International Journal of Pharmaceutics 513 (2016) 148–152

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

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

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ARTICLE INFO

Article history:
Received 9 July 2016
Received in revised form 1 September 2016
Accepted 6 September 2016
Available online 6 September 2016

Keywords:
Hydrophilic-hydrophobic polymer
Drug crystal
Molecular interaction
Solid dispersion

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.

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, 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

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http://dx.doi.org/10.1016/j.ijpharm.2016.09.017
0378-5173/

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.

Table 1
Formulation compositions of SDs powder (F1–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

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 (150 × 4.6 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 °C, 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, 76 × 26 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° to 50° 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

Fig. 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%