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Model-Based Solvent Selection during Conceptual Process Design of a New Drug Manufacturing Process

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Abstract:

Using models, we have demonstrated an efficient approach to identify optimal solvent compositions during conceptual design of an active pharmaceutical ingredient (API) process. A ternary solvent system was considered for a reaction, extraction, distillation, and crystallization sequence. Two thermodynamic models, NRTL-SAC and NRTL, as well as Aspen modeling tools, were employed to predict the liquid−liquid, vapor−liquid, and solid−liquid phase behaviors. We used these modeling tools to identify a solvent composition space for the reaction that allows for reasonable reaction volume while continuously removing a byproduct into a second aqueous phase. This composition also reduces API loss during subsequent aqueous extractions. Furthermore, the composition of the organic phase allows for an efficient azeotropic distillation during solvent exchange, resulting in a shorter cycle time needed to achieve the desired composition for final crystallization. Overall solvent usage for the process is also significantly reduced. This approach was applied retrospectively to a late-stage API process under experimental development and was validated with the production of API of excellent quality at the pilot scale with solvent compositions of the process in agreement with those predicted by the models.

Introduction

A recent pilot-plant campaign in our facility presented interesting challenges with respect to process design. The process involved heterogeneous catalytic hydrogenation followed by removal of inorganic impurities and crystallization of the product. While the challenges were met via traditional experimentation, the situation provided an opportunity to retrospectively apply model-based conceptual process design techniques to demonstrate their applicability in the design of pharmaceutical processes.

Model-based conceptual process design techniques have been widely used for integrating reaction and separation steps for chemical processes design.[1,2] However, these techniques have not been commonly practiced in the pharmaceutical industry. One possible reason is that thermodynamic models for the phase behavior of small organic molecules such as APIs have only been developed recently. Another reason is that modeling tools for batch operations used in manufacture of pharmaceuticals have not been readily available until recently. With the introduction of the NRTL-SAC model,[3] which can be used to predict phase behavior of API molecules, and the increasing availability of simulation models for batch unit operations, this situation is changing.

In this study, an example is provided to illustrate the difference between process design using a conventional experimental approach and a model-based process synthesis approach. A ternary solvent composition consisting of specific amounts of toluene, water, and isobutanol was selected for the recent pilot-plant campaign based on experimentally determined API solubility and the impurity profile in the reaction. This selection represents one single point in the ternary solvent composition phase diagram. In contrast, using the model-based process synthesis approach, feasible regions (design space) in the ternary solvent composition phase diagram can be predicted. More importantly, in the early stages of process development, model-based process synthesis approach can be used to more efficiently direct experimental efforts. The required accuracy may not be high at this stage, but in later stages of process development, the thermodynamic models should be refined to increase their accuracy.

Two thermodynamic models, NRTL-SAC and NRTL, were employed, as well as Aspen modeling tools, including Aspen Properties, Aspen Plus, and Aspen Split, to predict the liquid−liquid, vapor−liquid, and solid−liquid phase behavior. The NRTL-SAC (Non-Random Two Liquid-Segment Activity Coefficient) model is a parameter-based method for estimating solubilities in different solvents. It was developed in 2004[3] based on the Polymer NRTL model,[4] which was in turn based on the original NRTL model.[5] The original NRTL model accounted for the energetics of the interactions between various molecules as well as the nonrandomness of their mixing.[5] The Polymer NRTL model was created by extending the NRTL model to polymers by including the entropy of mixing from Flory−Huggins theory.[4] The NRTL-SAC model introduces the capability of treating new molecules for which no model parameters exist by treating them as oligomers of conceptual segments. These conceptual segments represent the molecule's ability to

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(1) Smith, R. *Chemical Process Design*; McGraw Hill: New York, 1995.

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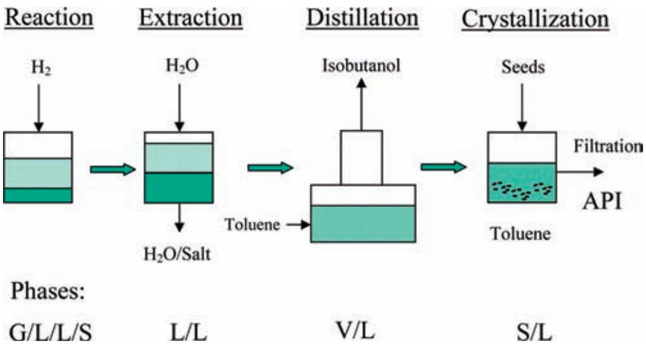

