DEVELOPMENT OF ORAL FORMULATIONS USING SPRAY DRIED SOLID DISPERSION TECHNOLOGY

A Thesis submitted to Gujarat Technological University

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Doctor of Philosophy

in

Pharmacy

By
Kaushika Mahendra Patel
189999901012

under supervision of
Dr. Shreeraj H. Shah

GUJARAT TECHNOLOGICAL UNIVERSITY

AHMEDABAD

February-2024

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ABSTRACT

Solid Dispersion (SD) technology is one of the most widely preferred solubility enhancement methods, especially for Biopharmaceutics classification system Class II and IV drugs. Since the last decade, its application for the dual purpose of solubility hike and modified release using novel carriers has been in demand for its added advantages. Spray drying is a commercially accepted technique with high aspects of scalability and product characteristics. The current study used spray dried dispersion to design Gastro-retentive formulation for antifungal drug Posaconazole and, delayed release formulation for the Proton pump Inhibitor Esomeprazole. The SD carriers explored were Soluplus®, possessing outstanding solubilization properties that enhance bioavailability and is suitable for innovative processing, and Gelucire 43/01, a lipid polymer utilized in a non-effervescent-based floating gastro-retentive DDS for the modified release of API. The SD carrier Hydroxy propyl methyl cellulose acetate succinate- medium grade (HPMCAS-MF) enhanced solubility, inhibited precipitation of saturated drug solutions, and allowed enteric release owing to its solubility above pH 6. The formulations were optimised using Design of Experiment (DOE), considering significant process & formulation variables. All the experimental batches were evaluated for %yield, % drug content, flow properties, saturation solubility, and *in-vitro* drug release in suitable dissolution media. The optimized batch was characterized for API-polymer/s compatibility based on DSC (Differential Scanning Calorimetry) and PXRD (Powder X-ray Diffraction). The optimized batch was characterized for particle size analysis, SEM (Scanning Electron Microscopy), residual solvent analysis, and stability testing as per ICH Guidelines. In case of POS gastro-retentive formulation, *in-vivo* roentgenography and pharmacokinetic study were performed in New Zealand white rabbit and male Sprague-Dawley rats respectively. The design space was developed via overlay plot based on constraints specified to attain the desired response and validated using three checkpoint batches with desirability 1. The undertaken research work provided a broad outcome in the area of SD technology for modified release formulations, using novel SD carriers with an added advantage beyond the solubility enhancement.

Key words: Spray dried solid dispersion, solubility, Soluplus®, Gelucire 43/01, HPMCAS-MF, Esomeprazole, Posaconazole.

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CHAPTER-5

List of Abbreviations

SD	Solid Dispersion
SDD	Spray Dried Dispersion
POS	Posaconazole
ESM	Esomeprazole
FTIR	Fourier Transform Infrared Spectroscopy
SEM	Scanning Electron Microscopy
PXRD	Powder X-Ray Diffraction
HS GC-MS	Head-space Gas Chromatography-Mass Spectrometry
ICH	International Conference on Harmonization
ASD	Amorphous Solid Dispersion
HPMCAS	Hydroxyl Propyl Methyl Cellulose Acetate Succinate
CR	Controlled release
DSC	Differential Scanning Calorimetry
PBS	Phosphate Buffer Solution
FFR	Feed Flow Rate

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CHAPTER 1
Introduction

Since solid oral dosage forms are easier to manufacture, have better stability, uniform dose distribution, and are smaller than other dosage forms, oral route is the most preferrable route of administration [1]. One of the important factors influencing the bioavailability of a formulation is its aqueous solubility [2]. Based on statistical data, about 40% of marketed formulations and 60% of compounds under synthesis have low water solubility and suffer bioavailability issues [3–5]. During the development phase, one of the main issues that compounds encounter is dissolution [6–9]. Consequently, the main challenge facing formulation scientists is to devise a practical method to improve the solubility of the API (Active Pharmaceutical Ingredient) in order to accelerate the rate of dissolution of formulation [10, 11].

1.1 Importance of Solubility Enhancement

One of the toughest aspects of improving therapeutic bioavailability is developing drugs with improved solubility [5, 12]. Table 1.1 details several methods for improving solubility that are currently in use [13–16].

Table 1.1 Solubility Enhancement Techniques

Mechanism	**Methods**
Physical modification	-Reduction in Particle size by micronization and nano-sizing
The alteration of crystal morphology	-Amorphous form -Polymorphism -Co-crystallization
Drug dispersions	-Eutectic mixture -Solid dispersion -Solid solution -cryogenic techniques like or URF (Ultra Rapid freezing), SFL (Spray Freezing into Liquid) or SFV/L (Spray freezing into vapour over liquid) -Inclusion complexation

Chemical modification	-change in pH -Addition of buffer -Derivatisation -Salt formation
Other methods	-Use of surfactant or solubilizer -Supercritical Fluid Technology -Cosolvency -Hydrotrophy -Use of novel excipients

1.2 Solid dispersion (SD)

One of the recommended approaches to address API's poor water solubility and restricted bioavailability is solid dispersion (SD) [17–20]. A SD consists of a minimum of two components: a drug that is poorly soluble and an SD carrier that is mostly hydrophilic [11, 21–23]. Multi-component SD may also be designed, in which more than two components are employed at the same time to optimize both formulation and therapeutic effectiveness [24]. Drug solubility is significantly improved by ternary SD that contains surfactant [25]. To improve solubility, the medication might be molecularly distributed in an amorphous or crystalline carrier [26, 27]. The medications have the benefit in terms of apparent solubility since they can be entrapped in their amorphous forms, which are theoretically the highest energy solid state of a material [28]. Using a polymer matrix, amorphous solid dispersion (ASD) stabilizes the formulation while simultaneously increasing the pace and amount of dissolution [23, 29, 30]. Higher dosage incorporation of poorly soluble drugs in the formulation is made possible by ASD's longer-lasting super saturation [22, 31].

The advantages of solid dispersion (SD) include reduced particle size and higher porosity, improved wettability, drug dispersion in an amorphous state, ease of production compared to chemical approaches like pro-drug or salt form, acceptance of SD over liquids obtained through solubilization method, and greater efficiency over particle reduction techniques [32].

The challenges faced by SD are as below [32]

- ✓ Lack of stability in Physical characteristics
- ✓ Observable alterations in crystallinity and a reduction in the rate of disintegration as a result of the aging process.

- ✓ During storage, SD is susceptible to changes in humidity and temperature because of its thermodynamic instability. By increasing total molecular mobility, lowering the glass transition temperature (Tg), or interfering with the interactions between the drug and carrier, these variables may encourage phase separation and crystallization of SD and lower the drug's solubility and rate of dissolution.
- ✓ The potential for SD instability over the storage term may have implications for drug quality and therapeutic efficacy.

1.3 Solid Dispersion Carrier

In SD technology, several polymers can be screened as per the requirement of formulation. There has been constant evolution in the category and characteristics of SD carriers. Initial generations of SD carriers, namely first, second and third generations, consisted of hydrophilic carriers with better wettability and solubility enhancement. The fourth generation focused on use of swellable polymers to felicitate the sustained or controlled release of API from the carrier. Whereas, recently the objective is to utilize the novel SD carriers with excellent stabilization properties along with the enhanced solubility of drug. The different SD carriers are discussed in Table 1.2 and Fig 1.1 [23, 33].

TABLE 1.2 Summary of SD carriers

CARRIERS	SALIENT FEATURES
FIRST GENERATION	Crystalline carriers like sugars, organic acid, and urea. Thermodynamically more stable Improved drug release due to better wettability and size reduction Eg. Eutectic mixture
SECOND GENERATION	Amorphous solid dispersion of drug and polymeric carrier These polymers are biologically inactive and less absorbed in GIT Cellulose derivatives like hydroxypropyl methylcellulose (HPMC), hydroxy ethyl cellulose, hypromellose acetate succinate (HPMCAS), cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), hydroxypropyl cellulose (HPC), methyl cellulose, chitosan, carboxymethyl cellulose, ethyl cellulose, carboxymethyl ethyl cellulose, cyclodextrin and derivatives, lactose, poloxamers, polyvinylpyrrolidone (PVP)

	polymethacrylates (Eudragit E, L, S, FS), polyvinylpyrrolidone-vinyl acetate copolymer (PVP/VA 64), polyvinyl acetate phthalate (PVAP), and polyethylene glycols (PEG) derivatives Eg: solid solution, solid suspension
THIRD GENERATION	These include carrier with surface active or self-emulsifying properties like Tween 80, poloxamer 408, Gelucire

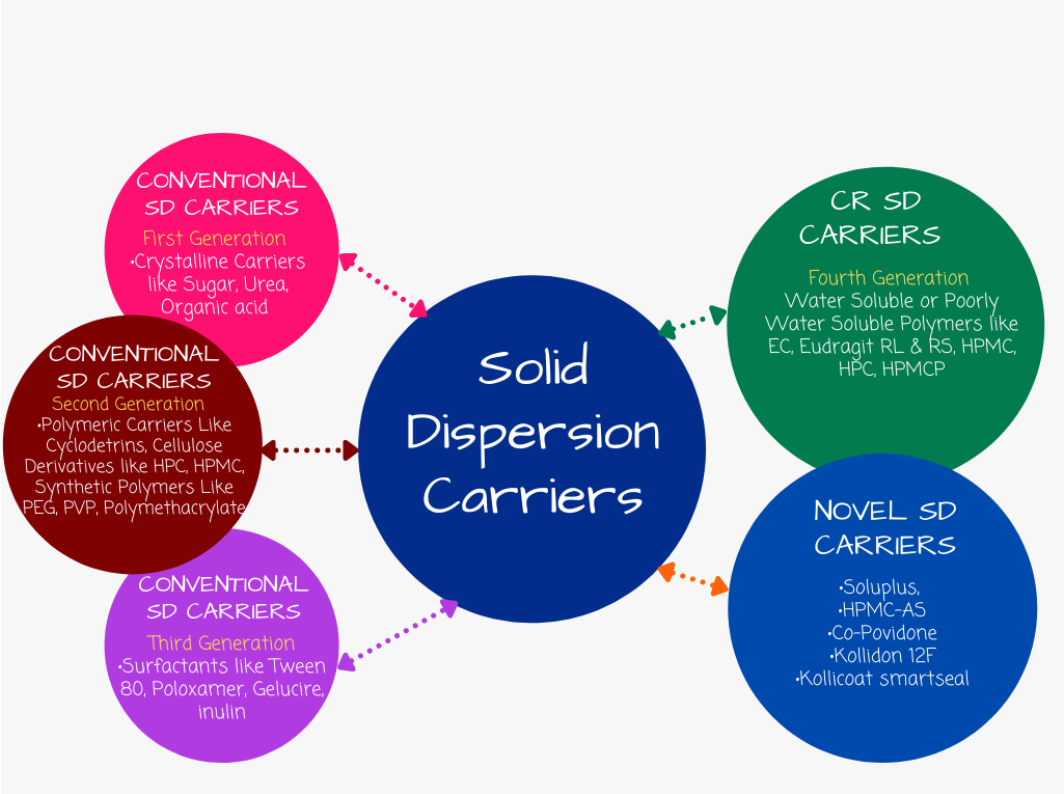

FIGURE 1.1 A summary of SD carriers

By using hydrophilic carriers to entrap the drug, the SD approach was first developed to improve the *in-vitro* release rate and the bioavailability of drugs with low aqueous solubility [34]. However, in the design of controlled release (CR) or sustained release (SR) formulations, hydrophobic and hydrophilic swellable polymers are also favoured as SD carriers to delay the dissolution of medication [34, 35]. Since the drug molecules disperse in the carrier or carriers to achieve the appropriate release rate, controlled release SD (CR SD) avoids the potential of a drug burst [36]. The primary constraints noted in CR SD are the scale-up of the pilot plant and the product's commercial viability despite substantial research [37]. To create CR SD, several preparation techniques and SD carriers are being investigated. A variety of carriers, including EC, HPMC, HPC, HPMCP, and various grades of Eudragit, are used in the preparation of CR SD [38, 39].

Selecting the appropriate SD carrier is of utmost importance in order to get the desired kind and attributes of SD. As Fig. 1 illustrates, there is a broad variety of SD carriers [40, 41]. Many new polymers have been studied recently and are being employed widely in SD technology. HPMCAS is the amphiphilic cellulosic SD carrier that is most often employed. The preferred SD carrier is the block graft copolymer Soluplus® because of its superior solubility, extrudability, and stabilizing qualities [42–53]. Due of its low Tg temperature and strong solubility in both polar and nonpolar solvents, copovidone (PVP VA64) is another adaptable SD carrier that is used for both HME and Spray Drying procedures [54]. In the manufacture of SD, kollidon 12PF, a low molecular grade soluble povidone, is utilized as a dispersant, solubilizer, and crystallization inhibitor [55]. In addition to its taste masking and hygroscopic qualities, Kollicoat® Smartseal has shown its superiority as an SD carrier [56].

1.4 Solid Dispersion Manufacturing Techniques

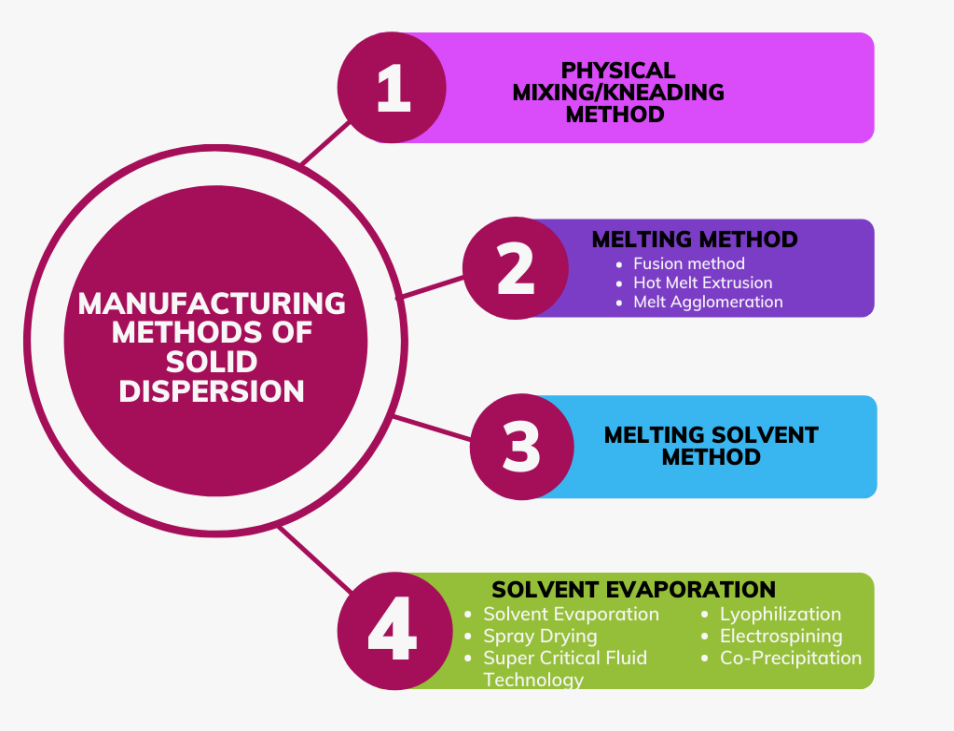

FIGURE 1.2 Manufacturing Techniques for Solid dispersion

There is a wide range of techniques available to improve the solubility of API namely nano-particle based formulations, lipid-based formulations, SD Technology, Reduction in particle size, salt formation or use of prodrug [57]. Out of the wide option of methods available, Solid dispersion (SD) is widely recognized technique for enhancing the solubility of pharmaceutical drugs [8]. The physicochemical characteristics of the API and the SD carrier

as well as the preparation method used have a crucial role in deciding the type and characteristics of SD formed. Thus, the selection of suitable technique to prepare SD and optimization of the process parameters is significant to achieve desirable formulation characteristics [58]. The different methods used to prepare SD [16, 59, 60] are summarized in Fig 1.2. The extensively used and preferred techniques in SD development are HME, Spray Drying, Co-precipitation and Supercritical Fluid [13, 32].

1.5 Amorphous Solid Dispersion (ASD)

1.5.1 Amorphous State

Pharmaceutical materials in an amorphous state are thermodynamically metastable and easily transform into a higher stable form i.e. crystalline form. Due to the substantial disparity in free energy between the amorphous and crystalline forms, the quasi-equilibrium thermodynamic viewpoint suggests that the solubility of the amorphous form exceeds that of the crystalline form [61]. It is shown that fast cooling may produce an amorphous material with a glassy character and a supercooled liquid. As the material cools, its viscosity rises at the same time as its molecular mobility steadily decreases. This is referred to as the Tg temperature, and the glassy condition of the substance. In contrast, glassy materials exhibit metastability, meaning they exist in a state that is neither fully crystalline nor in equilibrium with the supercooled liquid phase of the material. Consequently, it is essential to conduct extensive physical stability testing prior to the production of pharmaceutical products [62]. The glass transition is linked to alteration in a number of thermodynamic parameters, including process volume, entropy, and enthalpy. It was also described as a thermodynamic transition of second order. For such research, there is a wealth of literature available that addresses amorphous drug delivery devices [63]**.**

1.5.2 Amorphous Solid Dispersion

The bioavailability of a drug may potentially be enhanced by the use of amorphous solid dispersion when the drug is available in an amorphous state. The choice of an appropriate polymer carrier aids in improving the drug's solubility, speed of dissolution, and physical stability in the solid form. The use of a polymer carrier facilitates the conversion of a crystalline compound into its amorphous state, while concurrently enhancing the stability of

the ASD by increasing the Tg and reducing molecular mobility. Drug–polymer interactions and the breakdown of intermolecular interactions in the drug's crystal structure are undoubtedly what contributes to the stability of an ASD. The crystal lattice structure interferes with polymer-to-polymer interactions and compromises the stability of ASD. The improvement in ASD's bioavailability is due to both thermodynamic and kinetic factors. A greater surface area may be produced by the steric hindrance, which also inhibits crystallization and prevents the nucleation of new crystals. The surface area and dissolution may be correlated using the Noyes-Whitney equation. The rate of dissolution rises in correlation with surface area. The first stage of dissolution involves the molecule being wettable, which may be made easier by polymers that dissolve in water. The absorption kinetics of the molecule are accelerated by the supersaturated solution that has been generated and the improved gastrointestinal transit time, even if the complete dissolution release profile is not attained. Moreover, ASD has the potential to enhance the rate at which naturally existing micelles, nanoparticles, or microparticles in the gastrointestinal (GI) tract penetrate the system. [23, 62, 64–69].

1.6 Modified Release Solid Dispersion

The use of SD for the combined goals of improved solubility and tailored release using innovative carriers has been in demand over the last 20 years due to its additional benefits. The appropriate formulations required to improve the therapeutic uses and bioavailability of poorly aqueous-soluble drugs from SD have been studied. By adding SDs in an appropriate dosage form during or after SD manufacturing, several formulations may be developed [70, 71].

MR dosage form is defined as the one formed by modifying the existing conventional formulation with respect to release rate, release time or site of release.

Modified release can be achieved by different release mechanisms

(1) Extended Release [ER, XR, XL]: The main purpose is reduction in dosing frequency through prolonging the drug release profile [36, 72].

(a) Sustained Release [SR]: SR formulation provide an IR (Immediate Release) dose for normal onset of action, followed by maintenance dose to sustain the Pharmacological effect for known desired prolonged period of time usually 8-12 hrs [73].

(b) Controlled Release [CR]: Release the drug at a predefined controlled rate, for a specific time duration, locally or systematically [36].

(2) Delayed Release [DR]: DR formulation release the drug at any time other than immediately after administration as observed in IR formulations [74].

(3) Targeted/ Site specific Release: The site-specific formulation releases the drug at a specific site in the body like colon, buccal cavity, stomach, etc. The targeted formulation is designed to release the drug at specific target at cellular or receptor level [75].

The modified release formulations overcome major limitations of IR formulations providing several advantages as described in Fig 1.3.

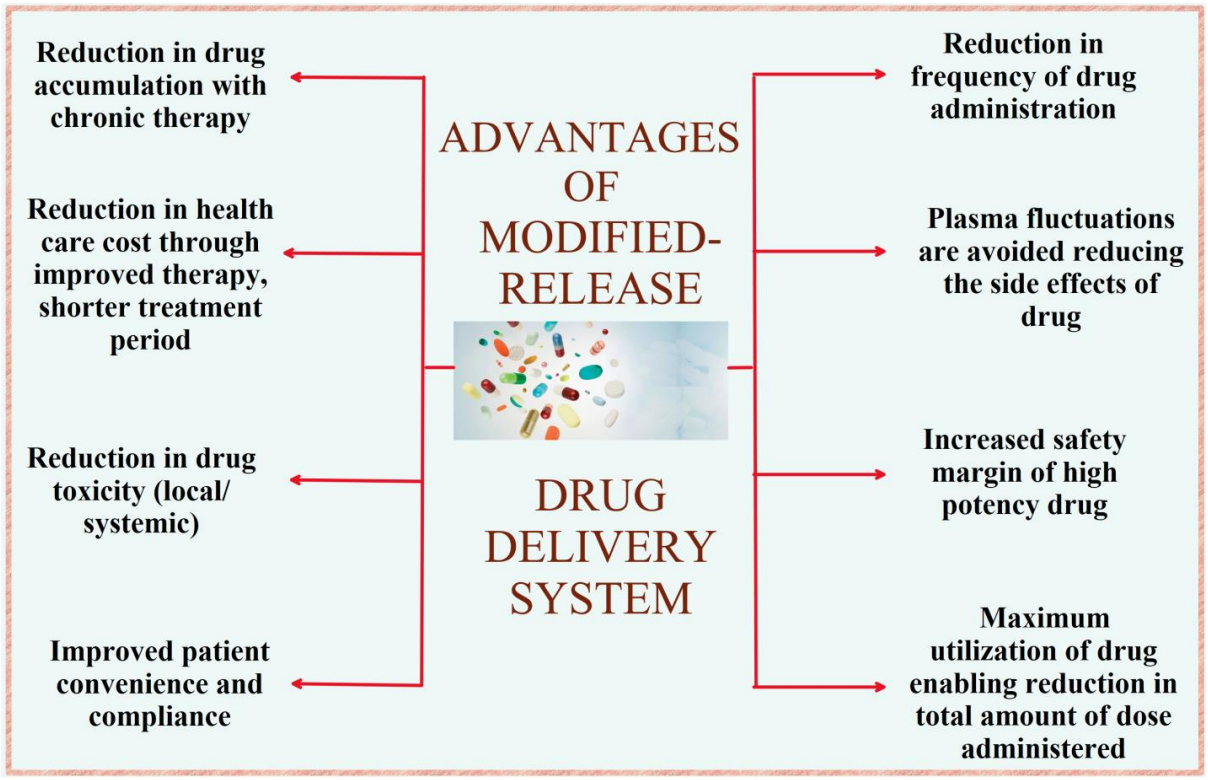

FIGURE 1.3 Advantages of Modified Release DDS

1.7 Current Status of Solid Dispersion based Products

The solubility enhancement based on conversion of API to amorphous form is one of the widely utilized formulation approach in the last two decades and about 30% commercialized products have been developed based on it. The summary of marketed products based on SD technology is described in Table 1.3 [13, 26, 32, 69, 76–78].

TABLE 1.3 List of Marketed Formulations based on SD

Sr No	Brand name	API	Carrier	Manufacturer	Year of approval
1	Nivadil®	Nilvadipine	HPMC	Fujisawa Pharmaceutical Co., Ltd	1989
2	Sporanox®	Itraconazole	HPMC	Janssen Pharmaceuticals, Inc., USA	1992
3	Prograf®	Tacrolimus	HPMC	AstellasPharma, US Inc.	1994
4	Norvir ®	Ritonavir	PVP-VA	Abbott	1996
5	Rezulin®	Troglitazone	PVP	Developed by Sankyo, manufactured by Parke-Davis division of Warner-Lambert	1997
6	Crestor®	Rosuvastatin	HPMC	Astra Zeneca	2002
7	Afeditab	Nifedipine	Poloxamer or PVP	Elan Corp, Ireland	2002
8	Cymbalta®	Duloxetine	HPMCAS	Eli Lilly	2004
9	Kaletra®	Lopinavir/ Ritonavir	PVP/VA	Abbot Labarotaries, USA	2005
10	Cesamet®	Nabilone	PVP	Meda Pharmaceuticals Inc., USA	2006
11	Nimotop®	Nimodipine	PEG	Bayer (Pty) Ltd., USA	2006
12	Fenoglide®	Fenofibrate	PEG/Poloxamer	Santarus, Inc.	2007
13	Eucreas®	Vildagliptin	HPC	Novartis Pharmaceuticals	2007
14	GalvumetTM	Metformin HCL	HPC	Novartis Pharmaceuticals	2007
15	Torcetrapib	Torcetrapib	HPMC AS	Pfizer, USA	2007
16	Intelence®	Fenofibrate	HPMC	Janssen Therapeutics, USA	2008
17	Modigraf®	Tacrolimus	HPMC	Astellas Pharma Europe B.V.	2009
18	Samsca®	Tolvaptan	HPMC	Otsuka Pharma	2009
19	Certican®/ Zortress®	Everolimus	HPMC	Novartis	2010
20	Onmel®	Itraconazole	HPMC	Sebela Ireland Ltd	2010
21	Incivek® (US), Incivo® (EU)	Telaprevir	HPMCAS	Vertex Pharmaceuticals	2011
22	Zelboraf®	Vemurafenib	HPMCAS	Roche	2011
23	Kalydeco®	Ivacaftor	HPMCAS/SLS	Vertex Pharmaceuticals	2012

24	Noxafil®	Posaconazole	HPMCAS	Merck	2013
25	Astagraf XL®	Tacrolimus	HPMC	Astellas Pharma Inc	2013
26	Belsomra®	Suvorexant	Copovidone	Merck	2014
27	Gris-PEG®	Griseofulvin	PEG 6000	Pedinol Pharmacal Inc.	2014
28	Isoptin SR-E®	Verapamil	HPC/HPMC	Abbott Labarotaries, USA	2015
29	Orkambi®	Lumacaftor/ Ivacaftor	HPMCAS/SLS	Vertex Pharmaceuticals	2015
30	Envarsus® LCP-Tacro®	Tacrolimus	Poloxamer/ HPMC	Veloxis Pharmaceuticals	2015
31	Zepatier®	Elbasvir/ Grazoprevir	HPMC	Merck	2016
32	Epclusa®	Sofosbuvir/ Velpatasvir	Copovidone	Gilead Sciences	2016
33	Venclexta®	Venetoclax	Copovidone	AbbVie	2016
34	Stivarga®	Regorafenib	Povidone K-25	Bayer	2017
35	Mavyret™	Glecaprevir/ Pibrentasvir	Copovidone K-28	AbbVie	2017
36	Lynparza®	Olaparib	Copovidone	AstraZeneca	2018
37	Tasigna®	Nilotinib	Soluplus	Novartis	2018
38	Orilissa®	Elagolix	Soluplus	AbbVie	2018
39	Erleada®	Apalutamide	HPMC-AS	Janssen	2018
40	Vitrakvi®	Larotrectinib sulfate	HPMC-AS	Bayer Healthcare Pharmaceuticals	2018
41	Trikafta®	Elexacaftor (Crystalline)/ Ivacaftor/ Tezacaftor	HPMC, HPMC-AS	Vertex	2019
42	Symdeko®	Tezacaftor/Ivacaftor and Ivacaftor	HPMC, HPMC-AS	Vertex	2019
43	Braftovi®	Encorafenib	Copovidone Poloxamer 188	Pfizer	2020
44	Oriahnn™	Elagolix/estradiol/norethindrone acetate	PEG 3350	AbbVie	2020

With the increasing utilization and faith in SD technology, the corresponding increase in the number of patents applied and granted on the same is also rising in the recent years [79]. Extensive research has been already executed on the various aspects pertaining to SD

technology [80]. The few of the recent patents related to formulations based on SD since 2019 are discussed below in Table 1.4.

TABLE 1.4 Summary of Recent Patents based on Solid Dispersion

Sr no	Patent no. Title & year	Summary of invention	API	SD carrier
1	**US 11,202,778 B2** AMORPHOUS SOLID DISPERSIONS OF DASATINIB AND USES THEREOF **2021**	The present invention describes the formation of ASD of protein kinase inhibitor Dasanitib using suitable polymeric carriers. The pharmaceutical formulation prepared thereof may be suitable for patients suffering from proliferative disorder like cancer or from diseases like H. pylori infection, achlorhydria or hypochlorhydria.	Dasatinib	Eudragit L100-55 Eudragit E100 Methocel E5
2	**EP 3 705 115 B1** COMPOSITION CONTAINING SELEXIPAG **2021**	The present invention includes a solid dispersion containing a selective prostacyclin (PGI2) receptor agonist Selexipag and solid unit dosage form for oral administration containing API in a non-crystalline state for the treatment of pulmonary arterial hypertension. The SD are prepared by hot melt extrusion method using appropriate carrier and then incorporated into tablet or capsule.	Selexipag	Copovidone, Hypromellose
3	**AU 2021106377 A4** MECHANISTIC APPROACH OF SOLUBILITY ENHANCEMENT: DEVELOPMENT OF HYDROTROPIC SOLID DISPERSION **2021**	The present invention includes the use of novel Hydrotropic solubilization technique to improve the solubility of poor water solvency drugs belonging to NSAID category like Meloxicin and Ketoprofen for replacing the use of toxic & costly organic solvent with safe & eco-friendly hydrotropic agent. The invention also focuses on development of SD by solvent evaporation method for rapid onset of action and improved bioavailability and then further on formulation of topical analgesic gel.	Meloxicin and Ketoprofen	Sodium benzoate Sodium Salicylate

4	**US011103503B2** PHARMACEUTICAL COMPOSITIONS OF LURASIDONE **2021**	The present invention includes ASD of slightly soluble drug Lurasidone and the pharmaceutical formulations thereof to reduce or eliminate the prior prevalent food effect along with the method of preparation of such compositions. The orally developed formulation showed better and consistent bioavailability than commercially available formulation in both fasted and fed state, along with sustaining sufficient plasma level even in fasting condition. The methods opted to develop SD is HME, Spray drying or Co-precipitation.	Lurasidone	HPMCAS, HPC, PVP/VA Copolymer
5	**US 11,129,815 B2** SOLID DISPERSIONS COMPRISING TACROLIMUS **2021**	Tacrolimus is indicated for prophylactic action of organ rejection during Kidney transplantation as Immunosuppressant. The present invention includes SD of Tacrolimus with improved and reproducible bioavailability, SD or solid solution in hydrophilic carrier with melting point at least 2^{o} C and pharmaceutical composition as well as solid oral dosage forms for delayed release comprising SD or solid solution. Drug release in the distal part avoids GIT related side effects as well as extensive metabolism in proximal part of GIT.	Tacrolimus	Hypromellose PEG 6000 Poloxamer 188
6	**US 10,874,671 B2** PHARMACEUTICAL COMPOSITIONS OF NILOTINIB **2020**	The present invention covers ASD of Nilotinib fumarate or tartrate prepared by Spray Drying OR Hot Melt Extrusion and the pharmaceutical compositions developed thereof. The oral formulations showed improved bioavailability in fasting condition as there is no prominent difference in the pharmacokinetic parameters obtained with and without food.	Nilotinib	HPMC-AS HPMCP 55 PVP K30 HPMC E3

7	**US 10,668,020 B1** PULLULAN BASED VINPOCETINE TABLETS, LYOPLANT - TABS, AS A BUCCAL SOLID DOSAGE FORM **2020**	In the current invention, Vinpocetin polymeric SD were formed by using PVP-VA 64 as carrier by lyophilization or freeze drying or solvent evaporation method. The SD was incorporated in buccal tablet containing pullulan as natural filler for the treatment of cerebral degenerative diseases to provide enhanced bioavailability by improving solubility and avoiding first pass metabolism.	Vinpocetin	PVP - VA64
8	**WO 2020/012498 A1** SOLID DISPERSION COMPRISING AN ANTICANCER COMPOUND FOR IMPROVED SOLUBILITY AND EFFICACY **2020**	The current invention focuses on development of SD of low soluble anticancer drug with improved solubility, oral pharmacokinetics and *in-vitro* & *in-vivo* effect by solvent evaporation technique.	IIIM-290	Hydrophilic SD carrier
9	**US 2019/0365738 A1** AMORPHOUS SOLID DISPERSION OF VALBENAZINE TOSYLATE AND PROCESS FOR PREPARATION THEREOF **2019**	The current invention discloses an ASD of Valbenazine tosylate, a process for preparation of ASD and a pharmaceutical composition comprising ASD. The ASD were prepared by Spray drying method using methanol as solvent. The spray dried ASD were incorporated into suitable oral pharmaceutical formulation	Valbenasine	HPMC Copovidone HPMC-AS PVP K-30
10	**EP 3 569 225 A1** SOLID DISPERSION CONTAINING RITONAVIR **2019**	The present invention describes SD of Ritonavir with a cationic polymer to suppress crystallization of drug in GIT fluid and preparation of oral pharmaceutical composition preferably tablet thereof. The composition of BCS Class IV drug Ritonavir in combination with another HIV protease inhibitor was developed to improve the bioavailability of formulation to treat HIV infection. The designed	Ritonavir	Eudragit® E

		composition of film coated tablet showed better stability as compared to commercially available soft capsules.		
11	**WO 2019/220352 A1** AMORPHOUS SOLID DISPERSION OF LAROTRECTINIB SULFATE AND PROCESS THEREOF **2019**	The present invention relates to the manufacturing process of ASD and the pharmaceutical compositions prepared thereof. Lorotrectinib is Tropomyosin receptor kinase inhibitor for the treatment of solid tumours. The prepared ASD improves the stability and biopharmaceutical characteristics of amorphous API. The ASD were incorporated in oral dosage forms like capsule and solution.	Larotrectinib	HPMC-AS HPMC HPMCP HPC PVP K-30 COPOVIDONE

The use of solid dispersion (SD) technology has been shown to boost the solubility of drugs that have low aqueous solubility, thereby resulting in an improvement in the rate of dissolution under in-vitro conditions. The establishment of a strong correlation between the *in-vivo* bioavailability of a drug and the in-vitro solubility enhancement is crucial in order to achieve the intended therapeutic efficacy of the formulation [81–85]. A summary of recent *in-vivo* studies performed on solid dispersion-based formulation to achieve the corresponding pharmacological activity is discussed in Table 1.5.

TABLE 1.5 Recent *In-vivo* studies of SD based formulations

Sr no	**Active Ingredient**	**SD Carrier**	**Therapeutic Activity**	**Inference**	**Reference**
1	IIIM-290	PVP K30	Anticancer	CSIR discovered anticancer lead was formulated as SD to improve solubility limited bioavailability and it showed about 1.5 times dose reduction during *in-vivo* study using Ehrlich solid tumor model	[86]
2	Zinc (II)-curcumin complex	PVP K30	Anticancer	The prepared SD proved to be an efficient, simplified and novel chemo-sensitizing agent for cancer treatment.	[87]

3	Curcumin	HPMC	Hepatoprotective	Curcumin in ASD based formulation showed improved bioavailability, safety as well as greater potential as hepatoprotective and antioxidant in mice	[88]
4	Curcumin	PVP K30	Anti-inflammatory	Cur-PVP ASD based on molecular interaction was found to be effective to improve solubility limited bioavailability, stability and anti-inflammatory action compared to raw crystalline curcumin.	[89]
5	Selaginella doederleinii	PVP K30	Anticancer	A potential ASD based anti-cancer agent with enhanced solubility & dissolution and improved bioavailability was developed that lead to considerable decrease in tumor size and micro vascular density during the *in-vivo* study in mice	[90]
6	(−) - Oleocanthal	(+) - Xylitol	Anticancer	OC-xylitol SD was formulated to serve dual purpose of taste masking and dissolution enhancement. It proved to be an efficient nutraceutical product to treat and prevent breast cancer during *in-vivo* study using xenograft mice model.	[91]
7	Triacetylated andrographolide	Kollidon (VA64)	Anti-inflammatory	The SD prepared with Kollidon VA64 using HME technique showed desired dissolution profile and prevented re-crystallization of drug. It was confirmed that the SD was essential approach to improve the *in-vivo* anti-inflammatory action of TA.	[92]

1.8 Spray Drying Technique for Solid Dispersion Preparation

Spray drying method utilizes atomization, where a liquid stream (solution, suspension, or emulsion) is divided in to small droplets that are constantly deposited into a glass chamber.

There, the drops evaporate into powder when they come into contact with the heated gas, which is subsequently separated from the powder by a cyclone or a bag-filter [3, 93–99].

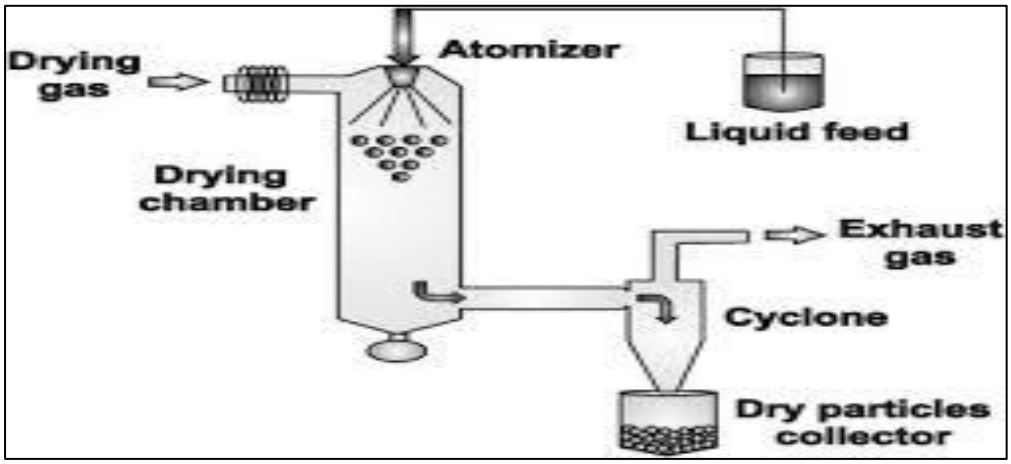

FIGURE 1.4 Overview of spray Drying Technique

1.8.1 Advantages of Spray Drying Technique

- ✓ Compared to other SD technologies like melt extrusion, it is a moderate drying process that uses low exposure durations and low temperatures.
- ✓ Rapid drying avoids phase separation between the medication and polymer components.
- ✓ It may generate consistent, spherical particles with manageable dimensions and enhanced flow and compressibility, making them appropriate for use in industrial operations.
- ✓ Products having a significant amount of amorphous drug content may be produced by carefully selecting the operation parameters and polymeric carriers.

1.8.2 Critical Process Parameters (CPP) for Spray Drying

Several critical process parameters of spray drying technique along with the characteristics affected by them are enumerated in Fig 1.5. & Table 1.6.

1.8.2.1 Selection of solvent and feed rate

The choice of solvent should be considered extremely carefully in order to produce homogeneous and stable solid dispersions, as spray dryers are typically scaled depending on their evaporation capabilities for a specific solvent. Solvents with lower boiling points are

readily evaporated, hence enhancing the production of solid particles. The dissolution rates of a medication may be significantly influenced by many factors, including the drug concentration in the feed solution, the selection of polymer and surfactant, and the ratio of polymer to surfactant to drug. The following factors should be considered when choosing a solvent: boiling point, drug and polymer solubility, and solvent toxicity as determined by the ICH classification (e.g., class III solvents are more chosen than class I solvents due to reduced toxicity potential). Table 1.6 lists the several solvents that are recommended for spray drying [9, 100, 101].

TABLE 1.6 List of commonly used solvents in spray drying technology

List of solvents	Boiling point (°C)	Dielectric constant	Solubility in water (g/100 g)	Density (g/ml)	ICH limit (ppm)
Acetone	56.2	20.7	Miscible	1.049	Class 3
Chloroform	61.7	4.81	0.795	1.498	60
Ethanol	78.5	24.6	Miscible	–	Class 3
Methanol	64.6	32.6	Miscible	0.791	3000
Dimethyl sulfoxide (DMSO)	189	47	25.3	1.092	Class 3
Dimethyl formamide (DMF)	153	36.7	Miscible	0.944	880
Water	100	78.54	–	0.998	–
Methylene chloride	39.8	9.08	1.32	1.326	600
Glycerin	290	42.5	Miscible	1.261	–
Ethyl acetate	77	6	8.7	0.895	Class 3

1.8.2.2 Role of feed atomization on final product

The primary objective of the atomizer is to decrease the concentration of the bulk liquid supply into minuscule droplets, therefore creating a substantial surface area that facilitates particle separation and solvent evaporation. The atomizer and feed inlet are properly positioned in the drying assembly to provide consistent mixing of the drying gas and feed solutions. Ultrasonic atomizers, rotary atomizers (rotating wheel atomization), pressure nozzles (hydraulic atomization), and two-fluid nozzles (pneumatic atomization) are some of the most common types of atomizers used in the pharmaceutical industry. The selection of an appropriate atomizer is contingent upon the specific attributes of the feed material as well

as the desired specifications for the resulting dried product. The present research landscape is primarily concerned with the use of four fluid spray nozzles in the spray drying process as an alternative to commonly used solvents for two drugs [65, 101].

1.8.2.3 Effect of inlet/outlet temperatures on final product characteristics

The outlet temperature is one of the most influential aspects on product morphology, which includes particle size &surface, density, stickiness of particles, residual solvent or moisture levels, % yield, and many other. Since solvents may plasticize the solid dispersion by increasing molecular mobility and inducing crystal formation, a secondary drying of the powder is typically essential after the spray drying technique is done. High quantities of residual solvent and poor flow characteristics are produced by spray drying at a lower output temperature [65, 76, 101–103].

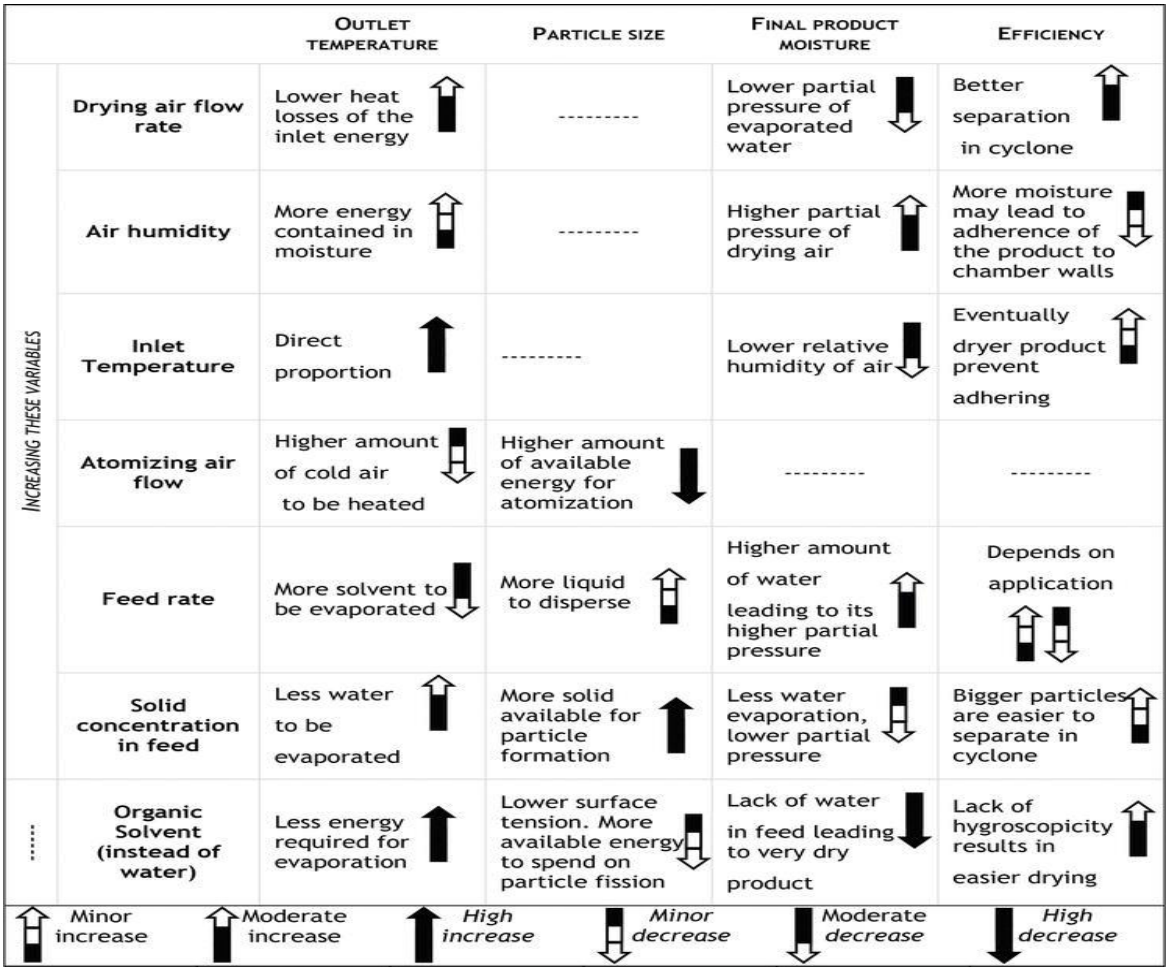

FIGURE 1.5 Summary of Critical Process Parameters of Spray Drying Technique

TABLE 1.7 The influence of Critical process parameters (CPP) in Spray drying [9]

Sr no	CPP	Significance
1	High aspirator rate	The increase in drying energy may result in an elevation of the output gas temperature. The residual moisture content in the finished product may be reduced. It provides enhanced and consistent particle separation capabilities.
2	High viscosity/ High solid content	Reducing the amount of solvent available for vaporization might result in an elevation of exhaust temperature. The presence of a higher concentration of solid matter inside a droplet may lead to an enlargement of particle size. Bigger particles facilitate their separation and enhances overall yield The reduction of moisture content in the final product is achieved by this process.
3	High humidity of drying gas	Moist particles have the potential to attach to the glassware, resulting in a decrease in process yield. It might lead to an increase in humidity levels in the final product.
4	High Fluid feed rate	Results in a reduction in the outlet temperature Leads to an increase in droplet size and, therefore, particle size Causes an increase in the moisture content of the finished product
5	High flow rate of spray gas	Reduction in the outlet temperature, Production of smaller droplets from the nozzle and a concurrent decrease in particle size.
6	High inlet temperature	The outlet temperature exhibits a proportionate increase. The yield is enhanced, resulting in a less adhesive product.
7	Organic solvent use	The use of organic solvents results in the production of smaller particles as a consequence of their reduced surface tension.

1.8.3 Critical Formulation Parameters for Spray Drying

In order to ensure the maintenance of an amorphous form of API during storage, the field of solid dispersion development is progressing towards including a third or perhaps more components alongside the polymeric carrier, which is often referred to as ternary solid dispersion. Adjuvants, which are substances added to a solid dispersion to enhance its dissolving and physical stability by increasing its wettability and reducing its tendency to crystallize during storage, are most often surfactants or co-solvents. In addition to surfactants, glidants and drying agents are used during the spray drying process to improve the flow properties and yield of the powder, while also reducing the tendency of particles to

adhere to the spray drying chamber. Additional additives, such as disintegrants, pH modifiers, salt formers, and complexing agents, may be used into the spray drying process [65, 101].

