The Influence of Drug Morphology on the Aerosolisation Efficiency of Dry Powder Inhaler Formulations

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Received 21 June 2007; revised 1 August 2007; accepted 16 August 2007

Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/jps.21195

ABSTRACT: The physicochemical properties of two forms of spray dried bovine serum albumin (BSA) have been investigated using particle sizing, surface energy measurement, atomic force microscopy (AFM) and colloid probe microscopy. The BSA powder had similar particle size distributions and surface energy but significantly different morphologies and roughness, classified as smooth and corrugated BSA. Adhesion forces between the corrugated BSA and α-lactose monohydrate indicated median adhesion forces were significantly less than for smooth/carrier interaction forces. These observations correlated well with aerosolisation from BSA/carrier blends, where the corrugated BSA particles gave a higher fine particle fraction than the smooth BSA, suggesting reduced BSA/carrier adhesion and increased drug liberation. The use of corrugated drug particle morphology in drug carrier DPI systems may lead to improved aerosol performance through reduced drug carrier contact area. © 2007 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 97:2780–2788, 2008

Keywords: dry powder inhalation; colloid probe microscopy; particle morphology

INTRODUCTION

The delivery of dry powders to the respiratory tract has become a popular delivery vehicle for both topical and systemic disease states. The most common formulation approach is to blend the active pharmaceutical ingredient (API) with a larger inert carrier, such as α-lactose monohydrate (lactose). This ordered mixing process aims to reduce the high cohesion forces that are present between the micron sized API particles, improve powder flow and allow accurate metering.[1] During the inhalation manoeuvre, energy supplied by the patient to the dry powder inhaler (DPI) must overcome the adhesive forces between drug and carrier, allowing liberation of drug from the device, dispersion of the API particles and respiratory penetration. However, the micron sized nature of the API particles (typically $\leq$6 μm aerodynamic diameter)[2] results in high API-carrier adhesion forces and poor aerosolisation performance, due to the majority of API particles remaining adhered to the carrier and being consequently swallowed. This results in the relative poor performance of current DPI devices on the market today.[3]

The culmination of these formulation challenges has resulted in a significant research focus on DPI carrier technology. In general, research has specifically focussed on the influence of the surface physicochemical properties of the carrier (such as morphology or surface area)[4–8] or the addition of ternary components to the API/carrier blend (such as magnesium stearate or inert fines).[9–15] In addition, a great deal of research has focussed on producing particles with increased stability and reduced interparticulate adhesion. For example, techniques such as super critical fluid extraction,[16] high gravity percipitaion[17] and sonication[18]

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Journal of Pharmaceutical Sciences, Vol. 97, 2780–2788 (2008)

technology have all been utilised to ensure rapid micromixing of solvent and antisolvent to produce stable particles with diameters conducive to respiratory therapy. Furthermore, controlled spray drying, with or without excipients, has shown promise as a method of producing drug particles with specific morphology and density parameter. Examples include Nektars PulmoSphere[19] and Alkermes Air technologies.[20]

Interestingly, although great effort has been put into particle engineering of API molecules, little research has focussed on the influence of the API morphology on the aerosolisation properties of drug from drug/carrier blends. Work, conducted by Larhrib et al.,[21] suggested increased crystal elongation ratios of salbutamol resulted in improved aerosolisation efficiency from salbutamol/carrier blends. Similar results were observed by Ikegami et al.,[22] when studying the performance of drug-lactose carrier blends containing steroid KSR-592. However, in this later study, the relative change in performance may be difficult to directly attribute to morphology as the steroid underwent polymorphic transformation.

Other previous studies have investigated the influence of drug morphology on the aerosolisation performance in drug-only systems.[23–27] However, most of these investigations have focussed on elongated particles which have reduced aerodynamic diameters (compared to their volume diameter) due to air-stream orientation effects. Noteworthy, studies by Chew et al.[26] and Chew and Chan[27] have shown surface morphological modification of primarily spherical BSA particles influenced aerosolisation performance; presumably through a reduction in contact area. Interestingly, in these previous studies the aerosolisation mechanism would be by deagglomeration of a fine particle mass and be heavily dependent on the packing fraction of the powder and the interplay between BSA particles. Although such factors are present in carrier-based systems, the contact geometry of the particles with the carrier particles will play a primary role.

As part of an ongoing study, the authors investigated the effect of BSA particle morphology on the aerosolisation efficiency of BSA from lactose carrier blends. Two primary BSA particle systems were prepared by spray drying: smooth and corrugated. The BSA particles were characterised in terms of morphology, BSA–carrier adhesion and blend aerosolisation performance.

MATERIALS AND METHODS

Materials

Bovine serum albumin (BSA) (Lot: 42K1578, Fraction V, minimum 98%) was supplied by Sigma Chemical Co. (MO, USA). Water was purified by reverse osmosis (MilliQ, Millipore Australia Pty Ltd., Sydney, Australia). All organic solvents were supplied by Biolab Ltd. (Victoria, Australia) and were of analytical grade. α-Lactose monohydrate (lactose; Lactochem™ crystals) was kindly supplied by Friesland Foods Domo (The Netherlands). The lactose crystals were dry-sieved through a nest of sieves to produce a 63–90 μm fraction, which was used throughout the study.

Preparation of BSA Microparticles

Smooth and corrugated BSA microparticles were prepared by spray drying from aqueous solution using a Buchi 191 mini spray dryer (Flawil, Switzerland). Settings were as follows: feed rate 1.4 $mL\,min^{-1}$ and aspiration rate 43.1 $m^3\,min^{-1}$. In addition, the aqueous BSA concentration and atomisation air pressure were 60 $mg\,mL^{-1}$ and 800 kPa, and 10 $mg\,mL^{-1}$ and 300 kPa for the smooth and corrugated particles, respectively, while the inlet/outlet temperatures were 55/36°C and 45/33°C, respectively. The preparation of microparticles is well established. Reproducibility (volume median diameters) of the powders produced using the spray dryer was in good agreement with previous studies using similar conditions.[26,27]

Particle Size Analysis

The particle size distributions of the smooth and corrugated BSA samples and 63–90 μm sieve fractioned lactose were assessed using laser diffraction. Approximately 10 mg of each sample was dispersed in chloroform and sonicated for 5 min in a water bath (Model FXT8; Unisonics Pty Ltd., Sydney, Australia). The dispersed samples were subsequently added to a small volume sample dispersion unit (Hydro SM, Malvern, UK) for analysis. Particle size distributions were measured between an obscuration of 5–25% in triplicate and were expressed in terms of median volume diameter ($d_{0.5}$).