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Influence of Formulation Factors on Particle Size Distributions and Respiratory Tract Deposition of Metered Dose Inhalers



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PURPOSE

The goal of this study was to evaluate the influence of metered dose inhaler (MDI) suspension formulation changes on the particle size distribution (PSD) and respiratory tract deposition of albuterol sulfate MDIs. Using a commercial MDI product as a model system, formulation variables were modified using a statistical Design of Experiments (DoE) approach. The following factors were studied: ethanol concentration, oleic acid concentration, and drug primary particle size.

The MDIs were characterized using in *vitro* techniques, and a mathematical model was used to estimate the amount of drug deposited in the airways and lung.

METHODS

MDI FILLING

Albuterol sulfate was micronized using a jet mill (Fluid Energy or Glenn Mills, depending on target particle size), and primary particle size distributions of the milled materials were determined by static-laser light diffraction (Sympatec HELOS) with dry dispersion.

Four HFA-134a MDI batches (Table 1) were manufactured via a one-step pressure filling process at 3-L scale using a suspension filler (Pamasol). The following components were used: 17-mL uncoated aluminum cans (Presspart), 28-µL metering valves (Aptar Pharma), and actuators (3M Healthcare).

X ₅₀ (µm)	Ethanol (% w/w)	Oleic acid (% w/w)
1.4	7	0.005
1.4	20	0.11
2.5	7	0.11
2.5	20	0.005

Table 1: Design of Experiments (DoE)

METHODS, CONT'D

The four MDI batches presented here represent the "four corners" of a DoE comprising 22 MDI batches.

PSDs of the MDIs were determined using two methods, and the cascade impaction data was used for lung deposition modeling.

LASER DIFFRACTION

- One volumetric PSD was measured from each of two MDIs from each batch using static laser-light diffraction (Sympatec HELOS).
- Measurements were made at 3 ms intervals at a distance of 2 cm from the laser beam for a period of 200 ms.

CASCADE IMPACTION

- Aerodynamic PSDs were determined using a Next Generation Impactor (NGI) at a flow rate of 30 L/min.
- An Alberta Idealized Throat (AIT, Copley; coated with glycerol) was used.
- Three cans were tested from each MDI batch. Each NGI experiment consisted of two actuations, and collected samples were assayed by LC-MSD.

MODELING

A multiple-path particle dosimetry (MPPD) model was previously developed based on airway morphometry measurements of human lung geometry and ventilation distribution [1]. The model calculates lung deposition by airway generation, lobe, or region based on the deposition mechanisms of inertial impaction, sedimentation, and diffusion. Breathing parameters were defined as a tidal volume of 500 mL and an inspiratory time of 1 sec to generate a flow rate consistent with the impactor studies.

Oropharyngeal (OP) deposition estimates are based on upper respiratory tract deposition in human volunteers [2].

RESULTS

LASER DIFFRACTION

For a given drug primary particle size, Volume Median Diameter (VMD) increased with increasing ethanol and oleic acid content. The effect was strong, with VMD increasing by approximately 80% for both drug PSDs. VMD, which is primarily a function of droplet size, was little affected by drug PSD.

CASCADE IMPACTION

For NGI experiments, fine particle dose (FPD < $5~\mu$ m) dropped by approximately 50% with increasing ethanol and oleic acid concentration. FPD was also highly dependent on the drug PSD. At a drug PSD of $1.4~\mu$ m, FPD averaged $48.0~\mu$ g. At a drug PSD of $2.4~\mu$ m, FPD averaged $28.2~\mu$ g. Mass median aerodynamic diameter (MMAD), which does not directly account for changes in induction port deposition, was much less sensitive to the factors studied.

MDI Batch Number	1	2	3	4		
API X ₅₀	1.4	1.4	2.5	2.5		
Ethanol (% w/w)	7	20	7	20		
Oleic acid (% w/w)	0.005	0.11	0.11	0.005		
Volume Median Diameter (µm)	4.52	8.15	4.09	7.39		
AIT deposition (%)	23.9	56.9	38.6	68.7		
FPD < 5 µm (µg)	62.0	34.0	37.2	19.3		
Mass Median Aerodynamic Diameter (µm)	1.77	2.00	2.69	2.52		
Geometric Standard Deviation	1.52	1.59	1.66	1.91		
MPPD predictions (%)						
Tracheobronchial Deposition (TB)	6.2	4.0	8.2	4.5		
Pulmonary Deposition (PU)	20.9	13.1	22.5	10.6		
Lung (TB + PU)	27.0	17.2	30.8	15.1		
Total (AIT + TB + PU)	50.9	74.1	69.4	83.8		

Table 2: PSD and Modeling Results

RESULTS, CONT'D

MODELING RESULTS

Using the particle size data from the NGI experiments, MPPD modeled lung deposition (Table 2) ranged from 17 to 31% for the different MDI formulations. Total respiratory tract deposition, including deposition in the lung and mouth/ throat region, ranged from 51 to 84%. The highest pulmonary deposition (21 to 23%) occurred for the two cases with the lowest VMDs. Airway generation profiles (Fig. 1) varied in the lower airway region as a function of formulation.

