MODELING OF ACTIVE INGREDIENT LOADING IN MICRO-PARTICLE CONTROLLED-DELIVERY SYSTEMS

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SUMMARY

In this work we have applied the GC-Flory equation of state to calculate the loading of an active ingredient (AI) in a polymer matrix, produced by solvent evaporation from a liquid emulsion. We use a simplified multiphase flash formulation based on excess Gibbs free energy models. We give a number of case studies of relevance to the development of computer-aided techniques for polymer screening, solvent selection and replacement of the external medium phase for micro emulsion formation. We also present model extensions, in particular the GC-Flory parameter table is extended in order to include missing amine group parameters.

INTRODUCTION

Micro-particle controlled-delivery systems consist of a polymeric matrix and an encapsulated active ingredient, which could be a flavour, a pharmaceutical, or a pesticide, to list only some of the diverse applications of such systems. The design of an effective micro-particle control-delivery system requires – among others – special understanding of the thermodynamics of multicomponent systems and has been the subject of significant research in the recent years. The present study focuses on the solvent evaporation manufacturing process. In this process an organic phase consisting of a volatile solvent with dissolved polymer and the AI to be encapsulated, is emulsified in an aqueous phase containing dissolved surfactant. The surfactant is utilized in order to stabilize the polymeric droplets and usually concentrations above the CMC are employed, which means that surfactant micelles are also present in the manufacturing solution. The manufacturing process is shown in Figure 1.

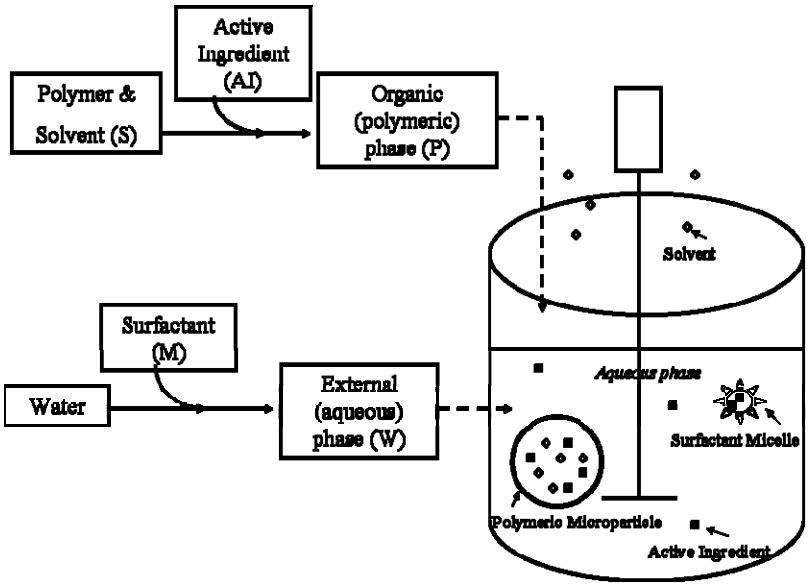

Figure 1: Schematic diagram of the oil-in-water emulsion solvent evaporation manufacturing process, illustrating the distributing of the AI (squares) between the polymeric micro-particles (circles), the

surfactant micelles ('suns') and water (external medium), during the evaporation of the solvent (diamonds).

The formation process of micro-particles using the solvent evaporation method appears to be relatively simple, without the involvement of complicated chemical reactions. However, the mechanisms of formation are quite subtle and depend greatly on the nature of the system and polymer, solvent and active ingredient properties. Because of the ranges and sizes of the molecular structures involved, the number of possible formulation alternatives for any type of product is extremely large. Therefore, a systematic strategy to limit the search space of promising products needs to be developed to minimize time and costly resources.

In this work we try to develop an approach for selecting (synthetic) polymer materials and solvents for processing based on the technique known by the acronym CAMD (Computer-Aided Molecular Design). Having formulated the property constraints and a version of the generic problem formulation, the success of CAMD methodologies depends to a large extent on the ability to predict and/or obtain the necessary pure component and mixture properties (performance characteristics), which are included in the property constraints and in the process model [1].

