A New Shadowgraphic Imaging Method for the Suspension Stability Analysis of Pressurized Metered Dose Inhalers

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Introduction

Pharmaceutical suspensions contained in pressurized metered dose inhalers (pMDIs) are widely used for pulmonary drug delivery. However, solid drug suspensions are inherently unstable [1] and can destabilize mainly by two related mechanisms: particle migration and agglomeration. Particle migration by creaming or sedimentation can lead to inconsistencies between delivered drug doses throughout the use of the inhaler, while particle agglomeration can affect both the amount and the site of drug deposition in the airways [2]. No commercial instruments are fully suitable for the characterization of pressurized suspensions that destabilize on a timescale of minutes or faster. Hence, **a new shadowgraphic imaging method** dedicated to the stability analysis of such pharmaceutical suspensions was developed in this study.

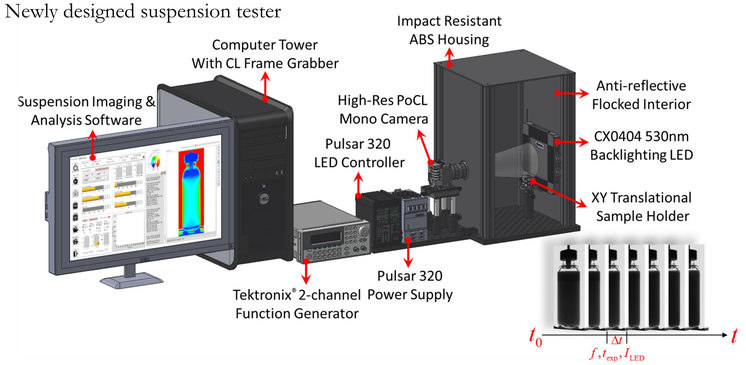
Materials and Methods

❖ **Materials:**

- ❑ Model particle: spray dried 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC).
- ❑ Sample vessel: round borosilicate glass vials with > 900 kPa pressure rating and crimpable top
- ❑ Suspension sample: 50 mg of spray dried DSPC power + 25 g HFA-134a propellant

❖ **Methods:**

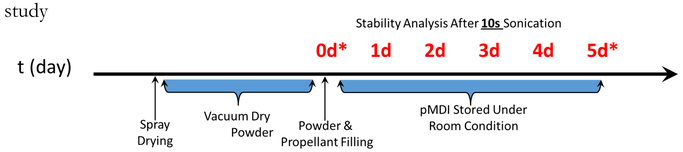
- ❑ Newly designed suspension tester



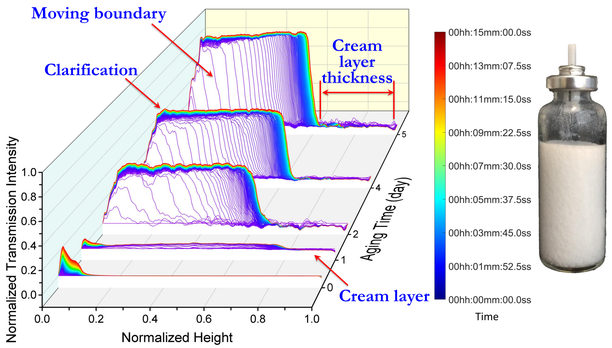
- ❑ Transmission profiles and instability index [3, 4]

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

- ❑ Aging study



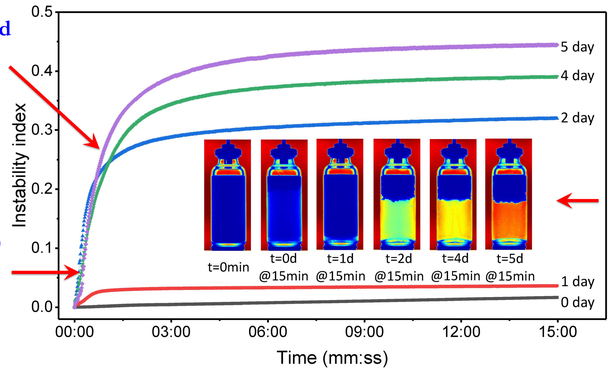
Results



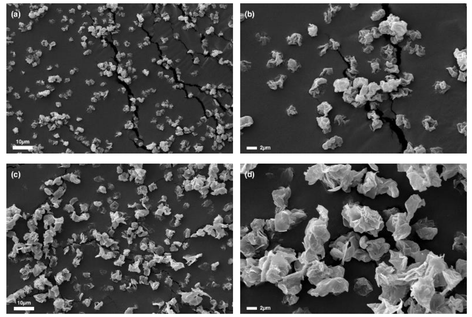
- Fresh suspension was relatively stable during the 15 min observation
- Clarification starts quickly from sample bottom after 2 days aging
- Final cream layer thickness increased gradually
- High spacial and temporal resolution record whole destabilization process

Different slopes stand for different rate of destabilization

High temporal resolution (> 1 fps) able to resolve fast destabilization processes



Final instability index (0<σ<1) corresponds to final suspension status

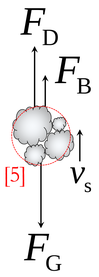


Fresh sample: separate particles with irregular and wrinkled surface morphology

Aged DSPC particles in propellant: layered structure and significantly increased particle size

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

Faster Settling Velocity [5]



Conclusions

❖ Wide range of temporal resolution (0.001 – 100 fps)

- ❑ High resolution up to 100 fps able to make fast stability measurements on unstable samples
- ❑ Low resolution suitable for monitoring stable samples for days

❖ High spatial resolution (2560×2048 pixel)

- ❑ Record of suspension sample with all local details
- ❑ Simultaneous sample illumination to measure whole sample at once without delay

❖ Suspension stability analysis

- ❑ Qualitative normalized relative transmission as unique fingerprints of each sample
- ❑ Quantitative instability index for cross-sample stability comparison to assist formulation optimization

❖ Pharmaceutical applications

- ❑ Stability analysis of samples with a wide range of stability
- ❑ Non-destructive stability monitoring of suspensions
- ❑ Applicable to stability analysis of emulsions

References

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