“FORMULATION, DEVELOPMENT AND EVALUATION OF ORODISPERSIBLE FILMS FOR VARIOUS THERAPEUTIC AGENTS”

A Thesis submitted to Gujarat Technological University

for the Award of

Doctor of Philosophy

in

Pharmacy

By

Ms. Amin Prakruti Mukund

Enrollment No. 169999901001

Under supervision of

Dr. Manishkumar P. Patel
Asst. Professor,
L.M. College of Pharmacy,
Ahmedabad, Gujarat.

GUJARAT TECHNOLOGICAL UNIVERSITY
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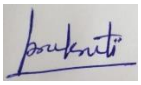

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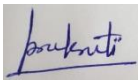

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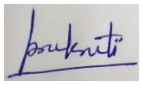

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ABSTRACT

Orodispersible films (ODF'S) have been identified as an alternative approach to conventional dosage forms. The orodispersible films are considered to be convenient to swallow, self-administrable, and fast dissolving dosage form, this system provides more rapid drug absorption from the pre gastric area which may provide quick onset of action, all of which make it as a versatile platform for drug delivery. This delivery system has been used for both systemic and local action. The present investigation was undertaken with the objectives of formulating orodisoersible films of antitussive agent Dextromethorphan hydrobromide (DXM) and Varenicline tartrate (VAR), is a highly selective partial agonist of the nicotinic acetylcholine receptor α4β2 subtype, used in smoking cessation, to enhance convenience and compliance of problematic subpopulation such as paediatric and geriatric patient. The present research reveals the effectiveness of quality by design methodology to optimize the formulation variables for the development of DXM and VAR oro-dispersible films. Various polymers screened and select hydroxypropylmethyl cellulose E15 and Kollicoat IR, PEG 400 as plasticizer, citric acid as saliva stimulating agent. Kyron T 314 resin for taste masking, sweetening agent such as aspartame and stevia and saliva stimulating agent citric acid. The films were prepared by solvent casting method using a systematic approach of design of experiments and evaluated for various parameters like weight variation, thickness, folding endurance, surface pH, drug content, tensile strength, % elongation, in vitro disintegration time and % in vitro drug release. Optimised formulation of Dextromethorphan Hbr shows in-vitro disintegration time 35 sec± 2, and in-vitro drug release studies indicated 99.5 %± 0.6 release within 10 minutes. Therefore, developed ODFs of DXM could be a good alternative formulation approach for the management and treatment of cold and cough, which benefits rapid absorption, consumer compliance and convenience. Optimised formulation of Varenicline tartrate shows 35+5 in-vitro disintegration time and in-vitro drug release studies indicated 98.23%+1.25 release within 10 minutes. taste masking of both the formulation evaluated by Insent Taste Sensing System TS-5000Z. It was concluded from the result that both the formulation (ODF's) shows good masking of bitterness than API. No significant change in the physical parameters, in vitro disintegration time and drug content was observed during storage for 90 days.

Key words: Orodispersible films **,** quality by design, hydroxypropylmethyl cellulose E15, Kollicoat IR, taste masking, Kyron T 314.

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*I dedicate my dissertation work to my dearest Masi, **Mrs. Maniben B. Patel** for her continuous encouragement and unconditional love.*

Prakruti Amin

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List of Abbreviation

DXM Hbr Hbr: Dextromethorphan Hydrobromide

VAR: Varenicline as Varenicline tartrate

ODF: Orodispersible films

GIT: Gastrointestinal Tract

NDA: New Drug Application

ANDA: Abbreviated New Drug Application

FDA: U.S. Food and Drug Administration

UV Spectroscopy: Ultra violet spectroscopy

FT-IR: Fourier Transform InfraRed Spectroscopy

HPMC: Hydroxy Propyl Methyl Cellulose

HPC: Hydroxy propyl cellulose

PVP: Poly vinyl pyrrolidone

PVA: Poly vinyl alcohol

PG: Propylene Glycol

PEG: Poly Ethylene Glycol

ICH: International Conference on Harmonization

QbD: Quality by Design

QTPP: Quality Targeted Product Profile

CQA: Critical Quality Attributes

QRM: Quality Risk Management

REM: Risk Estimation Matrix

PAT: Process Analytical Technology

DoE: Design of Experiment

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CHAPTER 1. INTRODUCTION

1.1. Introduction to dosage form

Oral drug delivery is the most common route of drug administration for the general population [1]. It is easier, on account of self-medication, accurate dosing, pain avoidance, non-invasiveness, adaptability, patient compliance and effective cost for the pharmaceutical companies. The advantages of this route include possible bypass of first-pass effect, avoidance of presystemic elimination within the gastrointestinal tract (GIT) and depending on the particular drug, a better enzymatic flora for drug absorption[2]. These facts justify why the oral delivery market holds 52% of the market share remaining the largest sector in the overall drug delivery market and 60% of all dosage forms available are the oral solid dosage form[3].

But there are some commonly associated problems with oral administration of drugs like minimizing the risk of partial loss of active ingredients due to tablet or capsule crushing or imprecise liquid administration which leads to dosage inaccuracy and drug therapy overdosing or inefficiency[4].

Many paediatric and geriatric patients are unwilling to take these solid preparations due to fear of choking and. have serious swallowing difficulties. It is estimated that almost 28% of the general population have frequent problems in swallowing medicines that is often the cause of poor patient compliance[5].

In order to overcome these issues, fast dissolving delivery systems are gaining considerable attention. Imagination is the capacity to deliver new and interesting thoughts, one such thought is the advancement of Novel Drug Delivery Systems (NDDS). A vast variety of pharmaceutical research is directed at developing new dosage forms. Most of these efforts have focused on either formulating novel drug delivery systems or increasing the patient compliance and attempts to ensure efficacy, safety and patient acceptability[6].

As discovery and development of new chemical agents is a complex, expensive and time consuming process, so recent trends are shifting toward designing and developing innovative drug delivery systems for existing drugs thereby the product patent life cycle, thereby giving a new life to existing molecules, Among the dosage forms developed for facilitating ease of medication, the orally disintegrating systems

have been the favourite of product development scientists Due to their thin size and flexibility they are found to be gaining attention.

Nowadays, there has been significance development in transmucosal routes of drug administration because this route has a potential to displace such problems as asassociated with oral administration of the drugs[7].

1.2.Introduction to oral cavity

Drug delivery via the oral cavity is highly conventional by patients. The oral cavity, or more commonly known as the mouth or buccal cavity, serves as the first portion of the digestive system. It consists of several different anatomically different aspects that work together effectively and efficiently to perform several functions. These aspects include the lips, tongue, palate, and teeth. The oral cavity is surrounded by the lips and is composed of two separate regions, the vestibule, the area between the cheeks, teeth, and lips, and the oral cavity proper. The oral cavity proper is mostly filled with the tongue and bounded anteriorly and on the sides by the alveolar processes containing the teeth and posteriorly by the isthmus of the fauces. Anteriorly, the roof forms by the hard palate and posteriorly by the soft palate. The uvula hangs downwards from the soft palate. The mylohyoid muscles constitute the floor of the oral cavity. The lining of the oral cavity is referred to as the oral mucosa, the mucosa is sensibly permeable and has a rich blood supply, it is robust and shows short recovery times after stress or damage. Furthermore, these factors make the oral mucosal cavity a very attractive and feasible site for local and systemic drug delivery[8]. The mucosal epithelial structure contains two different areas, the membrane of the stratified epithelium, which is a lipophilic area and space between cells, and a more hydrophilic area. The oral mucosa has a capability between the intestinal mucosa and the epidermis in terms of permeability to substances[9]. The mucosal epithelium offers two main drug absorption pathways, the paracellular pathway (intercellular) and the transcellular pathway (intercellular) The lipophilic structure of the cell membranes facilitates the passage of molecules with a high partition coefficient through the cells, while the polar nature of the intercellular space facilitates the penetration of more hydrophilic molecules. The hydrophobic, hydrophilic, or amphiphilic nature of the drug molecule determines its absorption.

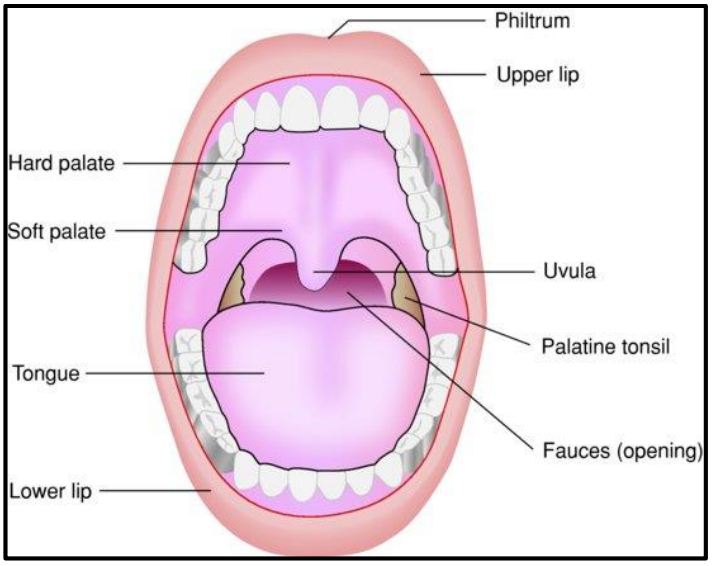


Figure 1.1: Oral cavity pathways

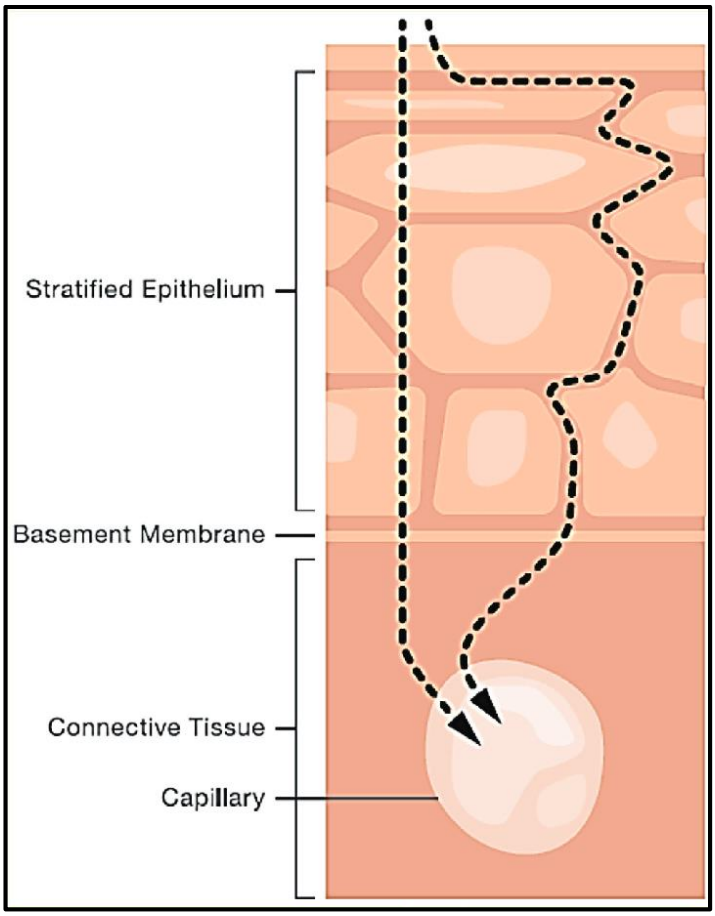


Figure 1.2: Mucosal pathways-intracellular and intercellular[10]

Fast dissolving delivery systems including orally disintegrating tablets (ODT) and fast dissolving films or orodispersible films or dissolvable oral thin films (OTFs) have continued to expand in sales and launched as patient compliant, and convenient

products efficiently addressing issues for pharmaceuticals as well as nutraceuticals that have been traditionally administered as oral solid dosages.

These are drug delivery systems that they are quickly releasing the drug by dissolving or adhering in the mucosa with saliva within a few seconds due to it contains water-soluble polymers when it placed in the mouth cavity or on the tongue". The sublingual mucosa has high membrane permeability due to its thin membrane structure and high vascularization. Due to this rapid blood supply, it offers very good bioavailability [11, 12]. In addition, the oral mucosa is a very effective and selective route of systemic drug delivery because of the large surface area and ease of application for absorption [13].

These either dissolve or disintegrate generally within a minute without needing water or chewing and upon melting; the dose of medicine is swallowed. Absorption of drug by oral mucosa into systemic circulation is an attractive approach because it is highly vascularized and hence highly permeable [14].

Among them oral film strips have hit the mainstream in the last few years. Fast-dissolving thin oral films are rapidly gaining interest in the pharmaceutical industry over disintegrating tablet technology because they are handy with patients having difficulties in swallowing or chewing solid dosage forms. Several other names of these thin films have been appeared, for example orodispersible films (ODFs), oral soluble films, mucoadhesive films, oral strips, oral films [oral thin films], buccal films, wafers, and trans mucosal films [9].

In Technology Catalysts' recently-released report on 'orally disintegrating tablet and film technologies' (3rd Edition), the company identified over fifteen companies actively developing OTF delivery technologies that enable the shift from a tablet form to a fast-dissolving and highly water-soluble wafer or film. With the filing of an Abbreviated New Drug Application ("ANDA") with the US Food and Drug Administration ("FDA"). This is a major cost of goods saver for generics.

1.3. Orodispersible film

A thin film that readily dissolves in the oral cavity is commonly referred as orodispersible film by the European Medicines Agency (EMA) (Hoffmann et al., 2011) or simply soluble film by the FDA (Food and Drug Administration, 2013)[15]. Although, oral films initially appeared as innovative breath freshening formulations,

it rapidly evolved to give response to different market needs, namely an easy-to-carry and easy-to-swallow drug delivery system [16].

In the European Pharmacopoeia (Ph. Eur.) they are described as ‘‘single or multilayer sheets of suitable materials, to be placed in the mouth where they disperse rapidly”.

For the most part, fast dissolving oral films are ultra-thin film 50-150 μm. having size of postage stamp, which dissolves within a few seconds in the oral cavity after being in contact with the saliva leading to fast absorption and instant bioavailability of the drugs [17]. Orodispersible films or non-adhesive fast dissolving films are normally composed by low molecular weight (Mw) (approx. between 1.000 to 9.000 Da) hydrophilic polymers. The majority of the orodispersible films are not necessarily designed to be mucoadhesive, but they may exhibit some degree of mucoadhesiveness, due to the innate characteristics of the polymers used. This mucoadhesion may also vary depending on the chemical properties and Mw of the film forming polymer used [1].

Additionally, ODF’s are intended to exhibit a fast disintegration in the oral cavity, be swallowed and absorbed to the systemic circulation in the gastro-intestinal tract.

Actually, this is somehow obvious in both official definitions: “single- or multilayer sheets of suitable materials, to be placed in the mouth where they disperse rapidly” (Ph. Eur. 7.4, “Orodispersible films”) and a “thin layer or coating which is susceptible to being dissolved when in contact with a liquid” (FDA, dosage form) (Food and Drug Administration, 2013; Hoffmann et al., 2011).

ODFs are fast disintegrating thin films having an area ranging from 5 to 20 cm^2 in which drug is incorporated in the form of matrix using hydrophilic polymer. Active pharmaceutical ingredient can be incorporated up to 1 to 30% w/w of the active pharmaceutical ingredient along with other excipients i.e., plasticizers, colorants, sweeteners, taste masking agents, etc. Plasticizer increases workability, spread ability and flexibility of films thereby reducing the glass transition temperature of polymers[18, 19].

1.3.1. Ingredients for formulation of orodispersible films

The general composition of an ODF is given in Table 1.1.

General composition of ODF	
Components	Concentration (%)

Active pharmaceutical ingredient	1 to 30
Hydrophilic polymer	40–50
Plasticizer	0-20
Saliva stimulating agents	2-6
Color, filler, flavor	0-40

Table 1.1. Composition of ODF

All excipients used in formulation should be chemically inert and approved for use in the formulation of oral films.

- **Active pharmaceutical ingredient**

The API can be incorporated into the films as particles or molecularly dispersed/dissolved. Particularly for dispersed APIs, particle size, particle size distribution and polymorphism become critical quality attributes. It is well known that these factors may affect solubility, rate of dissolution and ultimately bioavailability. As drug load is limited, high potency low-dose drugs are preferred [20]. A critical drug load can result in recrystallization or excessive influence on mechanical or disintegration properties of the films [21]. The drug is the core ingredient of these polymeric films and generally comprises of 5-30% (w/w) of the films [12]. Various classes of drugs can be incorporated into ODFs e.g. anti-histamine, anti-diarrheal, anti-depressants, vasodilators, anti-asthmatic, anti-emetic, etc [22].

List of polymers commonly used in the manufacture of polymeric films

- **Film forming polymers**

The oral films are essentially complex polymeric matrices that may be used efficiently as drug release platforms. The oral film must disintegrate in the saliva of the oral cavity. The successful development of an ODF is a function of justified selection and concentration of polymers as the mechanical strength of films is strongly associated with these factors. These polymeric matrices may be composed by several components in order to achieve well-designed drug-delivery platforms, but usually hydrophilic polymers are its main core. Polymers are the backbone of film formulations and are responsible for the strength of the film. The concentration of used polymers is also important factor while developing an ODF. The integrity of fast

dissolving oral films is dependent upon careful selection of polymer nature and concentration. Generally, polymer concentration used in preparing ODFs is around 45% w/w of total weight of dry thin strip, however, it can be increased up to 60–65% w/w in order to attain the film of desired attributes and characteristics. Polymer used as a film forming agent in formulation of ODFs should possess certain properties, listed in Table 1.2[23].

Properties
Non-irritant
Should not hinder with the disintegration time of ODF
Affordable
Non-toxic
Should possess adequate shelf-life
Should possess good spread ability
Should exhibit sufficient tensile strength
Should have good mechanical properties

Table 1.2: Ideal properties of polymers.

Various polymers are available for the preparation of thin films. Polymers can be used alone or in blend. The selection of the polymer (or mixtures) for the development of oral film matrices is a critical step and may vary taking into account the desired target product profile.

Hydrophilic polymers have been widely studied and tested for this application as film should be water soluble. These water-soluble polymers are used as film formers to produce a thin film with rapid disintegration good mechanical strength, and good mouthfeel effects. Both natural and synthetic polymers are used for film preparation. The list of polymers commonly used in the manufacture of polymeric films, is depicted in Table 1.3.

Type of polymer	**Examples**
Natural	Natural Starch, polymerized rosin, pullulan, sodium alginate, Pectin, gelatin, and maltodextrins
Synthetic	Polyvinyl alcohol, hydroxy propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose, polyvinyl

	pyrrolidone, and hydroxy propyl cellulose

Table 1.3: Most commonly used natural and synthetic polymers in ODFs.

HPMC is a very good film former and different grades viz Methocel E3, Methocel E5, Methocel E15 Premium LV, etc. are available.

- **Plasticizers**

The addition of a plasticizer is often necessary to obtain flexible, non-brittle ODFs[24]. They tend to reduce the brittleness of the strip by lowering glass transition temperature [Tg] of polymers thereby improving the flexibility of the films. The choice of plasticizer will depend on upon its compatibility with the polymer and also nature of the solvent employed in the casting of the strip. The flow of polymer will be improved when used along with plasticizer and additionally the strength of the polymer also gets improved. Propylene glycol (PG), Poly ethylene Glycol (PEG),Glycerol, sorbitol, low-molecular-mass macrogols, phthalates like dimethyl, diethyl and dibutyl phthalate, citrates derivatives such as tributyl, triethyl, acetyl citrate, triacetin and castor oil are some of the commonly used plasticizers [22, 25-27].

As ODFs still have a relatively high-water content after drying, water itself acts as plasticizer. Most of them have more effects that have to be considered, for example, sorbitol is also used as sweetener. Plasticizers may affect solubility of the API and drug absorption. High concentrations of plasticizers may cause an impaired moisture resistance, resulting in stability problems or tacky films. Macrogol 400 as well as the esters of citric acid are inappropriate for plasticizing maltodextrin films because of the lack of miscibility. Increasing the content of glycerol or propylene glycol in maltodextrin ODFs decreased the elastic modulus and increased the elongation at break. Concentrations higher than 18% w/w caused blooming phenomena and stickiness. The taste of glycerol plasticized ODFs was preferred over the taste of propylene glycol plasticized films.

- **Saliva stimulating agent**

The purpose of using saliva stimulating agents is to increase the rate of production of saliva that would aid in the faster disintegration of the rapid dissolving strip formulations. Generally, acids which are used in the preparation of food can be utilized as salivary stimulants. e.g., Citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid. These agents are used alone or in combination between 2 to 6%w/w of weight of the strip[24].

- **Flavouring agents**

Flavouring agents are necessary for taste and odour masking of the drug and to increase the appeal of the film. Also, the choice of flavours depends on age, taste and liking of the people. Younger people like fruit punch, raspberry etc. while the geriatric patient prefer orange, lemon and mint flavour. Cooling agents can also be added to enhance the flavour strength.

- **Sweetening agents**

Both natural and synthetic sweeteners are used to improve palatability of the mouth dissolving formulations[28-30]. The types of sweetening agents used in preparation of mouth dissolving formulations are enlisted in Table 1.4.

Natural	Synthetic
Sucrose- Mannitol	First generation- Saccharin
Fructose	Cyclamate
Dextrose- Sorbitol	Aspartame
Glucose	Second generation- Acesulfame-K
Isomaltose	Sucralose
Liquid glucose	Alitame and Neotame

Table1.4: Types of sweetening agents

- **Colouring agents**

When formulation ingredients or drug candidates are pre-sent in insoluble or suspension form pigments Various colouring agents used are FD & C colours, EU colours, natural colours and custom Pantone-matched colours. FD&C approved colours are used in the concentration not exceeding 1% w/w in the manufacturing of oral thin films, such as titanium oxide, silicon dioxide, zinc dioxide etc.

The design of efficient films as carriers for drug delivery requires a proper selection of the polymer and excipients used for their fabrication. These essential components affect the ability of the films to swell, disintegrate and modulate the release of the therapeutic molecule included in the formulation. Similarly, the type of polymer can influence the mechanical properties of the produced film, which should be elastic and resistant enough to be handled and applied at the target site without causing any discomfort.

1.3.2. Manufacturing methods for oral disintegrating film

Formulation of Oral Film involves the intricate application of aesthetic and performance characteristics. The manufacturing of orally dissolving films is done by various methods such as:

1. Solvent casting method
2. Hot melt extrusion method
3. Semisolid casting method
4. Rolling method
5. Solid dispersion extrusion

1. **Solvent casting method**

Solvent casting is the century old film making process. It is a generally applied technique for preparing orodispersible films**.** The method of solvent casting technique involves preparation of the film base which involves the mixing of suitable film forming excipients along with drug in a suitable solvent or solvent system. Once the solution is prepared, the film casting process is performed wherein a film of desired thickness is casted onto a moving inert substrate, where suitable rollers are employed for guiding the solution onto the substrate. Another way, it is then carefully casted on petri dish or plate made up of glass, Teflon or suitable material and dried. The final step concludes by drying the films and removes the trace of solvent to obtain the finished product. After the films are dried, the cutting, stripping and packaging is done[18].

The properties of the API play a critical role in the selection of a suitable solvent. The physicochemical properties of the API should be considered. These properties include compatibility of the API with other film-forming excipients, compatibility with solvents, the polymorphic nature of the API selected, and temperature sensitivity.

Manufacturing and packaging ODFs require special precaution to be taken to control the effect of moisture. Figure1.3 indicates critical factors involved in ODF manufacturing using the solvent-casting method. Stability of the film and its mechanical properties are significantly affected by the presence of moisture and temperature.

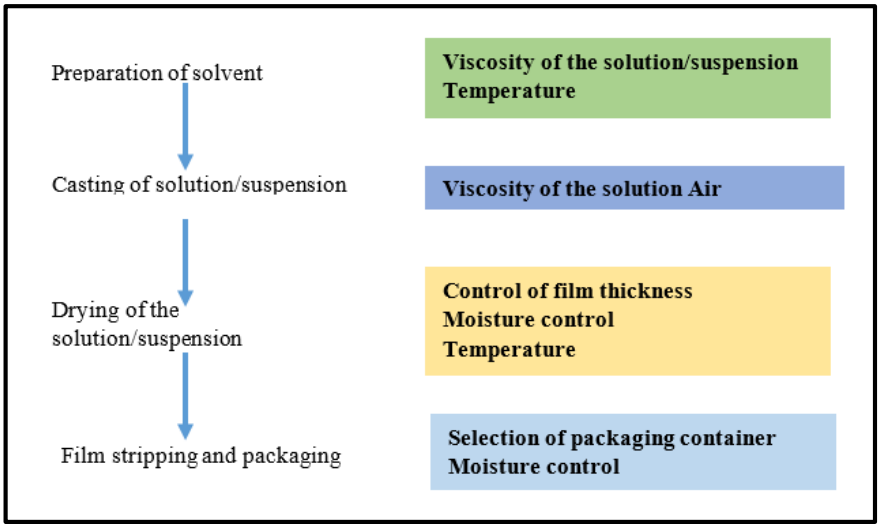


Figure 1.3: Crucial factors involved in manufacturing orodispersible films using the solvent-casting method

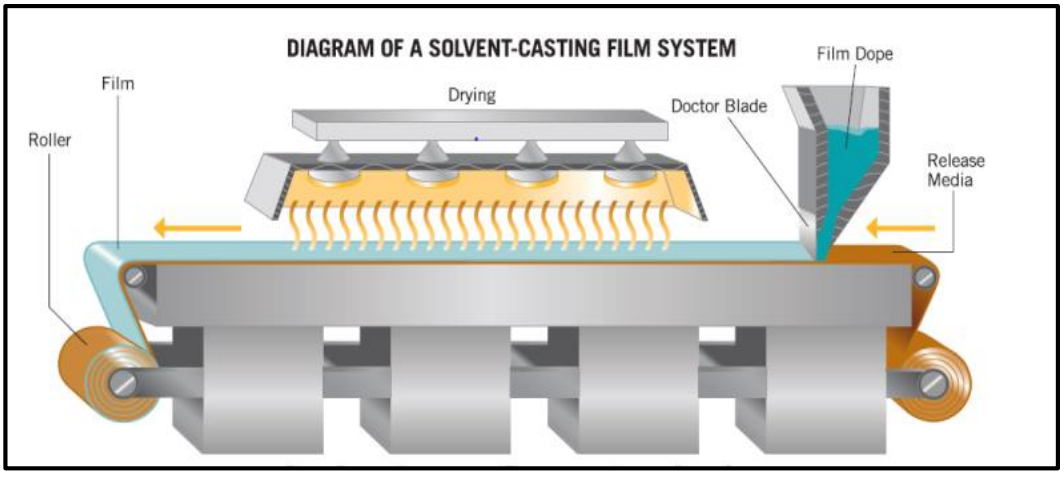


Figure 1.4: Solvent casting method

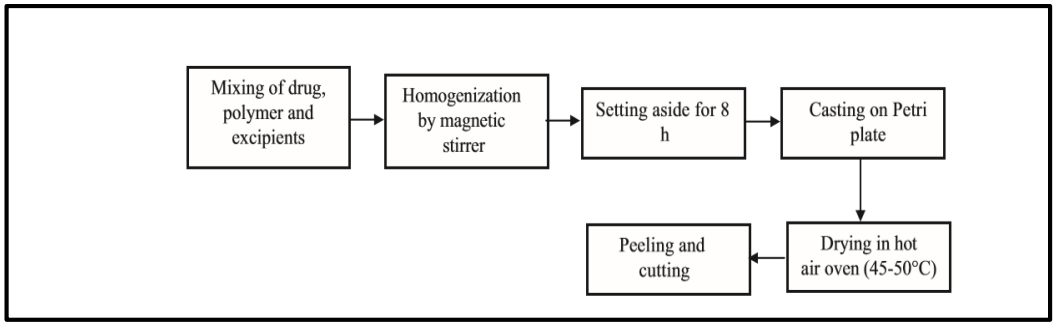


Figure 1.5: Flow chart of solvent casting method

Advantages

- Better uniformity in thickness and better clarity.
- Films possess fine gloss and free from defects.
- Films possess more plasticity and better physical properties.
- Solvent-casting is ideal for manufacturing films containing heat-sensitive API's because the temperatures required to remove the solvents are relatively low compared to those needed for a hot-melt extrusion process.

2. **Hot melt extrusion**

In hot-melt extrusion, the dry ingredients for the film are heated and homogenized by the action of an extruder screw until they are molten and mixed. In this melted material is forced through a flat extrusion die that presses extrudate into the desired film shape [31]. In pharmaceutical formulations twin screw extruder has proved to be beneficial due to homogenous and consistent mixing of multiple formulation ingredients leading to improved dissolution rate and bioavailability. This solvent free process, however processing of thermolabile substance is the major drawback of this process due to high temperature during extrusion [32].

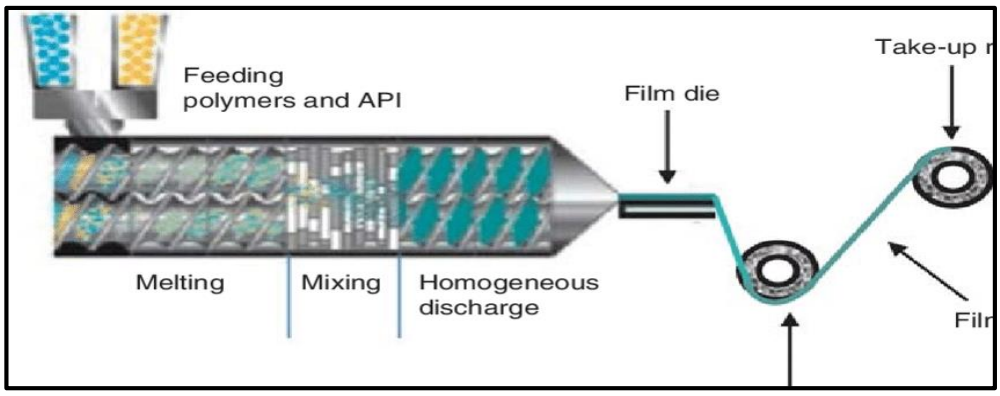


Figure 1.6: Schematic representation of hot melt extrusion technique

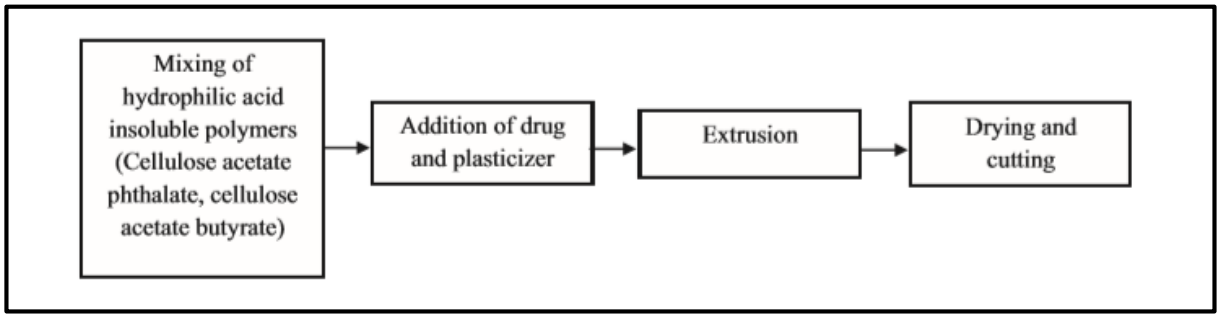


Figure 1.7: Flow chart of hot-melt extrusion method

3. Semisolid casting

In semisolid casting method firstly solution of water-soluble film forming polymer is prepared. The resulting solution is moved to a solution of acid insoluble polymer (e.g., cellulose acetate phthalate, cellulose acetate butyrate), which was prepared in ammonium or sodium hydroxide Then applicable amount of plasticizer is added so that a gel mass is obtained. Finally, the gel mass is casted in to the films or ribbons using heat-controlled drums. The thickness of the film is about 0.015-0.05 inches. The ratio of the acid insoluble polymer to film forming polymer should be 1:4[33].

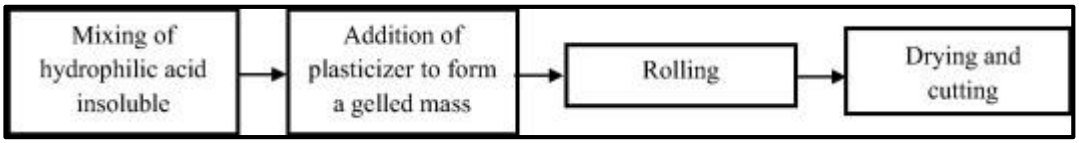


Figure 1.8: Flow chart of Semisolid casting method

4. Solid dispersion extrusion

The term solid dispersion refers to the dispersion of one or more APIs in an inert carrier in a solid state in the presence of amorphous hydrophilic polymers.

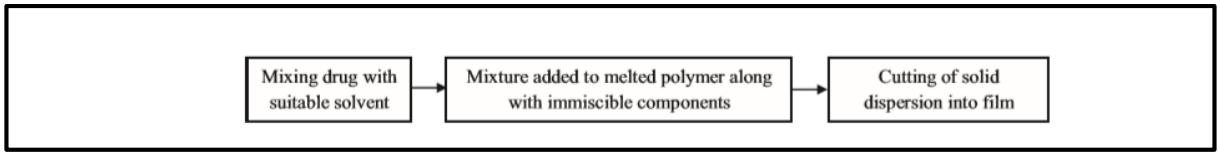


Figure 1.9:Flow chart of Solid dispersion extrusion

5. Rolling Method

In this technique suspension or a solution containing drug is rolled on a carrier. The solvent used essentially is water or a mixture of water and alcohol. The films are dried on the heated rollers and sliced into desired shapes and sizes. Other ingredients such as API, polymer, plasticizer and other required ingredients are dissolved in small quantities of aqueous solvent utilizing the high-shear processor.

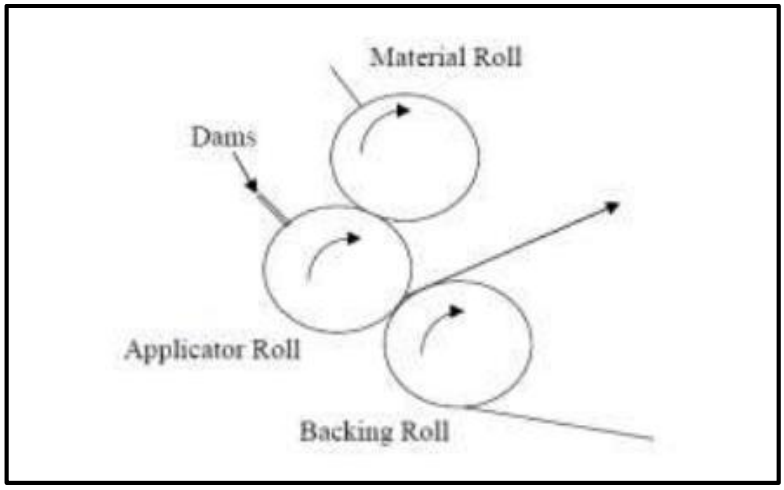


Figure 1.10: Rolling method

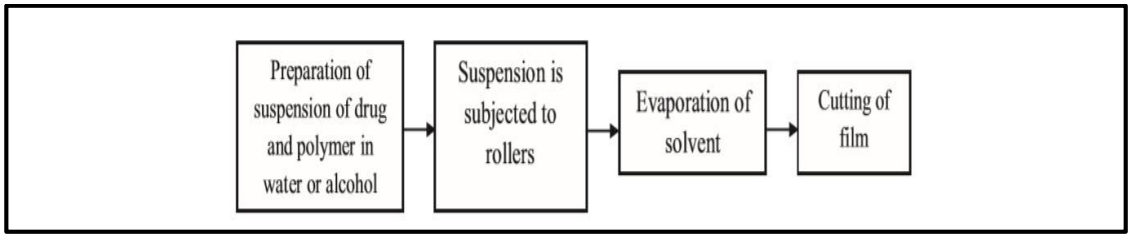


Figure 1.11: Flow chart of Rolling Method

The acceptability of ODFs was described by considering the features of the final product including thin, flexible, easy to administer, stable and physically appearance, composition, taste and mouthfeel[34]. ODFs are considered to be age-appropriate oral dosage forms mainly with respect to its disintegration in the oral cavity upon administration without water. For the convenience of the patients a short disintegration is favourable. Residual water and plasticizers will influence mechanical properties of ODFs [35]. Furthermore, ODFs offer the possibility to implement taste masking technologies in order to minimise the averseness of the taste of the Active Pharmaceutical Ingredient (API). Mouthfeel and texture are also considered key characteristics potentially affecting the acceptability of ODFs, particularly with regards to the presence of residual particles following disintegration.

In addition to the above-mentioned ODF characteristics, other features could potentially positively or negatively affect the patient acceptability of the dosage form, and should be explore. For instance, the handling, placement and disintegration of ODFs are key stages to identify the full product features with high potential impact on patient experience. For example, the “stickiness/adhesiveness” of the film potentially contributes to placement in the mouth and subsequently the overall mouthfeel of the

product. Krampe and colleagues have referred to the "gummy" nature of the films after wetting as potentially contributing to the mouthfeel of the dosage form[34]. Moreover, in the case of patients experiencing poor manual dexterity, poor hand sensitivity or reduced pinch strength, high ODF stickiness may result in the inability to properly handle the dosage form. These properties are largely related to the intrinsic properties of the carrier polymers, e.g., hygroscopicity and interfacial attributes.

The ODF formulation is designed to disintegrate fast once placed in the mouth. Wettability, disintegration, and dissolution time of the film may change depending on the saliva production rate of the user [36]. These parameters are considered to govern the performance of ODF drug products. Therefore, in the case of patients affected by severely impaired saliva production (dry mouth syndrome), ODFs may not be the dosage form of choice for drug administration [3].

1.4.Quality by design

Over the past year's pharmaceutical companies have been facing an increasingly difficulty in economic climate. An increase in the hurdles for the approval of new molecular entities, patent expiration and increasing health care cost have resulted in more focus in the cost associated with manufacturing and development of pharmaceuticals.

Traditional development focused on the formulation and delivery of the product to the next phase of clinical studies. Most of the formulation development tended to the interactive and empirically designed. Thus, changes were driven by need to modify the process during scale up or due to formulation failing to meet desire shelf life of product. Thus, manufacturing process were fixed and quality of product was measured by end product testing, commonly referred to as quality by testing. In this case quality is not build in the product and is achieved by end product testing. This approach is inefficient and does not facilitate continual improvement. In this system, product quality is ensured by raw material testing, drug substance manufacturing, a fixed drug product manufacturing process, in-process material testing, and end product testing. The quality of raw materials including drug substance and excipients is monitored by testing. If they meet the manufacturer's proposed and FDA approved specifications or other standards such as USP for drug substance or excipients, they can be used for the manufacturing of the products. Because of uncertainty as to whether the drug

substance specification alone is sufficient to ensure quality, the drug substance manufacturing process is also tightly controlled. Finished drug products are tested for quality by assessing whether they meet the manufacturer's proposed and FDA approved specifications. If not, they are discarded. Root causes for failure are usually not well understood.

In summary, product quality and performance are, in the traditional framework, achieved predominantly by restricting flexibility in the manufacturing process and by end product testing. The present regulatory review system places little or no emphasis on how the design of an effective and efficient manufacturing process can ensure product quality. As a result, the complexities of process scale-up, particularly for complex dosage forms are often not recognized. Finally, the burdensome regulatory requirement of supplements imposed on manufacturers for executing minor and incremental changes to manufacturing processes and controls inhibits continuous improvement and strategies for the implementation of continuous "real time" assurance of quality. Pharmaceutical quality, patient safety and efficacy are best controlled by a fundamental understanding of the formulation and manufacturing of pharmaceutical preparations.

QbD was first proposed by a well-known researcher Joseph Moses Juran. Later it has been accepted by ICH, US-FDA and other regulatory bodies. The principles of QbD are best explained by ICH Q8, ICH Q9 and ICH Q10, which gives the guidelines on Science and Risk-based assessment, product's life cycle and its approach, and the various method designs. US-FDA also highlights the key role of QbD in Process Analytical Technology (PAT) which is nothing but a Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance[37]. So, US FDA announced a new pharmaceutical regulatory concept, quality by design (QbD), which has challenged the pharmaceutical industry to design the quality of the final product instead of testing the product. The ICH guideline Q8 definition for QbD is "A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management [38]."

1.4.1. Enablers of quality by design

Two of the primary enablers of QbD are knowledge management and quality risk management. They play the critical role in development and implementation of QbD. They are instrumental in achieving product realisation and control and continual improvement.

1.4.2. Quality risk management

In the development of QRM enables resources to be focused on the critical areas that affect product and process. It is one of the tools for identifying, scientifically evaluating and controlling potential risk of quality. QRM helps to identifying material attributes and process parameters that have potential effect on CQA. It identifies and rank parameters /attributes that have potential impact on CQA and able to differentiate between true versus perceived risk, so high-risk area can be identify and mitigated them. The general outcome of QRM are acceptable risk, significant risk and unacceptable risk.

1.4.3. Knowledge Management

It is systematic approach to acquiring, analysing, storing and disseminating information related to product, process and component. It also emphasising on a transparency of information from development to commercial and vice versa. Prior knowledge avoids so many problems, issues and risk that may be addressed during manufacturing. So, good understanding of the documents relating to prior knowledge referenced in risk assessment and DoE.