We will therefore try to develop an approach to predict the final amount of AI in the polymeric droplets (AI loading) at the end of the solvent evaporation manufacturing process. Previous efforts along those lines include the work of Tse et al. [2], which we have further simplified by assuming constant equilibrium factors that are obtained via the infinite dilution activity coefficient values of the AI in the equilibrium phases.

MODELING

a) PT-Flash - the infinite dilution activity coefficient assumption

We assume that during the solvent evaporation manufacturing process of micro-particles, three different phases are at equilibrium, namely a polymer-rich, a water-rich and a micelle phase. This leads to F-1 'summation of mole fraction' equations:

$$\sum_{i=1}^{C} z_i \frac{K_{jF}^{i} - 1}{1 + \sum_{l=1}^{F-1} \beta_l (K_{lF}^{i} - 1)} = 0,\ j = 1, 2, ..F-1, where: F = 3 \qquad (1)$$

The above set of equations has to be solved for the unknown phase fractions β_l, where z_i is the total amount of component *i* in moles and K_{jF}^{i} the equilibrium factor of component *i* between phase *j* and reference phase *F*.

One can further assume that certain components are virtually insoluble in certain phases. Thus, water (W) is almost insoluble in the polymer (P) and the micelle (M) phases. Further, polymer and solvent are quite insoluble in the aqueous and micelle phases. Finally, the surfactant is present only in trace amounts in the phases outside the micelles. Following this assumption, the set of equations (1) is simplified to equations (2a) and (2b):

$$z_{AI} \frac{K_{P/W}^{AI} - 1}{1 + \beta_P (K_{P/W}^{AI} - 1) + \beta_M (K_{M/W}^{AI} - 1)} + \frac{z_P + z_S}{\beta_P} - \frac{z_W}{1 - \beta_P - \beta_M} = 0 \qquad (2a)$$

$$z_{AI} \frac{K_{M/W}^{AI} - 1}{1 + \beta_P (K_{P/W}^{AI} - 1) + \beta_M (K_{M/W}^{AI} - 1)} + \frac{z_M}{\beta_M} - \frac{z_W}{1 - \beta_P - \beta_M} = 0 \qquad (2b)$$

Here $K_{P/W}^{AI}$ and $K_{M/W}^{AI}$ are the equilibrium factors (or partition coefficients) with respect to AI between polymer/water and micelle/water phases respectively. Up to this point the approach resembles [2].

A further simplification can be applied if we (as we have done here) assume that K-factors with respect to the AI are constants and given by the ratio of the infinite dilution activity coefficient of the AI in the equilibrium phases.

$$K_{i/j}^{AI} = \frac{x_{AI}^{i}}{x_{AI}^{j}} \approx \frac{\gamma_{AI,j}^{\infty}}{\gamma_{AI,i}^{\infty}} \quad (3)$$

The above implies that the K-factors are concentration-independent, which seems to be a valid assumption for this range of AI concentrations in the micro-particle, since, even in cases that the amount of AI is higher, it can still be assumed that the ratio of AI in each of the phases is of the same order of magnitude. For the estimation of infinite dilution activity coefficient values of the AI in the polymer and micelle phases, a group-contribution model (GC-Flory EoS) has been chosen.

After solving the equations (2a) and (2b), the amount of AI in the polymer phase, at any stage of the solvent evaporation / micro-particle formation process can be calculated from the equation:

$$AI - Loading = \frac{m_{AI}^{P}}{m_{P}^{P} + m_{S}^{P} + m_{AI}^{P}} \times 100 = \frac{x_{AI}^{P} MW_{AI}}{x_{P}^{P} MW_{P} + x_{S}^{P} MW_{S} + x_{AI}^{P} MW_{AI}} \times 100 \quad (4)$$

