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

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Introduction

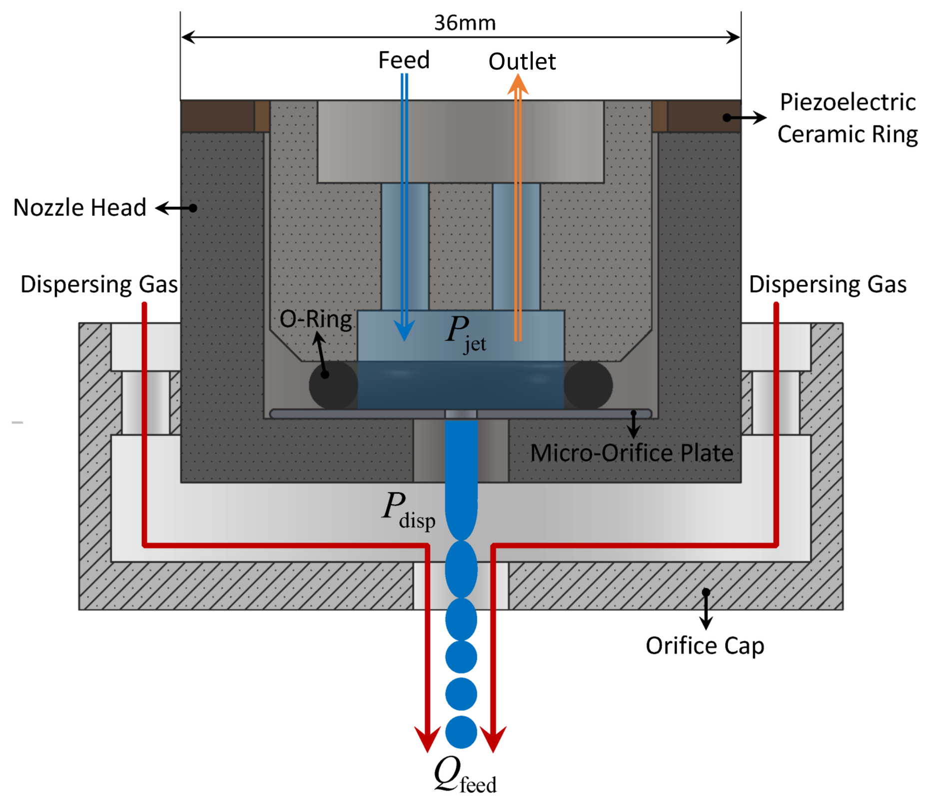
- Suspension-based pMDI are widely used for the treatment of airway diseases [1].
- Inherent instability of pressurized suspensions pose challenges to formulation development [2].
- Nano-suspensions [3], porous particles [4], and polymeric surfactants [5] to improve stability.
- Engineering particles with improved surface roughness is what we are proposing.

Materials and Methods

- **Materials:**
  - Model particle: Monodisperse spray-dried trehalose-trileucine particles
  - Model propellant: HFA227ea
- **Methods:**
  - Particle Engineering

$$Pe_i = \frac{\kappa}{8D_i} \qquad \tau_D = d_0^2/\kappa \qquad E_i = \frac{c_{s,i}}{c_{m,i}} \approx 1 + \frac{Pe_i}{5} + \frac{Pe_i^2}{100} - \frac{Pe_i^3}{4000} \quad (0 \le Pe_i \le 20) \qquad \frac{\tau_{c_{c,i}}}{\tau_D} = \left[1 - \left(\frac{c_{0,i} \cdot E_i}{c_{c,i}}\right)^{\frac{2}{3}}\right]$$

