

# The Changes in Dispersion of Salmeterol Xinafoate-Lactose Mixtures During Storage at Different Relative Humidities

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## Summary

The aims were to investigate *in vitro* dispersion changes of salmeterol xinafoate (SX)-lactose powders for inhalation during 18 months storage at 33%, 55% and 75% RH by a twin stage impinger and a next generation impactor. Agglomerate strength, surface energy, particle size changes were determined by an aerosizer, an inverse gas chromatograph, and a Mastersizer 2000/Spraytec, respectively. The FPF of the mixture containing 20% ML (M20F) significantly decreased from 11.3% to 7.7% at 75% RH ( $P=0.008$ ) within eight weeks. SX at the throat and mouthpiece, preseparator and stage 1 of next generation impactor significantly increased ( $P<0.05$ ) while that in the remaining stages significantly decreased ( $9.7 \pm 0.9\%$  to  $6.1 \pm 0.7\%$ ) ( $P<0.05$ ). Agglomerate strength of M20F increased. The total surface energy and work of cohesion of ML and SX, and the work of adhesion between SX-ML and ML-CL, significantly increased after storage ( $P<0.05$ ); this was consistent with the stronger agglomerate formation. Using a Spraytec, particles with the VMD of 4-25  $\mu\text{m}$  increased while those less than 4  $\mu\text{m}$  slightly decreased for M20F after storage. The particle size of ML increased after storage. The study concluded that the critical factors for decreased dispersion of SX formulations were RH of 75% or greater and the presence of high concentrations of ML. Decreased dispersion was possibly due to capillary forces and/or solid bridge formation of ML leading to the formation of larger and stronger agglomerates.

## Background

The changes in dispersion capability of drug from dry powder inhaler (DPI) formulations are often encountered by pharmaceutical manufacturers (Borgstrom et al. 2005). Drug dispersion is principally governed by the magnitude of interparticulate drug-drug and drug-excipient forces such as contact potential and Coulombic, van der Waals' forces, capillary forces, mechanical interlocking and solid bridging (Stewart 1986). These interparticulate forces can vary in different relative humidities (RH) at different rates and extents depending on material properties and storage duration. For example, forces like contact potential, van der Waals' forces and Coulombic forces develop very quickly, while solid bridges develop after long term storage at high RH and depend on temperature and humidity cycling. High RH may increase interparticulate forces due to increased capillary interactions resulting in the formation of larger agglomerates (Hogg 1989) which are less susceptible to breakage (Boerefijn et al. 1998). Micronized lactose monohydrate was also found to dissolve under the influence of high RH (75% RH or greater) (Podczek et al. 1997), and thus the liquid bridges which were formed at high RH conditions were often followed by solid bridges due to crystallization of the dissolved lactose (Padmadisastra et al. 1994). Therefore, the hypothesis of this study was that the interparticulate forces may increase during storage at high RH, both in the short and long term, with resultant decrease in performance of the inhalation powder by the formation of larger and stronger agglomerates.

There are a number of previous studies which evaluated the influence of storage humidity on dispersion of DPI formulations (Borgstrom et al. 2005; Young et al. 2003; Hindle and Makinen. 1996; Braun et al. 1996; Young and Price. 2004; Lida et al. 2004; Zeng et al. 2007; Harjunen et al. 2003; Maggi et al. 1999). These studies concentrated on the effect of RH either on drug alone (D) or on binary mixtures for short periods of time (maximum 7 days exposed in open pans at storage humidity). These studies did not include ternary mixtures even though these formulations have greater dispersion capability (Adi et al. 2006).

## Aims and Objectives

The aims of this study were (a) to investigate the influence of relative humidity (RH) on the *in vitro* dispersion (expressed as Fine Particle Fraction, FPF) of a five powder formulations for inhalation [salmeterol xinafoate (SX) alone and four SX (2.5%)-coarse lactose (CL) mixtures containing 0%, 5%, 10% and 20% micronized lactose (ML)] during long term storage (18 months) at 33%, 55% and 75% RH and (b) to understand the mechanism of dispersion change during storage by investigating factors such as particle size changes, agglomerate strength, surface energy and work of adhesion.