1.4.4. Elements of quality by design

ICH Q8(R2) Pharmaceutical development Annex discusses the various element of QbD.

Identification of quality target product profile (QTPP)

The preferred tool for strategic drug development using the QbD approach is the establishment of a quality target product profile (QTPP. ICH Q8 defines QTPP as "A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product". The QTPP formed basis of design for the development of of the product and is developed with the end in mind. It describes the goals to development team and dynamic and nature that is QTPP is updated and revised at various stages of development as new information is obtained during the development process, QTPP is a subset of TPP it is more oriented towards the chemistry, manufacturing and control

(CMC) aspect development. These quality requirements are called quality attributes that measures the performance of each formulation. QTPP is a quantitative surrogate for the aspect of clinical safety and efficacy and QTPP can be used to design to optimise both the formulation and process. A typical QTTP include dissolution, potency, impurities, stability, release and other product specification requirement.

Identification of CQA

A CQA is defined by ICH Q8 (R2) is "a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality". CQA is generally associated with raw material (drug substances and excipients), intermediate (in process excipients) and drug product. To develop a final product with desired CQAs, the quality needs to be designed into the product based on an understanding of critical material attributes (CMAs) and critical process parameters (CPPs), concepts which have been developed by the QbD approach [39, 40].

A CMA is a physical, chemical, biological or microbiological property or characteristic of an input material that should be within an appropriate limit, range, or distribution to ensure the desired quality of output material. A CPP is defined as "A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored and controlled to ensure the process produces the desired quality" limit, range, or distribution to ensure the desired quality of output material. A CPP is defined as "A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored and controlled to ensure the process produces the desired quality" Therefore, the mix of the CQAs and CPPs allows the explanation of design space [41].

Quality risk assessment

The risk identification at the initial stage perceives risk and as further process/product understanding is gained. The actual risk is clear and control strategy can be better defined. The risk assessment used as earlier phases of development therefore tends to be more qualitative and serve as the means to priorities the experimentation. Typical tool includes risk ranking and filtering, input process-output diagram and Ishikawa diagram and so on. An Ishikawa diagram is also known as fishbone and cause affect diagram. It is a graphical tool used to display and explore opinion about sources of

variation in a process. The purpose of Ishikawa diagrams to map the key sources that contribute to the problem being examined and their interrelationship.

The manufacture of ODF products involves solvent casting of a liquid mixture containing film former, plasticizer, anti-adherent, sweetener, colour and flavour onto a substrate. A variety of film formers and other excipients are used in the formulation development of ODF[1]. Variability in formulation (e.g., plasticizer and film former concentration) and process variables (e.g., drying temperature, air flow rate) may result in product quality failures over the shelf life. For e.g., inadequate in-process controls during drying may lead to the formation of uneven film surfaces. Variation in plasticizer concentration may impact the ODF critical quality attributes (CQA) such as dry thickness, % elongation at break, yield stress, young's modulus, folding endurance, dissolution rate, moisture content, moisture uptake and stickiness. Suppose if we consider an ideal ODF to be flexible, easy to administer, easy to handle and physically stable [22]. These characteristics can be translated into a high tensile strength, high elongation at break and low Young's modulus[42]. Furthermore, a short disintegration time is favourable. A subsequent step of the QTTP is the identification of the critical process parameters (CPP). CPP include the process variables, e.g., concentration film forming agents and amount of plasticizer that influence the CQA. By combining the CQA and CPP a design space can be created. As long as the formulation and process variables remain within the design space, a product will be obtained that meets the quality requirements. The CQA in the present study were acceptable taste, assay, content uniformity short disintegration time and fast drug dissolution (QTPP). For every CQA software gives a unique matrix of probabilities that helps to determine the best crossed model. The varied CPP in this study were the percentage of film forming agent and percentage of the plasticizer. Each CPP was subjectively positioned as high-, medium-, or low-risk(s) level thinking about the likelihood of risk and severity of associated impact on the CQAs.

Risk Assessment

Risk assessment studies were executed to identify the critical material attributes (CMA) or CPPs having significant influence on CQAs of ODF. An Ishikawa fish-bone diagram (Figure 1.12) was portrayed to enlist the potential high-risk factors that affect quality of final formulation.

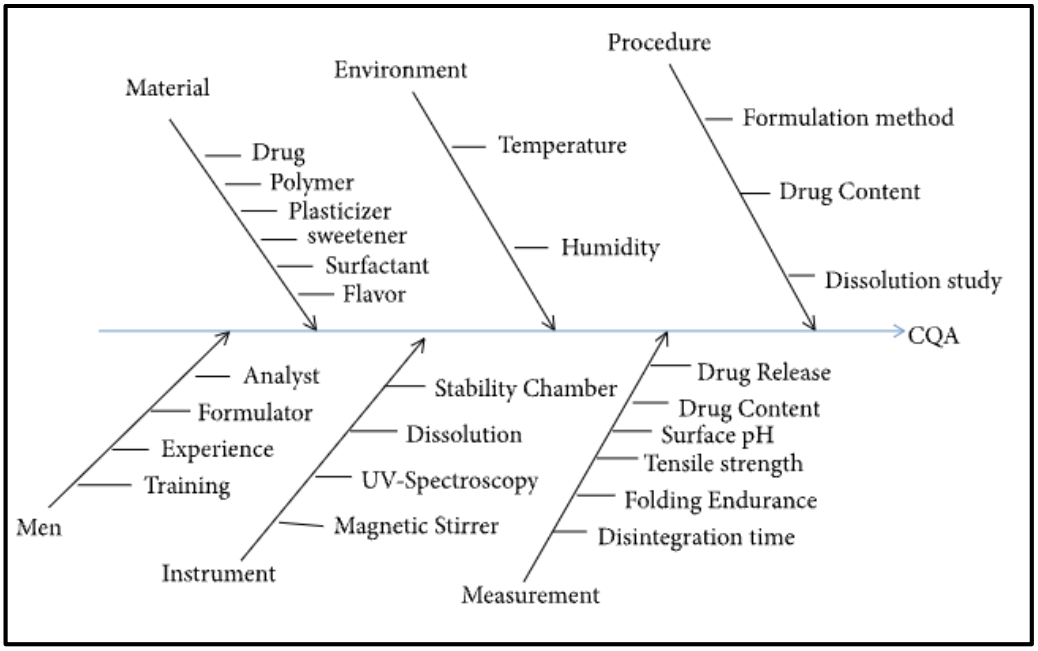
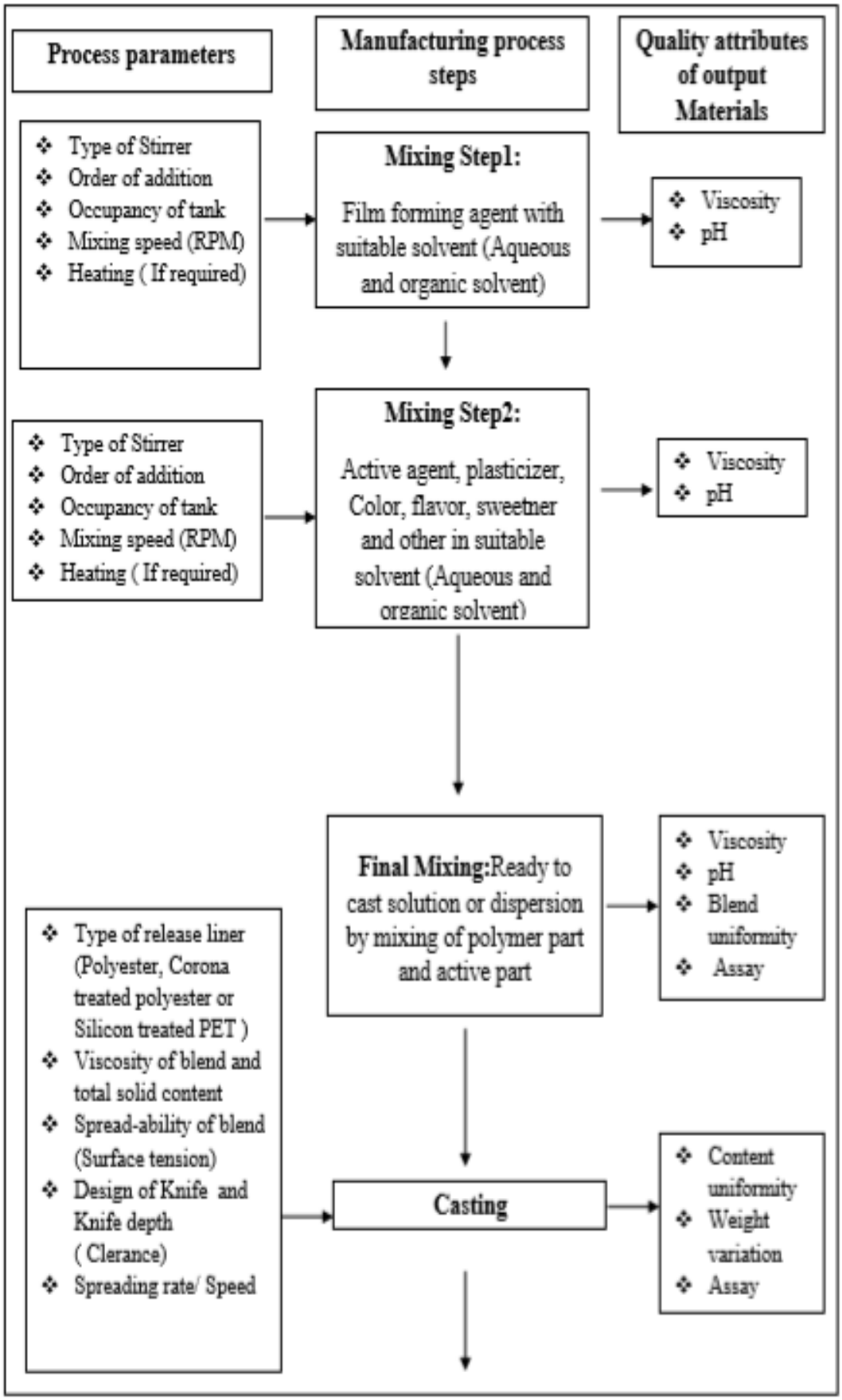


Figure 1.12: Ishikawa (fish-bone) diagram


Process parameters
Manufacturing process steps
Quality attributes of output Materials
Type of Stirrer
Order of addition
Occupancy of tank
Mixing speed (RPM)
Heating (If required)
Mixing Step1:
Film forming agent with suitable solvent (Aqueous and organic solvent)
Viscosity
pH
Type of Stirrer
Order of addition
Occupancy of tank
Mixing speed (RPM)
Heating (If required)
Mixing Step2:
Active agent, plasticizer, Color, flavor, sweetner and other in suitable solvent (Aqueous and organic solvent)
Viscosity
pH
Final Mixing:Ready to cast solution or dispersion by mixing of polymer part and active part
Viscosity
pH
Blend uniformity
Assay
Type of release liner (Polyester, Corona treated polyester or Silicon treated PET)
Viscosity of blend and total solid content
Spread-ability of blend (Surface tension)
Design of Knife and Knife depth (Clerance)
Spreading rate/ Speed
Casting
Content uniformity
Weight variation
Assay

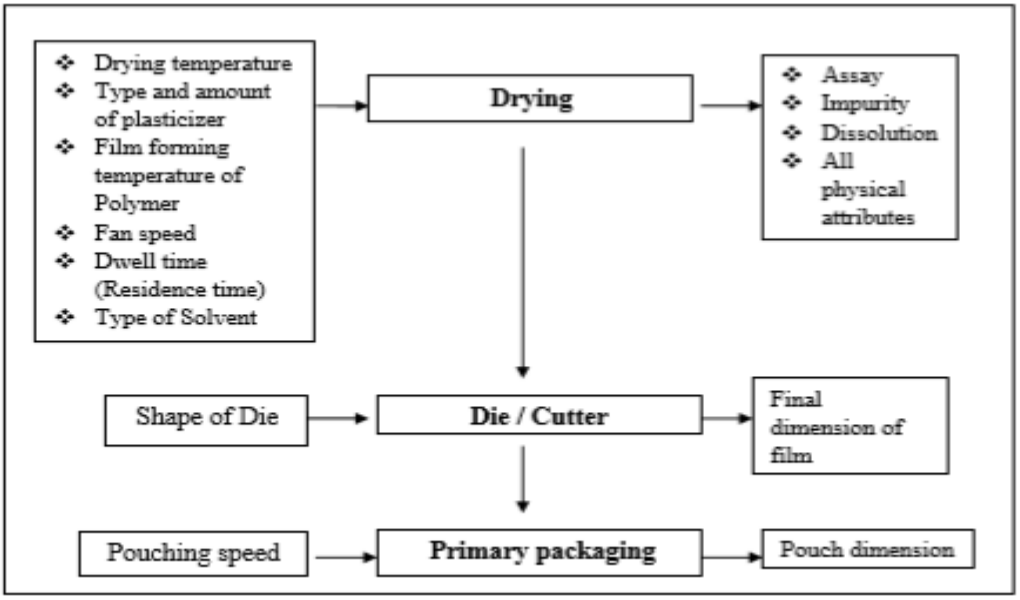


Figure 1.13: Effect of process parameters on quality attributes of film

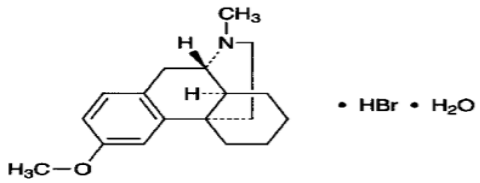
1.5. Introduction to drug

1.5.1. Dextromethorphan Hydrobromide

Common cold, cough and sore throat are minor disorders of respiratory system, usually arises due to infection in respiratory tract and autoimmune response. The number of patients suffering from cold, cough and sore throat usually increases during monsoon and winter season, owing to fluctuations in the environmental conditions. Children and women under 35 years are more prone to suffer from cold, cough and sore. Underdeveloped immune system increases the risk of exposure It is expected that children are three times more susceptible to cold and cough than an average adult. The aforementioned advantages of drug administration via the oral cavity offer new possibilities in the administration of drugs to "problematical" subpopulations like children and the elderly. These patients have special drug administration requirements as they are often unable to swallow solid dosage forms (e.g. tablets, capsules). Poor taste can also lead to medication being refused or spat out. Furthermore, the paediatric subpopulation is a very heterogeneous group. to cold related infection viruses in children mostly.

Dextromethorphan (3-methoxy-N-methylmorphinan) is one of the most commonly used antitussive drug (cough suppressant) in children. It is used to relive cough due to common cold, hay fever, upper respiratory tract infection, sinus, sore throat and

bronchitis. Dextromethorphan has an opioid like structure. However, being the d-isomer, it does not possess the analgesic/addictive properties of opioids. Dextromethorphan was approved as a non-prescription cough medication in 1958 by the FDA. In current scenarios, dextromethorphan can be found in more than 125 OTC cough and cold patented products. It is available as pills, gels, caps, lozenges, liquids and syrups but its availability as a solid dosage form is limited. Since liquid dosage forms are bulky and stability is a key issue, It is given either alone or in combination with analgesics (acetaminophen), expectorants (guaifenesin) and/or antihistamines (brompheniramine, chlorpheniramine and diphenhydramine). It's mainly active against the dry cough and is used in combination with expectorants to have significant effects for productive cough. Drug profile of DXM Hbr is depicted in Table 1.5.

Name of drug	Dextromethorphan Hydrobromide
Appearance	An almost white crystalline powder
Structure	
CAS number	125-69-9
Category	Cough suppressant
Molecular Weight	370.32g/mol
Chemical Formula	$C_{18}H_{25}NO \cdot HBr \cdot H_2O$
IUPAC Name	4-methoxy-17-methyl-17-azatetracyclo[7.5.3.01,10.02,7]heptadeca-2(7),3,5-triene;hydrate;hydrobromide
Solubility	Freely soluble in ethanol (95%) and in chloroform: sparingly soluble in water: Practically insoluble in ether.

Log P	3.6
Melting Point	°125 C
λ_{max}	278nm
Biological half life	The plasma half-life is normally about 11 hours, and antitussive activity can last for 5—6 hours.
Mechanism of action	After oral administration, dextromethorphan hydrobromide is rapidly absorbed from the GIT. The onset of action is between 15-30 minutes and the peak serum level is achieved within 2.5 hrs. Methyl analog of DEXTRORPHAN that shows high affinity binding to several regions of the brain, including the medullary cough center. This compound is an NMDA receptor antagonist (Receptors, N-Methyl-D-aspartate) and acts as a non-competitive channel blocker. Dextromethorphan hydro bromide is one of the widely used Antitussives, and is also used to study the involvement of glutamate receptors in neurotoxicity.
Dose	The oral dose of dextromethorphan in adults is 10- 20 mg every four hours, 30 mg every 6-8 hours, with a maximum of 120 mg in 24 hours. Children from 6-12 years are given 5 -15 mg every 4-8 hours to the maximum of 60 mg in 24 hours. Children from 2-6 years of age is given 2.5-5 mg every 4 hours, 7.5 mg every 6-8 hours to the maximum of 30 mg in 24 hours
Solubility	Freely soluble in ethanol (95%) and in chloroform: sparingly soluble in water: Practically insoluble in ether.
BCS Class	II

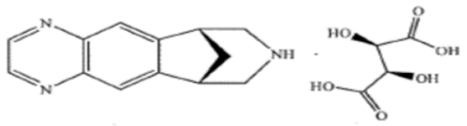
Absorption	Dextromethorphan is rapidly absorbed from the GI tract, with antitussive activity appearing within 15—30 minutes.
Volume of distribution	Approximately 5–6 L/kg.
Metabolism	Dextromethorphan is administered orally. It undergoes rapid and extensive hepatic metabolism to demethylated metabolites including the active metabolite, dextrorphan. Dextromethorphan is primarily metabolized by cytochrome P450 2D6 isoenzymes.
Route of elimination	Renal
Toxicity	CNS depression
Food interaction	Caution should be exercised when taking dextromethorphan with drinking grapefruit juice or eating grapefruits, especially white grapefruit juice, but also including other citrus fruits such as bergamot and lime, as well as a number of non-citrus fruits generally are recommended to be avoided while using DXM Hbr.

Table 1. 5: Drug profile of Dextromethorphan Hydrobromide

1.5.2. Varenicline as Varenicline tartrate

Smoking is the number one cause of preventable disease and death in the United States. A number of smoking cessation pharmacotherapies have led to rises in quitting and thus to important benefits to public health. There are now various FDA-approved medications that are effective in helping individuals quit smoking, including nicotine replacement therapy (NRT), bupropion sustained release treatment and varenicline. It was found in a large meta-analysis varenicline is to be the most effective monotherapy available and nicotine replacement, the most commonly used medication for smoking cessation. Varenicline is a novel and a potent and selective partial agonist for α4β2 nicotinic acetylcholine receptors, has been used for smoking cessation treatment. Both nicotine and varenicline bind to this receptor subtype. Varenicline blocks the ability

of nicotine to activate α4β2 receptors and this to stimulate the central nervous mesolimbic dopamine system, believed to be the neuronal mechanism underlying reinforcement and reward experience upon smoking. Varenicline is a partial agonist at α4β2 neuronal nicotinic acetylcholine receptors where it binds with high affinity and selectivity to produce an effect sufficient to alleviate symptoms of craving and withdrawal (agonist activity), while simultaneously resulting in blockade of the rewarding and reinforcing effects of smoking by preventing nicotine binding to α4β2 receptors (antagonist activity). Varenicline is a prescription medication used to treat smoking addiction. This medication is the first approved nicotinic receptor partial agonist. Its recommended oral dose is 0.5 and 1mg, available as film coated tablet. Literature depicted that varenicline showed significant benefit over NRT in measures of craving and withdrawal by decreasing the urge to smoke, negative effect and restlessness. VRC tartrate (Champix® and Chantix®: Pfizer) has been approved by USFDA as an aid of smoking cessation. The approved regime of VRC is 1mg for 12 weeks, starting with 1- week titration period. The drug profile is depicted in Table 1.6.

Name	Varenicline as Varenicline tartrate
Appearance	Varenicline tartrate is off-white to brown colour powder.
Structure	
CAS number	249296-44-4
Category	For use as an aid in smoking cessation.
Molecular Weight	361.65 g/mol
Chemical Formula	$C_{13}H_{13}N_3 \cdot C_4H_6O_6$
IUPAC Name	7,8,9,10-tetrahydro-6,10-methano-6H-pyrazino[2,3-h] (3) benzazepine, (2R,3R)-2,3-dihydroxybutanedioate (1:1)
Solubility	Freely soluble in water
Log P	0.9
pKa	9.23
Melting point (°C)	195.8 to 197.5°C

Identification	FTIR, UV, HPLC
BCS Class	I
Hygroscopic	Non-Hygroscopic
Indication	Smoking-Cessation Aid
Mechanism of action	Varenicline is a partial agonist at $\alpha_4\beta_2$ neuronal nicotinic acetylcholine receptors where it binds with high affinity and selectivity to produce an effect sufficient to alleviate symptoms of craving and withdrawal (agonist activity), while simultaneously resulting in blockade of the rewarding and reinforcing effects of smoking by preventing nicotine binding to $\alpha_4\beta_2$ receptors (antagonist activity).
Absorption	Maximum plasma concentrations of varenicline tartrate occur typically within 3-4 hours after oral administration
Protein binding	Less than 20%.
Volume of distribution	415 litres
Metabolism	Metabolism is limited (<10%). Most of the active compound is excreted by the kidneys (81%). A minor amount of varenicline is glucuronidated, oxidated, N-formylated, as well as conjugated to form a hexose.
Excretion	Varenicline undergoes minimal metabolism, with ed unchanged in the urine. Renal elimination of is primarily through glomerular filtration along with ular secretion possibly via the organic cation OCT2.

Table 1.6: Drug profile of Varenicline tartrate

1.6. Polymer profile

1.6.1. HPMC E 15

Hydroxypropyl methylcellulose (HPMC), also known as hypromellose, is widely implemented in pharmaceutical manufacturing as a binder, thickening agent, hydrophilic matrix material and film-forming material (Table 1.7). It is classified into several grades based on viscosity, degree of hydroxypropyl substitution and degree of methoxy substitution. The low viscosity HPMC grades (e.g., HPMC E3, HPMC E5 and HPMC E15) are often used for ODFs preparation and suitable for extrusion-based 3D printing of oral dosage forms. Moreover, the use of HPMC, which is a hydrophilic polymer, can further be advantageous in terms of enhancing the solubility and dissolution of poorly water-soluble drugs in the manufacture of solid dispersion[43, 44].

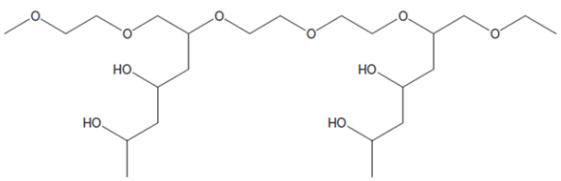
Formula	$C_{56}H_{108}O_{30}$
Molar mass	Variable
Solubility	Soluble in water
Physical state	Solid
pH	5-8
Viscosity	2 % in water, at 20°C, calculated: 12 - 18 cp
Odour	Odourless
Colour	White Powder

Table 1.7: Profile of HPMC

1.6.2. *Kollicoat*® IR

Kollicoat® IR is a poly (vinyl alcohol)-poly (ethylene glycol) graft copolymer (PVA-PEG). It was introduced to pharmaceutical research as an excipient and a film coating polymer by BASF Chemical Co. (Ludwigshafen, Germany) with the aim of producing an immediate release dosage form. The poly (vinyl alcohol)-poly (ethylene glycol) graft copolymer consists of ~ 75% PVA units and 25% PEG units, with PEG providing the backbone of the branched copolymer and PVA forming the branches. It also has 0.3% of colloidal silicon dioxide to improve its flow properties. It is used in instant release coating of tablets, pellets and particulate matter. It is also applicable as a binder

and in binding solutions for wet granulation. The polyvinyl alcohol moiety has good film-forming properties and the polyethylene glycol part acts as an internal plasticizer. The molecule is hydrophilic and thus readily soluble in water. As its structure is non-ionic, its solubility does not change when the pH increases or decreases along the gastrointestinal tract[45].*Kollicoat*® IR-based mucoadhesive films have considerable advantages compared to PVA, such as freely soluble in water, easy to formulate, very flexible due to integrated plasticizer, and high elongation at break[46]. *Kollicoat*® IR forms clear, colorless films that are flexible and that dissolve rapidly in water. *Kollicoat*® IR films are not tacky, unlike PVA and PEG films or their mixed polymer films. *Kollicoat*® IR films have a high pigment binding capacity and can be printed readily. In comparison with films of cellulose derivatives, films of *Kollicoat*® IR have a much higher elongation at break. *Kollicoat*® IR was developed for use as a hydrophilic film-forming polymer, it has an advantage that, as a non-ionic polymer, its solubility is pH-independent. Its surface activity and low viscosity when it is dissolved in water are advantageous to its use in fast dissolving dosage form. Polymer profile of *Kollicoat*® IR is depicted in Table 1.8.

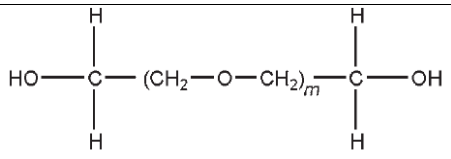
Structural formula:	
Molecular weight	approx. 45,000 AMU
Solubility	Solutions of *Kollicoat*® IR with concentrations of up to 40% can be prepared in water and aqueous systems, e.g. weak acids or alkalis. Solutions of up to 25% can be prepared in a 1:1 ethanol-water mixture. The polymer is insoluble in organic solvents.
Viscosity	The viscosity of a 20% solution is determined according to EN ISO 2555 at 23°C and a shear rate of 100 rpm.
Physical form	*Kollicoat*® IR is a white to faintly yellow, free-flowing, spray-dried powder.
Film formation	An aqueous solution is cast onto a smooth surface. When the water has evaporated, a clear, colourless, flexible film remains.

Chemical nature	The polymer consists of 75% polyvinyl alcohol units and 25% polyethylene glycol units. The product also contains approx. 0.3% colloidal silica to improve its flow properties.
Properties of aqueous solutions	
Viscosity	*Kollicoat*® IR dissolves rapidly in water. It is though the viscosity of aqueous solutions of *Kollicoat*® IR increases with the polymer concentration, however remains much lower than that of equivalent solutions of, for instance, cellulose derivatives.
Surface Tension	*Kollicoat*® IR reduces the surface tension of water. This makes aqueous solutions easy to spray, and the spray droplets exhibit good wetting behaviour on the tablet surface.
Film properties	*Kollicoat*® IR forms clear, colorless films that are enormously flexible and dissolve very rapidly in water. *Kollicoat*® IR films are not tacky, have a high pigment binding capacity and can easily be imprinted. *Kollicoat*® IR has a much higher elongation at break than cellulose derivatives.

Table 1.8: Profile of *Kollicoat*® IR

1.6.3. PEG-400 [47]

The USP32–NF27 describes polyethylene glycol as being an addition polymer of ethylene oxide and water. Polyethylene glycol grades 200–600 are liquids; grades 1000 and above are solids at ambient temperatures (Table 1.9). Liquid grades (PEG 200–600) occur as clear, colorless or slightly yellow-colored, viscous liquids. They have a slight but characteristic odour and a bitter, slightly burning taste. PEG 600 can occur as a solid at ambient temperatures.

Structural formula	
Formula	C2nH4n+2On+1, n=8.2to9.1
Chemical Name	**a**-Hydro-o-hydroxypoly(oxy-1,2-ethanediyl)
Molecular weight	380–420g/mol
Viscosity	90.0 cSt at 25 °C, 7.3 cSt at 99 °C

Freezing point (^{0}C)	4-8
pH (5% w/v solution)	4.0–7.0
Density	1.11–1.14 g/cm^3
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)

Table 1.9: Profile of PEG 400

1.6.4. Citric acid

Citric acid is a weak organic acid that has the chemical formula $C_6H_8O_7$. It occurs naturally in citrus fruits (Table 1.10). 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.

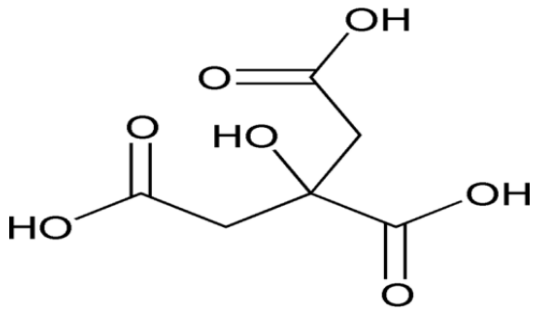
Formula	C6H8O7
Structural formula	
Molar mass:	192.124 g/mol
Melting point	153 °C
Density	1.66 g/cm³
Boiling point	310 °C
Solubility	Soluble 1 in 1.5 parts of ethanol (95%) and 1 in less than 1 part of water; sparingly soluble in ether

Table 1.10: Profile of citric acid

1.6.5. Aspartame

Aspartame is used as an intense sweetening agent in beverage products, food products, and table-top sweeteners, and in pharmaceutical preparations including tablets, powder mixes, and vitamin preparations (Table 1.11). It enhances flavor systems and

can be used to mask some unpleasant taste characteristics; the approximate sweetening power is 180–200 times that of sucrose. Unlike some other intense sweeteners, aspartame is metabolized in the body and consequently has some nutritive value. Aspartame is a methyl ester of the aspartic acid/phenylalanine dipeptide.

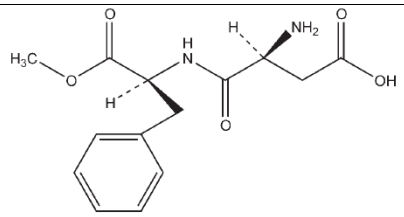
Structural Formula	
Empirical Formula	$C_{14}H_{18}N_2O_5$
Molecular Weight	294.30
Functional Category	Sweetening agent.
Description	Aspartame occurs as an off white, almost odourless crystalline powder with an intensely sweet taste.
Solubility	Slightly soluble in ethanol (95%); sparingly soluble in water. At 20^0C the solubility is 1% w/v at the isoelectric point (pH 5.2). Solubility increases at higher temperature and at more acidic pH, e.g., at pH 2 and 20^0C solubility is 10% w/v.

Table 1.11: Profile of aspartame

1.6.6. Stevia

The product is obtained by water extraction and concentration from the leaves *of Stevia rebaudiana Bertoni.* The active substance is a mixture of several steviol glycosides with the main glycosides stevioside and rebaudioside A. In the United States rebaudioside A-based natural sweeteners obtained a GRAS approval in 2008. Stevia is a white to light powder, having no less than 95% of the total of seven named steviol glycosides. The powder is freely soluble in water and insoluble in oils. The stability regarding pH and heat in food processing is good[48].

CHPTER 2. REVIEW OF LITERATURE

2.1 Review of literature on orodispersible film

Muhammad Irfan, et al., (2016) describes recent trends are shifting toward designing and developing innovative drug delivery systems for existing drugs. Out of those, drug delivery system being very eminent among paediatrics and geriatrics is orally disintegrating films (ODFs). These fast-disintegrating films have superiority over fast disintegrating tablets as the latter are associated with the risks of choking and friability. This drug delivery system has numerous advantages over conventional fast disintegrating tablets as they can be used for dysphasic and schizophrenic patients and are taken without water due to their ability to disintegrate within a few seconds releasing medication in mouth. Various approaches are employed for formulating ODFs and among which solvent casting and spraying methods are frequently used. Generally, hydrophilic polymers along with other excipients are used for preparing ODFs which allow films to disintegrate quickly releasing incorporated active pharmaceutical ingredient (API) within seconds. Orally disintegrating films have potential for business and market exploitation because of their myriad of benefits over orally disintegrating tablets [23].

KarkI S, et al., (2016) The thin films are considered to be convenient to swallow, self-administrable, and fast dissolving dosage form, all of which make it as a versatile platform for drug delivery. This delivery system has been used for both systemic and local action *via* several routes such as oral, buccal, sublingual, ocular, and transdermal routes. the aim of this review is to provide an overview of the critical factors affecting the formulation of thin films, including the physico-chemical properties of polymers and drugs, anatomical and physiological constraints, as well as the characterization methods and quality specifications to circumvent the difficulties associated with formulation design. It also highlights the recent trends and perspectives to develop thin film products by various companies [17].

Muhammad B. H. M, et al., (2016) described rapid disintegrating drug delivery system was developed as an alternative to capsules, tablets and syrups for geriatric and paediatric patients having problems in swallowing. To overcome the need, number of orally disintegrating tablets which disintegrate within one minute in mouth

without chewing or drinking water were commercialized. Then later, oral drug delivery technology had been improved from conventional dosage form to modified release dosage form and developed recently rapid disintegrating films rather than oral disintegrating tablets. Oral disintegrating film or strips containing water dissolving polymer retain the dosage form to be quickly hydrated by saliva, adhere to mucosa, and disintegrate within a few seconds, dissolve and releases medication for oromucosal absorption when placed in mouth. Oral film technology is the alternative route with first pass metabolism. This review give a comprehensive detail of materials used in ODF, manufacturing process, evaluation tests and marketed products [12].

Eman M et al., (2016) carried out the research with aim of improvement of water solubility, dissolution rate, oral bioavailability, and reduction of first pass metabolism of olanzapine (OL), Carboxylic acid dispersions at various molar ratios was carried out using rapid solvent evaporation. Dispersions with highest equilibrium solubility were formulated as fast dissolving oral films. Modelling and optimization of film formation were undertaken using artificial neural networks (ANNs). The results indicated co-amorphization of OL-ascorbic acid through H-bonding. The co-amorphous dispersions at 1:2 molar ratio showed more than 600-fold increase in solubility of OL. The model optimized fast dissolving film prepared from the dispersion was physically and chemically stable, demonstrated short disintegration time, fast dissolution and optimum tensile strength. In vivo data indicated high and maximum plasma concentration compared with the marketed references [49].

Rajni B, et al., (2014) prepared fast dissolving strip of Clobazam using solvent casting method. A full 3^2 factorial design was applied for optimization using different concentration of film forming polymer and disintegrating agent as independent variable and disintegration time, % cumulative drug release, and tensile strength as dependent variable. In addition, the prepared films were also evaluated for surface pH, folding endurance, and content uniformity. The results indicate that the film prepared using 100 mg of PVA and 6% of SSG showed the highest dissolution rate, suitable *in vitro* disintegration time, and satisfactory tensile strength. In vivo studies also indicated absence of significant difference between optimised formulation and marketed tablets and both exhibited comparable drug plasma level-time profiles [50].

Nusaiba K et al., (2016) studied orally disintegrating films containing nanoparticles loaded with acetaminophen. All films disintegrated in less than one minute, but acetaminophen was not free in the dissolution media even after six days. These results may indicate that although the nanoparticles released from the films immediately when impressed in solution the drug is sustained in the nanoparticles for longer time [14].

Alessandra A et al., (2018) carried out the work on hydroxypropyl methylcellulose (HPMC) fast-dissolving thin films for oral administration is investigated. Furosemide has been used as a model drug for *in vitro* release tests using three different set-ups: The Franz cell, the millifluidic flow-through device, and the paddle type dissolution apparatus (USP II). In order to enable drug incorporation within HPMC films, a multifunctional excipient, hydroxypropyl-β-cyclodextrin (HP-β-CD) has been included in the formulation, and it was compared with film without HP-β-CD The effect was studied on film swelling, erosion, and release properties. The research shows that furosemide release is faster for films including HP-β-CD due to larger erosion effects [51].

Mahesh A et al., (2010) prepared and studied the fast-disintegrating films of levocetirizine hydrochloride by solvent casting method. The films contained water-soluble polymers such as *Kollicoat*® IR or pullulan, aspartame and sucralose as sweeteners and pre-gelatinized starch as disintegrant. Levocetirizine hydrochloride was incorporated into these films by in-situ complex formation with hydroxy propyl beta-cyclodextrin. The optimized films were evaluated for weight variation, film thicknesfolding endurance, tackiness, tensile strength, assay, content uniformity, *in vitro* disintegration and dissolution, in vivo disintegration and taste masking ability by human gustatory sensation test. Results revealed that the organoleptic properties of levocetirizine dihydrochloride were improved by complexation with hydroxy propyl beta-cyclodextrin and the complex could be successfully formulated into a fast disintegrating film [52].

Yellanki S et al., (2011) studied mouth-dissolving film of phenobarbital for quick effect in treatment of epilepsy occurring in pediatric population. Suitable film former such as HPMC E15, Pectin, HPC, Xanthan gum and propylene glycol as solubilizer and plasticizer. The study reveals that use of plasticizers in combination could give

better results to films in respect to physicochemical parameters. Effect of superdisintegrants in formulation of mouth dissolving films at different concentrations has been investigated. Study shows that Sodium starch glycolate (SSC) as superdisintegrant in concentration range of 1% (w/v), showed good *in vitro* disintegration and dissolution time.In comparison with available marketed formulation, it has found that formulated films showed improved dissolution [53].

Takeuchi H et al., (2013) developed pharmaceutical thin films that disintegrate rapidly in the oral cavity. Films containing acetaminophen as a model drug were prepared by the solution/solvent casting method. HPMC and L-HPC used as film former and MCC and Pregelatinized starch as disintegrants. The study revealed that microcrystalline cellulose is a suitable disintegrant for the films. The mechanical strength of these polymeric films increased with increasing concentrations of acetaminophen incorporated into them, and the use of more than 30 % acetaminophen increased the disintegration time excessively. The addition of micronized L-HPC, as both a disintegrant and a film former, caused very rapid disintegration in water. Excess amounts of L-HPC increased the disintegration time and decreased the mechanical strength [54].

Maren P. et al., (2012) developed an orodispersible film (ODF) of Dimenhydrinate for the treatment of vomiting and nausea, especially for the pediatric population.Captisol®, HP-β-CD) and malt dextrin are used to improve the solubility of dimenhydrinate and could prevent the recrystallization of the drug substance in solid state of the film. An *in vitro* taste assessment done by electronic taste sensing systems Captisol formulation was rated as the best formulation with respect to taste evaluationby electronic taste sensing systems. Thus, it had the same advantages as the other cyclodextrin- and maltodextrin-based formulations, as the manufacturing resulted in homogenous ODFs showing no recrystallization of the drug compound. Regarding the maintenance of DMH in a non-crystallized state, maltodextrin Kleptose® Line caps was able to achieve the same effects in the ODFs as the cyclodextrins. Therefore, this maltodextrin with high amylose content offers an interesting alternative in ODF manufacturing with respect to pediatric formulations [55].

Mashru R. et al., (2005) prepared fast dissolving films for sublingual route containing salbutamol sulphate and polyvinyl alcohol as polymer. The films were evaluated for mechanical properties, *in vitro* release study and morphology study. A 33 factorial design was applied to study the effect of polyvinyl alcohol, glycerin and mannitol on % drug release and mechanical properties of the films. It was observed that polyvinyl alcohol had positive effect on tensile strength and mannitol had negative effect on tensile strength. Mannitol produced positive effect on drug release whereas polyvinyl alcohol produced negative effect on drug release [25].

Sayed s. et al., (2013) investigated fast dissolving sublingual films of Terbutaline sulfate using film polymers such as maltodextrin, Na alginate, carbapol 430, xanthan gum, HPMC E5, PVP K-25, and Na CMC. Propylene glycol and sorbitol were used as plasticizers and mannitol as filler. The result revales that Polymer type rather than total polymer concentration or plasticizer amount showed a significant effect on the tested film properties In vivo study is carried out for prepare film and conventional oral tablet by applying randomized, single dose, crossover study in four healthy volunteers pharmacokinetic profile of terbutaline sulfate from the film formula of choice gave a significantly faster drug absorption rate and recorded a relative bioavailability of 204.08% [56].

2.2 Review of literature on Drug

2.2.1 Dextromethorphan Hydrobromide

Sayed H.A. et al., (2014) prepared fast dissolving films containing dextromethorphan hydrobromide (DM) for oral use. Hydroxylpropyl methylcellulose E15 (HPMC) was used as the film forming polymer and cross povidone (CPV), microcrystalline cellulose (MCC) were used as super disintegrants. Films were prepared by solvent casting method. The prepared film evaluated for various physicochemical properties such as tensile strength, percentage of elongation, taste palatability, surface pH, weight and their content uniformity. Prepared ODF are elegant, transparent, flexible, smooth, homogeneous and palatable films. The research work shows that formulation excipients had a pronounced impact on the film physicochemical properties as well as the drug dissolution rate. the presence of saccharin and menthol may increase patient's palatability toward the formulated DM-loaded oral films[57].

Kunwarpuriya A. et al., (**2015)** investigated fast dissolving films of the antitussive drug Dextromethorphan hydrobromide, to enhance the convenience and compliance by the elderly and pediatric patients. The films were prepared using hydroxypropyl methylcellulose E5 polymer by solvent casting method. Glycerine as plasticizer, sucralose as sweetener and crosspovidone and sodium starch glycolate as super disintegrants were also included. In-vitro disintegration time was found to be less than 30 seconds and in-vitro drug release studies indicated 97% release within 5 minutes [58].

