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Molecular Thermodynamic Modeling and Design of Microencapsulation Systems for Drug Delivery

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ABSTRACT: A systematic design strategy is given for computer-aided design of microparticle drug-delivery systems produced by solvent evaporation. In particular, design of solvents, polymer material, and external phase composition are considered for the case when the active ingredient is known. The procedure is based on fundamental thermodynamic relations and group contributions to properties of pure species (solvent, active ingredient and polymer) and their mixtures. The method is intended for pharmaceuticals with complex molecular structures, for which limited experimental information is known. Case studies of solvent design are given.

INTRODUCTION

Perhaps the best-known contributions of John Prausnitz to describing the thermodynamic properties of mixtures may be activity coefficient models for solvents[1−3] and polymers.[4] These models, as well as forms developed from them[5−8] have inspired whole research programs around the world and are now routinely used in most research laboratories and process industries. In addition, part of his attention has been directed toward delivery systems for controlled release of active substances, involving studies of distribution of heavy organic solutes among aqueous phases and polymers[9] and swelling properties of gels.[10−12] These are the aspects of molecular thermodynamics we address here.

Microparticle controlled-delivery systems consist of a polymeric matrix with dissolved and/or dispersed active ingredient (AI). These are applied extensively for timed-release of organic compounds such as flavors, pharmaceuticals, and pesticides.[13] Such systems are often produced by solvent evaporation from a complex mixture of several phases. In the process, a (typically organic) phase, composed of the AI and a polymer dissolved in a volatile solvent, is emulsified in a normally aqueous external phase using a surfactant often at concentrations above its critical micelle concentration (CMC), resulting in two or three coexisting phases. Alternatively, the systems may be an aqueous phase, composed of a water-soluble AI and polymer emulsified in a hydrophobic external phase. For example, this process has been extensively studied for the production of microparticles based on biodegradeable polymers and copolymers such as polyhydroxy acids.[14,15]

Thus, selecting the proper polymer solvent and external phase solvent is essential for the formulations and processes of manufacturing particles to achieve prescribed release characteristics and desired AI loadings, while making minimal environmental impact with favorable economics. Using a strategy to estimate the outcome of chemical formulations can be valuable in the initial stages of microparticle product and process design. Previously we[16] (and others[17]) have outlined such an approach.

Formulation must ensure appropriate loading of AI into the microparticles. The loading is directly related to the partitioning of the AI among the phases present during evaporation. Major constraints on processing are that AI loss to the external and micellar phases should be minimized as solvent is evaporated, residual amounts of the solvents in the particles must be limited, and droplet size distributions must be appropriate for desired particle sizes.

Key properties for controlling these elements are mutual solubilities of all of the components and phase viscosities. These properties depend on the chemical structure of the solvents used, so a systematic method to select solvents would be valuable. The relation of solvent structure to properties requires structure-based property estimation methods. It is now possible to obtain reliable results for the most important properties used for modeling of these phenomena, allowing efficient reduction of the number of potential solvents, if not also a specific choice. Our purpose here is to describe such a strategy with a few illustrations.

Previous work has addressed microencapsulation processes and systems[16,17] based on a thermodynamic structure for predicting the final loading of AI in polymeric particles formed by evaporation of solvent from microemulsion droplets. For AI's with relatively simple molecular structures, the effects of varying the solvent identity, polymer chain length, and repeat unit structure can be captured with predictions from available activity coefficient models.

For more complicated AI's, the available activity coefficient models need to predict effects of a complex range of interactions among functional groups. Often the parameters necessary to characterize these effects have not been determined. Our prior work[18−20] showed how to estimate the solubility of complex AI based on selection of an optimal reference solvent. That method uses limited experimental data to estimate solubilities in other solvents. It is semipredictive in that it relies on knowing the solubility of the AI in one or more solvents. This limitation

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inhibits decisions when no data are known but provides a basis for reliably leveraging minimal experimental information and suggests appropriate measurement schemes. Combining this approach with the underlying thermodynamic modeling behind the AI loading computations is straightforward, allowing estimation of AI distribution in a great variety of systems.

Further, the prior works[16,17] focused on determining system properties from known chemical structures of the components (AI, solvent, polymer etc.). However, rational design of solvents is more directly addressed when considering the reverse problem of computer-aided molecular design (CAMD) where solvent structures are determined that possess specified properties. CAMD requires specification of systems properties, and determines which chemical structures (of solvents, polymers, etc.) will result in a product having the prespecified properties.

Thus, we integrate previous loading calculations[16,17] with reference solvent methods[18−20] capable of handling more complex AI's. We do so in order to establish an effective strategy for CAMD of solvents for applications. It is our expectation that these can be considered as alternatives to approaches based on convenience or habit. The paper reviews the foundations of the calculations, describes the particular methods for property estimation, articulates the strategy, and provides examples.

