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A new approach to select solvents and operating conditions for supercritical antisolvent precipitation processes by using solubility parameter and group contribution methods

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ABSTRACT

A new approach is proposed to select operating temperature and pressure for supercritical antisolvent particle precipitation based on solubility parameter calculated by group contribution methods and using only the critical properties of the solvent. Solubility parameters are also used to choose the most suitable organic solvent for a given application. Supercritical antisolvent precipitation operating conditions of 36 systems are investigated including 8 organic solvents (methanol, ethanol, acetone, DMSO, DCM, chloroform, NMP and acetic acid) and 6 solid solutes (atenolol, tartaric acid, flunisolide, paracetamol, amoxicillin and cholesterol) in the temperature and pressure ranges of 25–85 °C and 50–250 bar. The results show a good agreement between the experimental and calculated data for these systems. Although particle precipitation depends on several parameters such as mass-transfer rates and hydrodynamics, the focus of this work is on the role of thermodynamics to indicate the preliminary conditions for a successful antisolvent precipitation process. Validation and results of this new approach suggest that it can be a useful tool for a qualitative and completely predictive evaluation of supercritical antisolvent particle precipitation in a cheaper way than carrying out experimental runs.

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1. 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].

Supercritical precipitation processes have been extensively applied to obtain a great variety of pharmaceutical nanoparticles with mean diameters in the range of 30–500 nm. Also different morphologies are frequently attained such as spherical, needle-like, hollow core, rod-like, plate-like particles and so on [3–5]. Among the supercritical precipitation processes for the production of pharmaceutical nanoparticles of much interest are the gas antisolvent (GAS) process, the supercritical antisolvent (SAS) process, also referred as aerosol solvent extraction system (ASES) or precipitation by compressed antisolvent (PCA), the solution enhanced dispersion by supercritical fluids (SEDS) process, the atomized rapid injection for solvent extraction (ARISE) process, the rapid expansion of a supercritical solution (RESS) process, and the particles from gas-saturated solutions (PGSS) process [6].

Particularly in the antisolvent processes, one of the problems is to find the appropriate ratios of the solvent to the supercritical antisolvent for a given solid solute. 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 and pressure [7]. Knowledge of phase behaviour for systems involved in supercritical antisolvent precipitation is required to find appropriate temperature and pressure operating conditions. As an alternative to experimental investigation, solubility parameters can be used a priori to evaluate the possibility to dissolve a solute in an organic solvent, to check that the solute is not soluble or weakly soluble in the antisolvent, and to indicate the most suitable solvent for a given application.

Several thermodynamic models for describing phase behaviour of systems containing dense gases, organic solvents and solids are found in the literature including comparisons of their accuracy [8]. The binary interaction parameters of these models are usually fitted to solubility experimental data and phase behaviour of ternary

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systems are predicted using only these parameters. Therefore, it is difficult to accurately calculate the operating conditions of supercritical antisolvent precipitation processes based on the ternary system solute – solvent–antisolvent.

In view of these arguments, a preliminary analysis of supercritical antisolvent precipitation processes should require the use of physico-chemical properties of the components involved. However, employment of solubility parameter comes up as an alternative to do it without experimental data.

The concept of solubility parameters was introduced by Scatchard [9] and greatly extended by Hildebrand [10]. Since then, the universality of the solubility parameter has been pointed out and its general applicability has been presented by means of numerical relations [11]. Solubility parameters provide one of the simplest methods for correlating and predicting the solubility behaviour of two components in a mixture based on the knowledge of pure components physicochemical properties.

The use of solubility parameters at supercritical conditions has already been shown in the literature [12–15]. For example, Kagliwal et al. [15] used solubility parameters for evaluation of experimental conditions for separation of bioactives from seabuckthorn seeds by supercritical CO_2. However, the pressure effect on solubility parameters was not taken in account.

This work aimed at proposing a new completely predictive approach to find the most suitable solvents and to indicate preliminary possible operating conditions for supercritical antisolvent precipitation processes based on solubility parameters calculated by group contribution methods and using only the critical properties of the solvents. Validation of this approach is accomplished by comparison with data obtained from literature. It is important to say that the focus of this work is only on the assessment of thermodynamics aspects related to supercritical antisolvent precipitation processes as a prior step before carrying out expensive experimental runs. Nevertheless, a whole evaluation of particle precipitation processes requires also investigating the role of several parameters related to nucleation kinetics, solvent diffusion rate, atomization, mixing, hydrodynamics and precipitation rates. Considering the simple approach proposed here as the first step before experimental investigation, one can avoid spending time with unsuccessful operating conditions for supercritical antisolvent precipitation process.

2. Modelling

Supercritical antisolvent precipitation of pharmaceuticals should be preceded of understanding the phase behaviour of the ternary system solvent–solute–supercritical antisolvent. This understanding comprises the choice of solvent and the operating conditions. Among several approaches for assessing the interactions between components involved in supercritical antisolvent precipitation processes, this work emphasizes the analysis based on their solubility parameters. Supercritical antisolvent precipitation is based on the assumption that the solute is practically insoluble in the mixture solvent–antisolvent; if this hypothesis is verified the presence of solute can be neglected and the fluid phase system formed in the precipitator can be treated as a binary one. Therefore, the considerations about the process operating point can be performed on the corresponding *P–x* isothermal diagram and typical supercritical antisolvent precipitation will be operated at pressures above the binary mixture critical point [16].

In the method proposed in the present work, the solubility tracking conditions can be achieved by the performances of the solubility parameters of the solute, the solvent and the antisolvent. The assumption that the solute is practically insoluble in the mixture solvent–antisolvent can be assigned to a large difference between the solubility parameter of the solute and the solubility parameter of the mixture. Pressures above the binary mixture critical point can be seen in qualitative terms as a condition in which the difference between the solubility parameters of the solvent and the antisolvent is quite small. On the other hand, if the solute has a non-negligible solubility in the mixture antisolvent–solvent the difference between the solubility parameters of the solute and this mixture should be small.

2.1. Solubility parameter

The thermodynamic criteria of solubility are based on the free energy of mixing ΔG_M. Two substances are mutually soluble if ΔG_M is negative. By definition,

$$\Delta G_M = \Delta H_M - T \cdot \Delta S_M \tag{1}$$

where ΔH_M is the enthalpy of mixing and ΔS_M is the entropy of mixing. Since ΔS_M is generally positive there is a certain boundary positive value of ΔH_M below which the dissolution is possible.

Scatchard [9] introduced the concept of "cohesive energy density", defining this property as the cohesive energy per unit volume. Hildebrand [10] provided a comprehensive treatment of this concept and proposed the square root of the energy density as a parameter that can describe the behaviour of specific solvents. He proposed the term "solubility parameter" and the symbol "δ". The solubility parameter of a pure component is defined by Eq. (2):

$$\delta = \left(\frac{\Delta U_{vap}}{V_{liq}}\right)^{0.5} = \left(\frac{\Delta H' - R \cdot T + P \cdot V_{liq}}{V_{liq}}\right)^{0.5} \tag{2}$$

where ΔU_{vap} is the energy of complete vaporization, which is the energy change upon isothermal vaporization of the saturated liquid to the ideal gas state, and V is the molar volume. The solubility parameter can be estimated from the right side of the Eq. (2) where $\Delta H'$ is the difference between the enthalpy of oil as an ideal gas at temperature T and the enthalpy of liquid oil at the same temperature T and oil saturation pressure. Although the concept of solubility parameter was first applied to nonpolar liquids, it has been further extended to a much wider range of liquids.

Often the liquid molar volume is neglected with respect to the vapour one. The pressure influence on the vapor phase is also neglected so that the enthalpy of the vapor is considered as the enthalpy of an ideal gas. Therefore, the solubility parameter is usually simplified to

$$\delta = \left(\frac{\Delta U_{vap}}{V_{liq}}\right)^{0.5} = \left(\frac{\Delta H_{vap} - R \cdot T}{V_{liq}}\right)^{0.5} \tag{3}$$

Solubility parameters enable a qualitative analysis of a system containing a drug of interest, since they indicate which solvent should be chosen and what temperature and pressure conditions lead to larger differences between the solubility parameters of the drug and the mixture containing the solvent and the antisolvent.

2.2. Solubility parameters of the solutes

Due to the complexity of their molecular structure, in this work a group contribution method is used to calculate the solubility parameters of the solute. Fedors method [17] was selected due to the large number of different groups for which parameters are provided. Also, this method allows calculating the solubility parameters of cyclic compounds from the properties of linear compounds

with similar structure, by means of a cyclization increment. Solubility parameters of solutes are calculated by

$$\delta = \sqrt{\frac{\sum_i (\Delta E)_i}{\sum_i (\Delta V)_i}} \quad (4)$$

where δ is the solubility parameter of the solute expressed in $(cal/cm^3)^{0.5}$ at 25 °C, $\sum_i(\Delta E)_i$ is the sum of cohesive energies (cal/mol) and $\sum_i(\Delta V)_i$ is the sum of molar volumes (cm^3/mol).

The solubility parameter of the solute is corrected only by temperature since pressure does not exert a large influence on the properties of solids. The following equation can be used for the correction of temperature [18]:

$$\delta_2 = \delta_1 \cdot \left(\frac{T_c - T_2}{T_c - T_1}\right)^{0.33} \quad (5)$$

where δ_2 and δ_1 are the solubility parameters of the solute at temperatures T_2 and T_1 and T_c is the critical temperature of the solute estimated by a group contribution method [19].

2.3. Solubility parameters of the solvents

The solubility parameters of the solvents at different temperatures and pressures are calculated by Eq. (3). Regarding the influence of the enthalpy of vaporization on the calculation of the solubility parameter two different methods were used. The first one, namely method M1, allows calculating the enthalpy of vaporization by group contribution at 25 °C [20]. The second method (M2) involves the calculation of the enthalpy of vaporization at the normal boiling temperature. Both methods are based on two steps. The first step comprises the calculation of the enthalpy of vaporization at a particular temperature. In the second step the enthalpy of vaporization is corrected to a new temperature. The correction between both temperatures is expressed by the following empirical relationship proposed by Watson within an approximation of 2% to the experimental values [21]:

$$\Delta H_2^{vap} = \Delta H_1^{vap} \cdot \left(\frac{1 - T_{r2}}{1 - T_{r1}}\right)^{0.38} \quad (6)$$

where $T_r = T/T_c$

Table 1
Constants of the Reynolds equation of state for CO_2 [22].

Constants		Constants	
A_1	2.2488×10^{-1}	A_{11}	1.2115×10^{-1}
A_2	-1.3718×10^{2}	A_{12}	1.0784×10^{-7}
A_3	-1.4430×10^{4}	A_{13}	4.3962×10^{-11}
A_4	-2.9631×10^{6}	A_{14}	-3.6505×10^{4}
A_5	-2.0606×10^{8}	A_{15}	1.9491×10^{7}
A_6	4.5554×10^{-5}	A_{16}	-2.9187×10^{9}
A_7	7.7043×10^{-2}	A_{17}	2.4359×10^{-2}
A_8	4.0602×10^{1}	A_{18}	-3.7546×10^{1}
A_9	4.0295×10^{-7}	A_{19}	1.1898×10^{4}
A_{10}	-3.9436×10^{-4}	A_{20}	5.0×10^{-6}

Table 2
Systems selected from literature to investigate the new approach on selecting solvent and operating conditions for supercritical antisolvent precipitation process by solubility parameter. The solubility parameter of the selected solutes at 25 °C is also shown.