Nining et al., (2021) studied the effect of Citrus maxima pectin as superdisintegrant in orodispersible film formulation. due to its hydrophilicity, its high methyl content, and its great affinity for water. It allows the acceleration of the disintegration time of the orodispersible film. Orodispersible film of dextromethorphan hydrobromide was formulated in 5 formulas with varying concentrations. Films were evaluated for various parameters. The result revealed that orodispersible film of DXM Hbr Hbr showed disintegration time of 48.5-59 seconds, a tensile strength of 20.59 - 32.45 kg/cm2, and elongation of 38.8 - 44%. The results also showed that the increasing concentration of Citrus maxima pectin will accelerate the disintegration time, increase the elongation, and decrease the tensile strength [59].

Patel D.M. et al (2016) prepared fast dissolving film of cetirizine and dextromethorphan by solvent casting method using HPMC E5 LV, polyethylene glycol 400, aspartame- neotam-tartaric acid- citric acid- menthol- ion exchange resins for taste masking of dosage form. The optimised batch showed that fast dissolving films contain more than 95% of drugs as per percent drug content study, mouth dissolving time 17 seconds with more than 96% of drugs release occurs within 30 min. The bitter taste of the film was masked with Neotame and an ion exchange resin [60].

2.2.2 Varenicline as Varenicline tartrate

Chloe J et al., (2018) covered the formulation of varenicline as a partial agonist at α4β2 receptors, the primary neural substrate for nicotine reward. Then, they discuss evidence from preclinical studies indicating varenicline's efficacy in blocking nicotine reward, followed by clinical trials demonstrating safety and efficacy in sustaining abstinence in smokers. Finally, they cover post-market surveillance,

including contraindications in heavy machine operators, putative cardiovascular risk, and the repealed warning for adverse neuropsychiatric events[61].

Kwak S. et al., (2018) developed an immediate release-type tablets containing VRC-S a smoking cessation agent, were prepared by the wet granulation method. Formulation and stability studies were performed. The *in vitro* dissolution and in vivo pharmacokinetic (PK) behaviour of the tablets were compared with those of the commercial product (Champix) as a reference. The optimised batch was stable for 6 months under accelerated conditions. The dissolution of VRC was pH independent, revealing f2 values of 76.49 and 68.38 at pH 1.2 and pH 6.8, respectively. After the oral administration of optimised batch tablet and Champix to healthy human volunteers, pharmacokinetic parameters, including time to reach the maximum plasma concentration (Tmax), maximum plasma concentration (Cmax), and area under the curve from 0 to infinity (AUCinf), were compared. The values of 90% CI were 0.972–1.035 for Cmax and 0.982–1.075 for AUCinf, which was indicative of the bioequivalence of both products. Therefore, research concluded that VRC-S–containing immediate release tablet might be a promising candidate to replace the currently used commercial product for the treatment of smoking cessation [62].

Kenneth C et al., (2008) studied degradation of the amine-based smoking cessation drug varenicline tartrate in an early development phase osmotic, controlled-release (CR) formulation yields predominantly two products: N-methylvarenicline (NMV) and N-formylvarenicline (NFV). NMV is produced by reaction of the amine moiety with both formaldehyde and formic acid in an Eschweiler-Clarke reaction, while NFV is formed by reaction of formic acid alone with varenicline. The osmotic tablet formulated using Mannitol, varenicline as the tartrate salt, dibasic calcium phosphate and magnesium stearate. Tablets were coated with a pan-coater using 10% solids solutions with one of four coatings with varying ratios of CA, PEG, and butylated hydroxyl toluene (BHT). It was observed that PEG undergoes oxidative degradation to generate two reactive, low molecular weight products: formaldehyde and formic acid. Both these products can migrate from a coating to a tablet core upon extended storage conditions. It was concluded that, the drug can be made stable by keeping the ratio of PEG to CA low enough so that the PEG stays phase compatible with the CA.

Also, antioxidants in the coating and oxygen scavengers in the packaging also serve to prevent the PEG degradation, and consequently provide for drug stability[63] .

2.3. Review of literature on Polymers

Chauan I et al (2019) formulated and evaluated the Zolmitriptan loaded fast disintegrating oral film by solvent casting method. Hydroxy propyl methyl cellulose (HPMC E-15), polyvinyl pyrrolidone K-30 (PVP K-30), hydroxy propyl cellulose (HPC), Lycoat RS 720 was chosen for film formation in different proportions. Glycerol was used as plasticizer to induce plasticity and flexibility in films. Other excipients like citric acid as a saliva stimulating agent, aspartame as a sweetener, amaranth as coloring agent, cherry strawberry as flavouring agent was also used for the formulation of film. A 2^2factorial design was applied to selectedthe optimized formulation. Among the various formulations, prepared with HPMC E 15 + Lycoat RS 720)was chosen as optimized formulation as it showed 27.63 s of disintegration time. Satisfactory physico-mechanical characteristics like 1.215 N/mm^2 of tensile strength and 13 % elongation with other convincing evaluation parameters were also observed for optimized formula. In vivo studies also indicated that the pharmacokinetic parameters of optimized film significantly differ ($P< 0.05$) from drug sol (reference) exhibiting non-comparable drug plasma level-time profiles. Eventually, it can be concluded that fast disintegrating oral film approach is suitable for the delivery of Zolmitriptan. This formulation not only enhances the bioavailability of drug, but also produces quick action for the migraine patients [64].

Vipul K et al (2016) prepared mouth dissolving films of Granisetron hydrochloride (GH) using film forming polymers like PVP-K30, pullulan, maltodextrin and lycoat 720 and plasticizer like propylene glycol, poly ethylene glycol 400 and glycerin were used for selection of suitable polymer plasticizer combination MDF prepared using lycoat RS 720 and PEG-400 by solvent casing method showed acceptable mechanical characteristic and faster dissolution. Prepared MDF was clear, transparent, light green colour, non-sticky with a smooth surface without any interaction between drug and excipients. The high % drug release of the film in simulated saliva less in-vivo dissolving time in human volunteer. indicates that it can be used for drug delivery system of granisetron hydrochloride having first pass metabolism [65].

Alayoubi A et al., (2017) studied four different films of epinephrine using lycoat RS720 have been prepared by solvent casting technique The polymer percentages were (20%, 25%, 27% and 30%) of the total formulation weighs. The result of this study shows that, the formulation with the highest concentration of the polymer Lycoat (30%) formed smooth and clear film. The optimized formulation showed good mechanical properties attaining high level of flexibility, thickness uniformity and rapid disintegration (20 s) and dissolution time (90% within 7.2 min). They also carried out human volunteer's study for disintegration test and taste masking of epinephrine. From the study, it was concluded that epinephrine was successfully incorporated into fast dissolving film strip for potential use in paediatrics [66].

Li X et al., (2014) prepared sildenafil citrate (SC)-loaded polyvinyl alcohol (PVA)-polyethylene glycol (PEG) graft copolymer (*Kollicoat*®1 IR)-based orally dissolving films (ODFs) using a solvent casting method. The SC-loaded ODF with a loading capacity up to 6.25 mg in an area of 6 cm^2 was prepared and evaluated in terms of mechanical properties, disintegration time and dissolution rate. Different plasticizers and disintegrants were optimized on the basis of characteristics of blank ODFs. The blank ODF composed of *Kollicoat*® IR, glycerol and sodium alginate (ALG-Na) (10:1.5:2, w/w) had are markably short disintegration time of about 20s. The SC-loaded ODF showed a longer disintegration time (about25s), but exhibited improved mechanical properties when compared to the blank ODF. SC was homogenously dispersed throughout the ODF and the crystalline form of drug had been changed, existing strong hydrogen bonding between the drug and carriers. The*Kollicoat*®1IR/ALG Na based ODFs containing SC might be an alternative to conventional tablet for the treatment of male erectile dysfunction [67].

Visser J et al., (2014) Prepared extemporaneously ODFs containing casting solution of water-soluble APIs (enalapril maleate and prednisolone disodium phosphate) and a poorly water-soluble API (diazepam) for which ethanol 96% was used as co-solvent. Different combinations of film forming agents and other excipients and different casting heights were tested for their suitability for production of ODFs. Result shows that, the best suitable casting solution contained hypromellose, carbomer, glycerol, disodium EDTA and trometamol. The water-soluble APIs as well as ethanol

influenced the viscosity of the casting solution, mechanical properties and disintegration time of the ODFs [68].

2.4. Review of literature for application of Quality by design

Mazumder Set al., (2017) investigated the impact of formulation and process variables on the quality of oral disintegrating films (ODF) using Quality by Design (QbD) approach. Lamotrigine (LMT) was used as a model drug. Formulation variable was plasticizer to film former ratio and process variables were drying temperature, air flow rate in the drying chamber, drying time and wet coat thickness of the film. A Definitive Screening Design of Experiments (DoE) was used to identify and classify the critical formulation and process variables impacting critical quality attributes (CQA). Laboratory-scale DoE formulations were prepared and evaluated for mechanical properties (%elongation at break, yield stress, Young's modulus, folding endurance) and other CQA (dry thickness, disintegration time, dissolution rate, moisture content, moisture uptake, drug assay and drug content uniformity). The main factors affecting mechanical properties were plasticizer to film former ratio and drying temperature. Dissolution rate was found to be sensitive to air flow rate during drying and plasticizer to film former ratio. Data were analyzed for elucidating interactions between different variables, rank ordering the critical materials attributes (CMA) and critical process parameters (CPP), and for providing a predictive model for the process. Results suggested that plasticizer to film former ratio and process controls on drying are critical to manufacture LMT ODF with the desired CQA [69].

Branca M. A. Silva et al., (2017) This work exemplifies the application of QbD principles using retrospective data (rQbD) and illustrates its added value for increasing knowledge of investigational medicinal products being developed (e. g. tablets and capsules) and particularly ODFs. it is investigated the root-cause for the observed slower drug release in Orodispersible Films (ODFs) during storage. Risk assessment tools were used to identify parameters affecting ODFs critical quality attributes, namely percent drug release and residual water content. The parameters room temperature, room relative humidity, drying temperature and mixing equipment were used in the statistical modelling of the available data. The estimated models were then used to define the feasible working region. Statistical modelling indicates that initial residual water content of the ODFs is mainly affected by 2nd order interactions of

room temperature, room relative humidity and drying temperature, while the stability of drug release profile is mostly influenced by room temperature and an interaction between room relative humidity and drying temperature. Depending on the drying temperature employed the effect of room temperature and room relative humidity change significantly [70].

Visser J et al., (2015) extemporaneously prepared orodispersible films (ODFs) using film forming agents, hypromellose and carbomer 974P and the plasticizer glycerol. Trometamol and disodium EDTA were added to stabilize the solution. To optimize this formulation a quality target product profile was established in which critical quality attributes (CQAs) such as mechanical properties and disintegration time were defined and quantified. As critical process parameters (CPP) that were evaluated for their effect on the CQAs the percentage of hypromellose and the percentage of glycerol as well as the drying time were chosen. Response surface methodology (RMS) was used to evaluate the effect of the CPPs on the CQAs of the final product. The result shows that main factor affecting tensile strength and Young's modulus was the percentage of glycerol, elongation at break was mainly influenced by the drying temperature. Disintegration time was found to be sensitive to the percentage of hypromellose. From the results a design space, it can be concluded that an optimal formulation for plain ODF to which active pharmaceutical ingredients can be added have a slightly higher percentage of HMPC (9.81–9.84% vs 9.00%) and a reduced percentage of glycerol (12.27–12.35% vs. 22.1%) as compared to the initial formulation [71].

Dangre P. et al., (2019) fabricated of fast dissolving buccal film of clonidine hydrochloride by employing quality by design (QbD) based approach. The patient oriented quality target product profiles were earmarked and on that basis critical quality attributes were identified. Preliminary screening studies along with initial risk assessment eased the selection of film-forming polymer (HPMC E 15) and plasticizer (PEG 400) as CMAs for formulation of films. A 3^2 full factorial plan was utilized for assurance of impact, i.e., HPMC E15 (X1) and PEG 400 (X2), as independent variables (factors) on thickness (mm) (Y1), disintegration time (s) (Y2), folding endurance (Y3), and tensile strength (kg) (Y4). The optimized FDBF showed excellent features, like more than 90% drug dissolution within 8 min. and uniform

distribution of drug over the film formulation. It was concluded that, the accelerated stability test confirmed robustness of optimized CLH FDBF. Therefore, FDBF for CLH could be sorted as promising alternative for its administration with better patient compliance [72].

Lawrence X. Yu et al., (2008) discussed the pharmaceutical Quality by Design (QbD) and describe how it can be used to ensure pharmaceutical quality. The QbD was described and some of its elements identified. Process parameters and quality attributes were identified for each unit operation during manufacture of solid oral dosage forms. The use of QbD was contrasted with the evaluation of product quality by testing alone. The result of study indicates that QbD is a systemic approach to pharmaceutical development. It means designing and developing formulations and manufacturing processes to ensure predefined product quality. Using QbD, pharmaceutical quality is assured by understanding and controlling formulation and manufacturing variables. Product testing confirms the product quality. Implementation of QbD will enable transformation of the chemistry, manufacturing, and controls (CMC) review of abbreviated new drug applications (ANDAs) into a science-based pharmaceutical quality assessment [73].

2.5. Review of literature on Transdermal patch

Jagtap et al., (2018) prepared transdermal patch of Selegiline HCl and Nicotine to sustain the release and improve bioavailability of drug. Different formulations were prepared by varying the grades of Ethyl Cellulose and concentration of PVP by solvent casting method. A 32 full factorial design was applied to check the effect of varying the grades of Ethyl Cellulose ($X1$) and PVP concentration ($X2$) on the responses, that is, tensile strength, percentage drug released and diffusion coefficient as a dependent. The prepared formulations were evaluated for various parameters like thickness, tensile strength, folding endurance, % elongation, % moisture content, % moisture uptake, % drug content, *in vitro* drug release, *in vitro* permeation, and drug excipient compatibility. The optimised batch, which contained Ethyl Cellulose and PVP (1:1), showed satisfactory release, and was more similar to the theoretical predicted dissolution profile [74].

Mahajan et al., (2018) prepared the transdermal patch of piroxicam by using sustained release hydrophilic and lipophilic polymers containing permeation enhancer. The transdermal patches of piroxicam were prepared using the combination of polymers, hydroxypropyl methylcellulose E15, polyvinylpyrrolidone (PVP) K30, and ethyl cellulose in different concentration with sodium lauryl sulphate as the permeation enhancer and polyethylene glycol 400 as the plasticizer was used for the formulation of transdermal drug delivery system which demonstrated sustained release of the drug through the patches. The result demonstrated that optimised batch containing hydrophilic and lipophilic polymers (3:1 ratio) showed the maximum release and permeation of drug for a longer time period up to 12 hours which made it suitable for the development of sustained release patches of piroxicam [75].

José Juan Escobar Chávez et al, prepared and characterize both physically and biopharmaceutically, a nortriptyline hydrochloride (NTP-HCl) patch formulated in chitosan. Crystallization was not observed in the patches after storage and NTP-HCl was homogeneously distributed throughout the chitosan matrix. The addition of chemical enhancers to the patches increased the skin permeation of NTP-HCl. The addition of chemical enhancers to the patches increased the skin permeation of NTP-HCl. Characterization of chitosan patches was carried out for, *in vitro* skin permeation studies by passive diffusion and iontophoresis and rheological and bioadhesion studies. The study revealed that transdermal patch with chitosan, PF-127 and 1- provided a reasonable flux of NTP-HCl across the skin. Iontophoresis applied to the patches did not increase the penetration of NTP-HCl across the skin [76].

Lewis S. et al., prepared two types of nicotine transdermal patch, monolayer and bilayered. The monolayered patch bore a rate- controlling membrane, whereas the bilayered, served as matrix type. The solvent-casting technique was used to formulate the sodium alginate patch, containing nicotine. Ethyl cellulose film was used as the rate controlling membrane. *In vitro* release studies of transdermal patches showed a biphasic release pattern, with diffusion as the dominating mechanism of drug release for the matrix type, while the membrane-controlled released nicotine, gradually over the 24 h study. The study shows that, recommended initial dosage of transdermal nicotine to assist in cessation of smoking, is upto 22 mg/24 h. Studies have reported

that craving for nicotine, however, responded better to higher transdermal nicotine doses [77].

Summary of literature review

Research work carried out by different researchers in the area of orodispersible film was quite impressive and definitely has become the source of information for selection of excipients and conditions for formulation and development of the ODF. Methods and experimental designs were also found useful for undertaking present research work. Finally, it can be said that orodispersible films are exciting approaches to novel drug delivery systems or increasing the patient compliance. In that sense orodispersible films are a relatively new and very promising drug delivery system. Their versatility offers future potential for expanded applications across different delivery routes in multiple pharmaceutical, biopharmaceutical, and medical markets.

2.6 Patent Summary

Patent summary report is summarized in Table 2.1.

Sr. No	Patent Number	Title	Ref.
1	US 14/238,381	Orodispersible films for the manufacturing of individualised medicine or for large scale production	[78]
2	EP 01959912A	Fast dissolving orally consumable films containing an ion exchange resin as a taste masking agent	[79]
3	US 7648712	Fast dissolving orally consumable films containing a taste masking agent	[80]
4	US20130039932	Quickly soluble oral film dosage containing steviosides as a unpleasant taste masking agent	[81]
5	US 10/423398	Fast dissolving orally consumable films containing a sweetener	[82]
6	US 10092651	High-content fast dissolving film with masking of bitter taste comprising sildenafil as active ingredient	[83]

7	US8314235B2	Process for preparing varenicline, varenicline intermediates, pharmaceutically acceptable salts thereof	[84]
8	US 13/581491	Highly pure varenicline or a pharmaceutically acceptable salt thereof substantially free of methylvarenicline impurity	[85]

Table 2.1: Patent Summary

CHAPTER 3. RATIONAL AND HYPOTHESIS

3.1 Rational

3.1.1 Rational for Selection of Drug Delivery System

A thin film that readily dissolves in the oral cavity is commonly referred as orodispersible film by the European Medicines Agency (EMA) or simply soluble film by the FDA (Food and Drug Administration, 2013). Orodispersible films are ultra-thin film [50-150 μm] having size of postage stamp, which dissolves within a few seconds in the oral cavity after being in contact with the saliva leading to fast absorption and instant bioavailability of the drugs. Good acceptance from the users and an increasing demand of over-the-counter oral film products has led to the development of prescription drugs into oral thin films Given the specific advantages offered by these films and their ability to overcome the current unmet needs, the future holds significant potential. 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. The building success and popularity of ODF's recently in the global market makes it indispensable due to its consumer preference. The ODF technology is just in the beginning stage and has a bright future because of both patient compliance and pharmaceutical acceptability.

Orodispersible films have predominance over major drawbacks of rapid disintegrating tablets related to fear of choking, friability. These orodispersible films are specialised in a way that the water is not required for administration because they quickly fragment within a few seconds, discharging the drug in mouth. Orodispersible films, at the point when set on tongue, immediately hydrates by soaking in saliva following disintegration and/or dissolution discharging active pharmaceutical agents from the dosage form. No high-cost lyophilisation, high mechanical strength, rapid disintegration, and decreased choking risks are the quality attributes/or hallmarks of ODFs. The rationale of possessing distinctive properties and quick disintegration time ranging from seconds to at least one minute have earned exceptional significance in pharmaceutical trade business and patient compliance. Moreover, a unit dose of strip can be carried independently without requiring the secondary holder. Most of the antitussive agents are available in liquid dosage form. It is vital to address the poor

stability or instability of liquid dosage forms, particularly the aqueous formulations where attention towards the precise measurement of the amount of medicament and shaking the bottle every time before administration may accord to less acceptance by the patients. ODF provides a bigger surface area and better platform for quick disintegration and dissolution thereby releasing the drug in the oral cavity.

Advantages of ODF's

- More patient compliance.
- No first-pass effect.
- Enhance bioavailability with rapid onset of action.
- No risk of choking.
- Immediate Release dosage form: provides greater absorption at faster rate to achieve high maximum arterial levels required for relief.

3.1.2 Rational for selection of drug

- **Rational of formulation and development of orodispersible film of antitussive agent**

- Dextromethorphan hydrobromide (DXM Hbr) is a non-opioid antitussive agent, used to temporarily relieve cough due to the common cold, hay fever, upper respiratory tract infections, sinus inflammation, sore throat, or bronchitis. DXM Hbr affects the signals in the brain that trigger cough reflex.
- DXM Hbr oral recommended dose is 10 to 30 mg.
- Its molecular weight is 370 g/mol.
- Absolute bioavailability of DXM Hbr is about 11% due to hepatic first pass effect.
- DXM Hbr is commercially available in the market in many dosage forms as conventional tablets, capsules, chewable tablets, extended-release tablets in combination with guaifenesin and syrups but its availability as ODFs is limited.

- Liquid dosage forms provide rapid drug release and consequently rapid absorption and rapid action but they have bulk size and stability problems. ODF formulations of DXM Hbr have the advantages of both solid and liquid dosage forms and are useful for immediate relief of cough with improved patient compliance and to help patients of all age groups who have difficulty in swallowing.
- Also, disintegration and dissolution may enhance the rate of drug absorbance which may enhance bioavailability of the drug.
- The United State Food and Drug Administration (FDA) approved dextromethorphan as a prescription antitussive drug on September 24, 1954, and subsequently as an over-the-counter cough suppressant in 1958.
- ODF of DXM Hbr designed to be placed on the patient's tongue without being swallowed to deliver the dose would substantially simplify dose administration and improve patient compliance

❖ **Rational of formulation and development of orodispersible film of smoking cessation aids**

Varenicline (VAR) is a highly selective partial agonist of the nicotinic acetylcholine receptor α4β2 subtype. VAR, a partial agonist, blocks the full-agonist activity of nicotine by competitive binding. It helps in relief of withdrawal and craving symptoms. Because of weakening these symptoms, it endorses smoking cessation. Clinical trials have reliably found that this therapy raises the success of quitting smoking by 50–70. VAR tartrate (Champix® and Chantix®; Pfizer) has been approved by the USA-FDA as an aid to smoking cessation. Smoking cessation treatments are among the most cost-effective disease prevention. Pharmacological treatments approved for smoking cessation in the USA and the European Union include various forms of nicotine replacement therapy (NRT), sustained-release (SR) bupropion and, most recently, varenicline. Bupropion SR and NRT are both recognized as first-line pharmacotherapies for smoking cessation in the US and Europe and the most commonly used in the UK and the USA is NRT.

- Nicotine (NIC) cannot be developed as an oral pill due to its susceptibility to first-pass metabolism in the liver and efforts have been made to develop

alternative drug delivery systems for NRT. These include chewing gums, lozenges, mouth sprays, nasal sprays, transdermal patches (e.g., Nicorette), and oral films such as NiQuitin® strips. Though these can achieve successful quitting of smoking, they have their limitations, and therefore novel delivery systems are required.

- The transdermal patch provides slow and sustained NIC release; however, it does not match the fast delivery of NIC from cigarette smoking. Itching, edema, and erythema have also been associated with transdermal patches. Sleep disturbances have also been commonly reported with 24-hour patches.
- NIC chewing gum can sometimes result in slow onset and prolonged plasma NIC levels which cannot be matched with the rapid pharmacological effect and high maximum arterial NIC levels required for relief.
- Oral sprays allow rapid NIC absorption, but they require constant administration, and hence the bioavailability at the therapeutic level is not sustained.
- NRT strips such as NiQuitin® deal with the challenge of chewing gum for people with dental issues or who wear dentures.
- Electronic NIC delivery systems (ENDS) which can possibly cause harm to human cells due to presence of low concentrations of free radicals in e-cigarettes.
- Immediate release dosage form such as ODF of VAR provides greater absorption at faster rate to achieve high maximum arterial levels required for relief.

3.2. Hypothesis of research work

Hypothesis of present research work of formulation and development of orodispersible films is given in Figure 3.1.

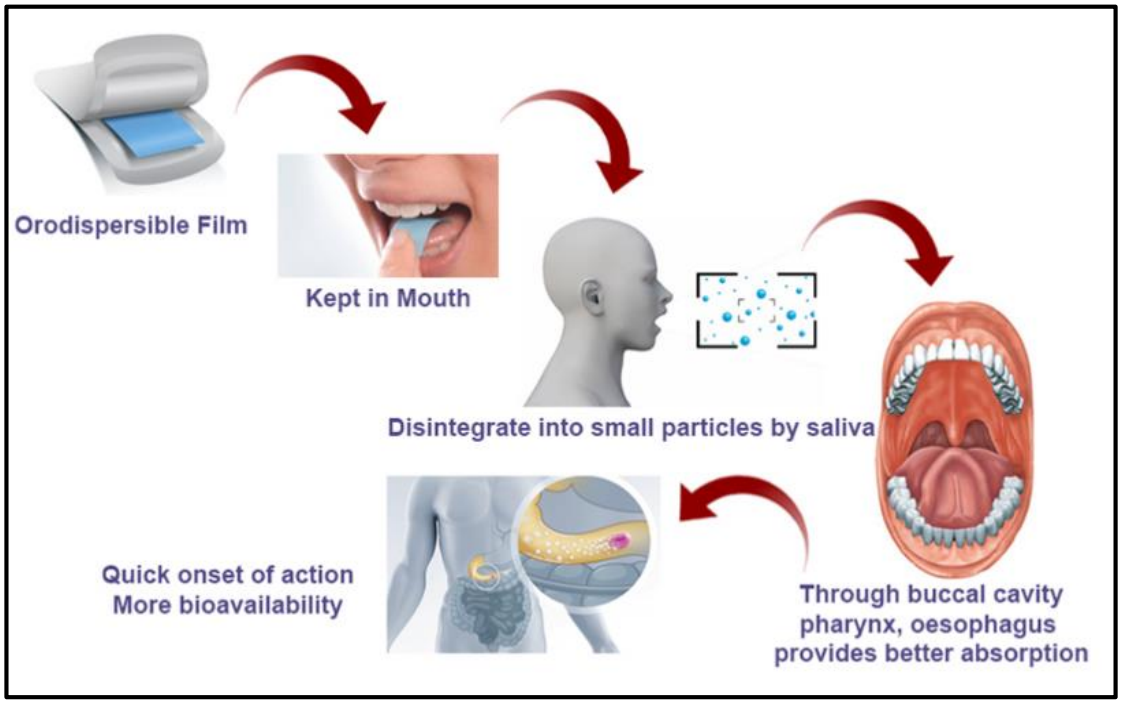


Figure 3.1: Hypothesis of ODF

CHAPTER 4. AIM AND OBJECTIVES

4.1 AIM OF STUDY

The aim of the present study is formulation development and evaluation of orodispersible films of Dextromethorphan hydrobromide and Varenicline tartrate.

4.2. OBJECTIVES

- ✓ The main objective of the present study is to formulate and evaluate orodispersible film of Dextromethorphan Hydrobromide and Varenicline tartrate by quality by design approach using ideal polymers by suitable methods.
- ✓ Preformulation Studies of selected APIs and excipients. Analytical method development for APIs.
- ✓ Formulation of fast dissolving Orodispersible film of Dextromethorphan Hydrobromide and Varenicline tartrate by quality by design approach using ideal polymers by design of experiment.
- ✓ Compatibility studies between the drug and excipients by FTIR.
- ✓ Taste masking of film.
- ✓ Evaluation of formulated film strips using different parameters like appearance, surface pH, uniformity of weight, drug content, film thickness, folding endurance of the film, *in-vitro* drug release studies etc.
- ✓ To evaluate the film with respect to *in vitro* drug disintegration time and *in-vitro* drug release studies
- ✓ Statistical analysis of all the results.
- ✓ To conduct stability studies as per the ICH guidelines.
- ✓ Compare with suitable market formulation

CHAPTER 5. LIST OF MATERIALS AND EQUIPMENTS

5.1. Materials and Equipments used

The materials and equipment's, utilized in the present study are mentioned in Table no. 5.1, 5.2 and 5.3 respectively.

Sr. No.	Component Name	Category	Company
1	Dextromethorphan Hydrobromide	Antitussive agent	Abbott Healthcare Pvt. Ltd
2	Varenicline as Varenicline tartrate	Aid in smoking cessation.	Lupin
3	Hydroxy Propyl cellulose	Film forming polymer	Abbott Healthcare Pvt. Ltd
4	PVP K30	Film forming polymer	Abbott Healthcare Pvt. Ltd
5	Polyvinyl Alcohol	Film forming polymer	Abbott Healthcare Pvt. Ltd
6	HPMC E5 LV	Film forming polymer	Colorcon Asia Pvt. Ltd. Mumbai
7	HPMC E15 LV	Film forming polymer	Colorcon Asia Pvt. Ltd. Mumbai
8	Hydroxy propyl cellulose	Film forming polymer	Abbott Healthcare Pvt. Ltd
9	Polyethylene Glycol	Plasticizer	Abbott Healthcare Pvt. Ltd

10	*Kollicoat*® IR	Film forming polymer	Amneal Pharmaceuticals
11	Lycoat RS 720	Film forming polymer	Chemtip Laboratories
12	Pullulan	Film forming polymer	Pharmaceutics lab., K.B.I.P.E.R.
13	Citric acid	Saliva Stimulating agent	Pharmaceutics lab., K.B.I.P.E.R.
14	Aspartame	Sweetener	Pharmaceutics lab., K.B.I.P.E.R.
15	Stevia	Sweetener	Purchase Sugar Free Green Stevia Powder
16	Kyron T-134	Resin	Ajanta Pharma Ltd
17	Double Distilled Water	Vehicle	Pharmaceutics lab., K.B.I.P.E.R.

Table 5.1: List of materials

Sr. No.	Name of Instrument	Make/Manufacture
1	Digital weighing balance (Sartorius P124S)	Swisser Instrument, India
2	Dissolution apparatus USP type 2	Electro lab ltd, Mumbai
3	Vernier Caliper	Sheetal scientific, Mumbai, India
4	Double Beam UV – Visible Spectrophotometer	UV-1800, Shimadzu, Japan
5	pH meter	Janki Impex Pvt. Ltd, Ahmedabad Labtronik. pH Cal, Electroquip, India
6	Magnetic Stirrer	Janki Impex Pvt. Ltd, Ahmedabad
7	Stability Chamber	Thermolab, Mumbai, India
8	Fourier Transform Infrared Spectrophotometer	FTIR 8400S, Shimadzu, Kroyoto, Japan
9	Texture Analyser	Brookfield Texture Analyzer Texture Pro version 2.1
10	E- tongue	Insent Taste Sensing System TS-5000Z

Table 5.2: List of Equipment's

Sr. No.	Software	Version
1	Design Expert®	Version 10.0.1, Stat ease Inc., Minneapolis, MN
2	Minitab 17®	Version 17, Minitab Inc., State college, Pennsylvania, USA

Table 5.3: List of software

5.2. PLAN OF WORK

- **Literature survey and Patent Search related to Drug, Polymer and ODF Technology.**
- **Selection of Drug, Polymer and Methodology for formulation and development of ODF drug delivery system. Procurement of drug and excipients**
- **Preformulation study of drug**
  - Analytical method development for API (VAR by UV spectrophotometry)
  - Drug excipient compatibility study
  - Melting point determination
  - Preparation of standard curve using UV- visible spectroscopy
  - Solubility
- **Preparation of ODF**
  - Dose calculation
  - Exploration of polymers for preparation of film
  - Selection of plasticizer for optimization of film.
  - Taste masking of film by suitable method
  - Design and Optimization of orodispersible film using Quality by design approach.
  - Determination of Quality Target Product Profile and Critical Quality Attribute
  - Risk Assessment by Ishikawa, Risk Estimation Matrix
  - Optimisation of formulation by application of suitable design of experiment.
  - Stability study of formulation
- **Characterization of Drug loaded ODF**
  - Appearance
  - Thickness
  - Uniformity of weight
  - Physical appearance and texture analysis of the films
  - Folding endurance
  - Mechanical properties
  - Surface pH
  - Drug content

- *In vitro* disintegration
- *In vitro* dissolution
- Statistical analysis
- Validation batches (Check Point Analysis) and its characterization.
- Comparison of optimized ODF with conventional marketed formulation
- Accelerated stability study

CHAPTER 6. EXPERIMENTAL WORK

6.1 Preformulation Studies

Preformulation is a group of studies that focus on the physicochemical properties of a new drug candidate that could affect the drug performance and the development of a dosage form. Every drug has intrinsic chemical and physical properties which has been considered before development of pharmaceutical formulation[86]. This property provides the framework for drug combination with pharmaceutical ingredients in the fabrication of dosage form. Objective of preformulation study is to develop the elegant, stable, effective and safe dosage form by establishing kinetic rate profile, compatibility with the other ingredients and establish [87].

6.1.1. Identification of Drug

Received sample of the drugs DXM Hbr was evaluated for colour, odour and texture. Taste of the drug was not determined since this requires permission from the human ethical committee. Reported data for taste of the drug was utilized [88].

6.1.2. Melting point

The substance under test was reduced to a very fine powder. Substance was filled in glass capillary tube (closed at one end) and tied to the thermometer such that the closed end of the capillary was near the middle of the thermometer bulb, and the remaining procedure was followed as mentioned in Method I for Melting Range or Temperature in IP 1996.

6.1.3. Flow Properties [89]

Bulk density (BD) and tapped density (TD) determined by standard procedure using standard density apparatus respectively.

The Carr's index (%) was calculated by using following equation

$$CI = [(BD - TD)/TD] * 100 \quad \text{------(1)}$$

Hausner's ratio, the ratio of bulk density to tapped density, was determined using following equation

$$\text{Hausner's ratio} = TD / BD \quad \text{------(2)}$$

Angle of Repose: Defined as the angle between free surfaces of a pile of powder to the horizontal plane, angle of repose for the current study was measured using fixed cone method wherein sample was meticulously poured through the funnel forming cone at the base until its apex touched the tip of the funnel Mean radius (r) and height (h) of the heap were measured basis which angle of repose (AR) calculated using equation.

$$tan\ \theta = h/r \qquad \text{--------(3)}$$

6.1.4. Solubility Study

Solubility of DXM Hbr was determined using the equilibrium method in various solvent such as double distilled water, 0.1 N HCl (pH 1.2), 4.5 Acetate Buffer, 6.8 Phosphate Buffer and ethanol. Briefly, an excess amount of sample was added to 1 mL of solvent. Test tubes containing the mixtures were sealed and kept in ambient conditions with intermittent shaking for 24 hours to achieve equilibrium. The mixtures were centrifuged for 10 minutes, and the supernatant was passed through a 0.45 μm Whatman® membrane filters paper The filtrate was diluted appropriately with water, and the concentration of the drug was measured using UV-spectrophotometer [90].

6.1.5. FT-IR analysis

The drug was subjected to FT-IR studies for the purpose of characterization. IR technique is one the most powerful techniques which offers the possibility of chemical identification. Drug was mixed with potassium bromide (KBr) in 1:100 proportions and a spectrum was obtained in a range of 400–4000 cm^{-1}. Potassium bromide was used as a blank while running spectrum [91].

6.1.6. UV visible spectrophotometry determination of absorption maximum (λmax)

The DXM Hbr was subjected to UV spectroscopic analysis to find out the wavelength (max) at which it shows maximum absorbance. Stock solution of the drug (1 mg/ml) was prepared in a phosphate buffer (pH 6.8) and a 100 μg/ml solution was scanned over the wavelength range 200–400 nm to determine λmax [92].

UV spectrophotometric determination for bulk and *in vitro* analysis

Suitable analytical methods were used for qualification and quantification of APIs (For sample analysis in bulk and *in vitro* characterization, UV spectrophotometry was used.

Apparatus

UV spectrophotometric analysis was performed on a Shimadzu UV-1800 spectrophotometer, with 1.00 cm quartz cells.

Preparation of Standard Stock Solution of DXM Hbr

Accurately weighed 10mg DXM Hbr was dissolved in 100 ml of suitable solvent to obtain a solution of 100 µg/ml.

6.1.7. Preparation of Calibration Curve

From the above prepared stock solution, aliquots were taken and appropriately diluted to obtain 10 to 60 µg/ml concentrations of DXM Hbr. Absorbance of each solution was measured 279.4 nm against 6.8 pH phosphate buffer as blank at specific λmax of 279.4nm. Analytical method parameters for DXM Hbr is listed in Table 6.1.

Parameter	**For DXM Hbr**
Sample Preparation	
Solvents	Distilled Water,0.1N HCl, Phosphate Buffer pH6.8
Stock Solution	100 µg/ml
Concentration range	5-40 µg/ml
Instrumentation	
Instrument Model	Shimadzu UV-1800
Sample Holder	1.00 cm quartz cells
Analytical Wavelength	279.4 nm
Measurement Type	Absorbance

Table 6.1: Analytical method parameters for DXM Hbr

6.1.8. Drug - excipients compatibility studies

Drug-Excipients interaction plays a vital role in achieving stability of drug in dosage form **[93]**. Fourier transform infrared spectroscopy (FT-IR) was used to study the physical and chemical interactions between drug and excipients. Drug excipient compatibility studies of DXM Hbr with polymers were studied using Fourier Transform Infrared Spectrophotometry to determine possibility of any drug-excipients interaction/incompatibility Pure drug DXM Hbr, and drug-excipient mixture were analysed using FT-IR spectrum and the characteristic peaks of functional groups present in the drug were correlated among the spectrum.

6.1.9. Polymer screening

The oral films are essentially complex polymeric matrices that may be used efficiently as drug release platforms [94]. The successful development of an ODF is a function of justified selection and concentration of polymers as the mechanical strength of films is strongly associated with these factors. Fast dissolving Film is prepared using hydrophilic polymers that rapidly dissolves on the tongue or buccal cavity, delivering the drug to the systemic circulation via dissolution when contact with saliva. Hence, the selection of the polymer was primarily based on the aqueous solubility, disintegration time and mechanical strength [94].

Various polymers are screened or the formulation of DXM Hbr such as hydroxypropyl methyl cellulose (HPMC) E5LV, HPMC E15LV, polyvinylpyrrolidone K 30, polyvinyl alcohol and hydroxypropyl cellulose. Five monopolymeric films trial batches T1 -T5 were prepared to screen polymers on the basis of film characteristics such as film forming capacity, appearance, spreadability, peelability and mechanical characteristics.

Material (mg/film)	**T1**	**T2**	**T3**	**T4**	**T5**
HPMC E5 LV	100	--	-	--	--
HPMC E15 LV	--	100	--	--	--
PVP K30	--	--	100	--	--

PVA	--	--	--	100	--
HPC	--	--	--	--	100
Citric Acid	4	4	4	4	4
Aspartame	5	5	5	5	5
PEG 400 (ml)	0.5	0.5	0.5	0.5	0.5
Glycerin (ml)	0.5	0.5	0.5	0.5	0.5
Water (ml)	20	20	20	20	20

Table 6.2: Trials for polymer screening for DXM Hbr

6.1.10. Selection of plasticizer

The addition of a plasticizer is often necessary to obtain flexible, non-brittle ODFs. They tend to reduce the brittleness of the strip by lowering glass transition temperature [Tg] of polymers thereby improving the flexibility of the films. The choice of plasticizer will depend upon its compatibility with the polymer and also nature of the solvent employed in the casting of the strip. Various plasticizers are screened such as PEG 400 and Glycerine,

6.1.11. Taste masking of DXM Hbr ODF using Drug-Resin Complex

The success of ODF depends on patient acceptance, palatability and the challenging aspect in the formulation of orodispersible film is to mask the bitterness of active pharmaceutical ingredients, since most drugs have bitter taste. The distasteful sensation of a drug can be masked either by the addition of flavours, sweeteners and effervescent agents or by reducing direct contact with the patient's taste buds through coating or granulation. Flavor is often overpowered by the taste of the medicine and the use of effervescent agents is not always convenient. Moreover, coating and granulation of the active ingredient may often rupture during compression and chewing of the tablet, as well as contribute to a gritty feel. Masking the bitter taste of actives using ion exchange resins is one among the economical methods reported. Several studies have shown that the complexation of a bitter tasting active with ion

exchange resin prevents the release of active from the complex in the saliva. Resins are inert and not absorbed by the body [95-97].

Selection of resin

Resins were selected on the basis of nature of the drug and requirement of formulation. Ideally, cation and anion exchange resins are used depending on the acidic and basic nature of the drug.

Dextromethorphan Hydrobromide has amine as a functional group, which is the cause of their obnoxious taste. If this functional group is blocked by complex formation the bitterness of the drug reduces drastically. Weak cation exchange resins such as Kyron T-314 was selected for the study.

Preparation of drug resin complex (DRC)

For present study, drug: resin was taken in 1:0.25, 1:0.50, 1.0.75, 1:1, 1:1.25 and 1:1.50 ratio. An accurately weighed quantity of resin was taken in a 100 ml beaker containing 25 ml of deionised water. Resin was allowed to swell for 30 min. Appropriate amount of drug (as per selected ratio was added into the same beaker. The beaker was placed on a magnetic stirrer for 30 min at 30°. The solution was filtered using whatman filter paper. The filtrate was analysed using appropriate dilution for determination of unbound drug at 279.4 nm using UV spectrophotometer. Percentage of drug bound to resin was calculated from amount of unbound drug.

