



Surface modification of lactose inhalation blends by moisture

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ARTICLE INFO

Article history:

Received 17 November 2009
Received in revised form 21 January 2010
Accepted 8 February 2010
Available online 13 February 2010

Keywords:

Lactose
Dry powder inhalation
Relative humidity
Deliquescence
Ostwald ripening
Solid bridge

ABSTRACT

We present an investigation of the effects of relative humidity (RH) on lactose powders during storage, with the aims of determining the humidity conditions under which lactose inhalation blends are stable, and characterising the surface changes that occur as a result of water condensation. Lactose inhalation powders manufactured by milling and sieving were stored in environments of RH from 32% to 100% (at room temperature) and changes in surface properties were observed using BET nitrogen adsorption, environmental scanning electron microscopy and laser diffraction particle size analysis. We found that the specific surface area of all lactose powders decreased during storage, with the rate of decrease and final drop being larger at higher RH (ranging from a 62% decrease at 100% RH to a 34% decrease at 32% RH, at room temperature). The specific surface area decrease corresponded to a reduction in the volume of fine particles (<5 μm) in the blend. Two effects were found to contribute to the decrease in specific surface area: the smoothing of coarse particles, attributed to the surface fine particles undergoing deliquescence due to their enhanced solubility by the Kelvin effect (i.e. due to their greater curvature and consequently greater surface energy), and solid bridging between fine particles in agglomerates, such that loose fine particles disappeared from the powder blend, having bonded with coarser particles. These changes in particle properties resulting from moisture exposure are expected to influence the fine particle fraction of drug released from the powder blends, and the observation that lactose inhalation blends were unstable even at 32% RH could potentially be a concern for the pharmaceutical industry.

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1. Introduction

1.1. Dry powder inhalation

Drug particles must have an aerodynamic diameter of 1–5 μm to be delivered to therapeutic sites by inhalation; any larger and they will deposit too early by inertial impaction, any smaller and they will have insufficient mass to settle and will remain in suspension and be exhaled (Newman and Clarke, 1983). However, particles in this size range have a poor flowability, which can lead to inaccurate measurement of doses (Podczeczek, 1998; Young et al., 2005). One solution is to blend the drug particles with a secondary component, a coarse (median size 20–100 μm), inert carrier, usually alpha lactose monohydrate (ALM) (Podczeczek, 1998), in a typical carrier:drug weight ratio of 67.5:1 (Steckel et al., 2004). This can produce carrier particles with drug particles scattered over the surface (Young et al., 2005), however when these blends are released from dry powder inhalers (DPIs) they have a low dose efficiency, which is believed to be a result of poor drug-carrier separation (Islam and Gladki, 2008). Carrier particle surface roughness influ-

ences the de-agglomeration; if the carrier particle has a smooth surface then it is likely to have a large contact area with the drug particle and strong interparticulate forces, whereas small asperities on the surface of a carrier particle will reduce the contact area with the drug, therefore decreasing the forces of adhesion (Kawashima et al., 1998; Podczeczek, 1998). Asperities of a similar size to the drug particles, however, have shown poor drug delivery efficiency due to contact points on multiple sides of the drug particle, and due to the particles becoming shielded from air flow (Kawashima et al., 1998; Zeng et al., 2000). Milled ALM carrier particles naturally have asperities of equivalent size to drug particles due to the presence of fine surface ALM particles (debris from the milling process), so increasing their smoothness is desirable provided that completely smooth particles are not obtained. Kawashima found that carrier lactose with a higher specific surface area (for the same sieve fraction, suggesting a greater surface roughness) had a reduced drug delivery efficiency, shown by the proportion of inhaled drug that was deposited in the correct part of the lung dropping from 30% to 5%. Zeng et al. (2000) observed the same trend by producing particles of a similar size but with varying roughness. Iida et al. (2003) reduced lactose particle roughness using ethanol, and found that the smoother the particles became, the greater their drug delivery efficiency, until an optimal surface roughness was reached. Lactose particles have been smoothed after manufacture in a variety

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of ways, both mechanically and chemically (Iida et al., 2001, 2003, 2004a). Alternatively, the use of a ternary component to “valley fill” the gaps between asperities has been found to reduce the relative height of the asperities and to effectively smooth the surfaces (Iida et al., 2004b; Iida, 2005; Zeng et al., 1998; Huber and Wirth, 2003). The use of fine ALM particles (micronised to have an aerodynamic diameter of 1–5 μm) to valley fill the carrier particles before the addition of drug is preferable for cheapness and has shown improved drug delivery efficiency (Zeng et al., 1998, 2001), however this may be because the drug is released from agglomerates of fines rather than from carriers (Podczeczek, 1999). In this paper, we examine the use of relative humidity (RH) as a technique for smoothing ALM carrier particles.

1.2. Effects of RH on ALM

The critical humidity (the RH at which deliquescence occurs; Huynh-Ba, 2008) of ALM, a water-soluble, crystalline solid (Rowe et al., 2003) is almost 100% at room temperature (Waterman and Adami, 2005), which means that at 100% RH an ALM inhalation blend will sorb water until completely dissolved. However particle size can influence solubility: smaller particles have a greater curvature, and consequently a higher surface energy, which can promote dissolution in a saturated solution, and thus at RH < 100% (Cleaver and Wong, 2004). “Ostwald ripening” is the phenomenon of smaller particles dissolving in a saturated solution and being incorporated into larger particles, which have a lower interfacial energy (Ostwald, 1896). When the smaller particles have dissolved in this way the solution becomes supersaturated, which then promotes the precipitation of the solid (Cleaver and Wong, 2004).

