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Improved respirable fraction of budesonide powder for dry powder inhaler formulations produced by advanced supercritical CO_2 processing and use of a novel additive

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ABSTRACT

A budesonide (BDS) suspension was obtained via advanced supercritical carbon dioxide ($scCO_2$) processing. Thereafter, the suspension was freeze-dried (FD) to produce BDS particles for dry powder inhaler formulations ($scCO_2$/FD processing). The $scCO_2$/FD processed BDS powder showed low crystallinity by powder X-ray diffraction and a rough surface by scanning electron microscopy. The respirable fraction of BDS was assessed using a twin impinger and revealed that the amount of the $scCO_2$/FD processed sample that reached stage 2 was 4-fold higher than that of the supplied powder. To extend the utility of $scCO_2$ processing, BDS particles for dry powder inhalers were fabricated by combining the $scCO_2$ system with various additives. When BDS was processed via $scCO_2$/FD in the presence of the novel additive, namely, monoglyceride stearate (MGS), the residual BDS/MGS particles remaining in the capsule and devices decreased, followed by an increase in the respirable fraction of BDS 6-fold higher than with the supplied powder. The $scCO_2$/FD processed BDS/MGS particles had a smooth surface, in contrast to the $scCO_2$/FD processed BDS particles. A combination of BDS and an appropriate additive in $scCO_2$ treatment may induce changes in particle surface morphology, leading to an improvement in the inhalation properties of BDS.

1. Introduction

The pulmonary route is preferred for delivering drugs or compounds used to treat asthma and chronic obstructive pulmonary disease because this route has a more rapid onset of therapeutic action, has a low incidence of side effects, and is a non-invasive route of administration (D'Arcy and McElnay, 1989; Labiris and Dolovich, 2003; Hickey, 2013). Pulmonary delivery relies on nebulizers, metered dose inhalers, or dry powder inhalers (DPIs), with the latter providing a convenient means of drug delivery and benefits including easy handling and relatively high patient compliance (Pedersen, 1996; Weiss et al., 2015). Particle engineering is the primary technique for improving the aerosol performance of DPI formulations, by controlling the aerodynamic diameter to within a suitable range (0.5–7 μm) (Adjei and Garren, 1990; Yakubu et al., 2013; Yazdi and Smyth, 2016). Because micronized particles are highly heterogeneous, charged, and cohesive, major issues in downstream processing and product performance can result (Buckton et al., 1988; Ward and Schultz, 1995). To improve flowability and dosing accuracy and to minimize dose variability, the following approaches are used: adhesive mixtures of the drug are attached to the surface of coarser carrier particles, such as lactose and mannitol (Bennett et al., 1999); the preparation is designed to have good flowability and a dispersible aggregate containing the drug nanoparticles (Miyazaki et al., 2017); and the particle surface is modified using a lubricant, such as magnesium stearate, to reduce interparticulate cohesion (Zhou et al., 2010). The carrier approach is limited by the strong interactions between carriers and drug particles, which reduce the separation and dose uniformity. In this work, we focused on

Abbreviations: BDS, budesonide; DPI, dry powder inhaler; DPPC, dipalmitoylphosphatidylcholine; DSC, differential scanning calorimetry; FD, freeze-dried; HPLC, high-performance liquid chromatography; MGHPO, monoglyceride of hydrogenated palm oil; MGL, monoglyceride laurate; MGP, monoglyceride palmitate; MGS, monoglyceride stearate; PXRD, powder X-ray diffraction; RESAS, rapid expansion from supercritical to aqueous solution; RESS, rapid expansion of supercritical solutions; $scCO_2$, supercritical carbon dioxide; SEDS, solution-enhanced dispersion by supercritical fluids; FE-SEM, field emission scanning electron microscopy; Span 40, sorbitan monopalmitate.

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designing particles with good flowability using lubricant additives. Crystallization by a supercritical fluid method was used to form fine primary particles for DPI formulations.

A supercritical fluid is any substance at a temperature and pressure above its critical point. It can diffuse through solids like a gas and dissolve materials like a liquid (Sapkale et al., 2010). Supercritical carbon dioxide ($scCO_2$) has already been proven to be a good replacement for organic solvents in the production of drug delivery systems because it is inexpensive, abundant, nontoxic, and suitable for the development of environmentally friendly processes (Martín and Cocero, 2008). The methods of forming fine particles using $scCO_2$ are categorized into using $scCO_2$ as a good solvent or using it as an antisolvent. Rapid expansion of supercritical solution (RESS) is a typical example of the former and is an organic solvent-free approach (Jung and Perrut, 2001; Asghari and Esmaeilzadeh, 2012). However, a crucial problem with RESS is that it is limited by the poor solubility of drugs and excipients in $scCO_2$, and the collection of particles is difficult. Approaches to overcome these problems include adding a small amount of organic solvent as an entrainer to increase drug solubility (Mishima et al., 1999) and spraying $scCO_2$ into an aqueous solvent (Pathak et al., 2004), known as rapid expansion from supercritical to aqueous solution (RESAS). The following advantage has been reported: crystal growth or particle coalescence during RESS may be inhibited by expanding into solution by surfactant stabilizers and a stable suspension of particles in aqueous solution was obtained (Young et al., 2000). In contrast, few drug nanoparticles are obtained by RESS or RESAS. Solution-enhanced dispersion by a supercritical fluid (SEDS) method is a typical example of the latter method (York and Hanna, 1995), but it is quite difficult to scale up this process (Bałdyga et al., 2010). Although particle preparation using $scCO_2$ for DPI has been reported (York, 1999; Schiavone et al., 2004; Lobo et al., 2005), additives to improve flowability have not been reported.

