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Agglomerate properties and dispersibility changes of salmeterol xinafoate from powders for inhalation after storage at high relative humidity

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ABSTRACT

Purpose: This study investigated changes in agglomeration and the mechanism of dispersibility decrease of salmeterol xinafoate (SX) from SX–lactose mixtures for inhalation after storage at 75% RH for 3 months.
Methods: The dispersibility, PSD and *in situ* PSD of aerosol plumes of SX alone and SX–coarse lactose (CL) mixtures containing 0, 5, 10 and 20% micronized lactose (ML) before and after storage were determined by a Next Generation Impactor (NGI), a Mastersizer 2000 and a Spraytec, respectively.
Results: The PSD of ML increased after storage at 75% RH, but dispersibility of SX using the stored ML increased. After storage, the %SX of the mixture containing 20% ML (M20F) significantly increased ($P < 0.05$) in the throat and mouthpiece, preseparator and stage 1 of NGI, while it significantly decreased in the remaining stages ($P < 0.05$). *In situ* analysis of aerosol plumes of M20F supported this result with an increased presence of particles of 4–25 μm and a decreased respirable particle distribution of <4 μm after storage.
Conclusions: The decreased dispersibility of M20F after storage was due to the formation of less dispersible agglomerates, probably occurring through enhanced capillary interaction and/or solid bridging of ML, entrapping and preventing the release of SX particles.

1. Introduction

Changes in dispersibility of dry powder inhalers during storage at high relative humidity (RH) are often encountered by pharmaceutical manufacturers (Borgstrom et al., 2005; Young et al., 2007). The dispersibility of powders is influenced by interparticulate forces (Louey and Stewart, 2002) which can be modified by environmental RH (Podczeck et al., 1996, 1997a,b; Young et al., 2003a, 2004). High RH may increase interparticulate forces due to increased capillary interactions resulting in the formation of larger agglomerates (Hogg, 1989) that are less breakable (Boerefijin et al., 1998). Micronized lactose monohydrate has been found to dissolve under the influence of high RH (75% RH or greater) (Podczeck et al., 1997a). Thus, the liquid bridges which are formed at these high RH conditions are often followed by solid bridges due to recrystallization of the dissolved lactose (Padmadisastra et al., 1994a,b).

Many investigations on the effect of storage RH on dispersibility (Braun et al., 1996; Hindle and Makinen, 1996; Young et al., 2003b; Lida et al., 2004; Young and Price, 2004; Borgstrom et al., 2005; Young et al., 2007; Zeng et al., 2007) were limited to either drug alone formulations or binary mixtures of drugs. These studies did not include dry powder inhaler formulations that contained ternary components (Staniforth, 1996; Zeng et al., 1996), although the addition of ternary components, for example, micronized lactose, has been shown to improve dispersibility (Lucas et al., 1998; Louey and Stewart, 2002; Adi et al., 2006). Moreover, in most studies, formulations were exposed to storage RH for only short periods of time (maximum 7 days).

A recent extended study on different types of dry powder formulations (Das et al., 2009) has reported that the salmeterol xinafoate (SX) dispersibility was influenced predominately by the presence of micronized lactose in the formulation and the storage relative humidity. A significant decrease in fine particle fraction (FPF) of SX after storage at 75% RH was observed in the ternary formulation containing 20% ML within 4 weeks and the decrease reached lower static levels within 3 months. Calculations revealed that increased capillary interactions were likely to occur between lactose particles and that deagglomeration required increased shear pressures after storage at 75% RH. The extent of particulate interactions increased, but the study did not identify the mechanism of decreased dispersibility. For example, the study outcomes could be consistent with increased lactose–lactose interactions resulting in (a) increase in the particle size distribution (PSD) of lactose or in (b) the formation of strong lactose agglomerates entrapping the SX and

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decreasing its dispersibility. An increase in the size distribution of lactose will influence dispersibility in different ways. Small changes in particle size in the cohesive range, essentially less than about 10 μm, have been shown to influence dispersibility of SX (Adi et al., 2006). However, significant agglomeration of micronized lactose, producing stronger free flowing agglomerates, will likely decrease SX dispersibility due to the capacity of the agglomerate to act as a secondary carrier and strongly bind the SX to its surface. Decreased dispersibility has been observed in formulations containing ternary lactose acting as secondary carriers (Adi et al., 2006). Thus, particle size changes may potentially result in either decreased or increased dispersibility of drugs. However, the entrapment of a drug within a lactose agglomerate network will decrease dispersibility. An understanding of the mechanism is essential to establish the body of knowledge to enable quality by design and to ensure that appropriate strategies are employed in the development of powders for inhalation.

The purpose of this study was to identify the mechanism of dispersibility change during storage at high RH of an SX formulation containing Inhalac 120 as the coarse lactose carrier and micronized lactose monohydrate as the fine added excipient. The study used a combination of particle sizing approaches to achieve the outcome.

2. Materials and methods

2.1. Materials

Inhalation grade micronized salmeterol xinafoate (SX) (batch no., B068803, Glaxo SmithKline, Ware, UK) was used as model drug. Coarse α-lactose monohydrate, CL (Inhalac ®120, Meggle AG, Wasserburg, Germany) was used in "as supplied" form as the coarse carrier. Micronized α-lactose monohydrate (Lactose New Zealand, Hawera, New Zealand) was prepared using a fluid energy mill (K-tron Soder, NJ, USA) as described in a previous study (Adi et al., 2006). Methanol (HPLC grade, Merck KGaA, Darmstardt, Germany), milli-Q grade water (Millipore Corporation, Melsheim, France) and ammonium acetate (BDH laboratories, Victoria, Australia) were used for HPLC analysis.

