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ORIGINAL ARTICLE

Zein-based solid dispersion for potential application in targeted delivery

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Abstract The study aims to design and evaluate the ability of zein in solid dispersion (SD) system to enhance drug dissolution rate for a further application of colonic delivery of poorly water-soluble drug. The SD samples were prepared by solvent method and the investigation of drug release was performed at pH 7.4. The wettability, molecular interactions and drug's crystal behaviours of SDs were studied by contact angle measurement, Fourier transform infrared spectroscopy (FTIR) and powder X-ray diffraction (PXRD), respectively. Zein-based SDs showed its potential in enhancing the rate of drug release. The PXRD results pointed out a rearrangement of drug's crystalline structure in some SD samples through the appearance of new peaks on PXRD diffractogram, while a formation of a hydrogen bond between prednisolone (PRL) and zein was also confirmed by FTIR spectra. It was evident that a strong relationship between the amount of zein and the dissolution rate of PRL in SD system attributed to zein hydrophobicity, recrystallization and molecular interaction which were factors inducing the enhanced drug release rate. In conclusion, zein is a potential carrier for controlled release SD systems, especially further application for poorly water-soluble drugs in colonic delivery like PRL due to the resistance of zein at low pH environment.

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Keywords Zein · Solid dispersion · Prednisolone · Controlled release · Colonic delivery

Abbreviations

BCS	Biopharmaceutics classification system
FTIR	Fourier transform infrared spectroscopy
HPLC	High performance liquid chromatography
PRL	Prednisolone
PXRD	Powder X-ray diffraction
SD	Solid dispersion

Introduction

In recent decades, development of the pharmaceutical industry has risen intensively with several promising drug applications. However, more than 70% of new chemical entities are categorized as poorly water-soluble drugs, leading to the poor bioavailability (Müller et al. 2006; Patel and Agrawal 2011; Sahbaz et al. 2015). With regards to the advantages including reduced particle size, increased wettability and porosity, as well as drug changes to a lower level of crystalline state or amorphous state, solid dispersion (SD) has been considered as one of the successful strategies to improve dissolution profiles of poorly water-soluble drugs (Chiou and Riegelman 1971; Tran et al. 2009, 2010b, 2011b). The choice of suitable carriers, solvent or melting method and other excipients for a drug formulation in two-component or multi-components system is prerequisite for an effectively stable SD product (Nguyen et al. 2015a, b; Tran et al. 2010a).

Applications of biopolymers like natural proteins are exponentially increasing in controlled and targeted drug delivery and tissue engineering (Matalanis et al. 2011; Nitta and Numata 2013; Oh et al. 2009). Protein-based

carriers provide a number of advantages over lipid, carbohydrate, or synthetic polymers, for example, biodegradability, high drug binding capacity and availability of a large surface area for drugs to be entrapped (Hawkins et al. 2008; Jahanshahi and Babaei 2008; Kratz 2008). Zein, the protein extracted from corn which belongs to the characteristic class of proteins known as prolamin, has been examined as a possible raw material for polymer applications since the early part of the twentieth century (Müller et al. 2011). It is considered as generally recognized as safe (GRAS) and food grade ingredient by Food and Drug Administration. Zein contains three-fourth of lipophilic and one-fourth of hydrophilic amino acid residues (KR 2012). This property may attribute to its solubility in binary solvents containing a lower aliphatic alcohol and water, for instance, aqueous ethanol and aqueous isopropanol, or in high concentration of urea, alkaline pH ≥ 11 or anionic surfactant, and its insolubility in water alone (Paliwal and Palakurthi 2014). The appropriate temperature and ratio of solvent mixture have a dramatic effect on the cloud point of zein. Due to its high hydrophobicity, zein has been successfully applied as a potential carrier for encapsulation and controlled release of poorly water-soluble compounds (KR 2012). Zein has been tested for controlled delivery of essential oils, dyes, anti-microbial agents, anti-cancer drugs, gene delivery as micro/nanoparticles, etc. (Brahatheeswaran et al. 2012; Gong et al. 2010; Wu et al. 2012).