THERMODYNAMIC MODELING OF DISTRIBUTIONS AMONG SOLVENT, POLYMER AND SURFACTANT PHASES

System. We begin by briefly repeating portions of previous developments.[16] The systems of interest involve five components:

AI: active ingredient
PO: polymer
SO: solvent component (compatible with both the polymer and AI)
MI: surfactant (which may serve as a stabilizer or form micelles)
EX: external phase component

in three possible phases:

P: polymer phase
X: external phase
M: micellar phase

The system will have at least two liquid phases, X (rich in EX) and P (rich in PO and SO). If AI and PO are hydrophobic, solvent SO is typically organic and EX would be polar or water. If AI and PO are hydrophilic, solvent SO can be polar or water and EX would be organic. Finally, if the concentration of MI is high enough it may form a third phase of micelles, M, rich in surfactant (MI) with only small amounts of EX and SO. All of these cases can be treated within the framework.

Phase Equilibrium Relationships. Phase compositions are obtained with a 3-phase pressure−temperature flash calculation, which determines phase compositions (identified here as by the sets of mole fractions x^{M}, x^{P}, and x^{X}, where superscripts denote phases) when pressure, temperature, and a set of overall compositions, z, are specified. The solution satisfies the phase equilibrium, material balance, and mole fraction summation constraints. There are various ways to express these relations, one of which is given by eqs 1 to 3

$$x_i^{M}\gamma_i^{M} = x_i^{P}\gamma_i^{P} = x_i^{X}\gamma_i^{X} \qquad i = 1, \ldots, 5 \tag{1}$$

$$z_i = x_i^{X} + \sum_{j \neq X} \beta_j (x_i^{j} - x_i^{X}) \qquad i = 1, \ldots, 5 \tag{2}$$

$$0 = \sum_i (x_i^{j} - x_i^{X}) \qquad j = \mathrm{M}, \mathrm{P} \tag{3}$$

Here eq 1 is for equilibrium, eq 2 is the component balances, and eq 3 constrains the summations of mole fractions. The phase fractions, β_j, are the (molar) fraction of the system found in phase j. Superscripts (j) on Lewis/Randall normalized activity coefficients and mole fractions denote phases, whereas subscripts (i) denote components. Using eq 1 we can define separation factors (K_{ij}) for component i in phase j and express it in terms of activity coefficients

$$K_{ij} = \frac{x_i^{j}}{x_i^{X}} = \frac{\gamma_i^{X}}{\gamma_i^{j}} \tag{4}$$

Substituting these into eqs 2 and 3 gives two equations to be solved for two independent (molar) phase fractions, β_M and β_P

$$0 = \sum_i \frac{z_i(K_{ij} - 1)}{1 + \sum_{k \neq X} \beta_k (K_{ik} - 1)} \qquad j = \mathrm{M}, \mathrm{P} \tag{5}$$

Solving to obtain the mole fractions of all components in all phases (x^{M}, x^{P}, and x^{X}) is iterative, with the technique being more complex if the K-factors depend on phase compositions. However, convergence is typically not difficult.

While this problem can be solved in the general case, simplification occurs if we assume complete insolubilities[16] (infinite dilution) since, as described above, certain components are often essentially insoluble in certain phases. Thus, component EX is normally almost insoluble in the polymer (P) and micellar (M) phases, and components PO and SO do not dissolve in the external (X) and micellar (M) phases. Finally, the surfactants are present only in trace amounts in the phases outside the micellar phase.[17] The consistent thermodynamic property limits for these insolubilities are

$$\begin{aligned} \gamma_i^{X} &= \infty, i \neq \mathrm{EX}, \mathrm{AI} \\ \gamma_i^{P} &= \infty, i \neq \mathrm{SO}, \mathrm{PO}, \mathrm{AI} \\ \gamma_i^{M} &= \infty, i \neq \mathrm{MI}, \mathrm{AI} \end{aligned} \tag{6}$$

Reformulation of eq 5 is necessary,[16] but the calculational objectives are similar. In the end, the necessary quantities to solve the problem are the separation factors

$$K_{\mathrm{AI},j}^{\infty} = \frac{\gamma_{\mathrm{AI}}^{X\infty}}{\gamma_{\mathrm{AI}}^{j\infty}} \qquad j = \mathrm{M}, \mathrm{P} \tag{7}$$

This is where property modeling becomes involved.

Separation Factors. There are an extremely large number of substances of interest. In the absence of molecular computations, solution-of-groups methods[3] remain the only realistic means for providing the activity coefficient ratios of eq 7. Unfortunately, these methods often require many model parameters describing the effects of unlike interactions. Since at least some parameter values are usually unknown, estimates must be found by fitting to experimental data. As an example of what could be involved, consider hydrocortisone acetate ([2-[(8S,9S,10R,11S,13S,14S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-2,6,7,8,9,11,12,14,15,16-decahydro-1H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl] acetate), shown in Figure 1.

