A Novel Software Tool for Crystallization Process Development

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Abstract
A new software application has been developed to assist both chemists and chemical engineers in the early stage of crystallization process development. The software enables the users to quickly identify feasible process alternatives through generation of solid-liquid equilibrium phase diagrams. It provides a convenient platform to integrate modeling, experimental, and synthesis activities involved in the crystallization process development workflow. Packaged as a collection of tools, it can accommodate various needs in a flexible manner instead of following a rigid workflow. An example illustrates the use of the software in a typical crystallization process development project.

Keywords: Software, crystallization, process development, phase diagram

1. Introduction
With the advances in chemistry and biochemistry, the chemical processing industries are faced with new challenges of producing high molecular weight chemicals, which are normally recovered as solids via crystallization. Developing a crystallization process is often a daunting task due to various problems such as low yield, inefficiency, difficult crystal separation, and expensive downstream purification due to high impurity level. On the other hand, today’s competitive environment calls for the development of a reliable and optimal process with minimum time, effort, and money. This is especially true for specialty chemical and pharmaceutical companies, which are often forced to reduce their selling price amid tighter regulations and reduced economic life cycle due to rapid introduction of competing products (Pisano, 1997).
Process vision and systematic procedures are crucial in meeting such challenges (Basu, 1998; Basu et al., 1999). In this connection, a systematic procedure for synthesizing crystallization-based separation processes that uses solid-liquid equilibrium (SLE) as the thermodynamic basis has been developed (Wibowo and Ng, 2000). Furthermore, the workflow in the development of crystallization processes has been studied (Wibowo and Ng, 2002). It is crucial that experimental efforts be integrated with modeling and synthesis efforts, especially when dealing with new chemical entities for which physical and chemical information is not available. In such cases, interaction between scientists and engineers is a key to the success of the overall development.

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To facilitate the execution of the activities involved in the crystallization process development workflow and to ensure effective flow of information among stakeholders, SLEEK™ (Solid-Liquid Equilibrium Engineering Kit) – a new software application for crystallization process development – has been developed. It is specifically targeted to assist chemists and chemical engineers in understanding, analyzing, and communicating the complex phenomena and tradeoffs that are a part of solid-liquid systems through visualization of SLE phase behaviors. Based on this understanding, thermodynamically feasible crystallization processes can be effectively designed.

2. Software for Crystallization Process Development

2.1 Organization
The software is organized in three hierarchical levels: cases, projects, and workspaces. A case is analogous to a unit of knowledge such as an experiment performed in the laboratory or a design for a process alternative. There are three different types of cases: analysis, design, and regression, which correspond to the Modeling, Synthesis, and Experimental classes of work objectives in process development. Projects are meaningful collections of experiments or cases, together with their findings. The workspace contains settings, global parameters such as selected unit sets, and property packages (selection of components, chemical reactions, and thermodynamic models), in addition to collections of projects and case studies.

The database structure is designed to promote both accumulation and sharing of SLE knowledge. Chemical compound and mixture information is stored in the built-in SLEEK database, the user-local database, the centrally managed user in-house database, and workspaces. The SLEEK database contains information on many pure components including all of the ICH Class 3 regulated solvents. The databases support the unusual necessities of solids data such as properties of polymorphs. Transfer of information is accomplished directly through the application interface. Users can easily transfer component information from one user-local database to another by simply sharing a workspace. Such an organization ensures total flexibility to accommodate any need, regardless of the workflow.

2.2 Functionalities
The software provides a team of chemical scientists and engineers with the tools they need to work together on a crystallization process development project. Regression tools provide the closest link to the experimental efforts by allowing the selection of the “best” representation of the physical phenomena, whether that is the most accurate or the most fundamental. Analysis functionalities include generation and visualization of SLE phase diagrams of multicomponent and liquid-phase reacting systems that may contain polymorphic solids or solid complexes. For multicomponent mixtures, high dimensional phase diagrams are represented using a series of cuts and projections. Multiphase flash calculation results are also provided to give the numerical results. Analysis tools are also available for classification of solvent-solute mixtures for solvent screening, even for evaluation of mixed-solvent systems. Design case studies give the crystallizer outputs for continuous and batch crystallizers, which are useful for selection of operating conditions and policy.
2.3 Workflow
In a typical process development project, a team may iterate many times between experiment, analysis, and design before the project is completed. Each team may have a different order of accomplishing the tasks, which may also depend on the particular compound, situation, or stage of development. Whether the objective is first to try a quick simulation to help decide what experiments to perform, or to measure the phase diagram in the laboratory before doing the design calculations, SLEEK is designed to handle the right amount of data at the right time. The goal is to quickly gain understanding of the chemical and physical process principles and implement optimal decisions, as opposed to providing a simulation environment.

