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Optimal Solvent Screening for the Crystallization of Pharmaceutical Compounds from Multisolvent Systems

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ABSTRACT: In this study, an effort has been made to predict the solid−liquid equilibrium (SLE) behavior of different solids (pharmaceuticals) in many common solvents and their mixtures. A modified optimization of a recent thermodynamic model, the NRTL−SAC model, was used in all stages of calculation (VLE, LLE, and SLE predictions). The batch cooling−antisolvent crystallization process was simulated for seven model molecules from the initial temperature to the final temperature and for the volume fraction of each solvent. The feasible region of temperature for each crystallization case was calculated based on the bubble-point temperature of the solvent mixture and the melting point of the model molecules. The NRTL−SAC model was used in conjunction with the optimization procedure to test the complete miscibility of solvents during each part of crystallization. After estimating the optimum solvent mixture (combination) for a specific model molecule, the results for single, binary, and ternary solvent mixtures were compared. The results obtained from the binary and ternary combinations were similar in terms of crystallization yields per mass of solvent mixture and far superior to those obtained with single solvents. The proposed algorithm demonstrates flexibility, simplicity, and accuracy in predicting the phase behavior and eventual optimal solvent screening for the crystallization of pharmaceutical components.

INTRODUCTION

In the production of many pharmaceuticals and chemicals the selection of a solvent for the crystallization process is very important.[1] The solubility of an active pharmaceutical ingredient in a solvent or solvent mixture can affect the drug release and absorption in the body and its transport in a living organism. Drug availability for experimental solubility determination during the early stages of new drug development is very restrictive.[2] In addition, difficulties in experimentation and inherent experimental errors are other complexities. On the other hand, accurate thermodynamic models can provide guidelines for the optimal selection of solvent combinations. Some thermodynamic methods, such as the nonrandom two-liquid (NRTL),[3] Wilson,[4] universal quasichemical (UNIQUAC),[5] and van Laar[6] models rely on huge amounts of experimental data. For ternary and quaternary systems of solvents, the use of these models requires vast numbers of experimental runs to determine the binary interaction parameters.[7] Predictive thermodynamic models, such as the universal functional activity coefficient (UNIFAC),[8] nonrandom two-liquid segment activity coefficient (NRTL−SAC),[2] and conductor-like screening segment activity coefficient (COSMO−SAC) models,[9,10] require information on the molecular structures of the solute and solvents. The UNIFAC model has shown a good predictive ability for a wide range of vapor−liquid equilibrium (VLE) and liquid−liquid equilibrium (LLE) systems. However, it fails to deal with systems in which the molecules have complex and unknown functional groups.[2] The NRTL−SAC model, proposed by Chen and Song,[2] was derived from the polymer nonrandom two-liquid (NRTL) model.[11] In this model, the molecules of solute and solvent are characterized by segments of three types: hydrophobic (X), hydrophilic (Z), and polar (Y). The polar segments are, in turn, divided into polar attractive ($Y-$) and polar repulsive ($Y+$) types. These conceptual segments were determined using experimental data on VLE and LLE in some systems. The four conceptual segments assigned to each molecule (solute or solvent) can be used as a descriptor of that molecule when used in VLE, LLE, and solid−liquid equilibrium (SLE) calculations. This model is simple and flexible in modeling the thermodynamic phase equilibria of binary and multicomponent systems. The advantage of this model, compared to other predictive methods such as UNIFAC, is its simplicity in defining a molecule with only four segment types, no matter how complex the chemical structure of a molecule is.

The VLE and SLE predictive abilities of the NRTL−SAC model were verified in some recent studies. Chen and Crafts used the NRTL−SAC model to find the segment numbers of paracetamol and sulfadiazine.[12] In another study, they showed that this model can be used in VLE calculations of common solvents.[2] Sheikholeslamzadeh and Rohani found the conceptual segment numbers of 3-pentadecylphenol, lovastatin, and valsartan in single and binary solvents.[13] Sheikholeslamzdeh and Rohani also studied different systems of solvents in binary, ternary, and quaternary mixtures to verify the applicability of the NRTL−SAC model in predicting the VLE and VLLE behaviors of those systems.[14] They showed that the NRTL−SAC model best describes such complex systems of solvents in good agreement with the experimental data. The results showed that the NRTL−SAC model could provide better results in ternary

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and quaternary mixtures than the UNIFAC model. Mota et al. used the NRTL−SAC model to estimate the segment numbers of budesonide, allopurinol, and furosemide in different solvents.[15]

In this work, the NRTL−SAC model is written in separate programs for the prediction of VLE, LLE, and SLE behaviors in multisolvent systems with seven model pharmaceutical molecules. A new optimization procedure is developed to calculate the best solvent or mixture of solvents to maximize the crystallization yield in cooling−antisolvent mode. It should be noted that, in the current study, the process modeling and optimization are based on the initial and final points of operation only. The path of cooling and addition of antisolvent are not considered here, and in addition, the initial and final operating points of crystallization are at equilibrium. It is worth noting that, throughout this work, the term component refers to a solid, solute, or solvent under study. A model molecule (an active pharmaceutical ingredient or any chemical compound) can be in the form of a solute (dissolved in a solvent or a solvent mixture) or a solid (crystallized or amorphous form of a solute).

THERMODYNAMIC BACKGROUND

Group-contribution models divide the contribution of the activity coefficient to two parts: the combinatorial and residual parts. The combinatorial part includes the contribution of the chemical structure and the size (volume and surface) of the component. The residual part includes the contribution of the group size and binary interaction between pairs of functional groups. The total activity of a component in a solution is the sum of the two parts

$$\ln \gamma_i = \ln \gamma_i^{C} + \ln \gamma_i^{R} \tag{1}$$

in which γ_i is the activity coefficient of component i in the solution, γ_i^{C} is the combinatorial part, and γ_i^{R} is the residual part. According to Chen and Song, the NRTL−SAC model is based on the derivation of the original NRTL model for polymers.[2] In the NRTL−SAC model, the combinatorial part is calculated as

$$\ln \gamma_i^{C} = \ln \frac{\varnothing_i}{x_i} + 1 - r_i \sum_j \frac{\varnothing_j}{x_j} \tag{2}$$

where x_i is the mole fraction of component i, r_i is the total segment number in component i, and $\varnothing_i$ is the segment mole fraction in the mixture. The residual term is defined as

$$\ln \gamma_i^{R} = \ln \gamma_i^{lc} = \sum_m r_{m,i}(\ln \Gamma_m^{lc} - \ln \Gamma_m^{lc,i}) \tag{3}$$

In eq 3 the two terms $\ln \Gamma_m^{lc}$ and $\ln \Gamma_m^{lc,i}$ are the activity coefficients of segment m in the whole solution and in component i, respectively. These two terms can be determined using the equations

$$\ln \Gamma_m^{lc} = \frac{\sum_j x_j G_{j,m}\tau_{j,m}}{\sum_k x_k G_{k,m}} + \sum_{m'} \frac{x_{m'} G_{m,m'}}{\sum_k x_k G_{k,m'}} \left(\tau_{m,m'} - \frac{\sum_j x_j G_{j,m'}\tau_{j,m'}}{\sum_k x_k G_{k,m'}}\right) \tag{4}$$

$$\ln \Gamma_m^{lc,l} = \frac{\sum_j x_{j,l} G_{j,m}\tau_{j,m}}{\sum_k x_{k,l} G_{k,m}} + \sum_{m'} \frac{x_{m',l} G_{m,m'}}{\sum_k x_{k,l} G_{k,m'}} \left(\tau_{m,m'} - \frac{\sum_j x_{j,l} G_{j,m'}\tau_{j,m'}}{\sum_k x_{k,l} G_{k,m'}}\right) \tag{5}$$

where i refers to the component and j, k, m, and m' refer to the segments in each component. $x_{j,i}$ is the segment-based mole fraction of segment j in component i only. The parameters in eqs 2−5 can be found from the definitions in the literature.[2]

