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Excipient-free nanoporous microparticles of budesonide for pulmonary delivery

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ABSTRACT

The aim of this study was to investigate the application of a spray-drying process for the production of nanoporous microparticles (NPMPs) to budesonide, and to characterise the particles produced in terms of their suitability for pulmonary delivery.

Budesonide was spray dried with and without ammonium carbonate from ethanol/water or methanol/water solutions. The solid-state characteristics and micromeritic (particle size, density, surface area) properties of spray dried powders were assessed. *In vitro* deposition studies were performed to assess aerosol performance.

The densities of the NPMPs were significantly lower and the surface areas significantly higher than for non-porous spray dried or micronised material. NPMPs of budesonide demonstrated improved aerosolisation properties compared to spray dried non-porous, micronised material and two budesonide commercial products. All spray dried materials were amorphous in nature. The glass transition temperature (~90 °C) was sufficiently high to suggest good physical stability at room temperature. When stored at 25 °C/60% RH NPMPs showed a reduced tendency to recrystallise compared to the equivalent non-porous spray dried powder. The physical stability and amorphous nature of NPMPs was retained, under these storage conditions for at least one year and the *in vitro* aerosolisation properties were not affected by the storage conditions.

Excipient-free porous microparticles, prepared by the novel process described, show good potential for drug delivery by oral inhalation with improved *in vitro* deposition properties compared to non-porous particles.

1. Introduction

Porous microparticles have been shown to have potential for pulmonary drug delivery. Large porous particles, such as those produced by Edwards et al. (1997, 1998a,b), have low bulk densities and smaller aerodynamic diameters than represented by their geometric diameters, thus having improved aerosolisation efficiency compared to conventional products, facilitating greater deposition in the respiratory tract, while avoiding macrophage uptake due to their large size (typically greater than 10 μm) (Edwards et al., 1998a,b). Other porous particles, of small geometric diameters (typically less than 10 μm), have also been produced by Duddu et al. (2002). These hollow porous Pulmosphere™ microparticles may be used in dry powder inhalers and in pressurised metered dose inhalers, where they form "homodispersions" in the liquefied propellant (Hirst et al., 2002). The methods described by these groups for producing porous particles all involved spray-drying processes, with the production of hollow porous particles by spray drying an emulsion consisting of a bioactive agent, a surfactant and a "blowing agent". The blowing agent is typically a volatile liquefied gas (e.g. HFA propellant) or volatile liquid such as carbon tetrachloride. In the spray-drying process, it has been postulated that the blowing agent is vaporised and forced through the thin surface wall to form pores in the particles (Tarara et al., 2003). The surfactant is required to stabilise the emulsion and will remain as a residual/contaminant in the particles. In their assessment of Exubera™, a spray dried dry powder inhalable form of insulin, a FDA advisory committee expressed concern about excipients in Exubera's formulation, which members feared could irritate the lungs (Gibaldi, 2006). It is of importance therefore to develop particle engineering technologies which will allow for the omission of excipients from the recovered active pharmaceutical ingredient particles.

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We recently presented an alternative method for producing porous particles. The process involves spray drying an active from a solution containing ammonium carbonate as a pore-forming agent or process enhancer, to produce excipient-free porous particles (Healy et al., 2008). Excipient-free "nanoporous microparticles (NPMPs)" (with pores in the size range 20–500 nm) of the model drug, bendroflumethiazide (BFMT) were prepared by spray drying from alcoholic solutions containing ammonium carbonate.

Other groups have proposed the use of ammonium carbonate as a pore former/blowing agent when spray drying emulsion (rather than solution) feeds (Edwards et al., 1998a,b), or have used ammonium bicarbonate when spray drying polymer solutions (also containing DL-leucine and DPPC) (Gervelas et al., 2007); however there are no previous reports by other groups in the literature of ammonium carbonate being used as a process enhancer for the production of excipient-free porous particles of active drug by spray drying simple solutions.

We have previously reported on the production, physicochemical characteristics and *in vitro* deposition properties of spray dried non-porous microparticles of budesonide (Tajber et al., 2009a,b), a therapeutically relevant active which is delivered by oral inhalation and used in the preventive treatment of asthma. In the present study we report on the application of the NPMP technology to budesonide to produce porous microparticles and we test the properties of these porous particles, relative to non-porous material. We also examine the effect of spray drying from mixed solvent systems containing no other additives (such as ammonium carbonate), to determine if the use of ammonium carbonate is a requirement in the production of NPMPs. To our knowledge there are no previous reports of the production of excipient-free porous microparticles from such simple mixed solvent systems.

