**Modelling Antisolvent Impact on Active Pharmaceutical Ingredient Batch Crystallization**

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**Highlights**

* Batch crystallization of fesoterodine fumarate active pharmaceutical ingredient
* Mathematical model of the process was developed, optimized and validated
* Larger, but more agglomerated particles are formed by increasing antisolvent amount
* Solubility decreases and crystallization kinetic rates increase with antisolvent amount

**1. Introduction**

Crystallization of active pharmaceutical ingredients (API) is one of the most important separation and purification operations in pharmaceutical industry. However, it is also one of the most complex ones, due to various thermodynamic, transport, and kinetic phenomena taking place in a heterogeneous system [1-2]. Fesoterodine fumarate is an API used to treat overactive bladder. High temperature-dependent solubility, high secondary nucleation rate, and slow crystal growth rate have been acknowledged for fesoterodine fumarate crystallization from 2-butanone in our previous work [3]. The present work examines the impact of antisolvent cyclohexane on the various properties of cooling batch crystallization of fesoterodine fumarate in 2-butanone.

**2. Methods**

The experimental part of the work was performed in a 2 L batch reactor. It consisted of in-line attenuated-total reflectance Fourier-transform infrared spectroscopy (ATR-FTIR) calibration of fesoterodine fumarate solutions in two different solvent compositions (2-butanone with 5 wt. % cyclohexane and 2-butanone with 10 wt. % cyclohexane). Equilibrium solubility between -10 and 40 °C in both compositions was determined by ATR-FTIR. A specified number of cooling crystallization and dissolution experiments in both solvent mixtures under various operating conditions were performed for estimation of kinetic parameters of crystallization and dissolution, as well as model validation. Experiments were monitored by ATR-FTIR and final products were analyzed by microscopic, thermal, and X-ray techniques.

In-house mechanistic mathematical model of the crystallization process based on population balance equation methodology was developed. Equilibrium solubility, mass and energy transfer resistances, and kinetic equations for nucleation, crystal growth, crystal dissolution, and crystal agglomeration were incorporated into the model. Values of unknown kinetic parameters were estimated via nonlinear regression of simulated and experimental quantitative results.

**3. Results and discussion**

Increase in the amount of antisolvent in the mixture from 0 to 10 wt. % resulted in decrease in fesoterodine fumarate solubility in the studied temperature range (Figure 1). This stems from the fact that fesoterodine fumarate is a polar solute, while cyclohexane is a very nonpolar solvent. Due to similar physical properties of 2-butanone and cyclohexane, no major difference in convective solid-liquid mass transfer coefficient, average turbulent energy dissipation rate, and overall heat transfer coefficient were calculated for different solvent mixtures. Kinetic rates of secondary nucleation, crystal growth, crystal dissolution, and crystal agglomeration all increased. Mass transport limitations on crystal growth and crystal dissolution kinetics were shown to be negligible under the used operating conditions. This indicates that the amount of antisolvent influences these two processes due to different rates of various mechanisms on crystal surface, such as integration of molecules into the crystal lattice. Overall, the increased rate of crystal agglomeration has a prevailing effect on final particle size distribution and particle morphology, which may be important for further pharmaceutical operations.



**Figure 1.** Solubility curves of fesoterodine fumarate in 2-butanone, 2-butanone with 5 wt. % cyclohexane, and 2-butanone with 10 wt. % cyclohexane, represented by sixth degree polynomials.

**4. Conclusions**

The impact of antisolvent cyclohexane on fesoterodine fumarate batch crystallization in 2-butanone was evaluated by combined experimental-modelling approach. Major influence on thermodynamic and kinetic properties of the system was observed and taken into account for model simulations. The present work thus shows a comprehensive mechanistic approach to take into account various possible ways how solvent composition may impact a crystallization process. It also presents further possibilities for model-based process optimization and intensification by tuning the amount of antisolvent and values of other operating variables.

**References**

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