The critical formulation parameters in spray drying are as follows [9]

- ✓ Feed composition (selection of API and carrier(s) in Binary/Ternary SD)
- ✓ Type of solvent (aqueous, organic or hydroalcoholic)
- ✓ Viscosity and surface tension of spray solution
- ✓ Selection of appropriate adjuvant like surfactant or cosolvent, glidant or drying agent, salt former, complexing agent, etc

1.8.4 SWOT analysis of Spray Dring Technique

The SWOT analysis of spray drying technique is shown in Fig 1.6. [65]

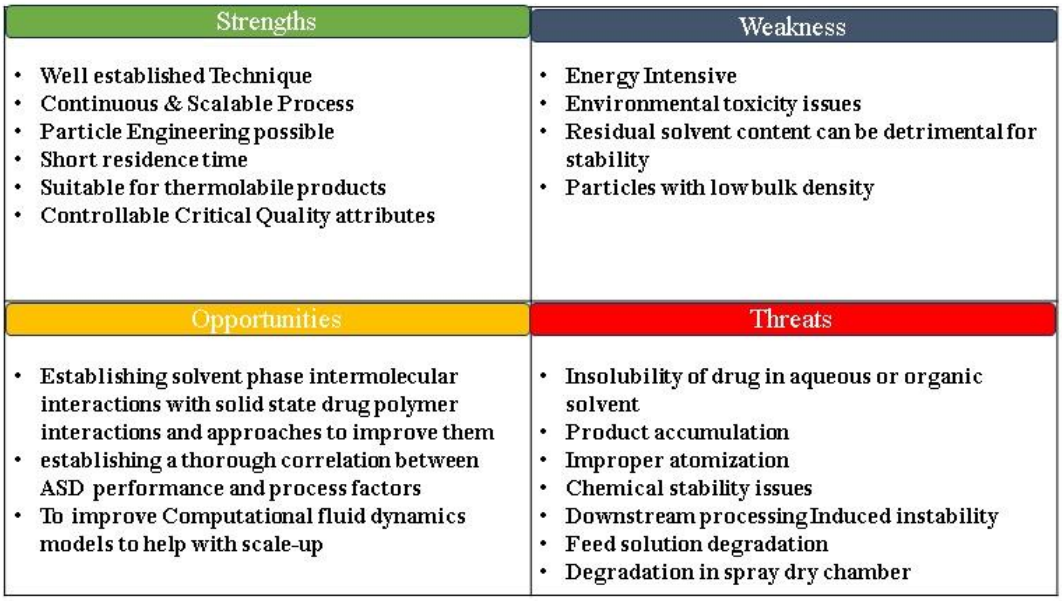

FIGURE 1.6 SWOT Analysis of Spray drying technique

1.9 Characterization of Solid Dispersion (SD)

The SD should be evaluated for different characteristics using specific analytical technique as discussed in Table 1.8 [23, 29, 101, 104].

TABLE 1.8 Characterization of SDD

CHRACTERIZATION	ANALYTICAL TECHNIQUE
AMORPHOUS FORM OF ASD	Powder X-ray diffraction (PXRD) Differential Scanning Calorimetry (DSC) Polarised Light Microscopy (PLM) solid state NMR
CRYSTALLISATION BEHAVIOUR	Scanning electron microscopy (SEM) Transmission electron microscopy (TEM)
PHASE BEHAVIOUR AND DRUG DISTRIBUTION OF TERNARY SDD	Combination of DSC with time-of-flight mass spectrometry and atomic force microscopy
INTERACTION BETWEEN THE COMPONENTS OF SD	FTIR (Fourier Transform Infrared Spectroscopy)
***IN-VITRO* RELEASE OF DRUG FROM SD BASED FORMULATION**	Dissolution rate study

1.9.1 Thermal/ Calorimetric Analysis [23, 105]

1.9.1.1 Differential scanning calorimetry

Principle: When a sample experiences a physical transformation, such as a phase transition, the amount of heat required to be transferred to or from the sample in order to maintain it at the same temperature as the reference material may differ.

Advantages: Appropriate for monitoring melting, the conditions in which experiments are conducted are straightforward.

Limitations: less susceptible to measurement of heat capacity.

1.9.1.2 Modulated Differential scanning calorimetry

Principle: employs two simultaneous heating rates: a sinusoidal or modulated heating rate that enables the simultaneous measurement of the sample's heat capacity, and a linear heating rate that yields data comparable to standard DSC.

Advantages: Differentiating between complex and overlapping heat processes, studying phase separation, and precisely quantifying amorphous phases.

Limitations: Strongly condition-dependent, melting: Intricate interpretation and imprecise measurement.

1.9.1.3 Dynamic mechanical thermal analysis

Principle: The measurement of the resultant strain resulting from the application of oscillatory stress involves the establishment of a function that relates the determined strain to the corresponding frequency or temperature.

Advantages: The viscoelastic characteristics of polymers are obtained by a time-efficient method that does not damage the sample.

Limitations: The characterization of low viscous materials is not appropriate, since they exhibit a limited ability for stress management.

1.9.1.4 Isothermal micro calorimetry

Principle: The ongoing evaluation of the heat output and total heat generated or consumed by an instance at a relatively constant temperature.

Advantages: extremely sensitive, long-lasting, and non-destructive method

Limitations: It takes hours or days to analyse this laborious procedure.

1.9.2 Spectroscopic techniques

1.9.2.1 Solid state Nuclear Magnetic Resonance

Principle: When wide radio frequency radiation pulses are applied to nuclei, they excite them and cause them to spin. As a consequence, when the nuclei return to their equilibrium states, free induction decay is generated.

Advantages: Simple sample preparation, modest sample size, little sample modification, and non-destructive

Limitations: The absence of sensitivity, high cost, and challenges associated with quantifying chemical noise and signal overlap.

1.9.2.2 Fourier transform Infra-red technique

Principle: Atomic-level chemical bonds and functional groups in a sample vibrate at a steady pace. A certain wave number is absorbed by a particular bond and functional group in the sample when continuous wavelength infrared light hits it; the detector then produces the absorbed spectrum.

Advantages: Quantitative analysis in all situations, Minimal sample size and non-destructive

Limitations: The presence of moisture and decreased accuracy might lead to erroneous findings.

1.9.2.3 Raman Spectroscopy

Principle: It is based on the Raman phenomenon, whereby the scattered light produced by the inelastic collisions of sample molecules with a monochromatic laser beam is what creates the Raman spectrum.

Advantages: Quantitative analysis, Non-destructive and Small sample size, not interfered by water, highly specific like a chemical fingerprint of a material

Limitations: There is virtually little Raman impact. Sensitive and highly tailored apparatus is required for the detection since the powerful laser light might damage the sample or cover the Raman spectrum when it heats the sample.

1.9.3 Microscopic and macroscopical techniques

1.9.3.1 X-Ray Powder Diffraction

Principle: The cathode ray tube's filtered and collimated beams are directed towards the sample, resulting in diffracted and constructive interference that fulfills Bragg's law ($n\lambda=2d \sin \theta$).

Advantages: Determine crystallinity of the compound, best method for phase analysis, non-destructive.

Limitations: Crystallinity determination is the best nondestructive approach for phase analysis.

1.9.3.2 Scanning electron microscopy

Principle: Significant quantities of kinetic energy are carried by accelerated electrons in a scanning electron microscope (SEM). When the incident electrons in the solid sample decelerate, this energy is released as a range of signals resulting from electron-sample interactions.

Advantages: Completing SEI, BSE, and EDS studies takes less time when using three-dimensional and topographical imagery.

Limitations: huge, pricey, and requires housing away from any potential influence from electricity, magnetism, or vibration.

1.9.3.3 Polarized light microscopy

Principle: Ordinary and exceptional light beams that are perpendicular to one another are produced when polarized light strikes the double refracting material. To create a high contrast picture, these rays are merged utilizing constructive and destructive interference using an analyzer.

Advantages: Reproducible, simple to use, and without risk of damage

Limitations: Agglomerates are not a good fit, and recovering samples may be time-consuming.

1.9.3.4 AFM

Principle: It works in three steps surface sensing, detecting and imaging, using a sharp tip cantilever to scan over the surface of a sample. The attractive and repulsive forces between the tip and the surface cause the cantilever to deflect towards or away from the surface respectively. Any of these slight deflections of cantilever are traced by deflections of laser beam which It operates in three stages: surface sensing, detecting, and imaging. A cantilever

with a sharp tip is used to scan a sample's surface. The cantilever deflects toward or away from the surface depending on the attractive and repulsive forces acting between the tip and the surface. Any of these tiny cantilever deflections are tracked by the laser beam's deflections, which are placed on the cantilever and captured by a position-sensitive photo diode to provide an accurate topographic picture.

Advantages: The instrument has a maximum lateral resolution of 1 nm, enabling it to discern the recurring lattices within a crystal structure and facilitating a thorough and complete comprehension of the material.

Limitations: High cost and long scan times that may cause sample temperature changes.

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CHAPTER 2

Review of Literature

2.1 Review of Literature of Posaconazole

Hens et al aimed to investigate precipitation of Posaconazole's supersaturated solution upon intestinal transit, and studied how the type & pH of formulation affected these processes. A cross-over research delivered 2 oral suspensions with strength 40 mg in 240 mL water at pH 1.6 and pH 7.1, followed by aspiration of gastric and duodenal fluids. Blood samples were withdrawn simultaneously. Additionally, drug was also given at half strength at pH 1.6. When API was administered in acidic condition, it reached supersaturated concentrations within 45 minutes. However, precipitation in intestine was widespread. Experiments with neutral solution led to subsaturated concentrations, with a mean duodenal $AUC_{0\text{-}120}$ min and C_{max} double than acidic condition. The mean value of $AUC_{0\text{-}8}$ h was twice as high after acidified suspension administration. After intragastric injection of posaconazole solution, considerable intestine precipitation (up to 92%) was seen, similar to the acidified suspension. This research first showed the gastrointestinal behavior and systemic exposure effects of a weakly basic medication under various settings [1].

Bitencourt et al provided a quick, reproducible UV-spectrophotometric technique for posaconazole analysis in raw materials using methanol as solvent at 260 nm detection wavelength, The plasma curve in concentration range 5-25 μg/mL showed linearity (R^2 = 0.9999). Low RSD results (0.49 to 0.82%) indicated reproducibility and moderate precision. The recovery test showed sufficient accuracy, with a mean recovery rate of 98.20%. Both specificity and robustness were observed. The average sample quantity was 100.82%. The suggested approach was found adequate for regular analysis in quality control labs. No statistical difference was detected between the UV spectrophotometric approach and the previously established HPLC, making it a trustworthy alternative [2].

Leung et al delivered an update on the clinical use of Azole antifungal Posaconazole (PCZ). PCZ was reported to be effective against Aspergillus fumigatus, certain Candida species Blastomyces dermatitidis, Crytopcoccus neoformans, and Trichosporon. It also inhibited

Candida, Coccidioides, certain Fusarium spp., Histoplasma, Scedosporium, and Zygomycetes. It was observed to show synergistic effect with Caspofungin or Amphotericin B against A. fumigatus, C. glabrata, and C. neoformans. PCZ suspension is meant to be administered with meals, nutritional supplements, and carbonated drinks to increase absorption. Its bioavailability increased with divided oral dosages. PCZ inhibits CYP3A4, hence drug-drug interactions with other substrates or efflux inhibitors &/ or inducers should be monitored. The most frequent side effects were reported to be headache, tiredness, nausea, vomiting, and increased liver enzymes. Immunocompromised individuals with gastrointestinal tracts ailments who have failed traditional antifungal medications or are suspected of a breakthrough fungal infection should utilize PCZ oral suspension. In 2014, a delayed-release tablet and IV injection were introduced, allowing PCZ to be used in various patient categories, including those who cannot take oral formulations [3].

Krishna et al reported a four-part, randomized crossover trial conducted in healthy volunteers of marketed Posaconazole oral suspension under various conditions to study its effect on stomach pH, dosage frequency, prandial condition, meal timing, and motility effect. A 400 mg dose of posaconazole was administered in part 1 either by itself, in combination with an acidic drink, or in conjunction with a proton pump inhibitor (PPI). In part 2, both the Boost nutritional supplement and 400 mg twice day and 200 mg four times day of posaconazole were administered for seven days. In Part 3, patients were instructed to fast and received 400 mg of posaconazole (SD) before to, during, and after a high-fat meal. Posaconazole 400 mg and nutritional supplement were given as an SD alone, with metoclopramide, and with loperamide in part 4. Instead to drug alone, posaconazole with an acidic beverage raised plasma concentration and AUC by 92% and 70%. High gastric pH reduced C_{max} and AUC by 46% and 32%. The administration of nutritional supplement with 400 mg or 200 mg Posaconazole increased C_{max} and AUC by 65% and 66%, and up to 137% and 161%, respectively in comparison to posaconazole alone, Treatment increased C_{max} and AUC 96% and 111% before a high-fat meal. Administration raised C_{max} and AUC 339% and 387% during and after meals. Increasing stomach motility decreased C_{max} and AUC by 21% and 19%. For those with absorption concerns, posaconazole should be given with a high-fat meal, nutritional supplement, acidic beverage, or split doses and avoided with proton pump inhibitors [4].

2.2 Review of Literature of Esomeprazole

Putta et al. studied Physico-chemical characteristics, developed & validated quantitative analytical estimation of Esomeprazole Magnesium Trihydrate by UV spectrophotometric method. Esomeprazole Magnesium Trihydrate is a proton pump inhibitor that reduces stomach acid output in peptic ulcer disease. The melting point of EMT was found to be 177.33°C in physico-chemical experiments. The sequence of methanol, ethanol, acetone, buffer pH 9.0, and distilled water was the order in which esomeprazole was soluble. When esomeprazole magnesium trihydrate was estimated analytically in bulk fluids, the maximum absorbance (λ_{max}) in methanol (200–400 nm) was found to be 203.5 nm. Based on linear regression analyses, the estimated API was varied from 2.00 to 10.00 µg/ml concentration. The approach was verified for intra-day fluctuation and quantitation research limitation. The SD values of inter-day and intra-day variance investigations showed little fluctuation. The limit of quantification for esomeprazole was obtained 1.00 µg/ml. The UV Spectrophotometric technique for Esomeprazole was found to be simple, accurate, and repeatable based on the analytical parameters [5].

Research was undertaken to provide a detailed description of a newly developed esomeprazole (ESO) delayed release gastro-resistant formulation that exhibited enhanced storage stability. The coating of drug, sub-coating, and enteric coating, were conducted using a fluid bed coater. The formulation processes, which encompass several factors such as the size and number of non-pareil sugar spheres, the concentration of binder in drug layer, the type and amount of sub-seal coating polymer, and the % weight gain with enteric polymer, were modelled using feed-forward back-propagation artificial neural networks (ANNs). The use of tiny initial spheres prepared using mesh 45/60 resulted in the agglomeration of pellets, whilst an increase in % weight gain of sub-seal coating reduced in the dissolution rate of ESO. Eudragit L30 D-55 enteric-coating demonstrated effective gastro-resistance in 0.1N HCl and pH 4.5 medium, releasing more than 85% of ESO in less than 30 min in intestinal pH above 5.5. The research discovered that only hydroxypropyl methyl cellulose (HPC) had the ability to stabilise ESO delayed-release formulations, as shown by its impact on assay, dissolving, impurities, and gastro-resistance performance at a 40±2°C temperature and 75±5% relative humidity (RH). The results of the study revealed that the drug, sub-seal, and enteric-coating layers exhibited a smooth and uniform outer surface when seen under

scanning electron microscopy. Additionally, the analysis conducted using x-ray diffraction verified the absence of any polymorphic changes [6].

A study was conducted on poorly water-soluble esomeprazole zinc (EZ). The study aimed to enhance the dissolution rate and bioavailability of esomeprazole zinc (EZ) by the synthesis of solid dispersions in polyethylene glycol 4000 (PEG4000) utilising a solvent approach. Various ratios of EZ to PEG4000 were used in the synthesis process. The research revealed that, in contrast to pure EZ or physical mixes, the dissolution rate of EZ was much higher in the solid dispersion system. The ratio of EZ to PEG4000 was clearly associated to the increase in dissolving rate. The maximum dissolution rate was produced by the solid dispersion system (EZ/PEG 4000 = 1/8 w/w), which was almost 14.7 times more than that of the pure EZ. Through the use of scanning electron microscopy (SEM) and differential scanning calorimetry (DSC), it was determined that EZ was in an amorphous condition in this solid dispersion. According to *in-vivo* administration experiments, EZ enteric-coated tablets (Nexium) and SDEZ in enteric capsule (SDEZ-EC) have different C_{max} and T_{max} values, and these differences were statistically significant. This finding is consistent with the *in-vitro* dissolution and implies that SDEZ-EC had a lower absorption rate than Nexium [7].

2.3 Review of Literature of Excipients in SD

Surti et al. attempted to develop a spray-dried solid dispersion (SDSD) to increase the solubility of the antidiabetic drug repaglinide. Since drug must be available at the absorption site in order to be absorbed, aqueous solubility is critical for drug delivery. One common method for increasing the solubility and, therefore, the rate of drug dissolution for weakly soluble substances is solid dispersion (SD). To generate SDSD, repagnilide was dried by spray drying in a solution of hypromellose acetate succinate (HPMCAS). Process parameters, screening formulation, and optimisation were all done using the Plackett-Burman and Box Behnken designs, respectively. SD was described by means of DSC, XRD, and SEM. The in-vivo oral glucose tolerance test, flow properties, yield percentage, and in-vitro dissolution of SDSD were evaluated. The batch that was optimised was an SDSD that had an input temperature of 90 °C, a drug: polymer ratio of 1:3.82, and 2.56% aerosil. The results demonstrated a rapid decrease in blood glucose levels, with a drop of 85% observed within a time frame of less than 15 minutes. Furthermore, the observed reduction in blood glucose levels was shown to be significantly greater when compared to both the pure active

pharmaceutical ingredient (API) and the commercially available product. Consequently, it was shown that using HPMCAS to create a spray-dried solid dispersion is an effective way to increase the solubility and dissolution of repaglinide [8].

Lu et al. developed gliclazide oral CR using Spray Dried Dispersion technique. Gliclazide, a BCS Class II 2nd-generation sulfonylurea, treats type 2 diabetes. Gliclazide SDD were produced utilising SD carriers HPMC-AS of H, M, and L grades and copovidone S-630 in varied ratios to make the drug amorphous and hydrophilic. Physicochemical characterization parameters for the dispersions were within the specified range. SDD saturation solubility and micro dissolution were compared to crystalline medication in FaSSIF pH 6.5 under non-sink condition. Drug solubility increased 1.5–4-folds and supersaturation lasted longer. Compaction simulator added optimized SDD into HPMC matrix. The release kinetics analysis projected that the formulation will dissolve at different rates in *in-vitro* USP apparatus I testing under normal circumstances. The stability investigation indicated disintegration patterns with similarity factors above 85 after six months. Thus, HPMC-AS and copovidone were potential SD carriers for stable, uniform monophasic SDD loading into HPMC's hydrophilic CR matrix architecture [9].

A study was conducted to develop CR matrix formulation of Glipizide based on Spray dried dispersion using various grades of HPMC-AS and Plasdone S-630 as SD carriers. The SSD were manufactured using automated spray dryer under optimized process variables and the obtained SDD were compressed into tablet using compaction simulator. The drug was entrapped in amorphous form within homogenous system with about 60% drug loading efficiency and the same was confirmed through well-established physico-chemical characterization evaluation parameters. Supersaturated micro-dissolution testing of different SDDs in FaSSIF revealed extended super saturation up to 3 hrs with approximately 5-14 folds solubility enhancement in comparison to the crystalline form of drug. Amongst the study of two SD carriers, HPMC-AS showed higher super saturation. Again, the M & H grades of HPMC-AS maintained that state effectively for prolonged time. The improved rate and extent of drug release was obtained from matrix tablet during the 24 hours dissolution study with the achievement of controlled release following zero and slow first order release kinetics. It was confirmed that the combined effect of HPMC-AS as well as HPMC prevented the re-precipitation of drug in crystalline form the super saturated solution and helped to develop stable and controlled release formulation [10].

A published experiment developed artemether (ARTM) solid dispersion (SD) formulation using hot melt Extrusion technique. A combination of SD carriers Soluplus, PEG 400, Lutrol F127, and Lutrol F68 with lower melting point than API were used to prepare SD. Three surfactants namely, PEG 400, Lutrol F127, and Lutrol F68; as well as process variables including residence time, screw rotation speed, and mixing temperature were all carefully examined. XRD, FT-IR, and SEM were used to examine how well ARTM dissolved in the melted excipient. The drug's melting enthalpy progression was quantitatively examined using differential scanning calorimetry (DSC). The findings demonstrated that the rate of dissolution improved with the increase in the ratio of polymer and surfactant with respect to API. It was determined that the drug dissolves in the polymer melt via a convective diffusion mechanism and that the rate of dissolution may be greatly increased by laminar distributive mixing. The produced solid dispersion's water solubility and dissolving rate were greatly increased. IC_{50} values showed a significant improvement in in vitro antimalarial tests. Therefore, hot-melt extrusion (HME) is a method that shows promise for enhancing ARTM's solubility and dissolution profile [11].

A research study was executed to explain the increase in the solubility and dissolution rate of Curcumin, a drug that is poorly soluble in water, using a unique solubility enhancement excipient called Soluplus®. Curcumin-Soluplus® blends were made using a variety of techniques, such as the physical mixing, co-grinding, size reduction, and solid dispersion. The polymer ratio used for generating the drug and polymer combinations ranged from 10% to 50% w/w. Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), X-ray diffraction (PXRD), and scanning electron microscopy (SEM) were used to assess Curcumin-Soluplus® combinations. The solid dispersion > co-grind > milling physical mixture > physical mixture was found to be the order of improved solubility. Furthermore, when the polymer ratio increased, solubility and drug dissolution rate improved. The FTIR results confirmed that there was no chemical interaction between the Soluplus® and Curcumin in co-grinding, milling, and physical mixes. Curcumin was found to be in an amorphous condition in the mixtures made using the solid dispersion approach by the DSC and PXRD. Within two hours, the drug prepared using the solid dispersion technique was released into a 0.5% w/w sodium lauryl sulphate medium after rapid and complete dissolution. It was determined that Curcumin's solubility and *in-vitro* release performance had been significantly improved by Soluplus® [12].

Peng et al. investigated Lopinavir (LPV), a BCS Class 4 medication, having poor water solubility & permeability *in-vivo*. They developed unique LPV solid dispersions (SD) to increase bioavailability and characterized their behaviour. The SDs of drug with polymer along with sorbitan monolaurate (SBM) as the wetting agent, in 1:4:0.4 proportion respectively, significantly enhanced LPV dissolution in a non-sink condition after solvent evaporation, for preliminary formulation screening. Hot-melt extrusion (HME) further improved dissolution. In the optimised formulations, Kollidon VA 64 and Soluplus were used as matrices. Extrudates had much greater dissolution rates than solvent-evaporated SDs. Stability tests conducted for six months with storage conditions of 25 °C temperature & 60% RH confirmed that stronger intermolecular interactions between drug and polymers during hot melt extrusion process were the cause. Differential scanning calorimetry, fourier transform infrared spectroscopy, and equilibrium tests showed that whereas Soluplus's amphiphilic structure generated both an H-bond and a micelle, Vinyl acetate 64 only established hydrogen bonding with API. Furthermore, the LPV bioavailability of soluplus extrudate was 1.70 times higher than that of VA64 and 3.7 times higher than that of LPV crystal. Soluplus improved LPV permeability across rat gut and Caco-2 cell monolayers, according to *in-situ* permeability and Caco-2 cell transport experiments, due to the inhibition of P-gp. The LPV bioavailability was enhanced by Soluplus matrixed extrudate via H-bonding with LPV, water-induced micelle formation, and *in-vivo* inhibition of P-gp. Its unique qualities make it an excellent carrier for drugs that aren't very soluble in water, such P-gp substrates [13].

An investigation was conducted on Efavirenz (EFV), a first-line anti-HIV medication that is primarily utilised in antiretroviral therapy. It belongs to BCS class II with low solubility & high permeability, and is almost water insoluble. The purpose was to enhance the solubility and dissolution rate of API by developing an amorphous solid dispersion (ASD) of the drug in a polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (Soluplus®) by spray-dried SD technology. In this study, a range of analytical techniques including particle size measurements, drug-polymer interaction studies, and Raman microscope mapping were used to generate and evaluate spray-dried ASD of drug in Soluplus® at different weight ratios of 1:1.25, 1:7, and 1:10. In various mediums, solubility and dissolution were assessed. For a duration of 12 months, stability study was performed at accelerated conditions of 40°C/75%RH and ambient conditions. The XRD and DSC investigations verified the amorphous nature of EFV. Analyses using FTIR spectroscopy

suggested a potential molecular interaction of drug with polymer. The solubility and dissolution rate were greatly improved by the spray-dried solid dispersions, with the degree of improvement being dependent on the polymer concentration. When subjected to moisture protection, it has been shown that spray-drying is a preferrable method to develop a stable dispersion of amorphous EFV in SD carrier Soluplus® [14].

The described study used a solid dispersion (SD) approach to increase the water solubility of the hydrophobic API Nimodipine. A new hydrophilic polymeric carrier called Soluplus® was used in the work. Supercritical fluid technology (SCF) was used to create Nimodipine-Soluplus® SDs (1:10) by impregnation technique. The resulting product was compared to those made using the traditional hot-melt (HM) process. The % drug release studies and solubility of the pure drug, solid dispersions, and related physical blends were compared and characterised. The pure API solubility in the SD produced with SCF technology was 77 times more than that of the SD developed with HM, and 7.7-fold higher than that of the physically mixed SD. Additionally, they had the largest cumulative release percentage of nimodipine during the course of the study. The findings verified the drug's amorphous transfer into the polymer matrix, as guaranteed by the powder X-ray diffraction (PXRD) & thermal analysis. Apart from the FTIR spectra showing the formation of hydrogen bonds between nimodipine and Soluplus®, there was also a decrease of the peak associated with nimodipine's N–H stretching and the ester group's C=O. To improve nimodipine's oral bioavailability, solid dispersion using Soluplus® utilising SCF technology may be a viable formulation option [15].

A study was conducted to develop gastro-retentive low density minitablets of Cefuroxime axetil using the melt granulation technique. The two different grades of gelucire, namely 50/13 and 43/01, were used to achieve the target of maintaining a constant plasma drug concentration along with floating behaviour. Using hydrophilic grade gelucire 50/13, Immediate release (IR) minitablets were prepared to achieve the loading dosage. Using hydrophobic gelucire 43/01 grade, whereas maintenance dosage was obtained through floating sustained release (SR) minitablets. The granules that were synthesised for IR and SR underwent scanning electron microscopy and micromeritic investigations. The analysis using Fourier transform infrared spectroscopy (FTIR) confirmed the compatibility of the drug with certain carriers. More than 85% of the loading dosage was dissolved in 30 minutes, according to an *in-vitro* dissolution investigation using optimised IR minitablets. Minitablets with SR optimisation demonstrated 0% latency for floating periods over 12 hours. The drug

release kinetics study showed that SR minitablets followed linear kinetics with non-Fickian diffusion control. Hard gelatin capsules with a 0 size were filled with the optimised batch of minitablets. The capsule's *in-vitro* disintegration investigation revealed an IR release, followed by SR for up to 12 hours. The dissolution data remains mostly unchanged during 3 months stability study as per ICH storage conditions at 40 °C and 75% RH. A proportional rise in growth inhibition against Escherichia coli was seen in the microbiological analysis of dissolution samples of optimised minitablets contained in capsules, up to 12-hour samples. An albino rabbit's *in-vivo* bioavailability study revealed a three-fold increase in oral bioavailability [16].

Panda et al. demonstrated that gas-generating single-unit tablets for floating delivery of several active pharmaceutical components had been studied. In the discussed study, gastro-retentive multi-particulate DDS of Nimodipine was developed using floating approach without gas-generating agents. The multiple-unit minitablets were formulated to maximise residence duration, sustain-release, and oral bioavailability. Melt granulation was used to prepare solid drug dispersion with lipophilic carriers such as hydrophobic grades of Gelucire namely, Gelucire 43/01 & Gelucire 39/01, Compritol ATO 888, and Precirol ATO 05. Sylysia 350 was used as an adsorbent in proportion 1:1 to lipophilic carrier. 15 mg minitablets were prepared by direct compression of granules and then filled inside a '0' capsule. DSC showed no drug-excipient interaction. The formulations with appropriate flow properties, minimum floating lag time, and floating retention up to 12 h were characterised for different parameters. The floating multi-particulate system of Nimodipine, encapsulated in optimised single-dose (capsule), with composition of 60 mg drug, 120 mg Gelucire 43/01, and 120 mg Sylysia 350 demonstrated floating lag time of 24.48 s, and 12 h sustained release. A pharmacokinetic analysis of the optimised formulation (F9) revealed higher bioavailability compared to Nimodipine in water showing about 2.5 times the AUC with greater retention time. The stability investigation revealed that the product was sufficiently stable with no significant changes in parameters after 6 months. It was concluded that minitablets of Nimodipine consisting of Gelucire 43/01 may maintain drug release with sufficient gastro-retention of 12 hrs using non-effervescent based approach [17].

The purpose of described investigation was to achieve the key objectives of formulating and analysing solid dispersions of the poorly water-soluble drug etoricoxib using lipid carriers via the process of spray drying. The features of solid dispersions were investigated by several analytical techniques, including diffuse reflectance infrared Fourier transform spectroscopy

(DRIFTS), differential scanning calorimetry (DSC), hot stage microscopy (HSM), powder X-ray diffraction (XRPD), and dissolution investigations. The XRPD profiles of solid dispersions did not show any peaks for etoricoxib, indicating the conversion of crystalline form of the drug into an amorphous one. The drug's dissolution in the lipid carriers was confirmed through the HSM analysis of the solid dispersions, further supported by the DSC curves of the solid dispersions lacking the etoricoxib peak. The existence of hydrogen bonds in solid dispersions was observed in DRIFTS spectra. The *in-vitro* dissolution study predicted higher dissolution rate of solid dispersions compared to pure API, spray-dried etoricoxib, and drug-lipid carrier physical combinations. Thus, spray-dried solid dispersions consisting of lipid carriers greatly increased the dissolution rate of drug etoricoxib [18].

2.4 Review of Literature of SD based Formulations

The study discussed the difficulties encountered during the development of a weakly basic drug formulation because of the pH variations the drug experiences in the gastrointestinal system. The drug solubility is shown to decline when the drug transits from the stomach's low pH to the small intestine's higher pH. Even the initial solubility is reported to decrease in an acidic stomach, whether from food or drugs that induce an achlorhydric situation. Lower *in-vivo* exposures are meant to a reflect this reduced drug solubility. A solubility-enabling strategy was proposed to mitigate the impact of stomach pH fluctuations. It had been shown that solid dispersions of amorphous drug in a polymer matrix was an efficient way to increase bioavailability, and they may be able to lessen the achlorhydric and food effects that were observed with traditional formulations. Solid dispersions are considered highly susceptible to processing paths that regulated particle characteristics, stability, drug release profile, and biological performance due to metastable state. The authors reported that the regulation of product qualities and reduction in development risks may be grasped by understanding different processing pathways effect on the solid dispersion properties. This work used both spray drying and hot melt extrusion to entrap a weakly basic drug that was much less soluble at higher pHs into a solid dispersion. These two processing procedures produced solid dispersions with similar qualities, and the effects on the dispersions' *in-vivo* performance and dissolution behaviour were studied[19].

Keen et al. developed CR SD containing drugs Itraconazole and Carbamazepine using PVP as SD carrier and Compritol 888 as release modifying agent & plasticer by two different

methods namely Holt melt extrusion and KinetiSol Dispersing. The use of lipid carrier glyceryl behenate allowed convenient processing of high MW PVP during HME technology. The entrapment of drug in amorphous form within the SD was confirmed based on DSC, PXRD and thermal analysis. The compritol ratio was selected 1.5 parts in compressed tablet prepared from extruded SD and it was reduced to 0.25 parts in KSD due to smaller SA to volume ratio of tablet. In-vitro dissolution testing of SD with and without compritol was conducted in purified water using USP dissolution apparatus I. The hydrophocity imparted by compritol allowed complete drug release in controlled manner by preventing re-crystallization of drug within the tablet. But the trend was reversed leading to incomplete drug release when the total weight of tablet increased gradually from 100 mg to 600 mg. Thus, it was confirmed that glyceryl behenate was a promising lipid excipient to prepare solid dispersion based oral controlled release formulation [20].

Park et al designed pH-independent controlled release formulation consisting of nanosized solid dispersion that is adsorbed on hydrophilic silica known by brand name Aeroperl® 23 24 300/30 to modify solubility and release rate of Valsartan. FT-IR (Fourier Transform Infrared) study proved that Ternary SD system formed had intermolecular hydrogen bonding and changed crystalline drug into an amorphous state. The dissolution study in 0.1 N HCL with acidic pH of 1.2 showed that the in-vitro release rate of drug from SD system prepared using carrier poloxamer 407 was drastically increased when compared to pure drug or commercially available Diovan® tablet. The dissolution enhancement was obtained due to nanosizing of SD system from 600 nm to 150 nm within the first 2 hrs of dissolution process. The CR tablets loaded with VAL SD and consisting of HPMC 4000 confirmed pH-independent zero-order drug release kinetics along with the desired stability profile during accelerated stability testing for six months with least inter-subject variability in Cmax in healthy human volunteers when compared to the outcomes of commercial product Diovan® 37 [21].

Xu et al studied ER dosage forms consisting of drugs which are potent and aqueous insoluble in nature comprising of novel combination of lipid excipient as SD carrier along with a matrix of hydrogel polymer. Tacrolimus SD was prepared with glyceryl behenate and Pluronic F127 as the SD carriers using hot melt method. Afterwards the SD was embedded within hydrogel matrix consisting of HPMC and lactose. The powder mixture obtained was directly compressed into tablets. The dissolution study revealed that the in-vitro release rate of drug was considerably enhanced due to the lipid solid dispersion carrier, and the addition

of hydrophilic polymer HPMC contributed to the development of stable formulation. ER tablets consisting of Tacrolimus SD showed the controlled drug release up to 24 hrs and the release profile fitted to the K-Peppas model (n = 0.85) indicating that the rate controlling mechanisms were diffusion and erosion based. The release profile of the formulation could be manipulated based on the composition of hydrogel matrix, especially the type and the proportion of HPMCs. The SD was melted and combined with hydro-gel polymer HPMC in a single step using Hot melt technique to obtain uniform distribution of the melted SD within the tablet hydro-gel matrix and achieve desired release profile [22].

Sustained release (SR) oral tablets based on the solid dispersion of poorly aqueous-soluble drug Disulfiram (DSF) was developed and characterized by Shergill et al. The main purpose of the formulation was to enhance aqueous solubility to improve the bioavailability along with the reduction of the metabolism and degradation of orally administered drugs due to the low pH and enzymatic activity of the stomach. SD were prepared from two different polymers namely Kolliphor P188 and P237 using hot melt method with DSF loading of 43 and 46% respectively in amorphous form. The tablets were manufactured from two different sustained release polymers namely Kollidon SR and Hypromellose to obtain sustained release of drug sand protect it from degradation in acidic environment of stomach. The addition of Kollidon SR in 80% ratio to the SR tablet prevents the degradation of drug in gastric pH for about 1 hr and 10 minutes. Kollidon SR resulted in only 16% degradation after 2 hrs compared to HPMC in same ratio that led to 75% degradation after 2 hrs. The drug release profile from the formulation depends on the percentage loading and the sustained release polymer used. Thus, it was concluded that HPMC provided much rapid drug release rate compared to another polymer Kollidon [23].

Nguyen et al designed a sustained release SD of Isradipine using swellable polymers PEG 6000 & HPMC 4000 by melting method to enhance drug dissolution rate along with sustaining the drug release rate from the formulation. HPMC 4000 was used for the swelling capability along with the common SD carrier PEG 6000 to provide an environment suitable for the swelling of HPMC 4000 which improved the drug dissolution by converting the crystalline nature of API to an amorphous one by forming molecular interaction. In this research, the most crucial problem of SR dosage forms was addressed which is dealing with poorly aqueous-soluble drugs that lead to poor bioavailability. The addition of such low aqueous soluble drugs into SR SD carriers could overcome the above-mentioned problems

by improving the solubility and dissolution rate of insoluble drug leading to enhanced oral absorption along with obtaining sustained drug release using suitable SD carrier [24].

The less published fact of the synergistic effect of dissolution enhancement and controlled drug release was focused by Tran et al using model drug Isradipine (IS). Solid dispersion containing the model drug was prepared by the melting method using PEG 6000 as the SD carrier. The prepared SD was added into polymer PEO N-60K to obtain the controlled release of drug. The physical mixture and SD were exposed to physico-chemical characterization by PXRD (Powder X-Ray Diffraction) to study the physical form of drug in SD, and FTIR to determine the drug-excipients interactions. The designed formulation was successful in increasing and controlling the dissolution rate of drug simultaneously throughout the GIT in both gastric and intestinal environment. Such an approach would be helpful to researchers to obtain the desired steady state blood levels of drugs with minimum peaks and troughs for prolonged time duration after a unit dose incorporation [25].

Moneghini et al. studied microwave irradiation (MW) technique to prepare solvent free SR SD (Sustained release solid dispersion) utilizing Ibuprofen (IBU) as a model drug and Imwitor 900 (glyceryl monostearate, GM) as a lipophilic SD carrier in varying ratios. The physical characteristics of SD performed by different evaluation parameters like Differential Scanning Calorimetry (DSC), PXRD and hot-stage microscopy (HSM) demonstrated a significant correlation of the solid state of IBU before and after treatment with MW technique. The % drug release from the irradiated solid dispersion samples was evaluated through the *in-vitro* dissolution rate studies and it revealed that the GMS was capable to achieve sustained drug release profile based on matrix erosion. Hence it was confirmed that the microwave irradiation is a novel and interesting technique to prepare drug-carrier systems [26].

SR microspheres of Nitrendipine comprising of SD were manufactured in single step process with the purpose of improving bioavailability of poorly soluble drug and achieving extended time to reach C_{max} value. Solid dispersion carrier HPMCP (Hydroxy Propyl Methyl Cellulose Pthalate) and sustained-release polymers Eudragit RS PO and ethylcellulose were utilized together to manufacture the microspheres using spherical crystallization technique also referred as quasi-emulsion solvent diffusion method. The prepared microspheres were characterized for the micromeritics and the release rate study. The rotation speed was shown to have a significant impact on the particle size of microspheres. During the dissolution

study, it was discovered that the drug release from microspheres was significantly influenced by the amount of dispersion agents or retarding agents included into the microspheres. The desired controlled release of drug from microspheres can be obtained by selecting suitable combination ratio of dispersing agents to retarding agents. Additionally, the in-vivo absorption study of developed microspheres was performed in 6 healthy dogs. The physicochemical characterization done by PXRD and DSC (Differential Scanning Calorimetry) confirmed the conversion of crystalline form of drug into amorphous one due to SD formulation. The accelerated stability study performed for duration of 3 months at storage conditions of 40°C and RH of 75% showed insignificant change in drug release rate and % assay of the microspheres. The bioavailability of the SR microspheres in comparison to marketed formulation (Bay press tablets) and IR formulation, and the Fr values obtained were 107.78% and 309.82% respectively [27].

The described investigation was conducted to prepare solid dispersions of a low aqueous soluble drug Nifedipine. SDs was manufactured using Methocel and coated upon sugar spheres using fluidized-bed coater. First of all, a common solvent system consisting of mixture of acetone:water in 7:3 ratio for the spraying of nifedipine and HPMC together was finalized based on optimization. The nifedipine SDs containing HPMC in Nifedipine:HPMC ratio of 1:1 and 1:3 showed broad peak in comparison to the peak demonstrating the MP of pure nifedipine upon characterization with DSC. The results of the *in-vitro* release analysis of the formulation showed that the release rate of nifedipine was increased when the ratio of the solid dispersion (SD) carrier hydroxypropyl methylcellulose (HPMC) was elevated. The incorporation of surfactant Tween 80 in dissolution medium while conducting the dissolution study enhanced the drug release rate. It was observed that the higher proportion of HPMC in SD formulation reduced the solubilization effect of Tween 80 [28].

A study was undertaken by **Patil et al.** with the aim of developing a solid dispersion of Metformin HCl. The study used HPMC K100M as the solid dispersion carrier and employed both the solvent evaporation and co-grinding methods. The effect of drug: carrier ratio on the release rate of metformin hydrochloride was understood by the dissolution study. The characterization of dispersion was conducted using FTIR, UV, DSC and PXRD study. The formulation was subjected to optimization and the optimized batch was considered for stability study as per ICH guidelines. The Release data were fit into pharmacokinetic release equations to interpret the drug release pattern. Considering all the characterizations, SD with

1:4 and 1:5 drug: polymer ratio was selected as the most promising formula for prolonged-release oral dosage form of metformin [29].

Sahoo et al. developed sustained release formulation of Verapamil HCl incorporating solid dispersion (SD) to obtain twice a day administration. The % drug release from tablets was controlled by using SR polymer Eudragit RLPO or Kollidon in varying ratios of drug: polymer. The physical mixtures and solid dispersions were prepared varying ratios of 1:1, 1:2, and 1:3 of Verapamil HCl: Eudragit RLPO / Kollidon® SR by simple mixing and solvent evaporation methods respectively. The physico-chemical characteristics of solid dispersion and absence of interaction between drug and carrier were confirmed based on graphs of FTIR, X-ray diffraction (XRD), and differential scanning calorimetry (DSC). The sustained release formulation was designed as tablet consisting of solid dispersions or physical mixtures of Eudragit RLPO/ Kollidon® SR. The % drug release rate from formulation was checked for time duration of 12 hrs in simulated Intestinal fluid using USP dissolution apparatus type II- Rotating Paddle. The *in-vitro* study showed that Eudragit helped to extend the release rate profile of drug to achieve twice a day administration whereas Kollidon® SR prolonged the release rate to achieve thrice a day administration. Based on the drug release study and the release kinetic equations, it was confirmed that SR tablet containing solid dispersions of Eudragit RLPO was more suitable to control the release of verapamil [30].

Tahseen et al. formulated sustained release tablet of Carvedilol using solid dispersion technology to increase the solubility of Carvedilol using SD carriers Poloxamer 407 and PVP K30. The sustained release profile of drug from the forulation was obtained with the help of sustained release polymer HPMC K15 in appropriate concentration. The tablets were directly compressed and analyzed for physicochemical properties. The dissolution study was performed in acidic medium for initial 2 hr followed by 12 hrs release study in simulated intestinal fluid in USP Type II Rotating paddle apparatus. The increase in HPMC concentration reduces the Carvedilol release. The batches F1 and F4 made with 20mg of HPMC K15 showed 97% drug release up to 12 hr whereas batches F2, F3, F5 and F6 containing 40mg and 60mg of HPMC K15 showed 98% drug release up to 14hr. Batches F1 and F4 containing SD consisting of Poloxamer 407 and PVP K30 demonstrated early $t_{50\%}$ of 6.4 hrs compared to 9.5 hrs of tablet formulation F7 containing only drug. Hence it was confirmed that SD technique is a successful and capable method for achieving sustained release for the low aqueous soluble drugs [31].

Halder et al. had undertaken a study with an aim to prepare sustained release solid dispersion (SRSD) of Carvedilol with 25% w/w drug loading to enhance dissolution. The research also examined the suitability of several drying methods that are accessible in industrial settings. SRSD of Carvedilol was designed using different proportions of polymers Kolliphor® P188 and Eudragit® RSPO and their physicochemical characterization was undertaken. The increase in dissolution rate was confirmed based on the dissolution study in sink and supersaturated conditions. Based on solubility study, the batch consisting of Kolliphor® P188 and Eudragit® RSPO in 2:1 ratio showed the maximum solubility and was proposed as optimized proportion to prepare SRSD of Carvedilol to undertake further characterization. The physical characterization based on the crystallinity study confirmed the amorphous form of CAR with higher solubility. The compatibility study between CAR and SD carriers based on FTIR showed no significant deviation verifying the absence of significant interactions. Also, the developed formulation revealed immediate formation of nano-particles upon dispersion in water. The *in-vitro* drug release study showed dissolution rate enhancement with controlled release of CAR compared to the crystalline form of CAR. The release rate data of Carvedilol were fitted into different release kinetics equations with the Korsmeyer Peppas equation giving the best correlation. Thus, the main release controlling mechanism is diffusion. There was no significant effect of method of preparation of formulations i.e., rotary vacuum drying or freeze drying on the drug release rate and mechanism. Hence, it can be concluded that the selected Sustained release SD approach is suitable for designing the formulation of CAR with improved biopharmaceutical characteristics [32].

Jujube et al. studied the characteristics of controlled release solid dispersions (CR-SDs) consisting of drug Aceclofenac, release controlling polymer polyethylene oxide, solid dispersion carriers namely poloxamer 407 & Gelucire 44/14, and pH modifying agent sodium carbonate. The immediate release (IR) and controlled release (CR) solid dispersions were designed and it was summarized that IR SDs containing the sodium bicarbonate improved the dissolution rate of Aceclofenac to a significant level, whereas the CR SDs containing PEO sufficiently maintained constant drug release rate. CR SDs had large droplet size and higher surface charge in comparison to immediate release solid dispersions. The pH modifying agent acts as release rate modifier by changing the crystalline behaviour and hydrogen-bonding interaction of drug and by controlling the micro environmental pH. Near-infrared images were captured that demonstrated an alteration of the PEO concentration to

maintain the pH modifier inside the system to obtain the constant release rate of Aceclofenac. Finally, it was summarized that the dissolution rate of solid dispersions of poorly water-soluble drug Aceclofenac consisting of PEO is significantly affected by micro-environmental pH, particle size and charge, pH modifying agent and the concentration of PEO [33].

Uegaki et al. not only developed controlled-release solid dispersion granules but also explained the release mechanism behind the controlled release of low aqueous soluble drug Nifedipine. To procure the objective, the SR granules were prepared using Hydrated Silicon Dioxide (HSD) and PVP by wet granulation method. Then, the solubility enhancement effect of PVP as SD carrier on Nifedipine was estimated. To optimize the rapidly dissolving granule of NIF, firstly suitable binder was selected and then the effect different ratios of drug and binder were studied. Immediate release granules of Nifedipine (NIF) containing binder erythritol and lubricant HSD were formulated. DSC study concluded the reduced crystallinity of API in the granules. The composition of immediate release granules was cross checked by conducting experiments with other 6 poorly water-soluble drugs to confirm the output. It was confirmed that the optimized composition led to dissolution enhancement of all drugs from the granule just as observed in NIF formulation. These studies prove that use of HSD in solid dispersion granules help to obtain rapid dissolution rate of the low aqueous soluble drugs. Afterwards the role of PVP in the drug dissolution rate from the IR granules was studied. The sustained release effect of polymer PVP on the IR SD granules consisting of these 7 drugs was recorded as no effect (rapid dissolution), middle effect or sustained effect. FTIR was used to examine the intermolecular interactions between the drug and HSD or PVP in order to comprehend the SR mechanism of the medication from the SD granules. Finally, it was interpreted that the appropriate balance between these interactions is essential to achieve the extended release of the drug [34].

Cai et al. worked on traditional Chinese medicine named Borneol that is helpful in enhancing *in-vivo* bioavailability and availability to the brain. The drawback of Borneol is gastric irritation in high doses. To check the applicability of Borneol, the model drug taken was gastrodin which is the principal biologically active constituent of the Chinese drug "Tianma" (Rhizoma Gastrodiae). SR SDs co-loaded with both were formulated using EC and HPMC as SR polymers. The solid dispersions were characterized based on SEM, Differential Scanning Calorimetry (DSC) and powder X-ray diffractometry (PXRD) to check the entrapment of API within the SR SD. The analysis confirmed that both medicines

were entrapped in an amorphous state within SD carrier. The dissolution study of both drugs concluded that the in vitro release pattern follows Higuchi model. Afterwards, the SDs were analysed for gastric irritation and the brain targeting and it was interpreted that the capacity of SR SDs to cross BBB was slightly weaker with brain targeting index of 1.83 compared to 2.09, but the gastric mucosa irritation was significantly reduced. Thus, it was summarized the SR technology is effective to overcome stomach irritation caused by borneol in addition to maintaining appropriate transportation ability for oral brain-targeting drug delivery [35].

