



Phase Transition and Volume Expansion in CO₂-Expanded Liquid Systems

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Binary mixtures of conventional solvents are very useful in the dense gas processing of pharmaceuticals. However, the lack of experimental data for ternary systems of organic solvents and dense carbon dioxide hinders the full exploitation of solvent engineering for particle formation by dense gas processing. In this work, volume expansion and mixture critical points for binary and ternary systems of organic solvents and carbon dioxide were experimentally determined at different temperatures and pressures. Results show an exponential behavior of the liquid volume expansion with pressure as the mixture come close to the mixture critical point.

1. Introduction

Dense gas antisolvent precipitation of pharmaceuticals has been investigated extensively in the last decades and several promising gas-expanded liquid techniques have been proposed (Foster et al. 2012). The principle of these techniques is based on the expansion by a dense gas, usually CO₂, of a liquid phase consisting of a drug dissolved in an organic solvent. The dense gas acts as an antisolvent for the system. As the antisolvent concentration increases the solvent expands and the dissolution capacity of the solvent phase, which is a unique function of its density, is reduced, as the antisolvent has little or no affinity for the solute. High antisolvent concentrations result in precipitation of the solute. The nature of the final precipitate is a function of the rate of volumetric expansion or pressurization, the antisolvent density, solute concentration and solute solubility (Thiering et al. 2000). The volumetric expansion of the liquid phase increases with increasing pressure and the degree of expansion depends on the type of solvent used and operating temperature. As the liquid phase approaches the mixture critical point, the volume expansion significantly increases and becomes infinite at the mixture critical point. The volumetric expansion for binary and ternary systems is an important parameter when choosing a suitable solvent for dense gas precipitation and is addressed in this study.

Carbon dioxide has been recognized as an environmentally friendly solvent and widely used in supercritical fluid applications because it has mild critical conditions ($T_c=304.25$ K, $P_c=73.8$ bar) and is inexpensive, nontoxic, nonflammable, and readily available (Chiu et al. 2008). All these characteristics make CO₂ the most useful dense gas in research and industry.

Besides the volume expansion, the mixture critical points of organic solvents and dense carbon dioxide mixtures have been experimentally determined at different temperatures and pressures (Kordikowski et al., 1995; Jin, 2001; Lazzaroni et al., 2005). Bakhbakhi (2011) observed that although an increase in temperature reduces the solubility of some solids in the gas expanded liquid phase, there was an crossover point beyond which an increase of temperature improves the solute solubility. Also some ternary systems tend to present liquid-liquid immiscibility at lower temperatures, this way relatively high temperatures were chosen for the experiments.

Binary mixtures of conventional solvents are very useful in the dense gas processing of pharmaceuticals: they allow control over the solvent power and physical properties of the solvent and over particle morphologies. Moreover, supercritical solvents are used in a great number of industrial sensitive applications like in food, waste treatment, polymers and monomers processing and biochemical industries (Bezaze et al., 2011). The lack of experimental data for ternary systems of organic solvents and dense carbon dioxide hinders the full exploitation of solvent engineering for particle formation by dense gas processing and is a major motivation for this study.

2. Materials and Methods

2.1 Materials

Carbon dioxide (99.9% purity) was provided by Coregas (NSW, Australia). HPLC-grade methanol, acetone and DMSO were purchased from Sigma-Aldrich (NSW, Australia) and used without any further purification.

2.2 Methods

The experimental runs were carried out in a bench unit designed at the Supercritical Fluids Research LAB, at University of New South Wales. The apparatus schematic is similar to one described by Foster et al. (2012) for GAS process. A high pressure equilibrium cell (Jerguson model 18T-32) equipped with a sapphire window and immersed in a water-bath was used to observe the volume expansion and the phase transition points for different binary and ternary systems. Organic solvent was fed to the cell using a graduated syringe. A syringe pump (Teledyne-ISCO) was employed to pressurize the cell and a pressure transducer with digital display (Druck) and uncertainty of 0.1 bar was used to monitor the pressure inside the cell. The volume expansion points were measured using a rule with an uncertainty of 0.25 mm. An expansion valve, followed by a solvent trap, was used to depressurize the system.

Each run consisted of loading the cell with a known volume of solvent of interest, slowly pressurizing the system with carbon dioxide to the desired pressure and allowing the system to rest for a few moments until reaching equilibrium. A measurable pressure change during this resting period would indicate that the liquid and gas were not in equilibrium. The volume expansion was calculated by using the internal cross section area of the cell and by measuring the difference in height of the meniscus at the starting and final points (desired pressure). This procedure was repeated until the system was close to its critical point, which occurred when the meniscus was not distinguishable enough to allow precisely measuring of its position. The system was recompressed to ensure that both phases were totally miscible. Slow depressurization using the expansion valve was done until the phase boundary was clearly visible again. At this point, the pressure was measured as the critical pressure of the mixture.

