



Phase equilibria for the mixtures of the deep eutectic solvent L-menthol + thymol plus CO₂ at high pressure



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ABSTRACT

The Vapour-Liquid Equilibrium (VLE) of different mixtures of CO₂ + L-menthol, CO₂ + thymol and CO₂ + L-menthol + thymol has been determined at 35, 40, 50 and 60 °C and pressures up to 220 bar using a variable volume view cell. Menthol + Thymol form a deep eutectic solvent (DES) mixture at a 1:1 molar ratio. For selected conditions, the composition of the vapour phase was determined by ¹H NMR. By interpolation of the experimental values, ternary diagrams were built. The mutual solubility between CO₂ and DES decreased as the proportion menthol:thymol approached the eutectic composition (1:1). Mutual miscibility also decreased with temperature and increased with pressure. The composition of the mixture of menthol + thymol (1:1) does not remain stable at 60 °C but it does at lower temperatures. The intermolecular interactions between menthol and thymol are responsible for this behaviour. The Peng-Robinson equation of state was used to correlate the results with promising results.

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Introduction

Deep Eutectic Solvents (DES) are liquid mixtures of two solid substances at a given temperature for which the eutectic point temperature is below that of an ideal mixture, presenting significant negative deviations from ideality. [1] For their special properties, DES have received much interest in the last years as a new kind of sustainable solvents[2] and an alternative to ionic liquids. DES have significant advantages over the former as its production is easy and non-costly, they do not require further purification and they also have tuneable properties. Many of the properties of DES are those obtained from the individual components, they can have a natural origin (NDES) or therapeutic properties (THEDES) if one of the components is an active drug. THEDES often show an enhanced efficiency in terms of bioavailability, solubility and transport of the drug as well as a better control release.[3] More-

Abbreviations: DES, Deep Eutectic Solvent; NDES, Natural Deep Eutectic Solvent; THEDES, Therapeutic Deep Eutectic Solvent; HDES, Hydrophobic Deep Eutectic Solvent; HBA, Hydrogen Bond Acceptor; HBD, Hydrogen Bond Donor; scCO₂, Supercritical CO₂; PGSS, Particle from Gas Saturated Solution; RESS, Rapid Expansion of a Supercritical Solution; Men, L-Menthol; Thy, Thymol; PR-EOS, Peng-Robinson Equation of State.

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over, it is assumed that the toxicity is low (providing none of the components is toxic).

Many DES are formed by mixtures of quaternary ammonium salts and other ionic compounds and they are generally hydrophilic. Hydrophobic DES (HDES) are a subclass of traditional DES that is receiving increasing attention.[4] Among them, the DES formed only by non-ionic substances (molecular DES, neutral-based HDES or type V DES) are of particular importance as they overcome the problems of the former such as high viscosity[5] and instability in contact with water by selective leaching of one of the two components.[6] These DES are composed of at least a hydrogen-bond donor (HBD) and an acceptor (HBA) that form stronger intermolecular interactions in the mixture than they do separately, resulting in strong negative deviations from ideality. Hydrophobic DES are finding an increasing number of applications, such as in extraction[6,7] and separation[5] chemical reactions[8], electroplating, [2] gas absorption,[9] drug delivery,[10] membranes,[11] and lignocellulosic biomass processing[2] among others.

A promising but relatively unexplored possibility is the combination of DES and supercritical carbon dioxide (scCO₂). If scCO₂ dissolves the DES and forms a supercritical phase, this mixture can be used to impregnate porous and/or polymeric substrates. The higher diffusivity, lower viscosity and reduced interfacial tension of the supercritical DES mixture in comparison to pure DES or a liquid solution will lead to a more homogeneous dispersion of the DES

on the support. Even if the DES is not fully soluble in scCO_2 , CO_2 dissolves into liquid DES to some extent and will volumetrically expand the DES, reducing its viscosity, which opens up many possibilities for processing with CO_2 . [12] For example, Silva et al. [13] impregnated a gauze with a DES formed by lauric and myristic acids in scCO_2 . They used the Particle from Gas Saturated Solution (PGSS) technique in which CO_2 is dissolved in the liquid DES and the Rapid Expansion of a Supercritical Solution (RESS) technique, which requires the dissolution of the DES in scCO_2 . In both cases, the mixture of DES and CO_2 (liquid or supercritical) was expanded into a chamber at low pressure over the gauze. The DES was dispersed over the gauze in a very homogeneous way. Because the physical properties of the DES are different to those of the separated components and because of the good dispersion, THEDES impregnated on the gauze had better permeability and solubility in water compared to its individual components. In another example, they dissolved the DES menthol:ibuprofen 3:1 in scCO_2 and impregnated alginate sponges. [12] Other examples of the DES + CO_2 applications are CO_2 capture, [9] polymer treatment [14,15] and encapsulation. [16].

In spite of the potential of the DES + CO_2 mixtures, fundamental studies on the phase behaviour of these systems have not been performed. [4] Most data report the solubility of CO_2 in DES for absorption applications, showing a relatively large CO_2 uptake. [9,17–19] This information is also needed for the proper design of the PGSS process. However, solubility data of DES in CO_2 are scarcer in spite of its importance for applications such as RESS or impregnation. Ji et al. [20] determined the solubility of phenol in CO_2 extracted from phenol + quaternary ammonium salts mixtures, which form DES. In this case, one of the components (quaternary salt) could not be dissolved in CO_2 . It would be interesting to assess whether selective solubilization of one component occurs when both components are soluble in CO_2 (molecular DES).

There is no deep study of the phase behaviour of any DES + CO_2 system or comparison with the corresponding binary mixtures of the individual components plus CO_2 . Thus, several questions remain unanswered: a) how does the mutual miscibility of DES and CO_2 changes in relation to that of the constituent components. b) how is the mutual miscibility affected by pressure and temperature c) whether the composition of a DES remains unaltered upon the addition of CO_2 (i.e. does a DES act as a pseudocomponent?). It seems obvious that these queries can only be addressed if a systematic study of the phase behaviour of a DES + CO_2 system is conducted, which is the main aim of the present report.

The mixture L-menthol (Men) + thymol (Thy) is potentially interesting. It was used for the liquid extraction of riboflavin. [21] Menthol can be used in DES for extraction [7] and is a typical HBA for THEDES. [3] Thymol also has therapeutic properties. [22] This mixture forms a hydrophobic DES whose properties have been extensively investigated. For this reason, it can be a good model mixture to further study the phase behavior of DES + CO_2 systems. Abranches et al. [23] studied the solid–liquid phase diagram for Men + Thy and clearly detected a eutectic composition at the Men:Thy mole ratio (1:1). Melting points of menthol and thymol are 42 and 50 °C, respectively, [24] but the eutectic mixture has an estimated melting temperature of –48 °C, whereas the melting point corresponding to the ideal mixture would be 14 °C. [23] The mixture Men:Thy (2:1) has also been proposed as DES [21], having a melting temperature of –6 °C, [23] although according to the phase diagram this composition does not correspond to the eutectic one. [23] However, following the definition by Martins et al. [1] a mixture at a composition different from the eutectic one can be considered a DES, as long as it is liquid at the operating conditions. In this work it is necessary to make this distinction as both mixtures Men:Thy studied are DES, but only Men:Thy (1:1) is a DES at the eutectic composition.

The chemical structure of Men and Thy is very similar but the mixture presents strong deviations from ideality, caused by the intermolecular hydrogen bonding between –OH groups [25] where menthol acts as hydrogen bond acceptor and thymol as hydrogen bond donor (Fig. 1). This nonideality diminishes as the temperature increases as the extent of H-bonding decreases, which could have some impact on the phase behaviour of this DES with CO_2 .

