Pharmaceutical Particle Engineering Achieves Highly Dispersible Powders for Pulmonary Drug Delivery

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ABSTRACT

We studied the formation process of spray-dried particles and used the findings to design highly dispersible dry powder formulations for pulmonary drug delivery.

A novel experimental method allows the direct measurement of droplet evaporation rates and observation of particle morphologies as a function of processing conditions. The experimental results are compared to a numerical model and are interpreted in the context of the Peclet number.

Control of particle density and morphology was achieved using a proprietary excipient that produces particles with superior aerosol properties.

OBJECTIVE

- Particle engineering for pulmonary drug delivery

INTRODUCTION

Particles are the fundamental building blocks of solid dosage form medications. Spray-drying efficiently produces powder in the size range that can be dispersed into a respirable aerosol with an optimal mass median aerodynamic diameter for pulmonary drug delivery. Proper design and adequate control during particle manufacture are essential for product consistency and stability.

Dispersibility is a key parameter because it determines the level of energy the inhalation device must provide to disperse the powder, and affects dose delivery efficiency and variability. Since dispersibility is governed by particle size, density, morphology, surface roughness, and surface energy, it is desirable to understand how to control these properties. This paper presents an approach to successful particle design and optimization of processing conditions, based on a detailed investigation of the particle formation processes.

METHODOLGY

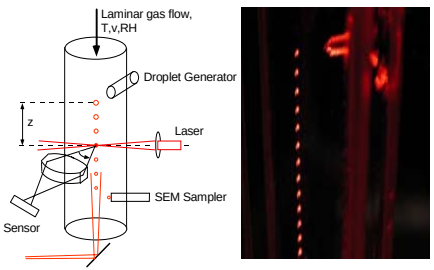
Experimental

Monodisperse droplets are produced by a droplet-on-demand generator and injected into a laminar gas flow of controlled temperature, velocity, and relative humidity. Initial droplet diameters are between 10 and 30 µm.

The droplets move along a highly repeatable trajectory and can be sized at different distances, z, from the point of injection. The distance a droplet travels as a function of time is measured using stroboscopic illumination.

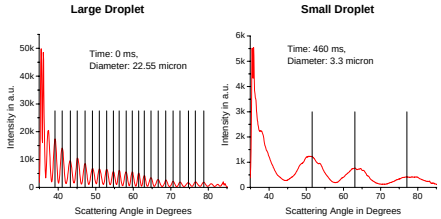
The size of the droplets, the time-scale of the process, and the gas phase conditions are representative of typical spray-drying conditions. Droplets are spaced far enough apart to avoid droplet – droplet interactions

Figure 1. Production of Representative Model Droplets in a Controlled Gas Phase



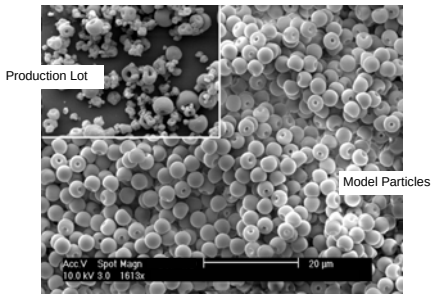
The droplet diameter is determined by measuring the average peak separation in the phase function of the elastical light scattering. The correlation between peak separation and droplet size was established with a numerical light-scattering model using Mie theory.

Figure 2. Droplet Sizing Using a Laser Light-Scattering Method



Dry particles are sampled onto membrane filters suitable for SEM analysis The experimental technique produces monodisperse particles with consistent morphology. The high level of control and repeatability allows systematic studies of particle formation.

