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Improvement in the water solubility of drugs with a solid dispersion system by spray drying and hot-melt extrusion with using the amphiphilic polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer and D-mannitol

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ABSTRACT

The aim of this study was to prepare and characterize solid dispersion particles with a novel amphiphilic polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer, as a water-soluble carrier. Solid dispersion particles were prepared by hot-melt extrusion and spray drying. Indomethacin (IMC) was used as a model comprising drugs with low solubility in water and D-mannitol (MAN) was used as an excipient. The physicochemical properties of prepared particles were characterized by scanning electron microscopy, thermal analysis, powder X-ray diffraction (PXRD) analysis, FTIR spectra analysis, and drug release studies. Stability studies were also conducted under stress conditions at 40 °C, 75% relative humidity. We found that dissolution behavior of the original drug crystal could be improved by solid dispersion with the polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer. The PXRD pattern and thermal analysis indicated that the solid dispersion prepared with the polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer and IMC was in an amorphous state. FTIR spectra analysis indicated that the interaction manner between the polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer and IMC may differ with the preparation method and formulation of solid dispersions. Stability studies proved that the amorphous state of IMC in solid dispersion particles was preserved under stress conditions for more than two weeks.

1. Introduction

In recent years, several novel drugs with low solubility in water are being developed in the pharmaceutical industry because of their high affinity to the drug potency target. Many problems such as low bioavailability or difficulties in formulation have occurred due to low water solubility. Therefore, enhancement in the solubility of such drugs would be important to the pharmaceutical industry. To solve this problem, several pharmaceutical engineering techniques such as grinding, salt formation, formation of an inclusion compound with cyclodextrins, and solid dispersion have been studied (Takeuchi et al., 2005).

Solid dispersion system is a useful for improving the dissolution property of drugs with low solubility in water. In general, solid dispersion particles are prepared with polymers as carriers for dispersing drug molecules in a polymer matrix (Dahlberg et al., 2008; Vasconcelos et al., 2007). The drug solubilizes in water with an amphiphilic polymer, thereby improving the solubility and dissolution rate and hence the bioavailability. The ideal *co*-dispersed system between the drug and polymer might preferably form a polymer micelle, leading to improvements in the apparent dissolution behavior of the drug. Utilizing the amorphous form of drugs can be a useful approach to improve dissolution behavior and bioavailability of active pharmaceutical ingredients with low solubility in water (Chiou and Riegelman, 1970; Goldberg et al., 1966; Hancock and Parks, 2000; Konno et al., 2008; Leuner and Dressman, 2000; Six et al., 2004). However, amorphous compounds are thermodynamically unstable and may crystallize over pharmaceutically relevant timescales. Amorphous compounds can often be stabilized by combining the active ingredient with a carrier polymer to form an amorphous molecular level solid dispersion (Chiow and Riegelman, 1971; Konno et al., 2008; Leuner and Dressman, 2000;

Abbreviations: IMC, Indomethacin; MAN, D-mannitol

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Serajuddin, 1999). It has also been reported that the drug is at a high thermodynamic activity level having particles with a large surface area in solid dispersions or solid solutions (Alonso et al., 1988; Fini et al., 2002; Gupta et al., 1991).

For solid dispersion preparation, spray drying and hot-melt extrusion are commonly used. Spray drying is used for methods ranging from simple spray drying operations of bulk active pharmaceutical ingredients and excipients to particle engineering such as granulation and microencapsulation (Ré, 2006; Vehring, 2008). One of the characteristics of spray drying is fast solvent evaporation, which leads to a rapid increase in viscosity and permits kinetic trapping of the active ingredients in the carrier (Paudel et al., 2013). Hot-melt extrusion is widely applied to process technology in the production of plastic, rubber, and food products (Kruder, 1985; Chokshi et al., 2005). It is also applied in the pharmaceutical industry because of its advantages over other methods: (1) It is a solvent-free processing method and thus is environment-friendly and cost-effective, (2) The method offers the possibility of a continuous process and therefore an efficient scale-up from a small-scale laboratory extruder to a large-scale production size melt extruder (Chokshi et al., 2005).

Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer [Soluplus®, SOL, Fig. S1(A)] is a novel amphiphilic polymer that is designed and developed for solid solutions. It is reported that SOL shows excellent solubilizing properties for BCS class II drugs and offers the possibility of producing solid solutions of several drugs with low solubility in water using extrusion, solvent evaporation, spray drying, and freeze-drying techniques (Hardung et al., 2010; Nagy et al., 2012; Shamma and Basha, 2013). SOL is an interesting and advantageous polymer in processing solid dispersions because of its amphiphilic chain orientation and structure. SOL exists in a granular, thermoplastic form with narrow particle size distribution providing advantages in processing by hot-melt extrusion and spray drying. Therefore, in this study, we prepared solid dispersion particles with indomethacin [IMC, Fig. S1(B)] and the novel amphiphilic polymer SOL by spray drying and hot-melt extrusion. IMC is one of the poorly water soluble drugs [solubility in unbuffered water (pH 4.37, 25 °C):22 μg/mL, pKa: 3.96 ± 0.30 (most acidic, 25 °C), calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02] which is often used as a model drug for the solid dispersion. The physicochemical properties of IMC and the prepared particles were characterized. In addition, particles with D-mannitol (MAN), used as an excipient for improving wettability of the formulations, were prepared and evaluated. Furthermore, stability studies under stress conditions at 40 °C, 75% relative humidity (RH) were performed.

