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Effects of wet-granulation process parameters on the dissolution and physical stability of a solid dispersion

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ABSTRACT

This study investigated how the process parameters of wet-granulation affect the properties of solid dispersions (SDs), such as dissolution and physical stability. SDs of nilvadipine (NIL) and hypromellose prepared by spray-drying were wet-granulated and dried under various conditions. The NIL concentration at 4 h and area under the curve from dissolution tests were taken to indicate dissolution. Then, the NIL crystallinity calculated from powder X-ray diffraction patterns of SD granules stored at 60 °C for 3 months was evaluated to indicate physical stability. A statistical analysis revealed that the amount of granulation liquid (w/w%) and the ratio of water to ethanol in the liquid (v/v%) significantly affected the dissolution property, and that the drying temperature had a significant effect on the physical stability. Although exposure to water makes the wet-granulation process seem less suitable for granulating a SD, the results indicated that the process can be used to develop SD granules by selecting appropriate conditions, such as a lower proportion of granulation liquid, a higher water to ethanol ratio in the liquid, and a higher drying temperature.

1. Introduction

Recently, more than 70% of new chemical entities in the pharmaceutical pipeline are classified in the biopharmaceutical classification system as having low solubility, namely, as class II or IV (Lipp, 2013). Class II or IV candidates have low solubility in the gastrointestinal tract, which typically results in low and varying bioavailability. So even if they have the potential to be safe and efficacious enough to meet unmet medical needs, they are difficult to be developed as marketed drugs (Gardner et al., 2004; Lipinski, 2000). Indeed, the low solubility of drug substances is one of the greatest challenges for pharmaceutical scientists in formulation and drug-delivery technology, and to overcome this hurdle various solubilization techniques have been developed. These include particle size reduction (Merisko-Liversidge and Liversidge, 2011; Moribe et al., 2013); inclusion complexes with cyclodextrins (Higashi et al., 2011, 2010); lipid-based formulations, including self-emulsifying drug-delivery system (SEDDS) (Sakai et al., 2009, 2010); crystal engineering approaches, including salt and cocrystal formation (Shiraki et al., 2008; Thakuria et al., 2013); and amorphization, including coamorphous and solid dispersion (SD) (Chen et al., 2015; Higashi et al., 2015; Hirasawa et al., 2003; Lobmann et al., 2011; Taylor and Zhang, 2016; Ueda et al., 2015; Vasconcelos et al., 2007).

Of these techniques, amorphization of crystalline drugs is recognized as one of the most promising strategies for improving aqueous solubility because of its higher free energy. However, the excess free energy in the amorphous state also provides a driving force for crystallization during dissolution in the gastrointestinal tract or storage of the drugs, which impairs the improved bioavailability (Murdande et al., 2010a,b). Over the last few decades, SDs have become an increasingly popular approach for addressing the solubility constraint because drug molecules in SDs are homogeneously dispersed into a polymer matrix and can maintain their amorphous state for long periods (Taylor and Zhang, 2016; Vasconcelos et al., 2007). Several approaches for preparing a SD are well known, such as spray-drying (Curatolo et al., 2009; Friesen et al., 2008; Qi et al., 2013), hot-melt extrusion (Djuris et al., 2013; Stankovic et al., 2015), co-grinding (Ito et al., 2010), or co-precipitation (Dong et al., 2008; Shah et al., 2012). A suitable

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preparation method needs to be selected depending on the physicochemical attributes of drug substances. For instance, the use of evaporation-based approaches, such as spray-drying, may be limited for drugs that have less than 10 mg/mL solubility in volatile organic solvents (e.g. ethanol, methanol, acetone, methylene chloride, tetrahydrofuran, and their mixtures) due to low productivity (Miller and Gil, 2011). Hot-melt extrusion may not be able to convert crystalline drugs with a melting point of over 200 °C to the amorphous state, because at that temperature the extrusion process sometimes causes polymer degradation (Lipp, 2013). An additional reason for the popularity of SDs is that they have the potential to overcome the "solubility-permeability trade-off", by which an increase in a drug's solubility is accompanied by a concomitant decrease in permeability. Thus, while solubilization techniques using common solubilizers, such as surfactants, cyclodextrins, or cosolvents, improve the equilibrium solubility of drug substances, they have a risk of impairing their membrane permeability. In contrast, SDs increase the apparent solubility of drugs by attaining supersaturation, which helps to maintain the membrane permeability and thus overcomes the solubility-permeability trade-off (Dahan et al., 2016; Hens et al., 2015; Raina et al., 2015).

