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Hydrophilic-hydrophobic polymer blend for modulation of crystalline changes and molecular interactions in solid dispersion

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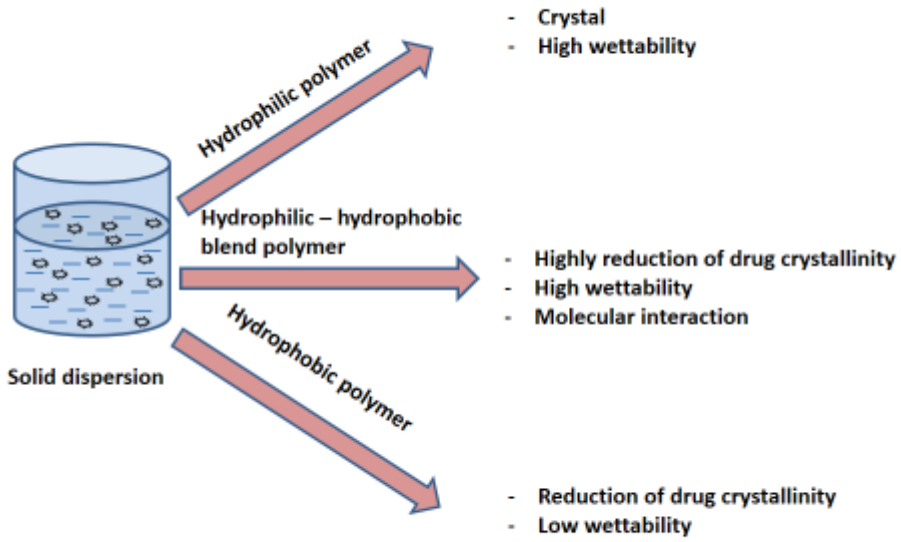
Graphical abstract



Abstract

This research study aimed to develop a new strategy for using a polymer blend in solid dispersion (SD) for dissolution enhancement of poorly water-soluble drugs. SDs with different blends of hydrophilic-hydrophobic polymers (zein/hydroxypropyl methylcellulose – zein/HPMC) were prepared using spray drying to modulate the drug crystal and polymer-drug interactions in SDs. Physicochemical characterizations, including power X-ray diffraction and Fourier transform infrared spectroscopy, were performed to elucidate the roles of the blends in SDs. Although hydrophobic polymers played a key role in changing the model drug from a crystal to an amorphous state, the dissolution rate was limited due to the wetting property. Fortunately, the hydrophilic-hydrophobic blend not only reduced the drug crystallinity but also

resulted in a hydrogen bonding interaction between the drugs and the polymer for a dissolution rate improvement. This work may contribute to a new generation of solid dispersion using a blend of hydrophilic-hydrophobic polymers for an effective dissolution enhancement of poorly water-soluble drugs.

Keywords: hydrophilic-hydrophobic polymer, drug crystal, molecular interaction, solid dispersion.

1. Introduction

Oral administration has been as an effective route in drug delivery systems due to its convenience and flexibility in dosage form design and patient compliance (Ummadi et al., 2013). Oral drug delivery still has some major limitations, including poor bioavailability, which subsequently affect the therapeutic efficacy and safety of the dosage form (Pridgen et al., 2015). Solubility is one of the key factors influencing the bioavailability of drugs (Leuner and Dressman, 2000; Tran et al., 2013) and is associated with an overwhelming number of challenges in drug development. Most of the new drug development have resulted from poor water solubility (Bosselmann and Williams III, 2012; Kalepu and Nekkanti, 2015). Currently, it is estimated that approximately 40 % of new drugs from new chemical substances show limited solubility in water (Ha et al., 2011; Kumar and Singh, 2013). Therefore, improving the solubilization of poorly water-soluble drug has been considered a crucial challenge in modern pharmaceutical science. Solid dispersion (SD) is a promising method that provides various advantages over other strategies in solubility enhancement of low aqueous soluble drugs (Dalvi et al., 2015; Tran et al., 2011). Vasconcelos et al. defined SD as dispersing poorly water-soluble drugs into a hydrophilic matrix (Vasconcelos et al., 2007). Moreover, SD is widely used as a powerful technique to markedly enhance solubility and increase the dissolution rate of poorly water-soluble drugs due to drug particle size reduction, wettability improvement, higher