Solute	Solvent	CO_2 composition	Pressure (bar)	Temperature (°C)	Reference
Atenolol (δ = 23.93)	Methanol	0.955	95	40	[27]
	Acetone	0.1–1	50–150	25–55	*
	DMSO	0.1–1	50–150	25–55	*
	DCM	0.1–1	50–150	25–55	*
	Ethanol	0.968	95	40	[27]
	Acetic acid	0.1–1	50–150	25–55	*
Tartaric acid (δ = 36.14)	Methanol	0.1–1	100–250	25–80	*
	Ethanol	0.93–0.96	100–250	40	[28]
	Acetone	0.93–0.96	100–250	40	[28]
	DCM	0.1–1	100–250	25–80	*
	Chloroform	0.1–1	100–250	25–80	*
	NMP	0.1–1	100–250	25–80	*
Flunisolide (δ = 26.50)	Methanol	0.860	100	60–80	[29,30]
	DMSO	0.1–1	80–200	40–80	*
	Acetone	0.917–0.957	100	40–80	[29,30]
	Acetic acid	0.1–1	80–200	40–80	*
	Chloroform	0.1–1	80–200	40–80	*
	NMP	0.1–1	80–200	40–80	*
Paracetamol (δ = 33.25)	Ethanol	0.993	100–250	40–85	[31]
	DMSO	0.1–1	100–250	25–85	*
	Acetone	0.1–1	100–250	25–85	*
	DCM	0.1–1	100–250	25–85	*
	Acetic acid	0.1–1	100–250	25–85	*
	NMP	0.1–1	100–250	25–85	*
Amoxicillin (δ = 35.47)	DMSO	0.996	100–250	40–80	[32]
	Ethanol	0.1–1	100–250	25–80	*
	NMP	0.970	150	40–80	[33,34]
	Acetone	0.1–1	100–250	25–80	*
	DCM	0.1–1	100–250	25–80	*
	Acetic acid	0.1–1	100–250	25–80	*
Cholesterol (δ = 20.28)	DCM	0.956	112	40–80	[35]
	Ethanol	0.1–1	100–250	40–80	*
	NMP	0.1–1	100–250	40–80	*
	Acetone	0.1–1	100–250	40–80	*
	Acetic acid	0.1–1	100–250	40–80	*
	DMSO	0.1–1	100–250	40–80	*

* Additional solvent used in this work for comparison with solvent of Ref. [2].

Table 3
Physical properties of the solvents [16].

Solvent	T_c (K)	T_b (K)	P_c (bar)	w
Methanol (MeOH)	512.6	337.9	80.97	0.564
Ethanol (EtOH)	513.9	351.4	61.48	0.645
Acetone (AC)	508.2	329.4	47.01	0.307
Dimethylsulfoxide (DMSO)	720	462	57.05	0.350
N-methylpyrrolidone (NMP)	721.6	351.4	44.03	0.539
Dichloromethane (DCM)	510	337.9	63	0.199
Chloroform ($CHCl_3$)	592	391.1	57.86	0.467
Acetic acid (AA)	536.4	334.3	54.72	0.222

The calculation of the solubility parameter as shown in Eq. (3) requires the calculation of the molar volume, which was done is this work using the Peng–Robinson equation of state [22]:

$$P = \frac{RT}{V-b} - \frac{a\ (T)}{V\cdot(V+b)+b\cdot(V-b)} \tag{7}$$

To determine the pure component parameters "a" and "b" the following properties are required: critical temperature (T_c), critical pressure (P_c) and acentric factor (w).

2.4. Solubility parameter of the antisolvent

Supercritical CO_2 is the antisolvent chosen to be investigated in this work and its solubility parameter should be evaluated at this condition.

The work of Giddings et al. [23] is the most widely referenced on the extension of the solubility parameter for supercritical fluids. Giddings et al. [23] suggested that the "solvent power" of a gas depends in part on its state relative to its critical condition. The influence of the state, that is, the relative compression and temperature, they termed a "state effect" or "physical effect". Besides, there is a "chemical effect", unique for each chemical specie and dependent on its polarity, acid–base properties and hydrogen bonding tendencies. Classical solubility differences among liquids depend mainly on the "chemical effect" as most liquids are in similar states or can be simply reduced to such without much alteration of their solvent characteristics. With some manipulations, by correlating data from liquid and assuming the equivalence of gases and liquids in a common density, they derived the following expression:

$$\delta = 0.326\cdot(P_c)^{0.5}\cdot\left(\frac{\rho_r}{\rho_{r(liq)}}\right) \tag{8}$$

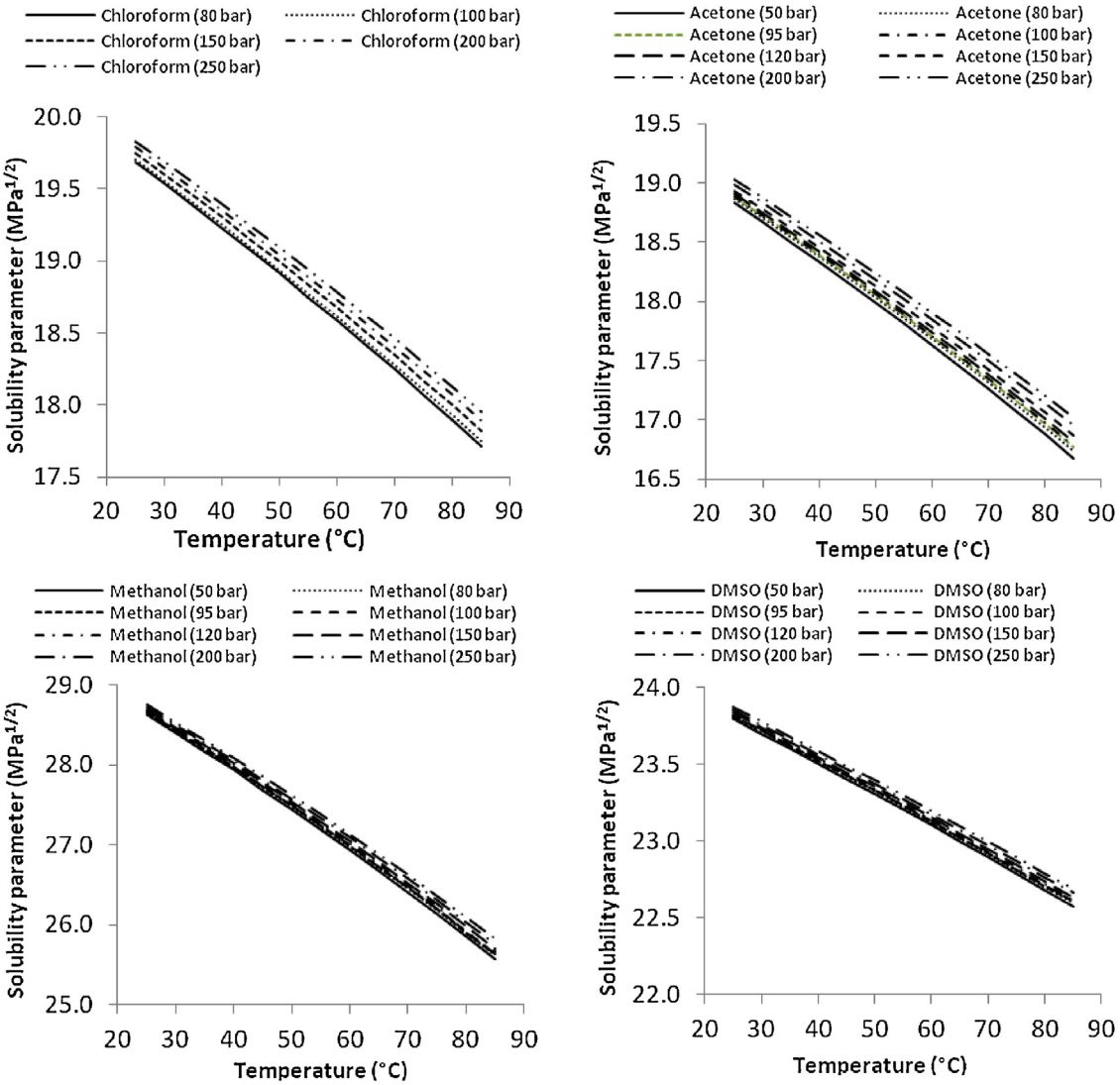

Fig. 1. Solubility parameters of chloroform, acetone, methanol and DMSO as a function of temperature and pressure calculated by methods M1 and M2.

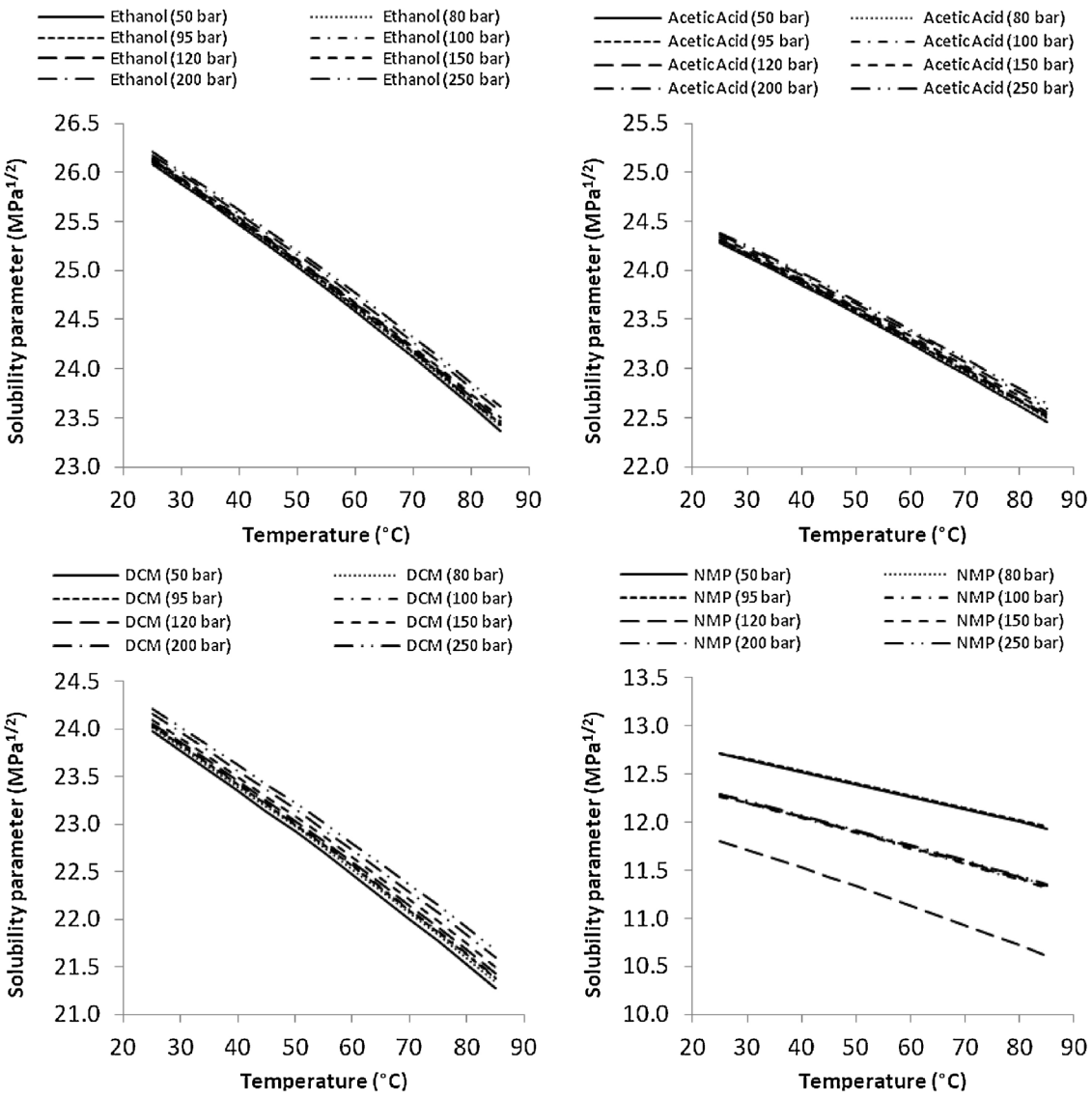

Fig. 2. Solubility parameters of ethanol, methanol, acetone, DCM, chloroform and NMP as a function of temperature and pressure calculated by methods M1 and M2.

