Solid Self-Emulsifying Drug Delivery System of Domperidone for Improved Biopharmaceutical Characteristics

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of
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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The thesis titled “Solid Self-Emulsifying Drug Delivery System of Domperidone for Improved Biopharmaceutical Characteristics” submitted by Saadia Shams Chowdhury (ID 18346063) of Summer, 2018 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy

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Ethics Statement

The study does not involve any kind of animal or human trial.

Abstract

The aim of this study was to use a solid-self emulsifying drug delivery system (S-SEDDS) to increase the solubility and dissolution rate of Domperidone (DMP), a poorly soluble, weakly basic anti-emetic medication. Several ratios of Kollisolv, Kolliphor® P188, and Glycerin were trialed and an S-SEDDS-DMP was formulated using the optimized ratio. Dynamic Light Scattering (DLS), Scanning Electron Microscopy (SEM), Differential Scanning Calorimetry (DSC), X-ray Powder Diffraction (XRPD), Fourier-transform infrared spectroscopy (FT-IR), and *in-vitro* dissolution rate experiments were used to characterize the S-SEDDS-DMP. The lack of incompatibilities between DMP and the utilized polymers was established by FT-IR and DSC tests. DSC, SEM, and XRPD analyses demonstrated that the drug in the produced S-SEDDS changed from crystalline to amorphous. It may be stated that the S-SEDDS approach was a successful tool for improving DMP dissolution.

Keywords: Domperidone; Solubility; Solid self-emulsifying drug delivery system (S-SEDDS); Bioavailability; Dissolution; BCS Class II drug

Dedication

To my parents

Acknowledgement

First and foremost, I would like to thank Almighty Allah.

This research paper could not have been completed without the constant support of several individuals and I would like to express my sincere gratitude to all of them.

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List of Acronyms

DMP	Domperidone
SEDDS	Self-emulsifying drug delivery system
S-SEDDS	Solid Self-emulsifying drug delivery system
BCS	Biopharmaceutical Classification System
NCE	New Chemical Entity
SEM	Scanning Electron Microscopy
DLS	Dynamic Light Scattering
DSC	Differential Scanning Calorimetry
XRPD	X-ray Powder Diffraction
FTIR	Fourier Transform Infrared Spectroscopy

Chapter 1

Introduction

1.1 Domperidone

Domperidone (DMP) is an antiemetic drug, used in the treatment of upper gastrointestinal motility problems, nausea and vomiting management, and as a supplementary therapy in Parkinson's disease patients. DMP blocks a neurotransmitter, dopamine, which mediates receptive relaxation of the stomach, partially preventing the effect of dopamine (Reddymasu et al., 2007).

1.2 Solubility

The drug's solubility is a critical physicochemical property that influences its absorption and therapeutic effectiveness. The rate at which a drug from a certain dosage form goes into solution is also determined by drug solubility (Khadka et al., 2014). It is a crucial factor in determining the amount of drug that will enter the systemic circulation and have the intended therapeutic effect (Savjani et al., 2012).

Only solubilized drug molecules can pass through cellular membranes and reach the region of pharmacological action (vascular system for instance). Any drug that is to be absorbed should be in the form of an aqueous solution at the absorption site. Because solubility and permeability are essential factors in drug absorption *in vivo*, they can be manipulated or increased using enhancing approaches. Poorly soluble drugs, which belong to BCS class II, also provide several *in vitro* formulation challenges, such as severely limited drug delivery

methods. More than 40% of the NCEs (new chemical entities) created recently in the pharmaceutical industry are essentially insoluble in water (Chaudhary et al., 2012).

Furthermore, a drug's solubility is determined by various parameters, including the content of the dissolution medium, the physical form of the solid, the temperature and pressure of the environment, particle size, molecular size, polarity, and polymorphism. Physical and chemical alterations, as well as other approaches, are used to improve solubility. Particle size reduction (micronization and nanosuspension), crystal habit change, solid solutions, solid dispersions, and cryogenic procedures are examples of physical approaches. pH adjustment, complexation, buffer usage, derivatization, and salt production are examples of chemical alterations. The suitable procedure is determined by the drug's properties, excipients, and the intended pharmaceutical formulation (Manogna et al., 2017).

1.2.1 Solubility of Domperidone

Protein binding for DMP is 92%, and the elimination half-life is 5-7 hours. Domperidone has a low aqueous solubility (0.986 mg/L), and its oral bioavailability has been estimated to be between 13 and 17 percent. One potential explanation for its limited bioavailability is its poor water solubility (Reddymasu et al., 2007).

Additionally, DMP has a high melting point (244°C to 248°C), indicating that it has a high crystal lattice energy. This is one of the reasons for low aqueous solubility. As a result, any technique that breaks the crystalline structure of DMP will be more successful in enhancing its water solubility (Ibrahim et al., 2011).

1.2.2 Importance of enhancement of solubility

According to Savjani et al. (2012), improving drug solubility and hence oral bioavailability remains one of the most difficult aspects of the drug development process, particularly for oral-drug delivery systems. There are several ways available and documented in the literature to improve the solubility of drugs that are poorly water-soluble. The approaches are chosen based on factors, such as the qualities of the drug under evaluation, the nature of the excipients to be used, and the nature of the desired dosage form.

Bioavailability can be improved by increasing the drug's solubility and dissolution rate in gastrointestinal fluids, particularly for class II (low solubility and high permeability) compounds. The rate-limiting step for BCS class II medications is drug release from the dosage form and solubility in the gastrointestinal fluid, not absorption, hence increasing solubility enhances bioavailability for BCS class II drugs (Krishnaiah, 2010; “Solubility Enhancement Techniques: A Review,” 2021).

1.3 Biopharmaceutical Classification System

In terms of research, the Biopharmaceutical Classification System (BCS) has improved the application and validity of drug solubility and permeability. Drug absorption is now well understood to be dependent on bioavailability and bioequivalence throughout the drug development process supplied by the United States Food and Drug Administration. The Biopharmaceutical Classification System (BCS) is a useful tool for making decisions throughout the early stages of drug development. The BCS was developed in 1995 and quickly established a standard for regulating oral dosage form’s bioequivalence (P Chavda, 2017).

The BCS is a scientific framework that categorizes drugs based on two parameters: a. aqueous solubility and b. intestinal permeability. If the drug substance's absorption is permeation rate restricted, solubility will not be a controlling parameter, and therefore the *in vitro* dissolution research can be utilized to establish the bioavailability (BA) or bioequivalence (BE) of the therapeutic product via *in vitro* - *in vivo* connection (IV–IVC) (Arrunátegui et al., 2015). Each class of BCS includes a specifically specified rate-limiting step with modification options, allowing the formulator to select and optimize a specific dosage form for the drug ingredient belonging to that class of BCS. Here, we will primarily concentrate on some of the new BCS principles (P Chavda, 2017).