In this report, the phase behaviour of the (L-menthol + thymol) DES + CO_2 is experimentally determined using a high-pressure variable-volume view cell. This mixture can be considered a good model to understand the behaviour of hydrophobic DES plus CO_2 . Moreover, it would be desirable to predict the phase behaviour of ternary mixtures DES + CO_2 from that of the corresponding binary ones as data are abundant in literature. To explore this possibility the understanding of the behaviour of the ternary mixtures in relation to the binary ones is needed. For this reason, the systems L-menthol + CO_2 and thymol + CO_2 are also measured. To our knowledge, there are no reports of this kind in the literature.

Two ratios of Men:Thy equal to 1:1 and 2:1 were set. Both solubilities of the liquid DES in CO_2 (dew points) and of CO_2 into the liquid (bubble points) were measured at temperatures of 35, 40, 50 and 60 °C. The data were correlated using the Peng Robinson equation of state [26] and the classical mixing rule allowing a linear dependence of the binary interaction parameters with temperature.

Experimental

The materials employed were CO_2 (Carbueros Metálicos, 99.995 %), L(-)-menthol (CAS: 99–89–78, Acros, 99.5 pure) and thymol (CAS: 89–83–8, Alfa Aesar, > 98 % pure). Commercial materials were used without further purification. DES were prepared by physical mixing of the corresponding quantities of L-menthol and thymol weighed using a balance A&D GR-200. The components were added to a beaker and mixed using a magnetic stirrer for a few minutes. The temperature was slightly increased to facilitate the melting. The proportion $n_{\text{Men}}/n_{\text{Thy}}$ can be set to 1 or 2 with an uncertainty of ± 0.1 %. This DES is hydrophobic so it should contain no significant amount of water. i.e. van Osch et al. [21] reported water contents of 0.03 % (w/w) for this DES.

Determination of the phase boundaries for the different systems studied was done using a high-pressure variable-volume view cell. A scheme of this device is depicted in Fig. 2. The volume of the cell can be varied between 6 and 21 mL using a movable piston connected to a manual pressure generator. Pressure is determined by means of a DRUK pressure transducer PTX7511-1 with an uncertainty of $\pm(0.01 + 0.0015P)$ MPa. Temperature is measured in the cell by a type-J thermocouple and kept constant using a heating tape and a PDI controller. The uncertainty of the temperature determination is ± 0.2 K. The inner part of the cell can be visualized through a sapphire window using a boroscope and a digital

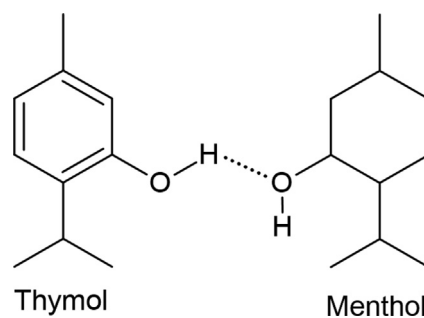


Fig. 1. Intermolecular H-bond between menthol and thymol.

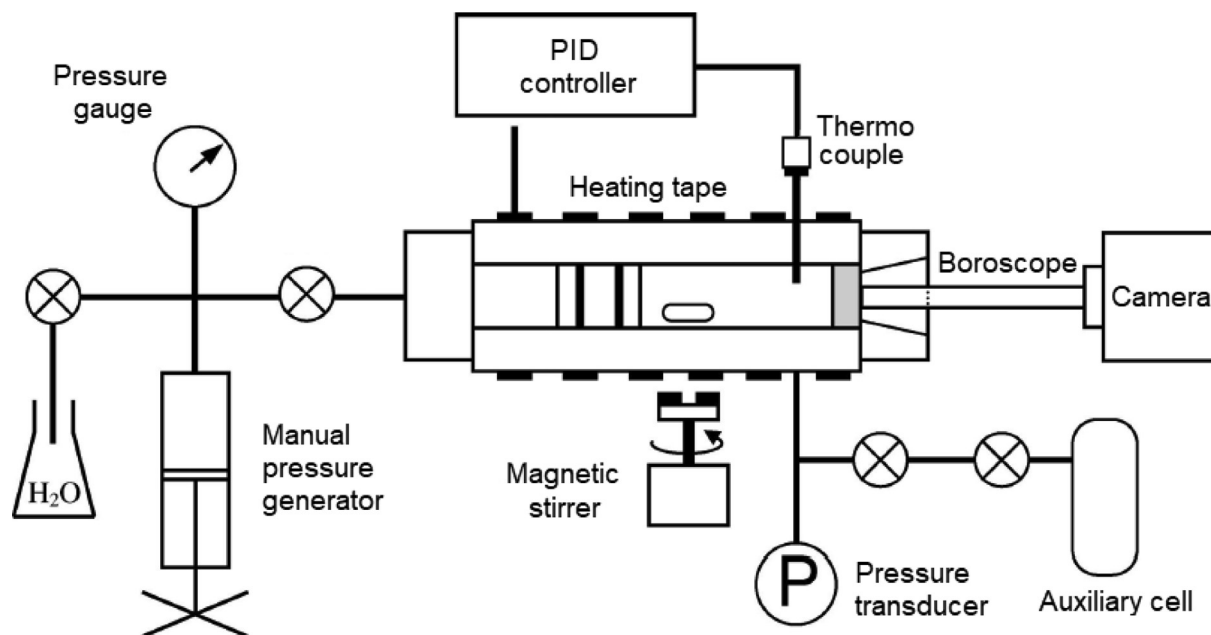


Fig. 2. Scheme of the high-pressure variable-volume view cell used in this work.

camera connected to a computer. The contents of the cell are stirred with a magnetic flea and an external magnetic stirrer. Details of the cell are given elsewhere.[27,28].

The measurements of the phase boundary were done following the synthetic approach: samples of known composition were prepared in the cell and their phase behaviour was studied varying pressure at a constant temperature. The DES, Men or Thy were placed in the cell before it was sealed. Then CO₂ was introduced into the cell by pressure-drop by means of an auxiliary cell. The mass of the different components was determined by weighing and the molar fraction calculated.

Solubility of Men, Thy or the 1:1 and 2:1 Men:Thy DES in CO₂ (dew points) was measured by decreasing the pressure from a homogeneous solution until the cloud point was observed due to the precipitation of the solute. The estimated uncertainty in the molar fraction of the solute was $\pm 0.1\%$. Solubility of CO₂ in liquid Men, Thy or DES (bubble points) was determined as follows: from a homogeneous solution, the pressure was slowly decreased until bubbles started to appear. Then the pressure was slowly increased at a rate of ca. 0.05 bar/min until the last bubble disappeared and the pressure was recorded. A reproducibility of ± 0.5 bar is estimated for the determination of the pressure of the bubble point.

In order to determine the Men:Thy ratio in the gas phase, the pressure was decreased to a biphasic state where a clear meniscus was observed. Then the view cell was connected to a 4-way sampling valve (Valco instruments) with a loop of 500 μL . The valve was slowly purged with the vapour phase from the cell for 1 minute, keeping the pressure manually constant with the piston. The meniscus was continuously observed to make sure that the vapour phase was withdrawn. Then, the sample was trapped in the loop and further depressurized over a small volume of CDCl₃. The loop was also rinsed with this solvent. ¹H NMR analysis of the sample was performed using a Bruker AVIII 300 MHz BACS-60 and 64 scans. The resulting spectra present the bands for menthol and thymol, from them, those that are not overlapped are selected and integrated, see Fig. 3. The Men:Thy molar ratio in the vapour phase, $y_{\text{Men}}/y_{\text{Thy}}$, was determined from integration of the signals for menthol and thymol. Sampling at the same conditions of pressure and temperature was performed 2–3 times in individual experiments.

