Journal of Research in Pharmacy

Research Article

www.jrespharm.com

Strategic application of a mixed polymeric micellar solid dispersion system to domperidone for improved biopharmaceutical characteristics

Shimul HALDER [1*], M. A. K. AZAD [2], Md. Shamiul ISLAM [3#], Istiak HOSSEN [2#], Madhabi Lata SHUMA [4], Eva Rahman KABIR [2]

1 Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Dhaka, Dhaka-1000, Bangladesh.
2 Department of Pharmacy, BRAC University, Mohakhali, Dhaka-1212, Bangladesh.
3 Department of Pharmacy, Faculty of Pharmacy, University of Dhaka, Dhaka-1000, Bangladesh.
4 Department of Pharmacy, Stamford University Bangladesh, Siddeswari, Dhaka-1217, Bangladesh.

* Corresponding Author. E-mail: shimulpht@du.ac.bd (S.H.); Tel. +880-29661900-73.
\# Contributed equally

Received: 31 July 2022 / Revised: 13 November 2022 / Accepted: 13 November 2022

ABSTRACT: The main objective of this work was to improve the biopharmaceutical properties of Domperidone (DMP)-loaded mixed polymeric micellar solid dispersion (MMSD). The apparent solubility of DMP in polymer solutions was used to choose suitable amphiphilic polymers for the preparation of an MMSD system. Different ratios of Soluplus® and Kolliphor® P188 (ranging 0–80 %w/w) have been used to prepare the MMSD-DMP by solvent evaporation method and physicochemically characterized. Among the tested different ratios of Soluplus® and Kolliphor® P188, the optimal ratio of polymers was selected based on the solubility and surface properties. The solubility of optimized MMSD-DMP in water was found more than 17 times higher compared to that of the crystalline DMP. The crystallinity evaluations of the optimized formulation revealed amorphization of DMP, resulting in enhanced solubility. The drug release pattern did not change significantly between formulations of MMSD-DMP produced by rotary vacuum drying and freeze drying. From these findings, MMSD approach might be a promising dosage option for DMP, offering enhanced biopharmaceutical behaviors leading to improved oral absorption.

KEYWORDS: Domperidone; mixed polymeric micellar solid dispersion; Soluplus®; Kolliphor® P188; solubility, dissolution.

1. INTRODUCTION

Domperidone (DMP) acts particularly on a D2 receptor and blocks the activity of dopamine [1]. DMP is used as a medication for nausea, vomiting, and gastroparesis [2,3]. In addition, DMP has been used to treat orthostatic hypotension in Parkinson's disease and to increase breast milk production in nursing mothers [4,5]. The biopharmaceutical classification system (BCS) classifies DMP as a class II drug having low dissolution and water solubility (0.986 µg/mL), resulting in poor bioavailability and leading to dissolution-rate limited oral absorption [6,7]. About 25%–40% of all currently known medications and newly produced active pharmaceutical ingredients (API) have poor water solubility. To achieve an effective plasma drug concentration for poorly water-soluble drugs, a large amount of dose of the medication must be provided. Although high doses of poorly water-soluble medicines have a lower systemic bioavailability, they have higher local toxicity at aggregate deposition locations due to the high concentration of the drugs [8]. This issue can be solved by employing a formulation technology that increases the drug's solubility [9]. The employment of a surfactant, pH modification, nano-suspension technology, hydrotrophy, solid dispersion, and salt formation are only a few of the very useful methods for increasing the solubility of a poorly water-soluble drug. Among the several ways discussed above; Solid dispersion (SD) technique is used widely to increase the water solubility, dissolution rate, and bioavailability of the drugs with poor water-solubility [10].

SD involves the molecular dispersion of one or more APIs in an inert carrier, which helps to improve the solubility of the drug [11]. Micellar SD is a new potential SD strategy that increases the bioavailability

How to cite this article: Halder S, Azad MAK, Islam MS, Hossain I, Shuma ML, Kabir ER. Strategic application of a mixed polymeric micellar solid dispersion system to domperidone for ımproved biopharmaceutical characteristics. J Res Pharm. 2023; 27(2): 860-872.

ISSN: 2630-6344

http://dx.doi.org/10.29228/jrp.366

significantly of drugs with poor water-solubility. In this method, biocompatible polymers form self-micelles in water that trap drug molecules of poorly water-soluble drugs and increase the water solubility of the drugs [12]. However, using single polymer based micelles in this technique can result in instability, uncontrolled distribution, and limited drug loading capacity [13]. This challenge can be solved by adopting mixed polymeric micelles, which offer improved thermodynamic and kinetic stability, increased drug loading capacity, controlled micelle size, and easy adjustment of many aspects [14,15].

At present different studies suggested that mixed polymeric micelles have the prominent advantages in terms of better thermal stability, high drug loading, core-shell structure with higher hydrophobic core, and targeted delivery compared with single polymeric micelles [16–20], thereby biopharmaceutical properties can greatly improve. However far is known about the feasibility of mixed polymeric miceller solid dispersion (MMSD) system to enhance the biopharmaceutical behavior of DMP.

The main goal of this present study is to develop DMP-loaded MMSD (MMSD-DMP) to improve the physicochemical characteristics of DMP as well as to enhance the dissolution behavior of DMP. To develop MMSD-DMP, suitable amphiphilic block copolymers were chosen based on assessing the apparent solubility of DMP in different polymer solutions. MMSD-DMP with 20% (w/w) drug loading was prepared using two biocompatible polymers and the polymer ratio was optimized. The optimized MMSD-DMP was then physicochemically characterized in terms of morphology, crystallinity, drug-polymer interaction, and micelle-forming potency. Surface tension was also determined by using the Rubingh model to predict the suitability of the formation of mixed micelles. The dissolution behavior of DMP samples were carried out to clarify the possible enhancement in dissolution behavior of DMP in water. Furthermore, the suitability of different drying processes in evaporating the solvents employed in the manufacture of MMSD-DMP was also studied in this work.

2. RESULTS AND DISCUSSION

In the new field of formulation development and drug delivery, scientists are still experiencing difficulties with drugs that have poor water solubility. For overcoming the drawbacks of poorly water-soluble drugs [21], SD has fortunately emerged as a promising strategy for combating them. SDs usually have two parts: the carrier and the active pharmaceutical ingredient (API). Choosing the right carrier is important for getting the best drug release and best therapeutic results [22]. Using a mixture of carriers could speed up the rate at which the drug dissolves, stop it from re-crystallizing, and keep the SD stable [21].MMSDs offer various advantages over typical SDs, including dosage reduction, consistent therapeutic efficacy, less side effects, and the ability to use a lower dose while enhancing therapeutic effectiveness [22]. Several studies have demonstrated that the synergistic impact of polymers in ternary systems might result in both head-to-head and electrostatic interactions [23]. This is due to hydrophilic groups linked to the surface by cohesive forces, which lowered surface tension, resulting in the formation of an inner hydrophobic core and enhanced solubility [16–18]. Therefore, the current study aimed to use mixed carriers in the preparation and characterization of MMSD-DMP to improve biopharmaceutical properties.

