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

Hui Wang,[1] Penny Tan,[2] David Barona,[1] Grace Li,[2] Susan Hoe,[2] David Lechuga-Ballesteros,[2] David Nobes,[1] and Reinhard Vehring[1]

[1]Department of Mechanical Engineering, University of Alberta, Edmonton, Alberta, Canada

[2]Pearl Therapeutics Inc., Redwood City, California, USA

KEYWORDS: shadowgraphic imaging, pressurized metered dose inhaler (pMDI), suspension stability, instability index

INTRODUCTION

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

MATERIALS AND METHODS

The main components of the suspension tester are a 2D collimated backlighting LED (CX0404-0530C5, Advanced Illumination Inc., Rochester, VT, USA), a 12-bit high-resolution (2560×2048 pixel) monochrome CCD camera (SP-5000M-PMCL, JAI Inc., San Jose, CA, USA), and a function generator (AFG1022, Tektronix Inc., Beaverton, OR, USA) that produces synchronizing signals. Round borosilicate glass vials (Adams & Chittenden Scientific Glass, Berkeley, CA, USA) with > 900 kPa pressure rating and crimpable top are used as standard sample vessels. The instrument (Figure 1) acquires sequential shadowgraphic images of the sample under pre-defined experimental settings.

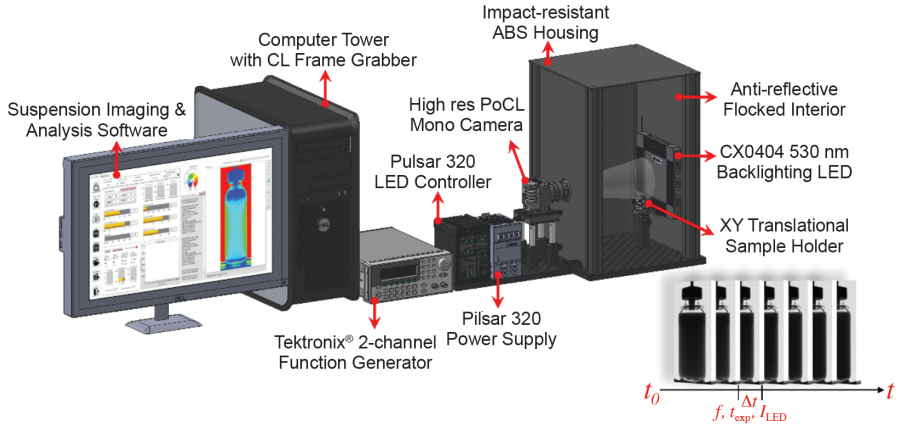

Figure 1. CAD model of the instrument for stability analysis of pressurized pharmaceutical suspensions.

From each of the shadowgraphic images, an absolute transmission profile, $T^{a}_{t,h}$, as a function of time, t, and position in the sample, h, can be obtained. The relative transmission, $\Delta T^{a}_{t,h}$, is then calculated by subtracting the initial transmission profile, $T^{a}_{t0,h}$, from all the subsequent profiles according to $\Delta T_{t,h} = T^{a}_{t,h} - T^{a}_{t0,h}$. The relative transmission is further normalized by its maximum value $\Delta T^{Max}_{t,h}$, which is the intensity difference between the transmission of a clear propellant T^{a}_{Clear} measured in a standard sample vessel and the initial transmission of the tested sample $T^{a}_{t0,h}$ according to:

$$\Delta T^{N}_{t,h} = \frac{\Delta T_{t,h}}{\Delta T^{Max}_{t,h}} = \frac{\Delta T_{t,h}}{T^{a}_{Clear} - T^{a}_{t_0,h}}. \qquad \textit{Equation 1}$$

By integrating the normalized relative transmission profile along the sample height, an instability index function

$$\sigma(t) = \int_{h=0}^{h=1} \left| \Delta T^{N}_{t,h} \right| \qquad \textit{Equation 2}$$

that quantifies the overall transmission change over time is obtained [3, 4]. The slope of the instability index plot represents the rate of destabilization. The instability index is a dimensionless number from 0 to 1 and can be used to compare and rank suspensions with different stability.