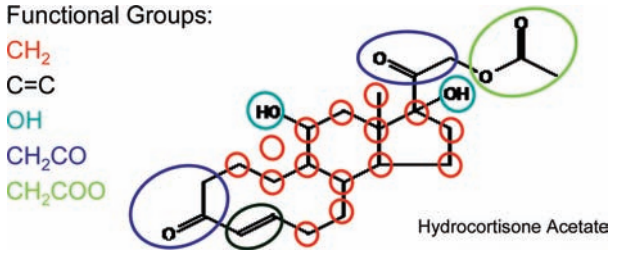

Figure 1. [2-[(8S,9S,10R,11S,13S,14S,17R)-11,17-Dihydroxy-10,13-dimethyl-3-oxo-2,6,7,8,9,11,12,14,15,16-decahydro-1H-cyclopenta[a]-phenanthren-17-yl]-2-oxoethyl] acetate or hydrocortisone acetate and its functional (main) groups.

As indicated, this AI has 5 different (main) groups. One can determine the partitioning of hydrocortisone acetate between solvents if the activity coefficients of hydrocortisone acetate in the solvents can be obtained. One such solvent would be n-hexane with subgroups CH_3 (2) and CH_2 (4), though both are in the (single) main group CH_2 for which parameters are needed. Using the 1-parameter UNIFAC method[8,21,22] for this solvent would involve 20 interaction parameters. When the solvent is water that includes an additional group, 30 interaction parameters are needed. If the solvent is a mixed solvent of water with methanol, the number becomes 42. Unfortunately if parameters for even a single solute functional group are unavailable in tabulations such as those for UNIFAC or its later extensions, reliable estimates cannot be made without experiment.

Fortunately, the situation is not as bad as it seems. For infinite dilution cases, differences between activity coefficients are not affected by solute−solute interactions, so only parameters for solute−solvent and solvent−solvent interactions are needed. This can substantially reduce the number of parameters needed. For example, for hydrocortisone acetate in *n*-hexane, there are only 8 parameters rather than 20, and for aqueous systems the reduction is from 30 parameters to 20 parameters.

If new values are needed, we have shown[18−20] how to efficiently obtain group contributions for solutes with unknown groups from limited amounts of data. If low concentration solubility data are known in a reference solvent (pure or mixed) which has similar groups to the solvent of interest, it is then possible to reliably estimate infinite dilution activity coefficients of the solute in the solvent of interest. This can be successful even when groups are present for which parameters are not available; group contribution values need not be known to high accuracy when they make only small contributions. We have shown how the technique successfully leverages limited data to determine differences in the solubility of sparingly soluble complex chemicals as pure solvent chemical constitution, or mixed solvent composition is varied, and how to focus on the most important groups. Use of the technique is illustrated below.

Solvent Selection. The goal of a solvent selection methodology is not to determine the best solvent. Rather the goal is to identify a (reduced) range of promising solvents which would be most feasible for a process. We intend to do so by (1) specifying a pure component and mixture properties set, such as boiling and melting temperatures, density, compatibility with other components, toxicity, etc., and (2) limiting the chemical structure to a set of groups in the basis set, such as hydrocarbon ring(s), and (3) number and kinds of allowed functional groups, such as hydroxyl and ketone. Then by generating and testing structures for compliance with the specified constraints we identify those structures that have the desired properties, at least when predicted from property models. An example of implementation of such constraints will be given below.

CASE: *N*-(4-HYDROXYPHENYL)ACETAMIDE

The formulation of partially hydrophobic drugs by conventional solvent evaporation methods can result in significant partitioning of the drug from the P phase into the X phase, leaving insufficient drug loaded into the polymer microparticles. Innovative evaporation methods have been reported to circumvent this problem.[14,15] The conditions for their implementation depend on the properties of the constituents, such as described above. To illustrate prediction of the final loading of AI for a practical case, we analyze here the preparation of microparticles containing *N*-(4-hydroxyphenyl)acetamide, based on a patent application.[23]

