The Effect of Lactose Quality Attributes on Predicted Inhaled Drug Deposition in Tiotropium Bromide DPI Formulations

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INTRODUCTION

Dry powder inhalers (DPIs) commonly contain micronized drug particles blended with carrier particles. This is intended to reduce the cohesive properties of the drug particles [1] and therefore increase their aerosolization efficiency and penetration into the respiratory tract. When selecting carrier particles it is important to consider several quality attributes, including particle size, morphology, surface roughness and adhesive interparticulate interactions with the drug(s). During early phase development the likely success of inhalation therapy is often extrapolated from *in vitro* measurements of aerodynamic particle size distribution (APSD) which may be related to regional drug deposition in the lungs. The actual location of *in vivo* particle deposition is more complex to model since it is affected by particle characteristics, airway geometry and breathing pattern [2].

In this study we evaluated the effectiveness of powder dispersion by measuring the polydispersibility index (PDI) and the specific surface area (SSA) for DPI formulations and attempted to identify correlations with drug mass likely to deposit in various regions of the respiratory tract.

METHODS

DPI formulations and capsule filling

Lactose monohydrate carrier particles (milled Lactohale 200, 201 and 206; milled Respitose ML001 and ML006; and sieved Respitose SV003 (DFE Pharma, Goch, Germany)) were tumble mixed (INVERSINA 2L, Bioengineering AG, Wald, Switzerland. 30 rpm for 10 minutes) with tiotropium bromide (anhydrous Form 11, 95% of particle smaller than 5 μm by volume, Teva API Division) to create six DPI formulations (Table 1). Each dry mix was sieved (60 mesh, Mini Sifter, Russell, Pineville, USA) prior to tumble mixing. Each formulation theoretically contained 99.69%

lactose and 0.31% micronized tiotropium bromide. Blend homogeneity was confirmed by sampling 30 minutes after mixing. The target weight of formulation (7 mg) was volumetrically filled using manual injectors into each capsule (VCAPS, Size 3, Lonza, Morristown, NJ) and theoretically contained 21.7 mcg of anhydrous tiotropium bromide (equivalent to 18.0 mcg of tiotropium).

Lactose physical properties

The specific surface area (SSA, m^2/cm^3, m^2/cc) and particle size distribution (PSD) of each lactose monohydrate sample was measured by laser diffraction (Spraytec, Malvern Instrument, 2.5kHz, rapid mode). The d10, d50, and d90 (μm) were used to calculate the polydispersibility index (PDI = (d90 – d10)/d50).

Aerosol evaluation

Capsule contents were aerosolized (n = 3) into a Next Generation Impactor (NGI, Copley Scientific, Nottingham, UK) using a high resistance DPI (RS01 DPI UHR Model-7, Plastiape, Osnago, Italy) at 41 L/min for 5.9 seconds. Tiotropium bromide was quantitatively rinsed from the capsule, device, mouthpiece connector, induction port, pre-separator and NGI stages and the amount of drug in each location was calculated following high performance liquid chromatography using a validated in-house method.

Predicted respiratory tract deposition

Tiotropium bromide deposition in the NGI was used to estimate the mass of drug deposition expected in naso-oro-pharyngo-laryngeal (NOPL), tracheobronchial (TB), and pulmonary (P) zones according to the to the particle size classifications of the National Council on Radiation Protection and Measurements [3] using CITDAS V3.10 software (Copley Scientific).

Relationships between the physical properties of lactose and predicted drug deposition location in the respiratory tract were evaluated using response surface regression analysis (linear+square, Minitab LLC. Inc., State College, PA, USA). Influences were considered statistically significant at $p < 0.1$.

RESULTS AND DISCUSSION

Table 1 shows the particle size metrics and SSA of each lactose grade alongside the mass of tiotropium bromide predicted to deposit in the NOPL, TB, and P regions of the respiratory tract when each lactose is incorporated into six model DPI formulations. Figure 1 shows the results of regression modeling of the location of drug deposition in the respiratory airways based on lactose physical properties.