2.1. Selection of polymers for MMSD system

A critical step in improving the biopharmaceutical properties of poorly water-soluble drugs in the MMSD system is the selection of appropriate polymers as a carrier. Amphiphilic polymers, which feature both a hydrophilic and a lipophilic unit in their structure, are gaining popularity as pharmaceutical excipients now a days. Interactions between poorly soluble pharmaceuticals and lipophilic units of amphiphilic polymers can lead to the development of polymeric micelles with a hydrophobic core and a hydrophilic shell, which can help improve the solubility of poorly water-soluble medications by encapsulation [24]. The apparent solubility of DMP in water was tested in the presence of several concentrations of pre-dissolved polymers such as α-tocopheryl polyethylene glycol 1,000 succinate (TPGS), Soluplus®, Kolliphor® P188, and Kolliphor® P407 ranging from 2 to 25 mg/mL in the present study for the selection of suitable polymers in the MMSD system for DMP. Because of their commercial availability and biocompatibility; TPGS, Soluplus®, Kolliphor® P188, and Kolliphor® P407 are commonly utilized as pharmaceutical excipients with amphiphilic characteristics to increase the solubility of poorly water-soluble medicines [25–27]. As shown in Figure 1, a rise in the aqueous solubility of DMP was detected when the polymer concentration increased. There was a linear association (A_L-type) between increased DMP solubility and increasing polymer concentration in all of the studied polymers. The improvement of DMP solubility by Soluplus® and Kolliphor® P188 were statistically significant (p<0.01) when compared to TPGS and Kolliphor® P407. Soluplus® and Kolliphor® P188; at a concentration of 25 mg/mL, improved the aqueous solubility of DMP by 75 and 72.5-fold, respectively, whereas TPGS and Kolliphor® P407, at the same

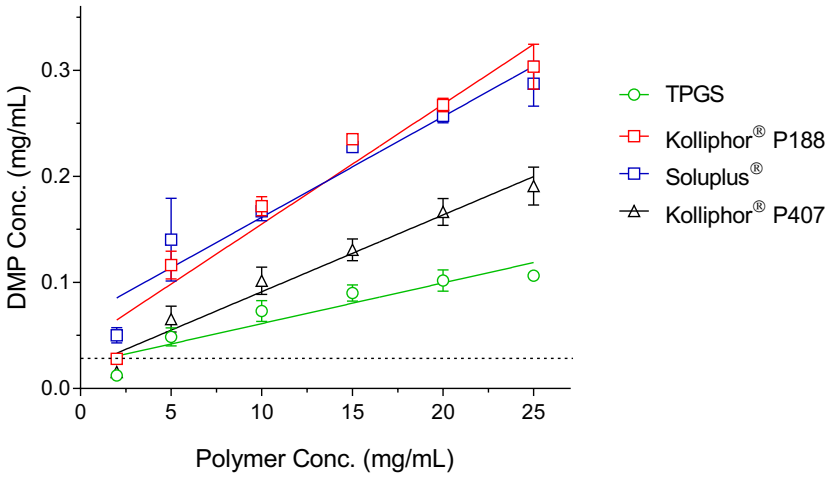

Figure 1. Apparent solubility of DMP in aqueous solution of Soluplus®, Kolliphor® P188, Kolliphor® P407 and TPGS at various concentrations (2–25 mg/mL).

concentration, improved it by 25 and 47 times, respectively. The higher dispersibility and miscibility of DMP dispersed in the polymers resulted in increased apparent solubility of DMP with amphiphilic block copolymers [13,28]. Moreover, the stability constants (K_s) were determined using a linear regression analysis of the phase solubility diagram produced and the data are presented in Table 1. The K_s is significantly higher for Soluplus® and Kolliphor® P188 compared to TPGS and Kolliphor® P407; justifying the positive effect towards solubility enhancement of DMP.

Table 1. Apparent solubility data of complexes of DMP with different polymers.

Complex/Parameter	S_0	Slope	R^2	K_s	C.E.
DMP-Soluplus®	0.00397	0.0095	0.8973	1009.81	0.009594
DMP-Kolliphor® P188		0.0113	0.9350	1198.59	0.011429
DMP-TPGS		0.0038	0.8506	409.96	0.003851
DMP-Kolliphor® P407		0.0072	0.9428	771.20	0.007294

S_0, solubility of DMP in water; K_s, stability constant; C.E., complexation efficiency

These findings suggested that DMP could interact better with Soluplus® and Kolliphor® P188; and become entrapped in the micelle's hydrophobic core; thereby improve the solubility higher. Therefore, based on the apparent solubility, Soluplus® and Kolliphor® P188 were chosen as the carrier for the development of MMSD-DMP to improve the physicochemical behavior of DMP.

2.2. Selection of an appropriate ratio of polymers

The physicochemical characteristics of MMSD-DMP prepared with different ratios of Soluplus® and Kolliphor® P188, including equilibrium solubility and surface properties, were investigated in order to determine the best ratio of Soluplus® and Kolliphor® P188 for further study. Considering crystalline DMP's poor aqueous solubility (3.97 µg/mL), all formulations (F1–F5) showed improved DMP solubility. Table 2 shows the equilibrium solubility of the prepared MMSD-DMP formulations. F1 showed the greatest improvement in solubility among all formulations. DMP solubility increased significantly with equal amount of Kolliphor® P188 and Soluplus®, reaching 69.64 ± 0.72 µg/mL, a 17.7-fold increase. Soluplus® is a non-ionic graft polymer made up of polyvinyl caprolactam-polyvinyl acetate polyethylene glycol. Polyethylene glycol (PEG) is the backbone and vinylcaprolactam/vinyl acetate is the side chain of Soluplus®. It can enhance the solubility of BCS class II drugs by self-assembling into micelles above the critical micelle concentration (CMC) of 0.0076 mg/ml [29,30]. On the other hand, Kolliphor® are made of block polymer of polyoxyethylene–polyoxypropylene–polyoxyethylene (PEO-PPO-PEO) which is used as a solubilizing agent, as well as emulsifying agent. Kolliphor® P188 consists of hydrophobic PPO block and hydrophilic PEO blocks, which help to act as surface-active agents [31]. It has a critical micelle concentration of 0.743 mg/mL [32]. This indicates that the combination of these two biocompatible polymers, might contribute to the enhanced

Table 2. Selection of suitable ratio of the polymers.