We summarize the procedure here, identifying the components and phases in the above notation. First, the *N*-(4-hydroxyphenyl)acetamide (AI) is ground in a motorized ball mill and sieved through a 38 μm mesh sieve. As previously[16] described, 18.3 g of cellulose acetate butyrate (CAB), the polymer component (PO), is dissolved in 81.7 g of propanone (SO). A total of 98.4 g of hexane is added to an aliquot of the CAB solution (100 g) with constant stirring to form the initial polymer phase (P) that consists mainly of SO and PO. Twenty grams of the sieved AI are then added to P under constant agitation to ensure even dispersion with some dissolution. Separately, small amounts of magnesium octadecanoate, insufficient to form a micellar phase (M), are dissolved in a hydrocarbon solvent (EX). This solution is used as the external liquid phase (X). Then 150 mL of X are decanted into a tall 600 mL beaker, and the P phase is added to it. Agitation to form a dispersion of phase P in phase X is performed for 2 min, followed by decreased stirring speed to obtain the desired dispersed phase size. The suspension of P in X is then introduced into a rotary evaporator and the SO removed under vacuum to obtain a suspension of polymer-coated AI particles in the range of (10 to 180) μm in phase X. The particles are then centrifuged, the X phase decanted, and the particles are washed with heptane. Any AI that partitioned to X before or during SO evaporation is lost to the formulation in the decanting and washing. The final product consists of microparticles that are filtered with paper, dried at 45 °C, and sieved with mesh sizes of (50, 90, 125, and 180) μm. It is expected that during the agitation and evaporation processes, most of the hexane and some of the AI will partition to the X phase. The final AI loading is mostly determined by the AI-distribution between CAB and EX, since the SO has been removed at that point. A summary of this system with our notation is the following:

COMPONENTS

SO: propanon
MI: magnesium octadecanoate
PO: CAB
EX: hydrocarbon
AI: *n*-(4-hydroxyphenyl)acetamide

PHASES

P: polymer phase with PO, SO, and AI
X: external phase with EX and AI

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Table 1. Predicted Properties of Candidate Solvent (SO) Components

solvent (SO) group assignment	solvent (SO) name	T_m K	T_b K	ρ^L g·cm^{-3}	$\gamma_{SO}^{CAB\infty a}$	$\Omega_{SO}^{CAB\infty a}$	$\gamma_{SO}^{X\infty}$	$\gamma_{EX}^{SO\infty}$
1 × CH_3 + 1 × CHO	ethanal	159.7	269.7	0.756	0.00258	2.92	10.68	4.63
1 × CH_3 + 1 × CH_3COO	methyl acetate	155.1	308.5	0.890	0.01082	7.29	7.028	3.27
1 × CH_3 + 1 × HCOO	methyl formate	158.3	285.1	0.925	0.00980	8.14	14.35	4.95
1 × CH_3 + 1 × CH_3CO	propanone	171.6	305.4	0.776	0.00880	7.56	7.675	5.58
1 × CH_3 + 1 × CH_2 + 1 × CHO	propanal	177.9	314.7	0.778	0.00802	6.89	5.524	4.12

[a] $\Omega_{SO}^{CAB\infty} = \gamma_{SO}^{CAB\infty}(M_{CAB}/M_{SO})$, where M_i is the molecular weight of component i.

The MI component is not of concern here, since no MI phase appears. The amount found in the final product depends on its partitioning among the particle, the surface, and X. It is expected that it would mostly partition to X.

Previously we[16] examined this situation by predicting the ultimate loading of *N*-(4-hydroxyphenyl)acetamide in CAB microparticles with the SO being propanone, when EX was hexane or water. Hexane gave much more favorable partitioning of the AI.

These components were selected on the basis of easy availability, but, given the issues of AI loss from partitioning and the toxicological risks of SO remaining in the product, alternatives for SO and EX might be explored. The possibilities are interrelated since changing SO and EX may even require changing PO and MI, constituting a more extensive design problem. Here we consider changing SO and then EX.

Potential Solvents (SO). Several features characterize a good solvent, SO, some of these are

a. low boiling point, to facilitate evaporation
b. low melting point, to ensure only a fluid state
c. higher density than the external phase component, EX
d. good compatibility of the solvent with the polymer, CAB
e. low loss to the external phase, X
f. low uptake of external phase component, EX, into the polymer phase, P
g. low toxicity

These involve no specification of AI distribution into SO, so there is no issue with regard to group contributions for *N*-(4-hydroxyphenyl)acetamide.

In addition to the above pure component and mixture properties, we consider constraints on the chemical constitution of the solvents or their structural feasibility.[24] In group-contribution based CAMD, a single component compound (such as ethanol) is formed from structural groups. We are not interested in all possible combinations of structural groups. Rather, we preselect the allowed structural groups into a basis set. The size and composition of the basis set depends on the intended application, the availability of accurate property prediction models, and perhaps the available computational resources. In addition to explicitly identifying the groups, constraints can include the number of times a group can appear in SO.

Criteria a−g can be formulated in terms of quantities calculable from group contribution methods. Therefore, determining SO compounds satisfying these constraints can be formulated as a traditional "generate-and-test" CAMD problem. It is convenient to use a benchmark solvent (SO^R) and then explore among replacements. Also, in place of a formal CAMD f steps

1. Determine the basis set of groupprocess, a simplified procedure can use the following sequence os.
2. Evaluate components that satisfy the pure component property constraints.
3. Check the polymer compatibility constraints for all candidates satisfying the constraints of step 2.
4. Check the external phase constraints, for all candidates satisfying the constraints of step 3.
5. Check the toxicology constraint, for all candidates satisfying the constraints of step 4.

