

MONITORING PHARMACEUTICAL SOLUBILITY IN THE BINARY SOLVENT/ANTISOLVENT FOR SAS PROCESS USING PENG-ROBINSON EQUATION OF STATE

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Abstract

A new approach is proposed to monitor the solid pharmaceutical solubility from the bubble point pressure and liquid density of the binary mixture solvent/antisolvent using the Peng-Robinson equation of state. The results show a good agreement between the experimental and the calculated pressure as a function of the antisolvent molar fraction. It is also calculated the limit pressure for the liquid-liquid immiscibility region at a given temperature. From this point, the liquid mixture density becomes constant as the antisolvent molar fraction increases.

Keywords: Solubility, pharmaceuticals, SAS process, cubic equation of state, solvent/antisolvent immiscibility

INTRODUCTION

Supercritical fluids have many industrial applications, including chemical reactions, extraction of essential oils, supercritical chromatography, manufacturing of semiconductors, micronization of pharmaceutical excipients, production of drug delivery systems and so on [1]. In recent years, biopharmaceutical drugs have been the target of intense investigation by the pharmaceutical industry owing to their encapsulation in nanoparticle systems. There are several methods which can be used for micronizing pharmaceuticals but only supercritical processing offers a good control on the size distribution of the micronized particles, is operated at mild temperatures, avoiding thermal degradation, and leaves no residual solvent in the final product [2].

A very promising application of supercritical fluid technology in the production of nanomaterials and particle design is the production of liposomes, which are phospholipid vesicles that can improve activity and safety of therapeutic molecules [3, 4, 5]. To assure liposome formation utilizing this technology, there is a need to understand the phase equilibria and to know the solubility of phospholipids in the chosen supercritical fluid. As experimental measurements can offer several difficulties, the prediction of phase behavior can provide important data to understand the process of these vesicles formation and production [6, 7].

Among the supercritical precipitation processes for the production of pharmaceutical nanoparticles, micronization techniques currently of much interest are the supercritical antisolvent micronization (SAS), the rapid expansion of a supercritical solution (RESS), and the particles from gas-saturated solutions process (PGSS). In the SAS process, one of the problems is to find for a given solid solute the appropriate ratios of the solvent to the supercritical antisolvent. The choice of a good combination of solvent and antisolvent can be a hard task and one of the requirements is the assurance that both form a single liquid phase at a given temperature [8].

This work aimed at proposing a new approach to monitor the solid pharmaceutical solubility in the ternary system solvent-solute-supercritical antisolvent by using information from the bubble point pressure and liquid density of the binary mixture solvent/antisolvent calculated with the Peng-Robinson cubic equation of state. It is also shown how to calculate the limit pressure for the liquid-liquid immiscibility region at a given temperature, since the liquid mixture density becomes constant as the antisolvent molar fraction increases.

MODELING

Supercritical antisolvent micronization (SAS) of pharmaceuticals should be preceded of understanding the phase behavior of the ternary system solvent-solute-supercritical antisolvent. However, experimental data on this ternary system are not easily found in the literature mainly because thermodynamic behavior is much less investigated than the particle processing and its properties. So, it is usual to assume that the ternary phase diagram formed by this ternary system could be predicted by the corresponding binary systems. In this case, vapor-liquid equilibrium is taken in account for the binary system solvent-supercritical antisolvent and solid-vapor equilibrium is considered for the binary system solid solute-supercritical antisolvent. It is not needed to investigate the phase equilibrium behavior of the third binary system because the solubility of the solid solute in the organic solvent, which is a limiting factor for a successful precipitation process, is required a priori to be high [9].

Vapor-liquid equilibrium

Before SAS particle processing it is important to know whether a certain solvent is completely miscible with the supercritical antisolvent. Further, liquid-liquid immiscibility should be prevented because its occurrence avoid that the expansion takes place and in this case particle formation by precipitation is inhibited. A complete understanding of vapor-liquid equilibrium for the system solvent-supercritical antisolvent demands calculation of both bubble point pressure and composition as long as the liquid density at this condition. Experimental data in the literature show that liquid density decreases with increasing the supercritical antisolvent mole fraction. However, when a liquid-liquid immiscibility appears, the liquid density becomes constant even with addition of more supercritical antisolvent [10]. This phenomenon can also be observed in a pressure versus molar fraction phase diagram for the binary system when the isothermal bubble curve slopes upward in an almost vertical line, though it is easier to detect it in a diagram of liquid density as a function of supercritical antisolvent mole fraction. Therefore, monitoring this turning point is crucial to establish the operational limits for SAS.

