COMPARISON OF THE USE OF DIFFERENT SOLUBILITY MODELS FOR THE COOLING CRYSTALLIZATION OF ACETAMINOPHEN

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Abstract

In this paper we evaluate the sensitivity of using different solubility models on the cooling crystallization of acetaminophen. Empirical, correlative thermodynamic (namely NRTL) and predictive thermodynamic (namely MOSCED) models are considered. Equilibrium solubility model prediction determines the predicted supersaturation profile. The different solubility equations are used within a population balance model for prediction of crystal size properties. Incorrect prediction of the supersaturation profile results in incorrect prediction of crystal size distribution. The NRTL model was found to be more accurate at predicting equilibrium solubility and consequently crystal size. After the solubility sensitivity is evaluated, two methods are proposed to make the crystallization model more robust against solubility model errors.

Introduction

Crystallization is a traditional and widely used industrial process for the production of particulates. These particulates may include agrochemicals, biological proteins, fine chemicals, and pharmaceuticals. A key advantage of utilizing crystallization as a separation process is its role in the production of high purity products, important for specialized industries. Making the crystallization process more relevant is the FDA's strict regulations on the required purity for biological proteins and pharmaceuticals.

The thermodynamic driving force for crystallization is the difference in the chemical potential between the solute and the solution. Since chemical potential is difficult to quantify, solution supersaturation, a more readily measurable quantity, is used conveniently as an approximation. The trajectory the supersaturation follows affects the final crystal's size, crystal size distribution (CSD), habit (shape), and purity. Not only can the crystal's size and habit affect the particle product's performance, as in the case of the biological availability/activity of pharmaceuticals, but the production of inadequately sized particles can cake the filter downstream causing operational problems.

Traditionally, industrial crystallizers were run either on a trial and error basis, or by utilizing 'thumb rules". These methods commonly produced suboptimal recipes which resulted in failed batches and economic losses. In addition, these methods often proved to be less reliable when used during scale up. There has recently been increased interest in the development of crystallization models to predict operating conditions that produce crystals with desirable characteristics (Nowee et al., 2007). The use of a crystallization models allows the development of optimal recipes without the use of excessive laboratory time or resources. In addition, the crystallizer model in combination with the recent availability of robust *in situ* crystallization equipment can be implemented into a model based control scheme in order to keep the crystallizer operating on the correct trajectory.

In this work, the cooling crystallization of acetaminophen in ethanol is investigated. Acetaminophen also known as paracetamol, is the active ingredient in a commonly used painkiller, Tylenol®. Acetaminophen is advantageous to use because not only is it inexpensive, it also has been studied heavily in the literature. The temperature dependent solubility of acetaminophen in ethanol was investigated by Romero et al. (1996), Fernandez (1999), Granberg and Rasmuson (1999), and Worlitschek and Mazzotti (2004). Its thermodynamic properties were studied by Hojjati and Rohani (2006). Although the cooling crystallization of acetaminophen was previously studied by several groups including Hendrickson and Grant (1998) and Fujiwara et al. (2002), very few works such as that by Worlitschek and Mazzotti (2004) looked into simulating the crystal size distribution (CSD), or used a thermodynamically-based solubility model. However, the latter workers did not evaluate the effect of different solubility models on the CSD prediction, leaving the open question as to which of these available solubility models is most appropriate This paper compares the use of empirical, thermodynamical, and generalized thermodynamic solubility models to evaluate how these affect the resultant supersaturation profile and CSD, and then details how to make the crystallization model more robust against solubility model error.