This procedure was validated by taking a sample of an homogeneous mixture of known composition and checking that the NMR reproduces the Men:Thy proportion. The full composition was not determined due to uncertainty in the determination of the concentration of Men and Thy in the recovered sample and the difficulty of determining the amount of CO₂ trapped.

Results and discussion

Liquid-vapour P-x diagrams

Vapour-Liquid equilibria data for the different systems CO₂ (1) + Liquid (2) measured in this work at different pressures and temperatures are presented next. The component “Liquid” is referred to menthol, thymol, DES(Men:Thy) = 1:1 or DES(Men:Thy) = 2:1 depending on the system studied. The mole fraction solubility (dew points), y_2 , are gathered in Table 1 whereas the mole fraction solubility of CO₂ in liquid (bubble points), x_1 , are gathered in Table 2. Data dispersion for the dew points was evaluated at each temperature by the standard deviations of the measurement (P_{exp}) with respect to the fit to a quadratic polynomial (P_{fit}) using the expression:

$$\sigma = \left(\frac{(P_{\text{fit}} - P_{\text{exp}})^2}{n - 3} \right)^{1/2} \quad (1)$$

The solubility of menthol in CO₂ was measured by Sovová et al. [29] and by Thakur and Gupta[30] using semicontinuous methods. Mukhopadhyay and De measured the solubility of L-menthol and thymol using a static analytic method.[31] Our data agree reasonably well with the literature data except for the set of Mukhopadhyay and De for menthol, whose solubility in CO₂ lay a bit above the values obtained in this work. Also, the data by Thakur and Gupta deviate at high pressure and 35 °C. P-x plots showing the comparisons can be found in figures S1 and S2.

Figs. 4 and 5 show the measured pressures for the bubble points and dew points in the systems CO₂ (1) + Men (2) and CO₂ (1) + Thy (2) respectively. The graphics are presented as a pressure – composition diagram showing the bubble points at the left (x_1 is the mole

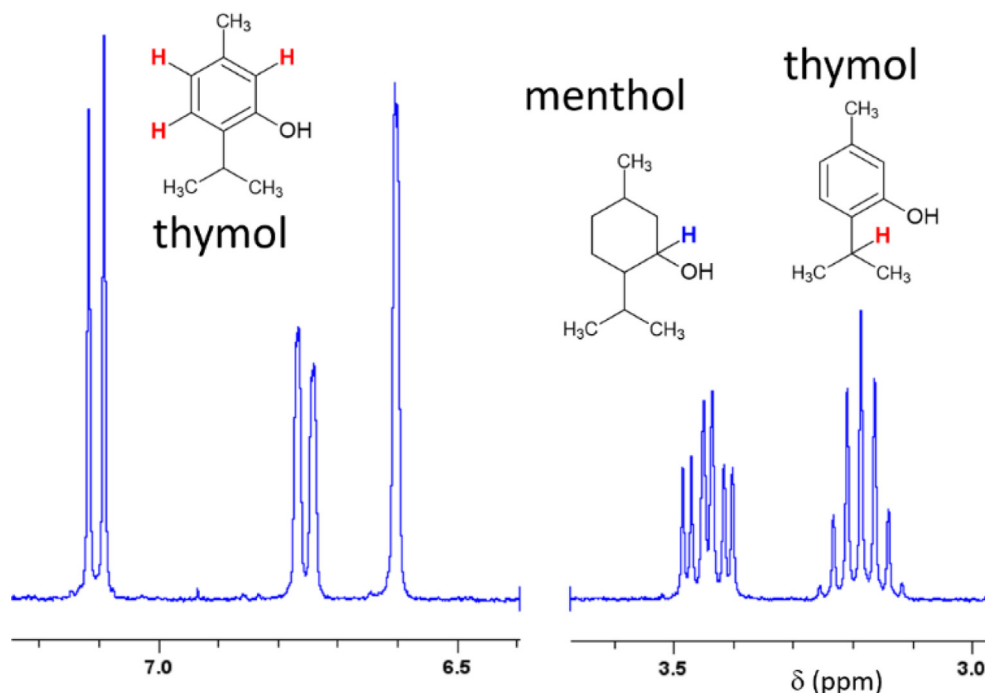


Fig. 3. Non-overlapping bands for the spectra of a mixture menthol + thymol in CDCl_3 . The aromatic signals for thymol (2 doublets and one singlet), are integrated between δ [6.5,7.2]; the tertiary hydrogen of thymol (septuplet) is integrated between δ [3.05,3.3] and the proton of the tertiary alcohol of menthol (triplet of doublets) is integrated between δ [3.35,3.55].

fraction of CO_2 in the liquid phase) and the dew points at the right (y_1 is the mole fraction of CO_2 in the vapour/supercritical phase).

Although the melting point of menthol is $42\text{ }^\circ\text{C}$ [24], it is well known that in presence of CO_2 , melting points can decrease significantly (i.e. for naphthalene the melting point depression is ca $20\text{ }^\circ\text{C}$ under 150 bar of CO_2 [27]). In fact, during the experiment, menthol started to melt in the cell at room temperature as soon as CO_2 was added. Thus, it is plausible to consider a VLE within the measured range of composition for the system CO_2 + menthol. In the case of thymol, the melting point is $50\text{ }^\circ\text{C}$ so it is not possible to assure VLE at the lowest temperatures. Nevertheless, when the phase behaviour of CO_2 + thymol was studied and the pressure was decreased from the one-phase region, thymol always precipitated as a liquid (cloud point). Solidification was not observed when bubble points were measured.

Attending to the dew points, solubility of Men or Thy in CO_2 increases with pressure at constant temperature as it is commonly observed as pressure increases the density of the supercritical fluid and the density enhances the solvation of the solute. For most conditions solubility decreases with temperature at constant pressure for the same reason, as density of CO_2 decreases when temperature increases. For the bubble points, the solubility of CO_2 in liquid Men or Thy increases with pressure and decreases with temperature.

Figs. 6 and 7 show the measured pressures for the bubble and dew points for the systems CO_2 (1) + DES(Men:Thy) = 1:1 and CO_2 (1) + DES(Men:Thy) = 2:1, respectively. The graphics are also presented as pressure – composition diagrams, as in Figs. 4 and 5.

For all the measuring conditions, temperature is above the melting point of the DES so no solid phases should be present. The shape of the diagrams is similar to those of the binary systems and the same trends with temperature and pressure are observed. However, the CO_2 + DES(Men:Thy) = 1:1 system shows a crossover point at around 200 bar and $y_1 = 0.96$. Crossover is a very well-known phenomenon of solute-supercritical fluid phase equilibria consisting on a change in tendency of the solubility dependence with temperature at constant pressure.[32] It is explained by a

compromise between two opposite effects: increasing temperature increases the vapour pressure of the solute (increasing its solubility) but also lowers the density of the supercritical fluid and the solvation of the solute (decreasing its solubility). At pressures lower than the crossover point, the latter effect prevails whereas, at higher pressures, the former effect prevails. For the system CO_2 + DES(Men:Thy) = 2:1, the dew point curves also tend to a crossover point. For the bubble points, some isotherms present an abrupt change of slope at high CO_2 mole fraction for the lowest temperatures. This behaviour may be related to interference with LL equilibria as it has been observed before for other systems at similar conditions.[33,34].

Solubility comparison

Fig. 8a shows a comparison of the solubility of Men, Thy, DES (Men:Thy) = 1:1 and DES(Men:Thy) = 2:1 in CO_2 at $40\text{ }^\circ\text{C}$. It can be clearly seen that the solubility of each solute in CO_2 follows the order Men > Thy > DES(Men:Thy) = 2:1 > DES(Men:Thy) = 1:1. The solubility of Men or Thy in CO_2 is significantly higher than those of the eutectic mixtures. However, the difference between the two CO_2 + DES(Men:Thy) curves is minor. In Fig. 8b, the corresponding solubilities of CO_2 in each of the liquid Men, Thy, DES (Men:Thy) = 1:1 and DES(Men:Thy) = 2:1 are compared. As for the previous case, the solubility of CO_2 in the liquid also follows the order Men > Thy > DES(Men:Thy) = 2:1 > DES(Men:Thy) = 1:1, at least for pressures below the crossover point.