Vapor-liquid equilibria for the binary system solvent-supercritical antisolvent can be described by the following equations:

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

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

where $\hat{\phi}_i^\alpha$ is the fugacity coefficient of the component i in the phase α , x_i and y_i are molar fraction of component i in the liquid and vapor phases, respectively. Subscripts L and V denotes for liquid and vapor phases, respectively. Component 1 and 2 are the antisolvent and the solvent, respectively. The following constraints should also be applied to both phases:

$$\sum_{i=1}^2 x_i = 1 \quad (3)$$

$$\sum_{i=1}^2 y_i = 1 \quad (4)$$

Eqs. (1) to (4) represent a set of four non-linear equations. Fixing temperature and the molar fraction of component 1 in the liquid phase, remain exactly four unknowns: the bubble pressure, the molar fraction of component 2 in the liquid phase, and both components molar fractions of the vapor phase.

In the present work only the vapor-liquid equilibria for the binary system solvent-supercritical antisolvent have been considered. Solid-vapor liquid equilibria has been discussed in a previous work [11].

Equation of state

The Peng-Robinson equation of state [12] has been selected to describe liquid and vapor phases behavior.

$$P = \frac{RT}{v-b} - \frac{a}{v(v+b) + b(v-b)} \quad (6)$$

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

$$b_i = 0.07780 \frac{RTc_i}{Pc_i} \quad (7)$$

$$\alpha_i = \frac{a_i}{b_i RT} \quad (8)$$

$$a_i = 0.45724 \frac{R^2 T c_i^2}{P c_i} f(Tr_i) \quad (9)$$

$$f(Tr_i) = \left[1 + m_i (1 - \sqrt{Tr_i}) \right]^2 \quad (10)$$

$$Tr_i = T / T c_i \quad (11)$$

$$m_i = 0.37464 + 1.54226 w_i - 0.26992 w_i^2 \quad (12)$$

Based on a previous experience [13], classical mixing rules are used to calculate the fugacity coefficient of the components in the mixture, with two adjustable parameters, as follows:

$$a = \sum_i \sum_j x_i x_j a_{ij} \quad (13)$$

where

$$a_{ij} = \sqrt{a_i a_j} (1 - k_{ij}) \quad (14)$$

and

$$b = \sum_i \sum_j x_i x_j b_{ij} \quad (15)$$

where

$$b_{ij} = \frac{b_i + b_j}{2} (1 - \eta_{ij}) \quad (16)$$

In this work, k_{ij} and η_{ij} are the parameters fitted to binary vapor-liquid experimental data.

Critical properties are first calculated by group contribution using a procedure recommended in literature [14]. Table 1 shows the pure component properties used in this work.

Parameter estimation

Since the liquid mixture density and the bubble point pressure can be used to predict the occurrence of liquid-liquid immiscibility, the objective function for parameter estimation should take in account both simultaneously. However, a good fit to experimental data is not achieved by the Peng-Robinson equation of state when the liquid mixture density and the bubble point pressure are considered in the same objective function. Therefore, in this work it is assumed that if the PR EOS well describes the bubble point curve it will be able to give also a good prediction of the liquid density of the binary mixture solvent/antisolvent. The solvent-supercritical antisolvent binary interaction parameters are calculated by fitting the

experimental vapor-liquid equilibrium data available in the literature and are considered temperature-independent, that is a unique couple of parameters are used for all isothermals.

Table 1: Pure component properties.

