

PREDICTION OF SOLID-LIQUID-VAPOR EQUILIBRIUM FOR SUPERCRITICAL PROCESSING OF PHARMACEUTICALS USING A CUBIC EQUATION OF STATE AND GROUP CONTRIBUTION METHODS

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Abstract

In this work is examined whether it is possible to predict solid-liquid-vapor phase equilibrium of ternary systems used in the SAS processing by the Peng-Robinson equation of state coupled with the LCVm mixing rules and the UNIFAC method for excess Gibbs free energy calculation. The enthalpy of fusion and the melting point temperature are estimated by group contribution methods. The results show a good agreement between experimental and calculated data and the main conclusion is that the PR-LCVm can be used in a totally predictive way. As a consequence, this EOS can be used to monitor the behavior of the antisolvent molar fraction as a function of the ternary mixture solid-liquid-vapor phase equilibrium.

Keywords: Pharmaceuticals, supercritical solvents, cubic equation of state, group contribution

INTRODUCTION

Recently, there is an interest in producing nanomaterials utilizing alternative technology. There are several techniques for scaling-nanoparticles, however, the nanoparticles produced by supercritical technology are more uniform in terms of morphology and size distribution. Another advantage of the production of nanoparticles using supercritical fluid is the elimination of multi-stage, since they may be produced in a single step, without toxic organic solvent [1]. Nowadays, the utilization of supercritical fluid based technology is considered as a promising substitute to the traditional methods for pharmaceutical processing, since it is an efficient and environmental-friendly technique. The utilization of supercritical fluids in the pharmaceutical field has been under intense investigation since the 1980s [2, 3]

Supercritical antisolvent micronization (SAS) has been widely studied to produce nanoparticles of pharmaceuticals, biopolymers, explosives, and so on [4]. The morphology of the precipitated nanoparticles obtained by SAS process depends on the operating point that is often at pressures much higher than the mixture critical point of the ternary system solvent-solute-supercritical antisolvent. Usually it is assumed that the ternary phase diagram formed

by this ternary system behaves like the binary system solvent-antisolvent. However, the literature shows that this hypothesis is not confirmed for all cases [5]. To obtain a successful SAS production of nanoparticles it is crucial to well understand the ternary phase diagram formed by the system solvent-solute-supercritical antisolvent [6].

Understanding of ternary phase equilibria behavior also represents a crucial step for assessing the feasibility to produce solid lipid nanoparticles (SLN) and selecting the correct operating conditions for PGSS [7]. The interpretation of the lipid phase behavior under a compressed gas and after expansion process prevents the overheating of termolabile drugs as well as allows producing particles on solid form [8, 9]. Considering that on SLN manufacturing by PGSS a compressed gas is dissolved in molten pure lipid or a mixture of lipids, from a thermodynamic point of view, the system can be suitably described by a solid-liquid-vapor (SLV) phase equilibrium [8]. However, taking into account the highly asymmetry among fluid, lipids and drug molecules, the thermodynamic modeling of these systems is a challenging task.

The main goal of this work is to investigate the possibility to predict solid-liquid-vapor phase equilibrium of ternary systems used in supercritical fluid particle processing by the Peng-Robinson equation of state coupled with the LCVM mixing rules and the UNIFAC method for excess Gibbs free energy calculation.

MODELING

The main thermodynamic problem in SAS process is to find for a given solid solute the appropriate combinations of the organic solvent and the supercritical antisolvent. It is not easy to predict a priori whether a certain solvent is miscible with the supercritical antisolvent. To assure a successful precipitation process, it is essential to know the solubility of the solid solute as a function of the solvent and the antisolvent compositions. In this way the change of the solvent composition can be finely tuned to achieve supersaturation.