Lu et al. developed a SR formulation consisting of SD of drug Ivermectin within a lipid matrix polymer hydrogenated castor oil using Solvent-melting technology aimed for subcutaneous route. The physical characterization of SD was done by SEM, PXRD and FTIR, whereas the drug release rate from SR SDs was analysed using HPLC. The Pharmacokinetic parameters of drug and its effectiveness against the ear mange mite were determined using rabbit as animal model after a unit subcutaneous incorporation of SD formulation. It was observed that the Ivermectin was able to trap amorphously in a lipid matrix in ratio lower than 1:3 for IVM: HCO. The drug excipient interaction was absent except for hydrogen bond within the amorphous SDs (ASDs). They showed extended drug release from formulation when compared to physical mixtures of drug and HCO. The release rate of API was found to reduce when the drug: carrier ratio was lowered. The release rate mechanism was diffusion controlled. The Cytotoxic study revealed that SD showed low toxicity to MDCK cells compared to pure IVM. The plasma concentration of IVM in SD with 1:3 ratios was maintained more than 1 ng/ml for 49 days. Increased values of pharmacokinetic parameters AUC, Mean Residence Time and T_{max} were observed for SD of 1:3 compared to IVM group. The solid dispersion enhanced bioavailability of IVM by 1.1-folds in comparison to drug alone in rabbits along with longer determination to combat rabbit ear mites than commercial IV formulation. Hence, the study proved that solid lipid dispersion technique is effective for the development of SC IVM formulations [36].

A work was conducted to develop SR SD of Metoclopramide HCl using solvent evaporation method. Different synthetic SR excipients like polymethacrylates (Eudragit RSPO & Eudragit RLPO) as well as natural polymers like guar gum & Egg albumin were used in combination to prepare SR SD. The SD were characterized by different evaluation properties like solubility, partition coefficient, assay, % cumulative drug release and flow property characteristics. All of these parameters were observed to be in an acceptable range. The SDs was exposed to X-Ray Diffraction and SEM and it was interpreted that the drug was

dispersed into a solid dispersion carrier in an amorphous form. The SR SD was also evaluated for pharmacokinetic parameters by in-vivo studies on Albino Wistar rats. The *in-vitro* dissolution study of SD proved that the sustained release of Metoclopramide HCl for at least 12 hrs was obtained along with the increase of bioavailability leading to reduction in dosing interval and dosing amount. Eventually the formulation reduced plasma level fluctuations minimizing dose related side effects. Apart from that, the formulation was cost effective and improved the patient compliance and drug efficiency [37].

Fan et al. conducted a study to design SR SD of curcumin in one step process by hot melt extrusion technology. The formulation was evaluated based on several in vitro as well as *in-vivo* parameters to serve the objective. Firstly, the crucial parameters related to process like temperature, speed of screw and rate of cooling were optimized. The Physicochemical characterization of SR SD was carried out based on DSC, PXRD and FTIR. It was concluded that SR pH independent polymers Eudragit RS & Eudragit RL used to sustain the release have good dispersibility with drug. The DSC study proved that the physical form of dispersed Curcumin within the SD was amorphous form. The Stability study performed for 6 months showed no difference in the physical characteristics of curcumin. The study using release kinetics models confirmed that the drug release mechanism from the SR SD was combination of diffusion and dissolution mechanisms. The in-vivo study proved that the bioavailability of the Curcumin in SR SD enhanced to 223.44% compared to curcumin alone. Hence it was justified that HME is a successful technique to prepare SR SD of Curcumin or any other poorly water-soluble drug, which not only improve bioavailability of drug but also stabilize effective plasma concentration [38].

Riekes et al. prepared FDC of ezetimibe and lovastatin drugs as Enteric coated formulation with the aim of preventing the degradation of drug into its hydroxy acid derivative in the acidic medium. The formulation was enteric coated using fluid bed coating. The manufacturing process included two-steps in which firstly the glass solution of two drugs and SD carrier Soluplus® was coated on sucrose beads and then further it was top-coated with pH dependant polymers of Eudragit L100 and Eudragit L100-55. The formulation analysed based on PXRD, SEM (Scanning Electron Microscopy), diffraction & dissolution studies in both gastric and intestinal pH interpreted the effect of bead size, enteric polymers and coating time. The study on bead size concluded that reduced bead size may tend to agglomeration of beads leading to drug release at low pH, especially because of uneven top coating. Both the grades of enteric polymers used prevented major proportion of drug to

release in stomach and allowed immediate release in the intestinal pH. The optimized coating time for perfect thickness was obtained 0.25 and 0.5 hrs respectively above pH 5.5 and above pH 6. The drugs were entrapped in molecular form within SD using carrier Soluplus® and it was concluded that Eudragit L100 formulations provide more proportion of drug release in stomach due to concave pores on the surface. The formulations were revealed to accelerated Stability studies of half year and the results showed no change in physicochemical properties and in-vitro release data of both drugs when compared to initial data [39].

Zhao et al. designed enteric solid dispersion (SD) of Nimodipine to overcome the limitations of low bioavailability and reduced clinical efficacy of the conventional solid dosage forms of NMD. Nimodipine (NMD) belong to the category of dihydropyridine calcium channel blocker, acting selectively on cerebral blood vessels. It is prescribed to prevent and treat cerebro-vascular disorders, especially delayed ischemic neurological disorders which are associated with circardian rhythm. The solid dispersions of NMD were prepared by Co-evaporation and melting method using HPMCAS and HPMCP. The delayed release tablet consisting of SD was prepared using Kollidon SR, Eudragit RS PO and PEO, N-12K. The prepared SDs were characterized by DSC and PXRD to interpret the physical nature of the dispersed API within the polymer matrix. The dissolution study of SD showed significantly enhanced dissolution of around 80% when compared to pure drug and physical mixture. A DR tablet was prepared by directly compressing the SD of NMD. The dissolution study of DR formulation containing NMD-SD showed nominal drug release (LT 10%) in 0.1 N HCl in the initial 2 h study and showed the drug release of around 32.1%, 75% and higher than 90% at pH 6.8 at the time points of 4, 10 and 14 hrs respectively. So, it was concluded that the proposed formulation was feasible for industrial applicability [40].

Overhoff et al. designed enteric powder consisting of solid dispersions (SD) of Itraconazole using HPMCP and Eudragit L100-55 by Rapid Freezing method. The influence of different composition characteristics that affect the release of drug from enteric SD under sink and non-sink conditions like polymer type, drug:polymer ratio, and particle structure were evaluated. The drug- polymer miscibility study was evaluated by Modulated DSC. The curves showed that 60% ITZ was completely miscible for both polymers and 70% was miscible in HP-55. Glass transition temperatures of high potency composition correlated with predicted Tg's based on Gordon–Taylor equation, and the pure amorphous regions in the exotherms revealed the phase separation during particle formation. The differentiation between completely miscible i.e., low potency and partially miscible i.e., high potency

compositions was checked based on different evaluation tests namely dissolution study, PXRD, SEM and surface area analysis. The Dissolution studies of completely miscible ITZ compositions revealed that the miscibility is playing a significant effect on drug release, especially under sink conditions, and the drug release through the pH dependant polymer follows square root diffusion. The dissolution study in supersaturated conditions revealed that the partially miscible components had highest saturation equilibrium solubility between 10.6 - 8 times compared to 15 - 19.6 times observed in low potency compositions and they also exhibited higher cumulative extents of super saturation. However, these completely miscible compositions precipitated rapidly which drastically lowered AUCs with $p < 0.05$. So, it was concluded that the parameter significantly affecting drug release in sink condition is the miscibility of the solid dispersion, whereas the one affecting supersaturated dissolution profiles is potency [41].

Controlled release solid dispersion granules of weakly basic drug Verapamil HCl were manufactured by solvent evaporation method to ensure that drug release occur unhampered at higher pH values. Different Sustained release polymers like ethyl cellulose, HPC and pH dependent polymers like Eudragit L and Eudragit S were utilized to prepare solid dispersion granules to obtain constant drug release rate, and to avoid the drug release rate from decreasing at the basic pH. CR formulation was designed by adding Eudragit L in EC network which may help to prevent the undetermined drug release at acidic pH and increase release of weakly basic drug at basic pH. The enteric polymers used in SD namely Eudragit L and Eudragit S showed different behaviour in terms of solubility and the release of API. The drug release data were fitted to Higuchi and first-order kinetic models and calculated correlation coefficients were almost same for both equations making it difficult to differentiate between the mechanisms. As a result, the mathematical models were implemented and it was confirmed that the release controlling mechanism in SD was diffusion, except for batches with greater proportion of enteric polymer. The SD was exposed to 2 years stability studies based on real time, and the results confirmed no change in the amorphous nature, IR spectra and Differential Thermal Analysis of formulation. Even the dissolution study of the formulations showed almost same drug release profiles after 24 months of the stability studies, eventually proving that the designed formulation was stable with dispersed drug in amorphous form [42].

Vo et al. prepared a gastro-retentive drug delivery system that would serve dual purposes of high residence in gastric environment through several approaches and potential induction of

in situ supersaturation overcoming poor and unstable bioavailability of drugs with low solubility. The aim was achieved by preparing floating pellets with bioadhesive nature, within which SD containing amorphous drug is loaded in a one step process using HME. The model drug selected was Felodipine with matrix-forming polymers used Hydroxypropyl cellulose (Klucel™ MF) and hypromellose (Benecel™ K15M). The foam pellets used sodium bicarbonate to obtain the expansion of CO_2 during the melt-extrusion process. The effect of proportion of formulation components upon the nature of pellet was understood based on 2n full factorial experimental design. The HME process successfully trapped the drug in an amorphous form within the polymeric matrix. All the foam pellets had high porosity and showed immediate floating in simulated gastric fluid without any lag time, and the pellets remained floating for about half day. The pellet-specific floating force obtained was 4800 μN/g which became greater prominently during initial hour, and it remained comparatively constant for about nine hrs. The most important factor affecting floating force was the proportion of sodium bicarbonate in the pellets. The *ex-vivo* bio adhesion study was performed using porcine stomach mucosa and the bio-adhesive force of the pellets obtained was around 5 mN/pellet, which was minimum 5 times greater compared to the gravitational force obtained by the pellets saturated with water. The *in-vitro* drug release study was performed in 0.1 N HCl and the sink condition was maintained using 0.5% sodium lauryl sulphate. The dissolution study of all 11 formulations showed controlled release up to 12 hrs with the percentage release of 5–12%, 25–45%, 55–80%, and ≥75% at time points of 1, 3, 5 and 8 hrs respectively. A supersaturated drug solution was formed in simulated dissolution medium, and almost 10-folds higher concentration was obtained and maintained compared to pure felodipine. The amount of Drug loaded in SD and HPMC proportion significantly affected dissolution after 3 h [43].

The study was performed to design gastro-retentive floating tablet consisting of SD of low aqueous soluble and permeable drug to increase the solubility along with retention the drug in gastric medium for achieving better absorption profile. The drug studied was antibiotic named Cefpodoxime proxetil belonging to third generation cephalosporin category. The oral bioavailability of drug is only 50% and half-life of drug is in range of about 2.09 - 2.84 hrs. The carriers selected to prepare SD were PEG 4000 and PEG 6000. The optimization was performed using face centred cube design (FCCD) and the optimized batch found out was SD8. It was observed that the highest solubility of 18.93 mg/ml and the drug release rate of 94.66% in gastric medium were obtained from the optimized batch compared to physical

mixtures and API alone. It was proved that increase in the concentration of carrier leads to solubility enhancement and the increase in drug release of SD following first order kinetics. The optimized batch SD8 was incorporated in gastro retentive floating tablet based on effervescent approach containing HPMC of grade K15 M as the water swellable polymer and sodium bicarbonate as effervescent agent. The tablets were prepared by directly compressing the mixture and evaluated for various quality control parameters like thickness, hardness, friability, assay, weight variation, *in-vitro* floating lag time & total floating time, % swelling index and dissolution study [44].

A study was conducted to develop wax based floating pellets consisting of Sustained release (SR) Solid dispersion (SD) of drug protocatechuic acid. It is weakly acidic drug of hydrophilic nature. The low-density approach was preferred to achieve extended gastric retention of drug along with the improvement in bioavailability. The matrix pellets were prepared with mixture of octadenol and MCC using extrusion-spheronization method coated with drug & ethyl cellulose (EC) SD using one step fluidized bed coating technique. The optimized batch showed sustained release for desired period of 12 hrs along with sufficient floating capability in gastric medium without any floating lag time. The drug release kinetics study predicted non-fickian release mechanism. The optimized pellets showed spherical structure with compact core during the structural analysis based on SEM. The FTIR, DSC and PXRD studies interpreted that the protocatechuic acid was dispersed in an amorphous form within the core of pellets without any significant interaction with the polymeric carriers. The stability study of optimized formulation confirmed the integrity and stability of amorphous SD of drug in the pellets [45].

2.5 Review of Literature of spray dried dispersion (SDD) based Formulations

Two solvent-based techniques for manufacturing amorphous solid dispersions (ASDs) from poly (vinylpyrrolidone-co-vinyl acetate) and weakly soluble spironolactone were compared in this work. The same equipment was used to continuously manufacture drug-loaded ASDs by electrospinning (ES) and spray-drying (SD) methods using solvent phase comprising of dichloromethane and ethanol. The concentration of the solution and the use of high voltage were the two primary variations between the two preparation techniques. To generate a fibrous product during electrospinning, a solution of greater concentration at higher voltage was utilised. On the contrary, during spray drying, a diluted solution without electrostatic force were used. Results from powder X-ray diffraction (PXRD) and differential scanning

calorimetry (DSC) indicated an amorphous structure for both ASD products. On the other hand, the ES sample showed almost 100% dissolution, but the SD sample did not fully dissolve. The samples' Raman microscopy mapping and polarised microscopy pictures demonstrated that the SD particles had crystalline traces, which had the ability to start precipitation during dissolution. Raman spectroscopy tests verified the appearance of the crystalline active medicinal component, whereas borescope examination of the dissolution fluid revealed the precipitated particles. The size and form of the developed samples, the pace at which surplus solvents evaporated, and the effect of the electrostatic field during the manufacture of ASDs, were important characteristics for the micro-morphological variations. The parameters under investigation proved to have a significant impact on ASDs dissolution rate. The authors concluded that it is important to concentrate on choosing the right ASD preparation technique in order to prevent the crystalline residues from impairing the dissolution capabilities [46].

Poudel et al. investigated a potent antihypertensive drug candesartan cilexetil (CC) that is a prodrug and a weakly soluble (BCS Class II) drug with restricted bioavailability. By adopting the spray drying process for generating several drugs loaded amorphous solid dispersions (ASDs) with PVPK30, a hydrophilic carrier, and sodium carbonate, a pH modifier, the authors aimed to increase the bioavailability of API. Tests for moisture content, solubility, and *in-vitro* drug release rate were used to screen the ideal formulation. In contrast to pure API, the researchers discovered a refined composition of cellulose acetate/polyvinylpyrrolidone K30/sodium carboxymethyl cellulose (CC/PVPK30/SC) that exhibited a significant increase in solubility by a factor of 30,000 and a more than nine-fold improvement in dissolution when formulated at a weight ratio of 1:0.5:1 (w/w/w). The use of solid-state analysis revealed that the crystallinity of CC underwent a transformation into an amorphous state inside the pH-modulated CC amorphous solid dispersion, without any unfavourable interactions. Additionally, stability experiments showed that under accelerated settings of up to 4 weeks and real-time stability conditions of up to 12 weeks, the optimised formulation remained stable with excellent drug content and drug release. In addition, rats treated with CCSDpM showed improvements in pharmacokinetic parameters, such as candesartan's AUC and Cmax, of 4.45 and 7.42 times, respectively, when compared to rats treated with CC. These findings implied that CCSDpM was a very successful treatment for improving oral absorption [47].

Tadalafil (TDL), a phosphodiesterase-5 inhibitor (PDE5I) recommended for erectile dysfunction (ED), was investigated by **Ahmed et al**. TDL's low rate of dissolution and water solubility, however, may restrict its use. The purpose of the research was to manufacture amorphous solid dispersion (ASD) utilising glycyrrhizin, a natural drug carrier, using spray-drying. Particle size & distribution analysis, polydispersity index (PDI) measurement, product yield, % drug content, Drug-polymer interaction study by Fourier Transformed Infrared (FTIR) spectroscopy, Differential scanning calorimetry (DSC) & X-Ray diffraction (XRD); Scanning Electron Microscopy (SEM), and *in-vitro* dissolution study were performed to determine particle and physicochemical characterizations. Male rats' sexual behaviour was studied in order to assess the produced ASD's aphrodisiac properties. The developed spray-dried dispersion was an effective drug-carrier binary combination, according to the findings. In contrast to the drug, which indicated a crystalline and spiky structure, PXRD and SEM revealed that the ASD of TDL with GLZ appeared in the amorphous nature and biconcave spherical shape. The solubility rate was 4.07 times higher in the optimised ASD3 formulation as compared to pure TDL. The parameters evaluated for optimized batch were 1.92 mm particle size, 0.32PDI, 97.78 % yield, and 85% drug content. The *in-vivo* study's findings show that ASD3 considerably increased aphrodisiac activity. According to the stability analysis, after a month of room temperature storage, the produced ASD3 did not exhibit any significant changes in its drug concentration or dissolution [48].

The preparation and testing of solid dispersions designed for repeated parenteral or oral administration of hazardous metabolites of paracetamol and glucosamine, including their physicochemical and pharmacokinetic properties, was the goal of the research. Using the spray drying method, solid dispersions were made at various glucosamine to paracetamol molar ratios. Equilibrium solubility study, *in-vitro* dissolution rate, Differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), X-ray diffraction (XRD), and scanning electron microscopy (SEM), were used to characterise the solid dispersions. The produced dispersions' *in-vivo* pharmacokinetics and toxic metabolites were assessed and contrasted with those of pure API and physical mixtures. The plasma drug concentration saw a 6.5-fold increase due to its rapid water solubility and more than seven-fold increase in dissolution rate when compared to paracetamol alone. The administration of oral doses to animals on the third day resulted in a significant increase of almost two-fold in the area under the curve (AUC) during the 0 to 24-hour timeframe, as shown in the dispersions. On the second and third days after dosing with solid dispersions and physical

mixes, respectively, there was a decrease in the quantity and concentration of hazardous pathway metabolites, which was followed by their total elimination. The analgesic effects of paracetamol were accelerated by the safer and more efficient administration of repeated doses made possible by the spray-dried dispersions. It was anticipated that the synergy between glucosamine's joint-protective properties and paracetamol's analgesic effects would enable the successful treatment of chronic pain-related conditions like osteoarthritis [49].

The study conducted by Li et al. was to examine the potential benefits of delaying the precipitation of weakly basic pharmaceuticals in a supersaturated condition. This delay was specifically explored following the transition of these APIs from acidic pH to near-neutral proximal small intestine fluid. The objective was to enhance the transitional solubility and bioavailability of these drugs. This research examined the influence of supersaturation on drug dissolution and permeation *in-vitro* and IVIVC for the weakly soluble basic drug ketoconazole. IDAS2 was used to assess dissolution rate in acidic and basic pH and penetration through Caco-2 cell monolayers. The weakly basic poorly soluble drugs were temporarily supersaturated *in-vitro* by the pH change from acidic to basic, resembling the *in-vivo* stomach to intestine transition. HPMCAS was added to dissolution media to increase the amplitude and duration of pH-driven supersaturation of the weakly basic drug ketoconazole in *in-vitro* IDAS2. The rat pharmacokinetic model showed HPMCAS affects ketoconazole oral bioavailability. Drug dissolution and penetration under 2-stage (pH shift from stomach pH 1.6 to intestinal pH 6.5) and 1-stage (constant intestinal pH 6.5) conditions were compared *in-vitro* to measure pH-induced drug supersaturation. The 2-stage procedure increased *in-vitro* dissolution and permeation of the weakly basic drugs dipyridamole, ketoconazole, and itraconazole by 393%, 161%, and 71%, respectively, compared to the 1-stage conditions. Warfarin, a BCS 2 acidic drug, decreased solubility by 9% and penetration by 21% under 2-stage circumstances. The gastric to intestinal pH shift did not supersaturate minoxidil or metoprolol, and their permeation was unaffected by the change. The polymeric precipitation inhibitor HPMCAS raised ketoconazole's *in-vitro* dissolution and permeation AUC by 187% and 119%, respectively, and its plasma $AUC_{0\text{-}24h}$ and C_{max} by 54% and 49% in rats after oral administration. The present study discovered that the innovative in-vitro dissolution-absorption methodology, which replicates the in-vivo gastrointestinal conditions impacting the release and absorption of orally administered drugs, exhibited sensitivity and physiological relevance. This methodology proved effective in investigating formulation excipients that utilize supersaturation to enhance systemic drug absorption [50].

Despite its proven therapeutic benefit, polypeptide-k, an antidiabetic phytochemical extracted from dried and ripened Momordica charantia seeds, has not seen significant use in clinical settings. This was mostly ascribed to its poor water solubility. In order to improve polypeptide-k's water solubility, a solid dispersion comprising the protein was developed in the research using the spray drying technology. Employing the Box Behnken Design as the optimisation strategy, variables were assessed. These include feed flow rate, inlet air temperature, tween-80 to API ratio, and trehalose to API ratio. The responses measured were angle of repose, product yield, moisture content, and solubility. The depictions of the ANOVA test confirmed that the ratio of tween-80 to PPK had a significant impact on the moisture content, solubility, and flow characteristics of the final formulation, whereas the ratio of trehalose to PPK considerably influenced the yield and flow properties of the product. While feed flow had a major impact on both moisture content and product yield, inlet air temperature had a considerable impact on moisture content. When compared to pure polypeptide-K, the optimised batch of formulation showed increased solubility in water and several aqueous buffers. PXRD and SEM were used to conclude that the formulation's higher surface area and smaller particle size were responsible for improved solubility [51].

Tyrosine kinase inhibitor gefitinib is meant to be taken orally; nevertheless, it has unfavourable side effects and a low absorption. Gefitinib (ZD) and ternary blends of various polymer ratios were prepared in organic solvent system to increase its solubility and enable colon targeting. Solid dispersions were produced using the spray drying (SD) method. To target the colon, the methyl methacrylate polymer Eudragit S 100 was added; and to increase the solubility of ZD, hydrophilic polymers like polyvinylpyrrolidone (PVP) & hydroxypropyl methyl cellulose (HPMC) were used. Various analytical techniques including SEM, DSC, PXRD, FTIR, dissolution, and cytotoxicity investigations were used to assess and describe the developed formulations. The spray-dried particles showed, according to SEM photographs, that the rod-shaped ZD crystals had collapsed into smaller spheres. ZD was found to be amorphous in the spray-dried dispersions, according to DSC, FTIR, and XRPD analyses. Studies on ZD dissolution and release showed that at pH 7.2, HPMC-based solid dispersion significantly ($P < 0.05$) increased ZD dissolution and release (up to 95% in 15 hours); at gastric and intestinal pH, almost no drug was released. In addition, compared to PVP-based solid dispersions, the HPMC-based ones showed improved mucoadhesive qualities. It was interesting to note that hydrophilic polymers-based solid dispersions did not

further inhibit the Caco-2 cell line in comparison to the pure drug according to cell viability experiments utilising the neutral red assay [52].

The slow dissolution rate and restricted permeability qualities of photosensitive amlodipine free base motivated **Jang et al.** to develop and analyse an amorphous solid dispersion (ASD) system to study how it may be used to enhance oral absorption. The solid dispersion was made by spray-drying a solution of amlodipine free base and dextrin (1:10 by weight) in which at least 0.9% w/w of SLS was included as an absorption enhancer. The spray-drying process was optimized, and the formulation, characterization, and in-vivo absorption studies of amlodipine solid dispersion (Amlo-SD) were evaluated. Amlo-SD particles were round, smooth, and measured an average of 12.90µ in diameter. The amlodipine in the Amlo-SD was amorphous and dispersed uniformly. The Amlo-SD was kept at room temperature for six months, during which time its physicochemical stability was maintained and its photostability was much improved. When compared to amlodipine, Amlo-SD showed substantially better solubility at pH 1.2 and 6.8. When Amlo-SD was administered to rats, plasma concentrations of Amlodipine were significantly higher than when Amlodipine was administered alone. Amlo-SD's AUC was elevated by a factor of 2.8 with SLS but only by a factor of 2.0 without it; this difference seems to be connected to the permeability-enhancing action of SLS. It was concluded that Amlo-SD using SLS technology is a practical replacement for existing amlodipine formulations [53].

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CHAPTER 3

Rationale of Project

3.1 Rationale of Posaconazole Gastro-retentive Formulation

3.1.1 Rationale for selection of Posaconazole

Posaconazole is a broad-spectrum triazole antifungal agent with potent activity against various pathogenic fungi, including yeast and moulds as well as against emerging, hard-to-treat and endemic infections. Posaconazole has potent in vitro activity against yeasts, including Candida species, Cryptococcus neoformans and Cryptococcus gattii, Aspergillus species as well as causative agents of Mucormycosis.

Posaconazole is efficacious as

- ✓ prophylaxis against invasive fungal infections (IFIs) in immuno-compromised patients at high risk.
- ✓ salvage therapy against invasive aspergillosis and mucormycosis.
- ✓ treatment for patients with refractory invasive fungal infections (IFIs), including aspergillosis.
- ✓ antifungal prophylaxis for neutropenic patients and hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host disease (GVHD).

Posaconazole is approved for use in the United States for the prophylaxis of invasive Aspergillus and Candida infections in immune-compromised patients and the treatment of oropharyngeal candidiasis, including infections refractory to itraconazole or fluconazole, or both.

In the European Union, the agent is approved for use as treatment for refractory IFIs, as first-line treatment for oropharyngeal candidiasis in immunocompromised patients or patients with severe disease, and as prophylaxis for IFIs in patients receiving remission-induction chemotherapy for acute myelogenous leukemia or myelodysplastic syndromes and HSCT recipients.

The profile of POS drug is described in Table 3.1 with important physico-chemical parameters

TABLE 3.1 Posaconazole Drug Profile

Drug	**Posaconazole**
Mol. Weight	700.7774 g/mole
Chemical Formula	$C_{37}H_{42}F_2N_8O_4$
Solubility	soluble in DCM, DMSO, DMF and very slightly soluble at pH 1 and insoluble from pH 2 to 14 in aqueous solutions
BCS CLASS	II
Mechanism of action	blockage of the cytochrome P-450 dependent enzyme, sterol 14α-demethylase, in fungi leading to the inhibition of the synthesis of ergosterol, a key component of the fungal cell membrane. This results in inhibition of fungal cell growth and ultimately, cell death.
Log P	5.4
Tmax	3-5 hrs
Vd	1774 L
Absolute bioavailability	8-47 %
Protein binding	98%–99%
Half-life	mean half-life (t½) of 35 hours
Elimination	Feacal>>renal; extensively in unchanged form
Metabolism	UDP glucuronidation (phase 2 enzymes) (UGT1A4).

Posaconazole is available as brand name Noxafil® in the form of injectable solution, oral suspension and delayed-release tablet. The dosage regimen of marketed formulations is listed in Table 3.2.

Table 3.2 Noxafil® (Posaconazole) Dosage and Administration

Indication	**Dose and Duration of Therapy**
Prophylaxis of Invasive Aspergillus and Candida Infections	**Oral Suspension:** 200 mg (5 mL) three times a day. **Delayed-Release Tablets:** **Loading dose:** 300 mg (3 delayed release tablets of 100 mg Posaconazole each) twice a day on the first day.

	Maintenance dose: 300 mg (3 delayed release tablets of 100 mg Posaconazole each) once a day, starting on the second day. **Injection:** **Loading dose:** 300 mg intravenously twice a day on the first day. **Maintenance dose:** 300 mg intravenously once a day thereafter. (Duration of therapy is based on recovery from neutropenia or immunosuppression.)
Oropharyngeal Candidiasis	**Oral Suspension:** Loading dose: 100 mg (2.5 mL) twice a day on the first day. Maintenance dose: 100 mg (2.5 mL) once a day for 13 days
Oropharyngeal Candidiasis Refractory to Itraconazole and/or Fluconazole	**Oral Suspension:** 400 mg (10 mL) twice a day Duration of therapy is based on the severity of the patient's underlying disease and clinical response.

3.1.2 Rationale for preparation of spray dried solid dispersion of Posaconazole

Posaconazole is a BCS class II drug with low aqueous solubility and high intestinal Permeability. So SDD of Posaconazole will enhance the solubility and may improve the bioavailability.

3.1.3 Rationale for selection of Posaconazole Gastro-retentive Formulation

The several limitations are observed in the marketed oral suspension of POS as mentioned below

- ✓ The low & variable bioavailability (8-47%) due to high lipophilicity of Posaconazole, possibly some first-pass effect, special conditions of the patients (e.g., malabsorption based on cytotoxic chemotherapy and bone marrow transplantation), increased gut motility and/or increased gastric pH
- ✓ Co-administration with high-fat food, absence of severe diarrhea, constitutive low gastric pH values, and absence of highly potent enzyme-inducing drugs is required to achieve therapeutic concentration
- ✓ After oral administration relatively high gastric POS concentration is achieved due to weakly basic property (pka 3.6 and 4.6) and the acidic environment of stomach in fasting condition. Upon entry into small intestine, supersaturation and precipitation of Posaconazole occurs reducing the concentration. Intestinal precipitation of Posaconazole along with pH

dependent dissolution leads to limited and variable bioavailability and inter-subject variability

- ✓ High dose and dosing frequency (effective in divided daily dosing) is required to procure the required bioavailability.

The sustained release Gastro retentive formulation of POS will be retained in the acidic environment of stomach for at least 5-8 hrs. This may inhibit the precipitation of Posaconazole upon entry in intestinal pH and retain the formulation in the acidic pH**,** where the solubility of drug is relatively higher compared to the basic pH of intestine.

3.1.4 Rationale for selection of SD carriers

Soluplus® is a highly preferred and widely utilized due to outstanding solubilization properties that enhance bioavailability and suitability for innovative processing techniques including HME, spray drying, and Super Critical Fluid technology. Soluplus® is a novel graft copolymer of vinyl caprolactam (57%) and vinyl acetate (33%), with 13% macrogol (PEG 6000), serving dual functions as an active solubilizer for pharmaceuticals with limited water solubility due to micelle generation and a matrix polymer for a solid solution. It has been studied widely as an SD carrier for solubility enhancement, especially for BCS Class II drugs.

Gelucire is a family of vehicles derived from mixtures of mono, di, and tri glycerides with PEG esters of fatty acids available in a wide range of grades based on HLB value and melting point, offering variable applications in oral and topical formulations. The use of hydrophilic grades in solubility and dissolution rate enhancement and of hydrophobic grades in sustained release is well established. Gelucire 43/01 grade is a lipid extensively utilized in a non-effervescent based floating gastro-retentive DDS for the modified release of API. Hence, the combination of Soluplus® and Gelucire 43/01 was selected to serve the dual purpose of solubility enhancement and gastro-retention of weakly basic drug Posaconazole.

3.2 Rationale of Esomeprazole Delayed-release Formulation

3.2.1 Rationale for selection of Esomeprazole

Esomeprazole is a proton pump inhibitor (PPI) used for the management of gastroesophageal reflux disease (GERD), for gastric protection to prevent recurrence of stomach ulcers or

gastric damage from chronic use of NSAIDs, and for the treatment of Zollinger-Ellison (ZE) and H. pylori infection.

It is the S-enantiomer of omeprazole, that suppresses gastric acid secretion by specific inhibition of the H^+/K^+ ATPase in the gastric parietal cell. This effect leads to inhibition of both basal and stimulated gastric acid secretion. As the binding to the (H^+, K^+)-ATPase enzyme is irreversible and new enzyme needs to be expressed in order to resume acid secretion, esomeprazole's duration of antisecretory effect persists longer than 24 hours.

The profile of ESM drug is described in Table 3.3 with important physico-chemical parameters.

TABLE 3.3 Esomeprazole Drug Profile

Drug	**Esomeprazole**
Mol. Weight	367.4 g/mol
Chemical Formula	C17H18N3O3SNa
Solubility	soluble in ethanol, DMSO, DMF, very slightly soluble in water
BCS CLASS	II
Dose	20 or 40 mg
Mechanism of action	suppresses gastric acid secretion by specific inhibition of the H+/K+ ATPase in the gastric parietal cell
Tmax	1.5 hours
Vd	16 L
Absolute bioavailability	64% after a single dose of 40 mg
Protein binding	97%
Half-life	1.1 - 1.4 hours
Elimination	80% of an oral dose of esomeprazole is excreted as inactive metabolites in the urine, and the remainder is found as inactive metabolites in the feces.
Metabolism	Esomeprazole is extensively metabolized in the liver by the cytochrome P450 (CYP) enzyme system

3.2.2 Rationale for preparation of spray dried solid dispersion of Esomeprazole

Esomeprazole is a BCS class II drug with low aqueous solubility and high intestinal Permeability. So SDD of Esomeprazole will enhance the solubility and may improve the bioavailability.

3.2.3 Rationale for selection of Esomeprazole Delayed-release formulation

All PPIs are acid labile with pH dependent stability profile. They rapidly degrade in acidic media while they are sufficiently stable under alkaline conditions. So, PPIs are mainly formulated as gastro-resistant, delayed-release formulations.

The marketed delayed release formulation consists of enteric coated pellets in capsule or compressed as tablet. The pellets require multiple layer coating of drug and different polymers, resulting in the lengthy and time-consuming formulation process including various steps.

Hence the delayed release tablet consisting of SDD of Esomeprazole may reduce processing steps and time along with providing same benefits as MUPS (Multi-Unit Particulate System).

3.2.4 Rationale for selection of SD carrier

The biggest limitation of ASD is the precipitation of amorphous drug from the supersaturated solution into crystalline form during the processing, storage or stability study at higher temperature or humidity drastically reducing the solubility and dissolution rate of API. Hypromellose acetate succinate (HPMCAS) is the most extensively utilised and favourable amphiphilic cellulosic SD carrier that is capable to overcome this major setback of ASD utilization in the dosage form by improving the stability of ASD. HPMCAS is an enteric polymer commercially available in three grades, namely L, M & H, with fine (F) or granular (G) form, differing in their acetyl (5-14%) and succinoyl (4-18%) substitution, and dissolving at pH $\geq$ 5.5, 6.0 and 6.8, respectively. Polymer performance in ASD is governed based on physico-chemical properties like glass transition (T_g), thermal stability, and solubility. The noteworthy characteristics of HPMCAS are high T_g (119 °C-122 °C), amphiphilic nature, melt viscosity values about 2.4-3.6 mPa.S, and insolubility in water and simulated gastric fluid. It is reported that polymers with high T_g promote stability of ASD. It is crucial to select a SD carrier which not only improves drug solubility, but also simultaneously inhibits drug precipitation, and HPMCAS has proved its worth in achieving both. In the dissolution study using buffer with a pH of 6.8, the SD of HPMCAS-MF demonstrated the greatest drug solubility due to its solubility above pH 6. This attained property remained constant throughout the shelf-life testing at high temperature and humidity conditions. HPMCAS-MF inhibited the recrystallization of dispersed drug from a supersaturated solution more than any other polymer studied.

CHAPTER 4

Aim & Objectives

4.1 Aim

The aim of present research work is to extent the use of spray dried solid dispersion from solubility enhancement to site specific release and delayed release.

4.2 Objectives

The objectives of research are to improve solubility of BCS class II drug by entrapping in spray dried solid dispersion and then to incorporate the solid dispersion into suitable formulation to achieve desired release profile.

Two different formulations are planned, as mentioned below, to utilize versatile polymers that offer solubility enhancement along with site-specificity.

FORMULATION 1: Gastro-retentive formulation of Posaconazole

FORMULATION 2: Delayed release formulation of Esomeprazole

The following steps would be undertaken to develop the formulations

1. Analytical method development of APIs in relevant solvent and dissolution media.
2. Selection of solid dispersion (SD) carriers and excipients for formulations.
3. Spray-dried solid dispersion formation by spray drying method.
4. Optimization of process parameters and formulation parameters by Design of Experiment (DOE).
5. Drug-polymer Interaction studies based on Fourier transform Infrared Spectroscopy (FTIR).
6. Determination of Physical Form of entrapped API in SD by Differential Scanning Calorimetry (DSC) & Powder X-Ray Diffraction (PXRD).
7. Characterization of developed product based on solubility study, % yield, % drug content, *in-vitro* dissolution study, particle size analysis, surface morphology study by

Scanning Electron Microscopy (SEM), residual solvent analysis by GC-MS (Gas Chromatography-Mass Spectrometry), and other relevant evaluation studies.

8. *In-vivo* study for the Posaconazole gastro-retentive formulation.

CHAPTER 5

Development of Posaconazole Gastro-retentive Formulation

5.1 Materials & Methodology

Posaconazole (POS) and Soluplus® were received as gift samples from Amneal Pharmaceuticals Pvt. Ltd., Ahmedabad, India, in purified form. Gelucire 43/01 was a generous gift sample from Gattefossé, Mumbai, India. All other excipients and solvents of analytical grade were purchased. Aerosil (colloidal silicon dioxide) used as an adsorbent was purchased from SD Fine Chemicals. The organic solvents used as a solvent phase for spray drying, namely dichloromethane (DCM) and Isopropyl alcohol (IPA), were of HPLC grade and procured from Purvi Enterprises, Ahmedabad, India. The purified water for pharmaceuticals used in the solvent phase was made available from the distillation plant on the university campus.

5.1.1 UV-VIS Spectroscopy

A UV-VIS spectrophotometer (UV-1800; Shimadzu, Kyoto, Japan) was used to conduct a quantitative measurement of POS in both methanol and simulated gastric dissolving media. A set of Posaconazole solutions was prepared by diluting a stock solution with a concentration of 1000 µg/ml. These solutions were then subjected to spectrophotometric analysis in the wavelength range of 200–400 nm, while a reagent blank was used as a reference. Standard calibration curves were produced at wavelengths of 259 nm and 255 nm using Beer-Lambert plots and known concentrations of POS in methanol and 0.1N HCl, respectively. A linear standard curve with a high coefficient of determination ($R^2 = 0.9999$) was established in both solvents to quantify the concentration of POS [1, 2].

5.1.2 Fourier-transform infrared spectroscopy (FTIR)

It is a pre-requisite to execute a DECS (Drug-Excipient compatibility study) before finalizing the excipients to combine with a particular API in a dosage form. Hence, a compatibility investigation was done on a newly made physical mix of POS and carriers, Gelucire 43/01 and Soluplus®, in a 1:1:1 proportion, prior to starting the development of SDD. After undertaking a one-month stability assessment, the compatibility of this combination was then contrasted with that of the identical blend. Dry potassium bromide (KBr) in an amount of 500 mg was added to a mixture. Powder mixes were compressed using a hydrostatic press at pressures ranging from 68.5 to 103.4 MPa to create small discs. The sample's infrared spectrum was measured using a Fourier-transform infrared (FTIR) instrument with a 400–4,000 cm^{-1} scanning range (IR Prestige-21, Shimadzu, Japan) [3].

5.1.3 Preparation of POS SDD by spray drying technique

a. Selection of solvent system for spray drying

POS is soluble in solvents DCM (Dichloromethane), Methanol & ethanol; whereas Gelucire 43/01 is solubilized in DCM only [4–6]. Soluplus® is soluble in most of the solvents including DCM, Methanol, IPA (Iso-Propyl Alcohol) & water, due to its excellent solubilization properties [7]. On the contrary, PEO WSR 303 is soluble in water after overnight soaking, due to its swelling behaviour. Hence Posaconazole, Gelucire and Soluplus® were dissolved in DCM to form organic phase. PEO was soaked in water overnight to form aqueous phase. IPA was used to make both the organic & aqueous phases miscible with each other upon constant stirring. The final solvent phase utilized for spray drying was Water: DCM: IPA (1:1:3).

b. Preparation of ASD by spray drying technique

A magnetic stirrer was used to dissolve Posaconazole (POS) in a solvent system of DCM (Dichloromethane): water: IPA (1:1:3), along with SD carriers Gelucire 43/01 and Soluplus®, hydrophilic gum PEO WSR 303 (Poly Ethylene Oxide Water Soluble Resin), and anti-adherent Aerosil (Colloidal Silicon Dioxide). Based on the API and polymer solubility and the concentration required to prevent precipitation, a solvent phase was created. The waxy excipient Gelucire 43/01's moisture content and stickiness were reduced with the help

of the adsorbent Aerosil. After being thoroughly mixed on a magnetic stirrer, the resultant dispersion was spray dried. With the atomization air pressure set at 2 kg/cm^2 and the aspirator speed set at 65 m^3/hr, a micro spray drier (Cronimach Machinary, model no. CRO-MSD161, Evaporation capacity: 1 L/hr H20) was utilized for spray drying in a co-current mode. The 0.7 mm dual-fluid nozzle is part of the Peristaltic pump that powers the dryer [8, 9]. The different process parameters & formulation components were selected based on preliminary trials and listed in Table 5.1 along with their specific role.

5.1.4 Experimental design

a. Selection of Process parameters based on preliminary trials

Based on the pressure of compressor attached with spray dryer, the maximum compression air pressure obtained was 2 kg/cm^2. Based on the review of literature and the fact that decrease in the aspiration rate may reduce yield, the compression pressure was selected as 2 kg/cm^2 leading to atomization pressure of 30 PSI. The inlet temperature was kept constant at 40°C due to the melting point of 43°C of Gelucire 43/01. The corresponding outlet temperature obtained was in range of 35-38^{o} C. The feed flow rate was varied during preliminary trials to allow sufficient exposure time to the droplets to convert to solid particles devoid of moisture. Based on the moisture content of product, 1.5 ml/min FFR was finalized for all the batches [10]. The summary of all the finalized process parameters is depicted in Table 5.1

TABLE 5.1 Finalized Formulation & Process variables for Spray Drying of POS SDD

Formulation Components for POS SDD	
Formulation Component	**Role**
Posaconazole	API
Gelucire 43/01	For floating and sustained release drug delivery system
Soluplus® (PVCap-PVAc-PEG)	possess excellent solubilization properties that may help to enhance bioavailability
PEO WSR 303	Hydrophilic swellable polymer to allow the sufficient drug release from hydrophobic Gelucire
Aerosil 200	Lubricant to reduce the stickiness of Gelucire during spray drying

(Colloidal Silicon Dioxide)	
Solvent System Water: DCM: IPA (1:1:3)	Water to soak PEO (overnight soaking), DCM to dissolve Posaconazole, Gelucire & Soluplus IPA to miscible water and DCM phases
Constant Formulation parameters for FFD	
PEO WSR 303	0.1 % W/V
Aerosil 200	10% W/W of Gelucire
Solvent phase	500 ml
Process Parameters for Spray Drying for FFD	
Inlet Temp	40°C
Outlet temperature	36-38°C
Compressed air pressure	2 kg/cm2
Atomization pressure	30 PSI
Feed flow rate	1.5 ml/min

b. Preliminary studies

The solubility study of POS API in several solvents was conducted to compare its solubility at different pH of GIT. Several preliminary batches of POS SDD were prepared for the finalization of formulation components along with their required proportions, and to optimize the process parameters for spray drying. These batches are discussed in Table 5.2. The screening of significant variables and their corresponding levels was executed based on the interpretations of preliminary trials.

TABLE 5.2 Preliminary Batches for Spray Drying of POS SDD

Drug/Excipient Components	Role	PB1	PB2	PB3	PB4	PB5	PB6	PB7	PB8	PB9	PB10	PB11	PB12	PB13
POS	API	-	1g	0.5g	0.5g	0.5g	0.5g	0.5 g	0.5 g	0.5 g	0.5 g	0.5 g	0.5 g	0.5 g

Water:DCM:IPA (1:1:3)	DCM:Methanol (1:4)	Aerosil 200	PEO WSR 301	Gelucire 43/01	Soluplus®	Gelucire 50/13
Solvent Phase	Solvent Phase	Anti-adherent	Swellable gum to enable drug release from gelucire matrix	Hydrophobic polymer as SR & floating polymer	Hydrophilic polymer as SD carrier	Hydrophilic polymer as SD carrier
-	q.s. 100 ml	1% of gelucire	-	1.25 g	-	1.25 g
-	q.s. 100 ml	2% of gelucire	-	0.5 g	-	0.5 g
-	q.s. 100 ml	5 % of gelucire	-	0.25 g	-	0.25 g
-	q.s. 100 ml	5 % of gelucire	-	0.75 g	-	0.25 g
-	q.s. 100 ml	10 % of gelucire	-	1 g	-	-
-	q.s. 100 ml	10 % of gelucire	-	1.5 g	-	-
-	q.s. 100 ml	10 % of gelucire	-	1.5 g	0.5 g	-
-	q.s. 100 ml	10 % of gelucire	-	1.25 g	0.5 g	-
q.s. 100 ml	-	10 % of gelucire	0.125 g	1 g	0.5 g	-
q.s. 100 ml	-	10 % of gelucire	0.1 g	1 g	0.5 g	-
q.s. 100 ml	-	10 % of gelucire	0.1 g	1.25 g	0.5 g	-
q.s. 100 ml	-	10 % of gelucire	0.1 g	1.5 g	0.5 g	-
q.s. 100 ml	-	10 % of gelucire	0.1 g	1.5 g	1g	-

c. Optimization of formulation variables utilizing Full Factorial Design (FFD)

The formulation variables were further optimized using Design of Experiment (DOE) to create a quadratic model of analysis after the choice of process variables [11]. For this, the Full Factorial Design (FFD) process was used. Nine trials were conducted overall, as per Design Expert 11 (StatEase, Minneapolis, MN). The POS: Soluplus® ratio (X1) and POS:

Gelucire 43/01 (X2), with suitable levels of low, medium, and high, were selected as two independent variables for the study. Table 5.3 shows the experimental runs that were generated using 3-level 2-factor FFD. The solubility (mg/ml) of API and the % CDR in 0.1 N HCl after eight hours (Q_8) were the chosen dependent variables for the product optimization, and they are both summarized in Table 5.3.

TABLE 5.3 3^2 FFD Matrix for POS SDD

Run	X1	X2	X1 POS: Soluplus® Ratio	X2 POS: Gelucire 43/01 Ratio
1	-1	-1	1:0.5	1:2.75
2	0	-1	1:1	1:2.75
3	+1	-1	1:1.5	1:2.75
4	-1	0	1:0.5	1:3
5	0	0	1:1	1:3
6	+1	0	1:1.5	1:3
7	-1	+1	1:0.5	1:3.25
8	0	+1	1:1	1:3.25
9	+1	+1	1:1.5	1:3.25

Independent Variables in FFD

Sr No	Variables	Levels of Variables		
		-1	0	+1
1	POS: Soluplus Ratio	1:0.5	1:1	1:1.5
2	POS: Gelucire Ratio	1:2.75	1:3	1:3.25

Dependent Variables in FFD

Sr No	Response
1	Solubility (mg/ml)
4	% Drug Release at 8 hrs (Q_8)

d. Validation of experimental design:

Based on the constraints selected for the independent and dependent variables, three check point batches with desirability 1 were selected to navigate the design space generated for optimization. The model was validated for accuracy by comparing the % error between the models predicted values and observed values for the selected dependent variables. The constraints for the screening of checkpoint batches are mentioned in Table 7. The basic purpose was to minimize the total weight of SDD to accommodate maximum dose of Posaconazole in single capsule formulation. The constraint selected for soluplus® ratio was

between 0.5-0.75, to achieve at least twice solubility in comparison to pure API. The constraint selected for Gelucire 43/01 ratio was 2.75-2.9, so that sufficient floating efficiency can be achieved along with the lower SD carrier proportion.

e. Determination of optimized batch:

The final optimized batch was selected based on the validated model and graphical optimization using the overlay plot. The formulation composition delivering the considerable rise in the solubility of the SDD compared to API alone and favourable % CDR at 8 hrs in gastric pH was selected as optimized formulation for the further characterization.