porosity and amorphous formations of the drug (Vasconcelos et al., 2007). In preparation of SDs, hydrophilic polymers obviously play an important role in establishing a delayed barrier to avoid recrystallization of drugs (Yonemochi et al., 2013). Despite a wide range of applications of hydrophilic polymers in SD, hydrophilic polymers could not always change drug crystals to amorphous forms and therefore, they need a modification process for improving the dissolution rate of poorly water-soluble drugs (Nguyen et al., 2015; Nguyen et al., 2016). There have been studies of ternary solid dispersion using hydrophilic polymer blends to improve drug solubility (Al-Obaidi et al., 2011; Goddeeris et al., 2008; Janssens et al., 2008). Furthermore, although hydrophilic-hydrophobic polymer blends addressing crystal growth inhibition by the presence of hydrophobic polymer in hydrophilic synthetic polymer have been also investigated (Ilevbare et al., 2012; Liu et al., 2014; Marks et al., 2014), the studies focused on changes in drug structural behaviors rather than drug dissolution profiles (Li et al., 2013). Unlike those studies, in which the drug release occurred at a slow rate, we developed the SD system using a zein/HPMC blend for the current study and attempted to indicate that the presence of a suitable hydrophobic polymer in the SD could maximize the dissolution rate of a SD containing a poorly water-soluble drug.

Hydroxypropyl methylcellulose (HPMC) is firmly recognized as a safe agent with non-toxic, non-irritation properties and has been applied in a variety of dosage forms (Huichao et al., 2014). HPMC is widely employed as a hydrophilic matrix material with different levels of viscosity depending on the composition of methoxyl and hydroxypropyl in the structure. On the other hand, zein (a natural biopolymer that is poorly soluble at pH < 11) was selected as a hydrophobic polymer (Paliwal and Palakurthi, 2014). Isradipine (IDP) was used as the model drug in this study. IDP belongs to Biopharmaceutical Classification System (BCS) II that possesses low oral bioavailability (17-28%) and poor solubility (< 10 mg/l) (Christensen et al., 2000).

2. Materials and Methods

2.1 Materials

Hydroxypropyl Methylcellulose (HPMC 4000) was purchased from Dow Chemical Company (USA). Zein was purchased from Acros Organics™ (USA). Sodium hydroxide (NaOH) were obtained from Guanghua Sci-Tech Company (China). Hydrochloric acid (HCl) was purchased from Xilong Chemical Industry Incorporated Company (China). KH_2PO_4 was purchased from Wako Pure Chemical Industries (Japan). Methanol and acetonitrile for high performance liquid chromatography (HPLC) were purchased from Fisher Scientific (USA).

2.2 Methods

2.2.1 Preparation of SDs

A solvent evaporation method using spray drying was utilized to prepare SDs. To investigate the enhancement of the dissolution rate of SDs, different SDs were performed with different ratios between zein and HPMC 4000 in which the amount of hydrophobic polymer was adjusted in the formulations to achieve a high dissolution rate of IDP and the capability of the formulations to promote crystal changes and molecular interactions were measured (**Table 1**). Zein was dissolved in ethanol 90% under stirring until a transparent solution appeared. Similarly, HPMC 4000 was slowly dispersed in hot water (60 °C) to form a swelling polymeric solution. Then, HPMC solution was immediately transferred into a low-temperature environment (-4 °C) until a clear solution formed.

For SDs containing zein (or HPMC) and drugs (F1 and F2), IDP was dissolved in the polymer solution until a homogenous solution formed. For SDs containing the zein/HPMC blend (F3 and F4), zein solution was added into HPMC 4000 solution and stirred for 5 min. This blend was adjusted with absolute ethanol to gain a clear solution and was kept stirring for 3 h. IDP was then continuously dispersed in the solution. The solvent of the formulation was

removed using a Spray-dryer (SD-1000, EYELA, Tokyo Rikakikai Co., Ltd) with atomizing at 200 kPa. The operation was controlled with an inlet temperature of 45 °C, and the outlet temperature was in the range of 37-40 °C. The flow and feed rate were set up at 0.95 m^3/min and 50 ml/h, respectively.

2.2.2. HPLC analysis

The quantity of IDP was determined using an Ultimate 3000 HPLC (Thermoscientific Inc., USA). HPLC analysis was utilized with a reverse phase column (150x4.6 mm, C18). The mobile phase consisted of methanol, water, and acetonitrile in a ratio of 46:20:34 (v/v/v) with a flow rate of 1 mL/ min. The running time and UV/Vis detector were set at 5 min and a wavelength of 325 nm.

2.2.3. Dissolution studies

The *in vitro* dissolution behavior was performed by a paddle apparatus at 37 ± 0.5 ºC, 50 rpm (PT-DT70, Germany). Buffer pH 1.2 and pH 6.8 were used as dissolution media. Each 900 mL of pH 6.8 or pH 1.2 was added into a dissolution vessel. A 1 mL sample was collected from the media at predetermined intervals of 15, 30, 45, 60, 90, 120 min and replenished by adding 1 mL of fresh solution media. A 100 µL sample was diluted with 900 µL of methanol for HPLC testing.