2.2. Methods

2.2.1. Preparation of powder formulations

SX (2.5%)–CL mixtures containing 0, 5, 10 and 20% micronized lactose (M0F, M5F, M10F and M20F) were prepared according to a previously validated mixing method (Alway et al., 1996; Liu and Stewart, 1998). The batch size for these formulations was 5 g. The micronized SX or SX and ML were placed between equal amounts of CL in a test tube. Placing three ceramic beads (approximately 10 mm diameter) inside, the test tube was stoppered and inverted several times to prevent the drug from sticking to the sides of the test tube which was followed by vigorous shaking for 5 min by hand. A ball-milling effect for breaking up agglomerates was provided by the ceramic beads.

2.2.2. Homogeneity of powder mixtures

The homogeneity of mixtures was determined to ensure that the mixing procedure produced homogenous and consistent powder mixtures that approached target SX content with low variability. Twenty samples (20 ± 0.5 mg each) were accurately weighed into suitable volumetric flasks and dissolved in 40% (v/v) methanol/water (HPLC grade) and the amount of SX was determined by a validated UV assay. The average drug content and the variability between samples, expressed by the coefficient of variation (CV), were used to quantify the homogeneity of each powder mixture. A mixture with mean drug content within 95–105% of the theoretical value and a CV <5% was regarded to have an acceptable degree of homogeneity. These specifications indicated that 95% of samples would fall within 10% of the mean (Crooks and Ho, 1976).

2.2.3. Storage conditions

A saturated solution of sodium chloride (NaCl) (BDH laboratories, Melbourne, Victoria, Australia) was used to produce 75% RH in sealed containers (Callahan et al., 1982). Five formulations: SX alone (D) and four SX–CL mixtures containing 0, 5, 10 and 20% ML (M0F, M5F, M10F and M20F, respectively) and CL and ML were stored in open pan as bulk powder at 75% RH for 3 months. Over the study period, the RH and temperature, monitored by a thermohygrometer (Shinyei TRH-CZ, Osaka, Japan), were observed to be 75 ± 2% and 25 ± 2 °C, respectively.

2.2.4. Dispersibility using a Next Generation Impactor (NGI)

In vitro dispersibility of the five powder formulations before and after storage (at 75% RH for 3 months) was carried out using a NGI according to the method described in the British Pharmacopoeia for DPIs (Appendix XXI F, http://www.pharmacopeia.co.uk). Using a Rotary vein pump and a solenoid valve timer, the *in vitro* measurements were carried out at 60 l/min. The pump was set using a calibrated flow meter (TSI instruments Ltd., Buckinghamshire, UK). The collection cups were coated with silicone oil before each measurement to eliminate particle bounce. The preseparator was filled with 15 ml of purified water. Accurately weighed 20 ± 0.5 mg of powder or 0.50 ± 0.03 mg of pure drug was loaded in to a size 3 gelatine capsule (Capsugel, Sydney, Australia), which was placed into a Rotahaler (Glaxo SmithKline, Melbourne, Australia). The Rotahaler was connected to a mouthpiece adaptor that was inserted into a United States Pharmacopoeia (USP) throat which was connected to the NGI. The dispersibility was carried out at 60 l/min for 4 s. The RH and temperature during experiment was 45% RH and 25 °C, respectively. The NGI experiments were conducted rapidly (<5 min) to minimise any effects of RH change. Samples from the 11 parts (capsule + rotahaler, throat + mouthpiece, preseparator, stages 1–7 and micro-orifice collector, MOC) were collected in separate volumetric flasks using 40% (v/v) methanol/water to rinse. Each formulation was tested in triplicate. The amount of SX in each part was determined using a validated HPLC assay. The aerodynamic cut-off diameters at a flow rate of 60 l/min for preseparator, stage 1, stage 2, stage 3, stage 4, stage 5, stage 6 and stage 7 were 12.41 μm, 8.06 μm, 4.46 μm, 2.82 μm, 1.66 μm, 0.94 μm, 0.55 μm and 0.34 μm, respectively (Marple et al., 2003a,b).

The amount of drug recovered from all stages of NGI, preseparator, throat, device and capsule was defined as the recovered dose (RD). The emitted dose (ED) was the percent of recovered dose that was collected from all sections except device and capsule. The amount of SX in each stage was then calculated as a percent of RD. The % fraction of RD that was collected in stage 3 to MOC was regarded as FPF.

2.2.5. In vitro drug dispersibility by twin stage impinger (TSI)

In vitro aerosol deposition was determined using a twin stage impinger (TSI, Apparatus, A; British Pharmacopoeia, 2000) (Copley Scientific Ltd., Nottingham, UK) and a Rotahaler (Glaxo SmithKline, Melbourne, Australia). A vacuum pump (Model OD 5/2, Dynavac Engineering, Melbourne, Australia) fitted to the mouthpiece of TSI was used to create the airflow and the flow rate was adjusted to 60 l/min before each measurement. A thermohygrometer (Shinyei TRH-CZ, Osaka, Japan) was used to measure the surrounding temperature (25 ± 2 °C) and RH (45 ± 2% RH). 7.0 and 30.0 ml of 40% (v/v) methanol (HPLC grade) were placed in the stage 1 and 2 of the TSI, respectively. Size 3 hard gelatine capsules (Capsugel, Sydney, Australia), loaded with the powder formulations (20 ± 0.5 mg)