Sample	Ratio (%) DMP:SP: KP 188	Equilibrium solubility (µg/mL)
Crystalline DMP		3.94 ± 0.05
F1	20 : 40 : 40	69.64 ± 0.72
F2	20 : 53.33 : 26.67	52.52 ± 0.61
F3	20 : 26.67 : 53.33	55.58 ± 1.52
F4	20 : 60 : 20	49.85 ± 3.67
F5	20 : 20 : 60	57.02 ± 2.38

DMP, domperidone; SP, Soluplus®; KP 188, Kolliphor® P 188.

dissolution behavior of DMP as well as improved oral absorption. Moreover, it was reported that due to kinetically stable nature, polymeric micelles dissociate very slowly that might affect the charting into different cells in vivo irrespective of administration route [33].

Table 3. Surface parameters of MMSD-DMP system at 25 °C.

	CMC (wt. %)		β	Adsorbed mole fraction	
	Experimental	Calculated		Experimental	Calculated
F1	1.14×10^{-3}	1.43×10^{-4}	-60.24	0.47	0.07
F2	1.25×10^{-3}	1.54×10^{-4}	-54.86	0.54	0.04
F3	1.98×10^{-3}	1.23×10^{-3}	-40.96	0.5	0.14
F4	9.88×10^{-3}	2.81×10^{-3}	-43.35	0.55	0.02
F5	2.48×10^{-3}	1.96×10^{-3}	-30.09	0.48	0.21

To further investigate the micellization potency of Soluplus® and Kolliphor® P188, the surface properties of micelles in MMSD formulations using Rubingh's equation were also evaluated and the results are shown in Figure 2 and Table 3. From the CMC values, the experimental CMC values were almost identical with theoretical value in F1, F2, F3, and F5, however in F4, some negative deviations were observed from theoretical value. Nevertheless, the low CMC value indicated the better stability and resistant against precipitation and dissociation of drug in blood stream [34]. Several studies have demonstrated that the synergistic effect of polymers in ternary systems might result in both head-to-head and electrostatic interactions. From the calculated surface properties of micelles, higher negative value of β-parameter suggested the existence of synergism between surfactants blends with stronger cohesive interaction between the polymers [35]. From Table 3, formulations F1 and F2 exhibited higher negative β values indicated favorable condition for improvement in solubility of DMP. This is due to the hydrophilic groups that were attached to the surface by cohesive forces, which lowered surface tension, generating an inner hydrophobic core and improving solubility. Formulations having a low-CMC value are more stable, and the drug is less susceptible to precipitation and dissociation in blood serum [34]. Although the gap between the theoretical and calculated CMC values is minimal, the CMC value of all formulations is low. Therefore, on the basis of improved solubility and surface properties of micelles, formulation F1 was chosen as the optimal one for further physicochemical characterization.

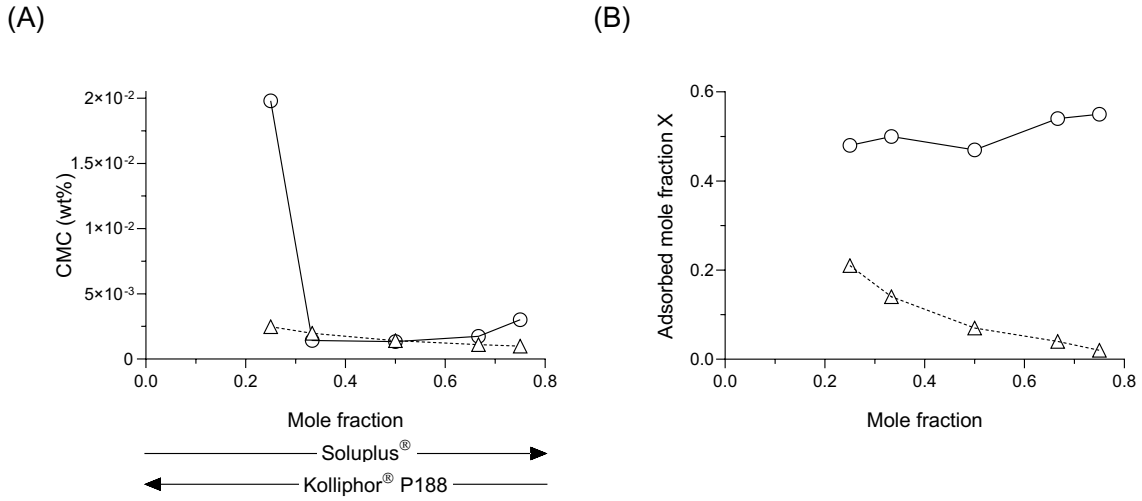

Figure 2. CMC values as a function of mole fraction of polymers (A), and dependence of the mixed adsorbed mole fraction of MMSD system (B). Each black line and dotted line indicate experimental and theoretical values, respectively.

2.3. Physicochemical characterizations

Because of the higher energy state, amorphous forms can have higher solubility and dissolution rates than crystalline states. As a result, determining crystallinity is critical for determining product quality. XRPD and DSC studies were used to study the crystalline state of MMSD-DMP (Figure 3). The XRPD pattern of crystalline DMP revealed several sharp peaks, with the strongest peak at around 13°, indicating the crystalline condition of DMP (Figure 3A). MMSD-DMP/RVD and MMSD-DMP/FD, on the other hand, showed a halo diffractive pattern, and the peaks detected in crystalline DMP were minimal in the diffractogram, indicating that DMP was in an amorphous condition. In DSC analysis, although crystalline DMP had a particular endothermic peak at about 250°C (Figure 3B), which corresponded to the melting point of DMP [36], the endothermic peak in MMSD-DMP/RVD and MMSD-DMP/FD at the melting point of crystalline DMP was lost in DSC analysis. According to PLM images, crystalline DMP has a rough block-like structure (Figure 4A-I), MMSD-DMP/RVD has small birefringence (Figure 4A-II), and MMSD-DMP/FD has loss of polarization, which could be indicative of inner DMP in the form of an amorphous state as evidenced by negligible birefringence (Figure 4A-III). Polarization in PLM observations can indicate a crystalline material [37], hence the lack of polarization in MMSD-DMP could indicate an amorphous condition of DMP in MMSD. The high free energy in the amorphous state may trap the drug molecule in MMSD and inhibit drug precipitation or recrystallization in the supersaturated state, which would be beneficial to improving the dissolving behavior of lipophilic drugs [38]. According to PLM, XRPD, and DSC investigations, the amorphization of DMP during the preparation procedure led to superior dissolving behavior.

