Effect of Lactose Processing on Dry Powder Inhaler Dispersion

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Introduction

Most Dry Powder Inhaler (DPI) products are formulated as interactive mixtures of micronized drug (<5μm in size) and larger carrier particles, typically lactose monohydrate. The carrier particles prevent powder aggregation and aid in flow and metering. When the patient actuates the inhaler device, powder is fluidized and enters the patient's airways. Micronized drug separates from its carrier and is carried into the lung while the carrier particles impact the throat and are cleared. Batch to batch variation of drug and lactose can adversely affect the formulation, leading to inconsistent operation of the inhaler.

Particle size (Chew and Chan, 1999; Steckel and Muller, 1997), surface area (Cline and Dalby, 2002; Sethuraman and Hickey, 2002), morphology (Chew and Chan, 2001; Dickhoff et al., 2005; Flament et al., 2004; Heng et al., 2000; Iida et al., 2004; Zeng et al., 2000), and surface energy (Cline and Dalby, 2002) have all been related to drug deposition efficiency with varying degrees of success.

When viewed separately, these variables can sometimes produce contradictory results. For instance, some studies have shown that surface corrugation improves deposition efficiency (Chew et al., 2005), while others have provided evidence to the contrary (Iida et al., 2004; Zeng et al., 2000).

Complementary analytical techniques may elucidate the relationships between physicochemical and performance variables.

Materials

Several batches of milled (ML) and sieved (SV) lactose monohydrate, Respitose® were provided by DMV International.

Micronized salbutamol sulfate, model drug used for dispersion and blending studies was supplied by Pfizer.

N-pentane, n-hexane, n-heptane, n-octane, n-nonane, THF, chloroform, acetone (all have purity 99+%, Sigma-Aldrich, St. Louis, MO) were used to probe the powder surfaces in IGC experiments.

Materials

- *In vitro Deposition Efficiency*

1% and 2% albuterol sulfate in lactose were prepared by 4 min blending in a small-scale planetary mixer at 150 rpm. Content uniformity RSD was < 5% in each case. 30mg were loaded into #3 gelatin capsules (Elanco, IN). A Dry powder inhaler (Rotahaler®, GSK) was attached to the mouthpiece of a twin liquid impinger. The powder was emitted at 60L/min for 10 seconds. Each stage was assayed using Shimadzu UV160U at 224.6nm. Several SV and ML batches were tested.

- *Inverse Gas Chromatography*

Dispersive surface free energies and specific free energy contributions were determined via IGC according to the procedure developed by Schultz et al., 1987. Measurements were performed using a HP5890 gas chromatograph with flame ionization detector, 4mm ID deactivated glass columns, 30mL/min N_2 flowrate, 40°C.

- *Scanning electron microscopy*

Powder samples from each lactose batch were mounted on aluminum stubs and coated with gold-paladium using a Polaron sputter coater. The samples were then examined under a JEOL 6300 scanning electron microscope. Micrographs were taken of several different areas at 60X to 4000X magnification.

- *Rotating Drum*

Rotating drum experiments were performed using ~30g powder samples in a 20-cm ID x 4.8cm width drum connected to a variable velocity motor. Dynamic angle of repose was determined using digital video capture methods and analyzed using ImageJ image analysis software. To asses the flow of the different batches mean time to avalanche and mean avalanche duration were recorded for each lactose batch. The angle of the powder in the rotating drum was recorded for every frame captured. A Fourier transform power spectrum analysis was used to resolve dominant frequencies characteristic of each powder.

- *Blending Studies*

1% Albuterol in lactose blends (15g batch size) were prepared by a short step of geometric dilution followed by avalanching in 60mL bottle on ball mill, with 15rpm rotation speed (gentle avalanching). At certain timepoints, 5 samples (5-15mg) were removed and assayed for albuterol using Shimadzu UV160U at 224.6nm.

Results & Discussion

1. In vitro deposition efficiency

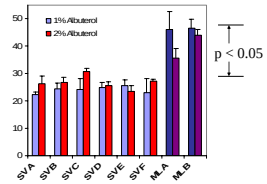

Figure 1. Fine Particle Fraction of 1% & 2% albuterol in lactose batches (mean±SD, n>3). Statistically significant differences were observed between ML and SV batches.

2. Particle Size & Surface Area

ML lactose (Span ~3.1) was more broadly distributed in size than SV (Span = 1.1-1.2), median diameters were similar (54-61μm); and surface areas (ML~0.9m²/g and SV~0.4m²/g) differed.

3. XPRD & DSC

Lactose batches had similar XRPD and DSC profiles. Presence of polymorph or amorphous content was not detected.

4. Dispersive surface free energy via Inverse Gas Chromatography

Dispersive surface free energy varied insignificantly with a combined average of 41.7 ± 1.0 mJ/m² at 40°C (n=6).

5. SEM and associated surface fines

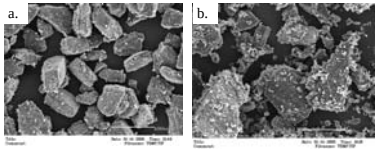

Figure 2. Electron photomicrographs of sieved (a) and milled (b) lactose samples. Clear differences in morphology between but not within SV and ML batches.

6. Bulk Flow

SV exhibited significantly better predictors of bulk flow than ML batches (p<0.05).

Table 1. Static Indicators of Flow

	Sieved Lactose	Milled Lactose
Carr Index (%)	18.4 ± 2.3	45.7 ± 1.8
Static Angle of Repose	29.1 ± 2.0	32.2 ± 0.4

7. Rotating Drum Experiments

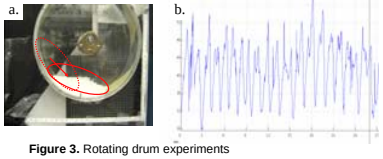

Figure 3. Rotating drum experiments

Rotating drum flow data was expressed as mean time to avalanche (T) and mean avalanche duration (D). While significant differences between T and D for ML and SV lactose were not noted, the magnitude of avalanches observed was quite different. ML lactose displayed more uniform flow than SV, as shown in Figure 4.

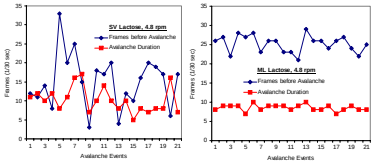

Figure 4. Avalanching behavior of lactose. (a) Sieved Respitose, (b) milled Respitose.

8. Blending Study

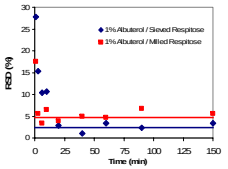

Figure 5. Content uniformity of 1% abuterol in lactose blends after blending in low-shear ball mill (without media) rotated at 15 rpm. Under low shear blending conditions, SV lactose ultimately achieves a lower RSD than ML.

The dynamic (rotating drum) and static (angle of repose) flow data are consistent with aggregate flow (Concessio and Hickey, 1997). This study indicates that particle geometry and flow considerations play an important role in powder dispersion. The more widely distributed ML lactose has higher bulk density which may facilitate fluidization during inhaler actuation. Through the formation of unstable aggregates that flow as large particles, ML lactose appears to display better dynamic flow which improves dispersion.

Conclusion

In conclusion, SV and ML lactose of similar composition, structure and median particle size but differing particle size distribution dispersed 1 and 2%w/w albuterol differently. These differences paralleled those in flow and the presence of fine lactose particles. Other surface analytical methods are being utilized to further assess the geometric and/or energetic features of lactose with respect to particle adhesion, cohesion and dispersion.

Acknowledgements

Martin Telko gratefully acknowledges receipt of a USP Fellowship.

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