Basis Set. To facilitate the handling of constraints related to structural feasibility of a set of molecular groups, it is customary to restrict the problem to either cyclic or acyclic structures; here we consider only acyclic structures. We also have constrained the allowed molecular groups to the 22 groups of alcohols, ketones, aldehydes, esters, ethers, and amides. Further, the solvent must contain a minimum of 2 and a maximum of 8 groups. Finally, special constraints can be placed on the functional groups, where the candidates must have no more than 6 functional groups, and each functional group should appear only once in the compound.

Pure Component Property Constraints. The quantitative property constraints are as follows

a. $T_{b,SO} < 320$ K
b. $T_{m,SO} < 250$ K
c. $\rho_{SO}^{L} > 0.725$ g·cm^{-3}
d. $\Omega_{SO}^{CAB\infty} < 10$
e. $\gamma_{SO}^{X\infty} > 5$
f. $\gamma_{EX}^{SO\infty} < 6$
g. $-\log(LC_{50}) < 3.5$

The constraints a−c were used to generate initial solvent candidates based on the group contribution method of Constantinou and Gani.[25,26] Five compounds, including the benchmark, propanone, were found. The group assignments, solvent names, predicted melting points (T_m), boiling points (T_b), and liquid densities (ρ^L) are given in the first five columns of Table 1. Note that the collections of groups were simple enough that component names can be easily written, though this may not always occur in CAMD results. Also the entries are all low-end homologues where group contribution property estimates may be less accurate. Here, for example, there are substantial errors in the melting temperatures, though the values are all well below the set criterion. Also, the boiling points are not very accurate, with estimates too low by (10 to 30) K, but the ranking of the compounds is reasonably well-predicted. The boiling points and densities of Table 1 suggest that ethanal and methyl formate would be particularly attractive alternatives to propanone.

CAB Solubility Constraint. Table 1 also lists infinite dilution activity coefficients for this problem. Good compatibility (d) can be indicated by greater solubility of the solvent, SO, in the polymer (CAB), which is described by lower values of the

Table 2. LC_{50} Values for Solvent Candidates

	$-\log(LC_{50})$	name(s)
$1 \times CH_3 + 1 \times CHO$	3.17	ethanal
$1 \times CH_3 + 1 \times CH_3COO$	2.18	methyl acetate
$1 \times CH_3 + 1 \times HCOO$	n.a.	methyl formate
$1 \times CH_3 + 1 \times CH_3CO$	1.23	propanone
$1 \times CH_3 + 1 \times CH_2 + 1 \times CHO$	3.31	propanal

weight-based activity coefficient, $\Omega_{SO}^{CAB\infty}$. The UNIFAC-FV[4] model was used to estimate the mole fraction activity coefficient, $\gamma_{SO}^{CAB\infty}$, which was then converted. CAB with an average molecular weight of about 50 000 or 180 repeat units, a density of 1.2 $g \cdot cm^{-3}$, and a butyric content of 47 % forms the basis of the calculations. Calculations using the Entropic FV method[6] yield values slightly different from those in Table 1, but again the trends are generally consistent. For this constraint, ethanal is significantly more compatible with the polymer than the others, for which there is little difference among them.

External Phase Constraints. Table 1 also gives calculated infinite dilution activity coefficients of solvent candidates in octane ($\gamma_{SO}^{X\infty}$) and of octane in replacement candidates ($\gamma_{EX}^{SO\infty}$) at 298.15 K using the Original UNIFAC model.[8,21,22] Different alkyl chain lengths will not give substantially different values. Less SO loss to the X phase (e) and limited EX uptake in the P phase (f) are associated with larger activity coefficients. Thus, ethanal and methyl formate have quite high values of $\gamma_{SO}^{EX\infty}$, and though propanone has the highest $\gamma_{EX}^{SO\infty}$, the others are fairly close. On the basis of these mixture properties, we can conclude that a ranking of the candidates would be ethanal, followed closely by methyl formate, and then propanone, when CAB is the polymer and the external phase component is a hydrocarbon.

Toxicology Constraint. Traditionally, chemical toxicity has been evaluated using experimental studies on animal models. The results of such studies are often reported as values of the lethal concentration (LC_{50}) in water killing 50 % of the animal population in question within a specified time, e.g., 96 h. Although conversion of these values to human toxicity is not without controversy, for preliminary assessments such as here, LC_{50} values can be indicative of a chemical's toxicological effects. We have employed the group contribution method of Martin and Young[27] to predict $-\log(LC_{50})$ values for the solvent candidates with lower values being most desirable. The results are shown in Table 2; propanone has the lowest value, whereas ethanal and propanal have the highest. Since there seem to be no data for methyl formate, measurements should be made if this candidate was to be retained in the analysis.