5.1.5 %Yield

The prepared solid dispersions by spray drying were weighed. The estimation of product yield was conducted by dividing the quantity of SDD produced by the combined weight of the active pharmaceutical ingredient (API) and excipients that were added to the corresponding batch [12].

$$\%\, Yield = \frac{Total\ amount\ of\ SDD}{Total\ amount\ of\ drug\ and\ carrier} * 100 \dots\dots\dots\dots\dots (5.1)$$

5.1.6 Drug content estimation (% Assay)

The proportion of POS loaded in the solid dispersion was analysed by performing assay of the developed formulation. SDD equivalent to 50 mg of POS was dissolved in solvent methanol. The sample was filtered with the help of Whatman filter paper, appropriately diluted and subjected to UV analysis at 255 nm to determine the sample's drug concentration. Considering the % drug content entrapped in SDD, the amount of POS SDD equivalent to 50 mg POS was utilized further in the equillibrium solubility study [13].

5.1.7 Equilibrium solubility study

As the formulation was gastro-retentive meant to retain in gastric pH, an excessive amount of the sample (drug/SDD) was mixed in 10 ml of 0.1 N HCl in a glass bottle with a stopper. The sample was put in a water bath at 37±0.5°C, which is about the same temperature as a human body, and agitated at a rate of 40 strokes per minute for 48 hours. The sample was

rotated at a speed of 2000 rpm for 10 minutes. After that, the supernatant was filtered (0.45µ) and dissolved, and the concentration at 259 nm was measured with a UV spectrophotometer (Shimadzu U-1800, Japan). Using above method, the solubility was measured for all the batches prepared [14].

5.1.8 Dissolution studies

The *in-vitro* release study of POS SDD was performed in a USP Apparatus II (paddle) at 50 rpm in order to determine the site specificity and drug release pattern [15]. SDD equivalent to 150 mg of drug in a capsule shell was added to 900 ml of 0.1 N HCl dissolution medium for 8 hours at 37±0.5 °C. At specified times, aliquots of 10 ml were taken out, filtered, and the dissolved drug was measured by UV spectroscopy at wavelengths of 259 nm. The % CDR (cumulative drug release) was calculated for up to 8 hours. The DD-solver excel add-in was used to determine release kinetics of all the batches for all of the possible models, such as zero order, first order, Higuchi, Hixon-Crowell, and Korsmeyer-Peppas, to find the best model for the formulation's release profile.

5.1.9 *In-vitro* Buoyancy Study

As the formulation was meant to be gastro-retentive, buoyancy lag time, duration of buoyancy and % buoyancy was determined in the USP dissolution apparatus II with 900 ml simulated gastric fluid (0.1 N HCl). The known amount of SDD was agitated with a paddle rotating at 50 rpm for 8 h. The floating and the sediment portions were recovered separately. Buoyancy percentage was calculated as the ratio of the floating proportion with respect to the total amount. The floating lag time described the time required to attain the floating of SDD from the time of incorporation of SDD into the apparatus. The total floating time was the time from the addition of SDD into apparatus till the time the floating was retained [16].

5.1.10 Powder flow properties

Particularly when blending powders, compressing tablets, and filling capsules, the pharmaceutical industry pays great attention to the flow properties of solid dispersion. In order to evaluate the POS SDD's flow properties, the powder's angle of repose (θ), bulk density, tapped density, Carr's index, and Hausner's ratio were measured [12, 17].

The flow properties were analysed using a calculation of utilising the fixed funnel method. This method included dispensing a predetermined sample size via a funnel onto a piece of graph paper in the shape of a cone. The following equation was used to calculate θ from the measured height (h) and radius (r).

$$\tan\theta = \frac{h}{r} \dots\dots\dots\dots\dots\dots (5.2)$$

A density apparatus was used to measure SDD bulk and tapped densities (Metalab Industries, Mumbai, India), and using their values Hausner's ratio and Carr's compressibility index (%) were calculated.

By accurately converting a precise weight of each formulation (2 g) into a graduated cylindrical measure, the bulk density of SDD formulations was ascertained. Without compacting, the volume of the solid dispersion was recorded in the cylinder measure, and the following equation was used to get the bulk density.

$$Bulk\ density = \frac{weight\ of powder}{Bulk\ volume} \dots\dots\dots\dots\dots\dots (5.3)$$

By accurately weighing each formulation (2 g) and then transferring that weight to a graduated cylindrical measure, the tapped density of the ESM SDD was calculated. The cylinder was tapped (about 100 times) until there was no longer any volume change. The following equation was used to get the tapped density.

$$Tapped\ density = \frac{weight\ of powder}{Tapped\ volume} \dots\dots\dots\dots\dots\dots\dots (5.4)$$

The flowability of the ESM SDD was assessed using Hausner's ratio. The following equation was used to compute Hausner's ratio.

$$Hausner's\ Ratio = \frac{Tapped\ Density}{Bulk\ Density} \dots\dots\dots\dots\dots\dots (5.5)$$

Another factor used to forecast the flowability of powder is Carr's Compressibility index (CI). The below mentioned Equation was utilized to determine the ESM SDD CI.

$$Carr's\ Index = \frac{Tapped\ Density - Bulk\ Density}{Bulk\ Density} * 100 \dots\dots\dots\dots\dots\dots\dots (5.6)$$

5.1.11 Differential scanning calorimetry (DSC)

DSC was performed of optimized SDD to ascertain the thermal behaviour of the POS and Carriers in the developed formulation and also to detect the interaction between the API and

carriers. The PerkinElmer Thermal Analyzer was used to obtain an overlay of the DSC thermograms at a scanning rate of 20 °C/min for heating from 30 °C to 350 °C in an inert environment flushed with nitrogen at a rate of 10 ml/min [13].

5.1.12 Powder X-ray Diffraction (PXRD) Analysis

A Powder X-ray Diffractometer D8 DISCOVER (Bruker) was used to record the powder X-ray diffraction spectra of the POS SDD and compared with the PXRD spectra of pure POS and SD carriers. The SDD sample in fine powder form was subjected to X-rays. Scan angles were ranged from 0° to 80° across a 2θ range [38].

5.1.13 Particle size measurement

Particle size measurements were conducted on the optimized batch in order to determine the size of the SDD. Dynamic light scattering (DLS) was used to evaluate the mean particle size of the SDD using the Particle Size Analyzer (HORIBA Scientific SZ-100). The apparatus was equipped with a laser that emitted light at a specific wavelength of 633 nm. Additionally, a backscattering detector was strategically positioned at an angle of 173°. A dispersion sample was created by dispersing SDD (specific substance) in neugel (Liquid paraffin), resulting in a viscosity of 13.000 mPa·s. The experiment was conducted in triplicate at a temperature of 25 °C, which corresponds to the standard room temperature. The average of the measurements obtained from the replicates was used to determine the results [18].

5.1.14 Scanning Electron Microscopy (SEM)

The surface morphology of SDD powder was investigated using scanning electron microscopy (SEM) with a concentrated electron beam (Ultraplus, Zeiss, Germany). The sample was placed onto a glass slide, immersed in methanol, and afterwards subjected to desiccation inside a desiccator. To achieve uniform layering and overloading, the sample underwent a gold-palladium coating process for a duration of 2 minutes. This process was carried out utilizing a gold-sputter module inside a low-pressure evaporator, with a current of 20 mA. Microphotographs were captured utilizing scanning and magnification techniques at a distance ranging from 8 to 11 mm and a voltage of 5 kilovolts [12].

5.1.15 Residual solvent analysis

Due to the different solubilities of the POS and excipients, DCM and water were used as solvents to dissolve. The two solvent phases were then mixed together on a magnetic stirrer with the aid of IPA. Given that DCM and IPA are categorized as class II (with a limit of 600 ppm) and class III solvents (with a limit of 5000 ppm), respectively, the residual solvent analysis was carried out using the HS-GC/MS (Headspace-Gas Chromatography/Mass Spectrometry) (Shimadzu GCMS-QP2020 NX) technology. The SDD sample was dissolved in an appropriate solvent, heated for a specific amount of time, and then transferred to a vial. The unstable substances contained in the container's gaseous state were then subjected to examination [19].

5.1.16 Formulation of dosage form comprising optimized SDD

Optimized formulation of SDD equivalent to 150 mg dose of Posaconazole was manually filled in hard gelatin capsule shell. The dosage form was assessed for *in-vitro* dissolution study and stability study.

5.1.17 Stability Studies

The optimized batch of POS SDD was encapsulated and stored in a High-Density Polyethylene (HDPE) bottle with a silica gel container closure system. This final dosage form was then subjected to an Accelerated stability study, following the guidelines set by the International Conference on Harmonization (ICH). The study was conducted at a temperature of 40°C ± 2°C and a relative humidity (RH) of 75% ± 5% for a duration of 6 months. The stability chamber used for this study was provided by Patel Instrument Pvt Ltd. [20]. The study examined the dosage form to see whether there were any statistically significant variations in its physical characteristics, solubility in 0.1 N HCl, drug dissolution profile, and drug content at regular time intervals (1, 3, 6, and 12 months).

5.2 Results & Discussion

5.2.1 UV-VIS Spectroscopy

The POS spectra obtained in UV-VIS spectrophotometer for 0.1 N HCl and methanol are shown in Fig 5.1. The linear (R^2 = 0.998) standard curves prepared in methanol and 0.1 N HCl are described in Fig 5.2.

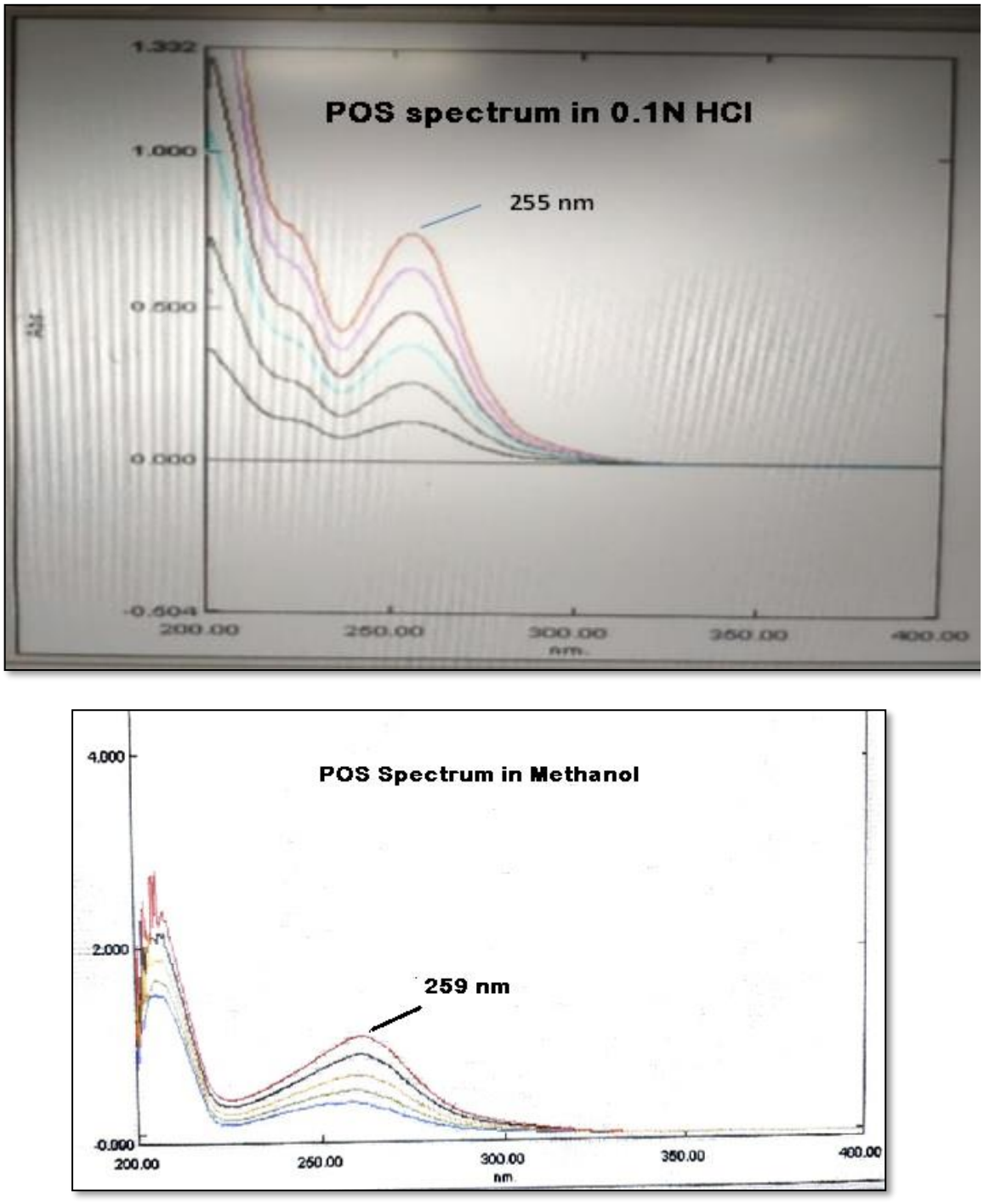
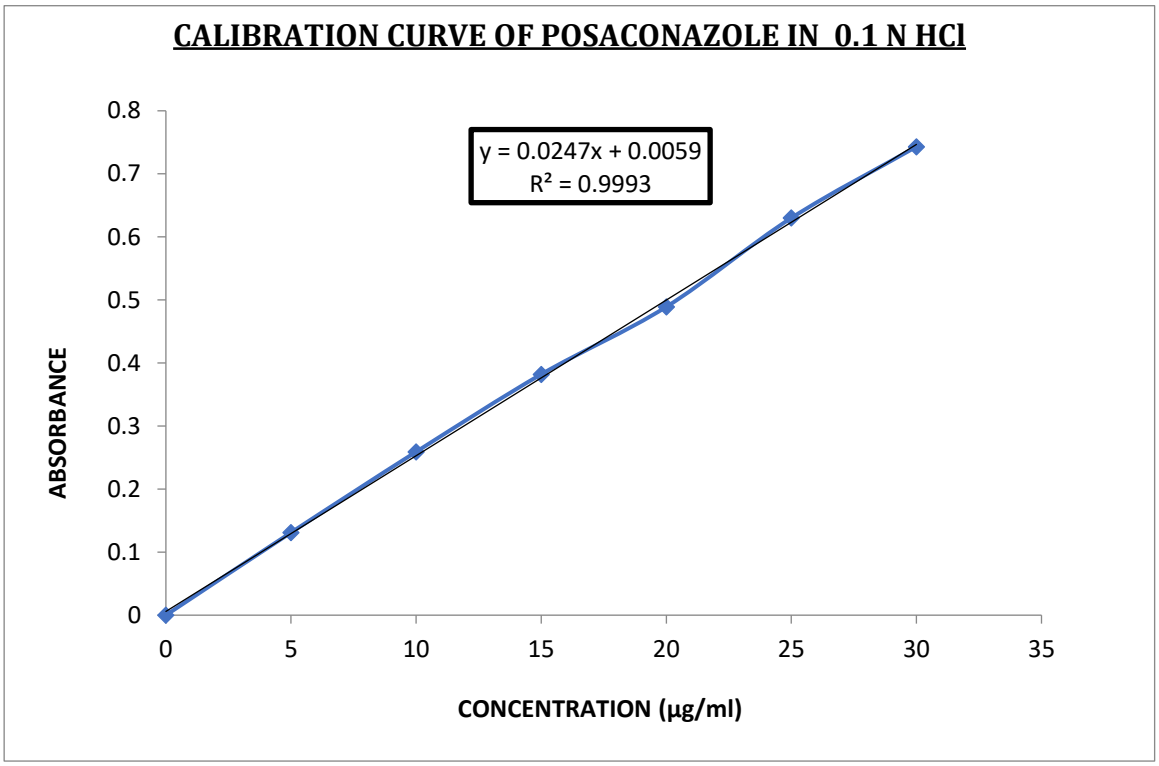


FIGURE 5.1 UV Spectra of Posaconazole



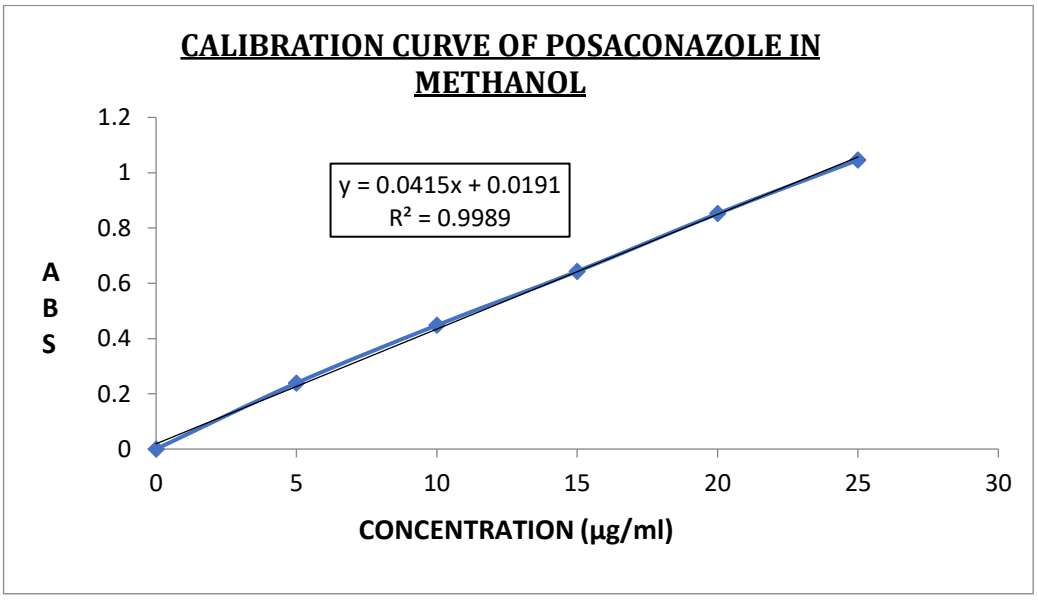


FIGURE 5.2 Calibration curves of Posaconazole

5.2.2 Fourier-transform infrared spectroscopy (FTIR)

Figure 5.3 illustrates the Fourier Transform Infrared (FTIR) spectra acquired for the drug and carriers Soluplus® & Gelucire 43/01, that were generated both at the beginning and after undergoing an accelerated stability study for one month. The two curves exhibited a high degree of overlap, suggesting that the combination of the active pharmaceutical ingredient

(API) and the chosen polymeric carrier are mutually compatible, as shown by the absence of any substantial peak loss even after a prolonged duration of 30 days. Therefore, it was feasible to use selected SD carriers for Posaconazole.

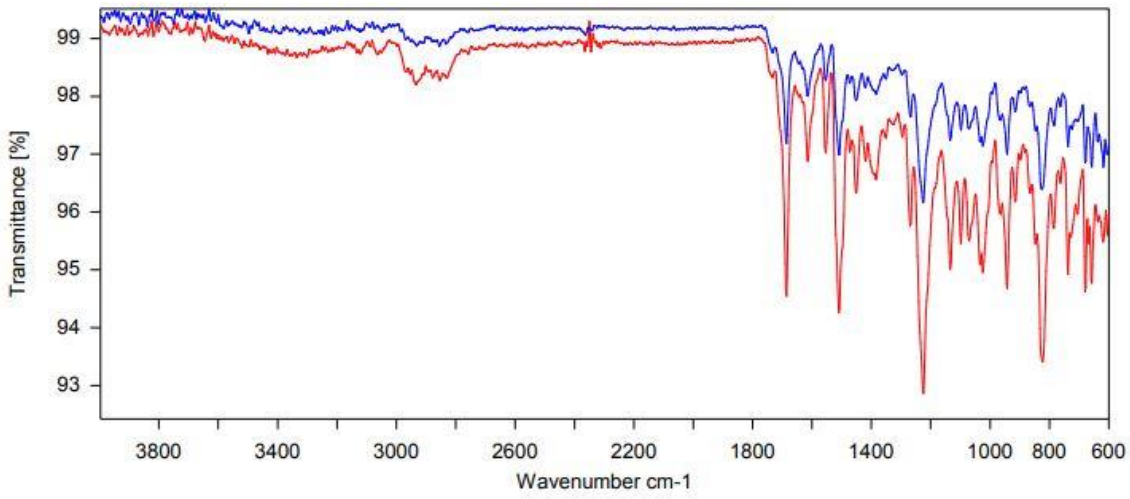


FIGURE 5.3 FTIR Spectra of Posaconazole and SD carriers

5.2.3 Experimental design

a. Preliminary studies

The solubility study of POS API conducted in several solvents simulating different pH of GIT is summarized in Table 5.4. Several preliminary batches of POS SDD prepared for the finalization of formulation components along with their required proportions, and to optimize the process parameters for spray drying are discussed in Table 5.5 along with the inferences. Based on the observations of preliminary batches, the process parameters were finalized for spray drying. It was concluded that the significant variables for optimization were proportions of SD carriers Soluplus® & Gelucire 43/01. Based on the interpretations of preliminary trials, it was confirmed that the levels of these variables to be considered in optimization process were greater than 1:2.5 for Gelucire 43/01, and it will commence from 1:0.5 for Soluplus®. The proportion of Aerosil required in final design batches was confirmed by residual moisture content of 3 batches with 2%, 5% and 10% w/w with respect to Gelucire 43/01amount. Karl-Fisher Tritation method was used for the analysis. The screening of significant variables and their corresponding levels was executed based on the interpretations of preliminary trials.

TABLE 5.4 Solubility Study of Posaconazole

Media	**Solubility (mg/ml)**	**Inference**
Purified Water	< 0.001	Practically insoluble
0.1 N HCl	**0.79**	**Very Slightly soluble**
pH 3.0	0.003	Practically insoluble
pH 4.5 Acetate buffer	< 0.001	Practically insoluble
pH 5.5 Phosphate Buffer	< 0.001	Practically insoluble
pH 6.8 Phosphate buffer	< 0.001	Practically insoluble

TABLE 5.5: Inference from Preliminary Batches of POS SDD

Preliminary Batch	**Inference**
PB1	Sticky mass was obtained
PB2	SD were comparatively less sticky but with high moisture content. **[8.75±0.25% MC using Karl Fisher Tritation]** The SD were not able to float
PB3	sticky SD were obtained with lower residual moisture content **[6.5±0.5% MC using Karl Fisher Tritation]** The SD were not able to float
PB4	Sticky mass was obtained
PB5	Non-sticky SD were obtained **[2.5±0.5% MC using Karl Fisher Tritation]** All the SD were not able to float
PB6	Non-sticky SD were obtained SD were able to float for more than 24 hr
PB7	Non-sticky SD were obtained The floating property was maintained
PB8	Non-sticky SD were obtained The floating tendency was reduced compared to batch 6
PB9	Thick viscous solution was formed that lead to deposition of sticky mass in drying chamber
PB10	Non-sticky SDD were obtained Floating was obtained for 2-4 hrs only in 1:2 Drug: gelucire proportion
PB11	Non-sticky SDD were obtained Floating was obtained for 4-5 hrs only in 1:2.5 Drug: gelucire proportion
PB12	Non-sticky SDD were obtained Proper floating was achieved and retained for at least 12 hrsThe % drug content in SDD was obatined 91%

	The % drug content in SDD was obtained 89% The solubility of Posaconazole SDD in 0.1 N HCl was obtained 1.5 mg/ml compared to 0.7 mg/ml of Posaconazole drug alone The SDD were enclosed in capsule shell and the in-vitro drug release study in 0.1N HCl showed controlled release up to 8 hrs
PB13	Non-sticky SDD were obtained Proper floating was achieved and retained The % drug content in SDD was obtained 91% The solubility of Posaconazole SDD in 0.1 N HCl was obtained 3.3 mg/ml compared to 0.7 mg/ml of Posaconazole drug alone The SDD were enclosed in capsule shell and the in-vitro drug release study in 0.1N HCl showed controlled release upto 8 hrs

b. Optimization of formulation variables utilizing Full Factorial Design (FFD)

DoE is a component of QbD, which is the most accurate model for comparing and evaluating statistical parameters. POS SDD were optimized using a 3-level 2-factor Full Factorial Design (3^2 FFD).

The optimization of SDDs was conducted by varying key formulation variables, keeping the process parameters constant for all the batches, using Full Factorial Design (FFD) for response surface optimization. FFD was chosen for the optimization based on the preliminary trials, since it allowed for the screening of two significant independent variables at three levels in 9 runs.

It was concluded that the significant variables for optimization were proportions of SD carriers Soluplus® & Gelucire 43/01. Soluplus® played an important role in enhancing the solubility od SDD. Whereas, Gelucire 43/01 was relevant with respect to the floating characteristic of SDD. Based on the interpretations of preliminary trials, it was confirmed that the levels of these variables to be considered in optimization process were 1:2.75, 1:3 & 1:3.25 for Gelucire 43/01, and 1:0.5. 1:1 and 1:1.5 for Soluplus®.

The 9 batches designed as per FFD were assessed for a variety of evaluation parameters, including % assay, saturation solubility in gastric medium, yield, and % CDR study in 0.1 N HCl, as per the methods discussed previously. The design matrix as per Design Expert along with the evaluation parameters is described in Table 5.6. Since all of these batches' assay (90–110%) met the necessary acceptance requirements, the difference in the data was

statistically insignificant. Also, the difference in yield obtained in all batches was statistically indifferent due to constant process parameters. Hence, saturation solubility and CDR at 8 hours in gastric media were thus the chosen dependent variables to consider for statistical analysis. The formulation should provide site-specific drug release in stomach to prevent the precipitation from saturated solution upon intestinal transit.

5.2.4 % Yield

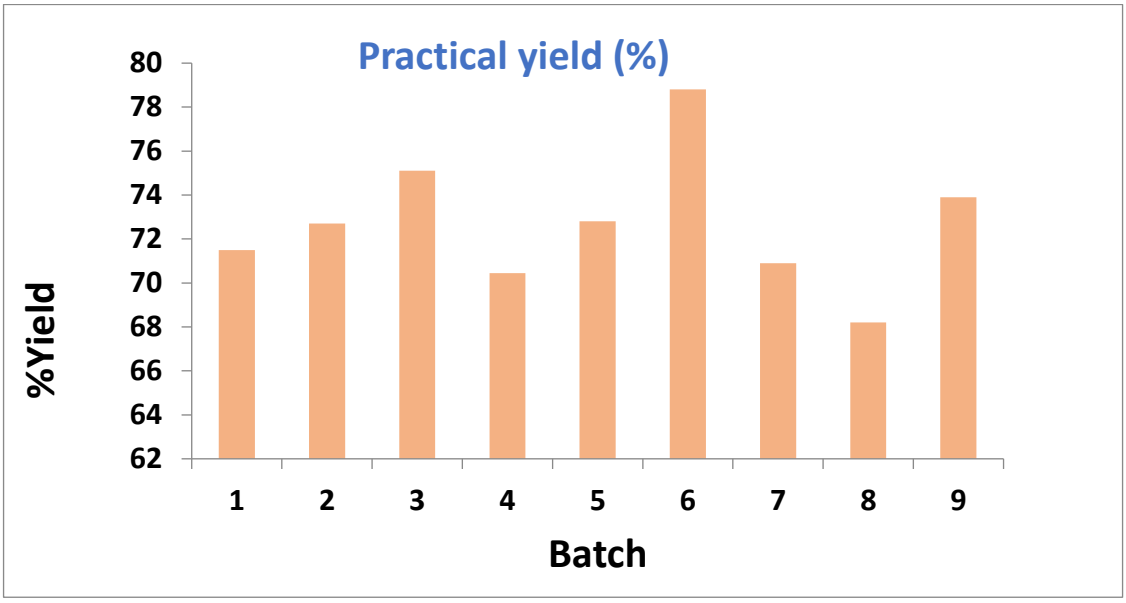


FIGURE 5.4 Bar graph of %Yield of POS SDD

The practical yield that was obtained after the spray drying of the solution comprising POS, SD carriers, and aerosil is summarized in Table 5.6. All of the batches exhibited % yield within the range of 68.2-78.8% with no significant fluctuation since the process parameters were previously optimized during the preliminary testing to maximize the process yield. All of the experimental batches had consistent FFR and inlet temperature, which reduced fluctuation in product yield. The information shown in Figure 5.4 indicates that an increase in the ratio of carriers to drug led to a partial improvement in yield percentage. The data is suggestive of the fact that the % yield was improved to some extent upon the increase in the ratio proportion of carriers with respect to drug. But, the difference in %yield of formulation batches was statistically insignificant.

TABLE 5.6 3^2 Full Factorial Design (FFD) with Evaluation Data

Run	X1	X2	X1 POS: Soluplus Ratio	X2 POS: Gelucire Ratio	% Yield	% Drug content (n=3)	Solubility (µg/ml) (n=3)	Q_8 (0.1 N HCl) (n=2)
B1	-1	-1	1:0.5	1:2.75	71.5	93.96±3.36	1504±12	102.56±0.75
B2	0	-1	1:1	1:2.75	72.7	94.85±4.58	1865±36	103.92±0.744
B3	+1	-1	1:1.5	1:2.75	75.1	98.45±1.23	2176±86	105.86±0.47
B4	-1	0	1:0.5	1:3	70.44	96.49±2.97	1945 ±33	97.25±1.04
B5	0	0	1:1	1:3	72.8	93.84±2.51	2332±27	98.47±0.64
B6	+1	0	1:1.5	1:3	78.8	92.09±3.7	2556±55	102.31±0.78
B7	-1	+1	1:0.5	1:3.25	70.9	94.00±2.36	2303±38	91.10±0.62
B8	0	+1	1:1	1:3.25	68.2	96.6±1.94	2641±43	92.53±0.28
B9	+1	+1	1:1.5	1:3.25	73.9	95.6±1.88	2936±41	94.25±0.21
API							710±15	

INDEPENDENT VARIABLES IN FFD

SR NO	VARIABLES	LEVELS OF VARIABLES		
		-1	0	+1
1	POS: Soluplus® Ratio	1:0.5	1:1	1:1.5
2	POS: Gelucire Ratio	1:2.75	1:3	1:3.25

DEPENDENT VARIABLES IN FFD

SR NO	RESPONSE
1	Solubility (µg/ml)
2	% CDR in 0.1 N HCl in 8 hours (Q_8)

5.2.5 Drug content estimation (% Assay)

The findings of the % assay, which was carried out to identify the percentage drug content in the SDD, are shown in Table 5.6. The information demonstrated that the % drug content is within the 90–110% permissible range for all the experimental batches. Fig. 5.5 shows the comparison statistics of 9 batches.

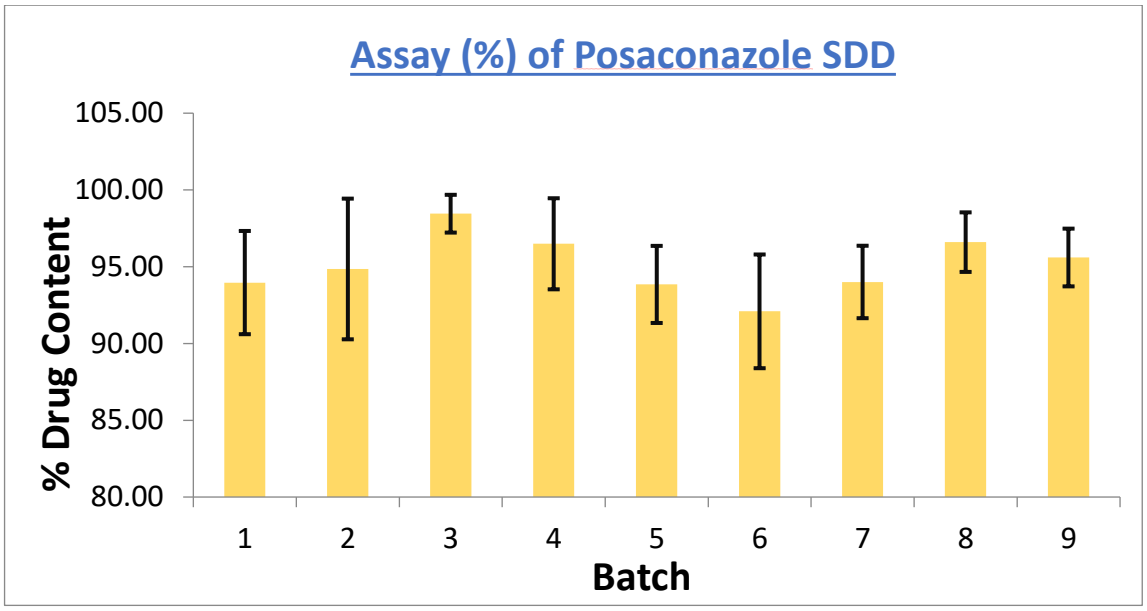


FIGURE 5.5 Bar graph of %Assay of POS SDD

5.2.6 Equilibrium solubility study

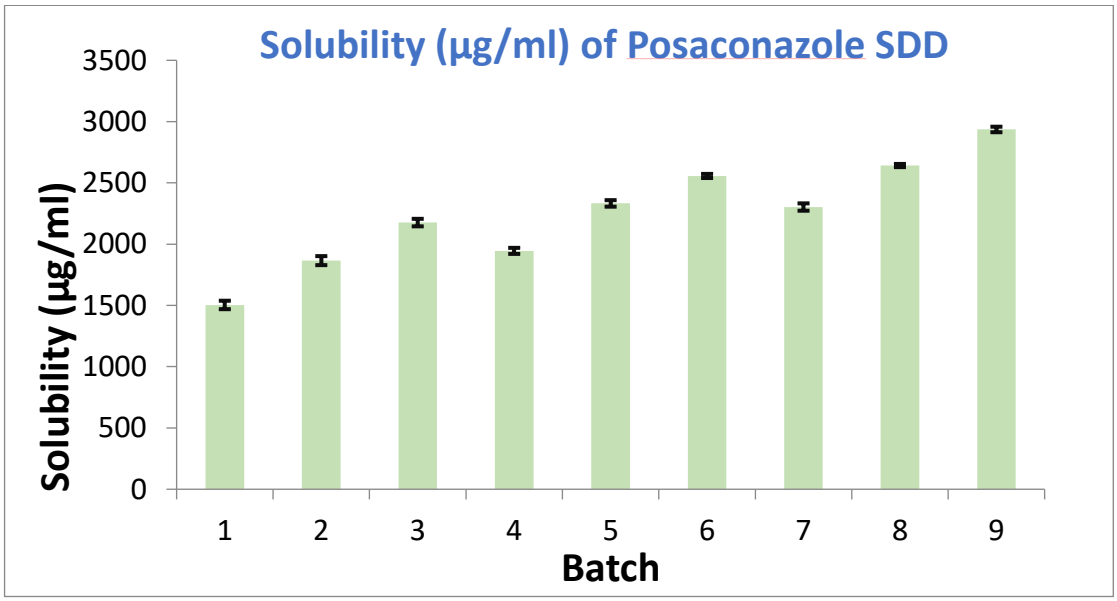


FIGURE 5.6 Bar graph of solubility of POS

All the experimental batches had their solubility values (µg/ml) calculated and shown in Table 5.6. According to the findings, there was a considerable increase in the solubility of POS API (710±15 µg/ml) when the proportion of SD carriers Soluplus® and Gelucire 43/01 was increased. The batches that had been developed demonstrated solubility that was two to three times greater than that of the API. The bar graph in Figure 5.6 illustrates the relative solubility improvement in comparison with API.

5.2.7 Dissolution studies

Table 5.8 provides an overview of the findings from the cumulative drug release study, which was conducted in a gastric medium (0.1 N HCl) during an 8-hour period, and the release kinetics study, which was conducted using DD-Solver software. All batches showed constant drug release within eight hours, with a CDR of more than 90%. The design space and batch B4 findings, which contained the closest optimisation quantity, indicated that the release kinetics are in agreement with the non-fickian diffusion (n<0.89) Korsemeyer-Peppas model. This interpretation could be confirmed from the adjusted R^2-value, which was almost identical to 0.999, the lowest AIC (Akaike Information Criteria) value, and the MSC (Model Selection Criteria) value, which was more than 4. Because the n component was closer to the 0.89 value, the drug release kinetics follow zero-order rather than first-order kinetics, and the erosion mechanism was more prominent than the diffusion mechanism.

The data shown in Fig 5.7 show the % CDR from POS SDD after 8 hours in 0.1 N HCl. Table 5.8 provides a summary of the dependent variable namely % CDR at 8 hours (Q_8) for each of the 9 batches. Fig. 5.7 displays the bar graph that shows the comparison statistics of Q_8 of all 9 batches.

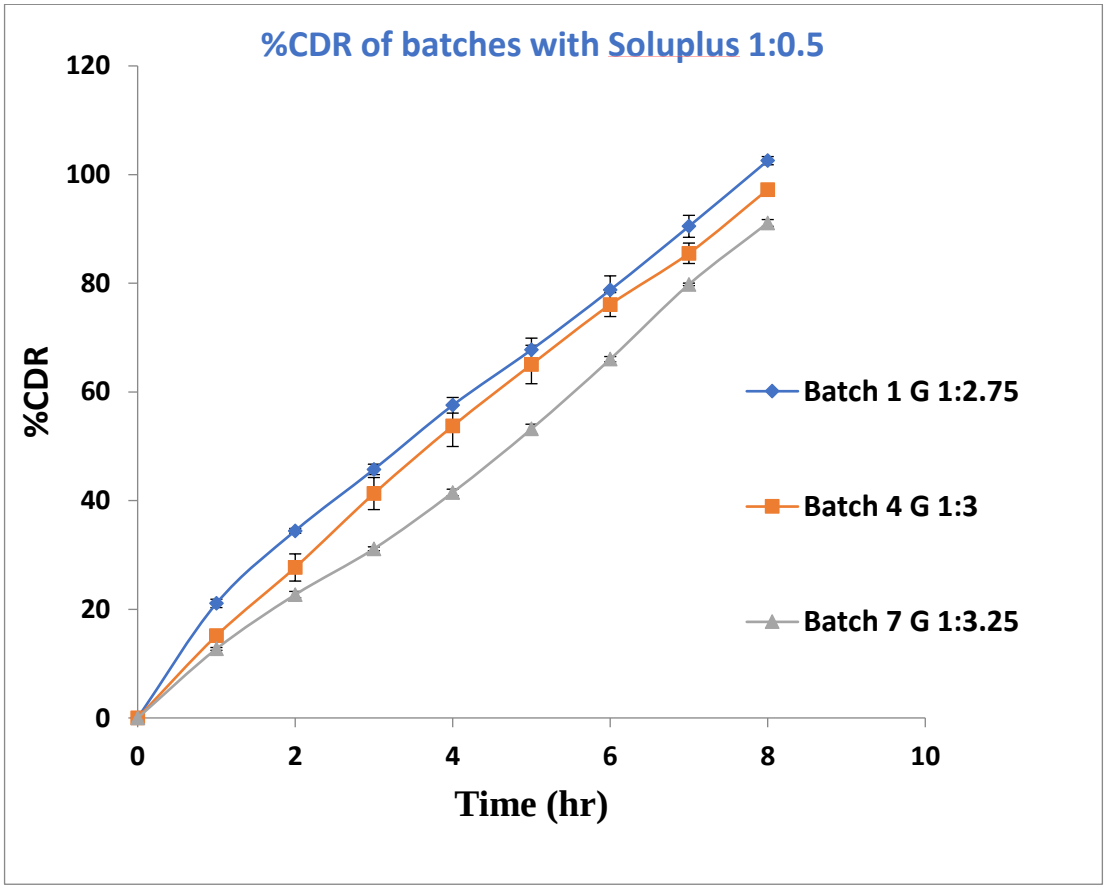
TABLE 5.7 *In-vitro* Drug Release study of POS SDD

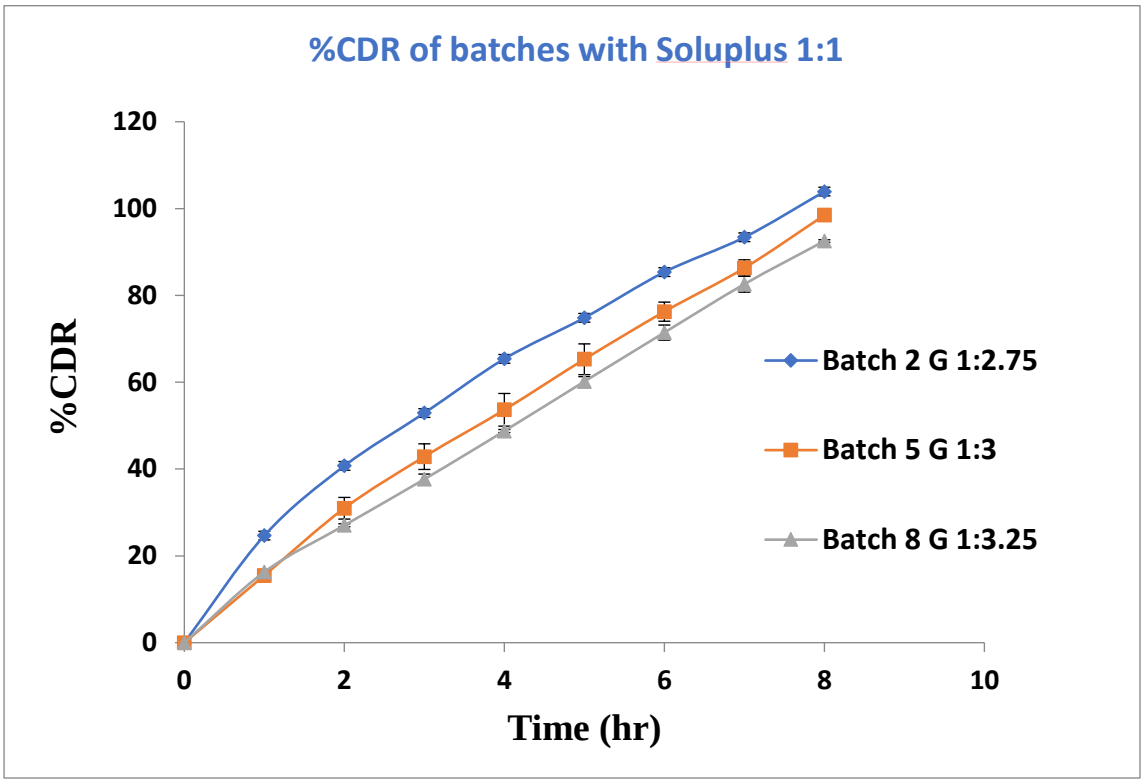
Time	B1	B2	B3	B4	B5	B6	B7	B8	B9
0	0	0	0	0	0	0	0	0	0
1	21.08± 0.77	24.67± 0.69	22.54± 0.09	15.13±0 .26	15.5± 1.98	18.47± 0.52	12.70±0 .26	16.29±0 .34	12.58±0 .94
2	34.44± 0.44	40.73± 0.87	34.99± 0.86	27.69±2 .49	30.97±2	31.19± 1.02	22.68±0 .6	27.04±0 .35	25.9±0. 53
3	45.75± 0.96	52.90± 0.62	46.32± 1.21	41.3± 2.95	42.85±1 .85	42.71± 0.35	31.13±0 .35	37.66±1 .19	38.33±1 .91
4	57.54± 1.44	65.38± 0.23	58.97± 2.26	53.71±3 .76	53.65±2 .04	54.35±2. 91	41.49±0 .61	48.76±0 .35	52.42±1 .15
5	67.77± 2.14	74.84± 0.62	70.18± 2.28	65.05±3 .54	65.29±2 .06	66.97± 2.26	53.18±0 .88	60.16±1 .13	63.98±0 .05
6	78.76± 2.59	85.37± 0.63	81.93± 2.91	76.08±2 .2	76.26±1 .31	78.5± 3.14	66.03±0 .49	71.44±1 .74	74.45±0 .14

7	90.48± 2.02	93.39± 0.48	93.56± 1.82	85.52±1 .88	86.31±1 .15	91.01± 1.28	79.8± 0.23	82.6± 1.84	83.4± 0.14
8	102.56± 0.75	103.92± 0.74	105.86± 0.47	97.25±1 .04	98.47±0 .64	102.31± 0.78	91.1±0. 62	92.53±0 .28	94.25±0 .21
zero order									
Parameter	**No.1**	**No.2**	**No.3**	**No.4**	**No.5**	**No.6**	**No.7**	**No.8**	**No.9**
Rsqr adj	0.9956	0.9863	0.9960	0.9982	0.9975	0.9984	0.9980	0.9989	0.9980
AIC	49.6320	59.3610	49.7522	38.8471	42.4134	41.0790	32.9982	35.8377	36.0762
MSC	3.1632	2.0331	3.2189	4.3925	3.9781	4.1978	4.9736	4.6085	4.6975
First order									
Parameter	**No.1**	**No.2**	**No.3**	**No.4**	**No.5**	**No.6**	**No.7**	**No.8**	**No.9**
Rsqr_adj	0.9506	0.9684	0.9403	0.9512	0.9533	0.9378	0.9225	0.9535	0.9510
AIC	56.8052	53.0492	59.1258	56.4490	56.0242	59.2400	59.4132	54.9728	56.2736
MSC	2.3662	2.7344	2.1774	2.4368	2.4658	2.1799	2.0386	2.4823	2.4534
Higuchi									
Parameter	**No.1**	**No.2**	**No.3**	**No.4**	**No.5**	**No.6**	**No.7**	**No.8**	**No.9**
Rsqr_adj	0.9374	0.9716	0.9354	0.9092	0.9182	0.9136	0.8505	0.9057	0.8971

										MSC	AIC
										2.1280	58.9488
										2.8406	52.0942
										2.0986	59.8346
										1.8164	62.0327
										1.9043	61.0774
										1.8515	62.1957
										1.3810	65.3317
										1.7760	61.3302
										1.7111	62.9544
Hixson-Crowell										***Korsmeyer-Peppas***	
n	MSC	AIC	Rsqr_adj	**Parameter**	n	MSC	AIC	Rsqr_adj	**Parameter**		
0.795	5.7241	26.5838	0.9984	**No.1**							
0.679	7.1967	12.8886	0.9997	**No.2**							
0.801	5.5418	28.8461	0.9981	**No.3**							
0.880	6.9174	16.1229	0.9995	**No.4**							
0.854	6.8342	16.7086	0.9995	**No.5**							
0.870	6.3334	21.8584	0.9991	**No.6**							
1.065	5.1603	31.3185	0.9969	**No.7**							
0.894	6.3796	19.8971	0.9991	**No.8**							
0.910	5.5893	28.0501	0.9981	**No.9**							
					MSC	AIC	Rsqr_adj	**Parameter**			
					3.0852	50.3343	0.9759	**No.1**			
					3.6555	44.7600	0.9874	**No.2**			
					2.8418	53.1463	0.9693	**No.3**			
					3.2524	49.1086	0.9784	**No.4**			
					3.2771	48.7221	0.9793	**No.5**			
					2.8553	53.1621	0.9683	**No.6**			
					2.5143	55.1324	0.9519	**No.7**			
					3.2277	48.2643	0.9779	**No.8**			
					3.2507	49.0974	0.9779	**No.9**			

Weibull									
Parameter	**No.1**	**No.2**	**No.3**	**No.4**	**No.5**	**No.6**	**No.7**	**No.8**	**No.9**
Rsqr_adj	0.9679	0.9770	0.9608	0.9865	0.9815	0.9699	0.9757	0.9816	0.9926
AIC	53.7407	51.0093	56.1296	45.6527	48.4696	53.5103	49.7629	47.4036	40.0461
MSC	2.7067	2.9611	2.5103	3.6364	3.3052	2.8166	3.1109	3.3234	4.2565
β	1.336	1.235	1.384	1.463	1.409	1.470	1.619	1.407	1.499





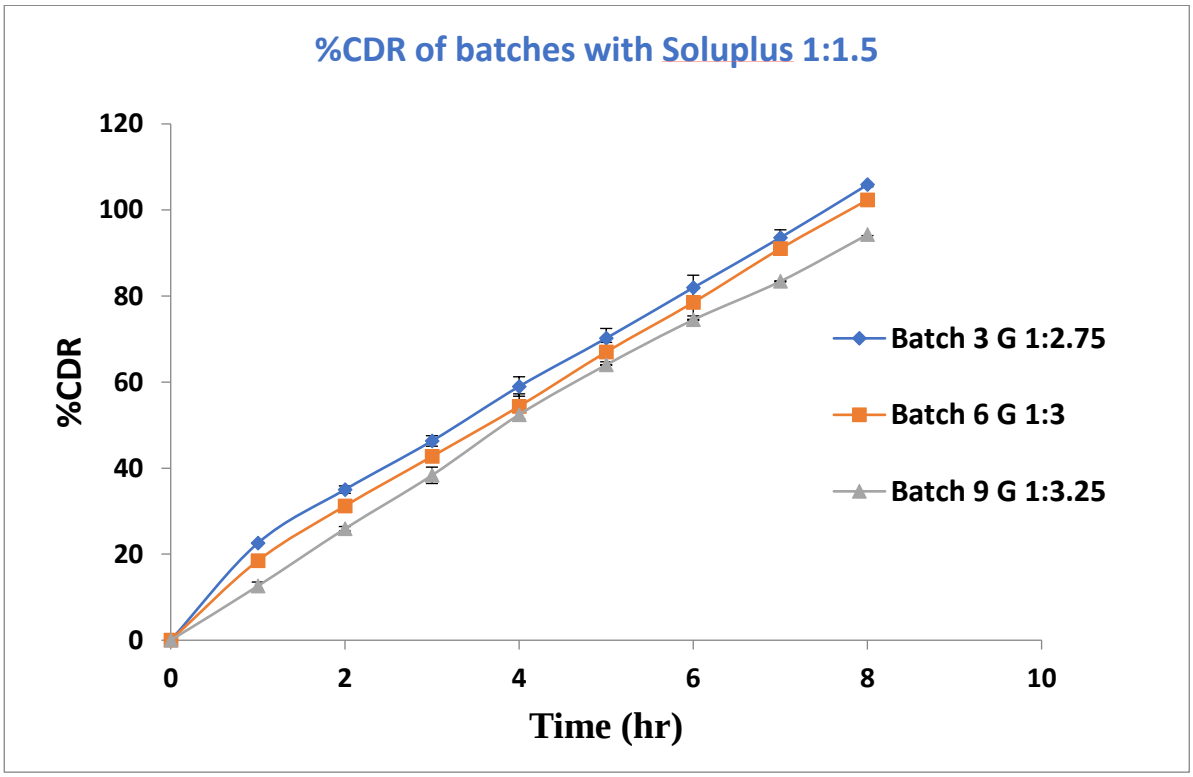


FIGURE 5.7 % CDR of POS SDD

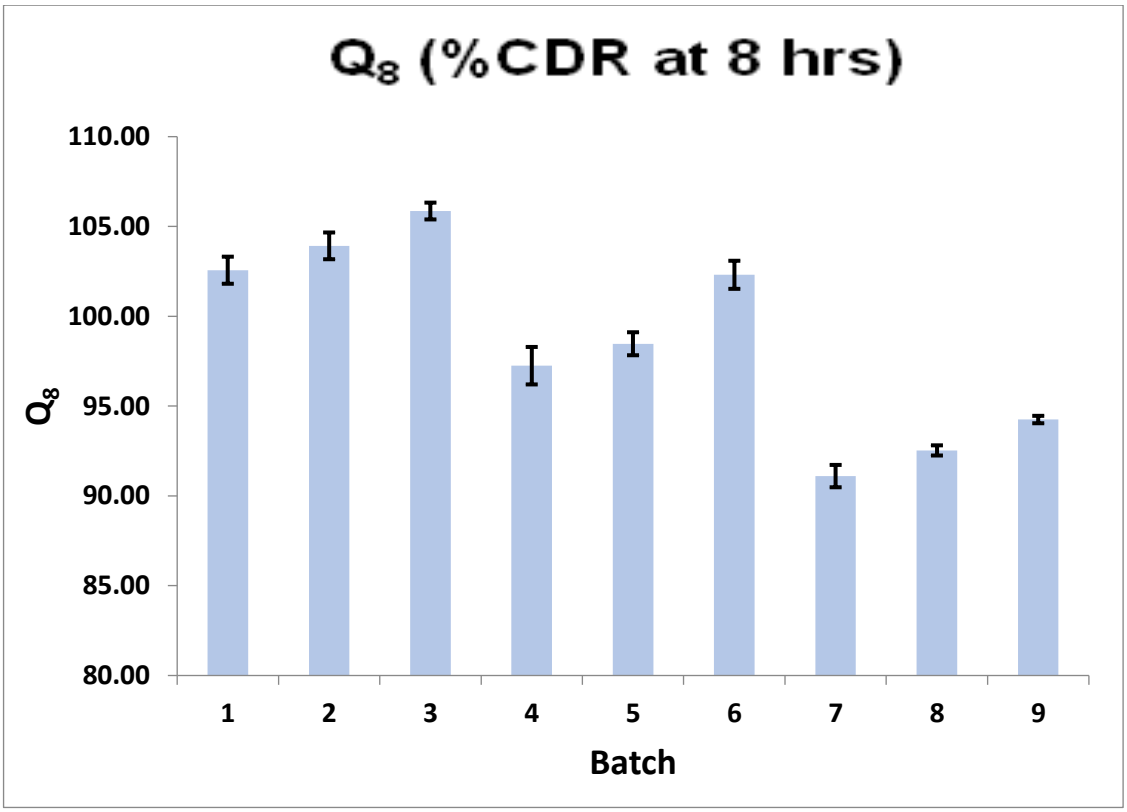


FIGURE 5.8 Bar Graph of Q_8 of POS SDD

5.2.8 *In-vitro* Buoyancy Study

Table 5.8 discusses the results from the buoyancy study of POS SDD that was carried out in accordance with the methodology section's description. Each batch exhibited the necessary gastro-retentive formulation floating tendency, with a total floating time exceeding 8 hours. The outstanding floating behavior of the low viscosity polymer Gelucire 43/01 was responsible for the observed lag time of zero.