Considering that the solvent and the antisolvent do not dissolve in the solid phase, there is only pure crystalline solute in this phase. As a consequence, the solid-liquid-vapor phase equilibria for the ternary system solute-solvent-supercritical antisolvent can be described by the following equations:

$$x_1 \cdot \hat{\phi}_1^L = y_1 \cdot \hat{\phi}_1^V \quad (1)$$

$$x_2 \cdot \hat{\phi}_2^L = y_2 \cdot \hat{\phi}_2^V \quad (2)$$

$$x_3 \cdot \hat{\phi}_3^L = y_3 \cdot \hat{\phi}_3^V \quad (3)$$

$$f_3^s = x_3 \cdot \hat{\phi}_3^L \cdot P \quad (4)$$

$$x_3 = 1 - x_1 - x_2 \quad (5)$$

$$y_3 = 1 - y_1 - y_2 \quad (6)$$

where $\hat{\phi}_i^\alpha$ is the fugacity coefficient of the component i in the phase α , f_3^s is the fugacity of the pure solute, x_i and y_i are molar fraction of component i in the liquid and vapor phases, respectively. Subscripts L, V and S denotes for liquid, vapor and solid phases. Component 1, 2 and 3 are the antisolvent, the solvent and the solute, respectively.

Equations (5) and (6) may be incorporated into Eqs. (3) and (4) to yield the following system of non-linear equations.

$$F_1 = x_1 \cdot \hat{\phi}_1^L - y_1 \cdot \hat{\phi}_1^V = 0 \quad (7)$$

$$F_2 = x_2 \cdot \hat{\phi}_2^L - y_2 \cdot \hat{\phi}_2^V = 0 \quad (8)$$

$$F_3 = (1 - x_1 - x_2) \cdot \hat{\phi}_3^L - (1 - y_1 - y_2) \cdot \hat{\phi}_3^V = 0 \quad (9)$$

$$F_4 = f_3^s - (1 - x_1 - x_2) \cdot \hat{\phi}_3^L \cdot P = 0 \quad (10)$$

Fixing temperature and pressure, Eqs. (7) to (10) represent a set of four non-linear equations with four unknowns: the molar composition of the fluid phases.

The following constraints should also be considered before solving this system of non-linear equations:

$$x_1 + x_2 \leq 1 \quad (11)$$

$$y_1 + y_2 \leq 1 \quad (12)$$

$$x_1 \neq y_1 \quad (13)$$

$$x_2 \neq y_2 \quad (14)$$

Solving this system of non-linear equations using the traditional methods is a hard task. Therefore, an alternative is to treat this system as an optimization problem whose objective function to be minimized is the quadratic sum of the F_i functions given by Eqs. (7) to (10) subject to the constraints (11) to (14):

$$\min J = \sum_{i=1}^4 F_i^2 \quad (15)$$

It is important to say that constraints (13) and (14) are coupled, i.e., they should occur simultaneously but not individually. These constraints should be transformed in the following inequalities

$$|x_1 - y_1| \geq \Delta_1 \quad (16)$$

$$|x_2 - y_2| \geq \Delta_2 \quad (17)$$

where Δ_i are the penalty values to the solution.

This optimization problem can be solved by the sequential quadratic programming (SQP) or the genetic algorithm (GA) methods. SQP is an iterative method for nonlinear optimization used on problems for which the objective function is continuously differentiable and the constraints are also continuously differentiable, subject to linearization of the constraints [10]. GA is an evolutionary algorithm-based method used to optimize a set of equations by a program's ability to perform a given computational task [11,12]. In this work the GA method was adopted.

The proposed optimization problem is inherently difficult to be solved due to the existence of several local minimum for the objective function. Therefore, further simplifications should be considered. It is reasonable to assume that the solute concentration in the vapor phase is negligible because the solute vapor pressure is quite low at the system temperature. So, the vapor phase is considered as a binary mixture of solvent and supercritical antisolvent and the only phase that contains the three components simultaneously is the liquid phase.

The fugacity of the pure solute is obtained by

$$f_3^S(T, P) = f_3^L(T, P) \cdot \exp \left[\frac{\Delta H_3^{fus}}{RT_3^{fus}} \left(1 - \frac{T_3^{fus}}{T} \right) + \frac{P \cdot (v_3^L - v_3^S)}{RT} \right] \quad (18)$$

where ΔH_3^{fus} is the fusion enthalpy and T_3^{fus} is the melting point temperature of the pure solute, v_3^S and v_3^L are the molar volumes of the pure solute in the solid phase and in the liquid phase at temperature and pressure of solid-liquid equilibrium, respectively. Usually, the difference between v_3^S and v_3^L is relatively small and therefore the third term of Eq. (18) can be neglected.