3. Results and Discussion

In this study the binary systems consisted of carbon dioxide with either methanol, dimethyl sulfoxide (DMSO) or acetone as the organic solvents were investigated. The ternary systems were composed of carbon dioxide with binary mixtures of these solvents in three different ratios: 75:25, 50:50 and 25:75 (% v/v). Experimental runs were carried out at 40, 50 and 60 °C for pressures from the atmospheric until close to the critical point of the system. The initial volume injected into the system ranged from 4 to 7 ml, depending on the system. Reproducibility of the method used was checked by comparison with published data. Figures 1 and 2 show a good agreement between the results of this work and those by Lazzaroni et al. (2005) and Jin (2001), respectively.

Volume expansion data measured for the binary systems are shown in Figures 3-5. At low pressures only a small increase of the liquid volume can be observed, but as the pressure goes up an exponential increase in the volume expansion occurs. The results show a volume expansion of approximately 1000 % for acetone, 400 % for methanol and 210 % for DMSO at 40 °C and near the corresponding critical point. At any given pressure, increases in temperature caused a decrease in the volumetric expansion for all systems. This can be explained by the decrease of CO₂ solubility in the organic phase. Varying the temperature also changes the pressure at the critical point for each system. This behavior is better observed in the system CO₂-DMSO, for which the maximum volume expansion was higher at higher temperatures (Figures 3-5).

In the ternary systems (Figures 6-14), volume expansion values were in between the values observed for the pure substances and CO₂. However, the relationship of the volume expansion with the volume ratio used is not linear, meaning that intermolecular interactions between the organic solvents cannot be neglected. Some of these intermolecular interactions have clear effects that are worth mentioning. In order to better explore the results, one temperature and an arbitrary pressure values were fixed and the volume

expansions for these conditions were obtained through interpolation for each of the tested compositions. These values were then compared with dots linearly traced between the volume expansion of the pure components in the system. If the interpolated data are close to the linear ones for most of the conditions tested, then the intermolecular interactions in that system do not interfere with the carbon dioxide solubility.

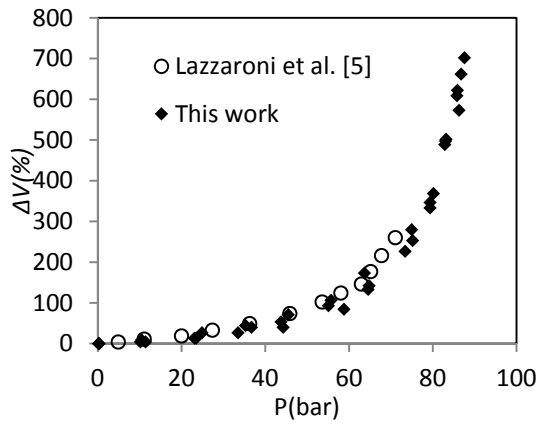


Figure 1: Percent volume change vs pressure of CO_2 for acetone at 40 °C.

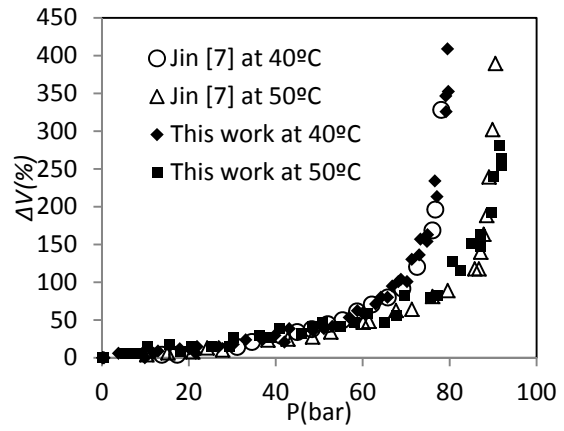


Figure 2: Percent volume change vs pressure of CO_2 for methanol at 40 and 50 °C.

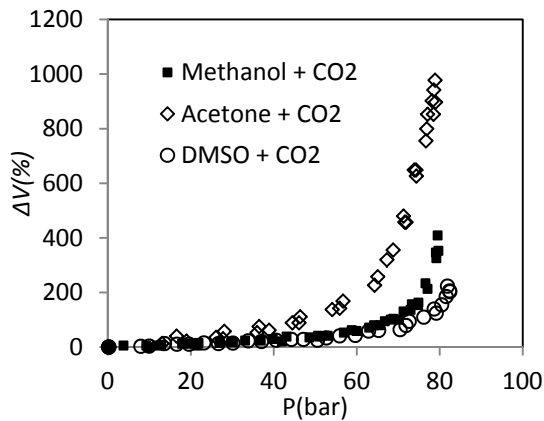


Figure 3: Percent volume change vs pressure of CO_2 for multiple solvents at 40 °C.