Supersaturation and Solubility

As stated previously, the driving force for crystallization is the difference in chemical potential between the solid and liquid phases. Supersaturation is usually used instead of chemical potential because it is easier to measure. Supersaturation can be defined as either a relative or an absolute quantity, where the former is represented by the ratio of the solvent concentration to the equilibrium concentration, and the latter represented by the difference between the solution concentration and the equilibrium concentration. Supersaturation can be generated by one of three primary methods, namely evaporation, cooling, and antisolvent addition. In evaporative crystallization, the solution is heated which causes the solvent to evaporate. This loss of solvent from the solution makes the solution more concentrated which simultaneously causes the generation of supersaturation. Cooling crystallization is reliant on the fact that most solutes experience a decrease in solubility as temperature drops. Finally, in antisolvent crystallization, supersaturaion is generated by the addition of a carefully chosen antisolvent that reduces the solubility of the solute in the original solvent. This antisolvent may either be a liquid, gas, or a supercritical fluid. Two or more of these mentioned techniques can be combined in the same operation enabling enhanced results.For instance, adding antisolvent to a cooling crystallization operation provides that operation with an extra degree of freedom, where a calculated antisolvent addition can work as a seeding mechanism. .

A good solubility model accurately predicts how the equilibrium concentration of the solute changes over the course of the crystallization batch. This accurate solubility prediction is required for a crystallization model to in turn become accurate in predicting crystal product properties like size. Solubility models can be based on either empirical or thermodynamic foundations. An empirical solubility model is an equation fitted to experimental solubility data, and typically has no underlying physical meaning, while on the other hand, a thermodynamic solubility model both fits the data and has physical meaning. Common types of thermodynamic models include those based on excess Gibbs energy such as Wilson, NRTL, or UNIQUAC. In addition, generalized thermodynamic models such as the MOSCED (Modified Separation of Cohesive Energy Density) model can also be used. The MOSCED model is a thermodynamic model used to calculate infinite dilution activity coefficients. The advantage of the MOSCED model is that no experimental data is needed to calculate the infinite dilution activity coefficients. The MOSCED model further calculates temperature dependent infinite dilution activity coefficients, such that a temperature-dependent activity coefficient model is not required. The MOSCED model was originally developed for binary liquid solutions, but was later extended to liquid-solid systems by Drauker et al. (2007). The MOSCED model carries 5 fitting parameters: λ, α, β, q, and τ (Lazzaroni et al., 2005). In this work, values for individual MOSCED parameters for acetaminophen and ethanol are adopted from

Lazzaroni et al. (2005). Once the two infinite dilution activity coefficients are known, they can be substituted into an excess Gibbs energy model to find the binary interaction parameters for that system. With the MOSCED model, no experimental data is needed to calculate these binary interaction parameters. In order to calculate an equilibrium solute concentration, the activity coefficient equation is solved simultaneously with a solid solubility equation to calculate both the mole fraction and the activity coefficient of the solute. We present full details of these solubility models and their implementation in the crystallization model in a separate paper (Widenski et al., 2008).

Comparison of Solubility Models

Several different solubility models were used for the purpose of evaluating the effect of these models on the predicted final crystal properties. The first on the list is an empirical correlation solubility model developed by Fernandez (1999) for acetaminophen in ethanol. We next evaluate excess Gibbs energy models, in activity coefficient form. These activity coefficient models considered are the Van Laar, Wilson, and NRTL. All three have binary interaction parameters while the NRTL model has a third parameter, α, the nonrandomness parameter. The last solubility model considered is the generalized MOSCED model combined with the Wilson activity coefficient model. The computer package gPROMS (Process Systems Enterprise Ltd, London) with its parameter estimation facility gEST was used to estimate the optimal values of the binary interaction parameters for each activity coefficient model.