Here MW_i is the molecular weight and x_i^P the mol fraction of each component in the polymer phase. In the case of the polymer and the solvent, that we have assumed that are insoluble in the other two phases, their mole fractions are obtained simply from:

$$x_i^P = \frac{z_i}{\beta_P}, i = P, S \quad (4a)$$

Finally, summation of mol fractions will provide the value of the AI mol fraction in the polymer phase:

$$x_{AI}^{P} = 1 - \frac{z_P}{\beta_P} - \frac{z_S}{\beta_P} \quad (4b)$$

b) The GC-Flory EoS

The GC-Flory EoS [3] and [4] is a group-contribution method based on a modified form of the Flory equation of state for polymer systems. In this work, the revised model form of the GC-Flory EoS is used, for which, the equations can be found in [3]. The use of group-contribution models permit the prediction of AI loadings in micro-particle systems based only on pure component information, such as the chemical structure, the molecular weight and the density. The only mixture data that are needed as input are the manufacturing temperature and the masses of all components. The GC-Flory EoS has the additional advantage over free volume activity coefficient models like UNIFAC-FV, that it does not require precise data for the density of the components at the studied temperature. Moreover, it has been shown [3] that at the same time as being simple, it provides good prediction for polymer systems, especially in the infinite dilution region where many thermodynamic models fail. Finally, GC-Flory has been recently applied in similar controlled-delivery systems with very satisfactory results [5].

In order to cover complex AI and surfactant molecules with the GC-Flory EoS, an amine main group with three subgroups has been introduced. The group definition is based on the UNIFAC group description and the group parameter estimation is done following the procedure described in [3], where experimental data for thermal expansivities and enthalpies of vaporization are used for estimation of the pure component parameters ($C_{i,}$ ε_{mm}), while VLE data of low molecular weight compounds are used to estimate the group interaction parameters (ε_{mn}).

c) Modeling of the aqueous (external) phase

Aqueous systems are difficult to model, so extra care is necessary when estimating water parameters for thermodynamic tools. An evaluation of the GC-Flory model in binary aqueous systems showed that the model cannot describe adequately both diluted regions, while UNIFAC [6] is shown to be most suitable for predicting the infinite dilution activity coefficients of AI's in aqueous phases. Often, however, the solubility of AI's in some solvents – often water – can be found either from literature or other sources. If so, the infinite dilution activity coefficient of AI in the aqueous phase can also be retrieved from the experimental data.

In particular, solid solubility data at low concentrations (typically $x_{AI} < 0.01$ [7]) can be translated into infinite dilution activity coefficient values via the equation:

$$\ln \gamma_{AI}^{\infty} = \ln x_{AI}^{id} - \ln x_{AI} \quad (5)$$

where x_{AI} is the experimental solubility of the AI and x_{AI}^{id} is the ideal solubility, approximately given by

$$\ln x_{AI}^{id} = -\frac{\Delta H_{fus}(T_0 - T)}{RT_0T} \quad (6)$$

where ΔH_{fus}, and T_0 are the (pure AI) heat of fusion and melting temperature respectively. These are property constants characterizing the pure AI, and can often be found in the literature [8]. When available, experimental solubility data can of course be expected to give more reliable results. Especially for slightly hydrophilic AI's, the final AI loading in the micro-particle can be very sensitive to small changes in activity coefficient predictions.

RESULTS

a) AI's with varying degrees of hydrophilicity

We have selected four systems for which both experimental data and previous modeling efforts are available in the open literature. Two model AI's (benzyl alcohol and n-octanol), as well as a pesticide (geraniol) and a fragrance (farnesol) are examined, in systems that consist of polystyrene as polymer, dichloromethane as solvent and CTAB as surfactant in water. The manufacturing process is described in detail in [2].