Figure 1. **Process flow diagram for the API process.**

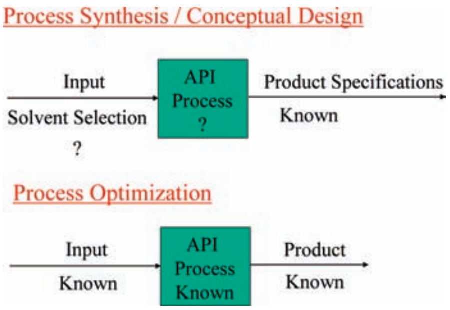

Figure 2. **Modeling objectives schematic.**

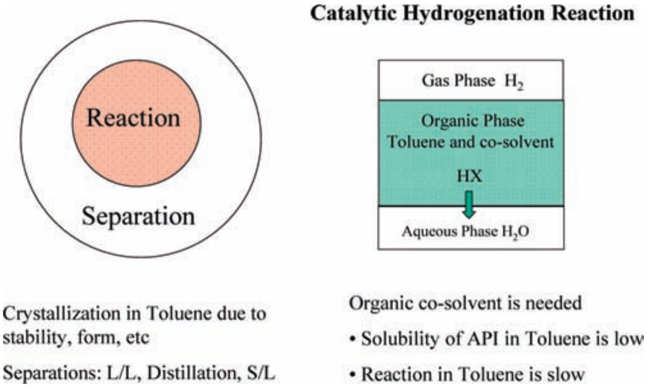

Figure 3. **Process synthesis schematic for the API reaction step.**

interact with polar and nonpolar solvents as well as form hydrogen bonds.[3] This model has been extended so that it is capable of modeling electrolytes[6] and has been tested on a variety of pharmaceutical molecules.[7,8] This model permits, for the first time, the capability of introducing new pharmaceutical compounds into model mixture calculations and accurately modeling the interactions of these compounds with other components of the system. This tool, combined with the other property estimation methods, can potentially open new doors into increasingly accurate process modeling.

Materials and Methods

Manufacture of the Active Pharmaceutical Ingredient. The process flow diagram for this API process is presented in Figure 1. The API is produced by the hydrogenation of the final intermediate in the presence of solvent and catalyst. A small amount (2−3%) of an aryl bromide is present in the final intermediate and undergoes conversion to API, leading to the formation of HBr. The formation of HBr changes the pH of the reaction mixture and affects the final API product quality and must be removed from the reaction mixture. In order to do so, an aqueous solution with 2 wt % of Na_2CO_3 is added to the reaction mixture to form two liquid phases. The HBr migrates from the organic phase to the aqueous phase and reacts with the Na_2CO_3 to form $NaHCO_3$ and NaBr. The aqueous phase is then removed during the workup.

The final step in the manufacture of most APIs, including the one in question, is solution crystallization. Solvent selection for this step is critical because the purity, physical stability, and form of the crystal are strongly dependent upon the solvent used for this step. For this API, toluene had been previously demonstrated to be the best solvent for the crystallization step. Although toluene is best for crystallization, it was not the best choice for the reaction in terms of solubility, reactivity, impurity formation, etc. A mixture of solvents was used in the reaction step to increase the solubility of API and thus reduce the reaction volume. This selection necessitated a solvent swap to remove the cosolvent before crystallization. The impurity removal discussed earlier required liquid−liquid immiscibility between the reaction media and water.

Modeling Strategies Used In Process Design. Since the solvent composition and phase behavior change from the reaction to the separation due to the requirements of each unit operation, a conceptual process design is needed to integrate the overall process and to reduce the solvent composition space (process design space) to a smaller more manageable region.

The scope of the conceptual process design and the scope of process optimization in terms of input to the API process and the output from the API process are described in Figure 2. In the conceptual process design stage, the starting material and the API product specifications are known, but the most suitable solvents and operating conditions are unknown. In addition, the separation operations after the reaction need to be determined. After the conceptual process design stage, the unknowns including the solvent and the API process operating conditions become defined. Afterwards, process optimization can be utilized to improve factors such as cycle time, solvent usage, and process yield.

Conceptual Process Design. The purpose of the conceptual process design is to come up with a feasible process to generate high-quality product at acceptable cost. The reaction is studied first since it is the heart of the process,[1] as shown in Figure 3. After reaction study, a separation sequence is proposed to generate the product to meet the product specifications. Modeling tools should be used to synthesize the possible process options. Several processes consisting of a reaction and a series of separation steps should be proposed. Experimental work should be coupled with this modeling work to verify the feasibility of the process from the conceptual process design work, as shown in Figure 4. Modeling work can be used to rapidly examine a large design space in order to hone in on the best processing options which should be verified experimentally. This is illustrated in Figure 4 which shows modeling being used for conceptual process design and process optimization in

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(6) Chen, C.-C.; Song, Y. *Ind. Eng. Chem. Res.* **2005**, *44*, 8909.
(7) Chen, C.-C.; Crafts, P. A. *Ind. Eng. Chem. Res.* **2006**, *45*, 4816.
(8) Kokitkar, P. B.; Plocharczyk, E.; Chen, C.-C. *Org. Process Res. Dev.* **2008**, *12*, 249.
(9) Stephenson, R. M. *J. Chem. Eng. Data* **1992**, *37*, 80.

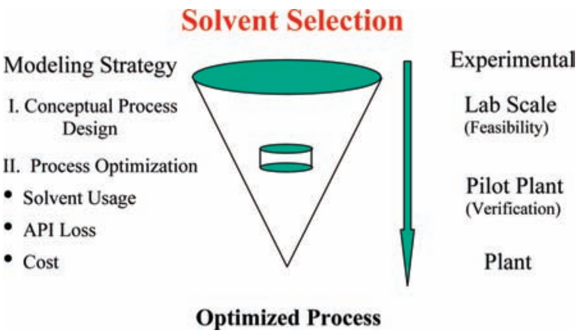

Figure 4. **Modeling strategy and experimental approach schematic.**

parallel with lab work to narrow the design space as the process is developed in the lab and scaled up to manufacturing scale.