where δ is the solubility parameter of the gas in $(\text{cal/cm}^3)^{0.5}$, P_c is the critical pressure in psia, ρ_r is the reduced density, defined as ρ/ρ_c, where ρ is the density and ρ_c is the critical density, and $\rho_{r(liq)}$ is the reduced density of the gas at its normal boiling point, considered constant and equal to 2.66. The "state effect" is represented by $\rho_r/\rho_{r(liq)}$ and the term $0.326\,(P_c)^{0.5}$ is related to the "chemical effect".

As outlined by Eq. (8), calculation of the solubility parameter of the supercritical fluid requires as an input the gas density ρ.

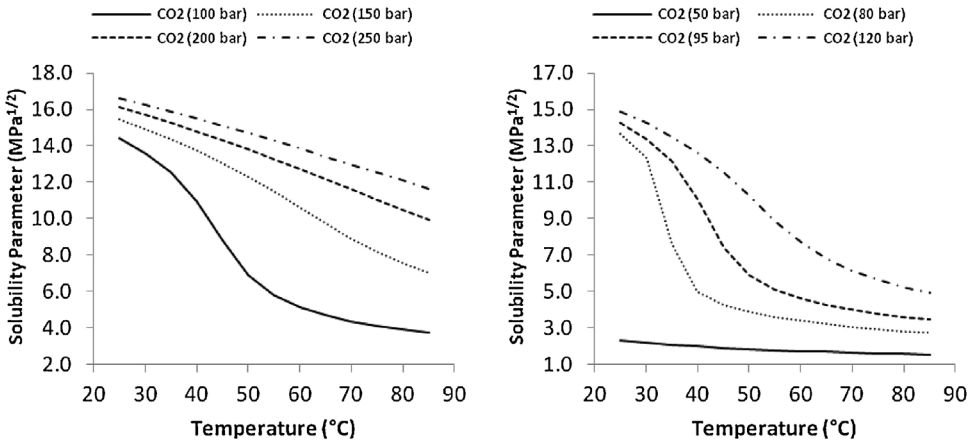

Fig. 3. Solubility parameter of CO2 calculated as function of temperature and pressure.

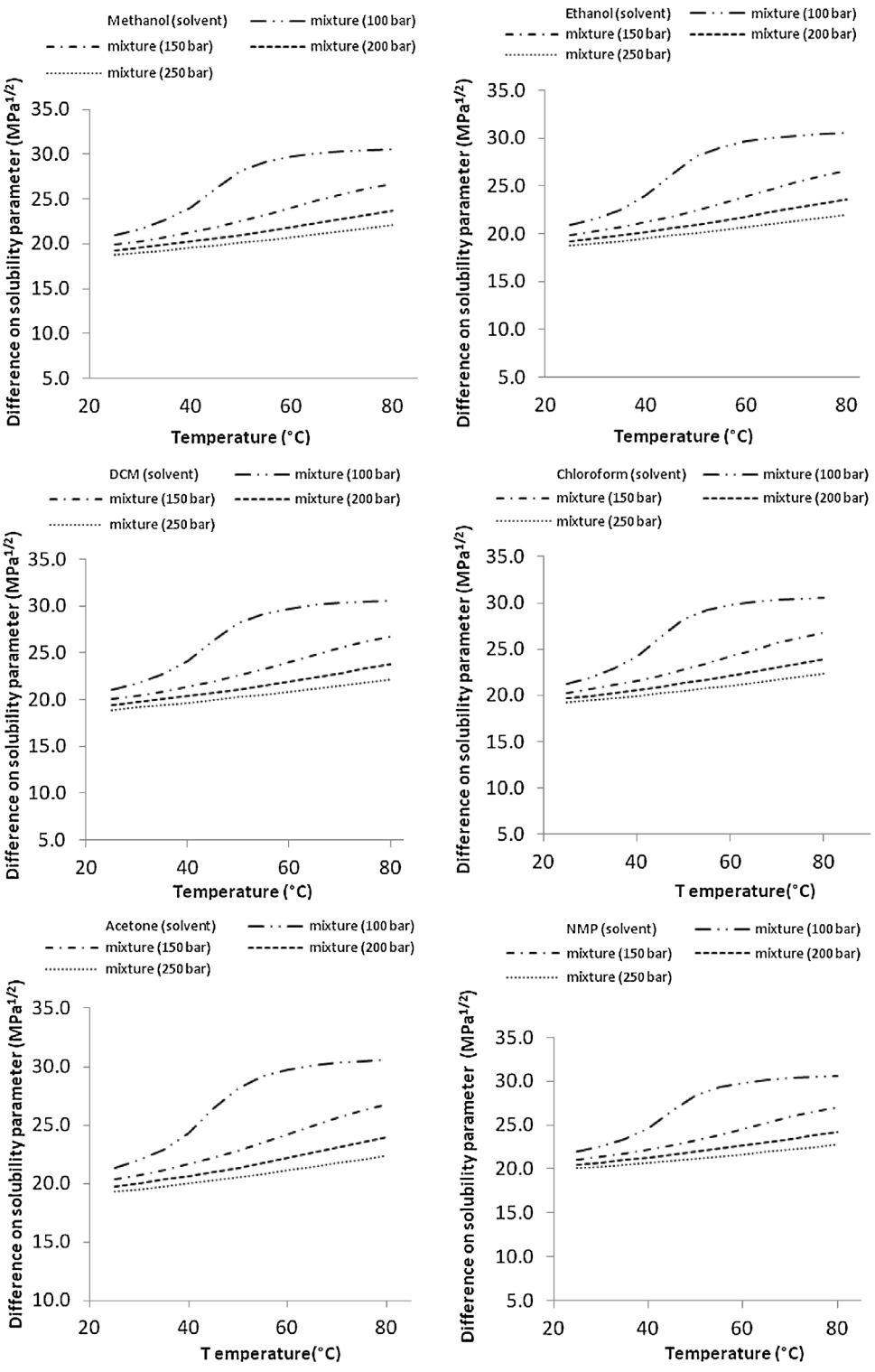

Fig. 4. Influence of pressure and temperature on the difference in the solubility parameter of tartaric acid and mixture CO2 mol fraction with different solvents (ethanol, methanol, acetone, DCM, chloroform, NMP).

Therefore, accuracy of the solubility parameter of the supercritical fluid is deeply dependent on the precision of the description of its pressure–volume–temperature behaviour. According to Shim [24], the Reynolds equation of state [25] is suitable for CO_2:

$$P = \rho^2 \cdot M_1 + \rho^3 \cdot M_2 + \left[(\rho^3 \cdot M_3 + \rho^5 \cdot M_4) \cdot \exp(-A_{20} \cdot \rho^2)\right] + \rho \cdot R \cdot T + \rho^4 \cdot (A_9 \cdot T + A_{10}) + \rho^5 \cdot (A_{11} \cdot T + A_{12}) + \rho^6 \cdot A_{13} \quad (9)$$

where T is the temperature (°C), P is the pressure (atm), ρ is the density (g/cm^3) and

$$M_1 = A_1 \cdot T + A_2 + \frac{A_3}{T} + \frac{A_4}{T^2} + \frac{A_5}{T^3} \quad (10)$$

$$M_2 = A_6 \cdot T + A_7 + \frac{A_8}{T} \quad (11)$$

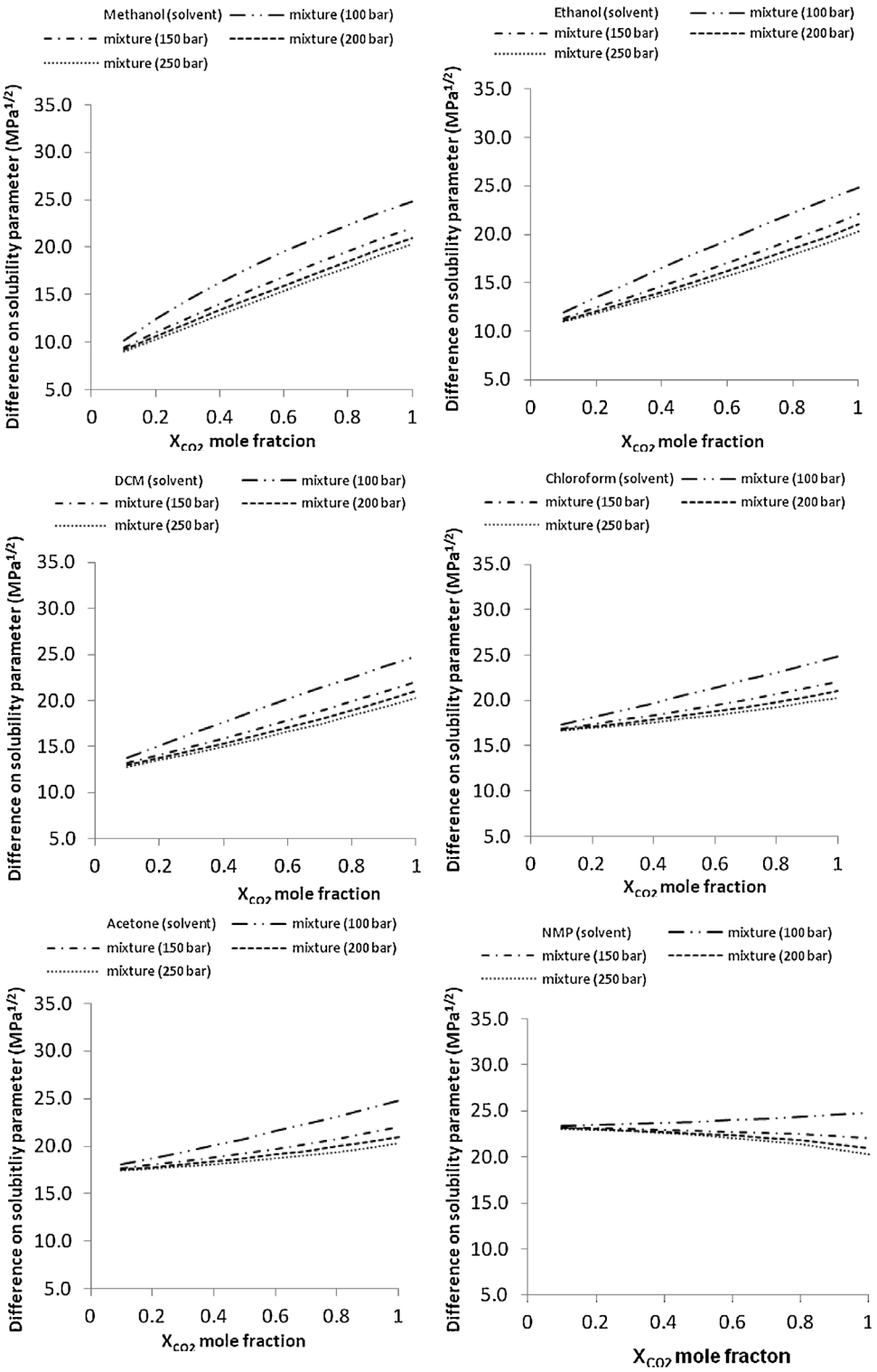

Fig. 5. Influence of pressure and mol fraction of CO2 on the difference in the solubility parameters of tartaric acid and different mixtures of CO2 and organic solvents (ethanol, methanol, acetone, DCM, chloroform and NMP) at 40 °C.

$$M_3 = \frac{A_{14}}{T^2} + \frac{A_{15}}{T^3} + \frac{A_{16}}{T^4} \quad (12)$$

$$M_4 = \frac{A_{17}}{T^2} + \frac{A_{18}}{T^3} + \frac{A_{19}}{T^4} \quad (13)$$

The constants A_i of the Reynolds equation of state for CO_2 are shown in Table 1.