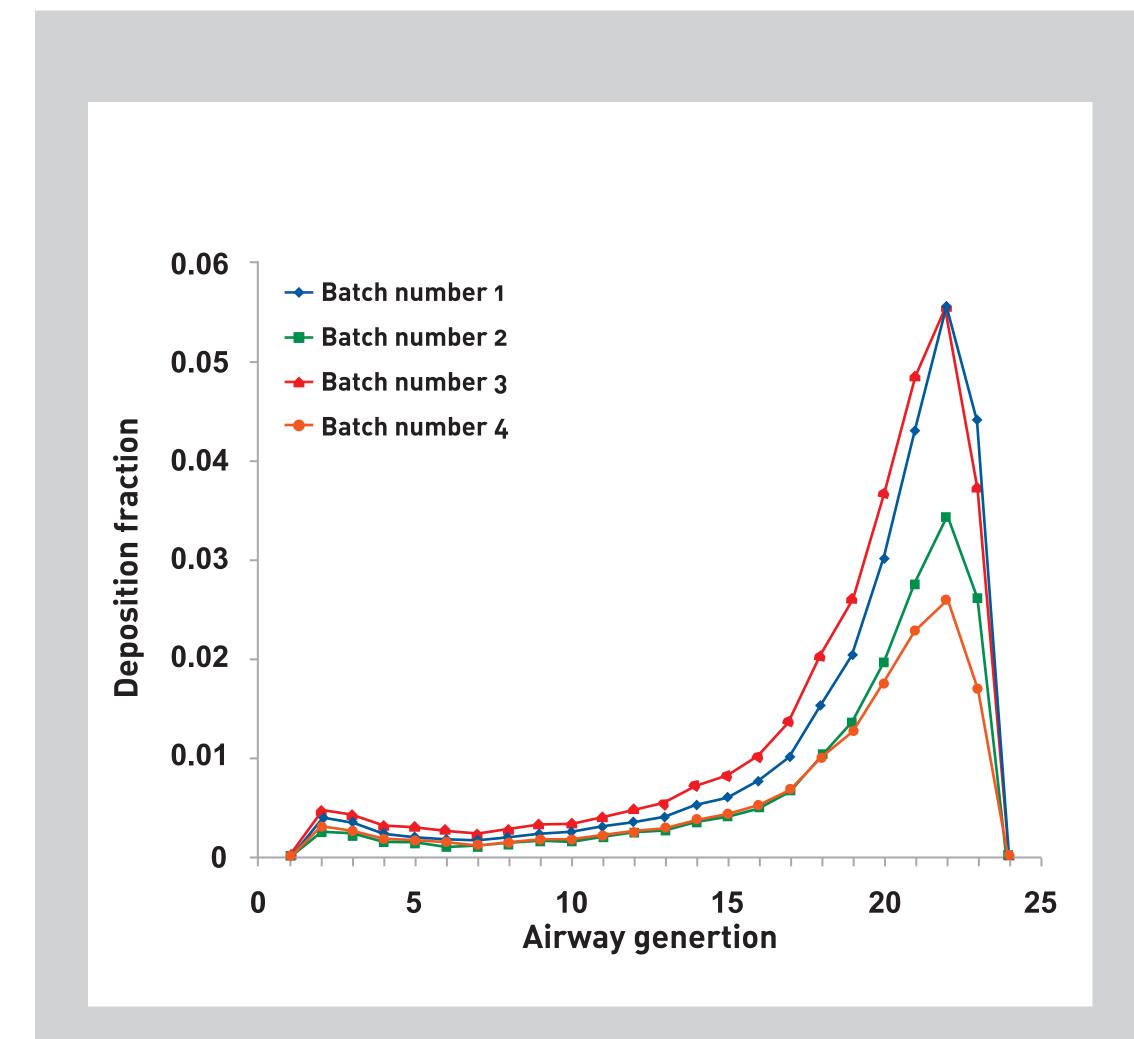


Figure 1: Airway Generation Estimates

CONCLUSIONS

In *vitro* performance and estimated airway deposition showed a strong dependence on MDI formulation variables. Data analysis of the completed set of 22 MDI batches from the DoE will allow assessment of all main effects and 2-factor interactions.

ACKNOWLEDGMENTS

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