Monodisperse Droplet Chain Technique to Support Development of Co-solvent Based Inhalation Products

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INTRODUCTION

Microparticles used in inhalation products can be designed in order to enhance properties such as dispersibility, dosage uniformity, and chemical or physical stability [1]. Large-scale empirical studies can be minimized by employing process models and numerical models to effectively design microparticles [1]. To this end, a monodisperse droplet chain in combination with a numerical model was developed to provide a small-scale testbed that could determine the effects of process parameters over a droplet's drying sequence and on the morphology of the final dried microparticles.

EXPERIMENTAL METHOD

The droplet chain method is based on droplets injected into a laminar drying gas flow field. As the droplets fall, the solution evaporates until only the solute remains in the

form of a dry microparticle. In order to capture the change in droplet diameter as a function of time, a series of monodisperse droplets are injected into the temperature controlled flow at a constant frequency to create a droplet chain. The dispensing device is a piezoceramic droplet dispenser (MicroFab Technologies, Plano, Texas, USA), controlled by driver electronics (MD-E-3000 Microdrop Technologies, Mühlenweg, Norderstedt, Germany). An imaging system with a high magnification lens (35-41-41-000, Excelitas, Fremont, California, USA), attached to a camera (GO-5000M-USB, JAI, Shanghai, China) monitors the droplets. Its acquisition rate is synced to the droplet dispensing frequency. This creates the appearance of a stable 'stationary' droplet chain. At each droplet position, the droplet is illuminated by a collimated light source (M530L3-C1, ThorLabs, Newton, New Jersey, USA) and the image of the droplet is analyzed to derive the volume equivalent diameter. This imaging system is placed on a linear motorized stage (MN10 – Precision Lead Screw, Velmex Inc, Bloomfield, New York, USA) oriented such that the imaging system can move along the length of the droplet chain to capture droplet diameter as a function of time. Thermocouples placed at the inlet and outlet of the flow tube and a hygrometer allow monitoring of the temperature and humidity of the drying gas, respectively. A schematic of this system is shown in Figure 1.

Evaporation experiments were conducted various ratios of ethanol-water mixtures, where only 3 ml of solution was required per experiment. Particle collection experiments were conducted for leucine dissolved in ethanol-water co-solvents. The mixtures were weighed out using a mass balance (ME204E, Mettler Toledo, Mississauga, Ontario, Canada) to determine the percent composition by mass. The captured images were

processed with a MATLAB code (Matlab R2016b, Natick, Massachusetts, USA) and calibrated with a standard image inserted into the flow tube.

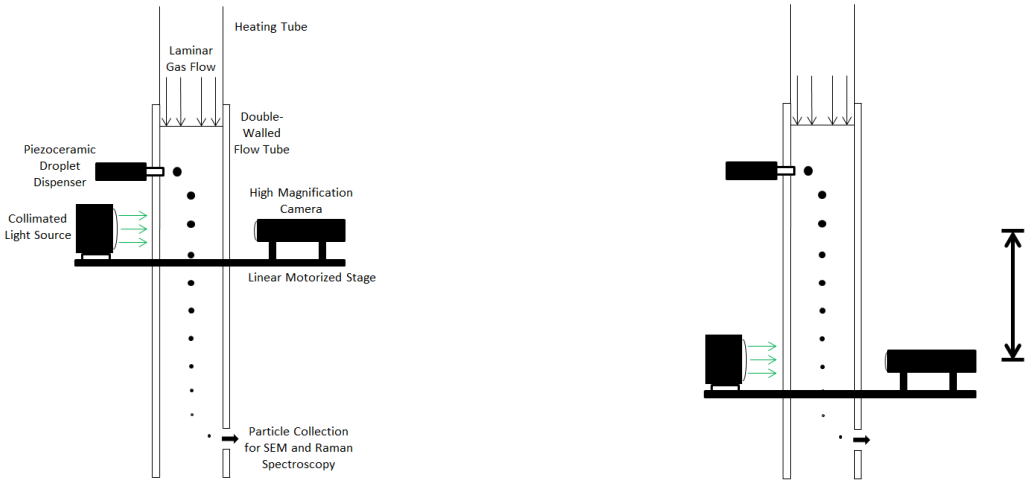


Figure 1. Schematic of the monodisperse droplet chain generator, which enables recording of the change in droplet diameter over time, as well as collection of dried microparticles for further analysis.