Herein, the purpose of this study was to explore the influence of hydrophobic carrier—zein, on the dissolution behavior of drug in colonic environment using SD approach. Prednisolone (PRL) is a synthetic adrenal corticosteroid chemically defined as 11,17,21-trihdroxyprena-1,4-diene-3,20-dione (Vogt et al. 2007). PRL has been widely used for treatment of colon disease like colitis (Park et al. 2002). This BCS class II drug with slight solubility (0.22–0.24 mg/mL at 25 °C) (Palanisamy and Khanam 2011; Vogt et al. 2007) was chosen as a model drug because a further development of colonic delivery of PRL could take a full advantage of zein in resistance to drug release at acidic pH. Various ratios of PRL-zein SD were used to investigate the improvement of dissolution rate. The structural crystallinity of drug was characterized by powder X-ray diffraction (PXRD). The potential molecular interaction between PRL and zein in SD was also investigated by Fourier transform infrared spectroscopy (FTIR).

Materials and methods

Materials

Zein was purchased from Acros Organics™ (New Jersey, USA), Prednisolone (PRL) was supplied by Tianjin Tianyao Pharmaceuticals Co., Ltd (China). Ethanol, Sodium hydroxide (NaOH), Disodium hydrogen phosphate dodecahydrate ($Na_2HPO_4{\cdot}12H_2O$), Potassium dihydrophosphate (KH_2PO_4) and Acetic acid (CH_3COOH) were provided by Guangdong Guanghua Sci-Tech Co., Ltd (Shantou, Guangdong, China). Sodium chloride (NaCl) and Hydrochloric acid (HCl) were supplied by Xilong Chemical Co., Ltd (Shantou, Guangdong, China). Sodium acetate was kindly gifted by Korea United Pharm Inc. (South Korea). Methanol for high performance liquid chromatography (HPLC) was purchased from Fisher Scientific (Pittsburgh, Pennsylvania, USA). All other chemicals and reagents were of analytical grade.

Methods

HPLC analysis

The concentration of Prednisolone (PRL) was determined by HPLC system (Dionex Ultimate 3000 HPLC, Thermoscientific Inc., USA) with Luna 5 µ C18 analytical column (150 × 4.6 mm). The mobile phase consisted of 60:30 (v/v) mixture of methanol and deionized water; the flow rate was 1.2 mL/min and the running time was 5.5 min. The UV detector was set at 254 nm to analyze the column effluent. The entire solution was filtered through a 0.45 µm membrane filter and was degassed prior to use. 20 µL of samples were injected into HPLC system for analysis.

Preparation of zein-based SD system

Zein-based SDs containing PRL were prepared by solvent—evaporation method with various ratios between PRL and carrier (Table 1). Firstly, zein was slowly added to a sufficient amount of binary solvent of ethanol and water (90:10 v/v) under stirring by magnetic stirrer (Thermo Scientific Cimarec Digital Stirring Hot Plate, USA). While zein was totally dissolved, PRL was dispersed into the solution under continuous stirring condition until a clear solution was observed. The sample was then evaporated in oven at 40 °C until a solid mass was formed. Finally, the

Table 1 Formulation compositions of PRL-zein SD powders

Formulation	Ratio	Weight for one dose (mg)		Solvent (mL)
		Drug	Zein	
F1	2:1	100	50	15
F2	2:2	100	100	18
F3	2:1.3	100	65	18
F4	2:1.5	100	75	20

zein-based SD powder was sieved through 0.5 μm mesh for the uniform of particles.

Dissolution study

The study was performed by the Dissolution Tester (Pharma Test, PT-DT70, Germany) with USP apparatus II (50 rpm, 37 ± 0.5 °C). The zein-based SD powders equivalent to 5 mg PRL were exposed to 900 mL of pH 7.4 for 120 min. 1 mL of the samples was withdrawn at predetermined intervals and replaced with fresh medium to keep the constant dissolution volume. The concentrations of PRL were then analyzed by HPLC as described above.

