION & DEVELOPMENT OF MOUTH DISSOLVING FILM FOR PSYCHOSIS TREATMENT: Psychosis is mental illness marked by hallucinations, dementia, and seizures. In order to reduce possibility of lasting brain damage, it must be treated quickly. Antipsychotic medication pharmacotherapy is still most common treatment for psychosis. therapy of psychosis is different from treatment of other diseases. orally dissolving film

100 formulation of newer antipsychotic is ideal medication candidate. Antipsychotics formulated as orally dissolving strip, which must be placed on patient's tongue without swallowing for dose delivery, would greatly simplify dose administration and enhance patient compliance. goal of this study was to design, develop, and characterise antipsychotic medication mouth dissolving films.. 6.1.3 RATIONAL OF FORMULATION & DEVELOPMENT OF QUETIAPINE FUMARATE MOUTH DISSOLVING FILM FOR PSYCHOSIS TREATMENT: The prevalence of psychotic disorders has risen dramatically. Furthermore, schizophrenia and bipolar disorder afflict between 2.4 and 5.7 million American adults, or around 1.1 and 2.6 percent of population aged 18 and older, respectively. ODT is most popular dosage form in tablet form, however film has greater advantages than tablet because to bigger surface area, which allows for faster disintegration and hence

dissolution in oral cavity. preparation of fast dissolving film is novel approach for rapid and rapid release of medicine for treatment of psychotic disorder. Patients who have rapid psychotic crisis and need to calm down will benefit from proposed drug delivery. Quetiapine fumarate is used to treat schizophrenia and bipolar disorder. However, because medicine is substantially metabolised by liver, its oral bioavailability is limited, making it good option. With half-life of 6 hours, quetiapine (QTP) is used to treat schizophrenic attacks and bipolar disorder. QTP is medication that is quickly absorbed and well tolerated. QTP has low risk of extrapyramidal symptoms. Within 1.5 hours, peak plasma concentration of quetiapine fumarate is reached. Quetiapine fumarate has bioavailability of roughly 9%, half-life of 6 hours, and is broadly dispersed throughout body. drug binds to plasma proteins in about 83 percent of cases. Because it is extensively metabolised in liver to sulfoxide metabolite and parent acid metabolite by sulfoxidation and oxidation, both of which are pharmacologically inactive and have low bioavailability, quetiapine fumarate was chosen as model drug for fast disintegrating drug delivery to avoid extensive firstpass metabolism. This implies that QTP quick dissolving film, which gives speedy relief from psychotic symptoms while minimising side effects, is required. The goal of this study was to create rapid disintegrating quetiapine fumarate film by combining several polymers with shorter disintegration time and increased drug

101 release, with goal of benefiting patients who have trouble swallowing traditional dose forms. improve drug bioavailability and fast onset of action. 6.2 OBJECTIVES OF RESEARCH WORK: The prime objectives were to develop MDF drug delivery system that: 1. To make release of drug at oral mouth cavity and hence dose and dose frequency can be decreased thereby obtaining greater therapeutic efficacy. 2. To Show better in-vitro release/diffusion performance than conventional dosage forms.

102 6.3 PLAN OF RESEARCH WORK: 6.3.1. Literature survey and Patent Search related to Drug, Polymer & MDF Technology. 6.3.2. Selection of Drug, Polymer and Methodology for formulation & development of MDF drug delivery system 6.3.3. Preformulation study of Drug ✓ Organoleptic characteristics of drug ✓ Melting Point ✓ Solubility ✓ Partition Co-efficient ✓ Identification of drug by λ_{max} , FT-IR study. ✓ Preparation of Calibration Curve of Drug ✓ Drug- polymer Compatibility study FT-IR study 6.3.4. Preparation of MDF. 6.3.5. Preliminary Trial Batches for selection of materials 6.3.6. Formulation of Drug loaded MDF Using Factorial Design (DoE) approach 6.3.7. Characterization of Drug loaded MDF ✓ Thickness ✓ Weight variation ✓ Drug Content ✓ Measurement of mechanical property ✓ Folding endurance ✓ Physical appearance and texture analysis of films ✓ In vitro disintegration ✓ In vitro dissolution ✓ Flux and Permeability Co-efficient Study ✓ Kinetics of drug release ✓ Stastical analysis ✓ Validation batches (Check Point Analysis) and its characterization of drug loaded MDF ✓ FT-IR Study of Optimized MDF Formulation ✓ Comparison of optimized MDF with conventional marketed formulation. ✓ Ex- vivo study subjected to IAEC approval and permission

103 ✓ Accelerated stability study 6.3.8. Thesis writing and paper publication in esteem journal. 6.4. EXPECTED OUTCOME The distribution of medicament to target site at therapeutically relevant level, with negligible or little discomfort and adverse effects to patient, are cornerstones of good pharmaceutical formulation. route of drug delivery plays significant role in this regard. oral route is most popular method of drug delivery due to its ease of usage. However, there are some possible downsides, such as poor bioavailability due to first pass effect and proclivity for producing abrupt high and low plasma concentrations of medication, which can lead to poor patient compliance. To overcome disadvantages of oral route, continuous intravenous infusion has been discovered to maintain consistent and sustained medication concentration within therapeutic range for long time. However, this method of drug delivery has several disadvantages, including as needle pain and unintentional needle sticks, necessitating recurrent hospitalisation and medical care during treatment. Due to patient compliance, mouth dissolving film is now recommended route of medication delivery. following are key predicted outcomes of this research: ✓ Development of Mouth Dissolving Film (MDF) ✓ Formulation of effective formulation for treatment of psychosis patients ✓ Patient's compliance due to development of MDF.

104 7. MATERIALS & EQUIPMENTS USED

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The accompanying materials, synthetics and instruments might be utilized for Quetiapine Fumarate Mouth Dissolving Film for Psychosis Treatment

according to following Table. 7.7.1. List of Materials Table 7. 1 List of Materials MATERIALS SOURCE Quetiapine Fumarate Zota Healthcare LTD, Surat. HPMC E5 Zota Healthcare LTD, Surat. PEG 400 Zota Healthcare LTD, Surat. Citric Acid Zota Healthcare LTD, Surat. Aspartame Zota Healthcare LTD, Surat. Mannitol Zota Healthcare LTD, Surat. Orange Flavour Zota Healthcare LTD, Surat. Methyl Paraben Zota Healthcare LTD, Surat. Propyl Paraben Zota Healthcare LTD, Surat. Vanillin

Zota Healthcare LTD, Surat. 7.7.2. List of Equipments Table 7. 2 List of Equipments EQUIPMENTS MODEL AND SOURCE UV – Visible Spectrometer UV-1700, Shimadzu Corporation. Mechanical Stirrer Remi instrument division Electronic Balance Ohaus corporation NJ, USA Humidity Cabinet Analytical Technologies, Bangalore. Scanning Electron Microscope JEOL JSM-6380KVM Oxford Instruments, England FT-IR Spectrophotometer Shimadzu Corporation Compound Microscope Acculab Dissolution Apparatus I, USP I Macro scientific works private limited, Delhi. Malvern Malvern Instruments LTD.

105 7.8. Methodology 7.8.1. Preformulation of Quetiapine Fumarate The reason for preformulation study is to assemble data that will assist makers with building stable measurements shapes that can be efficiently manufactured. 7.8.1.1. Organoleptic Characteristics of QTP FMT The organoleptic attributes of QTP FMT, like tone and scent, were inspected truly. 7.8.1.1.1. Taste Evaluation Study by Spitting In solitary measurements and single visually impaired review, 8 solid grown-up male volunteers between ages of 24 and 42 partook. All subjects gave composed informed agree before review, and they were told with regards to review's objective, dangers, and term. Each volunteer got QTP FMT at irregular. volunteers were told to clean their mouths with 200 cc of refined water before to preliminary. volunteers were approached to place medication in their mouth for 30 seconds, record deterioration season of film test, and give score in light of boundaries recorded in Table 3, in particular mouth feel, taste or sharpness, film delayed flavor impression, simplicity of dealing with, and by and large acknowledgment of detailing. Following 3 minutes,

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volunteers were told to let out example with salivation and flush their mouths with 200 ml refined water. Following 2 hours, indistinguishable system was finished subsequent example (either test or reference test). Thus, spitting of detailing and salivation was told to volunteers to forestall openness of medication. Table 7. 3 Parameters, Score and Results of Taste Evaluation Study 7.8.1.2. Determination of Melting Point of QTP FMT Melting point of QTP FMT was evaluated by capillary method. 106 7.8.1.3 Identification and Determination of Wavelength max (λ_{max}) of QTP FMT

To create stock arrangement of 100 g/ml, appropriately gauged amount of 100 mg of medication test was broken down in combination of water and acetonitrile (1:1) (3 of every 200,000)

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and volume moved toward 100 ml utilizing water and acetonitrile in 100 ml volumetric carafe. Then, at that point, 1 ml of stock arrangement was pipetted into 10 ml volumetric cup, and volume was

expanded to imprint to get convergence of 10 g/ml. resultant arrangement was then filtered with UV-noticeable spectrophotometer (Mdel-1700, Shimadzu, Japan) somewhere in range of 200 and 400 nm. UV range test

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was recorded, and most extreme worth got was contrasted with UV range expressed in authority monograph. greatest frequency of Quetiapine fumarate was found to be 248 nm. 7.8.1.4. Solubility study of QTP FMT Preformulation

dissolvability testing was performed, which involved dissolving abundance medicine in glass vials containing 20mL suitable dissolvable framework and sifting supernatant arrangement following 24 hours at room temperature utilizing 0.45 m pore size channel. initial 10 mL of filtrate were disposed of, and rest of weakened

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with water and spectroscopically estimated at 248 nm. Different solvents, like water, CH_3CO , ethanol, chloroform, ether, and pH 7.4 Phosphate support, will be utilized all through strategy. 7.8.1.5. Determination of Partition Co-efficient:

Not entirely set in stone by immersing 10mL of n-octanol in isolating channel with 10mL phosphate cradle pH 7.4 for 24 hours. 10mg of medicine will be put to isolating pipe, trailed by 4 hours of moderate shaking. layers of dissolvable were isolated utilizing channel, and how much drug broke up in each stage was estimated at 248

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nm against clear. 7.8.1.6. Preparation of Calibration Curve for QTP FMT 7.8.1.6.1. Calibration Curve for QTP FMT IN 0.1N HCL solution Preparation of Stock solution

In 100 mL volumetric jar, 100 mg of drug was precisely gauged. volume was then expanded to 100 ml by adding 0.1N HCL answer for accomplish 100 g/ml arrangement. 1 ml of stock arrangement (100 g/ml) was pipetted and weakened to 10

107 ml with 0.1N HCL arrangement into different volumetric jars and made up to 10 ml with 0.1N HCL answer for get convergences of 1.0 to 5.0 g/ml. Preparation of standard working solution 1ml was taken from stock arrangement (100g/ml) and weakened to 10ml with 0.1N HCL arrangement. Proper aliquots of arrangement were taken into different volumetric flagons and made up to 10ml with 0.1N HCL answer for accomplish convergence of 1.0 to 5.0 g/ml. By dissolving exactly gauged 100 mg of medicine in 100 ml volumetric flagon, medication alignment bend in 0.1 N HCL was made. volume was consequently expanded to 100ml utilizing 0.1N HCL answer for get answer of 100g/ml, which was then examined in UV spectrophotometer, affirming that example complied to Brew's Regulation. 7.8.1.6.1.

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Calibration Curve for QTP FMT in Saline buffer pH 7.4 Preparation of Stock solution

In saline support pH 7.4, 100g/

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ml stock arrangement of QTP FMT was produced by dissolving 10 mg of medication in 10 ml of methanol and afterward filling leftover volume with saline cradle pH 7.4.

By examining appropriate weakenings with high relationship coefficient, limit of QTP FMT was distinguished. Different standard weakenings were ready from stock answer for get arrangements

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of 2,4,6,8, and 10 g/ml, and their absorbance values were estimated at fixed max with boundary set at 0.5nm for

transfer speed and information pitch. Preparation of Standard working solution The previously mentioned arrangement was sequentially weakened with saline cradle pH 7.4 answer for get arrangements of 10, 20, 40, 50, and 100 g/ml. absorbance at 248 nm was utilized to assess how much QTP FMT. 7.8.1.7.

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Identification of QTP FMT by FT-IR Spectroscopy Potassium bromide IR circles will be made utilizing 1mg of QTP FMT on

water powered pellet press and checked at 4000-400

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cm-1 in FTIR. IR spectra acquired will be contrasted with reference range of QTP FMT. 7.8.1.8. Drug- Excipients Compatibility Studies by FT-IR A combination of QTP FMT, HPMC E5, Stake 400, Citrus extract, Aspatame, and Mannitol will be

utilized to make potassium bromide IR circle, which will be filtered in 4000-400

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cm-1 region in FTIR and contrasted with reference range of QTP FMT. 108 7.8.1.9. Particle Size Study: Unadulterated Medication Molecule size examination had done utilizing Optical Magnifying lens and Malvern Instrument. 7.8.2. Formulation and Development of QTP FMT MDF by using QbD Approach 7.8.2.1. Setting up Quality Target Product Profile (QTPP) and Selection of Formulation and Process Variables by Preliminary Trial Batches of QTP FMT MDF:

The impact of polymer type and focus, plasticizer type and fixation, crumbling specialists, and other excipients on MDF will be researched in primer preliminaries. To foster QbD Approach, these starter clumps of quick deteriorating films were assessed utilizing different boundaries, for example, morphological review, weight variety, breaking down

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time, surface pH, collapsing perseverance, thickness, drug content consistency, percent uniform medication dissemination, and in-vitro drug discharge study. 7.8.2.2. Dose calculation of QTP FMT for mould Dose of drug = ORAL DOSE * ORAL BIOAVAILABILITY/ BODY SURFACE AREA 7.8.2.3.

Solvent casting method Same as Above Table 7. 4 Materials and their concentration used for Preliminary trial Batches of QTP FMT MDF SL. NO ROLE OF MATERIAL MATERIALS TO BE USED CONCENTRATION 1 Drug QTP FMT 100 mg 2 Polymers HPMC E5, HPMC E50, Acacia, Tragacanth, Gelatin, Xanthum Gum, PVA, PVP and Pullnan 0.5 gm to 1.0 gm 3 Plasticizers PEG 200, PEG 400, Poloxamer 407, PG, IPA 0.5 gm to 1.0 gm

109 4 Disintegrating Agent Cross Providone, Kryon T-314, Banana Powder 0.5 gm to 1.0 gm 5 Solvent Distilled water Q.S. 6 Sweeting Agent Aspartame, Mannitol Q.S. 7 Flavouring Agent Vanillin Q.S. 8 Preservative Citric acid, Methyl paraben, Propyl paraben Q.S. 7.8.2.4.

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Preliminary Trial Batches of QTP FMT MDF 7.8.2.4.1. Selection of Polymer and concentration for QTP FMT MDF: The different polymers & their concentrations were used to prepare QTP FMT MDF to fix polymer type and concentration. details are as follows: Table 7. 5 Polymer and concentration for QTP FMT MDF 7.8.2.4.2.

Selection of plasticizer for QTP FMT MDF To fix plasticizer type and fixation, QTP FMT MDF was arranged utilizing few plasticizers and focuses. Coming up next are various plasticizers that were utilized:

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Table 7. 6 Plasticizer type and concentration for QTP FMT MDF PLASTICIZER TYPE USED PEG 200 Poloxamer 407 PG IPA

PVA PLASTICIZER CONCENTRATION 0.5- 1.0ml 10-20 mg 1-2 ml 0.5- 1.0ml 10-20 mg POLYMER TYPE USED HPMC E5 Acacia PVP PULLNAN HPMC E50 Tragacanth Xanthum gum POLYMER CONCENTRATION USED (gm) 0.5-1.0

110 USED 7.8.2.4.3. Selection of disintegrating agent for QTP FMT MDF To fix polymer type and focus, numerous polymers and fixations were used to make QTP FMT MDF. Coming up next are different polymers that were utilized: Table 7. 7 Disintegrating agent type and concentration for QTP FMT MDF 7.8.2.5.

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Risk Assessment of Critical Quality Attributes (CQAs) from Preliminary trial Batches to Develop QbD Approach

Process portrayal will recognize acceptable alterations in material and cycle boundaries, and hazard evaluation will be utilized to choose plan and interaction factors that might influence item quality for CQAs. At last, Interaction Configuration Space might have option to give quality affirmation by understanding and fostering control plan. In view of

information space, basic quality characteristics are named high, medium, or generally safe. High danger boundaries are generally respected significant

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for Plan of Analyses since they have more prominent impact than others and should be in multivariate reaches that can be acknowledged. 7.8.2.6. Formulation and Development of QTP FMT MDF by Design of Experiment (DoE) Using QbD Approach A plan space

could address detailing and interaction information, for example, characteristics connecting with drug fixing, materials, gear, protected innovation, and finished item quality. Hazard evaluation on MDF quality should be possible for this reason in light of comprehension of interaction and definition related components. For high-hazard boundaries, fundamental exploration and later Plan of Trial and error (DoE) would be led. We will propose configuration space for creating strong definition in light of impact of significant quality highlights of objective item profile. MDF will be portrayed for assortment of boundaries.