Using equations 1-4, we calculate the AI loading during solvent evaporation and micro-particle formation. Figure 2 describes the variation of the AI infinite dilution activity coefficient with the polymer phase composition. In the beginning of the evaporation, small values of the infinite dilution activity coefficient indicate that the AI is highly soluble in the solvent/polymer solution. Therefore it does not distribute significantly into the other two phases. However, as solvent evaporates, the non-idealities increase – as indicated by the infinite dilution activity coefficient which exceeding unity - resulting in the drift of the AI towards the aqueous and the micelle phases.

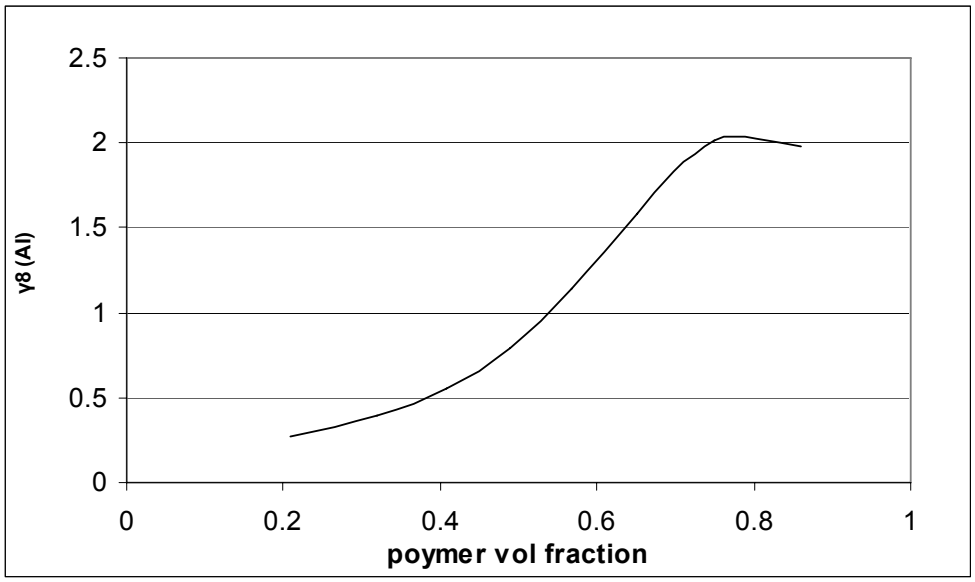

Figure 2: Predicted infinite dilution activity coefficient of n-octanol with respect to the composition of the polymer phase.

Figure 3 shows the overall accuracy of our calculations in all four of the afore-mentioned systems. Our predictions are evaluated against experimental data, as well as predictions with Entropic-FV [9] and UNIFAC-FV from [2]. UNIFAC is used for the aqueous phase in all cases. Our approach performs either equally good (for benzyl alcohol and octanol) or better (for geraniol and farnesol) than both the other models. It also manages to capture the effect of the hydrophobicity of the AI in the micro-particle loading.

