iSPERSE™: Formulation and *In Vitro* Characterization of a Novel Dry Powder Drug Delivery Technology

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INTRODUCTION

Efficient and reproducible dispersion and aerosolization of particles is critical to the optimal performance of dry powder inhaler (DPI) formulations for pulmonary administration (1). First-generation DPI formulations mix micronized drug with lactose carrier particles (typically 80 to 120 microns in diameter). These lactose blends are generally inefficient and highly flow rate dependent with respect to their dispersibility, resulting in a low delivery efficiency (typically < 20% delivered to the lungs) and a high degree of patient-to-patient variability, as well as limiting their use primarily to high potency drugs that have a relatively wide therapeutic index and safety margin (1, 2). Second-generation DPI platforms based on particle engineering approaches (3) (as opposed to active devices) have included production of large and porous particles (2, 4, 5) and corrugated particles with high degrees of surface rugosity (6, 7) and coating of particles with hydrophobic force-modifying excipients such as magnesium stearate (2, 8). While approaches like large, porous particles allow for the production of aerosolizable powders that can show good dispersibility over a wide range of flow rates (2, 4, 5, 9), the reduction in particle density (typically well below 0.4 g/cc tapped density) reduces the amount of drug per unit volume that can be administered. The objective of this abstract is to investigate the properties of a novel dry powder drug delivery technology termed iSPERSE™ (inhaled small particles easily respirable and emittable), including particle size, density and dispersibility of powders delivered from a simple, passive DPI. The ability to deliver large masses of powder across a wide range of inhalation flow rates will be discussed.

METHODS

Placebo and drug-containing dry powders were produced with drug classes including antibiotics, beta-agonists and steroids. Salt-based iSPERSE excipients were selected from pharmaceutically acceptable organic and inorganic salts. Starting materials were dissolved in aqueous or organic solvent systems and dry powders were prepared by spray drying on a B-290 Mini Spray Dryer (BÜCHI Labortechnik AG; Flawil, Switzerland). Solutions were atomized using a two-fluid nozzle and dried with hot, dry room air. The atomization gas was 800 L/h and the aspirator rate was at 80 or 90%, which corresponds to a flow rate of approximately 30 to 35 m^3/h. Inlet temperature of the process gas was 100 or 180°C and outlet temperature was from 50 to 87°C with a liquid feedstock flow rate of 3 to 9 mL/min. Powders were collected from a cyclone for further analysis.

Final powders were characterized for tapped density using a Tap Density Tester model TD1 (SOTAX; Horsham, PA). Volume median diameter (VMD) was determined using a HELOS laser diffractometer and a RODOS dry powder disperser (Sympatec; Princeton, NJ) across a range of pressures (0.2, 0.5, 1.0, 2.0, and 4.0 bar). Powder dispersibility was evaluated by comparing VMD at 0.5 bar to VMD at 4.0 bar. Powder dispersibility of emitted powder was also tested by measuring VMD and percentage of capsule emitted powder mass (CEPM) across flow rates representative of patient use (60 LPM and 2L, 30 LPM and 1L, 20 LPM and 1L, 15 LPM and 1L). Size 3 hydroxypropyl methylcellulose (HPMC) capsules (20 to 50 mg fill weight; V-Caps; Capsugel; Greenwood, SC) were used with a capsule-based passive DPI (RS01 Model 7HR; Plastiape S.p.A.; Osnago, Italy). Emitted VMD was measured by laser diffraction via the Spraytec (Malvern; Worcestershire, UK) at 1 kHz for the duration of the simulated inhalation maneuver and the percentage of CEPM was measured by weight change of the capsules. The aerodynamic particle size distributions of powders emitted from the RS01 DPI were measured with an eight stage Andersen cascade impactor (ACI; 2L at 60 LPM; gravimetric analysis of powder mass on glass fiber filters on inverted plate stages). A quantitative HPLC assay was not used for the impaction studies at this time since these methods were not yet developed for all molecules.

RESULTS AND DISCUSSION

To demonstrate the versatility of the iSPERSE technology, formulations were prepared of placebo and drug-containing powders comprising various salt-based and other excipients, in addition to different drugs (antibiotic: ciprofloxacin, tobramycin; beta-agonist: salmeterol xinafoate, albuterol sulfate; steroid: fluticasone propionate) over a wide range of drug loads (0.6% to 95% by weight). Across these different variables, formulations exhibited consistent iSPERSE properties of being relatively dense, geometrically small, dispersible and aerodynamically suitable for lung delivery (Table 1). Powder F, a formulation of drug and salt-based excipient alone (*i.e.*, without non-salt excipients such as amino acids often used in the formulation of inhalable dry powder aerosols) also possessed iSPERSE characteristics. These data suggest that the inclusion of specific salt-based excipients act to increase particle dispersibility and to reduce cohesive forces independent of particle morphology. The relatively high density of the iSPERSE powders allows for the possibility of filling up to 100 mg in a size 3 capsule. Further, the use of a simple spray drying process confers advantages with respect to conventional milling-based processes (10).