Component	T_c (K)	P_c (atm)	ω
Carbon Dioxide	304.2	72.830	0.224
Methanol	516.2	63.005	0.635
Chloroform	536.4	52.998	0.218
Formic Acid	580.1	72.934	0.473
Acetic Acid	592.7	57.143	0.447
Isopropanol	508.3	46.978	0.665
N-methylpyrrolidone	721.6	44.609	0.539
Dichloromethane	510.0	62.176	0.199
Dimethylsulfoxide	720.0	56.303	0.350
Ethanol	516.2	63.005	0.635
Ethyl Acetate	523.0	37.798	0.362
Acetone	508.1	46.385	0.307

Bubble pressure calculation was performed to fit the vapor-liquid equilibrium data and the following objective function was adopted:

$$OF = \min \sum_{i=1}^{NEP} \frac{(P_i^{cal} - P_i^{exp})^2}{P_i^{exp}} \quad (17)$$

Bubble pressure calculated errors are expressed in mean relative deviation ($\Delta P\%$) as follows:

$$\Delta P\% = \frac{100}{NEP} \cdot \sum_{i=1}^{NEP} \frac{|P_i^{exp} - P_i^{cal}|}{P_i^{exp}} \quad (18)$$

To accomplish parameter estimation a genetic algorithm (GA) was applied. It is an evolutionary algorithm-based method used to optimize a set of equations by a program's ability to perform a given computational task [15].

After parameter estimation, the liquid mixture density mean relative deviation ($\Delta \rho\%$) is calculated by

$$\Delta \rho\% = \frac{100}{NEP} \cdot \sum_{i=1}^{NEP} \frac{|\rho_i^{exp} - \rho_i^{cal}|}{\rho_i^{exp}} \quad (19)$$

RESULTS

Vapor-liquid equilibrium data for several binary systems of pharmaceutical interest were selected from the literature as shown in Table 2. For some of these systems, there are k_{ij} and η_{ij} binary interaction parameters values fitted to binary vapor-liquid experimental data available in the literature. In these cases, the bubble pressure was calculated with the binary interaction parameter values taken from the literature and with the values estimated in the present work. Table 3 shows a comparison of this calculation in terms of the mean relative deviation in pressure. The differences are probably due to the use of different objective functions during the parameter estimation procedure but no detailed information is given in the literature about the objective functions and the optimization method adopted. Using the k_{ij} and η_{ij} values obtained by Eq. (17), $\Delta\rho\%$ is calculated using PR-EOS and compared with those values available in the literature.

Table 2: Experimental vapor-liquid equilibria data of binary systems.

Binary systems	T (K)	Reference
CO ₂ -Methanol	313.20	[16]
CO ₂ -Chloroform	313.20	[17]
CO ₂ -Formic Acid	313.15	[18]
CO ₂ -Acetic Acid	313.15	[19]
CO ₂ -Isopropanol	334.90	[20]
CO ₂ - N-methylpyrrolidone	313.00	[21]
CO ₂ -Dimethylsulfoxide	314.49	[22]
CO ₂ -Ethanol	298.15	[10]
CO ₂ -Dichloromethane	311.41	[23]
CO ₂ -Acetone	313.13	[24]
CO ₂ -Ethyl Acetate	298.15	[10]

Table 3: Binary interaction parameters regressed for the antisolvent-solvent systems in this work and taken from the literature.

Binary Systems	k_{ij}	η_{ij}	$\Delta P\%$	$\Delta\rho\%$	Reference
CO ₂ -Dimethylsulfoxide	-0.0056	-0.0432	9.83	13.31	This work
	0.0150	-0.0250	4.87	12.23	[10]
	-0.0043	-0.1045	1.95	-	[9]
CO ₂ -Ethanol	0.0502	-0.0433	9.50	2.21	This work
	0.0890	0	2.16	1.80	[10]
	0.0645	0.0317	2.26	6.62	[9]
CO ₂ -Dichloromethane	-0.0624	0.0176	3.71	-	This work
	0.0631	-0.0120	3.42	-	[9]
CO ₂ -Acetone	-0.0800	-0.0338	13.71	7.22	This work
	0.0214	0.0293	0.74	4.47	[9]
CO ₂ -Ethyl Acetate	0.0275	0.0687	4.18	1.52	This work
	-0.0200	0.0100	5.46	1.25	[10]

Table 4 shows the values of k_{ij} and η_{ij} binary interaction parameters fitted to binary vapor-liquid experimental data available in the literature and the results of bubble pressure calculation in terms of the mean relative deviation in pressure. In these cases, no binary interaction parameters values are available in literature for comparison.

In this work the bubble point pressure calculation is not the final goal. Monitoring the liquid mixture density it is possible to predict the occurrence of liquid-liquid immiscibility transition that is detected when the liquid mixture density becomes constant at a given temperature.

Table 4: Binary interaction parameters regressed for the antisolvent-solvent systems using Peng-Robinson equation of state.

