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Research Articles

One step preparation of spherical drug particles by contamination-free dry milling technique with corn starch beads

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ABSTRACT

The novel dry milling technique has been developed by using a mechanical powder processor for improving the dissolution properties of poorly water-soluble drugs. It was found that the drug crystals were well pulverized by co-processing with fine particles of corn starch (CS). The morphological observation and particle size evaluation revealed that the processed products formed the composite particles with ordered-mixed structure, having double-layered particles with a core of CS and a coating layer of phenytoin (Phe), as a model drug. This result suggested that the drug crystals were selectively micronized and the resultant miniaturized Phe particles were adhered/fixed on the surface of un-milled CS particles. The mechanical characteristics detected by the indentation test assumed that the brittle Phe crystals sandwiched between elastic CS particles would be successfully crushed down by high shearing stress in the processor. The newly-established dispersion-sedimentation test indicated that the fine Phe particles were immediately detached from the composite particles in aqueous phase, constructing the suspension. The dissolution behavior from the processed particles was found to be improved and strongly dependent on the size and amount of detached Phe particles. Such milling and ordered-mixturization have been also successfully done by using recrystallized larger Phe particles than 100 μm. These results would propose the contamination-free dry milling technique without using hard milling balls or beads. The mechanism of the current milling and ordered-mixing phenomena is also provided in this report.

1. Introduction

During the past decade, new drug candidates produced in discovery researches have become more hydrophobic and less water-soluble as a result of progress in highly sensitive in vitro affinity assay using the sophisticated high-throughput screening equipment (Fagerberg and Bergstroem, 2015). Many “enable formulation” technologies have been developed and applied in the pharmaceutical researches so far in order to make such poorly water-soluble drug substances bioavailable (Buckley et al., 2013). Enabling formulation-approaches include the use of solubilization technologies such as co-solvent, self-micro-emulsifying drug delivery systems, liposomes, amorphous solid dispersions and mesoporous carriers, and so on (Rahman et al., 2013; Singh et al., 2011; Van Hoogevest et al., 2011). However, the traditional approaches such as pH adjustment and salt formation are still useful, and the reduction of particle size is a first choice among them to develop the drug products in pharmaceutical industry due to their wide applicability to the drug substances (Leleux and Williams, 2014).

On occasion when producing the powder of drug substance at the final step in its synthesis process, the drug particles are usually crystallized as enough large size in order to facilitate the solid-liquid separating operation by filter to be performed in the next step. Whereas, the small-sized crystals are usually preferable to enhance the mixing uniformity between components in the formulation. In fact, the filtered crystals are generally pulverized at the last step in the manufacturing process of drug substance, and the milled crystals are supplied to the manufacturing process of the drug product. In particular the poorly water-soluble drugs have been ground into the fine particles with single micron size so as to improve the dissolution behavior from the formulation as much as possible. A dry grinding method, in which the drug particles collide with a hard grinding medium at high speed under an air environment, is widely used in the pharmaceutical industry (Naik and Chaudhuri, 2015) due to the following reasons: 1) The milling technique has been conventional and well established. 2) Various types of the milling apparatus have been widely available corresponding to the particle size desired. 3) Drying process is not required before supplying the pulverized

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product to the next manufacturing step such as mixing and granulation process.

As a conventional method of dry grinding, i) pin mill, hammer mill and ball mill methods in which the drug particles to be crushed by colliding with hard grinding media (i.e. pins, plates and balls), and ii) jet mill method in which the drug particles to be crushed by colliding each other through air jet stream with high speed have been applied in practical field. However, the former media-milling method has potential safety risk that the part of grinding media could be broken or abraded under the operation and the small metal or ceramic wear of a material (i.e. zirconium, iron, silicium) would be transferred into the drug products (Li et al., 2015; Juhnke et al., 2012). Such undesirable contamination by the foreign matter would be critically disadvantageous to guarantee the quality of the pharmaceuticals. In addition, the fine-particulate products ground from the both i) and ii) methods have poor handling properties as a powder (flowability and packability), occasionally causing troublesome operation in the next manufacturing process (blending, tableting).

In order to solve these problems simultaneously, the authors tried to develop the novel dry milling technique by using a mechanical powder processing apparatus, which could provide the powdery products with powerful shearing stress. The mechanical powder processor, formerly known as a mechanofusion or hybridization system (Qu et al., 2015; Kumon et al., 2006; Zhang et al., 2008), has been originally applied to precisely mix two components with different particle size (Phillipe et al., 2005). Small guest particles are arranged and fixed onto the surface of large host particles, resulting in the blended powder with exactly same composition ratio in every particle. If one processed particle is picked out, the blend with exact same ratio of two components could be provided. This unit process and its product are named “ordered mixing” and “ordered mixture (OM)” after well-regulated mixing style, respectively (Staniforth et al., 1982). The current technique based on mechanical powder processing is characterized that the surface property of the processed particles, called OM particles hereafter, is significantly different from that of host particles. Thus, it is utilized to improve the powder flow property of cohesive particles (Mullarney et al., 2011; Zhou et al., 2010a), to improve the aerosolization properties of inhalational powder (Zhou et al., 2010b; Yang et al., 2012), to control the release profile of well water-soluble drugs (Kondo et al., 2013; Hoashi et al., 2013), and to enhance the dissolution behavior of poorly water-soluble drugs (Sonoda et al., 2008; Tay et al., 2012) in the pharmaceutical industry so far.