Contact angle measurement

For the assessment of wettability, contact angle of zein-based SD powder was measured based on the imaging method. This method was commonly used to measure contact angle by dropping a drop of liquid directly on a plane surface of the solid (Javadzadeh et al. 2007). The experiment was performed at room temperature. Zein-based SD samples and pure PRL were prepared in aqueous ethanol (90:10 v/v) and spread an exactly equal amount on microscope slides (1 mg/cm^2). Next, these slides were put in an oven at 50 °C to evaporate the solvent. A drop of pH 7.4 was placed on the surface of the solid mass. Images of the fluid droplet were recorded by means of a digital camera (Canon-SX 260 HS, USA). Digital photos were analyzed by Adobe Photoshop CS6 and determined by measuring the tangent to the curve of the droplet on the surface of the compact.

Powder X-ray diffraction (PXRD)

The pure PRL, zein and zein-based SD powders of different ratios were analyzed by X-ray diffractometer (Bruker D8 Advance, Germany) using Cu-Kα radiation at a voltage of 40 kV, 50 mA. The samples were scanned in increments of 0.02° from 5° to 45° (diffraction angle 2-theta) at 1 s/step, using a zero background sample holder.

Fourier transform infrared spectroscopy (FTIR)

A FTIR spectrophotometer (Bruker Vertex 70, Germany) was used to investigate the spectra of pure PRL, zein and zein-based SD samples. The wavelength was scanned from 500 to 4000 cm^{-1} with resolution of 2 cm^{-1}. KBr pellets were prepared by gently mixing 1 mg of sample with 200 mg KBr.

Scanning electron microscopy

Morphology of pure drug, zein and SD powder were investigated using Scanning electron microscopy (SEM, Jeol JSM IT 100, Japan). To allow surface visualization, before SEM analysis, the samples were coated with a thin layer of gold. All samples were examined under accelerating voltage of 10.0 kV.

Statistical analysis

The results were presented by mean ± SD. The contact angle measurement and dissolution studies data were analyzed using one-way ANOVA. Statistical significance is defined as $p < 0.05$. All calculations were performed using SigmaPlot 12.5 (Systat Software Inc.)

Results and discussion

Dissolution study

The dissolution profiles of pure PRL and zein-based SD powders at pH 7.4 are displayed in Fig. 1. Zein was successful in increasing drug dissolution rate compared to the release rate of pure drug. With regard to the pure PRL, the release rate was lower than 40% in the first 45 min, then was increased up to about 70% at the end of the 2 h period. Meanwhile, F1 formulation (PRL:zein 2:1) had a higher dissolution rate than the pure drug ($p < 0.05$). The percentage of drug release reached 64% after 45 min and finally achieved about 88% in 2 h. The presence of zein in SD system had an effect on the significant increase of the drug release rate. However, when the amount of drug and zein was equivalent (F2, PRL:zein 2:2), the dissolution rate was dropped down to 75%. This situation may be attributed to the low solubility of zein in pH < 11 (Paliwal and Palakurthi 2014). The more zein was present in the system, the more the formulation resisted to the lower pH media. Therefore, modification of the appropriate ratio between PRL and zein would be considered for enhancing the drug release rate up to more than 90%.

To verify the role of dissolution enhancement from zein, the release rate of F3 and F4, whose ratios stayed in between F1 and F2, were investigated. With the ratio of PRL:zein at 2:1.3, F3 showed the highest dissolution rate among all of the formulations ($p < 0.001$) with above 70% of drug released in the first 45 min. The rate of drug release continued to rise up, and finally reached nearly 100%. However, when increasing the amount of zein to the ratio 2:1.5 (F4), the release rate performed a slight decrease about 10% in comparison to F3. Although the release of drug from F4 was quite equal to that from F3 during the