Binary systems	k_{ij}	η_{ij}	$\Delta P\%$
CO ₂ -Methanol	0.0792	0.0271	1.85
CO ₂ -Chloroform	0.0834	0.0000	9.62
CO ₂ -Formic Acid	-0.0281	-0.0975	7.11
CO ₂ -Acetic Acid	-0.0064	-0.0658	2.77
CO ₂ -Isopropanol	0.0758	-0.0401	2.25
CO ₂ - N-methylpyrrolidone	-0.0801	-0.0057	27.15

Figure 1 shows the objective function surface (J) obtained as a function of parameters k_{ij} and η_{ij} . It can be seen the existence of several local minimum points that make the optimization of the objective function a hard task. For this type of surface, the SIMPLEX method is not appropriated because it depends strongly on the initial guess of the parameters values and it is not able to go out from a local minimum point in searching of a global minimum point. For this reason, the genetic algorithm (GA) method, which is an evolutionary algorithm-based method, was successfully adopted in this work.

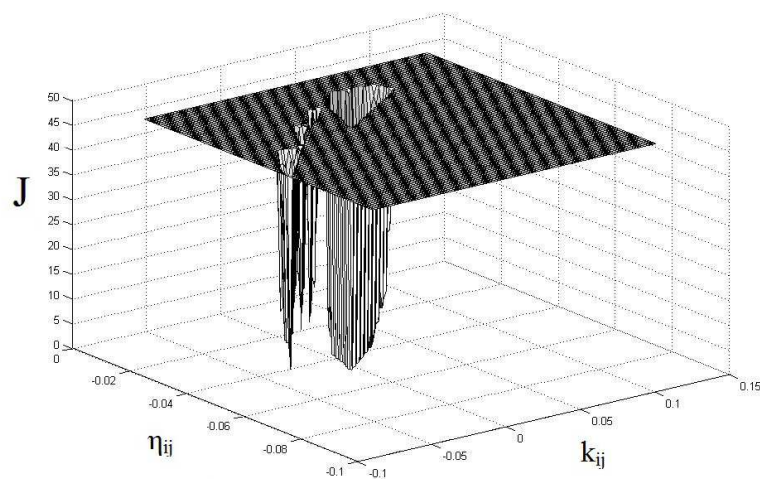


Figure 1: 3-D surface plot for the objective function (J) dependence on the parameters.

Figures 2 to 7 show the bubble pressure curves at 40°C for the systems CO₂-methanol, CO₂-chloroform, CO₂-formic acid, CO₂-acetic acid and CO₂-N-methylpyrrolidone, and at 61.9°C for CO₂-isopropanol respectively, calculated from the PR-EOS, whose binary interaction parameters values are shown in Table 4 . In most cases there is a good agreement between experimental and calculated data, except for the system CO₂-N-methylpyrrolidone.

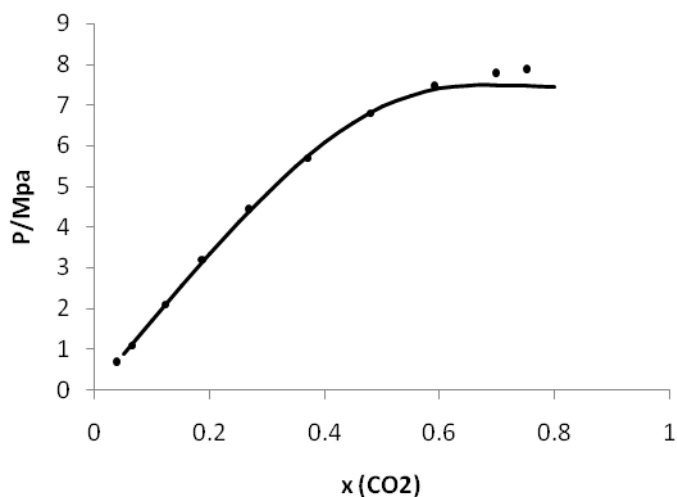


Figure 2: Bubble pressure curve for CO₂-methanol at 40°C calculated using the PR-EOS.