Amount of Drug (g)	**Amount of Resin (g)**	**Ratio**	**Solvent Vehicle**
1	0.25	1:0.25	Water
1	0.50	1:0.50	Water
1	0.75	1:0.75	Water
1	1.00	1:1	Water
1	1.25	1:1.25	Water
1	1.50	1:1.50	Water

Table 6.3: Preparation of drug resin complex

6.2.Preparation of ODF

ODF of DXM Hbr was prepared by solvent casting technique. Various steps involved for preparation of or dispersible film are as follows:

Preparation of Film Drug and Polymer Solution

For DXM Hbr, aqueous solution 'A' was prepared by dissolving HPMCE15 LV polymer in15 mL distilled water with stirring to produce solution. It was kept for 24 h to remove all the air bubbles and form a clear solution. Aqueous solution 'B' was prepared by dissolving a physical mixture of drug and resin, aspartame, citric acid and PEG 400 in specific proportions in distilled water. The aqueous solutions 'A' and 'B' were mixed and stirred overnight. The solutions were cast onto a 9 cm diameter glass petri plate.

Drying of the Solution:

Petri dish and were dried in the oven at 45 ^{0}C for 6 hr till a peelable film was formed.

Cutting the Final Dosage Form

The dried films were then cut into 2*2 cm

Packaging of the Films

The samples were packed in aluminium foil.

6.3. Formulation and Development of orodispersible film using Quality by Design approach

Defining QTPP and CQAs [98-101]

The manufacture of ODF products involves solvent casting of a liquid mixture containing film former, plasticizer, sweetener, colour and flavour onto a substrate. A variety of film formers and other excipients are used in the formulation development of ODF. Variability in formulation (e.g., plasticizer and film former concentration) may result in product quality failures over the shelf life. Therefore, the QbD approach was used to identify the critical quality characteristics from the patient's point of view and translate them into the CQAs that the final product should have. The first step for developing a product using this efficient approach is defining the quality target product profile QTPP (Table 6.4), prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product. Variation in plasticizer concentration may impact the ODF critical quality attributes (CQA) such as physical a. attributes (appearance, odour, flavour and size), identification, assay, content uniformity, disintegration time and dissolution. The description of CQA is given in Table 6.5.

QTPP Elements	**Target**	**Justification**
Dosage Form	ODF (Fast Dissolving Films)	Patient Compliance
Dosage Design	Immediate Release Fast Dissolving Films	For suitable replacement of marketed product
Route of Administration	Oral	Same route of administration
Dosage Strength	Similar to marketed product	Pharmaceutical Equivalence
Pharmacokinetics	Similar to marketed product	
Stability	Similar to marketed product	

Drug Product Quality Attributes	**Physical Attribute**	Pharmaceutically Equivalent to Marketed Product	
	Identification		
	Assay		
	Disintegration Time		
	Content Uniformity		
	Dissolution		
Administration/Concurrence with labelling		Similar food effect	To achieve similar Pharmacokinetics
Alternative methods of administration		None	None

Table 6.4: QTPP of the ODF

Quality Attributes of the Drug Product		**Target**	**Is this a CQA?**	**Justification**
Physical Attributes	**Appearance**	Acceptable to patient. No visual film defects observed	**No**	Color, Shape and Appearance are not directly linked to safety and efficacy. Therefore, not critical. The target is set to ensure patient acceptability.
	Odour	No unpleasant Odour	**No**	
	Flavour and Taste	Acceptable taste	**Yes***	A bitter or unacceptable taste may alter the dosage regimen as the patient will be reluctant to take bitter taste formulation. Safety and Efficacy is directly linked.

	Size	Acceptable to patient	**No**	Shape and Appearance are not directly linked to safety and efficacy. Therefore not critical. The target is set to ensure patient acceptability.
Identification		Positive	**Yes***	Identification is critical for safety and efficacy of the patient. But, since formulation and process variables do not impact identity, this CQA will not be addressed.
Assay		100% w/w of label claim	**Yes**	Drug content in the film will affect safety and efficacy as process variables affect the assay of the drug product. Hence it will be evaluated throughout development
Content Uniformity		Conforms to Pharmacopoeial Standards	**Yes**	Drug content uniformity in the film will affect safety and efficacy. Hence it will be evaluated throughout development
Disintegration Time		Conforms to Pharmacopoeial Standards	**Yes**	For FDF, disintegration time is the most important CQA. Any changes in disintegration time changes the dissolution rate of the drug. Hence it is critical.

Dissolution	NLT 90% in 10 minutes	**Yes**	Failure to meet the dissolution specification can impact bioavailability. Both formulation and process variables affect the dissolution profile.

Table 6.5: Quality target product profile (QTPP)

Risk Assessment Studies for DXM Hbr [102-104]

The risk assessment studies were carried out in the form of producing risk estimation matrix depicted in Table 6.6.

Drug Product CQA	**Polymer**	**Plasticizer**	**Sweetener**	**Flavour**	**Saliva Stimulant**
Assay	Low	Low	Low	Low	Low
Content Uniformity	Low	Low	Low	Low	Low
Disintegration Time	**High**	**High**	Low	Low	Low
Dissolution	**High**	**High**	Low	Low	Low

Table 6.6: Risk Assessment Studies for DXM Hbr

Risk estimation matrix showing the impact of each dependent variable on CQA

Formulation Variables	**Drug Product CQAs**	**Justification**
Polymer	**Assay**	Film forming polymer will not affect the Assay and CU the FDF. Hence risk is ranked low.
	Content Uniformity	
	Disintegration Time	Polymer constitute major portion of the film formulation. Hence are impact the DT and

	Dissolution	Dissolution of the FDF. Proper selection of polymer is most important factor for FDF formulation development. Hence risk is ranked high.
Plastisizer	**Assay**	Plastisizer will not affect the Assay and CU the FDF. Hence risk is ranked low.
	Content Uniformity	
	Disintegration Time	Plastsizer directly affect the wetting behaviour of the FDF and lead to disintegration. Faster disintegration would promote a faster dissolution rate. Hence proper Plastsizer selection is very important. And, the risk is ranked high.
	Dissolution	
Sweetener	**Assay**	Sweetener will only impact the taste of Fast dissolving film. It will not affect any other CQAs of the FDF. Hence the risk is ranked low.
	Content Uniformity	
	Disintegration Time	
	Dissolution	
Flavour	**Assay**	Flavouring Agent will not affect the Assay, CU, DT and Dissolution of FDF. Hence risk is ranked low.
	Content Uniformity	
	Disintegration Time	
	Dissolution	
Saliva Stimulant	**Assay**	Saliva Stimulating Agent will not affect the Assay, CU, DT and Dissolution of FDF. Hence risk is ranked low.
	Content Uniformity	
	Disintegration Time	
	Dissolution	

Table 6.7: Justification for the initial risk assessment of formulation variables

Dose calculation:

Diameter of Petridish (D) = 9.0 cm

Radius of Petridish (r) = D/2 = 4.5 cm

- Area of Petridish (A) = πr^2

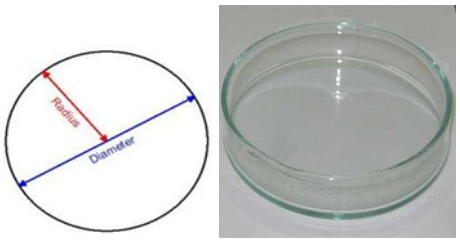
$$= 3.14 \times (4.5)^2$$

$$A = 63.58 \text{ cm}^2$$

Now, if 2 × 2 cm^2 film contains 10 mg of DXM Hbr

Than for 63.58 cm^2…….?

= 63.58× 10/4 =158.95=159 mg of DXM Hbr require per batch



Application of Plackett Burman Design [105-107]

The Plackett–Burman factorial design was employed in this study to correlate dependent and independent variables. A four-factor 12-run Plackett–Burman screening design was generated usingMinitab 17® (Version 17, Minitab Inc., State college, Pennsylvania, USA). The software package was used to estimate the response of dependent variables and optimized conditions. 12 batches were prepared according to composition presented in Table 6.11. All the batches contained 10 mg of API per film. In a multivariable system PBD is powerful and useful mathematical tool for the determination of key factors on a particular response generated by conducting a smaller number of experimental trials, but this method does not determine the exact quantity, it provides some essential evidence about each factor by performing comparatively few experiments. The purpose of PBD is to evaluate the effect of the

processing variables and identify the key one influencing the responses like folding endurance, disintegration time and dissolution at the end of 2 min (Q2).

In the present study, each variable was investigated at two levels namely high level (+ 1) and low level (− 1) as shown in Table 6.9. The effects of 4 independent variables on dependent variables (response) were investigated by 12 runs of experiments. Table 6.10 shows the factors under investigation as well as the level of each factor used in the experimental design. The factor ranges were selected based on prior knowledge from the initial trial experiments. The formulation of prepared batches is showed in Table 6.11.

Plackett - Burman Design			
factors	4	Replicates	1
Base Runs	12	Total runs	12
Base Blocks	1	Total blocks	1

Table 6.8: Placket burman experimental design metrics in coded level

Sl No.	**Independent Variables**	**Levels**	
		-1	**1**
1	HPMCE15LV	50	150
2	PEG400	0.25	0.75
3	Citric Acid	2	6
4	Aspartame	2.5	7.5

Table 6.9: Levels in the DoE

Run	**HPMCE 15LV**	**PEG 400**	**Citric acid**	**Aspartame**	**HPMCE 15LV**	**PEG 400**	**Citric acid**	**Aspartame**
	Coded Values				**Actual Values**			
1	-1	-1	1	1	50	0.25	6	7.5
2	-1	-1	-1	1	50	0.25	2	7.5
3	-1	-1	-1	-1	50	0.25	2	2.5
4	1	1	-1	1	150	0.75	2	7.5

5	-1	1	1	-1	50	0.75	6	2.5
6	1	1	1	-1	150	0.75	6	2.5
7	1	-1	1	-1	150	0.25	6	2.5
8	-1	1	-1	-1	50	0.75	2	2.5
9	-1	1	1	1	50	0.75	6	7.5
10	1	1	-1	1	150	0.75	2	7.5
11	1	-1	-1	-1	150	0.25	2	2.5
12	1	-1	1	1	150	0.25	6	7.5

Table 6.10: Factors in the design of experiment

Material (mg/film)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Dextromethorphan Hydrobromide	10	10	10	10	10	10	10	10	10	10	10	10
Kyron T-314	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5
HPMC E15 LV	50	50	50	150	50	150	150	50	50	150	150	150
PEG 400	0.25	0.25	0.25	0.75	0.75	0.75	0.25	0.75	0.75	0.75	0.25	0.25
Citric Acid	6	2	2	2	6	6	6	2	6	2	2	6
Aspartame	7.5	7.5	2.5	7.5	2.5	2.5	2.5	2.5	7.5	7.5	2.5	7.5
Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Table 6.11: Formulation batches of DoE

6.4. Evaluation of Orodispersible Films

- **Film weight**

Uniformity of mass was determined according to the European Pharmacopoeia (Ph. Eur. 8.0): uniformity of mass for single-dose preparations (method 2.9.5). Three randomly chosen ODFs were weighted individually on an analytical balance. Subsequently the average mass was calculated [94].

- **Film thickness**

The thickness of the ODFs was measured at five different points: in the corners and in the middle using a Vernier Calliper. Average thickness and standard deviation of each oral film formulation was determined [108].

- **Folding endurance**

The folding endurance is related to the flexibility of a film, and measured manually by firmly folding the films back and forth through the middle. The number of double folds on the same crease, required to produce crack in the film was noted as the value of folding endurance [109].

- **Surface pH of Films**

The surface pH of films was determined to investigate the possible side effect because of change in pH in vivo, since an acidic or alkaline pH may cause irritation to oral mucosa. As an acidic or alkaline pH may cause irritation to the oral mucosa, it is determined to keep the surface pH as close to neutral as possible. Strip was wetted with the help of water. The pH was measured by bringing the electrode in contact with the surface of the oral strip. This study was performed on three strips of each formulation and mean ± SD calculated [64].

- **Determination of drug content**

A 4 cm^2 strip was sliced into small pieces to be dissolved in 100 ml phosphate buffer (pH 6.8) and shaken persistently. Subsequently, the contents were sonicated until complete dissolution of the film After filtration, the drug was diluted appropriately

and estimated spectrophotometrically (Shimadzu 1800, Japan) at a wavelength of 279.4 nm (DXM Hbr).

- ***In vitro* disintegration time**

The disintegration time is the time when a film starts to break or disintegrate. The *in vitro* disintegration time of ODF, s was determined visually by taking three (4 cm^2) film sections of each formulation in a glass dish of 25 ml phosphate buffer of pH 6.8 at 37 °C with swirling every 10 s. The time required for complete film disintegration, where no residue is left on the screen, was recorded using a stop watch. The mean values were calculated [64].

- ***In vitro* Dissolution Study.**

For DXM Hbr the study was conducted using USP dissolution apparatus I in 50 mL buffer solution of pH 6.8 at 37 ± 0.5 °C and 50 rpm. One film section of 4 cm^2 area was placed in each basket, and samples were withdrawn every 2 min up to 10 min for spectrophotometric analysis at λmax at 279.4 nm (none of the used ingredients interfered with the drug peak). The experiments were conducted in triplicate, and mean values were calculated.

6.5. Evaluation of taste masking

Taste assessment using a multichannel taste sensor, an instrument commonly named the electronic tongue (E -Tongue), is becoming established as a novel alternative to human volunteers. The E -Tongue consists of an array of liquid electrochemical sensors coated with an organic membrane that governs the sensitivity and selectivity of each individual sensor

Evaluation of taste masking of the formulation done by Insent Taste Sensing System TS-5000Z which was outsourced.

- **Sensors**

All measurements were performed using the taste sensing system TS-5000Z (Insent Inc., Japan). This electronic tongue was equipped with four lipid membrane sensors labelled according to the different taste qualities and corresponding four reference electrodes. Bitterness sensor 1 (CPA1 CO0) for acidic bitterness, Bitterness sensor 2 (CPA1 AN0) and Bitterness sensor 3 (CPA1 BT0). Both AN0 and BT0 for basic

bitterness. The fourth sensor represented the gustatory stimuli such as astringency (CPA1 AE1). BT0 sensor was specially designed by Insent Inc., Japan for the current study. BT0 comprises of phosphoric acid di-ndecyl ester as artificial lipid and Bis (1-butylphenyl) adipate as plasticizer. It is specially recommended for bitter hydrochloride salts, DXM Hbr is one such bitter drug. The "aftertaste" can be measured for bitterness, umami and astringency. In current study, these were detected using sensors AN0 and BT0. 0.2 ml of inner solution was filled into each sensor before beginning of the experiments. All sensors were preconditioned in standard solution for one day before the measurement.

Preparation of Sample Solution

Purpose of preparation of sample solution was to evaluate the taste of Immediate Release Oral Film using Taste Sensors. Prepared 10mM KCL, as a diluent. 5 mg, 10 mg and 15mg of DXM Hbr was diluted to 100 ml with 10 mM KCL. Sample of Oral Film prepared by cutting film in 2X2 cm2 and dissolved in 100 mL of 10 mM KCL.

Electronic Tongue System and Measurement Set Up

Establishment of linearity for API

Before the measurements on Insent Tasting System TS 5000 Z, the system was qualified before actual measurement of formulations. Linearity range for DXM Hbr was established by studying different concentrations. (5 mg, 10 mg and 15mg of DXM Hbr was diluted to 100 ml with 10 mM KCL.)

Measurement of Bitterness using E-Tongue system [110-112]

Selection of Sensors

Suitable sensors were selected for measurement of bitterness in drug sample and prepared formulation. Selected sensors are mentioned in the Table 6.12.

Sensor	Taste Information
BT0	Evaluates basic bitterness
AN0	Evaluates basic bitterness
C00	Evaluates Bitterness and Acidic bitterness
AE1	Evaluates astringency and aftertaste from astringency

Table 6.12: Selected sensors for measurement of bitterness of API and Formulation

The handling of sensors was as per instructions provided from Insent TZ system. Prior to the beginning of experiments, each sensor (TecLabS Europe, Germany) was filled with 0.2 mL of saturated silver chloride solution, also called inner solution. The reference electrode was completely filled up with inner solution. All sensors were preconditioned in standard solution for one day before actual measurements. Sensors were regularly checked for their mV values as per requirement of the system. Actual measurement step involves first measuring mV values for a reference solution (Vr) and then the actual sample (Vs) (Solution to be evaluated for taste). These values indicate the "Initial Taste" for the given samples. In order to detect "After taste" electrode is rinsed first with washing solution and again measuring mV values (Vr'). Thus, each sample is measured four times. Cleaning procedure of sensor involves its rinsing with washing solution. It causes desorption of the some of the adsorbed substance and hence change in membrane potential after cleaning gives values of "After taste". Initial taste is indicated by relative value (Vs-Vr). Whereas, Vr'-Vr indicates "After taste" of the sample. Later value is referred as CPA (Change in Membrane Potential caused due to adsorption) values.

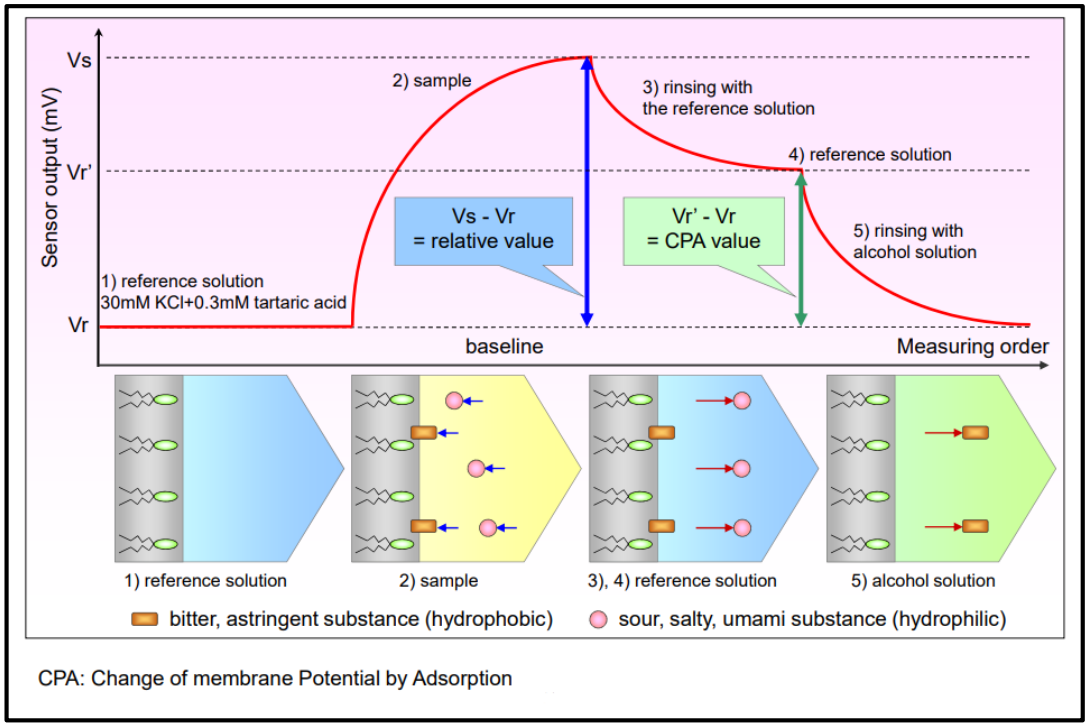


Figure 6.1: Measurement Procedure for Test Masking of Optimize formulation using e-Tongue

6.6.Stability Studies

The stability studies were conducted according to ICH guidelines, to investigate the effect of temperature, relative humidity on drug in different formulations. Final optimized formulation was subjected to aggravated conditions of temperature and relative humidity, by wrapping it in aluminium foil and packaging it in glass container. The films were kept in stability chamber, at 40±0.5 C temperature and 75 ± 5% RH for 3 months. After 1, 2 and 3 months. Samples were withdrawn at specific time interval and evaluated. The films were characterized for physical appearance, mechanical properties, drug content and *in vitro* drug release profile at regular intervals of 10 days. The study was continued for 3 months. Periodically, samples were withdrawn at different predetermined time intervals (0, 1, 2, 4, 6, 9, and 12 weeks) and examined physically for any changes in color, appearance thickness, and surface pH as well as chemically for their drug content.

Formulation and development of orally disintegrating film of Varenicline(VAR)

6.7. Preformulation Studies for VAR

Preformulation studies of VAR were performed as methods mentioned in section 6.1.

6.8.UV visible spectrophotometry determination of absorption maximum (λmax)

The VAR was subjected to UV spectroscopic analysis to find out the wavelength (max) at which it shows maximum absorbance. Stock solution of the drug (10 mg/100ml) was prepared in phosphate buffer (pH 6.8) and 100 µg/ml solution was scan over the wavelength range 200–400UV spectrophotometric determination for bulk and *in vitro* analysis [113].

UV spectrophotometric determination for bulk and *in vitro* analysis

Suitable analytical methods were used for qualification and quantification of APIs (For sample analysis in bulk and *in vitro* characterization, UV spectrophotometry was used [114].

Preparation of Calibration Curve

From the above prepared stock solution, aliquots were taken and appropriately diluted to obtain 5,10,15,20,25,30 and 35 and 40 µg/ml concentrations of VAR. Absorbance of each solution was measured 236nm.nm. against 6.8 pH phosphate buffer as blank at that specific λmax. Analytical method parameters for APIs are listed in table 6.13.

Parameter	**For VAR**
Sample Preparation	
Solvents	Distilled Water,0.1N HCl, Phosphate Buffer pH 6.8
Stock Solution	100 µg/ml
Concentration range	5-40 µg/ml

Instrumentation	
Instrument Model	Shimadzu UV-1800
Sample Holder	1.00 cm quartz cells
Analytical Wavelength	236nm.
Measurement Type	Absorbance

Table 6. 13: Analytical method parameters for API(VAR)

Developed analytical method of VAR was further taken for validation as given below.

6.8.1. Method Validation for VAR [114]

- **Linearity**

The absorbance difference (ΔA) was measured at 236 nm as described in above and calibration plots of VAR were obtained and regression equations for respective plots were calculated for the estimation of linearity.

- **Precision (repeatability)**

INTRADAY: Three solutions (0.3 µg/ ml, 3 µg/ ml, 9 µg/ ml) were prepared as described in procedure and six replicate readings of each were taken by UV spectrophotometer on the same day. The repeatability was expressed in terms of % relative standard deviation.

INTERDAY: Three solutions (0.3 µg/ ml, 3 µg/ ml, 9 µg/ ml) were prepared as described in procedure and six replicate readings of each were taken by UV spectrophotometer on three consecutive days. The repeatability was expressed in terms of % relative standard deviation.

- **LOD and LOQ**

Regression equations for linearity plot were derived in triplicates and standard deviation of the intercepts was calculated

LOD=3.3× SD / mean of slope of regression equations in triplicates -------- (3)

LOQ=10×SD / mean of slope of regression equations in triplicates --------- (4)

- **Accuracy of method**

The accuracy of the method was determined by calculating the recoveries of VAR by the standard addition method. Known amounts of standard solutions of VAR were added at 50, 100 and 150 % level to prequantified sample solutions of VAR (15 µg/ ml). Concentration of VAR was estimated by applying obtained values to the respective regression line equations.

6.9. Drug - excipients compatibility studies

Drug-excipients interaction plays a vital role in achieving stability of drug in dosage form. Fourier transform infrared spectroscopy (FT-IR) was used to study the physical and chemical interactions between drug and excipients. Drug excipient compatibility studies of VAR with polymers were studied using Fourier Transform Infrared Spectrophotometry to determine possibility of any drug-excipients interaction/incompatibility Pure drug, VAR and drug-excipient mixture were analysed using FT-IR spectrum and the characteristic peaks of functional groups present in the drug were correlated among the spectrum.

- **Preliminary trials for development of ODF for VAR**
- **Polymer screening**

The selection of polymers is one of the most critical and important parameters in the successful preparation of oral films due to their tensile strength, which depends on the type and amount of polymer used. As ODFs are rapidly dispersed and dissolved in the oral cavity, the film-forming polymers used must be water-soluble. At the same time, the films obtained must be durable, which will not cause any damage during transport and storage.

The various polymers and their fixations were utilized to plan VAR ODF to fix the polymer type and focus. The subtleties are as per the table 6.14.

Ingredients	**F1**	**F2**	**F3**
Kollicoat® IR (mg)	300		
Lycoat® (mg)		300	
Pullulan (mg)			300
PEG 400 (% of polymer)	2	2	2
Distilled Water (ml)	15	15	15
Drying Time	24 hr	24 hr	24 hr
Drying temperature	60°C	60°C	60°C

Table 6.14: Preliminary polymer screening for VAR ODF

❖ **Selection of plasticizer for VAR ODF**

The addition of a plasticizer is often necessary to obtain flexible, non-brittle ODFs. They tend to reduce the brittleness of the strip by lowering glass transition temperature [Tg] of polymers thereby improving the flexibility of the films. The choice of plasticizer will depend on upon its compatibility with the polymer and also nature of the solvent employed in the casting of the strip. Various plasticizers are screened such as PEG 400, glycerine, propylene glycol. The different plasticizer and their fixations were utilized to get ready VAR ODF to fix the plasticizer type and focus. The different plasticizer utilized were as per Table 6.15.

Ingredients	**F4**	**F5**	**F6**
Kollicoat® IR(mg)	300	300	300
Glycerin (% of polymer)	10	-	-
PEG-400 (% of polymer)	-	10	-
PG (% of polymer)	-	-	10
Distilled water (ml)	15	15	15
Drying Time	24 hr	24 hr	24 hr

Drying temperature	60°C	60°C	60°C

Table 6.15: Compositions for selection of plasticizer for VAR ODF

- **Selection of drying time**

Process variables e.g., drying temperature and time may result in product quality failures over the shelf life. For e.g., inadequate in-process controls during drying may lead to the formation of uneven film surfaces. Therefore, selection of drying temperature and time is an essential process parameter for the formulation of orodispersible film as per table 6.16.

Ingredients	**F7**	**F8**	**F9**
Kollicoat® IR (mg)	300	300	300
PEG 400 (% of polymer)	2	2	2
Distilled water (ml)	15	15	15
Drying Time	24 hr	12 hr	6 hr
Drying temperature	60°C	60°C	60°C

Table 6.16: Compositions for selection of drying time

- **Selection of sweetener concentration [115, 116]**

The success of ODF depends on patient acceptance, palatability and the challenging aspect in the formulation of orodispersible film is to mask the bitterness of active pharmaceutical ingredients, since most drugs have bitter taste. The distasteful sensation of a drug can be masked either by the addition of flavours, sweeteners and effervescent agents or by reducing direct contact with the patient's taste buds through coating or granulation. In the present research work, natural sweetener stevia used to mask the bitter taste of VAR. studies are carried out to understand effect of concentration of sweetener on characteristics of film. The trial details are shown in table 6.17.

Ingredients	**F10**	**F11**	**F12**
Kollicoat® IR (mg)	300	300	300

PEG 400 (% of polymer)	5	5	5
Stevia (mg)	1	5	10
Distilled water (ml)	15	15	15
Dryin-g Time	6 hr	6 hr	6 hr
Drying temperature	60°C	60°C	60°C

Table 6.17: Compositions for selection of sweetener concentration

6.10. Formulation and Development of VAR ODF by Design of Experiment (DoE) Using QbD Approach

In recent years, the development process of pharmaceutical preparation has changed. Quality by design (QbD) is a methodology used to build quality into products, by design. The QbD approach is used to ensure the pharmaceutical development is conducted in arrange to have in the end a systematic understanding of how process parameters affect a product. According to ICH (International Conference Harmonization) Q8, QbD can be defined as "a systematic approach towards development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management". A very common tool or element used in the QbD is the quality target product profile (QTPP), which can be defined as "a dynamic product description that summarizes the quality characteristics expected to guarantee the product performance, stability, safety, and efficiency". Mainly, QTPP includes the critical quality attributes (CQAs) and critical process parameters (CPPs). CQAs might be continued as attributes that characteristic of product quality and CPPs refers to critical process parameters or variables that can impact these characteristics. Therefore, the mix of the CQAs and CPPs allows the explanation of design space. The preparation of ODF and QTPP may be organized based on earlier reported studies considering the essential requirements for manufacturing as well as techniques available for its characterization to get the desired film properties. A prepared ODF should be handled without being harmed, ought to be physically stable and give a simple and pleasant administration. These properties may be translated into product quality attributes, such as appropriate

organoleptic and mechanical properties. For the present research work QTPP and CQA for VAR ODF was mention in table 6.18 and 6.19 respectively.

QTPP	TARGET	JUSTIFICATION
Dosage form	Fast dissolving Film	Immediate release of drug in pregastric region to avoid hepatic first pass effect.
Route of administration	Oral	Pharmaceutical equivalence requirement: Same route of administration
Dose	1 mg	Pharmaceutical equivalence requirement: Same strength
Pharmacokinetics	Fasting and Fed Study 90% CI of PK parameters, AUC 0-2,AUC 2-24, AUC 0-∞ and Cmax should fall within bioequivalence limits.	Bioequivalence Requirement
		Initial plasma level: Clinically significant therapeutic effect followed by a sustained plasma concentration.
Stability	At least 24 month at RT	Equivalent or better than RLD
Drug product quality attributes	Physical Attributes	Pharmaceutical Equivalence requirement
	Identification	
	Assay	
	Content Uniformity	

	Degradation Product	
	Residual Solvents	
	Drug release	
	Microbial Limits	
	Water content	
Container closure system	Suitable	Hermetically sealed foil packaging to prevent moisture transfer and breakage during shipment
Labelling	Orodispersible film	RLD labeling.
Alternative method of administration	None	As listed in RLD labeling

Table 6.18: Quality targeted product profile for VAR ODF

Quality Attributes of the drug product	Target	Is this a CQA???	Justification
Physical Attributes	Acceptable to patients	No	They do not affect the safety and Efficacy of the product
Tensile strength (N/mm^2)	44808	Yes	Determinant of strength of film
Load at Yield	10-20%	Yes	Determinant of strength of film
Q10 (%)	90-99%	Yes	Important to ensure the safety and efficacy of product
%Elongation at break	85-95%	Yes	Determinant of strength of film.

Table 6. 19: Critical quality attributes for VAR ODF

Risk Assessment

Risk assessment studies were executed to identify the critical material attributes (CMA) or CPPs having significant influence on CQAs of ODF. An Ishikawa fish-bone diagram (Figure 6.2) was portrayed to enlist the potential high-risk factors that affect quality of final formulation. The list encompasses nuance of key material attributes and/or process variables for development of ODF containing VAR.

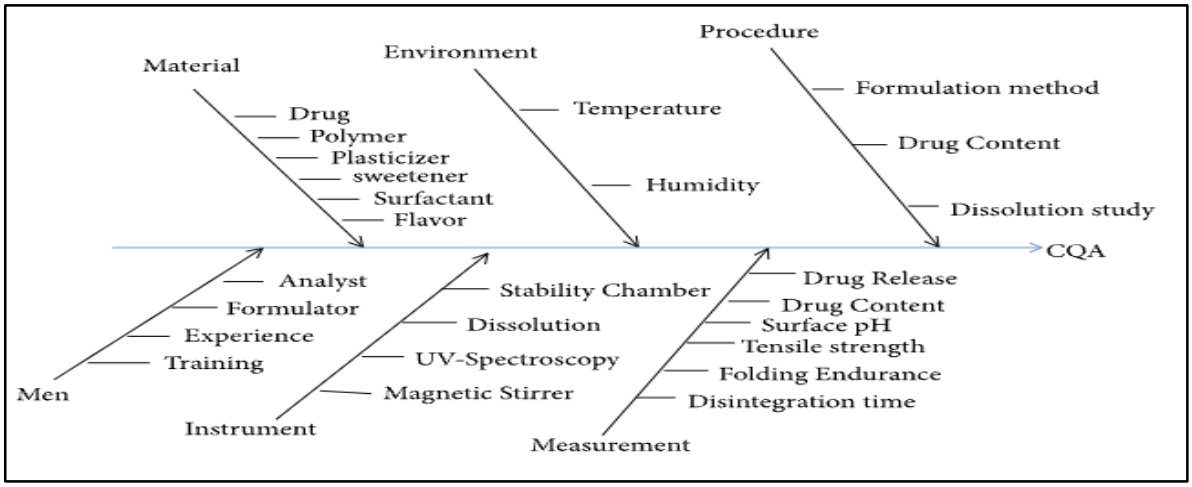


Figure 6.2: Ishikawa fish-bone diagram depicting the cause-and-effect relationship among the formulation and process variables.

❖ **Optimization of Formulation using 3^2 full factorial design [117-120]**

Based on preoptimisation studies, highly influential material attributes and process parameters were taken and optimization was carried out. A 3^2 full factorial design with 2 factors and 3 levels was selected for optimization of ODF. Concentration of *Kollicoat*® IR (X_1), and PEG 400 (X_2) as significant independent variables affecting the CQAs and Tensile strength (Y_1), Load at yield (Y_2), Q2 (Y_3), Q5 (Y_4), Q10 (Y_5) and % elongation at break (Y_6) were taken as dependent variables. Design Expert Software [Version 12.0.1, Stat ease Inc., Minneapolis, MN) was used to evaluate the effect of significant factors on dependent variables (CQAs). The effect of independent variable one each dependent variable can be studied using following polynomial equation.

$$Y= \beta_0+\beta_1X_1+\beta_2X_2+\beta_3X_1X_2+\beta_4X_1^2+\beta_5X_2^2\ldots..\beta nXn.$$

Here, Y is the response, β_0 is intercept and β_1 to β_n are coefficients for independent variables. In equation, positive sign of the coefficientsuggests a symbiotic effect on the response while the negative sign suggests an inimical effect on the response.

The response may be linear; two factor interaction, quadratic or cubic. Polynomial equations were generated for each CQA. The response surface plot is useful in learning about the main and the interaction effects of the independent variables, whereas the 2D contour plots give a visual representation of values of the responses. In order to visualize the effect of independent variables on each response 3D response plot and 2D contour plots were constructed. Optimization was done both graphically and numerically and a design space was generated where all the desired criteria of CQA were met. From design space, six check point batches were selected and formulated to validate the methodology. Observed and predicted response was compared and PRESS values were calculated. The experimental matrix depicting the actual values and coded values of selected independent variables as received by design expert is depicted in Table 6.20 and6.21.

Sr. No.	**Independent Variables**	**Levels**		
		-1	**0**	**1**
1	*Kollicoat*® IR (mg)	300	600	900
2	PEG 400 (%)	2	5	8

Table 6.20: Independent variables of DoE

Run	**Coded Values**		**Actual Values**	
	A: *Kollicoat*® IR	**B: PEG 400**	**A: *Kollicoat*® IR**	**B: PEG 400**
1	-1	-1	300	2
2	-1	0	300	5
3	-1	1	300	8
4	0	-1	600	2
5	0	0	600	5
6	0	1	600	8
7	1	-1	900	2

8	1	0	900	5
9	1	1	900	8

Table 6.21: Coded values and actual values of DoE

Optimization of Design

The computation for optimized formulation was carried using design expert software (Design Expert®, Stat Ease, Version 12.0.1). The optimized formulation was obtained by applying constraints (goals) on the dependent variables. The models were evaluated in terms of statistically significant coefficients and R^2 values. Both numerical and graphical methods were applied to find the optimum conditions and an overlay plot was generated.

Validation of design using check point batch

A checkpoint analysis was performed to confirm the role of the derived polynomial equation and contour plots in predicting the responses. Values of independent variables were taken at 3 points and the theoretical values of CQAs were calculated by substituting the values in the polynomial equation.

6.11. Formulation and Development of orodispersible film

Preparation of ODF

ODF of VAR was prepared by solvent casting technique. Various steps involved for preparation of or dispersible film are as follows:

Preparation of Film Drug and Polymer Solution

Aqueous solution 'A' was prepared by dissolving *Kollicoat*® IR in 15 ml of distilled water with stirring to produce solution. Aqueous solution 'B' was prepared by dissolving physical mixture of drug, stevia, citric acid and PEG 400 in specific proportion in distilled water. The aqueous solutions 'A' and 'B' were mixed and stirred for 1 h. The solutions were cast on to 9 cm diameter of glass petri plate.

Drying of the Solution:

Petri dish and were dried in the oven at 45 ^{0}C for 6 hr till a peel able film was formed.

Cutting the Final Dosage Form

The dried films were then cut into 2*2 cm

Now, if 2 × 2 cm^2 film contains 1 mg of DXM Hbr

Than for 63.58 cm^2= 63.58× 1/4 =15.895=15.9 mg of VAR require per batch

Packaging of the Films

The samples were packed in aluminium foil.

6.12. Characterization of VAR -ODF

- **Thickness**

Thickness of every oral film was determined at five different places using Vernier calliper micrometre. Average thickness and standard deviation of each oral film formulation was determined.

- **Films Weight**

Three films of 2 × 2 cm2 size were cut randomly from each film formulation. Films were weighed individually on electronic balance and the mean weight for each batch was calculated.

- **Folding endurance**

It was determined by folding the film of uniform cross-sectional area and thickness until it breaks. The number of times film was folded without breaking computed as the folding endurance value. This test ensures the tensile strength of the film.

- **Surface pH**

The surface pH of films was determined to investigate the possible side effect because of change in pH in vivo, since an acidic or alkaline pH may cause irritation to oral mucosa. As an acidic or alkaline pH may cause irritation to the oral mucosa, it is determined to keep the surface pH as close to neutral as possible. This test was evaluated by placing the film in a petri dish. Then it was moistened with 0.5 ml of phosphate buffer and kept for 30 s. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibration for 1 min. The average of three determinations for each formulation was taken.

- ***In vitro* Disintegration time**

Disintegration time was measured by placing the film strip (2 × 2 cm^2) in a petri dish 6 cm in diameter containing 6 ml of phosphate buffer of pH 6.8. The medium was kept mildly agitated by swirling every 10 s. Time required for complete disintegration of the film was noted. The disintegration time is the time when a film starts to break or disintegrate. All the measurements were done in triplicate and average values was reported.

- **Drug content determination**

A 4cm^2 strip was sliced into small pieces to be dissolved in 100 ml phosphate buffer (pH 6.8) and shaken persistently for 24 h. Subsequently, the whole solution was for 15 min. After filtration, the drug was diluted appropriately and estimated spectrophotometrically (Shimadzu 1800, Japan) at a wavelength of at 236 nm (VAR) respectively. The experiment was performed in triplicate for all formulations and the average values were recorded [121].

- **Tensile Strength [122, 123]**

Tensile strength, elongation at break, was computed to evaluate the tensile properties of the strips Tensile strength of the film was checked by texture pro version v 2.1(Brookfield). During measurement the strips were pulled at the top clamp by adding weights in pan till the film broke. The tensile strength represented by the weight in grams required to break the film was determined using the following equation.

$$TS = F/A$$

where F is the maximum load applied on the film in Newton's(N) and A is the original cross-sectional area measured in squared centimetre (cm^2).

When stress is applied the film sample stretches and is referred to as strain. Strain is basically the deformation of the film divided by the original dimension of the film. Percent elongation at break (%) was calculated by dividing the length at the time of break of the strip by the initial length of the strip and multiplying by 100 using the following equation.

$$E\% = \frac{L - L_0}{L_0} \times 100,$$

where $L0$ is the initial length of the strip and L is the length at the time of break. The mechanical properties of the film give idea about to what extent the film can withstand

the force or stress during processing, packaging, transport and handling. The desirable characteristics of film are moderate tensile strength, low elastic modulus, high % strain and high load at yield.

- ***In vitro* Dissolution Study**

A novel dissolution method employing with mini-vessels (50 mL) was used for real-time monitoring of release from ODF's with the help of magnetic stirrer. The *in vitro* dissolution studies were conducted using 50mL glass beaker with 25mL of dissolution media (buffer solution of pH 6.8) The temperature of the dissolution medium was maintained at 37.0 + 0.5 0C and the stirring speed controlled at 50 rpm. Film (2×2cm2) was placed on one side of the beaker using double-sided tape. 5mL samples were withdrawn at 2-minute time intervals and every time replaced with 5mL of fresh dissolution medium. The samples were analysed by measuring UV absorbance at 236nm [124].

6.13. Evaluation of taste masking

It was performed as mentioned in section 6.5.

6.14. Stability Studies

The stability studies were conducted according to ICH guidelines, to investigate the effect of temperature, relative humidity on drug in different formulations. Final optimized formulation was subjected to aggravated conditions of temperature and relative humidity, by wrapping it in aluminium foil and packaging it in glass container. The films were kept in stability chamber, at 40±0.5°C temperature and 75 ± 5% RH for 3 months. After 1, 2 and 3 months, Samples were withdrawn at specific time interval and evaluated. The films were characterized for physical appearance, mechanical properties, drug content and *in vitro* drug release profile at regular intervals of 10 days. The study was continued for 3 months.

6.15. Preparation of transdermal patch

A transdermal patch of VAR was developed to check its effect on drug release to improve patient compliance. Formulation was prepared as per the formula given in Table 6.22. Prepared patch was evaluated for various parameters like appearance, folding endurance, % drug content and *in vitro* drug release.