Interestingly these results suggest that the best solvents from physical properties are less attractive from a toxicological point of view. Thus, no solvent satisfies all of the imposed constraints, so the resolution would need to be based on the importance of a toxicity indicator. Use of this CAMD method precisely displays the information forming the basis of such a formulation decision.

Table 3 compares data obtained from literature[28] with the predictions using group contributions from Table 1 for other properties.

Table 3 illustrates a set of important points. First, the predicted values from Table 1 do not quantitatively reproduce the measured values. The solvents found are low-end homologues, and it is common for such compounds to not be well-described by group contributions. Note, however, that the predictions reliably rank the substances over the property value ranges. For example, those with higher boiling points (here $T_b > 320$ K) are predicted to have boiling points above 300 K while those with lower boiling points (here $T_b < 320$ K) are predicted to have boiling points below 300 K. Further, the order of predicted densities is in full agreement with experiment. Even the melting points show general agreement. All of the compounds with melting temperatures less than 250 K are correctly predicted to be in this range.

Potential External Phase Components for *N*-(4-Hydroxyphenyl)Acetamide. Next, we consider candidates for the external phase component (EX). Some properties that set the criteria for EX are

a. high boiling point, to avoid evaporation
b. low melting point, to ensure fluid state
c. lower density than the solvent phase
d. low compatibility with CAB
e. AI distribution favoring the polymer phase

Again, we use a simplified selection process rather than a full generate-and-test program

1. Determine the basis set of groups.
2. Evaluate the pure component property constraints.
3. Check the CAB solubilization constraint for all candidates satisfying the constraints of step 2.
4. Check the AI distribution constraint for all candidates satisfying the constraints of step 3.

Basis Set. The search is restricted to acyclic structures. The functional groups may be ketone, ether, alcohol, ester, or alkane, giving a basis set of 12 functional groups. The number of groups per molecule is limited to the range from minimum 2 to maximum 12, the number of functional groups is 6 or less, and no functional group can appear more than once in a candidate.

Pure Component Property Constraints. The quantitative property constraints are as follows:

a. $T_{b,EX} < 403.15$ K
b. $T_{m,EX} < 223.15$ K
c. $\rho_{EX}^{L} < 0.725$ $g \cdot cm^{-3}$
d. $\Omega_{RE}^{CAB\infty} < 40$
e. $\ln(\gamma_{AI}^{EX\infty}/\gamma_{AI}^{CAB\infty}) > 0$

Step 1 gives 8 candidates, all alkanes. Table 4 summarizes the candidate group assignments, with names of molecules including the benchmark, *n*-octane.

CAB Solubility. We have calculated the infinite dilution activity coefficients (molar) of the generated molecular structures for the external medium, $\gamma_{EX}^{CAB\infty}$, and converted them to their weight-based counterparts, $\Omega_{EX}^{CBA\infty}$, as above. We seek the lowest value. These are given in Table 4. The benchmark *n*-octane is the best, but, as expected, all values are quite large and similar. We have also included Table 5 comparing predictions with literature data[28] for some of the compounds having some of the groups in Table 4.

The conclusions are similar to those from Table 3. Both the boiling point and density values are ordered correctly. The predicted melting points identify the two compounds with the lowest value, but that for 3,3-diethylpentane is too low. As was shown in Table 3, melting point predictions are somewhat uncertain, suggesting that critical decisions should not be based upon predicted melting temperatures.

AI Distribution. While the criterion for partitioning is easy to state as the ratio of infinite dilution activity coefficients, it cannot be directly computed here because not all parameters for the

Table 3. Candidate Solvent (SO) Component Properties: Predictions versus Measurements

	T_m		T_b		ρ^L	
	K		K		g·cm^{-3}	
compound	measured[28]	predicted[25]	measured[28]	predicted[25]	measured[28]	predicted[26]
ethanal	150.2	159.7	294	269.7	0.780	0.756
methyl acetate	175.2	155.1	330.1	308.5	0.928	0.890
methyl formate	174.2	158.3	304.9	285.1	0.967	0.925
propanone	178.5	171.6	329.4	305.4	0.787	0.776
propanal	170.0	177.9	321.2	314.7	0.791	0.778

