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

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Introduction

Inhalable microparticles can be designed and engineered to enhance properties such as general morphology, dispersibility, dosage uniformity, and chemical or physical stability. Large-scale empirical studies can be minimized by employing process and numerical models to effectively design microparticles [1]. To this end, a monodisperse droplet chain in combination with a numerical model was developed to determine the effects of process parameters of **co-solvent systems** over a droplet's drying kinetics and on the morphology of the final dried microparticles.

Refer to the poster titled "*Interaction of Evaporating Multicomponent Microdroplets with Humid Environments*" for more information on the numerical model used in this study [2].

Droplet Chain

❖The Droplet Chain is a set of **monodisperse droplets** being injected into a laminar drying gas.

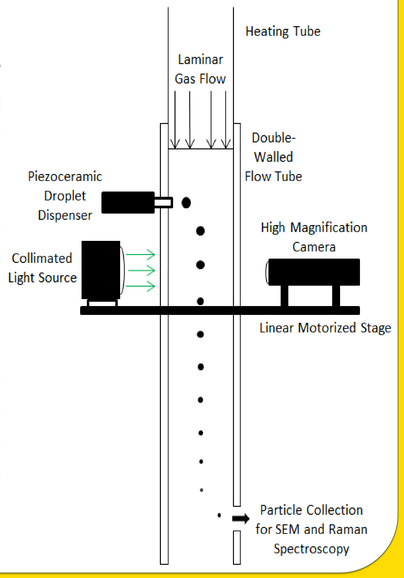
❖The drying behavior of the falling droplets was studied using a camera, a high magnification lens and a collimated light source.

❖Two thermocouples at the inlet and outlet of the flow tube and a hygrometer allowed monitoring of the temperature and humidity of the drying gas.

❖The **monodisperse dried particles** can be collected at the end of the flow tube on aluminum SEM stubs for further **microscopy** and **spectroscopy analysis**.

❖Experiments were conducted at various ratios of ethanol/water mixtures with leucine as the excipient, where only **3 ml of solution was required per experiment** with a production rate of about **50 µg/hr solid particles**.

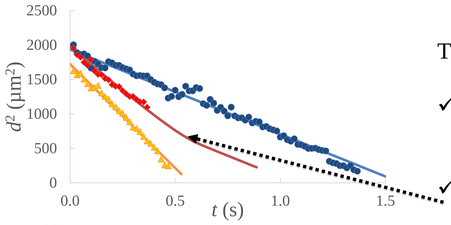
Advantages:
- ✓ Good for fast evaporation rates
- ✓ Can collect solid particles
- ✓ Minimal amount of sample needed

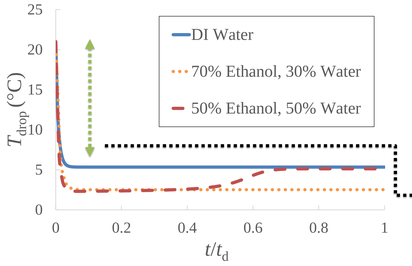


Results and Discussions

❖The drying kinetics of three different compositions of water/ethanol mixtures evaporating in dry air at 21 ˚C are shown here.

❖The droplet size histories for these cases are shown below. **The experimental data show great agreement with the results of the numerical model**.



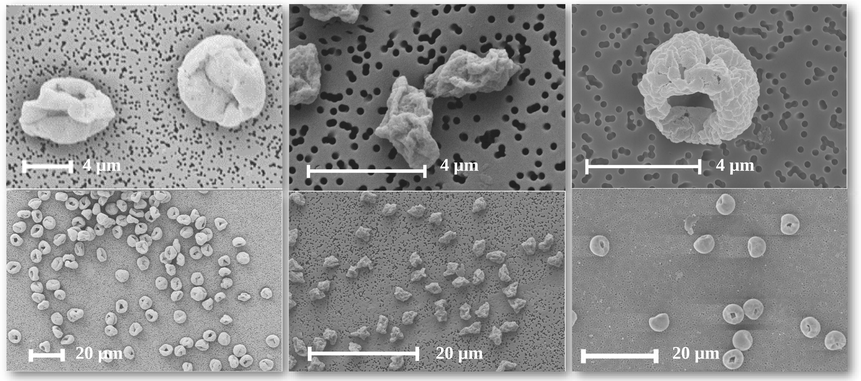


The following can be inferred from these figures:

- ✓ The evaporation rates increase by increasing the ethanol content.
- ✓ There is a change in evaporation rate during the drying for the 50% water:50% ethanol case.
- ✓ At 30% water:70% ethanol, azeotropic behavior is observed at room temperature and there is no sensible change in the evaporation rates.

Evaporative cooling

4 mg/ml leucine in water	0.21 mg/ml leucine in ethanol	4 mg/ml leucine in 50% water:50 ethanol by mass



SEM micrographs of monomorph and monodisperse particles produced using the Droplet Chain setup

❖ In all cases a hollow particle is formed, as expected for a pure leucine particle [3].

❖ The solvent composition clearly affects the final particle morphology as observed for the leucine particles in pure water and a mixture of water and ethanol. Due to the lower saturation values of leucine in ethanol, a more corrugated surface is observed in the water/ethanol mixture as compared to the pure water case.

Conclusions

❖ A **monodisperse droplet chain** can be used to measure evaporation rates of co-solvent systems for a variety of drying gas parameters to **assist formulation** and **process development** of inhalable pharmaceutical particles.

❖ **Monodisperse microparticles** with the **same morphology** can be collected for microscopy and spectroscopy analysis.

❖ This approach uses **minimal sample quantities** suitable for assaying formulations with expensive actives early in development.

❖ This technique combined with the *in silico* model has the potential to **lower risk** and **reduce costs** in early development of inhalable pharmaceuticals.

References

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