Ingredients	Amount
Drug (mg)	1
HPMC E5 (gm)	0.5
PVP (gm)	0.2
Propylene Glycol (%)	0.025
Solvent (water: methanol)	3 : 1

Table 6.22: Composition of Transdermal patch of VAR

CHAPTER 7. RESULT AND DISCUSION

Formulation and development of orally disintegrating film of DXM Hbr

7.1. Preformulation Studies for Dextromethorphan Hbr (DXM Hbr)

7.1.1. Identification of Drug/ Organoleptic properties

Received drug sample was evaluated visually and tested for colour, odour and taste. The observations are recorded in Table 7.1. This qualitative evaluation of the drug is an important characteristic in oral drug delivery systems i.e., palatability. Patient compliance is dependent on satisfactory taste determined by the target audience. Formulations under consideration in this study are intended to administer orally where taste of drug may influence the formulation composition. If, the drug is bitter than it may require taste masking to make it palatable.

Properties	**DXM Hbr Hbr standard**	**DXM Hbr HBR sample**
Colour (appearance)	White crystalline solid	White crystalline solid
Odour	Odourless	Odourless
Taste	Bitter	Bitter

Table 7.1: Organoleptic characteristics of Drugs

Observed characteristics are relevant to the reported data of DXM Hbr. Closeness of the reported organoleptic properties with the experimental one has met the part of identification tests and needs further investigation.

7.1.2. Melting point

Melting point information can be used for compound identification or in estimation of purity. It is general rule that pure substances will exhibit sharp melting points, while impure materials (or mixtures) will melt over a broad range of temperature. Melting point of DXM Hbr was found to be 121-123 °C, confirming the purity of the drug. This suggested that the received sample could be DXM Hbr.

7.1.3. Flow Properties

The flow properties of powders are critical for an efficient for solid dosage form. A good flow of the powder or granulation to be compressed is necessary to assure efficient mixing and acceptable weight uniformity for the solid dosage form.

Flow properties	
Bulk Density (g/ml)	0.249
Tapped Density (g/ml)	0.432
Carr's Index	31.944
Hausner Ratio	1.469
Angle of Repose	57.5°

Table 7.2: Flow property of drugs

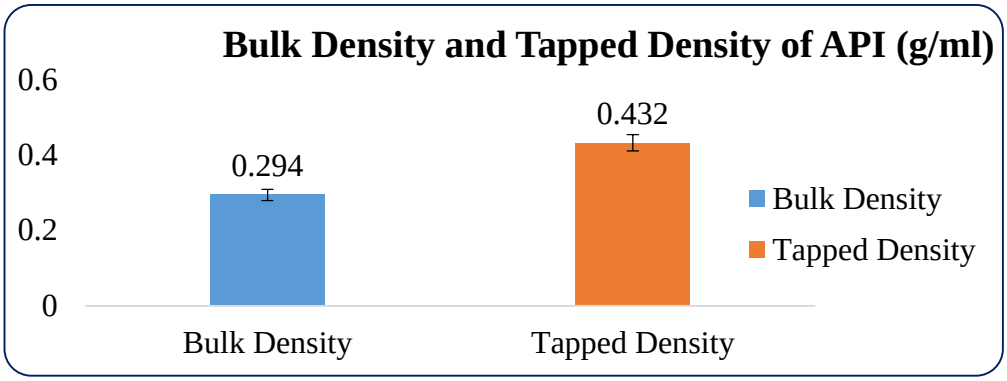


Figure 7.1: Bulk density and Tapped density of API (g/ml)

API having very poor flow in nature. But development of film formulation does not affect by API flow as the API is solubilise in appropriate solvent for film casting [125].

7.1.4. Solubility Study

The dissolving and dispersion liquids for drug delivery studies were picked in view of DXM Hbr solvency information in different liquids. Solubility of DXM Hbr Hbr in different solvent was reported in table 7.3.

Solvent	**Solubility (mg/ml)**
Distilled Water	14.7 ± 1.12

0.1 N HCl (pH 1.2)	9.7±0.98
4.5 Acetate Buffer	10.2±1.33
6.8 Phosphate Buffer	8.9±1.02
Ethanol	240.6±4.23

Table 7. 3: Solubility of DXM Hbr

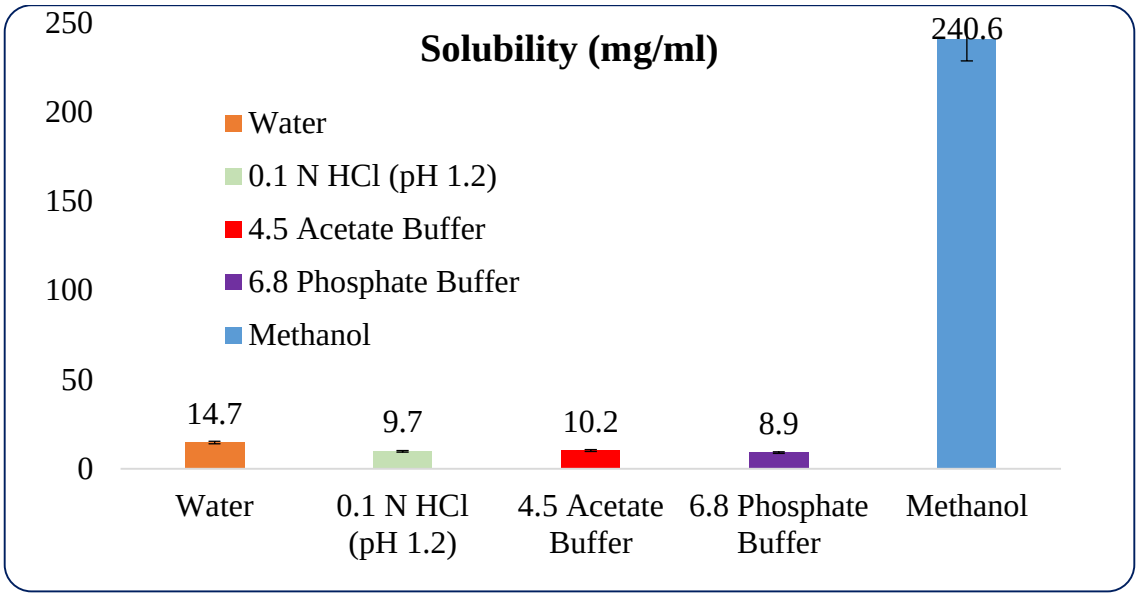


Figure 7.2: Solubility data of DXM Hbr

7.1.5. FTIR spectra of DXM Hbr

Identification of the drug sample DXM Hbr was confirmed from the FTIR spectrophotometer (Model-8400S, Shimadzu, Kroyoto, Japan). Spectra obtained by KBr pellet method. The FTIR spectrum of drug is shown in Figure 7.3 [126, 127].

Sr. No.	Inference	Standard wave no. (cm^{-1})	Observed wave no. (cm^{-1})
1	C=C (Aromatic)	1400 cm^{-1}	1303.79 cm^{-1}
2	C–O stretch	1000 – 1300 cm^{-1}	1035.70 cm-1
3	C–H (Aromatic bending)	900-675 cm^{-1}	823.56 cm^{-1}
4	C–N (Stretching)	1000 – 1350 cm^{-1}	1303.79 cm^{-1}
5	N- H (bending)	3500 – 3000 cm^{-1}	3473.56 cm^{-1}

Table 7. 4: FTIR spectra of DXM Hbr loaded samples

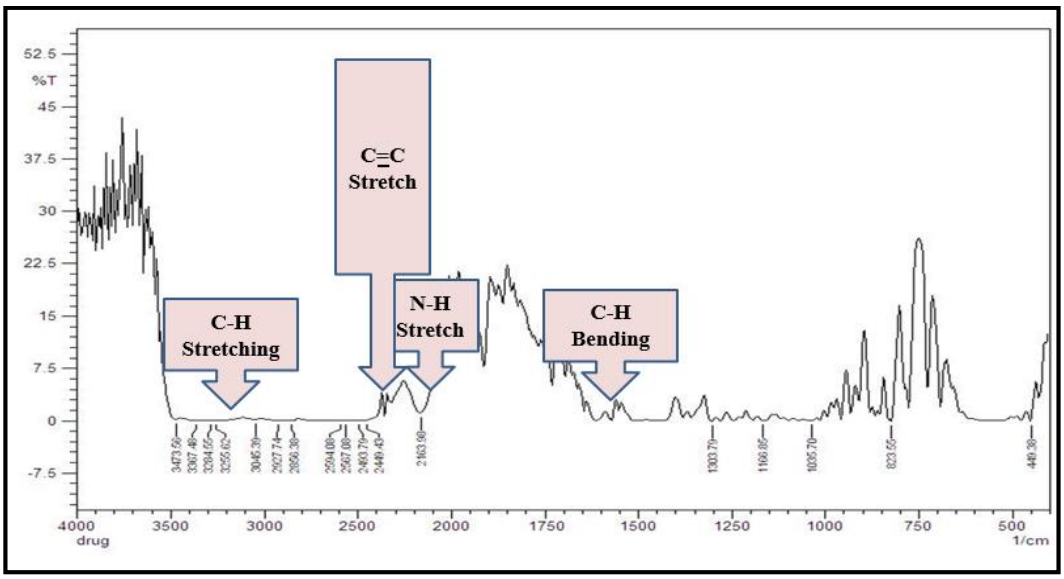


Figure 7.3: FTIR Spectra of Pure Drug

7.1.6. UV visible spectrophotometry determination of absorption maximum (λmax)

Stock solution of the DXM Hbr Hbr (1 mg/ml) was prepared in a phosphate buffer (pH 6.8) and a 100 µg/ml solution was scanned over the wavelength range 200–400 nm. DXM Hbr Hbr exhibited maximum absorption at 279.4 nm.

7.1.7. Calibration Curve

DXM Hbr Hbr Calibration Curve in Phosphate buffer pH 6.8

Accurately weighed 10mg DXM Hbr was dissolved in 100 ml of Phosphate buffer pH 6.8to obtain a solution of 100 µg/ml. From the above prepared stock solution, aliquots were taken and appropriately diluted to obtain 10,20,30,40,50, and 60 µg/ml concentrations of DXM Hbr. Absorbance of each solution was measured in triplicate at 279.4 nm. against 6.8 pH phosphate buffer as blank at that specific λmax. The absorbance of each concentration is shown in table 7.5 and the calibration curve is shown in figure 7.4.

Sr. No	Concentration (µg/ml)	Absorbance ± SD
1	0	0

2	10	0.065 ± 0.004
3	20	0.138 ± 0.003
4	30	0.193 ± 0.004
5	40	0.255 ± 0.002
6	50	0.310 ± 0.005
7	60	0.382 ± 0.003

Table 7.5: Absorbance of each concentration

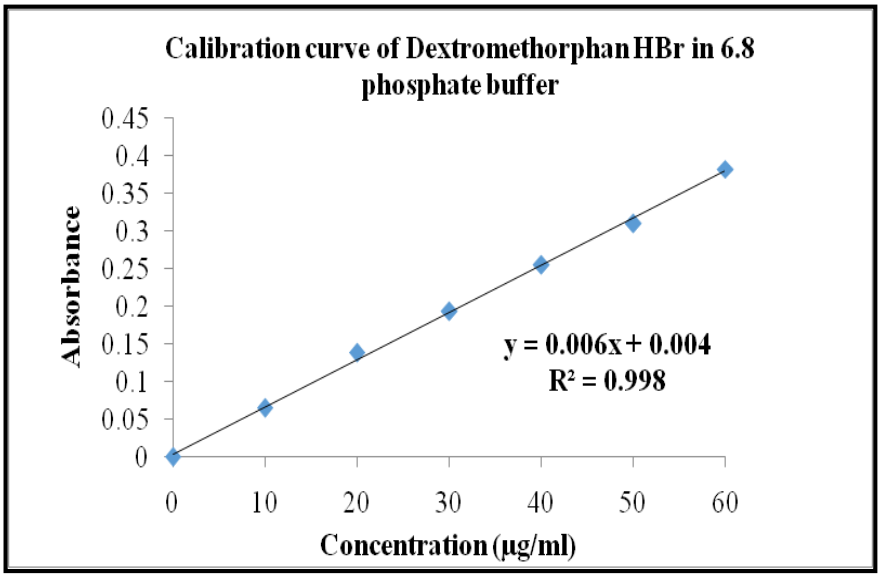


Figure 7.4: Standard Curve of DXM Hbr in Phosphate buffer pH 6.8

7.1.8. Drug-Polymers Interaction Studies

The individual drugs and polymer were separately scanned. All the spectra were compared for confirmation of common peaks. Dextromethorphan and with polymer showed no significant variation in intensity and position peaks, suggesting that drugs and excipients were compatible. Hence, it can be concluded that the drugs DXM Hbr is in free State. The spectra are reported in the Figure 7.5, Figure 7.6and Figure 7.7. The individual IR spectrum of the pure drug was found to be similar to that of its standard spectrum.

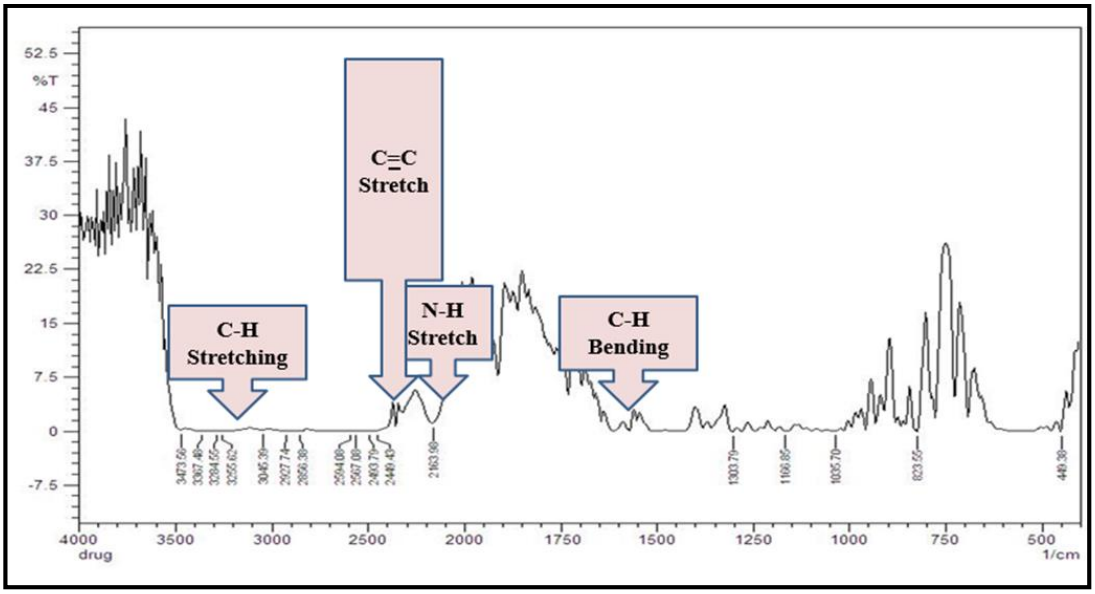


Figure 7.5: FTIR Spectra of Pure Drug (DXM Hbr)

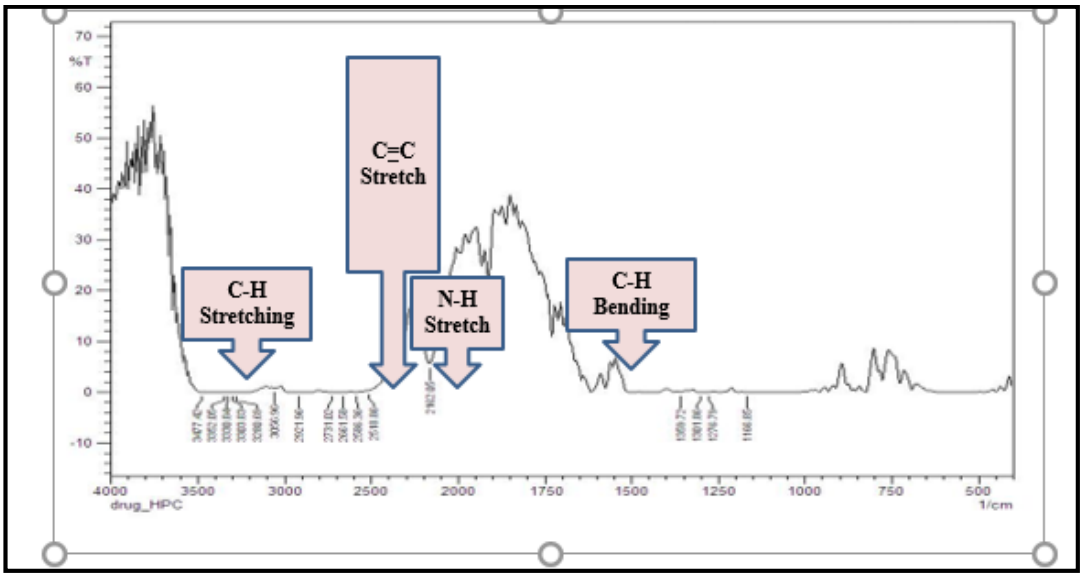


Figure 7.6: FTIR Spectra of Hydroxypropyl cellulose

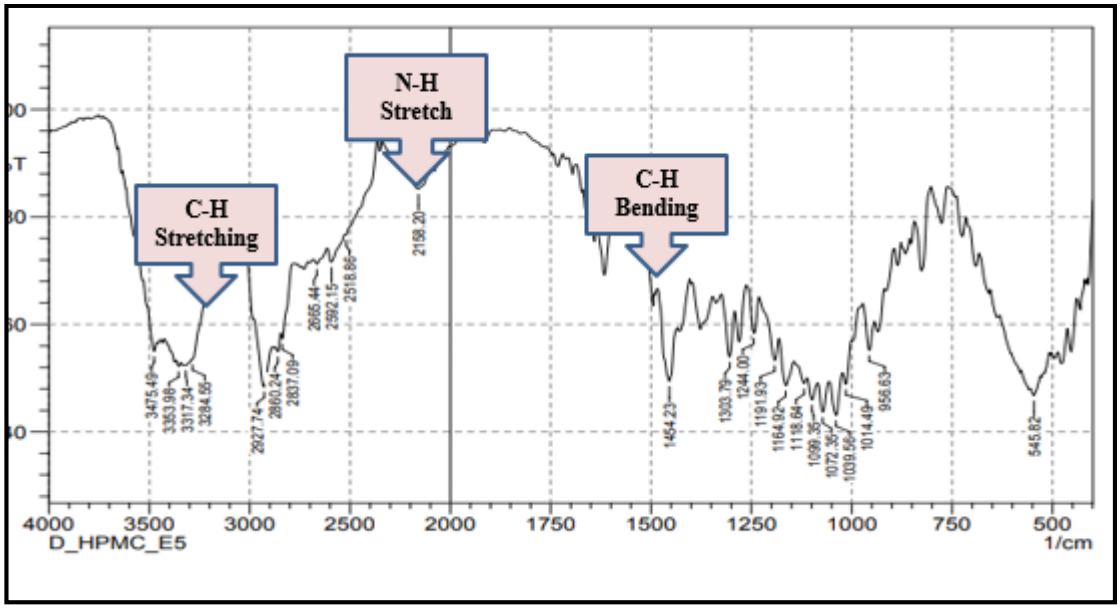


Figure 7.7: FTIR Spectra of DXM Hbr with Hydroxypropyl methyl cellulose E5

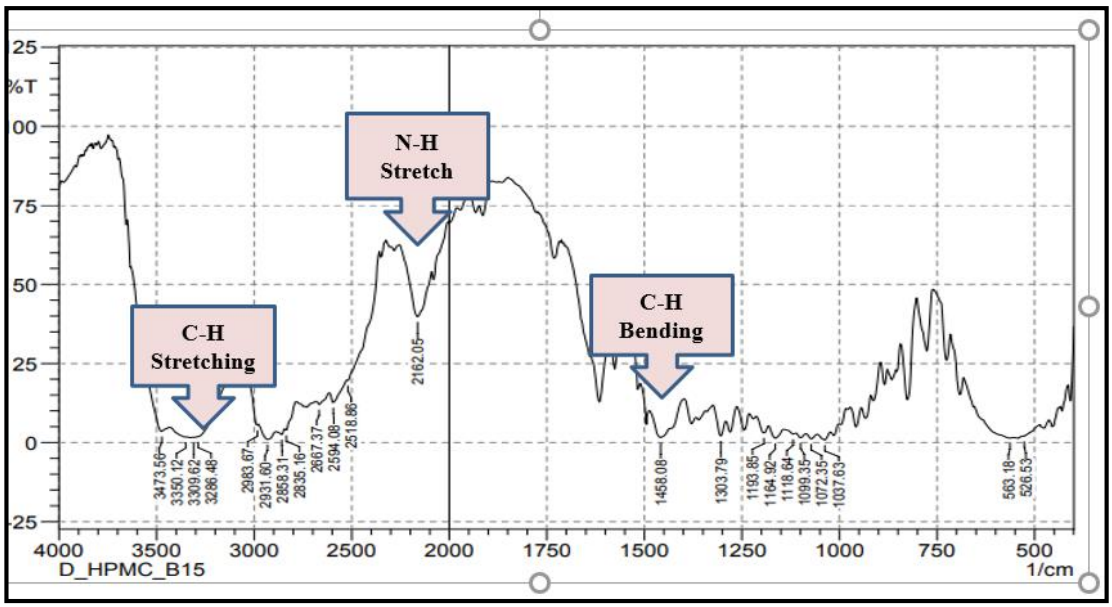


Figure 7.8: FTIR Spectra Dextromethorphan HBr with HPMC E15

7.1.9. Polymer screening

Various polymers are screened or the formulation of DXM Hbr such as hydroxypropyl methyl cellulose (HPMC) E5LV, HPMC E15LV, PVP K 30, polyvinyl alcohol and hydroxypropyl cellulose. Five monopolymeric films trial batches T1 -T5 shown in **Table 7.6** were prepared to screen polymers on the basis of film characteristics such as film forming capacity, appearance, spreadability, peelability and mechanical

characteristics. The films casted on glass petri dishes. PEG 400 was added as a plasticizer [127-129].

Parameters	T1	**T2**	**T3**	**T4**	**T5**
Appearance	Transparent	**Transparent**	Transparent	Transparent	Transparent
Texture	Smooth	**Smooth**	Smooth	Smooth	Smooth
Spradability	Good	**Good**	Average	Poor	Poor
Peelability	Easily Peelable	**Easily Peelable**	Easily Peelable	Not Easily Peelable	Not Easily Peelable
Stickiness	Non Sticky	**Non Sticky**	Sticky	Sticky	Sticky
Folding Endurance	116.67±4.18	**205.12±5.98**	98.23± 4.23	95.18±4.19	80.65± 3.68

Table 7.6: Result and observation of trial batches for selection of polymer

The film prepared using 100 mg of HPMC E5 LV and HPMC E15 LV was acceptable with respect to, film forming capacity, appearance, spreadability, peelability and mechanical characteristics. The films prepared by 100 mg of polyvinyl pyrrolidone K 30, polyvinyl alcohol and hydroxypropyl cellulose showed poor spreadability and mechanical characteristic and were sticky in nature. On the basis of good mechanical characteristic in terms of folding endurance HPMC E15 LV was selected for formulation development of ODF of DXM Hbr.

7.1.10. Selection of plasticizer

The addition of a plasticizer is often necessary to obtain flexible, non-brittle ODFs.

Discussion: PEG 400 was selected for the formulation development of ODF as it shows good film forming capacity, mechanical strength and non sticky films were produced.

7.1.11. Formulation and Development of orodispersible film

- **Taste masking of DXM Hbr ODF**

The drug-resin complex was optimized based on the different conditions of drug loading on to the resin. The selected ratio of drug and ratio of drug to resin and percentage drug loaded shown in table 7.7. The ratio of drug to resin was selected as 1:1.25 as there was no significant increase in the drug loading at a ratio of 1:1.50.

Sr. no.	Ratio	% Drug complex	Conclusion
1	1:0.25	31.5%	Not Satisfactory
2	1:0.50	45.3%	Not Satisfactory
3	1:0.75	67.8%	Not Satisfactory
4	1:1	83.4%	Not Satisfactory
5	**1:1.25**	**99.2%**	**Satisfactory**
6	1:1.50	99.4%	Satisfactory

Table.7.7: Results of Drug Resin Complex

7.2. Preparation of ODF

ODF were prepared using solvent casting method and characterized.

7.3. Application of Quality by Design in optimization of ODF

After application of QTPP, CQA and Risk assessment the design of experiment was applied to optimize the ODF.

Selection of Design (Plackett Burman Design)

Design of experiments (Design-Expert) has been used as a valuable tool for. identifying important parameters to optimize the formulation process. The amount (mg) of film former polymer HPMC E15LV (X_1) amount (ml) of plasticizer (PEG 400) (X_2), saliva stimulating agent (citric acid) (X_3) and sweetener (Aspartame) (X_4) were selected as independent variables, in this study. These four factors were evaluated, each at two levels. Each variable was represented at two levels, namely, "high" and "low" and they are depicted in Table 7.8. These levels define the upper and lower limits of the range covered by each variable. In addition to the variables of real interest, the Plackett–Burman design considers insignificant dummy variables, whose number should be one-third of all variables. The dummy variables, which are not assigned any values, introduce some redundancy required by the statistical procedure. Incorporation of the dummy variables into an experiment allows an estimation of the variance (experimental error) of an effect.

Factors (Independent variables)	**Levels (mg)**	
	-1	**+1**
X_1 =HPMC E15 LV (mg)	50	100
X_2 =PEG 400 (ml)	0.25	0.75
X_3= Citric acid (mg)	2	6
X_4= Aspartame (mg)	2.5	7.5

Table 7.8: Screening of independent variables in a Plackett–Burman design.

The formulation composition of prepared factorial batches is shown in Table 7.9.

Material (mg/film)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
DXM Hbr	10	10	10	10	10	10	10	10	10	10	10	10
Kyron T-314	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5
HPMC E15 LV	50	50	50	150	50	150	150	50	50	150	150	150

PEG 400	0.2	0.2	0.2	0.7	0.7	0.7	0.2	0.7	0.7	0.7	0.2	0.2
Citric Acid	6	2	2	2	6	6	6	2	6	2	2	6
Asparta me	7.5	7.5	2.5	7.5	2.5	2.5	2.5	2.5	7.5	7.5	2.5	7.5
Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Table 7.9: Formulation composition of prepared factorial batches

In a multivariable system PBD is powerful and useful mathematical tool for the determination of key factors on a particular response generated by conducting a smaller number of experimental trials, but this method does not determine the exact quantity, it provides some essential evidence about each factor by performing comparatively few experiments. The purpose of PBD is to evaluate the effect of the processing variables and identify the key one influencing the responses like folding endurance, disintegration time and dissolution at the end of 2 min (Q2).

In the present study, each variable was investigated at two levels namely high level (+ 1) and low level (− 1). The effects of 4 independent variables on dependent variables (response) were investigated by 12 runs of experiments. Table 7.8shows the factors under investigation as well as the level of each factor used in the experimental design. The factor ranges were selected based on prior knowledge from the initial trial experiments. The assessment comprised of evaluating the response in all the conditions showed in table 7.10.

Run Order	**HPMC E15 LV**	**PEG 400**	**Citric Acid**	**Aspartame**	**Disintegration Time (Sec)**	**Folding Endurance**	**Dissolution at 2 min (%)**
1	50	0.25	6	7.5	27 ± 1.9	102 ± 11.3	28.9±1.13
2	50	0.25	2	7.5	28 ± 2.3	108 ± 10.5	27.6±1.68
3	50	0.25	2	2.5	28 ± 1.4	106 ± 9.6	28.1±0.98
4	150	0.75	2	7.5	57 ± 3.6	271 ± 15.6	19.9±1.44

5	50	0.75	6	2.5	28 ± 1.1	115 ± 10.1	26.7±1.23
6	150	0.75	6	2.5	56 ± 4.5	268 ± 12.4	20.6±1.36
7	150	0.25	6	2.5	51 ± 5.6	254 ± 8.4	21.3±1.36
8	50	0.75	2	2.5	29 ± 3.2	114 ± 10.6	26.9±1.46
9	50	0.75	6	7.5	30 ± 1.8	119 ± 6.7	26.1±1.20
10	150	0.75	2	7.5	57 ± 2.2	270 ± 8.9	20.8±1.02
11	150	0.25	2	2.5	50 ± 2.9	259 ± 10.6	21.9±1.32
12	150	0.25	6	7.5	51 ± 2.6	261 ± 12.3	22.3±1.18

Table 7.10: Plackett–Burman experimental design matrix (in coded level) and experimental results.

Other parameters are also evaluated such as appearance, texture, spreadability, peelability, stickiness thickness, weight variation, surface pH and drug content The results are shown in table 7.11, 7.12 and 7.13.

Batch	**Appearance**	**Texture**	**Spradability**	**Peelability**	**Stickiness**	**Weight Variation ± SD (mg)**	**Thickness ± SD (mm)**	**Surface pH**	**Assay ± SD (%)**
F1	Transparent	Smooth	Good	Easily Peelable	Non Sticky	74.9 ± 2.5	0.32 ± 0.01	6.5 ± 0.1	99.5 ± 0.3
F2	Transparent	Smooth	Good	Easily Peelable	Non Sticky	69.4 ± 1.9	0.34 ± 0.02	6.6 ± 0.2	99.7 ± 0.4
F3	Transparent	Smooth	Good	Easily Peelable	Non Sticky	76.5 ± 2.5	0.31 ± 0.01	6.9 ± 0.1	98.5 ± 0.5

F4	Transparent	Smooth	Good	Easily Peelable	Non Sticky	102.3 ± 3.4	0.45 ± 0.02	6.8 ± 0.1	97.6 ± 1.6
F5	Transparent	Smooth	Good	Easily Peelable	Non Sticky	74.1 ± 2.1	0.35 ± 0.01	6.8 ± 0.1	98.9 ± 1.2
F6	Transparent	Smooth	Good	Easily Peelable	Non Sticky	109.5 ± 5.6	0.42 ± 0.03	6.4 ± 0.2	99.3 ± 1.9
F7	Transparent	Smooth	Good	Easily Peelable	Non Sticky	106.2 ± 4.5	0.44 ± 0.02	6.9 ± 0.1	99.9 ± 0.4
F8	Transparent	Smooth	Good	Easily Peelable	Non Sticky	71.3 ± 2.3	0.33 ± 0.02	6.5 ± 0.3	98.7 ± 0.6
F9	Transparent	Smooth	Good	Easily Peelable	Non Sticky	82.3 ± 1.9	0.32 ± 0.01	6.7 ± 0.2	99.1 ± 0.3
F10	Transparent	Smooth	Good	Easily Peelable	Non Sticky	103.2 ± 3.4	0.43 ± 0.03	6.8 ± 0.1	99.3 ± 0.5
F11	Transparent	Smooth	Good	Easily Peelable	Non Sticky	115.1 ± 2.9	0.45 ± 0.01	6.9 ± 0.2	98.6 ± 1.6
F12	Transparent	Smooth	Good	Easily Peelable	Non Sticky	110.5 ± 3.4	0.46 ± 0.02	6.8 ± 0.1	99.1 ± 0.8

Table 7.11: Results of factorial batches

Parameters	**Weight Variation ± SD (mg)**	**Thickness ± SD (mm)**	**Surface pH**	**Assay ± SD (%)**	**Disintegration Time ± SD (Sec)**	**Folding Endurance ± SD**
F1	74.9 ± 2.5	0.32± 0.01	6.5 ± 0.1	99.5 ± 0.3	27 ± 1.9	102 ± 11.3
F2	69.4 ± 1.9	0.34 ± 0.02	6.6 ± 0.2	99.7 ± 0.4	28 ± 2.3	108 ± 10.5

F3	76.5 ± 2.5	0.31 ± 0.01	6.9 ± 0.1	98.5 ± 0.5	28 ± 1.4	106 ± 9.6
F4	102.3 ± 3.4	0.45 ± 0.02	6.8 ± 0.1	97.6 ± 1.6	57 ± 3.6	271 ± 15.6
F5	74.1 ± 2.1	0.35 ± 0.01	6.8 ± 0.1	98.9 ± 1.2	28 ± 1.1	115 ± 10.1
F6	109.5 ± 5.6	0.42 ± 0.03	6.4 ± 0.2	99.3 ± 1.9	56 ± 4.5	268 ± 12.4
F7	106.2 ± 4.5	0.44 ± 0.02	6.9 ± 0.1	99.9 ± 0.4	51 ± 5.6	254 ± 8.4
F8	71.3 ± 2.3	0.33 ± 0.02	6.5 ± 0.3	98.7 ± 0.6	29 ± 3.2	114 ± 10.6
F9	82.3 ± 1.9	0.32 ± 0.01	6.7 ± 0.2	99.1 ± 0.3	30 ± 1.8	119 ± 6.7
F10	103.2 ± 3.4	0.43 ± 0.03	6.8 ± 0.1	99.3 ± 0.5	57 ± 2.2	270 ± 8.9
F11	115.1 ± 2.9	0.45 ± 0.01	6.9 ± 0.2	98.6 ± 1.6	50 ± 2.9	259 ± 10.6
F12	110.5 ± 3.4	0.46 ± 0.02	6.8 ± 0.1	99.1 ± 0.8	51 ± 2.6	261 ± 12.3

Table 7.12: Results of factorial batches in triplicate (n=3)

Time (min)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
0	0	0	0	0	0	0	0	0	0	0	0	0
2	28.9	27.6	28.1	19.9	26.7	20.6	21.3	26.9	26.1	20.8	21.9	22.3
4	52.1	53.7	52.5	42.5	50.8	41.9	43.9	51.2	52.3	43.9	44.3	45.5
6	77.5	79.8	78.1	70.6	76.2	68.7	70.8	76.4	76.1	70.4	71.5	73.6

8	96.7	98.1	97.6	85.3	94.2	84.2	85.8	95.2	95.6	86.1	86.9	85.1
10	99.5	99.2	98.9	95.2	98.3	94.9	96.4	98.6	98.2	96.5	97.2	96.7

Table 7.13: Results of dissolution study of factorial batches

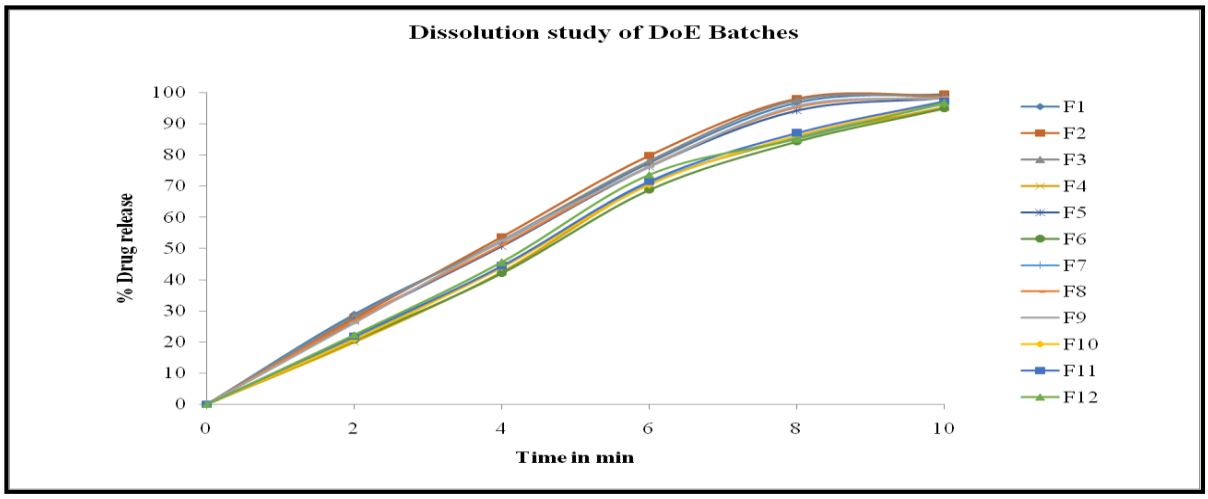


Figure 7.9: Dissolution profile of Factorial Batches

The Plackett Burman design is a useful and efficient mathematical approach to evaluate the effect of a large number of factors on a particular response generated by conducting a small number of experimental trials. Each variable was evaluated at two levels, high level (+1) and low level (-1). The factor ranges were selected based on prior knowledge about the system under study. The evaluation consisted of analyzing the response in all the conditions quoted in Table 7.10. The Plackett Burman design was chosen for identification of main factors that causes variability in product quality.

The disadvantage of design is that interactions between variables are generally confounded and cannot be easily determined, as there are not enough degrees of freedom. Also, unless treatments are replicated variability cannot be evaluated. While these are significant limitations when a large number of studies would be needed to implement higher resolution factorial designs, the Plackett Burman can be a pragmatic solution.

For the Plackett Burman Designs, the number of factors to be evaluated is up to 1 less than the number of runs or trials in the study. These designs do not exist for

all the possible number of runs. The original study paper published 8, 12, 16, 20, 24….96 and 100 runs. Thus, it is possible to study 7 factors in 8 runs, 11 factors in 12 runs and even 99 factors in 100 runs. To analyse the results, the expected values of a set of samples taken from a distribution of the absolute values of X (|X|) where X is distributed normally.

For the Plackett Burman –DoE, 4 parameters were chosen based upon risk estimation matrix and for each variable two treatment levels were identified by combination of prior experiences and the preliminary formulation studies in which small scale experiments were performed to determine the range of formulation and processing parameters. The levels were identified by a combination of prior experience and the preliminary formulation studies in which small set of experiments were done to determine the range of formulation and processing parameters. Once the variables and their levels have been chosen, the variables were randomly assigned to 12 experiment of the Plackett Burman DoE grid (Table 7.10). Further the influence of each factor on the response variable was also evaluated with the help of Pareto charts and normal plot. At this point the goal is to identify the CQAs for which future development efforts can be focused based upon the risk associated with each factor.

Effect of Independent variables on Disintegration time

The ANOVA table represented as Figure 7.10. suggested that Factors HPMC E15 LV and PEG 400 were significant factors contributing to the response of disintegration time. Citric acid and aspartame however, have p values >0.05 hence they were not considered critical for *in vitro* disintegration time. The Normal plot, half normal plot and residual plot showed uniform distribution of response and no outlier was observed in the presented graphs.

Analysis of Variance for Disintegration Time (Sec) (coded units)

Source	DF	Seq SS	Adj SS	Adj MS	F	P
Main Effects	4	1974.00	1974.00	493.50	287.87	0.000
HPMC E15 LV	1	1925.33	1925.33	1925.33	1123.11	0.000
PEG 400	1	40.33	40.33	40.33	23.53	0.002
Citric Acid	1	3.00	3.00	3.00	1.75	0.227
Aspartame	1	5.33	5.33	5.33	3.11	0.121
Residual Error	7	12.00	12.00	1.71		
Lack of Fit	6	12.00	12.00	2.00		
Pure Error	1	0.00	0.00	0.00		
Total	11	1986.00				

Figure 7.10: ANOVA table for *in vitro* disintegration time

Standardized pareto charts, representing the estimated effect of CPPs and CMAs on *in vitro* disintegration time can allow us to check the statistical significance of PBD. It consists of bars with a length proportional to the absolute value of the estimated effects divided by the standard error, which is the t- value of the student's t-test.

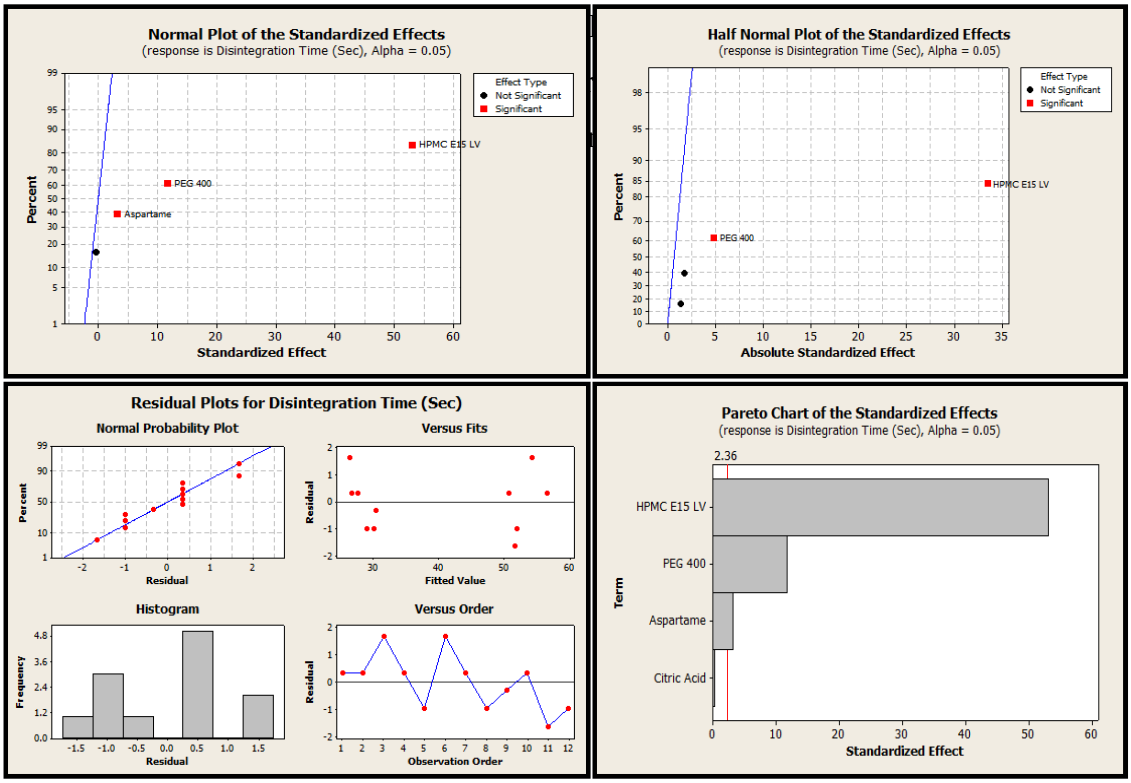


Figure 7.11: Normal plot, half normal plot, residual plot and Pareto chart for *in vitro* disintegration time

Main effect plot as shown in Figure 7.12, shows the effect of individual factor on the response. It can be observed that HPMC E15LV and PEG 400 showed significant positive relationship with response value. As the concentration of HPMC E15LV and PEG 400 increases the disintegration time also increase significantly. However, it can be observed from the graphs of citric acid and aspartame they have slightly negative and positive values [105, 131].