Thermodynamic Models and Modeling Tools. Thermodynamic models for the solvent and API system are needed to describe the following physical properties: liquid−liquid equilibrium (LLE), solubility of API in the mixture of solvents (SLE), and vapor−liquid equilibrium (VLE). Since the interaction between the API and the solvents has not yet been incorporated into the NRTL model, this model was used to predict the phase behavior of the solvent system (with the assumption that the API had little effect on this phase behavior), while the NRTL-SAC model was used to predict the solubility of the API in the solvents and solvent mixtures. Although hydrogen and salt are also present in this process, the effects of these components on the phase behavior are not considered at the conceptual process design stage. Aspen modeling tools such as Properties and Plus/Split were used for the process synthesis to predict LLE for the reaction and extraction, VLE for distillation, and residue curve maps (RCM) for the batch distillation and to generate the phase behavior shown in the triangle diagrams.

NRTL-SAC Thermodynamic Model for the API Physical Properties. The NRTL-SAC model uses as input between four and eight measured solubilities of the compound of interest in various solvents. These input solubilities should be taken from a wide variety of solvents to get some measure of how well the compound interacts with nonpolar solvents, polar hydrogen-bonding solvents, and polar solvents that do not form hydrogen bonds.[3] Also required as input to the model are the molecular weight, entropy of fusion, and melting temperature of the compound (the melting temperature and entropy of fusion are measured via differential scanning calorimetry or DSC). The solubility of a compound in one solvent is related to the solubility of the same compound in another solvent using a set of interaction parameters estimated from the measured data.[3] Individual solvents have been related to each other with the same set of interaction parameters through activity coefficient estimates from VLE and LLE data.[3]

The solubility of a given compound is related to its entropy of fusion, melting temperature, the solution temperature, and its activity coefficient in the solution by the van't Hoff equation:

$$\ln(x_1^{\text{sat}}) = \frac{\Delta_{\text{fus}}S}{R}\left(1 - \frac{T_{\text{m}}}{T}\right) - \ln \gamma_1^{\text{sat}} \qquad (1)$$

Given the entropy of fusion, the melting temperature, and the solution temperature, the only unknown in this equation is the activity coefficient. The NRTL-SAC model calculates the activity coefficient of the solute in the solution by breaking it into the sum of a combinatorial activity coefficient and a residual activity coefficient (eq 2). The combinatorial activity coefficient is calculated on the basis of Flory−Huggins theory (eq 6), and the residual activity coefficient is calculated on the basis of a modification of the original NRTL theory as shown below (eqs 3−5). A full description of the original NRTL model and NRTL-SAC can be found in refs 3 and 5

$$In(\gamma_I) = In(\gamma_I^C) + In(\gamma_I^R) \qquad (2)$$

$$In(\gamma_I^R) = In(\gamma_I^{lC}) = \sum_m r_{m,I}[In\Gamma_m^{lc} - In\Gamma_m^{lc,I}] \qquad (3)$$

$$In\Gamma_m^{lc} = \frac{\sum_j x_j G_{jm}\tau_{jm}}{\sum_k x_k G_{km}} + \frac{x_{m'}C_{mm'}}{\sum_{m'} x_k G_{km'}}\left(\tau_{mm'} - \frac{\sum_j x_j G_{jm'}\tau_{jm'}}{\sum_k x_k G_{km'}}\right) \qquad (4)$$

$$x_j = \frac{\sum_J x_J r_{j,J}}{\sum_I \sum_i x_I r_{i,I}}, \quad \chi_{j,I} = \frac{r_{j,I}}{\sum_i r_{i,I}}, \quad G_{ij} = \exp(-\alpha\tau_{ij}) \qquad (5)$$

Flory−Huggins

$$In(\gamma_I^{lC}) = In\frac{\phi_I}{x_I} + 1 - r_I\sum_J \frac{\phi_J}{r_J},$$

$$r_I = \sum_i r_{iI}, \quad \phi_I = \frac{r_I x_I}{\sum_J r_J x_I} \qquad (6)$$

In eqs 2−6, lowercase subscripts refer to the NRTL-SAC theoretical species segments that make up the solvent and solute molecules, and the uppercase subscripts refer to the actual solvent and solute molecules. The γ_I^C is the combinatorial activity coefficient and the γ_I^R is the residual activity coefficient. The expression for $\Gamma_m^{lc,I}$ has a similar form to that for $\Gamma_{\text{m}}^{\text{lc}}$ and has been eliminated for the sake of brevity (the interested reader can find the expression in ref 3). The $r_{m,I}$ are the lengths of the NRTL-SAC species on the molecule I (the NRTL-SAC parameters), the τ_{jm} are NRTL-SAC parameters describing the energetics of the interaction between the NRTL-SAC species, α is the NRTL parameter describing the nonrandom mixing of the molecules, and the x_j are the mole fractions.