In preliminary experiments we noticed lipid particles exhibited stability changes when suspended in HFA propellant, so selected these as our test formulation. An ethanolic solution of 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC; Lipoid GMBH, Germany) at a concentration of 15 mg/mL was spray dried using a modified Büchi B-191 lab-scale spray drier (Büchi Labortechnik AG, Flawil, Switzerland) at a feed flow rate of 5.0 mL/min into a drying chamber with 50°C inlet temperature to produce phospholipid micro-particles. A pressurized DSPC suspension was then prepared by weighing 50 mg of the dried DSPC powder into a glass vial, crimping on an aluminum metering valve, and then pressure-filling 25 g of HFA-134a propellant. The pMDI was monitored in a five-day aging study under room conditions. The suspension was evaluated for physical stability immediately following 10 seconds of manually shaking that simulates the shaking motion of pMDI users.

RESULTS AND DISCUSSION

Transmission profiles of the suspension at different time points during the aging study are shown in Figure 2. The fresh suspension was initially very stable during the 15 minute observation with a thin clarification region detected at the bottom of the vial. The clarification level increased quickly as the aging study progressed. The bottom half of the suspension clarified to more than 50% of its maximum transmission intensity after two days aging. Cream layers formed at the top of the aged suspension and the thickness of the cream layer also increased gradually.

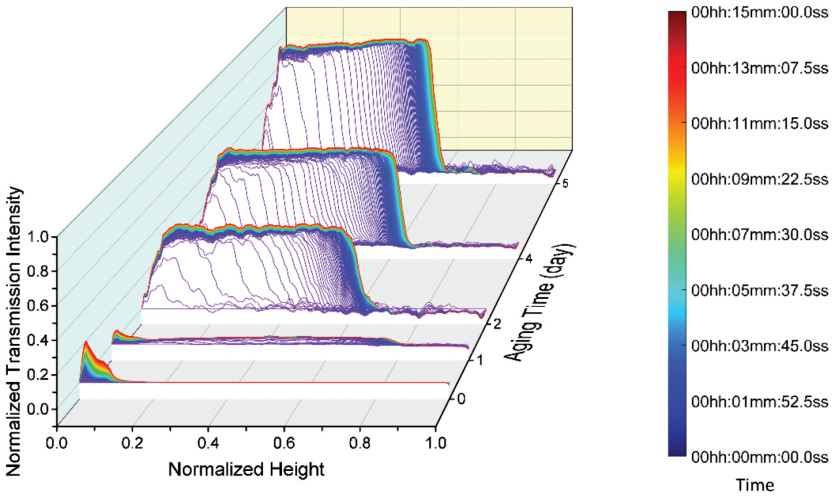

Figure 2. Destabilization processes of the pressurized DSPC suspensions changed significantly within the first five days after propellant filling as indicated by the normalized relative transmission profiles. Color bar to the right corresponds to the time of each stability measurement and has the units hour-minute-second.

Figure 3 shows the corresponding instability index plots for the different measurements presented in Figure 2. In combination with the inset shadowgraphic images acquired at the end of the measurement, it is clear that the suspension went through significant changes during the five-day aging period. The suspension was relatively stable within the first 24 hours with very slowly increasing instability index. However, its stability dropped suddenly after two days. The steep slopes of the index plots indicate that the destabilization process of the aged suspensions completed quickly within 1-2 minutes, which was easily resolved by the new suspension tester operating at 1.0 frames per second (fps). The whole creaming and clarification processes could not be observed by any other instrument we are aware of.