VLE, LLE, and SLE Prediction. For any component in equilibrium with itself in a multiphase system the fugacity in each phase must be equal to the corresponding value in the other phases[16]

$$f_i^{\alpha} = f_i^{\beta} = \cdots = f_i^{\gamma} \qquad i = 1, 2, ..., N \tag{6}$$

where N is the total number of solvents present in the system. For a vapor−liquid and solid−liquid equilibrium system eq 6 can be written in the following forms[17]

$$\text{SLE:} \quad x_i \gamma_i P_i^{sat} = f_i^{s} \tag{7}$$

$$\text{VLE:} \quad x_i \gamma_i P_i^{sat} = y_i P_{tot} \varphi_i \tag{8}$$

$$\text{LLE:} \quad (x_i \gamma_i)^{\alpha} = (x_i \gamma_i)^{\beta} \tag{9}$$

where x_i and y_i are the mole fractions of component i in the liquid and vapor phases, respectively. P_i^{sat} is the saturation pressure of component i inside the system at any arbitrary temperature and total pressure P_{tot}, and f_i^{s} is the fugacity of component i in the system. φ_i is the fugacity coefficient of component i in the vapor phase, which can be assumed to be equal to unity for low to moderate pressures. The gaseous mixture is assumed to be ideal (Lewis−Randall rule) for low and moderate pressures. According to eq 9, γ_i^{α} and γ_i^{β} are activity coefficients of component i in the two liquid phases of α and β, respectively. Each of eqs 7−9 is written for each phase equilibrium calculation in conjunction with the mass balance for the whole system. The resulting model equations enable the mole and phase fractions in the system under study to be determined.

To predict the SLE of a solid in a multisolvent system, the activity coefficient of the solute in solution must be known. The following equation gives the mole fraction of solute at equilibrium[16]

$$\ln x_s = -\frac{\Delta H_{fus}}{R}\left(\frac{1}{T_m} - \frac{1}{T}\right) - \ln \gamma_s \tag{10}$$

where x_s refers to the solute mole fraction; ΔH_{fus} is the heat of fusion; and T_m is the melting temperature of the solid under normal conditions, which can be measured using characterization methods such as differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA).[13] The values of γ_s are evaluated by activity coefficient thermodynamic models such as the NRTL−SAC model.

OPTIMIZATION METHOD AND PROCEDURE

To examine the best solvent or mixture of solvents for the crystallization of a certain component, a new optimization algorithm was developed with the objective functions

$$J_1(T, y) = S_{initial} - S_{final} = \frac{m_{initial,solute} - m_{final,solute}}{m_{solvent}} \tag{11}$$

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Table 1. Segment Numbers, Antoine Coefficients of Vapor Pressure, and Normal Boiling Points of the Solvents Studied in This Work,[19] along with the Class Numbers Assigned by the Food and Drug Administration (FDA)[18]

solvent	X	$Y-$	$Y+$	Z	A	B	C	T_b (K)	class
acetic acid	0.048	0.222	0.195	0.206	4.682	1642.540	−39.764	390.58	3
acetone	0.131	0.109	0.513	0.000	4.424	1312.253	−32.445	329.03	3
acetonitrile	0.018	0.131	0.883	0.000	4.279	1355.374	−37.853	354.62	2
anisole	0.536	0.010	0.653	0.000	4.177	1489.756	−69.607	426.24	3
benzene	0.615	0.000	0.281	0.000	4.018	1203.835	−53.226	352.83	1
1-butanol	0.425	0.004	0.000	0.490	4.546	1351.555	−93.340	390.64	3
2-butanol	0.343	0.069	0.000	0.393	4.329	1158.672	−104.683	372.31	3
n-butyl acetate	0.317	0.030	0.330	0.000	4.268	1440.231	−61.362	398.81	3
methyl *tert*-butyl ether	0.483	0.105	0.142	0.000	4.039	1149.261	−43.150	327.71	3
carbon tetrachloride	0.739	0.027	0.142	0.000	4.023	1221.781	−45.739	349.44	1
chlorobenzene	0.727	0.024	0.484	0.000	4.111	1435.675	−55.124	404.37	2
chloroform	0.393	0.000	0.167	0.000	4.208	1233.129	−40.953	334.02	2
cumene	1.161	0.000	0.000	0.000	4.054	1455.811	−65.948	425.04	3
cyclohexane	0.892	0.000	0.000	0.000	4.140	1316.554	−35.581	353.60	2
1,2-dichloroethane	0.394	0.000	0.691	0.000	4.585	1521.789	−24.670	356.56	1
1,1-dichloroethylene	0.529	0.000	0.208	0.000	4.097	1099.400	−35.950	304.29	1
1,2-dichloroethylene	0.188	0.000	0.832	0.000	4.147	1205.400	−42.550	333.20	2
dichloromethane	0.459	0.000	0.427	0.038	4.537	1327.016	−20.474	312.97	2
1,2-dimethoxymethane	0.277	0.030	0.077	0.057	4.037	1068.350	−50.409	315.06	2
N,*N*-dimethylacetamide	0.160	0.778	0.193	0.000	6.095	2725.960	28.209	419.07	2
N,*N*-dimethylformamide	0.180	0.752	0.254	0.000	3.931	1337.716	−82.648	422.97	2
dimethyl sulfoxide	0.000	1.114	0.000	0.000	4.491	1807.002	−60.995	463.35	3
1,4-dioxane	0.154	0.086	0.401	0.000	4.581	1570.093	−31.297	374.01	2
ethanol	0.251	0.030	0.000	0.630	5.247	1598.673	−46.424	351.12	3
ethyl acetate	0.339	0.058	0.441	0.000	4.228	1245.702	−55.189	349.81	3
ethylene glycol	0.000	0.343	0.000	0.852	5.337	2161.910	−64.720	469.80	2
diethyl ether	0.387	0.028	0.177	0.000	4.022	1062.640	−44.930	309.14	3
ethyl formate	0.256	0.305	0.000	0.000	4.133	1123.943	−54.903	326.86	3
formamide	0.000	0.089	0.341	0.252	7.585	3881.305	27.655	484.04	2
formic acid	0.000	0.090	0.000	0.420	2.001	515.000	−139.408	396.75	3
n-heptane	1.152	0.000	0.000	0.000	4.028	1268.636	−56.199	371.13	3
n-hexane	1.000	0.000	0.000	0.000	4.003	1171.530	−48.784	341.47	2
isobutyl acetate	0.620	0.183	0.541	0.000	4.537	1625.875	−32.494	390.87	3
isopropyl acetate	0.552	0.154	0.498	0.000	4.552	1490.877	−34.098	361.64	3
methanol	0.090	0.139	0.000	0.594	5.204	1581.341	−33.500	337.37	2
2-methoxyethanol	0.082	0.095	0.180	0.361	5.064	1853.556	−30.838	396.87	2
methyl acetate	0.239	0.000	0.338	0.000	4.204	1164.426	−52.690	329.69	3
3-methyl 1-butanol	0.419	0.000	0.538	0.314	5.080	1932.043	−28.698	408.99	3
methyl butyl ketone	0.673	0.224	0.469	0.000	5.667	2011.668	−45.364	400.33	2
methyl cyclohexane	1.053	0.000	0.246	0.000	3.948	1270.763	−51.734	373.62	2
methyl ethyl ketone	0.261	0.095	0.463	0.000	3.989	1150.207	−63.904	352.22	3
methyl isobutyl ketone	0.673	0.224	0.469	0.000	3.953	1254.095	−71.537	388.79	3
isobutanol	0.566	0.000	0.067	0.485	4.431	1236.991	−101.528	380.68	NA
N-methyl-2-pyrrolidone	0.252	0.790	0.281	0.000	12.657	4112.280	−66.866	391.76	2
nitomethane	0.122	0.000	1.032	0.051	4.405	1446.196	−45.633	373.91	2
n-pentane	0.898	0.000	0.000	0.000	3.989	1070.617	−40.454	308.83	3
1-pentanol	0.458	0.024	0.000	0.491	4.324	1297.689	−110.669	410.77	3
1-propanol	0.374	0.013	0.000	0.530	5.314	1690.864	−51.804	370.00	3
isopropyl alcohol	0.332	0.000	0.000	0.636	4.861	1357.427	−75.814	355.06	3
n-propyl acetate	0.514	0.134	0.587	0.000	4.144	1283.861	−64.378	374.20	3
pyridine	0.135	0.000	0.305	0.000	4.163	1371.358	−58.496	387.93	2
sulfolane	0.209	0.089	0.000	0.249	4.533	2255.469	−61.757	559.33	2
tetrahydrofurane	0.235	0.040	0.320	0.708	4.121	1202.942	−46.818	338.71	2
tetrahydronaphtalene	0.924	0.000	0.865	0.000	4.127	1690.912	−70.229	479.98	2
toluene	0.604	0.000	0.304	0.000	4.142	1377.578	−50.507	383.13	2
1,1,1-trichloroethane	0.548	0.000	0.287	0.000	5.886	2210.179	34.902	340.59	1
trichloroethylene	0.552	0.000	0.262	0.000	3.553	974.538	−85.811	360.06	2
m-xylene	0.758	0.021	0.316	0.000	4.134	1462.266	−58.045	411.76	2
water	0.000	0.000	0.000	1.000	6.210	2354.731	7.559	371.65	NA
trimethylamine	0.403	0.030	0.000	0.000	4.016	970.297	−34.060	275.66	NA