Ternary diagrams

Fig. 9 shows the ternary diagrams of the dew points for the system CO_2 + Men + Thy obtained from interpolation of the curves in Figs. 4 to 7. In this figure, the individual composition of Men, Thy and CO_2 are plotted. These diagrams do not cover the whole range of compositions but only those at high CO_2 concentrations, as this is the solvent. Fig. 9a shows the dependence of the solubility of the

Table 1Mole fraction solubility in CO₂ (y₂) of the different solutes studied at 35.0, 40.0, 50.0 and 60.0 °C (dew points for the system CO₂ (1) + Liquid (2)).

y ₂	P / bar			
	35.0 °C	40.0 °C	50.0 °C	60.0 °C
Liquid (2) = L-Menthol				
0.0067	–	89	109	125
0.0083	79	90	111	–
0.0098	83	93	114	134
0.0140	87	98	121	138
0.0180	89	100	121	141
0.0212	94	103	124	144
0.0285	108	116	131	149
0.0313	108	115	131	147
σ / bar	2.1	2.0	1.6	1.7
Liquid (2) = Thymol				
0.0047	82	93	112	128
0.0096	85	97	120	–
0.0115	87	100	122	142
0.0148	95	106	128	–
0.0201	110	120	140	159
0.0257	–	133	150	169
0.0268	–	137	154	171
0.0309	142	148	163	179
0.0319	150	154	167	181
σ / bar	2.4	1.2	0.9	0.5
Liquid (2) = DES(Men:Thy) = 1:1				
0.0076	87	97	118	–
0.0135	107	118	140	161
0.0160	116	125	143	161
0.0178	127	134	150	165
0.0192	132	137	153	167
0.0252	152	152	165	178
0.0322	173	172	179	194
0.0344	186	182	184	193
0.0408	200	193	191	199
0.0444	209	199	195	201
0.0473	219	207	201	207
σ / bar	2.2	1.8	1.7	2.6
Liquid (2) = DES(Men:Thy) = 2:1				
0.0051	85	95	114	130
0.0101	100	109	131	150
0.0163	108	115	137	154
0.0206	126	132	147	165
0.0226	132	136	151	166
0.0296	155	155	164	178
0.0302	164	163	169	180
0.0336	178	175	181	189
0.0363	187	181	183	191
σ / bar	3.4	3.4	3.4	3.3

Table 2Mole fraction solubility of CO₂ (x₁) in the different solutes studied at 35.0, 40.0, 50.0 and 60.0 °C (bubble points for the system CO₂ (1) + Liquid (2)).

x ₁	P / bar			
	35.0 °C	40.0 °C	50.0 °C	60.0 °C
Liquid (2) = L-Menthol				
0.3402	40.0	42.5	46.9	51.3
0.4836	61.2	65.5	73.9	82.3
0.5985	72.5	79.0	92.1	104.0
0.6681	80.5	88.1	104.1	118.4
Liquid (2) = Thymol				
0.2661	–	–	39.9	43.9
0.4112	55.8	60.4	69.4	77.8
0.5736	74.9	82.4	97.5	112.5
0.7136	125.3	126	136.1	149.2
Liquid (2) = DES(Men:Thy) = 1:1				
0.2392	37.1	38.7	42.4	46.1
0.3825	58.5	61.5	69.2	77.6
0.4734	78.6	82.8	93.9	103.6
0.6234	107.4	111.2	124.2	136.5
0.6632	117.4	121.9	128.3	139.1
Liquid (2) = DES(Men:Thy) = 2:1				
0.2715	42.6	45.2	49.6	53.6
0.4360	63.6	67.8	76.4	84.8
0.5921	80.7	89.0	104.4	118.3
0.7271	164.9	158.5	154.4	161.9

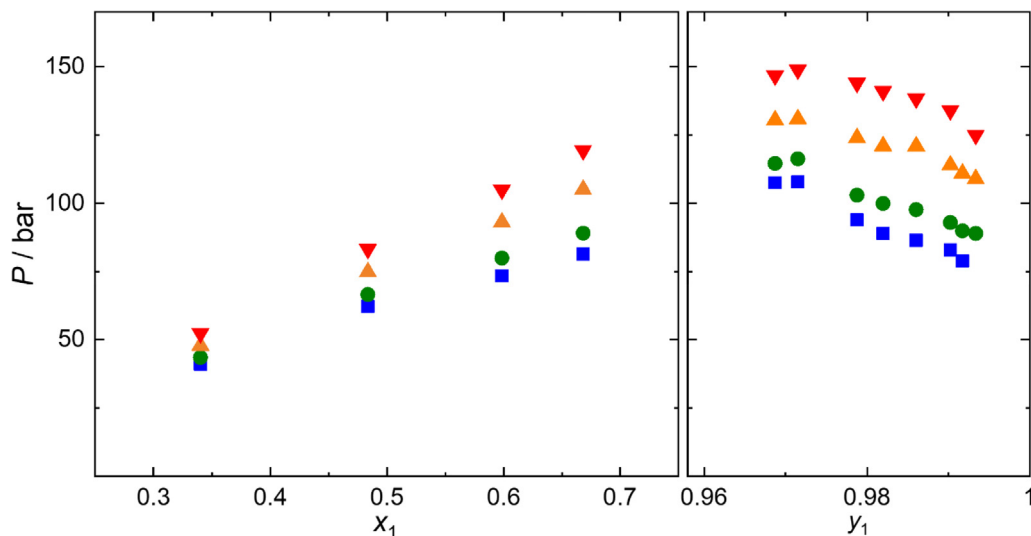


Fig. 4. Px diagram for the system CO₂ (1) + Men (2) at (■): 35.0 °C, (●): 40.0 °C, (▲): 50.0 °C, (▼): 60.0 °C. Left: bubble points; right: dew points.

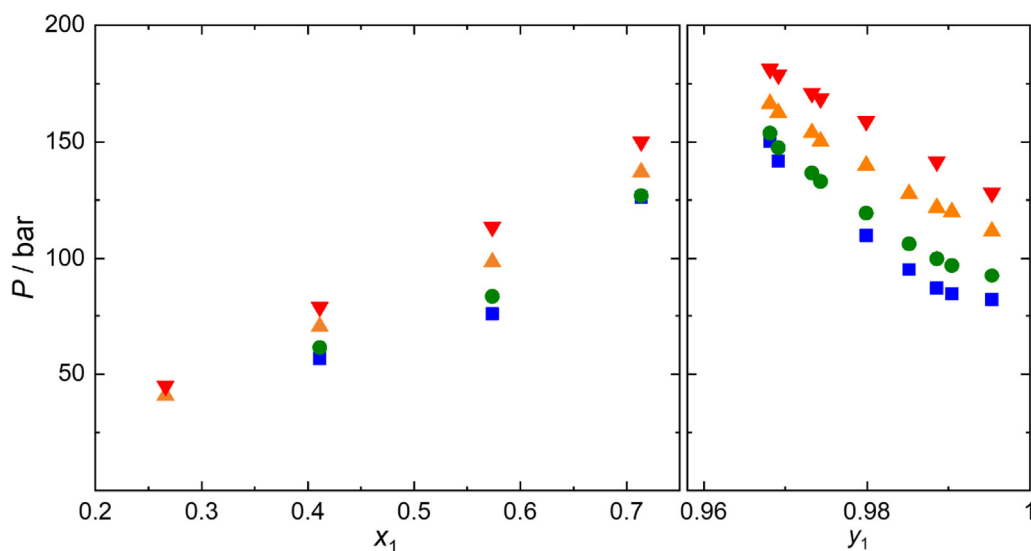


Fig. 5. Px diagram for the system CO₂ (1) + Thy (2) at (■): 35.0 °C, (●): 40.0 °C, (▲): 50.0 °C, (▼): 60.0 °C. Left: bubble points; right: dew points.

different solutes in CO₂ with the temperature at the constant pressure of 120 bar while 9b shows the dependence with pressure at 50 °C. The system is only miscible to the right of the curves that would connect the dew points at each temperature, that is, for very high CO₂ concentrations and splits into two phases at lower CO₂ concentrations.