Results and Discussion

Cosolvent Selection. It was previously demonstrated that toluene is the best choice for crystallization due to form and stability considerations. However, toluene is not the ideal solvent for the hydrogenation reaction for two reasons. First, the solubility of API in toluene is low, less than 10 mg/mL at the reaction temperature, which would lead to a very significant reactor size (1000 L for 10 kg of API). Second, the catalytic reaction rate in toluene is very slow and therefore, the reaction time will be long. Due to these two considerations, an organic cosolvent is needed to increase the API solubility and increase the reaction rate. The selection of the organic cosolvent must satisfy the requirements of both the reaction and the physical properties. The requirements of the reaction are minimizing the formation of side products and enabling acceptable reaction rates. The physical property requirements are high API solubility, low water miscibility to simplify phase separation, and boiling point lower than that of toluene. Several solvents including isobutanol, *n*-propanol, *n*-butanol, *sec*-butanol, meeting the physical properties requirements were tested in an Endeavor screening reactor to check the formation of side products and reaction rate. Isobutanol was selected as the organic cosolvent for this API process on the basis of the results of this screen.

Establishment of a Thermodynamic Model for the API. The NRTL-SAC parameters for the API were found using solubilities of this molecule in five pure solvents (*tert*-amyl alcohol, isobutanol, acetonitrile, isopropyl acetate, and isobutyl acetate) at 25 °C, as well as the solubility of this molecule in toluene at 60 and 90 °C. The entropy of fusion and melting temperature were measured via DSC and used as input to the model. The NRTL-SAC fit of the experimentally observed input solubilities was relatively good ($R^2 = 0.708$, root mean squared error 0.357). Figure 5 shows how the solubilities in these solvents were fit by NRTL-SAC as a function of their experimentally observed value.

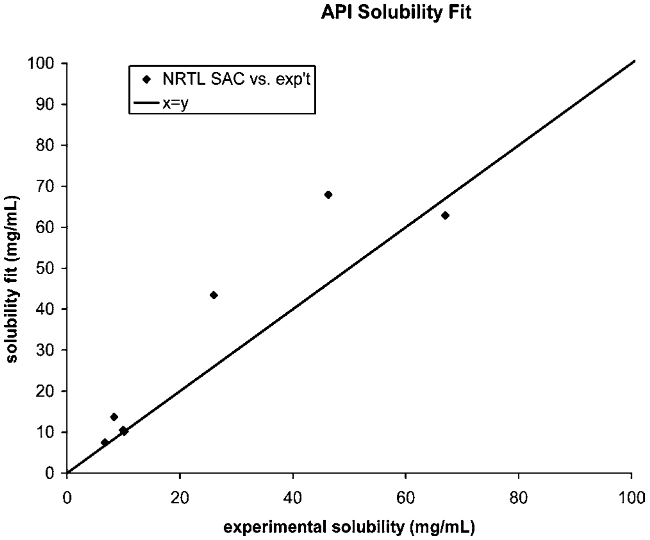

Figure 5. **Solubilities of the API fit by the NRTL-SAC model as a function of their experimentally observed values.**

Model Predictions for the API Solubility. The NRTL-SAC model was used to make predictions for the solubility of this molecule in toluene as a function of temperature and isobutanol as a function of temperature. These model predictions are shown in Figure 6. Fairly good agreement is seen between the model predictions and experimental measurements. The molecule's solubility is much higher in isobutanol than toluene and rises more rapidly in isobutanol as temperature is increased. Caution should be used when using any model to extrapolate room temperature solubility data to higher temperatures. In this case, high temperature solubility data was used as model input (the solubility in toluene at 60 and 90 °C), so more accurate results are expected at high temperatures for this reason. However, the results for the solubility in isobutanol as a function of temperature have not been experimentally verified and therefore should be (and were) used with caution.

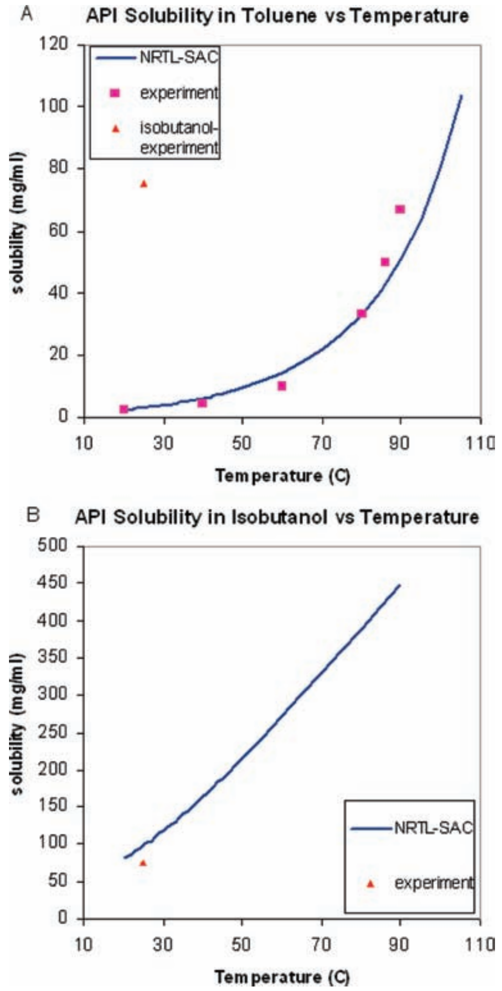

Figure 6. **(A) Solubility of the API in toluene as a function of temperature. NRTL-SAC model predictions are shown as a solid line, experimental measurements are shown as squares, and experimentally measured isobutanol solubility is plotted on the same axes as a triangle for reference. (B) Solubility of the API in isobutanol as a function of temperature. NRTL-SAC model predictions are shown as a solid line, the experimental measurement is shown as a triangle.**

