

A COMPARISON THROUGH EMPIRICAL AND MOLECULAR BASED EQUATIONS OF STATE FOR THE DESCRIPTION OF MICRONIZATION PROCESSES

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Supercritical fluids micronization techniques are used to process very different kinds of substances, such as polymers, catalysts, explosives, superconductors, coloring matter and pharmaceutical compounds. The main processes that use supercritical fluids as media for micronization are the Rapid Expansion of a Supercritical Solution (RESS), Particles from Gas Saturated Solution (PGSS) and Supercritical Anti-Solvent recrystallization (SAS). In all these techniques three phases are involved: solid, liquid and gas phase, thus making modelling quite complicated.

In order to give a wide description of the different situations that can occur in micronization processes, in this work three equations of state based on different physical models are used to represent these phase equilibria: a semi-empirical Peng-Robinson, a lattice fluid Sanchez-Lacombe and an off-lattice theory as Perturbed Hard Sphere Chain (PHSC) theory. In particular, organic solvent-supercritical antisolvent vapor-liquid equilibria, solubility of substances in supercritical fluid, melting point depression of pure substance in presence of dense gases and solubility of solids in organic high-pressure solvent - gaseous antisolvent systems are presented.

Vapor-liquid equilibrium data were used to obtain interaction parameters for the solvent-antisolvent systems and both equilibrium and volumetric properties are reproduced. Parameters for the solid-supercritical fluid systems were obtained by fitting of solubility experimental data and were used to reproduce melting point depression. For ternary systems, only binary interaction parameters are needed in order to reproduce experimental data.

INTRODUCTION

In the last few years, supercritical fluid technology has been used as a valid technique in micronization processes, especially for applications in pharmaceutical, food and fine chemical industries. Usually materials processed in these industries have to satisfy some basic requirements; in particular they should have a narrow particle size distribution curve and a high purity. High-pressure processes are the most suitable to realize these conditions, the first advantage being given by the possibility to control particle dimensions by small pressure changes; moreover, it is possible to obtain almost completely solvent-free products.

Thermodynamic behavior of the systems involved in micronization processes is of fundamental importance when trying to find optimal operating conditions. It is then necessary to use an equation of state to model the system thermodynamics, as many authors have done mainly with Peng-Robinson EoS [1-3]. Even if good results have been obtained, cubic equations of state are not the most suitable to represent phase equilibria involving complex molecules, and this is often the case of micronization processes.

From an engineering point of view, it is important to have an accurate model that can take into account these differences, since in industrial applications the model is considered useful if it is able to predict the system behavior, and not only if it can simulate experimentally tested conditions. To achieve this goal it is convenient to make a comparison between different models in order to define which one is the more reliable and the more suitable for each system.

The equations of state considered in this work are Peng-Robinson, Sanchez-Lacombe and PHSC EoSs. The cubic Peng-Robinson equation of state is suitable for simple sphere-like molecules, while Sanchez-Lacombe EoS, based on a lattice fluid model, has been developed mainly for polymers. The Perturbed Hard Sphere Chain (PHSC) theory, which is an off-lattice model, has already been applied to the simulation of high-pressure equilibria [4] with good results, encouraging its use in case of more complex chain-like molecules.

I - MODEL DESCRIPTION

The three equations used in this paper are the following: the classical Peng-Robinson [5]

$$P = \frac{RT}{v-b} - \frac{a(T)}{v(v+b)+b(v-b)}, \quad (1)$$

the lattice fluid Sanchez-Lacombe [6] written in terms of reduced variables

$$\tilde{P} = -\tilde{r}^2 - \tilde{T} \left[\ln(1 - \tilde{r}) + \left(1 - \frac{1}{r}\right) \tilde{r} \right], \quad (2)$$

and the more realistic theoretical model PHSC [7]

$$\frac{p}{r_r kT} = 1 + r_r \sum_{ij} f_i f_j b_{ij} g_{ij} (d_{ij}^+) - \sum_i f_i \left(1 - \frac{1}{r_i}\right) g_{ii} (d_{ii}^+) - \frac{r_r}{kT} \sum_{ij} f_i f_j a_{ij}, \quad (3)$$

For all the three equations mixing parameters are obtained with classical Van der Waals mixing rules. For a more detailed description of the models one is referred elsewhere [8].

