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PHARMACEUTICAL PARTICLE ENGINEERING ACHIEVES HIGHLY DISPERSIBLE POWDERS FOR PULMONARY DRUG DELIVERY. *REINHARD VEHRING, Willard R. Foss, David Lechuga-Ballesteros, Mei-Chang Kuo*

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 is essential for product consistency and stability of these powders, reducing development risks associated with poor product performance. This paper presents an approach to successful particle design and optimization of processing conditions, based on a detailed investigation of the particle formation processes.

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 and distribution, particle density, morphology, surface roughness, and surface energy, it is desirable to understand how to control these properties.

To study these properties, a novel experimental method is used that allows the direct measurement of evaporation rates of individual monodisperse droplets traveling in a heated, laminar gas flow, and observation of their morphologies in the dry state. Droplets are produced by a droplet-on-demand generator, injected into a gas environment that is representative of spray drying conditions, and their sizes are measured using laser light scattering at several points during the evaporation process. Dry particles are collected on a filter and analyzed by Scanning Electron Microscopy.

Experimental results on drying of different solutes of a glycoprotein with high molecular weight are presented and interpreted to explain the particle formation mechanism in the context of the Peclet number, which is the ratio of the diffusion coefficient of the protein and the evaporation rate. It is demonstrated that control of the Peclet number can be used to affect dispersibility by changing particle density. It is further shown that trileucine, a peptide with low solubility, can be used to encapsulate proteins or peptides to achieve superior aerosol performance, by modifying surface energy, rugosity, and particle density.

Application of the experimental findings to formulation and particle design of antibiotics (e.g. netilmicin sulfate), asthma therapeutics (e.g. albuterol), and proteins (e.g. hemoglobin) demonstrate that the fine particle dose with an aerodynamic diameter less than 3.3 μm can be improved from 25-35 % for formulations without dispersibility enhancer to more than 65-80 % with appropriately designed trileucine particles. The emitted dose from different inhalation devices improved from 20-50 % to more than 80–90 %.