Increasing Particle Surface Roughness as a Promising Strategy to Improve Colloidal Stability of Pharmaceutical Suspensions

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INTRODUCTION

Pressurized metered dose inhalers (pMDIs) containing pharmaceutical suspensions are the most widely prescribed form of medication for the treatment of airway diseases such as asthma and chronic obstructive pulmonary disease [1]. However, the inherent instability of solid suspensions can cause serious issues and has posed great challenges to the development of new formulations [2]. Various approaches have been applied to improve the colloidal stability of suspensions, including reducing the size of the suspended particle [3], making the particles hollow and porous [4], and adding polymeric surfactants [5]. An alternative approach to improving the colloidal stability of pMDI suspensions by intentionally introducing surface roughness to the particles is presented here.

MATERIALS AND METHODS

In order to isolate the effects of surface roughness on suspension stability, a monodisperse spray drying technique was used to produce uniform model particles for colloidal stability testing. Trileucine (BCBP2254V, Sigma-Aldrich, MO, USA), a surface-active shell former, was added to aqueous solutions of trehalose (177613, Fisher Sci., ON, Canada), a disaccharide, to intentionally introduce different levels of surface roughness to the spray-dried particles. Four feed solutions with a fixed total solids concentration of 5 mg/mL but different trileucine-trehalose mass ratios of 100:0, 99.6:0,

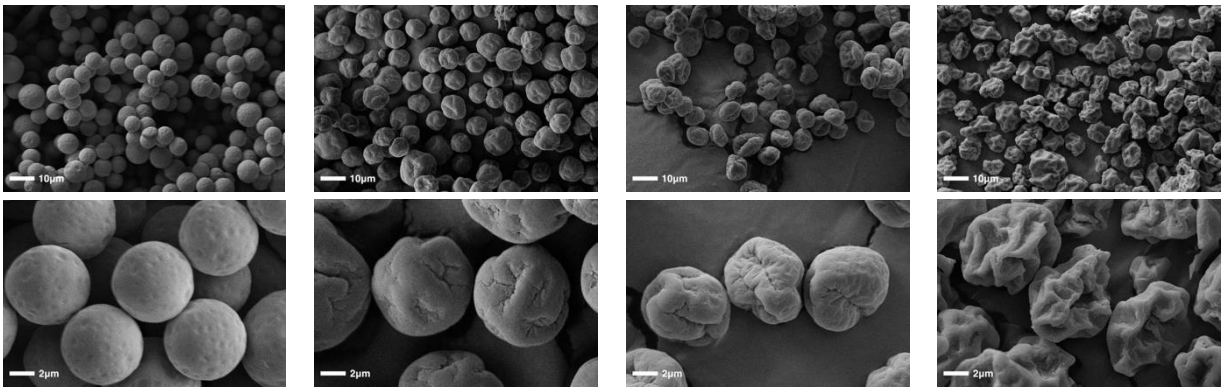
99.0:1.0, and 95.0:5.0 were spray-dried. Particle morphology, particle size distribution, and surface rugosity of the produced particles were characterized using scanning electron microscopy, time-of-flight aerodynamic particle sizing, and BET specific surface area measurement respectively. Pressurized suspensions were prepared by filling 50 mg ± 2 mg of the monodisperse particles into pressure-rated glass canisters and then pressure-filling these with 22.0 g ± 0.5 g HFA-227ea propellant. The colloidal stability of the suspensions was measured for 30 minutes immediately after 30 s of ultrasonic agitation (Branson, 2510-R-MTH, ON, Canada) using a shadowgraphic imaging technique [6] that measures the change in transmission intensity through suspension samples contained in transparent glass sample cells. A time-dependent instability index, $\sigma(t)$, ranging from 0 for unchanged samples to 1.0 for completely clarified samples was used to quantitatively compare the colloidal stability of different samples.

RESULTS AND DISCUSSION

The morphology of the particles shown in Fig. 1 highlights that they gradually changed from smooth to highly rugose when the concentration of trileucine was increased from 0% to 5.0% as designed. Particle size measurement showed that all four spray drying batches had similar mass median aerodynamic diameters (*MMAD* = 9 - 10µm) and good monodispersity with narrow geometric standard deviations (*GSD* < 1.2). The particle rugosity determined from specific surface area measurements provided quantitative evidence that the particle surface roughness increased significantly as more trileucine was added to the feed solution.

Table 1. Feed solutions for monodisperse spray drying. Characterization results include aerodynamic particle size distribution, surface rugosity, and instability index at 30min.

Feed Solution	Trehalose (mg/mL)	Trileucine (mg/mL)	*MMAD* (μm)	*GSD*	Rugosity	σ (t=30min)
0% Leu_3	5	-	10.1	1.1	1.12	0.27±0.02
0.4% Leu_3	4.98	0.02	10.0	1.1	1.27	0.23±0.02
1.0% Leu_3	4.95	0.05	9.9	1.1	1.35	0.18±0.01
5.0% Leu_3	4.75	0.25	8.7	1.1	2.77	0.03±0.01



0% Leu_3 0.4% Leu_3 1.0% Leu_3 5.0% Leu_3

Figure 1. Monodisperse spray-dried trehalose-trileucine particles show good monodispersity and increased surface roughness with the increased trileucine concentration.

