

## Summary

Microdroplet evaporation, in particular for microdroplets of insulin-polysorbate-water systems, is of interest to Novo Nordisk for analysis and design of systems forming inhalable insulin products. Microdroplet evaporation is also of interest in the broader context of forming micron scale powders by spray drying of insulin solutions using a variety of processes. The objectives of this project were to present a review of the relevant literature, show results of experiments to establish the phase equilibrium curve for insulin-water (surfactant) systems of interest, and then to derive and numerically solve a model for this process. The main deliverables are a computer program which can be used to evaluate the effect of various parameters on evaporation rates and droplet size.

Following a brief literature review, experiments were performed to determine the existence and nature of phase transitions in Novo Nordisk U1500 insulin solution as a function of temperature, *i.e.* to determine the phase diagram of the insulin-water-surfactant system of interest. Based on the results, a model has been formulated and numerically solved for the microdroplet system dynamics.

The model has only two free parameters for which rough estimates can be made based on phase field theory, *viz.* the maximum super saturation of insulin that can occur before solid phase nucleation commences, and the time constant with which the supersaturated solution relaxes towards equilibrium. An option has also been incorporated that allows specification of the number of drops present per unit volume of air which allows a “stand alone” estimate of droplet evaporation rates in devices where the quantity can be estimated, and where the air and the droplet may be assumed to move together. These parameters are varied in this work to determine their effects. For the purposes of determining the effects of the relaxation time and overshoot, ambient air temperature and water vapor concentration are kept constant, equivalent to assuming a relatively small number of drops per unit volume of air, as might occur during falling drop experiments. As expected, the ultimate size of the particle is smaller, the longer the relaxation time for solid formation. The maximum super saturation value is found to have no significant effect on the drop shrinkage rate. Typically for constant air temperatures of 373 K and zero humidity, a value of time constant  $\sim O(10^{-3})$  gave 50% reduction in diameter for a 5  $\mu\text{m}$  drop by the time a solid crust started formed at the surface in 6 ms. This means that if a few drops/ml of  $\sim 5 \mu\text{m}$  diameter fall in dry 373 K air, then the smallest drop size would be  $\sim 2.5 \mu\text{m}$ , when a solid crust would have formed.

If the number of drops per unit volume is large and the conditions in the air are now calculated for pockets of air moving with the drops, then the temperature of the surrounding air is reduced and the humidity increases with time. This both limits the drop surface temperature and reduces the rate of evaporation. The rates now depend on the number density of drops and the initial conditions in the air. For  $5 \cdot 10^5$  drops/ml which can be considered typical in some devices, 5  $\mu\text{m}$  drops take  $\sim 12$  ms to reduce to 50% of their original diameter.

While the results are indicative of what might be expected, the model needs to be calibrated against experiments. This can be done by falling drop experiments with relatively few drops/ml so the external conditions are approximately constant.