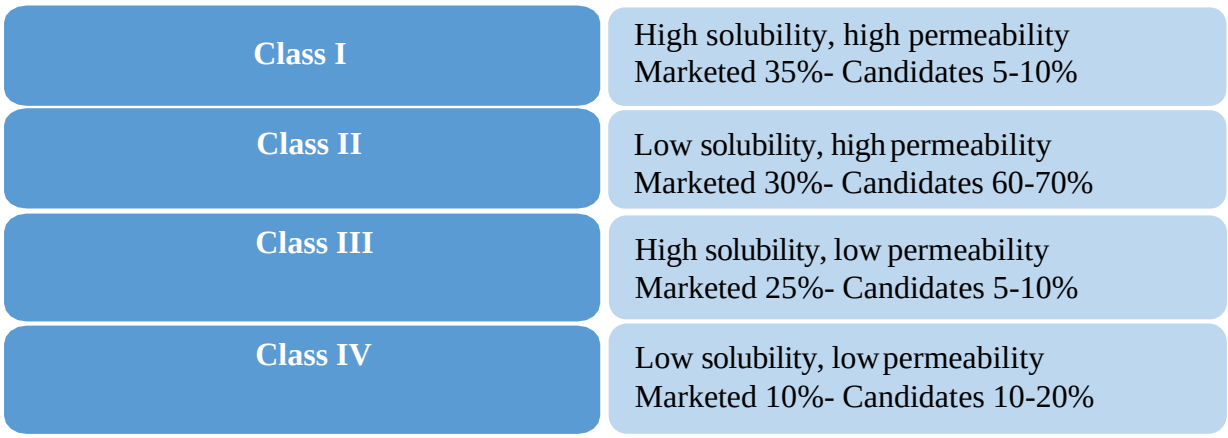


Figure 1: Percentage of marketed drug molecules according to the BCS classification system (Nikolakakis & Partheniadis, 2017).

1.3.1 BCS Class II

DMP is classified as a class II drug by the Biopharmaceutical Classification System (BCS) since it is weakly water-soluble and very permeable (Swami et al., 2010; Zhang et al., 2011). It is nearly insoluble in water (1 part in 50,000 parts of water) and has a pKa value of 7.9, indicating that it is a weakly-basic drug with a very slow dissolving rate at a very high pH

value (Council of Europe, 2014). This limits the rate of drug absorption and reduces bioavailability to 13-17% following oral dosing (Swami et al., 2010; Zhang et al., 2011).

1.4 Techniques of Enhancing Solubility of Domperidone

1.4.1 Physical Modification

i. By Using Cogrinding and Kneading Technique

By co grinding and kneading, solid dispersions of DMP were produced utilizing varied ratios of PVP and PEG as carriers. In a mortar and pestle, adequate amounts of drugs and carriers were mixed in varying mass ratios to create the co-grinding combinations. The kneading method employed a little amount of water-ethanol combination to disperse the drug and carriers. Solid dispersions were made with two carriers, PEG 4000 and PVP K25, using two distinct methods: cogrinding and kneading (Tyagi & Dhillon, 2012).

ii. By Complexation with The Large Ring Cyclodextrin

Large ring cyclodextrins (LR-CDs) have a moderately hydrophobic cavity that can trap molecules and form inclusion complexes. DMP solubility was increased thrice in LR-CD/DMP complexes compared to smaller CD/DMP complexes (Ismail et al., 2021).

iii. Using Modified Locust Bean Gum by Solid Dispersion Technique

Nagpal et al. (2016) investigated the potential of natural carrier MLBG for improving the solubility of DMP fast dissolving tablets. MLBG's wetting capacity, along with the drug's decreased particle size in solid dispersions, resulted in better drug solubility. The improved dissolution qualities of the drug's solid dispersion powder in fast dissolving tablets result in increased drug bioavailability as compared to pure DMP fast dispersible tablets.

iv. Using Melt Granulation Technique

Melt granulation is a method for effectively agglomerating drug powders using meltable polymers and surfactants. The advantage of this approach over traditional granulation is that neither water nor organic solvents are required. Because the drying stage is skipped, the technique takes less time and consumes less energy than wet granulation. Hydrophilic polymers polyethylene glycol-6000, 4000, and Myrj52 were used to make granules. When compared to the pure drug and marketed product, the melt granules' solubility and in-vitro dissolution characteristics improved significantly. DMP's internal energy changed with polymer and surfactant in melted granules, according to DSC data (Patel et al., 2011).

1.4.2 Chemical Modification

i. By Solvent Change *in situ* Micronization Technique

The particle size in this technique is less than 10µ. This approach is known as in situ micronization since the micron-size particles are generated immediately during the process without any size reduction. In comparison to milling, the particles are of uniform size, and the powder is less cohesive. The molecularly dissolved drug is transformed into the required particle size using a solvent change or pH change procedure, and the particles are stabilized and covered with a stabilizer. Stabilizers are lyophilic molecules or polymers that have a significant tendency to be adsorbed on freshly formed hydrophobic surfaces of particles, preventing the formation of micron-sized crystals through steric hindrance and increasing their water solubility. The in situ micronization procedure is used to improve the solubility of some medications that are poorly water-soluble (Varshosaz & Enteshari, 2018).

ii. Using Hydroxypropyl-β-Cyclodextrin by Inclusion Complexation Technique

DMP fast dissolving tablet was made by inclusion complexation utilizing HP-β-CD by kneading process. The application of HP-β-CD dramatically improved DMP solubility. Similarly, the introduction of SSG improved disintegration (Sodium Starch Glycolate) (Thapa et al., 2014).

iii. By Dispersion in Various Hydrophilic Carriers

DMP solubility tests were carried out using several hydrophilic carriers such as sorbitol, mannitol, PEG 4000, PEG 6000, pluronic F-68, and pluronic F-127. The use of hydrophilic carriers increased DMP solubility, and this increase was dependent on the type and concentration of the carrier. Pluronic F-127 and F-68 had the greatest solubilizing impact on DMP and were chosen for the creation of solid dispersions. FT-IR investigations revealed that DMP and pluronics are not incompatible. DSC and P-XRD analyses indicated that DMP was transformed from the crystalline to the amorphous state in the produced solid dispersions, resulting in increased drug solubility and dissolution rate. The formulation of solid dispersions significantly improved DMP solubility and dissolving rate. Increasing the quantity of carriers in the system improved solubility and dissolution rate even more. The solubility and dissolution rate of solid dispersions made with pluronic F-68 were greater than those prepared with pluronic F-127 (Aboutaleb et al., 2016)

iv. By Development of Self-Micro Emulsifying Drug Delivery System

One of the most recent techniques for the formulation of unit dose form for drugs with limited water solubility is solid SMEDDS. The choice of oil, surfactant, and cosurfactant mix is critical and varies from medicine to drug depending on solubility studies. Adsorption on a carrier transformed the liquid SMEDDS pre-concentration into a solid (Aerosil 300). The improved solid SMEDDS formulation of DMP demonstrated a considerable improvement in

dissolving rate when compared to the marketed tablet and pure drug, indicating SMEDDS's potential (Laddha et al., 2014).