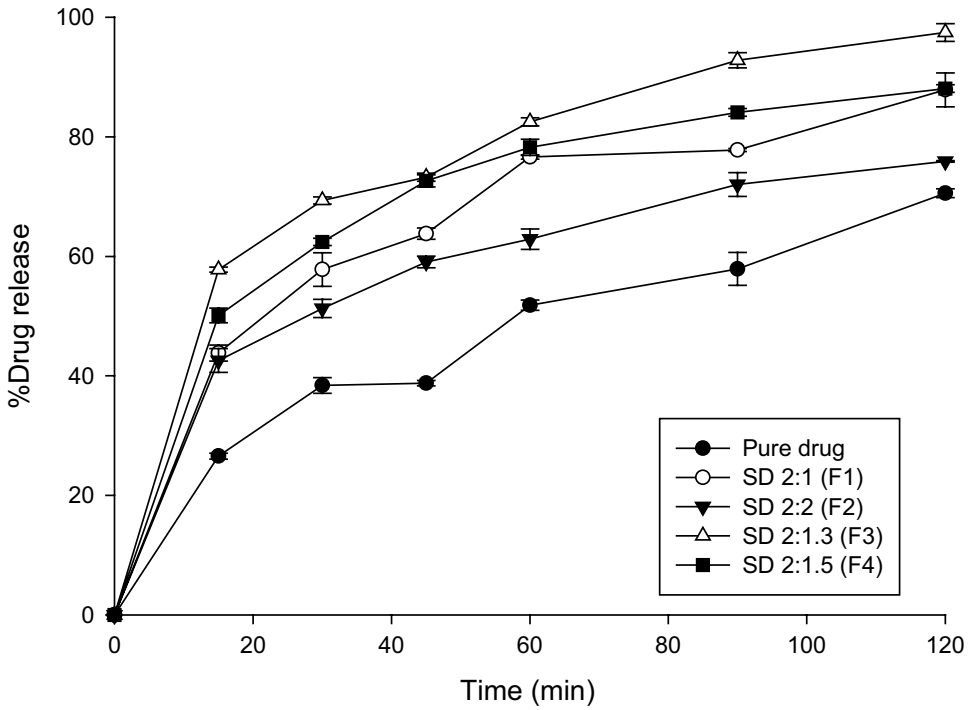

Fig. 1 Dissolution profiles of PRL from SDs of F1–F4 compared to the pure drug at pH 7.4

first 45-min-period, the final dissolution rate of F4 was about 88%. It is clearly seen that F4's release pattern was similar to F1 (PRL:zein 2:1) ($p > 0.05$, not significant). It may assume that the ratio 2:1.3 between drug and zein was the critical point which could give the highest release rate of PRL in SD system with zein. Generally, these results suggested that zein showed its ability to be used as a dissolution enhancer in SD systems and a greater amount of zein could result in a negative effect on drug release enhancement. Thus, for further applications of zein as SD carrier, it is necessary to decide an appropriate amount of zein to incorporate with the active agent for the highest dissolution rate.

Wettability study

The wettability of zein-based SD samples was studied by contact angle measurement since the lower the angle the better wettability of the sample should be. This instrument analysis revealed a strong relationship between the hydrophilic or the hydrophobic properties of the powder and the dissolution rates of the examined samples (Lazghab et al. 2005). The values of contact angles from all samples were strongly related to dissolution profiles of SD samples (Fig. 2). Specifically, the F3 (PRL:zein 2:1.3) formulation exhibited the smallest angle of about 9.19°, indicating its highest wettability resulted in the highest dissolution rate ($p < 0.001$). The sample SD with ratio 2:2 (F4), however, showed the biggest angle although its release rate was higher than pure drug. These data demonstrated that the presence of zein in the SD could improve the wettability of the formulation for enhancement of dissolution rate of poorly water-soluble drugs. However, it should be noted that a too high content of zein could increase hydrophobicity of SD and therefore, it could inhibit the drug dissolution rate.