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Table 1. continued

solvent	X	Y−	Y+	Z	A	B	C	T_b (K)	class
1-octanol	0.867	0.000	0.000	0.534	6.477	2603.359	−48.799	450.75	NA
n-octane	1.253	0.000	0.000	0.000	4.049	1355.126	−63.633	398.34	NA

Table 2. Segment Numbers and Physical Properties of Selected Components from the Literature

model molecule	melting temperature (K)	heat of fusion (kJ/mol)	entropy of change [J/(mol K)]	X	Y−	Y+	Z
lovastatin[13]	445.50	43.14	96.84	1.175	0.000	0.548	0.882
valsartan[13]	380.65	31.65	83.15	0.000	0.946	0.000	0.539
paracetamol[12]	443.20	27.60	62.28	0.416	0.016	0.168	1.861
budesonide[15]	534.00	34.70	64.98	1.000	0.178	0.005	1.079
allopurinol[15]	653.50	38.50	58.91	0.016	0.002	1.169	0.000
furosemide[15]	534.30	48.70	91.15	0.600	0.127	0.010	1.620
sulfadiazine[12]	538.80	31.20	57.91	0.757	0.000	0.000	1.940

$$J_2(T, y) = \frac{S_{\text{initial}} - S_{\text{final}}}{S_{\text{initial}}} \quad (12)$$

where $J_1(T,y)$ is an objective function based on the mass of solvent (or mixtures of solvents). The solubilities of the model molecules (S_{initial} and S_{final}) are expressed in units of mass of solute per mass of solvent. This objective function is defined in terms of the solubility at the initial and final states of crystallization and the mass of the solvent mixture. In eq 11, the $m_{\text{initial,solute}}$ and $m_{\text{final,solute}}$ denote the the initial and final masses, respectively, of dissolved solute in the solution, and m_{solvent} is the mass of solvent. In the absence of evaporation, the mass of solvent remains constant, as the process is operated under batch mode. $J_2(T,y)$ is an objective function based on the initial and final masses of solute. The main difference between the two objective functions is their dependency on the mass of solvent used in the crystallization process. For the first objective function, the mass of solvent consumed in addition to the mass of solute at both ends of crystallization is included in optimization, whereas the second objective function deals with the masses of the solute at the beginning and end of the process only. For each of these two objective functions, many constraints must be met for the crystallization process to be run safely and reliably. The optimization procedures with detailed formulations in single, binary, and ternary systems are demonstrated in Appendix A. The NRTL−SAC model is formulated on the molar basis calculation of the solubility. To transfer the results to the mass basis, we used a simple conversion factor that contains the ratio of molecular weights of the corresponding components.

The solvents used in the current study are listed in Table 1, along with their segment numbers, Antoine coefficients, and normal boiling points. The final column of this table lists the class of each solvent used in our study, based on the recommendation of U.S. Food and Drug Administration (FDA) for industries.[18] The solvents are divided into three classes, with the less recommended solvents for crystallization as class 1 and the favorable solvents as class 3. As an example, benzene is listed as class 1 because of its carcinogenic nature. There are many solvents in classes 2 and 3, which can be used in the pharmaceutical industry, but caution should be taken in separation and purification processes downstream of the crystallization process.

RESULTS AND DISCUSSION

The selected model molecules are listed in Table 2.[12−15] The physical properties of the model molecules with the four conceptual segment numbers used in our study are also included in Table 2. First, the results of optimization for the single-solvent case are discussed; then, those for binary and ternary systems of solvents are presented. As mentioned earlier, the computation times for finding the best solvent mixture in mixtures of two or more solvents are prohibitively high. Therefore, the quaternary case is not presented in the current study because the marginal improvement in the objective functions was found to be negligible, despite the enormous increase in computational time. The chemical structures of the model molecules used in this study are shown in Figure 1. For all of the calculations, a computer with a 2.67 GHz Core (2) Duo processor was used. The computations were primarily conducted in the Matlab environment. It should be noted that the mole ratios mentioned

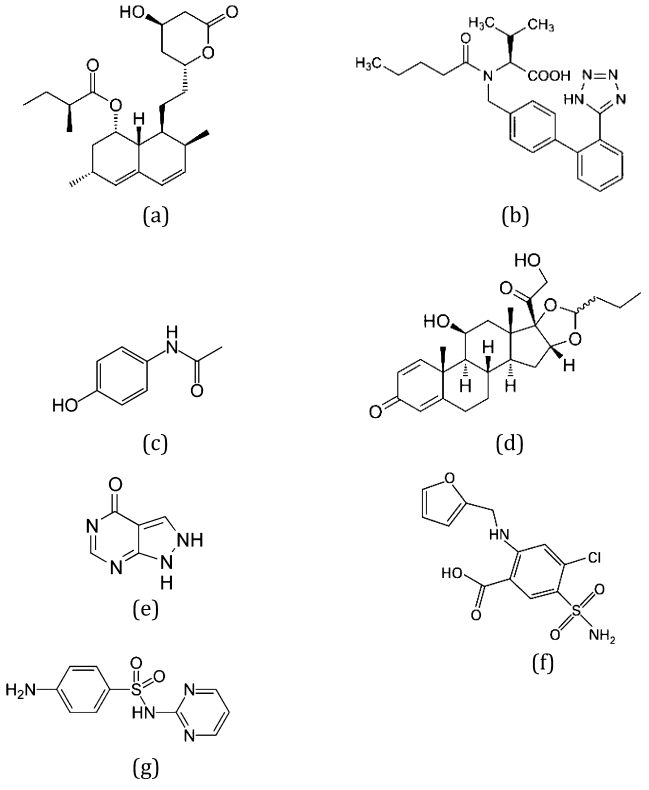

Figure 1. Chemical structures of model molecules used in the current study: (a) lovastatin, (b) valsartan, (c) paracetamol, (d) budesonide, (e) allopurinol, (f) furosemide, and (g) sulfadiazine.

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later represent the division of the two solvents' molar contents in a mixture (eq 3A). This quantity must not be treated as the mole fraction of solvents in the mixture.

Single-Solvent Screening. According to the description in previous sections, solvent screening was performed using single solvents and binary and ternary solvent mixtures. The first category deals with solvent selection from among single solvents. The selections were made among 62 solvents commonly used in research centers and industries.[2] For each of the objective functions defined in the Optimization Method and Procedure section, optimization was performed to find the best solvent for the crystallization process. In Table 3, the optimal solvent for the single-solvent crystallization of each component is listed. It should be noted that the initial and final temperatures for all of the simulations in the single-solvent case were chosen as 40 and 20 °C, respectively. The operating temperatures for the process were selected to satisfy the safety requirements of the crystallization process.