2. Materials and methods

2.1. Spray drying

All solutions prepared were spray dried with a Büchi B-290 Mini spray dryer. The Büchi B-290 spray dryer can operate in an open cycle or closed cycle mode. In the open cycle mode, the drying medium is exhausted to the atmosphere after the spray-drying process. The closed mode design is based upon recycling and reusing the gaseous medium, which is usually an inert gas such as nitrogen (Masters, 1991). The inert gas is loaded with solvent from the spray-drying process. After precooling in a preheat exchanger, the solvent is condensed in a refrigerator unit (B-295 inert loop). The cleaned gas stream then flows back to the spray dryer.

Solutions prepared from methanol/water solutions were spray dried with the spray dryer operating in the closed mode configuration with nitrogen as the drying gas and trapping solvent in the B-295 inert loop. The absence of oxygen prevents the formation of an ignitable mixture when spray drying the organic solvent. Solutions prepared from ethanol/water solutions were spray dried either with the spray dryer operating in the open mode using compressed air as the drying gas, or with the spray dryer operating in the closed cycle configuration using nitrogen as the drying gas and trapping solvent in the B-295 inert loop.

In all cases the gas flow rate was 670 Nl/h (based on air, 4 cm on the gas rotameter indicator), the pump setting was 30% and the aspirator setting was 100%.

2.2. Spray drying to produce porous particles of budesonide

Solutions of budesonide (micronised, Tianjin Tian Mao Technology Development Corp. Ltd., China) were prepared in ethanol (Cooley Distillery, Ireland)/water (deionised, Purite Prestige Analyst HP water purification system) or methanol (Lab Scan Analytical Sciences)/water, to which ammonium carbonate (Sigma–Aldrich, Ireland) was added. The alcohol content of the solvent systems used was 90% (v/v). The total solid concentration in solution was 1% (w/v). The ammonium carbonate was added in a concentration equivalent to 15% of the total weight of solids (such that budesonide concentration in solution was 0.85% (w/v)). In the case of the ethanolic solution spray dried (using air) with the dryer in the open mode; inlet temperature was set at 78 °C, with a resulting outlet temperature of 50 °C. In the case of the ethanolic solution spray dried (using nitrogen) with the dryer in the closed mode configuration, inlet temperature was set at 78 °C, with a resulting outlet temperature of 53 °C, while for the methanolic solution inlet temperature was 70 °C and outlet temperature was 45–48 °C.

Budesonide alone (i.e. without ammonium carbonate) was also spray dried as 1% solutions from 80% (v/v) ethanol and 20% (v/v) water or 80% (v/v) methanol and 20% (v/v) water solution. In the case of the ethanol/water system (spray dried in the open mode), inlet temperature was set at 78 °C, with a resulting outlet temperature of 50 °C, while for the methanol/water system (spray dried in the closed mode), inlet temperature was set at 70 °C, with a resulting outlet temperature of 46 °C.

2.3. Spray drying to produce non-porous particles of budesonide

A 1% (w/v) solution of budesonide was prepared in 95% (v/v) ethanol/5% (v/v) water and spray dried using a Büchi B-290 spray dryer in the closed mode with an inlet temperature of 78 °C and resulting outlet temperature of 52 °C.

2.4. Characterisation of physicochemical properties of materials

X-ray powder diffraction (XRD) and differential scanning calorimetry (DSC) measurements were made as previously described (Healy et al., 2008). XRD measurements were made on samples in low background silicon mounts, which consisted of cavities 0.5 mm deep and 9 mm in diameter (Bruker AXS, UK). The Siemens D500 Diffractometer used consists of a DACO MP wide-range goniometer with a 1.0° dispersion slit, a 1.0° anti-scatter slit and a 0.15° receiving slit. The Cu anode X-ray tube was operated at 40 kV and 30 mA in combination with a Ni filter to give monochromatic Cu Kα X-rays. Measurements were generally taken from 5° to 40° on the two θ scale at a step size of 0.05°/s. DSC was performed using a Mettler Toledo DSC 821^e. Samples (of weights between 6 and 11 mg) were accurately weighed and placed in closed 40 μl aluminium pans with three vent holes. Samples were run at a heating rate of 10 °C/min under nitrogen purge.

Particle size and density measurements were determined as previously described (Healy et al., 2008). Particle sizing was performed by laser diffraction using a Malvern Mastersizer 2000 particle sizer (Malvern Instruments Ltd., Worcestershire, UK) with Scirocco 2000 accessory. The dispersive air pressure used was 2 bar. Samples were generally run at a vibration feed rate of 50%. The particle size reported is the $d(0.5)$, which is the median particle size of the volume distribution. The values presented are the average of at least two determinations. Mastersizer 2000 software was used for analysis of the particle size. Bulk density ($b\rho$) was measured by filling the dry powder into a 1 ml graduated syringe with a funnel. The weight of the powder required to fill the 1 ml graduated syringe was recorded to calculate $b\rho$. The tap density ($t\rho$) of the powder was then evaluated by tapping the syringe onto a level surface at a height of 1 in., 100 times. The resultant volume was recorded to calculate $t\rho$. Each measurement was performed in triplicate.