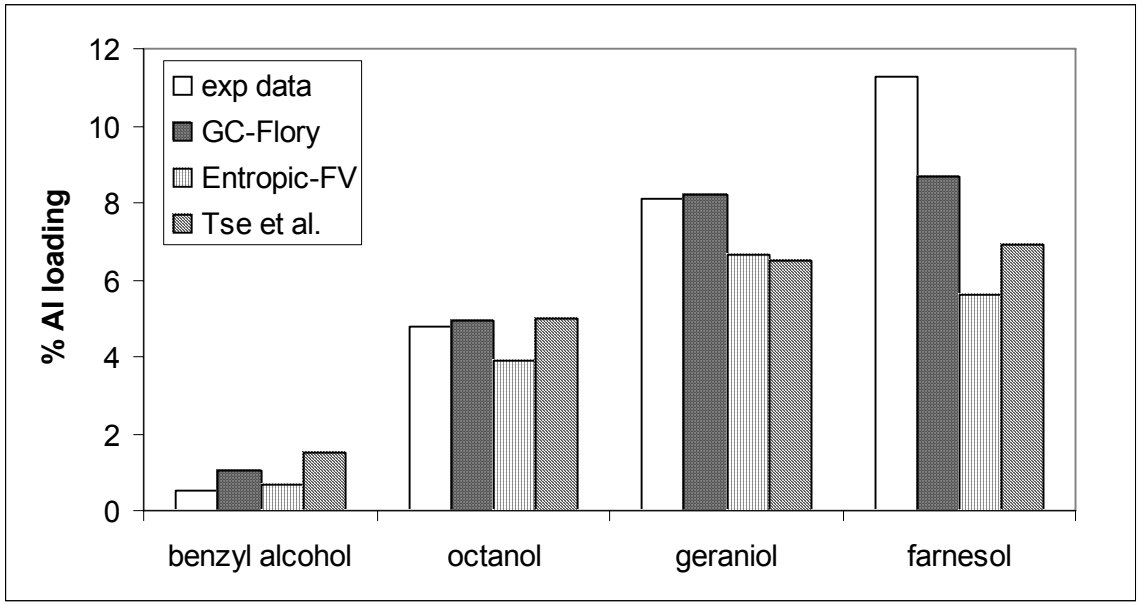

Figure 3: Comparison of experimentally measured [2] and theoretically predicted AI loadings for benzyl alcohol, n-octanol, geraniol and farnesol in PS micro-particles. Theoretical prediction made with GC-Flory, Entropic-FV and UNIFAC-FV [2].

b) Polymer Selection

Figure 4 shows how the above methodology can be applied in the polymer screening step of the product design. In all the three examined systems (the octanol system is not included because of lack of experimental data), the model manages to capture qualitatively the changes in the distribution of the AI between the phases in equilibrium when polystyrene is replaced with PMMA. Therefore, for example, if one wishes higher loadings of either benzyl alcohol or geraniol, polystyrene should be replaced by PMMA, whereas PMMA does not offer any advantage in the case of farnesol and one should evaluate other possible candidates for polymer replacement. The essential capability is to predict the change in AI loading as function of polymer structure.

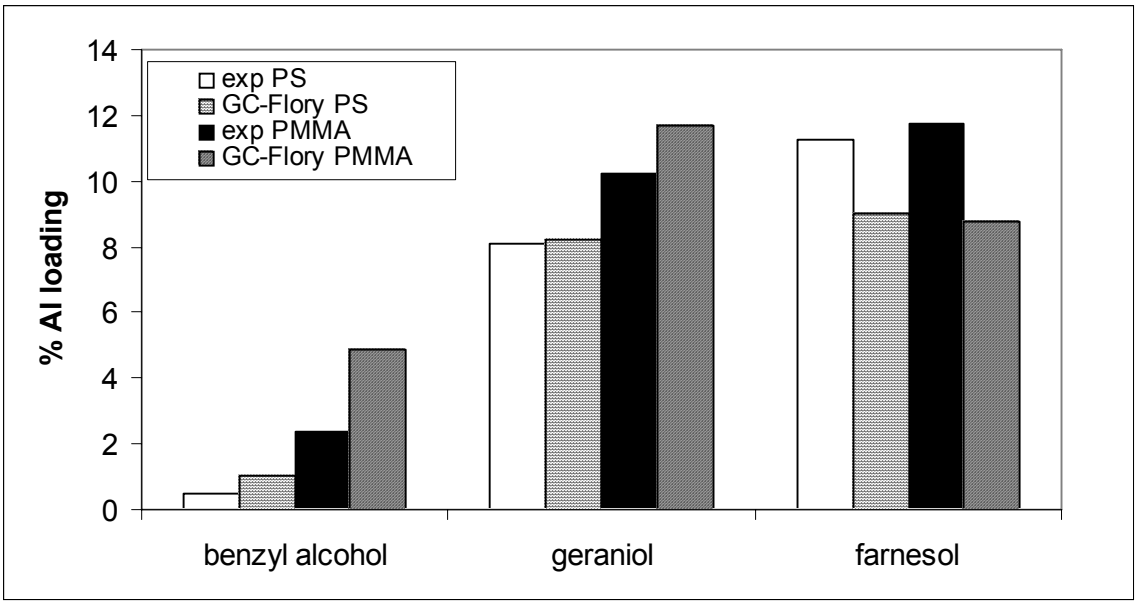

Figure 4: Comparison of experimental measurements [2] and predictions with GC-Flory of AI loadings for benzyl alcohol, n-octanol, geraniol and farnesol in PS and PMMA micro-particles.