Structure characterization

X-ray diffractions were performed on pure PRL, zein, and SD samples (F1–F4) to evaluate the structure behavior of PRL through zein-based SD systems. The XRD pattern of zein showed two broad peaks which confirmed its amorphous state at the positions between 5° and 35° of 2-theta, while numerous characteristic peaks of PRL indicated that drug was in typically crystalline nature (Fig. 3). Regarding the patterns of SD systems, F1 (PRL:zein 2:1) and F2 (PRL:zein 2:2) also showed some sharp and intrinsic peaks at diffraction angles, proving the crystalline form of these samples. The change of drug from a high crystalline state to amorphous or lower crystal energy could enhance its dissolution rate because no energy or just low energy is required to break up the crystal lattice during the dissolution process (Taylor and Zografi 1997). Moreover, increasing the ratio of carrier to drug in SD can decrease the drug crystallinity (Okonogi and Puttipipatkhachorn 2006). Interestingly, it is clearly seen that F2 was more crystalline than F1 due to the appearance of the new peak at 10° of 2-theta which had not existed on X-ray diffraction pattern of pure PLR.

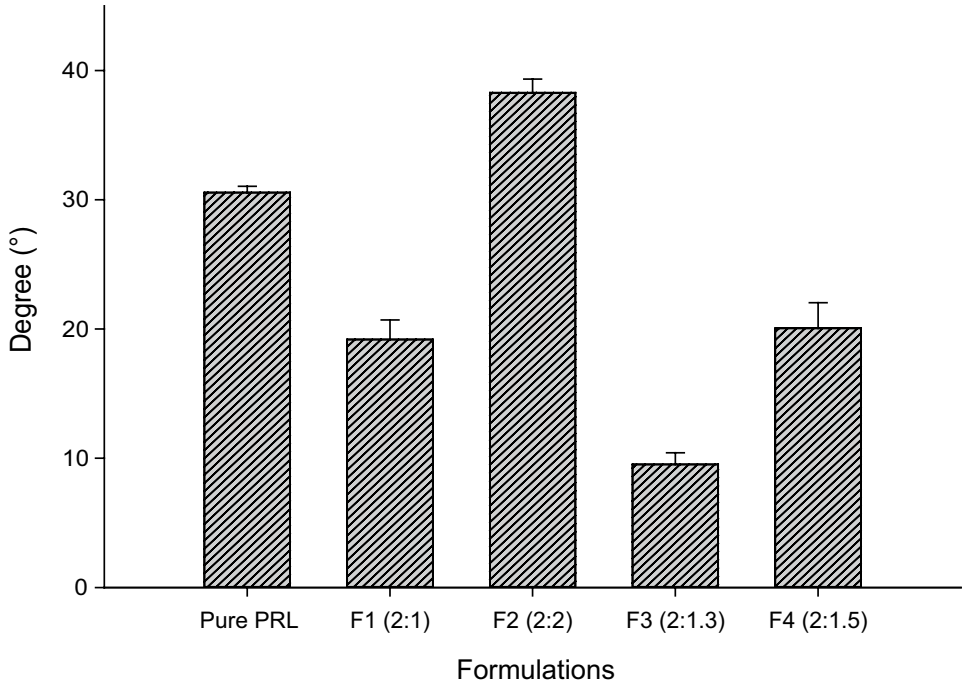

Fig. 2 Contact angle of pure PRL and zein-based SD samples

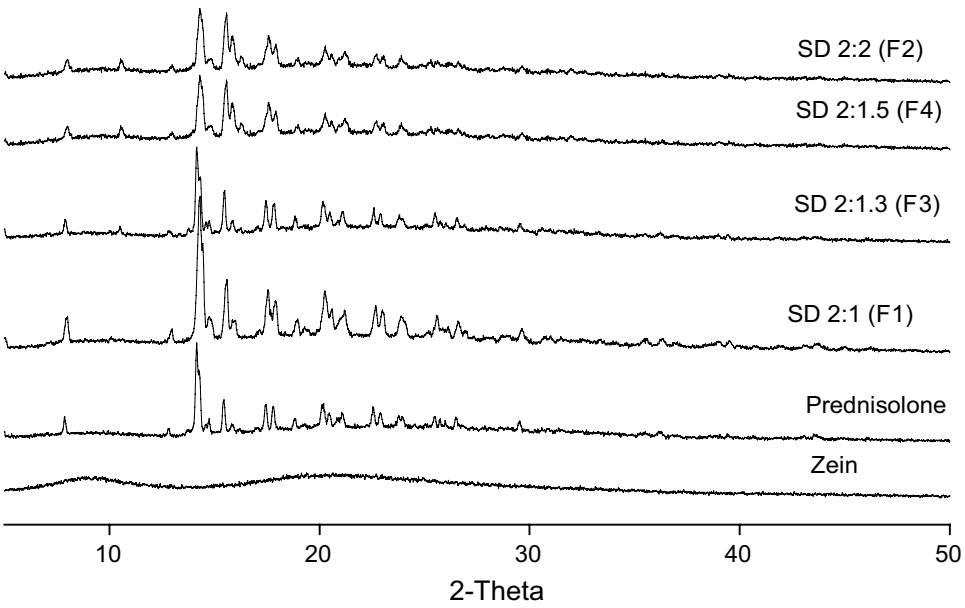

Fig. 3 PXRD patterns of pure PRL, zein and F1–F4 formulations

Comparing the diffractograms of SD samples in various ratios, it is clearly indicated that all formulations were in crystalline form as well. More importantly, the new peak at 10° of 2-theta appeared in all SD formulations, indicating the rearrangement in the crystalline structure of these samples during SDs formation. However, only small peaks were observed in the cases of F1 and F3 as compared to F2 and F4. These results suggested that the addition of zein should be halted at an appropriate ratio with drug to prevent a development of new crystal structures in formulations which may inhibit drug release (Tran and Tran 2013). Therefore, the interaction between PRL and zein in structure possibly occurred. It may be assumed that zein interacted with the active agent in SD system, leading to a rearrangement of drug crystalline structure.