Table 1.

Particle size PDI and SSA of lactose monohydrate and the predicted mass of tiotropium bromide deposited at various respiratory tract locations (NOPL, TB, and P).

Formulation / Lactose Grade	d10 µm	d50 µm	d90 µm	PDI	SSA, m^2/cm^3	Mass of predicted drug deposition per capsule, mcg		
						NOPL	TB	P
F1/Lactohale 200	13.39	68.95	148.70	1.962	0.257	0.920	1.559	1.158
F2/Lactohale 201	4.67	23.89	63.88	2.478	0.551	0.758	1.956	2.637
F3/Lactohale 206	30.11	83.2	161.85	1.583	0.142	0.502	1.303	2.728
F4/Respitose ML001	5.55	49.00	143.10	2.807	0.418	0.636	1.586	1.722
F5/Respitose ML006	2.74	17.02	45.91	2.536	1.600	0.629	2.097	3.089
F6/Respitose SV003	30.45	60.17	100.74	1.168	0.400	0.150	0.410	0.793

According to the regression model prediction ($p < 0.10$) based on the PDI, the mass of drug deposited in the NOPL, TB and P region is 0.042, 0.013 and 0.346 mcg, respectively. According to the regression model prediction ($p < 0.1$) based on the SSA, the mass of drug deposited in the NOPL, TB and P region is 0.914, 0.277 and 0.116 mcg, respectively. These results show that the deposition of aerosolized particles in the NOPL and TB regions are statistically related to PDI values, and predictable at the level of 80.2% in the P region.

Figure 1A shows that an increase in the SSA yields only a slight change in the mass of particles deposited in NOPL, while when SSA remains constant there is an approximately 1.3-fold increase in PDI over the range of 1.2 to 2.2, equivalent to a 0.30 mcg increase in the mass deposited in NOPL. Figure 1B indicates that the effect of SSA on the mass deposited in TB is negligible, while an approximately 1.1-fold increase in PDI over the range of 1.2 to 2.4 translates to an approximately 0.30 mcg increase in the mass of drug deposited in TB. Figure 1C indicates that the increase in the mass of drug deposited in P depends on the interaction between both variables (PDI and SSA). A SSA values greater than 1.4 m^2/cc is predicted to increase the mass deposited in P region independently of PDI values; whereas a SSA values less than 0.5 m^2/cc requires a higher PDI value (ideally greater than 1.8) in order to achieve higher mass deposition in the P region.

Figure 1D shows PDI is a main influencing physical property on the mass deposited in the NOPL region, which we attribute to a shorter residence time after aerosolization. Figure 1E suggests that PDI remains the main predictor of drug mass deposited in the TB region, but the interaction effect with SSA suggests SSA must exceed about 0.5 m^2/cc in order to achieve mass deposition in the TB region in the range of 1.5 to 2.5 mcg. Figure 1F indicates that achieving higher mass deposition in the P region generally requires a higher SSA value making the formulation's success highly dependent on the cohesive properties of the lactose particles. However, Figure 1F also suggests that the lowest SSA value of 0.142 m^2/cc (black closed circle) achieves a high predicted mass deposition of 2.728 mcg in the P region. We attribute this finding to the lactose carrier particles having a tightly controlled particle size without any fine particles, which we believe eliminates the negative effect of fine particles (increased cohesivity and poor aerosolization efficiency).