## Representative Data and Discussion

**Storage effect:** Upon storage, no significant difference occurred in the fine particle fraction (FPF) of any formulation at 33% and 55% RH (data not shown). Though other formulations showed no significant change in dispersion at 75% RH for six months (ANOVA,  $P>0.05$ ), the FPF of the mixture containing 20% ML (M20F) significantly decreased from 11.3% to 7.7% at 75% RH ( $P=0.008$ ) within eight weeks (Figure 1).

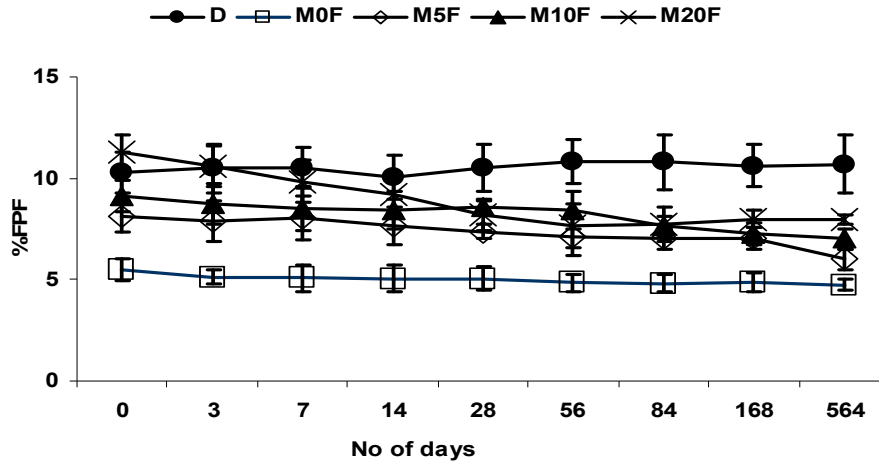


Figure 1: Fine Particle Fraction (FPF) of SX of five formulations: SX alone (D), and its four mixtures M0F, M5F, M10F and M20F containing 0%, 5%, 10% and 20% micronized lactose, respectively during storage at 75% RH for 18 months

**Dispersion determined by a next generation impactor:** Although other formulations did not show any significant changes after storage, the %SX at the throat and mouthpiece and preseparator significantly increased while it significantly decreased in stage 1 and 2 (4.46-12.41  $\mu\text{m}$ ) and in the remaining stages (stage 3 to micro orifice collector, MOC) (marginally significant,  $P=0.045$ ) (Figure 2). These results indicated the formation of larger agglomerates that are inaccessible to the lower stages of NGI and are consistent with that obtained using TSI.

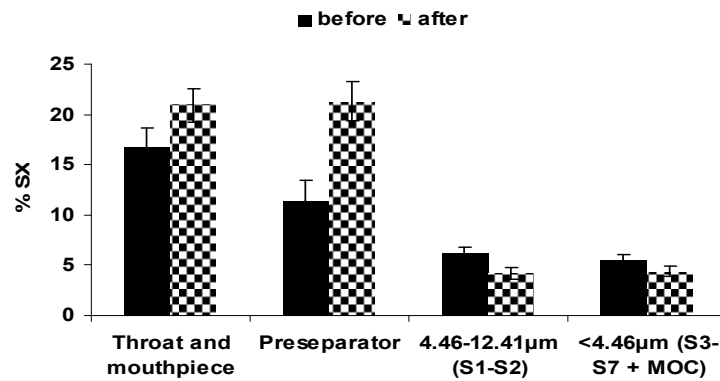


Figure 2: Comparison of % SX fraction at (A) throat and mouthpiece, preseparator, 4.46-12.41  $\mu\text{m}$  fraction and <4.46  $\mu\text{m}$  fraction before and after storage (at 75% RH for three months) mixture containing 20% micronized lactose (M20F) determined using a Next Generation Impactor (NGI) at an airflow of 60 L/min (the percent SX was calculated as percent fraction of recovered dose).

