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Development of a novel ultra cryo-milling technique for a poorly water-soluble drug using dry ice beads and liquid nitrogen

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ABSTRACT

A novel ultra cryo-milling micronization technique has been established using dry ice beads and liquid nitrogen (LN2). Drug particles were co-suspended with dry ice beads in LN2 and ground by stirring. Dry ice beads were prepared by storing dry ice pellets in LN2. A poorly water-soluble drug, phenytoin, was micronized more efficiently using either dry ice beads or zirconia beads compared to jet milling. Dry ice beads retained their granular shape without pulverizing and sublimating in LN2 as the milling operation progressed. Longer milling times produced smaller-sized phenytoin particles. The agitation speed for milling was optimized. Analysis of the glass transition temperature revealed that phenytoin particles co-ground with polyvinylpyrrolidone (PVP) by dry ice milling were crystalline, whereas a planetary ball-milled mixtures process with zirconia beads contained the amorphous form. The dissolution rate of phenytoin milled with PVP using dry ice beads or zirconia beads was significantly improved compared to jet-milled phenytoin or the physical mixture. Dry ice beads together with LN2 were spontaneously sublimated at ambient condition after milling. Thus, the yield was significantly improved by dry ice beads compared to zirconia beads since the loss arisen from adhering to the surface of dry ice beads could be completely avoided, resulting in about 85–90% of recovery. In addition, compounds milled using dry ice beads are free from abraded contaminating material originating from the beads and internal vessel wall.

1. Introduction

Classification of active pharmaceutical ingredients (API) according to the Biopharmaceutics Classification System (Amidon et al., 1995) places more than 35% of commonly prescribed drugs into the poorly water-soluble category (Wu and Benet, 2005). Lipinski et al. (2001) pointed out that lead compounds obtained through high-throughput screening (HTS) tend to have higher molecular weights and greater lipophilicity than those from the pre-HTS era. To address this, many technologies for aiding the solubilization of poorly water-soluble APIs have been developed, such as salt formation (Agharkar et al., 1976), pro-drugs, API particle size reduction (Junghanns and Muller, 2008; Merisko-Liversidge et al., 2003; Van Eerdenbrugh et al., 2008a,b; Wu et al., 2004), semi-solids (Cole et al., 2008), solid dispersion of the amorphous form (Curatolo et al., 2009), lipid-based formulation, and complexation with cyclodextrin (Rajewski and Stella, 1996). Of these technologies, milling to reduce the size of API particles is conventional, is utilized for a broad range of APIs, and is the approach tried first by pharmaceutical companies.

We previously reported a novel micronization technique for pharmaceutical powders using liquid nitrogen (ultra cryo-milling) (Niwa et al., 2010). Unlike conventional dry milling where the milling pot is cooled by liquid nitrogen, in our ultra-cryo milling technique the materials are suspended directly in liquid nitrogen together with hard small spherical balls (e.g., zirconia beads), and are broken down by intensive agitation. The original phenytoin crystals were effectively broken down into submicron particles that were much finer and more uniform in size and shape than conventional jet-milled particles. The spontaneous vaporization of liquid nitrogen at ambient temperature and pressure is very convenient because dry powders of the API are obtained after the milling process. Moreover, compared to jet milling, the dissolution rate of phenytoin was dramatically improved by co-grinding with pharmaceutical excipients using ultra-cryo milling (Sugimoto et al., in press). The submicron % of the particle size of phenytoin and excipient mixtures correlated well with the initial dissolution rate.

However, milling with beads leads to two concerns for pharmaceutical applications: contamination of the API by the material used for the beads and mixing vessel, and insufficient recovery of the ground materials. These beads are driven by agitation disk with the high-velocity revolution, given the corresponding momentum, and moves in the suspension at the corresponding speed. The beads collide with the rotation axis, disk, the inner wall of the vessel, and

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the other beads. As a result, the ground material can become contaminated with bead or vessel material. Contamination during the homogenization of food materials due to the abrasion of grinding tools has been reported (Cubadda et al., 2001). Although zirconia is chemically stable and hard, some abrasion cannot be avoided. Strict quality controls for pharmaceutical drug products are required for pharmaceutical companies. A second area requiring improvement is the recovery of the ground material. Since the ground materials are suspended together with the beads after milling, separation of the beads from the suspension is necessary. The ground materials adhere strongly to the beads as a result of the high-velocity collisions. The beads are rubbed each other well on a sieve while being flushed with liquid nitrogen in order to retrieve the adhered ground powders to the surface of the beads. However, 20–50% could not be retrieved.

We report herein an improvement to our novel cryo-milling technology which addresses these concerns. We have replaced the zirconia beads with beads of dry ice (solid carbon dioxide). At atmospheric pressure and ambient temperature, solid carbon dioxide sublimates directly to vapor (sublimation temperature: −79 °C; (Bailey, 1949). Dry ice is used for cooling foods, industrial cleaning, blasting, and for stripping paints, oils and biofilms (Silverman, 2006). Instead of using hard abrasive media such as sand to grind a surface, dry ice blasting uses soft dry ice accelerated to supersonic speeds to create mini-explosions on the target surface and lift the contaminant from the underlying substrate (Imura and Anezawa, 2006). The low temperature of liquid nitrogen (boiling point: −196 °C) (Brovik, 1960; Vesserman, 1966) allows dry ice to remain in the solid state, allowing the fracturing of materials under super cold conditions. Furthermore, following milling, there is no need to separate the beads from the ground material since the dry ice beads sublimate at ambient temperature and pressure. Thus, the ground material adhered to the beads is retrieved. To our knowledge, there have been no previous reports of the use of dry ice beads for milling.

