Agitation Method Affects Colloidal Stability of Pharmaceutical Suspensions

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Introduction

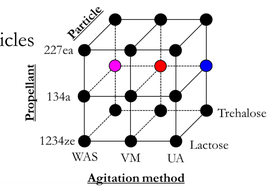
- pMDI suspension stability is crucial to ensure dosing uniformity [1] and product quality.
- Commercial instruments [2-3] have been applied to colloidal stability testing.
- Impact of initial agitation on the resultant suspension stability has been overlooked.
- Three different initial agitation methods, wrist action shaking, vortex mixing, and ultrasonic agitation, were tested using different suspension formulations and the results compared.

Materials and Methods

❖ **Materials:**

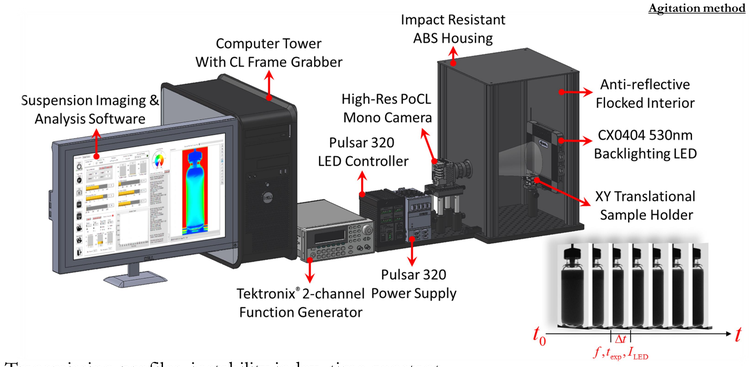
❑ Model particle: Monodisperse spray-dried trehalose and lactose particles

❑ Model propellant: HFA134a, HFA227ea, HFO1234ze



❖ **Methods:**

❑ Custom-designed suspension tester



❑ Transmission profiles, instability index, time constant

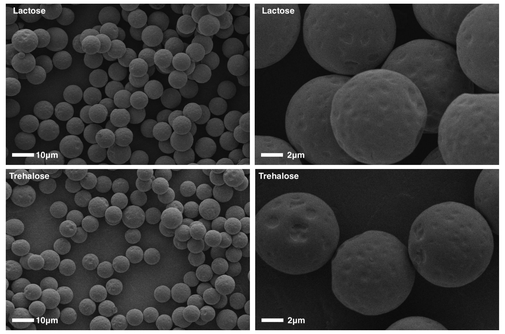
$$\Delta T_{t,h} = T^{a}_{t,h} - T^{a}_{t_0,h} \qquad \sigma(t) = \int_{h=0}^{h=1} \left|\Delta T^{N}_{t,h}\right| \quad (0 < \sigma < 1)$$

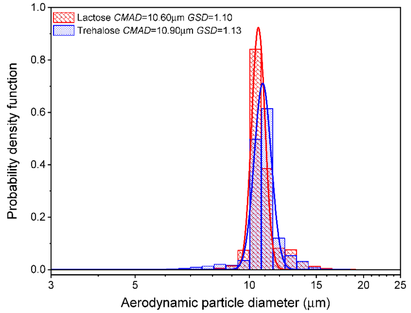
$$\Delta T^{N}_{t,h} = \frac{\Delta T_{t,h}}{\Delta T^{Max}_{t,h}} = \frac{\Delta T_{t,h}}{T^{a}_{Clear} - T^{a}_{t_0,h}} \qquad \tau(\sigma = 0.5)$$

❑ Agitation method

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

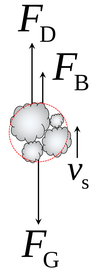
Results





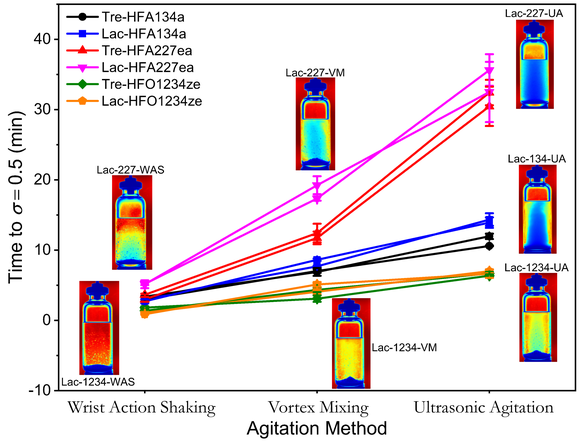
- Spherical, uniform, and solid saccharide particles as designed
- Similar particle size and both with narrow distribution

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



$$v_s = \frac{(\rho_P - \rho_L) d_{ve}^2 g}{18 \eta \chi}$$

- Model suspensions with different particle setting velocities → different suspension stabilities



- After W.A.S., all suspensions show **similarly low stability** – aggregated particles settle at high velocities regardless of the propellant
- V.M. and U.A. lead to **improved suspension stability**, especially for the suspensions in HFA227
- Suspension stability **highly depends on the initial agitation method**, especially when the primary particles have slow settling velocities

Conclusions

❖ A newly designed shadowgraphic imaging method

- ❑ High **spacial resolution** (2560 × 2048 pixel)
- ❑ High **temporal resolution** (> 1 fps)

❖ Suspension stability analysis

- ❑ Normalized relative transmission for understanding **destabilization processes** $\Delta T^{N}_{t,h}$
- ❑ Instability index $\sigma(t)$ and time constant τ for convenient cross-sample **stability comparison**

❖ Suspension stability highly depends on the employed initial agitation method

- ❑ Stability testing must be based on **quantified initial agitation energy/consistent agitation method**
- ❑ Meaningful suspension stability analysis results must be presented with a detailed description of the **applied agitation method**

References

[1] Ivey JW, Vehring R, Finlay WH: *Understanding pressurized metered dose inhaler performance.* Expert Opin Drug Deliv **2015**, 12: 901-916.

[2] Mengual O, Meunier G, Cayré I, Puech K, Snabre P: *TURBISCAN MA 2000: multiple light scattering measurement for concentrated emulsion and suspension instability analysis.* Talanta **1999**, 50: 445-456.

[3] Lerche D, Sobisch T: *Consolidation of concentrated dispersions of nano- and microparticles determined by analytical centrifugation.* Powder Technol **2007**, 174: 46-49.

Acknowledgements

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