Table 4. Predicted Properties of Candidate External Phase (EX) Components

		T_m	T_b	ρ^L_{EX}			
solvent (EX) group assignment	solvent (EX) name	K	K	g·cm^{-3}	$\gamma^{CAB\infty a}_{EX}$	$\Omega^{CAB\infty a}_{EX}$	$\ln[\gamma^{EX\infty}_{AI}/\gamma^{CAB\infty}_{AI}]^b$
2 × CH_3 + 6 × CH_2	*n*-octane	191.3	406.6	0.701	0.0969	42.3	6.65
4 × CH_3 + 4 × CH_2 + 1 × C	3,3-diethylpentane	202.2	412.7	0.718	0.1297	50.4	6.66
4 × CH_3 + 3 × CH_2 + 2 × CH	2-ethyl-4-methylhexane	171.6	412.6	0.712	0.1277	49.7	6.63
3 × CH_3 + 5 × CH_2 + 1 × CH	4-ethylheptane	189.7	422.0	0.714	0.1266	49.2	6.63
2 × CH_3 + 7 × CH_2	*n*-nonane	205.0	430.9	0.715	0.1265	49.2	6.63
6 × CH_3 + 4 × CH	2,3,4,5-tetramethylhexane	147.2	418.5	0.721	0.1676	58.8	6.76
5 × CH_3 + 2 × CH_2 + 3 × CH	3,4,5-methylheptane	169.6	427.5	0.722	0.1670	58.6	6.60
4 × CH_3 + 4 × CH_2 + 2 × CH	2,3-dimethyloctane	188.0	436.2	0.724	0.1657	58.1	6.60

[a] 298.15 K. [b] 303.15 K.

Table 5. Candidate External Solvent (EX) Component Properties: Predictions versus Measurements

	T_m		T_b		ρ^L_{EX}	
	K		K		g·cm^{-3}	
compound	measured[28]	predicted[25]	measured[28]	predicted[25]	measured[28]	predicted[26]
n-octane	216.4	191.3	398.8	406.6	0.699	0.701
3,3-diethylpentane	240.1	202.2	419.3	412.7	0.750	0.718
n-nonane	219.7	205.0	424.0	430.9	0.714	0.715
2,3-dimethyloctane	190.0	188.0	437.5	436.2	0.734	0.724

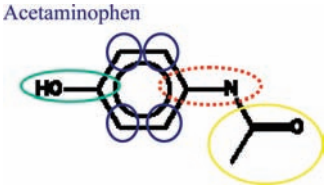

Figure 2. *N*-(4-Hydroxyphenyl)acetamide group assignment. Missing fragment within dashed oval.

groups of *N*-(4-hydroxyphenyl)acetamide with the groups of PO and EX are known. As shown in Figure 2, parameters for a group involving the nitrogen atom are missing from the published UNIFAC tables.

There are measured N-(4-hydroxyphenyl)acetamide solubilities in the literature for a hydrocarbon and a few functional solvents.[29−36] Such values can be used to estimate parameters by the reference solvent method.[18−20] With this, we have determined the necessary interaction parameters, *a*, given in Table 6.

Table 6. UNIFAC Parameters, *a*, for AC−NH− Group of *N*-(4-Hydroxyphenyl)Acetamide from Reference Solvent Data[a]

		a_{ij}	a_{ji}
i	*j*	K	K
AC−NH−	CH_2	−482.56	183.43
AC−NH−	ACH	0	0
AC−NH−	OH	−393.88	−110.91
AC−NH−	ACOH	0	0
AC−NH−	CH_2CO	−267.47	−244.21
AC−NH−	CH_3COO	299.54	242.35
AC−NH−	CH_2O	−654.17	−70.67

[a] R(AC−NH−) = 0.8978; Q(AC−NH−) = 0.516.

In Table 6, *i* and *j* denote UNIFAC groups. *R* and *Q* are the group volume and group surface area parameter, respectively, as determined previously.[18]

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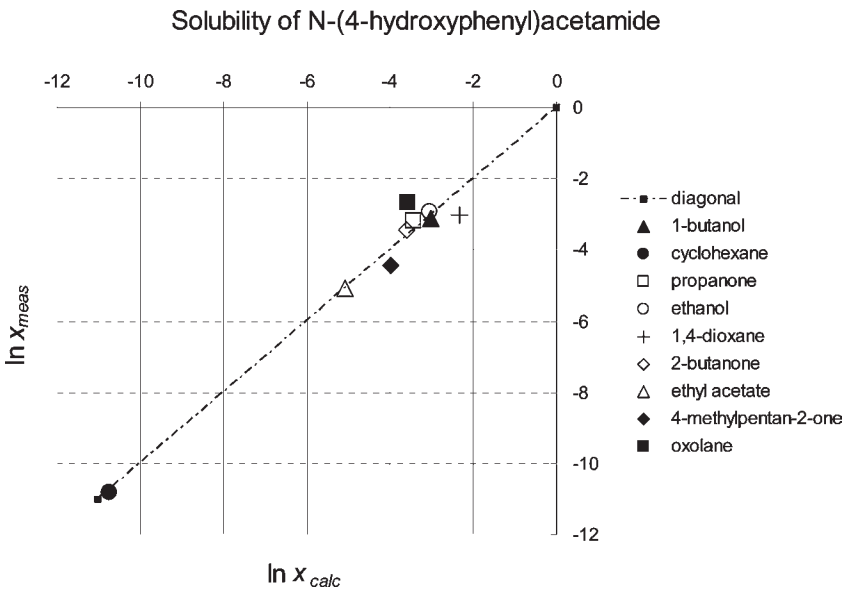