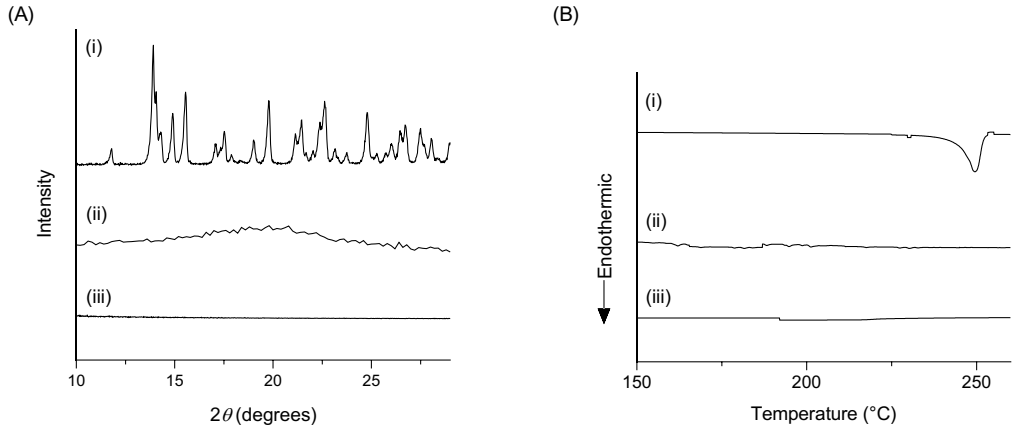

Figure 3. Crystallinity analysis of DMP samples using (A) XRPD and (B) DSC. (I) Crystalline DMP, (II) MMSD-DMP/RVD, and (III) MMSD-DMP/FD.

The surface morphology of the DMP samples was assessed using SEM observations (Figure 4B). The morphology of crystalline DMP was irregular shaped particles and predominantly dispersed (Figure 4B-I). On

the other hand, MMSD-DMP/RVD and MMSD-DMP/FD had the appearance of typical and flaky (Figure 4B). In comparison to the crystalline DMP, MMSD-DMP had homogenous particles, and the particle size was reduced significantly. DMP was found to be well-integrated into the polymer, implying that it was well-absorbed. In comparison to crystalline DMP, SEM micrographs clearly show that after the freeze-drying process, the surface area of pharmacological components increased significantly (Figure 4B-III). The increased surface area obtained by micronization of particles, according to the Noyes-Whitney equation, is a significant factor for improving the dissolving rate. The size distribution of polymeric micelles is thought to be one of the most important elements in improving a drug's biopharmaceutical characteristics [13].

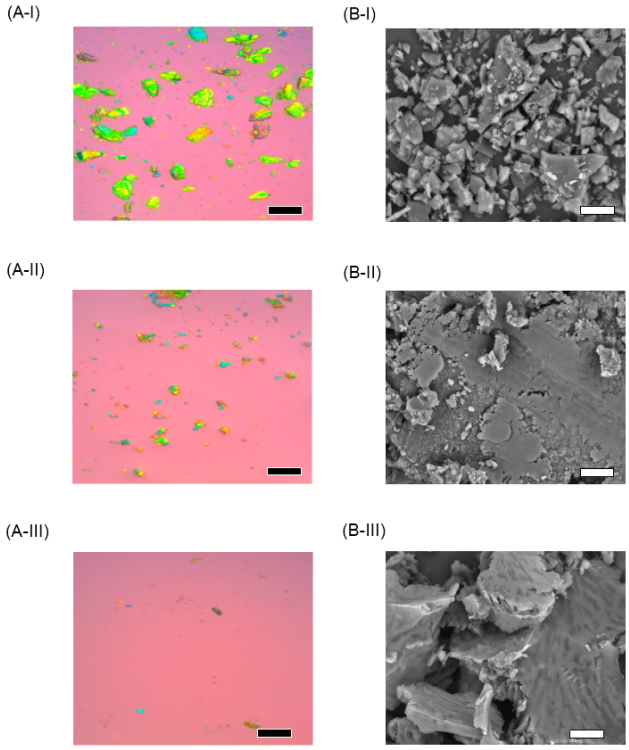

Figure 4. Microscopic images observed by polarized light microscope (A) and scanning electron microscope (B) and. (I) Crystalline DMP, (II) MMSD-DMP/RVD, and (III) MMSD-DMP/FD. Each black and white bar represents 100 µm and 50 µm, respectively.

DLS analysis was used to examine the micellization capabilities of MMSD-DMP in this work. DLS examination of water-dispersed MMSD-DMP samples (Figure 5) revealed the creation of uniformly nano-sized particles with a mean particle size of 134 nm for MMSD-DMP/FD with a PDI of 0.48 (Figure 5, block line); and 173 nm with a PDI of 0.40 for MMSD-DMP/RVD (Figure 5, dotted line), respectively.

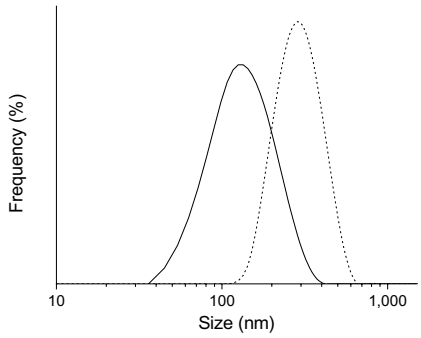

Figure 5. Particle size distribution of DMP samples. (Dotted line) MMSD-DMP/RVD and (block line) MMSD-DMP/FD.

Furthermore, due to their high drug solubility and increased dispersibility and diffusivity in the mucus layer by the hydrophilic chain on the surface of polymeric micelles, their size of 150 nm would aid rapid drug absorption after oral administration [39].

Therefore, the absence of crystalline DMP throughout the MMSD-DMP preparation process was confirmed by SEM pictures and DLS data. These benefits may contribute to DMP's better dissolution behavior.

2.4. Dissolution behavior

As previously stated, solubility is a key issue with crystalline DMP in therapeutic applications. To predict the drug release profile inside the physiological environment, in vitro dissolution tests are used to determine the rate and total amount of drug release from various dose forms [40]. As a result, dissolution investigations on DMP samples were conducted in distilled water to see whether different drying processes may improve the dissolution behavior of MMSD-DMP, as shown in Figure 6. The dissolved amount of DMP detected at 240 minutes was 0.47 µg/mL in water, indicating that crystalline DMP had a limited dissolving behavior. In contrast, the dissolution behaviors of DMP in MMSD-DMP/RVD and MMSD-DMP/FD were significantly improved, with 27.6- and 58.6-fold higher dissolution amounts at 240 min than crystalline DMP, respectively. No obvious precipitation or agglomeration of dissolved substances was observed. The findings were consistent with previous studies, which showed that increasing particle surface area as a result of pulverization can increase dissolution rate proportionally, and that decreasing diffusion layer thickness as a result of particle size reduction can contribute to dissolution acceleration [41]. Due to the uniform distribution of active components in an amphiphilic carrier, the MMSD method could increase wettability and dispersibility of poorly water-soluble compounds [10]. In theory, the one-phase SD system, defined as a solid solution, may be generated because DMP and the carrier polymers were entirely dissolved in organic solvent throughout the preparation procedure. Due to the thorough dissolving of the components during the production process of the MMSD-DMP formulation, DMP may be disseminated at a molecular level inside the SD system, resulting in the fast dissolution and dispersion of DMP molecules when the formulation is dispersed in water. Based on these findings, the dissolution characteristic of MMSD-DMP suggested quick dissolution and a higher dissolution amount of DMP when compared to crystalline DMP, potentially leading to an increase in DMP oral absorption.