The model was also used to predict solubilities of this API in a binary mixture of toluene and isobutanol. This solubility data was needed as this was the reaction solvent and the isobutanol was distilled away via a solvent swap before the crystallization. The model predictions for the solubility of the API in a binary mixture of toluene and isobutanol at 25 °C are shown in Figure 7 as a function of the mixture composition on the same axes with experimentally measured data. Fairly good agreement between the model predictions and the experimental measurements was also seen in this case. Although the model slightly overpredicts the data at large percentages of isobutanol, the model predictions and experimental measurements are in good qualitative agreement. In particular, both model and experiment show that the solubility increases rapidly at low percentage of isobutanol and then goes through a

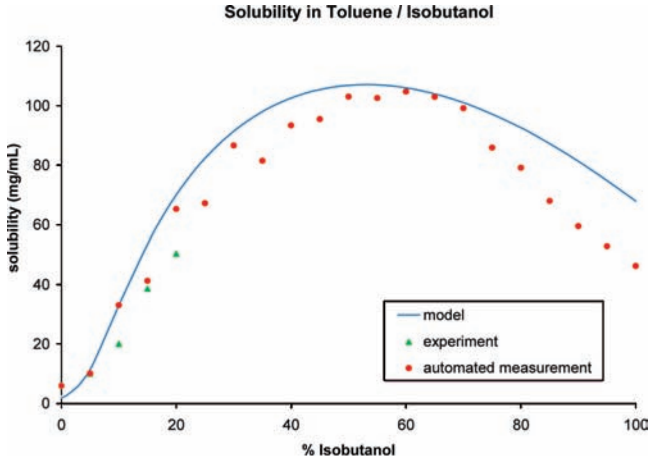

Figure 7. **Solubility of the API in a mixture of toluene and isobutanol at 25 °C as a function of mixture composition. The NRTL-SAC model predictions are shown as a solid line, experiments performed by hand are shown as triangles, and automated solubility measurements are shown as circles.**

maximum as the percentage of isobutanol is increased further. This shows that from a solubility perspective, there is little advantage to adding large amounts of isobutanol to the solvent mixture and a disadvantage to adding too much isobutanol to the solvent mixture. This nonideal solubility behavior has been observed for other API compounds by experimental measurement and model-based prediction with the NRTL-SAC model.[8]

On the basis of the good agreement between the model predictions and experimental data for the APIs solubility in toluene as a function of temperature and its solubility in the toluene/isobutanol mixture, the NRTL-SAC model for this API molecule was considered verified. The model was also tested by comparing its predictions to experimental data for the solubility of this molecule in the following mixtures: toluene/*tert*-amyl alcohol, toluene/*n*-butanol, toluene/2-butanol, and toluene/*n*-propanol. These results have been omitted for the sake of brevity, but the agreement between the model predictions and experimental measurements in these cases was similar to the agreement in the toluene/isobutanol case. While it is obvious that this model is not 100% accurate, the accuracy is good enough to help to make the correct decisions about process conditions such as solvent composition.

The accuracy of these predictions could be further improved by adding these solubility measurements in this binary solvent mixture to the model input. However, they were not, as this data was intended to be used to verify the model, and it was our desire to verify the model with a "blind" prediction of solubility data that had not been used as input. Once a particular solvent system has been selected, the accuracy of the model predictions can be improved even further by switching models from NRTL-SAC to NRTL. In this case, the NRTL binary interaction parameters between the API and the solvents would need to be regressed. Since we were interested in exploring the solvent design space with NRTL-SAC we deemed the regression of the NRTL binary interaction parameters for this system to be outside of the scope of this study.

Liquid and Liquid Equilibrium (LLE) for Water/Toluene/Isobutanol System. The phase behavior for the water, toluene, and isobutanol system is depicted in Figure 8, a triangle composition diagram. These results were generated with the NRTL model which was verified by comparison to experimental data available in the literature.[9] The unit of the axis for all ternary composition phase diagrams is mass fraction. The composition space for this system is divided into two regions: two-phase region (shaded) and the one-phase region (white). In the two-phase region, the composition in the organic phase and the composition in the aqueous phase are connected by tie lines, as shown in Figure 8. Toluene and isobutanol are completely miscible, water and isobutanol are partially miscible, and toluene and water are almost not miscible. Therefore, when there is a mixture of toluene (T) and isobutanol (I) with the weight ratio of T to I as high as 90 to 10 in the reactor, only a small amount of water is needed to bring this mixture into the two-phase region. In contrast, when a mixture of toluene and isobutanol with the weight ratio of T to I of 10/90 is present in the reactor, a relatively high amount of water is needed to bring this mixture into the two-phase region.

