Formulation Characterization of a Novel Levofloxacin Pulmonary Dry Powder Drug Delivery Technology

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INTRODUCTION

Progressive obstructive lung disease is the main cause of morbidity and early mortality in patients with cystic fibrosis (CF). *Pseudomonas aeruginosa* (PA) is the most significant pathogen contributing to initial and persistent infection in CF leading to unrecoverable loss of lung function and long-term pulmonary complications (1, 2). There are two aerosol antibiotics approved in the United States to treat CF patients with PA: tobramycin inhalation solution (TOBI®, Novartis Pharmaceuticals) and aztreonam lysine for inhalation (Cayston®, Gilead Pharmaceuticals), with a nominal dose of 300 mg and 75 mg, respectively. High concentrations of antibiotics at the target site of action in patients with pulmonary infections provides increased efficacy (3). However, there is a need for alternative therapies due to decreased efficacy over long-term use, drug intolerance, and new emerging pathogens (4). Additionally, nebulized therapies have documented disadvantages: high cost, and inconvenient and time-consuming administration (5).

Levofloxacin is a fluoroquinolone antibiotic with potent activity against pathogens in CF patients including PA (4). Studies show that nebulized levofloxacin is safe, well-tolerated, results in higher concentration in tissues than oral or intravenous dosing and demonstrates significant clinical efficacy in patients with CF with PA lung infection (2, 4, 6). The administration of levofloxacin dry powder via a dry powder inhaler (DPI) could reduce drug dose burden, simplify/lower costs and provide quick and convenient administration, while maintaining efficacy. The objective of this abstract is to summarize our investigation into the properties of a levofloxacin formulation using a novel dry powder drug delivery technology termed iSPERSE™ (inhaled small particles easily respirable and emittable). The powders were characterized for particle size, density and dispersibility of dry powders delivered from a simple, passive DPI. The ability to deliver large masses of levofloxacin powder across a wide range of inhalation flow rates will be discussed.

METHODS

Dry powders containing varying loadings of levofloxacin with leucine (amino acid) and sodium chloride (inorganic salt) were prepared by spray drying on a B-290 Mini Spray Dryer (BÜCHI Labortechnik AG; Flawil, Switzerland). The general spray drying conditions varied from an inlet temperature of 100-180˚C, compressed air as the drying medium at a rate of 667 LPH, feed solution concentration was 10 g/L pumped at a flow rate of 2.8-6.0 mL/ min. 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 (0.5, 1.0, and 4.0 bar). Powder dispersibility was evaluated by comparing VMD at 0.5 bar to VMD at 4.0 bar. Powder dispersibility was also tested by measuring VMD and the percentage of capsule emitted powder mass (CEPM; as measured by weight change of the capsules) when emitted from size 3 hydroxypropyl methylcellulose (HPMC) capsules (40 mg fill weight; V-Caps; Capsugel; Greenwood, SC) via a capsule-based passive DPI (RS01 Model 7HR; Plastiape S.p.A.; Osnago, Italy) across flow rates representative of patient use (60 LPM and 2L, 30 LPM and 1L, 20 LPM and 1L, 15 LPM and 1L). VMD was measured by laser diffraction via the Spraytec (Malvern; Worcestershire, UK) at 1 kHz for the duration of the simulated inhalation maneuver where powder was delivered directly into the sizing cell without the use of a USP throat. The aerodynamic particle size distributions of powders emitted from the RS01 DPI were measured with a two-stage Andersen Cascade Impactor (ACI) (2 L at 60 LPM; gravimetric analysis of powder mass on glass fiber filters on inverted plate stages) to determine fine particle fraction of the total dose (FPF_{TD}) smaller than 5.6 microns.

RESULTS AND DISCUSSION

To demonstrate the aerodynamic properties of the iSPERSE technology, drug-containing powders with levofloxacin loads up to 90% (w/w), leucine and sodium chloride were manufactured and tested (Table 1). A formulation with 100% levofloxacin was spray dried to show the effect of the addition of leucine and sodium chloride on powder properties. Across these different variables, formulations exhibited consistent iSPERSE properties of being relatively dense, geometrically small, dispersible and aerodynamically suitable for lung delivery. An optimized formulation with greater than 75% (w/w) levofloxacin loading is presented.

Table 1.

iSPERSE formulations and powder properties (mean ± SD; n=1-2).

Powder	Drug loading level (w/w)	Leucine to sodium chloride ratio	Tapped density (g/cc)	FPF_{TD}< 5.6 μm by ACI2 (%)	VMD at 1.0 bar by RODOS (μm)	Ratio of VMD at 0.5 to 4.0 bar by RODOS
A	< 75%	1:2	0.93 ± 0.09	59.3 ± 4.4	2.04	0.95
B	< 75%	1:2	0.92 ± 0.02	57.5 ± 1.5	2.04	1.03
C	< 75%	1:2	0.79 ± 0.08	46.2 ± 0.7	1.79	1.05
D	> 75%	2:1	0.72 ± 0.01	39.3 ± 2.1	2.27	1.01
E	> 75%	2:1	0.63 ± 0.06	51.7 ± 0.3	2.06	1.08
F	> 75%	2:1	0.82 ± 0.01	61.8 ± 0.8	1.64	1.10
G[a]	100%	N/A	0.60 ± 0.01	31.6 ± 1.5	2.87	1.39

[a]Powder G is spray dried levofloxacin with no leucine or sodium chloride

The VMD at 1.0 bar is smaller for the iSPERSE levofloxacin powders than for 100% levofloxacin, with the smallest VMD achieved by Powder F, the optimized powder. Levofloxacin powders containing leucine and sodium chloride are dispersible across dispersion pressures, having a ratio of VMD at 0.5 bar and 4.0 bar close to one, while levofloxacin alone shows dependency on the primary pressure used to measure VMD. The optimized iSPERSE levofloxacin (Powder F) had the highest FPF_{TD} smaller than 5.6 microns at 62%.The levofloxacin dry powders are relatively dense, with tapped density greater than 0.5 g/cc and as high as 0.9 g/cc.