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DISINTEGRATING AGENT TYPE USED Cross Povidone (g) Kyron T-314 (g) Banana Powder (g)

DISINTEGRATING AGENT CONCENTRATION (gm) 0.5 - 1.0

111 7.8.2.7. Characterization of QTP FMT MDF 7.8.2.7.1. Weight variation On scientific equilibrium, mouths dissolving oral movies were gauged, and normal load for each film was determined. It is best for movies to have weight that is basically steady. It's vital to ensure film has perfect proportion of excipients and Programming interface. 7.8.2.7.2. Thickness of Films thickness of film was estimated at five separate areas utilizing micrometer screw measure, and normal of three readings was inferred. This is important to give consistency in thickness of film, which is connected to portion precision in film. 7.8.2.7.4. Folding endurance Collapsing perseverance is estimated by collapsing similar piece of film again and over until it breaks. collapsing perseverance esteem is times film can be collapsed in similar spot without breaking. 7.8.2.7.5. Thickness: thickness of medication arranged fix is estimated with computerized micrometer at different focuses on fix, and normal thickness and standard deviation are determined to ensure that thickness of fix is kept up with. 7.8.2.7.6. Weight Uniformity: characterized fix region should be parted into particular areas and made appearance advanced equilibrium. Individual loads will be utilized to lay out normal weight and standard deviation. 7.8.2.7.7 Surface pH The film to be tried was drenched with 0.5 cc of refined water and put away for 30 seconds in Petri dish. Subsequent to bringing terminal of pH meter in contact with outer layer of definition and permitting 1 moment for equilibration, pH was recorded. For every detailing, normal of three conclusions was made. 7.8.2.7.8. In vitro disintegration test Whenever oral film comes into contact with water or spit, deterioration time starts to abbreviate. breaking down ideal opportunity for quick dissolving film ought to be somewhere in range of 5 and 30 seconds. One more way was to outwardly decide breaking down time by plunging film in 25 mL water in measuring utensil. container was delicately shaken, and second when film started to part or deteriorate was

112 recorded. 7.8.2.7.9. Drug content Determination: arrangement is shaken ceaselessly for 24 hours in shaker hatchery after precisely gauged amount

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of film (over 100 mg) is broken up in 100 mL of Phosphate cradle pH 7.4 in which drug is

solvent. After then, at that point, whole arrangement is sonicated. How much medicine in arrangement is estimated spectrophotometrically after sonication and resulting sifting. 7.8.2.7.10 Tensile Strength: Tensile strength= $F/a \times b (1+L/l)$ 7.8.2.7.11 Flux and Permeability coefficient: $K_p = J/C$ 4.8.2.7.16. In-vitro Permeation study A dispersion cell receptor compartment limit of 12 ml can be utilized to direct in-vitro saturation research. Between contributor and receptor compartments of dispersion cell, extracted cellophane paper was mounted. Over paraffin film, arranged patches were put. dispersion cell's receptor compartment was loaded up with phosphate cushion pH 7.4. whole gathering was mounted on attractive stirrer, and arrangement in receptor compartment was continually and consistently whirled with attractive

dots at 50 rpm while keeping temperature of 32 0.5 °C. Tests were taken at different times and spectrophotometrically assessed for drug focus. With indistinguishable volume of phosphate support, receptor stage was recharged. 7.8.2.7.12

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Kinetic Analysis of Release Data: 7.8.2.7.12.1. Zero Order Release $Q_t = Q_0 + K_0t$ 4.8.2.7.12.2.

First Order Release Equation $\log C = \log C_0 - Kt / 2.303$

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Plot: log cumulative percentage of drug remaining vs. time. 7.8.2.7.12.3. Higuchi Square Root of Time Equation: $Q = KH \times t^{1/2}$ 7.8.2.7.12.4.

Hixson-Crowell Model $W_0^{1/3} - W_t^{1/3} = k t$ 7.8.2.7.12.5. Korsmeyer- Peppas Release Mechanism $M_t / M_\infty = k t^n$

113 7.8.2.7.13. Validation or check point analysis of QTP FMT MDF Plan and portrayal of expected bunches from Overlay plots proposed by StatEase programming will be utilized for approval or designated spot examination. aftereffects of normal and noticed clumps will be analyzed. 7.8.2.7.14. Taste Evaluation Study by Spitting In solitary measurements and single visually impaired review, 8 sound grown-up male volunteers between ages of 24 and 42 partook. All subjects gave composed informed agree preceding review, and they were told with regards to review's objective, dangers, and span. Each volunteer got irregular portion of QTP FMT advanced MDF. volunteers were told to clean their mouths with 200 cc of refined water before to preliminary. volunteers were approached to place medication in their mouth for 30 seconds, record deterioration season of film test, and give score in view of boundaries recorded in Table 3, in particular mouth feel, taste or harshness, film lingering flavor, simplicity of taking care of, and generally acknowledgment of detailing. Following 3 minutes,

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volunteers were told to let out example with spit and wash their mouths with 200 ml refined water. Following 2 hours, indistinguishable method was finished subsequent example (either test or reference sample).So, spitting of definition and salivation was told to volunteers to forestall openness of medication. Table 7. 8 Parameters, Score and Results of Taste Evaluation Study 7.8.2.7.15. Scanning electron microscope

Checking electron microscopy was utilized to analyze surface morphology of better definition. filtering electron infinitesimal example holder with twofold sided taps was

114 covered with 150A gold layer for 2 minutes in vaccum of 310-1atm organ gas utilizing falter coater (JSM 6390, Make - JEOL). filtering electron magnifying instrument was then used to examine examples. 7.8.2.7.16. Skin Permeation Study (Ex-vivo Study) IAEC endorsement and assent will be expected for skin penetration examination (ex- vivo study). Skin from pale skinned person rodents will be painstakingly taken out. skin will be utilized as hindrance layer for examinations once hypodermal fat tissue has been taken out. For this examination, ideal plan from in vitro analyses will be utilized, with rodent skin filling in as film between contributor and receptor compartments. receptor compartment will be loaded up with phosphate cradle pH 7.4 and unsettled at 37 1 °C utilizing attractive stirrer. examples will be contrasted with clear utilizing UV spectrophotometer set to 248 nm. 7.8.2.7.17.

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Comparison of optimized QTP FMT MDF with Marketed QTP FMT formulation: The optimized formulation QTP FMT MDF will be compared with Marketed conventional QTP FMT. 7.8.2.7.18. Stability Studies The picked organization was put in

golden shaded jugs that were firmly shut and stopped up with cotton. They were hence kept up with for one month

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at 40°C/75% RH and surveyed for actual appearance, in vitro deterioration time, drug content homogeneity, and medication discharge learns at foreordained stretches. 115 8. RESULTS & DISCUSSION 8.1 PREFORMULATION STUDY OF QTP FMT 8.1.1. ORGANOLEPTIC PROPERTIES Table 8. 1 Organoleptic characteristics of Drugs S.No. Parameters 1.

White in color 2. Characteristics in odor 3. Bitter in taste The actual appearance of unadulterated medication was inspected outwardly as per Indian Pharmacopeia. Shading, scent, and taste were assessed by our faculties (eye, tongue, and nose) in this examination. 8.1.2. MELTING POINT The chose medication's dissolving point was determined utilizing advanced liquefying point instrument and hairlike combination technique. With utilization of burner, one finish of fine was fixed. narrow cylinder's open end was embedded into little piece of powder, and cylinder was delicately tapped to settle accumulated material. method was completed few times more. dissolving point gadget was then used to situate slender cylinder. Not entirely settled at what temperature medicine starts to liquefy. Table 8. 2 Determination of melting point of drugs S.No. Quetiapine FMT Melting Point Observed value (n =3) Standard value 1. 172-176 0 C 170-175 0 C The dissolving point was utilized to decide example's virtue. softening place of drug test was 170-1750C, which was inside reach and shown that example was unadulterated QTP FMT. 8.1.3. DETERMINATION OF WAVELENGTH OF QTP FMT To create stock arrangement of 100 g/ml, appropriately gauged amount of 100 mg of medication test was disintegrated in combination of water and acetonitrile (1:1) (3 of every 200,000) and volume moved toward 100 ml utilizing water and acetonitrile in 100 ml volumetric jar. Then, at that point, 1 ml of stock arrangement was pipetted into 10 ml volumetric cup, and volume was expanded to imprint to get convergence of 10 g/ml. resultant arrangement was then examined with UV-noticeable 116 spectrophotometer (Mdel-1700, Shimadzu, Japan) somewhere in range of 200 and 400 nm. UV range test was recorded, and greatest worth got was contrasted with UV range expressed in authority monograph. The λ max of QTP FMT and Quetiapine fumarate was viewed as 318 nm and 248 nm separately. Table 8. 3

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Wavelength maximum (λ max) of QTP FMT Drug λ max Actual λ max Observed λ max QTP FMT 250 248.5 Figure 8. 1 UV Spectrum of QTP FMT 8.1.4. SOLUBILITY STUDIES

The dissolving and dissemination liquids for medication delivery and pervasion examinations were picked in light of QTP FMT dissolvability information in different liquids. solvency of medication test was tried by dissolving 100 mg of medication test in different liquids in expanding sums. Dissolvability was estimated by recording how much dissolvable important to disintegrate medicine. Table 8. 4 Solubility of profile of QTP FMT S.No. Solvent Solubility QTP FMT Conc. (mg/ml) Mean \pm SD, n=3 Inference

117 1. HCl 11.67 ± 0.21 Soluble 2. NaOH 11.07 ± 0.15 Soluble 3. Ethanol 0.07 ± 0.02 Slightly Soluble 4. Methanol 0.86 ± 0.03 Sparingly Soluble 5. Water 0.66 ± 0.04 Slightly Soluble 6. DMSO 0.95 ± 0.05 Slightly Soluble Figure 8. 2 Solubility of profile of QTP FMT 8.1.5. PARTITION COEFFICIENT In n-ctanol as nn-watery stage and phosphate support arrangement pH 7.4 (PBS pH 7.4) as fluid stage, medication parcel coefficient was estimated. These two stages were blended in equivalent parts and held in isolated pipes until they were soaked with one another. In wake of blending, let framework be for 30 minutes. parcel coefficient was determined by isolating 10 mg of prescription into 10 ml parts of n- ctanl and PBS pH 7.4 in isolating channels. isolating channels were shaken for 24 hours on mechanical shaker. Two stages were isolated, and fluid stage was sifted through Whatman channel paper, and how much medication in watery stage was

118 evaluated spectrophotometrically at max 248 nm utilizing phosphate cushion arrangement pH 7.4 as clear after satisfactory weakening. Table 8. 5

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Determination of Partition Coefficient of selected Drugs S.No. Sample Partition Coefficient (Mean \pm SD, n=3) 1. QTP FMT 3.35 ± 0.53 8.1.6. Calibration Curve: 8.1.6.1.

QTP FMT Calibration Curve in 0.1N HCL Preparation of standard stock solution (100 μ g/ml) in 0.1N HCL In 100 mL volumetric carafe, 100 mg of medicine was precisely gauged. volume was then expanded to 100 ml by adding 0.1N HCL

answer for accomplish 100 g/ml arrangement. 1 ml of stock arrangement (100 g/ml) was taken and weakened to 10 ml with 0.1N HCL arrangement in independent volumetric carafes, bringing about centralization of 1.0 to 5.0 g/ml. Preparation of standard working solution 1ml was taken from stock arrangement (100g/ml) and weakened to 10ml with 0.1N HCL arrangement. Fitting aliquots of arrangement were taken into different volumetric flacons and made up to 10ml with 0.1N HCL answer for accomplish centralization of 1.0 to 5.0g/ml. By dissolving definitively gauged 100 mg of prescription in 100 ml volumetric cup, medication adjustment bend in 0.1 N HCl was made. volume was thusly expanded to 100ml utilizing 0.1N HCL answer for acquire answer of 100g/ml, which was then examined in UV spectrophotometer, affirming that example complied to Lager's Regulation. Table 8. 6 Calibration Curve of QTP FMT in 0.1 N HCl Conc. ($\mu\text{g/ml}$) Absorbance (nm) Mean \pm SD; n=3 0 0 ± 0.00 1 0.102 ± 0.001 2 0.118 ± 0.020 3 0.202 ± 0.013 4 0.223 ± 0.012 119 5 0.313 ± 0.090 6 $0.34/\pm 0.021$ 7 0.388 ± 0.027 8 0.417 ± 0.023 9 0.489 ± 0.011 10 0.513 ± 0.003 Figure 8. 3 Standard Curve of QTP FMT in 0.1 N HCl at 248 nm Table 8. 7 Summery Report of calibration curve for QTP FMT Parameters QTP FMT

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Wavelength (λ_{max}) 248 Beer's limit ($\mu\text{g/ml}$) 0-10 Corrélation coefficient (R²) 0.986 Slope 0.050 Obeys Beer law in conc. range of 0-10 mcg/ml R² value shows linearity 120 8.1.6.2.

QTP FMT Calibration Curve in Phosphate buffer pH 7.4 (pH of Salivary stimulating fluid): Preparation of standard stock solution (100 $\mu\text{g/ml}$) in Phosphate buffer pH 7.4 (pH of Salivary stimulating fluid) In 10 mL volumetric flagon, precisely gauge 100 mg of medicine. volume was then expanded to 100 ml by adding Phosphate cradle pH 7.4 to accomplish 100 g/ml arrangement. 1 ml of stock arrangement (100 g/ml) was pipetted and weakened to 10 ml in discrete volumetric flacons with Phosphate support pH 7.4 to get centralization of 1 to 10 g/ml. Preparation of standard working solution 1 ml was pipetted from stock arrangement (100 g/ml) and weakened to 10 ml with Phosphate support pH 7.4. Suitable aliquots of arrangement were put into different volumetric carafes and made up to 10 ml with Phosphate cushion pH 7.4 to get centralizations of 1 to 10 g/ml. The alignment bend for drug in Phosphate cushion pH 7.4 was made by dissolving 100 mg of medication in 100 ml volumetric carafe that was exactly gauged. volume was then expanded to 100 ml utilizing Phosphate cushion pH 7.4 to create answer of 100 g/ml, which was then filtered in UV spectrophotometer to affirm that example complied with Lager's regulation. Table 8. 8 Calibration Curve of QTP FMT in Phosphate buffer pH 7.4 Conc. ($\mu\text{g/ml}$) Absorbance (nm) Mean \pm SD; n=3 0 0 ± 0.00 1 0.015 ± 0.051 2 0.015 ± 0.120 3 0.033 ± 0.003 4 0.03 ± 0.041 5 0.053 ± 0.028 6 0.062 ± 0.110 7 0.067 ± 0.003 8 0.070 ± 0.004 121 9 0.083 ± 0.017 10 0.089 ± 0.023 Figure 8. 4 Standard Curve of QTP FMT in Phosphate buffer pH 7.4 Table 8. 9 Standard Curve of QTP FMT in Phosphate buffer pH 7.4 Parameters QTP FMT

100% **MATCHING BLOCK 105/131** **W** <https://docplayer.net/amp/213630941-Design-dev ...>

Wavelength (λ_{max}) 248 Beer's limit ($\mu\text{g/ml}$) 0-10 Corrélation coefficient (R²) 0.989 Slope 0.009 Obeys Beer law in conc. range of 0-10 mcg/ml R² value shows linearity 8.1.7.

Identification of QTP FMT by FTIR Spectra To distinguish substance, infrared spectroscopy was utilized on unadulterated medication test. medication pellet was made by compacting medication with IR grade potassium bromide in KBr press at 5.5 metric huge loads of tension. pellet was put in IR compartment and checked with FTIR spectrophptmeter (Mdel-8400 S, Shimadzu, Japan) between wave numbers 4000-450 cm^{-1} .

122 Table 8. 10 Interpretation of FTIR Spectra of QTP FMT S.No. Inference Standard wave no.(cm^{-1}) Observed wave no. (cm^{-1}) Interpretation 1. O-H stretching 3584-3700 3751 Alcohol 2. C-H stretching 3000-3100 3080 Alkene 3. C-H stretching 2840-3000 2881 Alkane 4. C=C stretching 1600-1650 1600 Conjugated alkene 5. C-H bending 1372-1290 1344 Alkane methylene group 6. C-N stretching 10201250 1032 Amine 7. Substituted benzene ring 780-800 795 1,3 di substituted Figure 8. 5 FTIR Spectra of Pure Drug 8.1.8. Compatibility study of QTP FMT with excipients by FTIR Spectra Table 8. 11 Interpretation of FTIR Spectra of QTP FMT S.No. Inference Standard wave no.(cm^{-1}) Observed wave no.(cm^{-1}) Interpretation 1. O-H stretching 3584-3700 3751 Alcohol 2. C-H stretching 3000-3100 3079 Alkene 3. C-H stretching 2840-3000 2882 Alkane 4. C=C stretching 1600-1650 1602 Conjugated alkene 5. C-H bending 1372-1290 1343 Alkane methylene group

123 6. C-N stretching 10201250 1033 Amine 7. Substituted benzene ring 780-800 794 1,3 di substituted Figure 8. 6 FTIR Spectra of Pure Drug with excipients A combination of QTP FMT, HPMC E5, Stake 400, Citrus extract, Aspatame, and Mannitol will be utilized to make potassium bromide IR circle, which will be checked in 4000-400 cm⁻¹ region in FTIR and contrasted with reference range of QTP FMT. At point when QTP FMT was joined with polymers, no adjustments in IR tops were noticed. These discoveries highlight polymers' similarity with QTP FMT.

