

Effect of Surface Energy Evolution on Particle Nucleation under GASP Conditions

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We address here the problem of particle nucleation and growth under so-called: Gas-Anti-Solvent-Precipitation (GASP) conditions. This complex environment is of considerable interest in many current technologies. In the pharmaceutical industry, which motivated the present work, GASP is used to produce the controlled precipitation of an Active Pharmaceutical Ingredient (API) from an organic solvent often sprayed into compressed CO₂. Of vital importance is the ability to predict and control the size distribution of the nucleated particles, with the usual goal of producing narrow distributions of ultrafine particles to facilitate rapid dissolution when administered. Our theoretical model is illustrated using the system: phenanthrene [as API-surrogate] precipitated from liquid toluene using CO₂ as anti-solvent at ca. 60 bar and 298K). Our preliminary results demonstrate the need to account for the time evolution of not only the supersaturation (as was already known) but also the surface energy of the particle/fluid interface (usually not considered).

In our well-mixed single droplet theoretical model we consider the time evolution of particle nucleation- and condensation-growth-rates, fully coupled to the evolving environmental conditions associated with CO₂ uptake and solution volume change. Particle nucleation rates are conveniently approximated using Classical Nucleation Theory (CNT), and single particle growth rates are based on a kinetic model including Gibbs-Kelvin(-Ostwald) curvature corrections for recently born particles. However, the numerical method used to solve the Population Balance Equation governing the particle number density distribution function (NDDF) is not restricted to any particular choice of rate laws for nucleation or growth, nor does it presume or restrict the mathematical form of the NDDF. Our model identifies the dependence of the characteristic particle size and nucleation/growth time scales of the problem as a function of the control parameters in the isobaric/isothermal GASP environment (mainly pressure level and initial API under-saturation). Besides revealing the relevant dimensionless numbers that govern the performance of such systems, we demonstrate the importance of *surface energy evolution* (SEE) in determining the critical nucleation size, and the associated nucleation rate, in this variable composition “carrier fluid”. Our model also reveals the effects of SEE on the finally observed particle NDDF. In this regard, we find that a non-monotonic time evolution of the critical nucleation size can give rise to multi-modal size distribution functions, without the need to involve physical processes other than particle nucleation. Our

results also show that, for the system under consideration (phenanthrene precipitated from a micron size toluene solution using CO₂ as anti-solvent) typical particle growth times are orders of magnitude longer than the corresponding characteristic nucleation times. Hence, in this case post-nucleation particle growth introduces only a small correction, and the finally observed precipitated particle NDDF basically betrays the integrated time history of the critical nucleus size convoluted with $\ln(\text{supersaturation})$. As a corollary, controlling the time evolution of the critical nucleus size (via both effective surface energy and supersaturation) enables NDDF-control, which in some cases can even yield (normally undesirable) multimodal API particle populations.

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