1.5 SEDDS

According to Kalepu et al. (2013), lipid-based drug delivery methods have gained popularity in recent years for enhancing the solubility of weakly water-soluble drugs as well as improving the oral bioavailability of lipophilic drugs. Among the most frequently employed lipid drug delivery methods, are nanoparticles (made of lipids) (nanoemulsions, solid lipid nanoparticles, lipid drug conjugates, nanosuspensions, liposomes, lipid nanocapsules, and liquid crystalline nanoparticles). SEDDS are one of the most promising and innovative lipid-based drug delivery systems. By raising the surface area of drug particles and boosting permeability across the membranes, self-emulsifying drug delivery systems (SEDDS) have emerged as possible drug delivery techniques for the solubility of poorly soluble drugs (Ijaz et al., 2016).

SEDDS formulations are isotropic formulations of natural or synthetic oil, surface-active compounds, or a single or many hydrophilic solvents and co-solvents with a drug that freely form oil-in-water nanoemulsions in aqueous conditions after slight stirring (Chen et al., 2018; Vithani et al., 2019). Lipophilic drugs are easily encapsulated inside minute-diameter droplets, resulting in a high surface area for absorption and enhanced bioavailability (Kazi et al., 2017). These formulations have demonstrated a strong capacity to increase intestinal absorption of a wide range of drugs. Many studies have shown that oil-in-water (O/W) emulsions improve drug absorption in the intestine, but the instability of this form has been a major barrier to their application. The appearance of self-emulsifying systems solved the problem of formulation stability since the emulsion is created only before administration (Gursoy & Benita, 2004). Furthermore, in research by Jianxian et al. (2020), SEDDS have

also been shown to considerably improve the oral bioavailability of drugs that are quickly metabolized but poorly soluble.

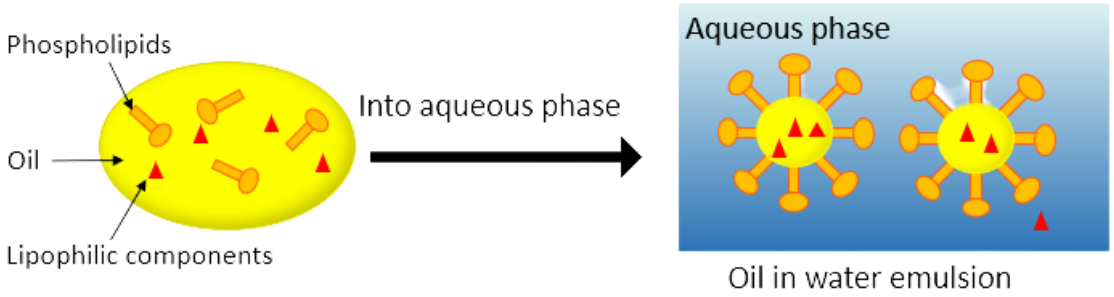


Figure 2: SEDDS

1.5.1 S-SEDDS

SEDDS can exist in both liquid and solid forms. However, SEDDS are typically confined to liquid dose forms since many excipients used in SEDDS are not solids at room temperature. S-SEDDS have been widely used in recent years because to the advantages of solid dosage forms since they typically provide more effective alternatives to traditional liquid SEDDS (Tang et al., 2008).

S-SEDDS refers to solid dosage forms with self-emulsification capabilities in the field of dosage forms. S-SEDDS concentrates on the inclusion of liquid/semisolid SE components into powders/nanoparticles by various solidification procedures (for example, adsorptions to solid carriers, spray drying, melt extrusion, nanoparticle technologies, and so on). These powders/nanoparticles, which correspond to SE nanoparticles/ dry emulsions/solid dispersions, are often processed further into additional solid SE dosage forms or, alternatively, packed into capsules (i.e., SE capsules). SE capsules are also those into which liquid/semisolid SEDDS are directly packed without the need of a solidifying excipient (Tang et al., 2008).

Because S-SEDDS are, to some extent, mixtures of SEDDS and solid dosage forms, many of their qualities (for example, excipient selection, specificity, and characterization) are the sum of the relevant properties of both SEDDS and solid dosage forms (Tang et al., 2008).

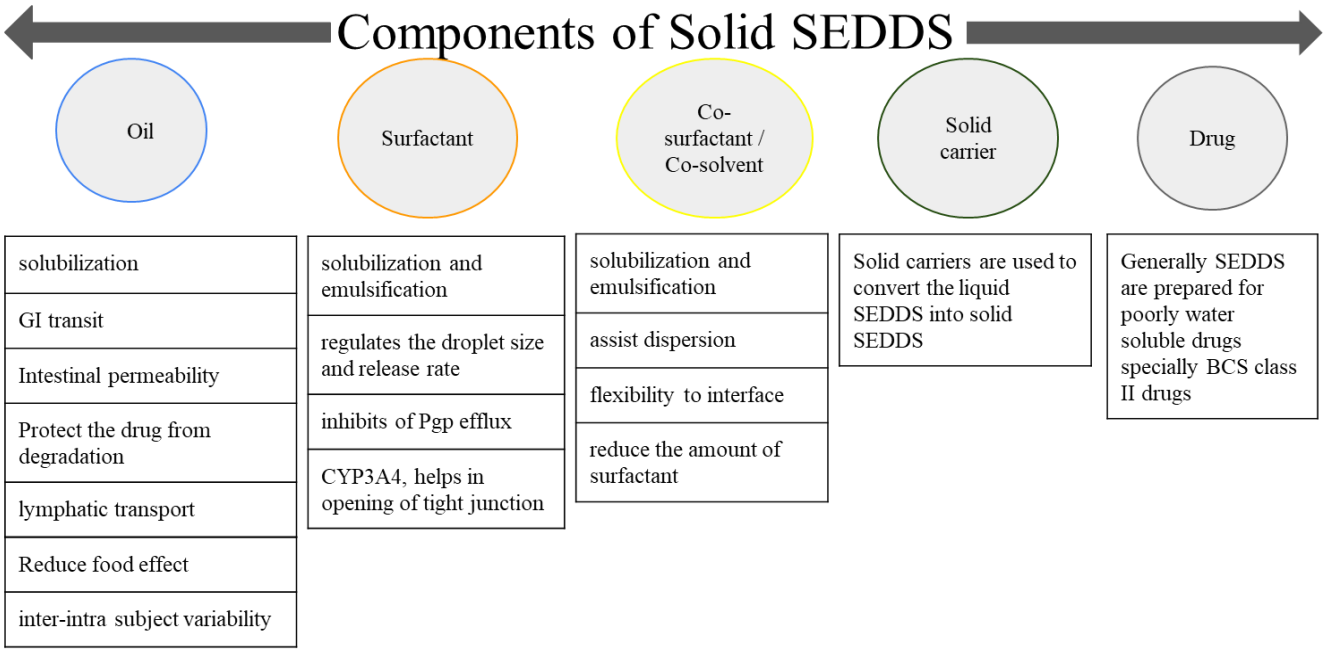


Figure 3: Role played by the components of S-SEDDS (adapted from Maji et al., 2021).