Molecular interactions

In order to investigate any possible interaction between pure PRL and zein in a formulation, FTIR is frequently

used (Tran et al. 2011a). FTIR spectra from F1 to F4 were analyzed together with the pure drug and zein (Fig. 4). Pure PRL displayed characteristic peaks of O-H stretch vibration at 3357, 3455 and 3498 cm^{-1}, indicating the presence of three hydroxyl groups and peaks at 2856 cm^{-1}. Besides, the position of 2932 cm^{-1} showed the presence of C–H stretching (alkanes) in its structure (Palanisamy and Khanam 2011). There were also carbonyl groups (C=O) and aromatics (C–C) peaks at 1710 and 1654, and 1612 cm^{-1}, respectively. In the FTIR spectrum of zein, an O–H stretch at 3418 cm^{-1}, two intense bands at 1649 and 1539 cm^{-1}, assigned to the amide bands, were observed (Müller et al. 2011).

Regarding the zein-based SDs, it can be seen that all characteristic peaks of the drug appeared on FTIR spectrum of F1. The result demonstrated that no interaction between zein and PRL occurred at this ratio. However, in F2 sample, a noticeable exception should be pointed out that peak at 3357 cm^{-1} of O–H stretch vibration of pure drug disappeared on its FTIR spectrum. Likewise, from the spectra of F3 and F4, the O–H stretch vibration at 3357 cm^{-1} was also absent. The situation may claim that molecular interactions between the active agent and zein might occur on hydroxyl groups and form a hydrogen bonding, thus, leading to the disappearance of 3357 cm^{-1} peak. Furthermore, no shifting peaks or new peaks in SD's spectra could be found, except for the decrease in intensities of absorption bands at 1710, 1654 and 1612 cm^{-1} in a linear portion to the ratio of carrier. Therefore, no significant interaction between drug and carrier occurred besides the formation of hydrogen bonding as mentioned above. It would be suggested that this hydrogen bonding was formed between the O–H group of PRL and the N–H group of zein (Zheng et al. 2007).