Starting with meager information such as melting point and enthalpy of fusion, the SLE phase behavior can be calculated using a simple thermodynamic model. With the help of design procedures coupled with visualization on the phase diagram, operations such as heating, cooling, solvent addition, and solvent removal can be put together to systematically generate process alternatives. To guarantee the feasibility of the design, it is critical to ensure that the predicted phase diagram is verified with phase equilibrium experiments and model regression. Once the phase diagram has been confirmed, the conclusions and optimizations acquired from the design tools can be esteemed with confidence. A typical workflow is illustrated below using an example.

3. Example: Development of Aspirin Purification Process
The last step in the production of aspirin (acetyl salicylic acid) is reacting salicylic acid with acetic anhydride to form aspirin and acetic acid. Upon addition of cold water, aspirin and unreacted salicylic acid would crystallize out because of their low solubilities. The solid mixture is then purified by recrystallization in an organic solvent. It is assumed that the solid mixture contains 70% aspirin and 30% salicylic acid (by weight). This example illustrates the application of the software in the development of a batch crystallization-based separation process for obtaining pure aspirin.

3.1 Solvent Selection
It is a common practice among chemists to select a recrystallization solvent based on general criteria such as solubility of the purified compound and impurities in hot and cold solvent, boiling point of the solvent, and the potential for chemical reaction between the compound and the solvent. In addition, solvents with low toxicity are preferred for pharmaceutical use. The software can be used to estimate the solubility of both aspirin and salicylic acid in various pure and mixed solvents.

Table 1 summarizes the calculation results for selected solvents using the regular solution model, which is known to provide a good estimate for organic systems (Myerson, 2002). The solvents can then be ranked based on the ratio of aspirin solubility at 65°C to its solubility at 25°C, as well as the ratio of salicylic acid to aspirin solubility at 25°C. Assuming no significant esterification reaction, ethanol shows all the characteristics of a good solvent, since it dissolves a lot of aspirin but only a small amount of salicylic acid at 65°C. The per-pass crystallization yield would also be high since only about 20% of the aspirin would remain dissolved at 25°C. On the other hand, acetic acid and ethyl acetate appear to be good solvents for purifying salicylic acid.
Table 1. Calculated solubilities using regular solution model.

<table>
<thead>
<tr>
<th>No</th>
<th>Solvent Name</th>
<th>Boiling Point (°C)</th>
<th>Aspirin Solubility (g/100g) 25°C</th>
<th>Aspirin Solubility (g/100g) 65°C</th>
<th>Salicylic Solubility (g/100g) 25°C</th>
<th>Salicylic Solubility (g/100g) 65°C</th>
<th>Solubility ratio 25°C Sal/Asp</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acetic acid</td>
<td>117.9</td>
<td>18.7</td>
<td>81.2</td>
<td>4.35</td>
<td>9.55</td>
<td>36.6</td>
</tr>
<tr>
<td>2</td>
<td>Ethyl acetate</td>
<td>77.06</td>
<td>6.02</td>
<td>28.5</td>
<td>4.73</td>
<td>3.37</td>
<td>11.7</td>
</tr>
<tr>
<td>3</td>
<td>Tetrahydrofuran</td>
<td>65.97</td>
<td>10.6</td>
<td>49.0</td>
<td>4.63</td>
<td>5.93</td>
<td>21.0</td>
</tr>
<tr>
<td>4</td>
<td>Ethanol</td>
<td>78.29</td>
<td>20.5</td>
<td>95.3</td>
<td>4.65</td>
<td>30.2</td>
<td>89.3</td>
</tr>
<tr>
<td>5</td>
<td>1-Propanol</td>
<td>97.2</td>
<td>19.6</td>
<td>80.4</td>
<td>4.10</td>
<td>23.2</td>
<td>68.0</td>
</tr>
</tbody>
</table>

3.2 Generation of Phase Diagrams

Although solubility comparison can be helpful for preliminary solvent screening, it does not provide a complete picture of the situation. For example, the presence of salicylic acid can significantly affect the solubility of aspirin. A phase diagram provides a more comprehensive picture by showing regions of composition where various pure products can be crystallized out.