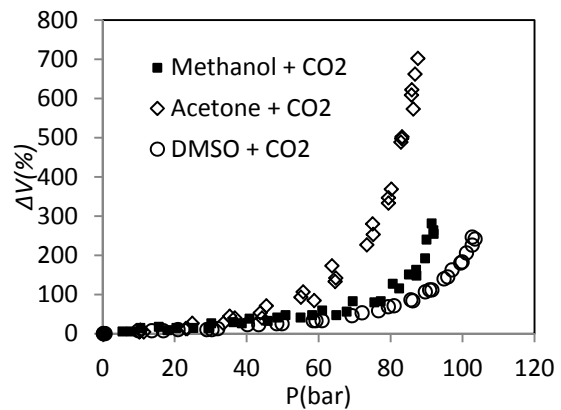


Figure 4: Percent volume change vs pressure of CO_2 for multiple solvents at 50 °C.

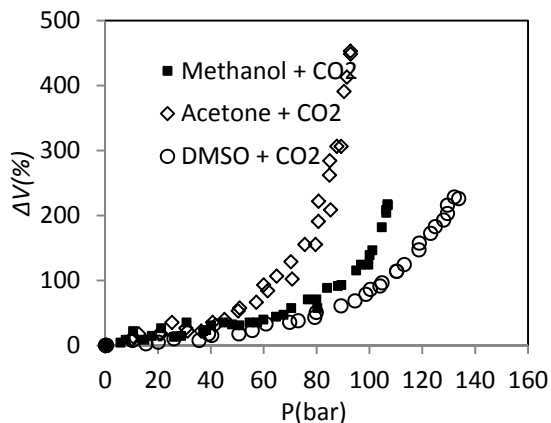


Figure 5: Percent volume change vs pressure of CO_2 for multiple solvents at 60 °C.

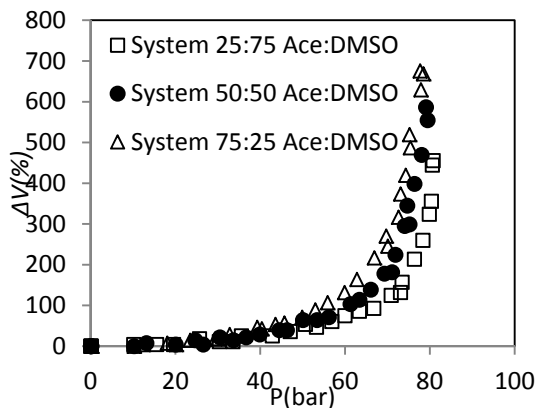


Figure 6: Percent volume change vs pressure of CO_2 for acetone : DMSO system at 40 °C.

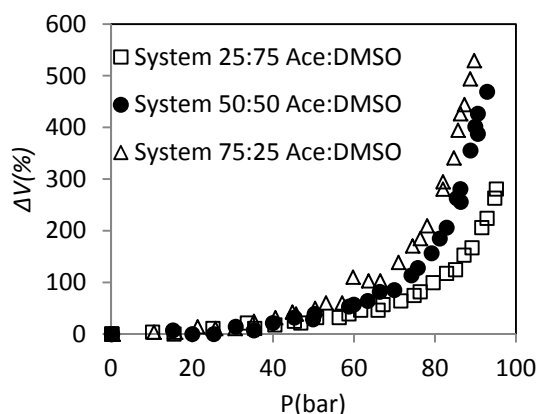


Figure 7: Percent volume change vs pressure of CO_2 for acetone : DMSO system at 50 °C.

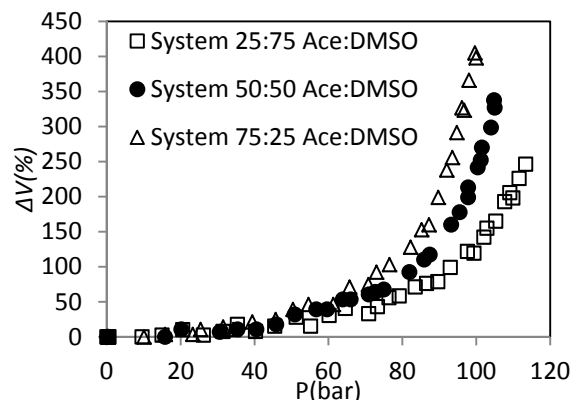


Figure 8: Percent volume change vs pressure of CO_2 for acetone : DMSO system at 60 °C.

