394g Direct Design of Batch Recipes and Concentration Control in Antisolvent Crystallization

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Increasing emphasis is being placed on designing and operating pharmaceutical crystallizers so as to produce a robust and consistent crystal product [1]. In batch crystallization in industry, usually the recipe is designed to follow a temperature and/or antisolvent addition profile. Rigorous determination of an optimal batch recipe requires accurate growth and nucleation kinetics, which can be determined in a series of continuous or batch experiments [2-4]. For agglomerating and other complex crystallization systems, it can be difficult to determine kinetics that are accurate enough to compute an optimal batch recipe. These complications have resulted in the common industrial practice of trial-and-error experimentation to design batch recipes for pharmaceutical crystallization. An alternative approach that does not require accurate kinetics or trial-and-error experimentation is to control the crystallizer so that it follows a supersaturation profile in the metastable zone [5-8]. The advantage of this approach is its lower sensitivities to most practical disturbances and to variations in the nucleation and growth kinetics, and that this method does not require the derivation of first-principles models and the associated determination of crystallization kinetics [9].

This paper describes applications of a concentration control system to follow a setpoint supersaturation profile in the metastable zone for batch antisolvent crystallization. This is an expansion of past studies in cooling crystallization, in which an automated system [5,8,10] was implemented that determined the metastable limit and the solubility curve using the Lasentec FBRM [11-13] and ATR-FTIR spectroscopy [5-8,13] coupled with chemometrics [14-16]. In the concentration feedback control system, the supersaturation is calculated from the in-process solution concentration measurement (using ATR-FTIR spectroscopy coupled with chemometrics) and a previously measured saturation concentration, which is obtained using an automated system [5,8,10]. The crystallizer follows the setpoint supersaturation profile by adjusting the antisolvent addition rate based on the concentration measurement. The batch recipe is implemented so that the antisolvent addition rate is an algebraic function of the supersaturation defined by the setpoint profile, and so is very easy to implement and requires no control tuning.

Both simulations and experiments demonstrate the robust performance obtained by the proposed concentration-control method for the design and implementation of batch recipes for antisolvent crystallization. The implementation in Visual Basic was designed so that the metastable zone determination and batch recipe design can operate in an automated manner, while providing a graphical user interface so that experts can choose to make adjustments based on their level of expertise.

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