For a mixture consisting of SC–CO_2 and a solvent, the solubility parameter of the mixed fluid is determined as follows [26]:

$$\delta = \phi_{CO2} \cdot \delta_{CO2} + \phi_{solvent} \cdot \delta_{solvent} \quad (14)$$

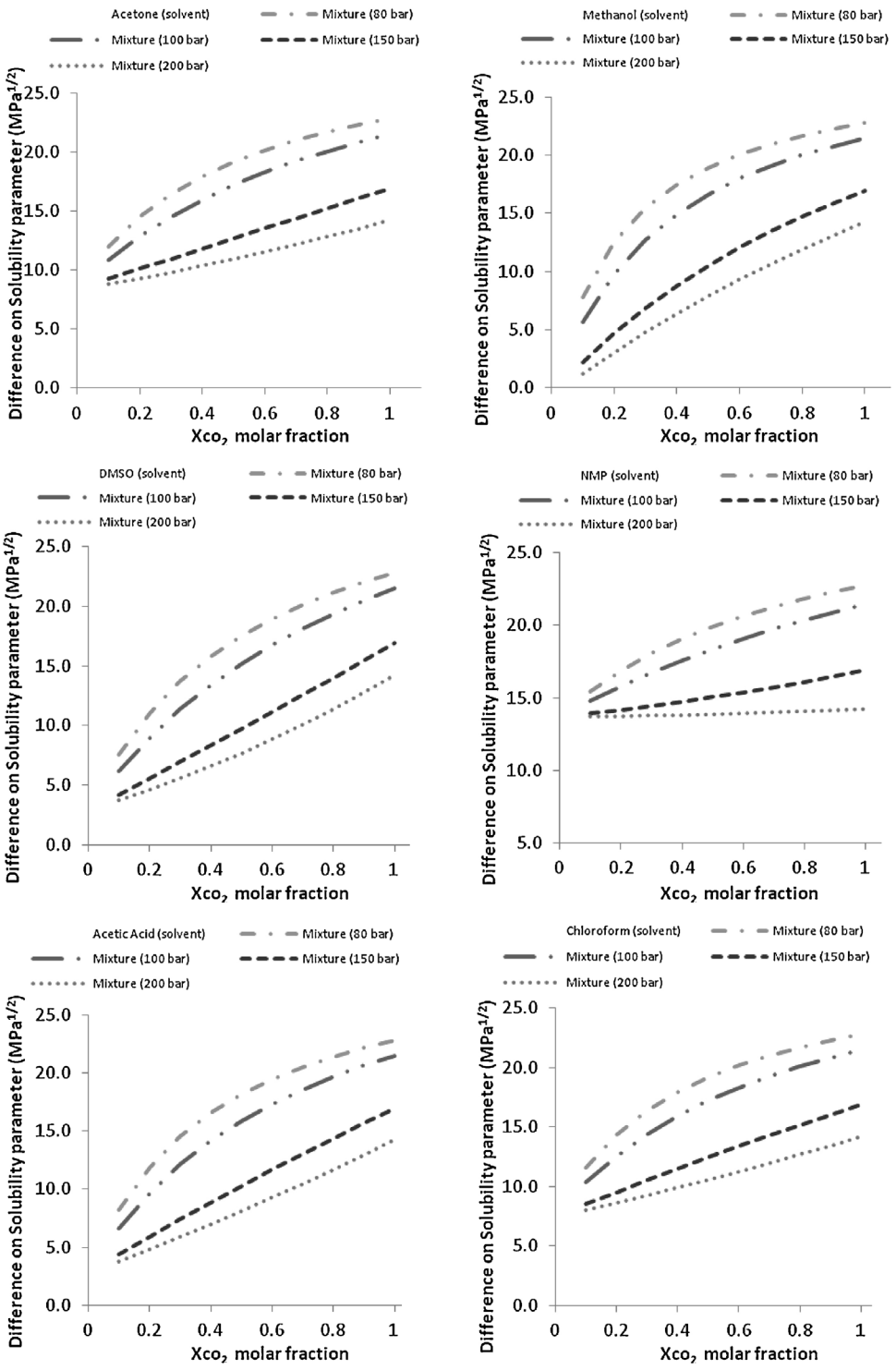

Fig. 6. Influence of pressure and molar fraction of CO2 on the difference in the solubility paramaters of Flunisolide and different mixtures of CO2 and organic solvents (DMSO, methanol, acetone, DCM, acetic acid, chloroform and NMP) at 70 °C.

where

$$\phi_i = \frac{x_i \cdot V_i}{\sum_j x_j \cdot V_j} \tag{15}$$

and x is the mol fraction and V is the molar volume.

3. Results and discussion

In this study we selected 6 solutes from the literature, each one with 6 organic solvents, resulting in 36 systems to be investigated concerning on the solvent and operating conditions for supercritical antisolvent precipitation process [2]. Relevant information of these systems and their characteristics are displayed in Table 2. The solubility parameter of the selected solutes at 25 °C is also shown at Table 2. It is worth noting that beside the systems

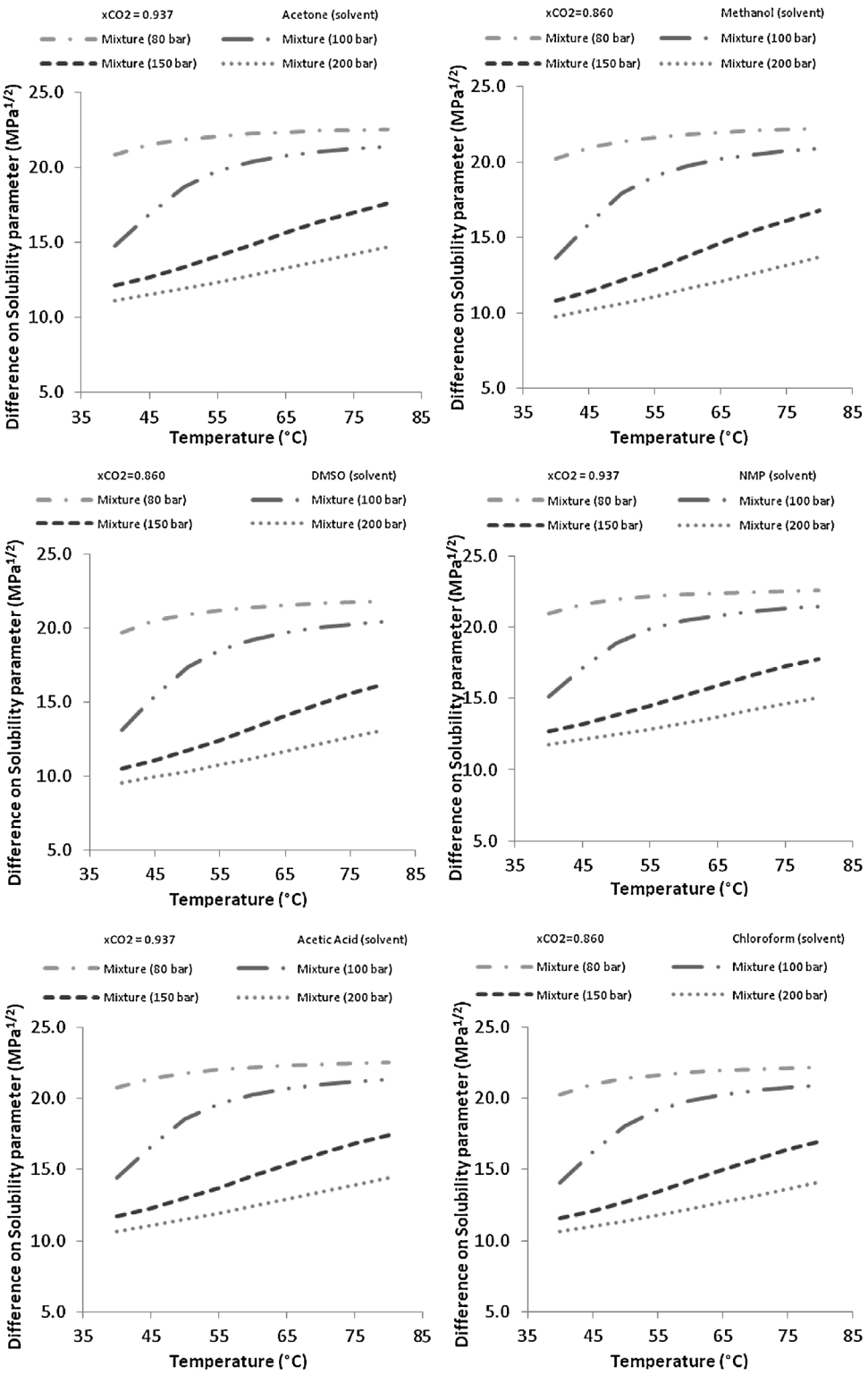

Fig. 7. Influence of pressure and temperature on the difference in the solubility parameters of flunisolide and different mixtures of CO2 and organic solvents (acetone, acetic acid and NMP with a molar fraction of CO2 equal to 0.937 and methanol, chloroform and DMSO with a molar fraction of CO2 equal to 0.860).

solute–solvent–antisolvent with experimental data available other systems whose solvents are easily found in the literature were included in this study. This procedure allows assessing the possibility of using several solvents, detached with an asterisk (*) in Table 2, as additional solvents. Therefore, for each solute an evaluation of 6 solvents was performed.

Table 3 displays the physical properties of the organic solvents selected in this work. The molecular structures of the solvents are not required since their physical properties are well known [19]. The critical pressure (P_c), the critical temperature (T_c) and the acentric factor (w) are used to calculate the molar volume of the solvent by Eq. (7).

