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Development of a novel pelletization technique through an extremely high-shear process using a mechanical powder processor to produce high-dose small core granules suitable for film coating

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ABSTRACT

We established an extremely high-shear melt pelletization technique using a mechanical powder processor to produce high-dose granules smaller than 300 μm with properties suitable for film coating. A mixture of ethenzamide and polyethylene glycol (used as a low-melting binder) at various weight ratios was mechanically treated under various jacket temperatures. When the jacket temperature was set to 50 °C or greater, the product temperature reached the melting point of the binder, resulting in pelletization. The drug powder were pelletized with a small amount of binder to yield pellets of approximately 150 μm with a drug content of more than 90%. The mechanism of melt pelletization through ultrahigh shearing involves a series of nucleation, consolidation, coalescence and breakage stages. The power consumption profile corresponding to each stage in the pelletization revealed that pellets between 75 and 300 μm were effectively obtained at a large power consumption peak. The resultant pellets showed comparative sphericity and smoothness, and higher durability than commercial core granules for film coating. In conclusion, this study demonstrates that the extremely high-shear melt pelletization technique can give drug pellets with desirable properties as core particles for the coating process.

1. Introduction

Pharmaceutical pellets, which are spherical granules consisting of a drug and an excipient, are widely prepared as core particles for precise film coating with controlled release (Vervact et al., 1995). In the pharmaceutical industry, core granules applied for controlled release coating should have particular properties, including spherical morphology, smooth surface and high mechanical strength (Erkoboni, 2010), in order to secure high reproducibility of release profiles and reduce the required coating amount. A high drug content is also an important criterion for core particles, as low-loading core granules give rise to enlargement of the final products through coating and tableting processes, leading to increases in the dose. Furthermore, in recent years, the manufacture of core particles as small as possible has become desirable, because fine particles are more likely to be distributed throughout the gastrointestinal tract than coarse particles (Davis et al., 1986; Meyer et al., 1988; Clarke et al., 1993), and controlled release particles with a smaller size would therefore reduce the variation in bioavailability and the risk of toxicity caused by local high drug concentrations. In addition, small modified release particles are easily applied to a tableting process for producing multiple-unit tablets, as they are more unlikely to suffer a decrease in tablet strength (Debunne et al., 2004) and be disrupted during compression (Ragnarsson et al., 1987) compared with large ones. Thus, core particles with the properties as described above are indispensable for the development of high-level controlled release products.

Pelletization techniques include extrusion/spheronization processes (Vervact et al., 1995; Erkoboni, 2010), high-shear granulation (Vonk et al., 1997; Ramaker et al., 1998) and rotary fluidized bed granulation (Korakianiti et al., 2000; Hamashita et al., 2007). In general, the extrusion/spheronization technique is most popular for the manufacture of core granules for film coating. In this approach, wet mass is passed through millimeter-order pores under high pressure, and the resultant extrudates are round via a spheronizer to obtain dense pellets loaded to a level of more than 80% (Erkoboni, 2010). However, it is difficult to produce pellets less than 500 μm in size, because the extrusion through a screen with small pores generates very high pressure, which can result in

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breakage of the screen. Despite reductions in extrusion pressure due to the addition of swelling materials (Kanbe et al., 2007) or glycerides (Dupont et al., 2002), pellets under 300 μm have not been prepared in an effective way. Therefore, an extrusion/spheronization technique is an unsuitable approach for producing fine core particles. Meanwhile, high-shear granulation and rotary fluidized bed granulation can provide relatively small granules through optimization of formulation, material properties and operating conditions. However, since kneading and densification powers of these processors are weaker than those of the extruder, small agglomerates, which are less subject to mechanical stress, are not sufficiently spheronized and densified. Furthermore, it is considered to be difficult to pelletize drug powder with low plasticity and strong adhesion without adding a large amount of plastic excipient (such as microcrystalline cellulose) under low mechanical stress. Thus, high-shear and rotary fluidized bed granulation techniques are unlikely to give small dense pellets containing a great deal of drug. Hence, we focused on an extremely high-shear process using a mechanical powder processor, which can overcome the technical issues of the small pelletization caused by weak mechanical stress in conventional techniques.

A mechanical powder processor, which is known as a mechanofusion or hybridization system, is an ultrahigh-shear mixer that can effectively provide powder with strong impacting, shearing and compressive stresses in a closed container (Pfeffer et al., 2001). Mechanical stress results from the passage of the material through the narrow gap between a vessel wall and a rotor blade and the centrifugal tumbling motion with swirling flow derived from a high-speed rotor, promoting breakage of agglomerated fine particles and mixing of different powders. Thus, the processor, which was originally used as a dry particle coater based on ordered mixing, has been utilized to improve the flowability of cohesive powder (Yang et al., 2005; Zhou et al., 2011), the dispersibility in air of inhalational powders (Zhou et al., 2010; Yang et al., 2012) and the solubility of poorly water-soluble drugs (Nagata et al., 2001; Sonoda et al., 2008). As far as we know, there is no report on the application of mechanical powder processing to granulation or pelletization. Since we previously reported that mechanical powder processing can modify rod-like drug crystals of several tens of microns into spherical particles through ultrahigh shearing (i.e., particle shape modification) (Kondo et al., 2013), the extremely high-shear process is expected to have the ability to spheronize and densify small agglomerates consisting mainly of drug powder.