TABLE 5.8 *In-vitro* Buoyancy Study of POS SDD

Batch	Amount of SD equivalent to 25 mg drug (g)	Floating lag time (s)	Floating duration (h)	Buoyancy± SD (%)
1	0.106	0	> 8 hrs	94.34±1.88
2	0.119	0	> 8 hrs	89.64±4.85
3	0.131	0	> 8 hrs	89.06±4.41
4	0.113	0	> 8 hrs	91.45±5.11
5	0.125	0	> 8 hrs	93.87±5.14

6	0.138	0	> 8 hrs	89.37±4.18
7	0.119	0	> 8 hrs	93.84±2.43
8	0.131	0	> 8 hrs	95.42±3.82
9	0.144	0	> 8 hrs	93.75±3.47

5.2.9 Regression Analysis & Validation of FFD

A description of the quadratic model regression analysis for each of the selected dependent variables is given in Table 5.9. The selected regression model was statistically significant and showed a strong fit with a small probability of extraneous variability, according to the statistical analysis of the Model F values and lack of fit for each dependent variable. Every time, there was a difference between the adjusted and predicted R^2 of less than 0.2, which suggests an acceptable level of variation. Adeq Precision's measurement of a signal to noise ratio more than four indicates that the paradigm in question may be used to explore the design space.

TABLE 5.9 Regression Analysis by Quadratic model and Model Validation

ANOVA ANALYSIS FOR SOLUBILITY			
Source	**F-value**	**p-value**	
Model	439.40	0.0002	Significant
A-Soluplus Concentration	879.85	< 0.0001	
B-Gelucire Concentration	1306.74	< 0.0001	
AB	0.5468	0.5132	
A^2	5.24	0.1061	
B^2	4.64	0.1202	
Std. Dev.	26.37	**R^2**	0.9986
Mean	2250.89	**Adjusted R^2**	0.9964
C.V. %	1.17	**Predicted R^2**	0.9881
		Adeq Precision	65.8110

ANOVA ANALYSIS FOR Q_8 (% drug release in 0.1N HCl)			
Source	**F-value**	**p-value**	
Model	80.82	0.0021	Significant
A-Soluplus Concentration	39.99	0.0080	
B-Gelucire Concentration	359.45	0.0003	
AB	0.0089	0.9308	
A^2	1.22	0.3507	
B^2	3.43	0.1610	

Std. Dev.	0.7418	**R^2**	0.9926
Mean	98.69	**Adjusted R^2**	0.9803
C.V. %	0.7516	**Predicted R^2**	0.9214
		Adeq Precision	25.2825
Constraints			
Name	**Goal**	**Lower Limit**	**Upper Limit**
A: Soluplus Concentration	is in range	0.5	0.75
B: Gelucire Concentration	is in range	2.75	2.9
Solubility	is in range	1504	2000
Q8	is in range	90	100
Check point Batches for Model Validation			
Soluplus Concentration (g)	**Gelucire Concentration (g)**	**Solubility (µg/ml)**	**Q_8 (%)**
0.537	2.898	1805.582	99.836
0.560	2.895	1817.649	99.950
0.618	2.898	1869.657	99.989
Check point Batches Optimization & Model Validation for Q8			
Batch	**Predicted Q_8 (%)**	**Observed Q_8 (%)**	**%Error**
CP1	99.836	98.5±0.34	1.33
CP2	99.950	99.65±0.6	0.3
CP3	99.989	99.96±0.51	0.03

Full and reduced models were generated for the first dependent variable, POS solubility, as represented in equations 5.7 & 5.8 respectively. As shown in Table 5.9 and represented in Fig 5.8, the findings showed that both independent variables, namely the proportions of Soluplus® and Gelucire 43/01 ratios, were statistically significant with a P-value of less than 0.05.

Solubility Full model = 2306.11+319.33 A+389.17 B – 9.75AB – 42.67 A2 – 40.17 B2 + ε.....(5.7)

Solubility Reduced model = 2306.11+319.33 A+389.17 B + ε……(5.8)

Wherein

A & B are Main Effects

AB is a 2-way Interaction Effect, A2 & B2 are Curvature effects

Ɛ is an Experimental error

The solubility of the API was mostly determined by the SD carrier, whose validity is predicated based on the coefficient values of components A and B. An improvement in the solubility of POS was likely caused by an increase in SD carrier, as shown by the positive sign, which indicated a direct relationship between the factor and response. The graphical representation of Response Surface Plots (RSP) and Contour Plots (CP), as shown in Figure 5.8, provided further evidence for the interpretation.

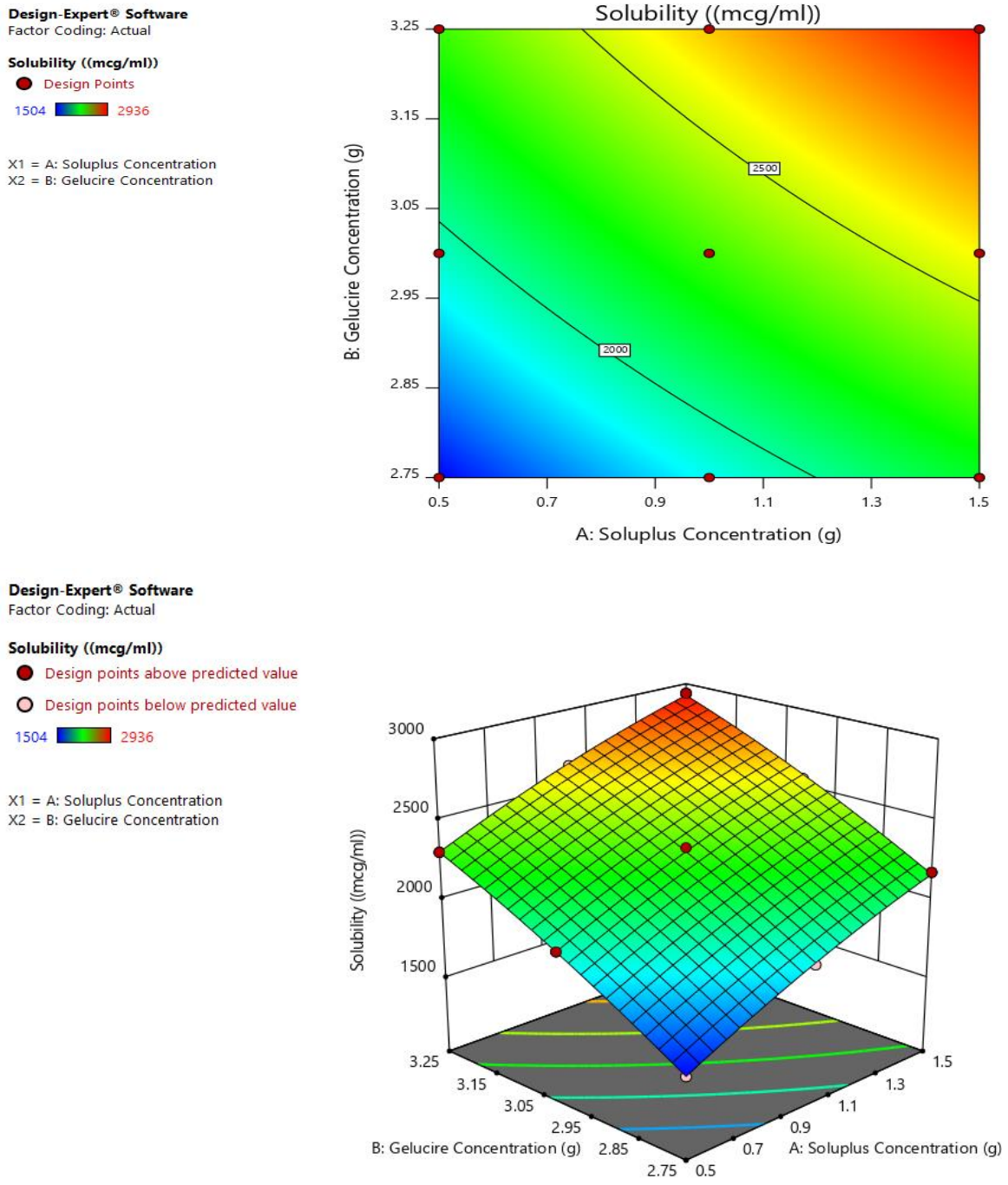


FIGURE 5.8 Contour Plot & Response Surface Plot of POS solubility

About the second response, it was discovered that Q_8 significantly affected the formulation drug release rate. The p-value and the plots shown in Table 5.9 and Fig. 5.9, respectively, suggested that both independent variables were significant. A positive coefficient for A indicates a direct relation between the concentration of Soluplus® and the % CDR of POS. The negative coefficient of B indicated the inverse relastionship between the concentration of Gelucire and the % CDR of POS. Gelucire 43/01 is thought to have retarded drug release from SDD due to its hydrophobic nature.

Q8 = 98.95+1.92 A- 5.74 B – 0.035AB + 0.578A2 – 0.971 B2 + ε……..(5.9)

Q8 Reduced Model = 98.95+1.92 A- 5.74 B + ε……(5.10)

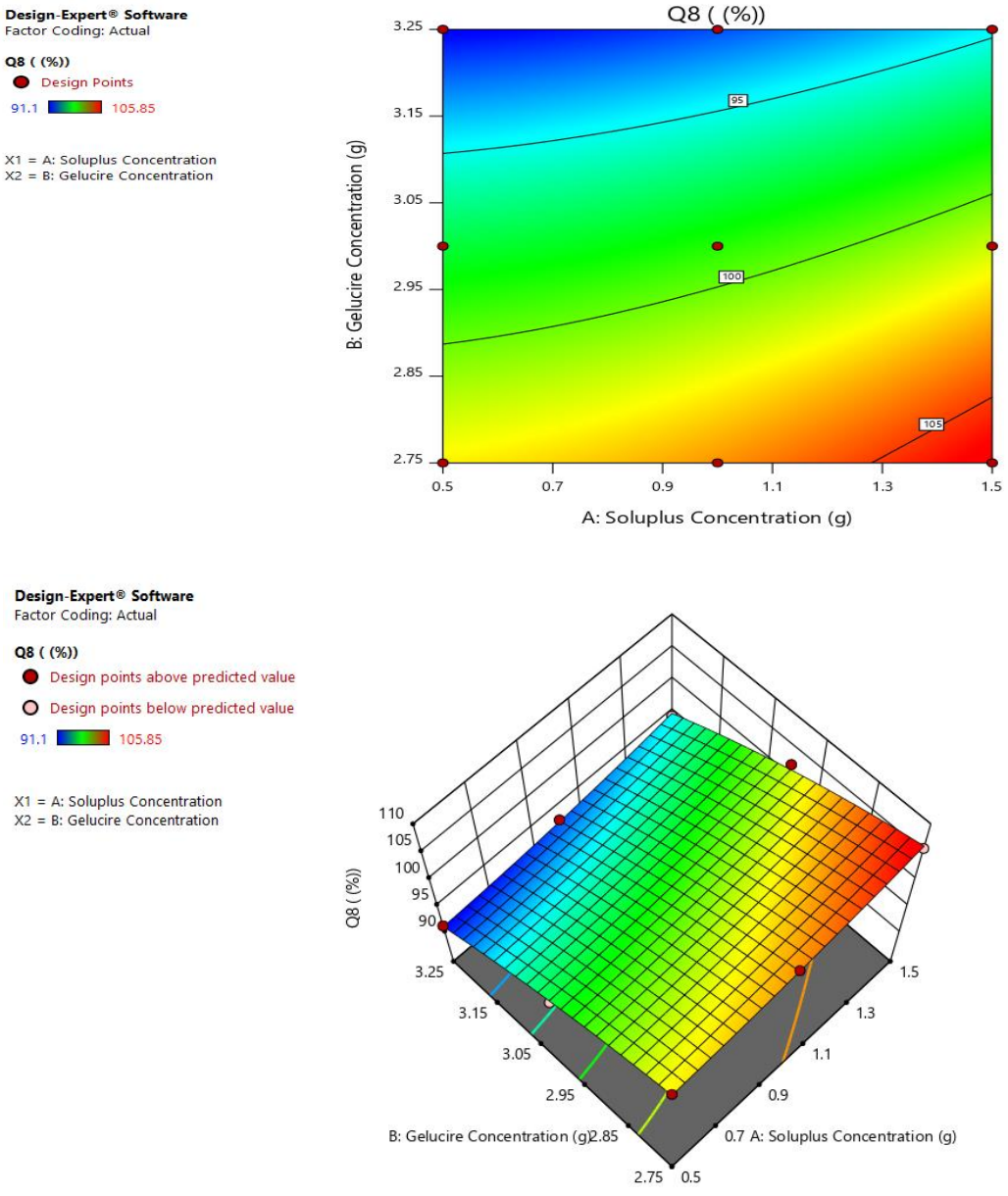


FIGURE 5.9 Contour Plot & Response Surface Plot of Q_8

The present study involved an examination of the impact of various factors on recorded responses as well as the constraints deemed appropriate by the experimenter. For model validation, three check point batches with a desirability score of 1 were specifically examined, as shown in Table 5.9. Fig 5.10 shows the overlay plot that was obtained and used to optimize the design space. The optimization space may be navigated by using the yellow-highlighted region on the graph.

Check point batch 1 (CP 1) was considered optimized batch for total SDD calculation based on 300 mg POS dose and used for the accelerated stability study following ICH Guidelines.

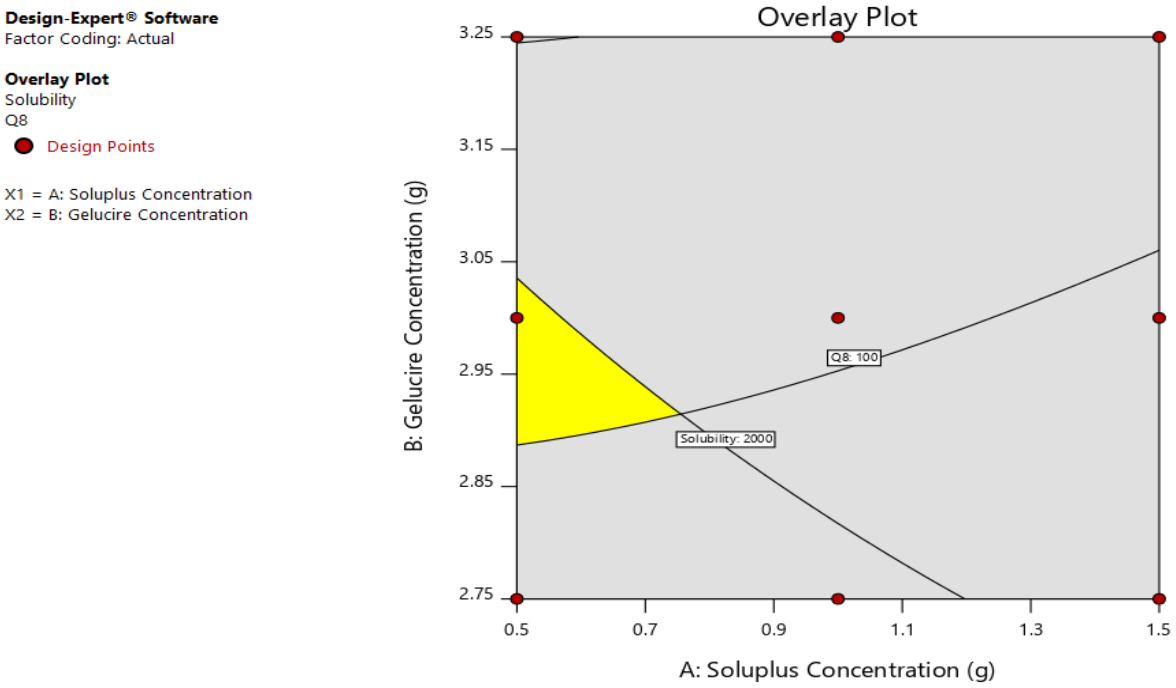


FIGURE 5.10 Overlay Plot for Design Space Optimization of POS SDD

5.2.10 Powder flow properties

Equations outlined in the methodology section were used to evaluate the batch CP1 in terms of its flow parameters. For SDD, the AOR was 29.17±0.54°. The tapped density was found to be 0.48±0.04 g/ml and the bulk density to be 0.45±0.017 g/ml, while the computed CI and Hausner's ratio were 1.09±0.01 and 9.79±1.03, respectively. Based on the Angle of Repose (<30), Hausner's Ratio (1.00–1.11), and Carr's Compressibility Index (5–15%) data, it was anticipated that the SDD would exhibit exceptional flow characteristics appropriate for the capsule formulation.

5.2.11 Differential scanning calorimetry (DSC)

A thermogram was generated using differential scanning calorimetry (DSC) to examine the drug's thermal properties alone and in combination with the polymer in the solid dispersion dosage form (SDD). An overlay of DSC thermograms of the pure POS, carriers and POS SDD are shown in Figure 5.11. The POS thermogram showed that the drug had a crystalline structure, as shown by the sharp endothermic peak that was measured at 170.91°C. Posaconazole API melted at 115 °C, recrystallized at 118 °C, and melted in its crystalline state at 171 °C, according to the DSC curve. The absence of a clear endothermic peak in the SDD was discovered by DSC analysis, indicating that the drug's crystalline structure had changed within the SDD to an amorphous state.

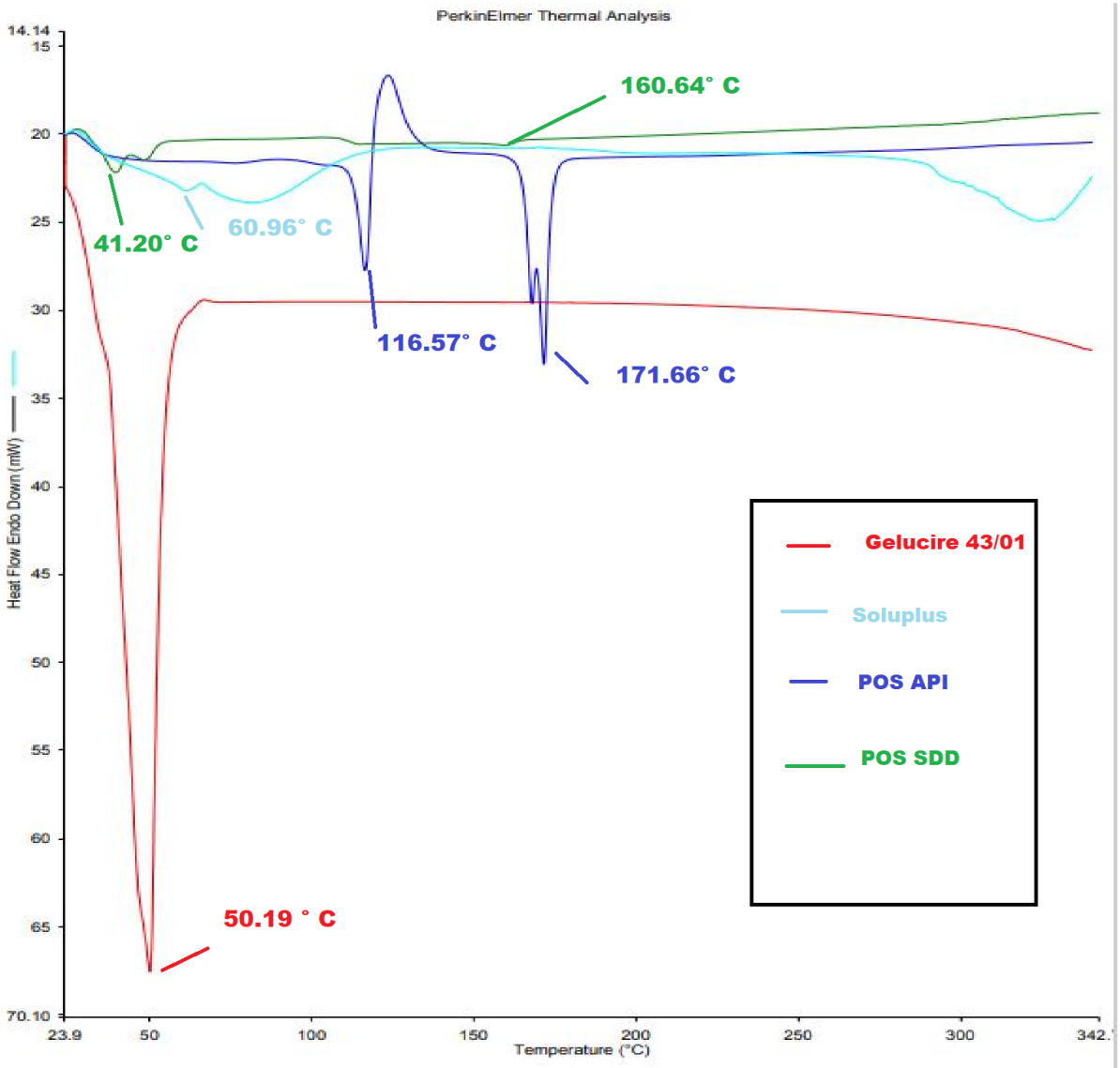
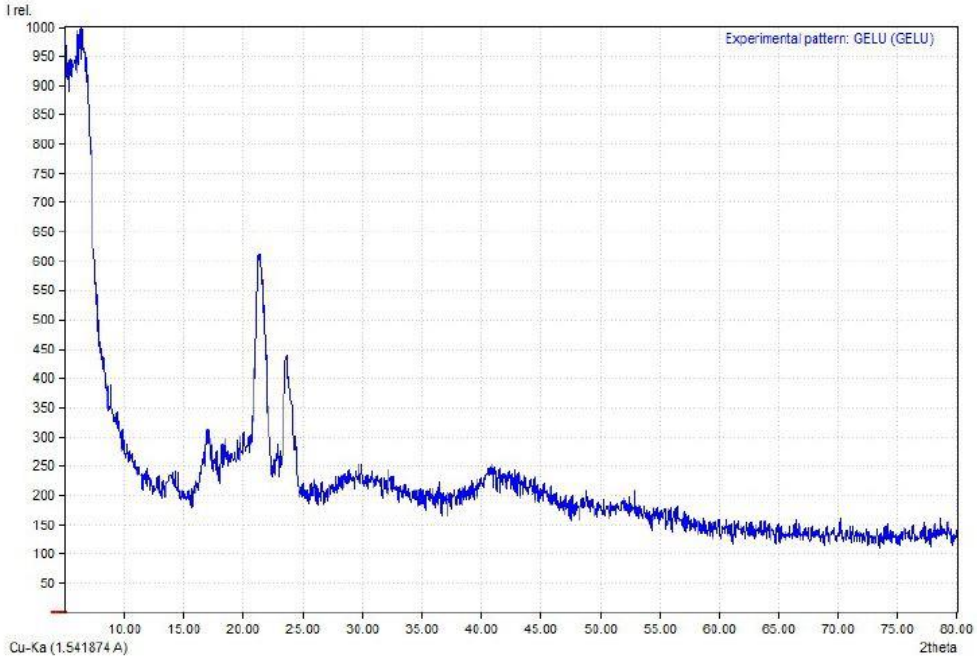


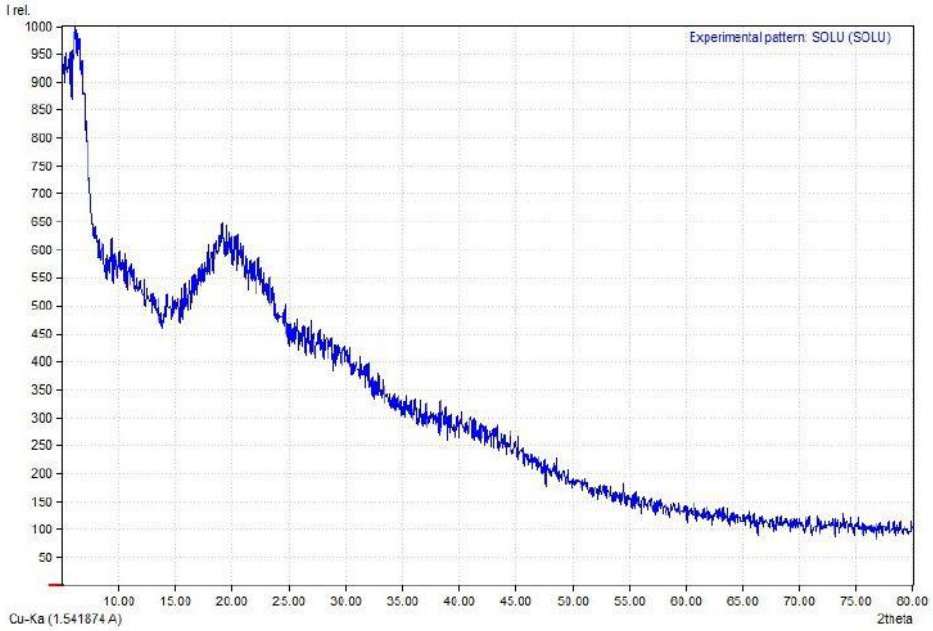
FIGURE 5.11 An overlay of DSC Thermograms of POS API, SD carriers & SDD

5.2.12 Powder X-ray Diffraction (PXRD) Analysis

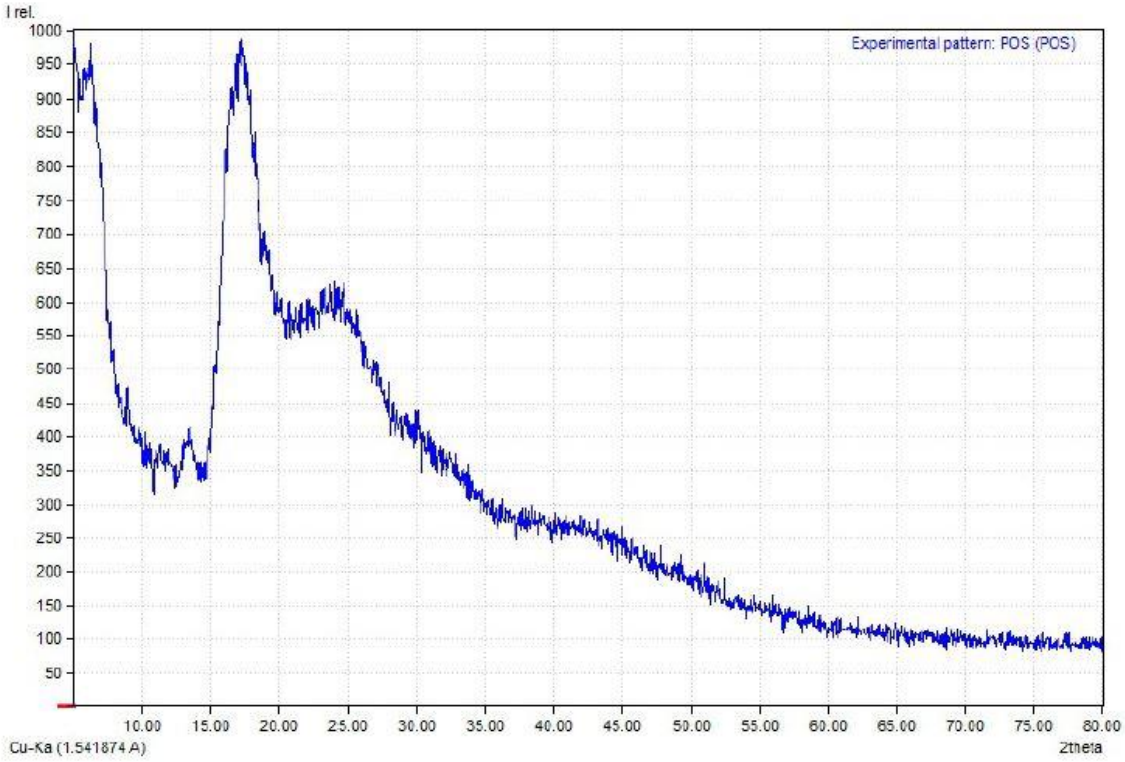
The diffraction pattern of the pure POS and SDD samples is shown in Fig. 5.12. The API showed a discernible peak at 16.33° 2θ value, indicating that it was crystalline. There were no obvious peaks in the SDD's PXRD pattern, which supported the belief that the drug within the SDD had changed from crystalline to amorphous. Enhancing the solubility and dissolution rate of API in SDD was dependent upon the conversion procedure



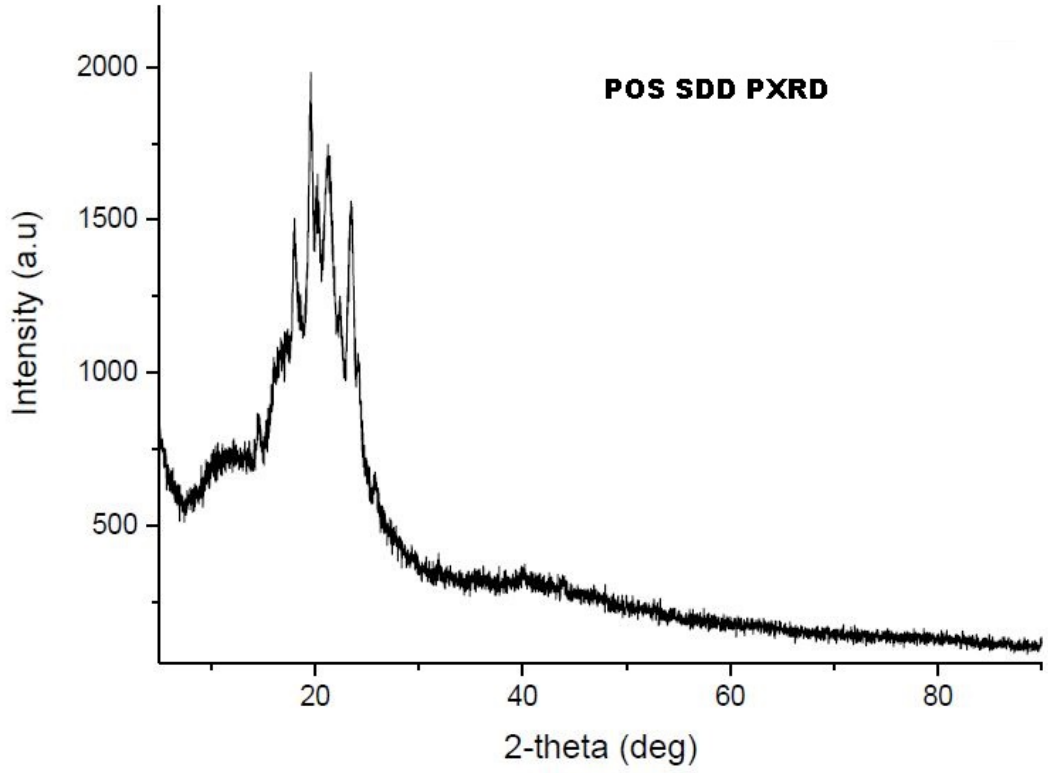
PXRD Scan of Gelucire 43/01



PXRD Scan of Soluplus



PXRD Scan of POS API



PXRD Scan of POS SDD

FIGURE 5.12 PXRD Spectra of POS API, SD carriers & SDD

5.2.13 Particle size measurement

As shown in Fig. 5.13, the optimized batch that was selected underwent evaluation to measure particle size. The results revealed that the Polydispersity Index (PDI) value of 2.357 indicated that the SDD's size distribution was polydisperse. The mean particle size of the batch was determined to be 3023.9 nm, with a standard variation of 1725.1 nm. Dynamic light scattering (DLS) was used to assess the hydrodynamic dimensions of the particle collection; the intensity-weighted mean value (Z-average) was 2067.5 nm. Particle size reduction might lead to a substantial increase in solubility.

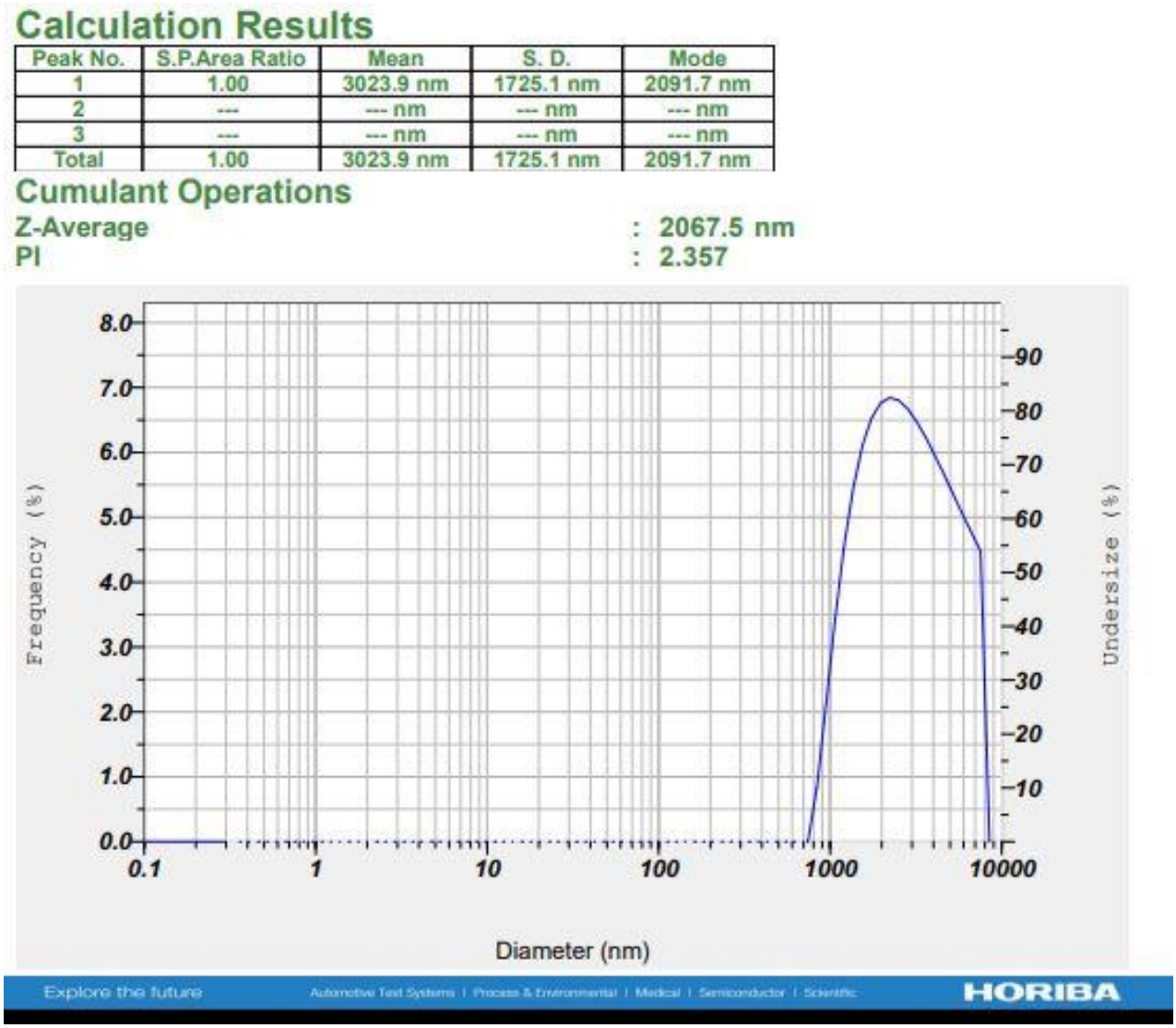


FIGURE 5.13 Particle size analysis of POS SDD

5.2.14 Scanning Electron Microscopy (SEM)

The surface morphology study performed on the optimized batch using scanning electron microscopy (SEM) is shown in Figure 5.14, along with the relevant magnification scale. The spherical form and fibrous texture of the SDD powder were confirmed by the visual representation. The spherical form of SDD may be responsible for the powder's advantageous flow characteristics.

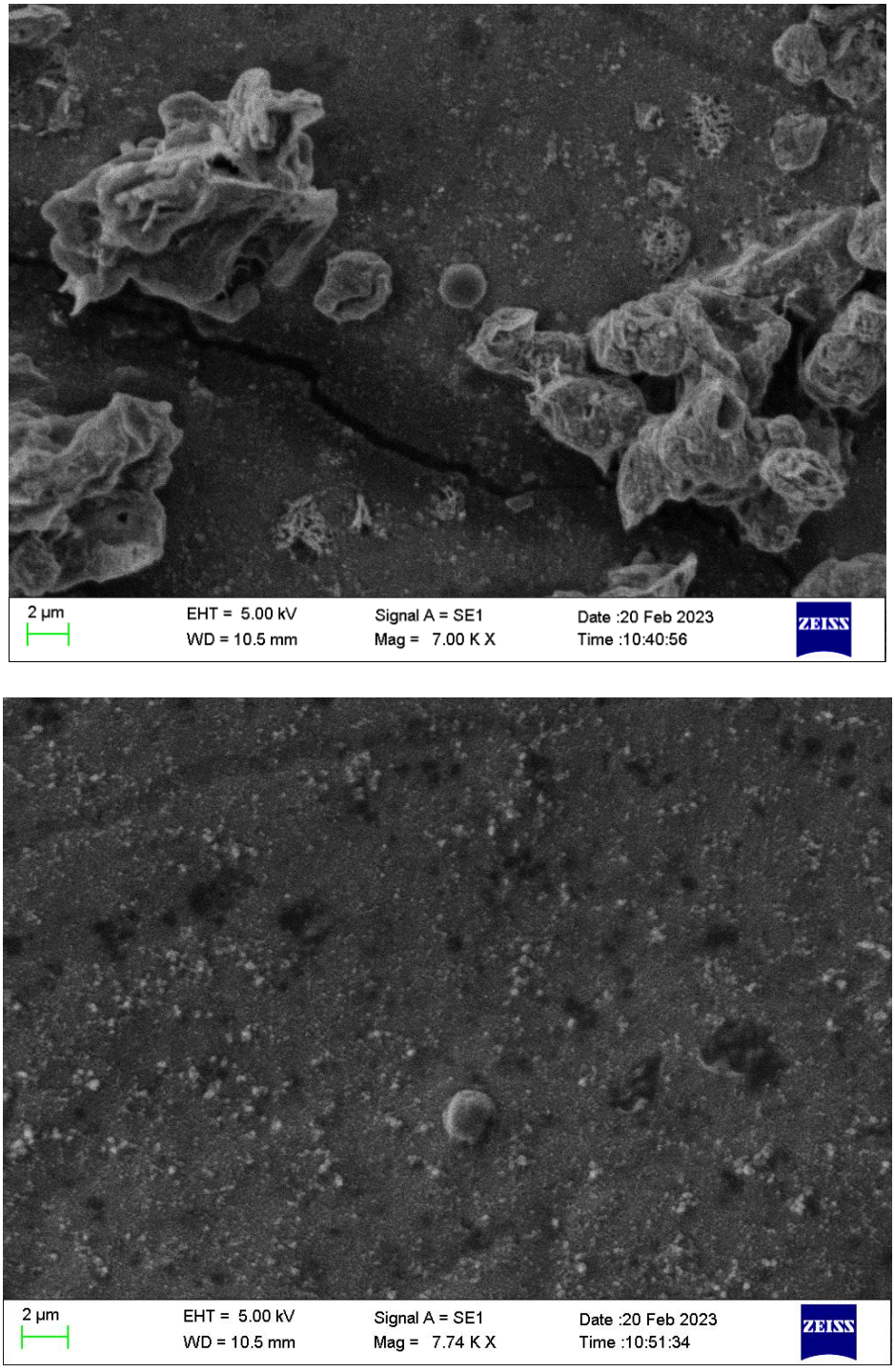
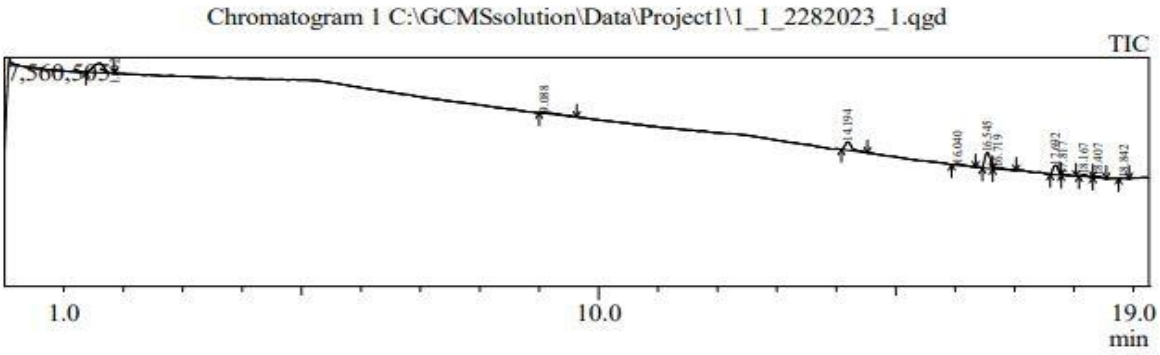


FIGURE 5.14 Surface morphology analysis of POS SDD using SEM

5.2.15 Residual solvent analysis

The chromatogram showed no residual solvent peaks of solvents used in spray drying process viz. DCM or IPA, as per the results of the HS-GC/MS analysis of the SDD sample. This finding led to the conclusion that the formulation is safe to administer. Fig. 5.15 shows all the peaks found during the analysis.



Peak Report TIC

Peak#	R.Time	Area	Height	A/H	Name
1	1.602	3906764	311155	12.56	Nickel tetracarbonyl
2	9.088	840286	36552	22.99	Argon
3	14.194	2135965	268527	7.95	Benzoic acid, 4-methyl-
4	16.040	486525	49499	9.83	Benzenemethanol, 4-(methoxymethyl)-
5	16.545	3236404	519881	6.23	4-Methylethcathinone
6	16.719	654329	55509	11.79	(R)-(-)-N-Ethyl-alpha-methylphenethyl
7	17.692	1956093	308639	6.34	Tapentadol
8	17.817	200656	30338	6.61	Benzoic acid, cyclohexylmethyl ester
9	18.167	331244	53790	6.16	Methylphenidate
10	18.407	297746	49336	6.04	Imidazole, 2,4-diethyl-1-methyl-5-phen
11	18.842	138976	23828	5.83	Butylone, N-acetyl-
		14184988	1707054		

Spectrum

FIGURE 5.15 Residual solvent analysis of POS SDD using HS-GC/MS

5.2.16 Stability Studies

The International Council for Harmonization (ICH) recommendations were used to conduct the accelerated stability testing, as shown in Table 5.10. For all the selected relevant parameters, the end results compared to the original data at time 0 were statistically significant. It was deduced that the oral formulation developed would remain stable for the requisite six months.

