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PRESERVING PROTEINS AND PEPTIDES DURING SPRAY DRYING OF INHALABLE PHARMACEUTICAL POWDERS.

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Powders for the pulmonary delivery of protein and peptide pharmaceutical substances are produced in a spray drying process. The proteins and peptides in these dry powder formulations are immobilized in an amorphous glassy state, extending their resistance to degradation from typically a few hours in solution to several years in the dry form. Droplet evaporation and spray drying literature has suggested that the presence of a solute in an evaporating droplet reduces the evaporation rate and increases the droplet temperature, with a possible detrimental effect on the pharmaceutically active ingredient. This paper studies the evaporation behavior of spray-dried, micron-sized droplets, with particular attention to the later stages of drying, where the solids content is high and the droplet temperature approaches that of the surrounding hot gas.

Studies on the evaporation behavior of solution droplets have mostly been restricted to conditions that are atypical of the spray-drying of powders intended for pulmonary delivery. Initial droplet sizes were large and so the resultant dry particle sizes were orders of magnitude larger than respirable particles. Temperatures were typically measured by suspending droplets on a thermocouple junction, significantly altering the heat transfer characteristics.

To investigate the thermal conditions inside evaporating solution droplets in the micron size range, a numerical model was developed that calculates the evaporation behavior for single solution droplets. Concentration profiles of multiple solutes inside the droplet were calculated, where accurate descriptions of changing material properties were included to account for changing solute concentrations. Calculations were performed through particle solidification, with special attention to the later stages of drying. The particle temperature and solute concentrations were examined at all stages of the drying process to assess the thermal and mobility environment to which the proteins are exposed.

The numerical results were verified using a novel experimental technique that allows for direct measurement of the droplet evaporation rates of individual solution droplets traveling in a heated, laminar gas flow. The model results compare well to the measured evaporation rates for both pure and solution droplet droplets subjected to gas temperatures from 25 to 150 °C, verifying the droplet temperature calculations. Interpolating the experimental results with the model through the rapid solidification stage demonstrates that the droplet temperatures do not deviate significantly from the wet bulb temperature until the very late stages of drying, where the solute concentration is sufficiently high to immobilize and protect the pharmaceutically active ingredient from degradation.

The results are in agreement with observations made on various spray-dried powder formulations of peptides and proteins. The impact of the spray drying process on the purity was found to be minimal, and successful stabilization of the active pharmaceutical ingredients was achieved.