2.2.4 Contact angle measurement

The wettability of SDs was characterized using a direct image processing method to determine the contact angle via the solid-liquid interface. SDs powder with predetermined equal masses were dissolved completely in ethanol 90 % and spread extensively on microscope slides (Duran, 76x26 mm) with 500 mg of the samples. Then, these samples were kept in an oven at 45 °C for solvent evaporation. Contact angle measurements were performed by dropping constant pH 1.2 and 6.8 on the surface of solid samples. Images were captured by utilizing digital camera (DSC-RX100 Mark III, Sony, USA).

2.2.5 Power X-ray diffraction (PXRD) analysis

The PXRD patterns of IDP, carriers and SDs were obtained at room temperature using a Powder X-ray diffractometer (D2 PHASER, Bruker, Germany) with Cu radiation. The X-ray generator was operated at 30 kV and 100 mA. The diffraction data were scanned in a 2θ range from 5^{o} to 50^{o} using a receiving slit of 0.1 mm with a step size of 0.020273 at 2θ/s.

2.2.6 Fourier transform infrared (FTIR) analysis

FTIR spectra of IDP, carriers and SDs were analyzed using a Fourier transform infrared spectrometer (VERTEX 70, Bruker, USA). Then, 1 mg of the sample was dispersed in 200 mg dry potassium bromide (KBr). The mixture was compressed under high pressure and placed in FTIR sample holder. The wavelength was scanned from 500 to 4000 cm^{-1} with a resolution of 4 cm^{-1}.

3. Results and discussion

3.1. Dissolution studies

Figure 1 presents the dissolution profiles of SDs in pH 1.2 media. Obviously, the percentage of drug release was significantly enhanced for all SD formulations compared to the pure drug (0%). While the formulations F1 and F2 contained only one polymer (zein or HPMC) the percentage of drug release improved by reaching to approximately 75 % and 51 % after 120 min, respectively, F4 considerably enhanced drug release better with more than 85 % drug release within 120 min. Meanwhile, in comparison to F2, the dissolution profile of F3 indicated a good performance of drug release. Therefore, this result revealed that a zein/HPMC blend in SD of F3 provided better enhancement of drug release than the SD containing only zein. Interestingly, the pertinent composition in blend with F4 importantly enhanced the dissolution rate of IDP in the gastric environment compared to other dissolution profiles. More than 55 %

of the drug was released within the first 15 min and steadily increased to nearly 86 % at the end of the dissolution process.

Figure 2 illustrates the dissolution rate of SDs carried out at pH 6.8 within 120 min. Obviously, most of the formulations showed an enhanced dissolution rate of IDP during the 2 h at pH 6.8 and also remained the same order of dissolution performances as they were in the gastric fluid. SDs of F1 and F2 were prepared without blending zein and HPMC. Hence, in the profile of F2, the formulation containing IDP and zein alone showed a moderate percentage of drug release, approximately 61 % after 2 h with 51 % drug released in the first 15 min. In contrast, SDs of F1 including IDP and HPMC 4000 performed better than F2, which could release drug up to 84 % over 120 min. The blend in formulation F3 where the amount of zein was reduced and replaced by HPMC 4000 (the drug/ zein/ HPMC ratio 1:3:1) showed higher drug release compared to zein alone (F2). So, it is evident from the dissolution profiles that a reduction in the amount of zein could lead to a higher dissolution rate of IDP. For this reason, SDs of F4 were prepared by decreasing a small amount of HPMC 4000 and replaced zein with a ratio 1:0.5:3.5 compared to F1. SDs of F4 showed the highest percentage of drug release up to 100 %. This result was enhanced significantly compared to F1, F2 and F3. Moreover, after the first 15 min, F4 had a significantly higher percentage of drug release than other formulations, which was specified to be approximately 65 %. Therefore, F4 proved that the zein/HPMC blend had an extremely strong effect on dissolution rate enhancement of a poorly water-soluble drug. In conclusion, F4 was considered to be an optimal model formulation for further investigations. Moreover, the drug release of SDs in intestinal fluid (pH 6.8) performed better than in gastric fluid (pH 1.2).

3.2. Contact angle

SD has been considered an effective method to enhance the wettability of poorly water-soluble drugs due to the formation of an amorphous state (Dalvi et al., 2015; Puri et al., 2010).