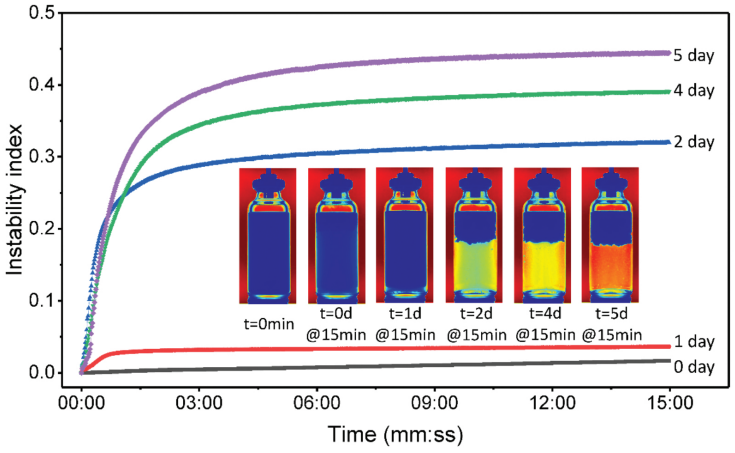

Figure 3. **Instability index plots for measurements at different time points indicate significantly reduced suspension stability over five days. Insets are the corresponding shadowgraphic images recorded at the end of the stability measurement period.**

Morphological analysis of the fresh and aged DSPC particles (Figure 4) shows rugose lipid particles with irregular shapes, and thin sheets of lipid, respectively. The aged particles are larger than the original particles. It is likely that DSPC molecules had a certain level of mobility in the propellant and re-oriented to form their favored layered structure. The much larger sizes lead to faster creaming velocities of the particles in the propellant and, therefore, cause a faster rate of destabilization [5].

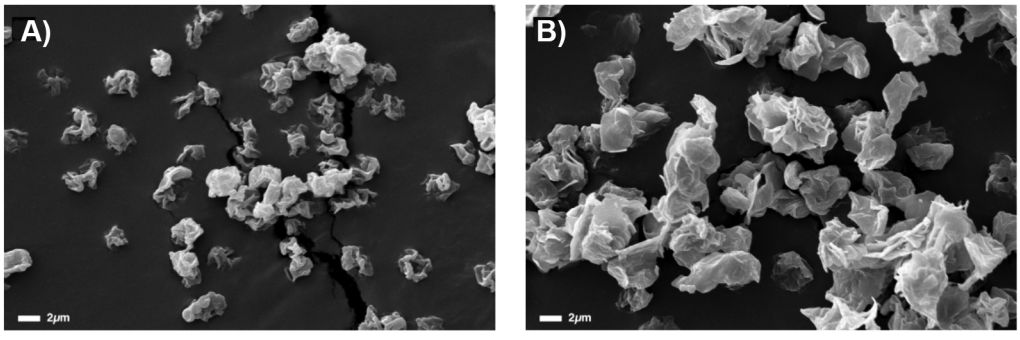

Figure 4. **SEM images of the A) fresh and B) aged DSPC particles show very different particle morphologies and increased sizes of aged particles.**

CONCLUSIONS

A new shadowgraphic imaging method developed for stability analysis of pressurized pharmaceutical suspensions is introduced. Pressurized suspensions that destabilize within minutes can now be measured with high temporal resolution (> 1 fps). The developed normalized relative transmission can be used to quantitatively describe the destabilization processes. The instability index provides a single parameter based on transmission changes, which is useful in comparing and rank-ordering the stabilities of multiple samples.

REFERENCES

1. Johnson KA: Interfacial phenomena and phase behavior in metered dose inhaler formulations. *Lung Biology in Health and Disease* 1996, 94: 385-415.

2. Wu L, Zhang J, Watanabe W: Physical and chemical stability of drug nanoparticles. *Adv Drug Deliv Rev* 2011, 63: 456-69.

3. Detloff T, Sobisch T, Lerche D: Instability index. *Dispersion Letters Technical* 2013, 4: 1-4.

4. Lesaint C, Glomm WR, Lundgaard LE, Sjöblom J: Dehydration efficiency of AC electrical fields on water-in-model-oil emulsions. *Colloids Surf Physicochem Eng Aspects* 2009, 352: 63-69.

5. Finlay WH: *The Mechanics of Inhaled Pharmaceutical Aerosols: An Introduction.* Academic Press; 2001.