Table 3. Optimal Single Solvent for Each of the Model Components with Their Starting and Ending Operating Temperatures at 40 and 20 °C, Respectively

model molecule	optimal solvent	J_1 [(g crytallized)/(g of solvent)]	optimal solvent	J_2[(g crytallized)/(g of initial solute) × 100]
lovastatin	DMF[a]	0.14	chloroform	70.51
valsartan	water	3.01	pyridine	83.64
paracetamol	methanol	0.23	pyridine	61.88
budesonide	ethyl formate	0.13	pyridine	61.00
allopurinol	acetonitrile	9.60×10^{-4}	sulfolane	63.55
furosemide	ethyl formate	0.03	formic acid	72.29
sulfadiazine	DMSO[b]	0.16	formic acid	61.86

[a]*N*,*N*-Dimethylformamide. [b]Dimethyl sulfoxide.

It can be seen from Table 3 that, for each pharmaceutical model molecule, there is a solvent that can produce the maximum amount of solid crystals based on one of the objective functions. It is worth noting that, for all seven solutes, the solvent that yielded the highest value for objective function J_1 was different from the solvent that yielding the highest value for the other objective function, J_2, which is because of the definitions of the two objective functions. The first objective function maximizes the amount of crystallized solid and minimizes the amount of solvent used. This is more clearly illustrated in Figure 2, which shows the solubility curves of valsartan in pyridine and water. From Table 3, it can be seen that water will maximize the first objective function, whereas pyridine optimizes the second objective function. To maximize the second objective function, the final solubility should be as low as possible, whereas the initial solubility has a minor effect in optimizing this objective function. This shows that one might find some solvents with near-zero solubilities in the final stage of crystallization, hence optimizing the yield based on the second objective function. However, for the first objective function, in addition to the final solubility, the initial solubility and solvent mass are also important. The final selection of the solvent can be improved by considering other parameters such as environmental and hazardous conditions associated with using each specific solvent. For example, solvent cost is an important issue when dealing with the large-scale production of pharmaceuticals or specialty chemicals. If this is the case, the first objective function can help an engineer determine the most favorable solvent for the process. On the other hand, if the price of the solvent is not crucial and the chemical is much more expensive, the yield based on the second objective function can help determine the best solvent.

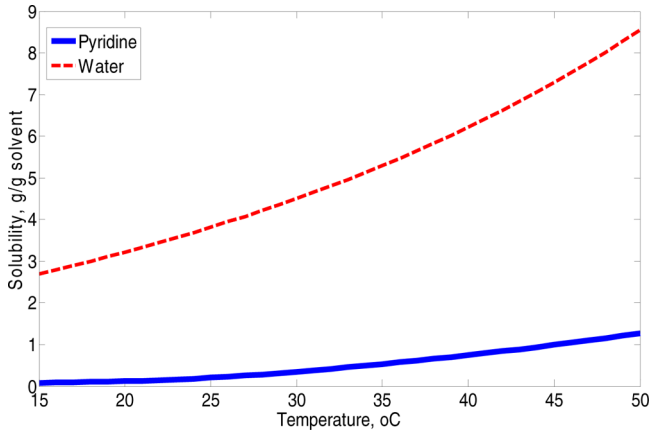

Figure 2. Solubility curves obtained for valsartan in pyridine and water using the NRTL−SAC model.

To compare the values of the two objective functions for the crystallization of the model molecules in 62 solvents, we used a scatter chart as shown in Figure 3, which represents the single-solvent solubility for sulfadiazine. The *x* axis shows the solvent identification number (i.e., that for water is 59), and the *y* axes on the left and right present the performance based on the first and second objective functions, respectively. As is evident from the figure, for all of the solvents, the second objective function is in the range of 45−62%, whereas the first objective function has a value of nearly zero for about 45 solvents. This means that, despite having a reasonable value for the second objective function, many of the solvents could not provide favorable results for the first objective function. Therefore, three solvent candidates with the most favorable yields for both objective functions were selected as *N*,*N*-dimethylacetamide, *N*,*N*-dimethylformamide (DMF), and dimethyl sulfoxide (DMSO). Of these three solvents, DMSO might be the best solvent, with values for the first and second objective functions equal to 0.16 (g crytallized)/(g of solvent) and 47.55%, respectively. However, if one based the selection on the first objective function only, DMF would be considered as the optimal single solvent.

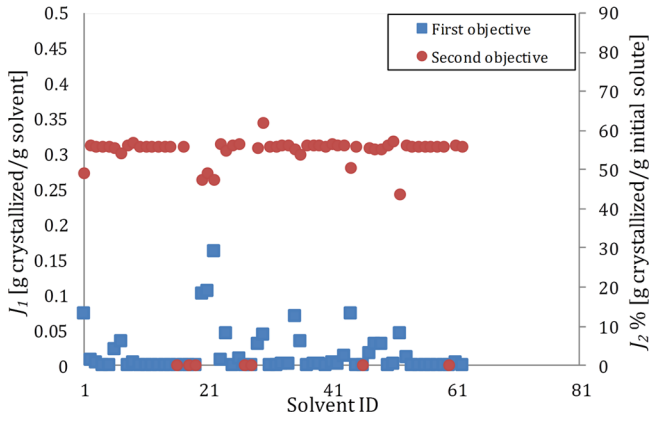

Figure 3. Comparative illustration of the values for two objective functions for sulfadiazine.

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Table 4. Optimal Operating Conditions for Cooling and Antisolvent Crystallization of the Binary Solvent for the First Objective Function (J_1)

model component	initial conditions				final conditions		
	optimal solvents (first, second)	mole ratio (r_1)	volume ratio (r_1')	temperature (°C)	mole ratio (r_1)	volume ratio (r_1')	temperature (°C)
lovastatin	DMSO, ethyl formate	0.54	0.47	65	36.90	32.43	15
valsartan	*n*-heptane, water	0.00	0.00	65	28.57	233.79	19
paracetamol	cumene, methanol	0.00	0.00	65	24.18	83.31	20
budesonide	cyclohexane, ethyl formate	0.00	0.00	64	32.14	42.98	19
allopurinol	acetonitrile, trimethyl amine	4.52	2.67	39	312.44	184.72	20
furosemide	ethyl formate, formic acid	64.74	138.61	64	0.00	0.00	15
sulfadiazine	cyclohexane, DMSO	0.08	0.13	65	117.86	179.34	15

Binary-Solvent Screening. In the case of binary-solvent screening, the first objective function was used for all possible combinations of solvents (i.e., 1891 binary combinations). For the binary-solvent case, one always can find a second solvent that leads to complete crystallization of the solute, which maximizes the second objective function. The results of optimizing the process conditions during the initial and final parts of the process using the first objective function are presented in Table 4. For each component, there is a pair of solvents that results in maximum crystallization of the solute per mass of solvent. In the first column, the two selected optimal solvents are listed, and their mole and volume ratios are given in the third and fourth columns. The solvent selections and conditions for each model molecule are discussed. The maximum amount of product crystals based on the first objective function and the corresponding value in terms of the second objective function are included in Table 4. As mentioned, the second objective function can be maximized with some different combinations of solvents, whereas the first objective is much more restrictive in terms of solvent selection. It should be noted that the value of zero for a mole or volume ratio of solvents in Table 4 means that part of the crystallization process is performed with the pure second solvent. The same thing applies when the ratio is a large number, which corresponds to negligible second solvent.

Lovastatin. In this case, the initial and final temperatures lie exactly on the constraint limits for temperature. After optimization of all possible solvent combinations, dimethyl sulfoxide (DMSO) and ethyl formate were found to form the optimal solvent mixture. In Figure 4, the solubility of lovastatin in mixtures of cumene and acetonitrile is demonstrated. As is evident from the results, for all temperatures, a value of 0.35 for the mole ratio of cumene to acetonitrile yields the maximum solubility. For the case of crystallization with these solvents, the initial and final states and temperatures can be found from Figure 4. This procedure was conducted for all binary combinations of solvents to maximize the crystallization of lovastatin. According to the results reported in Table 4, the volume ratio of DMSO to ethyl formate at the beginning of the crystallization is 0.47, and the final value is 32.43. This means that the crystallization process should be started with nearly half as much DMSO as ethyl formate at 65 °C to dissolve as much lovastatin as possible. However, at the end of the process at 15 °C, excess DMSO has to be added to the vessel to achieve the final ratio of solvents, thereby maximizing the crystal yield based on the first objective function. The temperature ranges are exactly the values that were initially set for the crystallization without any change. This shows that the bubble point of the solvent mixture from the start to the final part of the process and the melting point of the solute are higher than the operating temperatures. The optimum value of the first objective function for lovastatin is 1.08 g crytallized per gram of solvent.