1.5.2 Preparation of S-SEDDS

At room temperature, the oily/lipid component is often a fatty acid ester or a medium/long-chain saturated, partially unsaturated, or unsaturated hydrocarbon. Mineral oil, vegetable oil, silicon oil, lanolin, refined animal oil, fatty acids, fatty alcohols, and mono-/di-/tri-glycerides are some examples (Gursoy & Benita, 2004).

Non-ionic surfactants with a moderately high hydrophilic-lipophilic balance (HLB) value are the most commonly suggested surfactants. To generate stable SEDDS, the surfactant concentration should be between 30% and 60% (w/w) (Tang et al., 2008).

S-SEDDS have been prepared using a number of processes, including adsorptions to solid carriers, spray drying, melt extrusion, and nanoparticle technology. Adsorptions to solid carriers, spray drying, melt extrusion, and nanoparticle technology have all been employed in the creation of S-SEDDS (Tang et al., 2008).

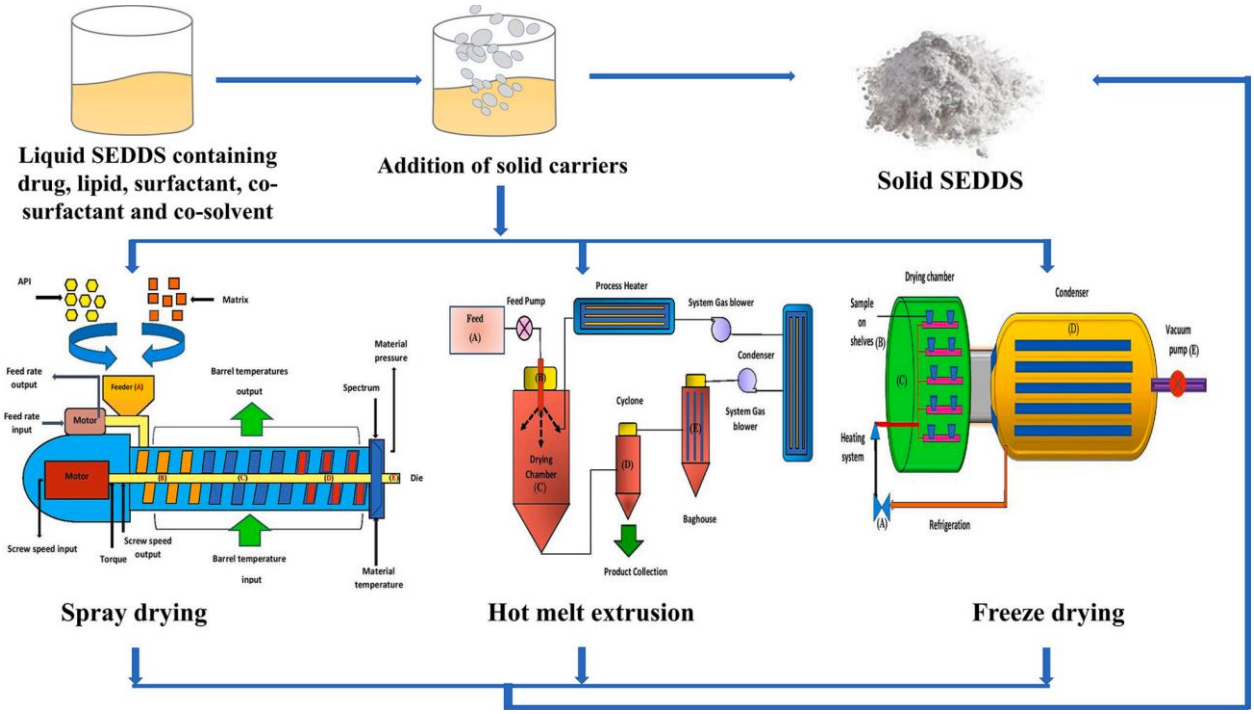


Figure 4: Solidifying techniques involved in the preparation of S-SEDDS(Maji et al., 2021).

1.6 Purpose of This Study

To enhance biopharmaceutical properties like dissolution and bioavailability of the poorly soluble hydrophobic drug, DMP, and to minimize the loss of dose of the drug by improving the solubility and dissolution in the aqueous system by formulating a Solid Self-emulsifying drug delivery system (S-SEDDS).

S-SEDDS development is a technique in lipid-based formulation design that, in addition to improving solubility, offers other advantages over liquid systems. S-SEDDS combines the

advantages of liquid SEDDS, such as increased solubility and bioavailability, with the advantages of solid dosage forms, such as ease of handling and administration, improved patient compliance, high stability and reproducibility, faster and easier production, and thus lower production cost) (Nikolakakis & Partheniadis, 2017).

Chapter 2

Methodology

2.1 Materials

DMP was procured from Beximco, Kolliphor ® P118 and Kollisolv from BASF Bangladesh, HPMC K4M from Evonik Bangladesh. All other chemicals and apparatus were procured from commercial sources.

2.2 Preparation of Standard Curve of DMP

The stock solution was prepared by dissolving 10 mg of DMP in 100mL methanol in a volumetric flask; therefore, the concentration of the stock solution was 0.1mg/mL. The stock solution was further diluted to prepare concentrations ranging from 2.5, 5, 10, and 20µg/mL.

Table 1: Preparation of varying concentrations of DMP for the standard curve

Sl no.	Preparation	Concentration
A	200 µL of the stock solution, and 800 µL of distilled water	20 µg/mL
B	100 µL of the stock solution, and 900 µL of distilled water	10 µg/mL
C	500 µL from B, and 500µL of distilled water	5 µg/mL

D	500 µL from C, and 500 µL of distilled water	2.5 µg/mL
E	200 µL from C, and 800 µL of distilled water	1 µg/mL

2.3 Optimization of Vehicle

2.3.1 Polymer Ratio

Thirty different combinations of Kollisolv, Kolliphor® P188, and Glycerin were trialed to find the most optimized ratio for the preparation of the self-emulsifying drug delivery system.