Table 1.

iSPERSE formulations and powder properties (mean ± SD; n=2-3).

Powder	Formulation Components	Tapped density (g/cc)	MMAD by ACI (μm)	GSD by ACI	VMD at 1.0 bar by RODOS (μm)	Ratio of VMD at 0.5 to 4.0 bar by RODOS
A	Mg[a] lactate, Na[b] chloride, leucine	0.8±0.02	3.56±0.02	1.82±0.01	2.23±0.07	1.0
B	Na sulfate, mannitol	0.9±0.00	4.01±0.07	1.68±0.02	1.93±0.03	1.4
C	Ciprofloxacin, Na chloride, mannitol	0.6±0.02	3.88±0.10	1.75±0.02	1.92±0.09	1.0
D	Tobramycin, K[c] citrate, maltodextrin	0.6±0.00	2.91±0.11	1.83±0.00	1.55±0.02	1.2
E	FP[d], SX[e], Na chloride, leucine	0.5±0.11	3.01±0.16	1.81±0.04	1.58±0.02	1.4
F	Albuterol sulfate, Mg sulfate	0.5±0.03	2.52±0.16	1.83±0.04	1.36±0.02	1.1

[a] Mg: magnesium; [b] Na: sodium; [c] K: potassium; [d] FP: fluticasone propionate; [e] SX: salmeterol xinafoate

Furthermore, the percent mass of iSPERSE placebo powders (Powders A, B) emitted from capsules remained primarily unchanged as a function of flow rate; CEPM of Powder A only varied by 1% and Powder B by 6% from 15 to 60 LPM (Figure 1A). The emitted particle size varied only slightly from 28.3 to 60 LPM with VMD changes of 7-8% (Figure 1B). Larger particle sizes were measured at 15 and 20 LPM than at 60 LPM, where VMD increased approximately 1 micron at the lower flow rates as compared to 60 LPM, however particle size remained less than 3.4 microns across the range of flow rates. These results on Powders A and B demonstrate the relative flow rate independence of both the amount of powder output and the respirable size of the particles that exited the DPI.

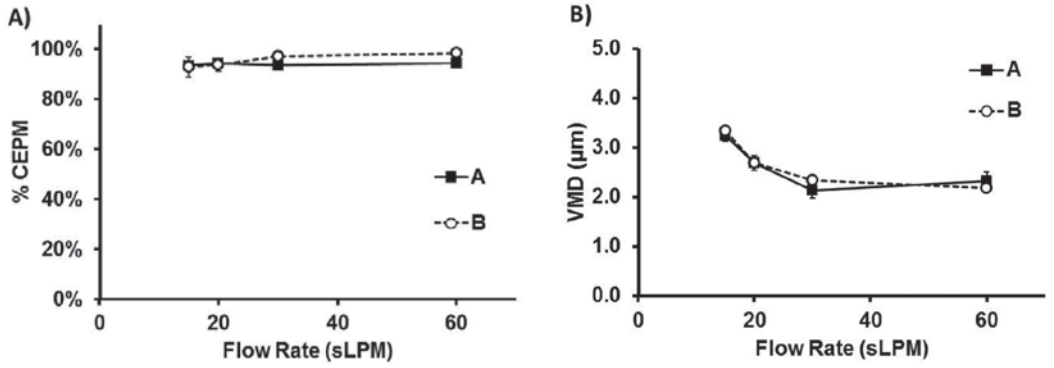

Figure 1. **A) Capsule emitted powder mass (CEPM) and B) emitted volume median diameter (VMD) of iSPERSE powders emitted from a DPI as a function of flow rate (mean ± SD; n=4-5; filled squares represent Powder A, open circles represent Powder B).**

CONCLUSIONS

The iSPERSE technology is a novel dry powder drug delivery system that allows for the delivery of large masses of drugs via a simple, passive DPI. This versatile delivery system can incorporate low to high drug loads along with specific salt-based excipients by using a simple spray drying process. The powder is composed of small, relatively dense, dispersible particles that, for Powders A and B, demonstrated flow rate independent capsule emptying and emitted particle size.

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