Rational Design of Microparticles for Respiratory Drug Delivery Using L-Leucine

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INTRODUCTION

Therapeutic aerosols are used extensively in the treatment of respiratory diseases. These aerosols, composed of billions of microparticles, deliver active pharmaceutical ingredients to the lung. Their behavior and efficacy can change depending on initial manufacturing conditions. These conditions in turn have an effect on the aerosol's physical properties. Despite the prevalent use of aerosols for respiratory drug delivery, little is known about how to control their solid-state properties. This study aims to characterize several of these properties and interpret them using existing particle engineering theory[1], the first step towards a rational approach to designing aerosol microparticles.

EXPERIMENTAL APPROACH

Microparticles composed of Trehalose and L-Leucine – in varying relative mass fractions – were manufactured using a Buchi B90 Nano Spray Dryer. Trehalose was used because it has been shown to be a good stabilizer for proteins or biological vectors. L-Leucine was used because of its ability to increase the dispersibility and respirable fraction of aerosol microparticles, thus making the aerosol easier to deliver.[2]

L-Leucine mass fractions were varied between 10 – 40% across six different lots. Pure Trehalose and L-Leucine lots were also manufactured. Total feed concentrations were varied to obtain a mass median aerodynamic diameter (MMAD) between 1 – 5 μm for all lots. All other spray dryer settings were kept constant throughout: inlet temperature (75^{0}C), drying gas flow rate (100 L/min), solution feed rate (80% spray), initial droplet diameter (4 μm spray cap).

The effect of L-Leucine mass fraction on morphology, crystallinity, and powder density were observed using scanning electron microscopy (SEM), Raman spectroscopy, and a novel density measurement technique.

Raman spectroscopy uses inelastic scattering to probe the solid-state of the microparticles. Raman spectra were collected and analyzed using custom equipment and methods described elsewhere.[3] Deconvolution of the spectra yielded amorphous and crystalline fractions of each excipient used.

Due to the small mass of powder generated, a novel density measurement technique was necessary. Using a non-rotating micrometer spindle as a piston, samples were compacted into a cavity of known volume (158 mm^3). Pressure on the powder bed was derived using a digital balance. Compressed bulk densities were quoted at 35.3 kPa of pressure.[4]

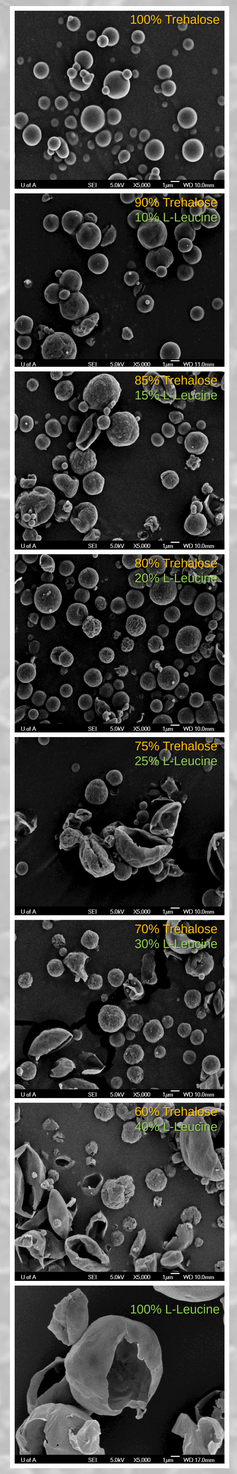

Figure 1: SEM micrographs demonstrating changing particle morphology at various L-Leucine concentrations

Table 1: MMAD and geometric standard deviation (GSD) of spray dried aerosols

$Y_{Trehalose}$	$Y_{L\text{-}Leucine}$	MMAD (μm)	GSD (μm)
1	0	4.19	1.71
0.90	0.10	5.37	1.99
0.85	0.15	4.70	1.76
0.80	0.20	3.91	1.83
0.75	0.25	3.95	2.03
0.70	0.30	2.96	1.72
0.60	0.40	2.69	1.86
0	1	2.13	2.28