c) Solvent Replacement

When preparing micro-particles containing a pharmaceutical agent, the choice of organic solvent is critical in developing a successful formulation. Apart from its ability to dissolve the polymer and its miscibility in the external phase, its toxicity should also be taken into account, since there will always be trace amounts of solvent in the final micro-particle formulation.

β-estradiol is a hormone used to treat menopausal symptoms in women and at present is only available in oral and transdermal forms. Variations in an individual's skin permeability and poor patient compliance have initiated research towards developing polymeric micro-particles with encapsulated β-estradiol. PLAGA (50:50) is one of the recommended polymers, since it is both FDA approved and biodegradable.

Dichloromethane is a good solvent for PLAGA because of its ability to dissolve large amounts of the polymer and at the same time has a low solubility in water. However, it is not biocompatible and this could lead to its rejection for some pharmaceutical formulations. The final β-estradiol loading of a PLAGA micro-particle is not affected by replacing dichloromethane with the less toxic ethyl acetate. Both experimental data and calculations show that (see Figure 5). On the other hand, addition of methanol to form a dichloromethane/methanol mixture leads to a decrease in the final loading. Even though there is a deviation between our predictions and the experimental data, the qualitative trend is the same.

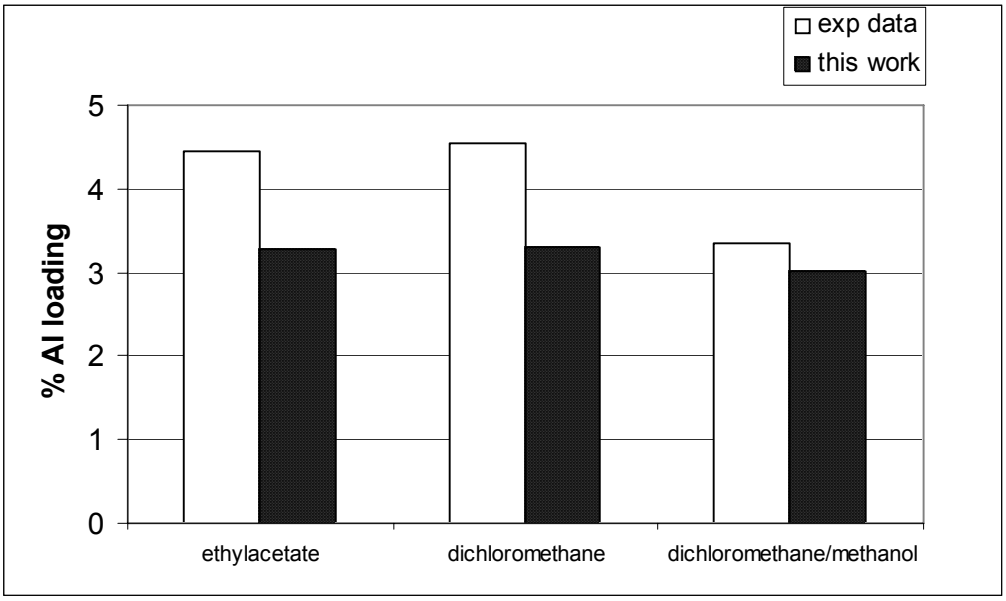

Figure 5: Comparison of experimental measurements [10] and predictions with GC-Flory of AI loadings for β-estradiol in PLAGA micro-particles manufactured under three different solvents.