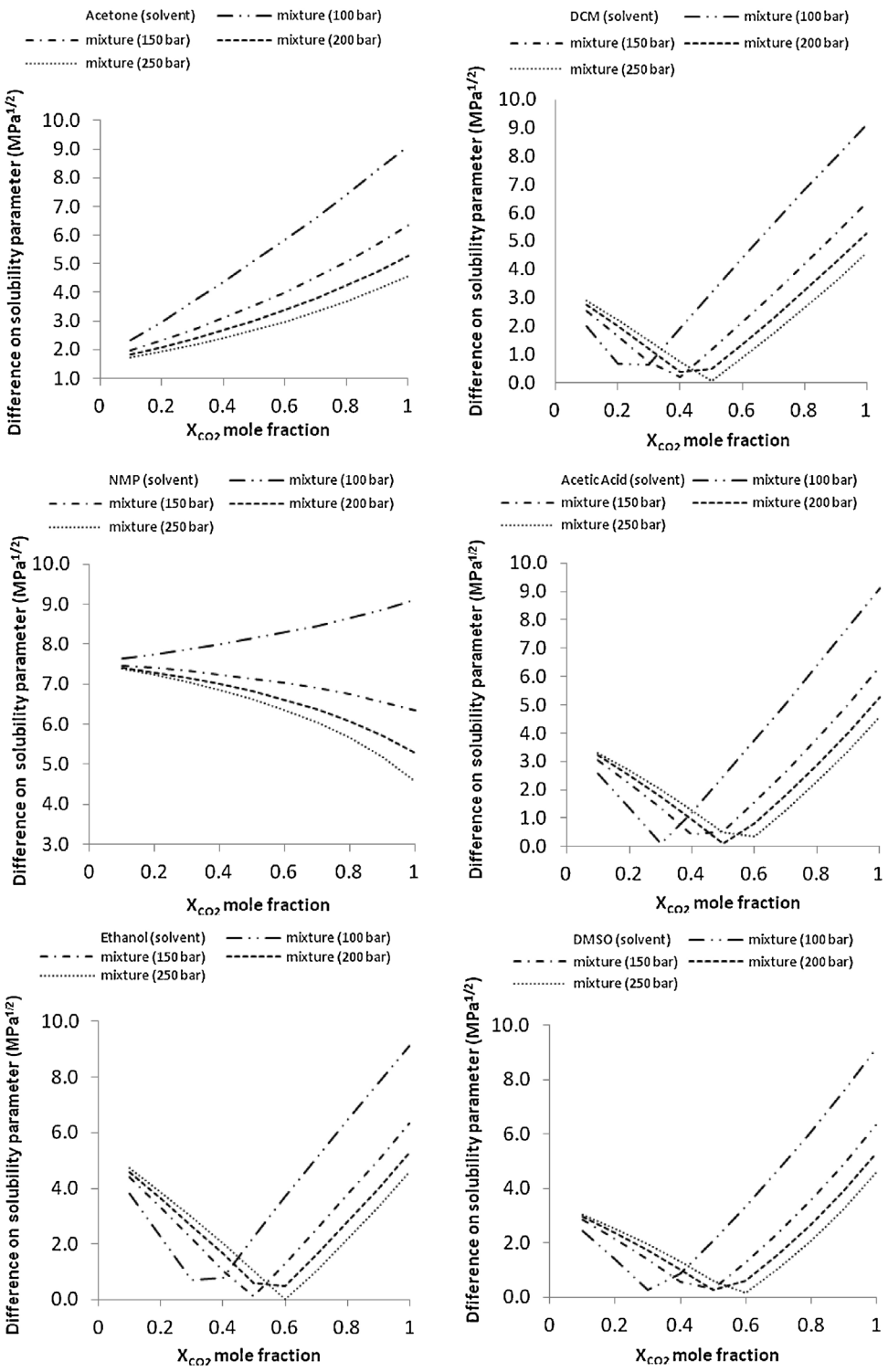

Fig. 8. Influence of pressure and molar fraction of CO2 on the difference in the solubility parameters of cholesterol and different mixtures of CO2 and organics solvents (DMSO, DCM, acetone, acetic acid, chloroform, NMP) at 40 °C.

The methodology detailed in Section 2.3 was applied to evaluate variations in the solubility parameter of the solvents as a function of pressure and temperature. It is worth noting that the performance of methods M1 and M2 to calculate the enthalpy of vaporization was also assessed. The results showed that the corresponding values of the solubility parameters remain practically unchanged for both methods although they provide different values for the enthalpy of vaporization. Therefore, this result allows concluding that the solubility parameters of the solvents are independent of the method used to calculate their enthalpy of vaporization.

Fig. 1 shows the solubility parameters of chloroform, acetone, methanol and DMSO as a function of temperature and pressure calculated by both methods. Fig. 2 shows analogous results for ethanol, acetic acid, DCM and NMP. The influence of pressure is negligible but for NMP. At constant temperature a large increase in pressure causes a slight increase in the solubility parameter of the solvents with the exception of NMP. On the other hand,

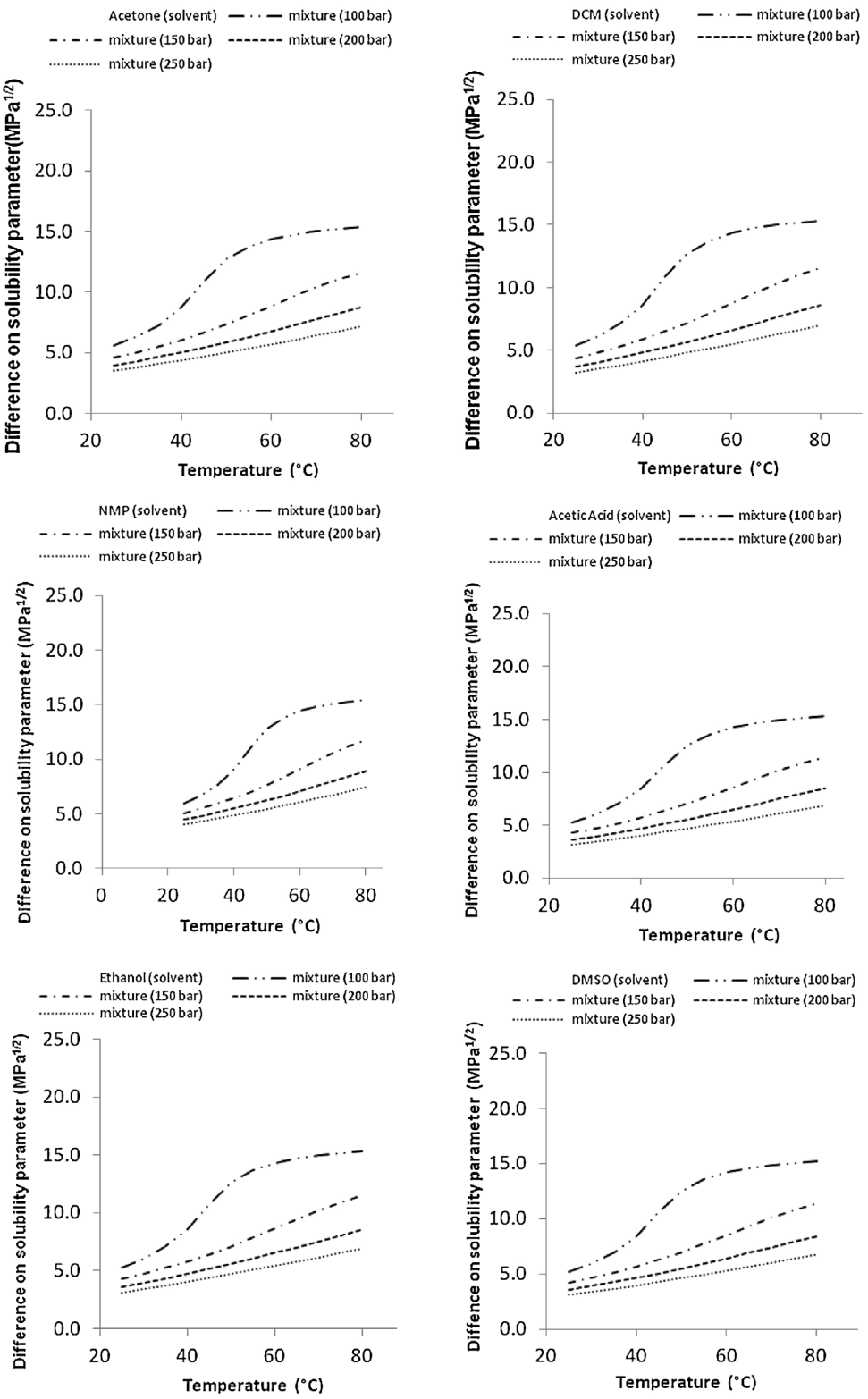

Fig. 9. Influence of pressure and temperature on the difference in the solubility parameters of cholesterol and different mixtures of CO2 and organic solvents (acetic acid, DMSO, acetone, DCM, ethanol and NMP) with a molar fraction of CO2 equal to 0.956.

the solubility parameters of the solvents are strongly temperature dependent. At constant pressure an increase in temperature causes a decrease in the solubility parameter. In Fig. 2 it is important to highlight the behaviour of NMP because at higher temperatures its solubility parameter shows lower values and larger pressure effects than the other solvents.

Fig. 3 shows the temperature and pressure effect on the solubility parameter of CO_2. To allow a good visualization of the difference in the values of the solubility parameter, the plots were separated into two pressure ranges. At constant temperature an increase in pressure corresponds to an increase in the solubility parameter. For isobaric conditions, a decrease in the solubility parameter occurs

