Agitation Method Affects Colloidal Stability of Pharmaceutical Suspensions

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INTRODUCTION

The colloidal stability of pharmaceutical suspensions contained in pressurized metered dose inhalers (pMDIs) is a crucial attribute that needs to be carefully characterized for considerations of dosing uniformity [1] and subsequent product quality. Commercial instruments including Turbiscan [2] and LUMiSizer [3] have been applied to colloidal stability testing, but the impact of initial agitation on the resultant suspension stability has rarely been discussed. Three different initial agitation methods—wrist action shaking (WAS), which simulates the manual shaking motion of pMDI users, vortex mixing (VM), which delivers moderate shear rate, and ultrasonic agitation (UA), which provides the most effective dispersing capability—were tested using different suspension formulations and the results compared.

MATERIALS AND METHODS

To avoid the potential complication introduced by polydisperse particles, a monodisperse spray drying technique [4] was used to prepare uniform model particles for the suspension stability testing. Briefly, feed solutions of pure trehalose (177613, Fisher Sci., ON, Canada) and lactose (L2643, Sigma-Aldrich, MO, USA) at a concentration of 5 mg/mL were pressure-fed through a 30μm orifice to form a liquid micro-jet, which was then forced to disintegrate into monodisperse droplets by a vibrating piezoelectric ceramic. The solution droplets were then dispersed in a drying chamber and the dried particles collected using a cyclone. Aerodynamic particle size

distribution and morphology of the dried particles were characterized using a time-of-flight aerodynamic particle sizer (APS) and scanning electron microscopy (SEM).

Pressurized suspensions were then prepared by filling 50 mg ± 0.5 mg of the spray-dried disaccharide particles into pressure-rated glass vials and subsequent pressure filling with 18 mL ± 0.4 mL of propellants. Three propellants with different liquid densities, HFO1234ze, HFA134a, and HFA227ea, were used to prepare suspensions with different stabilities. Each suspension sample was tested three times for each agitation method. Detailed descriptions of the agitation process applied before each stability measurement are listed in Table 1.

Table 1. Methods and settings used for initial agitation of suspensions. “Osc/min” stands for oscillation per minute; “RT” stands for room temperature.

Agitation Method	Setting	Time (s)	Brand	Model
Wrist Action Shaking	385 Osc/min @ 15°, RT	30	Burrell Sci.	75-CC
Vortex Mixing	3200 rpm, RT	30	Fisher Sci.	02215365
Ultrasonic Agitation	100 Watts @ 42kHz, RT	30	Branson	2510-R-MTH

A custom-designed shadowgraphic imaging technique [5] that detects the time-dependent change of transmission intensity across the suspensions contained in transparent glass vials in a bright field was utilized for the suspension stability characterization. All the suspensions were observed for 30 minutes for suspension stability immediately after 30 s agitation. A time-dependent dimensionless instability index, $\sigma(t)$, ranging from 0 for unchanged samples to 1.0 for completely clarified samples, was derived for each sample. For cross-sample comparison, the time for the instability index to reach 0.5, $\tau(\sigma = 0.5)$ was used as a quantitative suspension stability indicator, with the corresponding time constants for stable samples being longer than those for unstable ones.

RESULTS AND DISCUSSION

The results of the particle size measurement listed in Table 2 in combination with the particle morphology in Fig. 1 prove a good monodispersity and uniformity for the prepared trehalose and lactose particles. Since solid model particles with no internal voids were obtained, the particle density (ρ_P) was close to the true density of trehalose and lactose. Settling velocities of the particles in each propellant were then calculated according to $v_s = \frac{(\rho_P - \rho_L) d_{ve}^2 g}{18 \eta \chi}$, in which d_{ve} is the particle volume equivalent diameter, ρ_L is the liquid propellant density, g is the gravitational acceleration, η is the dynamic viscosity of the propellant, and χ is the dynamic shape factor to account for non-spherical particles. According to Table 2, the primary particles are expected to settle almost 3-4 times faster in HFA134a and HFO1234ze propellant than in HFA227ea.

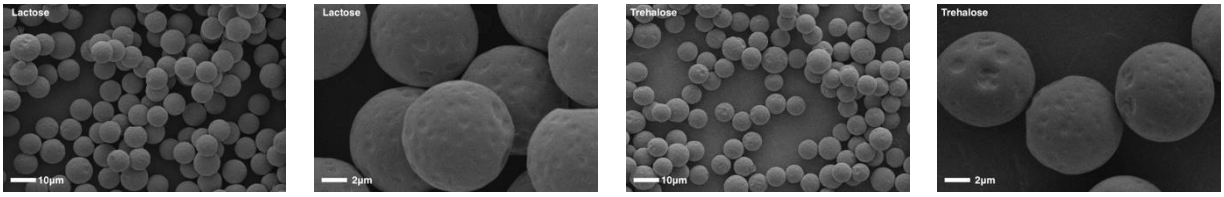

Figure 1. Monodisperse spray-dried trehalose and lactose particles with narrow geometric standard deviations (*GSD*) and similar mass median aerodynamic diameters (*MMAD*).