Obviously, all of the SDs data (**Figure 3)** indicated that the dissolution rate enhancement of IDP in both buffer environments was due to small contact angles. It should be noted that the highly hydrophobic property of zein could result in a higher contact angle of SDs (F2) or even in combination with HPMC (F3). However, a suitable incorporation of zein in the formulation (F4) significantly reduced the contact angle not only at pH 1.2 but also at pH 6.8, specifically at 26^{o} and 31^{o}, respectively, which had the highest wettability compared to other formulations. These analyses showed that the contact angle studies had a direct influence on dissolution studies. Therefore, the combination of zein and HPMC in blends would have a key impact leading to the dissolution rate enhancement of IDP in SDs.

To understand the effect of zein/HPMC blends in formulations, PXRD was used to investigate the crystal structure of pure IDP, zein, HPMC 4000, SDs of F1, F2, F3 and F4. Numerous peaks with high intensity were observed in the X-ray diffraction pattern for pure IDP (**Figure 4**). This result indicated that the drug is highly crystalline, which may lead to its poorly water-soluble property (Bobbala and Veerareddy, 2012). In contrast, no distinct peaks of zein were characterized in its pattern, which revealed its amorphous state. HPMC 4000 had a broad characteristic peak at 19.5 2θ, which also indicated its highly amorphous state. Under these considerations, zein/HPMC blends could form an amorphous structure for dissolving drugs and changing drugs from a crystalline state into an amorphous state. Obviously, in the diffractograms of F1 and F2, some characteristic peaks still remained at 9.5, 11.8, 19.3 and 23.12 θ at a lower intensity compared to the pure drug. However, F2 seemed to reduce more drug crystallinity than F1 with the presence of zein in the formulation, which indicated that zein facilitated the decrease of crystalline drug better than HPMC 4000. F3 still retained 2 characteristic peaks of IDP at 19.3 and 23.12 θ, whereas these peaks were diminished in intensity compared to F2 and F1. Interestingly, the diffractogram of F4 showed that numerous peaks of IDP disappeared in the pattern, which indicated a highly reduced level of drug

crystallinity in SDs. The result also supported the reason why F4 had the best performance of drug release than other formulations. In general, the utility of zein as a hydrophobic polymer showed its greater potential to form an amorphous state compared to a hydrophilic enhancer, such as HPMC. Nevertheless, SD of F2 with zein presented a limitation in enhancing wettability, which resulted in a lower drug dissolution rate than the use of HPMC in SD of F1, which was observed in previous contact angle and dissolution studies. However, the combination of zein and HPMC in SD showed better transformation into an amorphous state, especially with SD of F4.

FTIR studies were performed to investigate the physicochemical interactions between the drug and carriers in SDs according to the absence or shift of characteristic peaks. In the spectrum of IDP illustrated in **Figure 5**, a characteristic peak of N-H stretching was located at 3345 cm^{-1}, and a functional group observed at 1701 cm^{-1} was noticed by a carbonyl group with C=O bonding (Park et al., 2013). Additionally, two additional peaks at 1646 cm^{-1} and 1331 cm^{-1} indicated N-H bending and C-N stretching, respectively, in the spectrum of IDP (Havanoor et al., 2014). An existence of a peak at 2945 cm^{-1} was specified by the C-H group in the chemical structure (Ramasahayam et al., 2015). The spectrum of zein presented stretching of the hydroxyl group and amino group around the 3450 cm^{-1} position (Corradini et al., 2014). Moreover, two peaks at 1655 cm^{-1} and 1540 cm^{-1} were ascribed to the C=O group and N-H bond, respectively. In the spectra from HPMC 4000, a characteristic peak named O-H stretching was indicated at 3452 cm^{-1}. In addition, C-H stretching and C-O stretching occurred at 2926 cm^{-1} and 1118 cm^{-1}, respectively (Sekharan et al., 2011). Obviously, the spectrum of F1 did not show any changes in the presence of the amino group and the carbonyl group of IDP positioning at 3345 cm^{-1} and 1701 cm^{-1}. Meanwhile, the disappearance of the carbonyl group associated with a lower intensity of amino group in SD containing zein alone of F2 indicates that there was an interaction of hydrogen bonding between IDP and zein. However, this

formulation did not achieve a well-released dissolution profile due to its hydrophobic property. In the spectrum of F3, the utility of the zein/HPMC blend in SD resulted in the disappearance of the C=O group of from IDP, which revealed the interaction between the drug and carriers. Interestingly, the missing NH group and C=O group of IDP in the spectra of F4 (SD with drug/zein/HPMC ratio 1:0.5:3.5) demonstrated that the pertinent composition of the formulation resulted in the effectiveness in modulating the interaction. Hydrogen bonding interactions between IDP and zein in SDs of F2, F3, F4 resulted in crystalline changes, compared to the SD containing only HPMC. Therefore, the presence of a hydrophobic polymer in SD may induce a chemical interaction between the polymer and the poorly water-soluble drug, which facilitated increased drug dissolution.