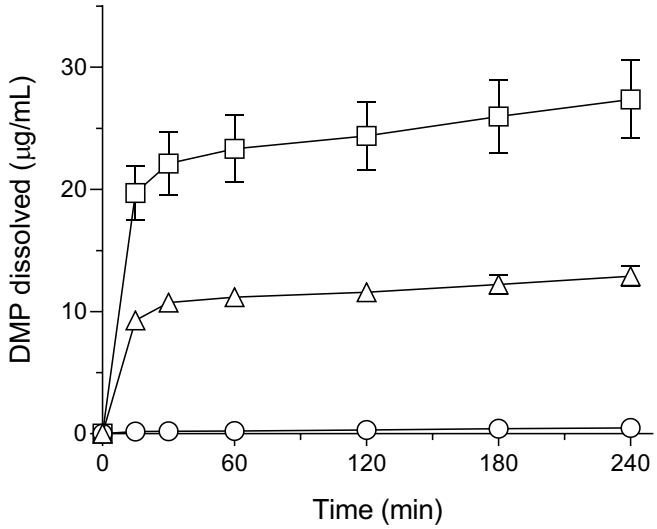

Figure 6. Dissolution tests of DMP samples in water. ○, crystalline DMP; △, MMSD-DMP/RVD; and □, MMSD-DMP/FD. Data represent the mean ± S.D. of 3 experiments.

2.5. Drug polymer ınteractions

Amorphous molecules may theoretically be molecularly disseminated in the matrix carrier in an SD formulation, and the interaction between these molecules could lead to improved drug amorphization [42]. The molecular state of crystalline DMP and processed MMSD-DMP was assessed using FT-IR analysis. Figure 7 depicts the FT-IR spectra. The asymmetric C-H stretching vibration was indicated by a prominent, well-defined distinctive infrared absorption band at "2910" cm^{-1} in the FT-IR spectrum of crystalline DMP (Figure 7-I). "3458.9" cm^{-1} (O-H stretching), "2935.6" cm^{-1} (aromatic C-H stretching), "1738.3" cm^{-1}, "1639.5" cm^{-1} (C=O stretching), and "1481.4" cm^{-1} (C-O-C stretching) were the highest peak values for Soluplus® (Figure 7-II). IR spectrum patterns in DMP samples are thought to reflect various chemical environments. The absorption maxima at "2883.38" cm^{-1} (C-H stretch aliphatic), "1348.15" cm^{-1} (in plane O-H bend), and "1107.06" cm^{-1} (C=O

stretching) in the IR spectra of Kolliphor® P188 are depicted in the diagram (Figure 7-III). The absence of a distinctive peak in the IR spectra of the MMSD-DMP/RVD and MMSD-DMP/FD, on the other hand, indicates negligible electrostatic interaction. The FT-IR spectra curves revealed that the inclusion of Soluplus® and Kolliphor® P188 correlates to the presence of minor hydrophobic interaction that may not influence the chemical structure of DMP, based on the results in comparison to FT-IR spectrum analysis. From a theoretical aspect, this is desirable since some drug-polymer interactions may actually slow down the dissolution process, and the thermodynamic driving force for dissolution will be stronger if the drug-polymer interactions are weak or non-existent [43,44].

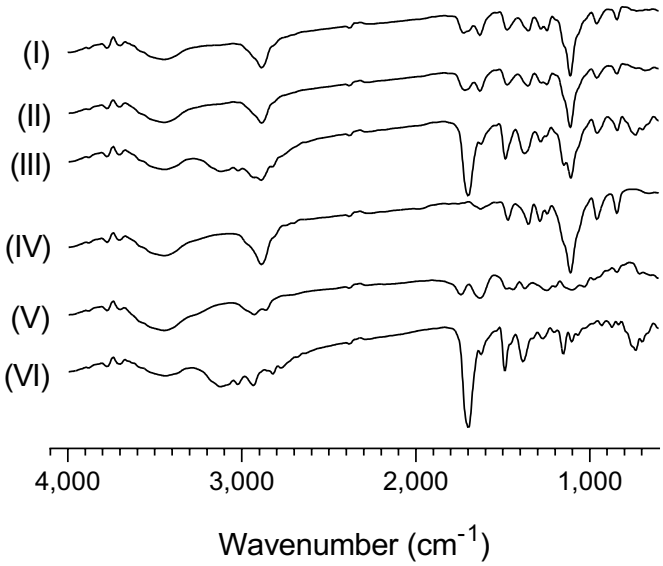

Figure 7. Drug-polymer interaction studies of DMP samples using FT-IR. Baseline-corrected and normalized IR data of DMP samples. (I) Crystalline DMP, (II) Soluplus®, (III) Kolliphor® P 188, (IV) Physical mixture, (V) MMSD-DMP/RVD, and (V) MMSD-DMP/FD.

3. CONCLUSION

With the goal of increasing biopharmaceutical characteristics, an MMSD formulation of DMP was developed using two biocompatible polymers, Soluplus® and Kolliphor® P188, and two industrially scalable techniques, namely solvent evaporation by RVD and freeze-drying. The findings of solid-state characterization revealed that DMP amorphized throughout the preparation procedure. The optimized formulation, resulted in much enhanced solubility due to the drug's immediate micellization. Based on these findings, the MMSD strategy, with the polymer blends as a carrier and a simple technique of manufacture, appears to be a potential way for improving DMP's biopharmaceutical performance. However, in spite of the tremendous advantages of the MMSD system in improving the biopharmaceutical properties of poorly water-soluble drugs, these techniques have some limitations; especially in the selection of an appropriate polymer, suitability of the preparation techniques, dependence on critical micelle concentrations, low drug-loading capacity, and stability of the final product. Therefore, further extensive investigations in both in vitro and in vivo will help to overcome the underlying problems of the MMSD system in commercialization.

4. MATERIALS AND METHODS

4.1. Materials

Reference DMP was obtained from Tokyo Chemical Industries, Japan, and Beximco Pharmaceuticals Ltd., Dhaka, Bangladesh, kindly donated working samples of DMP. BASF Bangladesh Co. Ltd. generously provided Soluplus®, Kolliphor® P188, and Kolliphor® P407. TPGS were a kind gift from BASF Japan Co. Ltd (Tokyo, Japan). All other chemicals and reagents were purchased commercially.