2. Materials and methods

2.1. Materials

Soluplus® [SOL, BASF Japan Ltd.] were kindly gifted by BASF Japan Ltd. (Tokyo, Japan). Indomethacin (IMC) was purchased from Kongo Chemical Co. Ltd. (Toyama, Japan). D-Mannitol (MAN, the reagent grade), acetonitrile (HPLC grade), ethanol and phosphoric acid (the reagent grade) were purchased from Kishida Chemical Co., Ltd. (Osaka, Japan). All other chemicals used were of reagent grade.

2.2. Solubility studies of IMC with Soluplus®

Five milliliters of SOL solutions (0.02–80 mg/mL) were added to an excess of IMC (50 mg), and the mixture was mechanically shaken (140 strokes/min) for 2 days at 37 °C. The equilibrium-attained system was filtered (pore size, 0.45 μm), and IMC concentration was determined by HPLC. HPLC conditions were as follows (Hess et al., 2001; Hirai et al., 1997): Column, YMC-Pack ODS-A 4.6 × 150 mm (YMC Co., Ltd. Kyoto, Japan); mobile phase, acetonitrile/0.2% phosphate solution = 60/40; temperature, 40 °C; detector, UV; wavelength, 320 nm; flow rate, 1 mL/min; injection volume, 20 μL. The HPLC system comprised of a Prominence LC-20AD intelligent HPLC pump, SPD-20A intelligent UV/VIS detector, a CTO-10AS intelligent column oven, a SIL-10AF intelligent sampler, a CBM-20A system controller, and an LC solution chromatography data system (all from Shimadzu Co., Kyoto, Japan).

Table 1
Formulations of physical mixture (PM) and hot-melt extrusion (EX) samples.

		IMC (g)	SOL (g)	MAN (g)
PM_5050	IMC: SOL = 50:50	1.0	1.0	0
PM_5050M	IMC: SOL: MAN = 50:50:25	1.0	1.0	0.5
EX_5050	IMC: SOL = 50:50	1.0	1.0	0
EX_5050M	IMC: SOL: MAN = 50:50:25	1.0	1.0	0.5
EX_1585	IMC: SOL = 15:85	1.5	8.5	0
EX_1585M	IMC: SOL: MAN = 15:85:15	1.5	8.5	1.5

2.3. Preparation of solid dispersion particles

Solid dispersion particles were prepared by hot-melt extrusion and spray drying. The physical mixture (PM) was prepared by geometric mixing of IMC, SOL, and MAN at determined weight ratios using a mortar and pestle (Table 1).

Hot-melt extrusion samples (EX) were prepared as PM at predetermined ratios of IMC, SOL, and MAN (Table 1). Hot-melt extrusion was performed using a co-rotating twin screw HAAKE Minilab II extruder (Thermo Fisher Scientific KK, Yokohama, Japan). The temperature was set at 150 °C, the screw speed was 50 rpm, and PM was manually fed into the extruder. The glass transition temperature (T_g) of SOL is reported as 71.1 °C, and the melting point and T_g of IMC is reported as 165 °C and 42 °C, respectively (Bochmann et al., 2016; Chokshi et al., 2008). In addition, we used MAN (T_g: 13 °C, Sugimoto et al., 2006) as an excipient for improving wettability of the solid dispersion formulations. The extrusion temperature was below the melting point of IMC and above T_g of IMC, SOL and MAN. Samples were pressed through a single orifice die and ground by a mortar and pestle. Particle sizes of 125–250 μm were collected by sieving. In order to evaluate the effect of particle size on release profiles, EX_1585 particle was ground by AO Jet mill (Seishin Enterprise Co. Ltd., Tokyo Japan) and named EX_1585JET. The conditions of jet milling were as follows: Pressure, 0.4 MPa (inlet) and 0.3 MPa (outlet); the injection rate, 5 g/h; the number of vibrations, 71 Hz.

The formulations of spray drying samples (SD) are shown in Table 2. The weight ratio of IMC and SOL, 50:50 or 15:85, were prepared. The solvent E60 and E100 represent 60 and 100 mL of ethanol, respectively, and EW represents the mixture of ethanol and water. IMC and SOL were dissolved in solvents, ethanol or a mixture of ethanol and water (water was added after IMC and SOL were dissolved in ethanol) to prepare the particles. The prepared solution was spray dried. IMC and SOL were dissolved in ethanol, and MAN was dissolved in water to prepare SD with MAN. Both the solutions were mixed; this mixture solution was spray dried and the solid dispersion powder was collected and used for evaluation. Spray drying was performed using a spray dryer (GS-310, Yamato Scientific Co., Ltd., Japan) at rate of 10 mL/min and sprayed into the chamber through a nozzle with a diameter of 400 μm, at a pressure of 0.12–0.15 MPa. The inlet and outlet temperatures of the drying chamber were maintained at 50 °C and 20 °C, respectively.

In order to evaluate the physicochemical properties of MAN polymorphisms further, two separate spray dried sample were prepared. Spray-dried MAN (SD MAN) was prepared with an ethanol/water solution. Water spray-dried MAN (water SD MAN) was prepared from a water solution (Table 2).

2.4. Morphology observations

Scanning electron microscopy (SEM) was used to examine particle