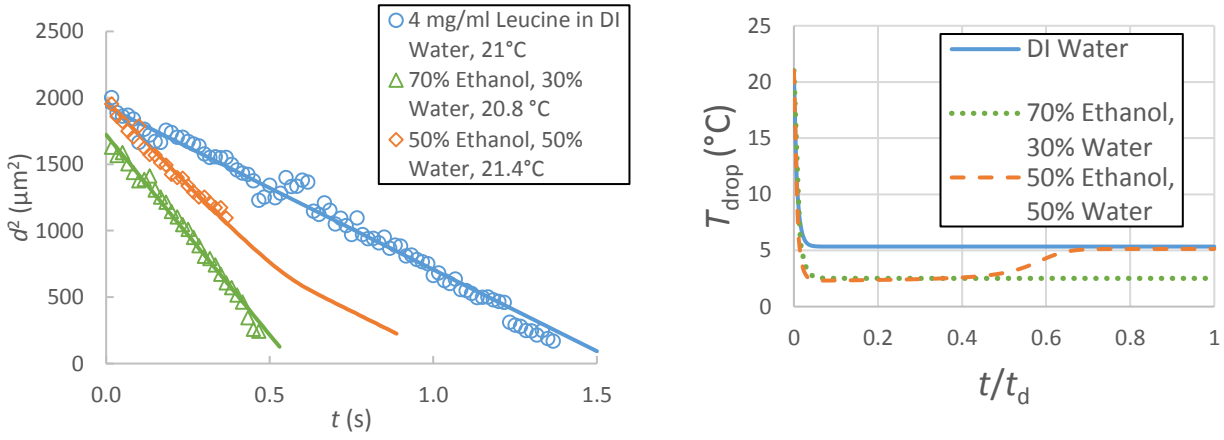
MODEL

A hybrid numerical/analytical model has been developed to calculate the evaporation rates of a co-solvent microdroplet. The model uses Maxwell's equation to describe diffusion controlled evaporation of a microdroplet [2]. The evaporation rates of each solvent are calculated separately and then added together to obtain the total evaporation rate of the co-solvent droplet. The effects of the latent heat of vaporization are also considered in calculating the instantaneous droplet temperature.

In using Maxwell's equation, spherical symmetry is assumed, and effects such as Stefan flow, thermal radiation and convective heat and mass transfer are neglected. These assumptions are reasonable as temperatures and settling velocities of the droplets are relatively low. Also, well-mixed or infinite diffusivity is assumed for the solvents inside the droplet. This means that their concentrations within the droplet are constant in the radial direction at each instance.

RESULTS AND DISCUSSION

The solvent evaporation rates were plotted in Figure 2(a) as the square of the diameter as a function of time, where the timestep (0.017 s) between consecutive droplets is the inverse of the droplet dispensing frequency [3]. The pure water evaporation experiment was conducted to verify the performance of the apparatus, as the evaporation rate of water is well-known [4]. The experimental results demonstrate that the evaporation rates of the co-solvent systems show excellent agreement with the numerical model's outputs. The fall in the droplets' temperature is shown in Figure 2(b). It is apparent from this figure that the 70% EtOH/30% water mixture shows azeotropic behavior (a state in which a mixture's composition cannot be altered by distillation) and no change is observed in the composition. This is not the case for the 50% EtOH/50% water mixture where a change in droplet composition is inferred.

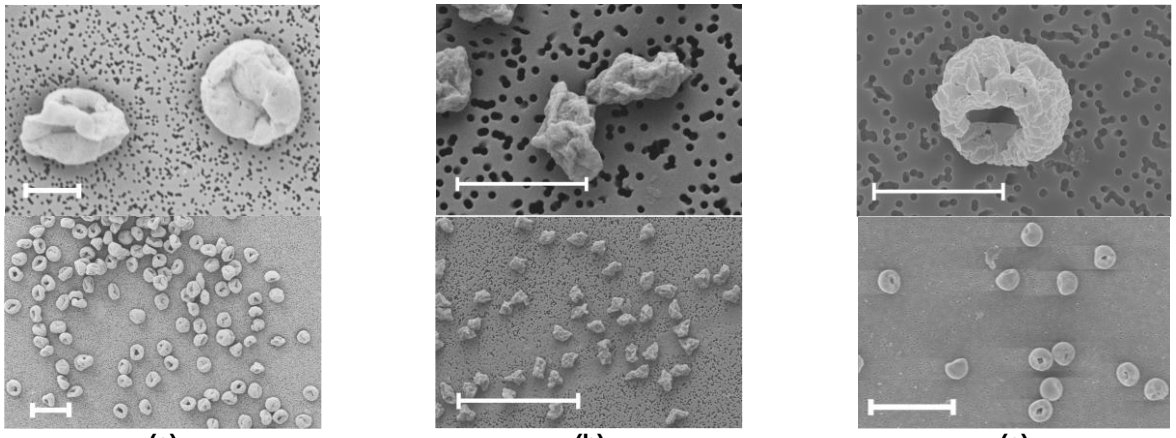


(a) (b)

Figure 2. (a) Selected results obtained with the monodisperse droplet chain generator, depicting droplet diameter squared vs. time. Symbols: measured data from processed images. Closed lines: theoretical model results. (b) Droplet temperature vs. time normalized with the drying time.

Figure 3 displays the morphology of leucine microparticles produced by the generator. It is apparent that the co-solvent ratio has a strong effect on particle morphology. With this apparatus it is possible to systematically study changes in particle morphology, because

the particles produced are monodisperse and nearly monomorph, as can be seen in the lower row of Figure 3.



(a) (b) (c)

Figure 3. Scanning electron microscope (SEM) images of particles produced from solutions with (a) 4 mg/mg leucine in water, (b) 0.21 mg/ml leucine in ethanol, (c) 4 mg/ml leucine in 50% water, 50% ethanol. Top row depicts morphology of particles, bottom row demonstrates that the particles are monodisperse with consistent morphology (Top row scale bar is 4 μm in length and bottom row scale bar is 20 μm in length).

CONCLUSIONS

A monodisperse droplet chain can be used to measure evaporation rates of co-solvent systems for a variety of drying gas parameters. This information is needed for numerical particle formation models which can assist in formulation and process development. Monodisperse microparticles can be collected and imaged with a scanning electron microscope (SEM) to determine morphology or be analyzed via Raman spectroscopy in order to determine the solid phase of the particles [5]. This approach uses minimal sample quantities suitable for scarce or expensive actives early in development.

These results in conjunction with a numerical evaporation model can be used to gain a mechanistic understanding of the relationship between process and formulation parameters and particle morphology and associated properties like adhesiveness and physical stability. This technique has the potential to lower risk and reduce cost in early development of inhalable pharmaceuticals.

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