Figure 1 shows the polythermal phase diagrams of aspirin, salicylic acid, and two different solvents, calculated using regular solution model. The left section of the triangle is the aspirin saturation region, where pure aspirin can be crystallized, while the right section signifies the salicylic acid saturation region. These regions are separated by the double saturation curve, where both aspirin and salicylic acid are co-saturated. A third region corresponding to the solvent saturation region is not visible due to its proximity to the solvent vertex. Comparison of the two diagrams suggests that ethanol is a better solvent for crystallizing aspirin, as indicated by a larger aspirin saturation region, while ethyl acetate is more suitable for obtaining salicylic acid crystals.

3.3 Regression

To ensure accuracy, the phase diagram needs to be validated by incorporating experimental solubility data. Figure 2a shows the assumed experimental data on aspirin solubility in ethanol at various temperatures, along with the regressed binary phase diagram. Since regular solution model does not have adjustable parameters, the NRTL

![Fig. 1. Ternary polythermal phase diagram of (a) aspirin-salicylic acid-ethanol system and (b) aspirin-salicylic acid-ethyl acetate system.](image-url)
model was used instead. Using the software’s regression tool, the binary interaction parameters between aspirin and ethanol were obtained. Similarly, data on solubility of salicylic acid in ethanol can be used to regress the binary interaction parameters between the two components. The ternary polythermal phase diagram of aspirin-salicylic acid-ethanol, calculated using NRTL model with the regressed parameters, is shown in Figure 2b. It is apparent that the aspirin saturation region is bigger than what was predicted by the regular solution model.

3.4 Process Design

With the phase diagram in hand, separation process alternatives can be generated. The feed is first dissolved in ethanol to give a solution indicated by point 1 (Fig. 2b). The solution is then cooled so that aspirin crystallizes out and the solution composition moves to point 2, which should be near the double saturation curve but still inside the aspirin saturation region to prevent co-saturation of salicylic acid. Clearly, the location of points 1 and 2 depends on how much ethanol is added to the feed. Using the sensitivity analysis tool, the solid recovery as well as dissolution and crystallization temperatures for various ethanol to feed ratios can be obtained. For example, for a ratio of 3:5 (by weight), the temperature at point 1 should be 75°C for complete dissolution. The minimum temperature at point 2 is 20°C, beyond which salicylic acid begin to co-precipitate. Such analyses make it possible to select the solvent to feed ratio such that the recovery and operating temperatures fall into a desirable range.

In an attempt to increase product recovery, possibilities of processing the mother liquor are investigated. Observation of the phase diagram reveals that solvent removal would move point 2 into the salicylic acid saturation region (point 3, Fig.2b), so that pure salicylic acid can be crystallized out. However, the relatively small salicylic acid saturation region would lead to a low recovery. Another option is to completely remove ethanol from the mixture, and dissolve the remaining mixture in ethyl acetate, which produces a larger salicylic acid saturation region (Fig.1b). As before, regression and sensitivity analysis can be performed to select operating conditions such as temperatures.
and solvent to feed ratio. The quantitative results allow the calculation of material balances, the summary of which is depicted in Figure 3 along with selected operating temperatures. The first crystallizer is operated at 25°C to avoid the need for refrigeration. Evaporation of ethyl acetate at the end yields a solid mixture of a similar composition to the original feed, which can be mixed with fresh feed in the next batch, thus minimizing the loss of aspirin. Although this process is subject to further validation and addition of more details, the identification of such a thermodynamically feasible alternative provides a good starting point for further development.

4. Conclusions

The development of a crystallization process consists of several stages. In the conceptual design stage, thermodynamically feasible process alternatives are generated and their economic potentials are evaluated. Taking into account crystallization kinetics and mixing effects, promising alternatives are further developed into a more detailed design, utilizing process systems engineering techniques for optimization, batch plant scheduling, and so on. The software tool offers a unique approach for developing crystallization processes at the conceptual design level, by providing the understanding of SLE phase behavior through visualization of phase diagrams and allowing incorporation of experimental data for better prediction. By first calculating the phase diagram using thermodynamic models, specific needs for experimental validation can be identified, thus minimizing the required development time and effort to achieve the desired level of accuracy. Information flow is enhanced because both the chemical analyst performing laboratory experiments and the engineers developing operational procedures use the same application. For experienced laboratories, research prowess is further increased by the ability of SLE data archival for future reference and sharing.

References

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