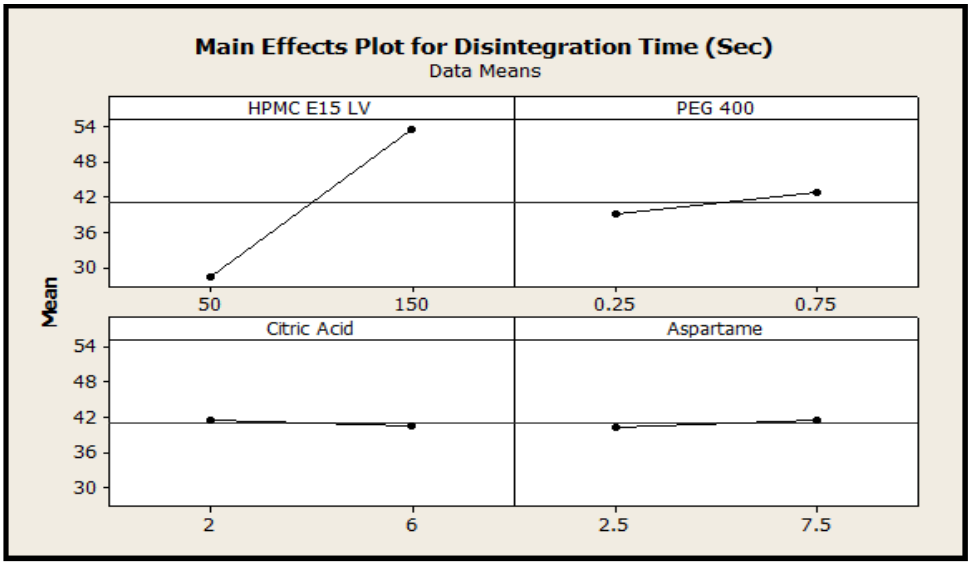


Figure7.12: Main effect plot for *in vitro* disintegration time

The contour plot and response surface plot for *in vitro* disintegration time showed that the response followed linear model. Variation in the results of disintegration time(30-55seconds) confirms proper selection of materials and their levels. The contour plot and response surface plot suggest negative linear relationship of factors with response (Figure 7.13)

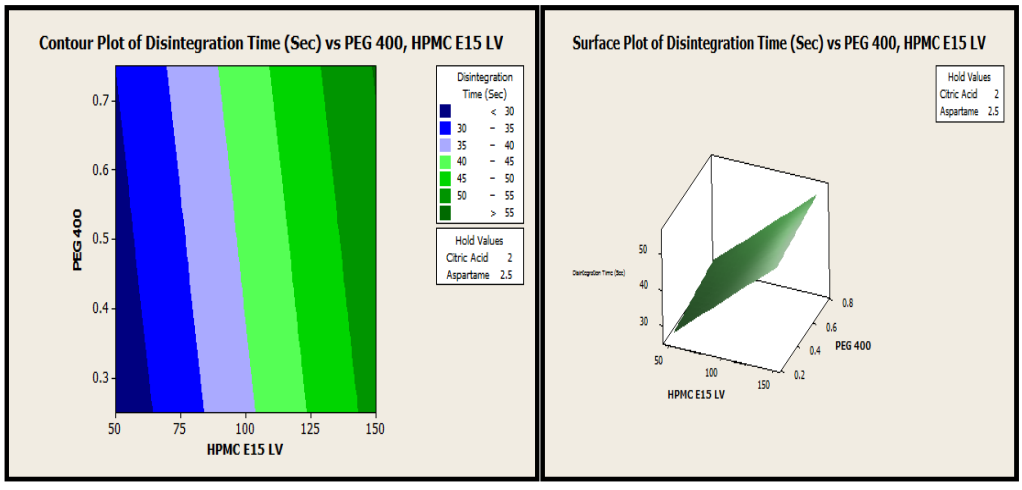


Figure 7.13: Contour plot and response surface plot for *in vitro* disintegration time

Effect of Independent variables on Folding endurance

The ANOVA table represented as Figure 7.14. suggested that Factor HPMC E15LV and PEG 400 were significant factors contributing to the response of folding endurance. Citric acid and aspartame however, have p values >0.05 hence they were not considered critical for folding endurance.

Analysis of Variance for Folding Endurance (coded units)

Source	DF	Seq SS	Adj SS	Adj MS	F	P
Main Effects	4	70779.7	70779.7	17694.9	3210.31	0.000
HPMC E15 LV	1	70380.1	70380.1	70380.1	12768.74	0.000
PEG 400	1	374.1	374.1	374.1	67.87	0.000
Citric Acid	1	6.7	6.7	6.7	1.22	0.305
Aspartame	1	18.7	18.7	18.7	3.40	0.108
Residual Error	7	38.6	38.6	5.5		
Lack of Fit	6	38.1	38.1	6.3	12.69	0.212
Pure Error	1	0.5	0.5	0.5		
Total	11	70818.3				

Figure 7.14: ANOVA table for folding endurance

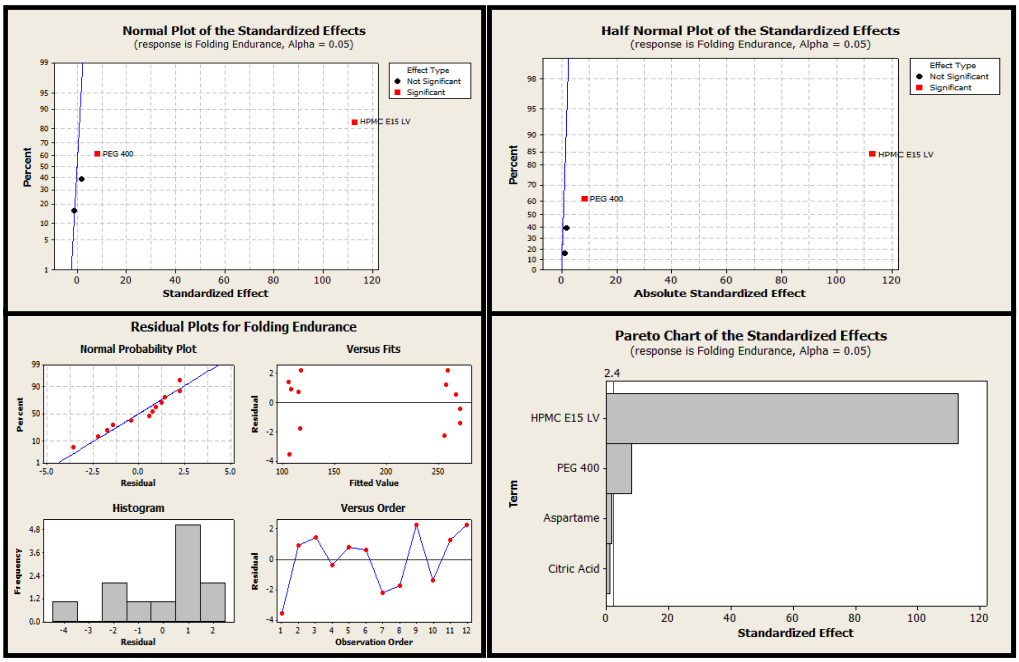


Figure 7.15: Normal plot, half normal plot, residual plot and Pareto chart for folding endurance

The Normal plot, half normal plot and Residual plot showed uniform distribution of response and no outlier was observed in the presented graphs.

Standardized pareto charts, representing the estimated effect of CPPs and CMAs on folding endurance can allow us to check the statistical significance of PBD. It consists of bars with a length proportional to the absolute value of the estimated effects divided by the standard error, which is the t- value of the student's t-test.

It can be observed from the Normal plot, half normal plot, residual plot and pareto chart only HPMC 15 LV and PEG 400 were considered as critical factors having significant effect on the response i.e., folding endurance

Main effect plot as shown in Figure 7.16, shows the effect of individual factor on the response. It can be observed that HPMC E15LV and PEG 400 showed significant positive relationship with response value. As the concentration of HPMC E15LV and PEG 400 increases the folding endurance also increase significantly. However, it can be observed from the graphs of citric acid and aspartame they have slightly negative values.

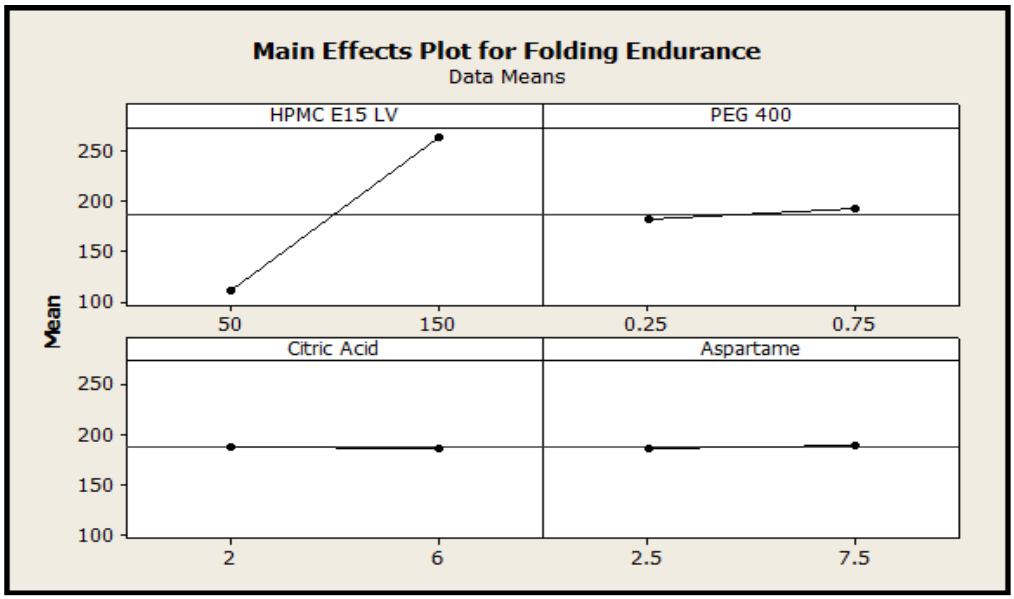


Figure 7.16: Main effect plot for folding endurance

The contour plot and response surface plot for folding endurance showed that the response followed linear model. Variation in the results of folding endurance confirms proper selection of materials and their levels. Positive relationship of HPMC E15LV and PEG 400can be observed from contour plot and response surface plot.

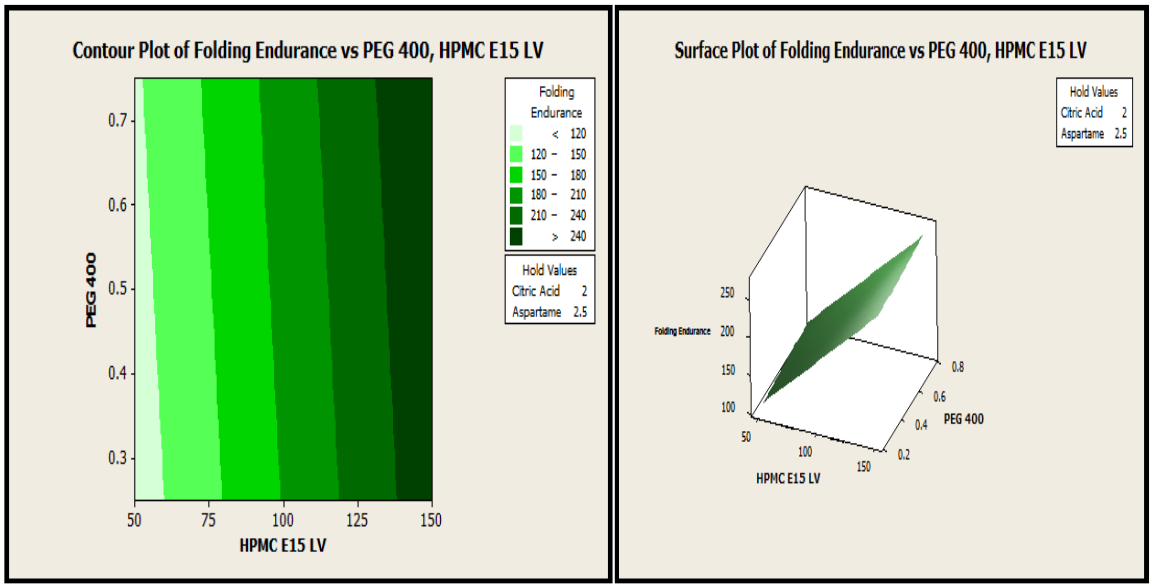


Figure 7.17: Contour plot and response surface plot for Folding Endurance

Effect of Independent variables on Q2 (Dissolution at 2 min)

The ANOVA table represented as Figure 7.18. suggested that Factor HPMC E15LV and PEG 400 were significant factors contributing to the response of Q2. Citric acid and aspartame however, have p values >0.05 hence they were not considered critical for folding endurance.

Analysis of Variance for Dissolution at 2 min (%) (coded units)

Source	DF	Seq SS	Adj SS	Adj MS	F	P
Main Effects	4	124.130	124.130	31.033	100.61	0.000
HPMC E15 LV	1	117.188	117.188	117.188	379.92	0.000
PEG 400	1	6.901	6.901	6.901	22.37	0.002
Citric Acid	1	0.041	0.041	0.041	0.13	0.727
Aspartame	1	0.001	0.001	0.001	0.00	0.960
Residual Error	7	2.159	2.159	0.308		
Lack of Fit	6	1.754	1.754	0.292	0.72	0.716
Pure Error	1	0.405	0.405	0.405		
Total	11	126.289				

Figure 7.18: ANOVA table for Q2

The Normal plot, half normal plot and Residual plot showed uniform distribution of response and no outlier was observed in the presented graphs (Figure 7.18).

Standardized pareto charts, representing the estimated effect of CPPs and CMAs on dissolution at 2 min can allow us to check the statistical significance of PBD. It

consists of bars with a length proportional to the absolute value of the estimated effects divided by the standard error, which is the t- value of the student's t-test.

It can be observed from the Normal plot, half normal plot, residual plot and pareto chart only HPMC 15 LV and PEG 400 were considered as critical factors having significant effect on the response i.e., dissolution at 2 min(Q2).

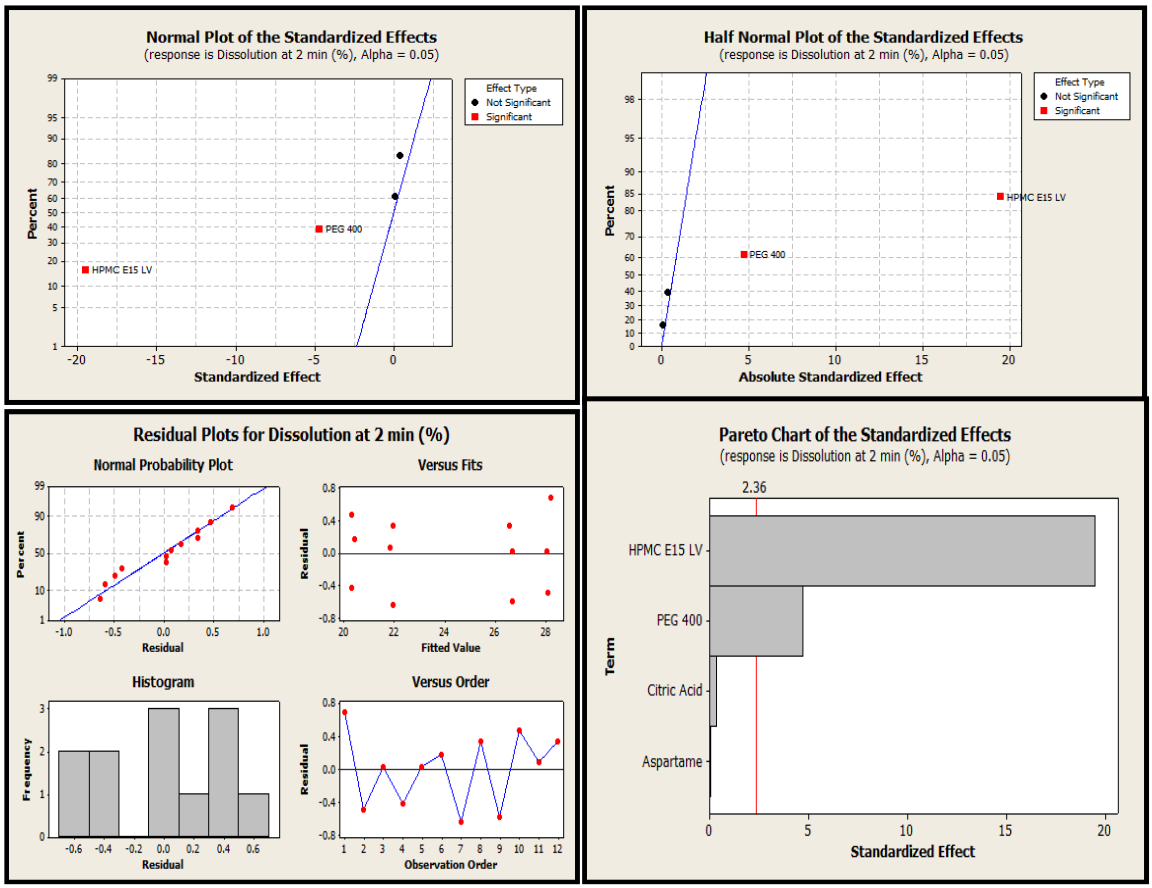


Figure 7.19: Normal plot, half normal plot, residual plot and Pareto chart for dissolution at 2 min. (Q2)

Main effect plot as shown in Figure 7.20., shows the effect of individual factor on the response. It can be observed that HPMC E15LV and PEG 400 showed significant negative relationship with response value. As the concentration of HPMC E15LV and PEG 400 increases the dissolution at 2 min decreases as it is a release retarding polymer. However, it can be observed from the graphs of citric acid and aspartame they do not have any significant relationship with the response. This can be contributed to the point that the plackett burman takes in to consideration only linear

relationship between dependent and independent variables. The main effect plot for dissolution at 2 min is shown in Figure 7.20.

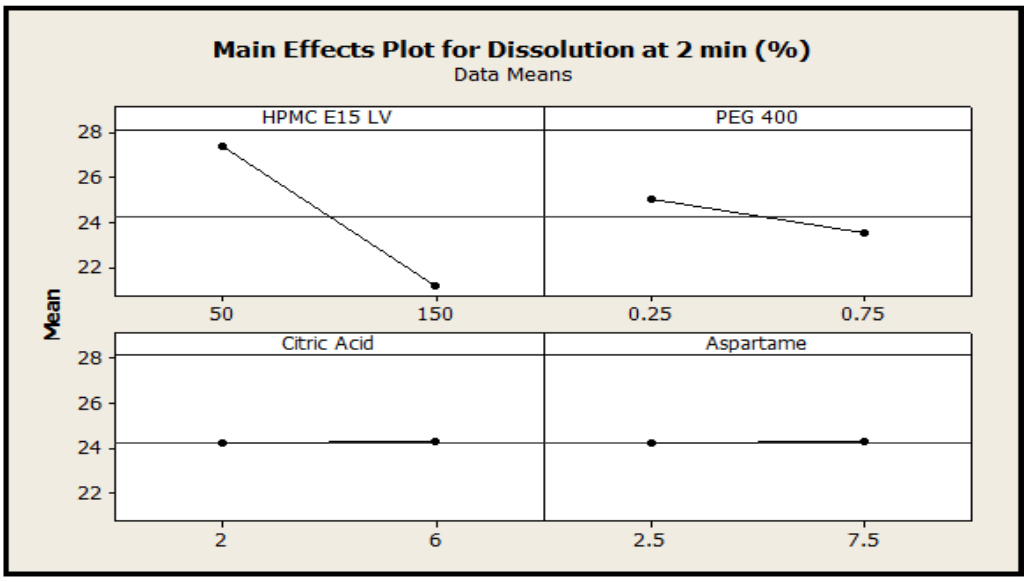


Figure 7.20: Main effect plot showing the relationship of independent variables on dissolution at 2 min (Q2)

The contour plot and response surface plot for dissolution at 2 min (Figure 7.21) showed that the response followed linear model. Variation in the results of disintegration time confirms proper selection of materials and their levels. Negative relationship of HPMC E15LV and PEG 400can be observed from contour plot and response surface plot.

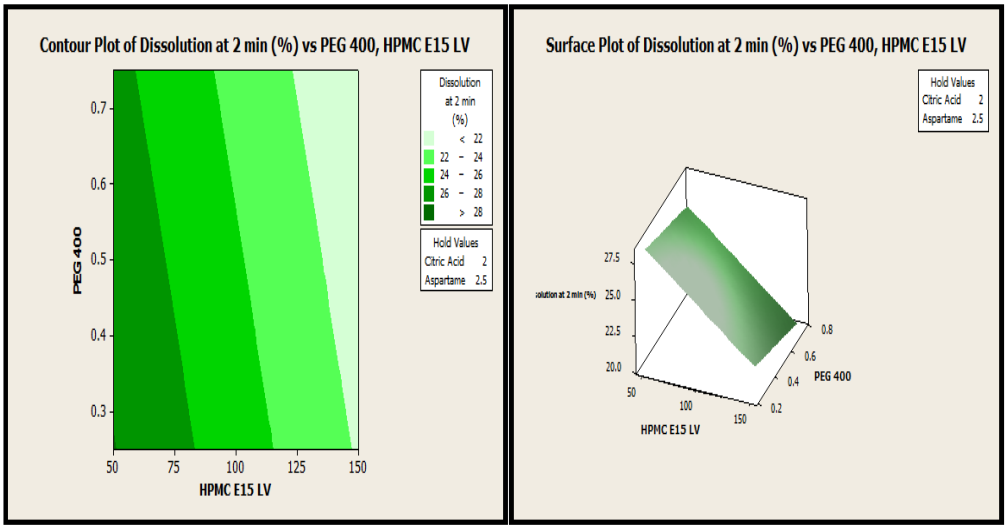


Figure 7.21: Contour plot and Response surface plot for dissolution at 2 min (Q2)

Optimization of film by Plackett-Burman Design

The Plackett–Burman factorial design was employed in this study to correlate dependent and independent variables. A four-factor 12-run Plackett–Burman screening design was generated using Minitab 17® (Version 17, Minitab Inc., State college, Pennsylvania, USA). The software package was used to estimate the response of dependent variables and optimized conditions. All the batches contained 10 mg of API per film. Optimization was performed by application of constraints. The *in vitro* disintegration time was limited to 25 seconds to 50 seconds, folding endurance was limited from 150 to 250 while the dissolution at 2 min was limited to 20% to 40 % values.

The overlay plot observed after application of the constraints is shown in the Figure 7.22., keeping the hold values of citric acid (2%) and aspartame (2.5%). Magnified overlay plot is shown in Figure 7.23. showing the optimized batch of ODF.

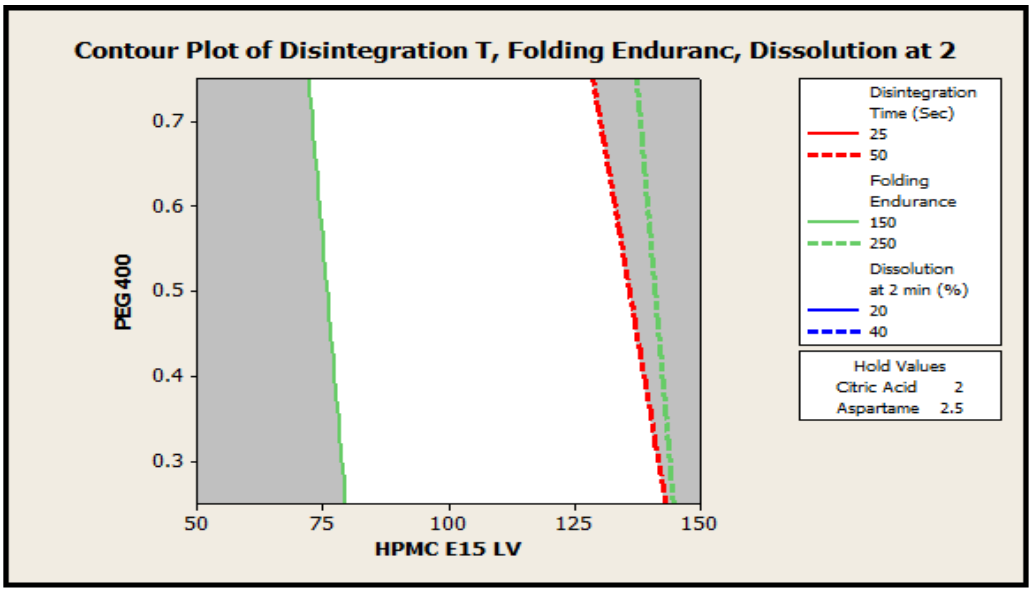
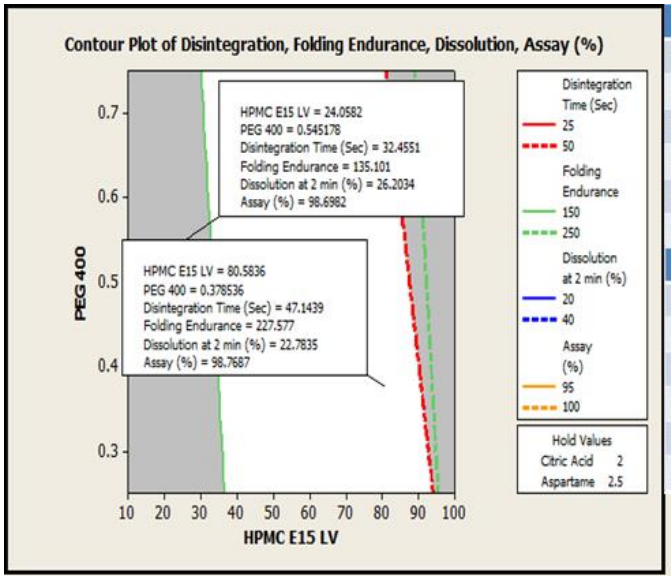


Figure 7.22: Overlay contour plot of plackett burman design



Batch-F13	Predicted	Actual
HPMC E15 LV	24.05 mg	
PEG 400	0.545 mg	
Disintegration Time (sec)	32	34
Folding Endurance	135	131
Dissolution at 2 min (%)	26	29
Assay (%)	98.7	99.2
Batch-F14	**Predicted**	**Actual**
HPMC E15 LV	80.58 mg	
PEG 400	0.378 mg	
Disintegration Time (sec)	47	45
Folding Endurance	227	230
Dissolution at 2 min (%)	22	24
Assay (%)	98.8	98.5

Figure 7.23: Magnified overlay contour plot of plackett burman design

The formulation obtained from overlay plot was checked for its prediction power and the predicted error was found to be less than 5% and the optimized formulation of orally disintegration film is shown in the Table 7.14.

Material (mg/film)	**F15**
Dextromethorphan Hydrobromide	10
Kyron T-314	12.5
HPMC E15 LV	40
PEG 400	0.5
Citric Acid	4
Aspartame	5
Water	q.s.

Table 7.14: Optimized formulation of ODF

7.4. Evaluation of DXM Hbr-ODF

The results of optimized batch are shown in the Table 7.15.

Parameter	**Results**
Weight variation (mg)	73.5 ± 2.1

Thickness (mm)	0.24 ± 0.03	
Surface pH	6.9 ± 0.1	
Drug content %	99.5 ± 0.4	
***In vitro* disintegration time (Sec)**	35 ± 2	
Folding endurance	174 ± 9	
% Drug Release	**Time (min)**	**% Drug Release**
	0	0
	2	26.5 ± 4.1
	4	48.3 ± 3.4
	6	66.9 ± 2.8
	8	88.5 ± 1.9
	10	99.5 ± 0.6

Table 7.15: Results of optimized batch of ODF

Comparison of optimized formulation with market product

The graphical representation of dissolution profile of optimized batch and market formulation is shown in Figure 7.24. It can be observed from the figure, that prepared optimized ODF releases the drug significantly faster compared to market formulation (Lastuss-CT). It can be observed from the graphs of *in vitro* drug release that, optimized ODF release more than 99% drug in 10 min while the market formulation release around 75% drug release in 10 min.

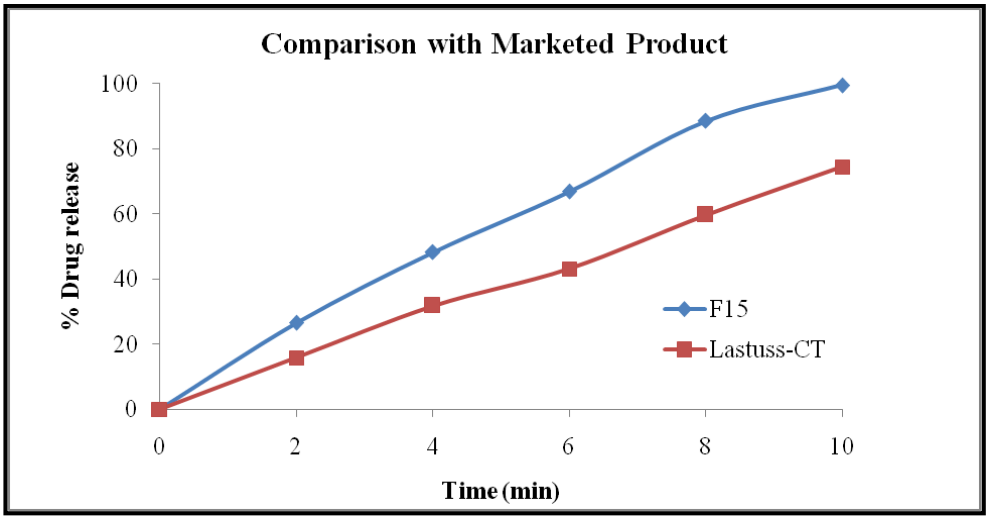


Figure 7.24: Graphical representation of comparison of *in vitro* drug release with market product

The comparative dissolution profile of optimized formulation and Market formulation is shown in the Table 7.16. it shows that the market formulation release around 74.5 ± 1.7% drug in 10 min while optimized formulation releases 99.5 ± 0.6% formulation in 10 min., suggesting the superiority of optimized formulation compared to market product.

Time (min)	F15	Lastuss-CT
0	0	0
2	26.5 ± 4.1	15.9 ± 5.9
4	48.3 ± 3.4	31.8 ± 4.8
6	66.9 ± 2.8	43.2 ± 3.5
8	88.5 ± 1.9	59.8 ± 2.4
10	99.5 ± 0.6	74.5 ± 1.7

Table 7.16: Comparative dissolution profile of optimized batch and Market product

7.5. Taste Masking of DXM Hbr-ODF

The results obtained for the taste masking of ODF of DXM Hbr compare to pure DXM Hbr is shown in the Figure 7.25. It can be observed that the bitter taste of DXM Hbr is significantly reduced in the prepared ODF formulation. This taste masking of the film can be contributed to preparation of drug- resin complex using Kyron T 314and use of Aspartame as a sweetening agent. Also, it was observed that, the sensor output of optimized ODF was significantly less than API, which means bitter taste of the drug was completely masked. However, the results obtained from e-tongue has to be confirmed by a human testing panel but that would require permission by the human ethics committee and it is out of scope for the present study.

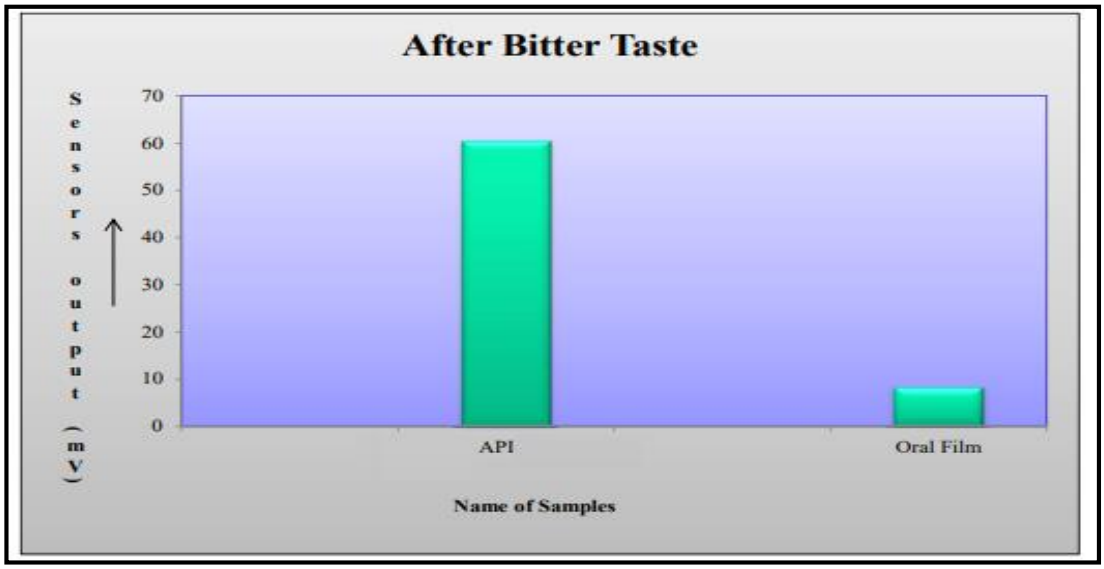


Figure 7.25: Results of taste masking of prepared optimized Oral film and API (DXM Hbr)

7.6. Stability Study

Results of stability studies for optimized ODF is shown in the table 7.17. It can be observed that no significant changes were observed during the time span of accelerated stability study. Other parameters like weight variation (mg), thickness (mm), surface pH, % drug content and *in vitro* disintegration time, folding endurance and % drug release at 10 min changed non-significantly. Considering the results depicted in Table 7.17. Prepared formulation was considered to be stable during the period of accelerated stability study [132, 133].

Parameter	**Initial**	**After 1 month**	**After 2 month**	**After 3 month**
Appearance	Transparent, Non sticky and flexible	Transparent, Non sticky and flexible	Transparent, Non sticky and flexible	Transparent, Non sticky and flexible
Weight variation (mg)	73.5 ± 2.1	73.6 ± 2.3	73.1 ± 2.6	73.4 ± 2.2
Thickness (mm)	0.24 ± 0.03	0.24 ± 0.02	0.24 ± 0.05	0.24 ± 0.04
Surface pH	6.9 ± 0.1	6.8 ± 0.2	6.8 ± 0.3	6.9 ± 0.1
Drug content %	99.5 ± 0.4	99.2 ± 0.5	99.1 ± 0.7	99.3 ± 0.9
***In vitro* disintegration time (Sec)**	35 ± 2	36 ± 4	37 ± 3	36 ± 5
Folding endurance	174 ± 9	178 ± 7	171 ± 3	175 ± 6
Drug Release at 10 min	99.5 ± 0.6	99.8 ± 0.4	99.3 ± 0.7	99.6 ± 0.9

Table 7.17: Results of stability study (n=3)

Updated risk assessment

The updated risk estimation matrix after successful application of QbD is shown in Table 7.18. It suggests that if formulation is prepared from the obtained optimized region reduces the risk of variation significantly.

Drug Product CQA	Polymer	Plasticizer	Sweetener	Flavour	Saliva Stimulant
Assay	Low	Low	Low	Low	Low
Content Uniformity	Low	Low	Low	Low	Low
Disintegration Time	Low	Low	Low	Low	Low
Dissolution	Low	Low	Low	Low	Low

Table 7.18: Updated risk assessment for optimized orally disintegrating film

RESULTS AND DISCUSSION

Formulation and development of orally disintegrating film of VAR

7.7. Preformulation Studies for VAR (VAR)

7.7.1. Identification of Drug/ Organoleptic properties

Received drug sample was evaluated visually and tested for colour, odour and taste. The observations are recorder in table 7.19. This qualitative evaluation of the drug is an important characteristic in oral drug delivery systems i.e., palatability. Patient compliance is dependent on satisfactory taste determined by the target audience. Formulations under consideration in this study are intended to administer orally where taste of drug may influence the formulation composition. If, the drug is bitter than it may require taste masking to make it palatable.

Properties	VAR standard	VAR sample
Colour (appearance)	White crystalline solid	White crystalline solid
Odour	Odourless	Odourless
Taste	Bitter	Bitter

Table 7.19: Organoleptic characteristics of Drugs

Observed characteristics are relevant to the reported data of VAR. Closeness of the reported organoleptic properties with the experimental one has met the part of identification tests and needs further investigation.

7.7.2. Melting point

Melting point information can be used for compound identification or in estimation of purity. It is general rule that pure substances will exhibit sharp melting points, while impure materials (or mixtures) will melt over a broad range of temperature. Melting point of VAR was found to be 121-123 °C, confirming the purity of the drug. This suggested that the received sample could be VAR.

7.7.3. Flow Properties

The flow properties of powders are critical for an efficient for solid dosage form. A good flow of the powder or granulation to be compressed is necessary to assure efficient mixing and acceptable weight uniformity for the solid dosage form.

Flow properties	
Bulk Density (g/ml)	0.241
Tapped Density (g/ml)	0.408
Carr's Index	30.988
Hausner Ratio	1.512
Angle of Repose	55.5°

Table 7.20: Flow properties of VAR

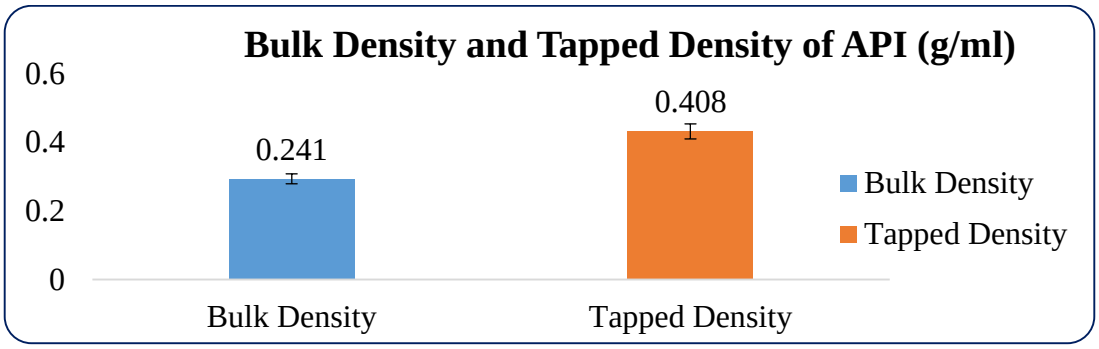


Figure 7.26: Bulk density and Tapped density of API (g/ml)

API having very poor flow in nature. But development of film formulation does not affect by API flow as the API is solubilise in appropriate solvent for film casting

7.7.4. Solubility Study

The dissolving and dispersion liquids for drug delivery studies were picked in view of VAR solvency information in different liquids. Solubility of VAR in different solvent was reported in table 7.21.

Solvent	**Solubility (mg/ml)**
Distilled Water	57.7 ± 1.12
0.1 N HCl (pH 1.2)	57.7±0.98
4.5 Acetate Buffer	52.2±1.33
6.8 Phosphate Buffer	54.9±1.02
Ethanol	59.6±4.23

Table 7.21: Solubility of VAR

7.7.5. FT-IR analysis

Identification of the drug sample VAR was confirmed from the FTIR spectrophotometer (Model-8400S, Shimadzu, Kroyoto, Japan). Spectra obtained by KBr pellet method. The FTIR spectrum of drug is shown in Figure 7.27[134].