124 8.2.2.

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Trial batches for QTP FMT MDF for CQAs for QTP FMT MDF Table 8. 12 selection of polymers type and concentration for QTP FMT MDF

Ingredients QTPO DT1 QTPO DT2 QTPO DT3 QTPO DT4 QTPO DT5 QTPO DT6 QTPO DT7 QTPO DT8 QTPO DT9 QTPOD T10 QTPOD T11 QTPOD T12 Drug (gm) 0.184 PVP (gm) 0.1 0.3 0.5 - - - - - EC (gm) - - - 0.1 0.3 0.5 - - - - - HPMC E5 (gm) - - - - - 0.1 0.3 0.5 - - - HPMC E50 (gm) - - - - - 0.1 0.3 0.5 PEG 200 (ml) 01 DW Q.S Strip Yes

125 Form Stickine ss - Appearance # * # * DISCUSSION: BATCH (QTPODT1-QTPODT3): PVP, strip framing polymer, was utilized in sums going from 100 to 500 mg. strip, which had 300mg focus, was tacky and clear. strip showed air entanglement as fixation was expanded to 1.0gm, giving it cloudy appearance. Likewise, strip struggled separating itself from petridish. BATCH (QTPODT4-QTPODT6): Strip shaping polymer EC at fixations going from 100 to 500 mg was used. strip was tacky and clear with grouping of up to 300mg. Because of production of knots in strips at 500 mg fixation, strips were non-tacky yet cloudy by all accounts. BATCH (QTPODT7- QTPODT9): strip framing polymer HPMC E5 was used in focuses going from 100 to 500 mg. strips were decided on their actual appeal as well as their tenacity. From petridish, it was found that strips were non-tacky, clear, and had adequate peelability. BATCH (QTPODT10-QTPO11): HPMC E50, strip framing polymer, was utilized in fixations going from 100 to 500 mg. strips were decided on their actual appeal as well as their tenacity. From petridish, it was found that strips were non-tacky, clear, and had OK peelability.

126 Table 8. 13 Results of QTPODT4- QTPODT12 Batch Surface Texture Weight uniformity (mg) (Mean ± SD) n=3 Avg. uniform Drug Distribution (%) ± SD, n = 3 Avg. Drug Content uniformity (%) ± SD, n = 3 QTPODT4 Smooth 98.00±0.14 98.32 ± 0.191 99.32 ± 0.72 QTPODT5 Smooth 98.00±0.57 98.65 ± 0.221 99.16 ± 0.53 QTPODT7 Smooth 96.00±0.35 98.24 ± 0.389 98.76 ± 0.19 QTPODT8 Smooth 97.00±1.13 98.46 ± 0.244 99.65 ± 0.08 QTPODT9 Smooth 98.00±0.56 98.30 ± 0.44 99.84 ± 0.02 QTPODT10 Smooth 99.00±0.48 99.45 ± 0.189 99.40 ± 0.43 QTPODT11 Smooth 100.00±0.34 99.54 ± 0.129 99.76 ± 0.67 QTPODT12 Smooth 101.00±0.35 99.12 ± 0.131 99.50 ± 0.19

127 Figure 8. 7 Results of QTPODT4- QTPODT12 Table 8. 14 Results of QTPODT4- QTPODT12 Batch Surface Texture

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Surface pH (Mean ± SD) n=3 Thickness (mm) (Mean ± SD) n=3 Avg. Tensile strength (N/cm²) ± SD, n = 3

QTPODT4 Smooth 6.98 ± 0.05 0.14 ± 0.01 1.02 ± 0.01 QTPODT5 Smooth 7.05 ± 0.24 0.14 ± 0.01 1.03 ± 0.05 QTPODT7 Smooth 6.80 ± 0.18 0.17 ± 0.02 1.64 ± 0.01 QTPODT8 Smooth 6.66 ± 0.06 0.16 ± 0.02 1.53 ± 0.02

128 QTPODT9 Smooth 6.36 ± 0.13 0.15 ± 0.01 1.06 ± 0.03 QTPODT10 Smooth 6.96 ± 0.02 0.16 ± 0.01 2.22 ± 0.02 QTPODT11 Smooth 6.84 ± 0.28 0.17 ± 0.01 2.38 ± 0.01 QTPODT12 Smooth 6.74 ± 0.05 0.17 ± 0.01 2.86 ± 0.03 Figure 8. 8 Results of QTPODT4- QTPODT12

129 Table 8. 15 Results of QTPODT4- QTPODT12 Batch Surface Texture

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Avg. In Vitro Disintegration Time (sec) ± SD, n = 3 Avg. Folding Endurance ± SD, n = 3

QTPODT4 Smooth 161.35 ± 4.245 90.00±5 QTPODT5 Smooth 169.5 ± 3.375 97.00±4 QTPODT7 Smooth 167.26 ± 1.156 90.00±1 QTPODT8 Smooth 180.27 ± 1.271 101.00±5 QTPODT9 Smooth 189.01 ± 2.576 109.00±4 QTPODT10 Smooth 121.68 ± 1.936 148.00±3 QTPODT11 Smooth 135.76 ± 2.127 162.00±1 QTPODT12 Smooth 141.65 ± 1.377 173.00±2

130 Figure 8. 9 Results of QTPODT4- QTPODT12 Inference From discoveries of previously mentioned fundamental preliminary clusters for polymer choice, it was found that polymer HPMC E50 created best outcomes in focus scopes of 100, 300, and 500mg. Therefore, HPMC E50 was picked for last MDF synthesis.

131 Table 8. 16 Selection of Polymer type and concentration for QTP FMT MDF Ingredi ents QTPO DT13 QTPO DT14 QTPO DT15 QTPO DT16 QTPO DT17 QTPO DT18 QTPO DT19 QTPOD T20 QTPO DT21 QTPO DT22 QTPO DT23 QTPO DT24 Drug (gm) 0.184 Xanthu m gum (gm) 0.1 0.3 0.5 - - - - - PULL NAN (gm) - - - 0.1 0.3 0.5 - - - - - Acacia (gm) - - - - - 0.1 0.3 0.5 - - - Tragac anth (gm) - - - - - 0.1 0.3 0.5 PEG 200 (ml) 01 DW Q.S Strip Yes No Yes No

132 Form Stickin ess + Appear ance # @ # @ BATCH (QTPODT13-QTPODT15): Xanthum gum, strip-framing polymer, was used in focuses going from 100 to 500 mg. pre- arranged strips were inspected, and it was found that they were tacky and cloudy for all intents and purposes, and that they were hard to eliminate from petridish. BATCH (QTPODT16-QTPODT18): PULLNAN, strip-shaping polymer, was utilized in focuses going from 100 to 500 mg. It was found that no strip had been shaped. BATCH (QTPODT19-QTPODT21): Acacia gum, strip-shaping polymer, was used in sums going from 100 to 500 mg. strips that shaped were tacky, dark, and hard to eliminate from petridish. BATCH (QTPODT22-QTPODT24): Strip-framing polymer acacia gum was utilized in dosages going from 100 to 500 mg. tacky, hazy strips that framed were hard to eliminate from petridish.

133 Table 8. 17 Selection of Plasticizer type and concentration for QTP FMT MDF Ingredi ents QTPL DT1 QTPL DT 2 QTPL DT 3 QTPL DT 4 QTPL DT 5 QTPL DT 6 QT PL DT7 QTPL DT 8 QTPL DT 9 QTPL DT 10 QTPL DT 11 QTPL DT 12 QTPL DT 13 QTPL DT 14 QTPL DT 15 HPMC E50 (gm) 0.3 Drug (gm) 0.184 PG (ml) 0.5 0.75 1.0 - - - - - IPA (ml) - - - 0.5 0.75 1.0 - - - - - PVA (gm) - - - - - 0.01 0.015 0.020 - - - - - Poloxa mer 407 (gm) - - - - - 0.01 0.015 0.020 - - - PEG 200 (ml) - - - - - 0.01 0.015 0.020

134 DW (ml) Q.S Strip Form Yes Stickine ss + - + Appeara nce # * @ Strip-shaping polymer acacia gum was utilized in dosages going from 100 to 500 mg. tacky, obscure strips that framed were difPEG 200 (1-2 ml), PVA and Poloxamer 407 (10-20 mg), and PG and IPA (0.5-1.0 ml) were utilized to make strips. Actual appearance and tenacity of created strips were analyzed. strips holding back PVA and Poloxamer 407 were found to be non-tacky, non-slick, straightforward, and simple to project. Stake 200, PG, and IPA strips, then again, were tacky, sleek, misty, and hard to cast.ficult to eliminate from petridish

135 Table 8. 18 Results of QTPODT4- QTPODT12

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Batch Surface Texture Weight uniformity (mg) (Mean ± SD) n=3 Surface pH (Mean ± SD) n=3 Thickness (mm) (Mean ± SD) n=3 Avg. Tensile strength (N/cm 2) (Mean ± SD), n = 3 Avg. Drug Content uniformity (%) (Mean ± SD), n = 3 Avg. uniform Drug Distribution (%) (Mean ± SD), n = 3 Avg. In Vitro Disintegration Time (sec) (Mean ± SD), n = 3 Avg. Folding Endurance (Mean ± SD), n = 3

QTPLDT7 Smooth 99.96±0.34 6.40±0.010 0.16±0.032 1.73 ± 0.145 98.40 ± 0.289 97.44 ± 0.289 168.36 ± 1.527 114.00 ± 1.732 QTPLDT8 Smooth 98.00±0.01 7.01±0.29 0.23±0.056 1.98 ± 0.172 99.32 ± 0.382 98.55 ± 0.289 176.47 ± 0.577 136.00 ± 2.645 QTPLDT9 Smooth 101.00±0.03 7.10±0.39 0.32±0.098 2.18 ± 0.065 99.32 ± 0.289 96.35 ± 0.382 187.02 ± 2.00 154.00 ± 2.00 QTPLDT10 Smooth 99.74±0.18 7.02 ± 0.00 0.18±0.013 2.25 ± 0.058 99.74 ± 0.50 99.36 ± 0.289 118.87 ± 0.577 193.00 ± 3.46 QTPLDT11 Smooth 99.65±0.34 7.35 ± 0.577 0.26±0.034 2.63 ± 0.307 99.43 ± 0.29 99.69 ± 0.289 127.56 ± 0.577 203.65 ± 1.53 QTPLDT12 Smooth 99.46±0.14 7.69 ± 0.577 0.31±0.028 2.89 ± 0.177 99.90 ± 0.29 99.83 ± 0.144 132.29 ± 1.528 219.65 ± 0.58

136 Figure 8. 10 Results of QTPODT4- QTPODT12 Inference In light of aftereffects of previously

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mentioned primer preliminary groups for plasticizer determination, it was found that Poloxamer 407 (mg) in focus scope of 10-15 mg created best outcomes. 137 Table 8. 19 Selection of disintegrating agent type and concentration for QTP FMT MDF Ingredients QTPDT1 QTPDT2 QTPDT3 QTPDT4 QTPDT5 QTPDT6 QTPDT7 QTPDT8 QTPDT9 Drug (gm) 0.184 HPMC E5 (gm) 0.3 PEG 400 (ml) 01

Cross Povidone (gm) 0.050 0.075 0.1 - - - - - Banana Powder (gm) - - - 0.050 0.075 0.1 - - - Kyron T-314 (gm) - - - - -
 - 0.050 0.075 0.1 DW Q.S Strip form Yes Stickiness - + _ Appearance # * DISCUSSION: strips were made with 0.05, 0.075,
 and 0.1 gm convergences of deterioration specialists Cross Povidone, Banana powder, and Kyron T-314. actual
 appearance and tenacity of pre-arranged strips were evaluated. strips holding back banana powder and cross povidone
 were tacky and seemed hazy or non-straightforward. strips holding back Kryon T-314, then again, were non-tacky and
 clear.

138 Table 8. 20 Results of QTPDT7- QTPDT9

| | | |
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| 87% | MATCHING BLOCK 111/131 | W https://docplayer.net/amp/213630941-Design-dev ... |
| Batch Surface Texture Weight uniformity (mg) (Mean \pm SD) n=3 Surface pH (Mean \pm SD) n=3 Thickness (mm) (Mean \pm SD) n=3 Avg. Tensile strength (N/cm ²) \pm SD, n = 3 Avg. Drug Content uniformity (%) \pm SD, n = 3 Avg. uniform Drug Distribution (%) \pm SD, n = 3 Avg. In Vitro Disintegration Time (sec) \pm SD, n = 3 Avg. Folding Endurance \pm SD, n = 3 QTPDT7 Smooth 98.00 \pm 0.88 6.4 \pm 0.27 0.15 \pm 0.003 1.18 \pm 0.065 99.32 \pm 0.289 96.32 \pm 0.382 72.17 \pm 0.22 193.00 \pm 3.46 QTPDT8 Flexible 104.00 \pm 0.29 7.02 \pm 0.28 0.20 \pm 0.003 1.092 \pm 0.152 99.90 \pm 0.29 99.24 \pm 0.144 66.32 \pm 0.23 197.65 \pm 0.58 QTPDT9 Flexible 110.00 \pm 0.53 7.01 \pm 0.87 0.22 \pm 0.003 2.638 \pm 0.058 99.73 \pm 0.50 99.24 \pm 0.289 26.20 \pm 0.10 198.00 \pm 3.63 139 | | |

Figure 8. 11 Results of QTPDT7- QTPDT9 Inference The crumbling time for clumps was best achieved with Kyron T-314 (mg), henceforth convergence of 100 mg was picked for last MDF detailing.

8.2.3. Preparation of QTP FMT Mouth Dissolving Film using Design of Experiment PREPARATION OF MOUTH DISSOLVING FILM OF QTP FMT USING 3 2 FACTORIAL DESIGN As expressed in plan course of action Tables, 3 2 complete factorial plan was utilized to explore impact of free factors X1 (Poloxamer 407) and X2 (HPMC E50) on subordinate factors Y1 Elasticity (N/cm²), Y2 Breaking down Time (sec), and Y3 percent CDR (in 6 min). Two elements were evaluated at three levels (1, 0 +1) in this plan, and each of nine potential test clumps were figured out. Table shows arrangement of every one of nine expected mixes of MDF of QTP FMT utilizing 3 2 full factorial plans. Table 8. 21 Independent variable and their levels Factor code Factor Name Low (-1) High (+1) Independent Variables X1 Amount of P-407 (gm) 0.01 0.020

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|--|-------------------------------|--|
| 100% | MATCHING BLOCK 112/131 | W https://docplayer.net/amp/213630941-Design-dev ... |
| X2 Amount of HPMC E50 (gm) 0.250 0.350 Dependent Variables Y1 Tensile Strength (| | |

N/cm²) Y2 Disintegration Time (sec) Y3 % CDR (in 6 min) 8.2.4. Validation Analysis of Predicted and Actual Batches QTP FMT MDF: To improve formulation, 3 2 complete factorial design is frequently used. Two factors were investigated

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| in this design, each at three levels, and experimental trials were conducted on all nine conceivable combinations. Poloxamer 407 concentration (X1) and HPMC E50 concentration (X2) were chosen as independent variables. | | |

dependent variables were

| | | |
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| 100% | MATCHING BLOCK 114/131 | W https://docplayer.net/amp/213630941-Design-dev ... |
| Tensile Strength (Y1), Disintegrating Time (Y2), and In-vitro drug release (Y3). | | |

Conclusions can be drawn using polynomial equations. Table shows results of experimental design batches.