The change in transmission intensity through the suspension samples contained in transparent glass vials over 30-minute observation is presented in Figure 2. A layer of settled particles was observed in all cases, as evidenced by the reduced transmission intensity at the bottom of the samples ($h < 0.1$). Because the particle density was higher than the propellant density, the top portions of the suspensions all clarified to a certain extent after 30 minutes. The suspension sample with 0.4% trileucine destabilized similarly to the suspension with pure trehalose, with the difference becoming significant only when the fraction of trileucine was increased to 1.0%. The formulation with 5.0% trileucine was the most distinctive case; it showed little transmission intensity change over the 30 min measurements and thus manifested a significantly improved

suspension stability. The normalized transmission intensity profiles agreed with the inset shadowgraphic images in that the suspension with pure trehalose clarified the most and the destabilization process slowed down gradually as the particle surface roughness was improved.

As listed in Table 1, the 30-minute instability indices for the tested samples provided a quantitative comparison for the colloidal stability of the suspensions. The change in surface roughness caused by a small amount of trileucine in 0.4% already made a difference in the stability of the corresponding suspensions. When the trileucine concentration was increased to 1.0% and 5.0%, the suspension stability was greatly improved by the increased surface rugosity, and the instability index decreased substantially from 0.27±0.02 for pure trehalose to 0.18±0.01 and 0.03±0.01, respectively.

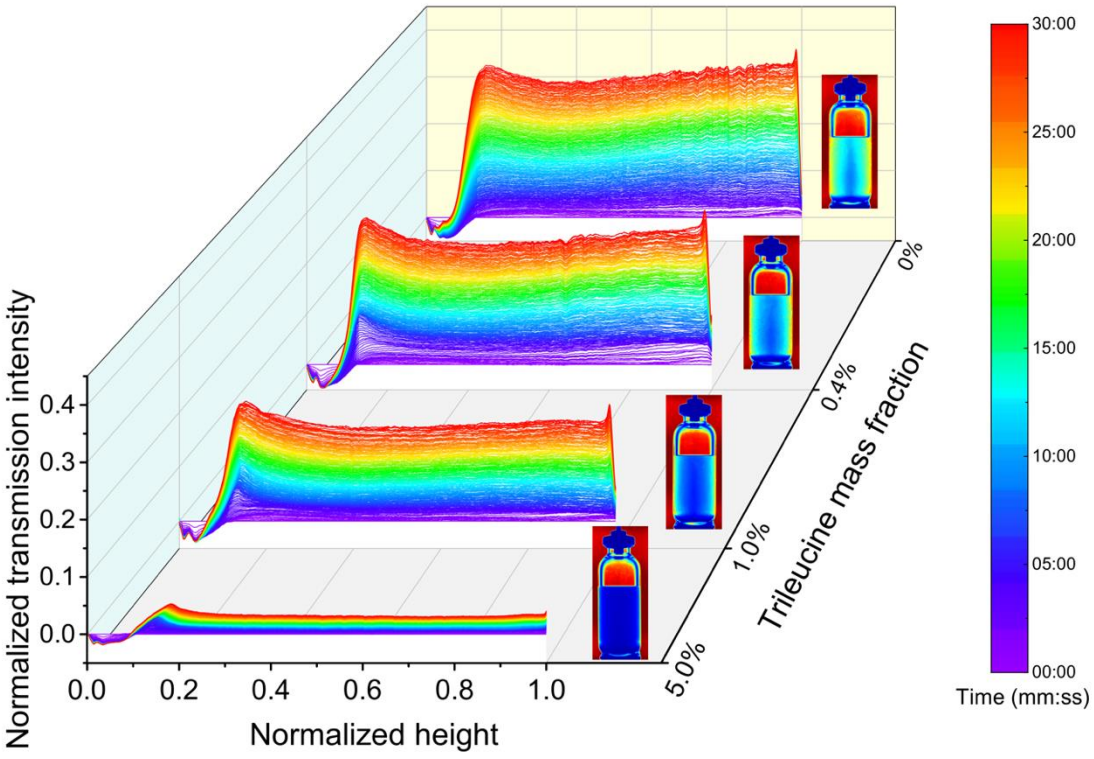


Figure 2. Normalized relative transmission profiles indicate a slower destabilization process as more trileucine was added to the formulation and the suspended particles became more rugose. Inset shadowgraphic images represent end state of the suspension after 30 minutes' measurement.

CONCLUSIONS

Effects of surface roughness on the colloidal stability of pressurized pharmaceutical suspensions were isolated and investigated using spray-dried monodisperse particles. Trileucine was used as a shell former to produce particles with different levels of surface roughness. It has been demonstrated that more rugose particles lead to more stable suspensions, and all of these show better stability than suspensions containing pure trehalose particles with relatively smooth surfaces. Therefore, increasing the surface roughness of particles, for example, by using shell formers like trileucine, is a promising technique that can potentially be used to stabilize their suspensions. Moreover, because this technique is likely not very dependent on the type of propellant and does not require the use of a surfactant, it offers a new means of transitioning to more environmentally friendly pMDIs.

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