Due to the key roles in enhancing dissolution rate of PRL with zein, factors that should be taken into account include the amount of zein in SDs, the rearrangement of PRL's crystalline structure and the formation of hydrogen bond between O–H group and N–H group. An appropriate amount of zein would maximize the dissolution rate of PRL. In contrast, an excess amount of zein in the formulation would facilitate an interaction between zein and PRL through the hydrogen bonding which may result in the recrystallization and the dissolution rate inhibition. Also, the wettability of SD samples could decrease with an inappropriate zein amount. Consequently, the dissolution rate of the active agent might be affected by the amount of zein as it has the water resistant property. Therefore, a modulation of an appropriate amount of zein in a suitable preparation method would facilitate an effective dissolution enhancement of poor water-soluble drugs.

Morphology studies

The SEM images demonstrate the structure of drug, zein and SD samples at different ratios (Fig. 5). PRL image shows a smooth surface with small particles aggregated. Besides, zein has a bigger particles size and a structure of amorphous state as confirmed by XRD diffractogram. The images of SD formulations proved that all samples are in crystalline state, in agreement with XRD results, and there was no significant difference between these SD powders when they were observed by SEM.

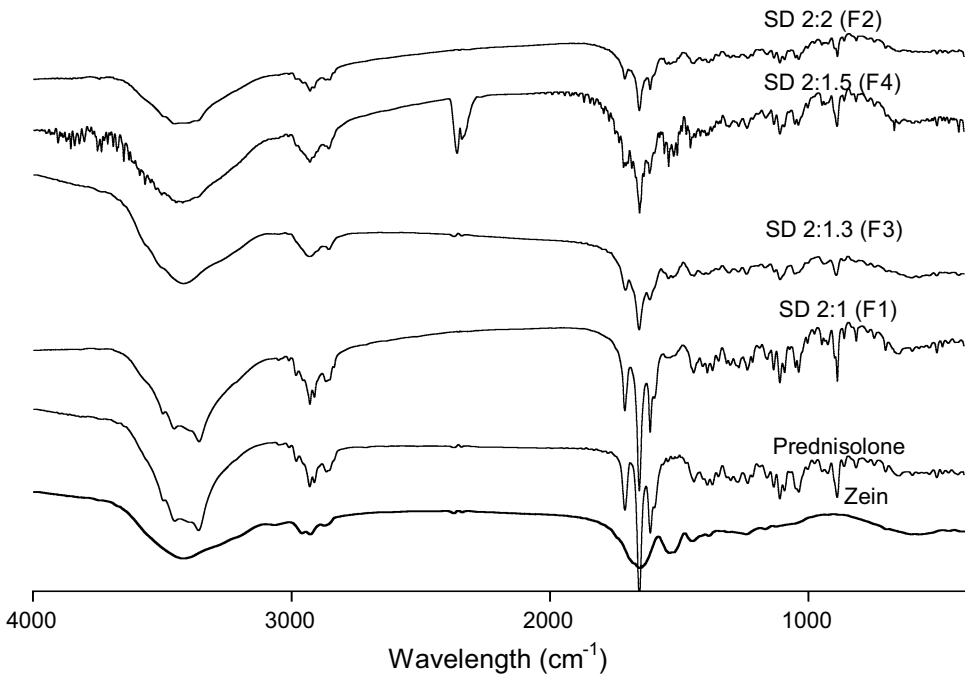

Fig. 4 FTIR spectra of pure PRL, Zein and F1–F4 formulations

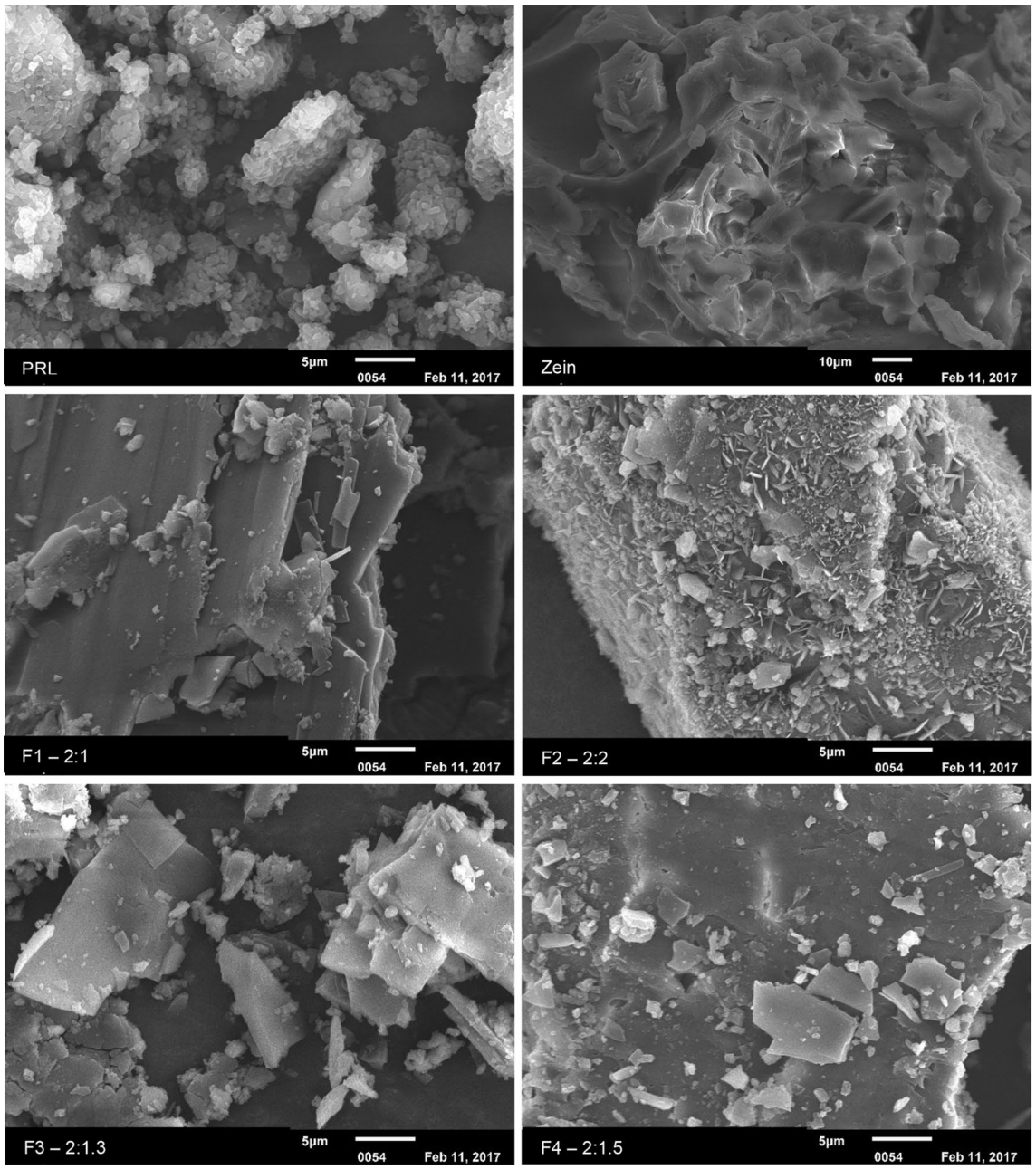

Fig. 5 SEM images of pure PRL, Zein and F1–F4 formulations

Conclusion

Design of zein-based SD in this research was successfully fabricated to increase dissolution rate of poorly water-soluble drugs, which hence may lead to the enhanced drug bioavailability and absorption. The improvement of drug release rate depended on an appropriate amount of zein in SD formulations. Changes of wettability, drug recrystallization, and molecular interaction due to the presence of zein could be attributed to the main mechanism of drug dissolution enhancement. Further studies and evaluations are required to explore zein as a promising carrier for targeting colon of poorly water-soluble drugs.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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