The tendency observed in Fig. 8 can also be appreciated in Fig. 9 more clearly. The shape of the boundaries clearly shows that the solubility of the two DES mixtures in CO₂ is lower than those of Men or Thy, being the lowest of them that of the eutectic composition, DES(Men:Thy) = 1:1 for most of the conditions. Temperature enhances the region of immiscibility while pressure decreases it.

Fig. 10 shows the ternary diagrams of the bubble points for the system CO₂ + Men + Thy obtained from interpolation of the curves in Figs. 4 to 7. Fig. 10a shows the dependence of the solubility of CO₂ in the different liquids with temperature at the constant pressure of 80 bar while 10b shows the dependence with pressure at 50 °C. In this case, the region of miscibility is to the left of the curves. The complete boundary would result from merging them with the dew point curves like those shown in Fig. 9.

As in Fig. 9, the region of immiscibility increases with temperature and decreases with pressure. The solubility of CO₂ in the liquid phase is lower for the mixtures Men + Thy than for the individual components being the eutectic composition the lowest of them. This difference is especially noticeable for the lowest temperatures and it becomes lower as temperature increases (Fig. 8a).

Some trends in the solubility of CO₂ in DES have been described in the literature. It is generally observed that at constant pressure, solubility decreases as the temperature increases,[17–19] as observed in this work. Regarding the dependence with composition, for the Choline Chloride + urea DES[17] the highest CO₂ solubility occurred at the eutectic composition, opposite to what is reported in our work. The Choline Chloride + urea DES is very different from the Men + Thy DES, due to the ionic nature of choline chloride. In this case, at the eutectic composition, charges seem to be screened making the CO₂ more soluble. Then this system cannot be taken as a model for type V DES due to the presence of ionic species.[35] Instead it seems that it is not possible to generalize the behaviour of a DES in comparison to the forming components.

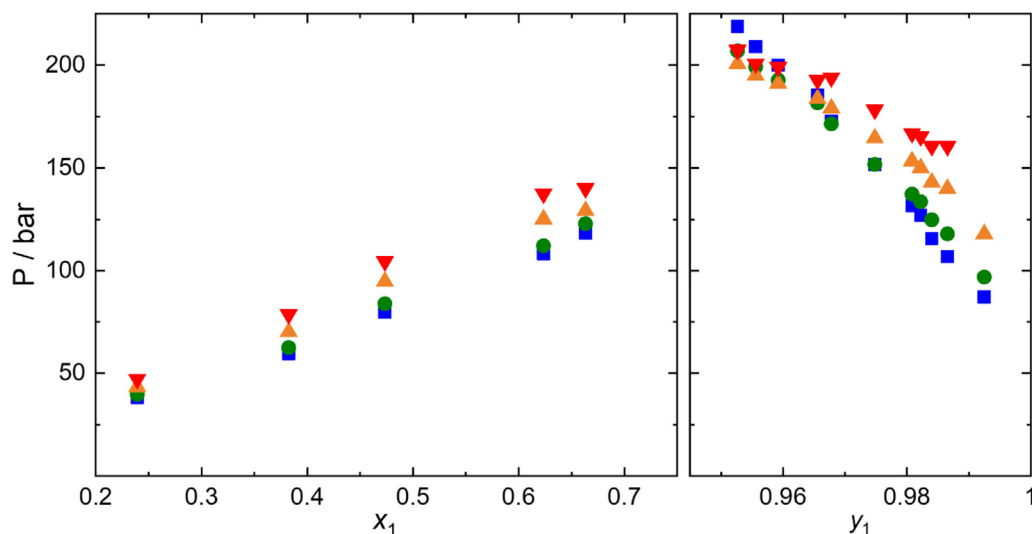


Fig. 6. P-x diagram for the system CO_2 (1) + DES(Men:Thy) = 1:1 at (■): 35.0 °C, (●): 40.0 °C, (▲): 50.0 °C, (▼): 60.0 °C. Left: bubble points; right: dew points.

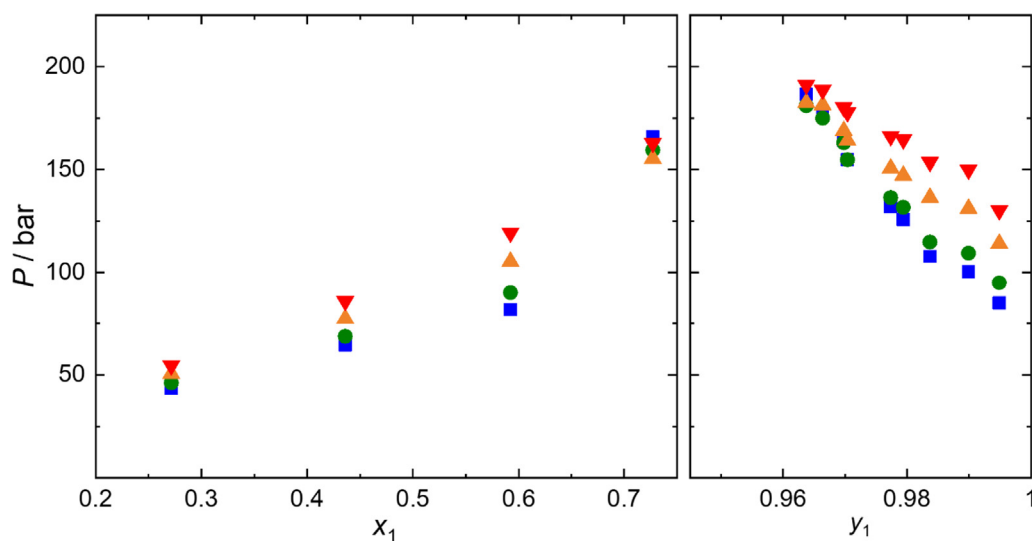


Fig. 7. P-x diagram for the system CO_2 (1) + DES(Men:Thy) = 2:1 at (■): 35.0 °C, (●): 40.0 °C, (▲): 50.0 °C, (▼): 60.0 °C. Left: bubble points; right: dew points.

As the size and structure of menthol and thymol are similar (Fig. 1), the volume effects of the mixtures would be minimized so the different behaviour should be related to the interactions formed upon mixing. The VLE region for the studied mixtures of DES plus CO_2 is significantly larger than those found for each of the components plus CO_2 . This can be explained by considering the strong interactions between Men and Thy molecules that stabilize the liquid mixture.[23] As this mixture is more stable, negative deviations from the Raoult's Law are expected for the system Men + Thy, being these mixtures less volatile. The vapour pressure thus contributes less to the solubility in CO_2 compared to the pure components Men or Thy. Following the same approach, the strong Men – Thy interactions are difficult to break so the CO_2 can solubilize less in the DES liquid phase. These hydrogen bonds are very sensitive to temperature and their quantity and strength decrease significantly to the extent that the mixture Men + Thy behaves ideally at the boiling temperature.²³ This agrees with our observations as the higher the deviation from ideality, the more different the behaviour of the DES with respect to its components. Applying this idea to the CO_2 solubilization in the liquid, the curvature of the

lines in the ternary diagram should be less pronounced as temperature increases, as it is observed in Fig. 10a.