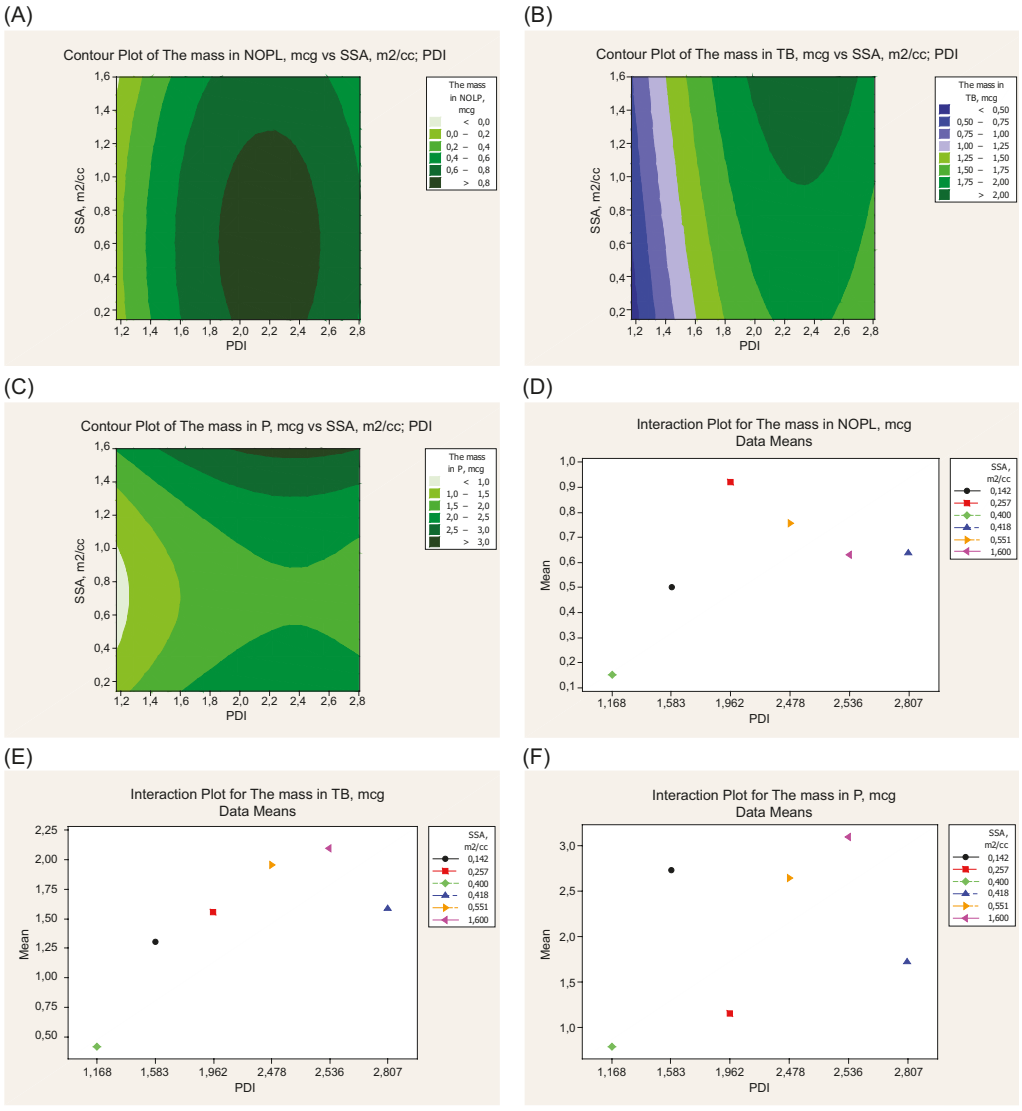

Figure 1. **Contour and interaction plots with $p < 0.1$ between PDI and SSA, and the predicted tiotropium bromide mass deposited in NOPL, TB, and P regions.**

CONCLUSIONS

The PDI and the SSA are important determinants of powder deagglomeration in inhaled air streams and are therefore considered to be critical quality attributes influencing the aerosolization efficiency of tiotropium bromide in lactose carrier-based DPI formulations. Larger lactose PDI values result in a more heterogeneous drug-carrier mixture with the ability to more readily relax (fluidize) in response to turbulent forces generated in a DPI. This results in more predicted deposition in the

NOPL and TB lung regions. The inclusion of a small percentage of fine carrier particles (fines) in a DPI formulation (which is associated with higher lactose SSA value) results in more predicted drug mass deposition in the P region, but the fines concentration must be optimized in order to eliminate the negative effects of cohesiveness which can result in reduced aerosolization efficiency.

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