Notwithstanding the high efficacy of SDs in improving the bioavailability of poorly soluble drugs, relatively few commercial products using SD techniques have been launched (Vasconcelos et al., 2016). One reason for this could be the difficulty of developing formulations with SDs. Although amorphous drugs in SDs are stabilized by an interaction between drug and polymer, there still remains a risk of the drug being recrystallized by water (moisture) or heat during the manufacture and storage of SD formulations, with the consequent loss of the advantage in improved solubility (Bhugra and Pikal, 2008; Singh and Van den Mooter, 2016; Vo et al., 2013). So far, many scientists have studied the process conditions required for preparing the SD itself by the aforementioned techniques and have examined how the parameters in the preparation process affect the properties of the prepared SDs (Dobry et al., 2009; Kojima et al., 2013; Liu et al., 2010; Patel et al., 2014; Saerens et al., 2014). However, developing SDs into marketed products generally requires subsequent formulation processes, such as granulating, mixing, or tableting, and is known to be difficult because their physical stability is lower than that of crystalline drugs. Nevertheless, few studies have attempted to investigate the effect of these formulation processes (Jijun et al., 2011; Leane et al., 2013).

Generally, SDs prepared by the spray-drying method, which is a well-established manufacturing technique, have a relatively small particle size and low bulk density that result in poor flowability. So, spray-dried powders require downstream processing, such as granulating, to improve the flowability for subsequent tableting or capsule-filling processes. In this study, we prepared a SD consisting of a poorly soluble drug, nilvadipine (NIL), and a water-soluble polymer, hypromellose (HPMC), by spray-drying. Then, we granulated the SD by the wet-granulating method, which is one of the commonly used granulation methods, and evaluated the effects of the wet-granulating process parameters on the properties of the SD, such as its dissolution and physical stability.

2. Materials and methods

2.1. Materials

NIL (anhydrate crystalline form) was purchased from Sagami Chemical Industry (Tokyo, Japan). HPMC of grade 2910 with a viscosity of 6 mPa·s was kindly provided by Shin-Etsu Chemical (Tokyo, Japan). Lactose monohydrate (Pharmatose® 200 M) was purchased from DFE Pharma Japan (Tokyo, Japan). Hydroxypropylcellulose (HPC, grade L) was purchased from Nippon Soda (Tokyo, Japan). Low-substituted HPC (L-HPC, grade NBD-022) was purchased from Shin-Etsu Chemical (Tokyo, Japan). Crospovidone (Kollidon CL®) was purchased from BASF Japan (Tokyo, Japan). Magnesium stearate (Parteck® LUB MST) was purchased from Merck Japan (Tokyo, Japan). All materials were of chemical grade and were used as received. All other reagents were commercially available and of analytical grade.

2.2. Preparation of NIL/HPMC SD

A mixture of NIL and HPMC at a ratio of 1/1 (w/w) was dissolved in a 3/1 (v/v) ethanol/water mixture by stirring at about 50 °C. The concentration of the drug in the solution was 50 mg/mL. The solution was spray-dried with a mini spray dryer B-290 (Büchi, Flawil, Switzerland) using the following conditions to prepare the NIL/HPMC SD: inlet temperature of 120 °C, solution feeding rate of 6 mL/min, nitrogen flow rate of 7.5 m^3/h. After spray drying, the obtained SD was secondary dried using a VT220 vacuum dryer (Kusumoto Chemicals, Tokyo, Japan) at 25 °C overnight.

2.3. Preparation of SD granules

The ratio for formulation of SD granules shown in Table 1 was selected from a preliminary formulation study as resulting in adequate properties for immediate release tablets. In the preliminary study, SD granules were prepared with different disintegrants such as croscarmellose sodium, L-HPC, and crospovidone, and at different ratios. Subsequently, the SD tablets were obtained by a hand press. Then, their hardness and disintegration time were evaluated according to the Japanese Pharmacopoeia method (data not shown). The SD and the excipients listed in Table 1 other than magnesium stearate were put into a mortar and manually mixed using a pestle for 3 min. The obtained physical mixture (PM) was wet-granulated with a granulation liquid, such as water or water/ethanol mixture, for a certain time. The resulting granule was dried in a VT220 vacuum dryer (Kusumoto Chemicals, Tokyo, Japan) to reduce the amount of liquid (water and ethanol) to less than 4%, then sieved through a 22 mesh metal screen and lubricated by mixing with magnesium stearate to achieve SD granules. Table 2 shows the granulation and drying conditions of each batch (E1–E8), which followed a 2^4 fractional factorial experimental design

Table 1
Unit formula of solid dispersion (SD) granules with each ratio and function.

Component	Formulation ratio (w/w%)	Function
SD (NIL/HPMC)	40	Active ingredient
Lactose monohydrate	24	Filler
Hydroxypropylcellulose (HPC-L)	3	Binder
Low-substituted hydroxypropylcellulose (L-HPC)	25	Disintegrant
Crospovidone	7.5	Disintegrant
Magnesium stearate	0.5	Lubricant