Stability of the DES composition

The main drawback of measuring ternary systems using a synthetic approach is that it does not allow the determination of tie lines. It is then not possible to connect the compositions of the dew and the bubble points and to verify if the eutectic composition Men:Thy = 1:1 remains stable in presence of CO_2 , i.e. if none of the components is extracted selectively (the proportion 1:1 remains constant in the liquid and the vapour phase) which is equivalent to say that the DES behaves as a pseudocomponent. This latter possibility is plausible attending to the stronger intermolecular forces in the mixture Men + Thy at the eutectic composition. To explore this possibility the vapour phase was sampled and the molar ratio Men:Thy was determined by NMR. Table 3 gathers the results.

Validation experiments with a homogeneous mixture (entry 1 in Table 3) confirm the viability of the sampling procedure, rendering a Men:Thy average ratio equal to 1.025, very close to the

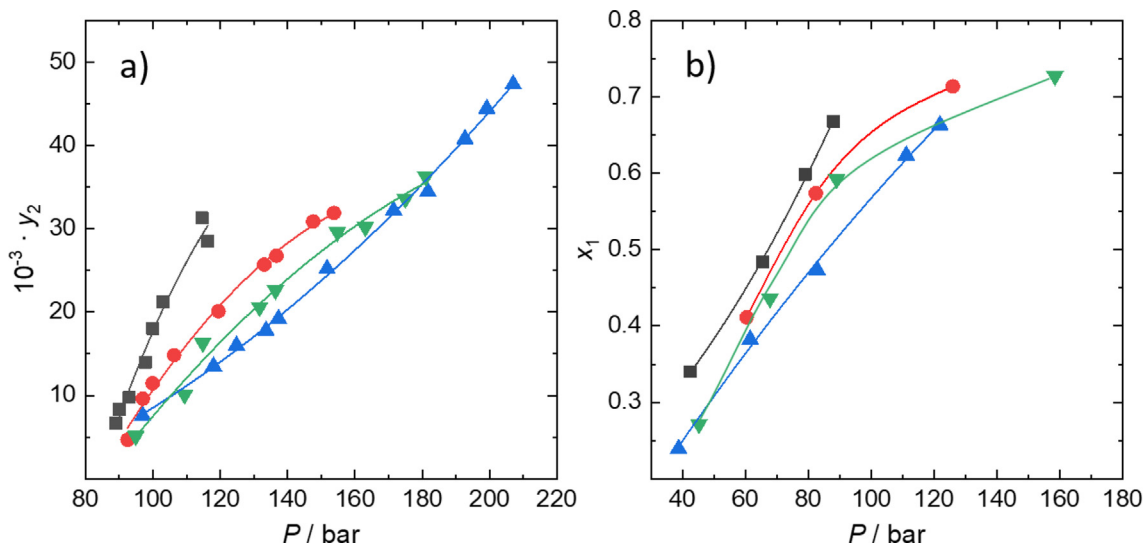


Fig. 8. Comparison of the phase behaviour of the systems (■): CO₂ + Men, (●) CO₂ + Thy, (▲): CO₂ + DES(Men:Thy) = 1:1 and (▼): CO₂ + DES(Men:Thy) = 2:1 at 40.0 °C. In all cases, component 1 is CO₂ and component 2 is either Men, Thy or the DES(Men:Thy). a) Solubility of component 2 in CO₂ (y_2). b) Solubility of CO₂ in component 2 (x_1). Lines are polynomial fitting to help visualization.

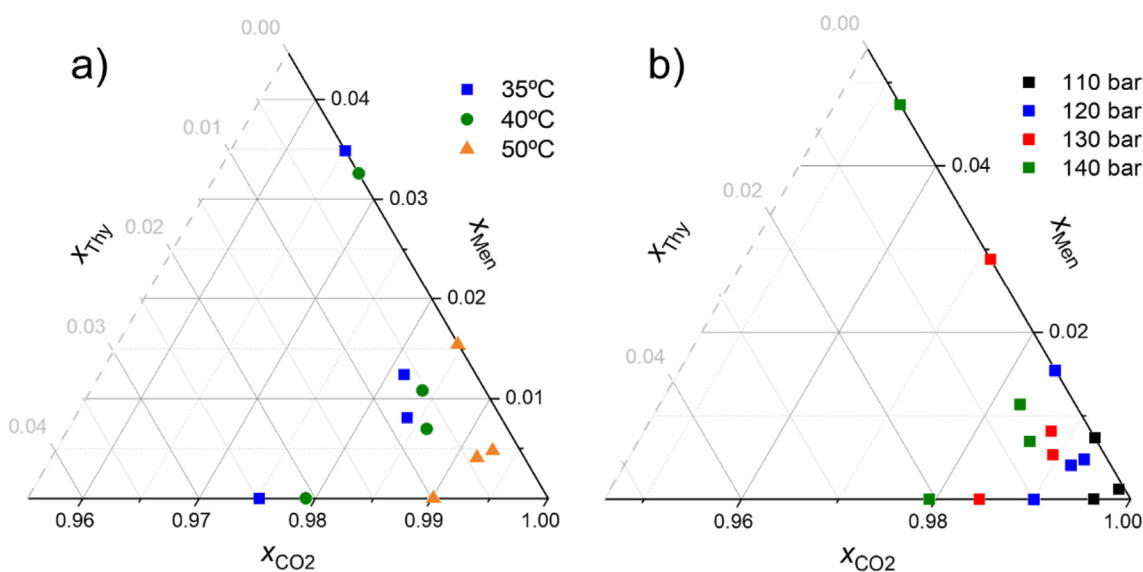


Fig. 9. Ternary diagrams of the dew points for the system CO₂ + Men + Thy. a) Dependence with temperature at the constant pressure of 120 bar, b) Dependence with pressure at the constant temperature of 50.0 °C.

theoretical one. Entries 2 to 4 show experiments for biphasic mixtures at different conditions, in every case the vapour phase was enriched in menthol. The Men:Thy ratio may depend on the overall composition, x_2 , but unfortunately a tendency could not be found so an average is presented instead. As it can be appreciated in entry 2, when the mixture Men + Thy at the eutectic composition of 1:1 is in equilibrium with CO₂ at 60 °C and 120 bar, the latter extracts menthol preferentially, as it is the most soluble component in CO₂. If temperature and pressure are lowered (entry 3), the values are more similar to the expected one indicating a behaviour closer to a pseudocomponent and the composition remains stable. That is consistent with stronger intermolecular interactions at lower temperatures as discussed previously. If the DES studied is the 2:1, the differences between the obtained values with the expected ones are even larger. For this mixture,

however, no pseudocomponent behaviour is expected as this is not the eutectic composition.