d) External medium replacement

Acetaminophen is the most widely used analgesic and antipyretic drug and is available in many different forms, like tablets, capsules, liquid, drops etc. When acetaminophen micro-particles are manufactured by the solvent evaporation process, water in the external phase should be replaced with some other chemical due to the high aqueous solubility of the drug. Otherwise, the drug will partition rapidly from the organic into the aqueous phase, resulting in micro-particles with little or no drug loading [11]. A mixture of hydrocarbons obtained from petroleum, known as 'heavy' or 'light mineral oil' (depending on the size of the hydrocarbons it contains) is commonly employed as the external phase for such pharmaceutical preparations [12]. Figure 7 shows experimental [13] and predicted loadings of acetaminophen in CAB micro-particles, where, for our predictions, the light mineral oil was taken to have properties similar to n-hexane. Our modeling results agree with the experimental data. The severe decrease in the AI loading, that our model predicts when the external phase is replaced with water, can be also verified by the experimental solubility values of acetaminophen in water [8].

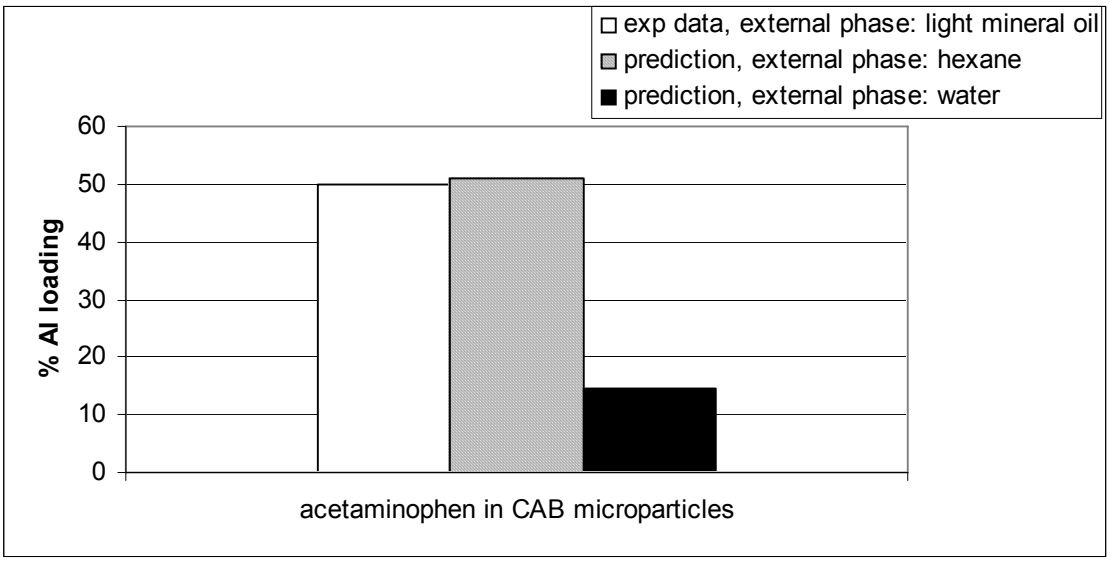

Figure 7: Comparison of experimentally measured [14] and theoretically predicted with GC-Flory AI loadings for acetaminophen in CAB micro-particles manufactured under two different external phases.

e) Effect of polymer molecular weight

Phenobarbiton, a barbiturate, is used to control epilepsy, to relieve anxiety and it is also used for short-term treatment of insomnia. Like acetaminophen, phenobarbiton is a water soluble compound, so an oily medium (kerosene) is used as the external phase [15]. Figure 8 shows experimental [15] and predicted loadings of phenobarbiton in PLA micro-particles, for three different molecular weights of the polymer. The predictions are in very good agreement with the experiment and follow the weak trend towards lowering the AI loading with respect to lower molecular weight.