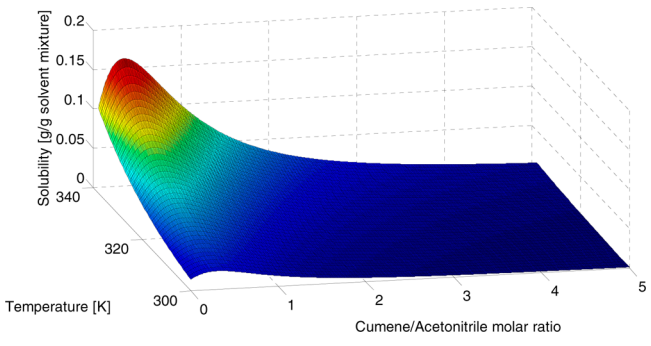

Figure 4. Solubility of lovastatin in mixtures of cumene and acetonitrile in the temperature range of 300−340 K.

Valsartan. The optimal pair of solvents for this component are *n*-heptane and water in mole ratios of 0.00 and 28.57 at the beginning and end of crystallization, respectively. From Table 4, it can be seen that the volume ratio of *n*-heptane to water under both conditions shows that one of the solvents has a high solubility (water) and the other has a very poor solubility (an antisolvent). It is worth noting that the miscibility conditions for the mixtures at both ends of the crystallization process were examined and satisfied.

Paracetamol. For this model molecule, the initial and final states of the solvent mole and volume fractions are at the extreme values, as in the valsartan case. The optimum pair of solvents for paracetamol is cumene and methanol. As the solubility of paracetamol in methanol is very high, specifically at higher temperatures, the initial conditions of the crystallizer should be pure methanol at the highest possible temperature. The final state is reached by adding cumene to achieve a cumene/methanol volume ratio of 83.31 to crystallize the solute. This high volume ratio of cumene to methanol shows the huge addition of cumene as an antisolvent. Also, the temperature should be selected as low as possible at the final stage.

Budesonide. The pair of solvents suitable for the highest crystal yield for this component is cyclohexane and ethyl formate. The procedure of the crystallization is the same as for paracetamol, but with different solvent ratios at the initial and final stages of operation.

Allopurinol. This component generally has a very low solubility in most solvents. Because of the N−H bonds in its chemical structure, two solvents having amine and nitrile groups were found to form the optimum pair of solvents for the crystallization process. Trimethylamine is the best at dissolving allopurinol, whereas acetonitrile at high concentration is a poor

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solvent. Therefore, in the initial stage of the process, a combination of the two solvents was identified for the maximum dissolution. The mixture of the two solvents has a high concentration of both nitrile and amine groups, which might be of help in attracting and dissolving the solid molecule. Other solvents were not able to dissolve this component compared with the two selected solvents. It is worth noting that the boiling points of trimethylamine and acetonitrile are very low, and as a result, the initial temperature was set at 39 °C for the initial operation.

Furosemide. The optimal pair of solvents for this component was found to be ethyl formate and formic acid as the solvent and antisolvent, respectively. The results show that, at the end of crystallization process, the volume fraction of solvent should reach to zero, as the antisolvent crystallizes almost all of the furosemide dissolved in the solution. The value of the first objective function for this process is 0.13 (g crytallized)/(g of solvent), which is very high. Trying other combinations of solvents resulted in lower yields. On the other hand, as the first objective function was defined based on the number of moles of solute per mole of solvent mixture, the lower molecular weight of the mixture of solvents corresponds to a lower mass of solvents consumed. The molecular weights of formic acid and ethyl formate are low and hence, make the crystallization operation economical.

Sulfadiazine. In this case, DMSO was found to be the best solvent, with cyclohexane as an antisolvent. The reason DMSO was selected for the crystallization might be the sulfide groups, which are similar in both solute and solvent. Cyclohexane is a relatively nonpolar solvent and is a poor solvent for this component.

Ternary-Solvent Screening. As mentioned in previous sections, the computation time increases rapidly as the number of solvents under study increases. From Table 5, it can be seen that the time required to optimize the 62 binary combinations of solvents for the model molecules varied from 1 to 25 h of CPU time. On the other hand, a careful study of all common 62 solvents revealed that around half of them had similar segment numbers. Therefore, 30 solvents from the pool of 62 solvents were chosen for ternary-solvent optimization. The optimum solvents in the binary case were also included in this subset. The optimum solvent mole and volume ratios are listed in Table 6 for each model molecule. It should be noted that r_i and r_i' refer to the ratios of the numbers of moles or volumes of solvent i to solvent i + 1 in each part of crystallization. The results of optimization for the solvents in the ternary case for the first objective function are reported in Table 6. This table lists the three-solvent combinations for each model molecule, along with their mole and volume ratios at the beginning and end of crystallization.

Lovastatin. DMSO was selected as the first solvent, which is similar to the binary case as the initial solvent for crystallization. The other two solvents screened are different from that in the binary case. However, the combination of the two other solvents (cyclohexane and trimethylamine) is such that the yields are nearly the same under the two sets of conditions, which shows that DMSO has a major effect on the crystallization of this component.

Valsartan. For this model molecule, *n*-heptane and water solvents are the same as in the binary case. Water was selected as the initial solvent for crystallization. The mole and volume ratios of the two other solvents with respect to water are zero. Ethyl formate is present in a very small amount with respect to *n*-heptane at the end of the process, which shows that the ternary optimization of solvents is nearly the same as in the binary case.

Paracetamol. For this component, methanol is the major solvent initially (the same as in the binary case); however, methanol content is nearly zero at the end of crystallization. The final part of crystallization runs with cumene as an antisolvent with a small amount of water.

Budesonide. As is evident from Table 6 and eqs 4A−6A (in Appendix A), the mole fractions of ethyl formate and formic acid are 0.96 and 0.04, respectively. This shows that a minute amount of formic acid is added to ethyl formate in the initial part of crystallization. To increase the yield, formic acid should be added to the system in a large amount as shown in Table 6. Here, the temperature range of crystallization is also nearly bounded by the two limits. The only difference between this case and the binary case is that formic acid was used as an antisolvent. The reason for this difference is the presence of DMSO in the system, which interacts with the other solvents similarly to cyclohexane in the binary case.

Table 5. Optimum Value of First Objective Function (J_1) for Model Components with the Corresponding Yield Based on the Second Objective and the CPU Time Allocated for Calculation for Binary-Solvent Optimization

component	J_1 [(g crytallized)/(g of solvent)]	J_2 [(g crytallized)/(g of initial solvent) × 100]	CPU time (h)
lovastatin	1.08	96.58	14.79
valsartan	14.24	100.00	2.94
paracetamol	0.97	100.00	15.41
budesonide	0.48	100.00	3.31
allopurinol	9.67×10^{-4}	95.17	0.42
furosemide	0.13	62.14	1.00
sulfadiazine	0.64	99.42	6.78

