Sheffield™ Brand Inhalation Grade Lactose Functionality Testing

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Introduction

Using a dry powder inhaler for drug delivery has many advantages over traditional routes including fast delivery of active, no needle use, and no pill swallowing. They also offer advantages over older respiratory delivery methods such as those using nebulizers or pressurized CFC containing aerosols. Dry powder inhalers also offer the potential for delivering a wider range of drugs than these older methods. Typically, with dry powder inhalers, the active ingredient and a carrier are blended together and used to fill the inhaler, or with some inhalers, single dose capsules. During use, the patient either inhales a dose by simply inhaling, or is assisted by a burst of air, depending on the inhaler type.

Lactose has been used as a carrier in these applications due to its inertness, cost, availability, particle size options, and patient tolerability. Two of the most important characteristics of the formula are dose uniformity, and from a cost standpoint, the amount of active that reaches the patients lungs in relation to the amount in the starting dose. The lactose used as a carrier will most certainly have an effect on both of these characteristics.

In this study, two grades of Sheffield™ Inhalation grade lactose (monohydrate and anhydrous) will be compared to a standard industry grade of spray dried inhalation lactose. They will be compared by blending the lactose with micronized albuterol, filling the inhaler, and emitting doses into an Anderson Cascade Impactor. The emitted dose (from the inhaler) along with the fine particle fraction in the impactor (simulates how much active would reach the lungs) will be measured.

Materials

The lactose grades used in this study were the following grades of Sheffield's™ Inhalation Lactose

Anhydrous 40M
Monohydrate 40M

An industry Spray dried Monohydrate was also used for comparative reasons

Industry Spray Dried A

Micronized Albuterol Sulfate was used as the active ingredient

Methods

Albuterol Method Development. Two HPLC methods were developed for the analysis of albuterol sulfate. The method used to analyze the samples from the blending studies is linear from 10-50 µg/ml with no individual standard deviations greater than 3%. The HPLC method that was utilized for the ACI sample analysis is linear from 0.1 to 1 µg/ml with no individual standard deviations greater than 2%.

Micronization of Albuterol. Micronization of albuterol sulfate was preformed using a jet mill with an inlet and opposing pressure of about 1000psi. The albuterol sulfate was characterized (pre- and post-micronization) by laser diffraction particle sizing. Laser diffraction showed a decrease in particle size from X_{50} of ~9.2 µm and X_{90} of ~34.66 µm (unmicronized) to a X_{50} ~1.87 µm and X_{90} ~4.68 µm (micronized).

Blending Procedure. Micronized albuterol sulfate was mixed separately with the three different grades of lactose in a ratio 1:100 (w/w), which is in close accordance with the ratio employed in the commercial Ventolin Rotacaps. Albuterol sulfate was mixed with lactose using geometric dilution followed by blending in the Turbula mixer. The blend homogeneity was determined as a function of blending time, six samples were taken post-blend (each 25+/- 5 mg) from different regions of the blend and analyzed by HPLC.

Anderson Cascade Impaction (ACI) Studies. A test method was developed for performing Anderson Cascade Impaction (ACI) testing of the lactose/albuterol dry powder using the current United States Pharmacopoeia convention as a starting point.

The ACI studies were conducted by sampling the aerosol powder from the dry powder inhaler (Aerolizer), at the flow rate determined, through an eight-stage cascade impactor (Anderson Samplers, Inc., Smyrna, GA, non-viable, inertial impactor). The stages will be coated in accordance with the specifications set out in the United States Pharmacopoeia. An Aerolizer will be tested with three collections preformed (n=3).

Five hard gelatin capsules (Size 3) were filled with 25 +/- 2 mg of each blend mixture. The impactor plates (-1 to 6) were coated with silicone oil. A filter paper was place in the last stage of the impactor and 10 ml of 0.01 N HCL was introduced in the preseparator. The impactor was assembled and an Aerolizer containing a filled capsule was fitted into a molded rubber mouthpiece attached to the throat of the impactor and aerolized at 60 +/- L/min for 4 seconds. The deposition test was repeated until four more capsules were actuated in the same manner. After all the 5 capsules had been actuated the impactor was dismantled and the impactor plates, filter paper, inhaler body, mouthpiece, throat, casing and preseparator were washed with 0.01 N HCL. Method development work was preformed to determine the amount of 0.01 n HCL required for washing of the plates so as to be within the working range for HPLC analysis. The concentration of albuterol sulfate in the samples was determined by HPLC. Each blended formulation was tested three times.

A recovery study was also preformed to ensure that the washing solvent was recovering the entire albuterol sulfate on the impactor plates. This was done by adding a known amount of albuterol sulfate solution to the impactor plates, washing the plates with 0.01 n HCL and analyzing the washings by HPLC. A recovery of 98% was obtained.

Results and Discussion

Blending Results. Blending of albuterol sulfate with three different inhalation lactose products, one from each category (Sheffield™ Anhydrous, Sheffield Monohydrate, and Spray Dried Monohydrate) resulted in good blend uniformity after 35 minutes. The three re-blends were then used in the remainder of the study.

Table 1: Blending Results

Lactose	Average % albuterol sulfate in unit dose sample after blending for 35 minutes
Lactose NF inhalation Monhydrate 40M	0.97
Lactose NF inhalation Anhydrous 40M	1.02
Industry Spray Dried Monohydrate A	0.96

Anderson Cascade Impaction Results. A variety of parameters were used to characterize the deposition profiles of albuterol sulfate from the blends in ACI studies. The recovered dose (RD) was calculated from the sum of drug collected in the inhaler device, preseparator, throat and mouth pieces, casing and 8 stages of the impactor, whereas the emitted dose (ED) was the amount of drug released from the inhaler device. Percent recovery and percent emission was determined by the ratio of RD and ED to the theoretical dose, respectively, the theoretical does being the dose collected in stages 1-6 of the impactor (<4.5 µm). Fine particle fraction (FPD) was calculated as a ratio of FPD to RD and also as a ratio of FPD to ED.