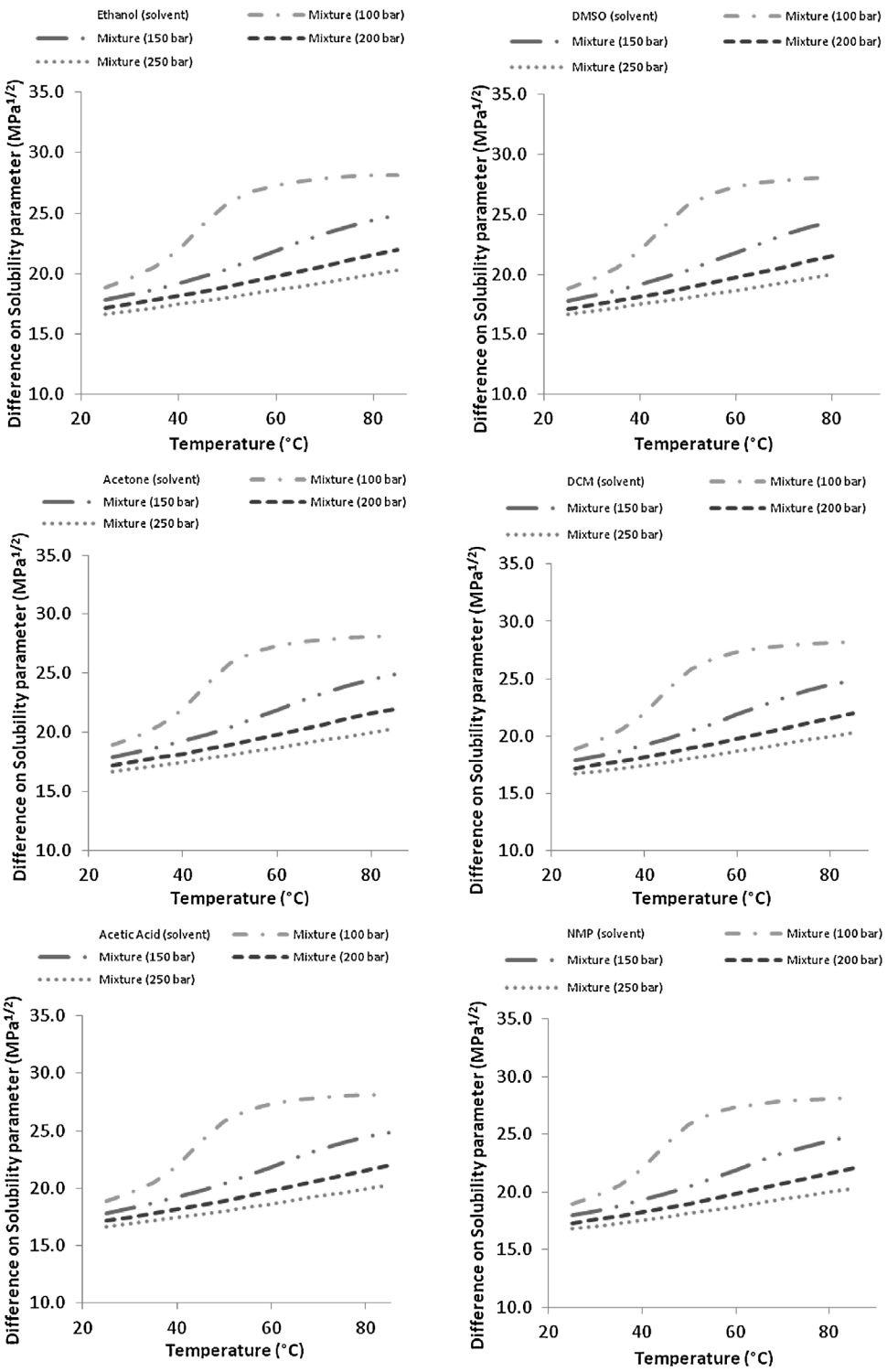

Fig. 10. Influence of pressure and temperature on the difference in the solubility parameters of paracetamol and different mixtures of CO2 and organic solvents (ethanol, acetic acid, acetone, DCM, DMSO and NMP with a molar fraction of CO2 equal to 0.993).

with an increase in temperature. An important point to be emphasized is that at the highest pressure levels (200 and 250 bar) there is almost a linear variation of the solubility parameter with temperature which does not occur at lower pressure levels. Furthermore, at the lowest pressure (50 bar) there is a very small variation of the solubility parameter with temperature. A possible explanation to this behaviour is that at higher pressures the molecules are closer and due to this reason the temperature effect on the solubility is more pronounced. However, this effect decreases when pressure gets lower because the molecules stay further from each other.

Fig. 4 shows the calculated results for the solubility parameters of tartaric acid and different mixtures of CO_2 (0.937 mol fraction) and organic solvents (ethanol, methanol, acetone, DCM, chloroform, NMP) as a function of pressure and temperature. As shown in Table 2, there are experimental data available in literature only for the mixtures containing ethanol and acetone. For the other solvents, the mixtures are proposed to investigate how the solubility

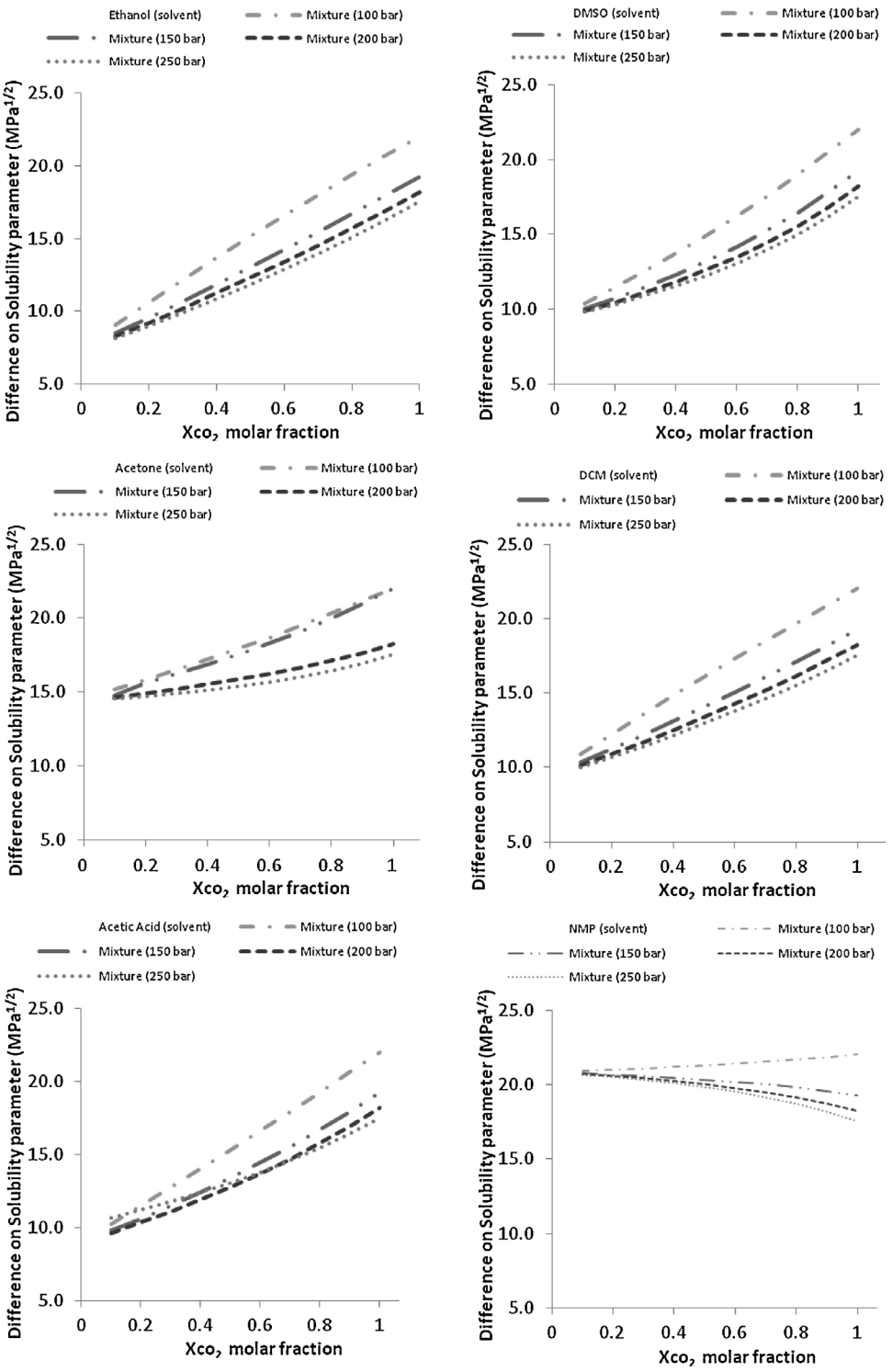

Fig. 11. Influence of pressure and molar fraction of CO2 on the difference in the solubility parameters of paracetamol and different mixtures of CO2 and organic solvents (ethanol, acetic acid, acetone, DCM, DMSO and NMP) at 40 °C.

parameter behaves for the same ranges of temperature and pressure.

As it is known, supercritical antisolvent precipitation techniques are based on the assumption that the solute is practically insoluble in the mixture solvent–antisolvent. In order to carry the precipitation out it is necessary that the solubility parameter of the solute be as far as possible from the solubility parameter of solvent–antisolvent mixture. In Fig. 4 it can be noticed that the values of the solubility parameter for the mixtures solvent/CO_2 are similar regardless of the solvent used. The reason for this behaviour is related to the fact that CO_2 is the dominant component with a molar composition as high as about 94%. Once solubility parameter is directly related to the intermolecular forces, the variation in the solubility parameter of the solute with temperature is almost unnoticeable as expected. In terms of temperature and pressure operating conditions for supercritical antisolvent precipitation process, it is desirable that the difference between the solubility parameters of the solute and of the mixture containing CO_2 and

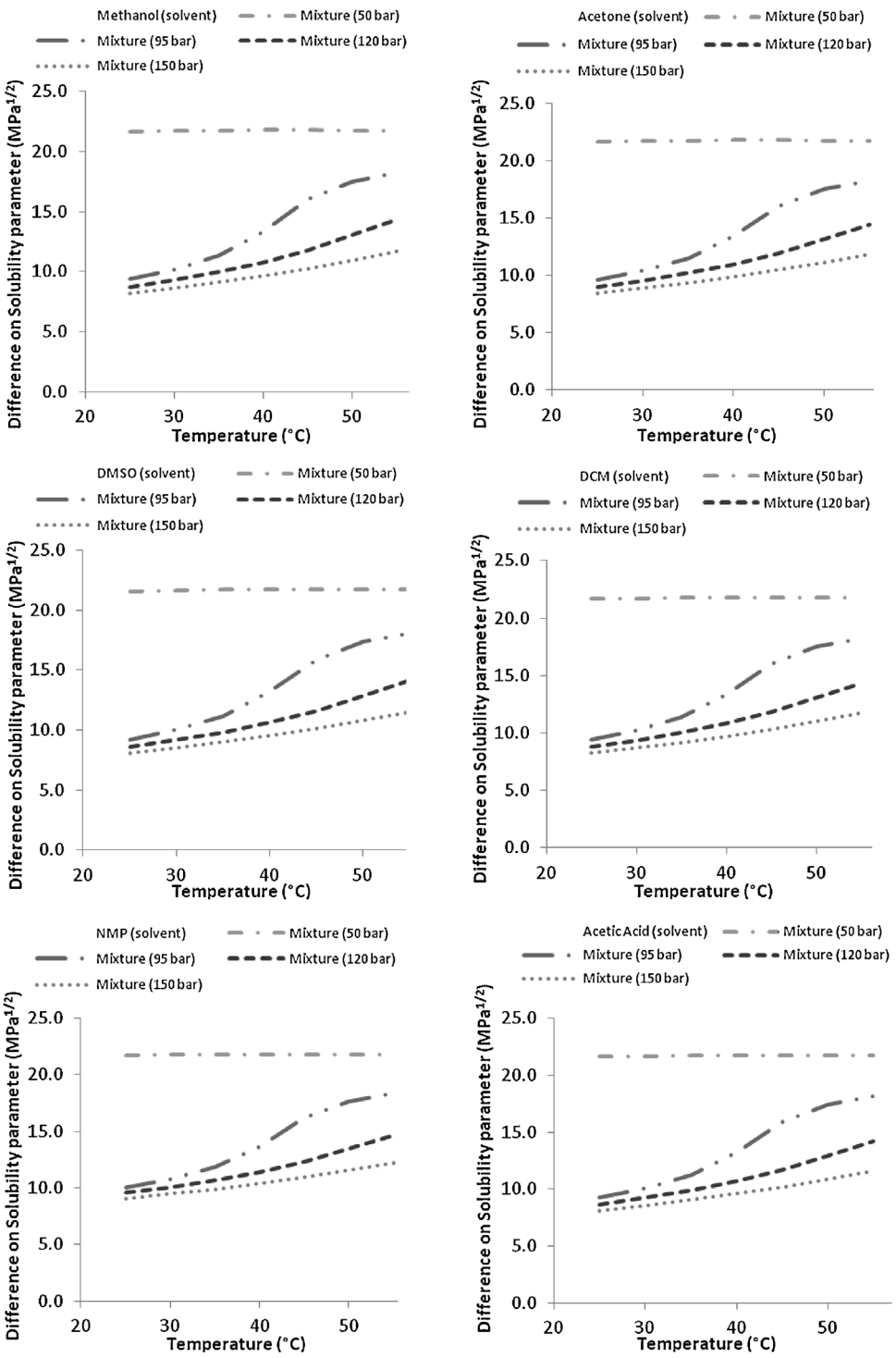

Fig. 12. Influence of pressure and temperature on the difference in the solubility parameters of atenolol and different mixtures of CO_2 and organic solvents (methanol, acetone, DMSO, DCM, NMP with a molar fraction of CO_2 equal to 0.955).

solvent be as large as possible. For instance, according to Fig. 4, the best condition to precipitate tartaric acid from an organic solution with methanol, ethanol, DCM, chloroform, acetone or NMP using supercritical CO_2 should be around 80 °C and 100 bar. Notice that at low temperatures this difference becomes independent on pressure for all selected solvents because the molar composition of CO_2 is as high as 94%.