Table 6. Optimal Solvents with Their Mole Ratios, Volume Ratios, and Temperatures for the Initial and Final Parts of Crystallization Based on the First Objective Function (J_1)

	initial conditions				final conditions		
model molecule	optimum solvents (first, second, third)	mole ratio (r_1, r_2)	volume ratio (r_1', r_2')	temperature (°C)	mole ratio (r_1, r_2)	volume ratio (r_1', r_2')	temperature (°C)
lovastatin	DMSO, cyclohexane, trimethyl amine	2.28, 3.29	1.50, 4.03	65	0.00, 3.364	0.00, 4.12	19
valsartan	ethyl formate, *n*-heptane, water	0.00, 0.00	0.00, 0.00	65	0.01, 381.91	0.00, 312.50	15
paracetamol	water, cumene, methanol	7.66, 0.00	1.00, 0.00	65	0.00, 19.76	0.00, 68.09	19
budesonide	DMSO, ethyl formate, formic acid	0.00, 28.00	0.00, 59.93	64	32.56, 0.00	42.98, 0.00	15
allopurinol	cyclohexane, acetonitrile, trimethyl amine	0.00, 17.55	0.00, 10.38	40	5.63, 0.04	11.66, 0.03	20
furosemide	DMSO, ethyl formate, 1,4-dioxane	0.16, 101.30	0.12, 95.94	65	0.18, 0.00	0.16, 0.00	15
sulfadiazine	DMSO, trimethyl amine, dichloromethane	9.83, 344.48	7.91, 475.93	65	25.53, 0.00	20.54, 0.00	20

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Allopurinol. The solvent combination for the ternary system provides a higher yield according to the first objective function (nearly 15% higher than in the binary case). Acetonitrile and trimethylamine are selected in both the binary and ternary systems, but cyclohexane is added at the end of the crystallization process to crystallize as much solute as possible in the ternary-solvent case.

Furosemide. Ethyl formate is selected in the ternary system for the initial part of crystallization, whereas the final part of crystallization runs with 1,4-dioxane instead of formic acid in the binary-solvent combination. It seems that the yield of the first objective function changed slightly, whereas the second objective function for the ternary optimization changed significantly.

Sulfadiazine. DMSO has poor dissolving power for sulfadiazine, which why it was selected in both the binary and ternary systems as a crystallizing antisolvent agent in the final part of the crystallization process. However, dichloromethane was also selected in combination with DMSO in the ternary system for the final part of the process. The initial part of crystallization runs with trimethylamine for the ternary case, which has excellent dissolving characteristics for sulfadiazine.

The results of optimization based on both objective functions are summarized in Table 7. There are some additional points that must be mentioned based on the calculations for the ternary-solvent case as follows:

- According to Table 8, the yield based on optimization of the first objective function does not change significantly compared to its value in the binary case, except for allopurinol. It can be seen that the maximum value of the first objective function for a specific component for binary, ternary, and also higher combinations is nearly the same.
- For nearly all seven model molecules, the optimum solvents in the binary and ternary mixtures were nearly the same. The solvents that were picked in the ternary case were almost all from the list of solvents in the binary case (Table 4).
- To find an optimal solvent or solvent mixture for a model molecule, the selection should be made from the pool of binary solvents, as the cost of solvent recovery and filtration increases with the presence of more solvents. In addition, the change in the value of optimization of the first objective function from binary to ternary solvent systems is not significant.

Table 7. Optimal Values of Crystal Yield for Ternary Mixture of Solvents Based on the First Objective Function and the Corresponding Second Objective Function

component	J_1 [(g crytallized)/(g of solvent)]	J_2 [(g crytallized)/(g of initial solute) × 100]	CPU time (h)
lovastatin	1.10	99.96	46.92
valsartan	14.25	100.00	12.34
paracetamol	0.97	100.00	76.20
budesonide	0.49	99.84	13.29
allopurinol	0.0014	96.42	1.31
furosemide	0.14	99.88	4.00
sulfadiazine	0.66	99.98	42.78

CONCLUSIONS

In this work, optimal solvent screening for the crystallization of seven pharmaceutical molecules based on a modified optimization algorithm and NRTL−SAC thermodynamic modeling of VLE, LLE, and SLE of 62 common industrial solvents was successfully accomplished. The algorithm showed good predictive capability in VLE, LLE, and SLE systems. Two different objective functions were defined for the optimization. The results of single-, binary-, and ternary-solvent screening calculations are reported in Table 8. It is evident that, in general, the best choice for maximizing crystallization based on the first objective function of a batch cooling−antisolvent process is a binary solvent system. As an example, the binary crystallization yields of valsartan and paracetamol increased by factors of 4 and 3, respectively, with respect to the results obtained with a single optimal solvent. The additional computational complexities created do not justify ternary solvent systems. The ternary solvent systems were found to affect only the second objective function, which, for some cases such as furosemide, resulted in an improved yield. It should be noted that, for some optimization cases, high dilution conditions occurred at either or both ends of crystallization, which shows the possibility of applying other processing methods, such as evaporative crystallization. This work shows the capability of the thermodynamic model in conjunction with the proposed optimization procedure to yield the best combination of solvents for optimal performance of a crystallization process, specifically in the pharmaceutical industry.

APPENDIX A

In this appendix, the mathematical formulation of the optimization procedure and the algorithm to find the constituents mole fractions for single solvents and binary and ternary solvent mixtures are demonstrated.

Single Solvent

For safety reasons, we required the program to choose the upper limit of the crystallization temperature to be less than the melting point of the solid. Therefore, the mathematical representation of the problem for single-solvent optimization is

Table 8. Optimal Objective Function Values for Single-, Binary-, and Ternary-Solvent Combinations

	single		binary		ternary	
component	J_1	J_2	J_1	J_2	J_1	J_2
lovastatin	0.14	70.51	1.08	96.58	1.10	99.96
valsartan	3.01	83.64	14.24	100.00	14.25	100.00
paracetamol	0.23	61.88	0.97	100.00	0.97	100.00
budesonide	0.13	61.00	0.48	100.00	0.49	99.84
allopurinol	9.60×10^{-4}	63.55	9.67×10^{-4}	95.17	0.0014	96.42
furosemide	0.03	72.29	0.13	62.14	0.14	99.88
sulfadiazine	0.16	61.86	0.64	99.42	0.66	99.98

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$$\max_{T_{initial}, T_{final}} J_u(T) \qquad u = 1, 2 \tag{1A}$$

subject to

$$\{T_{initial}, T_{final}\} + 5 < T_{melting}$$

$$\{T_{initial}, T_{final}\} + 10 < T_{solvent}{}^{sat}$$

$$T_{initial} > T_{final}$$

where $T_{initial}$ and T_{final} are the initial and final temperatures, respectively, of the crystallization operation. The vapor pressure of a pure component (Antoine equation) can be found from

$$\log_{10}(P_i^{sat}) = A_i - \frac{B_i}{T^{sat} + C_i} \qquad i = 1, 2, ..., N;$$

$$P \text{ (bar)}, T \text{ (K)} \tag{2A}$$

The values of the constants in eq 2A for all of the solvents were found from the National Institute of Standards and Technology database[18] and are listed in Table 1.

Binary Solvents

For the case of binary-solvent calculations, in addition to the constraints implemented in the single-solvent case, there are additional nonlinear constraints. The initial and final operating temperatures are calculated based on the bubble point and freezing point of the solvent mixture. According to the results obtained by Sheikholeslamzadeh and Rohani the NRTL−SAC model can be best used to predict the VLE behavior of multicomponent systems.[14] Therefore, we employed the NRTL−SAC model to predict the bubble-point temperature of the solvent mixture in addition to the SLE calculations. The VLE calculations for binary and multisolvent systems were coded using methods described elsewhere.[14] In addition to the initial and final temperatures as optimization variables, the initial and final mole fractions of the solvents (or their volume ratio) are also included in the optimization procedure. Therefore, we need to have a framework to relate the mole fractions of solvents and solute together. For a system of N solvents and a solute, the procedure for finding the mole fractions of the constituents of the solution is a trial-and-error method. If we assume that the mole fractions of a solute and solvent in solution are x_{solute} and $x_z{}^s$, respectively for $z = 1, ..., N$, then the ratios of the mole fractions of two solvents are

$$R_1 = \frac{x_1{}^s}{x_2{}^s}, \quad R_2 = \frac{x_2{}^s}{x_3{}^s}, \quad ..., \quad R_{N-1} = \frac{x_{N-1}{}^s}{x_N{}^s} \tag{3A}$$

