394a Control of Polymorph Crystallization Via Quasi-Emulsions

Xing Wang and Donald J. Kirwan

Identifying all possible solid forms of an Active Pharmaceutical Ingredient (API) is important for intellectual property protection. Further, consistent manufacturing and sale of only the approved solid form of the API is required by FDA regulations. It often happens in the pharmaceutical process development that one polymorphic form of crystals is produced in small scale development experiments; but after scaling-up the process, another form is generated. This situation has been related to effects of solvents, processing time and temperatures, and possibly to mixing conditions. The quasi-emulsion phenomenon (well-dispersed droplets of a viscous solute containing a crystallizable solute in a non-viscous anti-solvent) described previously [2004 AIChE Annual meeting, Austin, TX] as occurring under certain mixing conditions can play a role in polymorph formation. During quasi-emulsion precipitation (QEP) it is observed that crystal nucleation and growth are slowed as compared to a homogeneously-mixed solution. Control of polymorph formation can then be accomplished by use of selected mixing modes and solutions/solvents that favor or prevent quasi-emulsion conditions. In brief, we hypothesize that crystallization from a quasi-emulsion, where diffusion becomes important, will slow nucleation and growth rates and thermodynamically favor the formation of the stable polymorphic form. On the other hand, rapid mixing to homogeneity with high supersaturation will kinetically favor the formation of a metastable form in accordance with Ostwald's Rule of Stages. Quasi-emulsions in which the solvent and anti-solvent show different polarities may also affect polymorph formation through polar/non-polar interactions that affect hydrogen-bond formation which influences molecular packing in crystals.

With 60% (mass) polyethylene glycol 300 (PEG300)–40% H2O as the solvent and water as the anti-solvent, the control of polymorph formation in three model pharmaceutical compounds (methylparaben, p-aminobenzoic acid and sulfanilamide) has been demonstrated. The crystallization of the polymorphs of glycine with 80%PEG300 as anti-solvent and water as solvent is also discussed. These results experimentally supported the predictions from the QEP theory. Therefore, the quasi-emulsion model can be used to direct the development of industrial crystallization processes involving polymorphism. During the development of a process, mixing conditions can be selected to favor quasi-emulsion formation to try to ensure that the stable polymorph is formed and identified. Similarly, rapid mixing without quasi-emulsion formation will help to produce and identify metastable forms that might be produced in the process. It is also important to insure that mixing conditions (as they often do) do not change upon process scale-up as this could result in another polymorphic form being produced.