Table 8. 22 Batches Code of fast disintegrating films of QTP FMT Ingredients QTPOF1 QTPOF2 QTPOF3 QTPOF4 QTPOF5 QTPOF6 QTPOF7 QTPOF8 QTPOF9 Poloxamer (mg)- X1 +1 -1 0 0 +1 -1 -1 0 +1 HPMC E50 (mg)- X2 -1 -1 -1 0 0 0 +1 +1 +1 Table 8. 23 Batches concentrations of fast disintegrating films of QTP FMT Ingredients QTPOF 1 QTPOF 2 QTPOF 3 QTPOF 4 QTPOF 5 QTPOF 6 QTPOF 7 QTPOF 8 QTPOF 9 Drug (gm) 0.184 Poloxamer 407 (gm) 0.020 0.010 0.015 0.015 0.020 0.010 0.010 0.015 0.020 HPMC E50 (gm) 0.250 0.300 0.350 Kyron T-314 (gm) 0.1 Aspartame (gm) 0.040 Citric acid (gm) 0.070 Tween 20 (gm) 0.050 Vanillin (gm) 0.050 Distilled water (ml) 10

8.2.5.3 Optimization of Formulation 8.2.5.3.1 Formulation optimization by 3 2 factorial designs Master Planning Programming product variant 8.0.7.1 was utilized, and outcomes from underlying clumps yielded aggregate of nine mouth dissolving film types. Table shows outcomes. wide reach showed mouth dissolving film's veritable characteristics. Table 8. 24 Evaluation parameters of factorial design batches QTPOF1- QTPOF9 Formulation Code Avg. Weight (mg) (Mean ± SD), n=3 Avg. uniform Drug Distribution (%) (Mean ± SD), n = 3 Avg. Drug Content uniformity (%) (Mean ± SD), n = 3 QTPOF1 105.83 ± 0.236 96.33 ± 1.22 97.30 ± 0.16 QTPOF2 103.65 ± 1.13 97.42 ± 0.01 98.25 ± 0.31 QTPOF3 105.82 ± 0.19 96.90 ± 0.19 99.65 ± 0.16 QTPOF4 102.15 ± 0.40 95.00 ± 0.15 98.9 ± 0.24 QTPOF5 98.00 ± 0.02 97.73 ± 0.38 97.97 ± 0.11 QTPOF6 101.61 ± 0.24 96.40 ± 0.48 97.97 ± 0.55 QTPOF7 102.31 ± 0.14 96.00 ± 0.06 99.09 ± 0.01 QTPOF8 99.35 ± 1.04 98.00 ± 0.46 97.65 ± 0.76 QTPOF9 106.15 ± 0.16 96.62 ± 0.06 97.21 ± 0.36

Figure 8. 12 Evaluation parameters of factorial design batches QTPOF1- QTPOF9 Table 8. 25 Evaluation parameters of factorial design batches QTPOF1- QTPOF9 Formulation Code Avg. Surface pH (Mean ± SD), n = 3 Avg. Thickness (mm) (Mean ± SD), n = 3 Avg. Folding Endurance (Mean ± SD), n = 3 (Y 1) QTPOF1 6.70 ± 0.26 0.15 ± 0.01 144.00 ± 1 QTPOF2 6.74 ± 0.13 0.16 ± 0.02 146.00 ± 2 QTPOF3 6.82 ± 0.05 0.17 ± 0.03 149.00 ± 5 QTPOF4 6.7 ± 0.19 0.21 ± 0.01 155.00 ± 4 QTPOF5 6.72 ± 0.02 0.22 ± 0.02 158.00 ± 1 QTPOF6 6.81 ± 0.25 0.24 ± 0.01 159.00 ± 1 QTPOF7 6.74 ± 0.15 0.28 ± 0.02 164.00 ± 3 QTPOF8 6.71 ± 0.08 0.31 ± 0.3 167.00 ± 5 QTPOF9 6.70 ± 0.26 0.33 ± 0.04 169.00 ± 2

Figure 8. 13 Evaluation parameters of factorial design batches QTPOF1- QTPOF9 Table 8. 26 Optimization of fast disintegrating films of QTP FMT using 3 2 Full factorial design QTPOF1- QTPOF9 Formulation Code Y1: Tensile strength (N/cm 2) Y2: Disintegration Time (sec) Y3: %CDR (In 6 min) QTPOF1 1.092±1.14 23.47±0.3 98.34±1.0 QTPOF2 1.230±0.16 27.90±1.4 98.82±0.14 QTPOF3 1.582±1.47 24.15±1.6 99.06±1.25 QTPOF4 1.091±1.59 20.55±1.14 98.06±1.15 QTPOF5 1.091±1.15 22.51±1.67 96.30±1.26 QTPOF6 1.16±0.47 21.23±0.15 97.90±0.16 QTPOF7 2.637±1.26 28.20±1.05 95.61±1.16 QTPOF8 2.46±0.68 29.32±0.74 94.40±0.16 QTPOF9 2.230±1.16 32.31±1.59 92.61±1.37

Figure 8. 14 Optimization of fast disintegrating films of QTP FMT using 3 2 Full factorial design QTPOF1- QTPOF9 Stastical Analysis: Table 8. 27 Model Selection Responses Source SD R 2 Adj. R 2 Pred. R 2 PRESS Suggested Model Y1: TS Linear 0.46 0.613 0.484 0.250 2.5 2FI 0.50 0.618 0.389 -0.047 3.5 Quadratic 0.18 0.972 0.926 0.708 1.0 Suggested Cubic 0.18 0.990 0.918 -0.862 6.2 Aliased Y2: DT Linear 4.035 0.2596 0.013 -0.726 227.73 2FI 3.985 0.3982 0.037 -1.661 351.10 Quadratic 0.532 0.9936 0.983 0.922 10.34 Suggested Cubic 0.045 1.0000 1.000 0.9972 0.369 Aliased Y3: %CDR Linear 0.835 0.8934 0.858 0.743 10.09 2FI 0.721 0.9339 0.894 0.727 10.73 Quadratic 0.244 0.9955 0.988 0.964 1.43 Suggested Cubic 0.397 0.9960 0.968 0.2697 28.676 Aliased

Table 8. 28 Model coefficients and respective P-value Model term Y1: TS Y2: DT Y3: %CDR Full model Reduced Model Full model Reduced Model Full model Reduced Model coefficient p- value Coefficient Coefficient p-value Coefficient Coefficient p-value Coefficient Coefficient p- value Coefficient C 1.216 0.015 1.122 20.60 0.0017 - 97.806 0.001 - X1 -0.105 0.239* - 0.17 0.4948* # - -0.847 0.0034 - X2 0.574 0.004 0.5738 2.38 0.0016 - -2.265 0.0002 - X1X2 -0.067 0.501* - 2.14 0.0040 - -0.630 0.0141 - X11 -0.141 0.340* - 1.26 0.0445 - -0.573 0.0449 - X22 0.755 0.009 0.7545 6.14 0.0005 - -0.938 0.0122 - *Not significant (p<0.05), * # not significant but retained in model to maintain hierarchy

Table 8. 29 Regression analysis Model parameters Y1: PS Y2: PDI Y3: EE Full model Reduced Model Full model Reduced Model Full model Reduced Model df 5 2 5 5 5 5 F-value 20.89 42.97 92.61 92.61 131.33 131.33 P-value (model) 0.0154 0.0003 0.0017 0.0017 0.0010 0.0010 R 2 0.9721 0.9347 0.9936 0.9936 0.9955 0.9955 SSE 0.0930 0.2174 0.8492 0.8492 0.1786 0.1786 MSE 0.0310 0.0362 0.2831 0.2831 0.0595 0.0595 No. of term omitted 3 0 0 8.2.5.3.2 Effect on Responses Y1, Y2 & Y3 Y1: Tensile Strength (N/cm 2) Design-Expert® Software Factor Coding: Actual Tensile Strength (N/cm^2) Design Points 2.639 1.093 X1 = B: Amount of HPMC E50 X2 = A: Amount of P-407 250 270 290 310 330 350 10 12 14 16 18 20 Tensile Strength (N/cm^2) B: Amount of HPMC E50 (mg) A: Amount of P-407 (mg) 1.2 1.2 1.4 1.6 1.8 2 2.2 Design-Expert® Software Factor Coding: Actual Tensile Strength (N/cm^2) Design points above predicted value Design points below predicted value 2.639 1.093 X1 = B: Amount of HPMC E50 X2 = A: Amount of P-407 10 12 14 16 18 20 250 270 290 310 330 350 0.5 1 1.5 2 2.5 3 Tensile Strength (N/cm^2) B: Amount of HPMC E50 (mg) A: Amount of P-407 (mg) Y2: Disintegration Time (sec)

Design-Expert® Software Factor Coding: Actual Disintegration Time (Sec) Design Points 32.33 20.57 X1 = A: Amount of P-407 X2 = B: Amount of HPMC E50 10 12 14 16 18 20 250 270 290 310 330 350 Disintegration Time (Sec) A: Amount of P-407 (mg) B: Amount of HPMC E50 (mg) 22 22 24 24 26 26 28 30 Design-Expert® Software Factor Coding: Actual Disintegration Time (Sec) Design points above predicted value Design points below predicted value 32.33 20.57 X1 = A: Amount of P-407 X2 = B: Amount of HPMC E50 250 270 290 310 330 350 10 12 14 16 18 20 20 22 24 26 28 30 32 34 Disintegration Time (Sec) A: Amount of P-407 (mg) B: Amount of HPMC E50 (mg) Y3: % CDR (in 6 min) Design-Expert® Software Factor Coding: Actual CDR (in 6 min) (%) Design Points 99.07 92.63 X1 = A: Amount of P-407 X2 = B: Amount of

HPMC E50 10 12 14 16 18 20 250 270 290 310 330 350 CDR (in 6 min) (%) A: Amount of P-407 (mg) B: Amount of HPMC E50 (mg) 94 96 98 Design-Expert® Software Factor Coding: Actual CDR (in 6 min) (%) Design points above predicted value Design points below predicted value 99.07 92.63 X1 = A: Amount of P-407 X2 = B: Amount of HPMC E50 250 270 290 310 330 350 10 12 14 16 18 20 92 94 96 98 100 CDR (in 6 min) (%) A: Amount of P-407 (mg) B: Amount of HPMC E50 (mg) Figure 8. 15 Surface Response Plot & 3D Surface Plot The information showed was produced utilizing programming, and shape plot and reaction surface plot were made utilizing factorial plan. Figure shows Shape plot of variable's effect on responses Y1, Y2, and Y3, as well as Reaction surface plot of variable's effect on responses Y1, Y2, and Y3. Table 8. 30 Optimization Target Responses Target given for optimization Y1: TS Maximize

Y2: DT Minimize Y3: %CDR Maximize Table 8. 31 Checkpoint analysis Response Type of Value QTPOF10 QTPOF11 Desirability= 1 Desirability= 1 X1= 10.58 X1= 17.07 X2= 335.32 X2= 250 Y1: TS Predicted 1.9 1.3 Observed 2.01 1.21 % Error -5.79 6.92 Y2: DT Predicted 24.85 23.76 Observed 25.35 22.78 % Error -2.01 4.12 Y3: %CDR Predicted 96.43 98.94 Observed 98.81 99.92 % Error -2.47 -0.99 An anticipated worth and noticed worth are essentially indistinguishable because of designated spot clump. QTPOF11 is designated spot group with best. Accordingly, it is viewed as cluster that has been improved. mouth dissolving film was made with this group. Table 8. 32 Evaluation of mouth dissolving film: Sr. No Evaluation parameter Results 1. Weight variation(mg) 105.24±0.01 2. Thickness (mm) 0.20±0.02 3. Folding endurance 160±2.00 4. Surface pH 6.7±0.04 5. Drug content (%) 99.12±0.10

Figure 8. 16 SEM OF QTPOF11 Table 8. 33 Flux and permeability co-efficient of QTPF11 Time (Mins) Batch QTPF11 Flux J (mg/cm²/hr) Permeability co-efficient (kP) 0 0.000 0 1 0.773 0.035393 2 0.034 0.000454 3 0.008 0.000428 4 0.012 0.000672 5 0.023 0.00069 6 0.317 0.010454 7 0.053 0.002931 Table 8. 34 Kinetic analysis of release data of QTPOF11 Model Zero-Order First-Order Higuchi R 2 value 0.982 0.864 0.985 Slope 5.315 0.153 0.668 Intercept -0.221 0.575 1.884 The cumulative amount of drug permeated was fitted to Zero order and Higuchi model i.e. diffusion mechanism.

Figure 8. 17 FT-IR Study of Optimized MDF Formulation 8.6.2 Taste Evaluation Study by Spitting Table sums up discoveries of taste assessment examination. dirt and peevishness of definition in mouth were utilized to rate mouth feel in this review. In all details, normal mouth feel recommended smooth to exceptionally smooth sensation. Still up in air by capacity to eliminate

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| film from Alu pocket and spot it in mouth without utilization of water, which was considered patient-accommodating and | | |

phenomenal. Table 8. 35

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| Results of Taste and Palatability Evaluation Sample Type Mouth feel Taste (Bitterness) After taste Ease of handling Acceptance | | |

Test (Batch No. QTPOF11) 4.36 ± 0.56 5.00 ± 0.00 4.68 ± 0.45 5.00 ± 0.00 5.00 ± 0.00

Table 8. 36 Comparison of optimized MDF with conventional marketed formulation Time (in mins) % Drug release (QTPOF11) % Drug release of Marketed Product (Qticare-25) 0 0.0 0.0 1 0.477 ± 0.10 0.163 ± 0.11 2 8.924 ± 0.11 4.273 ± 0.07 3 16.75 ± 1.21 8.31 ± 0.22 4 55.51 ± 1.16 33.21 ± 1.31 5 84.35 ± 1.11 56.15 ± 1.11 6 99.25±0.16 61.00±0.33 Figure 8. 18 Comparison of optimized MDF with conventional marketed formulation 8.6.3 Evaluation of optimized batch under stability study

Table 8. 37 Evaluation of optimized batch under stability study Stability Conditions Sampling Time Disintegration Time (sec ± SD) Drug Content (% ± SD) Tensile Strength (kg/cm² ± SD) Visual Appearance 40° C ± 02° (Temp.) Initial 34.56 ± 00.51 99.12 ± 00.10 02.34 ± 0.01 Clear appearance 75% ± 05% RH 03 months 34.37 ± 02.73 99.53 ± 00.29 02.61 ± 0.01 Clear appearance

9. CONCLUSION To observe best polymer for making quick dissolving movies of ZPO HCL and QTP FMT, various clusters of movies were made with various convergences of polymer, breaking down specialist, and plasticizer. These quick breaking down films were read up for their shape, weight variance, thickness, surface pH, elasticity, collapsing strength,

percent drug content consistency, percent uniform medication dissemination, and in-vitro drug discharge examinations. plans of HPMC E5 and HPMC E50 100- 500 mg polymer were browsed among 21 clusters of ZPO HCL and QTP FMT MDF in light of assessed boundary. To observe best plasticizer for making ZPO HCL and QTP FMT quick dissolving film, many groups of movies were made with various measures of plasticizer. Clumps of polyethylene glycol 400 (Stake 400) and Poloxamer 407 in scope of 1-2 ml were picked in view of appraisal models. Besides, banana powder was picked as speedy dissolving specialist at dose of 75mg. These quick crumbling films were read up for their shape, weight change, thickness, surface pH, elasticity, collapsing sturdiness, percent drug content consistency, percent uniform medication circulation, and in-vitro drug discharge examinations. ZPO HCL and QTP FMT quick dissolving film was effectively made utilizing 3 2 full factorial plan with various definition mixes, and was found to have great collapsing perseverance, breaking down time, percent drug discharge, and other inspected measurements. upgraded plan ZMDOF10 and QTPOF11 was shown to be steady for multi month under sped up strength conditions. In two details, every one of measurements for taste assessment yielded positive discoveries. subsequent film was meager and clear, with smooth sensation and decent sweet to severe taste. 25-minute ex-vivo saturation investigation of streamlined group was directed using Franz Dispersion Cell. Toward finish of 15 minutes, over 80% of meds had been delivered. The consequences of medication polymer communication uncovered that there was no cooperation between medications and polymers. During 90-day steadiness testing, created definitions showed no adjustment of percent drug content or actual qualities. In view of in-vitro characterization and ex-vivo pervasion examination, it was resolved that Ziprasidone and QTP FMT had 80 percent entrance rate and could be provided orally as mouth dissolving film. Therefore, medication is delivered at oral mouth cavity with lower portion recurrence, bringing about better remedial adequacy.