Moreover, the following relations are obtained for each solvent's mole fraction

$$x_1{}^s = R_1 x_2{}^s = R_1 R_2 R_3 \cdots R_{N-1} x_N{}^s \tag{4A}$$

$$x_2{}^s = R_2 x_3{}^s = R_2 R_3 \cdots R_{N-1} x_N{}^s \tag{5A}$$

$$x_{N-1}{}^s = R_{N-1} x_N{}^s \tag{6A}$$

The sum of the mole fractions of all components is unity; therefore

$$x_1{}^s + x_2{}^s + x_3{}^s + ... + x_{N-1}{}^s + x_N{}^s + x_{solute} = 1 \tag{7A}$$

Upon substitution of eqs 4A−6A into eq 7A, one obtains

$$x_N{}^s(R_1 R_2 \cdots R_{N-1} + R_2 R_3 \cdots R_{N-1} + \cdots + R_{N-1} + 1) + x_{solute} = 1 \tag{8A}$$

or, in compact form

$$x_N{}^s \sum_{i=1}^{N-1} \prod_{j \geq i}^{N-1} R_j + x_N{}^s + x_{solute} = 1 \tag{9A}$$

First, the solute mole fraction is guessed, and with the known values of solvent mole ratios (or volume ratios), the mole fraction of the last solvent is found. The other solvent mole fractions are found using eqs 4A−6A. The trial-and-error calculation is repeated until the error between two consecutive mole fractions for each component in the solution is minimized. The procedure to find the solubility of a solute in a system of N solvents is described elsewhere.[14] This procedure is inside the optimization loop used in the present work. The optimization problem for the binary-solvent case is

$$\max_{T_{initial}, T_{final}, R_{initial}, R_{final}} J_u(T, R) \qquad u = 1, 2 \tag{10A}$$

subject to

$$30\ ^\circ\text{C} < T_{initial} < \min\{(T_{melting} - 5), 65\ ^\circ\text{C}\}$$

$$15\ ^\circ\text{C} < T_{final} < \min\{(T_{melting} - 5), 20\ ^\circ\text{C}\}$$

$$0 \leq \left\{ \frac{x_{1,0}{}^s}{x_{2,0}{}^s}, \frac{x_{1,f}{}^s}{x_{2,f}{}^s} \right\} \leq 1000$$

$$T_{final} < T_{initial}$$

$$T_{initial} < T_j{}^{sat}(P_{tot}, x_{1,0}{}^s, x_{2,0}{}^s) - 10$$

$$T_{final} < T_j{}^{sat}(P_{tot}, x_{1,f}{}^s, x_{2,f}{}^s) - 10$$

where $x_{1,0}{}^s$ and $x_{2,0}{}^s$ are the initial solvent mole fractions, which are functions of temperature. $x_{1,f}{}^s$ and $x_{2,f}{}^s$ are the final solvent mole fractions, which are functions of the final temperature of the crystallizer. T^{sat} is the bubble temperature of the system of solvents at a total pressure of P_{tot} and the given mole fractions of components. Therefore, it can be seen that another trail-and-error procedure should be performed with the optimization for each combination of solvents, simultaneously. This procedure is repeated for each possible combination of solvents, and finally, the values of optimization are compared, and the combination providing the maximum yield is selected as the optimal solvent combination. If each combination of solvents is denoted by $S_{m,n}$ in which m and n are solvent identifiers (which are defined for all of the solvents in the program environment), then the optimized value of operating conditions for each combination is contained in each element of the matrix (matrix in matrix)

$$\mathbf{OM}_u = \begin{bmatrix} 0 & \begin{bmatrix} T_{initial} & T_{final} \\ R_{initial} & R_{final} \end{bmatrix}_{1,2} & \cdots & \begin{bmatrix} T_{initial} & T_{final} \\ R_{initial} & R_{final} \end{bmatrix}_{1,n} \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & \begin{bmatrix} T_{initial} & T_{final} \\ R_{initial} & R_{final} \end{bmatrix}_{m,n} \\ 0 & 0 & \cdots & 0 \end{bmatrix} \tag{11A}$$

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$$\mathbf{OY}_u = \begin{bmatrix} 0 & S_{1,2} & \cdots & S_{1,n} \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & S_{m,n} \\ 0 & 0 & \cdots & 0 \end{bmatrix}_u \qquad u = 1, 2 \tag{12A}$$

OM is the optimization matrix that is made by optimizing $(m \times n)/2$ combinations of solvents. $\mathbf{OY}_u$ is the matrix of objective functions for $u = 1, 2$. It should be noted that both matrices are upper diagonal and the elements for the same solvent (i.e., $m = n$) are zero. In this study, the total number of nonzero elements of the matrix for the binary solvent was 1891 [calculated as $(62 \times 61)/2$].

Ternary and Quaternary Solvents

When the number of solvents in a crystallization process increases, the number of combinations increases substantially. As an example, if one has to examine all possible combinations of a ternary solvent mixture from a list of 62 solvents, a total of 37820 [$= (62 \times 61 \times 60)/(3!)$] cases should be considered for optimization. For each case, the optimization procedure consists of linear and nonlinear constraints in addition to VLE, LLE, and SLE calculations. This procedure is computationally very intensive. Therefore, we selected a subset from the 62 solvents for each model molecule to reduce the CPU time. The selection of solvents for ternary calculation was based on the optimal group of solvents found for binary combinations. Additional solvents having different segment numbers from the selected binary solvents were also used for ternary calculations. The additional solvents were selected from the solvents with similar segment numbers and less hazardous classes.

For the quaternary-solvent optimization, the computational time for all possible combinations would be much higher (the total number of cases for quaternary systems is 557845). In the case of three- or four-solvent mixtures, the mathematical formulation for optimization is almost the same as previously described. The difference is in the number of mole fractions present in calculations of VLE and SLE. Also, the nonlinear constraints of the framework change according to the number of components present in the system. Therefore, the optimization formulation for a system of N solvents and a solute can be expressed as

$$\max_{T_{\text{initial}}, T_{\text{final}}, \mathbf{R}} J_u(T, R) \qquad u = 1, 2 \tag{13A}$$

subject to

$$30\ ^\circ\text{C} < T_{\text{initial}} < \min\{(T_{\text{melting}} - 5), 65\ ^\circ\text{C}\}$$

$$15\ ^\circ\text{C} < T_{\text{final}} < \min\{(T_{\text{melting}} - 5), 20\ ^\circ\text{C}\}$$

$$0 \le \left\{ \frac{x_{1,0}{}^{s}}{x_{2,0}{}^{s}}, \frac{x_{1,f}{}^{s}}{x_{2,f}{}^{s}}, \ldots, \frac{x_{N-1,0}{}^{s}}{x_{N,0}{}^{s}}, \frac{x_{N-1,f}{}^{s}}{x_{N,f}{}^{s}} \right\} \le 1000$$

$$T_{\text{final}} < T_{\text{initial}}$$

$$T_{\text{initial}} < T^{\text{sat}}(P_{\text{tot}}, x_{1,0}{}^{s}, x_{2,0}{}^{s}, \ldots, x_{N,0}{}^{s}) - 10$$

$$T_{\text{final}} < T^{\text{sat}}(P_{\text{tot}}, x_{1,f}{}^{s}, x_{2,f}{}^{s}, \ldots, x_{N,f}{}^{s}) - 10$$

in which $\mathbf{R} = (R_1, R_2, \ldots, R_N)$ accounts for the initial and final ratios of solvents. This operation is performed for all of the combinations of solvents of interest. The mole fractions of solvents in the nonlinear constraint are found from the expressions

$$x_1{}^{s} = \left[\frac{R_1 R_2 \cdots R_{N-1}}{R_1 R_2 \cdots R_{N-1} + \cdots + R_{N-1} + 1} \right]$$

$$x_2{}^{s} = \left[\frac{R_2 R_3 \cdots R_{N-1}}{R_2 R_3 \cdots R_{N-1} + \cdots + R_{N-1} + 1} \right]$$

$$\vdots$$

$$x_{N-1}{}^{s} = \left[\frac{R_{N-1}}{R_2 R_3 \cdots R_{N-1} + \cdots + R_{N-1} + 1} \right] \tag{14A}$$