Table 2: Trialing of 30 different combinations of Oil:Surfactant:Cosurfactant

	Kollisolv (OIL)	**Kolliphor® P188 (SURFACTANT)**	**Glycerin C (CO-SURFACTANT)**
SL	**Ratio**	**Ratio**	**Ratio**
1	25	70	5
2	25	65	10
3	30	60	10
4	30	55	15
5	30	50	20
6	35	45	20
7	35	40	25
8	20	75	5
9	15	80	5
10	10	85	5
11	20	70	10
12	20	65	15
13	25	60	15
14	15	75	10
15	40	45	15
16	35	50	15
17	35	55	10

18	30	65	5
19	40	50	10
20	45	50	5
21	25	70	5
22	40	55	5
23	35	60	5
24	12	78	10
25	42	53	5
26	25	65	10
27	20	75	5
28	24	60	16
29	20	64	16
30	32	60	8

2.4 Construction of Pseudo-Ternary Phase Diagram

A pseudo-ternary phase diagrams of oil (Kollisolv), surfactant (Kolliphor® P188), and cosurfactant (Glycerin) was created in order to identify the fine emulsion area in the phase diagram. Different weight ratios of oil, surfactant, and cosurfactant were combined with water with stirring to estimate the solubility of DMP and stable emulsification formation, and the mixture was visually examined for phase separation, phase clarity, and precipitation. The fine emulsion zone was then identified.

2.5 Preparation of SSEDDS

The optimal oil, surfactant, and cosurfactant ratio from the pseudo-ternary phase diagram was chosen to prepare the S-SEDDS-DMP formulation.

In total, 500mg equivalent of DMP was prepared.

The SEDDS was weighed and, 10% of DMP, and 7% of HPMC was added. It was mixed well in a water bath (50℃) for 30 minutes and after it was completely dissolved, 10% Aerosil 200 was added. The formulation was dried using a vacuum drying oven for about 4 hours.

2.6 Dissolution study

The SEDDS with the best results in the pseudo-ternary diagram was then investigated for its *in-vitro* dissolution profile. The S-SEDDS (which contained 50mg equivalent of DMP) was placed in a vessel. The dissolution study was conducted at 37°C using the USP-II, paddle technique, with 900 ml of distilled water, poured into each vessel and revolving at 50 rpm. At each designated time point (10, 20, 30, 45, 60, and 120 minutes), 2 ml of the filtered sample was obtained and diluted 5 times using methanol. The concentration of S-SEDDS-DMP in water was determined using a UV spectrophotometer at 284nm. Each analysis had three duplicates. The same procedure was performed for raw DMP as well. Percentage of drug release was computed using the following equation:

$$\frac{\text{Concentration} \times \text{Dilution factor} \times 900}{1000} \times 100$$

2.7 Physicochemical Characterization

Several techniques were employed to determine the physicochemical characteristics.

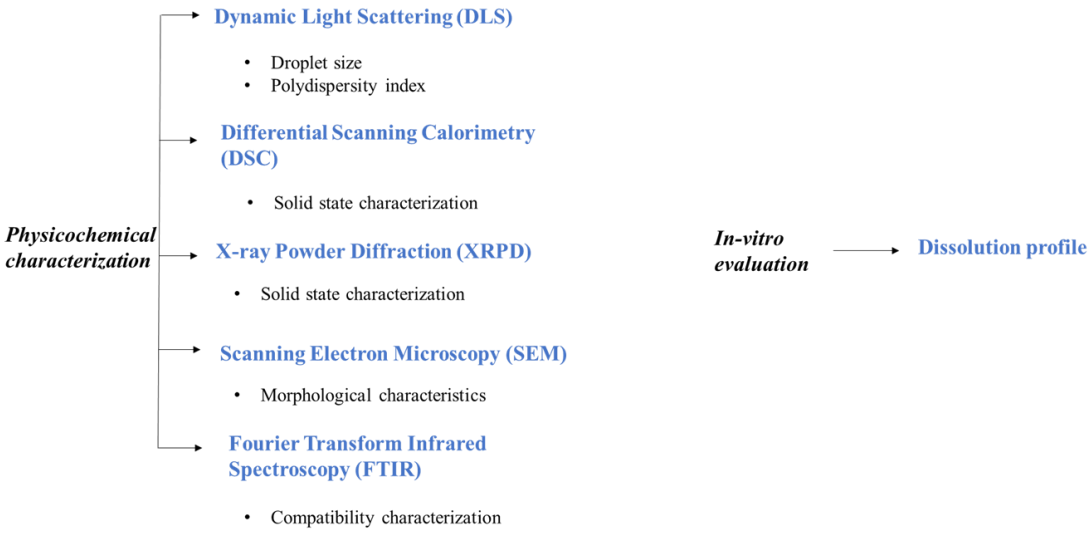


Figure 5: Techniques used for characterization and evaluation of S-SEDDS.

2.7.1 Dynamic Light Scattering (DLS)

The dynamic light scattering (DLS) method was used to assess the mean particle sizes distribution, polydispersity index (PDI) of the aqueous suspended S-SEDDS-DMP using a Zetasizer Ultra (MALVERN, Worcestershire, UK). S-SEDDS-DMP was disseminated in Milli-Q before being utilized for particle size distribution analysis. The analysis was carried out in triplicate (Halder et al., 2021).

2.7.2 Scanning Electron Microscopy (SEM)

SEM was done to obtain information on surface topography, and crystalline structure (Andrews, 1981). The SEM analysis was done on a Miniscope® TM3030 (Hitachi, Tokyo, Japan). The samples of crystalline DMP and S-SEDDS-DMP were put on an aluminum sample holder and secured with double-sided carbon tape. The samples were coated with platinum using a magnetron sputtering equipment, MSP-1S (Vacuum Device, Ibaraki, Japan) (Halder et al., 2021).

2.7.3 X-ray Powder Diffraction (XRPD)

XRPD analysis was performed for the comparison of crystalline DMP structure with the amorphous S-SEDDS-DMP.

The x-ray powder diffraction (XRPD) was done on a Mini Flex II (Rigaku, Tokyo, Japan) using Cu Kα radiation at 40 mA and 35 kV. The device was set to scan at 4°/min, and the DMP samples were scanned over a range of 2 angles ranging from 10° to 35° with a step size of 0.2° (Halder et al., 2021).

2.7.4 Differential Scanning Calorimetry (DSC)

DSC study was also performed for the comparison of crystalline DMP structure with the amorphous S-SEDDS-DMP. Thermal analysis of DMP samples was performed using a DSC Q1000 (TA Instruments, New Castle, DE, USA) with a heating rate of 5°C/min and purging nitrogen gas (50 ml/min). The DMP samples were put in aluminum sample pans and sealed. DSC thermal analysis was performed on accurately weighed (about 3 mg) samples. As a reference standard, indium (8-10 mg, 99.999% pure, onset at 156.6°C) was utilized to calibrate the system (Halder et al., 2021).

2.7.5 Fourier Transform Infrared Spectroscopy (FTIR)

FTIR was performed to check for any interaction between DMP and the polymers. Hence the compatibility between them was established.

The drug, polymers, and produced formulation, were all subjected to a qualitative FT-IR examination. Samples of 1-2 mg were combined with potassium bromide (IR grade) and crushed into discs under vacuum in a compressor unit before being scanned from 4000 to 400 cm-1 using an FT-IR spectrometer (Shimadzu IR-470, Japan) with an empty pellet holder as a reference (Aboutaleb et al., 2016).