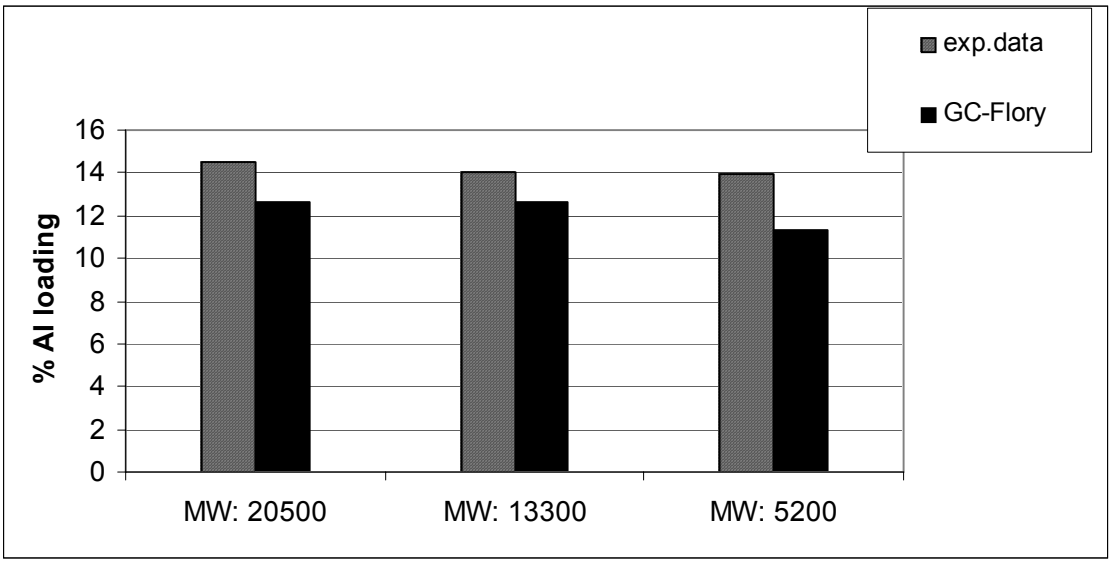

Figure 8: Comparison of experimentally measured [15] and theoretically predicted with GC-Flory AI loadings for phenobarbiton in PLA micro-particles for different molecular weight of the polymer.

CONCLUSIONS

The main steps for solving computer-aided molecular design problems are:

1. Problem formulation – what functions should the compound perform?
2. Re-formulation in terms of series of property constraints – what properties should the designed compound(s) possess?
3. Solution of the property based problem – the identification of compounds having the desired properties
4. Analysis of the obtained solutions – verification of the predicted results and examination of aspects not included as property constraints
5. Final candidate selection

Here we have described developments useful in Step 3, which is where we expect to find the most challenging scientific aspects. Our approach to predicting the product compositions of micro-particles containing an active ingredient has been described and used to suggest alternative components to a given formulation. The approach is based on phase equilibrium relationships, group contributions for activity coefficients, facilitated by use of infinite dilution conditions.

In particular, the GC-Flory EoS, as a model for the prediction of the loading of an AI in a micro-particle during the solvent evaporation manufacturing process, has been evaluated. Comparisons with data on available systems are quite good, suggesting that the technique should be viable for analysis and synthesis of combined polymeric/organic phase media. We have demonstrated this as part of a set of simple, yet realistic case studies. We have also outlined directions for future research. The GC-Flory EoS has been extended to include a wider range of molecules with complex structure. This is an example of a necessary direction for future work. Very limited experimental information is required namely the manufacturing temperature and the masses of all components in the input, which makes the method - in principle **-** purely predictive.

Furthermore, a predictive mathematical model has been applied to describe the controlled-release profile of AI's from micro-particles manufactured by the solvent evaporation technique. The applicability of the model has been highlighted through a case study and the critical parameters have been identified and estimated.

Such efforts on developing and integrating thermodynamic models with predictive controlled-release methods will greatly assist the application of 'reverse engineering' technology methods in chemical product development. More general problem formulations (Step 1) will often begin with a concept based on desirable release characteristics. Then these should be translated into – or phrased in terms of - property constraints to be satisfied by the formulated system.

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