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+ Sticky - Non-sticky * transparent # Semi-transparent @ non-transparent

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| <p>Formulation & Development Of ZPO HCL MDF Using Doe 81 5.3.1 Preparation Of Mouth Dissolving Film Of ZPO HCL Using 3 2 Factorial Design .. 81 5.3.2</p> | | <p>Formulation & Development of Quetiapine FMT MDF using DoE Preparation Of Mouth Dissolving Film Of Quetiapine Fmt Using 3 2 Factorial Design</p> | | |
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| <p>Preliminary Trial Batches of QTP FMT MDF 109 7.8.2.4.1. Selection of Polymer and concentration for QTP FMT MDF: 109 7.8.2.4.2.</p> | | <p>Preliminary Trial Batches of Quetiapine FMT MDF 3.2.4.1. Selection of Polymer and concentration for Quetiapine FMT MDF</p> | | |
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| <p>MDF 69 Table 5. 17 Preliminary trial batch for selection of Plasticizer type and concentration for</p> | | <p>MDF Tab. 16: Preliminary trial batch for selection of polymers type and concentration for</p> | | |
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| <p>for QTP FMT MDF 131 Table 8. 19 Preliminary trial batch for selection of Plasticizer type and concentration for QTP FMT MDF 133</p> | | <p>for Quetiapine FMT MDF Tab. 16: Preliminary trial batch for selection of polymers type and concentration for Quetiapine FMT MDF.</p> | | |
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| Standard Curve of QTP FMT in Phosphate buffer pH 7.4 121 Figure 8. 5 FTIR Spectra of Pure QTP FMT 122 Figure 8. 6 FTIR Spectra of Pure QTP FMT with excipients 123 | | Standard Curve of Quetiapine FMT in Phosphate buffer ph 7.4. 4.1.7. Identification of Quetiapine FMT by FTIR Spectra Fig. 3: FTIR Spectra of Pure Quetiapine FMT. www.wjpps.com Vol 10, Issue 7, 2021. ISO 9001:2015 Certified Journal 1462 Fig. 4: FTIR Spectra of Pure Quetiapine FMT with excipients. 4.1.8. | | |
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| <p>Mechanism of Action: Wicking due to fibrous structure, swelling with minimal gelling. Effective Concentrations: 1-3% Direct Compression, 2-4% Wet Granulation 1.4</p> | | <p>Mechanism of Action: Wicking due to fibrous structure, swelling with minimal gelling. Effective Concentrations: 1-3% (Direct Compression), 2-4% (Wet Granulation)</p> | | |
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| <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | | |
| 32/131 | SUBMITTED TEXT | 15 WORDS | 76% MATCHING TEXT | 15 WORDS |
| <p>Desu P et al. (2012) Formulation and evaluation of fast dissolving films of zolmitriptan</p> | | <p>Desu P, Sahu M. Formulation and evaluation of fast dissolving films of zolmitriptan.</p> | | |
| <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | | |
| 33/131 | SUBMITTED TEXT | 17 WORDS | 80% MATCHING TEXT | 17 WORDS |
| <p>Bhyan B et al. (2012) Formulation and evaluation of fast dissolving sublingual films of rizatriptan Benzoate</p> | | <p>Bhyan B, Jangra S. Formulation and evaluation of fast dissolving sublingual films of rizatriptan Benzoate.</p> | | |
| <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | | |
| 34/131 | SUBMITTED TEXT | 15 WORDS | 100% MATCHING TEXT | 15 WORDS |
| <p>et al. (2012) Development and characterization of pharmacokinetic parameters of fast- dissolving films containing levocetirizine.</p> | | <p>et al. Development and characterization of pharmacokinetic parameters of fast-dissolving films containing levocetirizine.</p> | | |
| <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | | |

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|---------------|---|----------|--|----------|
| 35/131 | SUBMITTED TEXT | 18 WORDS | 86% MATCHING TEXT | 18 WORDS |
| | ScientiaPharmaceutica 96 Panchal MS et al. (2012) Formulation and evaluation of mouth dissolving film of ropinirole hydrochloride | | ScientiaPharmaceutica., 2012; 80: 779 87. 7. Panchal MS, Patel H, Bagada A, et al. Formulation and evaluation of mouth dissolving film of ropinirole hydrochloride | |
| | W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ... | | | |
| 36/131 | SUBMITTED TEXT | 12 WORDS | 95% MATCHING TEXT | 12 WORDS |
| | Fast disintegrating films containing anastrozole as dosage form for dysphagia patients. | | Fast disintegrating films containing anastrozole as a dosage form for dysphagia patients. | |
| | W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ... | | | |
| 37/131 | SUBMITTED TEXT | 22 WORDS | 78% MATCHING TEXT | 22 WORDS |
| | Archives of pharmaceutical research 98 Nagar M et al. (2012) Formulation and evaluation of mouth dissolving film of antipsychotic drug aripiprazole | | Archives of pharmaceutical research, 2012; 25(12): 2171 82. 9. Nagar M, Nagar M, Chopra V. Formulation and evaluation of mouth dissolving film of antipsychotic drug aripiprazole. | |
| | W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ... | | | |
| 39/131 | SUBMITTED TEXT | 14 WORDS | 100% MATCHING TEXT | 14 WORDS |
| | et al. (2011) Formulation and evaluation of fast dissolving film of levocetirizine dihydrochloride. | | et al. Formulation and evaluation of fast dissolving film of levocetirizine dihydrochloride. | |
| | W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ... | | | |
| 48/131 | SUBMITTED TEXT | 12 WORDS | 100% MATCHING TEXT | 12 WORDS |
| | ondansetron hydrochloride by polymer carrier system and formulation of rapid disintegrating | | Ondansetron hydrochloride by Polymer Carrier System and Formulation of Rapid Disintegrating | |
| | W http://www.arjournals.org/index.php/ijaps/article/view/258 | | | |

| 40/131 | SUBMITTED TEXT | 11 WORDS | 100% MATCHING TEXT | 11 WORDS |
|--------|--|----------|---|----------|
| | And Characterization Of Ziprasidone Nanocrystals Prepared By Media Milling Technique | | AND CHARACTERIZATION OF ZIPRASIDONE NANOCRYSTALS PREPARED BY MEDIA MILLING TECHNIQUE; | |
| | <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | |

| 41/131 | SUBMITTED TEXT | 14 WORDS | 100% MATCHING TEXT | 14 WORDS |
|--------|--|----------|---|----------|
| | Release Characteristics of Quetiapine Fumarate Extended Release Tablets Under Biorelevant Stress Test Conditions; | | Release Characteristics of Quetiapine Fumarate Extended Release Tablets Under Biorelevant Stress Test Conditions; | |
| | <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | |

| 42/131 | SUBMITTED TEXT | 11 WORDS | 100% MATCHING TEXT | 11 WORDS |
|--------|--|----------|---|----------|
| | Water soluble film for oral administration with instant wettability 6 US8178674 | | Water soluble film for oral administration with instant wettability. US | |
| | <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | |

| 43/131 | SUBMITTED TEXT | 22 WORDS | 54% MATCHING TEXT | 22 WORDS |
|--------|--|----------|---|----------|
| | The following materials, chemical substances and devices might also be used for Ziprasidone Mouth Dissolving Film for Psychosis Treatment as per | | The following materials, chemicals and instruments may be used for Quetiapine Fumarate Mouth Dissolving Film for Psychosis Treatment as per | |
| | <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | |

| 44/131 | SUBMITTED TEXT | 57 WORDS | 37% MATCHING TEXT | 57 WORDS |
|--------|---|----------|--|----------|
| | Methodology 4.3.1 Preformulation of ZPO HCL The Preformulation find out about is often generate facts beneficial to improve secure dosage varieties that can be heavily produced for manufacturer. 4.3.1.1 Organoleptic Characteristics of ZPO HCL Physical look at was done to check Organoleptic Qualities of ZPO HCL like Tone and Smell. 4.3.1.2 Taste Evaluation Study by Spitting | | METHODOLOGY 3.1. Preformulation of Quetiapine Fumarate [105-106] The Preformulation study is mostly Generate data useful to develop stable dosage forms that can be mass-produced for manufacturer. 3.1.1. Organoleptic Characteristics of Quetiapine FMT Physical examine was done to check Organoleptic Characteristics of Quetiapine FMT like Colour and Odour. 3.1.1.1. Taste Evaluation Study by Spitting 8 | |
| | <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | |

| 45/131 | SUBMITTED TEXT | 40 WORDS | 80% MATCHING TEXT | 40 WORDS |
|--------|--|----------|-------------------|--|
| | Parameters, Score and Results of Taste Evaluation Study 44 4.3.1.3 Determination of Melting Point of ZPO HCL Melting point of ZPO HCL was evaluated by capillary method. 4.3.1.4 Identification and Determination of Wavelength max (λ_{max}) of | | | Parameters, Score and Results of Taste Evaluation Study. 3.1.2. Determination of Melting Point of Quetiapine FMT Melting point of Quetiapine FMT was evaluated by the capillary method. 3.1.3. Identification and Determination of Wavelength max (λ_{max}) of |
| | W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ... | | | |

| 46/131 | SUBMITTED TEXT | 25 WORDS | 45% MATCHING TEXT | 25 WORDS |
|--------|---|----------|-------------------|--|
| | ethanol, chloroform, ether, and pH 7.4 Phosphate cushion. 4.3.1.6 Determination of Partition Co-efficient: It was once decided via soaking 10mL of n-octanol in 10mL | | | ethanol, chloroform, ether and ph 7.4 Phosphate buffer. www.wjpps.com Vol 10, Issue 7, 2021. ISO 9001:2015 Certified Journal 1451 3.1.5. Determination of Partition Co-efficient It was determined by saturating 10mL of n-octanol with 10mL |
| | W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ... | | | |

| 47/131 | SUBMITTED TEXT | 41 WORDS | 60% MATCHING TEXT | 41 WORDS |
|--------|---|----------|-------------------|--|
| | Calibration Curve for ZPO HCL in Saline buffer pH 7.4 Preparation of Stock solution A 100g/ml stock arrangement of ZPO HCL was created in saline cushion pH 7.4 by dissolving 10 mg of medication in 10 ml of methanol and | | | Calibration Curve for Quetiapine FMT in Saline buffer ph 7.4 Preparation of Stock solution A 100 μ g/ml stock solution of Quetiapine FMT was prepared in saline buffer ph 7.4 by first dissolving 10 mg of the drug in 10 ml of methanol and |
| | W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ... | | | |

| 49/131 | SUBMITTED TEXT | 21 WORDS | 57% MATCHING TEXT | 21 WORDS |
|--------|---|----------|-------------------|---|
| | were made to acquire arrangements of 2,4,6,8, and 10 g/ml, and their absorbance values were estimated at fixed max with | | | were made to obtain solutions of 2,4,6,8 and 10 μ g/ml and their respective absorbance values were measured at fixed λ_{max} with |
| | W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ... | | | |

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|---|-----------------------|---|--------------------------|----------|
| 50/131 | SUBMITTED TEXT | 62 WORDS | 19% MATCHING TEXT | 62 WORDS |
| <p>potassium bromide IR circle will be produced using combination of ZPO HCL, HPMC E5, Stake 400, Citrus extract, Aspartame, and Mannitol, which will be examined in 4000-400 cm⁻¹ region in FTIR and contrasted with reference spectra of ZPO HCL. 46 4.3.1.11 Particle Size Study: Unadulterated Medication Molecule size examination had done utilizing Optical Magnifying lens and Malvern Instrument. 4.4</p> | | <p>Potassium bromide IR disc will be prepared using mixture of Quetiapine FMT, HPMC E5, PEG- 400, Citric Acid, Aspatame and Mannitol Hydraulic Pellet press will be scanned 4000-400 cm⁻¹ region in FTIR and obtained IR Spectrum was compared with a reference of Quetiapine Particle Size Study Pure Drug Particle size analysis had done using Optical Microscope and Malvern Instrument.</p> | | |
| <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | | |

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|---|-----------------------|---|--------------------------|-----------|
| 51/131 | SUBMITTED TEXT | 129 WORDS | 74% MATCHING TEXT | 129 WORDS |
| <p>morphological examination, weight variety, crumbling time, surface pH, collapsing perseverance, thickness, drug content consistency, percent uniform medication conveyance, and in-vitro drug discharge study to foster QbD Approach. 4.4.2 Dose calculation of ZPO HCL for mould Dose of drug = ORAL DOSE * ORAL BIOAVAILABILITY/ BODY SURFACE AREA > Area of mould is 24 cm² (12 cm x 2 cm). > Area of film is 6 cm² (3 cm x 2 cm). > Total number of films in each mould 24/6 = 4 > One film contains 25 mg of drug than 4 films containing 100 mg drug > So, one mould containing 100 mg drug 4.4.3 Solvent casting method Oral fast deteriorating films are ready by dissolving film arrangement materials (polymers) and plasticizer in</p> | | <p>morphological study, weight variation, disintegration time, surface ph, folding endurance, thickness, drug content uniformity, % uniform drug distribution and in-vitro drug release study to develop QbD Approach. 3.2.2. Dose calculation of Quetiapine FMT for mould Dose of drug = ORAL DOSE * ORAL BIOAVAILABILITY/ BODY SURFACE AREA Area of mould is 24 cm² (12 cm x 2 cm). Area of film is 4 cm² (2 cm x 2 cm). Total number of films in each mould 24/4 = 6 One film contains 25 mg of drug than 6 films containing 150 mg drug So, one mould containing 150 mg drug 3.2.3. Solvent casting method The oral fast disintegrating films are prepared by dissolving film forming agents (polymers), and plasticizer in</p> | | |
| <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | | |

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|--|-----------------------|--|--------------------------|----------|
| 52/131 | SUBMITTED TEXT | 21 WORDS | 60% MATCHING TEXT | 21 WORDS |
| <p>Preliminary Trial Batches of ZPO HCL MDF 4.4.4.1 Selection of Polymer and concentration for ZPO HCL MDF: The various polymers</p> | | <p>Preliminary Trial Batches of Quetiapine FMT MDF 3.2.4.1. Selection of Polymer and concentration for Quetiapine FMT MDF The different polymers &</p> | | |
| <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | | |

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|--|-----------------------|--|--------------------------|----------|
| 53/131 | SUBMITTED TEXT | 21 WORDS | 65% MATCHING TEXT | 21 WORDS |
| <p>Table 4. 6 Plasticizer type and concentration for ZPO HCL MDF PLASTICIZER TYPE USED PEG 200 PEG 400 PG IPA</p> | | <p>Table 3: Plasticizer type and concentration for Quetiapine FMT MDF. PLASTICIZER TYPE USED PLASTICIZER CONCENTRATION USED (gm) PEG 200 PEG 400 Poloxamer 407 0.5-1 1.0 PG IPA 3.2.4.3.</p> | | |
| <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | | |

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|---------------|---|----------|---|----------|
| 54/131 | SUBMITTED TEXT | 18 WORDS | 70% MATCHING TEXT | 18 WORDS |
| | The different polymer utilized were as per following: Table 4. 7 Disintegrating agent type and concentration for | | The different polymer used were as follows: Table 4: Disintegrating agent type and concentration for | |
| | W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ... | | | |
| 55/131 | SUBMITTED TEXT | 19 WORDS | 75% MATCHING TEXT | 19 WORDS |
| | Formulation and Development of ZPO HCL MDF by Design of Experiment (DoE) Using QbD Approach A plan space | | Formulation and Development of Quetiapine FMT MDF by Design of Experiment (DoE) Using QbD Approach A design space | |
| | W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ... | | | |
| 56/131 | SUBMITTED TEXT | 17 WORDS | 84% MATCHING TEXT | 17 WORDS |
| | DISINTEGRATING AGENT TYPE USED Cross Povidone (g) Kyron T-314 (g) Banana Powder (g) | | DISINTEGRATING AGENT TYPE USED DISINTEGRATING AGENT CONCENTRATION (gm) Cross Povidone (g) Kyron T- 314 (g) Banana Powder (g) 0.5 0.75 1.0 3.2.5. | |
| | W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ... | | | |
| 57/131 | SUBMITTED TEXT | 38 WORDS | 37% MATCHING TEXT | 38 WORDS |
| | Drug content Determination: After precisely gauged amount of film (over 100 mg) is broken down in 100 mL of Phosphate support pH 7.4 in which medicine is solvent, arrangement is shaken constantly for 24 hours in shaker | | Drug content Determination An accurately weighed portion of film (above 100 mg) is dissolved in 100 ml of Phosphate buffer ph 7.4 in which drug is soluble and then solution is shaken continuously for 24 hrs. in shaker | |
| | W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ... | | | |
| 58/131 | SUBMITTED TEXT | 16 WORDS | 58% MATCHING TEXT | 16 WORDS |
| | In-vitro Permeation study An in-vitro pervasion study can be completed utilizing dissemination cell receptor compartment | | In-vitro Permeation study An in-vitro permeation study can be carried out by using diffusion cell receptor compartment | |
| | W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ... | | | |

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|--|-----------------------|---|--------------------------|----------|
| 59/131 | SUBMITTED TEXT | 29 WORDS | 37% MATCHING TEXT | 29 WORDS |
| <p>paraffin film. receptor compartment of dissemination cell was loaded up with phosphate support pH 7.4. entire thing was mounted on attractive stirrer, and arrangement in receptor compartment was</p> | | <p>paraffin film receptor compartment of diffusion cell was filled with phosphate buffer ph 7. 4 whole assembly was fixed on a magnetic stirrer, and solution in receptor compartment was</p> | | |
| <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | | |

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|--|-----------------------|--|---------------------------|----------|
| 60/131 | SUBMITTED TEXT | 16 WORDS | 100% MATCHING TEXT | 16 WORDS |
| <p>Kinetic Analysis of Release Data: 4.6.12.1 Zero Order Release $Q_t = Q_0 + K_0t$ 4.6.12.2</p> | | <p>Kinetic Analysis of Release Data 3.2.7.12.1. Zero Order Release $Q_t = Q_0 + K_0t$</p> | | |
| <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | | |

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|--|-----------------------|---|--------------------------|----------|
| 61/131 | SUBMITTED TEXT | 34 WORDS | 51% MATCHING TEXT | 34 WORDS |
| <p>Wavelength maximum (λ_{max}) of ZPO HCL Drug λ_{max} Actual λ_{max} Observed λ_{max} ZPO HCL 317 317.47 Figure 5. 1 UV Spectrum of ZPO HCL 5.1.4 SOLUBILITY STUDIES</p> | | <p>Wavelength maximum (λ_{max}) of Quetiapine FMT. λ_{max} Drug Actual λ_{max} Observed λ_{max} Quetiapine FMT 250 248 Fig. 1: UV Spectrum of Quetiapine FMT. 4.1.4. SOLUBILITY STUDIES</p> | | |
| <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | | |

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|--|-----------------------|--|--------------------------|----------|
| 62/131 | SUBMITTED TEXT | 19 WORDS | 70% MATCHING TEXT | 19 WORDS |
| <p>From experiment, it was found that ZPO HCL was soluble in HCl, NaOH, Ethanol, Methanol and DMSO.</p> | | <p>From experiment, it was found that Quetiapine FMT was soluble in HCl, NaOH and slightly soluble in Ethanol, Methanol and DMSO. 4.1.5.</p> | | |
| <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | | |

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|--|-----------------------|--|--------------------------|----------|
| 63/131 | SUBMITTED TEXT | 26 WORDS | 84% MATCHING TEXT | 26 WORDS |
| <p>Determination of Partition Coefficient of selected Drugs S.No. Sample Partition Coefficient (Mean \pm SD, n=3) 1. ZPO HCL 4.61 ± 0.43 5.1.6 Calibration Curve: 5.1.6.1</p> | | <p>Determination of Partition Coefficient of selected Drugs. S.No. Sample Partition Coefficient (Mean \pm SD, n=3) 1. Quetiapine FMT 3.22 ± 0.47 4.1.6. Calibration Curve.</p> | | |
| <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | | |

| 64/131 | SUBMITTED TEXT | 43 WORDS | 89% MATCHING TEXT | 43 WORDS |
|--------|---|----------|--|----------|
| | Wavelength (λ_{max}) 317 Beer's limit ($\mu\text{g/ml}$) 0-10 Corrélation coefficient (R ²) 0.9977 Slope 0.1028 Obeys Beer law in conc. range of 0-20 mcg/ml R ² value shows linearity 58 5.1.7 ZPO HCL Calibration Curve | | Wavelength (λ_{max}) 248 Beer s limit ($\mu\text{g/ml}$) 0-10 Corrélation coefficient (R ²) 0.984 Slope 0.054 Obeys Beer law in conc. range of 0-10 mcg/ml R ² value shows linearity The calibration curve | |
| | W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ... | | | |

| 65/131 | SUBMITTED TEXT | 35 WORDS | 100% MATCHING TEXT | 35 WORDS |
|--------|--|----------|--|----------|
| | Wavelength (λ_{max}) 317 Beer's limit ($\mu\text{g/ml}$) 0-10 Corrélation coefficient (R ²) 0.9956 Slope 0.0117 Obeys Beer law in conc. range of 0-10 mcg/ml R ² value shows linearity 5.1.8 | | Wavelength (λ_{max}) 248 Beer s limit ($\mu\text{g/ml}$) 0-10 Corrélation coefficient (R ²) 0.984 Slope 0.054 Obeys Beer law in conc. range of 0-10 mcg/ml R ² value shows linearity | |
| | W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ... | | | |

| 66/131 | SUBMITTED TEXT | 24 WORDS | 82% MATCHING TEXT | 24 WORDS |
|--------|---|----------|---|----------|
| | Surface pH (Mean \pm SD) n=3 Thickness (mm) (Mean \pm SD) n=3 Avg. Tensile strength (N/cm ²) \pm SD, n = 3 | | Surface ph (Mean \pm SD) n=3 Thickness (mm) (Mean \pm SD) n=3 QTPDT1 Flexible 99 \pm 0.29 7.3 \pm 0.29 0.11 \pm 0.003 QTPDT2 Flexible 105 \pm 0.09 7.2 \pm 0.33 0.33 \pm 0.101 QTPDT3 Flexible 107 \pm 0.27 7.9 \pm 0.82 0.30 \pm 0.001 Avg. Tensile strength (N/cm ²) \pm SD, n = 3 1.231 \pm 0.145 1.584 \pm 0.172 1.093 \pm 0.181 | |
| | W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ... | | | |

| 67/131 | SUBMITTED TEXT | 16 WORDS | 100% MATCHING TEXT | 16 WORDS |
|--------|---|----------|--|----------|
| | SD, n = 3 Avg. In Vitro Disintegration Time (sec) \pm SD, n = 3 | | SD, n = 3 98.25 \pm 0.289 98.48 \pm 0.144 98.32 \pm 0.144 99.47 \pm 0.289 99.56 \pm 0.029 99.14 \pm 0.231 98.34 \pm 0.291 98.67 \pm 0.291 Avg. In Vitro Disintegration Time (sec) \pm SD, n = 3 167.67 \pm 1.456 180.48 \pm 1.371 189.12 \pm 2.876 121.29 \pm 1.536 135.87 \pm 2.527 141.76 \pm 1.877 161.56 \pm 4.345 169.26 \pm 3.575 | |
| | W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ... | | | |

| 68/131 | SUBMITTED TEXT | 24 WORDS | 82% MATCHING TEXT | 24 WORDS |
|--------|---|----------|-------------------|--|
| | Surface pH (Mean \pm SD) n=3 Thickness (mm) (Mean \pm SD) n=3 Avg. Tensile strength (N/cm ²) \pm SD, n = 3 | | | Surface pH (Mean \pm SD) n=3 Thickness (mm) (Mean \pm SD) n=3 QTPDT1 Flexible 99 \pm 0.29 7.3 \pm 0.29 0.11 \pm 0.003 QTPDT2 Flexible 105 \pm 0.09 7.2 \pm 0.33 0.33 \pm 0.101 QTPDT3 Flexible 107 \pm 0.27 7.9 \pm 0.82 0.30 \pm 0.001 Avg. Tensile strength (N/cm ²) \pm SD, n = 3 1.231 \pm 0.145 1.584 \pm 0.172 1.093 \pm 0.181 |
| | W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ... | | | |

| 69/131 | SUBMITTED TEXT | 16 WORDS | 100% MATCHING TEXT | 16 WORDS |
|--------|---|----------|--------------------|---|
| | SD, n = 3 Avg. In Vitro Disintegration Time (sec) \pm SD, n = 3 | | | SD, n = 3 98.25 \pm 0.289 98.48 \pm 0.144 98.32 \pm 0.144 99.47 \pm 0.289 99.56 \pm 0.029 99.14 \pm 0.231 98.34 \pm 0.291 98.67 \pm 0.291 Avg. In Vitro Disintegration Time (sec) \pm SD, n = 3 167.67 \pm 1.456 180.48 \pm 1.371 189.12 \pm 2.876 121.29 \pm 1.536 135.87 \pm 2.527 141.76 \pm 1.877 161.56 \pm 4.345 169.26 \pm 3.575 |
| | W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ... | | | |

| 70/131 | SUBMITTED TEXT | 65 WORDS | 38% MATCHING TEXT | 65 WORDS |
|--------|--|----------|-------------------|--|
| | Batch Surface Texture Weight uniformity (mg) (Mean \pm SD) n=3 Avg. uniform Drug Distribution (%) \pm SD, n = 3 Avg. Drug Content uniformity (%) \pm SD, n = 3 ZDT7 Flexible 107.13 \pm 1.33 101.45 \pm 0.38 99.30 \pm 0.14 ZDT8 Flexible 99.1 \pm 0.24 99.35 \pm 0.25 99.61 \pm 0.11 ZDT9 Flexible 99.10 \pm 0.15 99.15 \pm 0.13 99.18 \pm 0.37 | | | Batch Surface Texture Weight uniformity (mg) (Mean \pm SD) n=3 Surface pH (Mean \pm SD) n=3 Thickness (mm) (Mean \pm SD) n=3 QTPDT1 Flexible 99 \pm 0.29 7.3 \pm 0.29 0.11 \pm 0.003 QTPDT2 Flexible 105 \pm 0.09 7.2 \pm 0.33 0.33 \pm 0.101 QTPDT3 Flexible 107 \pm 0.27 7.9 \pm 0.82 0.30 \pm 0.001 |
| | W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ... | | | |

| 71/131 | SUBMITTED TEXT | 24 WORDS | 82% MATCHING TEXT | 24 WORDS |
|--------|---|----------|-------------------|--|
| | Surface pH (Mean \pm SD) n=3 Thickness (mm) (Mean \pm SD) n=3 Avg. Tensile strength (N/cm ²) \pm SD, n = 3 | | | Surface pH (Mean \pm SD) n=3 Thickness (mm) (Mean \pm SD) n=3 QTPDT1 Flexible 99 \pm 0.29 7.3 \pm 0.29 0.11 \pm 0.003 QTPDT2 Flexible 105 \pm 0.09 7.2 \pm 0.33 0.33 \pm 0.101 QTPDT3 Flexible 107 \pm 0.27 7.9 \pm 0.82 0.30 \pm 0.001 Avg. Tensile strength (N/cm ²) \pm SD, n = 3 1.231 \pm 0.145 1.584 \pm 0.172 1.093 \pm 0.181 |
| | W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ... | | | |

| 72/131 | SUBMITTED TEXT | 16 WORDS | 100% MATCHING TEXT | 16 WORDS |
|--------|--|----------|--------------------|---|
| | SD, n = 3 Avg. In Vitro Disintegration Time (sec) \pm SD, n = 3 | | | SD, n = 3 98.25 \pm 0.289 98.48 \pm 0.144 98.32 \pm 0.144 99.47 \pm 0.289 99.56 \pm 0.029 99.14 \pm 0.231 98.34 \pm 0.291 98.67 \pm 0.291 Avg. In Vitro Disintegration Time (sec) \pm SD, n = 3 167.67 \pm 1.456 180.48 \pm 1.371 189.12 \pm 2.876 121.29 \pm 1.536 135.87 \pm 2.527 141.76 \pm 1.877 161.56 \pm 4.345 169.26 \pm 3.575 |
| | <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | |

| 73/131 | SUBMITTED TEXT | 71 WORDS | 70% MATCHING TEXT | 71 WORDS |
|--------|---|----------|-------------------|--|
| | of MDF of ZPO HCL utilizing 3 2 full factorial plans. Table 5. 25 Independent variable and their levels Independent Variables Low level (-1) Medium level (0) High level (+1) X1=amount of PEG (ml) 1 1.5 2 X2=amount of HPMC E5 LV (gm) 0.250 0.300 0.350 Dependent Variables Y1= Folding endurance Y2 = Disintegration Time (sec) Y3= % CDR (%) 5.3.2 Validation Analysis of Predicted and Actual Batches | | | of MDF of Quetiapine FMT using 3 2 full factorial designs is shown in Table 3. Tab. 21: Independent variable and their levels. Independent Variables Low level (-1) Medium level (0) High level (+1) X1=amount of Poloxamer 407 (mg) 10 15 20 X2=amount of HPMC E50 (gm) 250 300 250 Dependent Variables Y1= Tensile Strength Y2 = Disintegration Time (sec) Y3= % CDR (%) 4.3.1. Validation Analysis of Predicted and Actual Batches |
| | <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | |

| 74/131 | SUBMITTED TEXT | 37 WORDS | 30% MATCHING TEXT | 37 WORDS |
|--------|--|----------|-------------------|--|
| | of Stake 400 (X1) and HPMC E5 LV (X2) were picked as free factors. Collapsing perseverance (Y1), crumbling term (Y2), and in-vitro drug discharge (Y3) were picked as reliant factors. Polynomial conditions can be utilized to | | | of Poloxamer 407 (X1) and the concentration of HPMC E50 (X2) were selected as independent variables. The Tensile Strength (Y1), disintegrating time (Y2) and In-vitro drug release (Y3) were selected as dependent variables. The polynomial equations can be used to |
| | <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | |

| 75/131 | SUBMITTED TEXT | 25 WORDS | 65% MATCHING TEXT | 25 WORDS |
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| | Surface pH \pm SD, n = 3 Avg. Thickness (mm) \pm SD, n = 3 Avg. Tensile strength (N/cm ²) \pm SD, n = 3 | | | Surface ph (Mean \pm SD) n=3 Thickness (mm) (Mean \pm SD) n=3 QTPDT1 Flexible 99 \pm 0.29 7.3 \pm 0.29 0.11 \pm 0.003 QTPDT2 Flexible 105 \pm 0.09 7.2 \pm 0.33 0.33 \pm 0.101 QTPDT3 Flexible 107 \pm 0.27 7.9 \pm 0.82 0.30 \pm 0.001 Avg. Tensile strength (N/cm ²) \pm SD, n = 3 1.231 \pm 0.145 1.584 \pm 0.172 1.093 \pm 0.181 |
| | <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | |

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| 76/131 | SUBMITTED TEXT | 19 WORDS | 60% MATCHING TEXT | 19 WORDS |
| <p>film from Alu pocket and spot it in mouth without utilization of water, which was considered patient-accommodating and</p> | | <p>film from Alu pouch and put it in mouth without need of water which was ranked patient friendly and</p> | | |
| <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | | |

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| 77/131 | SUBMITTED TEXT | 19 WORDS | 77% MATCHING TEXT | 19 WORDS |
| <p>Results of Taste and Palatability Evaluation Sample Type Mouth feel Taste (Bitterness) After Taste Ease of handling Acceptance</p> | | <p>Results of Taste and Palatability Evaluation. Test (Batch No. ZMDF5) Mouth Feel 4.25 ± 0.46 Taste (Bitterness) 4.00 ± 0.00 After taste 3.88 ± 0.35 Ease of handling Acceptance 5.00 ± 0.00 4.375 ± 0.52</p> | | |
| <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | | |

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| 78/131 | SUBMITTED TEXT | 19 WORDS | 66% MATCHING TEXT | 19 WORDS |
| <p>The accompanying materials, synthetics and instruments might be utilized for Quetiapine Fumarate Mouth Dissolving Film for Psychosis Treatment</p> | | <p>The following materials, chemicals and instruments may be used for Quetiapine Fumarate Mouth Dissolving Film for Psychosis Treatment</p> | | |
| <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | | |

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| 79/131 | SUBMITTED TEXT | 93 WORDS | 38% MATCHING TEXT | 93 WORDS |
| <p>volunteers were told to let out example with salivation and flush their mouths with 200 ml refined water. Following 2 hours, indistinguishable system was finished subsequent example (either test or reference test). Thus, spitting of detailing and salivation was told to volunteers to forestall openness of medication. Table 7. 3 Parameters, Score and Results of Taste Evaluation Study 7.8.1.2. Determination of Melting Point of QTP FMT Melting point of QTP FMT was evaluated by capillary method. 106 7.8.1.3 Identification and Determination of Wavelength max (λ_{max}) of QTP FMT</p> | | <p>volunteers were asked to spit out the sample with saliva after 3 min and asked to rinse their mouths with 200 ml of distilled water. The same procedure was repeated after 2 hour for second sample (either test or reference sample). So, spitting of formulation and saliva was instructed to volunteers to prevent exposure of drug. www.wjpps.com Vol 10, Issue 7, 2021. ISO 9001:2015 Certified Journal 1450 Tab. 1: Parameters, Score and Results of Taste Evaluation Study. 3.1.2. Determination of Melting Point of Quetiapine FMT Melting point of Quetiapine FMT was evaluated by the capillary method. 3.1.3. Identification and Determination of Wavelength max (λ_{max}) of Quetiapine FMT</p> | | |
| <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | | |

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| 80/131 | SUBMITTED TEXT | 35 WORDS | 33% MATCHING TEXT | 35 WORDS |
| <p>and volume moved toward 100 ml utilizing water and acetonitrile in 100 ml volumetric carafe. Then, at that point, 1 ml of stock arrangement was pipetted into 10 ml volumetric cup, and volume was</p> | | <p>and volume made upto 100 ml using water and acetonitrile in 100 ml volumetric flask to obtain a stock solution 100 µg/ml. Then 1 ml of this stock solution was pipetted out in a 10 ml volumetric flask and volume was</p> | | |
| <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | | |

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| 81/131 | SUBMITTED TEXT | 35 WORDS | 42% MATCHING TEXT | 35 WORDS |
| <p>was recorded, and most extreme worth got was contrasted with UV range expressed in authority monograph. greatest frequency of Quetiapine fumarate was found to be 248 nm. 7.8.1.4. Solubility study of QTP FMT Preformulation</p> | | <p>was recorded and obtained λ max was matched with the UV spectrum as reported in official monograph. The λ max of Quetiapine fumarate was found to be 248 nm respectively. 3.1.4. Solubility study of Quetiapine FMT Preformulation</p> | | |
| <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | | |

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| 82/131 | SUBMITTED TEXT | 33 WORDS | 35% MATCHING TEXT | 33 WORDS |
| <p>with water and spectroscopically estimated at 248 nm. Different solvents, like water, CH₃)₂CO, ethanol, chloroform, ether, and pH 7.4 Phosphate support, will be utilized all through strategy. 7.8.1.5. Determination of Partition Co-efficient:</p> | | <p>with water and assayed spectroscopically at 248 nm. The procedure will be followed by using different solvents like water, acetone, ethanol, chloroform, ether and ph 7.4 Phosphate buffer. www.wjpps.com Vol 10, Issue 7, 2021. ISO 9001:2015 Certified Journal 1451 3.1.5. Determination of Partition Co-efficient</p> | | |
| <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | | |

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| 83/131 | SUBMITTED TEXT | 26 WORDS | 60% MATCHING TEXT | 26 WORDS |
| <p>nm against clear. 7.8.1.6. Preparation of Calibration Curve for QTP FMT 7.8.1.6.1. Calibration Curve for QTP FMT IN 0.1N HCL solution Preparation of Stock solution</p> | | <p>nm against blank. 3.1.6. Preparation of Calibration Curve for Quetiapine FMT 3.1.6.1. Calibration Curve for Quetiapine FMT in Saline buffer ph 7.4 Preparation of Stock solution</p> | | |
| <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | | |

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| 84/131 | SUBMITTED TEXT | 15 WORDS | 88% MATCHING TEXT | 15 WORDS |
| <p>Calibration Curve for QTP FMT in Saline buffer pH 7.4 Preparation of Stock solution</p> | | <p>Calibration Curve for Quetiapine FMT in Saline buffer ph 7.4 Preparation of Stock solution</p> | | |
| <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | | |

| 85/131 | SUBMITTED TEXT | 30 WORDS | 38% MATCHING TEXT | 30 WORDS |
|--------|--|----------|-------------------|---|
| | ml stock arrangement of QTP FMT was produced by dissolving 10 mg of medication in 10 ml of methanol and afterward filling leftover volume with saline cradle pH 7.4. | | | ml stock solution of Quetiapine FMT was prepared in saline buffer ph 7.4 by first dissolving 10 mg of the drug in 10 ml of methanol and then, making up the final volume with saline buffer ph 7.4. |
| | <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | |

| 86/131 | SUBMITTED TEXT | 21 WORDS | 65% MATCHING TEXT | 21 WORDS |
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| | of 2,4,6,8, and 10 g/ml, and their absorbance values were estimated at fixed max with boundary set at 0.5nm for | | | of 2,4,6,8 and 10 µg/ml and their respective absorbance values were measured at fixed λmax with parameter set at 0.5nm for |
| | <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | |

| 87/131 | SUBMITTED TEXT | 21 WORDS | 64% MATCHING TEXT | 21 WORDS |
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| | Identification of QTP FMT by FT-IR Spectroscopy Potassium bromide IR circles will be made utilizing 1mg of QTP FMT on | | | Identification of Quetiapine FMT by FT-IR Spectroscopy Potassium bromide IR disc will be prepared using 1mg of Quetiapine FMT on |
| | <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | |

| 88/131 | SUBMITTED TEXT | 39 WORDS | 39% MATCHING TEXT | 39 WORDS |
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| | cm-1 in FTIR. IR spectra acquired will be contrasted with reference range of QTP FMT. 7.8.1.8. Drug- Excipients Compatibility Studies by FT-IR A combination of QTP FMT, HPMC E5, Stake 400, Citrus extract, Aspatame, and Mannitol will be | | | cm -1 in FTIR and obtained IR Spectrum will be compare with reference spectrum of Quetiapine FMT. 3.1.8. Drug- Excipients Compatibility Studies by FT-IR Potassium bromide IR disc will be prepared using mixture of Quetiapine FMT, HPMC E5, PEG- 400, Citric Acid, Aspatame and Mannitol Hydraulic Pellet press will be |
| | <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | |

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| 89/131 | SUBMITTED TEXT | 69 WORDS | 60% MATCHING TEXT | 69 WORDS |
| <p>cm-1 region in FTIR and contrasted with reference range of QTP FMT. 108 7.8.1.9. Particle Size Study: Unadulterated Medication Molecule size examination had done utilizing Optical Magnifying lens and Malvern Instrument. 7.8.2. Formulation and Development of QTP FMT MDF by using QbD Approach 7.8.2.1. Setting up Quality Target Product Profile (QTPP) and Selection of Formulation and Process Variables by Preliminary Trial Batches of QTP FMT MDF:</p> | | <p>cm-1 region in FTIR and obtained IR Spectrum was compared with a reference of Quetiapine Particle Size Study Pure Drug Particle size analysis had done using Optical Microscope and Malvern Instrument. www.wjpps.com Vol 10, Issue 7, 2021. ISO 9001:2015 Certified Journal 1452 3.2. Formulation and Development of Quetiapine FMT MDF by using QbD Approach 3.2.1. Setting up Quality Target Product Profile (QTPP) and Selection of Formulation and Process Variables by Preliminary Trial Batches of Quetiapine FMT MDF</p> | | |
| <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | | |

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| 90/131 | SUBMITTED TEXT | 40 WORDS | 61% MATCHING TEXT | 40 WORDS |
| <p>time, surface pH, collapsing perseverance, thickness, drug content consistency, percent uniform medication dissemination, and in-vitro drug discharge study. 7.8.2.2. Dose calculation of QTP FMT for mould Dose of drug = ORAL DOSE * ORAL BIOAVAILABILITY/ BODY SURFACE AREA 7.8.2.3.</p> | | <p>time, surface ph, folding endurance, thickness, drug content uniformity, % uniform drug distribution and in-vitro drug release study to develop QbD Approach. 3.2.2. Dose calculation of Quetiapine FMT for mould Dose of drug = ORAL DOSE * ORAL BIOAVAILABILITY/ BODY SURFACE AREA</p> | | |
| <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | | |

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| 91/131 | SUBMITTED TEXT | 54 WORDS | 76% MATCHING TEXT | 54 WORDS |
| <p>Preliminary Trial Batches of QTP FMT MDF 7.8.2.4.1. Selection of Polymer and concentration for QTP FMT MDF: The different polymers & their concentrations were used to prepare QTP FMT MDF to fix polymer type and concentration. details are as follows: Table 7. 5 Polymer and concentration for QTP FMT MDF 7.8.2.4.2.</p> | | <p>Preliminary Trial Batches of Quetiapine FMT MDF 3.2.4.1. Selection of Polymer and concentration for Quetiapine FMT MDF The different polymers & their concentrations were used to prepare Quetiapine FMT MDF to fix the polymer type and concentration. The details are as follows: www.wjpps.com Vol 10, Issue 7, 2021. ISO 9001:2015 Certified Journal 1453 Table 2: Polymer and concentration for Quetiapine FMT MDF.</p> | | |
| <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | | |

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| 92/131 | SUBMITTED TEXT | 21 WORDS | 75% MATCHING TEXT | 21 WORDS |
| <p>Table 7. 6 Plasticizer type and concentration for QTP FMT MDF PLASTICIZER TYPE USED PEG 200 Poloxamer 407 PG IPA</p> | | <p>Table 3: Plasticizer type and concentration for Quetiapine FMT MDF. PLASTICIZER TYPE USED PLASTICIZER CONCENTRATION USED (gm) PEG 200 PEG 400 Poloxamer 407 0.5-1 1.0 PG IPA 3.2.4.3.</p> | | |
| <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | | |

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| 93/131 | SUBMITTED TEXT | 16 WORDS | 100% MATCHING TEXT | 16 WORDS |
| Risk Assessment of Critical Quality Attributes (CQAs) from Preliminary trial Batches to Develop QbD Approach | | Risk Assessment of Critical Quality Attributes (CQAs) from Preliminary trial Batches to Develop QbD Approach | | |
| <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | | |

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| 94/131 | SUBMITTED TEXT | 42 WORDS | 38% MATCHING TEXT | 42 WORDS |
| for Plan of Analyses since they have more prominent impact than others and should be in multivariate reaches that can be acknowledged. 7.8.2.6. Formulation and Development of QTP FMT MDF by Design of Experiment (DoE) Using QbD Approach A plan space | | for Design of Experiments as they are having more effect than others and need to be in accepting multivariate ranges. [91] www.wjpps.com Vol 10, Issue 7, 2021. ISO 9001:2015 Certified Journal 1454 3.2.6. Formulation and Development of Quetiapine FMT MDF by Design of Experiment (DoE) Using QbD Approach A design space | | |
| <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | | |

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| 95/131 | SUBMITTED TEXT | 14 WORDS | 84% MATCHING TEXT | 14 WORDS |
| DISINTEGRATING AGENT TYPE USED Cross Povidone (g) Kyron T-314 (g) Banana Powder (g) | | DISINTEGRATING AGENT TYPE USED DISINTEGRATING AGENT CONCENTRATION (gm) Cross Povidone (g) Kyron T- 314 (g) Banana Powder (g) 0.5 0.75 1.0 3.2.5. | | |
| <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | | |

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| 96/131 | SUBMITTED TEXT | 21 WORDS | 64% MATCHING TEXT | 21 WORDS |
| of film (over 100 mg) is broken up in 100 mL of Phosphate cradle pH 7.4 in which drug is | | of film (above 100 mg) is dissolved in 100 ml of Phosphate buffer ph 7.4 in which drug is | | |
| <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | | |

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| 97/131 | SUBMITTED TEXT | 18 WORDS | 100% MATCHING TEXT | 18 WORDS |
| Kinetic Analysis of Release Data: 7.8.2.7.12.1. Zero Order Release $Q_t = Q_0 + K_0t$ 4.8.2.7.12.2. | | Kinetic Analysis of Release Data 3.2.7.12.1. Zero Order Release $Q_t = Q_0 + K_0t$ | | |
| <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | | |

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| 98/131 | SUBMITTED TEXT | 23 WORDS | 77% MATCHING TEXT | 23 WORDS |
| <p>Plot: log cumulative percentage of drug remaining vs. time. 7.8.2.7.12.3. Higuchi Square Root of Time Equation: $Q = KH \times t^{1/2}$ 7.8.2.7.12.4.</p> | | <p>Plot: log cumulative percentage of drug remaining vs. time. www.wjpps.com Vol 10, Issue 7, 2021. ISO 9001:2015 Certified Journal 1457 3.2.7.13.3. Higuchi Square Root of Time Equation $Q = KH t^{1/2}$</p> | | |
| <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | | |

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| 99/131 | SUBMITTED TEXT | 63 WORDS | 42% MATCHING TEXT | 63 WORDS |
| <p>volunteers were told to let out example with spit and wash their mouths with 200 ml refined water. Following 2 hours, indistinguishable method was finished subsequent example (either test or reference sample).So, spitting of definition and salivation was told to volunteers to forestall openness of medication. Table 7. 8 Parameters, Score and Results of Taste Evaluation Study 7.8.2.7.15. Scanning electron microscope</p> | | <p>volunteers were asked to spit out the sample with saliva after 3 min and asked to rinse their mouths with 200 ml of distilled water. The same procedure was repeated after 2 hour for second sample (either test or reference sample). So, spitting of formulation and saliva was instructed to volunteers to prevent exposure of drug. Table 6: Parameters, Score and Results of Taste Evaluation Study. 3.2.7.16. Scanning electron microscope</p> | | |
| <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | | |

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| 100/131 | SUBMITTED TEXT | 35 WORDS | 68% MATCHING TEXT | 35 WORDS |
| <p>Comparison of optimized QTP FMT MDF with Marketed QTP FMT formulation: The optimized formulation QTP FMT MDF will be compared with Marketed conventional QTP FMT. 7.8.2.7.18. Stability Studies The picked organization was put in</p> | | <p>Comparison of optimized Quetiapine FMT MDF with Marketed Quetiapine FMT formulation The optimized formulation Quetiapine FMT MDF will be compared with Marketed conventional Quetiapine FMT. 3.2.7.19. Stability Studies The selected formulation was packed in</p> | | |
| <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | | |

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| 101/131 | SUBMITTED TEXT | 51 WORDS | 43% MATCHING TEXT | 51 WORDS |
| <p>at 40°C/75% RH and surveyed for actual appearance, in vitro deterioration time, drug content homogeneity, and medication discharge learns at foreordained stretches. 115 8. RESULTS & DISCUSSION 8.1 PREFORMULATION STUDY OF QTP FMT 8.1.1. ORGANOLEPTIC PROPERTIES Table 8. 1 Organoleptic characteristics of Drugs S.No. Parameters 1.</p> | | <p>at 40°C / 75% RH for 1 month and evaluated for their physical appearance, in vitro disintegrating time, drug content uniformity and drug release study at specified of time. 4. AND DISCUSSION 4.1. PREFORMULATION STUDY OF Quetiapine FMT 4.1.1. ORGANOLEPTIC PROPERTIES Tab. 8: Organoleptic characteristics of Drugs. 4.1.2. MELTING POINT S.No. Parameters</p> | | |
| <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | | |

| 102/131 | SUBMITTED TEXT | 34 WORDS | 61% MATCHING TEXT | 34 WORDS |
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| | Wavelength maximum (λ max) of QTP FMT Drug λ max Actual λ max Observed λ max QTP FMT 250 248.5 Figure 8. 1 UV Spectrum of QTP FMT 8.1.4. SOLUBILITY STUDIES | | | Wavelength maximum (λ max) of Quetiapine FMT. λ max Drug Actual λ max Observed λ max Quetiapine FMT 250 248 Fig. 1: UV Spectrum of Quetiapine FMT. 4.1.4. SOLUBILITY STUDIES |
| | <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | |

| 103/131 | SUBMITTED TEXT | 26 WORDS | 92% MATCHING TEXT | 26 WORDS |
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| | Determination of Partition Coefficient of selected Drugs S.No. Sample Partition Coefficient (Mean \pm SD, n=3) 1. QTP FMT 3.35 \pm 0.53 8.1.6. Calibration Curve: 8.1.6.1. | | | Determination of Partition Coefficient of selected Drugs. S.No. Sample Partition Coefficient (Mean \pm SD, n=3) 1. Quetiapine FMT 3.22 \pm 0.47 4.1.6. Calibration Curve. |
| | <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | |

| 104/131 | SUBMITTED TEXT | 40 WORDS | 100% MATCHING TEXT | 40 WORDS |
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| | Wavelength (λ max) 248 Beer's limit (μ g/ml) 0-10 Corrélation coefficient (R 2) 0.986 Slope 0.050 Obeys Beer law in conc. range of 0-10 mcg/ml R 2 value shows linearity 120 8.1.6.2. | | | Wavelength (λ max) 248 Beer s limit (μ g/ml) 0-10 Corrélation coefficient (R 2) 0.984 Slope 0.054 Obeys Beer law in conc. range of 0-10 mcg/ml R 2 value shows linearity |
| | <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | |

| 105/131 | SUBMITTED TEXT | 36 WORDS | 100% MATCHING TEXT | 36 WORDS |
|---------|--|----------|--------------------|---|
| | Wavelength (λ max) 248 Beer's limit (μ g/ml) 0-10 Corrélation coefficient (R 2) 0.989 Slope 0.009 Obeys Beer law in conc. range of 0-10 mcg/ml R 2 value shows linearity 8.1.7. | | | Wavelength (λ max) 248 Beer s limit (μ g/ml) 0-10 Corrélation coefficient (R 2) 0.984 Slope 0.054 Obeys Beer law in conc. range of 0-10 mcg/ml R 2 value shows linearity |
| | <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | |

| 106/131 | SUBMITTED TEXT | 26 WORDS | 65% MATCHING TEXT | 26 WORDS |
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| | Trial batches for QTP FMT MDF for CQAs for QTP FMT MDF Table 8. 12 selection of polymers type and concentration for QTP FMT MDF | | | Trial batches for Quetiapine FMT MDF for CQAs for Quetiapine FMT MDF Tab. 16: Preliminary trial batch for selection of polymers type and concentration for Quetiapine FMT MDF. |
| | <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | |

| 107/131 | SUBMITTED TEXT | 24 WORDS | 82% MATCHING TEXT | 24 WORDS |
|---------|--|----------|-------------------|--|
| | Surface pH (Mean \pm SD) n=3 Thickness (mm) (Mean \pm SD) n=3 Avg. Tensile strength (N/cm ²) \pm SD, n = 3 | | | Surface pH (Mean \pm SD) n=3 Thickness (mm) (Mean \pm SD) n=3 QTPDT1 Flexible 99 \pm 0.29 7.3 \pm 0.29 0.11 \pm 0.003 QTPDT2 Flexible 105 \pm 0.09 7.2 \pm 0.33 0.33 \pm 0.101 QTPDT3 Flexible 107 \pm 0.27 7.9 \pm 0.82 0.30 \pm 0.001 Avg. Tensile strength (N/cm ²) \pm SD, n = 3 1.231 \pm 0.145 1.584 \pm 0.172 1.093 \pm 0.181 |
| | W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ... | | | |

| 108/131 | SUBMITTED TEXT | 20 WORDS | 100% MATCHING TEXT | 20 WORDS |
|---------|--|----------|--------------------|---|
| | Avg. In Vitro Disintegration Time (sec) \pm SD, n = 3 Avg. Folding Endurance \pm SD, n = 3 | | | Avg. In Vitro Disintegration Time (sec) \pm SD, n = 3 167.67 \pm 1.456 180.48 \pm 1.371 189.12 \pm 2.876 121.29 \pm 1.536 135.87 \pm 2.527 141.76 \pm 1.877 161.56 \pm 4.345 169.26 \pm 3.575 Avg. Folding Endurance \pm SD, n = 3 90 \pm 2 101 \pm 1 109 \pm 2 148 \pm 2 162 \pm 3 173 \pm 2 90 \pm 6 97 \pm 5 |
| | W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ... | | | |