4.2. Preparation of standard curve and determination of DMP content

In a volumetric flask, 10 mL of DMP stock solution was prepared by dissolving 10 mg of DMP in sufficient methanol to yield a final concentration of 1 mg/mL. In the concentration range of 8-30 µg/mL, DMP

follows the Beer-Lambert equation and DMP gives an acceptable absorbance value at 284 nm [45]. Therefore, the stock solutions were then diluted sequentially at various concentrations prior to use and the corresponding absorbance were determined at 284 nm using a UV-vis spectrophotometer (UV-1800, Shimadzu Corporation, Japan). The amount of DMP was calculated using the standard curve-derived equation.

4.3. Phase Solubility Study

The apparent solubility of DMP in polymer solutions was evaluated in triplicate using an established method provided by Higuchi and Connors to determine a suitable carrier [46]. At a polymer concentration of 2–25 mg/mL, an excess of DMP (ca. 10 mg) was added to the aqueous solutions of TPGS, Soluplus®, Kolliphor® P188, and Kolliphor® P407. The tubes were then sealed and shaken for 48 h using a shaking water bath (Water Bath Shaker, WBS-C, China) at 37 °C to maintain equilibrium. After 48 h, the samples were kept 10 min to settle and the resulting suspension were subjected to centrifugation at 10,000×g for 5 minutes. The resulting supernatants were then filtered and the DMP content was analyzed using the method described in the preceding section.

The stability constant (K_s) and complexation efficiency (C.E.) were calculated using the equations below;

$$K_s = \frac{slope}{So\ (1-slope)}$$

$$C.E. = \frac{slope}{(1-slope)}$$

Where, S_o is the equilibrium aqueous solubility of DMP, and the slope is attained by plotting DMP concentration versus different polymer concentrations.

4.4. Preparation of MMSD-DMP

In a beaker, the exact amount of DMP and the calculated amount of the selected polymers based on the apparent solubility were taken and dissolved in adequate amount of methanol. Stirring was done carefully for some time to ensure that the mixture was homogeneous. During the selection phase of the polymer ratio, the solution mixtures were dried with a rotary vacuum-dryer (RVD) (Heidolph Rotasap, Germany). In order to compare the influence of drying on the physicochemical behavior of MMSD-DMP, the freeze-drying (FD) method was employed in the preparation of optimized MMSD-DMP. In FD process, crystalline DMP (25 % w/w) and optimized polymer ratios were precisely weighed, dissolved in 1, 4-dioxane, and then frozen at –80°C. The frozen samples were then lyophilized for 24 h using an Eyela FD-1000 freeze dryer at a pressure of 15 Pa. (Tokyo Rikakikai, Tokyo, Japan). The freeze dryer's solvent trapper was kept at –50°C.

4.5. Equilibrium Solubility Study of DMP and MMSD-DMP Samples

The solubility tests were carried out according to a method evolved by Higuchi and Connors' with a little modification (6). Briefly, an excess amount of DMP samples (about 50 mg) was placed to a test tube containing 10 mL of distilled water and stored in an automated water bath shaker at 37°C for 24 hours. Aliquots of test solutions were collected after 24 h, centrifuged at 10,000×g for 5 minutes, and diluted with 50% methanol. The DMP content was analyzed using the method described in the preceding section.

4.6. Dissolution Study

The dissolution study of DMP samples were performed using the USP type II paddle method (Universal Dissolution Tester, Logan- UDT 804) at 37±0.5 °C, with 900 mL of distilled water at 50 rpm. The optimized MMSD-DMP was chosen for the in vitro dissolution investigation because it had the best results in the equilibrium solubility analysis. Briefly, samples (1 mL) were taken at predefined intervals (15 min, 30 min, 60 min, 120 min, 180 min, and 240 min) and centrifuged at 10,000×g for 5 minutes before being filtered through a 0.45 m membrane filter and diluted with 50% methanol. At 284 nm, the concentration of DMP was measured spectrophotometrically. The experiment was repeated three times.

4.7. Surface Morphology

Using scanning electron microscopy (SEM) methods (Miniscope® TM3030, Hitachi, Tokyo, Japan), the surface morphology of crystalline DMP and MMSD-DMP was investigated.

After fixing the samples to an aluminum sample holder using double-sided carbon tape, a magnetron sputtering equipment was used to cover them with platinum (MSP-1S, Vacuum Device, Ibaraki, Japan).

4.8. Polarized Light Microscopy (PLM)

The PLM images of DMP samples (suspended in silicone oil) were examined with a CX41 microscope (Olympus Co. Ltd., Tokyo, Japan) to properly evaluate the crystallinity of the samples under different conditions such as slightly uncrossed polars, differential interface contrast, and a red wave compensator.

4.9. X-ray Powder Diffraction (XRPD)

A Mini Flex II (Rigaku, Tokyo, Japan) was used to record the XRPD patterns of DMP samples that generate Cu Kα radiation at 40 mA and 35 kV. All the Samples were scanned at 2θ angles of short-range from 5° to 35° that maintained 0.2° step size and scanning speed of 4°/min.

4.10. Differential Scanning Calorimetry (DSC)

To determine the thermal behavior of DMP samples, 3 mg sample were put in closed aluminum pans and heated at a rate of 5°C/min using a DSC Q1000 (TA Instruments, New Castle, DE, USA) with nitrogen gas (50 mL/min) purged. Indium was used as a reference standard to calibrate the system (99.999 percent pure, 8–10 mg, onset at 156.6°C).

4.11. Micelle Size Distribution

The mean hydrodynamic diameter of MMSD-DMP samples suspended in water was determined using a dynamic light scattering (DLS) method with a Zetasizer Ultra (MALVERN, Worcestershire, UK). Correlation of photon from light scattering was used to calculate the mean diameter, and all measurements were taken at 25°C and an angle of 90°. The test was performed three times.

4.12. Fourier Transform Infrared Spectroscopy (FT-IR)

FT-IR analysis was carried out to determine the likelihood of hydrophobic interactions between the polymers and the drug. The samples were placed separately on the sample platform of the instrument (Perkin Elmer, L160000A, USA) and IR spectra were collected in the range of 4000–600 cm^{-1} using Spectrum 10 software. During the analysis, the baseline was corrected and normalized for each sample. To make the obtained spectra smooth, a smoothing function of 9 points was applied.

4.13. Critical Micelle Concentration (CMC) Measurement

4.13.1. Critical Micelle Concentration (CMC) Measurement

The CMC of mixed polymeric micelles were determined by means of surface tension measurement using stalagmometer at 25 °C by drop count method as per following formula. The corresponding CMC value to the polymers is where the tension becomes stable. Other surface properties including interactions between polymers, β were calculated according to Rubingh's model [47].

$$\sigma_2 = \frac{\rho_2 n_1}{\rho_1 n_2}\sigma_1$$

σ_2= surface tension of formulation
σ_1= surface tension of water
ρ_2= density of formulation
ρ_1= density of water
n_2= number of drops of formulation
n_1= number of drops of water experimental

4.14. Data analysis

All data are represented as mean ± standard deviation (S.D.). Graphpad, Prism 8.0, was used to create the graphs (GraphPad Software, LaJolla, CA). For statistical comparisons, a one-way analysis of variance with pairwise comparisons using Fisher's least significant difference approach was used. A *p* value of less than 0.05 was considered significant in all analyses.