For the description of liquid and vapor phases, the Peng-Robinson equation of state [13] has been selected with mixing rules from LCVM method coupled with UNIFAC model [14] to calculate the fugacity coefficient of the three components in the mixture.

$$P = \frac{RT}{v-b} - \frac{a}{v(v+b) + b(v-b)} \quad (19)$$

Pure component parameters for Peng-Robinson equation of state are obtained by the following expressions

$$b_i = 0.07780 \frac{RTc_i}{Pc_i} \quad (20)$$

$$\alpha_i = \frac{a_i}{b_i RT} \quad (21)$$

$$a_i = 0.45724 \frac{R^2 T c_i^2}{P c_i} f(Tr_i) \quad (22)$$

$$f(Tr_i) = \left[1 + m_i (1 - \sqrt{Tr_i}) \right]^2 \quad (23)$$

$$Tr_i = T / T c_i \quad (24)$$

$$m_i = 0.37464 + 1.54226 w_i - 0.26992 w_i^2 \quad (25)$$

The fugacity coefficient of solute in the liquid phase is calculated using the Peng-Robinson EOS with two types of mixing rules: the classical ones, with two adjustable parameters, and those from LCVM method coupled with UNIFAC activity coefficient model, with only one adjustable parameter, as follows.

Classical mixing rules

$$a = \sum_i \sum_j x_i x_j a_{ij} \quad (26)$$

$$a_{ij} = \sqrt{a_i a_j} (1 - k_{ij}) \quad (27)$$

$$b = \sum_i \sum_j x_i x_j b_{ij} \quad (28)$$

$$b_{ij} = \frac{b_i + b_j}{2} (1 - \eta_{ij}) \quad (29)$$

LCVM mixing rules

$$\ln \hat{\phi}_i = \frac{b_i}{b} \left(\frac{Pv}{RT} - 1 \right) - \ln \frac{P(v-b)}{RT} - \frac{\bar{\alpha}_i}{2\sqrt{2}} \ln \left[\frac{v(1+\sqrt{2})b}{v(1-\sqrt{2})b} \right] \quad (30)$$

$$b = \sum_i x_i b_i \quad (31)$$

$$\alpha = \left(\frac{\lambda}{A_v} + \frac{1-\lambda}{A_M} \right) \frac{G^E}{RT} + \frac{1-\lambda}{A_M} \sum_i x_i \ln \frac{b}{b_i} + \sum_i x_i \alpha_i \quad (32)$$

$$\bar{\alpha}_i = \left(\frac{\partial n \alpha}{\partial n_i} \right)_{T,P,n_j \neq n_i} = \left(\frac{\lambda}{A_V} + \frac{1-\lambda}{A_M} \right) \ln \gamma_i + \frac{1-\lambda}{A_M} \left(\ln \frac{b}{b_i} + \frac{b_i}{b} - 1 \right) + \alpha_i \quad (33)$$

A_V and A_M are constants related to Vidal and Michelsen mixing rules, respectively. For the Peng-Robinson equation of state, $A_V = -0.623$ e $A_M = -0.52$. γ_i is the activity coefficient calculated by the UNIFAC group contribution model and λ is the LCVM parameter that weight Vidal and Michelsen mixing rules contribution. In this work, λ is used in two ways: without estimation (considering its original value fixed at 0.36) and fitted to experimental data.

RESULTS

An isothermal flash calculation was performed for the ternary mixtures CO₂-toluene-phenanthrene and CO₂-toluene-naphthalene. Experimental equilibrium data was taken from the literature [15]. Equilibrium constants were calculated using PR EOS with classical mixing rules (2 adjustable parameters), PR-LCVM for $\lambda=0.36$ and PR-LCVM with λ fitted to experimental data. Parameter estimation was done using a genetic algorithm (GA). The performance of the models were compared based on the liquid molar fraction mean absolute deviation ($\Delta x\%$) given by

$$\Delta x\% = \frac{100}{NEP} \cdot \sum_{i=1}^{NEP} |x_i^{\text{exp}} - x_i^{\text{cal}}| \quad (34)$$

Table 1 shows the values of the interaction parameters of the Peng-Robinson equation of state with the classical mixing rules (PR-CMR) estimated for the binary systems which contains the same components of the ternary systems CO₂-toluene-phenanthrene and CO₂-toluene-naphthalene at 25°C.

