Levofloxacin Dry Powders Engineered for Efficient Pulmonary Delivery and Stability

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KEYWORDS: dry powder, spray drying, particle engineering, inhaled antibiotic, cystic fibrosis treatment

INTRODUCTION

Chronic pulmonary *Pseudomonas aeruginosa* (PA) infection is a significant cause of morbidity and mortality in cystic fibrosis (CF) patients [1]. Treatment is typically by nebulized therapies, with the associated disadvantages of time-consuming administration and device cleaning. Alternative delivery systems with reduced administration times are highly desirable to simplify treatment for CF patients.

The iSPERSE™ technology is a novel dry powder drug delivery system that represents an alternative therapy for CF patients with PA infection. The powder is composed of small, relatively dense and dispersible particles that can be formulated with high drug loads, allowing for more convenient and faster administration via a simple, passive dry powder inhaler (DPI).

The fluoroquinolone antibiotic levofloxacin has potent activity against pathogens in CF patients [2] and was selected for investigation in the iSPERSE system. The use of monovalent and divalent metal salt excipients was tested in powders with high drug load. These powders were tested for aerosol and physical properties, as well as stability upon storage across a range of conditions.

METHODS

Dry powders containing levofloxacin with sodium chloride or magnesium lactate (inorganic salts) and leucine (amino acid) were prepared by spray drying on a BÜCHI B-290 Mini Spray Dryer. Powders were assayed for content and purity using a reverse-phase high-performance liquid chromatography (HPLC) method, with the reported percent of label claim corrected for water content as measured by Karl Fischer coulometric titration. Particle size was determined using a Sympatec HELOS laser diffractometer and a RODOS dry powder disperser across a range

of pressures (0.5, 1.0, and 4.0 bar) to measure volume median diameter (VMD), with powder dispersibility evaluated by comparing VMD at 1.0 bar to VMD at 4.0 bar. The aerodynamic particle size distributions of powders when emitted from size 3 hydroxypropyl methylcellulose (HPMC) capsules (40 mg fill weight) via a capsule-based passive DPI (RS01 Model 7HR; Plastiape) were measured with an eight-stage Andersen Cascade Impactor (ACI; 2 L at 60 LPM; analytical analysis of powder mass on glass fiber filters using an HPLC method). Thermal analysis of the powders was performed with a differential scanning calorimeter (DSC) and thermogravimetric analysis (TGA) to measure glass transition temperature (T_g; inflection), crystallization temperature (T_c; onset), enthalpy of crystallization, and weight loss up to 140°C. Final powders were also characterized for tapped density. All testing was performed in duplicate, with the exception of particle size by laser diffraction and thermal analysis, which were single runs for each formulation.

Bulk powders were evaluated for packaged stability at refrigerated (5°C), long-term (25°C, 60% RH), and accelerated (40°C, 75% RH) conditions and assessed at time points of 0.5, 1, and 3 months for selected test methods.

RESULTS AND DISCUSSION

Drug-containing iSPERSE powders with levofloxacin loads of 70-85% (w/w), sodium chloride (Powder A) or magnesium lactate (Powder B), and leucine were manufactured and tested (Table 1). Both powders demonstrated iSPERSE properties desirable for efficient pulmonary delivery, including being geometrically small, dispersible and aerodynamically suitable for lung delivery. Chemical integrity of the molecule was maintained post-processing with both formulations. Both formulations were relatively dense with tapped density as high as 1.0 g/mL.

Table 1.

iSPERSE levofloxacin powder properties.

Powder	Content (% Label Claim)	Purity (%)	MMAD (μm)	aPSD GSD	VMD at 1.0 bar by RODOS (μm)	Ratio of VMD at 1.0 to 4.0 bar by RODOS	Tapped density (g/cc)
A	100.6	99.8	5.00	1.77	1.88	0.96	1.0
B	100.6	99.9	4.46	1.82	2.18	1.02	0.7

Thermal properties of the powders are shown in Table 2. A T_g of about 50°C above the storage condition is predictive of maintaining physical stability of amorphous solids; in this case the target T_g being 50°C considering long-term storage or 75°C for accelerated conditions. Both levofloxacin formulations have a T_g in excess of 50°C, however only Powder B has a T_g above 75°C. It is hypothesized that the divalent cation in Powder B provides a chelation effect with levofloxacin that results in a higher glass transition temperature and therefore greater predicted thermal stability of these formulations.