TABLE 5.10 Accelerated Stability Study of POS SDD as per ICH Guidelines

Test parameter	Specifications	Initial	1st Month	3rd Month	6th Month
Description	White colored Spray dried powder	White colored Spray dried powder	No change	No change	No change
% Assay (Drug Content)	NLT 90% and NMT 110% of label claim	98.17±0.83	97.41±0.555	96.64±0.445	94.66±0.76
Solubility (µg/ml)	NLT 90% and NMT 110% of label claim	1829±22	1766±16.08	1689±10.54	1604±7.42
% Drug release at 8 hrs	NLT 90% and NMT 110% of label claim	98.5±0.34	96.83±0.976	94.32±0.283	92.47±0.662

5.3 *In-vivo* study of POS SDD

The proposed *in-vivo* Radiographic study in rabbit and the Pharmacokinetic study in male Sprague-Dawley rats were approved by the Institutional Animals Ethics Committee (IAEC) and submitted to the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), New Delhi, India.

5.3.1 Roentgenography in Rabbit for site-specificity

The optimized POS SDD underwent an *in-vivo* gastro-retention study utilizing radiography technique in a healthy New Zealand white rabbit. The radio-opacity of the formulation was procured by substituting 10% of the drug component with barium sulphate (BaSo4) and employing the identical methodology outlined in the methods section [21]. The subject was housed in a solitary enclosure, and the investigations were carried out in a sterile environment within the animal house, which was kept at a consistent temperature of approximately 25 °C. The rabbit underwent a 12-hour fasting period prior to the study, during which it was allowed unrestricted access to water. The radio-opaque POS SDD, which was enclosed in a capsule shell, was administered to the animal via an oral gastric tube while in a fasted state, along with approximately 20 ml of water. The animal was deprived of food and water intake throughout the duration of the research. X-ray images

were captured of the animal's abdominal region in an upright position at various intervals of time, including 0 hours (prior to the administration of the formulation), 2 hours, 5 hours, and 7 hours, as the formulation was intended to have a release profile of 8 hours in a gastric environment [22].

Fig 5.16 displays X-ray images of the rabbit abdomen captured at various time intervals (0, 2, 5, and 7 hours) in order to verify the gastro-retention efficacy of the optimized formulation. Upon the prompt oral administration of POS SDD contained within a capsule shell to the animal, the undamaged capsule shell was distinctly noticeable in the X-ray depiction. After a period of two hours, the capsule shell underwent dissolution, resulting in the emergence of POS SDD powder, which was observed to be floating in the upper region of the rabbit's abdomen. The image obtained after a duration of 5 hours provided evidence that the SDD powder exhibited gastro-retentive characteristics throughout the aforementioned time period. The conclusive image obtained after 7 hours of observation provided evidence that the SDD powder underwent dissolution within a time frame of 5 to 7 hours. This was validated by its absence in the X-ray, thus affirming the previous finding. Therefore, the *in-vitro* drug release results of the optimized formulation were validated by the roentgenography investigation, which confirmed the retention of SDD in the gastric environment for the intended duration of 8 hours.

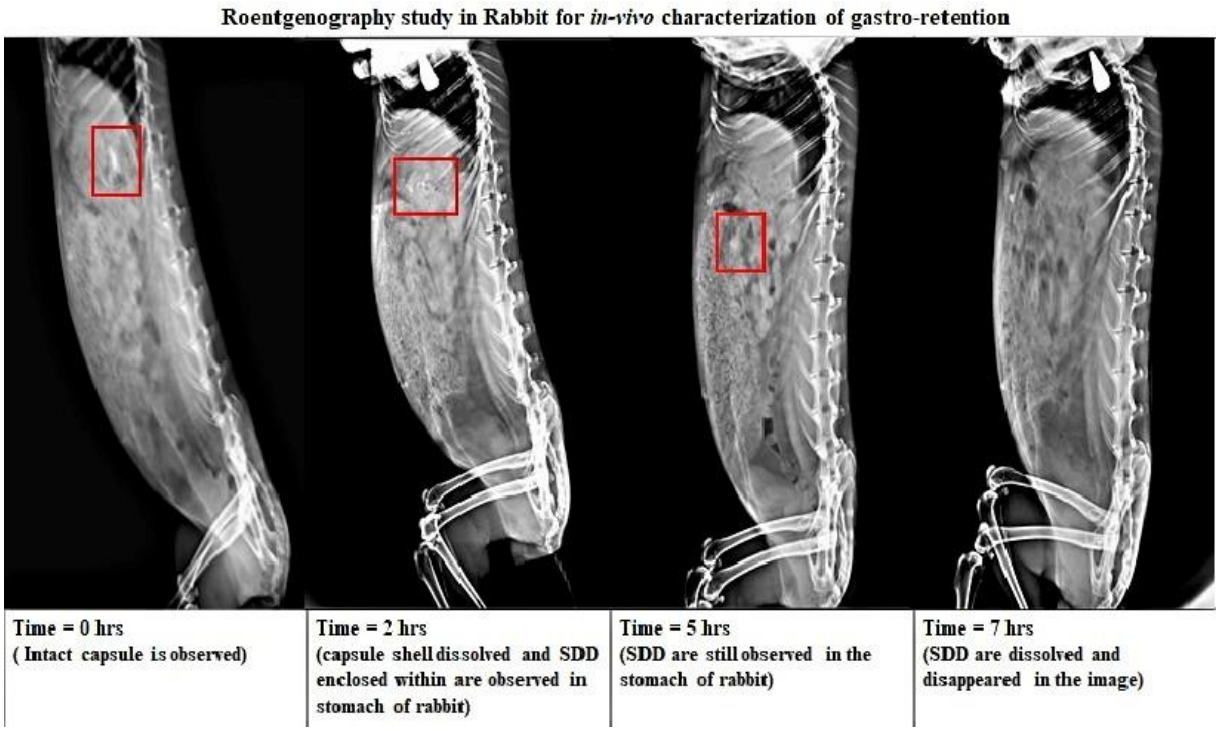


FIGURE 5.16 Roentgenography study of POS SDD in Rabbit

5.3.2 Pharmacokinetic study in Male Sprague Dawley Rats

The study utilized male Sprague-Dawley rats weighing 250 g (ranging from 225-275 g) on the day of experimentation. The rats were procured from the Preclinical Department of Zydus Research Centre, located in Ahmedabad, India. The animals underwent a minimum of 5 days of acclimatization in pairs and were provided with standard feed and unrestricted access to water [23].

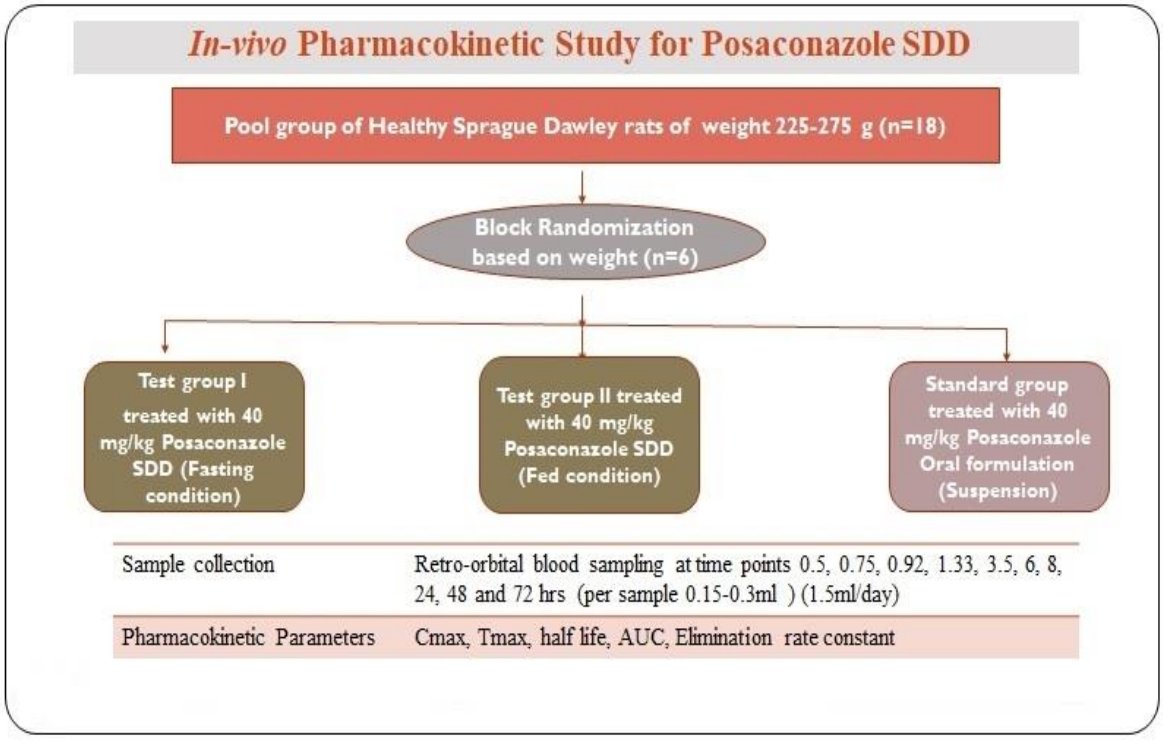


FIGURE 5.17 *In-vivo* Pharmacokinetic study plan of POS SDD

Three experimental cohorts, each consisting of six rats, were utilized for the study, as described in Fig 5.17. Two groups were subjected to the optimized POS SDD in the fasting and fed states, whereas the third group was administered the standard oral formulation (Noxafil suspension) after overnight fasting. The objective was to evaluate the impact of the food on the formulation's bioavailability and compare to a marketed product. Prior to the administration of the test or standard product, a blank blood sample was collected from three experimental groups at time 0 for the purpose of analysing drug plasma concentrations. The experimental animals were orally administered POS SDD/suspension via gavage at a dose of 40 mg/kg of POS. In order to facilitate administration, the POS SDD was dispersed within a solution containing 1% Sodium Lauryl Sulphate (SLS). The oral Noxafil suspension was also administered with 1% SLS for the appropriate comparison of parameters. The study

involved the retro-orbital blood sampling technique (0.15-0.3ml, NMT 1.5ml per day per rat) at specific time intervals of 0.5, 0.75, 0.92, 1.33, 3.5, 6, 8, 24, 48, and 72 hours from both test groups and the third standard group while the rats were under isoflurane anesthesia [24, 25].

The obtained specimens were promptly subjected to centrifugation in Eppendorf tubes at a speed of 5000 rpm for a duration of 10 minutes at a temperature of 4°C immediately after withdrawal, with the aim of segregating the plasma from the blood. The plasma sample featuring supernatant was transferred to a separate tube and subjected to centrifugation with Acetonitrile (ACN) in a 1:2 ratio at 10000 rpm for 5 minutes at 4 °C. This process was carried out to extract the POS in ACN for the purpose of detecting the POS plasma concentration. The plasma concentrations of POS in all the extracted samples were measured by High Performance Liquid Chromatography (Isocratic HPLC, Model: LC-2000) using column C18-5 (Sun Q, 4.6mm ID x 250mm L S/N A00026, Sun International Co., Ltd., Japan) with a flow rate of 1ml/min. The mobile phase used for analysis was ACN: Water (60:40) + 0.1% acetic acid. The calibration curve of POS was prepared in ACN in the range of 10 to 50 ppm from the stock solution of 1000 ppm as shown in Fig 5.18 [2, 26].

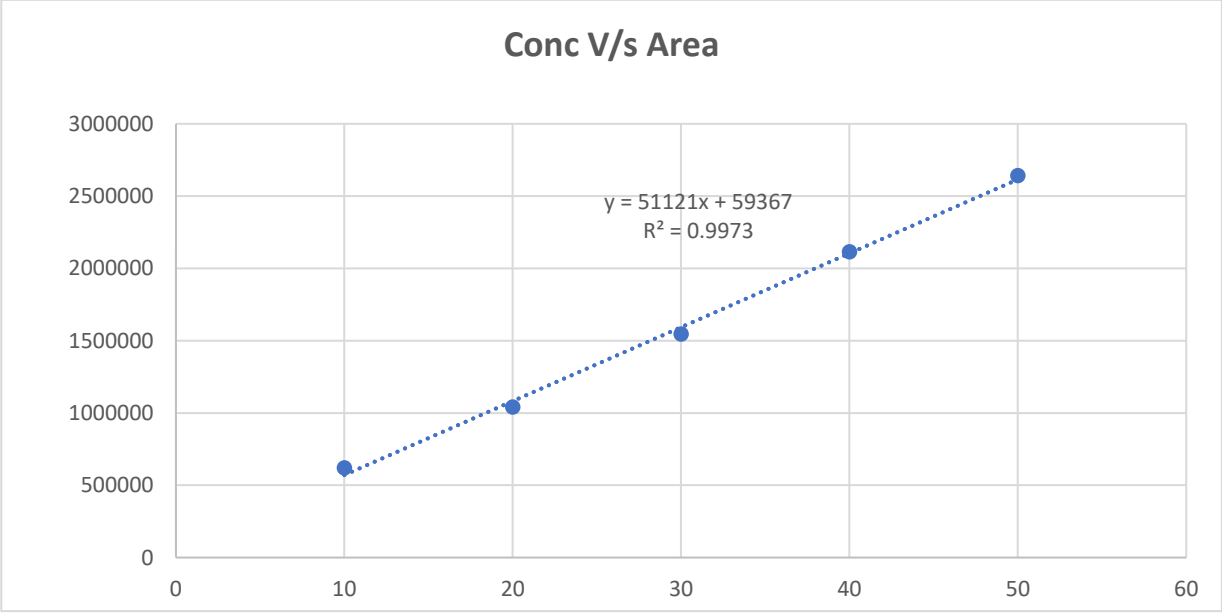


FIGURE 5.18 calibration curve of POS in ACN using HPLC

The plasma concentration-time profiles obtained after oral administration of the POS SDD formulation and Noxafil were subjected to non-compartmental pharmacokinetic analysis using PK Solver Pharmacokinetic software, as shown in Fig 19.

PKSolver 2.0 **Non-Compartmental Analysis of Plasma Data after Extravascular Input (Test- Fasting)**

Time Unit	h	Method	Linear Trapezoidal
Conc Unit	µg/ml	Analyst	user
Dose	10	Date	2023-6-13
Dose Unit	mg	Time	15:00:18

Time	Conc	ln(C)	AUC	AUMC	R	R_adj	Parameter	Unit	Value
0			0	0			Lambda_z	1/h	0.012113606
0.5	1.01477844	0.0146703	0.25369461	0.1268473			t1/2	h	57.22054683
0.75	1.12498914	0.11777338	0.52116556	0.29573869			Tmax	h	1.33
0.92	0.33772846	-1.0855131	0.64549655	0.39386711			Cmax	µg/ml	8.228245093
1.33	8.22824509	2.10757276	2.40152113	2.70099372	0.05768839	-0.1960065	Tlag	h	0
3.5	0.82588029	-0.1913054	12.2252472	17.7110432	0.5632431	0.14655349	Clast_obs/Cmax		0.215175392
6	0.74806178	-0.2902697	14.1926747	26.9347328	0.44839623	-0.0652544	AUC 0-t	µg/ml*h	170.5984123
8	1.42757376	0.35597633	16.3683103	42.8436935	0.04994598	-0.4962581	AUC 0-inf_obs	µg/ml*h	316.7576821
24	3.16680774	1.15272406	53.1233622	742.235499	-0.9988376	0.99535307	AUC 0-t/0-inf_obs		0.538577032
48	2.42613196	0.8862982	120.238639	3051.72813			AUMC 0-inf_obs	µg/ml*h^2	28568.08395
72	1.77051586	0.57127095	170.598412	5978.90585			MRT 0-inf_obs	h	90.18908006
							Vz/F_obs	(mg)/(µg/ml)	2.606149868
							Cl/F_obs	(mg)/(µg/ml)/h	0.031569874

FIGURE 5.19 (a) Non-compartmental Analysis of Test group in Fasting condition

PKSolver 2.0 **Non-Compartmental Analysis of Plasma Data after Extravascular Input (Test-Fed)**

Time Unit	h	Method	Linear Trapezoidal
Conc Unit	µg/ml	Analyst	user
Dose	10	Date	2023-6-13
Dose Unit	mg	Time	19:00:20

Time	Conc	ln(C)	AUC	AUMC	R	R_adj	Parameter	Unit	Value
0	0		0	0			Lambda_z	1/h	0.016262038
0.75	0.27501987	-1.2909119	0.10313245	0.07734934			t1/2	h	42.62363471
1.33	0.87067903	-0.1384819	0.43538513	0.47298706			Tmax	h	24
3.5	1.12788561	0.12034474	2.60382777	6.01256604			Cmax	µg/ml	1.884443701
6	0.84306601	-0.17071	5.06751729	17.2700607			Tlag	h	0
8	1.76559186	0.56848597	7.67617516	36.4531916			Clast_obs/Cmax		0.458141203
24	1.8844437	0.63363266	36.8764597	511.264261	-0.9499998	0.80499932	AUC 0-t	µg/ml*h	108.0786558
48	1.59286567	0.4655347	78.6041721	1971.47467			AUC 0-inf_obs	µg/ml*h	161.1680218
72	0.8633413	-0.1469452	108.078656	3634.89219			AUC 0-t/0-inf_obs		0.670596155
							AUMC 0-inf_obs	µg/ml*h^2	10721.94596
							MRT 0-inf_obs	h	66.52650962
							Vz/F_obs	(mg)/(µg/ml)	3.815453321
							Cl/F_obs	(mg)/(µg/ml)/h	0.062047048

FIGURE 5.19 (b) Non-compartmental Analysis of Test group in Fed condition

PKSolver 2.0 **Non-Compartmental Analysis of Plasma Data after Extravascular Input (Standard Noxafil)**

Time Unit	h	Method	Linear Trapezoidal
Conc Unit	µg/ml	Analyst	user
Dose	10	Date	2023-6-14
Dose Unit	mg	Time	15:07:15

Time	Conc	ln(C)	AUC	AUMC	R	R_adj	Parameter	Unit	Value
0	0		0	0			Lambda_z	1/h	0.014974784
0.5	0.11	-2.2072749	0.0275	0.01375			t1/2	h	46.28762596
0.75	0.35	-1.0498221	0.085	0.0534375			Tmax	h	24
0.92	0.58	-0.5447272	0.16405	0.121106			Cmax	µg/ml	3.16
1.33	0.94	-0.0618754	0.47565	0.486785			Tlag	h	0
3.5	1.26	0.23111172	2.86265	6.628102			Clast_obs/Cmax		0.487341772
6	2.55	0.93609336	7.62515	31.265602			AUC 0-t	µg/ml*h	163.55515
8	1.78	0.57661336	11.95515	60.805602			AUC 0-inf_obs	µg/ml*h	266.3946998
24	3.16	1.15057203	51.47515	781.445602	-0.9967396	0.98697983	AUC 0-t/0-inf_obs		0.613957973
48	2.32	0.84156719	117.23515	3027.8456			AUMC 0-inf_obs	µg/ml*h^2	19966.68812
72	1.54	0.43178242	163.55515	5694.7256			MRT 0-inf_obs	h	74.9515217
							Vz/F_obs	(mg)/(µg/ml)	2.506766407
							Cl/F_obs	(mg)/(µg/ml)/h	0.037538284

FIGURE 5.19 (c) Non-compartmental Analysis of Std group

FIGURE 5.19 Non-compartmental Analysis using PK-Solver

The plasma concentration versus time profiles for each group were generated and analyzed to detect the maximum concentration of the drug in the plasma (C_{max}) and the corresponding time at which this maximum concentration was reached (T_{max}). The Ke value was derived from the slope of the straight concentration-time curve using the method of least squares. The AUC_{0-72} was calculated using the linear trapezoidal rule to determine the area under the plasma concentration curve for each time interval from zero to 72 hours. The $AUC_{0-\infty}$ was determined via extrapolation to infinity utilizing the formula ($AUC_{0-72} + C_{72}/Ke$), where C_{72} represented the plasma concentration at 72 hours. Likewise, the $AUC_{0-\infty}$/dose was computed for each animal, normalized by dose. The estimation of the elimination half-life ($t_{1/2}$) was conducted from elimination rate constant. The calculation of oral clearance (Cl/F) involved dividing the dose by $AUC_{0-\infty}$, while the oral volume of distribution (Vd/F) was determined by dividing the oral clearance by the elimination rate constant (Ke) [27].

After oral administration of 40 mg/kg of POS to the rat groups, plasma concentrations increased with respect to time. The different pharmacokinetic parameters obtained are depicted in Table 5.11. The overlay plot of plasma concentration time profiles of all 3 groups generated using GraphPad Prism 8, shown in Fig 5.20, depicted two C_{max} and t_{max} values

after oral administration, as mentioned in Table 5.11 due to the enterohepatic recirculation of POS.

TABLE 5.11 Pharmacokinetic Data Analysis using PK Solver in Sprague-Dawley Rats

PK Solver 2.0 Non-Compartmental Analysis of Plasma Data after Extravascular Input			
Time Unit: h		**Dose**: 10 mg	
Conc Unit: **µg/ml**		**Method**: **Linear Trapezoidal**	
Parameter	**Fasting (mean±SEM)**	**Fed (mean±SEM)**	**Noxafil (mean±SEM)**
Ke (1/h)	0.011±0.001	0.019±0.017	0.019±0.002
$t_{1/2}$ (h)	62.194±3.521	37.565±3.233	37.899±4.429
t_{max1} (h)	1.330±0	3.500±0	6.000±0
C_{max1} (µg/ml)	8.513±0.165	1.163±0.0245	2.073±0.247
t_{max2} (h)	24 ±0	24 ±0	24 ±0
C_{max2} (µg/ml)	2.994±0.092	1.838±0.03	2.887±0.151
AUC $_{0\text{-}t}$ (µg/ml*h)	161.867±5.413	103.769±2.47	144.32 ±10.084
AUC $_{0\text{-}inf\_obs}$ (µg/ml*h)	314.021±1.638	145.322±9.69	212.101±28.408
MRT $_{0\text{-}inf\_obs}$ (h)	96.498±4.528	59.576±4.49	63.355±6.17
Vz/F_obs (Cl/F/Ke) (mg)/(µg/ml)	2.858±0.164	3.719±0.078	2.589±0.041
Cl/F_obs (Dose/AUC 0-inf) (mg)/(µg/ml)/h	0.032±0.0001	0.069±0.004	0.049±0.006

The higher value of C_{max1} of the developed POS SDD (8.513±0.165 µg/ml) as compared to the marketed oral formulation (2.073±0.247 µg/ml) confirmed the proposed solubility improvement of ternary SDD. The t_{max2} value of all 3 groups treated was 24 hrs, with the highest $t_{1/2}$ value in the developed formulation in the fasting state. $AUC_{0-\infty}$ value (314.021±1.638 µg/ml*h) was also highest for POS SDD in the fasting state, leading to the relative bioavailability of 148.9 % compared to Noxafil oral suspension. The estimation of the relative bioavailability of POS formulation was executed using the following equation.

$$\textbf{Relative bioavailability (Fr)} = \left[\frac{AUC_{test}}{AUC_{std}} * \frac{Dose_{std}}{Dose_{test}}\right] * 100 \text{.....(5.11)}$$

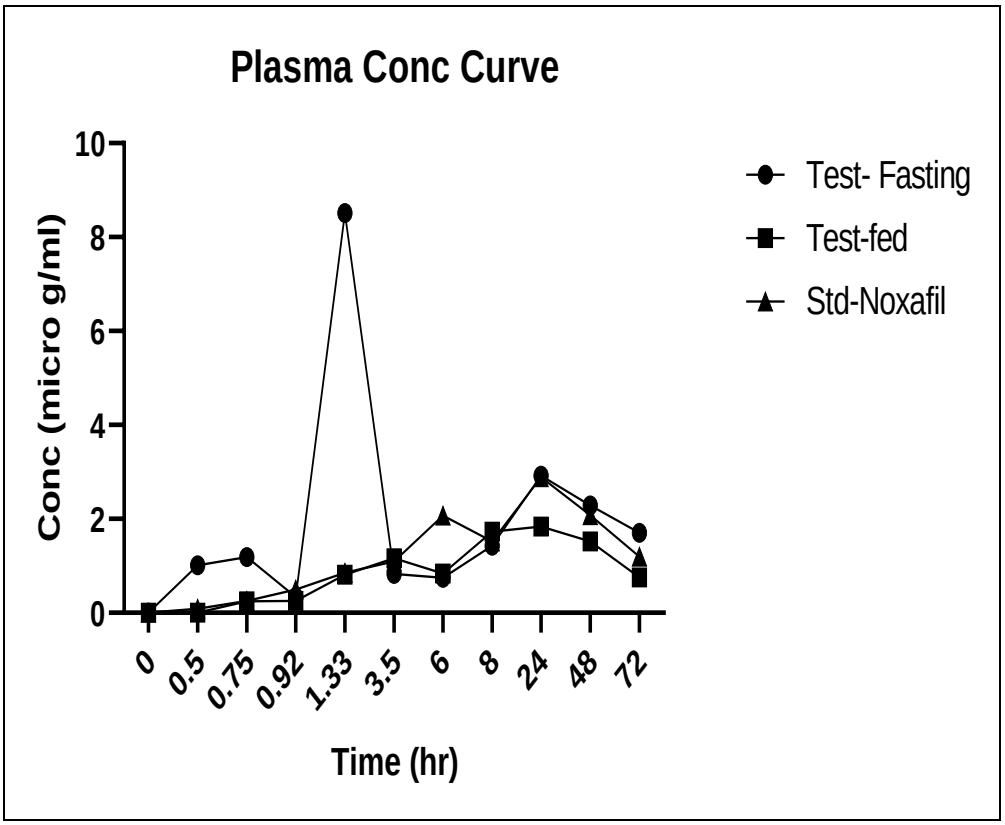
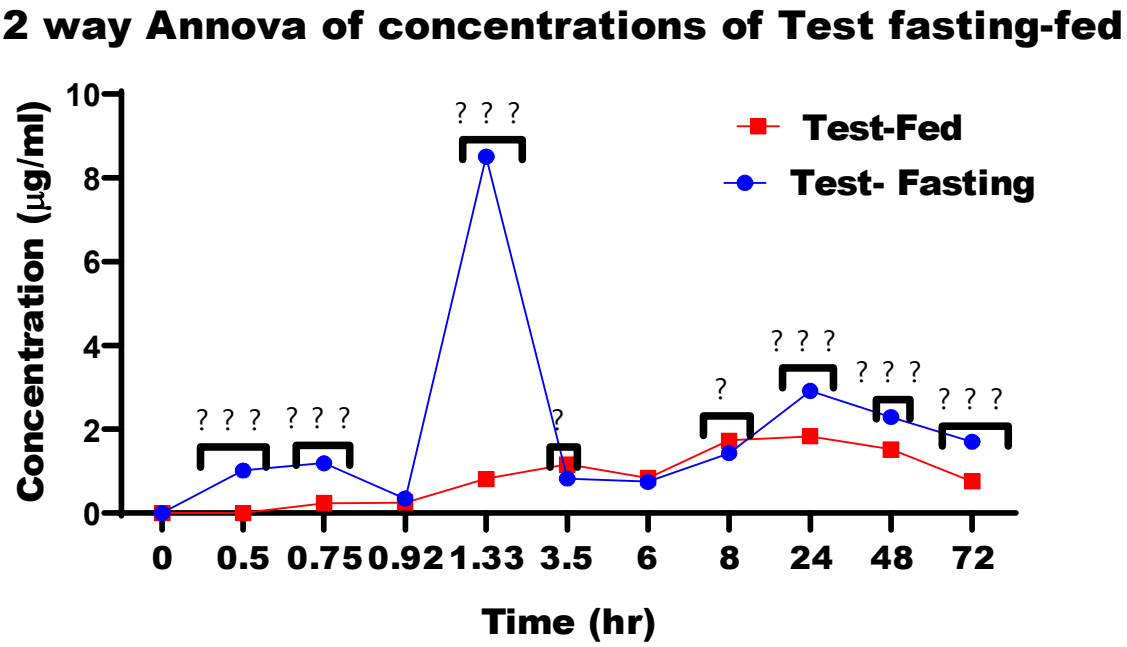
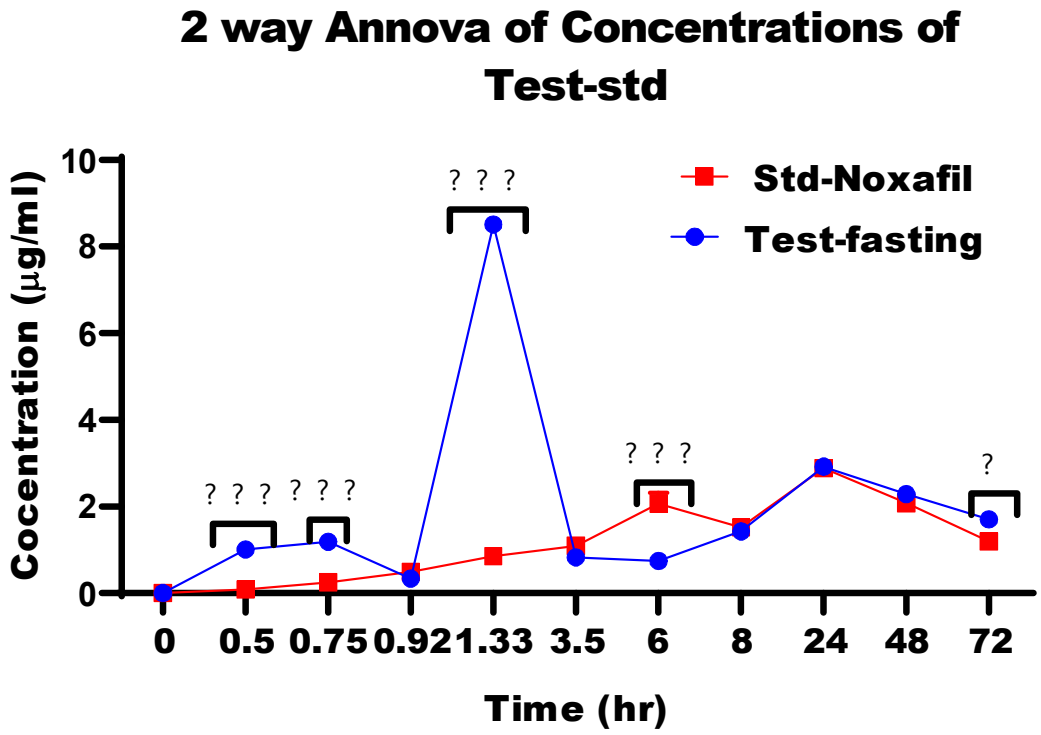
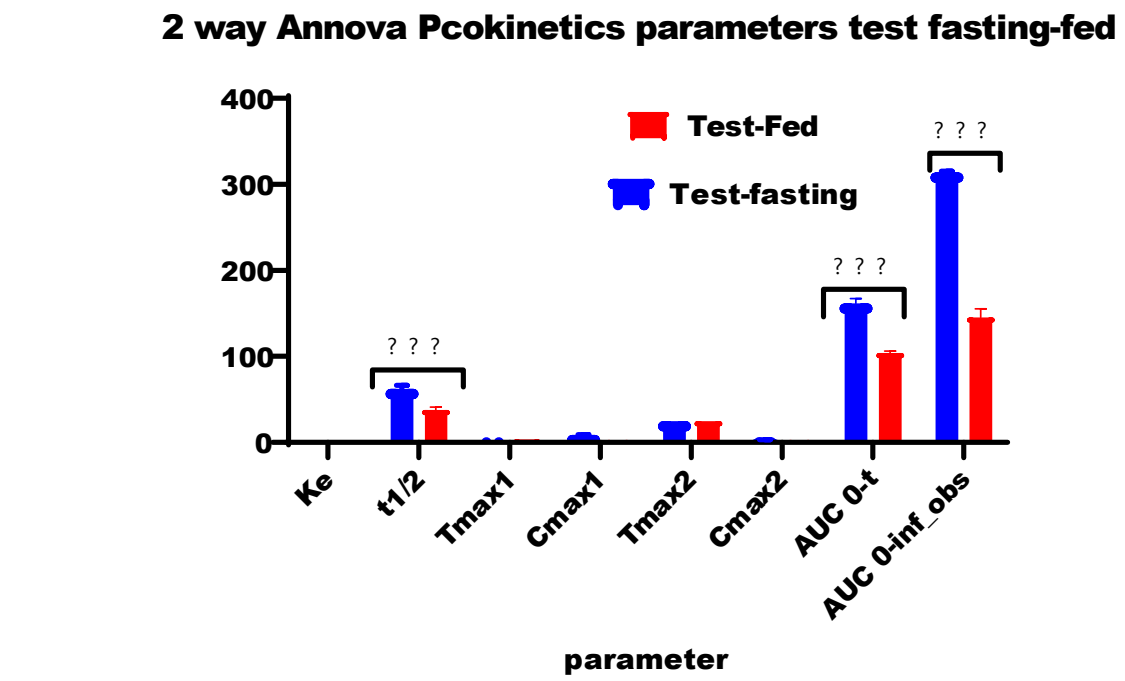


FIGURE 5.20 The overlay plot of plasma concentration-time profiles with GraphPad Prism 8

The data derived were checked for statistical significance using the Two-way ANOVA test, followed by Sidak's multi-comparison test with $\alpha = 0.05$ and P value <0.05. The comparison of concentration values at each time points in the plasma-concentration curve and comparison of each derived pharmacokinetic parameter between test and standard marketed formulations as well as between the fasting and fed states of the developed formulation were performed using GraphPad Prism 8. The curves generated in GraphPad prism 8 based on the data obtained from statistical analysis are depicted in Fig 5.21.


2 way Annova of concentrations of Test fasting-fed
Concentration (µg/ml)
Time (hr)
Test-Fed
Test- Fasting
0
0.5
0.75
0.92
1.33
3.5
6
8
24
48
72


2 way Annova of Concentrations of Test-std
Cocentration (µg/ml)
Time (hr)
Std-Noxafil
Test-fasting
0
0.5
0.75
0.92
1.33
3.5
6
8
24
48
72



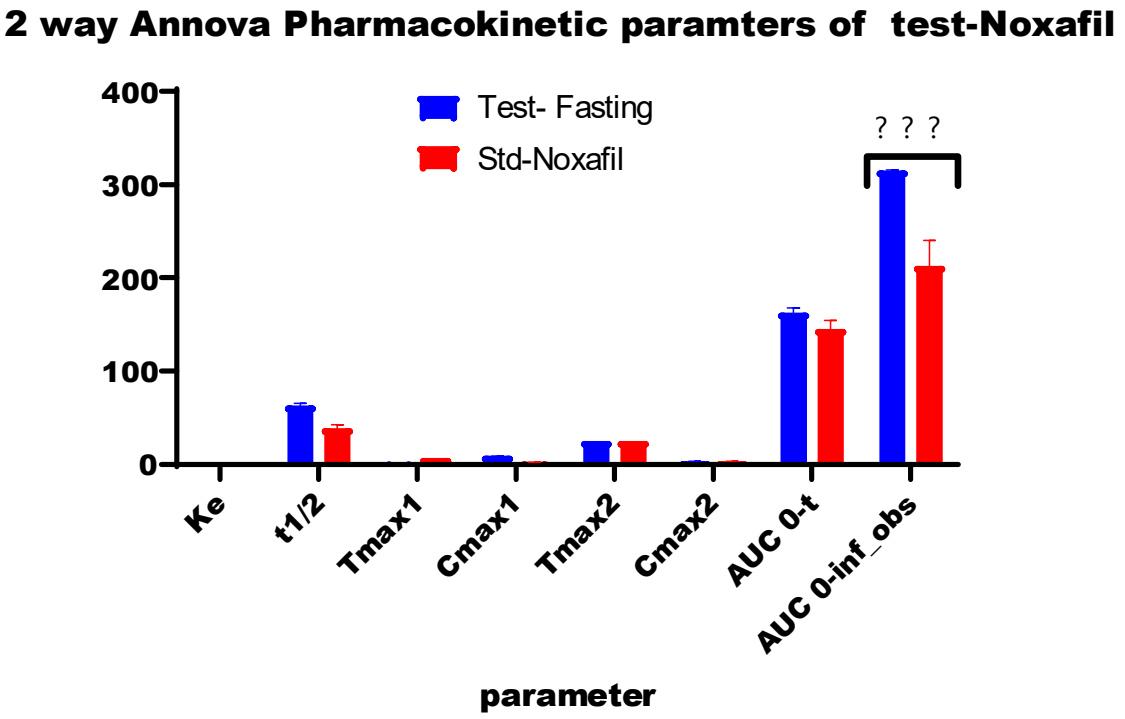


FIGURE 5.21 Two-way ANOVA studies of POS SDD

The study concluded that the test product showed significant difference in $AUC_{0\text{-}inf}$ value in the fasting group as compared to the standard group of Noxafil after overnight fasting. Whereas, the same statistical analysis performed between fed and fasting state administration of developed product concluded that the test product showed significant

difference in half life and AUC values, because in fasting condition the gastric pH is acidic allowing higher solubility of weakly basic drug, enabling higher concentration and AUC values compared to fed conditions. The ANOVA study performed for the significant difference in the concentration values at each time point summarized that the concentration of test product in fasting state is significantly higher at time points 0.5, 0.75, 1.33 & 6 hrs., compared to standard product Noxafil oral suspension; whereas the concentration of test product in fasting state is significantly higher at time points 0.5, 0.75, 1.33, 24, 48 & 72 hrs., compared to fed state administration. The two-way ANOVA studies performed for comparison are shown in Fig 5.21.

This supports the rationale for the research and addresses a known limitation of Noxafil oral suspension, which is the variable bioavailability caused by the precipitation of weakly basic API in the intestinal pH due to the significant increase in pH from 1.2 to >5 during gastrointestinal transit. It is recommended that Noxafil be administered under fed conditions in order to minimize pH variability. The gastro-retentive POS SDD that was created exhibited greater bioavailability during fasting conditions in comparison with fed conditions, in contrast to the Noxafil suspension. This can be attributed to the fact that weakly basic drugs are more soluble and dissolve more readily in an acidic environment compared to an alkaline pH. Continuous maintenance of this acidic environment may prove beneficial in reducing the variability in bioavailability.

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CHAPTER 6

Development of Esomeprazole Delayed-release Formulation

6.1 Materials & Methodology

The samples of Esomeprazole Magnesium Trihydrate (ESM) and SD carrier HPMCAS-MF were generously provided in a pure state by Amneal Pharmaceuticals Pvt. Ltd., located in Ahmedabad, India. The additional excipient, talc, which served as an adsorbent, was procured from SD Fine Chemicals. The organic solvents, methanol and acetone, which were used as the solvent phase for spray drying, were of HPLC Grade and were obtained from Purvi Enterprises located in Ahmedabad, India. The purified water used for pharmaceutical purposes in the solvent phase was sourced from the distillation facility located inside the university campus.

6.1.1 UV-VIS Spectroscopy

UV-VIS spectrophotometer (UV-1800; Shimadzu, Kyoto, Japan) was used to quantify ESM in methanol and simulated GIT dissolution media. Using Beer-Lambert plots, the standard calibration curve was generated using known ESM concentrations in methanol, 0.1N HCl, and PBS (Phosphate Buffer Solution) pH 6.8 at 301 nm, 278 nm, and 300 nm, respectively. The methanol calibration curve was utilized to determine % drug content and the physiological media were used to determine the solubility and % drug release in the GIT. The concentration range utilised was between 5 to 25 µg/ml. For the measurement of ESM, a linear ($R^2 = 0.998$) standard curve was prepared in each solvent [1].

6.1.2 Fourier-transform infrared spectroscopy (FTIR)

Prior to the finalization of components for the development of SDD, the physical mixture of ESM and carrier HPMCAS-MF in a 1:1 ratio was exposed to a compatibility study using FTIR instrument with a 400-4,000 cm^{-1} scanning range (IR Prestige-21, Shimadzu, Japan).

This study compared the compatibility of the same mixture following a one-month stability study. The mixture was mixed with 500 mg dry potassium bromide (KBr). Using a hydrostatic press, powder combinations were compacted into tiny discs using pressure varying between 68.5 and 103.4 MPa [2, 3].

6.1.3 Preparation of ESM SD by spray drying technique

a. Selection of solvent system for spray drying

Esomeprazole is soluble in solvents DCM (Dichloromethane), Methanol, ethanol, DMF (Dimethyl Formamide) [4, 5]; whereas HPMCAS is soluble in DCM, Acetone and Methanol [6]. Both API and Carrier are soluble in methanol, but HPMCAS is precipitated from methanol in the presence of ESM. Hence Acetone was used to keep the carrier dispersed in the solvent phase which was further stabilized with water due to the hydrophilic nature of HPMCAS. The final solvent phase utilized for spray drying was methanol: water: Acetone (1:2:7).

b. Selection of Process Parameters for spray drying

Based on the pressure of compressor attached with spray dryer, the maximum compression air pressure obtained was 2 kg/cm^2. Based on the review of literature and the fact that decrease in the aspiration rate may reduce yield, the compression pressure was selected as 2 kg/cm^2 leading to atomization pressure of 30 PSI. The inlet temperature was varied from 80 to 120^{o}C to allow rapid evaporation of solvent and procure free flowing product and its effect was studied on the %yield of SD. The corresponding outlet temperature obtained was in range of 60-100^{o}C. The feed flow rate was kept 5 ml/min to allow sufficient exposure time to the droplets to convert to solid particles devoid of moisture [7, 8]

c. Preliminary Batches of ESM SDD

Using a magnetic mixer, ESM and HPMCAS-MF were mixed into a solution of methanol, water, and acetone (1:2:7). The resulting mixture was sprayed dried while a magnetic mixer kept moving it (30). For spray drying, a mini spray dryer (Cronimach Machinary, model no. CRO-MSD161, evaporation capacity: 1 L/hr H2O) was used in a co-current mode, which means that the feed air and drying air went in the same direction. The atomization air

pressure was 2 kg/cm^2 and the aspirator speed was 65 m^3/hr. The dryer comprises of Peristaltic type pump with two-fluid nozzle of 0.7 mm diameter. ESM and HPMCAS-MF were dissolved in a solvent system comprising of methanol: water: Acetone (1:2:7) using magnetic stirrer. The ratio of API: Carrier was selected 1:1 for the preliminary trials. The PB1 (Preliminary Batch 1) comprising of only API & carrier was sticky leading to the incorporation of talc as anti-adherent in subsequent batches to reduce the moisture content of finished product. In the subsequent three PB (PB3, PB4 and PB5) the inlet temperature was varied to determine its effect on the % yield and to finalize a value for further formulation batches [5, 9–11]. The preliminary batches are described in Table 6.1

TABLE 6.1 Preliminary Batches for Spray Drying of ESM SDD

Formulation Components	**PB1**	**PB2**	**PB3**	**PB4**	**PB5**
ESM	0.5 g	0.5 g	1g	1g	1g
HPMCAS (1:1)	0.5 g	0.5 g	1g	1g	1g
Talc	-	1% W/W	1% W/W	1% W/W	1% W/W
Methanol: Water: Acetone (1:2:7)	q.s. 500 ml	q.s. 500 ml	q.s. 500 ml	q.s. 500 ml	q.s. 500 ml
Inlet Temperature	100°C	100°C	80°C	100°C	120°C
Outlet Temperature	80°C	80°C	60°C	80°C	100°C
Constant Process Parameters of Spray Dryer 1. Feed Flow Rate: 5 ml/min 2. Compression Pressure: 2 kg/ cm^2 3. Atomization pressure: 30 PSI					

6.1.4 Experimental design

a. Screening the influential factors based on preliminary trials:

The final formulation components and the significant process parameters like Feed Flow rate (FFR) and inlet temperature were considered for optimization based on the review of literature and the range for proceeding optimization design was confirmed based on the preliminary trials depicted in Table 6.1. The outlet temperature displayed in spray dryer was based on the cumulative effect of inlet temperature, aspirator setting and FFR [12, 13] .

b. Optimization of process parameters and formulation variables utilizing Box Behnken design (BBD):

Based on the independent variables and their levels required for the optimization process, Response surface-based DOE (Design of Experiment) known as Box Behnken Design was selected for establishing quadratic model of analysis [14, 15]. As suggested by the design expert 13 with single centre point replication, 15 experiments were conducted wherein formulation variable Esomeprazole: HPMCAS-MF ratio (X1) and process parameters like FFR (X2) and Inlet temperature (X3) were considered as independent variables with appropriate low and high levels along with centre point. The selected dependant variables for the product optimization were % yield, solubility (mg/ml) of API and % cumulative drug release (CDR) in gastric pH in 2 hours (Q_2). Table 6.2 depict the experimental runs generated utilizing BBD as per Design Expert 13 (StatEase, Minneapolis, MN).

TABLE 6.2: Box-Behnken Design (BBD) Matrix

Experimental Batch	X1	X2	X3	X1 ESM: HPMCAS-MF Ratio	X2 FFR (ml/min)	X3 Inlet temperature (°)
B1	-1	-1	0	1:1	4	100
B2	+1	-1	0	1:3	4	100
B3	-1	+1	0	1:1	8	100
B4	+1	+1	0	1:3	8	100
B5	-1	0	-1	1:1	6	80
B6	+1	0	-1	1:3	6	80
B7	-1	0	+1	1:1	6	120
B8	+1	0	+1	1:3	6	120
B9	0	-1	-1	1:2	4	80
B10	0	+1	-1	1:2	8	80
B11	0	-1	+1	1:2	4	120
B12	0	+1	+1	1:2	8	120
B13	0	0	0	1:2	6	100
B14	0	0	0	1:2	6	100
B15	0	0	0	1:2	6	100

INDEPENDENT VARIABLES IN BBD				
SR NO	**VARIABLES**	**LEVELS OF VARIABLES**		
		-1	**0**	**+1**

1	**ESM: HPMCAS-MF Ratio**	1:1	1:2	1:3
2	**Feed flow rate (FFR) (ml/min)**	4	6	8
3	**Inlet temperature of Spray dryer (°)**	80	100	120

DEPENDENT VARIABLES IN BBD	
SR NO	**RESPONSE**
1	**% Yield**
2	**Solubility (mg/ml)**
3	**% CDR in 0.1 N HCl in 2 hours (Q_2)**

c. Validation of experimental design:

Based on the constraints selected for the independent and dependent variables, three check point batches with desirability 1 were selected to navigate the design space generated for optimization. The model was validated for accuracy by comparing the % error between the models predicted values and observed values for the selected dependent variables [16].

d. Determination of optimized batch:

The final optimized batch was selected based on the validated model and graphical optimization using the overlay plot. The formulation composition delivering highest yield with the considerable enhancement in the solubility of the SDD compared to API alone and favourable enteric release with less than 8% CDR in gastric pH was selected as optimized formulation for the further characterization [17–19].

6.1.5 %Yield

The prepared solid dispersions by spray drying were weighed. The estimation of product yield was conducted by dividing the quantity of SDD produced by the combined weight of the active pharmaceutical ingredient (API) and excipients that were added to the corresponding batch [20].

$$\%\, Yield = \frac{Total\ amount\ of\ SDD}{Total\ amount\ of\ drug\ and\ carrier} * 100 \ldots\ldots\ldots\ldots\ldots (6.1)$$

6.1.6 Drug content estimation (% Assay)

The proportion of ESM loaded in the solid dispersion was analysed by performing assay of the developed formulation. SDD equivalent to 50 mg of ESM was dissolved in solvent methanol. The sample was filtered with the help of Whatman filter paper, appropriately diluted and subjected to UV analysis at 301 nm to determine the sample's drug concentration. Considering the % drug content entrapped in SDD, the amount of ESM SDD equivalent to 50 mg ESM was utilized further in the saturation solubility study [21–23].