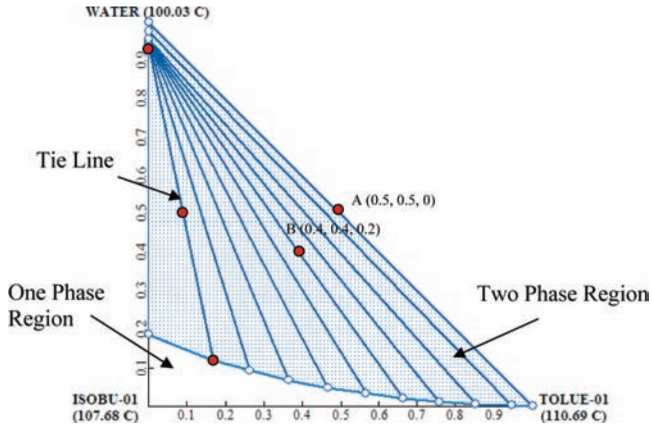

Figure 8. **Triangle diagram showing liquid−liquid equilibria in the water/toluene/isobutanol solvent system.**

Solvent Composition Selection for Reaction. The solvent composition selection for reaction is displayed in the shaded area in Figure 9. The model predictions and experimental data for the solubility of the API in an isobutanol/toluene mixture (Figure 6) show that with greater than 15% isobutanol the solubility will be greater than 40 mg/mL, making the reactor

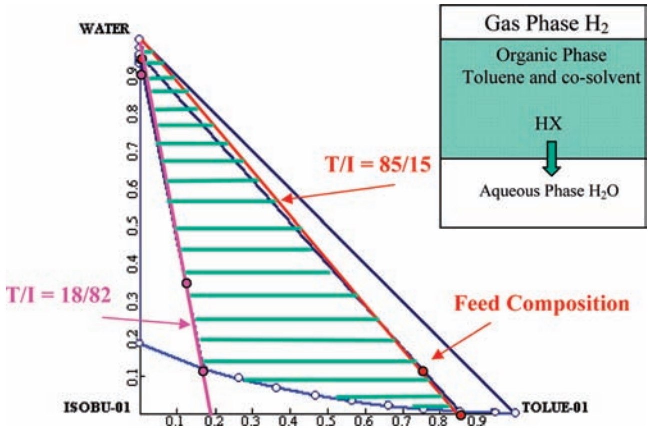

Figure 9. **Triangle diagram depicting solvent composition selection for reaction.**

size acceptable (250 L or less for 10 kg of API). However, the solubility decreases rapidly when the isobutanol is higher than 82%. The isobutanol level in the reactor should therefore be approximately 15% to 82%. The other consideration for the solvent composition for reaction is that two phases are required so that the reaction byproduct, HBr, will migrate from the organic phase to the aqueous phase. Any feed composition located inside the shaded region of Figure 9 will lead to two phases upon addition of water and keep the isobutanol level in the reactor between 15% and 82%.

Solvent Composition Selection for Extraction. This extraction of impurities by adding water to the reaction mix is illustrated by using material balance lines and tie lines in the LLE diagram below (Figure 10). Two cases are used: a reaction product mixture with a high weight ratio of T/I and one with a low ratio of T/I. The first case is shown by point 1 in the diagram. A material balance line can be drawn from point 1 to the water apex. After water is added to this reaction product mixture, the composition becomes point 2. The tie line passing through point 2 provides the composition of the two phases. The same procedures are applicable to the case with a low toluene to isobutanol ratio, illustrated by point 3, the feed composition, and point 4 after addition of water.

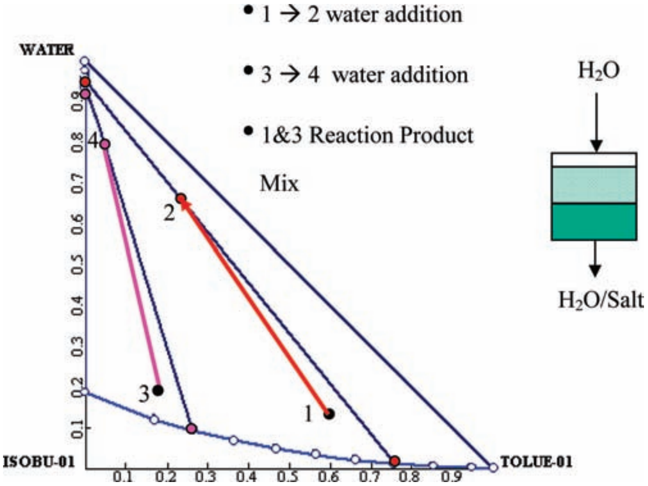

Figure 10. **Triangle diagram depicting solvent composition selection for extraction.**

The impacts of the weight ratio of toluene to isobutanol in the reaction product mix on the extraction can be drawn from these two cases. The isobutanol level in the aqueous phase at a low T/I ratio is higher than that at a high T/I ratio so the loss of API at a low T/I ratio is higher than that at a high T/I ratio since the API is more soluble in isobutanol. Thus, to reduce the loss of API a high T/I ratio is preferable in the extraction.