Acknowledgements: The authors would like to express their gratitude to Professor Dr. Satomi Onoue and Dr. Hideyuki Sato of the University of Shizuoka, Japan, for allowing the physicochemical characterization of the samples. The authors also express their thanks to the BASF, Bangladesh for proving the polymers.

Author contributions: Concept – S.H., E.R.K.; Design – S.H., M.A.K.A., M.L.S.; Supervision – S.H., M.A.K.A., E.R.K.; Resource – S.H., E.R.K.; Materials – S.H., M.A.K.A.; Data Collection &/or Processing – I.H., M.S.I.; Analysis &/or Interpretation – M.S.I., S.H.; Literature Search – I.H., M.S.I.; Writing – I.H., M.S.I., S.H.; Critical Reviews – S.H., M.A.K.A., S.M.I., I.H., M.L.S., E.R.K.

Conflict of interest statement: The authors have not disclosed any conflicts of interest.

REFERENCES

[1] Osinski MA, Uchic ME, Seifert T, Shaughnessy TK, Miller LN, Nakane M, et al. Dopamine D2, but not D4, receptor agonists are emetogenic in ferrets. Pharmacol Biochem Behav. 2005;81(1):211–9. [CrossRef]

[2] Zhang C-H, Zhao B-X, Huang Y, Wang Y, Ke X-Y, Zhao B-J, et al. A Novel Domperidone Hydrogel: Preparation, Characterization, Pharmacokinetic, and Pharmacodynamic Properties. J Drug Deliv. 2011;2011:1–9. [CrossRef]

[3] Silvers D, Kipnes M, Broadstone V, Patterson D, Quigley EMM, McCallum R, et al. Domperidone in the management of symptoms of diabetic gastroparesis: Efficacy, tolerability, and quality-of-life outcomes in a multicenter controlled trial. Clin Ther. 1998;20(3):438–53. [CrossRef]

[4] Bacchi S, Chim I, Kramer P, Postuma RB. Domperidone for Hypotension in Parkinson's Disease: A Systematic Review. J Parkinsons Dis. 2017;7(4):603–17. [CrossRef]

[5] Grzeskowiak L, Smithers L, Amir L, Grivell R. Domperidone for increasing breast milk volume in mothers expressing breast milk for their preterm infants: a systematic review and meta-analysis. BJOG An Int J Obstet Gynaecol. 2018 Oct;125(11):1371–8. [CrossRef]

[6] Patel D, Patel S, Patel C. Formulation and evaluation of fast dissolving tablet containing domperidone ternary solid dispersion. Int J Pharm Investig. 2014;4(4):174. [CrossRef]

[7] Bhalani DV, Nutan B, Kumar A, Singh Chandel AK. Bioavailability Enhancement Techniques for Poorly Aqueous Soluble Drugs and Therapeutics. Biomedicines. 2022; 10(9):2055. [CrossRef]

[8] Bikiaris DN. Solid dispersions, Part II: New strategies in manufacturing methods for dissolution rate enhancement of poorly water-soluble drugs. Expert Opin Drug Deliv. 2011;8(12):1663–80. [CrossRef]

[9] Ndlovu ST, Ullah N, Khan S, Ramharack P, Soliman M, de Matas M, et al. Domperidone nanocrystals with boosted oral bioavailability: fabrication, evaluation and molecular insight into the polymer-domperidone nanocrystal interaction. Drug Deliv Transl Res. 2019;9(1):284–97. [CrossRef]

[10] Sareen S, Joseph L, Mathew G. Improvement in solubility of poor water-soluble drugs by solid dispersion. Int J Pharm Investig. 2012;2(1):12. [CrossRef]

[11] Vo CLN, Park C, Lee BJ. Current trends and future perspectives of solid dispersions containing poorly water-soluble drugs. Eur J Pharm Biopharm. 2013;85(3 PART B):799–813. [CrossRef]

[12] Zhang Q, Polyakov NE, Chistyachenko YS, Khvostov M V., Frolova TS, Tolstikova TG, et al. Preparation of curcumin self-micelle solid dispersion with enhanced bioavailability and cytotoxic activity by mechanochemistry. Drug Deliv. 2018;25(1):198–209. [CrossRef]

[13] Ghezzi M, Pescina S, Padula C, Santi P, Del Favero E, Cantù L, et al. Polymeric micelles in drug delivery: An insight of the techniques for their characterization and assessment in biorelevant conditions. J Control Release. 2021;332:312–36. [CrossRef]

[14] Ahmad Z, Shah A, Siddiq M, Kraatz H-B. Polymeric micelles as drug delivery vehicles. RSC Adv. 2014;4(33):140–70. [CrossRef]

[15] Cagel M, Tesan FC, Bernabeu E, Salgueiro MJ, Zubillaga MB, Moretton MA, et al. Polymeric mixed micelles as nanomedicines: Achievements and perspectives. Eur J Pharm Biopharm. 2017;113(2017):211–28. [CrossRef]

[16] Bernabeu E, Gonzalez L, Cagel M, Gergic EP, Moretton MA, Chiappetta DA. Novel Soluplus®-TPGS mixed micelles for encapsulation of paclitaxel with enhanced in vitro cytotoxicity on breast and ovarian cancer cell lines. Colloids Surfaces B Biointerfaces. 2016;140:403–11. [CrossRef]

[17] R.S. B, A.S. J, D.T. M, A.G. J, P.A. RH, M.S. N. Soluplus based polymeric micelles and mixed micelles of lornoxicam: Design, characterization and In vivo efficacy studies in rats. Indian J Pharm Educ Res. 2016;50(2):277–86. [CrossRef]

[18] Raffin RP, Colomé LM, Hoffmeister CRD, Colombo P, Rossi A, Sonvico F, et al. Pharmacokinetics evaluation of soft agglomerates for prompt delivery of enteric pantoprazole-loaded microparticles. Eur J Pharm Biopharm. 2010;74(2):275–80. [CrossRef]

[19] Hornok V. Serum Albumin Nanoparticles: Problems and Prospects. Polymers. 2021; 13(21):3759. [CrossRef]

[20] Srivastava A, Prajapati A. Albumin and functionalized albumin nanoparticles: Production strategies, characterization, and target indications. Asian Biomed. 2020;14(6):217–42. [CrossRef]

[21] Tran PHL, Duan W, Lee B-J, Tran TTD. Current Designs of Polymer Blends in Solid Dispersions for Improving Drug Bioavailability. cCurr Drug Metab. 2018;19(13):1111–8. [CrossRef]