II - RESULTS

Vapor-liquid equilibrium has been calculated for many different solvent-antisolvent systems and it has been noticed that Peng-Robinson and PHSC EoSs reproduce experimental data very well and calculate bubble point curve without any significant difference, also close to critical conditions. Sanchez-Lacombe EoS instead does not give results as satisfactory, especially at high pressures, where its behavior is often distant from the experimental data.

While regressing VLE data, also liquid phase molar volumes have been calculated in order to reproduce volumetric expansion of the systems considered. In this case Peng-Robinson model gives bigger errors than Sanchez-Lacombe and PHSC, but it is important to define which formula has to be used to calculate volumetric expansion. In fact, when using the classical definition [9], the errors cancel out (Figure 1) and Peng-Robinson EoS appears to be a reliable model. Anyways, according to de la Fuente *et al.* [3] for a given antisolvent this

formula does not allow to distinguish between different solvents; for this reason they introduce a new formula to better choose which solvent is the best for a given system.

Using this new definition the errors of the model become evident as it is shown in Figure 2, making thus impossible again to distinguish between different solvents. More in general, since Peng-Robinson EoS is not able to reproduce volumetric data correctly it can not be used as a valid tool to predict volumetric expansion. PHSC and Sanchez-Lacombe EoSs are instead a good model to represent volumetric behavior, both of them giving satisfactorily results.

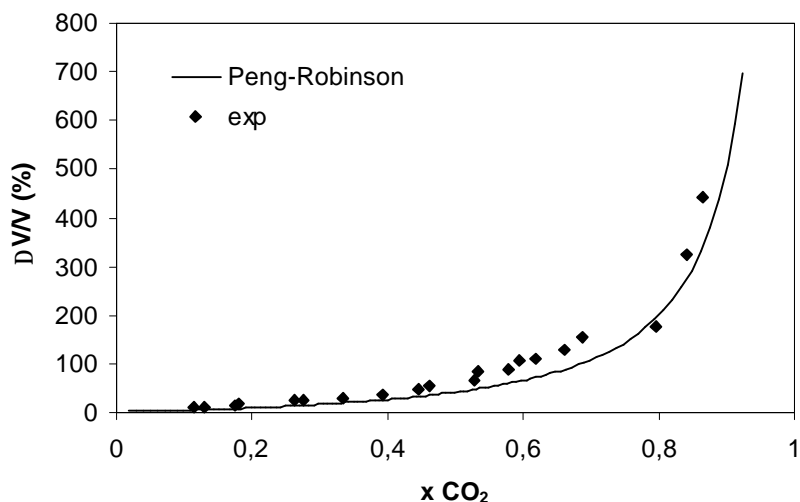


Figure 1: Volumetric expansion for the system CO₂-Acetonitrile calculated with Peng-Robinson EoS at T=298.15 K, according to the classical definition; experimental data from Kordikowski *et al.* [1]

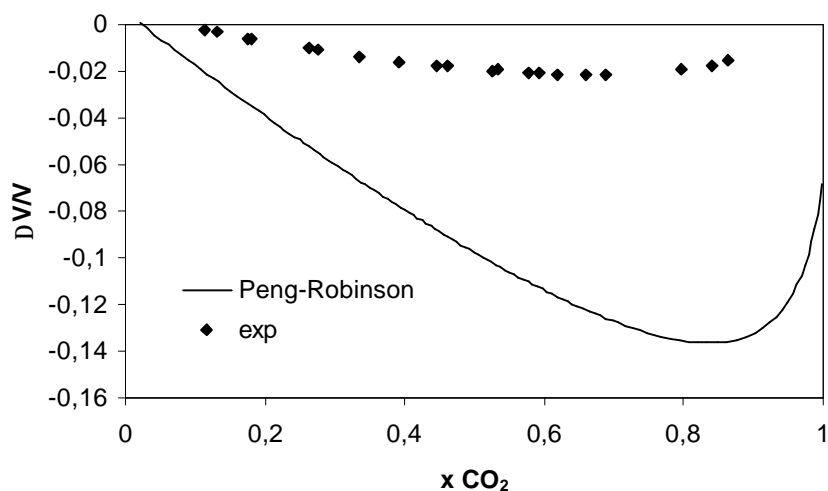


Figure 2: Volumetric expansion for the system CO₂-Acetonitrile calculated with Peng-Robinson EoS at T=298.15 K according to the formula proposed by de la Fuente *et al.* [3]; experimental data from Kordikowski *et al.* [1]