Table 2.

Thermal properties of iSPERSE powders.

Powder	Weight loss (%)	T_g (°C)	T_c (°C)	Enthalpy of crystallization (J/g)
A	3.6	58.0	75.6	32.0
B	5.6	79.0	91.3	15.2

Stability of iSPERSE levofloxacin powders was evaluated over storage conditions for three months. Levofloxacin content and purity were maintained in both formulations after storage at all conditions. Solid-form stability of the amorphous solids was demonstrated with consistent T_g and T_c (Figure 1). The aerodynamic particle size distributions of Powder A (Figure 2a) and Powder B (Figure 2b) were stable at the 3 month time point across storage conditions.

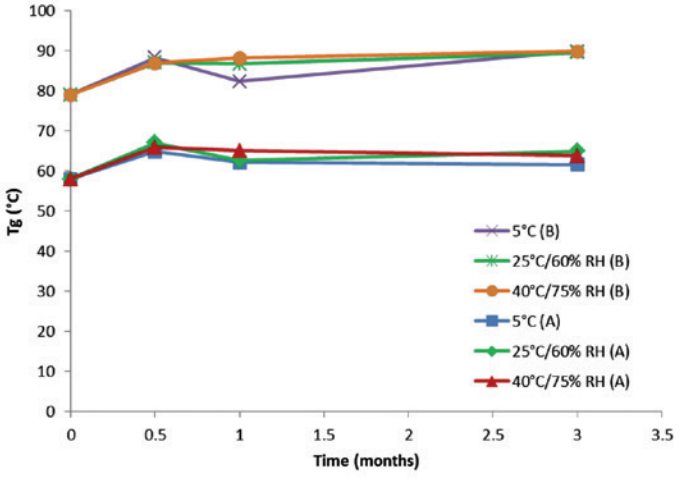

Figure 1. Glass transition temperature of Powders A and B at 0.5, 1, 3 months storage at refrigerated, long-term, and accelerated conditions (n = 1).

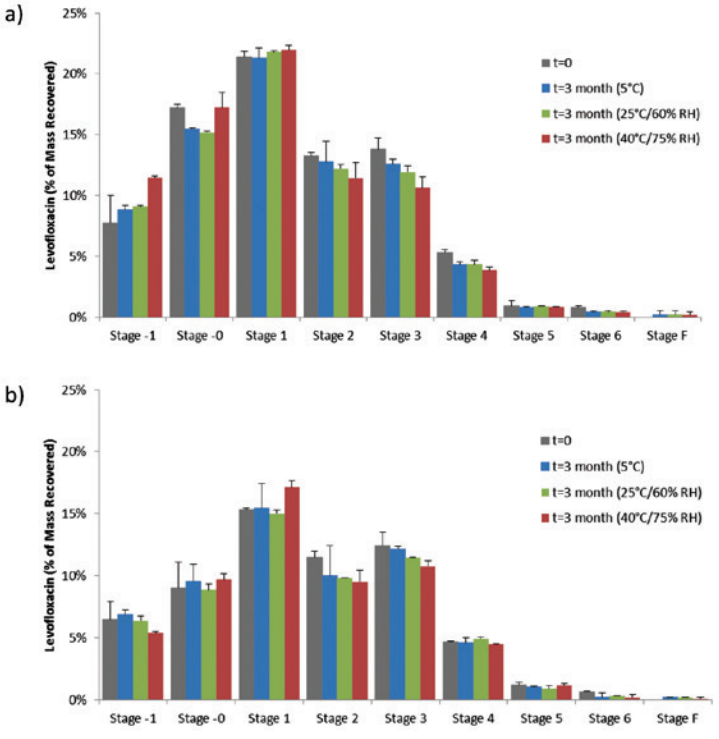

Figure 2. Aerodynamic particle size distribution of a) Powder A and b) Powder B at time = 0 and 3 months storage at refrigerated, long-term, and accelerated conditions (mean ± SD; n = 2).

CONCLUSIONS

iSPERSE dry powder formulations of levofloxacin represent a promising alternative oral inhaled therapy for CF patients that can simplify administration. Feasibility of the drug product has been demonstrated with desirable aerosol and physical properties, as well as stability across storage conditions. Furthermore, the use of divalent cations may impart enhanced thermal stability of levofloxacin across longer time courses in these amorphous pharmaceutical solids.

REFERENCES

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