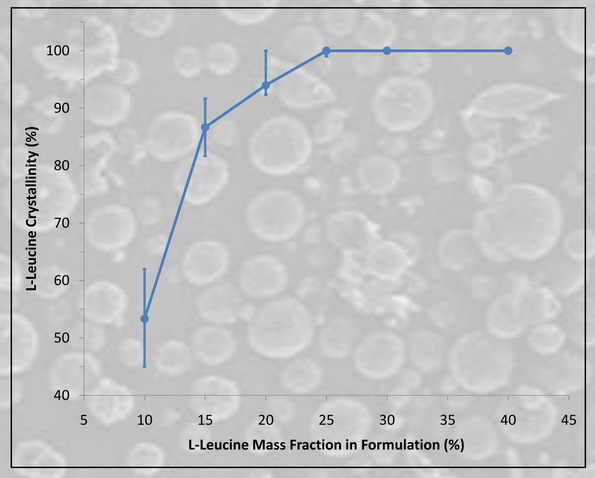

Figure 2: Change in L-Leucine crystallinity of spray-dried aerosol samples

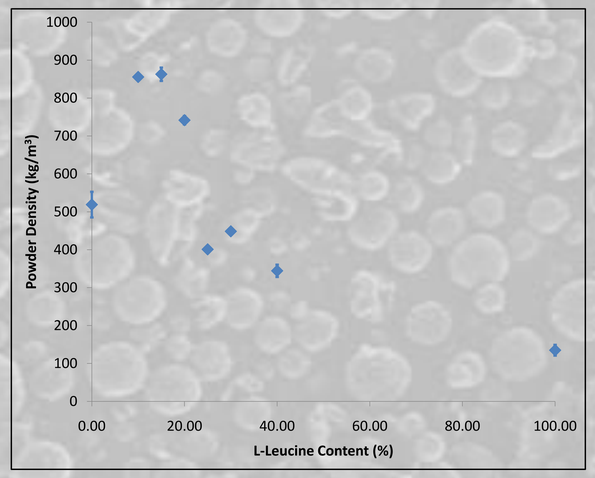

Figure 3: Compressed bulk density at 35.3 kPa

RESULTS

The effect of L-Leucine on the physical characteristics of spray-dried microparticles was successfully characterized. For most samples, the aerodynamic diameter fell within the acceptable range for respirable particles (1 – 5 μm), as intended.[5]

The morphology of the particles changed from solid, smooth spheres to hollow shells with increasing L-Leucine content. The surface of the particles also became more corrugated with increasing L-Leucine. Figure 1 demonstrates these transitions.

A distinct transition in crystallinity was derived from the Raman analysis. Trehalose was amorphous in all formulations, but L-Leucine crystallinity changed significantly. In Figure 2, samples with L-Leucine mass fractions greater than 0.20 were completely crystalline. Below this level the L-Leucine became amorphous (nearly 50% amorphous at an L-Leucine mass fraction of 0.10).

As shown in Figure 3, density decreased with increasing L-Leucine content. A significant decrease of 754.4 to 398.0 kg/m^3 was observed between L-Leucine mass fractions of 0.20 and 0.25, respectively. This decrease in density correlated with the L-Leucine mass fraction's increase in crystalline character. The density of the pure Trehalose sample deviated from the observed trend because of its cohesive nature. Pure Trehalose adhered to the micrometer piston head, causing large fluctuations in the observed density.

CONCLUSION

Characterizing the solid-state properties of aerosols is a necessary step in forming a systematic approach to microparticle design in pharmaceutical applications. In this study, we successfully demonstrated the effect of L-Leucine on particle morphology, crystallinity and powder density. Of particular interest is the relationship between crystalline structure and density. A minimum L-Leucine threshold was necessary to obtain crystalline character and reduce powder density.

Future studies include the investigation of spray drying kinetics and implementation of excipients like L-Leucine to spray dry biological therapeutics for respiratory drug delivery.

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