Fig. 5 shows for the same systems shown in Fig. 4 the calculated results for the solubility parameters of tartaric acid and different mixtures of CO_2 and organic solvents (ethanol, methanol, acetone, DCM, chloroform, NMP) as a function of pressure and molar fraction of CO_2 at 40 °C. This behaviour of the solubility parameters is useful for comparison of the solvents at the solute precipitation step of the supercritical antisolvent processes due to the antisolvent addition. It should occur at the largest possible difference between the solubility parameters of the solute and the solvent–antisolvent mixture. Therefore, this information is useful to monitor supercritical antisolvent precipitation processes.

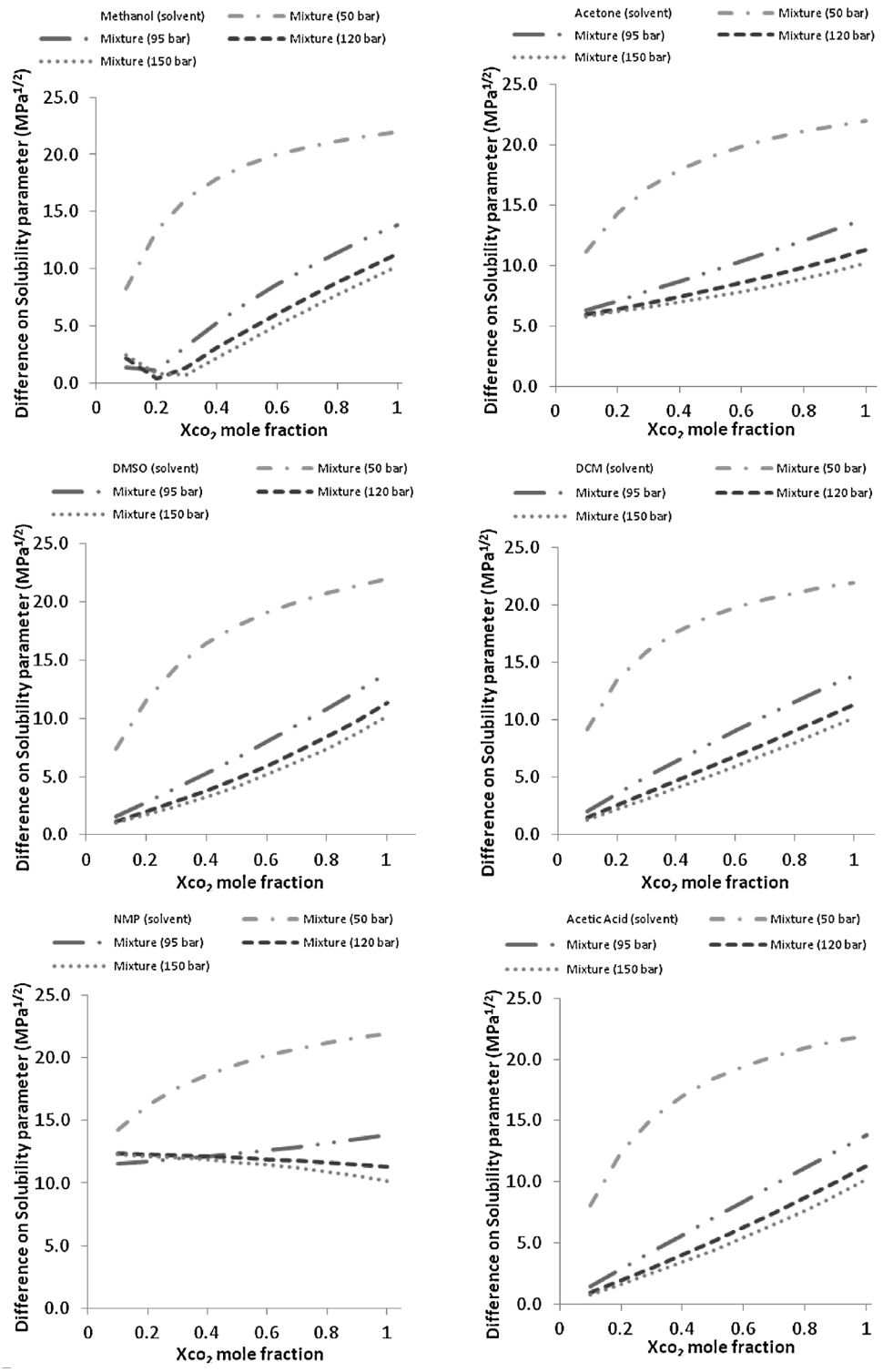

Fig. 13. Influence of pressure and molar fraction of CO2 on the difference on the solubility parameters of atenolol and different mixtures of CO2 and organic solvents (methanol, acetone, DMSO, DCM and NMP) at 40 °C.

Analogous to Fig. 5, it is shown in Fig. 6 the calculated results for the solubility parameters of flunisolide and different mixtures of CO_2 and organic solvents (DMSO, methanol, acetone, DCM, acetic acid, chloroform, NMP) as a function of pressure and molar fraction of CO_2 at 70 °C. Considering the precipitation step of supercritical antisolvent processes, which usually occurs at molar concentrations of CO_2 above 0.85, the best condition for precipitation is achieved at the minimum pressure level (80 bar) as shown in Fig. 6.

Supercritical antisolvent precipitation of flunisolide, as referred in the literature [2], was investigated for more than a single value of molar fraction of CO_2. For this reason two mixture containing solvent and antisolvent with different compositions were investigated which results are shown in Fig. 7. For the solvents acetone, NMP and acetic acid the molar fraction of CO_2 is 0.937. For the solvents methanol, chloroform and DMSO the molar fraction of CO_2 is 0.860. In Fig. 7 the influence of temperature and pressure on the

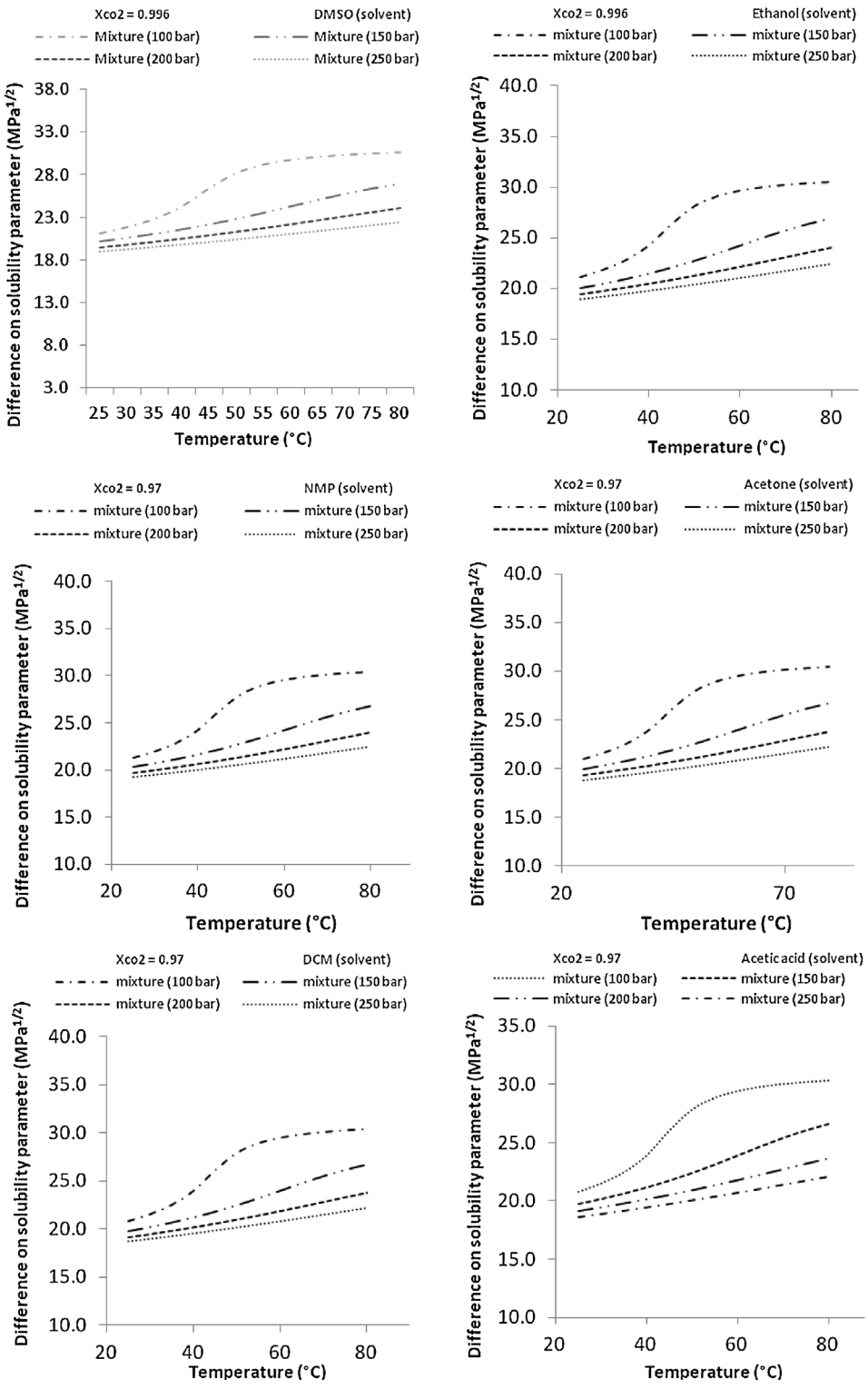

Fig. 14. Influence of pressure and temperature on the difference in the solubility parameters of amoxicilin and different mixtures of CO2 and organic solvents (ethanol and DMSO with a molar fraction of CO2 equal to 0.996, DCM, NMP, acetic acid and acetone with a molar fraction of CO2 equal to 0.970).

solubility parameter is evaluated aiming at determining the temperature and pressure best condition for solute precipitation. For all solvents the results show that the best condition corresponds to the highest temperature and the lowest pressure. This behaviour is independent of the solvent used since the concentration of CO_2 is very high for all systems. Due to the high concentration of CO_2, the behaviour of the solubility parameter of the mixture comes essentially from the solubility parameter of CO_2. Therefore, the solubility parameter of the mixture at 80 bar is very similar to that of pure CO_2 at this same pressure which can be seen in Fig. 3.