The properties of the powders upon emission from a DPI were further evaluated across a wide range of flow rates. The CEPM of optimized iSPERSE levofloxacin (Powder F) remains greater than 97% and primarily unchanged as a function of flow rate between 20 and 60 LPM and is still greater than 87% at 15 LPM (Figure 1A), while the VMD increased only slightly at lower flow rates (Figure 1B). These data demonstrate the excellent reproducibility and flow rate independence of both the amount of powder output and the size of the particles that exited the DPI. In comparison, the CEPM of spray dried 100% levofloxacin (Powder G) drops as flow rate decreases and has a high variability between measurements, with VMD increasing above a respirable size at flow rates lower than 60 LPM. The powder capsule fill weight was 40 mg, with the possibility of filling up to 100 mg in a size 3 capsule. These data suggest that the inclusion of leucine and sodium chloride act to increase particle dispersibility. Further, the use of a simple spray drying process confers advantages with respect to conventional milling-based processes (7).

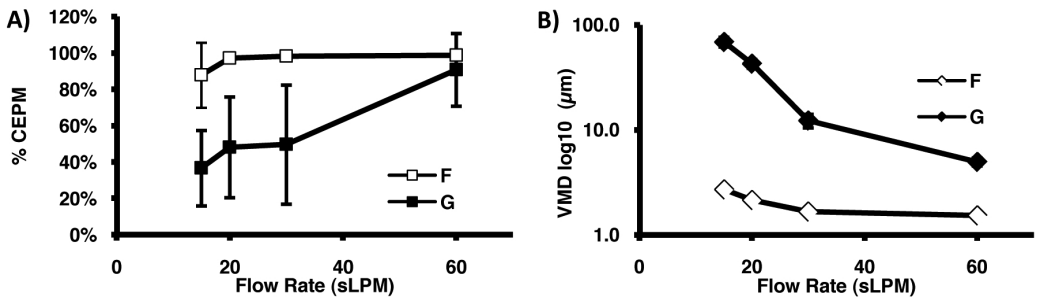

Figure 1. A) Capsule emitted powder mass (CEPM) and B) volume median diameter (VMD) of iSPERSE powders emitted from a DPI as a function of flow rate (mean ± SD; n=4-5).

CONCLUSIONS

The iSPERSE technology is a novel dry powder drug delivery system suitable for levofloxacin that represents an alternative therapy for CF patients with PA infection. Given the relatively high density of the powder, the iSPERSE levofloxacin powder may allow for the delivery of large masses across a range of inspiratory flow rates via a simple, passive DPI leading to faster and more convenient administration. The powder is composed of small, relatively dense and dispersible particles. This delivery system can incorporate high drug loads via a simple one-step spray drying process, reducing costs.

REFERENCES

1. Gibson, R.L. Burns, J.L., and Ramsey, B.W. (2003), "Pathophysiology and management of pulmonary infections in cystic fibrosis," *American Journal of Respiratory Critical Care Medicine,* 168, pp. 918-51.

2. Tsivkovskii R., Sabet, M., *et al*. (2010), "Levofloxacin reduces inflammatory cytokine levels in human bronchial epithelia cells: Implications for aerosol MP-376 (levofloxacin solution for inhalation) treatment of chronic pulmonary infections," *FEMS Immunology and Medical Microbiology,* 61, pp. 141-46.

3. Dudley, M.N., Loutit, J., and Griffith, D.C. (2008), "Aerosol antibiotics: Considerations in pharmacological and clinical evaluation," *Current Opinion in Biotechnology*, 19, pp. 637-43.

4. Geller, D.E., Flume, P.A., *et al.* (2011), "Pharmacokinetics and safety of MP-376 (levofloxacin inhalation solution) in cystic fibrosis subjects," *Antimicrobial Agents and Chemotherapy,* 55(6), pp. 2636-40.

5. Newhouse, M.T., Hirst, P.H., *et al.* (2010), "Inhalation of a Dry Powder Tobramycin PulmoSphere Formulation in Healthy Volunteers," *American College of Chest Physicians*, 124, pp. 360-66.

6. Geller, D.E., Flume, P.A., *et al.* (2011), "Levofloxacin inhalation solution (MP-376) in patients with cystic fibrosis with *Pseudomonas aeruginosa," American Journal of Respiratory Critical Care Medicine* 183, pp. 1510-16.

7. Shoyele, S.A. and Cawthome, S. (2006), "Particle engineering techniques for inhaled biopharmaceuticals," *Advanced Drug Delivery Reviews*, 58(9-10), pp. 1009-29.