In this study, dry ice beads were prepared, their utility for producing finer milled particles was evaluated, and the dissolution of the ground drug was determined and compared to particles ground by zirconia bead milling.

2. Materials and methods

2.1. Chemicals and materials

Phenytoin was purchased from Wako Pure Chemical Co., Ltd. (Osaka, Japan). Polyvinylpyrrolidone K-30 (PVP) was provided by BASF JAPAN, Co., Ltd. (Tokyo, Japan). Liquid nitrogen (LN2) was purchased from Iwatani Industrial Gases Co., Ltd. (Osaka, Japan). Dry ice pellets (shot dry®) were purchased from Iwatani Carbonix Co., Ltd. (Osaka, Japan). All other chemicals and solvents were of analytical reagent grade, and deionized-distilled water was used throughout the study. Zirconia hard small balls (0.6 mm diameter; YTZ-0.6) were purchased from Nikkato Co., Ltd. (Osaka, Japan).

2.2. Manufacturing equipment

A commercially available batch-type wet milling machine (RMB-04, Aimex Co., Ltd., Tokyo, Japan) generally used for wet-milling with beads was used for ultra cryo-milling in LN2, as illustrated in our previous paper (Niwa et al., 2010). LN2 was refilled during milling operation to compensate volatilized LN2: The weight of total milling machine was monitored on a scale and LN2 was added by every 50 g reduction to keep the constant volume of LN2 in the vessel. About one litter of LN2 was needed for processing for 15 min. A four hundred-milliliter-capacity vessel, rotation shaft and disks made of zirconia (zirconium oxide) were used for zirconia bead milling, while all equipment for dry ice bead milling was made of stainless steel.

2.3. Ultra cryo-milling using zirconia beads (zirconia milling)

Ultra cryo-milling was carried out by colliding and grinding the suspended materials with zirconia beads, as reported previously (Niwa et al., 2010). In brief, liquid nitrogen was used as the dispersing medium. Around 15 g of phenytoin or phenytoin premixed with pharmaceutical excipient was suspended in LN2. The rotation disks were spun at 1700 rpm. At appropriate intervals, LN2 was added to the vessel to compensate for evaporation. After 15 min of agitation, the drug slurry was separated from the beads by passing through a 212-μm sieve. The dried milled particles were collected after spontaneous evaporation of the LN2 under ambient conditions. In order to avoid adsorption of moisture from the air, the whole operation was performed under a flow of nitrogen gas.

2.4. Ultra cryo-milling using dry ice beads (dry ice milling)

Ultra cryo-milling with dry ice beads was conducted in the same manner as with zirconia beads, except for the following changes. The rotation disks were spun at 1660 rpm (tip speeds; 4.69 m/s), 2230 rpm (tip speeds; 6.41 m/s), and 2880 rpm (tip speeds; 8.28 m/s), and for longer time (e.g., 30, 60, 120, and 360 min. The resultant slurry of the drug was not sieved; rather, the dried milled particles were collected after spontaneous evaporation of the LN2 and dry ice beads under ambient conditions. The vessel was made of stainless steel.

2.5. Jet milling and planetary ball milling

Jet milling and planetary ball milling were also conducted to provide reference milled material. Fifteen grams of phenytoin was size-reduced using a jet mill machine (A-O, Seishin Enterprise Co., Ltd., Tokyo, Japan) operated at 0.7 MPa air pressure and a feed rate of 0.4 – 0.8 g/min. Five grams of phenytoin was milled with a planetary ball mill (PM100, Retsch, Germany) operated at 400 rpm with 10 numbers of 10 mm diameter stainless steel balls for 120 min.

2.6. Zirconia assay of zirconia-milled phenytoin

The zirconia in ground phenytoin generated by zirconia milling was quantified by high-resolution inductively coupled plasma mass spectrometry. Ground phenytoin mixed with sulfuric acid and nitric acid was heated at 80 °C and degraded until the phenytoin dissolved completely. The residual zirconia (ZrO_2) was calculated as the zirconium (Zr) content in the milled particles.

2.7. Morphology and particle size distribution (PSD)

The morphology and size of the milled particles were compared to the original bulk particles using a scanning electron microscope (SEM, JSM-6060, JEOL Ltd., Tokyo, Japan). The particles were coated by platinum sputtering (JFC-1600, JEOL Ltd.). The particle size distribution of the original and milled phenytoin dispersed in dry air, 0.4 MPa pressure, was measured by laser diffraction scattering using a diffractometer with a dry dispersing unit (LMS-30, Seishin Enterprise Co., Ltd., Tokyo, Japan). The diameters of the particles at 10%, 50%, and 90% of the cumulative volume distribution ($D_{10\%}$, $D_{50\%}$, $D_{90\%}$, respectively) were represented as the size distribution. In addition, the cumulative weight percentage of particles less than 1 μm in diameter was defined as "submicron %" in order to assess the milling efficiency.