Modelling of the data using Peng-Robinson equation of state

The data for the solubility of CO₂ into liquids (bubble points) can be modelled using equations of state.[36] In this work, bubble points were fitted to the Peng-Robinson Equation of State [26] (PR-EOS) using the software Aspen Plus V11. The parameters a and b in the PR-EOS for the mixture were evaluated from those of the pure components according to the classical mixing rule:

$$a = \sum_i \sum_j x_i x_j a_{ij} a_{ij} = (a_{ij} a_{jj})^{1/2} (1 - k_{ij}) \quad (2)$$

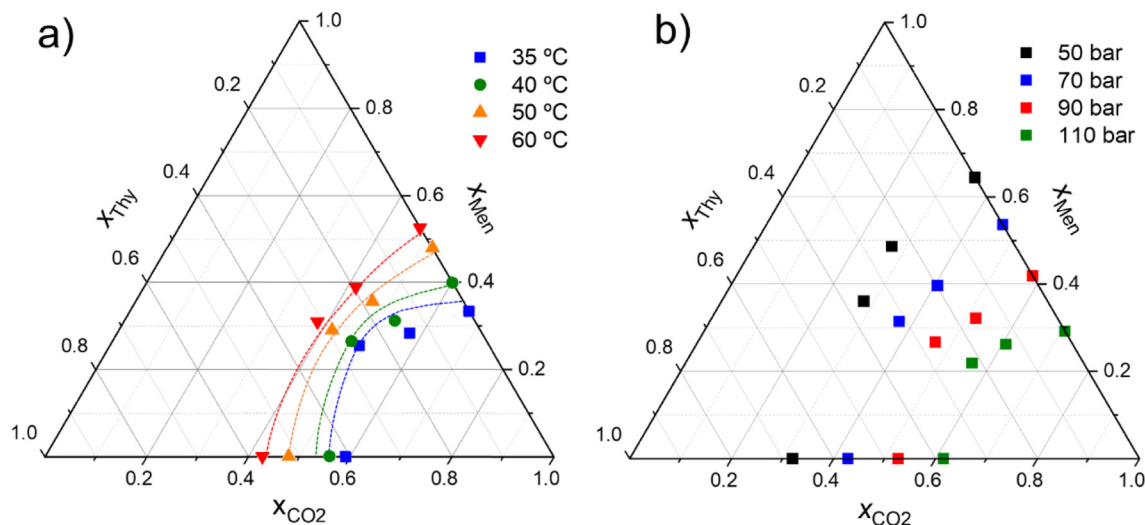


Fig. 10. Ternary diagrams of the bubble points for the system CO₂ + Men + Thy. a) Dependence with temperature at the constant pressure of 80 bar. Dotted lines: Calculation using the PR-EOS and parameters of Table 4. b) Dependence with pressure at the constant temperature of 50.0 °C.

Table 3

Proportion Men:Thy (mol/mol) in the vapour phase determined by ¹H NMR at different conditions. x₂ is the overall molar fraction of Men + Thy.

Entry	T / °C	P / bar	x ₂	y _{Men} /y _{Thy}
DES(Men:Thy) = 1:1				
1 ^a	40.0	135, 160	0.018 – 0.026	1.025 ± 0.005
2	60.0	120	0.015 – 0.034	1.19 ± 0.04
3 ^b	35.0	85	0.018 – 0.019	1.04 ± 0.04
DES(Men:Thy) = 2:1				
4	60.0	120	0.030 – 0.036	2.54 ± 0.16

^a Validation experiments. Sample of homogeneous phase taken, an average of 2 values at 135 and 160 bar.

^b Average of two values. For the rest of the entries an average of at least 3 values was done.

$$b = \sum_i \sum_j x_i x_j b_{ij} = \frac{1}{2} (b_{ii} + b_{jj}) \quad (3)$$

Being $k_{ij} = k_{ji}$ the binary interaction parameter between unlike components i and j . Due to the strong effect of temperature in intermolecular interactions, it was chosen to set a linear dependency of k_{ij} with T :

$$k_{ij} = k_{ij}^a + k_{ij}^b \cdot T \quad (4)$$

The parameters of the EOS for the pure components, constants a_{ii} and b_{ii} for CO₂, Men and Thy, were evaluated using the values of the critical constants and acentric factors already stored in the software. The fitting was done in two stages: first, the parameters k_{ij}^a and k_{ij}^b for the pairs Men – CO₂ and Thy – CO₂ were calculated from bubble points of the system CO₂ + Men and CO₂ + Thy respectively. In a second stage, the data for the ternary systems CO₂ + DES (Men:Thy) were used to correlate the values of k_{ij}^a and k_{ij}^b for the pair Men – Thy. The fitting method was in all cases the maximum-likelihood. The results obtained are summarized in Table 4 along with the Root Mean Square Error (%) for pressure and CO₂ molar fraction. As shown in Fig. 10a, the PR-EOS is able to reproduce the shape and the main features of the ternary diagram and a semiquantitative agreement with the experimental data is observed (Figure S4). This agreement is better at the highest temperatures. The PR-EOS also predicts an enrichment of the vapour phase in menthol, but in this case, it largely overestimates the ratio Men/Thy with values within 1.9 and 5.5 for the mixtures CO₂ + DES(Men:Thy) = 1:1 and above 6 for the mixtures CO₂ + DES (Men:Thy) = 2:1 (see supplementary information).

Table 4

Correlated parameters for the Peng-Robinson EOS using the binary and ternary mixtures studied in this work.

System	CO ₂ (1) + Men (2)	CO ₂ (1) + Men (2)	CO ₂ (1) + Men + Thy
Parameter	$i = \text{CO}_2, j = \text{Men}$	$i = \text{CO}_2, j = \text{Thy}$	$i = \text{Men}, j = \text{Thy}$
Correlated			
k_{ij}^a	0.1122	0.1832	-0.2637
k_{ij}^b	-2.42×10^{-5}	-3.45×10^{-4}	5.58×10^{-4}
RMSE% (P)	0.053	0.030	0.14
RMSE% (x _i)	5.0	4.5	15.9

According to Equation (4), the values obtained for the binary interaction parameters k_{ij} Men – Thy are negative for the four temperatures studied. Also, their absolute values decrease as temperature increases. These results suggest attractive intermolecular interactions between the two components which are diminished with temperature, in agreement with what has been discussed above. Further details of the procedure along with the comparison with the experimental data are gathered in the Supplementary information.

Conclusions

This extensive study of the phase behaviour of the mixtures involved in the system CO₂ + the DES formed by L-Menthol + Thymol allows obtaining many conclusions about the effect of the mixture on the mutual miscibility of CO₂ and the DES. The solubility of the DES in CO₂ and the solubility of CO₂ in

DES are lower than the solubilities of the individual components L-menthol or thymol. Mutual solubility of CO₂ and the Men:Thy DES increases with pressure and decreases with temperature for most of the conditions studied. By interpolation of the experimental data, ternary diagrams can be built showing a maximum deviation from ideality at the eutectic composition of Men:Thy = 1:1 and which seems to decrease with temperature. NMR analysis of the vapour phase indicates that the composition of the mixtures studied is not stable, as CO₂ extracts menthol preferentially, however at lower temperatures this preference is diminished. These observations can be explained by attending to the intermolecular H-bond between menthol (HBA) and thymol (HBD), which is the highest at the eutectic composition and decreases significantly with temperature. The data were fitted to the Peng–Robinson Equation of State showing that this can be a promising method to correlate this kind of data.

Our data show that Men:Thy DES can be dissolved in CO₂ and that CO₂ is substantially soluble in the DES at moderate temperature and pressure conditions, so different supercritical fluid techniques such as RESS, PGSS or impregnation in CO₂ could be used to incorporate the DES in different advanced drug delivery systems. The mutual miscibility of the DES and CO₂ is lower than that for the corresponding components, which has to be considered when designing the techniques mentioned above. Nevertheless, the possibility of dispersing directly the DES on the support overcomes the higher pressures required.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jiec.2023.01.034>.

Reference

- [1] M.A.R. Martins, S.P. Pinho, J.A.P. Coutinho, J. Sol. Chem. 48 (2019) 962–982, <https://doi.org/10.1007/s10953-018-0793-1>.
- [2] X. X. Chang, N. M. Mubarak, S. A. Mazari, A. S. Jatoi, A. Ahmad, M. Khalid, R. Walvekar, E.C. Abdullah, R. R. Karri, M.T.H Siddiqui, S. Nizamuddin, J. Ind. Eng. Chem. 104 (2021) 362–380. <https://doi.org/10.1016/j.jiec.2021.08.033>.
- [3] M.S. Rahman, R. Roy, B. Jadhav, M.N. Hossain, M.A. Halim, D.E. Rainey, J. Mol. Liq. 321 (2021) 114745–, <https://doi.org/10.1016/j.molliq.2020.114745>.

