

311b Using Complex Crystallizer Configurations in a Batch System to Affect Crystal Size and Morphology

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Crystallization outcomes were determined from two different types of crystallizer configurations: (1) a batch system that was cooled at four different rates and (2) a system in which a cooled, laminar-flow tubular unit preceded a batch vessel that was held at the same low temperature as the jacket of the laminar-flow unit. The latter configuration is referred to here as a laminar-flow tubular crystallizer (LFTC) because supersaturation was generated in the tubular unit preceding the batch-operated vessel. The crystalline systems studied were paracetamol (acetaminophen) and D-mannitol.

In addition to comparisons between the two crystallizer configurations, variations with specific process variables within each crystallizer type were also investigated. For example, the mean sizes of crystals produced in batch crystallizations were examined with respect to cooling rate and other process variables. Measurements of metastable limits demonstrated that as cooling rates increased, the metastable zone widths of the two solutes increased and nucleation rates increased, leading to reductions in mean crystal size.

The total time required to relieve all of the generated supersaturation (i.e., produce a fixed mass of crystals) was significantly less with the LFTC than with the batch unit. Additionally, paracetamol was produced as two different polymorphs in the LFTC, Forms I and II. The production of the different forms apparently resulted from the rapid rate at which supersaturation was generated in the LFTC, although the evidence suggests that solvent-mediated transformation of the less stable polymorph, Form II, to the more stable Form I took place in the batch vessel as it approached equilibrium.

There are two possible advantages of the LFTC, in addition to the production of smaller crystals. First, because rapid cooling in the tubular unit leads in some cases to high nucleation rates, there is much greater crystal surface area on which mass can be deposited, thereby shortening the operating time required to go from initial to final conditions. Clearly the higher heat-transfer coefficients associated with forced convection contribute to this advantage. Of course, if large crystals are essential in the product specifications, the advantage of reduced operated time is overwhelmed by the disadvantage of producing smaller crystals. Second, the data on paracetamol clearly show that it is possible to produce an unstable polymorph because of the exceedingly high rate at which supersaturation is generated. The possibility of extending such behavior to other systems must be evaluated on a case-by-case basis.