**Particle size distribution determined by a spraytec:** When determined by using a Spraytec, particles with the volume mean diameter (VMD) range of 4-25  $\mu\text{m}$  increased while those less than 4  $\mu\text{m}$  slightly decreased for M20F after storage (Figure 3). No change was observed with other formulations before and after storage. These results indicated the formation of larger agglomerates that are inaccessible to lower stages and are consistent with the results obtained by using TSI and NGI.

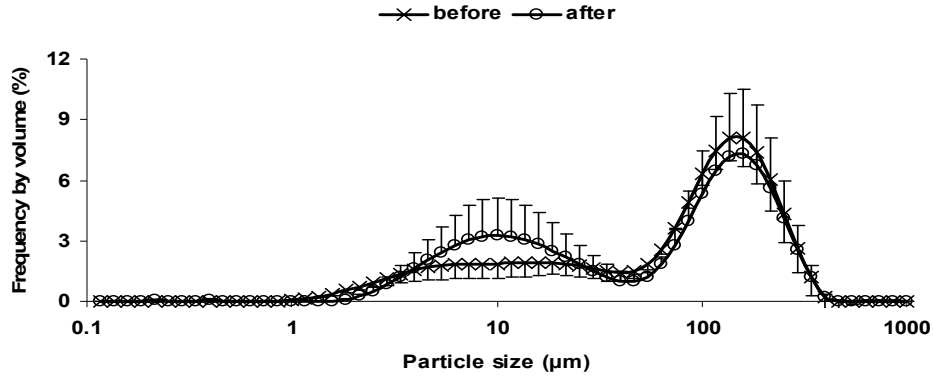


Figure 3: Comparison of particle size distributions (PSD) of the mixture containing 20% micronized lactose (M20F) before and after storage (at 75% RH for three months) determined using a Spraytec at an airflow of 60 L/min

**Particle size distributions of micronized lactose by Mastersizer 2000:** The calculated capillary forces were greater for ML-ML contact than other particle interactions and the propensity of ML-ML contacts was higher in M20F (Das et al. 2008). The PSD of ML shifted to higher particle sizes after storage (Figure 4A), which is an indication of the formation of large particles by strong cohesion and/or solid bridging of small ML particles resulting in decreased number of ML particles. Although no change was observed with other formulations after storage, the particle size distribution (PSD) of M20F showed that the frequency of medium sized particles (4.3-23.0 µm) increased while the frequency of smaller particles (0.6-3.4 µm) decreased (Figure 4B).

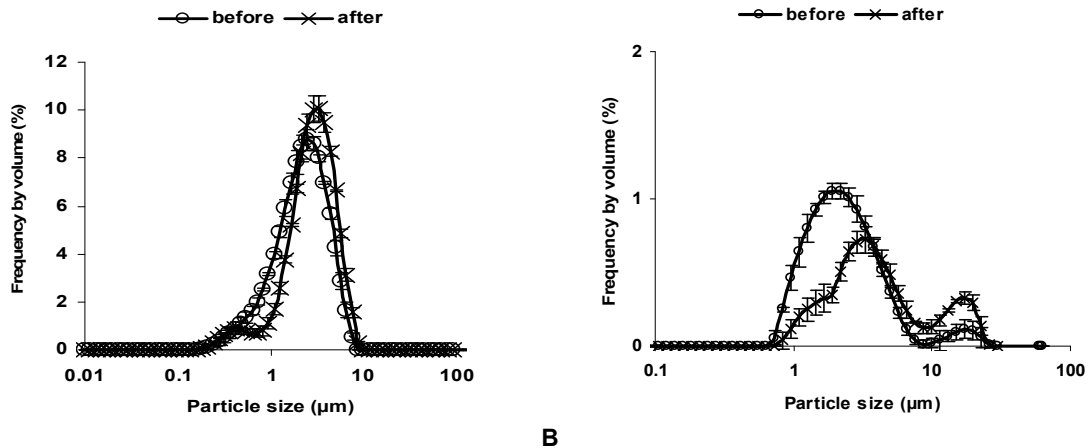
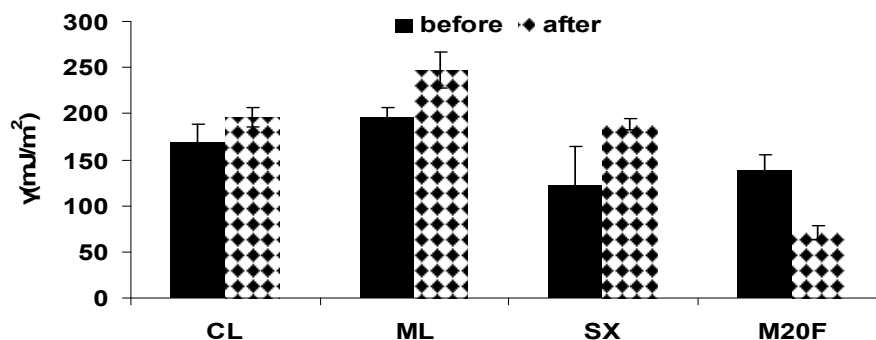