4. Conclusion

This research was successful in significantly enhancing the dissolution rate of a poorly water-soluble drug, such as IDP, in SDs using a hydrophilic-hydrophobic polymer blend. An SD containing an appropriate ratio of polymer blend could be a promising strategy for enhancing dissolution. The study also revealed that zein/HPMC blends had better performance than neat carriers in SDs throughout the increase of hydrophilicity, completely amorphous formation and well-performance of molecular interactions. FTIR and PXRD results demonstrated the ability of the SD system to enhance the dissolution rate of a drug by changing the drug structure from a crystalline form to an amorphous form by formulating an intermolecular hydrogen bond between the drug and carriers. The F4 with a ratio of 1:0.5:3.5 between IDP, zein and HPMC 4000, respectively, was considered to be the optimal formulation for further investigation.

Acknowledgements

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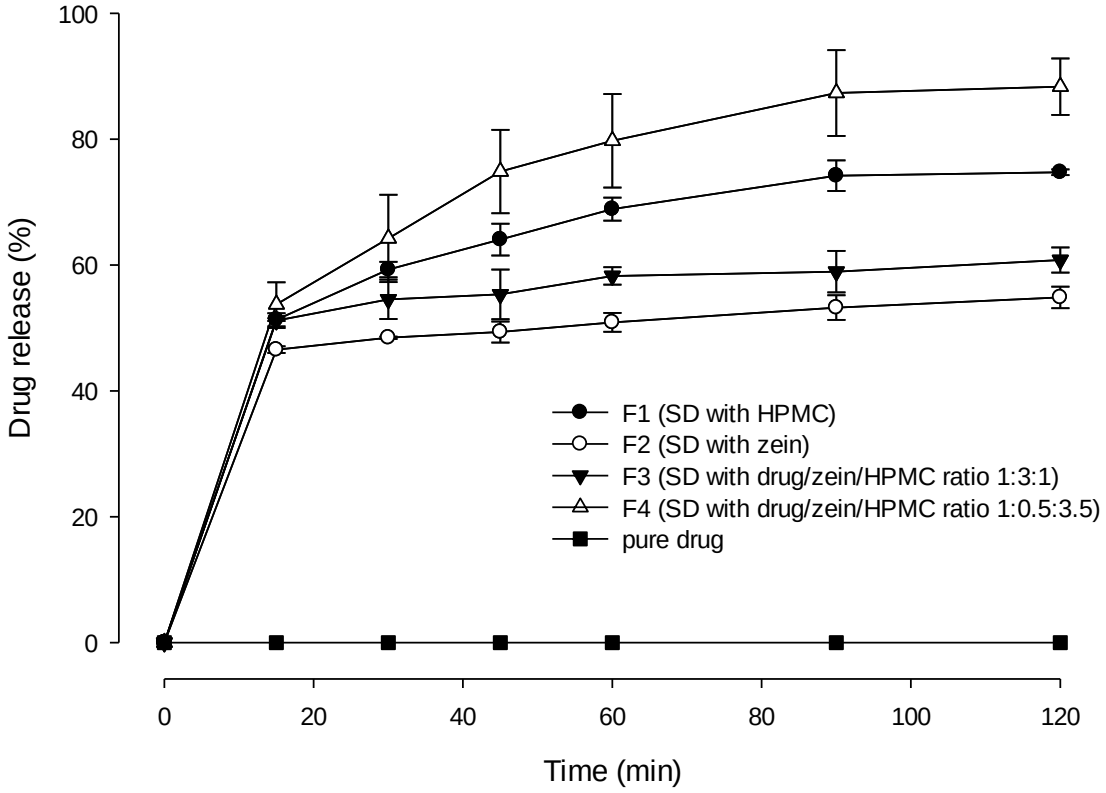

Figure 1. Dissolution profiles of pure IDP, SDs containing IDP of F1, F2, F3 and F4 at pH 1.2