Cleaver and Wong (2004) studied an Ostwald ripening effect in boric acid (H_3BO_3) powder. Rather than observing the enhanced dissolution of discrete fine particles, fine features on the surfaces of coarser particles were studied using atomic force microscopy (AFM). As RH (at room temperature) was increased, images showed the dissolution of small rounded surface features, and this was attributed to their preferential dissolution due to their high curvature. Surface smoothing was observed at 80% RH but not at 40% RH. At 90% RH caking of a packed boric acid powder bed was observed in isothermal conditions in a closed system (Cleaver et al., 2004). This was attributed to solid bridging by Ostwald ripening. Bérard et al. (2002) studied the surface topography of lactose in AFM after storage at 0%, 32% and 85% RH (at room temperature), and the mean roughness values were found to be 37.29 ± 14.79 , 25.95 ± 6.08 and 23.41 ± 5.65 nm respectively. The identical roughness values at 32% and 85% RH implied that the small surface asperities were able to dissolve in a saturated surface lactose solution both at 85% RH and at 32% RH, and then precipitate onto coarser particles such that the particle surfaces became smoother. Kontny et al. (1987) observed the smoothing and enlarging of sodium chloride and sodium salicylate crystals at low water sorption. Less than one monolayer was sufficient to enable molecules to move around by “surface dissolution” and reduce the surface area. This smoothing and enlarging was only seen on particles with disordered surfaces, such as those produced by milling.

So, exposure to RH is expected to cause the smoothing and caking of ALM particles. In this paper, we attempt to investigate the RH-induced smoothing of ALM particles in greater detail than has previously been considered.

2. Materials and methods

2.1. Materials

Lactohale[®] LH200 (milled ALM) was obtained from Friesland Foods Domo (The Netherlands). Respitose[®] SV003 (sieved ALM)

was obtained from DMV International (The Netherlands). LH200 and SV003 are designated “inhalation grades” and have similar equivalent sphere volume median diameters (66 and 56 μm , respectively, from Spraytec laser diffraction measurements), but LH200 has a broad particle size distribution (PSD) (consisting of coarse carrier particles and fine particles) whereas SV003 has a narrow PSD (predominately coarse carrier particles). Both LH200 and SV003 particles are angular with elongation ratios (length/breadth) of ~ 1.7 . Micronised (fine) ALM particles were obtained from Pfizer (UK) and from DMV International, and had an equivalent sphere volume median diameter of 4.1 μm and an elongation of ~ 1.3 . Throughout this article “fine particles” are defined as those with equivalent sphere diameters under 5 μm , and “coarse particles” are defined as those suitable for use as carrier particles (20–100 μm).

Microcrystalline cellulose (Celphere[®] SCP-100) was obtained from Asahi Chemical Industry Co., Ltd. (Japan).

2.2. Mixing lactose grades

Commercially available inhalation grades were used as supplied, and also blended with fine ALM. To prepare blends the fine ALM was added to the coarse grades in a glass container such that the final concentrations of the fines were 1.0%, 5.0%, 10.0%, 15.0% and 25.0% (w/w), respectively. Blends were mixed using a spinner-rotator (Turbula T2F, Willy A Bachofen AG, Basel, Switzerland) at 46 rpm for 30 min.

2.3. Storage of lactose

ALM blends were exposed to controlled humidity environments using either saturated salt solutions or a humidity chamber (Coy Laboratory Products Inc., MI, USA). Four different RH were chosen at which to store the powders: 32%, 55%, 75% and 100% (at room temperature). These RH were selected because they cover a broad range and can be generated easily by use of saturated salt solutions (O'Brien, 1948). A saturated salt solution was manufactured by dissolving as much salt as possible into water, and then adding extra salt to generate a layer of undissolved solid on the bottom of the container (Martin, 1962).

In order for a new drug product to be registered within the regions of the EC, Japan, and the United States it must submit to the guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH, 2003). The “ICH harmonised tripartite guideline for the stability testing of new drug substances and products” suggests that new drug substances should be evaluated under several storage conditions including “Accelerated” conditions of $40^\circ\text{C} \pm 2^\circ\text{C}/75\% \text{RH} \pm 5\% \text{RH}$ for 6 months. In addition to the RH described above, ALM blends were stored under ICH conditions to test their stability over extended periods.

2.4. BET surface area analysis

The specific surface areas of the ALM blends were measured using a BET (named after Brunauer, Emmett and Teller who developed the theory) gas adsorption isotherm method on a TriStar 3000 surface area analyser (Micromeritics Instrument Corporation, Norcross, USA). Prior to surface area analysis, the blends were dried overnight in vacuum oven at 50°C . An accurately weighted sample of powder of approximately 1 g was placed into the glass loop of the instrument, which was then filled with a glass rod and submerged into liquid nitrogen. An eight-point BET nitrogen adsorption analysis was carried out. Experiments were repeated at least three times using fresh powder.

The specific surface area of a powder is the surface area per unit mass, and consequently it will depend on both the particle size

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