| 109/131 | SUBMITTED TEXT | 78 WORDS | 81% MATCHING TEXT | 78 WORDS |
|---------|---|----------|-------------------|---|
| | Batch Surface Texture Weight uniformity (mg) (Mean \pm SD) n=3 Surface pH (Mean \pm SD) n=3 Thickness (mm) (Mean \pm SD) n=3 Avg. Tensile strength (N/cm ²) (Mean \pm SD), n = 3 Avg. Drug Content uniformity (%) (Mean \pm SD), n = 3 Avg. uniform Drug Distribution (%) (Mean \pm SD), n = 3 Avg. In Vitro Disintegration Time (sec) (Mean \pm SD), n = 3 Avg. Folding Endurance (Mean \pm SD), n = 3 | | | Batch Surface Texture Weight uniformity (mg) (Mean \pm SD) n=3 Surface pH (Mean \pm SD) n=3 Thickness (mm) (Mean \pm SD) n=3 QTPDT1 Flexible 99 \pm 0.29 7.3 \pm 0.29 0.11 \pm 0.003 QTPDT2 Flexible 105 \pm 0.09 7.2 \pm 0.33 0.33 \pm 0.101 QTPDT3 Flexible 107 \pm 0.27 7.9 \pm 0.82 0.30 \pm 0.001 Avg. Tensile strength (N/cm ²) \pm SD, n = 3 1.231 \pm 0.145 1.584 \pm 0.172 1.093 \pm 0.181 Avg. Drug Content uniformity (%) \pm SD, n = 3 Avg. uniform Drug Distribution (%) \pm SD, n = 3 Avg. In Vitro Disintegration Time (sec) \pm SD, n = 3 98.42 \pm 0.289 97.42 \pm 0.289 48.19 \pm 0.32 99.33 \pm 0.382 98.53 \pm 0.289 43.39 \pm 0.51 Avg. Folding Endurance \pm SD, n = 3 161 \pm 1.732 136 \pm 2.645 99.92 \pm 0.29 99.25 \pm 0.144 42.03 \pm 0.22 114 \pm 2.00 |
| | W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ... | | | |

| 110/131 | SUBMITTED TEXT | 62 WORDS | 50% MATCHING TEXT | 62 WORDS |
|---------|--|----------|-------------------|---|
| | mentioned primer preliminary groups for plasticizer determination, it was found that Poloxamer 407 (mg) in focus scope of 10-15 mg created best outcomes. 137 Table 8. 19 Selection of disintegrating agent type and concentration for QTP FMT MDF Ingredients QTPDT1 QTPDT2 QTPDT3 QTPDT4 QTPDT5 QTPDT6 QTPDT7 QTPDT8 QTPDT9 Drug (gm) 0.184 HPMC E5 (gm) 0.3 PEG 400 (ml) 01 | | | mentioned preliminary trial batches for selection of plasticizer it was observed that the best results were obtained in Poloxamer 407 (mg) in the concentration range of 10-15 mg. Tab. 19: Preliminary trial for selection of disintegrating agent type and concentration for Quetiapine FMT MDF Ingredients QTPDT1 QTPDT2 QTPDT3 QTPDT4 QTPDT5 QTPDT6 QTPDT7 QTPDT8 QTPDT9 Drug (mg) 184 184 184 184 184 184 184 184 184 HPMC E5(mg) 300 300 300 300 300 300 300 300 300 PEG 400 (ml) 1 1 1 1 1 1 1 1 1 |
| | W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ... | | | |

| 111/131 | SUBMITTED TEXT | 132 WORDS | 87% MATCHING TEXT | 132 WORDS |
|---------|---|-----------|-------------------|---|
| | Batch Surface Texture Weight uniformity (mg) (Mean ± SD) n=3 Surface pH (Mean ± SD) n=3 Thickness (mm) (Mean ± SD) n=3 Avg. Tensile strength (N/cm ²) ± SD, n = 3 Avg. Drug Content uniformity (%) ± SD, n = 3 Avg. uniform Drug Distribution (%) ± SD, n = 3 Avg. In Vitro Disintegration Time (sec) ± SD, n = 3 Avg. Folding Endurance ± SD, n = 3 QTPDT7 Smooth 98.00±0.88 6.4±0.27 0.15±0.003 1.18 ± 0.065 99.32 ± 0.289 96.32 ± 0.382 72.17±0.22 193.00 ± 3.46 QTPDT8 Flexible 104.00±0.29 7.02±0.28 0.20±0.003 1.092 ± 0.152 99.90 ± 0.29 99.24 ± 0.144 66.32±0.23 197.65 ± 0.58 QTPDT9 Flexible 110.00±0.53 7.01±0.87 0.22±0.003 2.638 ± 0.058 99.73 ± 0.50 99.24 ± 0.289 26.20±0.10 198.00 ± 3.63 139 | | | Batch Surface Texture Weight uniformity (mg) (Mean ± SD) n=3 Surface pH (Mean ± SD) n=3 Thickness (mm) (Mean ± SD) n=3 QTPDT1 Flexible 99±0.29 7.3±0.29 0.11±0.003 QTPDT2 Flexible 105±0.09 7.2±0.33 0.33±0.101 QTPDT3 Flexible 107±0.27 7.9±0.82 0.30±0.001 Avg. Tensile strength (N/cm ²) ± SD, n = 3 1.231 ± 0.145 1.584 ± 0.172 1.093 ± 0.181 Avg. Drug Content uniformity (%) ± SD, n = 3 Avg. uniform Drug Distribution (%) ± SD, n = 3 Avg. In Vitro Disintegration Time (sec) ± SD, n = 3 98.42 ± 0.289 97.42 ± 0.289 48.19±0.32 99.33 ± 0.382 98.53 ± 0.289 43.39±0.51 Avg. Folding Endurance ± SD, n = 3 161 ± 1.732 136 ± 2.645 99.92 ± 0.29 99.25 ± 0.144 42.03±0.22 114 ± 2.00 www.wjpps.com Vol 10, Issue 7, 2021. ISO 9001:2015 Certified Journal 1471 QTPDT4 QTPDT5 Flexible 104±0.29 7.0±0.28 0.29±0.003 Flexible 110±0.53 7.0±0.87 0.16±0.003 |
| | W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ... | | | |

| 112/131 | SUBMITTED TEXT | 14 WORDS | 100% MATCHING TEXT | 14 WORDS |
|---------|---|----------|--------------------|---|
| | X2 Amount of HPMC E50 (gm) 0.250 0.350 Dependent Variables Y1 Tensile Strength (| | | X2=amount of HPMC E50 (gm) 250 300 250 Dependent Variables Y1= Tensile Strength |
| | W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ... | | | |

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| 113/131 | SUBMITTED TEXT | 32 WORDS | 53% MATCHING TEXT | 32 WORDS |
| | in this design, each at three levels, and experimental trials were conducted on all nine conceivable combinations. Poloxamer 407 concentration (X1) and HPMC E50 concentration (X2) were chosen as independent variables. | | In this design two factors were evaluated, each at three levels and experimental trials were carried out at all nine possible combinations. The concentration of Poloxamer 407 (X1) and the concentration of HPMC E50 (X2) were selected as independent variables. | |
| | W | https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ... | | |
| 114/131 | SUBMITTED TEXT | 12 WORDS | 100% MATCHING TEXT | 12 WORDS |
| | Tensile Strength (Y1), Disintegrating Time (Y2), and In-vitro drug release (Y3). | | Tensile Strength (Y1), disintegrating time (Y2) and In-vitro drug release (Y3) | |
| | W | https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ... | | |
| 115/131 | SUBMITTED TEXT | 19 WORDS | 60% MATCHING TEXT | 19 WORDS |
| | film from Alu pocket and spot it in mouth without utilization of water, which was considered patient-accommodating and | | film from Alu pouch and put it in mouth without need of water which was ranked patient friendly and | |
| | W | https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ... | | |
| 116/131 | SUBMITTED TEXT | 19 WORDS | 77% MATCHING TEXT | 19 WORDS |
| | Results of Taste and Palatability Evaluation Sample Type Mouth feel Taste (Bitterness) After taste Ease of handling Acceptance | | Results of Taste and Palatability Evaluation. Test (Batch No. ZMDF5) Mouth Feel 4.25 ± 0.46 Taste (Bitterness) 4.00 ± 0.00 After taste 3.88 ± 0.35 Ease of handling Acceptance 5.00 ± 0.00 4.375 ± 0.52 | |
| | W | https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ... | | |
| 118/131 | SUBMITTED TEXT | 24 WORDS | 100% MATCHING TEXT | 24 WORDS |
| | A Review on new generation orodispersible tablets and its future prospective", International Journal of Pharmacy and Pharmaceutical Sciences, 2011, 3(1), 1-7. 39. | | A Review on new generation orodispersible tablets and its future prospective. International Journal of Pharmacy and Pharmaceutical Sciences, 2011;3(1):1-7. 20. | |
| | W | https://www.ijpp.org.in/article-download/full-text/4413 | | |

| 129/131 | SUBMITTED TEXT | 20 WORDS | 85% MATCHING TEXT | 20 WORDS |
|---------|---|----------|--|----------|
| | Orally Disintegrating Systems: Innovations in Formulation and Technology”, Recent Patents on Drug Delivery & Formulation, 2008, 2(3), 258-74. 57. | | Orally Disintegrating Systems: Innovations in Formulation and Tech- nology, Recent Patents on Drug Delivery & Formulation, 2, 2008, 258-274 [29] | |
| | <p>W https://ijpras.com/storage/models/article/LOjOBmJjWVrDHgS2NBu4og5HcTUP6E78mpzxCsVFapWosrXKYY1lC9D...</p> | | | |

| 117/131 | SUBMITTED TEXT | 20 WORDS | 100% MATCHING TEXT | 20 WORDS |
|---------|---|----------|---|----------|
| | Effect of taste masking technology on fast dissolving oral film: dissolution rate and bioavailability”, Nanotechnology, 2018, 29(30), 304001. 82. | | Effect of taste masking technology on fast dissolving oral film: dissolution rate and bioavailability, Nanotechnology, 2018 | |
| | <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f...</p> | | | |

| 119/131 | SUBMITTED TEXT | 42 WORDS | 93% MATCHING TEXT | 42 WORDS |
|---------|---|----------|--|----------|
| | Effect of taste masking technology on fast dissolving oral film: dissolution rate and bioavailability”, Nanotechnology, 2018, 29(30),304001. 86. Pagilla P. & Vishnu P., “Formulation and evaluation of lovastatin oral disintegration thin films”, GSC Biological and Pharmaceutical Sciences, 2018, 3(2), 35- 42. 87. | | Effect of taste masking technology on fast dissolving oral film: dissolution rate and bioavailability, Nanotechnology, 2018 Jul 27; 29(30): 304001. 3. Pagilla P, Vishnu P and Konde A. Formulation and evaluation of lovastatin oral disintegration thin films. GSC Biological and Pharmaceutical Sciences, 2018; 3(2); 35-42. 4. | |
| | <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f...</p> | | | |

| 120/131 | SUBMITTED TEXT | 47 WORDS | 83% MATCHING TEXT | 47 WORDS |
|---------|--|----------|--|----------|
| | Desu & Sahu M., “Formulation and evaluation of fast dissolving films of zolmitriptan”, Int Res J Pharm., 2012, 3(5), 373–76. 94. B Bhyan & Jangra S., “Formulation and evaluation of fast dissolving sublingual films of rizatriptan Benzoate”, Int J Drug Dev Res., 2012, 4(1), 133–43. 95. | | Desu P, Sahu M. Formulation and evaluation of fast dissolving films of zolmitriptan. Int Res J Pharm., 2012; 3(5): 373 76. www.wjpps.com Vol 10, Issue 7, 2021. ISO 9001:2015 Certified Journal 1474 5. Bhyan B, Jangra S. Formulation and evaluation of fast dissolving sublingual films of rizatriptan Benzoate. Int J Drug Dev Res., 2012; 4(1): 133 43. 6. | |
| | <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f...</p> | | | |

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|--|-----------------------|--|--------------------------|----------|
| 121/131 | SUBMITTED TEXT | 20 WORDS | 71% MATCHING TEXT | 20 WORDS |
| <p>Formulation & evaluation of fast dissolving buccal films of sertraline”, Int J Drug Dev Res., 2012, 4(1), 220–26. 96.</p> | | <p>Formulation and evaluation of fast dissolving sublingual films of rizatriptan Benzoate. Int J Drug Dev Res., 2012; 4(1): 133 43. 6.</p> | | |
| <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | | |

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|--|-----------------------|--|--------------------------|----------|
| 122/131 | SUBMITTED TEXT | 55 WORDS | 74% MATCHING TEXT | 55 WORDS |
| <p>Res., 2012, 5(4), 260– 70. 98. Choudhary D. & Patel V. et al., “Development and characterization of pharmacokinetic parameters of fast-dissolving films containing levocetirizine”, Scientia Pharmaceutica, 2012, 80, 779–87. 99. Panchal M. et al., “Formulation and evaluation of mouth dissolving film of ropinirole hydrochloride by using pullulan polymers”, IJPRAS, 2012, 1, 60–72. 100. Dixit</p> | | <p>Res., 2012; 4(1): 133 43. 6. Choudhary DR, Patel VA, Chhalotiya UK, et al. Development and characterization of pharmacokinetic parameters of fast-dissolving films containing levocetirizine. ScientiaPharmaceutica., 2012; 80: 779 87. 7. Panchal MS, Patel H, Bagada A, et al. Formulation and evaluation of mouth dissolving film of ropinirole hydrochloride by using pullulan polymers. IJPRAS, 2012; 1: 60 72. 8. Dixit</p> | | |
| <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | | |

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|---|-----------------------|---|--------------------------|----------|
| 123/131 | SUBMITTED TEXT | 55 WORDS | 66% MATCHING TEXT | 55 WORDS |
| <p>Fast disintegrating films containing anastrozole as dosage form for dysphagia patients”, Archives of pharmaceutical research, 2012, 25(12), 2171–82. 101. Nagar M. et al., “Formulation and evaluation of mouth dissolving film of antipsychotic drug aripiprazole”, Der Pharmacia Lettre, 2012, 4(4), 1221–7. 102. Joshi P. et al., “Formulation development and evaluation of mouth dissolving film of</p> | | <p>Fast disintegrating films containing anastrozole as a dosage form for dysphagia patients. Archives of pharmaceutical research, 2012; 25(12): 2171 82. 9. Nagar M, Nagar M, Chopra V. Formulation and evaluation of mouth dissolving film of antipsychotic drug aripiprazole. Der Pharmacia Lettre., 2012; 4(4): 1221 27. 10. Prabhu P, Malli R, Koland M, et al. Formulation and evaluation of fast dissolving film of</p> | | |
| <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | | |

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|--|-----------------------|---|--------------------------|----------|
| 124/131 | SUBMITTED TEXT | 21 WORDS | 62% MATCHING TEXT | 21 WORDS |
| <p>Formulation and evaluation of fast dissolving films of loratidine for sublingual use”, Int Res J Pharm., 2012, 3(7), 157–61. 105.</p> | | <p>Formulation and evaluation of fast dissolving films of zolmitriptan. Int Res J Pharm., 2012; 3(5): 373 76.</p> | | |
| <p>W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ...</p> | | | | |

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|----------------|---|----------|---|----------|
| 125/131 | SUBMITTED TEXT | 11 WORDS | 100% MATCHING TEXT | 11 WORDS |
| | M. et al., "Formulation and evaluation of fast dissolving film | | M, et al. Formulation and evaluation of fast dissolving film | |
| | W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ... | | | |
| 126/131 | SUBMITTED TEXT | 21 WORDS | 100% MATCHING TEXT | 21 WORDS |
| | et al., "Formulation and evaluation of fast dissolving film of levocetirizine dihydrochloride", Int J Pharma Investig., 2011, 1(2), 99–104. 114. | | et al. Formulation and evaluation of fast dissolving film of levocetirizine dihydrochloride. Int J Pharma Investig., 2011; 1(2): 99 104. 11. | |
| | W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ... | | | |
| 127/131 | SUBMITTED TEXT | 12 WORDS | 100% MATCHING TEXT | 12 WORDS |
| | ondansetron hydrochloride by polymer carrier system and formulation of rapid disintegrating | | Ondansetron hydrochloride by Polymer Carrier System and Formulation of Rapid Disintegrating | |
| | W http://www.arjournals.org/index.php/ijaps/article/view/258 | | | |
| 128/131 | SUBMITTED TEXT | 23 WORDS | 100% MATCHING TEXT | 23 WORDS |
| | Formulation, Optimization And Characterization Of Ziprasidone Nanocrystals Prepared By Media Milling Technique", International Journal of Pharmacy and Pharmaceutical Sciences; 2015,5(8), 1491. 137. | | FORMULATION, OPTIMIZATION AND CHARACTERIZATION OF ZIPRASIDONE NANOCRYSTALS PREPARED BY MEDIA MILLING TECHNIQUE; International Journal of Pharmacy and Pharmaceutical Sciences, 2015; 7 (8): | |
| | W https://docplayer.net/amp/213630941-Design-development-and-characterization-of-mouth-dissolving-f ... | | | |
| 130/131 | SUBMITTED TEXT | 19 WORDS | 100% MATCHING TEXT | 19 WORDS |
| | EFFECT OF COMPACTION PROCESS IN GRANULOMETRY; International Journal Of Pharmaceutical Sciences And Research" IJPSR, 2016, 7(2), 601-606. 147. | | EFFECT OF COMPACTION PROCESS IN GRANULOMETRY; International Journal of Pharmaceutical Sciences and Research; IJPSR, 2016; 7(2): 601-606, | |
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131/131

SUBMITTED TEXT

15 WORDS

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Release Characteristics of Quetiapine Fumarate Extended
Release Tablets Under Biorelevant Stress Test Conditions",
AAPS

Release Characteristics of Quetiapine Fumarate Extended
Release Tablets Under Biorelevant Stress Test Conditions;
AAPS

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