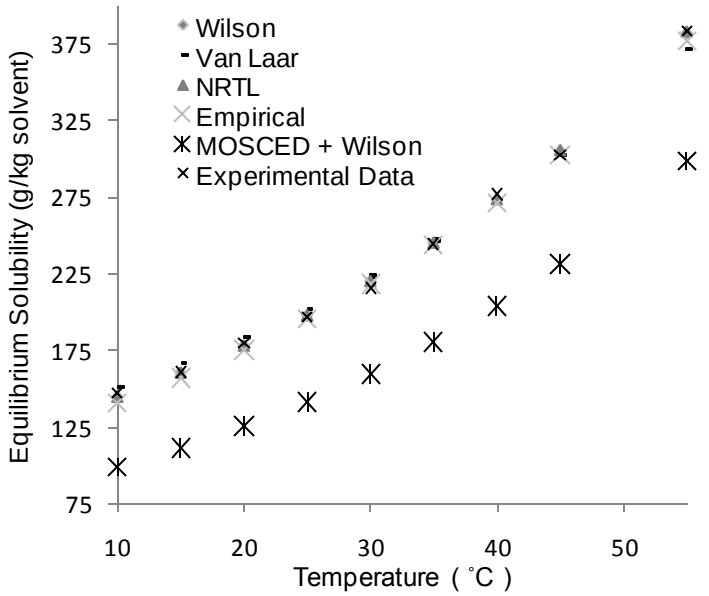

Figure 1. Equilibrium solubility curves for the different solubility models compared to experimental data from Worlitschek and Mazzotti (2004).

With the newly calculated binary interaction parameters, the prediction of the different models can now be compared. This is done graphically in Figure 1 against literature experimental data. The empirical model and each of the activity coefficient models all appear to provide good fits to the experimental data while the MOSCED model systematically underestimates the solubility over the entire temperature range of interest. The reason for the poor fit of the MOSCED model is because it is a generalized model. The tabulated MOSCED parameters are averaged over a wide variety of solvents in order to make the model as applicable to as many systems as possible. In the case where experimental solubility data is not available, the MOSCED model gives a first estimate to the solubility. However, if experimental data is available, it is preferable to fit binary interaction parameters of an activity coefficient model to get a more accurate solubility prediction.

Population Balance & Crystallization Kinetics

Since crystallization is a particulate process, a population balance is used to account for the number of crystals during the batch. The population balance for a constant volume batch crystallizer with no agglomeration or attrition, and where crystal growth follows McCabe's Law is written as:

$$\frac{dn(L,t)}{dt} + G\frac{dn}{dL} - B = 0 \qquad (1)$$

Where *G* is the growth rate, *B* is the nucleation rate, *L* is the length, and *n(L,t)* is the crystal distribution. The population balance is solved numerically in gPROMS using a backward finite difference discretization method.

Secondary nucleation is the dominant nucleation mechanism when supersaturation levels are less than the primary nucleation metastable limit., Secondary nucleation is caused by the presence of suspended particles in solution through several different mechanisms. It can occur due to the solvent washing away weakly held surface crystals (fluid shear), from severe crystal collisions (attrition), or due to weak collisions with crystallizer equipment or other crystals (contact nucleation). Crystal growth occurs when the solution's relative supersaturation is greater than one. Countering growth, dissolution occurs when the solution's relative supersaturation is less than one. Depending on the nature of the system, growth can either be diffusion or surface reaction controlled, while dissolution is normally diffusion controlled. Worlitschek and Mazzotti (2004) modeled acetaminophen crystal growth as being surface reaction limited with an Arrhenius function, and dissolution was modeled as a diffusion limited process. In this work, we use the constitutive equations for nucleation and growth presented in Worlitschek & Mazzotti (2004).

Simulation Results

The crystallization kinetics developed by Worlitschek and Mazzotti (2004) only consider secondary nucleation, and not primary nucleation. This implies that each crystallization batch must be seeded with crystals for either crystal growth or nucleation to occur. From their CSD data, the seed was approximated to being normally distributed with a mean size of 190 microns and standard deviation of 30. The amount of seed they use is not reported. It is important to have the correct amount of seed to use in the simulation because both the initial nucleation rate and the solute mass balance depend on the second moment of the seed. It was found that if insufficient seed was used, the supersaturation profile peaked too high, and if an excessive amount of seed was used the supersaturation rose too slowly. An optimum seed amount was found to be 1.15 x 10^{11} μm^2, providing the supersaturation data fit of Figure 2.