Figure 3. Solubility of *N*-(4-hydroxyphenyl)acetamide with ethyl acetate as reference solvent. Solubility data are for (▲) 1-butanol,[30] (●) cyclohexane,[29] (□) propanone,[30] (○) ethanol,[31] (+) 1,4-dioxane,[36] (◇) 2-butanone,[30] (Δ) ethyl acetate,[30] (♦) 4-methylpentan-2-one,[30] and (■) oxolane.[30] All data are treated as if taken at 303.15 K. ln x_{meas}: measured solubility value. ln x_{pred}: predicted solubility value.

The results of the estimation compared to measured data are shown in Figure 3 where ln x_{meas} and ln x_{calc} denote measured and calculated solubility values. In Figure 3 we have ignored the modest effect of temperature between the measurements at 298.15 K and our comparisons at 303.15 K. As can be seen, the *N*-(4-hydroxyphenyl)acetamide solubility is much lower in cyclohexane than in any solvent with functional groups.

Using these AC−NH− parameters for the candidate solvents, we obtain the partitioning results of the last column of Table 4, demonstrating that all of the CAMD criteria can be met by most hydrocarbons. The final selection could be based on cost, availability, and other nonphysical factors. Although this result was probably predictable, the CAMD method conveniently displays the options for decisions on formulation.

■ DISCUSSION

Our purpose has been to describe a general procedure for selecting optimal microparticle solvent (SO) and external phase component (EX) that can treat any pair of polymer (PO) and active ingredient (AI) components and could include a micellar phase. The steps of this CAMD problem consist of

1. Formulate the problem: Determine the functions each compound should perform.
2. Articulate the property constraints: List the chemical structures, pure component and mixture properties, and other attributes that the designed compounds should possess; express these as constraints on properties whose values can be estimated using only structure-based methods, such as group contributions.
3. Solve the property-based problem: From the basis set of groups, generate molecules that have the desired properties.
4. Analyze the results: Evaluate the obtained compounds for consistency, sensitivity, and similarity.
5. Select the final candidate(s): Weight the various characteristics to choose the optimal component(s) for experimental verification.

Our example assumed particular PO and AI to illustrate details of step 1 to step 4 and part of step 5. On-going developments of polymer property methods[37] for computer-aided polymer design[38,39] suggest that similar considerations can be made for identifying promising polymer structures.

The possibilities of the example case may be expanded with potential for improved results. We could have included properties such as PO structure, P phase morphology, diffusion of SO and AI, SO vaporization energy, temperature, and component[14] and mixture viscosities. If the models used contain temperature variations, no new information is needed to screen with temperature constraints. It is likely that adding too many constraints can limit or eliminate otherwise viable candidates. In such cases, relative weights of the constraints might need to be included or modified. Thus, CAMD can be expected to involve iteration as criteria are revised, because many problems do not have a unique solution, and "optimal" is often based on judgments among conflicting criteria.

For finite solute concentrations, mixed solvents, copolymers, and other product options, the CAMD concept and general procedures are the same, but the information demands can be much greater and the calculations more complex. These problems can be reduced as databases on pharmaceutical systems are augmented, if the experiments are designed, and the results are analyzed, tabulated, and archived, in ways that would allow expansion of property estimation techniques.

Our intention has been to demonstrate the capability of property models of solutions in design of pharmaceutical products and of other delivery systems. The principal limitation, unlike traditional petrochemical applications, is the inadequacy of parameter databases and the diversity of molecular interactions, which can make overwhelming demands on experiments. We have tried to show how inroads into this challenge[40] can be made using molecular thermodynamic modeling frameworks, and leveraging limited data, to obtain useful engineering results. Having been blessed to be members of John Prausnitz' vast academic family, we believe this perspective is part of our rich

inheritance, and we hope that this work might be considered a contribution to his enduring legacy.

CONCLUSIONS

A methodology has been described for integrating thermodynamic prediction of AI loading in solvent-evaporation polymer microparticle processing with computer-aided solvent design tools for evaluation of candidate components of a formulation. The fundamentals are based on phase equilibrium relations that simplify under infinite dilution conditions, pure component and mixture properties that can be estimated by group contributions, and utilization of limited reference solvent solubility data. Examples involving solvent selection illustrate the approach by systematic exclusion of suboptimal solvents to provide rapid decision making. Extensions to more complex systems are suggested.

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