6.1.7 Equilibrium solubility study:

As the formulation was delayed release meant to dissolve in intestinal pH, an excessive amount of the sample (drug/SDD) was mixed in 10 ml of PBS pH 6.8 in a glass bottle with a stopper. The sample was put in a water bath at 37±0.5°C, which is about the same temperature as a human body, and agitated at a rate of 40 strokes per minute for 48 hours. The sample was rotated at a speed of 2000 rpm for 10 minutes. After that, the supernatant was filtered (0.45µ) and dissolved, and the concentration at 300 nm was measured with a UV spectrophotometer (Shimadzu U-1800, Japan). Using above method, the solubility was measured for all the batches prepared [24–27].

6.1.8 Dissolution studies

The *in-vitro* release study of ESM SDD was performed in a USP Apparatus II (paddle) at 50 rpm in order to determine the site specificity and drug release pattern. SDD equivalent to 20 mg of drug in a capsule shell were added to 900 ml of 0.1 N HCl dissolution medium for 2 hours at 37±0.5 °C and then to PBS pH 6.8 for another 2 hours. At specified times, aliquots of 10 ml were taken out, filtered, and the dissolved drug was measured by UV spectroscopy at wavelengths of 278 nm and 301 nm respectively. The % CDR was calculated for up to 4 hours. The DD-solver excel add-in was used to determine release kinetics of all the batches for all of the possible models, such as zero order, first order, Higuchi, Hixon-Crowell, and Korsmeyer-Peppas, to find the best model for the formulation's release profile [28–30].

6.1.9 Powder flow properties

Particularly when blending powders, compressing tablets, and filling capsules, the pharmaceutical industry pays great attention to the flow properties of solid dispersion. In order to evaluate the ESM SDD's flow properties, the powder's angle of repose (θ), bulk density, tapped density, Carr's index, and Hausner's ratio were measured [31].

The flow properties were analysed using a calculation of utilising the fixed funnel method. This method included dispensing a predetermined sample size via a funnel onto a piece of graph paper in the shape of a cone. The following equation was used to calculate θ from the measured height (h) and radius (r).

$$\tan\theta = \frac{h}{r} \dots\dots\dots\dots\dots\dots (6.2)$$

A density apparatus was used to measure SDD bulk and tapped densities (Metalab Industries, Mumbai, India), and using their values Hausner's ratio and Carr's compressibility index (%) were calculated.

By accurately converting a precise weight of each formulation (2 g) into a graduated cylindrical measure, the bulk density of SDD formulations was ascertained. Without compacting, the volume of the solid dispersion was recorded in the cylinder measure, and the following equation was used to get the bulk density.

$$Bulk\ density = \frac{weight\ of powder}{Bulk\ volume} \dots\dots\dots\dots\dots\dots (6.3)$$

By accurately weighing each formulation (2 g) and then transferring that weight to a graduated cylindrical measure, the tapped density of the ESM SDD was calculated. The cylinder was tapped (about 100 times) until there was no longer any volume change. The following equation was used to get the tapped density.

$$Tapped\ density = \frac{weight\ of powder}{Tapped\ volume} \dots\dots\dots\dots\dots\dots\dots (6.4)$$

The flowability of the ESM SDD was assessed using Hausner's ratio. The following equation was used to compute Hausner's ratio.

$$Hausner's\ Ratio = \frac{Tapped\ Density}{Bulk\ Density} \dots\dots\dots\dots\dots\dots (6.5)$$

Another factor used to forecast the flowability of powder is Carr's Compressibility index (CI). The below mentioned Equation was utilized to determine the ESM SDD CI.

$$Carr's\ Index = \frac{Tapped\ Density - Bulk\ Density}{Bulk\ Density} * 100 \ldots\ldots\ldots\ldots\ldots\ldots\ldots (6.6)$$

6.1.10 Differential scanning calorimetry (DSC)

DSC was performed of optimized SDD to ascertain the thermal behaviour of the ESM and HPMCAS-MF in the developed formulation and also to detect the interaction between the API and carrier. The PerkinElmer Thermal Analyzer was used to obtain the DSC thermograms at a scanning rate of 20 °C/min for heating from 30 °C to 350 °C in an inert environment flushed with nitrogen at a rate of 10 ml/min [32]. The % crystallinity of ESM SDD was calculated based on the heat of fusion of sample (ΔH_f) and the heat of fusion of pure crystalline sample (ΔH_f°) obtained from the thermograms using following equation [33].

$$\%\ Crystallinity = \frac{\Delta H_f}{\Delta H_f^{\circ}} * 100 \ldots\ldots\ldots\ldots\ldots\ldots\ldots (6.7)$$

6.1.11 Powder X-ray Diffraction (PXRD) Analysis

A Powder X-ray Diffractometer D8 DISCOVER (Bruker) was used to record the powder X-ray diffraction spectra of the Esomeprazole SDD and compared with the PXRD spectra of pure ESM. The SDD sample in fine powder form was subjected to X-rays. Scan angles were ranged from 0° to 80° across a 2θ range [34].

6.1.12 Particle size measurement

Particle size measurements were conducted on the optimized batch in order to determine the size of the SDD. Dynamic light scattering (DLS) was used to evaluate the mean particle size of the SDD using the Particle Size Analyzer (HORIBA Scientific SZ-100). The apparatus was equipped with a laser that emitted light at a specific wavelength of 633 nm. Additionally, a backscattering detector was strategically positioned at an angle of 173°. A dispersion sample was created by dispersing SDD (specific substance) in neugel (Liquid paraffin), resulting in a viscosity of 13.000 mPa·s. The experiment was conducted in triplicate at a

temperature of 25 °C, which corresponds to the standard room temperature. The average of the measurements obtained from the replicates was used to determine the results [35].

6.1.13 Scanning Electron Microscopy (SEM)

The surface morphology of SDD powder was investigated using scanning electron microscopy (SEM) with a concentrated electron beam (Ultraplus, Zeiss, Germany). The sample was placed onto a glass slide, immersed in methanol, and afterwards subjected to desiccation inside a desiccator. To achieve uniform layering and overloading, the sample underwent a gold-palladium coating process for a duration of 2 minutes. This process was carried out utilizing a gold-sputter module inside a low-pressure evaporator, with a current of 20 mA. Microphotographs were captured utilizing scanning and magnification techniques at a distance ranging from 8 to 11 mm and a voltage of 5 kilovolts [36].

6.1.14 Residual solvent analysis

Due to the difference in the solubilities of ESM and HPMCAS-MF, methanol and acetone were used as solvents for their dissolution, respectively. Subsequently, the two solutions were mixed on a magnetic stirrer. The solvents methanol and acetone are classified as class II and class III solvents, respectively. To analyse the residual solvent content, a technique known as Headspace-Gas Chromatography/Mass Spectrometry (HS-GC/MS) [Shimadzu GCMS-QP2020 NX] was used. A suitable solvent was used to solubilize the SDD sample, which was then transferred into a vial and subjected to heating for a preset duration. The examination of the volatile components in the gas phase of the vial was conducted [34, 37].

6.1.15 Formulation of dosage form comprising optimized SDD

Optimized formulation of SDD equivalent to 20 mg dose of Esomeprazole was manually filled in hard gelatin capsule shell. The dosage form was assessed for *in-vitro* dissolution study and stability study.

6.1.16 Stability Studies

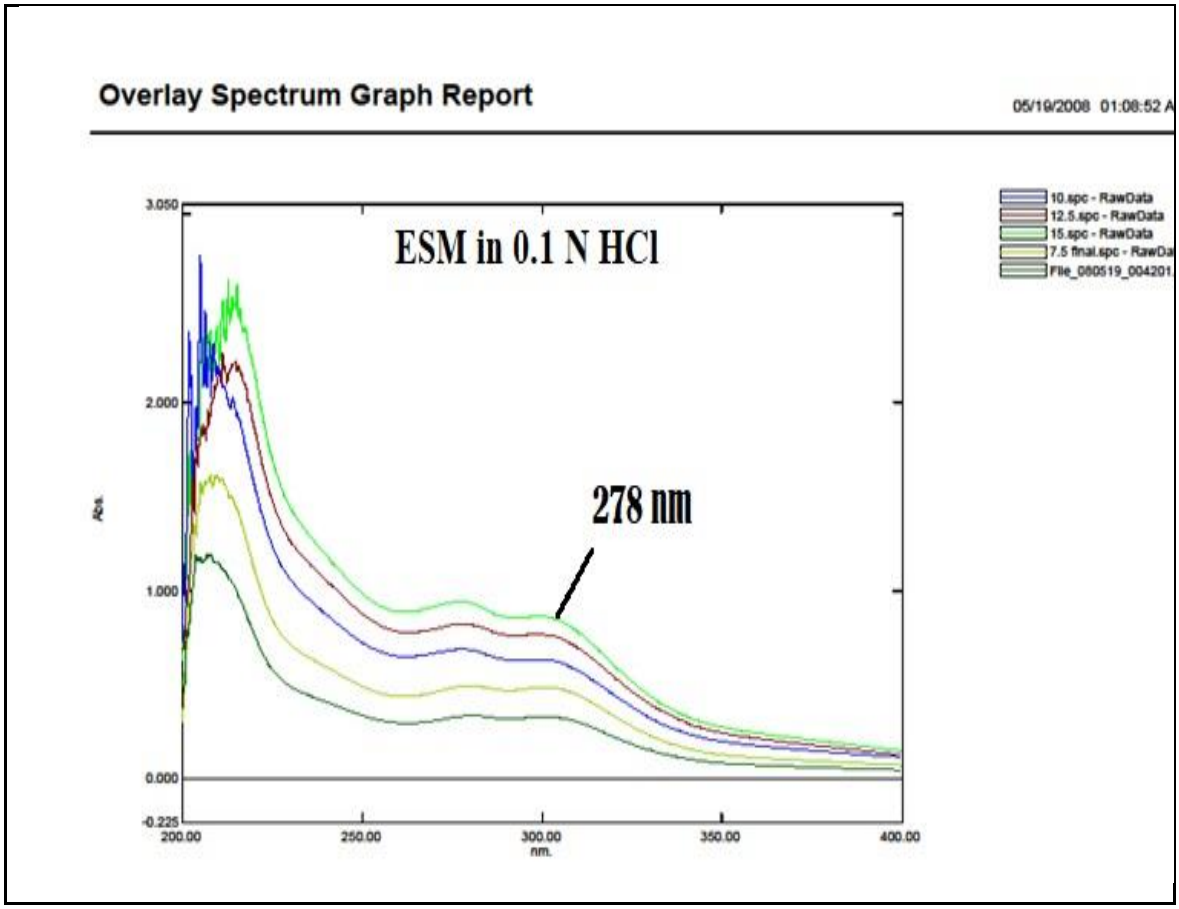
The optimized batch of SDD was encapsulated and stored in a High-Density Polyethylene (HDPE) bottle with a silica gel container closure system. This final dosage form was then

subjected to an Accelerated stability study, following the guidelines set by the International Conference on Harmonization (ICH). The study was conducted at a temperature of 40°C ± 2°C and a relative humidity (RH) of 75% ± 5% for a duration of 6 months. The stability chamber used for this study was provided by Patel Instrument Pvt Ltd. [38]. The study examined the dosage form to see whether there were any statistically significant variations in its physical characteristics, solubility in PBS pH 6.8, drug dissolution profile, and drug content at regular time intervals (1, 3, 6, and 12 months).

6.2 Results & Discussion

6.2.1 UV-VIS Spectroscopy

The ESM spectra obtained in UV-VIS spectrophotometer for gastric (0.1 N HCl) and intestinal (PBS pH 6.8) dissolution media are shown in Fig 6.1. The linear (R^2 = 0.998) standard curves prepared in methanol, 0.1 N HCl and PBS pH 6.8 are described in Fig 6.2.



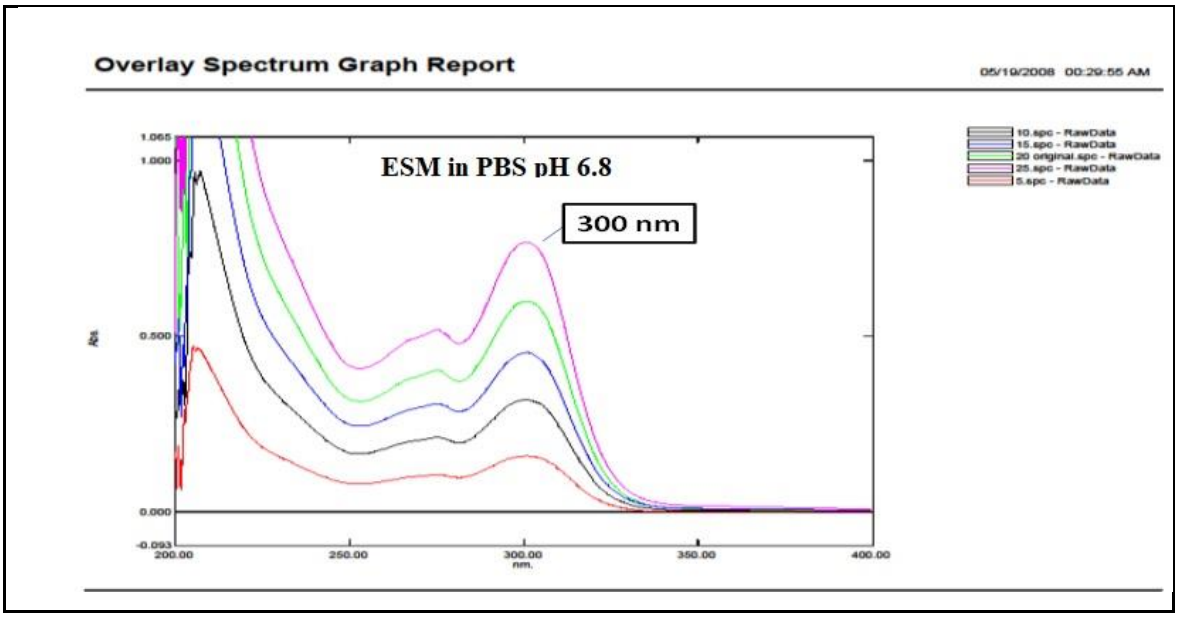


FIGURE 6.1 UV Spectra of ESM

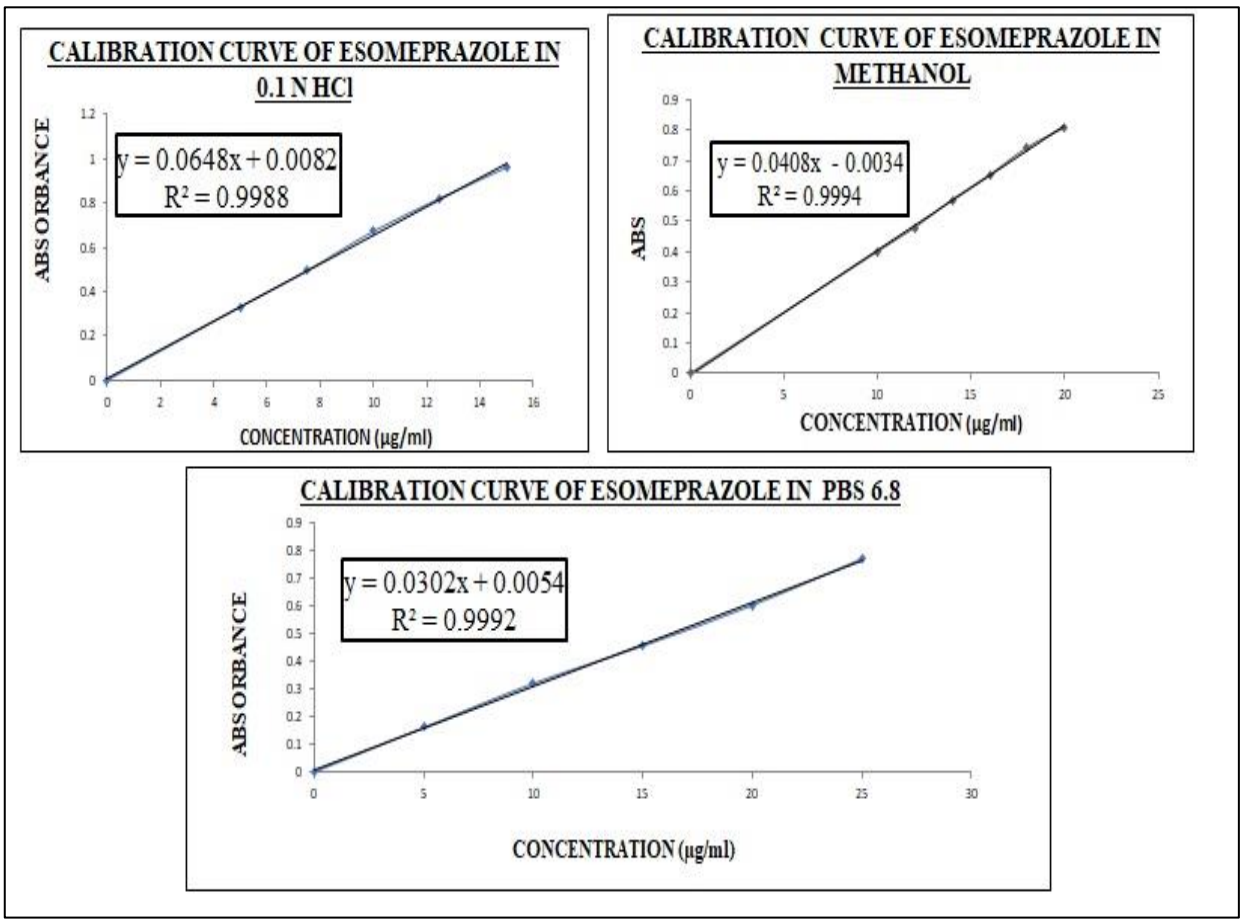


FIGURE 6.2 Calibration curves of ESM

6.2.2 Fourier-transform infrared spectroscopy (FTIR)

Figure 6.3 illustrates the Fourier Transform Infrared (FTIR) spectra acquired for the drug and polymer combination that were generated both at the start time and after undergoing a stability study for one month. The two curves exhibit a high degree of overlap, suggesting that the combination of the active pharmaceutical ingredient (API) and the chosen polymeric carrier are mutually compatible, as shown by the absence of any substantial peak loss even after a prolonged duration of 30 days. Therefore, it is possible to use HPMCAS-MF as a solid dispersion carrier for Esomeprazole.

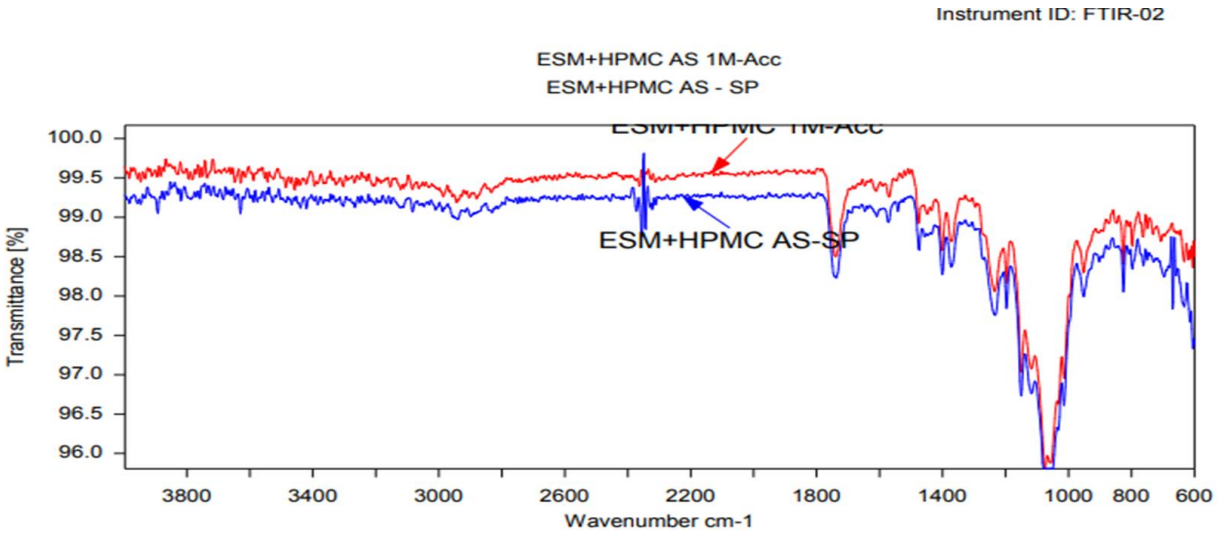


FIGURE 6.3 FTIR Spectra of ESM & HPMCAS-MF

6.2.3 Optimization by Box-Behnken Design

The use of Quality by Design (QbD) methodology is gaining prominence in the pharmaceutical industry due to its recognition of the crucial process and formulation characteristics derived from risk assessment. The Design of Experiment (DoE) is a constituent element of Quality by Design (QbD), which is widely regarded as the most precise framework for comparing and assessing statistical significance [39].

The optimization of SDDs was conducted by varying key process and formulation variables via the use of a Box-Behnken design (BBD) for response surface optimization. BBD was chosen for optimization based on the preliminary trials, since it allowed for the screening of three significant independent variables that were necessary for further optimization. The use of BBD facilitated the analysis of the cumulative impacts of significant process and

formulation factors, hence reducing the quantity of preliminary batches required for the optimization of the formulation. Moreover, the Box-Behnken design (BBD) is a second order design, utilized to create response curves by employing three levels of independent variables. This design allows for the effective optimization of the product while simultaneously minimizing the number of experimental runs required, compared to Central Composite Design (CCD:20 runs) and 3^3 Full Factorial Design (FFD: 27 runs) incorporating the same number of independent variables at same levels.

Since SD carriers increase BCS class II drug solubility, HPMCAS-MF percentage was the first and most relevant independent variable. ESM: HPMCAS-MF was 1:1 in all preliminary testing. In all batches, API solubility substantially increased. The product's solubility and cost determined the levels chosen for optimization: 1:1, 1:2, and 1:3. The early studies showed that FFR affects processing time and product moisture. decreased FFR (< 4) batches significantly slowed solvent evaporation, resulting in decreased yield percentages. Batches with greater FFR (≥8) retained moisture despite employing adsorbent. According to the ROL, increasing FFR increases droplet size and particle size, which is bad for solubility. For further adjustment to improve product production and SDD flow characteristics, the FFR was selected as the second independent variable with values 4, 6, and 8 ml/min. Spray drying intake temperature affects yield, moisture content, and output temperature. Initial studies at 80, 90, and 100 °C showed that increasing intake temperature increases yield. Lowering the intake temperature did not dry droplets sprayed in the drying chamber via nozzle well enough to optimum yield. Based on the situation, inlet temperature was set at 80, 100, and 120°C. Due to ESM stability, the maximum temperature chosen was 120°C to confirm the optimal degree of temperature beyond which the impact may reverse and produce decline. According to literature, ESM is exceptionally stable up to 140°C, supporting the above values [52].

The 15 batches designed as per BBD were assessed for a variety of evaluation parameters, including drug concentration, saturation solubility, yield, and CDR study, as per the methods discussed previously. Since all of these batches' assay (90–110%) met the necessary acceptance requirements, the difference in the data was statistically insignificant. Yield, saturation solubility, and CDR at 2 hours in gastric media were thus the chosen dependent variables to consider for statistical analysis. The retardation of drug release in the first two hours in the stomach is a statistically significant measure compared to overall %CDR since the proposed PPI formulation is DR. The formulation would act as an instant release

conventional dose form once it entered the small intestine. This data served as a basis for choosing Q2 as the dependent variable.

6.2.4 %Yield

Table 6.3 provides a summary of the practical yield that was achieved after the spray drying of the solution containing ESM, HPMCAS-MF and Talc. The data suggested that the process variables had alarming effects on the product yield relative to the drug:carrier ratio. According to the bar graph in Fig 6.4, the lower FFR that was selected based on the literature review offered a greater yield. Due to its effects on the product's particle size and moisture retention, the increase in FFR is further not ideal. Although the increase in input temperature was initially intended to substantially improve the yield, it eventually had a reverse effect.

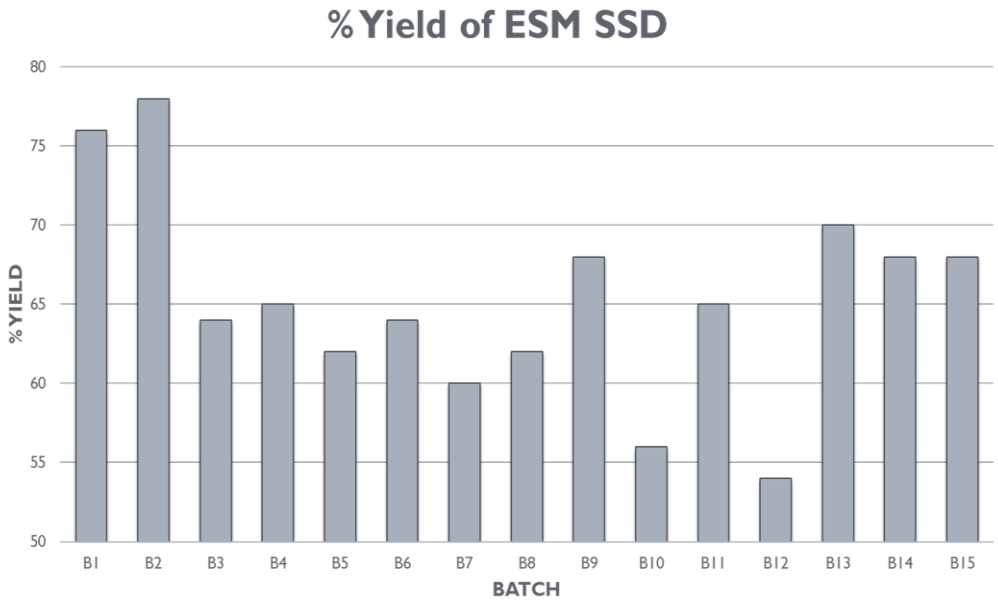


FIGURE 6.4 Bar graph of %Yield of ESM SDD

TABLE 6.3 Evaluation Data of Analysed Parameters and Responses selected for BBD

Batch	% Yield (Response 1)	% Assay (n=3)	Solubility (mg/ml) (n=3) Response 2	Q_2 (% CDR in 0.1 N HCl) (n=2) Response 3
B1	76	94.78±2.725	0.889±0.002	11.6±0.243
B2	78	95.6±5.123	1.737± 0.046	7.16±0.344
B3	64	97.19±1.345	0.857±0.002	10.97±0.145
B4	65	95.92±2.920	1.711±0.09	7.071±0.153

B5	62	94.17±3.26	0.874±0.001	10.2±0.146
B6	64	92.53±4.672	1.89±0.07	7.32±0.207
B7	60	94.27±2.774	0.865±0.001	10.59±0.096
B8	62	96.78±1.529	1.919±0.021	6.62±0.169
B9	68	94.63±1.91	1.207±0.002	8.59±0.097
B10	56	94.75±2.682	1.24±0.005	8.086±0.198
B11	65	96.24±2.252	1.260±0.003	8.13±0.051
B12	54	96.33±1.177	1.238±0.005	7.38±0.195
B13	70	94.02±2.396	1.213±0.001	8.33±0.05
B14	68	96.4±1.860	1.205±0.003	8.19±0.051
B15	68	95.83±2.322	1.221±0.003	7.88±0.1
API			0.519±0.001	11.6±0.243

6.2.5 Drug content estimation (% Assay)

The assay of SDD was carried out in methanol in order to ascertain the percentage of Esomeprazole entrapped in the product. The percentage of drug content was calculated and is shown in Table 6.3. The data confirmed that the % drug content falls within the permitted range of 90-110%. The comparative data of all batches are demonstrated in the bar graph shown in Figure 6.5.

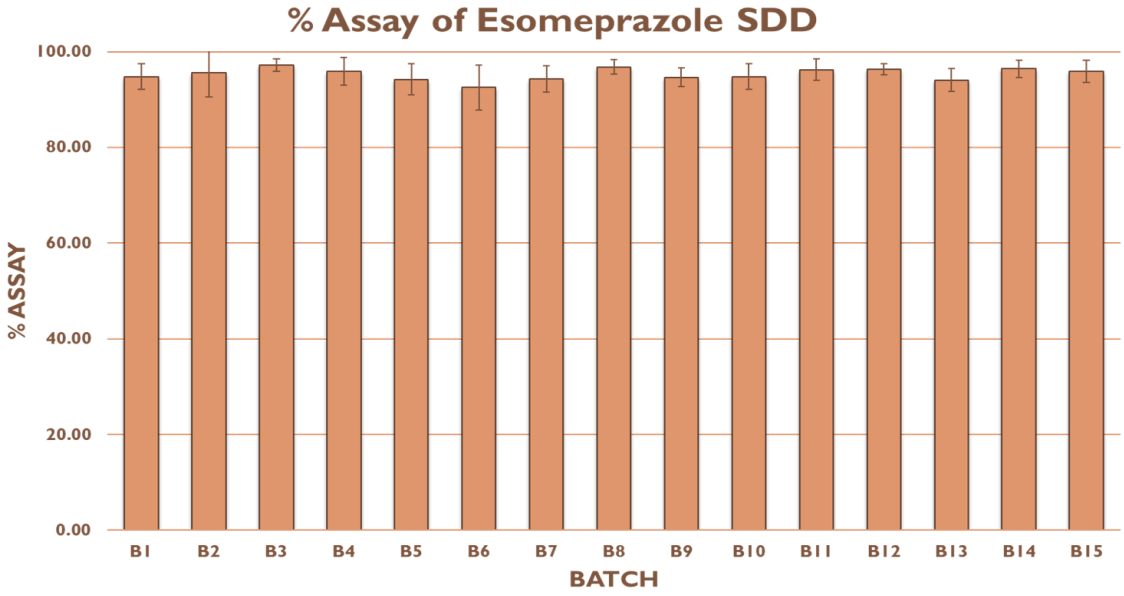


Fig 6.5 Bar graph of %Assay of ESM SDD

6.2.6 Equilibrium solubility study

The saturated solubility of ESM API and ESM in SDD was measured for all the 15 batches as described in methodology section. The solubility data in mg/ml are summarized in Table 6.3. The comparative solubility enhancement with respect to API are demonstrated in bar graph of Fig 6.6.

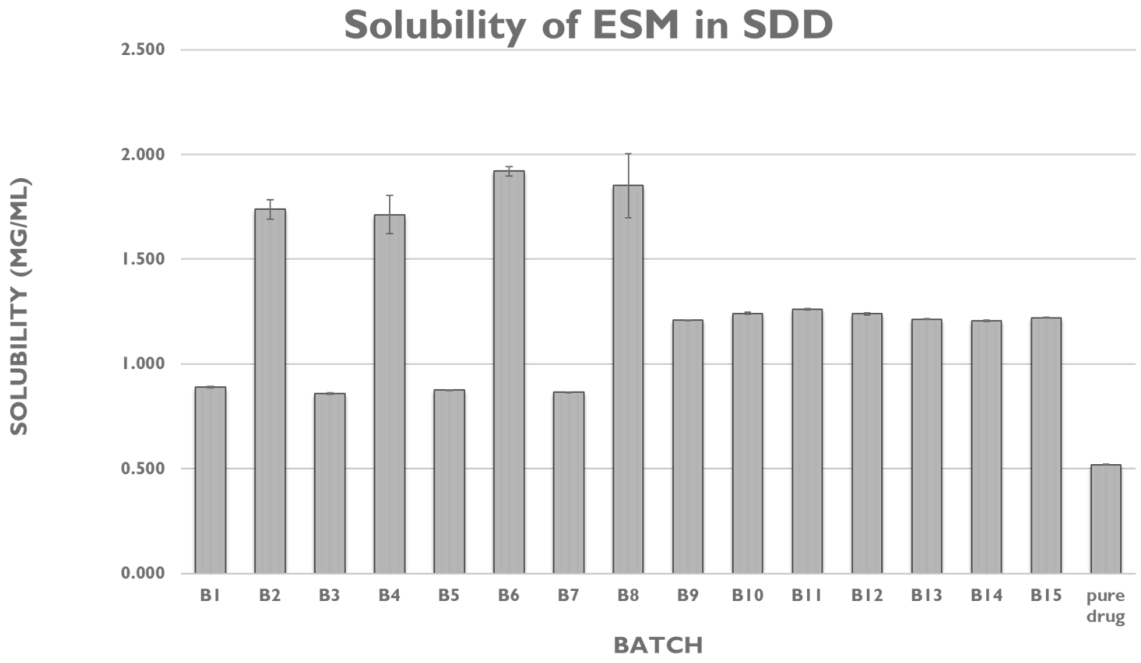


FIGURE 6.6 Bar graph of solubility of ESM

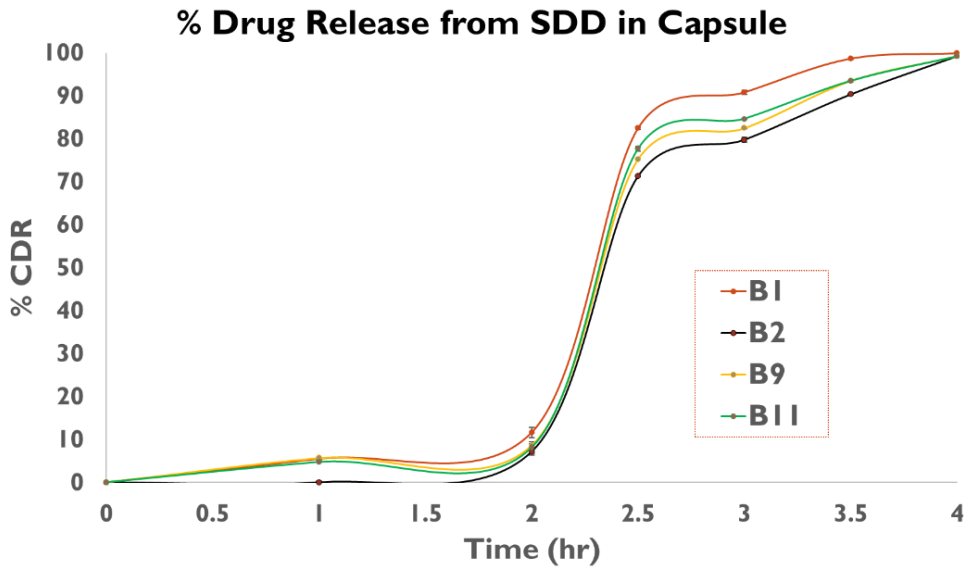
6.2.7 Dissolution studies

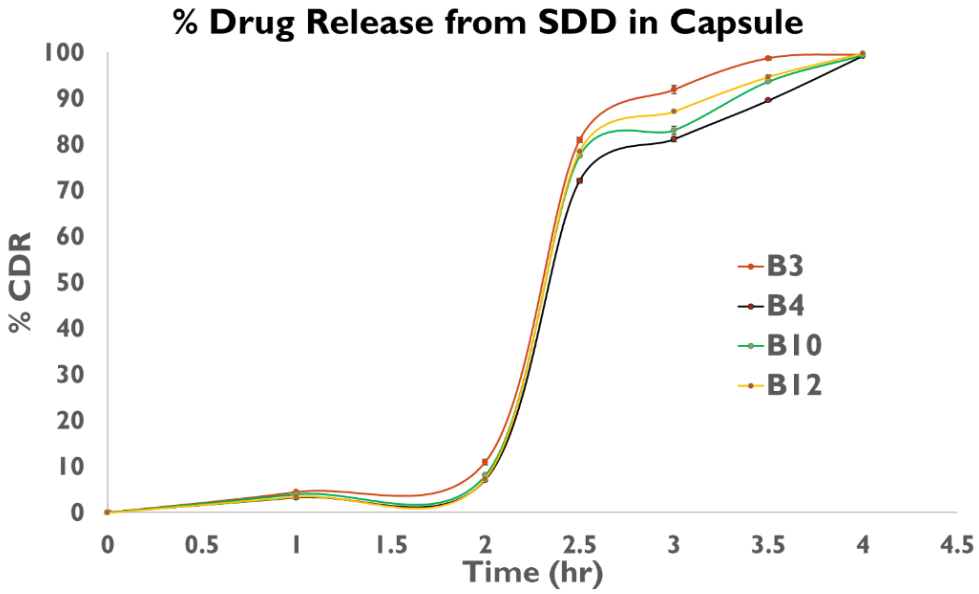
Table 6.4 discusses the cumulative drug release data in gastric medium (0.1 N HCl) for 2 hours and for a further 2 hours in PBS pH 6.8. The % CDR patterns for all batches are summarized in Fig 6.7. It is crucial for the delayed release formulation to retard the % CDR in 0.1 N HCl for 2 hrs (Q_2), which should not exceed 10% precisely. As opposed to this, the formulation should provide uncontrolled release of drugs once it reaches its intestinal pH. The batches with a Drug: HPMCAS-MF ratio of 1:1 exhibited somewhat lower release retardation in stomach pH compared to the intended value, but all the batches achieved about 99% CDR after 4 hours. Fig. 6.8 displays the bar graph comparing the Q_2 values for all 15 batches. The developed formulation's CDR was compared to the USP product monograph for DR formulation, which states that "NLT 75% (Q) of the labelled amount of esomeprazole is dissolved at 30 min in phosphate buffer pH 6.8," and "NMT 10% of the labelled amount

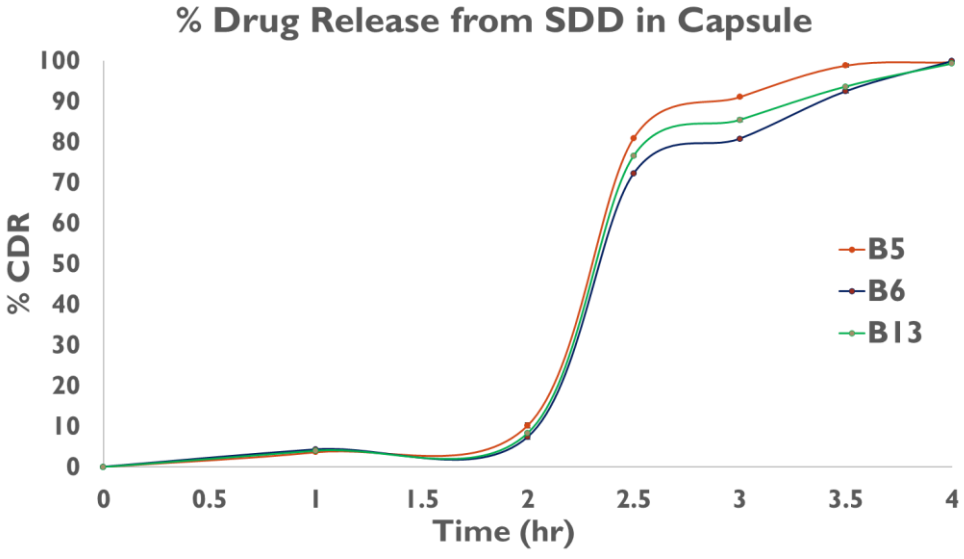
of esomeprazole is dissolved in 0.1 N hydrochloric acid, up to 2 hrs." The chosen optimum range complied with USP monograph.

TABLE 6.4: *In-vitro* Release study of ESM SDD

Dissolution Media	**Time (hr)**	**B1**	**B2**	**B3**	**B4**	**B5**	**B6**	**B7**	**B8**
	0	0	0	0	0	0	0	0	0
0.1 N HCl	**1**	5.47±0.196	0.00	4.47±0.246	3.25±0.491	3.63±0.147	4.29±0.982	5.13±0.196	1.10±1.562
	2	11.61±0.243	7.17±0.344	10.97±0.145	7.07±0.153	10.20±0.146	7.33±0.207	10.60±0.1	6.63±0.169
PBS pH 6.8	**2.5**	82.40±1.192	71.26±0.871	80.95±0.566	72.13±0.058	80.92±0.567	72.23±0.629	79.98±0.1	72.20±0.696
	3	90.71±0.254	79.72±0.033	91.86±0.571	81.12±0.467	91.02±0.166	80.78±0.739	89.99±0.096	80.98±0.141
	3.5	98.59±0.465	90.27±0.557	98.71±0.9	89.53±0.584	98.76±0.252	92.46±0.534	98.31±0.958	92.30±0.04
	4	99.83±0.256	99.15±0.032	99.51±0.353	99.22±0.1	99.58±0.379	99.87±0.643	99.27±0.126	98.90±0.252
Dissolution Media	**Time (hr)**	**B9**	**B10**	**B11**	**B12**	**B13**	**B14**	**B15**	
	0	0	0	0	0	0	0	0	
0.1 N HCl	**1**	5.65±0.147	4.01±0.098	4.74±0.147	3.46±0.1	4.01±0.1	3.77±0.147	4.26±0.15	
	2	8.59±0.097	8.09±0.198	8.13±0.051	7.39±0.195	8.33±0.05	8.12±0.051	7.88±0.1	
PBS pH 6.8	**2.5**	75.21±0.413	77.54±0.329	77.66±1.315	78.48±0.121	76.59±0.156	76.83±0.367	78.15±0.521	
	3	82.43±0.111	83.08±0.124	84.61±0.592	87.09±0.02	85.39±0.265	85.93±0.37	86.23±0.526	
	3.5	93.45±0.218	93.66±0.865	93.42±0.1	94.60±0.127	93.62±0.469	96.10±0.153	93.80±0.531	
	4	99.22±0.305	99.36±0.034	99.12±0.1	99.72±0.552	99.24±0.158	99.45±0.577	99.28±0.202	


% Drug Release from SDD in Capsule
% CDR
Time (hr)
B1
B2
B9
B11


% Drug Release from SDD in Capsule
% CDR
Time (hr)
B3
B4
B10
B12


% Drug Release from SDD in Capsule
% CDR
Time (hr)
B5
B6
B13

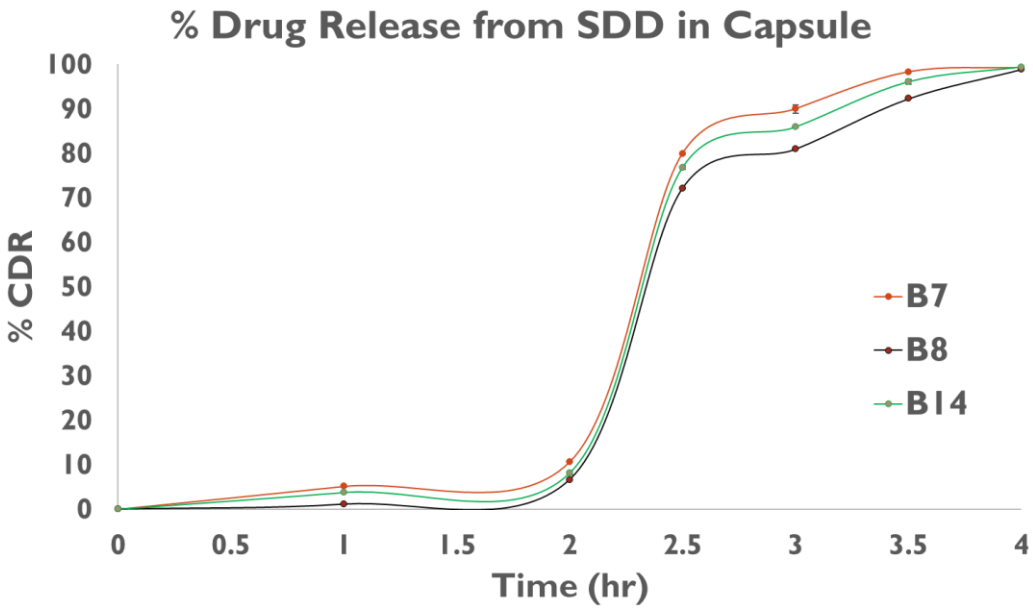


Fig 6.7 % CDR of ESM SDD

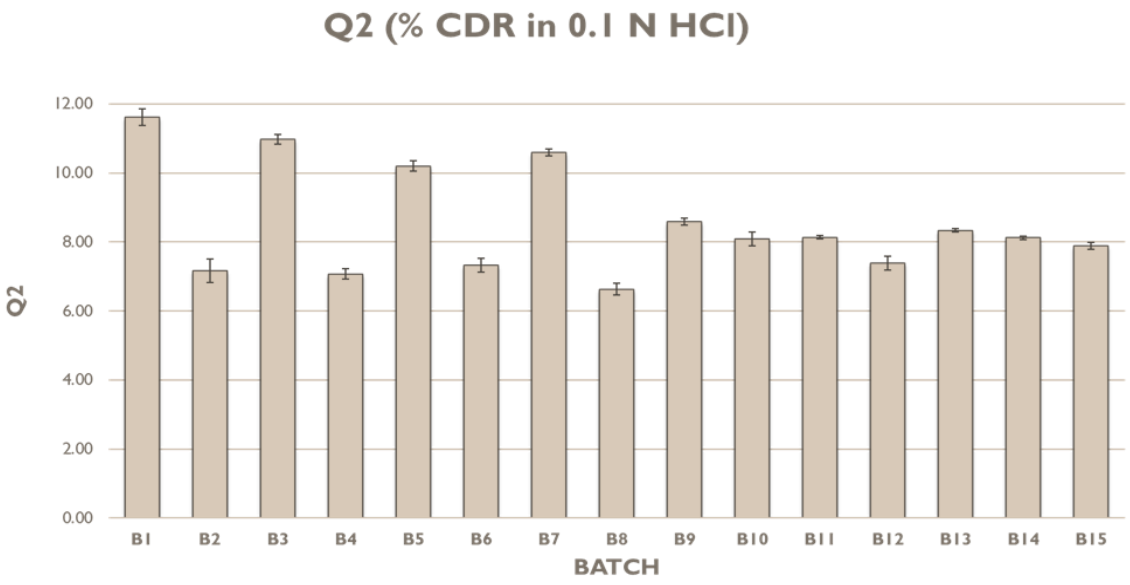


Fig 6.8 Bar Graph of Q_2 of ESM SDD

In Table 6.5, the release kinetics analysis of 15 design batches carried out using DD-Solver Excel add-in is reported. It was determined that the release kinetics after the lag time of 2 hrs fits the Korsmeyer Peppas (K-Peppas) model based on the values of adjusted R^2 -value close to 0.999, Akaike Information Criteria (AIC) value in range of 30-40, and MSC (Model Selection Criteria) value >4. This was based on the results of B9 and B11 comprising the nearest optimization quantity as per design space layout. The K-Peppas model explained how a drug would release from a polymeric framework, suggesting that the actual release

mechanism was unknown or complex. The presence of Fickian diffusion with a hindered release mechanism after a lag time of two hours was confirmed by the measured value of the n-exponent, which is less than 0.45.