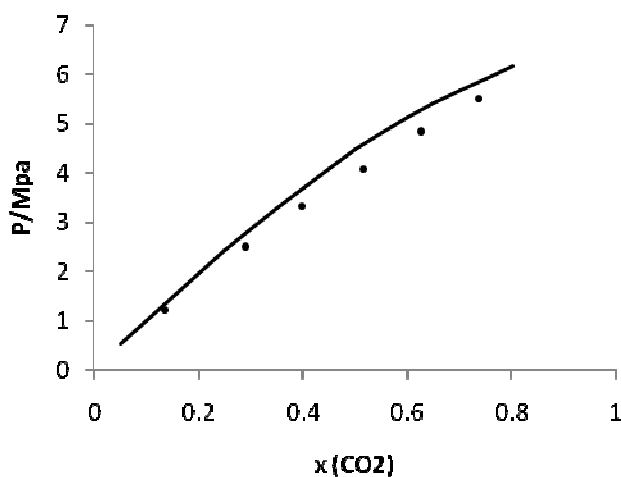


Figure 3: Bubble pressure curve for CO₂-chloroform at 40°C calculated from the PR-EOS.

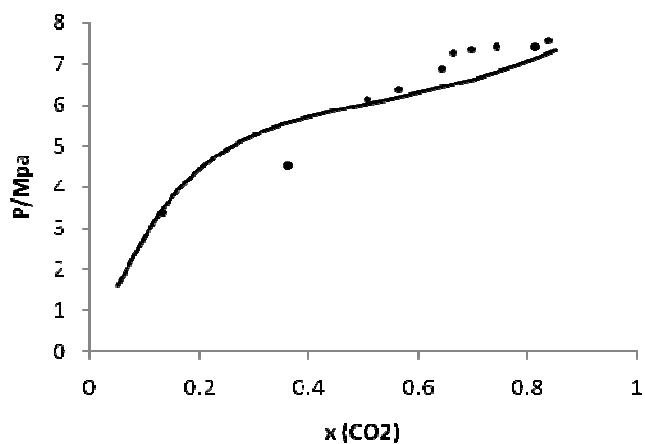


Figure 4: Bubble pressure curve for CO₂-formic acid at 40°C calculated using the PR-EOS.

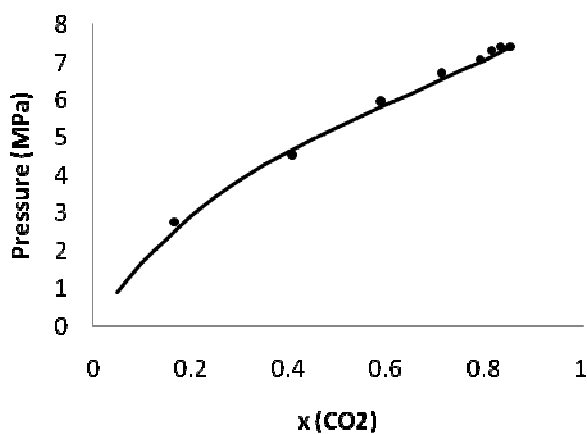


Figure 5: Bubble pressure curve for CO₂-acetic acid at 40°C calculated using the PR-EOS.

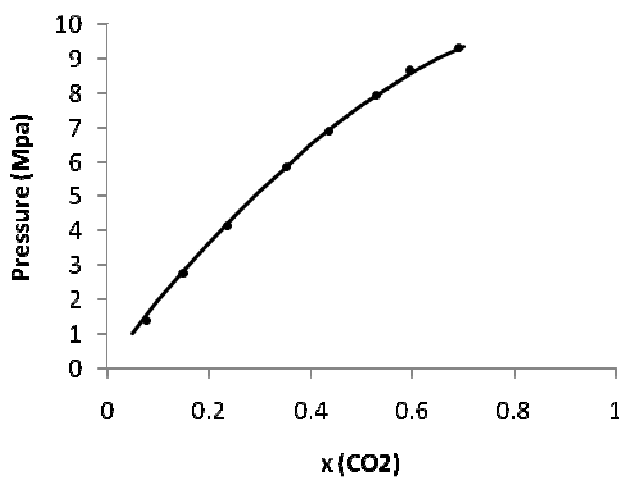


Figure 6: Bubble pressure curve for CO₂-isopropanol acid at 61.9°C calculated using the PR-EOS.