  - Monodisperse spray drying for model particle preparation

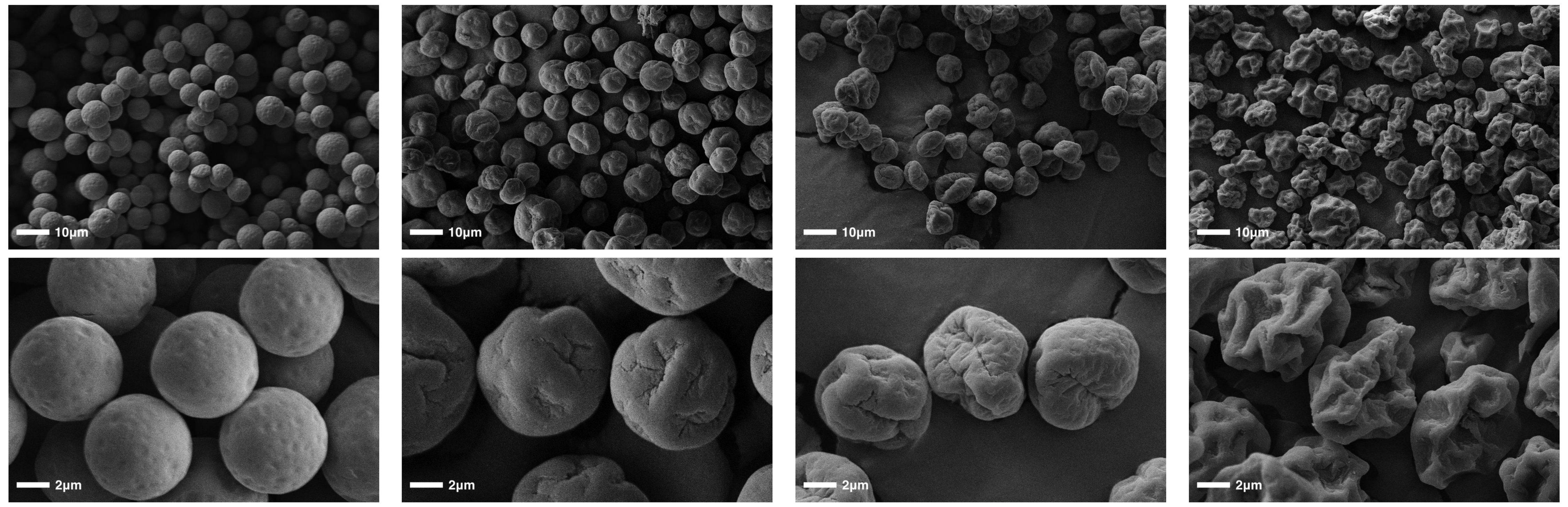


- Liquid solution pressurized through micro-orifice plate to form micro-jet
- Piezoelectric ceramic ring to force regular disintegration of liquid jet into monodisperse droplets
- Droplets dried in an environment with controlled temperature and humidity

  - Custom-designed shadowgraphic imaging technique for suspension stability characterization
    - Sequential images of pressurized suspensions contained in transparent glass vessels
    - Simultaneous sample illumination, high temporal and spatial resolution
    - Normalized relative transmission profiles for entire destabilization process recording
    - Instability index as a single parameter for direct cross-sample stability comparison

Results

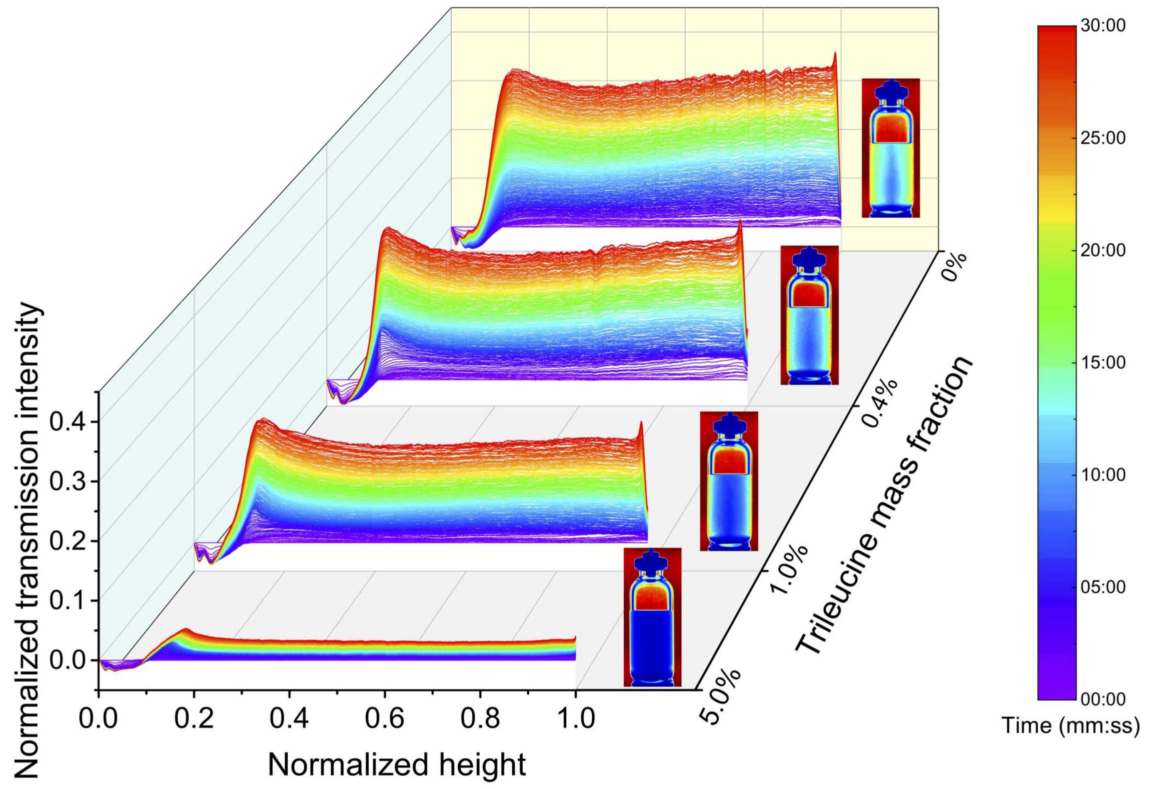
- **Characterization of spray-dried particles**