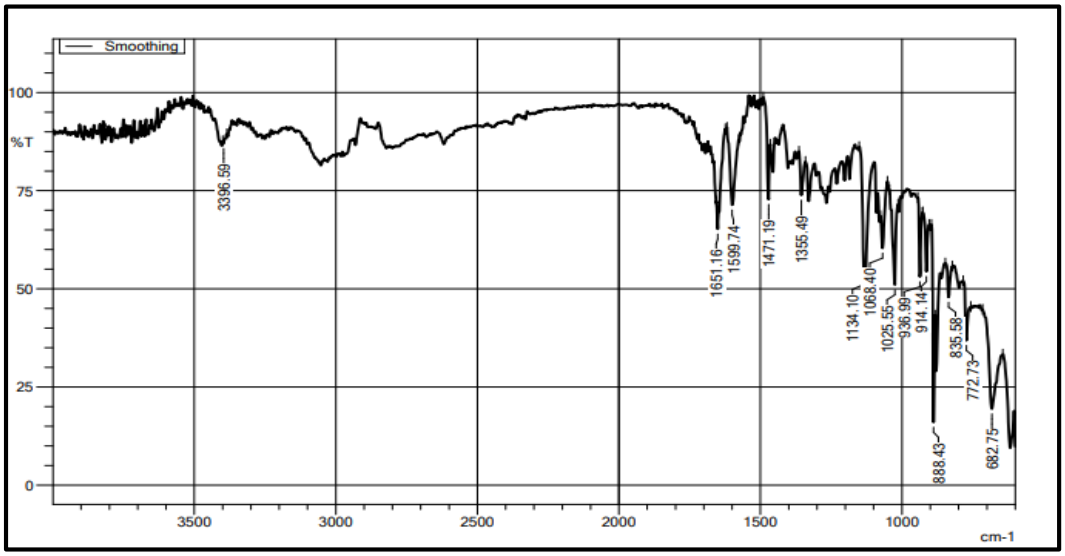


Figure 7.27: FTIR Spectra of Pure Drug (VAR)

Sl. No.	Inference	Standard wave no. (cm^{-1})	Observed wave no. (cm^{-1})
1	Bonded N–H/C–H/O–H stretching of amines and amides	3396 cm^{-1}	3396.39 cm^{-1}
2	aromatic C-H stretching	3040 and 888cm^{-1}	888.43,835.58 cm^{-1}
3	Diketones	1651 cm^{-1}	1651.16 cm^{-1}
4	C=C, C=N pyridine ring stretching	1599 to 1471 cm^{-1}	1599.74 cm^{-1}
5	broadening C=N stretching	3000 cm^{-1}	3002.69 cm^{-1}

Table 7.22: FTIR spectra of VAR loaded samples

7.8. UV visible spectrophotometry determination of absorption maximum (λmax)

Method development.

This work presents the validation of the UV VIS spectrophotometric method developed to examine varenicline content in the selected pharmaceutical formulation. For the spectrophotometric analysis, a Shimadzu UV spectrophotometer was used. The initial method development was conducted on pure substance using working standards solution. Although the light absorption characteristics of VAR are available in literature, we recorded the UV-absorption spectrum in methanol in order to select the appropriate analytical wavelength, while simultaneously verifying available data. VAR has two absorption maxima at 236 and 320 nm which were considered in further analysis. No significant differences between the spectrum in methanol and the spectra available in literature were observed.

System suitability

We tested the system's suitability for being an integral part of an analytical procedure. This was done with respect to the signal to-noise ratio for the VAR peak using a VAR solution of 10 μg/ml. The high value of signal-to-noise ratio of 2.00E+05 - indicates the use of a suitable analytical wavelength. All these results assure the adequacy of the proposed UV spectroscopic method for the routine analysis of VAR.

Sample solution stability.

The stability of the drug in solution during analysis was determined by repeated analysis of drug samples (10 μg/ml) during the same day and also after storage of the drug solution for three days under refrigeration. The results of such experiments indicate that there was no significant change in analysis over a period of 72 hours. Herein, the mean RSD between peak areas for the samples was found to be less than 0.5%, suggesting that the drug solution can be stored without any degradation over the time interval studied.

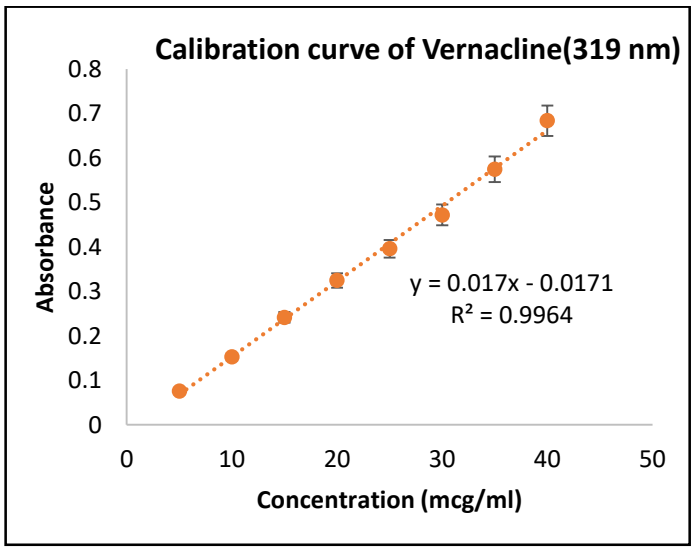
Stress testing of VAR.

Forced degradation studies was carried out to demonstrate the selectivity and stability-indicating property of the proposed method. In so-doing, stress testing of drug substances can detect the changes with time in the properties of the drug substance. In

our experiment, different stress conditions were applied, among these, acid and base hydrolysis, oxidation and irradiation with UV light. In doing this, VAR was treated with 30% solution of hydrogen peroxide, 1 mol/l solution of hydrochloric acid, 2 mol/l solution of sodium hydroxide and UV radiation (254nm). The applied conditions resulted in the significant decomposition of the analyzed substance, and λ_{max} of the degradation products were different from those of VAR. In the case of oxidation, absorption was observed at λ max similar to that of VAR was observed, but with a significantly larger area.

Linearity

The ability to obtain detector signals proportional to the concentrations of VAR in the samples was tested by the construction of five independent calibration curves. Each curve was generated by creating 6-concentration points; each concentration was analysed in triplicate, and regression analysis for the results was carried out using the least-square method. The results revealed a good linear calibration fit in the range of 5-40 µg /ml. The calibration equation is shown in the Figure 7.28 with the determination coefficient of 0.9999. Linearity was confirmed by significance testing of Pearson correlation (TV = 539.7 (28) > t = 1.71) and by Mandel fitting test (TV = 0.433 < F99% (1, 27) = 7.68), while normality was assessed by applying the Shapiro-Wilks test (TV= 0.9574, p = 0.26). The obtained low values of standard deviations of the regression coefficients are indicative for the significant validity of the calibration points used for constructing the calibration curve.



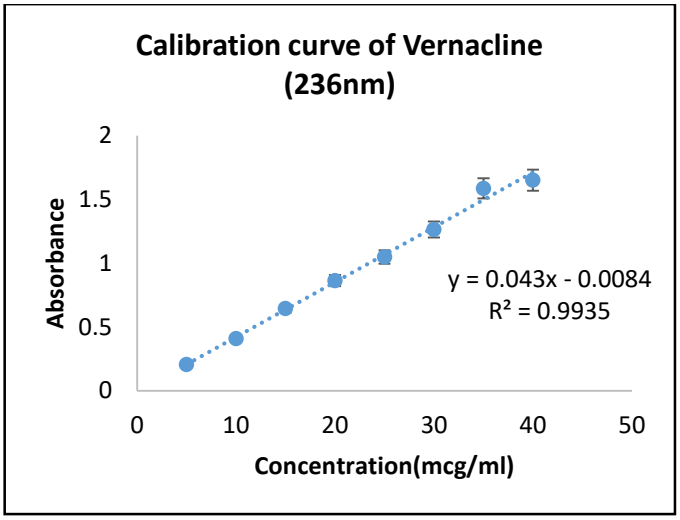


Figure 7.28: Calibration curve of VAR at 236nm and 319nm

Limit of detection (LOD) and limit of quantitation (LOQ)

The limit of detection (LOD) and limit of quantitation (LOQ) were calculated based on the signal-to-noise method. Determination of the signal-to-noise ratio was performed by comparing measured signals from samples with known low concentrations of VAR, with those of blank samples, and then establishing the minimum concentration at which the VAR can be reliably detected. A signal-to-noise ratio of 3:1 or 10:1 was taken into account for estimating the LOD and LOQ, respectively. The LOD and LOQ values were 10 and 33 ng/ml, respectively.

Precision

Precision was measured in accordance with ICH recommendation. Six subsequent solutions of VAR, at three different concentrations (9, 3, and 0.3 µg/ml) showed acceptable intra-day precision; the relative standard deviations (RSD, n = 6) of the concentrations, calculated from a calibration curve, did not exceed 3%. Inter-day precision was determined by multiple inter-day measurements of VAR at the same VAR concentration level (9, 3, and 0.3 µg/ml). The RSD values (n = 12) of less than 3% indicate acceptable reproducibility of the method (Table 7.23).

The labelled concentration (mcg/ml)	**The found concentration (mcg/ml)**	**RSD (%)**
Intraday precision		

9	9.009	0.54
3	3.009	0.67
0.3	0.297	2.59
Interday precision		
9	8.967	0.42
3	3.008	0.69
0.3	0.297	3.08

Table 7.23: Precision of proposed method

Accuracy

Accuracy was based on the recovery study of known amounts of VAR standard added (50%, 100% and 150% in relation to the label claim) to a placebo matrix for tablets (tablet model mixtures). The samples at each concentration level were mesured in triplicate, and the added amounts were calculated from a calibration curve. The recovery was expressed as percentages, calculated from the formula: concentration/nominal concentration × 100). The recovery values ranged from 99.73 to 101.23 (Table 7.24). The obtained results indicate acceptable method accuracy.

Tablet model mixture	**The labelled concentration(mcg/ml)**	**The found concentration (mcg/ml)**	**% Recovery**
M 150%	1.85	1.873	0.54
M 100%	1.25	1.247	0.67
M 50%	0.6	0.598	2.59

*mean value, n=3.

Table 7.24: Evaluation of the method accuracy by recovery study

Applicability of the method.

As shown above, the developed method gave satisfactory results with the analysis of VAR in bulk substance. Thus, VAR-containing tablets were subjected to analysis by the proposed method. In such an experiment, the label claim percentage was found to be 99.96 ± 1.31% RSD (intra-day analysis) and 99.46 ± 1.25% RSD

(inter-day analysis). These satisfactory values indicate that the proposed method can be applied for the routine quality control of VAR tablets. The developed UV VIS spectrophotometric method is selective, sensitive, accurate and precise. Statistical analysis for the results demonstrates that the method is suitable for the determination of VAR in bulk and tablet forms without the interference generated via degradation products. It is, therefore, recommended for routine use in laboratory quality control.

7.9. Drug-Polymers Interaction Studies

The individual drugs and polymer were separately scanned. All the spectra were compared for confirmation of common peaks. VAR and with polymer showed no significant variation in intensity and position peaks, suggesting that drugs and excipients were compatible. Hence, it can be concluded that the drugs VAR is in free State. The spectra are reported in the Figure 7.29. The individual IR spectrum of the pure drug was found to be similar to that of its standard spectrum.

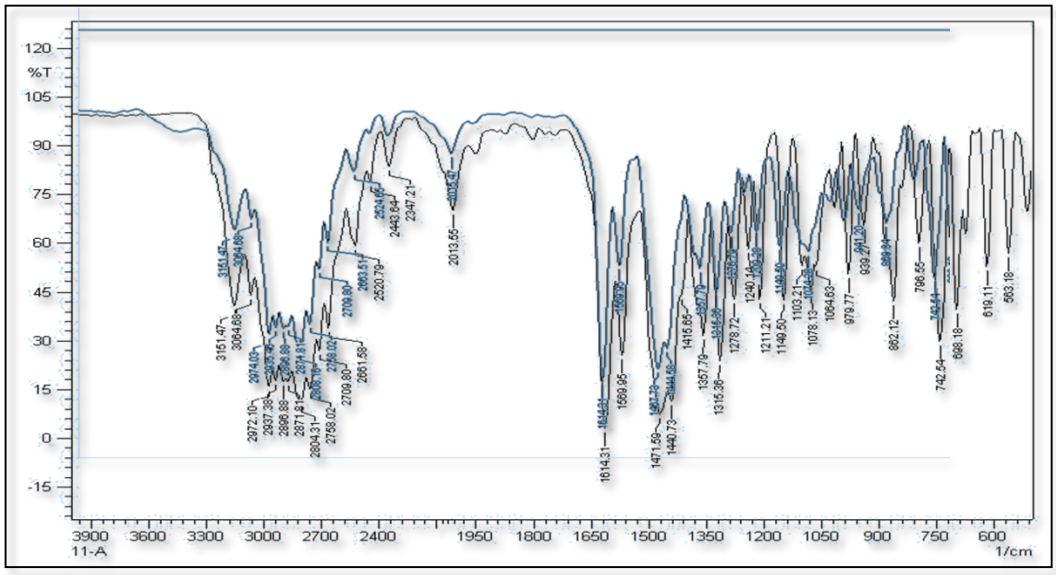


Figure 7.29: FTIR Spectra of VAR with Kollicoat® IR

Preliminary Studies

For Selection of Polymer

Considering the lowest disintegration time, higher folding endurance, suitable dissolution profile and transparency of prepared film *Kollicoat*® IR was selected for further studies [130, 134].

Ingredients	F1	F2	F3
Kollicoat® IR (mg)	300	-	-
Lycoat® (mg)	-	300	-
Pullulan (mg)	-	-	300
PEG 400 (% of polymer)	2	2	2
Distilled Water (ml)	15	15	15
Drying Time	24h	24h	24h
Drying temperature	60°C	60°C	60°C
Observations	Transparent,	Transparent.	Not Transparent,
Physical Characteristics	Non Sticky	Non sticky	Non sticky
Disintegration time (Sec)	34±0.98	41±1.12	51±1.56
Dissolution(sec.)	300±1.56	230±2.56	395±2.33
Spradability	++	++	+
Folding endurance	247±3.56	205±3.93	72±2.56

Table 7.25: Results of parameters for the selection of polymer

For selection of drying time

Considering the lowest disintegration time, higher folding endurance, suitable dissolution profile and transparency of prepared film drying time of 24h was selected for further studies (Table 7.26)

Ingredients	F4	F5	F6
Kollicoat® IR (mg)	300	300	300

PEG 400 (% of polymer)	2	2	2
Distilled Water (ml)	15	15	15
Drying Time	24h	12 h	6h
Drying temperature	60°C	60°C	60°C
Observations	Transparent,	Transparent.	Transparent,
Physical Characteristics	Non-Sticky	Non sticky	Non sticky
Disintegration time (Sec)	34±0.98	36.9±0.98	38.2±1.02
Dissolution(sec.)	300±1.56	230±2.56	230±3.85
Spradability	++	++	++
Folding endurance	247±3.56	205±6.12	315±5.66

Table 7.26: Results for the batches prepared to optimize drying time

For selection of polymer concentration

Considering the lowest disintegration time, higher folding endurance, suitable dissolution profile and transparency of prepared film *Kollicoat*® IR in the concentration of 300 mg to 900 mg was selected for further studies of design of experiments (Table 7.27)

Ingredients	F7	F8	F9
Kollicoat® IR (mg)	300	600	900

PEG-400 (% of polymer)	2	2	2
Distilled Water (ml)	15	15	15
Observations			
Thickness	0.066±0.102	0.078±0.332	0.088±0.525
Physical Characteristic	Transparent, Non sticky	Transparent, Non sticky	Transparent, Non sticky
Disintegration time (Sec)	41±0.89	58±0.55	75±1.02
In-vitro drug release	75 ± 2.30	97 ± 3.13	120± 2.90
Spradability	++	++	++
Folding endurance	255 ± 1.082	265 ± 2.03	273 ± 1.95

Table 7.27: Results for selection of polymer concentration for design of experiments

Selection of plasticizer

Considering the lowest disintegration time, higher folding endurance, suitable dissolution profile and transparency of prepared film PEG 400 was selected for further studies (Table 7.28)

Ingredients	F10	F11	F12
Kollicoat® IR(mg)	300	300	300
Glycerin (% of polymer)	10	-	-

PEG-400 (% of polymer)	-	10	-
PG (% of polymer)	-	-	10
Distilled water	15	15	15
Observations			
Physical Characteristic	Transparent, Sticky	Transparent, Non Sticky	Transparent, Sticky
Spradability	++	++	++
Disintegration time (Sec)	45.35±1.02	38.23±1.06	51.23±2.15
Folding endurance	175 ± 1.116	196 ± 2.014	142 ± 3.331

Table 7.28: Results of prepared batches for selection of plasticizer

Selection of plasticizer concentration

Considering the lowest disintegration time, higher folding endurance, suitable dissolution profile and transparency of prepared film PEG 400 in the concentration of 2% to 10% was selected for further studies of design of experiments. (Table 7.29)

Ingredients	F13	F14	F15
Kollicoat® IR(mg)	300	300	300
PEG-400 (% of polymer)	2	-	-
	-	5	-
	-	-	10

Distilled water (sec.)	15	15	15
Observations Physical Characteristic	Transparent, Sticky	Transparent, Non Sticky	Transparent, Sticky
Spradability	++	++	++
Disintegration time (Sec)	31.28±1.08	36.25±1.12	38.23±1.06
Folding endurance	315 ± 1.116	358.56	196 ± 2.014

Table 7.29: Results of batches prepared for deriving plasticizing concentration

Composition for selection of sweetener concentration

Different concentration of sweetening agent (Stevia) was taken in the preliminary study to observe its effect on the mechanical parameters of film. It can be observed from the Table 7.30 that the mechanical properties and *in vitro* disintegration time remains same and no significant changes were observed. So, stevia can be used as a sweetening agent in the formulation of ODF.

Ingredients	F16	F17	F18
***Kollicoat*® IR (mg)**	300	300	300
PEG-400 (% of polymer)	5	5	5
Stevia (mg)	1	5	10
Distilled water (sec.)	10	10	10
Observations **Physical Characteristic**	Transparent, Sticky	Transparent, Sticky	Transparent, Sticky

Spradability	++	++	++
Disintegration time (Sec)	38+1.56	37.25+1.21	35.15+1.28
Folding endurance	315 + 1.116	358.56	196 + 2.014
Taste Masking	Not evaluated	Not Evaluated	Not Evaluated

Table 7.30: Results of the batches prepared for optimization of sweetener concentration

7.10. Application of Quality by Design in optimization of ODF

Solvent casting method was used because of its ease of manufacture and lower cost. PEG 400 as an effective plasticizer to formulate oral orodispersible film (ODF) of Varenicline prepared by the solvent casting method was demonstrated. PEG 400 reduces the glass transition temperature (Tg) of *Kollicoat*®® IR and thus increase the elasticity of ODF formulation. Hence, concentration of plasticizer was selected as one of the independent variables for experimental design. *Kollicoat*® IR a film forming agent was selected as another variable as it may affect the mechanical properties & disintegration time of the ODF formulations.

Factorial design layout.	Factor 1	Factor 2	Response 1	Response 2	Response 3	Response 4	Response 5	Response 6
Run	A:*Kollicoat*® IR	B:PEG 400	Tensile Strength	Load at Yield	%Elongation at break	Q2	Q5	Q10
			N/mm2		%	%	%	%

1	-1	-1	3.24	4.87	75.7	20.12	59.1	98.9
2	-1	0	3.6	5.97	98.3	25.1	53.21	93.42
3	-1	1	4.41	6.65	116	22.44	52.01	91.77
4	0	-1	7.22	15.18	76.4	30.1	58.21	98.01
5	0	0	8.28	18.63	95.9	27.12	56.12	95.61
6	0	1	9.3	20.93	105.95	19.23	51.23	92.53
7	1	-1	6.32	15.18	76.8	31.25	60.25	100.2
8	1	0	7.36	19.88	89.3	26.52	57.11	96.51
9	1	1	9.88	29.64	100	25.01	54.12	93.41

Table 7.31: Factorial design layout

Batch	**Thickness (mm)**	**Drug Content (%)**	**Tensile strength (N/mm^2)**	**Folding endurance**	**Surface pH**	**Disintegration time(sec.)**
B1	0.1±0.005	92±1.41	4.28±0.45	225±2.51	6.7±0.05	28±2.51
B2	0.11±0.008	94.4±1.23	3.66±0.26	201±1.98	6.9±0.02	32±2.58
B3	0.12±0.002	96.8±1.35	3.8±0.38	245±2.56	7.1±0.059	34±3.12
B4	0.14±0.005	93.6±1.58	9.45±0.48	185±1.88	6.9±0.04	30±2.59
B5	0.15±0.0023	95.2±1.65	8.63±0.95	198±1.35	6.7±0.023	35±3.48

B6	0.15±0.0025	98.4±1.98	8.85±0.56	209±2.6	7.1±0.048	38±3.56
B7	0.16±0.0051	92.8±1.02	8.22±0.51	175±2.48	6.9±0.06	35±3.18
B8	0.18±0.0035	97.6±1.11	8.24±0.23	180±2.35	7.2±0.04	40±3.25
B9	0.2±0.0026	98.4±1.23	9.88±0.68	215±2.31	7.3±0.035	43±3.21

Table 7.32. Physicochemical responses of factorial batches

Influence of independent variables on Tensile strength

An ideal OFDF should exhibit an adequately high tensile strength value to be able to withstand normal handling. In spite of this, a very high value (very high rigidity) is not desired, because it could retard the drug release from the polymer matrix. The prepared OFDFs had tensile strength values from (3.24±0.26 to 9.88±0.68 (N/mm^2) as displayed in Table 7.32. The observation show that mechanical property of film strongly depends upon the selected independent variables. The mathematical relationship generated using multiple linear regression analysis for the variables all shown in Table 7.32. Model reduction was carried out by excluding non-significant terms ($P > 0.05$) in model equations resulting from the multiple regression analysis. Tensile strength values were analysed using the following polynomial equation:

Full model (Y_1) = $8.06 + 1.06 X_1 + 2.05X_2 + 0.60X_1X_2 + 0.31 X_1^2 - 2.46 X_2^2$

Reduced model (Y_1) = $8.26 + 1.14 X_1 + 2.05 X_2 + 0.59 X1X2 - 2.46 X2^2$

Concerning, response Y1 the results of multiple Quadratic regression analysis showed that the coefficients b1 and b2 bear a positive sign for coefficient value for X_1 i.e., 1.14 and positive sign for X_2 i.e., 2.05. So, it indicated that both X_1 and X_2 had a positive effect on Tensile strength; i.e. as the amount of polymer and plasticizer was increased the tensile strength increased relatively. These findings shows that polymer and plasticizer had a significant effect on the tensile strength of the prepared films.As can be observed from Figure 7.30, it was noticed that increasing the polymer concentration (X2) significantly increased the tensile strength values of the prepared

ODFs. This could have been because of the formation of a densely packed network of the used polymer chains at higher concentration, leading to formation of a stronger matrix.

Coefficients		
Coefficients	**Coefficient value**	**p value**
bo	8.26	2E-04
b1	1.14	0.001
b2	2.05	1E-04
b12	0.59	0.022
b22	-2.46	4E-04

Table7.33: Results of regression analysis for tensile strength

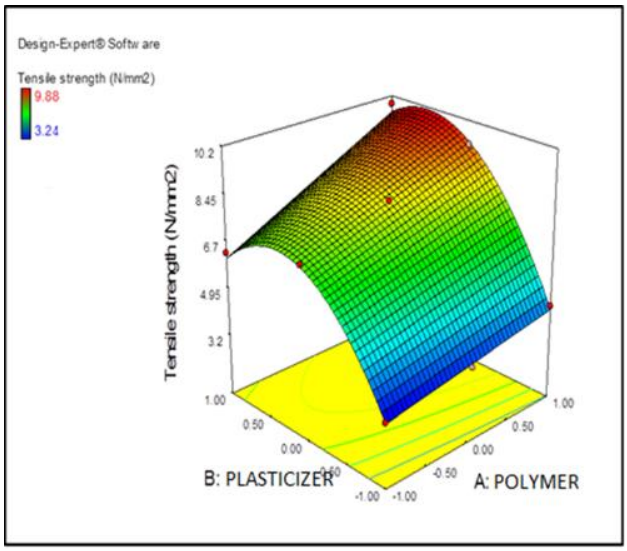


Figure 7.30: Response surface plot showing the influence of *Kollicoat*® IR concentration and PEG-400 concentration on TS (N/mm^2)

The response surface plot showing the interactions of independent variables on tensile strength is shown in Figure 7.30. It shows that the response follows quadratic model. It can be observed from the graph that the tensile strength is significantly affected by the change in concentration of plasticizer.

Effect of variable on load at yield

Load at yield is the load value at the point of yield; that is, where plastic deformation begins. **Full model (Y_2)** = 17.86 +3.66 X_1 +7.87 X_2 +3.17X1X2+0.58 X_1^2 -4.55 X_2^2

Reduced model (Y_2) = 18.25 + 3.66 X1 + 7.87 X2 + 3.17 X1X2-4.5

Concerning, response Y2 the results of multiple Quadratic regression analysis showed that the coefficients b1 and b2 bear a positive sign for coefficient value. For X_1 i.e., 3.66 and positive sign for X_2 i.e., 7.87. So, it indicated that both X_1 and X_2 had a positive effect on load at yield; i.e. as the amount of polymer and plasticizer was increased the load increased relatively. The fitted equation relating the response Y2 to the transformed factor is shown in the table 7.34.

Coefficients		
Coefficients	**Coefficient value**	***p* value**
bo	18.25	4E-04
b1	3.66	0.002
b2	7.87	1E-04
b12	3.17	0.007
b22	-4.55	0.007

Table 7.34: Results of regression analysis for load at yield

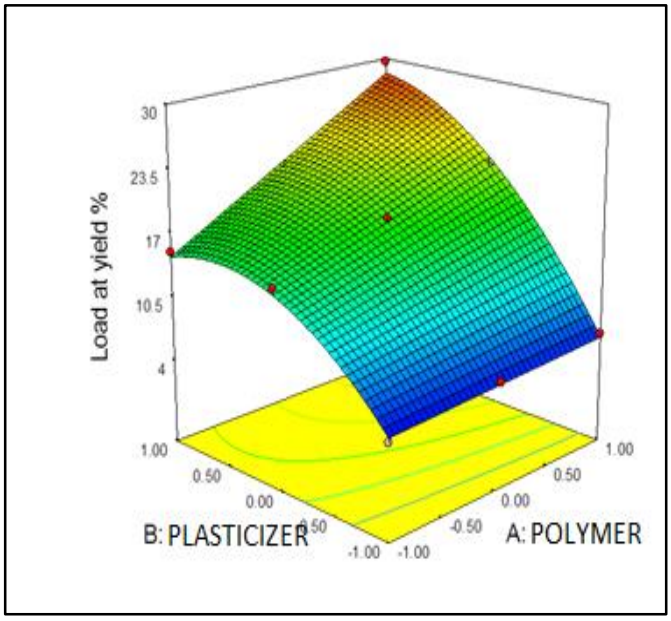


Figure 7.31: Response surface plot showing the influence of *Kollicoat*® IR concentration and PEG-400 concentration on load at yield

The response surface plot showing the interactions of independent variables on % load at yield is shown in Figure 7.31. It shows that the response follows quadratic model. It can be observed from the graph that the %load at yield is significantly affected by the change in concentration of plasticizer. The effect of polymer can be observed from the graph and the interaction of factors are also showing significant effect on response values.

Influence of independent variables on% Elongation at break:

OFDFs should possess a large elongation percentage, in order to exhibit the desired flexibility and stretchability, which is important for facile handling and application of the film to the oral cavity. ODF'S should possess moderate tensile strength, high % elongation (% E) and high percent of drug release. The results revealed that all the films showed he % elongation at break (EB) in the range of 75.7 to 105.95 %. Result of multiple Linear regression analysis showed that the coefficients b1 bear a positive sign and b2 bear a negative sign. The coefficient value for X1 i.e. 15.51 and positive sign for X2 i.e. -3.98. So it indicated X1 has more effect on % Elongation than X2. Negative sign of X2 indicates negative effect on % Elongation. It indicates that higher amount of plasticizer was increased in formulation, % Elongation was decreased. The fitted equation relating the response Y3to the transformed factor is shown in the table 35.

Full model (Y_3) = $94.54 + 15.51 X_1 - 3.98 X_2 - 4.27X1X2 - 2.69 X_1^2 - 0.067 X_2^2$

Reduced model (Y_3) = $94.50 + 15.51 X1 - 3.98 X2 - 4.27 X1X2 - 2.69 X2^2$

Coefficients		
Coefficients	**Coefficient value**	*p* -value
bo	94.50	< 0.0001
b1	15.51	< 0.0001
b2	-3.98	0.0016

b12	-4.27	0.0026
B22	-2.69	0.0410

Table 7.35: Results of regression analysis for % Elongation at break

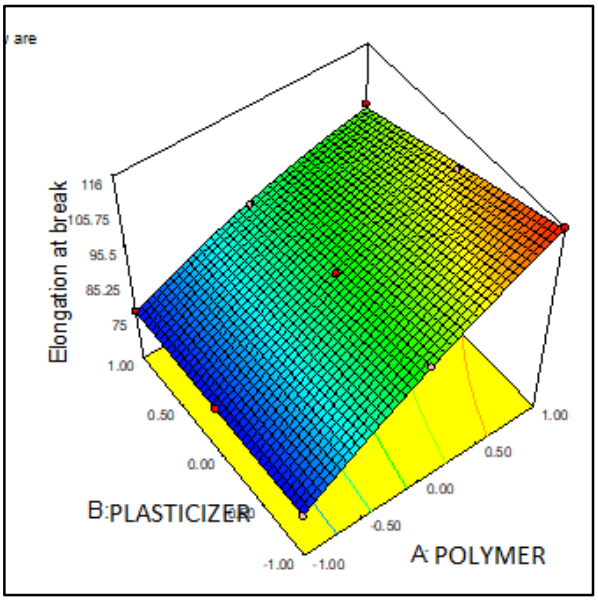


Figure 7.32: Response surface plot showing the influence of *Kollicoat*® IR concentration and PEG-400 concentration on % Elongation at break.

The response surface plot showing the interactions of independent variables on elongation at break is shown in Figure 7.32. It shows that the response follows quadratic model. It can be observed from the graph that the response is significantly affected by the change in concentration of plasticizer. The effect of polymer can be observed from the graph and the interaction of factors are also showing significant effect on response values.

Influence of independent variable on Q2 (% drug release at the end of 2 minutes)

For ODFs, time is an important factor, because the loaded drug should be dissolved within a few minutes. Figure 7.33 illustrates the dissolution profiles of all the prepared OFDFs; where, the % VAR dissolved after 10 min from all the prepared ODFs was found to be from 5.35±1.34 % to 100.2±1.23%.

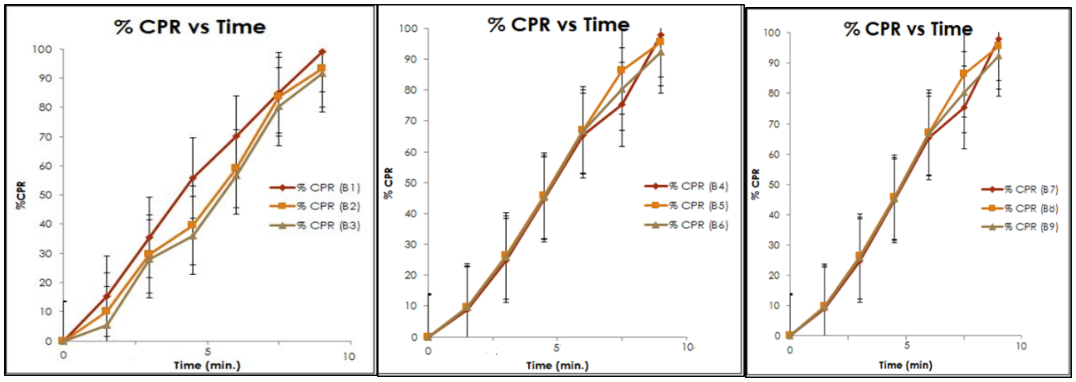


Figure 7.33: Dissolution profile of prepared ODF's for % VAR dissolved after 2 min(Q2)

Concerning the response, results of multiple Linear regression analysis showed that the coefficients b1 bear a positive and b2 bear negative sign for coefficient value for X1 i.e., 2.52 and negative sign for X2 i.e., -2.46. So, it indicated that X1 is increased then % of drug release is increased, but if amount of X2 is increase so the % drug release is decreased. The fitted equation relating the response Y4 to the transformed factor is shown in the table 7.36 below.

Full model (Y4) = 25.21 + 2.52 * A + -2.465 * B

Reduced model (Y4) = 25.21 + 2.52 * A + -2.465 * B

Coefficients		
Coefficients	**Coefficient value**	**P value**
bo	25.21	2E-04
b1	2.52	< 0.0001
b2	-2.465	0.019

Table 7.36: Results of regression analysis for *in vitro* drug release after 2 min

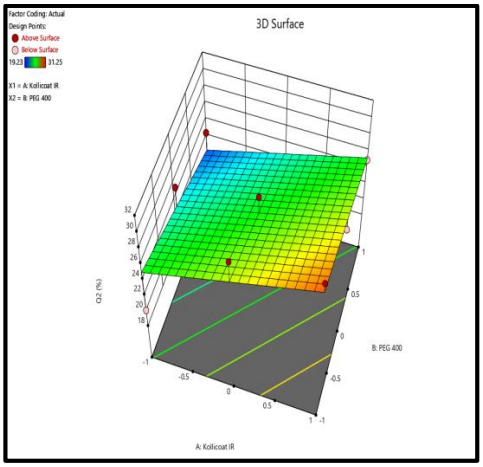


Figure 7.34: Response surface plot showing the influence of *Kollicoat*® IR concentration and PEG-400 concentration on % drug release at the end of 2 min. (Q2)

The response surface plot showing the interactions of independent variables on % drug release at 2 min(Q2) is shown in Figure 7.34. It shows that the response follows linear model. It can be observed from the graph that the response is significantly affected by the change in concentration of polymer and plasticizer. The signs of interaction effects are not visible from the response surface plot.

Influence of independent variable on Q5 (% drug release at the end of 5 minutes)

Concerning Y5, the results of multiple linear regression analysis showed that the coefficients b1 bear a positive and b2 bear negative sign for coefficient value for X1 i.e., 1.19 and negative sign for X2 i.e., -3.366. So, it indicated that X1 is increased then % of drug release is increased, but if amount of X2 is increase so the % drug release is decreased. The fitted equation relating the response Y5 to the transformed factor is shown in the table 7.37.

Full model (Y_5) = 55.7067 + 1.19333 * A + -3.36667 * B

Reduced model (Y_5) =55.7067 + 1.19333 * A + -3.36667 * B

Coefficients		
Coefficients	**Coefficient value**	**P value**
bo	55.70	0.0005

b1	1.19	0.0306
b2	-3.3667	0.0002

Table 7.37: Results of regression analysis for *in vitro* drug release after 5 min

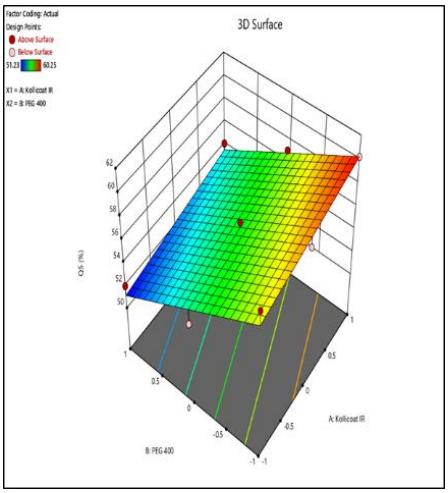


Figure 7.35: Response surface plot showing the influence of *Kollicoat*® IR concentration and PEG-400 concentration on % drug release at the end of 5 min. (Q5)

The response surface plot showing the interactions of independent variables on % drug release at 5 min(Q5) is shown in Figure 7.35. It shows that the response follows linear model. It can be observed from the graph that the response is significantly affected by the change in concentration of polymer and plasticizer. The signs of interaction effects are not visible from the response surface plot.

Influence of independent variable on Q10 (% drug release at the end of 10minutes)

Concerning, response Y6 the results of multiple linear regression analysis showed that the coefficients b1 bear a negative and b2 bear positive sign for coefficient value for X1 i.e., -3.40 and positive sign for X2 i.e., 1.17. So, it indicated that X1 is increased then % of drug release is decreased because of the increased amount of X1 results in increased thickness of the film which decreases the drug dissolution rate. But if amount of X2 is increase so the % drug release is increase because plasticizer also

acted as solubility enhancer. The fitted equation relating the response Y6 to the transformed factor is shown in the table 7.38.

Full model (Y_6) = 94.86 -3.40 X_1 +1.17 X_2 -0.16X1X2+0.79 X_1^2 +0.49 X_2^2

Reduced model (Y_6) = 18.25 + 3.66 X1 + 7.87 X2 + 3.17 X1X2-4.55

Coefficients		
Coefficients	**Coefficient value**	**P value**
bo	95.71	2E-04
b1	-3.4	< 0.0001
b2	1.17	0.019

Table 7.38: Results of regression analysis for *in vitro* drug release after 10 min (Q10)

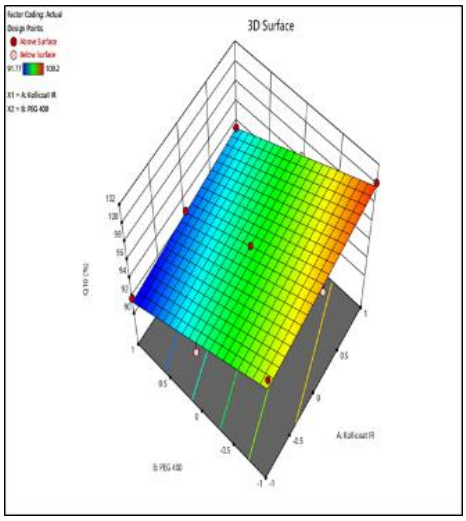


Figure 7.36: Response surface plot showing the influence of *Kollicoat*® IR concentration and PEG-400 concentration on % drug release at the end of 10 min. (Q10)

The response surface plot showing the interactions of independent variables on % drug release at 10 min(Q10) at break is shown in Figure 7.36. It shows that the response follows linear model. It can be observed from the graph that the response is

significantly affected by the change in concentration of polymer and plasticizer. The signs of interaction effects are not visible from the response surface plot.

In addition, the statistical analyses clarified that polymer concentration (X1) had a significant impact on % VAR dissolved after 10 min. Where, higher % VAR dissolved after 10 min was shown in ODFs with lower polymer concentration. Shaikh et al. reported similar findings, where they found that using a low polymer concentration led to needing a lower amount of water to dissolve the film and leading to faster drug release**.** PEG 400 plasticized the film while maintaining its affinity for water, the permeability of the film increased at the higher PEG 400 levels.

Selection of the Optimized ODF Loaded with VAR

The main purpose of Design-Expert® software is to find an optimized formulation with high quality properties. For this purpose, the optimum values were obtained by graphical and numerical optimization based on desirable conditions for all responses. To identify the optimal ODF, it was nearly impossible to fulfil all the desired responses at the same time, because the optimum condition fulfilled for one response could adversely affect other responses. However, the desirability function combined all the desired responses in one variable, in order to determine the optimum levels of the examined factors. After statistical analysis the desirability function was applied to select the best batch. The desirable values selected for dependent variables Y1, Y2, Y3, Y4, Y5 and Y6. Desirable values range selected was 5% varying from optimum value which is obtained as per software (Table 7.39)

Dependent variables	**Desirable limits**	
	Lower limit	**Upper limit**
R 1 **Tensile strength** **(N/mm2)**	**4**	**9**
R 2 **(% Load at yield)**	**10**	**20**
Q2 **(% Drug release)**	**25**	**35**

Q5 (% Drug release)	**55**	**60**
Q10 (% Drug release)	**95**	**100**
%Elongation at break	**85**	**98**

Table 7.39: Desirable limits as per software

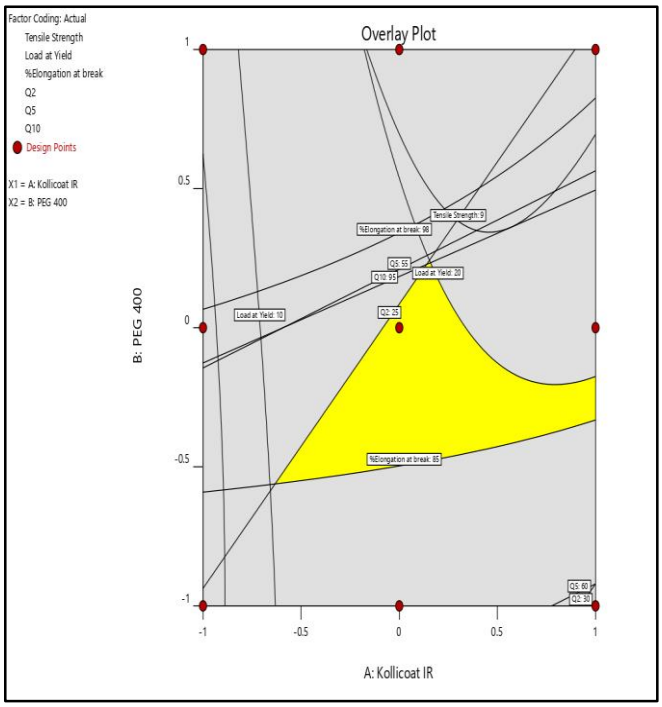


Figure 7.37: Overlay plot for effect of independent variables on responses.

Overlay plot of graphical optimization is shown in Figure 7.37, which expressed the requirements of desirable conditions for all responses. The optimum desirability of 1 was achieved when optimum factor levels were fixed at 108 mg of *Kollicoat*® IR, 0.5 mg of PEG 400. For these levels, the predicted values and experimental values made are reported in Table 7.40. Finally, their validation was calculated and there was no acceptable deviation between the experimental and predicted values based on suggested models.

