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 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.

Materials

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

Results & Discussion

1. 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®) 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 UV1600 at 224.8nm. Several SV and ML batches were tested.

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~0.8m2/g and SV~0.4m2/g) differed.

3. XRPD & 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 measurements yielded similar values and were not statistically significant (p < 0.05).

5. SEM and associated surface features

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

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<tr>
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<th>Sieved Lactose</th>
<th>Milled Lactose</th>
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<tbody>
<tr>
<td>Carr Index (%)</td>
<td>15.4 ± 2.3</td>
<td>21.8 ± 3.2</td>
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<tr>
<td>Static Angle of Repose (°)</td>
<td>29.1 ± 2.0</td>
<td>32.2 ± 0.4</td>
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7. 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.

8. Blending Study

Particle size distribution and flow properties of 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.

Conclusions

In conclusion, SV and ML lactose of similar composition, structure and median particle size but differing particle size distribution dispersed differently. These differences may be attributed to differences in flow and metering of the powder in the inhaler device. Other surface analytical methods are being utilized to further assess the geometric and energetic features of lactose with respect to particle aggregation and dispersion.

Acknowledgements

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References


Cline, D., and Dalby, R. (2002). Predicting the quality of powders for inhalation from surface energy and area. Pharm Res 19, 1215-1227.