Fig. 8 shows the calculated results for the solubility parameters of cholesterol and different mixtures of CO_2 and organic solvents (DMSO, methanol, acetone, acetic acid, chloroform, NMP) as a function of pressure and molar fraction of CO_2 at 40 °C. According to

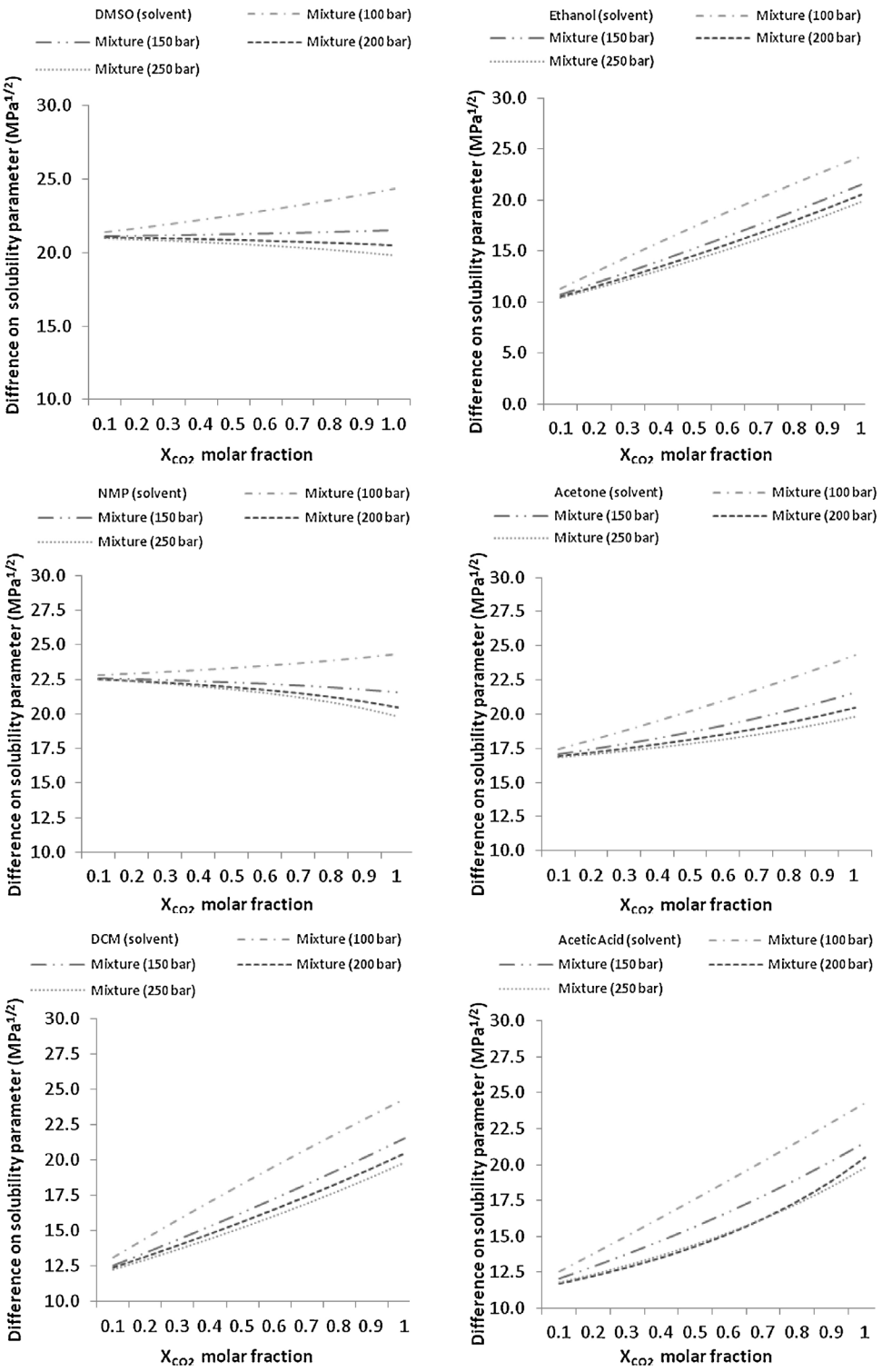

Fig. 15. Influence of pressure and molar fraction of CO2 on the difference in the solubility parameters of amoxicilin and different mixtures of CO2 and organic solvents (ethanol and DMSO, DCM, NMP, acetic acid and acetone) at 40 °C.

the literature, DCM is the only solvent experimentally evaluated with cholesterol [2]. The lowest differences between the solubility parameters of cholesterol and the organic solvents occur for acetone and DCM, which are the most suitable solvents for the step of solubilization of the solute. These solvents are suitable for the precipitation step of supercritical antisolvent processes and the best pressure condition is at 100 bar for a molar fraction of CO_2 lower than 0.2 or higher than 0.6. It is also important to highlight the similar behaviour of acetic acid and DMSO.

Let us assess the variation of the solubility parameter of cholesterol and the selected solvents with temperature for a fixed concentration of CO_2 in the solvent–antisolvent mixture equal to 0.956, as shown in Fig. 9. The results show that there is no change with respect to different solvents. Once again this behaviour is due

to the high concentration of CO_2. Regarding to the pressure and temperature range investigated the conditions recommended for solute precipitations are of low pressure and high temperature.

Fig. 10 presents the calculated results for the solubility parameters of paracetamol and different mixtures of CO_2 and organic solvents (ethanol, acetic acid, acetone, DCM, DMSO and NMP) as a function of pressure and temperature for a molar fraction of CO_2 equal to 0.993. As shown in the literature [2], ethanol is the unique solvent experimentally investigated for this solute. The pressure range was 80–250 bar and temperature range from 40 to 85 °C. As it can be seen in Fig. 10, if DMSO or acetone were chosen as the solvents the worst pressure condition for precipitation would be at 250 bar mainly for DMSO because the difference between the solubility parameter of paracetamol and of the mixture containing solvent and antisolvent would be the lowest. It is also observed that there is no difference in the results if DCM, acetic acid, NMP or ethanol is used with paracetamol.

At 40 °C, as shown in Fig. 11, the evaluation of the solubility parameter of paracetamol regarding to pressure and composition of the mixture containing solvent and antisolvent allows identifying ethanol as the best solvent because it provides the smallest difference between the solubility parameter of solute and this mixture, which is desired for the first step of solute solubilization. Regarding to variations of the solubility parameter with pressure and concentration of the solvent–antisolvent mixture there is no difference between ethanol, DMSO and acetic acid for mole fraction of CO_2 equal to 0.993, as observed in the experimental assessment [2].

To be consistent with the experimental data presented in the literature [2], Fig. 12 displays the results of the evaluations performed on solubility parameters of atenolol and different mixtures of CO_2 and organic solvents (ethanol, methanol, acetone, DCM, DMSO, acetic acid) with molar fractions of CO_2 equal to 0.955 for all solvents except for ethanol that has a molar concentration of 0.968. The profiles of the solubility parameter are very similar. However, it should be noted that the solubility parameters of all mixtures at 50 bar are almost temperature insensitive.

Fig. 13 shows the calculated results for the solubility parameters of atenolol and different mixtures of CO_2 and organic solvents (ethanol, methanol, acetone, DCM, DMSO and acetic acid) as a function of pressure and molar fraction of CO_2 at 40 °C. Regarding to the conditions for solubilization of the solute in the organic solvent, the results show a very similar behaviour when using DCM, DMSO or acetic acid. For these three solvents, good conditions for solubilization of atenolol exist at 40 °C. On the other hand, the results for methanol show that the solubilization should be achieved with a solution containing a molar fraction of CO_2 around 0.20 and for ethanol solubilization is reached with a lower concentration of CO_2 around 0.10. Regardless the solvent, the conditions for precipitation of solute from the mixture containing solvent and antisolvent should be achieved at the highest concentration of CO_2 in the solution and the lowest pressure (50 bar).

In Fig. 14 the effect of temperature and pressure on the solubility parameters of amoxicillin and different mixtures of CO_2 and organic solvents is shown for different mixture compositions. For the solvents DMSO and ethanol the molar fraction of CO_2 is 0.996 while for the solvents NMP, acetone, DCM and acetic acid it is 0.970. Fig. 14 reveals that the best condition for precipitation of amoxicillin corresponds to the highest temperature and the lowest pressure.

Fig. 15 shows the calculated results for the solubility parameters of amoxicillin and different mixtures of CO_2 and organic solvents (ethanol, acetone, acetic acid, DCM, DMSO, NMP) as a function of pressure and molar fraction of CO_2 at 40 °C. Regarding to the conditions for solubilization of the solute in the organic solvent, the results show that ethanol is the most suitable solvent because it provides the smallest difference between the solubility parameters of the solute and the mixture solvent–antisolvent compared to the other solvents. So, it assures the best performance for the first step of a supercritical antisolvent precipitation process. It is important to depict the unusual behaviour of the mixtures containing DMSO or NMP where the difference between the solubility parameters of the solute and the mixture decreases with an increase in the concentration of CO_2 in the mixture. The apparent reason is related to the fact that the solubility parameters of these pure solvents are much smaller than that of CO_2.

4. Conclusions

In this work, investigation of thermodynamic behaviour of systems involved in supercritical antisolvent precipitation has been done by a new approach based on the concept of solubility parameter. Calculation is done by group contribution methods using only critical properties of the organic solvents. Validation of this approach is accomplished by studying 36 ternary systems of high non-ideal behaviour with experimental data obtained from the literature in order to indicate the appropriate solvent for a successful supercritical antisolvent precipitation process. Comparison between experimental data and calculated results shows that this new approach is accurate to indicate the preliminary conditions of temperature and pressure to start the precipitation of a solute from a given solution containing an organic solvent and a supercritical antisolvent. It is shown that higher temperatures and lower pressures benefit solute precipitation for all systems investigated. However, this solubility parameter approach evaluates supercritical antisolvent precipitation process only under a thermodynamic point of view. Influence of mass-transfer rates or order process parameters on solute precipitation are not included in the scope of this work. Although this new approach is limited to the role of thermodynamics on supercritical antisolvent precipitation, it can be applied for a preliminary qualitative evaluation of supercritical antisolvent precipitation of complex molecules like pharmaceuticals prior to time-consuming and expensive lab work.

List of symbols

a	attraction parameter of Peng–Robinson equation of state
A_1, A_2, A_3, A_4, A_5	parameters of Eq. (10)
A_6, A_7, A_8	parameters of Eq. (11)
A_{14}, A_{15}, A_{16}	parameters of Eq. (12)
A_{17}, A_{18}, A_{19}	parameters of Eq. (13)
A_{20}	parameters of Eq. (9)
b	co-volume parameter of Peng–Robinson equation of state
P	pressure
T	temperature
V	molar volume
w	acentric factor

Greek letters

δ	solubility parameter
ΔE	cohesive energy
ΔG	free energy of mixing
ΔH	enthalpy of mixing
$\Delta H'$	residual enthalpy
ΔS	entropy of mixing
ΔU	energy of complete vaporization
ρ	density
ϕ	volume fraction

Subscripts

c	critical

i	component *i*
j	component *j*
liq	liquid
M	mixture
r	reduced
vap	vaporization

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