Table 2. Suspension formulations used for colloidal stability testing. Particle settling velocities (v_S) were calculated based on the measured aerodynamic particle sizes and propellant properties at 20 °C.

Particle	Propellant	*MMAD* (µm)	*GSD*	ρ_P (g/cm³)	ρ_L (20°C, g/cm³)	v_S (mm/min)	Replicates
Trehalose	227ea	10.60	1.10	1.53±0.02	1.41	1.08	×2
	134a				1.23	3.41	×2
	1234ze				1.18	4.08	×2
Lactose	227ea	10.90	1.13	1.52±0.05	1.41	1.10	×2
	134a				1.23	3.61	×2
	1234ze				1.18	4.32	×2

A summary of the suspension stability measurements for different combinations of formulation and agitation method is presented in Fig. 2. Trehalose and lactose particles behaved similarly when suspended in the same propellant and agitated using the same method, indicating similar particle-propellant surface interactions. When the same agitation method was applied, the suspension stability strongly depended on the particle settling velocity, such that lower settling velocity was correlated with more stable suspensions.

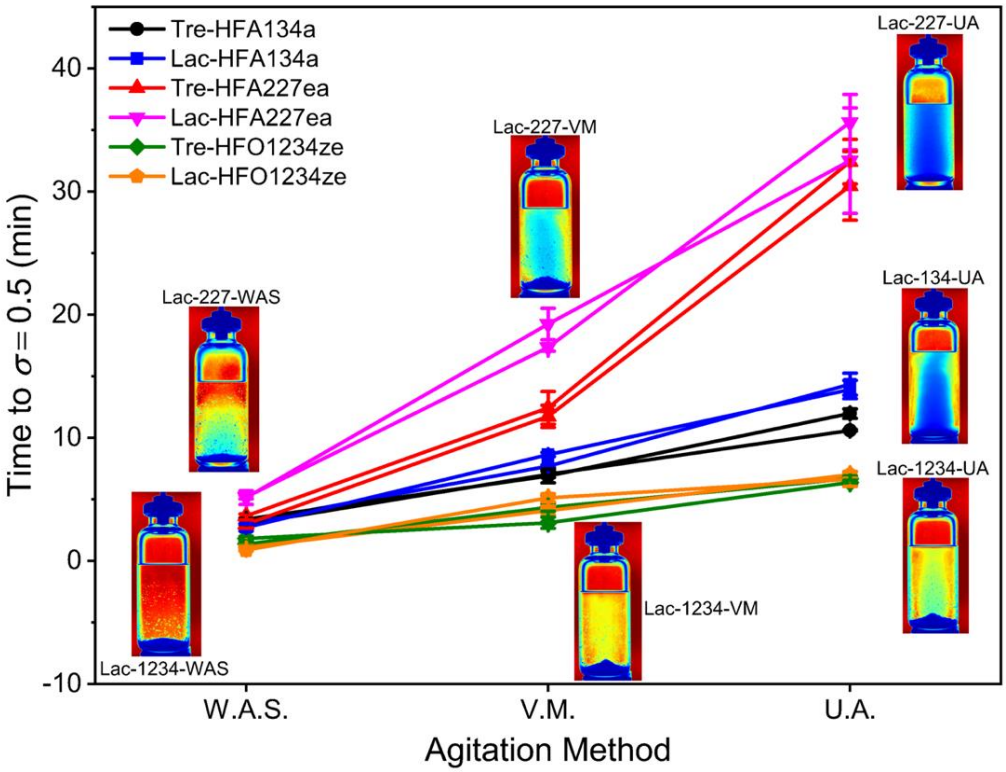

Figure 2. Time for the instability index to reach 0.5, $\tau(\sigma = 0.5)$, for different combinations of suspension formulation and applied agitation method. Inset shadowgraphic images show the state of the suspensions after 5-minute observation.

A clear dependence of suspension stability on the agitation method was observed when considering each suspension formulation. After wrist action shaking, all suspensions show similarly low stability, likely because aggregated particles were not fully dispersed

and thus settled at high velocities regardless of the propellant type. Increasing the agitation energy by vortex mixing and ultrasonic agitation led to improved suspension stability, especially for the suspensions in HFA227ea. For these, the time constants increased from 4 min ± 1 min after wrist action shaking to 33 min ± 6 min after ultrasonic agitation, indicating a significantly improved suspension stability. Because ultrasonic agitation is much more efficient than shaking in breaking up large agglomerates, the greater extent of de-agglomeration introduced by the ultrasonic agitation led to more stable suspensions. Less improvement of colloidal stability was observed for suspensions in HFA134a and HFO1234ze, perhaps because of the higher settling velocities for primary-sized particles in these propellants.

CONCLUSIONS

Three agitation methods delivering different dispersing energies were evaluated to study their effects on the colloidal stability of model pMDI suspensions. A clear dependence of suspension stability on the employed initial agitation method was observed. The same suspension can have significantly different colloidal stabilities when agitated differently. Colloidal stability testing of suspensions must be based on quantified initial agitation energy or at least consistent agitation method. Moreover, suspension stability analysis results must be presented together with a detailed description of the applied agitation method for any measurement of suspension stability to be fully meaningful.

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