Chapter 3

Results and Discussion

3.1 Standard Curve of DMP

When the absorbance was plotted against the concentration, a linear calibration curve with a correlation coefficient (R^2) of 0.9991 was obtained.

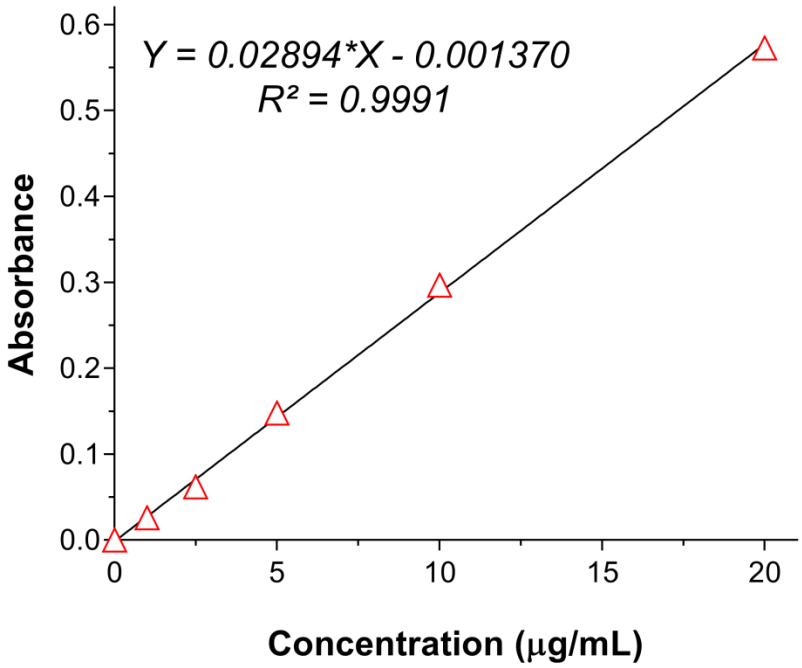


Figure 6: Standard curve of DMP

3.2 Optimization of SEDDS Composition

The optimized ratio of oil, surfactant, and cosurfactant, was found from the pseudo-ternary phase diagram, which showed the optimum ratio of oil, surfactant, and cosurfactant to be 25:60:15 respectively.

An increased concentration of the surfactant, Kolliphor® P188 was successful in enhanced emulsification, which was evident in the pseudo-ternary phase diagram.

According to a prior study, raising the concentration of surfactant increased the rate of self-emulsification, and a percentage of surfactant below 60% demonstrated inadequate emulsification. A greater surfactant concentration can stabilize the oil/ water interface and generate a fine emulsion with tiny droplet size and low viscosity (Halder et al., 2021). The results obtained from this study are therefore consistent with literature findings.

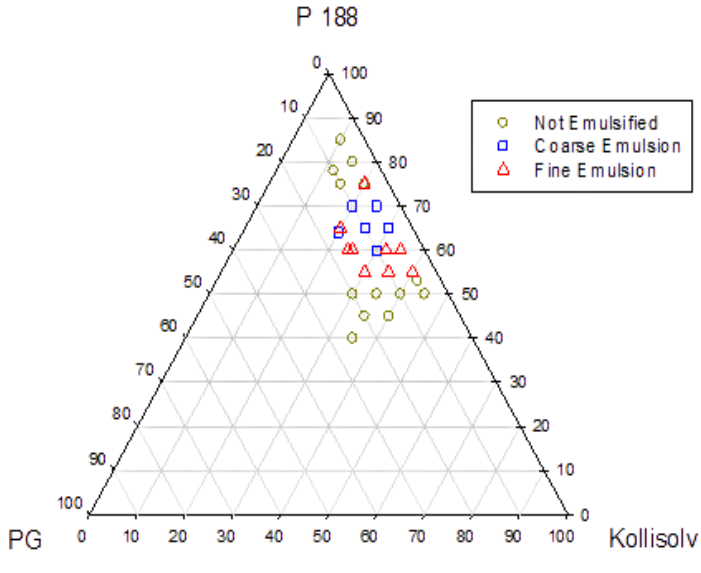


Figure 7: Pseudo-ternary phase diagram of SEDDS formulations in water

Table 3: Preparation of SEDDS

A (OIL) (Kollisolv)	**B (Surfactant) (Kolliphor® P188)**	**C (Co-surfactant) (Glycerin)**
Ratio 25	Ratio 60	Ratio 15

3.3 Dissolution Study

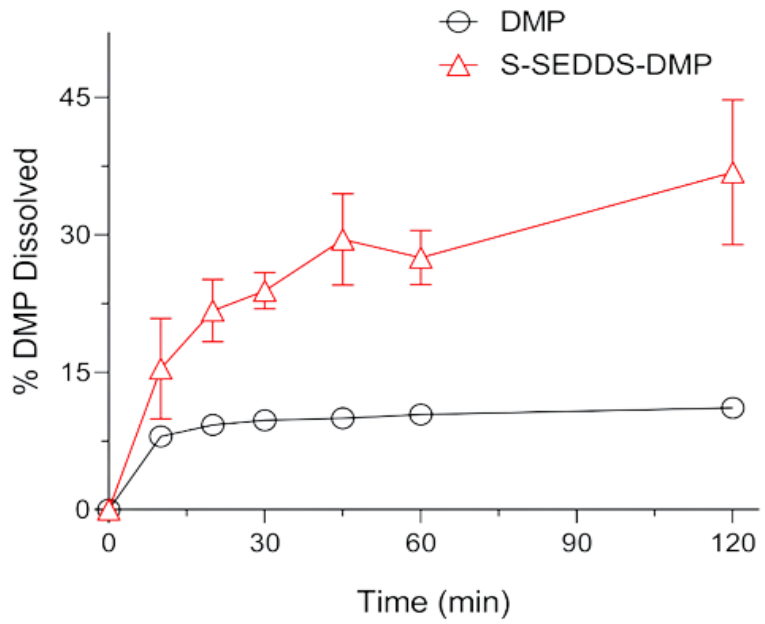


Figure 8: In vitro dissolution properties of DMP samples. Data represent the mean±S.D. of 3 experiments.

Crystalline DMP showed a 10% dissolution over a period of 2 hours, whereas, S-SEDDS-DMP showed about a 35% dissolution over a period of 2 hours.

Based on the pseudo-ternary phase diagram, S-SEDDS was formulated with the optimum ratio and its drug release profile was assessed. The formulation's drug release patterns were investigated in distilled water, and the concentration of the drug was calculated using the standard curve equation (Figure 5): $y = 0.029x - 0.002$

The dissolution profile showed an increase in % DMP released by S-SEDDS-DMP compared to crystalline DMP. This indicates that formulation of the S-SEDDS-DMP would result in a better release profile and therefore may have a better solubility compared to crystalline DMP.