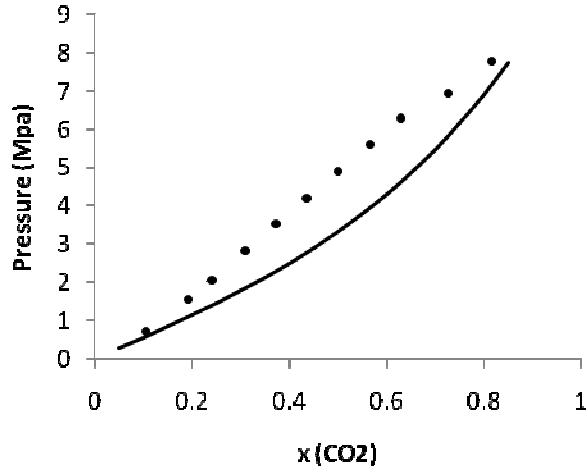


Figure 7: Bubble pressure curve for CO₂-N-methylpyrrolidone acid at 40°C calculated using the PR-EOS.

Figure 8 shows the liquid mixture reduced density curves as a function of CO₂ mole fraction for the systems CO₂-methanol, CO₂-chloroform, CO₂-formic acid, CO₂-acetic acid and CO₂-N-methylpyrrolidone at 40°C, and CO₂-isopropanol at 61.9°C predicted using the PR-EOS.

The liquid mixture reduced density (ρ_r^l) is the ratio of the liquid mixture density (ρ^l) to the liquid mixture critical density (ρ_c^l) calculated by

$$\rho_r^l = \rho^l / \rho_c^l \quad (20)$$

$$\rho_c^l = \frac{\sum_i x_i \cdot MW_i}{\sum_i x_i \cdot V_{c_i}} \quad (21)$$

where MW_i is the molecular weight and V_{c_i} is the critical volume of pure component i .

Figure 8 also shows that no liquid-liquid immiscibility region is detected since the liquid mixture density varies with mole fraction at a given temperature.

CONCLUSION

In this work a new approach is proposed to evaluate the behavior of ternary systems on the basis of the corresponding binary systems using the Peng-Robinson equation of state. This approach is useful to monitor the solid pharmaceutical solubility from the bubble point pressure and liquid density of the binary mixture solvent/antisolvent. A genetic algorithm (GA) method was successfully adopted for parameter estimation instead of the traditional SIMPLEX method due to presence of several local minimum points during the optimization

procedure of the objective function. The results show a good agreement between the experimental and the predicted values.

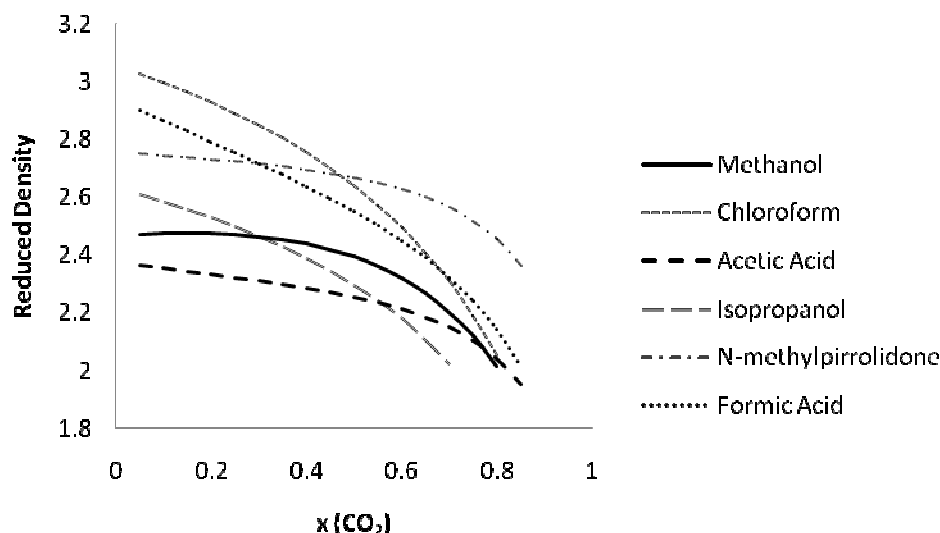


Figure 8: Liquid mixture reduced density curve for the systems CO₂-methanol, CO₂-chloroform, CO₂-formic acid, CO₂-acetic acid and CO₂-N-methylpyrrolidone at 40°C and CO₂-isopropanol at 61.9°C calculated using the PR-EOS.

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