Of the solubility models tested, the NRTL model was chosen because it was the most accurate activity coefficient model, and should give the best representation of experimental data. The empirical and MOSCED models were also chosen to depict how the magnitude of error in the solubility model affects the final CSD. These three models are compared under the linear cooling profile used by Worlitschek and Mazzotti (2004). This linear cooling profile decreases linearly from 30 ˚C to 10 ˚C over 10 hours and is then held constant at 10 ˚C for 4 hours.

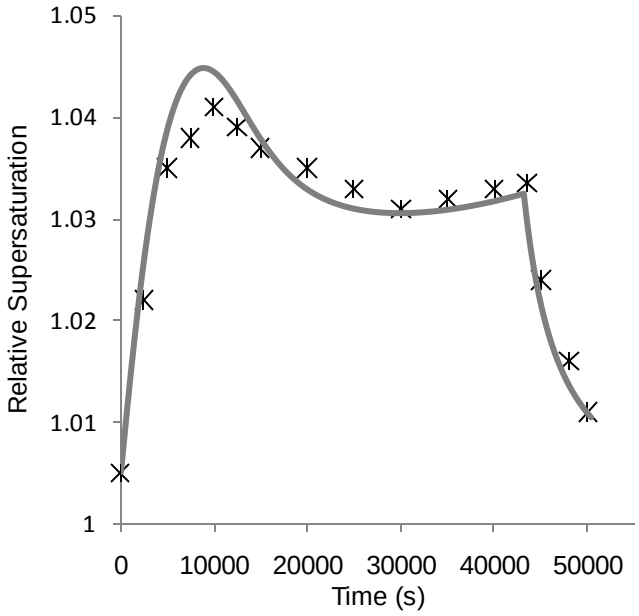

Figure 2. Relative supersaturation for linear cooling where the simulated profile using the NRTL model is plotted with experimental data from Worlitschek & Mazzotti (2004).

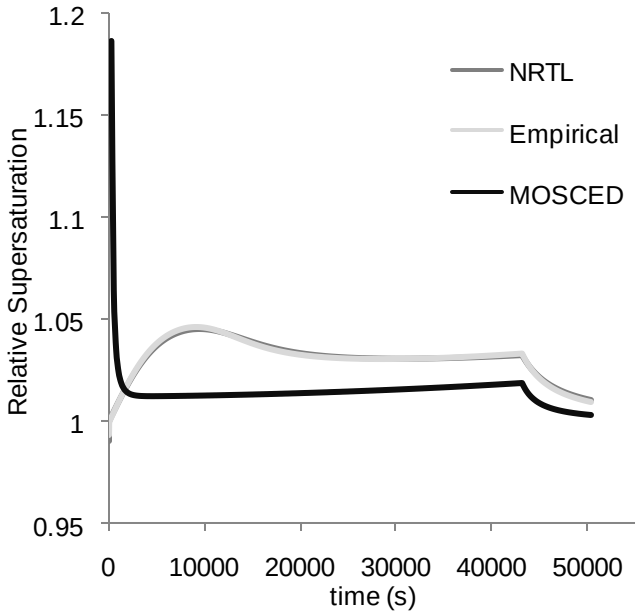

Figure 3. Relative supersaturation.