3.4 Physicochemical Characterization

3.4.1 Dynamic Light Scattering (DLS)

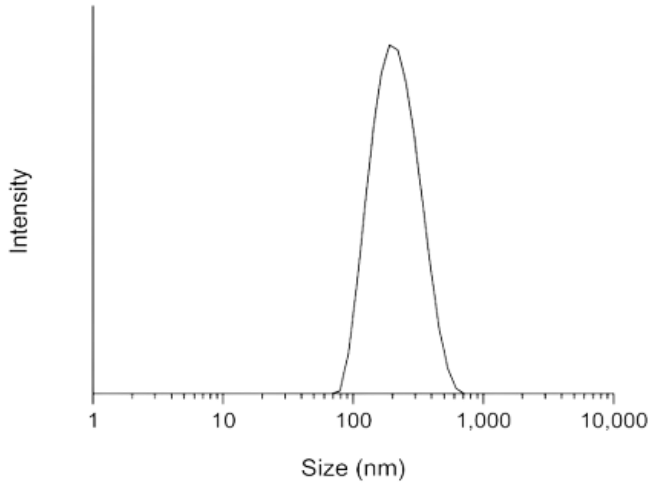


Figure 9: Particle size distribution of S-SEDDS-DMP sample in water.

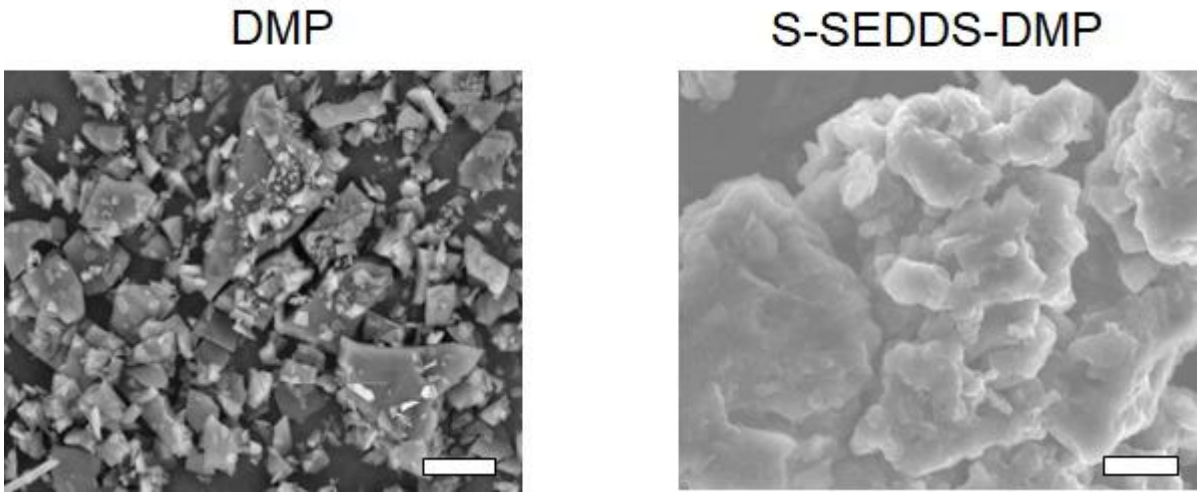
The mean diameter found was 265 nm and the poly-dispersity index was 0.242.

Particle size has a significant influence on medication solubility and absorption. The S-SEDDS-DMP DLS analysis demonstrated that the produced formulation had particle sizes ranging from 70 to 800 nm. However, the majority of particles have a mean diameter of 265 nm. According to the Noyes Whitney equation, the particle sizes are substantially smaller with higher disjoining pressure and increased surface area, which boosts the formulation's interfacial solubility compared to crystalline DMP. The polydispersity index was 0.242. A polydispersity value greater than 0.7 indicates that the particle size is broadly distributed (Jambhekar & Breen, 2013). Therefore, the study conducted was successful in reducing the particle size with a lower polydispersity index.

Because dissolution and absorption are closely coupled, the impact in this respect is that solubility increases as particle size decreases. As a result, we hypothesize that when

introduced into aqueous media, this S-SEDDS-DMP may be useful in enhancing the dissolving behavior of DMP due to the production of minute particles in dispersion phase (Halder et al., 2021).

3.4.2 Scanning electron microscopy (SEM)



Each white bar represents 100µm

Figure 10: SEM images of DMP and S-SEDDS-DMP samples.

Figure 9 shows SEM images of crystalline DMP and S-SEDDS-DMP. The existence of crystalline solids can be seen in the microscopic picture of crystalline DMP. However, these are absent in the S-SEDDS-DMP sample. Therefore, the S-SEDDS-DMP sample showed enhanced surface area and reduced crystallinity which may be indicative of better aqueous solubility. Amorphous materials may occur in irregular shapes that are distinguishable as transparent glass in nature. The S-SEDDS-DMP displayed a SEM picture with distinct surface morphology, suppressing the majority of the materials. Amorphous solids are weaker than crystalline solids due to their weak intermolecular force of attraction, therefore require less energy to break (Auerbach, 2021).

3.4.3 X-ray Powder Diffraction (XRPD)

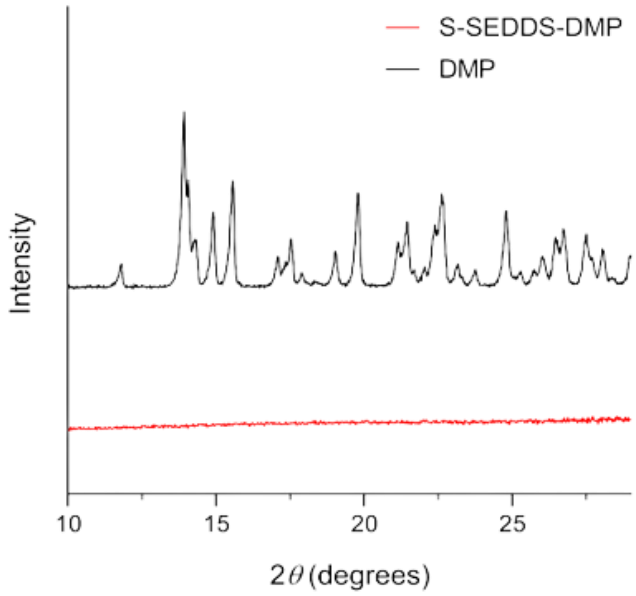


Figure 11: Crystallinity analysis of DMP and S-SEDDS-DMP samples.

In the XRPD study, crystalline DMP displayed a pattern of strong, high-intensity peaks, whereas, S-SEDDS-DMP showed no peaks.

The unique high intensity narrow peaks at 2θ ranging from 10° to 35° were created by the lengthy periodicity and regular arrangement of molecules throughout dimension (Figure 10).

Because amorphous materials do not have long range order, but rather have molecules randomly dispersed throughout dimension, x-rays are scattered in many directions, there is destructive interference, and therefore no peaks are observed.

S-SEDDS DMP XRPD patterns revealed no diffraction peaks as compared to DMP. This indicates that the crystallinity of the S-SEDDS-DMP formulation has decreased (Halder et al., 2021). A reduction in the crystallinity of the drug leads to enhanced solubility.