TABLE 6.5 Release Kinetics Study of ESM SDD by DD-Solver

Zero Order															
Para meter	B1	B2	B3	B4	B5	B6	B7	B8	B9	B10	B11	B12	B13	B14	B15
Rsqr adj	0.7968	0.8082	0.7946	0.8061	0.7918	0.8100	0.7976	0.8027	0.8076	0.7978	0.7959	0.7882	0.7990	0.7975	0.7917
AIC	58.0347	57.0343	58.1850	56.9735	58.3321	56.9257	57.9392	57.3441	57.0209	57.5869	57.6457	58.2059	57.5802	57.8056	57.9246
MSC	0.9407	0.7446	0.9367	1.0135	0.9289	1.0305	0.9500	1.0057	1.0066	0.9636	0.9509	0.9212	0.9689	0.9640	0.9330
First Order															
Para meter	B1	B2	B3	B4	B5	B6	B7	B8	B9	B10	B11	B12	B13	B14	B15
Rsqr_ adj	0.6362	0.6398	0.6319	0.6423	0.6275	0.6415	0.6354	0.6343	0.6454	0.6360	0.6360	0.6245	0.6367	0.6312	0.6310
AIC	62.1115	61.4446	62.2703	61.2601	62.4053	61.3696	62.0597	61.6630	61.3028	61.7023	61.6934	62.2129	61.7240	62.0032	61.9265
MSC	0.3584	0.1145	0.3531	0.4011	0.3470	0.3956	0.3614	0.3887	0.3949	0.3757	0.3726	0.3488	0.3769	0.3644	0.3613
Higuchi															
Para meter	B1	B2	B3	B4	B5	B6	B7	B8	B9	B10	B11	B12	B13	B14	B15
Rsqr_ adj	0.9193	0.9626	0.9235	0.9562	0.9257	0.9589	0.9270	0.9593	0.9455	0.9392	0.9360	0.9350	0.9408	0.9422	0.9341

MSC	AIC	Rsqr_ adj	Para meter	T_{lag}	n	MSC	AIC	Rsqr_ adj	Para meter	MSC	AIC
			Hixson-Crowell						**Korsemeyer-Peppas**		
0.5401	60.8394	0.6967	**B1**	2.157	0.120	3.2438	***41.9136***	0.9809	**B1**	1.8641	51.5714
0.2930	60.1955	0.6986	**B2**	2.000	0.244	5.4741	***23.9274***	0.9984	**B2**	2.3799	45.5866
0.5340	61.0037	0.6928	**B3**	2.370	0.085	3.4247	***40.7691***	0.9840	**B3**	1.9245	51.2703
0.5768	60.0302	0.6999	**B4**	2.000	0.231	5.2068	***27.6200***	0.9973	**B4**	2.5022	46.5525
0.5261	61.1519	0.6886	**B5**	2.305	0.101	3.6022	***39.6187***	0.9865	**B5**	1.9584	51.1255
0.5742	60.1196	0.7001	**B6**	2.000	0.243	4.9099	***29.7699***	0.9963	**B6**	2.5626	46.2009
0.5421	60.7946	0.6957	**B7**	2.267	0.113	3.4007	***40.7845***	0.9836	**B7**	1.9703	50.7978
0.5647	60.4308	0.6933	**B8**	2.000	0.234	6.0628	***21.9445***	0.9988	**B8**	2.5843	46.2942
0.5735	60.0530	0.7033	**B9**	2.000	0.206	4.5364	***32.3124***	0.9947	**B9**	2.2687	48.1865
0.5503	60.4800	0.6943	**B10**	2.000	0.187	4.8974	***30.0507***	0.9963	**B10**	2.1657	49.1726
0.5463	60.4774	0.6941	**B11**	2.000	0.181	4.9631	***29.5604***	0.9965	**B11**	2.1102	49.5303
0.5206	61.0099	0.6838	**B12**	2.000	0.175	5.7973	***24.0729***	0.9985	**B12**	2.1031	49.9328
0.5532	60.4900	0.6954	**B13**	2.000	0.190	5.4341	***26.3238***	0.9978	**B13**	2.1908	49.0267
0.5412	60.7654	0.6910	**B14**	2.000	0.195	5.4076	***26.7005***	0.9978	**B14**	2.2177	49.0301
0.5340	60.7180	0.6895	**B15**	2.000	0.175	5.3351	***27.1101***	0.9976	**B15**	2.0846	49.8633

Weibull															
Parameter	**B1**	**B2**	**B3**	**B4**	**B5**	**B6**	**B7**	**B8**	**B9**	**B10**	**B11**	**B12**	**B13**	**B14**	**B15**
Rsqr_adj	0.9893	0.9502	0.9921	0.9522	0.9915	0.9560	0.9882	0.9590	0.9621	0.9672	0.9709	0.9809	0.9742	0.9789	0.9768
AIC	***37.4045***	***47.5964***	***35.3519***	***47.1748***	***35.9196***	***46.6828***	***38.0688***	***46.3387***	***45.6528***	***44.8644***	***44.0026***	***41.3597***	***43.2081***	***41.9928***	***42.5528***
MSC	3.8879	2.0928	4.1985	2.4133	4.1307	2.4937	3.7887	2.5779	2.6307	2.7811	2.8999	3.3278	3.0221	3.2230	3.1290
β	2.804131	4.6095	2.885488	2.884797	3.016309	2.839707	2.760343	3.512454	2.59465	2.817376	2.705775	2.98696	2.813226	2.907898	2.795986

6.2.8 Regression Analysis & Validation of BBD

Table 6.6 shows the results of the quadratic regression analysis for each of the chosen dependent variables. It was clear from the Model F values and lack of fit analyses for each dependent variable that the model chosen for the regression study was significant and fits well with the fewest possible noise possibilities. Each time, the difference between the predicted adjusted R^2 was less than 0.2, which is considered to be a reasonable difference. Adeq Precision's measurement of a signal to noise ratio > 4 suggested that this paradigm may be used to explore the design space.

TABLE 6.6 Regression Analysis by Quadratic model for Dependent Variables

ANOVA ANALYSIS FOR SOLUBILITY			
Source	**F-value**	**p-value**	
Model	61.93	**0.0001**	**Significant**
A-HPMCAS Conc	538.27	< **0.0001**	
B-FFR	0.0854	0.7819	
C-Inlet Temp	0.0242	0.8826	
AB	0.0028	0.9600	
AC	0.2783	0.6204	
BC	0.2511	0.6376	
A^2	14.57	**0.0124**	

B^2	0.8817	0.3908	
C^2	2.99	0.1442	
Residual			
Lack of Fit	95.03	0.0104	**Not Significant**
Std. Dev.	0.0569	**R^2**	0.9911
Mean	1.29	**Adjusted R^2**	0.9751
C.V. %	4.42	**Predicted R^2**	0.8586
		Adeq Precision	22.3428
ANOVA ANALYSIS FOR % Yield			
Source	**F-value**	**p-value**	
Model	94.95	**< 0.0001**	**significant**
A-HPMCAS Conc	8.96	**0.0303**	
B-FFR	421.46	**< 0.0001**	
C-Inlet Temp	14.82	**0.0120**	
AB	0.3659	0.5717	
AC	0.0000	1.0000	
BC	0.3659	0.5717	
A^2	15.01	0.0117	
B^2	0.9381	0.3773	
C^2	375.23	< 0.0001	
Residual			
Lack of Fit	0.1875	0.8972	**not significant**
Std. Dev.	0.8266	**R^2**	0.9942
Mean	65.33	**Adjusted R^2**	0.9837
C.V. %	1.27	**Predicted R^2**	0.9694
		Adeq Precision	35.5583

ANOVA ANALYSIS FOR Q_2 (% drug release in 0.1N HCl)			
Source	**F-value**	**p-value**	
Model	36.37	**0.0005**	significant
A-HPMCAS Conc	283.07	**< 0.0001**	
B-FFR	4.82	0.0795	
C-Inlet Temp	2.64	0.1649	
AB	0.7013	0.4405	
AC	2.87	0.1511	
BC	0.1488	0.7155	
A^2	27.19	0.0034	
B^2	1.87	0.2300	
C^2	3.06	0.1406	
Residual			

Lack of Fit	2.67	0.2838	not significant
Std. Dev.	0.3188	**R^2**	0.9850
Mean	8.54	**Adjusted R^2**	0.9579
C.V. %	3.73	**Predicted R^2**	0.8006
		Adeq Precision	19.7612

The full and reduced models for dependent variable solubility based on regression analysis and P-Value <0.05 are described below.

Solubility Full model = $1.21 + 0.4665A - 0.0059B - 0.0031C + 0.0015AB - 0.015AC - 0.0142BC + 0.113 A^2 - 0.0278 B^2 + 0.0512 C^2 + \varepsilon$ ……. (6.8)

Solubility Reduced model = $1.21 + 0.4665A + 0.113 A^2 + \varepsilon$…….... (6.9)

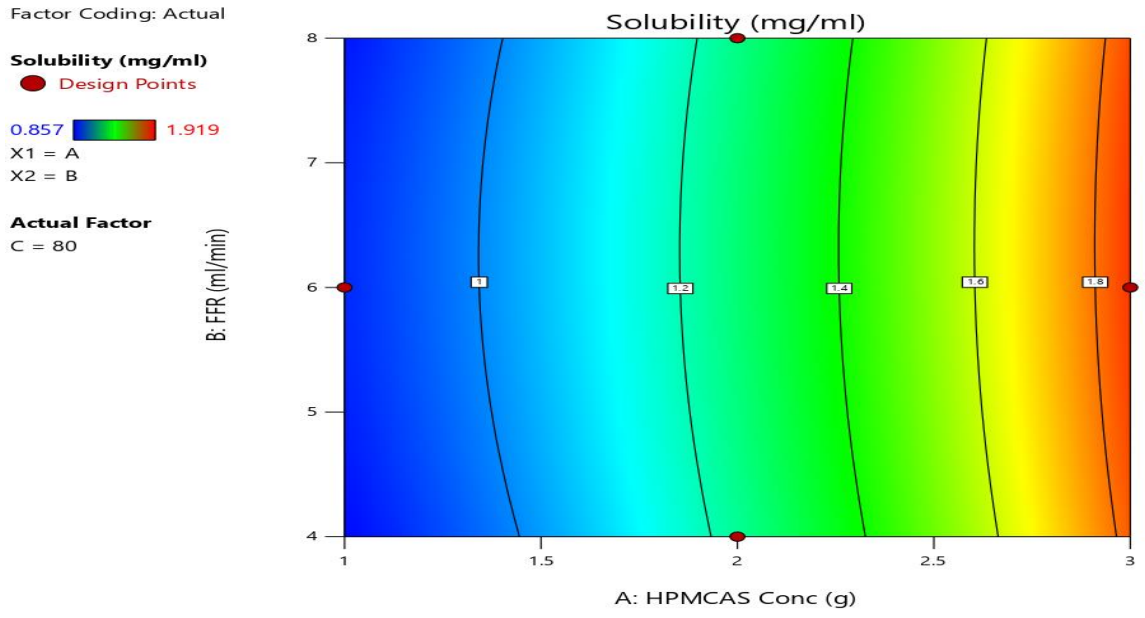
Wherein

A, B & C are Main Effects

AB, AC & BC are 2-way Interaction Effects

A^2, B^2 & C^2 are Curvature effects

ε is Experimental error



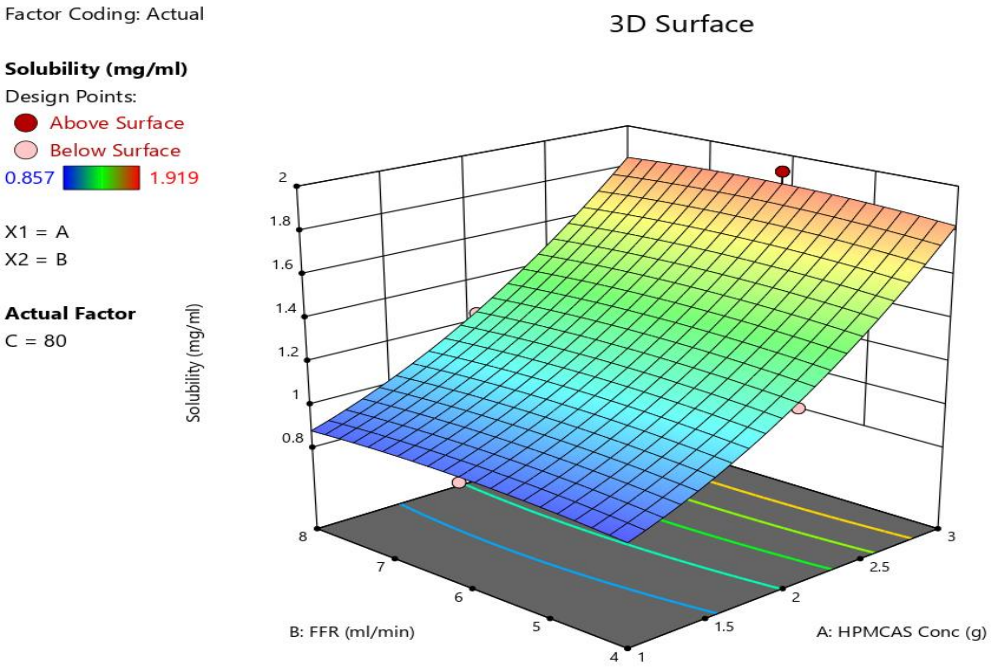


FIGURE 6.9 Contour Plot & Response Surface Plot of solubility

HPMCAS-MF concentration is the most significant variable with a P-value< 0.05 impacting the solubility of ESM, according to the reduced quadratic model, whereas factor B has no significant impact on the solubility of SD. The solubility of the API is dependent on proportion of SD carrier, and this is confirmed based on the highest coefficient value of factor A. The positive sign indicated that factor and response were directly related, and that an increase in SD carrier would improve ESM solubility. The view was further confirmed by the contour plots (CP) and response surface plots (RSP) depicted in Fig. 6.9. Additionally, it was clear from the regression data and graphs that the selected process variables had no impact on solubility.

For second response % Yield, it was concluded that all the chosen independent factors were significant based on P-values less than 0.05, but the process parameters, particularly FFR, had a significant impact because of greater coefficient values. The negative sign of factor B indicated that when the FFR increases, the product yield decreases proportionately. A contributing cause to the decreased yield may be the shorter exposure period of the sprayed dispersion in the drying chamber with an increased FFR. In the case of factor C, or inlet temperature, initially a rise in percent yield was seen as temperature was increased, but after reaching a certain optimal temperature, the trend changed, resulting in a loss in % yield. Plots of the contour and response surface in Fig 6.10 also indicated the similar results.

% Yield Full Model = $68.67 + 0.875A - 6B - 1.13C - 0.25AB + 0.0AC + 0.25BC + 1.67A^2 + 0.4167 B^2 - 8.33C^2 + \varepsilon$……. (6.10)

% Yield Reduced Model = $68.67 + 0.875A - 6B - 1.13C + 1.67A^2 + \varepsilon$……. (6.11)

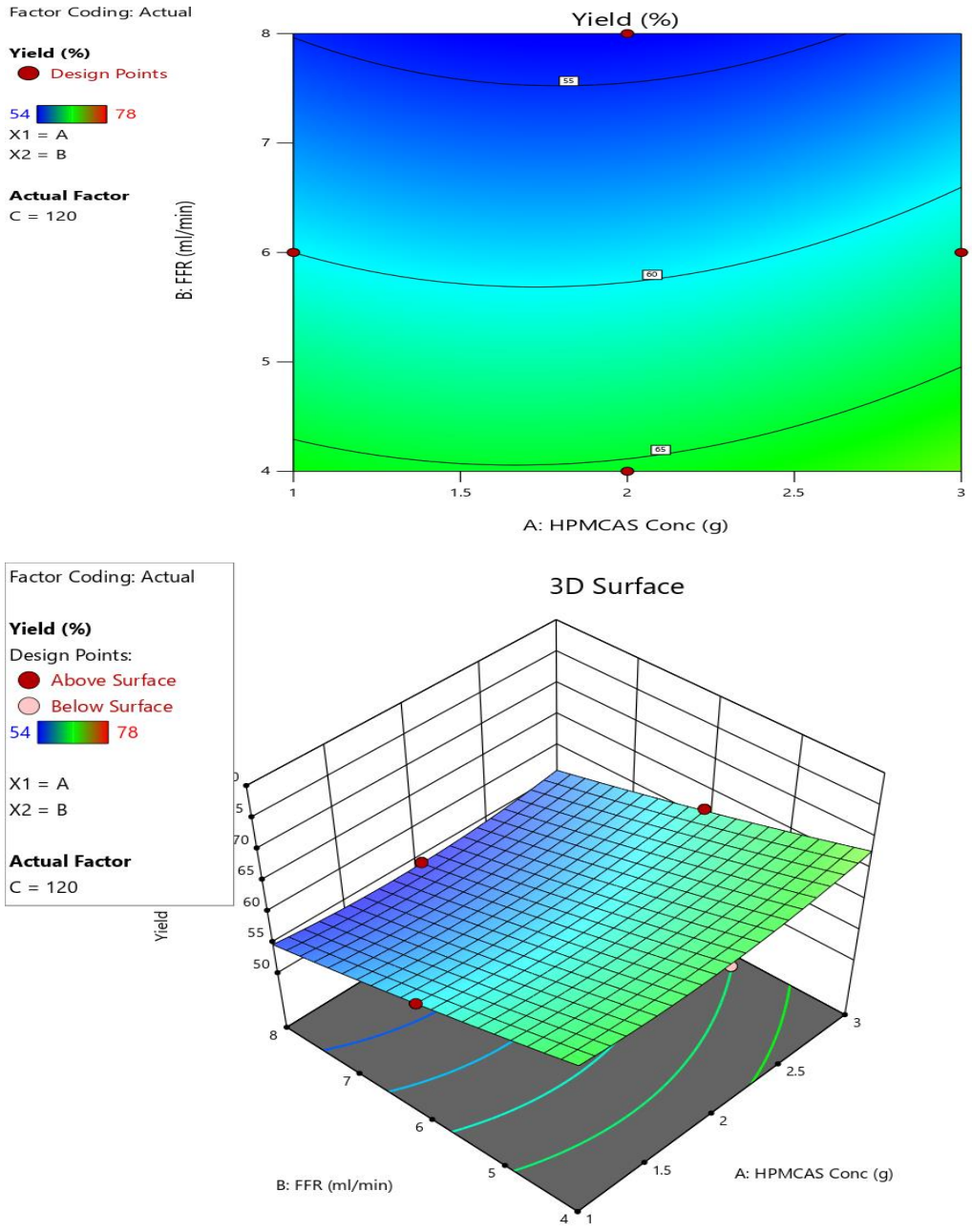


FIGURE 6.10 Contour Plot & Response Surface Plot of %Yield

Based on the reduced quadratic model, it was anticipated that the HPMCAS-MF concentration was once again playing a crucial role in the third response Q_2 having a significant influence on the delayed release of the formulation. The interpretation was

supported by the reduced equation, the p-value, and the graphs shown in Fig 6.11. HPMCAS-MF having solubility at pH greater than 6 was crucial in retarding the drug release in gastric pH and thus enhancing the stability of PPI. According to the theoretical and graphical optimization, the higher polymer ratio decreased the % CDR in 0.1 N HCl.

Q2 Full Model = 8.11 – 1.9A – 0.2475B – 0.1832C +0.1335AB – 0.27AC – 0.0615BC + 0.8653 A2 + 0.2268 B2 – 0.2902 C2 + ε……. (6.12)

Q2 Reduced Model = 8.11 – 1.9A + 0.8653 A2 + ε……. (6.13)

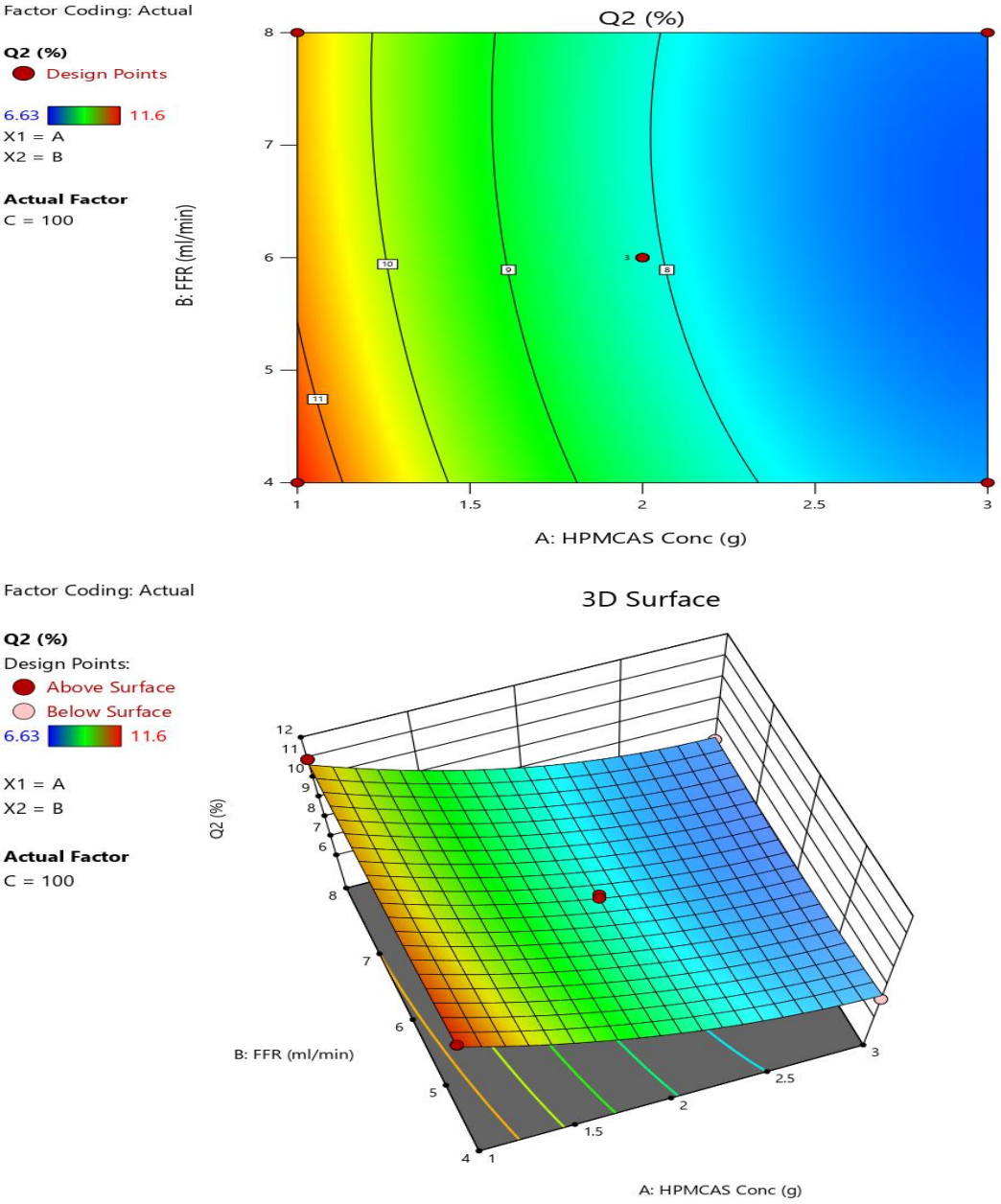


FIGURE 6.11 Contour Plot & Response Surface Plot of Q_2

The three check point batches with desirability 1 were examined for the model validation as listed in Table 6.7, taking into account the effect of variables on the responses recorded and the appropriate constraints selected. As illustrated in Fig 6.12, the overlay plot for design space optimization was generated. The yellow region in the plot may be used to navigate the space for optimization.

TABLE 6.7: Check Point Batches selected based on Constraints

Constraints			
Name	**Goal**	**Lower Limit**	**Upper Limit**
A: HPMCAS-MF Conc	is in range	1	3
B: FFR (ml/min)	is in range	4	8
C: Inlet Temp (°)	is in range	80	120
Solubility (mg/ml)	is in range	1.1	1.919
Yield (%)	is in range	75	78
Q_2 (%)	is in range	0	8

Check point Batch	**HPMCAS-MF conc (g)**	**FFR (ml/min)**	**Inlet Temp (°)**	**Solubility (mg/ml)**	**Yield (%)**	**Q_2 (%)**
CP1	2.361	4.099	94.649	1.379	75.133	7.971
CP2	2.387	4.122	98.819	1.391	75.396	7.902
CP3	**2.492**	**4.038**	**97.899**	**1.449**	**75.963**	**7.806**

The Check point batch 3 (CP3) was considered as optimized formulation for total SDD calculation with respect to ESM dose of 20 mg. The same batch CP3 was utilized for the further characterization and accelerated stability study as per ICH Guidelines.

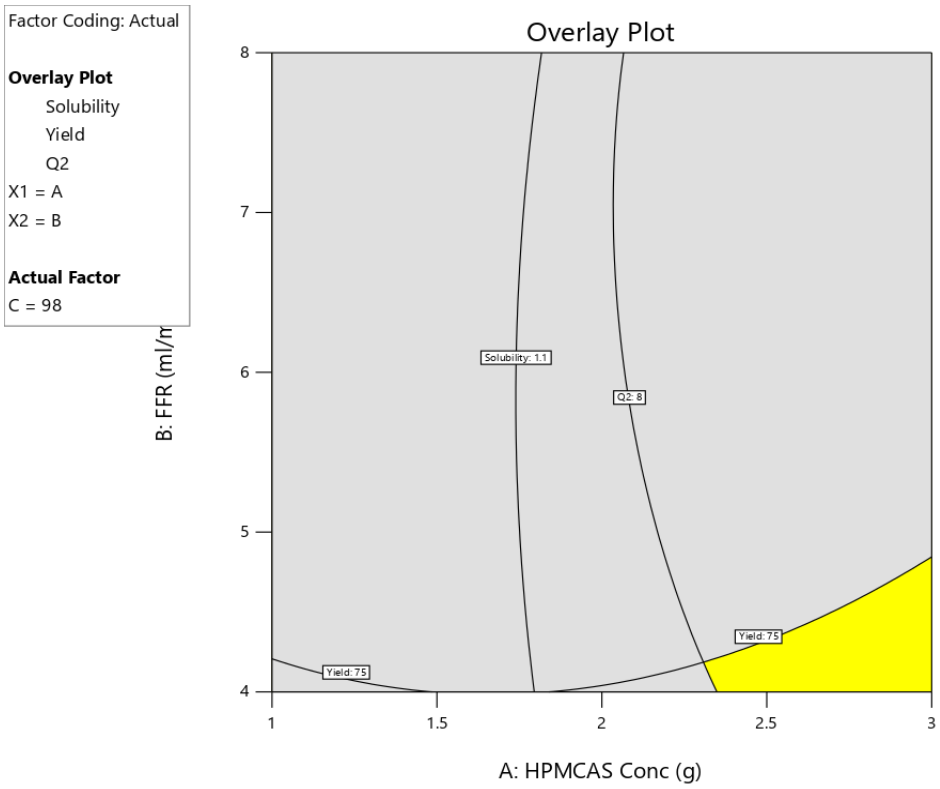


FIGURE 6.12 Overlay Plot for Design Space Optimization

6.2.9 Powder flow properties

The batch CP3 was evaluated for the flow characteristics using the equations presented in the methodology section. For SDD, the AOR was 29.17±0.54°. The results for bulk density and tapped density were 0.45±0.017 g/ml and 0.48±0.04 g/ml, respectively. Whereas the calculated values for the Hausner's ratio and Carr's Compressibility Index were 1.09±0.01 and 9.79±1.03, respectively. On the basis of the data of Angle of Repose (<30), Carr's Compressibility Index (5-15 %) and Hausner's Ratio (1.00–1.11), it was predicted that the SDD have good flow properties suitable for the capsule formulation.

6.2.10 Differential scanning calorimetry (DSC)

A DSC thermogram was generated to investigate the thermal behaviour of the drug alone and in combination with polymer in the SDD. The overlay spectra of DSC thermograms of pure API and SDD are shown in Fig 6.13. The drug appeared to be crystalline on the pure ESM thermogram, having an endothermic peak at 174.17°C. Pure crystalline drug has a fusion heat of 53.3 J/g. The SDD's DSC curve showed that there was no distinct endothermic

peak with an area of 11.383 mJ, suggesting that the drug's original crystalline nature had been reduced. The SDD sample's heat of fusion was measured as 7.588 J/g. Equation (6.7) was used to calculate the percentage crystallinity of ESM SDD, and the result was 14.23%, confirming the amorphization of pure ESM in SDD.

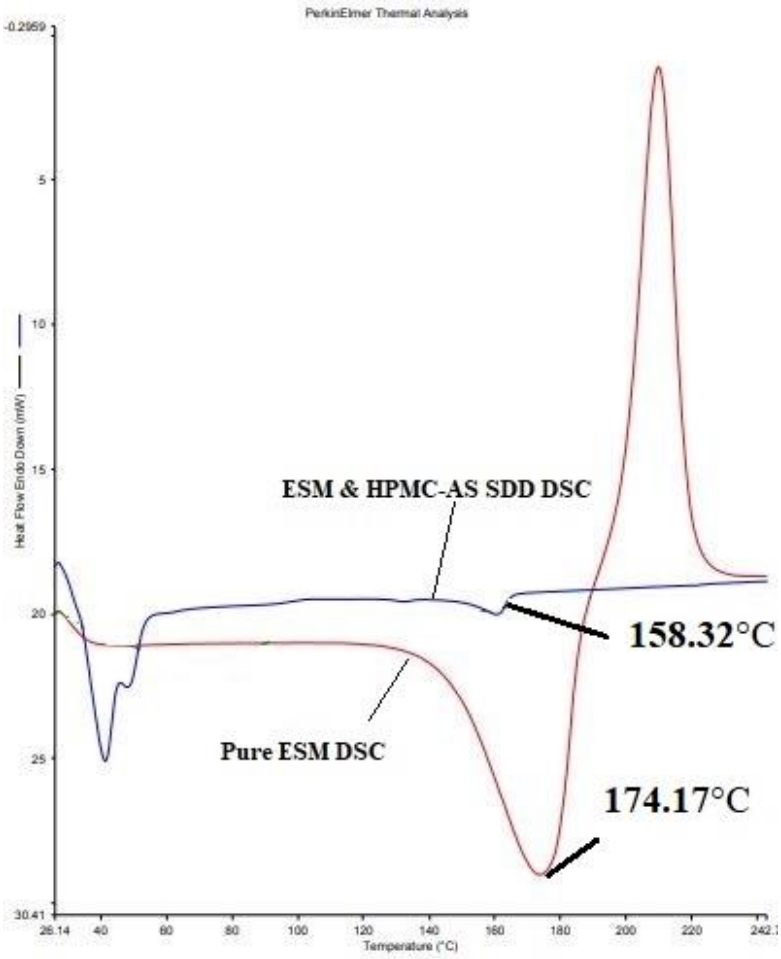
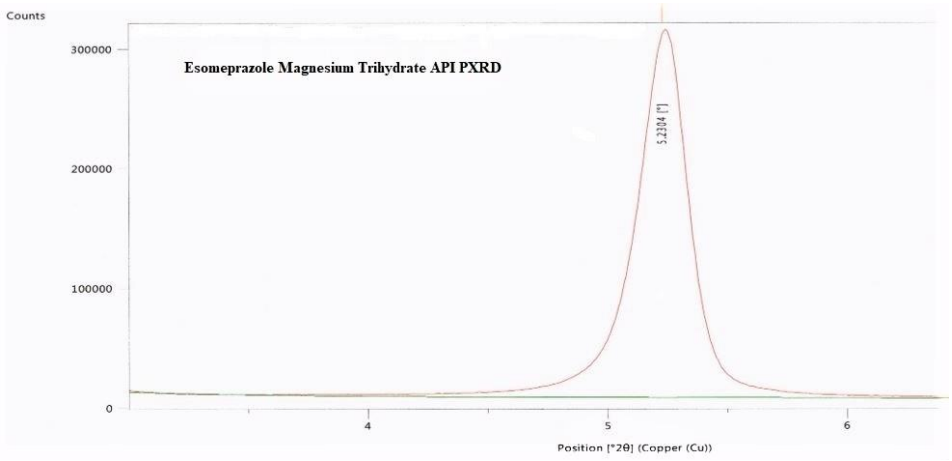


FIGURE 6.13 DSC Thermograms Overlay of ESM & SDD

6.2.11 Powder X-ray Diffraction (PXRD) Analysis

Fig 6.14 illustrates the diffraction pattern of pure ESM and spray dried SD. The pure API displayed a prominent peak at 2θ values of 5.2304°, indicating its crystalline nature. Conversely, the PXRD curve of SDD exhibited the absence of characteristic peaks, confirming the amorphous state of the drug in SDD. This transformation significantly contributes to the enhancement of solubility and dissolution rate of the API in the formulation.



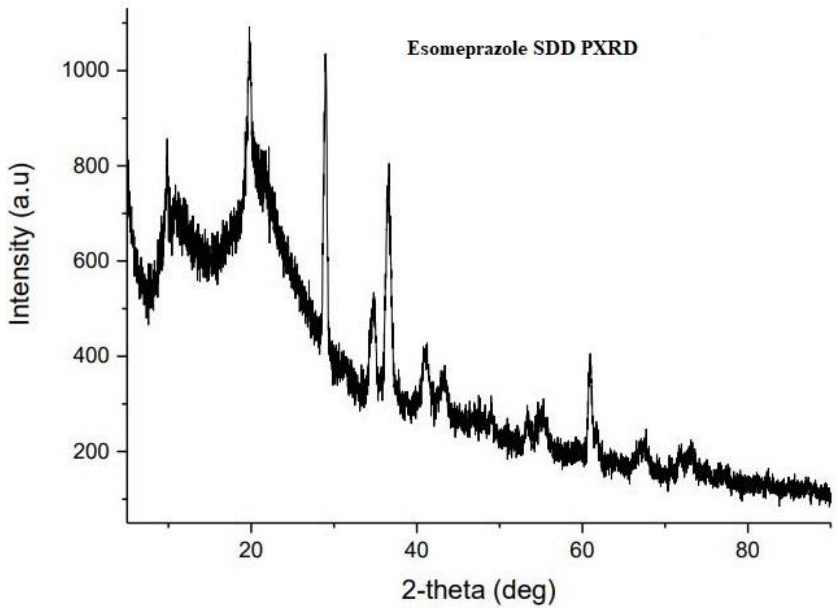


FIGURE 6.14 PXRD Spectra of ESM & SDD

6.2.12 Particle size measurement

Particle size measurement was conducted on Batch CP3, and the corresponding results are shown in Fig 6.15. The experimental findings demonstrated that the size distribution of the SDD was characterized as polydisperse, as conveyed by the Polydispersity Index (PDI) value of 2.221. The average particle size of the batch was found to be 2272 nm, along with a standard deviation of 593.6. The hydrodynamic dimensions of the particle sample were evaluated using dynamic light scattering (DLS), resulting in an intensity-weighted mean value of 1.818 µ (Z-average). The smaller particle size has the potential to greatly improve solubility.

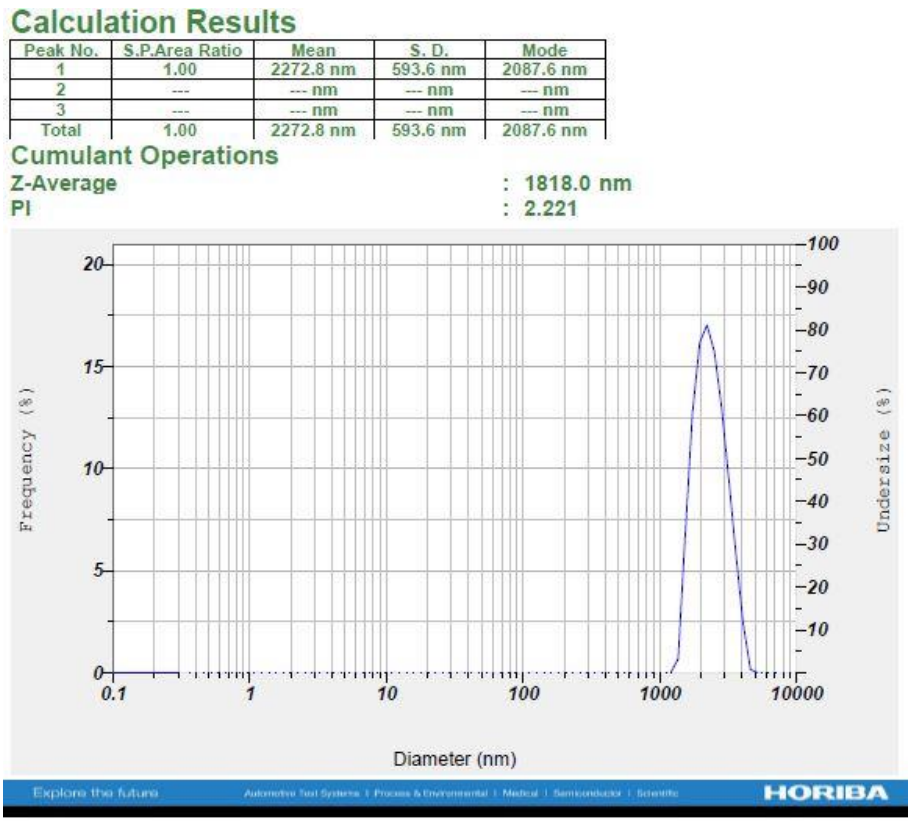


FIGURE 6.15 Particle size analysis of ESM SDD

6.2.13 Scanning Electron Microscopy (SEM)

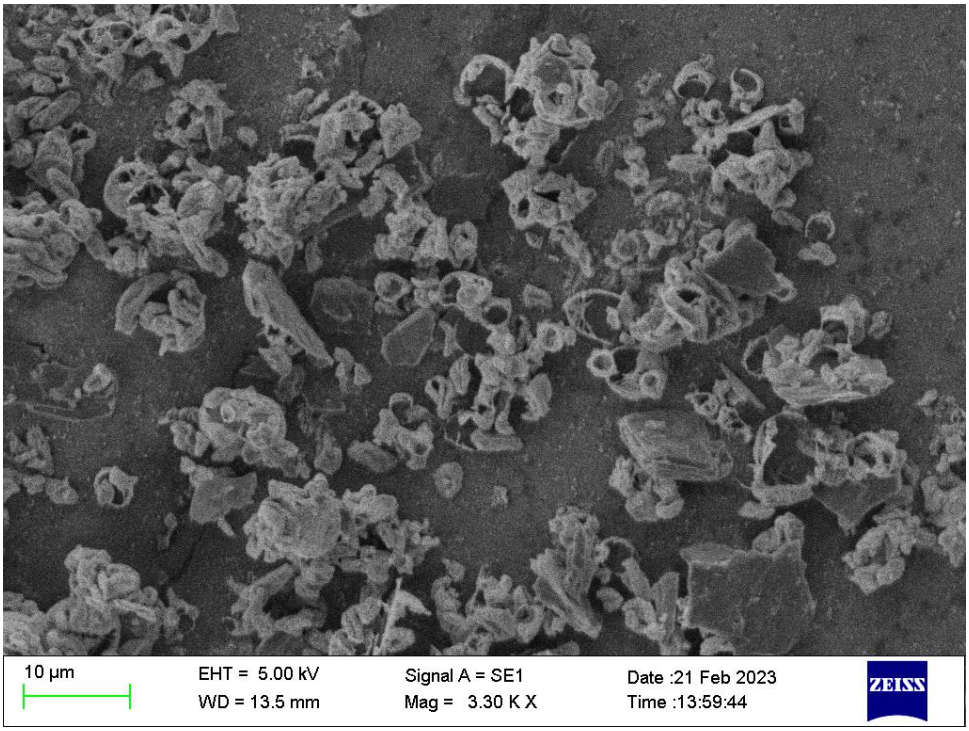
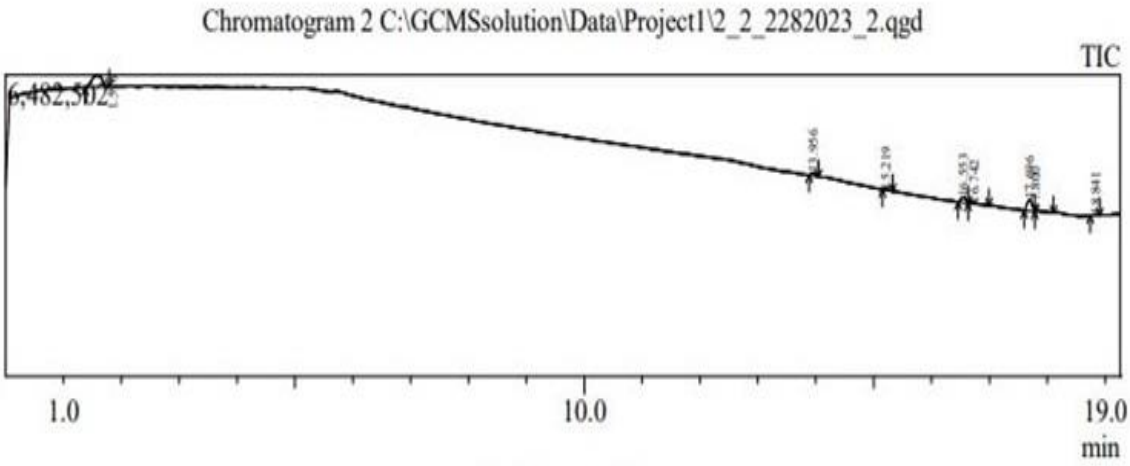


FIGURE 6.16 Surface morphology analysis of ESM SDD using SEM

Fig 6.16 displays the surface morphology analysis conducted using scanning electron microscopy (SEM) on the optimized batch. The accompanying magnification scale is also shown. The visual representation provided confirmed the spherical shape and fibrous texture of the SDD powder. The desired flow qualities of powder may be facilitated by the spherical form of the SDD.

6.2.14 Residual solvent analysis

In this work, methanol was used as a solvent to dissolve a drug that belongs to Class 2 (Solvents to be limited) and has a 3000-ppm formulation limit. Acetone, which is in Class 3 Solvents (Solvents with low toxic potential), was chosen to breakdown polymer, and it can be used in dosage form up to a limit of 5000 ppm [50]. Based on the HS-GC/MS study of the SDD sample, the chromatogram showed that there were no solvent bands left over, so the mixture was safe to give. All the peaks found during research are illustrated in Fig 3 to back the results.



Peak Report TIC

Peak#	R.Time	Area	Height	A/H	Name
1	1.596	3151431	254679	12.37	Nickel tetracarbonyl
2	13.956	358224	60523	5.92	Benzenamine, 2-methoxy-N,N-dimethy
3	15.219	177030	29291	6.04	4-Methoxy-3,5-dimethylpyridine-2-carl
4	16.553	768135	116759	6.58	4-Methylethcathinone
5	16.742	314405	26258	11.97	Argon
6	17.696	1599999	244230	6.55	Tapentadol
7	17.800	392216	46862	8.37	Argon
8	18.841	140324	23146	6.06	1,2-Benzenedicarboxylic acid, bis(2-m
		6901764	801748		

FIGURE 6.17 Residual solvent analysis of ESM SDD using HS-GC/MS

6.2.15 Stability Studies

The parameters that were observed during the Accelerated Stability testing based on the International Council for Harmonisation (ICH) guidelines are summarized in Supplementary Table 6.8. All the metrics indicated a lack of statistically significant change in the end results when compared to the original data at time 0. Based on the available evidence, it can be inferred that the oral formulation that was created exhibited stability during the designated time period of 6 months.

TABLE 6.8 Accelerated Stability Study of ESM SDD as per ICH Guidelines

Test parameter	**Specifications**	**Initial**	**1st Month**	**3rd Month**	**6th Month**
Description	Cream colored Spray dried powder	Cream colored Spray dried powder	Cream colored Spray dried powder	Cream colored Spray dried powder	Cream colored Spray dried powder
% Assay (Drug Content)	NLT 90% and NMT 110% of label claim	97.62±0.637	97.19±0.763	95.94±0.667	94.94±0.579
Solubility (mg/ml)	NLT 90% and NMT 110% of initial data	1.45±0.03	1.437±0.042	1.367±0.021	1.313±0.035
% Drug release at 2 hrs in 0.1 N HCl	NLT 90% and NMT 110% of initial data	7.86±0.09	7.69±0.0.162	7.27±0.113	7.055±0.417

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CHAPTER 7

Conclusions

7.1 Development of Posaconazole Gastro-retentive formulation

- ✓ In the present study, an SDD based oral gastro-retentive formulation was developed using an industrially feasible spray drying technique for the sustained release of the weakly basic drug Posaconazole in the gastric environment, where its solubility is higher compared to intestinal pH.
- ✓ The ternary ASD were prepared using carriers Soluplus®, which has an excellent solubilization properties, and lipid polymer Gelucire 43/01, which has floating and sustained release properties.
- ✓ The ratio of SD carriers was optimized based on DOE using 3^2 Full Factorial Design. The final optimized formulation was decided from the Design Space of an overlay plot having desirability 1 for the selected constraints. The optimized batch of SDD possessed almost 2-folds enhanced solubility compared to the API, along with controlled release in simulated gastric pH for 8 hours.
- ✓ The release kinetics evaluated by the DD Solver Excel Add-in confirmed K-peppas kinetics with non-fickian diffusion.
- ✓ The selected SDD batch fulfilled all the required characteristics desired for the compatibility and complexation between API and carrier confirmed by FTIR, DSC, and PXRD studies.
- ✓ The particle size of the optimized batch was in the micron range, supporting the improved solubility of the BCS Class II drug. The surface morphology study undertaken using SEM scan revealed spherical shape of SDD.
- ✓ The developed SDD was sufficient to obtain gastric retention with no floating lag time, > 8hrs floating duration and > 90% buoyancy, as confirmed from *in-vitro* buoyancy study.
- ✓ The developed SDD, equivalent to 20mg dose, encapsulated in capsule shell was stable as per ICH guidelines.
- ✓ The gastro-retention was confirmed through an *in-vivo* roentgenography study in New Zealand white rabbit. The pharmacokinetics study executed in male Sprague-Dawley

rats proved the efficiency of the developed formulation in comparison to the marketed formulation using PK Solver Excel Add-in. The statistical significance was confirmed based 2-way Annova studies followed by Sidak's multi-comparison test.

- ✓ The major limitation of variable bioavailability of standard Noxafil oral suspension may be overpowered by the developed novel formulation.

7.2 Development of Esomeprazole Delayed Release Formulation

- ✓ In the present study, spray dried dispersion based oral formulation was developed for the delayed release of PPI Esomeprazole magnesium.
- ✓ The significant process and formulation variables were optimized based on DOE concept using Box-Behnken Design, a preferred Response Surface optimization method. The final optimized formulation was decided from the Design Space of overlay plot having desirability 1 for the selected constraints. The optimized batch of SDD possessed almost 3-folds enhanced solubility compared to the API along with the at least 90% dose retention in final dosage form during the transit from gastric pH to intestinal pH.
- ✓ Both these targets were solely achieved by the SD carrier HPMCAS-MF having excellent solubilization properties and solubility above pH 6.
- ✓ Hence, this approach may be extended to any API having stability issues in upper GIT or for the API having absorption window in lower GIT.
- ✓ The selected SDD batch fulfilled all the required characteristics desired for the compatibility and complexation between API and carrier confirmed by FTIR, DSC and PXRD studies.
- ✓ The particle size of the optimized batch was in micron range supporting the improved solubility of BCS Class II drug. The surface morphology study undertaken using SEM scan revealed spherical shape of SDD.
- ✓ The developed SDD encapsulated in hard gelatin capsule dosage form was sufficient to procure the delayed release eliminating the need of enteric coating and/or multi-particulate dosage form prevalent in marketed formulation.

List of Publications

1. **Solid dispersion technology as a formulation strategy for the fabrication of modified release dosage forms: A comprehensive review.**
   Authors: **Kaushika Patel**, Shreeraj Shah, Jaymin Patel
   Publication date: 18 April 2022, Issue: June 2022
   Source: DARU Journal of Pharmaceutical Sciences **(Clarivate IF: 4.1)**
   Volume: 30, Issue: 1, Pages165-189
   Publisher: Springer International Publishing, DOI: 10.1007/s40199-022-00440-0

2. **Development of Delayed Release Oral Formulation Comprising Esomeprazole Spray Dried Dispersion utilizing design of experiment as an optimization strategy.**
   Authors: **Kaushika Patel**, Jaymin Patel, Shreeraj Shah
   Published date: 12 Sept, 2023
   Volume:24, Issue: 7, Pages: 186
   Source: AAPS PharmSciTech **(Clarivate IF: 3.3)**
   Publisher: Springer International Publishing, DOI: 10.1208/s12249-023-02642-4

3. **A Novel Posaconazole Oral formulation using Spray Dried Solid Dispersion Technology: in-vitro and in-vivo study**
   Authors: **Kaushika Patel**, Vijay Kevlani, Shreeraj Shah
   Published date: 11th Nov, 2023
   Source: Drug Delivery & Translational Research **(Clarivate IF: 5.4)**
   Publisher: Springer International Publishing