To describe completely the thermodynamics of micronization processes it is necessary to consider also solid-fluid equilibria, in which very different kinds of particles are involved. Solubility of solids in supercritical fluid has been reproduced with the three models for various systems: naphthalene-ethylene, naphthalene-CO₂, phenanthrene-CO₂, nC₂₈-CO₂, cholesterol-CO₂, *p*-hydroxybenzoic acid-CO₂ and vitamin D₂-CO₂. In this way it has been tried to give a wide description of the situations that can occur in micronization processes.

It is important to notice that for Sanchez-Lacombe EoS it necessary to use temperature dependent interaction parameters to reproduce solid-fluid equilibria, while for Peng-Robinson and PHSC EoS this has not been the case. Anyways, even using temperature dependent parameters, Sanchez-Lacombe model does not give good results as it is shown in Figure 3. For the system CO₂-phenanthrene this equation gives a maximum in solubility and a similar behavior has been observed for all the systems considered, making thus impossible to represent correctly this kind of processes.

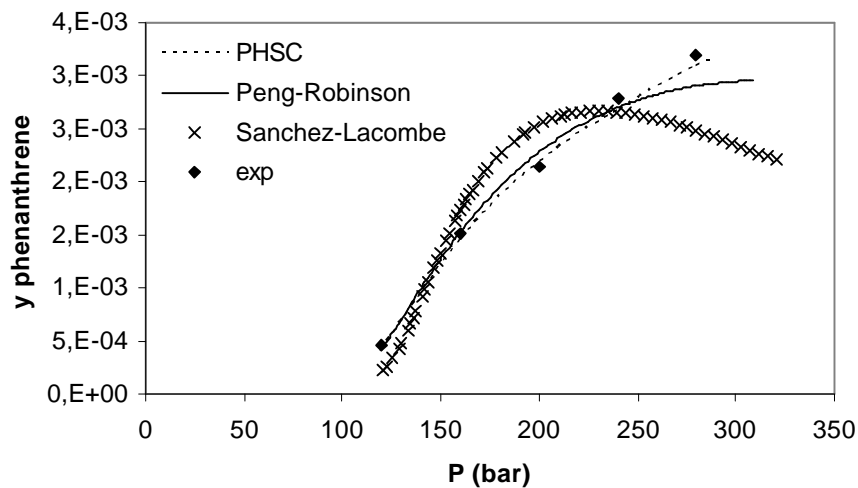


Figure 3: Solubility of phenanthrene in supercritical CO₂ at T = 328 K; experimental data from Kurnik *et al.* [10]

With Peng-Robinson model definitely better results have been obtained, but when dealing with complex molecules such as vitamins only PHSC EoS has given good results.

Another important feature of solid-fluid equilibria is melting point depression: for PGSS process in fact it is useful to reproduce the P-T curve and with Peng-Robinson and PHSC EoS it has been predicted using binary interaction parameters obtained from the regression of solubility data. With Sanchez-Lacombe model this has not been possible, since no temperature independent parameters were available. In Figure 4 P-T curves for the system naphthalene-CO₂ are presented: for both Peng-Robinson and PHSC EoS there is a good agreement with experimental data.

To conclude the analysis of micronization processes also solute-solvent-antisolvent systems have been considered. In Figure 5 results for the system CO₂-*p*-hydroxybenzoic acid-ethylacetate with Peng-Robinson EoS are reported, showing a correct representation of the ternary system behavior. Equilibrium curves have been calculated only using solid-fluid and solvent-antisolvent binary interaction parameters. Similar results have been achieved with PHSC EoS, while with Sanchez-Lacombe the calculation could not be performed using binary parameters obtained from the regression of vapor-liquid or solid-fluid equilibrium data.