We have focused on the fact that $scCO_2$ does not act as an antisolvent under higher pressures and lower temperatures that are above the critical point of $scCO_2$, and the particles are not precipitated by using a supercritical antisolvent unit. RESAS was incorporated into the antisolvent unit, overcoming the low drug solubility in $scCO_2$ and achieving continuous particle manufacturing. We previously reported that indomethacin particles of around 350 nm could be obtained using the combinational $scCO_2$ system and that the particles showed good redispersibility as a nanosuspension (Tozuka et al., 2010). We applied the $scCO_2$ system to budesonide (BDS). However, submicron-sized particles were not obtained. The driving force for crystal growth from individual molecules is supersaturation. Supersaturation of a drug in a solution can be obtained by decreasing the temperature or adding an antisolvent. The size of crystals depends on the balance between the nucleation rate and crystal growth, and the balance is determined by the extent of the supersaturation (Waard de et al., 2011). However, the $scCO_2$ method could not improve process conditions because the upper pressure limit of this apparatus is 25 MPa and $scCO_2$ must remain above 31.1 °C, which is the critical temperature of CO_2. In this study, we extend the utility of the $scCO_2$ method by using lubricant additives. Dipalmitoylphosphatidylcholine (DPPC) is widely used as a DPI additive (Edwards et al., 1997; Gervelas et al., 2007). Lung surfactant is 40% DPPC by weight (Pilcer and Amighi, 2010) and DPPC is not toxic to lung cells. In Japan, DPPC is used as a soy bean phosphatide, and the acceptable daily intake of soy bean phosphatide is 3.36 mg/day for inhalation (Japanese Pharmaceutical Excipients Directory, 2016). In the USA, the acceptable intake of 1,2-distearoyl-sn-*glycero*-3-phosphocholine is 6.4 mg for inhalation (Healy et al., 2014). DPPC can decrease interparticulate cohesion due to its long aliphatic chains (Cuvelier et al., 2015; Eedara et al., 2016). We focused on monoglyceride of hydrogenated palm oil (MGHPO) because it is a fatty acid ester with expected lubricant effects, is much cheaper than DPPC, is a widely used food additive that serves as an emulsifying agent, is permitted for human consumption, and is a novel pharmaceutical additive. Similar to DPPC, the improved inhalation properties of MGHPO may also arise from its long aliphatic chains.

2. Materials and methods

2.1. Materials

BDS ((+)-[(*RS*)-16α,17α-butylidenedioxy-11β,21-dihydroxy-1,4-pregnadiene-3,20-dione) was supplied by Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan. DPPC was purchased from Nippon Oil and Fats Co., Ltd., Tokyo, Japan. MGHPO and monoglyceride laurate (MGL) were supplied by Taiyo Kagaku Co., Ltd., Mie, Japan. Monoglyceride palmitate (MGP) was purchased from Tokyo Kasei Kogyo Co., Ltd., Tokyo, Japan. Monoglyceride stearate (MGS) and sorbitan monopalmitate (Span 40) were purchased from Nacalai Tesque, Kyoto, Japan. Supplemental Material 1 gives the structural formulas of these additives. The constituents of MGHPO were 0.6% MGL, 43.2% MGP, 52.0% MGS, and 4.2% others. All other chemicals and solvents were of reagent grade.

2.2. Preparation of BDS suspension by an improved supercritical CO_2 system

A suspension containing BDS particles was produced by a supercritical fluid operating system based on the RESAS method ($scCO_2$ processing). Supplemental Material 2 shows a schematic diagram of the apparatus developed for preparing the BDS particle suspension. The apparatus consisted of a reaction vessel and a crystallization unit, and functioned as a supercritical fluid operating system based on RESAS. The device comprised a CO_2 pump (maximum: 20 mL/min), drug solution pump (10 mL/min), reaction vessel (50 mL), and a back pressure regulator (Jasco Corp., Ltd., Tokyo, Japan). The apparatus used in this study is described in our previous report (Tozuka et al., 2010).

BDS and additives were dissolved in ethanol. The total concentration of the BDS and additive solution was 20 mg/mL. The percentage of additives was defined as the additive content as a proportion of the total amount of BDS and additives. The CO_2 solvent was introduced to the reaction vessel at 14 mL/min at a controlled temperature. When the vessel reached the desired pressure, both the CO_2 fluid and the BDS and additive solution were co-sprayed via a coaxial nozzle (outer nozzle: stainless steel tube, 1.59 mm o.d. × 0.8 mm i.d., Jasco Corp., Tokyo, Japan; inner nozzle: capillary column, 0.25 mm o.d. × 0.25 μm i.d., DB-23, J&W Scientific Inc., CA, USA). A new capillary column was used for every batch. Here, 200 mg of solid was used for one batch (20 mg/mL solid solution of 10 mL). Immediately after co-spraying, CO_2 fluid containing BDS, an additive, and ethanol was expanded from the reaction vessel into 30 mL aqueous media via the back pressure regulator. The amount of sample was adjusted so that the conditions were similar to those in the previous study using the same apparatus (Tozuka et al., 2010). All $scCO_2$ processed samples were obtained at 25 MPa and 40 °C.

2.3. Freeze-drying of the suspension after $scCO_2$ processing

The suspension was dispersed by sonication for 5 min after $scCO_2$ processing. To obtain particles for the pharmaceutical formulation, 30 mL of the dispersion was put in a 200 mL stainless