Table 1: Parameters of the PR-CMR EOS estimated for the binary systems at 25°C.

| Binary systems | k_{ij} | η_{ij} |
|-------------------------------|----------|-------------|
| CO ₂ -Toluene | 0.0900 | 0.0 |
| CO ₂ -Phenanthrene | 0.1010 | 0.0 |
| CO ₂ -Naphthalene | 0.1010 | 0.0 |
| Toluene-Phenanthrene | 0.0046 | 0.0 |
| Toluene- Naphthalene | 0.0013 | 0.0 |

Table 2 shows the results obtained for the system CO₂-toluene-phenanthrene. In this case PR-CMR EOS presents the best performance. Also it can be seen that there is no significant difference between PR-LCVM with or without fitting parameter λ to experimental data. Therefore, PR-LCVM can be used in a totally predictive way by fixing λ equal to 0.36 as originally suggested.

Table 2: Liquid molar fraction mean absolute deviations ($\Delta x\%$) for the system CO₂-toluene-phenanthrene at 25°C.

| EOS | $\Delta x(\%)$ | | |
|----------------------------|-----------------|---------|--------------|
| | CO ₂ | Toluene | Phenanthrene |
| PR-CMR | 1.95 | 1.78 | 0.01 |
| PR-LCVM ($\lambda=0.36$) | 3.00 | 2.49 | 0.01 |
| PR-LCVM ($\lambda=0.55$) | 2.37 | 2.63 | 0.01 |

Table 3 shows the results obtained for the system CO₂-toluene- naphthalene. In this case PR-LCVM EOS with λ fixed equal to 0.36 gives the best performance. The difference between PR-LCVM with or without fitting parameter λ to experimental data is considerable and should not be neglected. This result confirms the good predictive power of PR-LCVM.

Table 3: Liquid molar fraction mean absolute deviations ($\Delta x\%$) for the system CO₂-toluene-naphthalene at 25°C.

| EOS | $\Delta x(\%)$ | | |
|----------------------------|-----------------|---------|-------------|
| | CO ₂ | Toluene | Naphthalene |
| PR-CMR | 3.07 | 3.70 | 0.83 |
| PR-LCVM ($\lambda=0.36$) | 0.93 | 1.15 | 0.75 |
| PR-LCVM ($\lambda=0.50$) | 3.40 | 3.37 | 1.00 |

Figures 1 to 3 show the pressure versus liquid molar fraction curves for the system CO₂-toluene-phenanthrene at 25°C with a good agreement between experimental and calculated data for all models.

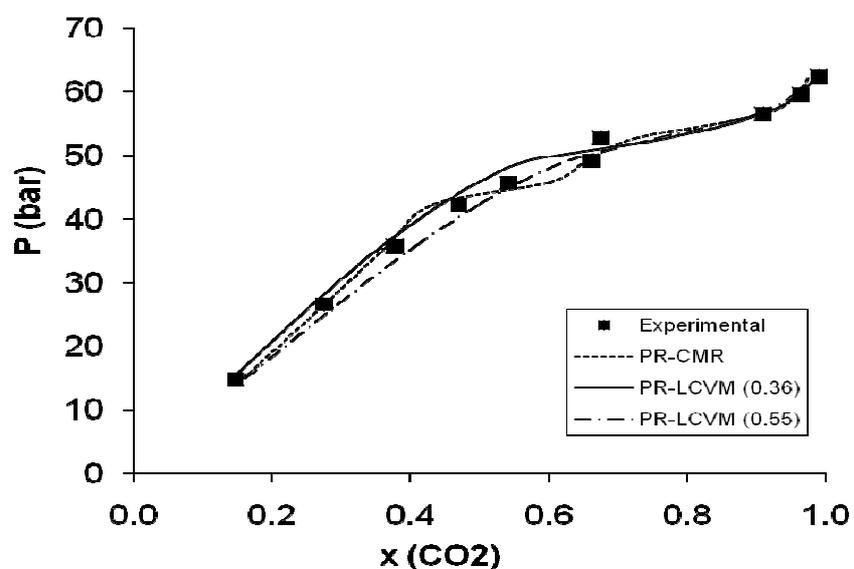


Figure 1: CO₂ molar fraction in the liquid phase calculated by a three-phase flash algorithm for CO₂-toluene-phenanthrene system at 25°C using the PR-EOS and PR-LCVM. Experimental data were taken from [15].