Solvent Composition Selection for Batch Distillation. The water, toluene, and isobutanol system exhibits very interesting azeotropic behavior: three binary minimal-boiling-temperature azeotropic mixtures and one ternary minimal-boiling-temperature azeotropic mixture exist.[10] The model predictions for the temperature and the composition at the azeotropic points at 1 atm are displayed in Figure 11.

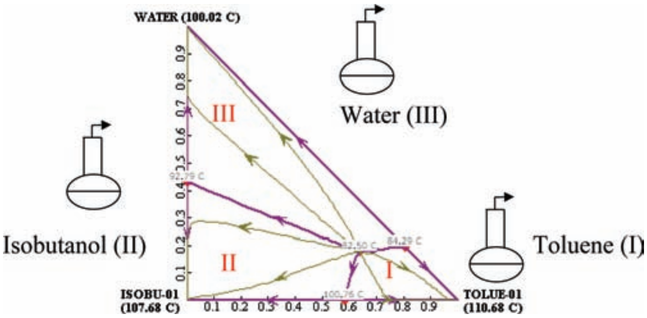

Figure 11. **Azeotropic behavior, distillation boundaries (purple), and residue curve maps (grey) for the water/toluene/isobutanol system.**

The ternary azeotropic point is classified as an "unstable node", and the three binary azeotropic points are classified as "saddle points".[2] Distillation boundaries exist from unstable nodes to saddle points so there are three distillation boundaries in this system, as shown in Figure 11. The three distillation boundaries divide the solvent composition space into three compartments: the toluene, isobutanol, and water compartments, as shown in Figure 11. Distillation boundaries in ternary systems exhibit the same behavior as those in binary azeotropic systems: feed below or above the azeotropic point cannot be distilled over the azeotropic point. For the ternary system shown in the diagram, when the feed composition is located inside one compartment, the kettle composition remains in that compartment and cannot be changed from that compartment to any other compartment by simple distillation. The residue curve maps (used to indicate how the composition changes during batch distillation) shown in Figure 11 illustrate this point. For example, consider a feed composition in the kettle located in compartment I near the ternary azeotropic point. During the batch distillation, the composition in the kettle will change and follow one of the trajectories. At the end of the batch distillation, the composition of the residue will be close to pure toluene. Thus, compartment I is called the toluene compartment. Similarly, any feed composition located in compartment II will end up as pure isobutanol, and compartment III, as pure water. The location of the ternary azeotopic point in Figure 11 is critical because it dictates the distillation boundary and the size of each compartment. Therefore, the model-based prediction of this azeotrope was verified on the basis of experimental data[10] as shown in Table 1.

Table 1. **Composition and temperature of ternary azeotropic mixture**

azeotropic point	data	ASPEN split analysis
isobutanol, wt%	16	18
toluene, wt%	67	59
water, wt%	17	23
temperature, °C	81.3	82.5

Integrated Composition Solvent Selection. The reactor feed composition is critical to having a feasible process as is illustrated by considering two cases: one for a low T/I ratio and the other for a high T/I ratio. A reactor feed composition with a low T/I ratio is represented by point 1 in Figure 12. After the reaction, water is added to the extractor, and the feed composition in the extractor is represented by point 2. After

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(10) Frolov, A. F.; Loginova, M. A.; Nazarova, V. F. *Russ. J. Phys. Chem.(Engl. Transl.)* **1969**, *43*, 1478.

the phase split, the composition in the aqueous phase is represented by point 3, while the composition in the organic phase is represented by point 4. After the extraction, the aqueous phase is removed, and the organic phase is sent to the batch distillation column. However, the feed composition for distillation is located in the isobutanol compartment which will lead to isobutanol instead of toluene becoming the solvent for crystallization at the end of batch distillation.

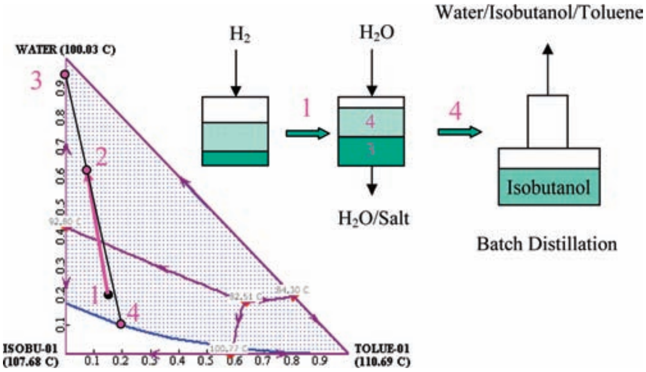

Figure 12. **Integrated solvent selection with the feed in the wrong compartment.**

A reactor feed composition with a high T/I ratio is represented by point 1 in Figure 13. Following the same sequence described in the first case, the feed composition in the batch distillation column is located in the toluene compartment. This will lead to toluene being the solvent in the pot at the end of the distillation.