Responses	CP 1			CP 2		
	Predicted Value	Experimental value	Relative error (%)	Predicted Value	Experimental value	Relative error (%)
R1	8.62	8.3	3.71	7.59	7.3	3.82
R2	19.58	19.25	1.67	15.99	15.44	3.43
R3	25.68	25.12	2.22	26.52	26.51	0.03
R4	55.69	55.21	0.869	56.21	56.5	0.513
R5	95.31	94.01	1.36	95.41	94.37	1.09
R6	95.69	96.23	0.56	97.55	96.20	1.38

Table 7.40: Comparative levels of predicted and experimental values of the responses obtained at optimum condition.

Optimized formulation of ODF of VAR is shown in Table 7.41.

Ingredients (per film)	OP1
Varenicline (mg)	1
Kollicoat® IR (mg)	108
PEG-400 (mg)	0.5
Distilled Water (ml)	10
Stevia (mg)	5
Citric acid (mg)	5

Table 7.41: Optimized formulation of VAR ODF

7.11. Formulation and development of orodispersible film

Preparation of ODF

Films were prepared using solvent casting method and optimized using factorial design.

7.12. Characterization of VAR-ODF

Results of optimized batch of ODF of VAR is shown in Table 7.42.

Parameters	Result
Thickness (mm)	0.150±1.25
Tensile strength (N/mm^2)	7.15
Folding endurance	198± 5.22
Drug content (%)	95.23±1.11
Surface pH	6.9±0.60
In vitro disintegration time(sec.)	35±5
%Elongation	95.30±3.5
Q2 (%)	26.42±1.28
Q5(%)	56.64±2.01
Q10 (%)	98.23±1.25
Load at Yield	19.58

Table 7.42: Results of optimized batch of VAR ODF

The texture profile of optimized ODF is shown in Figure 7.38.

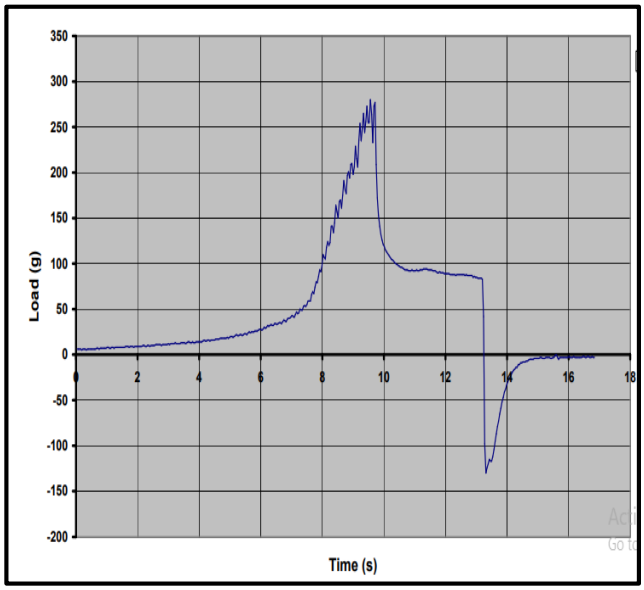


Figure 7.38: Texture profile of optimized batch

7.13. Taste Masking of VAR-ODF

The results obtained for the taste masking of ODF of VAR compare to pure VAR is shown in the Figure 7.39. It can be observed that the bitter taste of VAR is significantly reduced in the prepared ODF formulation. This taste masking of the film can be contributed to use of stevia as a sweetening agent. Also, it was observed that the sensor output of optimized ODF was significantly less than API, which means bitter taste of the drug was completely masked. However, the results obtained from e-tongue has to

be confirmed by a human testing panel but that would require permission by the human ethics committee and it is out of scope for the present study.

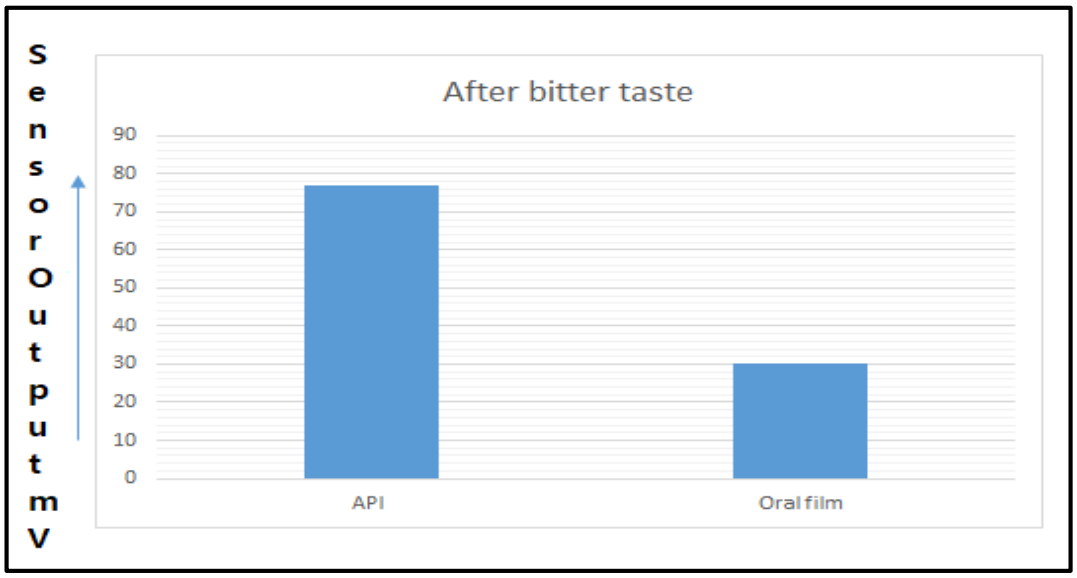


Figure 7.39: Results of taste masking of prepared optimized Oral film and API (VAR)

7.14. Stability Study

Results of stability studies for optimized ODF is shown in the table 7.43. It can be observed that no significant changes were observed during the time span of accelerated stability study. Other parameters like weight variation (mg), thickness (mm), surface pH, % drug content and *in vitro* disintegration time, folding endurance and % drug release at 10 min changed non-significantly. Considering the results depicted in Table 7.43. prepared formulation was considered to be stable during the period of accelerated stability study.

Parameters	**Before stability study**	**After stability study (30 days)**	**After stability study (90 days)**
Thickness (mm)	0.150±1.25	0.147±1.20	0.143±1.60

Tensile strength (N/mm^2)	7.15±2.25	7.10±2.30	6.95±2.40
Folding endurance	198± 2.22	193± 2.20	185± 1.20
Drug content (%)	95.23±1.11	94.30±1.10	93.20±1.11
Surface pH	6.9±0.60	6.9±0.40	6.8±0.50
***In vitro* disintegration time(sec.)**	35±5	33±5	32±5

Table 7.43: Results of stability study (n=3)

Updated risk assessment

The updated risk estimation matrix after successful application of QbD is shown in Table. 7.44.

Drug Product CQA	**Polymer**	**Plasticizer**	**Sweetener**	**Flavour**	**Saliva Stimulant**
Assay	Low	Low	Low	Low	Low
Content Uniformity	Low	Low	Low	Low	Low
Disintegration Time	Low	Low	Low	Low	Low
Dissolution	Low	Low	Low	Low	Low

Table 7.44: Updated risk assessment for optimized orally disintegrating film

7.15. Comparison with transdermal patch

The results of prepared transdermal patch are shown in Table 7.45. The drug release profile of Transdermal patch is shown in Figure 7.40. It suggested that the transdermal patch release drug for up to 24h.

Physical parameters	**Transdermal Patch**
Appearance	Smooth, uniform and flexible
Thickness (mm)	0.2795±0.3
Folding Endurance	35±1
%Drug Content	99.99± 0.8
***In-vitro* Drug Release (%)**	81.7±1.126

Table 7.45: Results of prepared Transdermal patch

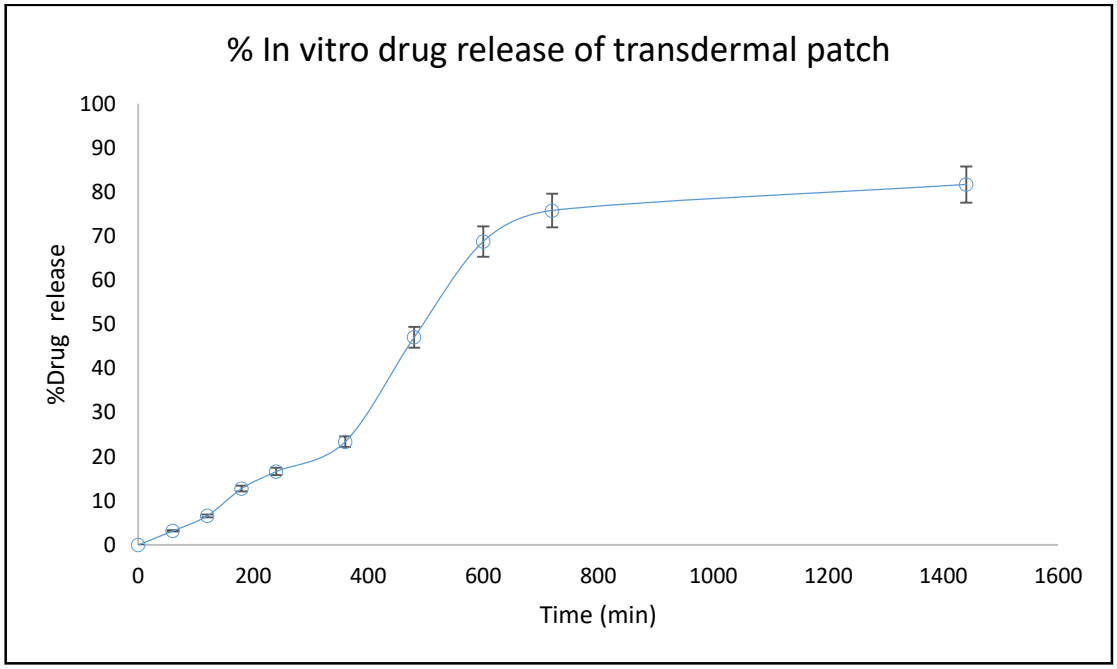


Figure 7.40: *In vitro* drug release profile of transdermal patch

CHAPTER 8. CONCLUSION

The present research reveals the effectiveness of quality by design methodology to optimize the formulation variables for the development of DXM Hbr orodispersible films. A Plackett–Burman statistical optimization design was employed to understand the film formulation development process and improve its quality. For DXM Hbr ODF. HPMC E15 and PEG 400 concentrations were the major factors influencing critical quality attributes of the film, such as such as mechanical properties, disintegration time, *in-vitro* dissolution This QbD-driven formulation development approach assisted in outlining control strategies to minimize the unfavourable impact of these CMPs on product quality and efficacy. Overall, practicing the QbD approach for formulation development of DXM Hbr fast-dissolving oro-dispersible films assured step-by-step, logical, risk-based formulation development where the quality of the product would be assured. For the present research work, HPMC E15LV was used as film forming polymer that showed rapid disintegration time of film. PEG 400 was used as plasticizer to enhance mechanical strength of film. Kyron T-314 was used to mask the bitter taste of drug along with it; other excipients such as sweetener and saliva stimulating agents were added. Optimized formulation showed thickness in the range of 0.24 ± 0.03mm, folding endurance 174 ± 9. *In vitro* disintegration time 35 ± 2 sec and the cumulative % drug release 99.5 ± 0.6 % at the end of 10 min. Optimized formulation was compared with suitable market formulation which showed higher drug release in 10 min. Taste masking was evaluated by Insent Taste Sensing System TS-5000Z. It was concluded from the result that Dextromethorphan Hbr ODF shows good masking of bitterness than API. Therefore, developed ODFs of DXM Hbr could be a good alternative formulation approach for the management and treatment of cold and cough, which benefits rapid absorption, consumer compliance and convenience.

Orodispersible films consisting of VAR with *Kollicoat*® IR as a film-forming agent and PEG 400 as plasticizer along with other excipients (stevia as sweetener, citric acid as saliva stimulating agent) were formulated using solvent casting method. On the basis of preliminary results, the amount of *Kollicoat*® IR (X1) and the amount of plasticizer (X2) were selected as independent variables in 3^2 full factorial design while tensile strength, % elongation at break, load at yield Q2, Q5 and Q10 were taken as dependent variables. Multiple linear regression analysis, ANOVA and graphical

representation of the influence of factor by contour plots and 3D response surface graphs were performed using 12.0.1 version of Design Expert®. Checkpoint batch were prepared to validate the generated model. Optimized batch was evaluated for various parameters. Optimized formulation shows thickness in the range of 0.150±1.25mm, folding endurance 198± 5.22, tensile strength 7.15 (N/mm^2), % elongation 95.30+3.5, load at yield 19.58. *In vitro* disintegration time was 35±5 sec and the cumulative % drug release was 98.23±1.25%. at the end of 10 min. and it was subjected to accelerated stability study. The optimized batch was found to be stable in the stability evaluation. VAR patch was prepared and evaluated for its drug release, it showed drug release for up to 24 h, which can be further evaluated and characterized for its potential use in smoking cessation in consumers.

In nutshell, orodispersible film improve the oral bioavailability of drugs with extensive first pass metabolism, by promoting the absorption of the drug substance through the oral mucosa reducing the dose necessary to achieve the therapeutic action, which may contribute also to a reduction of the side effects. DXM Hbr and VAR administered in the form of fast dissolving films will be potential novel drug dosage form for paediatric geriatric and also for general population by providing faster release and better patient compliance. By developing the effective delivery system for the existing drug, ODF's offer the opportunity to extend product life cycle for pharmaceutical companies.

CHAPTER 9.REFERENCES

1. Borges, A. F., et al. (2015). "Oral films: current status and future perspectives: I—galenical development and quality attributes." Journal of Controlled Release. 206: 1-19. 0168-3659
2. Madhav, N. S., et al. (2009). "Orotransmucosal drug delivery systems: a review." Journal of Controlled Release. 140(1): 2-11. 0168-3659
3. Scarpa, M., et al. (2017). "Orodispersible films: Towards drug delivery in special populations." International journal of pharmaceutics. 523(1): 327-335. 0378-5173
4. Patel, V. F., et al. (2011). "Advances in oral transmucosal drug delivery." Journal of Controlled Release. 153(2): 106-116. 0168-3659
5. Schiele, J. T., et al. (2013). "Difficulties swallowing solid oral dosage forms in a general practice population: prevalence, causes, and relationship to dosage forms." European journal of clinical pharmacology. 69(4): 937-948. 1432-1041
6. Dave, V., et al. (2017). "Formulation design and optimization of novel fast dissolving tablet of chlorpheniramine maleate by using lyophilization techniques." Bulletin of Faculty of Pharmacy, Cairo University. 55(1): 31-39. 1110-0931
7. Bala, R. and S. Sharma (2018). "Formulation optimization and evaluation of fast dissolving film of aprepitant by using design of experiment." Bulletin of Faculty of Pharmacy, Cairo University. 56(2): 159-168. 1110-0931
8. Satheesh Madhav, N. V., et al. (2012). "Recent trends in oral transmucosal drug delivery systems: an emphasis on the soft palatal route." Expert Opinion on Drug Delivery. 9(6): 629-647. 1742-5247
9. Sharma, D., et al. (2015). "Fast dissolving oral films technology: A recent trend for an innovative oral drug delivery system." International Journal of Drug Delivery. 7(2): 60-75. 0975-0215
10. Chan, R. (2016). "Oral thin films: Realms of Possibility." ON Drug Delivery Magazine. 69: 12-17
11. Hussain, M. W., et al. (2017). "Development and evaluation of fast dissolving film for oro-buccal drug delivery of chlorpromazine." Indian Journal of Pharmaceutical Education and Research. 51(4): S539-S547

12. Mahboob, M. B. H., et al. (2016). "Oral films: A comprehensive review." International Current Pharmaceutical Journal. 5(12): 111-117. 2224-9486
13. Özakar, R. S. and E. Özakar (2021). "Current overview of oral thin films." Turkish journal of pharmaceutical sciences. 18(1): 111
14. Al-Nemrawi, N. K. and R. H. Dave (2016). "Formulation and characterization of acetaminophen nanoparticles in orally disintegrating films." Drug delivery. 23(2): 540-549. 1071-7544
15. Barnhart, S. D. (2008). Thin film oral dosage forms. Modified-release drug delivery technology, CRC Press: 235-256.
16. Garsuch, V. and J. Breitkreutz (2009). "Novel analytical methods for the characterization of oral wafers." European Journal of Pharmaceutics and Biopharmaceutics. 73(1): 195-201. 0939-6411
17. Karki, S., et al. (2016). "Thin films as an emerging platform for drug delivery." asian journal of pharmaceutical sciences. 11(5): 559-574. 1818-0876
18. Bala, R., et al. (2013). "Orally dissolving strips: A new approach to oral drug delivery system." International journal of pharmaceutical investigation. 3(2): 67
19. Arya, A., et al. (2010). "Fast dissolving oral films: an innovative drug delivery system and dosage form." Int J ChemTech Res. 2(1): 576-583
20. Hariharan, M. (2009). "Orally dissolving film strips (ODFS): the final evolution of orally dissolving dosage forms." Drug Deliv. Tech. 9: 24-29
21. Gaisford, S., et al. (2009). "Monitoring crystallisation of drugs from fast-dissolving oral films with isothermal calorimetry." International journal of pharmaceutics. 380(1-2): 105-111. 0378-5173
22. Hoffmann, E. M., et al. (2011). "Advances in orodispersible films for drug delivery." Expert Opinion on Drug Delivery. 8(3): 299-316. 1742-5247
23. Irfan, M., et al. (2016). "Orally disintegrating films: A modern expansion in drug delivery system." Saudi pharmaceutical journal. 24(5): 537-546. 1319-0164
24. Patel, A. R., et al. (2010). "Fast dissolving films (FDFs) as a newer venture in fast dissolving dosage forms." Int. J. Drug Dev. Res. 2(2): 232-234

25. Mashru, R., et al. (2005). "Development and evaluation of fast-dissolving film of salbutamol sulphate." Drug development and industrial pharmacy. 31(1): 25-34. 0363-9045
26. Rathi, V., et al. (2011). "A BRIEF REVIEW ON ORAL FILM TECHNOLOGY." International Journal of Research in Ayurveda & Pharmacy. 2(4). 2277-4343
27. Keshavarao, K. P., et al. (2011). "Formulation and evaluation of mouth dissolving film containing Rofecoxib." IRJP. 2(3): 273-278
28. Khatoon, N., et al. (2013). "Overview on fast dissolving oral films." International Journal of Chemistry and Pharmaceutical Sciences. 1(1): 63-75
29. Siddiqui, M., et al. (2011). "A short review on "A novel approach in oral fast dissolving drug delivery system and their patents"." Adv Biol Res. 5(6): 291-303
30. Ghodake, P. P., et al. (2013). "Mouth dissolving films: Innovative vehicle for oral Maniruzzaman, M., et al. (2012). "A review of hot-melt extrusion: process technology to pharmaceutical products." International Scholarly Research Notices. 2012
31. Thakur, R. R., et al. (2012). "Orally disintegrating preparations: recent advancement in formulation and technology." Journal of Drug Delivery and Therapeutics. 2(3). 2250-1177
32. Heer, D., et al. (2013). "Recent trends of fast dissolving drug delivery system–an overview of formulation technology." Pharmacophore. 4(1): 1-9. 2229-5402
33. Krampe, R., et al. (2016). "Oromucosal film preparations: points to consider for patient centricity and manufacturing processes." Expert Opinion on Drug Delivery. 13(4): 493-506. 1742-5247
34. Preis, M., et al. (2014). "Mechanical strength test for orodispersible and buccal films." International journal of pharmaceutics. 461(1-2): 22-29. 0378-5173
35. Stegemann, S., et al. (2016). "Defining patient centric pharmaceutical drug product design." The AAPS journal. 18(5): 1047-1055. 1550-7416
36. Nadeem, M. and M. S. Babu "PHARMACEUTICAL SCIENCES." Quality Assurance. 3(4): 5

37. Rathore, A. S. and H. Winkle (2009). "Quality by design for biopharmaceuticals." Nature biotechnology. 27(1): 26-34. 1546-1696
38. Chang, R.-K., et al. (2013). "Generic development of topical dermatologic products, part II: quality by design for topical semisolid products." The AAPS journal. 15(3): 674-683. 1550-7416
39. Namjoshi, S., et al. (2020). "Quality by design: Development of the quality target product profile (QTPP) for semisolid topical products." Pharmaceutics. 12(3): 287. 1999-4923
40. Visser, J. C., et al. (2015). "Quality by design approach for optimizing the formulation and physical properties of extemporaneously prepared orodispersible films." International journal of pharmaceutics. 485(1-2): 70-76. 0378-5173
41. Preis, M., et al. (2013). "Oromucosal film preparations: classification and characterization methods." Expert Opinion on Drug Delivery. 10(9): 1303-1317. 1742-5247
42. Azad, M. A., et al. (2020). "Polymers for extrusion-based 3D printing of pharmaceuticals: A holistic materials–process perspective." Pharmaceutics. 12(2): 124. 1999-4923
43. Li, C. L., et al. (2005). "The use of hypromellose in oral drug delivery." Journal of pharmacy and pharmacology. 57(5): 533-546. 0022-3573
44. Janssens, S., et al. (2007). "The use of a new hydrophilic polymer, Kollicoat® IR, in the formulation of solid dispersions of Itraconazole." European journal of pharmaceutical sciences. 30(3-4): 288-294. 0928-0987
45. Hogan, J. E. (1995). Film-coating materials and their properties Summary. Pharmaceutical coating technology, CRC Press: 16-62.
46. Rowe, R. C., et al. (2009). Handbook of pharmaceutical excipients, Libros Digitales-Pharmaceutical Press.
47. Tiefenbacher, K. F. and K. Tiefenbacher (2017). "Technology of main ingredients—sweeteners and lipids." Wafer and Waffle. 123-225
48. Maher, E. M., et al. (2016). "In vitro/in vivo evaluation of an optimized fast dissolving oral film containing olanzapine co-amorphous dispersion with selected carboxylic acids." Drug delivery. 23(8): 3088-3100. 1071-7544

49. Bala, R., et al. (2014). "Design optimization and in vitro-in vivo evaluation of orally dissolving strips of clobazam." Journal of drug delivery. 2014. 2090-3014
50. Adrover, A., et al. (2018). "Experimental and modeling study of drug release from HPMC-based erodible oral thin films." Pharmaceutics. 10(4): 222. 1999-4923
51. Mahesh, A., et al. (2010). "Development of taste masked fast disintegrating films of levocetirizine dihydrochloride for oral use." Current drug delivery. 7(1): 21-27. 1567-2018
52. Yellanki, S., et al. (2011). "Dissofilm: a novel approach for delivery of phenobarbital; design and characterization." Journal of Young Pharmacists. 3(3): 181-188. 0975-1483
53. Takeuchi, H., et al. (2013). "Design of rapidly disintegrating drug delivery films for oral doses with hydoxypropyl methylcellulose." Journal of Drug Delivery Science and Technology. 23(5): 471-475. 1773-2247
54. Preis, M., et al. (2012). "Development of a taste-masked orodispersible film containing dimenhydrinate." Pharmaceutics. 4(4): 551-562. 1999-4923
55. Sayed, S., et al. (2013). "Fast-dissolving sublingual films of terbutaline sulfate: formulation and in vitro/in vivo evaluation." Molecular Pharmaceutics. 10(8): 2942-2947. 1543-8384
56. Auda, S. H., et al. (2014). "Design, Formulation and Characterization Of Fast Dissolving Films Containing Dextromethorphan." Digest Journal of Nanomaterials & Biostructures (DJNB). 9(1). 1842-3582
57. Kunwarpuriya, A., et al. (2015). "Formulation and evaluation of Dextromethorphan hydrobromide fast dissolving film." International Journal of Innovative Pharmaceutical Sciences and Research. 3(8): 2154-2347
58. Elfiyani, R. and S. Nurhasanah (2021). Citrus maxima Pectin as Superdisintegrant: Preparation and Evaluation of Dextromethorphan Hydrobromide Orodispersible Film. IOP Conference Series: Earth and Environmental Science, IOP Publishing.
59. Patel, D. M., et al. (2016). "Formulation and Evaluation of Fast-Dissolving Film of Cetirizine and Dextromethorphan." International journal of pharmaceutical sciences and nanotechnology. 9(3): 3305-3311. 0974-3278

60. Kwak, S. S., et al. (2018). "Immediate release tablet formulation of varenicline salicylate and comparative pharmacokinetic study in human volunteers." Drug Design, Development and Therapy. 12: 3377
61. Jordan, Chloe J., and Zheng-Xiong Xi. "Discovery and development of varenicline for smoking cessation." Expert opinion on drug discovery 13.7 (2018): 671-683.
62. Chauhan, I., et al. (2019). "Oral delivery of zolmitriptan loaded fast disintegrating film: formulation development, statistical optimization, in-vitro and in-vivo evaluation." Journal of Applied Pharmaceutical Sciences and Research. 13-22. 2581-5520
63. Waterman, Kenneth C., et al. "N-methylation and N-formylation of a secondary amine drug (varenicline) in an osmotic tablet." Journal of pharmaceutical sciences 97.4 (2008): 1499-1507.
64. Sapavadiya, V. K., et al. (2016). "Development and Optimization of Mouth Dissolving Film of Granisetron using 32 Factorial Design and Response Surface Methodology." International journal of pharmaceutical sciences and nanotechnology. 9(1): 3118-3129. 0974-3278
65. Alayoubi, A., et al. (2017). "Development of a fast dissolving film of epinephrine hydrochloride as a potential anaphylactic treatment for
66. pediatrics." Pharmaceutical development and technology. 22(8): 1012-1016. 1083-7450
67. Xu, L.-L., et al. (2014). "Formulation and in vitro characterization of novel sildenafil citrate-loaded polyvinyl alcohol-polyethylene glycol graft copolymer-based orally dissolving films." International journal of pharmaceutics. 473(1-2): 398-406. 0378-5173
68. Visser, J. C., et al. (2015). "Orodispersible films in individualized pharmacotherapy: The development of a formulation for pharmacy preparations." International journal of pharmaceutics. 478(1): 155-163. 0378-5173
69. Mazumder, S., et al. (2017). "Quality by Design approach for studying the impact of formulation and process variables on product quality of oral disintegrating films." International journal of pharmaceutics. 527(1-2): 151-160. 0378-5173

70. Silva, B. M., et al. (2017). "Retrospective Quality by Design (rQbD) applied to the optimization of orodispersible films." 528(1-2): 655-663. 0378-5173
71. Silva, B. M., et al. (2017). "Retrospective Quality by Design (rQbD) applied to the optimization of orodispersible films." International journal of pharmaceutics. 528(1-2): 655-663. 0378-5173
72. Dangre, P. V., et al. (2019). "Quality by design (QbD) assisted fabrication of fast dissolving buccal film for clonidine hydrochloride: Exploring the quality attributes." Advances in Polymer Technology. 2019. 0730-6679
73. Yu, L. X. (2008). "Pharmaceutical quality by design: product and process development, understanding, and control." Pharmaceutical research. 25(4): 781-791. 1573-904X
74. Jagtap, P. and R. Wagh (2018). "Development, evaluation and optimization of smoking cessation patch containing antidepressant drugs." Development.
75. Mahajan, N. M., et al. (2018). "Formulation development and evaluation of transdermal patch of piroxicam for treating dysmenorrhoea." Journal of Applied Pharmaceutical Science. 8(11): 035-041
76. Escobar-Chávez, J. J., et al. (2011). "Transdermal nortriptyline hydrocloride patch formulated within a chitosan matrix intended to be used for smoking cessation." Pharmaceutical development and technology. 16(2): 162-169. 1083-7450
77. Lewis, S. and N. Udupa (2006). "Design and evaluation of matrix type and membrane controlled transdermal delivery systems of nicotine suitable for use in smoking cessation." Indian journal of pharmaceutical sciences. 68(2). 2278-8875
78. Breitenbach, A., et al. (2014). Orodispersible films for the manufacturing of individualised medicine or for large scale production, US Patent 14/238,381.
79. Bess, W. S., et al. (2006). Fast dissolving orally consumable films containing an ion exchange resin as a taste masking agent, EP 01959912A.
80. Bess, W. S., et al. (2010). Fast dissolving orally consumable films containing a taste masking agent, US 7648712.
81. Park, J.-K., et al. (2016). Quickly soluble oral film dosage containing steviosides as a unpleasant taste masking agent, US 9492379.

82. Kulkarni, N., et al. (2003). Fast dissolving orally consumable films containing a sweetener, US 10/423398.
83. Jeong, H. J., et al. (2018). High-content fast dissolving film with masking of bitter taste comprising sildenafil as active ingredient, US 10092651.
84. Dixit, G., et al. (2012). Process for preparing varenicline, varenicline intermediates, pharmaceutically acceptable salts thereof, US 8314235.
85. Pradhan, N. S., et al. (2013). Highly pure varenicline or a pharmaceutically acceptable salt thereof substantially free of methylvarenicline impurity, US 13/581491.
86. Chaurasia, G. (2016). "A review on pharmaceutical preformulation studies in formulation and development of new drug molecules." International journal of Pharmaceutical sciences and research. 7(6): 2313-2320
87. Verma, G. and M. K. Mishra (2016). "Pharmaceutical preformulation studies in formulation and development of new dosage form: A review." Int. J. Pharma Res. Rev. 5(10)
88. Pharmacopoeia, I. (1996). "Government of India, ministry of health and family welfare." Delhi: Controller of Publications. 2(35): 448
89. Schulze, D. (2021). Flow properties of bulk solids. Powders and Bulk Solids, Springer: 57-100.
90. Gopinath, R., et al. (2011). "Pharmaceutical preformulation studies–current review." 2(5): 1391-1400
91. Bruni, G., et al. (2002). "Drug-excipient compatibility studies. Search of interaction indicators." 68(2): 561-573. 1388-6150
92. Vijayalakshmi, R., et al. (2010). "Simultaneous UV spectrophotometric determination of cetrizine and dextromethorphan in tablet dosage form." 7(S1): S314-S318. 2090-9063
93. Bruni, G., et al. (2002). "Drug-excipient compatibility studies. Search of interaction indicators." Journal of Thermal Analysis and Calorimetry. 68(2): 561-573. 1388-6150
94. Dixit, R. and S. Puthli (2009). "Oral strip technology: Overview and future potential." Journal of Controlled Release. 139(2): 94-107. 0168-3659

95. Bhise, K., et al. (2008). "Taste mask, design and evaluation of an oral formulation using ion exchange resin as drug carrier." Aaps Pharmscitech 9(2): 557-562. 1530-9932

96. Patra, S., et al. (2010). "Taste masking of Etoricoxib by using ion-exchange resin." Pharmaceutical development and Technology15(5): 511-517. 1083-7450

97. Douroumis, D. J. E. o. o. d. d. (2007). "Practical approaches of taste masking technologies in oral solid forms." Expert opinion on drug delivery 4(4): 417-426. 1742-5247

98. Gupta, M. S., et al. (2021). "Orodispersible films: Conception to quality by design." Advanced drug delivery reviews 178: 113983. 0169-409X

99. Borges, A. F., et al. (2015). "Outlining Critical Quality attributes (CQAs) as guidance for oral films." Pharmaceutical Development and technology165

100. Visser, J. C., et al. (2015). "Quality by design approach for optimizing the formulation and physical properties of extemporaneously prepared orodispersible films." INternational Journal of Pharmaceutics 485(1-2): 70- 76. 0378-5173

101.Krampe, R., et al. (2016). "Oromucosal film preparations: points to consider for patient centricity and manufacturing processes." Expert opinion on Drug Delivery 13(4): 493-506. 1742-5247

102. Dalal, R., et al. (2021). "Development and Optimization of Asenapine Sublingual Film Using QbD Approach." AAPS Pharm Sci Tech 22(7): 1-20. 1530-9932

103. Casian, T., et al. (2017). "QbD for pediatric oral lyophilisates development: risk assessment followed by screening and optimization." Drug development and Industrial Pharmacy 43(12): 1932-1944. 0363-9045

104. Mishra, V., et al. (2018). "Quality by design (QbD) approaches in current pharmaceutical set-up." Expert opinion on Drug Delivery 15(8): 737- 758. 1742-5247

105. Vanaja, K., et al. (2007). "Design of experiments: concept and applications of Plackett Burman design." Clinical Research and Regulatory Affairs 24(1): 1-23. 1060-1333

106. Shaikh, S. S. and A. J. A. C. L. Barrawaz (2021). "Quality by Design Approach in the Formulation of Glibenclamide Mucoadhesive Buccal Films." Analytical Chemistry Letters 11(4): 497-511. 2229-7928

107.Ahmed, T. A. J. J. o. l. r. (2015). "Preparation of transfersomes encapsulating sildenafil aimed for transdermal drug delivery: Plackett– Burman design and characterization." Journal of Liposome Research 25(1): 1- 10. 0898-2104

108. Hamza, M. (2017). "Development And Evaluation Of Orodispersible Films Of Lamotrigine: Hydroxypropyl B Cyclodextrin Inclusion Complex." Al-Azhar Journal of Pharmaceutical Sciences. 56(2): 31-46. 1110-1644

109. Koland, M., et al. (2010). "Fast dissolving sublingual films of ondansetron hydrochloride: effect of additives on in vitro drug release and mucosal permeation." Journal of Young Pharmacists. 2(3): 216-222. 0975- 1483

110. Gupta, H., et al. (2010). "E-tongue: a tool for taste evaluation." Recent patents on drug delivery and formulations 4(1): 82-89. 1872-2113

111.Haraguchi, T., et al. (2014). "Evaluation of ebastine-loaded orally disintegrating tablets using new apparatus of detecting disintegration time and e-tongue system." Journal of Drug Delivery Science and Technology24(6): 684-688. 1773-2247

112. Li, L., et al. (2007). "Utilization of a modified special-cubic design and an electronic tongue for bitterness masking formulation optimization." Journal of Pharmaceutical Sciences 96(10): 2723-2734. 0022-3549

113. Ibrahim, F., et al. (2022). "Spectroscopic strategies for quantitation of varenicline in pharmaceutical preparations and content uniformity testing."Royal society oprn science 9(9): 220628. 2054-5703

114. Kocak, E., et al. (2013). "Validation of spectrophotometric method to quantify veranicline content in tablets." Hacettepe Üniversitesi Kütüphaneleri 0970-7077

115. Bhyan, B., et al. (2011). "Orally fast dissolving films: innovations in formulation and technology." Int J Pharm Sci Rev Res 9(2): 9-15

116. Sharma, R., et al. (2007). "Development of taste masked film of valdecoxib for oral use." Indian Journal of Pharmaceutical Sciences 69(2): 320. 2278-8875

117. Raza, S. N., et al. (2019). "Formulation and evaluation of mouth dissolving films of losartan potassium using 32 Factorial design." Int. J. Pharm. Sci. Res 10(3): 1402-1411

118. Prajapati, V. D., et al. (2018). "Pullulan based oral thin film formulation of zolmitriptan: Development and optimization using factorial design." International Journal of Biological Macromolecules 107: 2075-2085. 0141-8130

119. El-Said, I. A., et al. (2021). "Optimization of taste-masked dapoxetine oral thin films using factorial design: in vitro and in vivo evaluation." Pharmaceutica Development and Technology 26(5): 522-538. 1083-7450

120. Sonawane, D. D. J. A. J. o. P. (2022). "Formulation and Evaluation of Perindopril Erbumine Mouth Dissolving Film Using 32 Factorial Design." Asian Journal of Pharmaceutics 16(3). 1998-409X

121. Nalluri, Buchi N., et al. (2013) "Development and evaluation of mouth dissolving films of sumatriptan succinate for better therapeutic efficacy." Journal of applied pharmaceutical science 3.8 : 161-166.2231-3354.

122.Takeuchi, Y., et al. (2020). "Mechanical characteristics of orally disintegrating films: Comparison of folding endurance and tensile properties." International Journal of Pharmaceutics 589: 119876. 0378-5173

123. Liew, K. B., et al. (2014). "Effect of polymer, plasticizer and filler on orally disintegrating film." Drug Development and Industrial Pharmacy 40(1): 110-119. 0363-9045

124. Geldart, D., et al. (2006). "Characterization of powder flowability using measurement of angle of repose." China Particuology 4(3-4): 104-107. 1672-2515

125. Auda, S. H., et al. (2014). "Design, Formulation And Characterization Of Fast Dissolving Films Containing Dextromethorphan." Digest Journal of Nanomaterials and Biostructures 9(1). 1842-3582

126. Fouad, E. A., et al. (2011). "In vitro investigation for embedding dextromethorphan in lipids using spray drying." Digest Journal of Nanomaterials and Biostructures. 1139

127. Hirpara, F., et al. (2012). "Optimization & screening of different film forming polymers and plasticizers in fast dissolving sublingual film." International Journal of Pharmacy and Pharmaceutical Sciences 1(2): 94-101

128.Galgatte, U. C., et al. (2013). "Investigation of different polymers, plasticizers and superdisintegrating agents alone and in combination for use in the formulation of fast dissolving oral films. "International Journal of PharmTech Research 5(4): 1465-1472

129.Mahesh, A., et al. (2010). "Development of taste masked fast disintegrating films of levocetirizine dihydrochloride for oral use." Current Drug Delivery 7(1): 21-27. 1567-2018

130. Tyssedal, J. and O. J. P. Samset, Statistics (1997). "Analysis of the 12 run Plackett-Burman design." Statistics (8).

131. Nirmala, D., et al. (2016). "Design and evaluation of fast dissolving oral films of Zolpidem by solvent casting method." Asian Journal of Pharmaceutical Research 6(2): 67-71. 2231-5683

132. Ali, M., et al. (2016). "Formulation and evaluation of fast dissolving oral films of diazepam." Journal of Pharmacovigilance 4(3): 1-5

133. Kassem, M. G., et al. (2012). "Varenicline." 37: 389-411. 1871-5125

134.Sultana, F., et al. (2013). "Preparation and evaluation of fast dissolving oral thin film of caffeine." International Journal of Pharmacy and Biologial Sciences 3(1): 153-161,2230-7605

ANNEXURE I

List of Publications

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Development and validation of the UV spectroscopic method for varenicline determination in pharmaceutical preparation

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Abstract---A simple and accurate UV visible spectroscopic method has been developed and validated for quantification of varenicline in bulk drug and pharmaceutical dosage forms. A shimadzu UV spectrophotometer was used considering availability and cost effectiveness of the proposed method. λmax of 236nm and 319nm were observed from the spectroscopic method. The calibration curve was linear (r = 0.99) in the studied range of concentration (5- 40 µg /ml) in both the absorption maxima. The selectivity and sensitivity of the elaborated method were satisfactory, and the limits of detection and quantification were less than 20% of the specification level. Moreover, the inter- and intra-day precisions was found to be less than 3% (RSD), while the recovery values expressing inter- and intra-day accuracy was varied from 99.73 to 101.23. The varenicline solution was stable over a period of 3 days on storage under refrigeration. The utility of the developed method was examined by analyzing the tablets containing VAR. As a result, the method was found to be selective, sensitive, precise and accurate.

Keywords---UV visible spectroscopic method, varenicline, smocking.

Introduction

Smoking is the number one cause of preventable disease and death in the United States (Young & Davis,2019). A number of smoking cessation pharmacotherapies

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Preformulation Studies of Varenicline for Formulation and Development of a Novel Orally Disintegrating Film

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Objective: The major goal of pre-formulation research is to create a drug delivery system that is stable, elegant, safe, and effective by determining the drug's kinetic profile, the formulation's compatibility with various excipients, and the physico-chemical characteristics of new drug molecules. This could offer crucial support for executing formulation design or the need for the molecular change. Therefore, in the current study, studies on Varenicline (VAR)'s appropriateness for oral formulation were conducted. Similar to cytisine, VAR functions as a partial nicotine receptor agonist. It blocks alpha-4-beta-2 nicotinic acetylcholine receptor subtypes and is a partial agonist. Through partial agonism, VAR reduces the urge and withdrawal symptoms associated with quitting efforts by inhibiting the dopaminergic activation brought on by smoking. It stops nicotine from stimulating the mesolimbic dopamine pathway, which is linked to nicotine addiction.

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Development And Characterization Of Orally Disintegrating Film Of Dextromethorphan For Improved Patient Compliance

Prakruti Mukund Amin , Manish Patel

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ABSTRACT

Fast-dissolving pills are becoming more and more common because they don't need water to be administered. Dextromethorphan is prescribed for sore throats. The study's goal was to develop and improve a fast-dissolving film for dextromethorphan taste masking utilizing a casting approach using HPMC E15 LV, polyethylene glycol 400, aspartame-tartaric acid- citric acid- menthol-ion exchange resins. Plasticizers, tartaric and citric acids, which stimulate salivation, menthol, and tartaric and citric acids as flavouring agents were all used in the formulation of the films. To disguise the bitterness of medications, Aspartame and Kyron T111, an ion exchange resin, were employed as sweeteners. According to a study on drug content in films that dissolve quickly, more than 95% of the medications are present. More than 96% of pharmaceuticals are released within 30 minutes, according to a formula film that demonstrated a 17-second oral dissolving time. Without using any organic solvent, films were made using the solvent casting process, and it was discovered that they satisfied the mouth dissolving time and other film criteria. Our findings indicate that the four films we developed all had satisfactory film characteristics. Conclusion: Without using any organic solvents, a fast-dissolving film containing dextromethorphan may be cast using the solvent casting process.

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