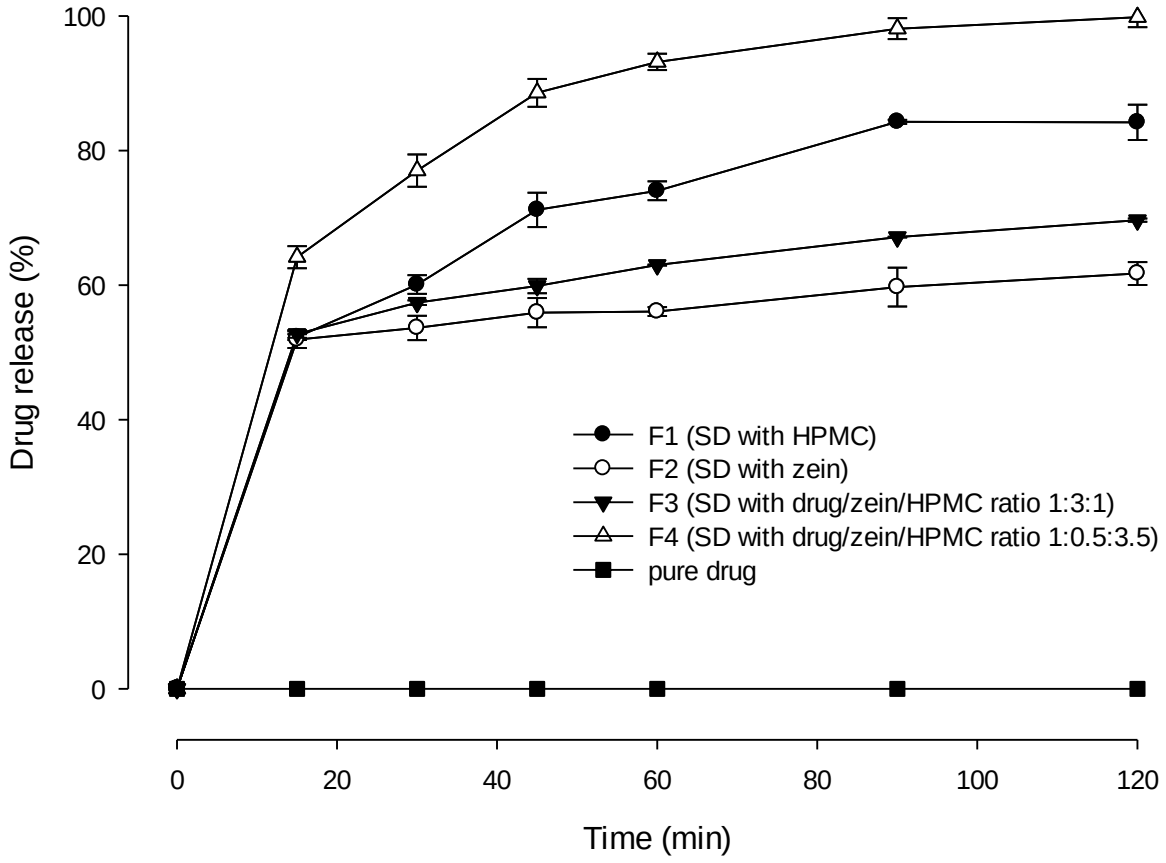

Figure 2. Dissolution profiles of pure IDP and SDs containing IDP of F1, F2, F3 and F4 at pH 6.8

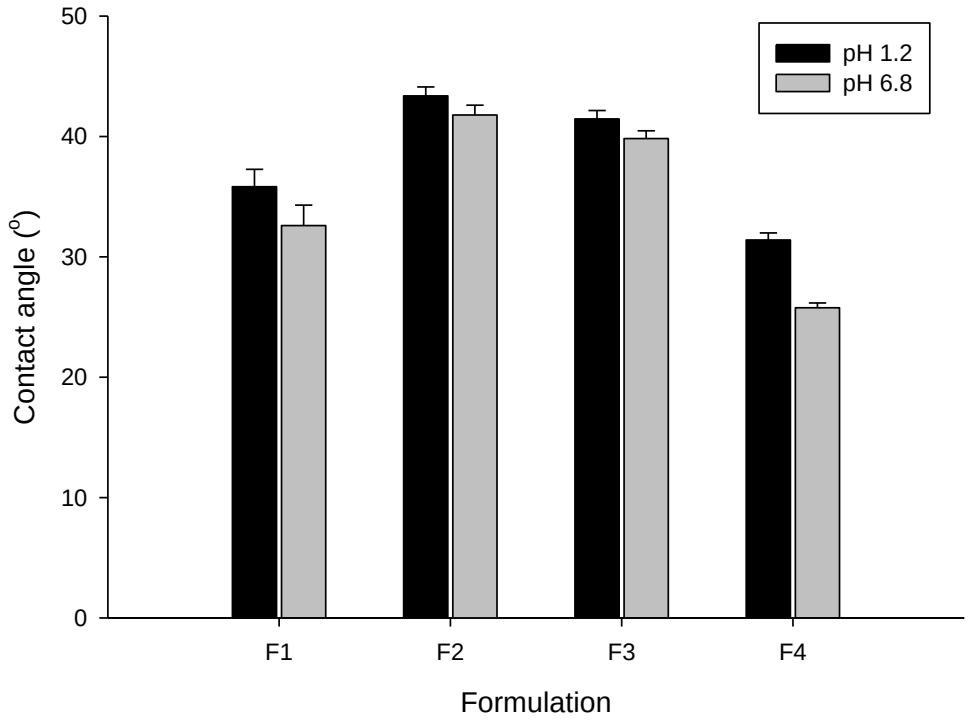

Figure 3. Contact angle measurement of droplets on SDs containing IDP of F1, F2, F3 and F4