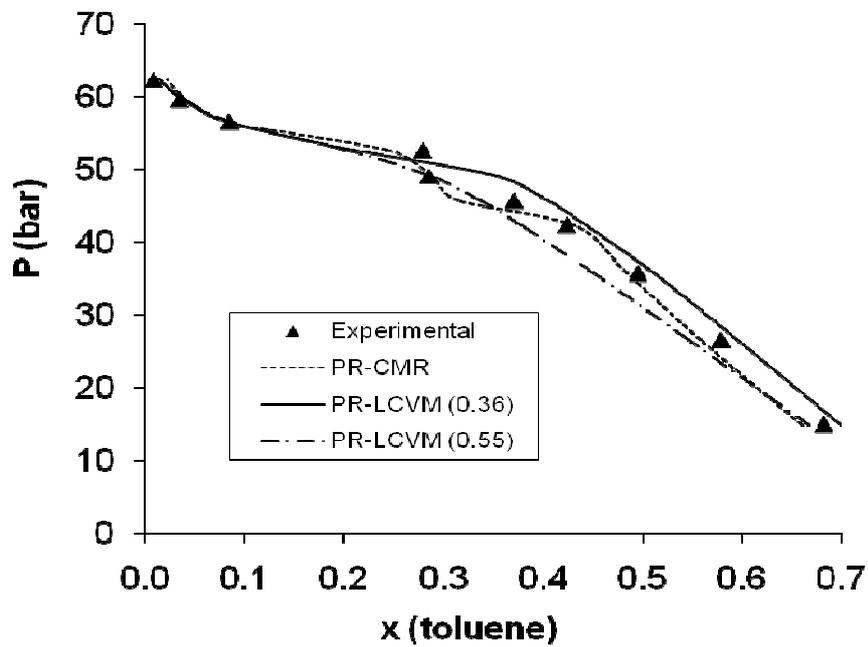


Figure 2: Toluene molar fraction in the liquid phase calculated by a three-phase flash algorithm for CO₂-toluene-phenanthrene system at 25°C using the PR-EOS and PR-LCVM. Experimental data were taken from [15].

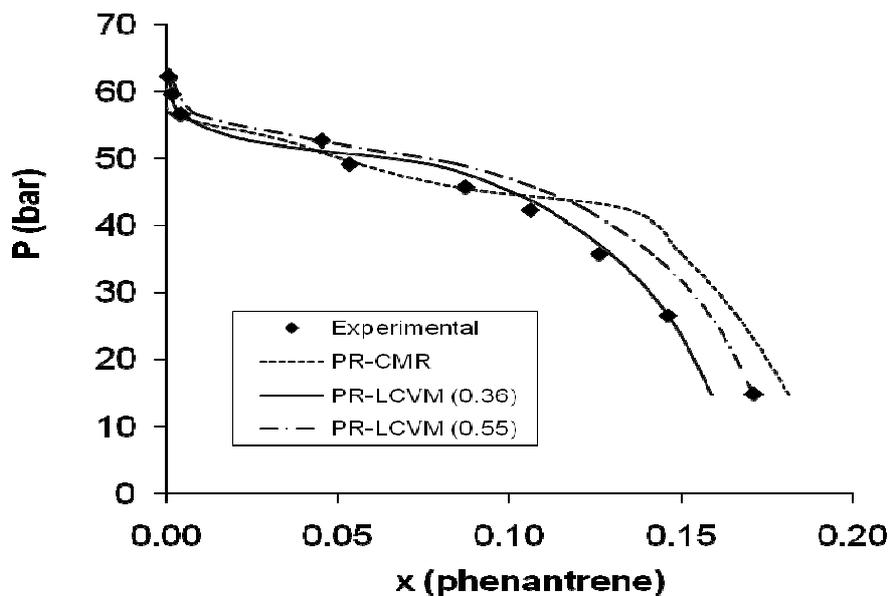


Figure 3: Phenanthrene molar fraction in the liquid phase calculated by a three-phase flash algorithm for CO₂-toluene-phenanthrene system at 25°C using the PR-EOS and PR-LCVM. Experimental data were taken from [15].