In this study, we developed a novel pelletization technique with an extremely high-shear process using a mechanical powder processor to produce high-dose core granules smaller than 300 μm with properties suitable for coating (spherical morphology, smooth surface and high mechanical strength). Since the processor is basically running in dry condition without adding water in the system, granulation through the melting of a solid binder under heating (so-called melt granulation) was investigated. In this approach, the drying step is unnecessary, as no solvent is used during the granulation step, reducing processing time and energy requirement. In addition, granulation of moisture-sensitive drug without organic solvents is an environment-friendly process. Melt granulation is also known as a method for preparing prolonged-release particles using a matrix former such as a hydrophobic wax (Vervaet and Remon, 2010). However, because it is hard to manufacture pellets with diverse release profiles (such as zero-order, site-specific and pulsatile release) using this approach, as an early stage in the development of coated particles widely applicable to controlled-release dosage, core pellets with high drug content were prepared through extremely high-shear melt pelletization in this work. Drug and low-melting binder powders mixed at various weight ratios were mechanically treated with a high-speed rotor under various jacket temperatures. The granulation process was analyzed using power consumption profile of the processor to clarify the mechanism of pelletization.

2. Materials and methods

2.1. Materials

Ethenzamide (ETZ) (API Corporation Ltd., Osaka, Japan) was used as the model drug. Polyethylene glycol 6000 (PEG) (Sanyo Chemical Industries, Ltd., Kyoto, Japan) was used as a low-melting binder. The melting point of PEG determined by a differential scanning calorimeter (DSC) (DSC-60, Shimadzu Co., Ltd., Kyoto, Japan) was about 56 °C. Spherical granules consisting of mannitol alone (Nonpareil-108 (200), particle fraction: 150–250 μm, Freund Industrial Co., Ltd., Tokyo, Japan), which are commercially available as core particles for film coating, were selected as a reference for the resultant pellets. All other chemicals and solvents were of analytical reagent grade.

2.2. Extremely high-shear melt pelletization via mechanical powder processing

A mechanical powder processor (NOB) (Nobilta NOB-MINI, Hosokawa Micron Co., Ltd., Osaka, Japan) based on a mechanofusion system was used as a granulator. The components and character of NOB were described in a previous article (Kondo et al., 2013).

ETZ and PEG were individually ground at a fixed air pressure of 0.6 MPa using a jet mill apparatus (A-O jet mill, Seishin Enterprise Co., Ltd., Tokyo, Japan), and were physically blended at various weight ratios (ETZ: 92.5–95.0% and PEG: 5.0–7.5%) for 5 min in a polyethylene bag. Water heated to various temperatures (40, 50 and 60 °C) was circulated in the jacket of NOB via a thermostat circulator (NCB-1200, Tokyo Rikakikai Co., Ltd., Tokyo, Japan), After the jacket temperature had reached a plateau, this mixture (approximately 10 g: corresponding to 100 mL loose bulk density) was placed into the vessel of NOB, and a cover equipped with a thermal detector was attached to the vessel. The container was inclined at 90° to start the operation. The width of clearance between the vessel and blade was fixed to 1.0 mm. Mechanical powder processing was conducted in a series of preliminary and main runs. In the preliminary run, the rotor speed was set to 1000 rpm for 1 min and was then increased from 1000 to 7000 rpm for 2 min in order to spread the powder throughout the vessel and avoid overloading the motor connected to the rotor. After that, the main run was performed at a fixed rotor speed of 7000 rpm for 10 min. The power consumption of the motor and the product temperature in the vessel during mechanical processing were recorded at fixed time intervals. After the operation finished, the vessel was turned upward, then the cover was removed to attach a recovery container to the vessel. This was turned upside down, and the product was collected by rotating the rotor at 1000 rpm for 1 min. Product yield was defined as the ratio of the weight of collected powder divided by that of charging powder. The products obtained at a PEG concentration of 6.25% and jacket temperatures of 40, 50 and 60 °C were designated as Temp40°C, Temp50°C and Temp60°C, respectively. Meanwhile, the products containing PEG at 5.00%, 6.25% and 7.50% prepared under a jacket temperature of 50 °C were designated as PEG5.00%, PEG6.25% and PEG7.50%, respectively.

2.3. Scanning electron micrographs

Sample powder was fixed on a brass stage using double-faced carbon tape, and was coated using a sputtering equipment (JFC-1600, JEOL Ltd., Tokyo, Japan) with platinum at a fixed current of 30 mA for 90 s. The morphological appearance of the particles was