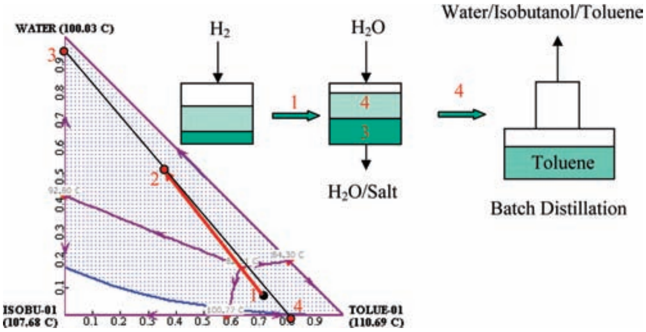

Figure 13. **Integrated solvent selection with the feed in the right compartment.**

The requirements for the solvent composition discussed above can be summarized as follows. For an acceptable reactor size and reaction rate, the weight ratio of toluene to isobutanol needs to be between 85/15 and 20/80. In order to have two liquid phases for the extraction, the feed composition to the reactor should be located in the two-phase region and does not need to be greater than 20% water since the salt being extracted is very soluble in water. In order to minimize loss of isobutanol and API in the aqueous phase, a high weight ratio of toluene to isobutanol should be used. Finally, in order for the batch distillation to end with the API in toluene in the kettle, the composition of the organic phase after extraction should be located in the toluene compartment. When these requirements were applied to the solvent composition space, a sweet spot was generated and is shown in Figure 14 below. These modeling results demonstrate a solvent composition for reaction that would integrate the overall API process from reaction to separation. The operating conditions previously used in the pilot plant were located within this region of the phase diagram. The modeling approach presented here is validated by this experimental verification of the model results and may therefore be used in the future for solvent selection.

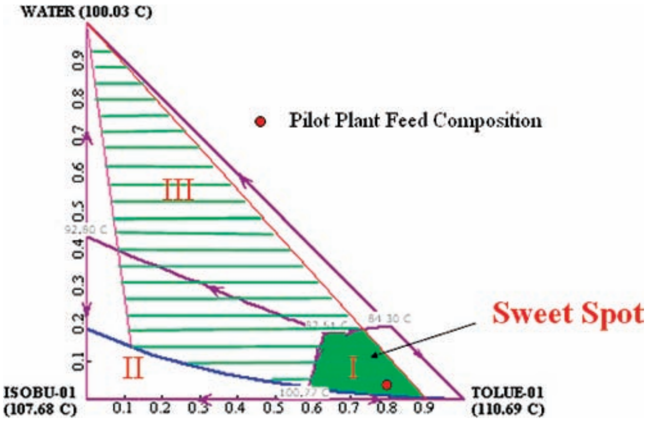

Figure 14. **Triangle diagram for the water/toluene/isobutanol illustrating the sweet spot for process operation.**

Pilot-Plant Operation and Model Verification. The feed composition to the reactor during the pilot-plant operation contained 79 wt % toluene, 18.5 wt % isobutanol and 2.5 wt % water. This composition is located in the sweet spot as shown in Figure 14. According to the modeling results presented here, this feed composition should lead to an efficient distillation with the result being a toluene solution in the kettle. The results of the distillation are given in Figure 15 which shows that the isobutanol concentration in the distillate is less than 0.2 vol % and the kettle temperature reaches 100 °C at the end of the distillation. This temperature is very close to the boiling temperature of pure toluene at 550 mmHg (99.69 °C).

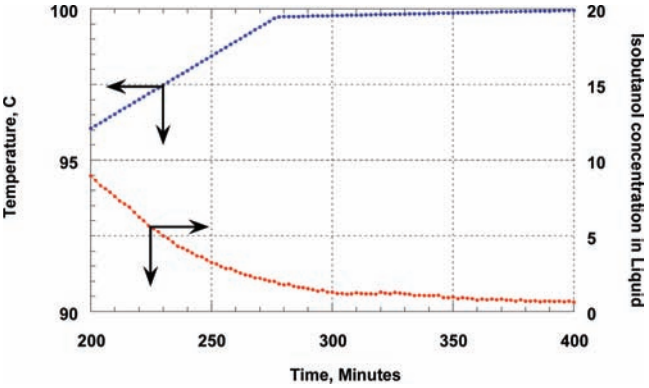

Figure 15. **Temperature and concentration profile during distillation at 550 mmHg in the pilot-plant operation.**

Also observed during the distillation in the pilot plant at 550 mmHg, was a boiling point at 70 °C. This boiling point indicates that a ternary minimal-boiling-temperature azeotropic mixture exists because this boiling temperature is lower than the boiling point of any binary minimal-boiling-temperature azeotropic mixture at 550 mmHg.

Effect of Solute on LLE and VLE. As mentioned earlier, the interaction between the solute and the three components was neglected when the LLE and VLE behavior was modeled. As the process evolves from the pilot-plant scale to the commercial scale, the thermodynamic models can be refined to evaluate this assumption. The NRTL binary interaction parameters between each of the solvents and the solutes could be regressed for this purpose so that the NRTL model could be used to evaluate the impact of solute on LLE and VLE. The scope of this evaluation could be extensive, and is beyond the scope of this work.

Conclusions

In conclusion, we have used the NRTL-SAC and NRTL models as well as modeling tools to design an API process in an integrated manner from reaction to crystallization. We identified a sweet spot, occupying less than 10% of the solvent composition space, which satisfies all processing requirements. A solvent composition within this region was used previously in a pilot-plant campaign to generate API of acceptable quality, thereby supporting the modeling results.

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