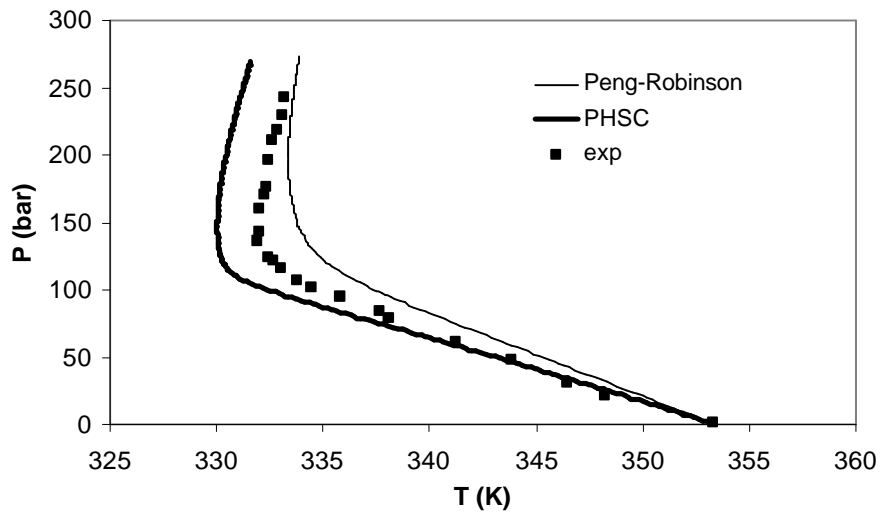


Figure 4: P-T curves for the system naphthalene-CO₂; experimental data from Cheong *et al.* [11]

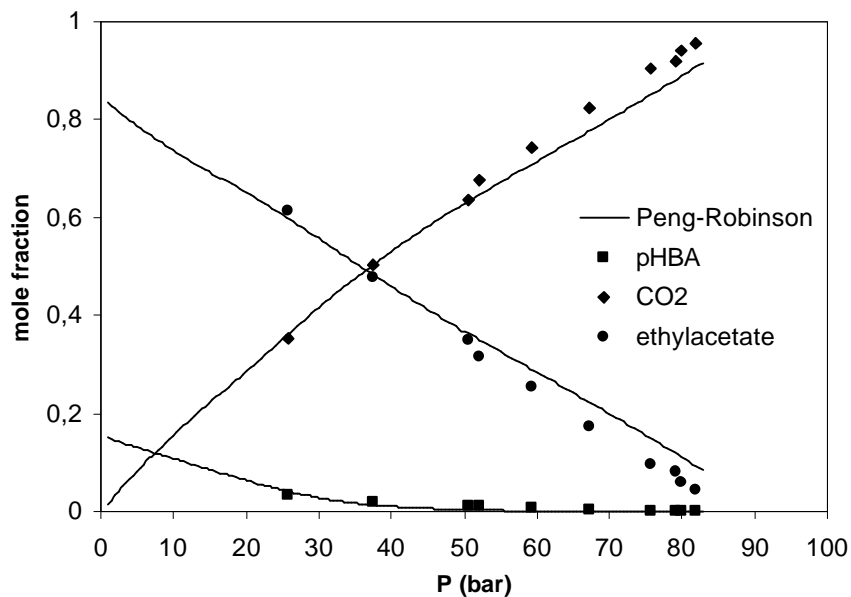


Figure 5: System CO₂-p-hydroxybenzoic acid-ethylacetate at T = 318.15 K; experimental data from Liu *et al.* [12]

CONCLUSION

Three different equations of state based on different physical models have been considered for the description of phase equilibria involved in micronization processes. Sanchez-Lacombe EoS presents great difficulties in representing high pressure equilibria, both vapor-liquid and solid-fluid equilibria. For this reason it seems that it can not be used to model supercritical fluid processes; but surely it has to be tested with more systems, for example systems containing polymers for which this equation has been developed.

Peng-Robinson and PHSC EoSs instead are suitable to describe high pressure equilibria, but from a comparison it appears clearly that particular attention should be paid to

the choice of the model when trying to represent volumetric properties or solid solubility in supercritical fluids. For these cases in fact the cubic equation shows its drawbacks, while PHSC is a more reliable model.

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