3.3. PXRD analysis

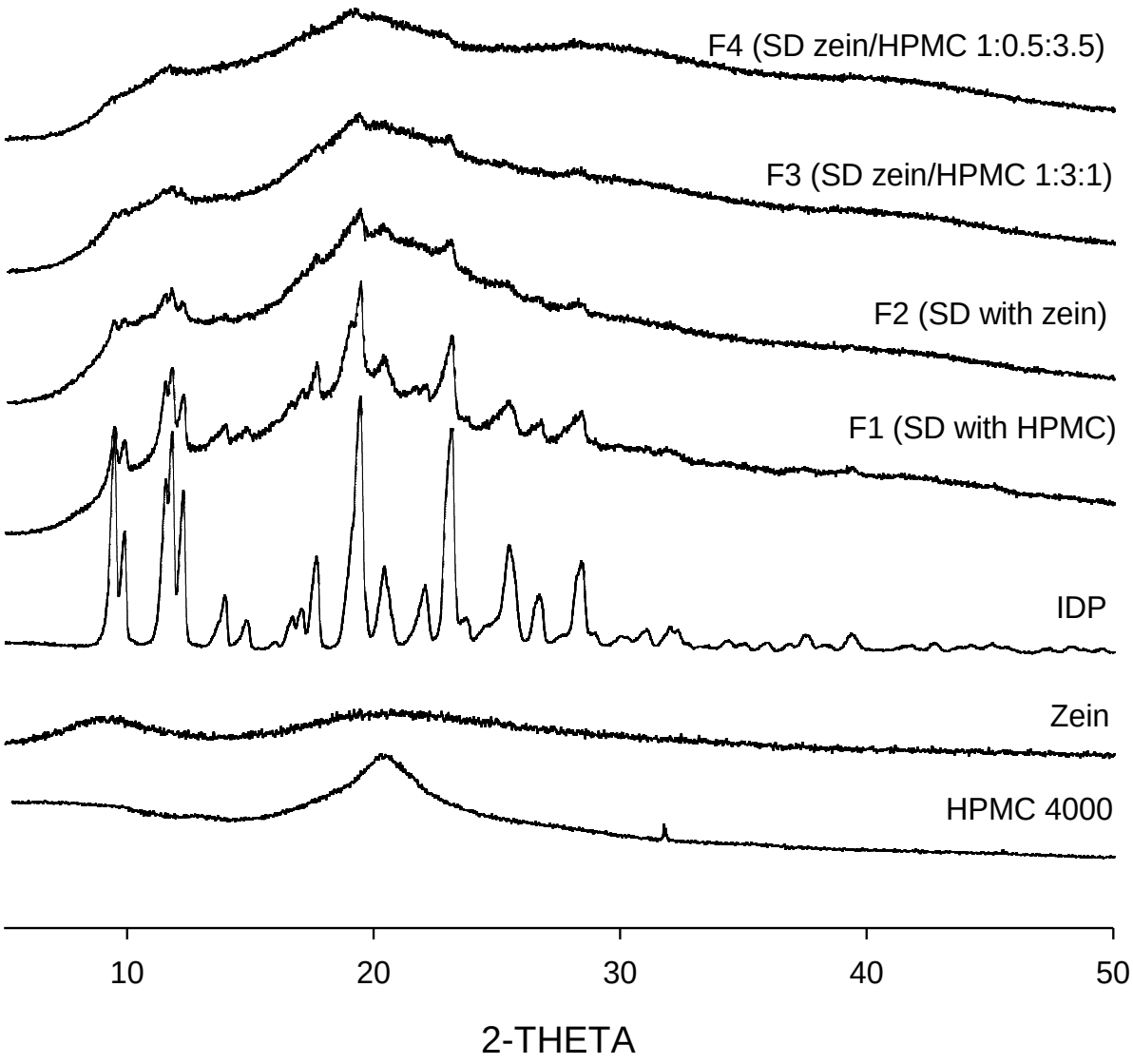

Figure 4. PXRD patterns of pure IDP, HPMC 4000, zein and SDs of F1, F2, F3, F4

3.4. FTIR analysis

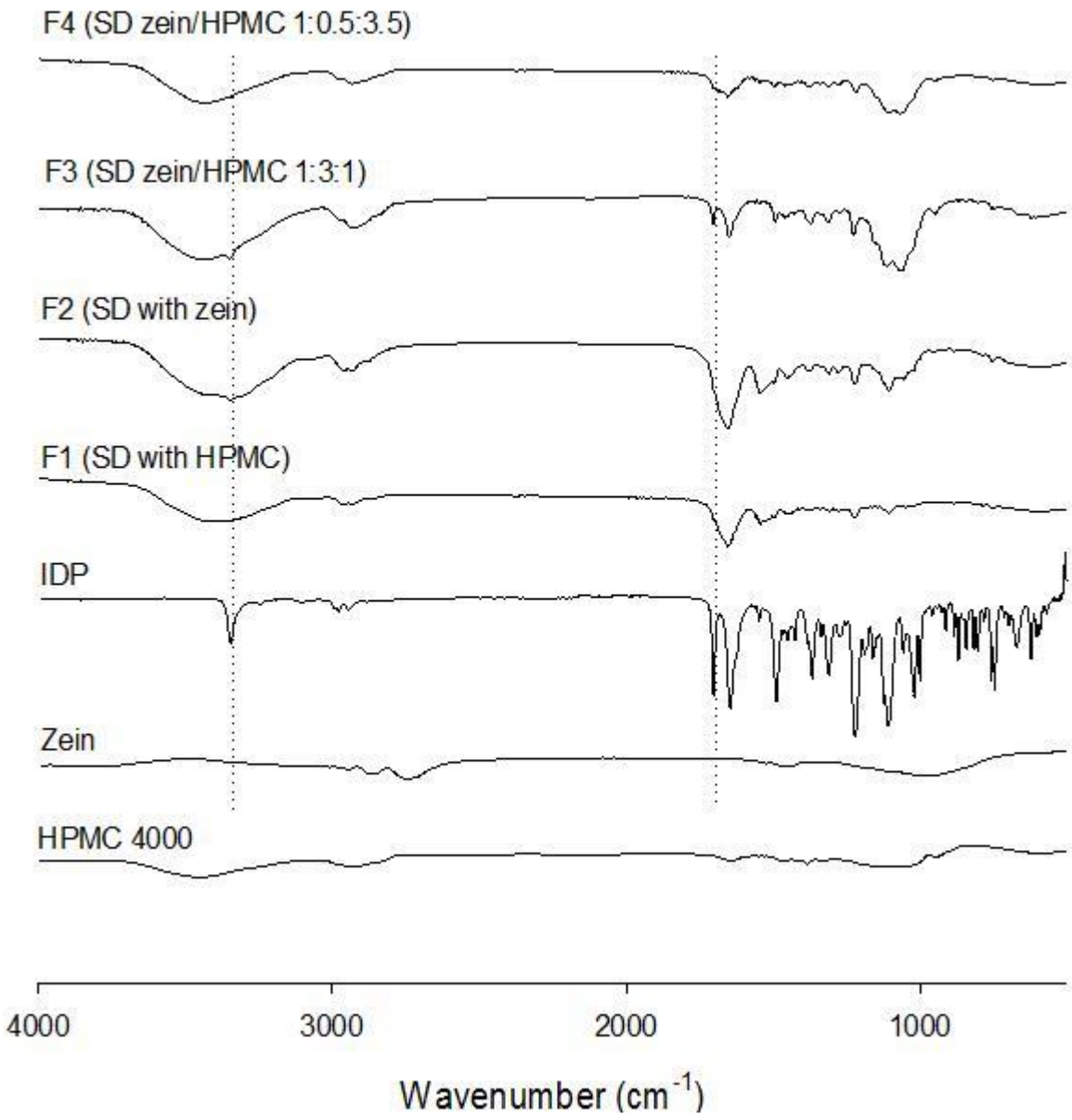

Figure 5. FTIR spectra of pure IDP, HPMC 4000, zein and SDs of F1, F2, F3, F4

Table 1: Formulation compositions of SDs powder (F1, F2, F3, F4)

Formulation	IDP (mg)	Zein (mg)	HPMC 4000 (mg)	Ratio	Total (mg)
F1	5	-	20	1 : 0 : 4	**25**
F2	5	20	-	1 : 4 : 0	**25**
F3	5	15	5	1 : 3 : 1	**25**
F4	5	2.5	17.5	1 : 0.5 : 3.5	**25**