- [4] M.H. Zainal-Abidin, M. Hayyan, W.F. Wong, J. Ind. Eng. Chem. 97 (2021) 142–162, <https://doi.org/10.1016/j.jiec.2021.03.011>.
- [5] D.J.G.P. van Osch, C.H.J.T. Dietz, S.E.E. Warrag, M.C. Kroon, ACS Sustain. Chem. Eng. 8 (2020) 10591–10612, <https://doi.org/10.1021/acssuschemeng.0c00559>.
- [6] C. Florindo, L.C. Branco, I.M. Marrucho, Fluid Phase Equilib. 448 (2017) 135–142, <https://doi.org/10.1016/j.fluid.2017.04.002>.
- [7] F. Bergua, M. Castro, J. Muñoz-Embid, C. Lafuente, M. Artal, J. Mol. Liq. 352 (2022), <https://doi.org/10.1016/j.molliq.2022.118754>.
- [8] S. Khandelwal, Y.K. Tailor, M. Kumar, J. Mol. Liq. 215 (2016) 345–386, <https://doi.org/10.1016/j.molliq.2015.12.015>.
- [9] F.P. Pelaquim, A.M. Barbosa Neto, I.A.L. Dalmolin, M.C.d. Costa, Ind. Eng. Chem. Res. 60 (2021) 8607–8620, <https://doi.org/10.1021/acs.iecr.1c00947>.
- [10] S. Emami, A. Shayanfar, Pharm. Dev. Technol. 25 (2020) 779–796, <https://doi.org/10.1080/10837450.2020.1735414>.
- [11] C.H.J.T. Dietz, M.C. Kroon, M. Di Stefano, M. van Sint Annaland, F. Gallucci, Faraday Discuss. 206 (2018) 77–92, <https://doi.org/10.1039/C7FD00152E>.
- [12] A.A. Barros, J.M. Silva, R. Craveiro, A. Paiva, R.L. Reis, A.R.C. Duarte, Curr. Opin. Green Sustain. Chem. 5 (2017) 82–87, <https://doi.org/10.1016/j.cogsc.2017.03.014>.
- [13] J.M. Silva, S. Akkache, A.C. Araújo, Y. Masmoudi, R.L. Reis, E. Badens, A.R.C. Duarte, Mat. Sci. Eng. C 99 (2019) 599–610, <https://doi.org/10.1016/j.msec.2019.02.012>.
- [14] I. M. Aroso, R. Craveiro, Â. Rocha, M. Dionísio, S. Barreiros, R. L. Reis, A. Paiva, A. R. C. Duarte, Int. J. Pharmaceut. 492 (2015) 73–79. <https://doi.org/10.1016/j.ijpharm.2015.06.038>.
- [15] I. M. Aroso, J. C. Silva, F. Mano, A. S. Ferreira, M. Dionísio, I. Sá-Nogueira, S. Barreiros, R. L. Reis, A. Paiva, A. R. Duarte, Eur. J. Pharm. Biopharm. 98 (2016) 57–66. <https://doi.org/10.1016/j.ejpb.2015.11.002>.
- [16] A. Roda, F. Santos, A. A. Matias, A. Paiva, A. R. C. Duarte, J. Supercrit. Fluids. 161 (2020) 104826. <https://doi.org/10.1016/j.supflu.2020.104826>.
- [17] X. Li, M. Hou, B. Han, X. Wang, L. Zou, J. Chem. Eng. Data 53 (2008) 548–550, <https://doi.org/10.1021/jc700638u>.
- [18] F. Rahbi, F. Mutelet, H. Sifaoui, J. Chem. Eng. Data 66 (2021) 702–711, <https://doi.org/10.1021/acs.jced.0c00844>.
- [19] L.F. Zubeir, D.J.G.P. van Osch, M.A.A. Rocha, F. Banat, M.C. Kroon, J. Chem. Eng. Data 63 (2018) 913–919, <https://doi.org/10.1021/acs.jced.7b00534>.
- [20] Y. Ji, Y. Hou, S. Ren, C. Yao, W. Wu, Fluid Phase Equilib. 429 (2016) 14–20, <https://doi.org/10.1016/j.fluid.2016.08.020>.
- [21] D. J. G. P. van Osch, C. H. J. T. Dietz, J. van Spronsen, M. C. Kroon, F. Gallucci, M. van Sint Annaland, R. Tuinier, ACS Sustainable Chem. Eng. 7 (2019) 2933–2942. <https://doi.org/10.1021/acssuschemeng.8b03520>.
- [22] M. F. N. Meeran, H. Javed, H. al Tae, S. Azimullah, S. K. Ojha, Front. Pharmacol. 8 (2017) 1–34. <https://doi.org/10.3389/fphar.2017.00380>.
- [23] D.O. Abranches, M.A.R. Martins, L.P. Silva, N. Schaeffer, S.P. Pinho, J.A.P. Coutinho, Chem. Commun. 55 (2019) 10253, <https://doi.org/10.1039/C9CC04846D>.
- [24] [24] <https://webbook.nist.gov/chemistry/>.
- [25] N. Schaeffer, D. O. Abranches, L. P. Silva, M. A. R. Martins, P. J. Carvalho, O. Russina, A. Triolo, L. Paccou, Y. Guinet, A. Hedoux, J. A.P. Coutinho, ACS Sustainable Chem. Eng. 9 (2021) 2203–2211. <https://doi.org/10.1021/acssuschemeng.0c07874>.
- [26] D.Y. Peng, D.B. Robinson, Ind. Eng. Chem. Fundam. 15 (1976) 59–64, <https://doi.org/10.1021/i160057a011>.
- [27] E. Pérez, A. Cabañas, Y. Sánchez-Vicente, J.A.R. Renuncio, C. Pando, J. Supercrit. Fluids 46 (2008) 238–244, <https://doi.org/10.1016/j.supflu.2008.01.009>.
- [28] Eduardo Pérez. PhD Dissertation. Universidad Complutense de Madrid, 2008.
- [29] H. Sovová, R.P. Stateva, A.A. Galushko, J. Supercrit. Fluids 41 (2007) 1–9, <https://doi.org/10.1016/j.supflu.2006.08.007>.
- [30] R. Thakur, R.B. Gupta, Ind. Eng. Chem. Res. 44 (2005) 7380–7387, <https://doi.org/10.1021/ie050417j>.
- [31] M. Mukhopadhyay, S.K. De, J. Chem. Eng. Data 40 (1995) 909–913, <https://doi.org/10.1021/jc00020a038>.
- [32] N.R. Foster, G.S. Gurdial, J.S.L. Yun, K.K. Liang, K.D. Tilly, S.S.T. Ting, H. Singh, J. H. Lee, Ind. Eng. Chem. Res. 30 (1991) 1955–1964, <https://doi.org/10.1021/ie00056a044>.
- [33] Y. Sánchez-Vicente, O. Alonso-Pastor, C. Pando, A. Cabañas, J. Chem. Thermodyn. 103 (2016) 152–156, <https://doi.org/10.1016/j.jct.2016.07.044>.
- [34] S. Liao, Y. Hou, S. Li, X. Chen, W. Wu, J. Supercrit. Fluids 55 (2010) 32–36, <https://doi.org/10.1016/j.supflu.2010.08.014>.
- [35] V. Alizadeh, L. Esser, B. Kirchner, J. Chem. Phys. 154 (2021), <https://doi.org/10.1063/5.0038093>.
- [36] R. Haghbaksh, S. Raeissi, J. Chem. Eng. Data 63 (2018) 897–906, <https://doi.org/10.1021/acs.jced.7b00472>.