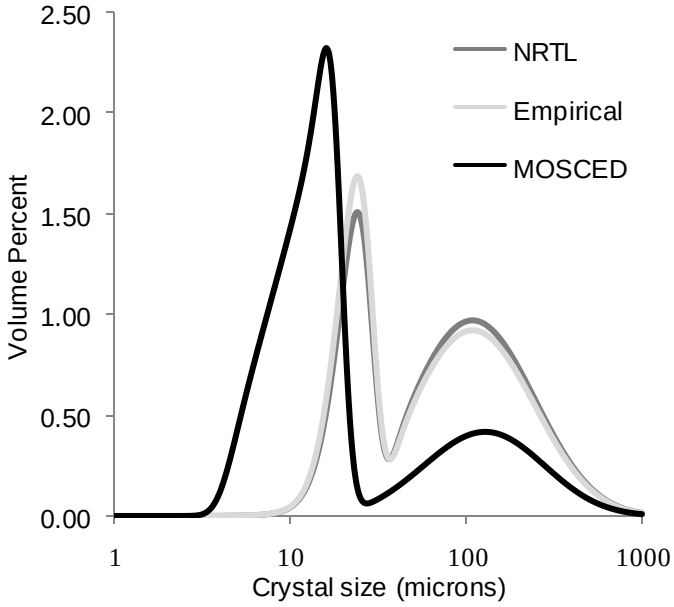

Figure 4. Volume percent CSD.

For the linear cooling temperature profile there is a large difference between the MOSCED and the other solubility models as seen in Figure 3. The MOSCED model greatly overestimates the initial relative supersaturation due to the model's bias for under-predicting the equilibrium solubility. After 5000 seconds the NRTL and empirical models are almost indistinguishable from each other while the MOSCED model is a poor prediction throughout the run.

By inspecting the final volume averaged CSD for each model (Figure 4), it can be seen that the NRTL and empirical models give approximately the same results, while again the MOSCED model being less accurate than the others. The reason for the slight differences in the first peak between the NRTL and empirical models is due to the relative supersaturation curve peaking at a higher value than the others causing increased secondary nucleation. The MOSCED model

predicts a large peak of small crystals due to excessive secondary nucleation in the beginning of the batch. This is due to the high initial supersaturation which causes the large amount of secondary nucleation. Since the MOSCED model predicts secondary nucleation earlier than the other three models, and peaks at a higher relative supersaturation value than the others, it also should predict that the first peak's maximum should have a larger crystal size than the others. However, this is not the case because the growth kinetics was modeled as being a function of absolute supersaturation. For a fixed relative supersaturation, the absolute supersaturation can have varying values depending on the value of the equilibrium concentration. Since the MOSCED model under-predicts the solubility of acetaminophen it will have a corresponding absolute supersaturation that is lower than the other models. This lower absolute supersaturation causes less growth of the crystals. The errors between the different solubility models do not result in large differences in the final CSD except for the MOSCED model which only is qualitatively accurate.

Robustness against Solubility Model Errors

Since crystallization models are often used to predict or to obtain optimal cooling profiles it would be advantageous to make the model more robust against solubility model errors or biases. One way to make the model more robust is to specify the initial supersaturation condition instead of an initial solution concentration. This will remove the solubility's model effect on the initial supersaturation. As seen earlier, this can be detrimental to the model. It is reasonable to be able to specify the initial supersaturation because that will be known when doing crystallization experiments. Also the relative supersaturation is usually kept small to stay within the metastable region. If the relative supersaturation is too high and the metastable region is exceeded, uncontrollable primary nucleation will occur. When the initial supersaturation is specified, each solubility model does a much better job at predicting the relative supersaturation profiles seen below in Figure 5.

Another way to make the model more robust is to make the growth kinetics a function of relative supersaturation instead of absolute supersaturation. The absolute supersaturation can thus be rewritten as:

$$\Delta c = c_{eq}^{ref}(S-1) \quad (2)$$

In order to make this change of variables a reference equilibrium concentration needs to be chosen. Since the crystallization cooling batch varies from 30˚C to 10˚C the reference equilibrium concentration was taken to be 176 g Acetaminophen/kg solvent at 20˚C. Substituting this into the growth kinetics resulted in the CSD profile shown in Figure 6. Now the MOSCED model does a much better job at predicting the final CSD. The grown secondary nucleates now have approximately the same size distribution for each solubility model. By making the growth kinetics a function of relative supersaturation instead of absolute supersaturation, the crystallization model is much more robust against solubility model errors.