In this research the mechanical powder processor was applied to pulverize the drug crystals due to its simple and easy operation. Further, the small-spherical media, so-called beads, were loaded together in the equipment in order to enhance the milling efficiency. Fine particles of corn starch (CS), which is one of the major additives for solid dosage form, were adopted as milling beads in place of conventional beads made of hard materials such as zirconia, stainless steel, and alumina to avoid a potential concern of contamination completely. It was discovered that only the drug particles have been selectively miniaturized when the mixed powders composed of the drug and CS were processed by high shearing stress. Furthermore, the products were found to be spherical composite particles with ordered mixture-type structure, in which micronized drug particles were deposited on the surface of CS core particle. Considering that the CS particles might play a role of milling beads for micronization of drug crystals, the author planned to develop the novel contamination “zero” dry milling technique using the “beads” of pharmaceutical additives. In this report, the pulverization process was clarified based on the morphological transformation during processing and the mechanical properties of drug and CS particles. In addition, the sizes of ground drug particles were evaluated by the newly-established dispersion-sedimentation test, in which the dispersed drug particles in the aqueous medium were separated in size by centrifugation. Finally, the dissolution behavior of the processed particles was measured to assess the solubilization effect. The final goal of this research is to develop a novel dry milling technique to produce the spherical drug particles with improved release properties, which is applicable to research and production activities in pharmaceutical industry.

2. Materials and methods

2.1. Chemicals

Phenytoin was used as a poorly water-soluble model drug, and purchased from Wako Pure Chemical Co., Ltd. (Osaka, Japan). The purity and mean size of intact phenytoin powder were >99.9% (extra pure grade) and 9.2 μm, respectively. Corn starch was used as a small sphere (bead) for dry milling process as well as a core particle of ordered mixture. Japanese Pharmacopoeia (JP) grade of corn starch (corn starch white) was provided by Japan Corn Starch Co., Ltd. (Tokyo, Japan). The intact materials of corn starch and phenytoin were directly used in the experiments. Phenytoin and corn starch were abbreviated to Phe and CS in this report, respectively. All other chemicals and solvents were of analytical reagent grade, and deionized-distilled water was used throughout the study.

2.2. Recrystallization of phenytoin

Phe was recrystallized to obtain the crystals with larger sizes than that available from the supplier. 3.0 g of Phe powder was dissolved in 100 mL of ethanol at 65 °C. This ethanolic solution was cooled to 25 °C at preset cooling speeds of 1) −20 or 2) −3.3 °C/h by using an incubator (NTS-4000, Tokyo Rikakikai Co., Ltd., Tokyo, Japan), and then stored in a refrigerator for 48 h. The precipitates were recovered by filtration, and the dried products were fractioned by using standard sieves with 45-μm, 125-μm, 250-μm and 850-μm opening. The crystals within 1) 45–250 μm fraction and 2) 125–850 μm fraction were separated from the recrystallized products through 1) rapid and 2) slow cooling procedures described above, respectively. 3 types of Phe with different crystal sizes (one intact and two recrystallized Phe) were named as small, medium, and large sized Phe (S-Phe, M-Phe, and L-Phe) in order of size.

2.3. Manufacturing instruments

As a dry milling apparatus, a mechanical powder processor (Nobilta-Mini, Hosokawa Micron Co., Ltd., Osaka, Japan) based on a mechanofusion principle was used in this research. This machine was mainly composed of a cylindrical vessel, a rotator equipped with 8-blades and a motor. It is characteristic that the vessel and rotator are horizontally positioned to allow sample powder to locate downward on the inner round wall of the vessel. Thus, the sample powder could receive powerful shearing force effectively while passing through the clearance between wall of vessel and blades of rotator. The schematic diagram of this machine is shown in our previous article (Kondo et al., 2013). The clearance between them was fixed to 1 mm in the present study.

2.4. Mechanical powder processing

The sample powder having 30 mL of bulk volume was placed into the vessel, and a cover equipped with a temperature indicator was attached. After the vessel was leaned to set horizontally, the rotation was started. The rotation speed was gradually increased up to 5000 rpm for 1.5 min to mix and distribute the sample powder throughout the vessel. The rotation was continued at fixed speed of