In-situ seeding in batch precipitation and crystallization

Peter H Karpinski  
Novartis Pharmaceuticals Corp., USA

A significant part of high added value materials are produced by batch precipitation or crystallization. The properties of such materials are largely determined by the way the batch process was conducted. Therefore, in order to obtain crystalline material of desired properties consistently, the entire precipitation/crystallization process must be carefully controlled. In the mid 1990’s, this author introduced the concept of in-situ seeding that simplifies the design and control of batch precipitation/crystallization and gives the results comparable with the conventional seeding approach. In this paper, the in situ seeding model is reviewed and illustrated with a case study for photosensitive imaging materials. Other model applications, its ramifications, useful hints, and proposed uses by taking the advantage of the current on-line crystal size distribution (CSD) monitoring capabilities, are discussed. The concept in question acknowledges that in many practical applications – e.g. the reactive precipitation of sparingly soluble materials or cooling crystallization of materials with a narrow metastable zone – nucleation is very difficult to control due to its near-catastrophic rate. Slightly different process conditions and/or a few seconds different duration of nucleation – frequently unavoidable in large-scale operations – may result in very different nuclei population that inevitably leads to the different final product. According to the model, instead of trying to control ‘impossible’ (rapid nucleation), the nucleation step is separated from the consecutive growth step by a hold step (i.e., no reagent addition or constant temperature segment), after which the outcome of the nucleation and hold steps is evaluated. During this hold segment, due to the Ostwald ripening, the nuclei population is evolving and establishes itself as a quasi-stable set of ‘effective nuclei’. The effective nuclei population is appraised in a dedicated series of nucleation-ripening experiments or – preferably – on line. The crystal size distribution of the effective nuclei, treated in the same way as the CSD of external seeds, is then utilized to adjust or redesign the course of the profile of the supersaturation-generating property rate, Q, (e.g. reagent addition rate, cooling rate) in time, t: Q=f (attributes of effective nuclei, CSD, G, t), where G is the growth rate, for the control of the successive growth step. The approach proposed eliminates external seeding and yet removes or significantly reduces the batch-to-batch variability.