3.4.4 Differential Scanning Calorimetry

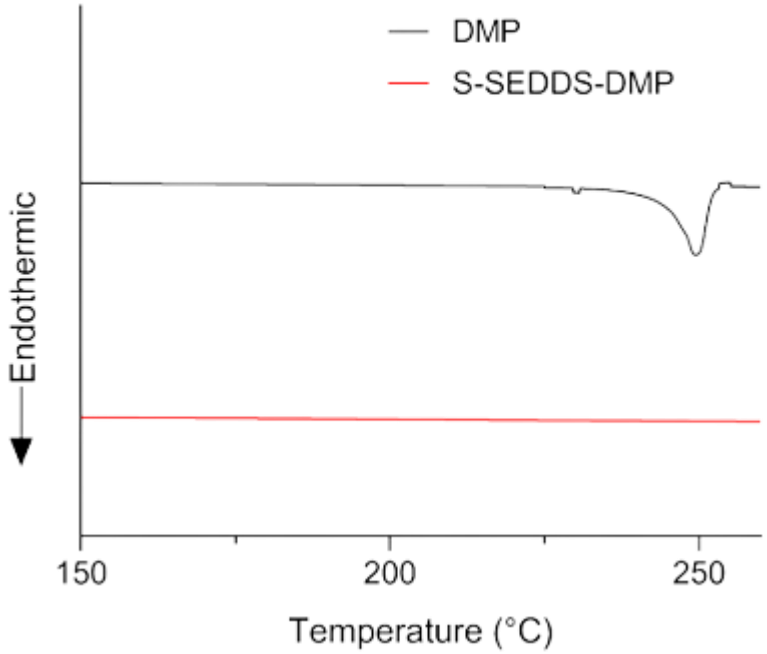


Figure 12: Differential Scanning Calorimetry of DMP and S-SEDDS-DMP samples.

An endothermic peak was observed at 250°C for DMP and no peak was observed for S-SEDDS-DMP.

A prominent endothermic peak was observed at 250°C corresponding to the melting point of DMP in the DSC thermal analysis of crystalline DMP. The typical melting endothermic peak for DMP is missing from the S-SEDDS-DMP thermograms. The peaks near disappearance indicate that DMP was dissolved in the polymers, and also indicates that the S-SEDDS-DMP formulation is free from any crystalline structure (Figure 11). This also indicates that DMP is present in the amorphous form. Amorphous solids require less energy to dissolve; therefore, the subsequent solubility and dissolution rate can increase (Rams-Baron et al., 2018).

3.4.5 Fourier transform Infrared Spectroscopy

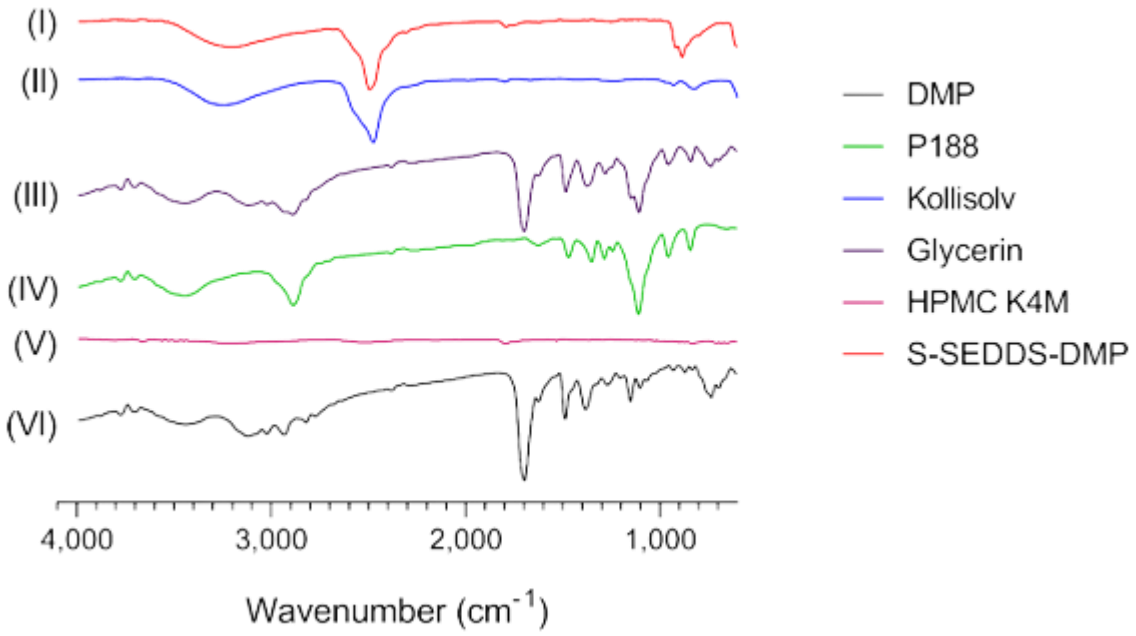


Figure 13: Fourier Transform infrared Spectroscopy (FT-IR) analysis to determine DMP-polymer compatibility

Pure DMP (DMP) and S-SEDDS-DMP were analyzed using Fourier transform infrared spectroscopy, showing distinct peaks for the drug and polymer.

FTIR analysis showed that there is no modification or interaction between the drug and carrier. This indicates that the drug and the polymers are compatible with each other.

Chapter 4

Conclusion

The poor biopharmaceutical characteristics of DMP are significant barriers to its therapeutic effectiveness; this is because of DMP's lipophilic nature. It appears to be poorly disseminated in GI fluid, limiting its clinical application. The current study used a pseudo-ternary phase diagram and emulsion forming potency to generate an optimal SEDDS formulation. After which, S-SEDDS- DMP was developed, optimized, and evaluated in this study. Based on the physicochemical properties, S-SEDDS- DMP demonstrated better dissolution behavior. The overall findings also demonstrated an improvement in solubility, and reduced crystallinity when compared to crystalline DMP.

From the various ratios, formulation with Kollisolv: Kolliphor® P188: Glycerin ratio (%) of 25: 60: 15 produced the greatest results. In terms of drug-polymer ratio optimization, a larger proportion of Kolliphor® P188 in the polymer ratio resulted in higher solubility in repeated studies. Thus, S-SEDDS-DMP remains a promising technique for improving DMP's dissolution behavior, maybe with further adjustment of polymer ratios and formulation.

Chapter 5

Future Work

Future work would include preparation of SEDDS with more variety of ratios of the polymers along with assessment of their stability, and comparing the prepared formulations with commercially available Domperidone tablets. Their stability in simulated gastric fluid would also be carried out. Additionally, i*n-vitro* pharmacokinetics studies would be performed. Lastly, *in- vivo* physicochemical analyses would be carried out to prove the *in-vitro* hypothesis of S-SEDDS-DMP in the improvement of oral solubility and bioavailability.

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