Single factor ANOVA demonstrated that there was no significant difference (p-value >0.05) in the percent emissions and FPF as a function of recovered dose between Monohydrate and Anhydrous 40M Lactose. However FPF as a function of emitted dose was higher for Monohydrate Lactose 40M as compared to Anhydrous Lactose 40M at 90% confidence interval (p<0.1).

Percent emissions and FPF (both as a function of recovered and emitted dose) was lower for the Competitor Lactose A as compared to both Monohydrate and Anhydrous Lactose 40M. There is not a large difference in particle sizes of these carrier lactose particles; however a difference in the deposition characteristics was recorded.

Table 2: Lactose Monohydrate Inhalation 40M as a Carrier

Parameter	1st Replicate	2nd Replicate	3rd Replicate	Average
Drug Content in the Capsules (µg)	1206	1159	1200	1188.3
Recovered Dose (RD) (µg)	1191	1127	1158	1158.7
% Recovery	98.9	97.2	96.5	97.5
Emitted Dose (ED) (µg)	1077.2	992.9	1015.3	1028.4
% Emission	89.3	85.7	84.6	86.5
Fine Particle Dose (FPD)	566.3	542.9	566.7	558.7
Fine Particle Fraction as a Function of RD (%)	47.5	48.2	49.0	48.2
Fine Particle Fraction as a Function of ED (%)	52.6	54.7	55.8	54.4

Table 3: Lactose Anhydrous Inhalation 40M as a Carrier

Parameter	1st Replicate	2nd Replicate	3rd Replicate	Average
Drug Content in the Capsules (µg)	1234	1263	1271	1256
Recovered Dose (RD) (µg)	1170	1270	1223	1121
% Recovery	94.8	100.5	94.6	96.6
Emitted Dose (ED) (µg)	1055.4	1178.1	1116.1	1116.6
% Emission	85.5	93.2	86.4	88.4
Fine Particle Dose (FPD)	513.9	599.6	582.9	565.5
Fine Particle Fraction as a Function of RD (%)	43.9	47.2	47.7	46.3
Fine Particle Fraction as a Function of ED (%)	48.7	50.9	52.3	50.6

Table 4: Industry Spray Dried Monohydrate A as a Carrier

Parameter	1st Replicate	2nd Replicate	3rd Replicate	Average
Drug Content in the Capsules (µg)	1164	1221	1197	1194
Recovered Dose (RD) (µg)	1103	1167	1162	1144
% Recovery	94.7	95.6	97.1	95.8
Emitted Dose (ED) (µg)	939	992.1	987.6	972.9
% Emission	80.7	81.3	82.5	81.5
Fine Particle Dose (FPD)	294.9	309.4	312.0	305.5
Fine Particle Fraction as a Function of RD (%)	26.7	26.5	26.9	26.7
Fine Particle Fraction as a Function of ED (%)	31.4	31.2	31.6	31.4

Figure 1: Percent Emission from Inhaler

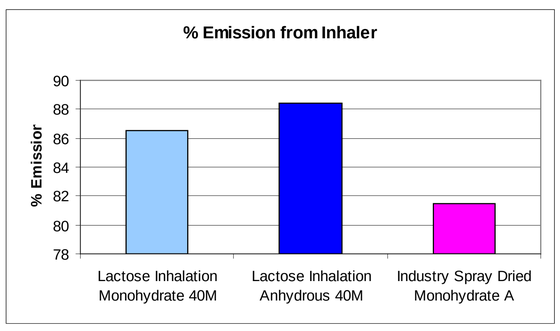
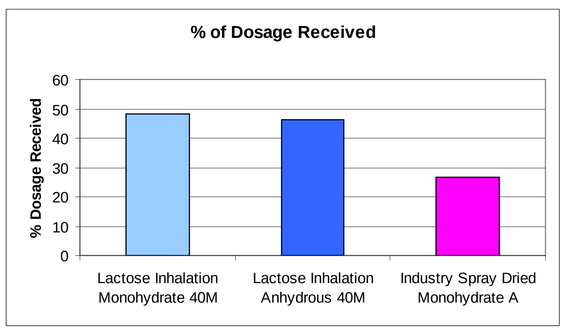


Figure 2: Percent of Dosage Received



Conclusions

For the blending part of the study, all materials exhibited an acceptable blend uniformity with the micronized Albuterol.

For the % emission from the inhaler, the Anhydrous lactose had the highest amount released. This is most likely because Monohydrate Lactose typically tends to stick to materials because of the higher moisture content. However, the Sheffield crystalline monohydrate had a higher emission than the spray dried. This is probably because the spray dried contains amorphous lactose which also tends to stick.

The percentage of lactose that theoretically would reach the lungs is based on the fine particle fraction in the Anderson Cascade Impactor. The Fine Particle Fraction as a function of emitted dose shows that the Sheffield™ Anhydrous and Monohydrate were similar at 54.4 and 50.6%. This is most likely due to the similar particle sizes of the products. The spray dried product was much lower at 31.4%. This also had a similar particle size curve but the lower result is most likely due to the porosity of the spray dried product which will hold the active and not allow its release in the air stream. The amorphous lactose content may also have an effect on active release. This warrants further study.

Based on these results, either grade of the Sheffield™ products tested resulted in high emission and fine particle fractions.

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