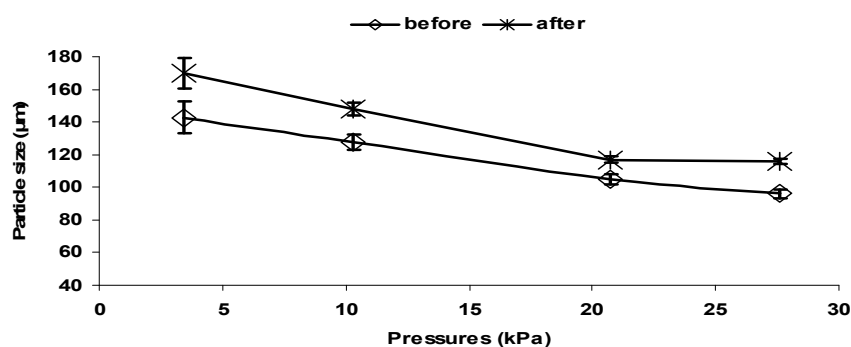
Figure 4: Comparison of particle size distributions (PSD) of the (A) mixture containing 20% micronized lactose (ML) (shown upto 30 µm), and (B) ML, before and after storage (at 75% RH for three months) determined using a Mastersizer 2000 at 1.0 bar pressure

**Surface energy determined by Inverse Gas Chromatography:** When the surface energy at infinite dilution was determined by inverse gas chromatography after conditioning the stored samples at 75% RH for two hours, the total surface energy increased for ML and SX, remained unchanged for CL and significantly decreased ( $P < 0.05$ ) for M20F (Figure 5). The increased emitted dose after storage possibly due to increased flow was in good agreement with the decrease in total surface energy of M20F at infinite dilution. The work of cohesion of ML and SX and the work of adhesion between SX-ML, SX-CL and ML-CL, significantly increased after storage ( $P < 0.05$ ), which helps formation of stronger agglomerate formation.



**Figure 5: Comparison of total surface energy ( $\gamma$ ) before and after storage at 75% RH for three months determined at infinite dilution with conditioning the before storage samples at 0% RH and after storage samples at 75% RH [coarse lactose (CL), micronized lactose (ML), salmeterol xinafoate (SX) and mixture containing 20% micronized lactose (M20F)]**

**Agglomerate strength determined by Aerosizer:** Although no significant difference was observed for other formulations (data not shown), a particle size-shear pressure profile determined using an Aerosizer showed that the agglomerate strength of M20F increased after storage (Figure 6), and reduced dispersion of SX.



**Figure 6: Agglomerate strengths of the mixture containing 20% micronized lactose before and after storage at 75% RH for three months determined at four shear pressures (3.4, 10.3, 20.7, 27.6kPa)**

## Conclusions

The study concluded that the critical factors for decreased dispersion of SX formulations were RH of 75% or greater and the presence of high concentrations of ML possibly due to capillary forces and/or solid bridge formation of ML leading to the formation of larger agglomerates of increased strength and the reduction in the number of ML particles.

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