[22] Tran PHL, Tran TTD, Park JB, Lee BJ. Controlled release systems containing solid dispersions: Strategies and mechanisms. Vol. 28, Pharmaceutical Research. 2011. p. 2353–78. [CrossRef]

[23] Prasad D, Chauhan H, Atef E. Amorphous stabilization and dissolution enhancement of amorphous ternary solid dispersions: Combination of polymers showing drug-polymer interaction for synergistic effects. J Pharm Sci. 2014;103(11):3511–23. [CrossRef]

[24] Khadka P, Ro J, Kim H, Kim I, Kim JT, Kim H, et al. Pharmaceutical particle technologies: An approach to improve drug solubility, dissolution and bioavailability. Asian J Pharm Sci. 2014;9(6):304–16. [CrossRef]

[25] Vasconcelos T, Marques S, Sarmento B. The biopharmaceutical classification system of excipients. Ther Deliv. 2017;8(2):65–78. [CrossRef]

[26] Ilie A-R, Griffin BT, Vertzoni M, Kuentz M, Kolakovic R, Prudic-Paus A, et al. Exploring precipitation inhibitors to improve in vivo absorption of cinnarizine from supersaturated lipid-based drug delivery systems. Eur J Pharm Sci. 2021;159:105691. [CrossRef]

[27] Gangarde YM, T. K. S, Panigrahi NR, Mishra RK, Saraogi I. Amphiphilic Small-Molecule Assemblies to Enhance the Solubility and Stability of Hydrophobic Drugs. ACS Omega. 2020;5(43):28375–81. [CrossRef]

[28] Pereira JM, Mejia-Ariza R, Ilevbare GA, McGettigan HE, Sriranganathan N, Taylor LS, et al. Interplay of Degradation, Dissolution and Stabilization of Clarithromycin and Its Amorphous Solid Dispersions. Mol Pharm. 2013 Dec 2;10(12):4640–53. [CrossRef]

[29] Shi NQ, Lai HW, Zhang Y, Feng B, Xiao X, Zhang HM, et al. On the inherent properties of Soluplus and its application in ibuprofen solid dispersions generated by microwave-quench cooling technology. Pharm Dev Technol. 2018;23(6):573–86. [CrossRef]

[30] Hu M, Zhang J, Ding R, Fu Y, Gong T, Zhang Z. Improved oral bioavailability and therapeutic efficacy of dabigatran etexilate via Soluplus-TPGS binary mixed micelles system. Drug Dev Ind Pharm. 2017;43(4):687–97. [CrossRef]

[31] Wang T, Markham A, Thomas SJ, Wang N, Huang L, Clemens M, et al. Solution Stability of Poloxamer 188 Under Stress Conditions. J Pharm Sci. 2019;108(3):1264–71. [CrossRef]

[32] Tian JL, Zhao YZ, Jin Z, Lu CT, Tang QQ, Xiang Q, et al. Synthesis and characterization of Poloxamer 188-grafted heparin copolymer. Drug Dev Ind Pharm. 2010;36(7):832–8. [CrossRef]

[33] Xu W, Ling P, Zhang T. Polymeric micelles, a promising drug delivery system to enhance bioavailability of poorly water-soluble drugs. Vol. 2013, Journal of Drug Delivery. 2013. [CrossRef]

[34] Dou J, Zhang H, Liu X, Zhang M, Zhai G. Preparation and evaluation in vitro and in vivo of docetaxel loaded mixed micelles for oral administration. Colloids Surfaces B Biointerfaces. 2014;114:20–7. [CrossRef]

[35] Fujimori M, Kadota K, Tozuka Y. Mixed Micelle System Produced by Interaction Between Transglycosylated Stevia and an Ionic Surfactant Improves Dissolution Profile of Mefenamic Acid. J Pharm Sci. 2017;106(4):1117–23. [CrossRef]

[36] Oudah MH, Rahi FA, Al-Lami MS. Preparation and characterization of domperidone nanoparticles for dissolution improvement. Iraqi J Pharm Sci. 2018;27(1):39–52. [CrossRef]

[37] Li C, Zhu Y. Quantitative polarized light microscopy using spectral multiplexing interferometry. Opt Lett. 2015;40(11):2622–5. [CrossRef]

[38] Onoue S, Suzuki H, Kojo Y, Matsunaga S, Sato H, Mizumoto T, et al. Self-micellizing solid dispersion of cyclosporine A with improved dissolution and oral bioavailability. Eur J Pharm Sci. 2014;62:16–22. [CrossRef]

[39] Ki B, Soo J, Kang S, Young S, Hong S. Development of self-microemulsifying drug delivery systems (SMEDDS) for oral bioavailability enhancement of simvastatin in beagle dogs. 2004;274(1–2):65–73. [CrossRef]

[40] Bai G, Wang Y, Armenante PM. Velocity profiles and shear strain rate variability in the USP Dissolution Testing Apparatus 2 at different impeller agitation speeds. Int J Pharm. 2011;403(1–2):1–14. [CrossRef]

[41] Dokoumetzidis A, Macheras P. A century of dissolution research: From Noyes and Whitney to the Biopharmaceutics Classification System. Int J Pharm. 2006;321(1):1–11. [CrossRef]

[42] Onoue S, Kojo Y, Aoki Y, Kawabata Y, Yamauchi Y, Yamada S. Physicochemical and pharmacokinetic characterization of amorphous solid dispersion of tranilast with enhanced solubility in gastric fluid and improved oral bioavailability. Drug Metab Pharmacokinet. 2012;27(4):379–87. [CrossRef]

[43] Boonsongrit Y, Mueller BW, Mitrevej A. Characterization of drug-chitosan interaction by 1H NMR, FTIR and isothermal titration calorimetry. Eur J Pharm Biopharm. 2008;69(1):388–95. [CrossRef]

[44] Pandey MM, Jaipal A, Charde SY, Goel P, Kumar L. Dissolution enhancement of felodipine by amorphous nanodispersions using an amphiphilic polymer: insight into the role of drug–polymer interactions on drug dissolution. Pharm Dev Technol. 2016;21(4):463–74. [CrossRef]

[45] Prabu S, Shirwaikar A, Shirwaikar A, Kumar C, Joseph A, Kumar R. Simultaneous estimation of esomeprazole and domperidone by UV spectrophotometric method. Indian J Pharm Sci. 2008;70(1):128–31. [CrossRef]

[46] Higuchi, T and Connors KA. Phase Solubility Studies. Adv Anal Chem Instrum. 1965;4:117–212. [CrossRef]

[47] Rubingh DN. Mixed micelle solutions. In: Solution Chem Surfactants, [Proc Sect 52nd Colloid Surf Sci Symp]. 1979. p. 337–54.