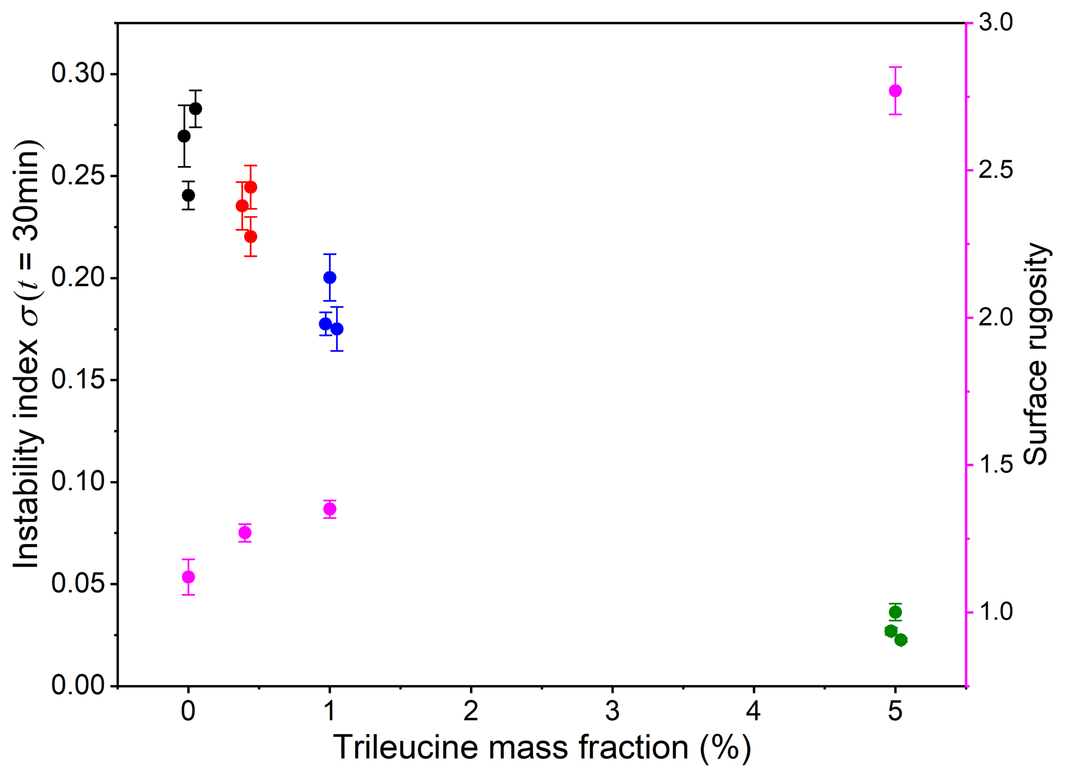


Monodisperse spray-dried trehalose-trileucine particles show good monodispersity and increased surface roughness with increased trileucine concentration from 0% to 5.0%.

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

- Similar particle size
- Good monodispersity
- Increasing rugosity
- Decreasing stability





- All samples show clarification and sedimentation
- Different destabilization processes observed for samples with 0%, 0.4%, and 1.0% Leu$_3$
- Stability of suspension with 5.0% Leu$_3$ significantly improved

- Low Leu$_3$ concentration at 0.4% and 1.0% already improved the suspension stability, and much more significantly at 5.0%
- The improving suspension stability agrees with trend of increasing particle surface rugosity

Conclusions

- Successful particle engineering of monodisperse trehalose-trileucine particle with controlled surface rugosity
  - Monodispersity avoids complication by polydispersity
  - Trileucine used as shell former/surface modifier
  - Higher trileucine concentration enable earlier shell formation, leading to higher surface roughness
- Improved suspension stability with increased particle surface roughness
  - More rugose particles → more stable suspensions
  - Shell formers, e.g., trileucine, can be formulated to stabilize suspensions
  - No surfactants needed
  - Promising approach in the transitioning to new pMDIs

References

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Acknowledgements

ALBERTA INNOVATES
NSERC CRSNG
UNIVERSITY OF ALBERTA
AstraZeneca