Figures 4 and 5 show the pressure versus liquid molar fraction curves for the system CO₂-toluene-naphthalene at 25°C. There is a good agreement between experimental and calculated data for the EOS investigated.

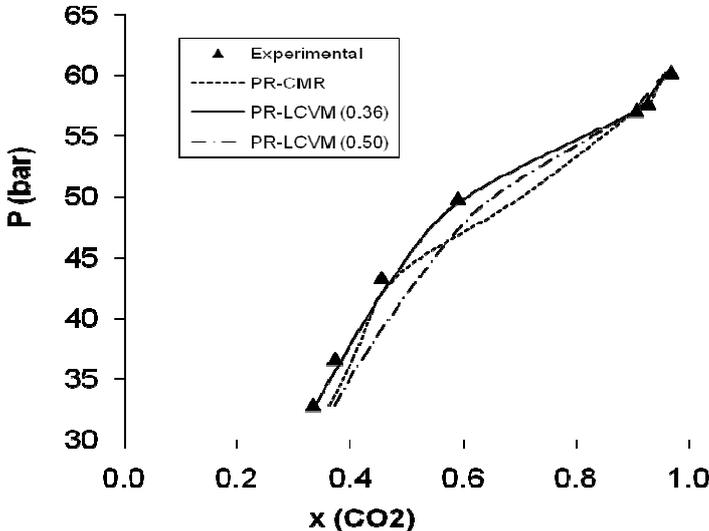


Figure 4: CO₂ molar fraction in the liquid phase calculated by a three-phase flash algorithm for CO₂-toluene-naphthalene system at 25°C using the PR-EOS and PR-LCVM. Experimental data were taken from [15].

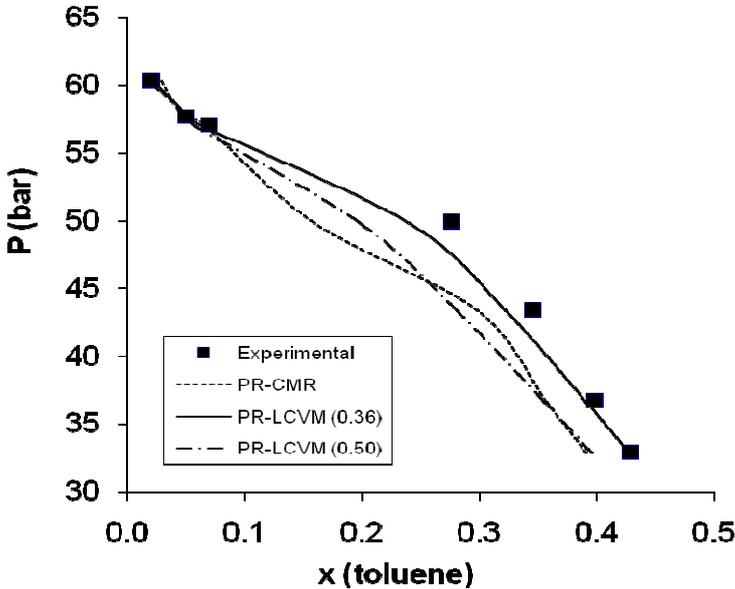


Figure 5: Toluene molar fraction in the liquid phase calculated by a three-phase flash algorithm for CO₂-toluene-naphthalene system at 25°C using the PR-EOS and PR-LCVM. Experimental data were taken from [15].

CONCLUSION

In this work the possibility to predict solid-liquid-vapor phase equilibrium of ternary systems used in supercritical fluid particle processing by the Peng-Robinson equation of state coupled with the LCVM mixing rules and the UNIFAC method for excess Gibbs free energy is investigated. The results are very promissory because show that the PR-LCVM EOS can be used in a totally predictive way with a good agreement between experimental and calculated data. Therefore, it is possible to monitor the behavior of the antisolvent molar fraction as a function of solid-liquid-vapor phase equilibrium of the ternary mixture. Further research is in progress to apply the PR-LCVM EOS to monitor the supercritical processing of pharmaceuticals without the need of ternary solid-liquid-vapor phase equilibrium experimental data.

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