For each optimization, these mole fractions are initialized, and a trial-and-error procedure is performed to stabilize the final results for each multisolvent system and its corresponding SLE containing the solute. For example, for the case of a ternary solvent mixture, the problem can be expressed as a three-dimensional upper diagonal matrix that contains all of the operating points of each ternary solvent combination under optimal conditions. Each nonzero element represents a 2×3 matrix that consists of the operating points. As shown in eq 15A, $\mathbf{OM}_k$ is the matrix that corresponds to all binary combinations with the kth solvent (the third solvent in a ternary solvent system)

$$\mathbf{OM}_k = \begin{bmatrix} 0 & \begin{bmatrix} T_{\text{initial}} & T_{\text{final}} \\ R_{\text{initial}}{}^{1} & R_{\text{final}}{}^{1} \\ R_{\text{initial}}{}^{2} & R_{\text{final}}{}^{2} \end{bmatrix}_{1,2,k} & \cdots & \begin{bmatrix} T_{\text{initial}} & T_{\text{final}} \\ R_{\text{initial}}{}^{1} & R_{\text{final}}{}^{1} \\ R_{\text{initial}}{}^{2} & R_{\text{final}}{}^{2} \end{bmatrix}_{1,n,k} \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & \begin{bmatrix} T_{\text{initial}} & T_{\text{final}} \\ R_{\text{initial}}{}^{1} & R_{\text{final}}{}^{1} \\ R_{\text{initial}}{}^{2} & R_{\text{final}}{}^{2} \end{bmatrix}_{m,n,k} \\ 0 & 0 & \cdots & 0 \end{bmatrix}_k \qquad k = 1, 2, \ldots, N \tag{15A}$$

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$$\mathbf{OY}_{k,u} = \begin{bmatrix} 0 & S_{1,2,k} & \cdots & S_{1,n,k} \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & S_{m,n,k} \\ 0 & 0 & \cdots & 0 \end{bmatrix}_{k,u} \qquad u = 1, 2 \tag{16A}$$

where N is the total number of solvents added to the binary combination. $R_{\text{initial}}{}^{i}$ and $R_{\text{final}}{}^{i}$ are the initial and final values, respectively, of the ith solvent ratio ($x_i^s/x_{i+1}{}^s$). For the quaternary system of solvents, the condition will be more complex, as the matrix of operating conditions will be four-dimensional. For this case, each element inside $\mathbf{OM}_{k,\vartheta}$ is a three-dimensional submatrix that contains just the values of three-solvent combinations for the first solvent picked in the four-dimensional matrix. This matrix is given by

$$\mathbf{OM}_{k,\vartheta} = \begin{bmatrix} 0 & \begin{bmatrix} 0 & \begin{bmatrix} T_{\text{initial}} & T_{\text{final}} \\ R_{\text{initial}}{}^{1} & R_{\text{final}}{}^{1} \\ R_{\text{initial}}{}^{2} & R_{\text{final}}{}^{2} \end{bmatrix}_{1,2,k} & \cdots & \begin{bmatrix} T_{\text{initial}} & T_{\text{final}} \\ R_{\text{initial}}{}^{1} & R_{\text{final}}{}^{1} \\ R_{\text{initial}}{}^{2} & R_{\text{final}}{}^{2} \end{bmatrix}_{1,n,k} \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & \begin{bmatrix} T_{\text{initial}} & T_{\text{final}} \\ R_{\text{initial}}{}^{1} & R_{\text{final}}{}^{1} \\ R_{\text{initial}}{}^{2} & R_{\text{final}}{}^{2} \end{bmatrix}_{m,n,k} \\ 0 & 0 & \cdots & 0 \end{bmatrix}_{k=1,\vartheta} & \cdots \\ \vdots & \vdots & & \vdots \\ 0 & 0 & & 0 \end{bmatrix}_{\vartheta} \tag{17A}$$

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Kokitkar, P. B.; Plocharczyk, Ed.; Chen, C.-C. Modeling Drug Molecule Solubility to Identify Optimal Solvent Systems for Crystallization. *Org. Process Res. Dev.* **2008**, *12*, 249.

(2) Chen, C.-C.; Song, Y. Solubility modeling with a nonrandom two-liquid segment activity coefficient model. *Ind. Eng. Chem. Res.* **2004**, *43*, 8354.

(3) Renon, H.; Prausnitz, J. M. Local compositions in thermodynamic excess functions for liquid mixtures. *AIChE J.* **1968**, *14*, 135.

(4) Wilson, G. M. Vapor−liquid equilibrium. XI. A new expression for the excess free energy of mixing. *J. Am. Chem. Soc.* **1964**, *86*, 127.

(5) Abrams, D. S.; Prausnitz, J. M. Statistical thermodynamics of liquid mixtures: A new expression for the excess Gibbs energy of partly or completely miscible systems. *AIChE J.* **1975**, *21*, 116.

(6) Ding-Yu, P. Extending the Van Laar Model to Multicomponent Systems. *Open Thermodyn. J.* **2010**, *4*, 129.

(7) Matsuda, H.; Matsumoto, S.; Kaguragi, K.; Kurihara, K.; Tochigi, K.; Tomono, K. Prediction of solubilities of pharmaceutical compounds in water + co-solvent systems using an activity coefficient model. *Fluid Phase Equilib.* **2010**, *290*, 153.

(8) Fredenslund, A.; Jones, R. L.; Prausnitz, J. M. Group-Contribution Estimation of Activity Coefficients in Nonideal Liquid Mixtures. *AIChE J.* **1975**, *21*, 1086.

(9) Lin, S.-T.; Sandler, I. S. A Priori Phase Equilibrium Prediction from a Segment Contribution Solvation Model. *Ind. Eng. Chem. Res.* **2002**, *41*, 899.

(10) Panayiotou, C. Equation-of-State Models and Quantum Mechanics Calculations. *Ind. Eng. Chem. Res.* **2003**, *42*, 1495.

(11) Chen, C.-C. A Segment-Based Local Composition Model for the Gibbs Energy of Polymer Solutions. *Fluid Phase Equilib.* **1993**, *83*, 301.

(12) Chen, C.-C.; Crafts, P. A. Correlation and prediction of drug molecule solubility in mixed solvent systems with a nonrandom two-liquid segment activity coefficient (NRTL−SAC) model. *Ind. Eng. Chem. Res.* **2006**, *45*, 4816.

(13) Sheikholeslamzadeh, E.; Rohani, S. Solubility prediction of pharmaceutical and chemical compounds in pure and mixed solvents using predictive models. *Ind. Eng. Chem. Res.* **2012**, *51*, 464.

(14) Sheikholeslamzadeh, E.; Rohani, S. Vapour−liquid and vapour−liquid−liquid equilibrium modeling for binary, ternary, and quaternary systems of solvents. *Fluid Phase Equilib.* **2012**, *333*, 97.

(15) Mota, F. L.; Carneiro, A. P.; Queimada, A. J.; Pinho, S. P.; Macedo, E. A. Temperature and solvent effects in the solubility of some pharmaceutical compounds: Measurements and modeling. *Eur. J. Pharm. Sci.* **2009**, *28*, 499.

(16) Gmehling, J.; Onken, U. *Vapor−Liquid Equilibrium Data Colletction*; DECHEMA: Frankfurt/Main, Germany, 1977.

(17) Smith, J. M.; Van Ness, H. C.; Abbott, M. M. *Introduction to Chemical Engineering Thermodynamics*, 7th ed.; McGraw-Hill: New York, 2005.

(18) *International Conference on Harmonisation (ICH)—Guidance for Industry. Q3C Impurities: Residual Solvents*; U.S. Food and Drug Administration: Washington, DC, 1997.

(19) *NIST Chemistry WebBook*; NIST Standard Reference Database 69; National Institute of Standards and Technology (NIST): Gaithersburg, MD, 2005.

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There were errors in Table 6 and Equation 1A in the version of this paper published October 3, 2012. The correct version published October 10, 2012.