Figure 3. Model Particles with Representative Morphologies



Particle Formation

The particle formation process can be described using the diffusion equation for the normalized radial coordinate, $R=r/r_s$, [1]

$$\frac{\partial c}{\partial t} = \frac{D}{r_s^2}\left(\frac{\partial^2 c}{\partial R^2} + \frac{2\partial c}{R\partial R}\right) + \frac{R\partial c \partial r_s}{r_s \partial R \partial t}$$

D is the diffusion coefficient of a component with the concentration c in the droplet. r_s is the droplet radius. This equation assumes no internal convection in the droplet. It also does not account for radial or temporal changes of the diffusion coefficient. The diffusion equation has an analytical solution for a constant evaporation rate, κ:

$$d^2(t) = d_0^2 - \kappa \cdot t \,.$$

This model does not account for the instationary evaporation at the beginning and end of the evaporation process, where the droplet temperature differs from the wet bulb temperature of the pure solvent. A solution to the diffusion equation is

$$c = c_m \frac{\exp\left(-0.5\mathrm{Pe}R^2\right)}{3\int_0^1 R^2 \exp\left(-0.5\mathrm{Pe}R^2\right)dR}$$

where the concentration is expressed as a function of the average concentration in the droplet, c_m. Pe is the Peclet number.

$$\mathrm{Pe} = -\frac{r_s \partial r_s}{D\partial t} = \frac{\kappa}{8D}$$

Because of the limitations of the analytical solution, a full numerical model was developed to describe the evaporation process. Details of this model are given in poster 3PA3.

Aerosol performance of the powders shown in Figure 7 was characterized using a Nektar Pulmonary Delivery System (PDS) or a Nektar Dry Powder Inhaler (DPI) for powder dispersion and an Andersen Cascade Impactor (ACI) under controlled ambient conditions (21°C and 40% RH). The dry powders were obtained by spray drying an aqueous solution both with and without trileucine in a Büchi 190 spray dryer.

SEM was used to monitor particle morphology. Powder surface composition was determined by X-ray Photoelectron Spectroscopy (XPS).

RESULTS

Figure 4. Evaporation Process for a Glycoprotein with a Peclet Number of 10

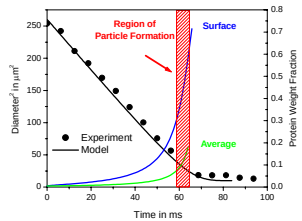


Figure 5. Increasing the Peclet Number Reduces the Particle Density

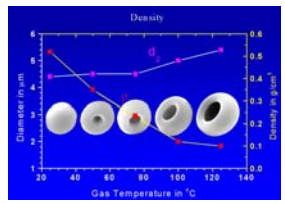
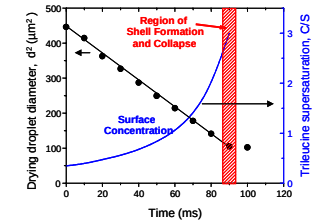
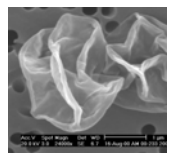


Figure 6. Further Reduction of Particle Density with Trileucine as Shell Former





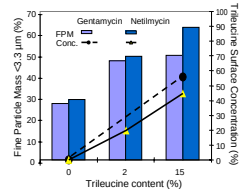
Early shell formation leads to low density particles:
ρ = 0.05 g/cm³

Particles with low density and high rugosity provide good dispersibility. The numerical model in combination with the experimental results allow a prediction of the amount of shell former which is necessary to provide the desired morphology and density.

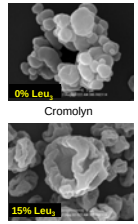
Figure 7. Application Examples: Particle Engineering Achieves Highly Dispersible Dry Powders for Pulmonary Drug Delivery

Example A: Antibiotics

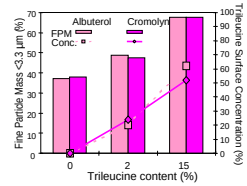
Netilmicin Sulfate



Example B: Asthma Therapeutics

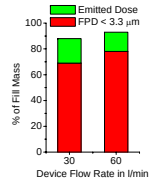


Cromolyn



Example C: Protein

Hemoglobin – Trileucine in a passive DPI



CONCLUSIONS

- The particle formation process for spray-dried microparticles has been investigated numerically and experimentally.
- Particle morphologies are a function of the Peclet number.
- The results were used to predict formulation compositions which lead to desirable particle density and morphology.
- Powder dispersibility was significantly improved for low density particles using trileucine as shell former.
- Highly efficient lung delivery can be achieved using dispersible powders in active and passive dry powder inhalers.

REFERENCES

1. Leong, K. H., *J. Aerosol Sci* **18**, 511, (1987)

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