Conclusions

Different models for solubility were presented and evaluated within a population balance crystallization model. The effect of the error of solubility models on the crystallization final CSD predictions was evaluated using four different solubility models. It was shown that small solubility model errors do not greatly affect the final CSD. However, large errors in the solubility model can be detrimental to the prediction as in the use of the MOSCED model. However, there are two ways to modify the model to make it more robust against solubility errors. By specifying the initial relative supersaturation and by making the crystallization kinetics a function of relative

supersaturation the crystallization model is much more robust against solubility model errors. With these changes to the model, the generalized MOSCED model now can predict the final CSD more accurately. The next step in the solubility sensitivity testing of crystallization models will be to evaluate the effect of these different solubility models on the predictions of antisolvent crystallization.

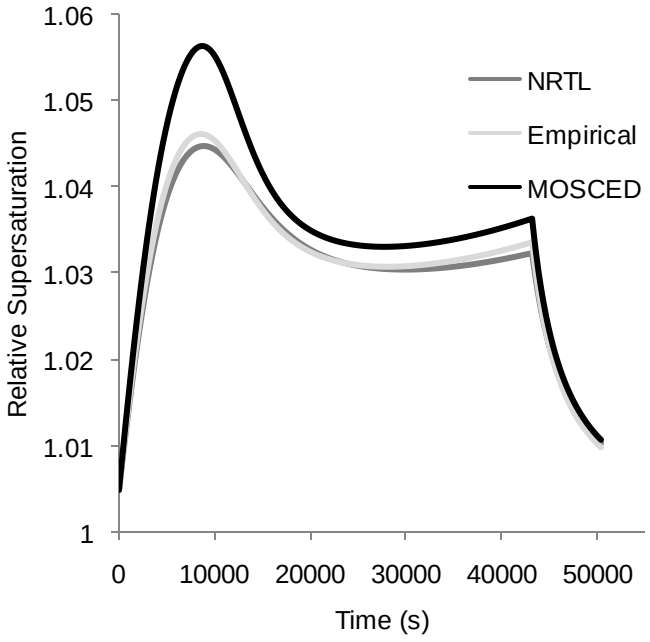

Figure 5. Relative supersaturation with a fixed initial relative supersaturation.

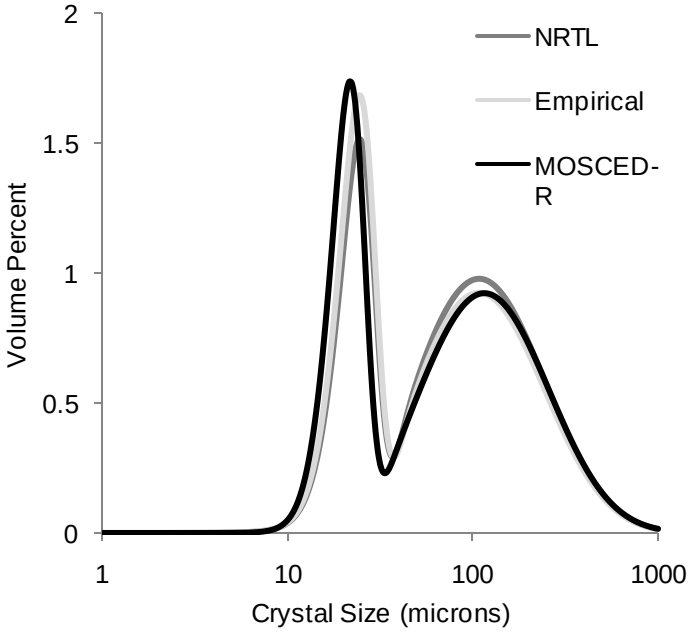

Figure 6. Volume percent CSD for the robust MOSCED crystallization model.

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