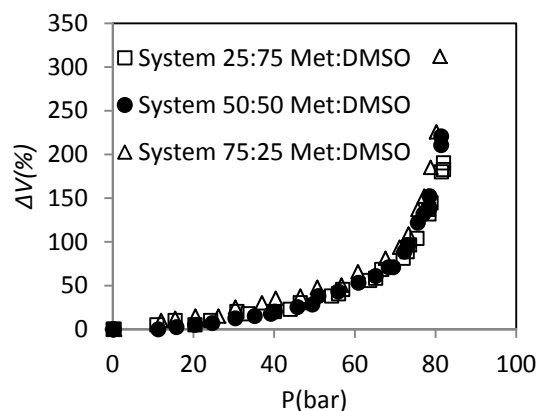


Figure 9: Percent volume change vs pressure of CO_2 for methanol : DMSO system at 40 °C.

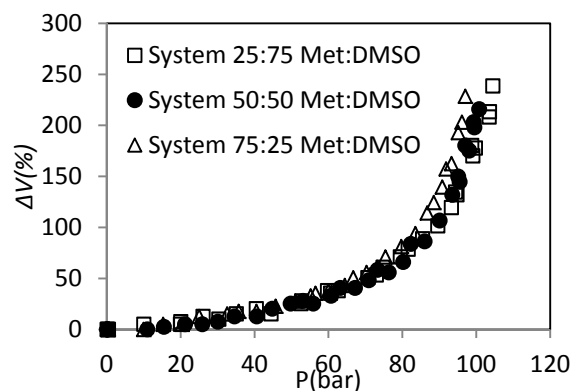


Figure 10: Percent volume change vs pressure of CO_2 for methanol : DMSO system at 50 °C.

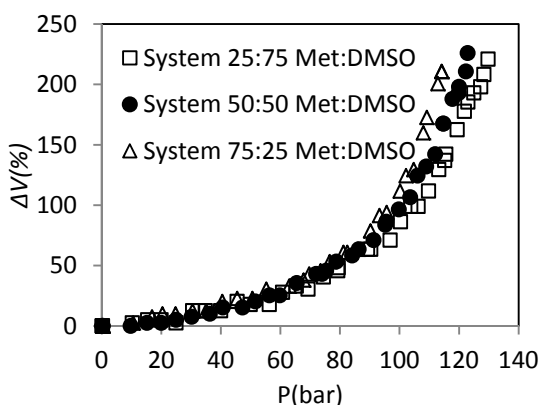


Figure 11: Percent volume change vs pressure of CO_2 for methanol : DMSO system at 60 °C.

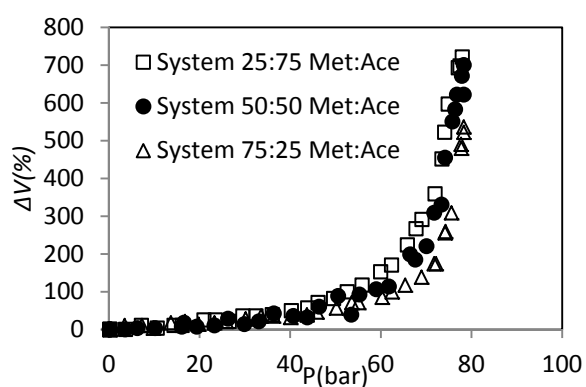


Figure 12: Percent volume change vs pressure of CO_2 for methanol : acetone system at 40 °C.

Starting with the ternary system CO_2 /acetone/DMSO (Figures 6-8), at 40 °C and 70 bar the volume expansion of pure acetone and pure DMSO were approximately 413% and 70% respectively. If the system behavior were linear, the volumetric expansion for the 50:50 system should be 241,5 %, but strong intermolecular interactions take place decreasing the solubility of CO_2 in the organic phase and therefore pushing down the volume expansion value. Indeed, the experimental interpolated value found was 184 %. Values below the predicted linear ones were found in all the tested compositions, temperatures and for a

wide range of pressures. The fact that both acetone and DMSO have large dipole moments and similar structure may contribute for these strong interactions.

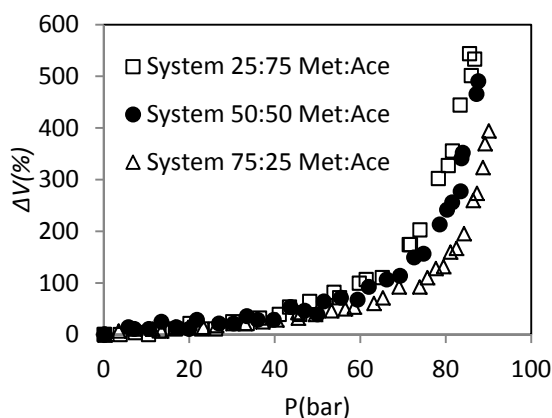


Figure 13: Percent volume change vs pressure of CO_2 for methanol : acetone system at 50 °C.

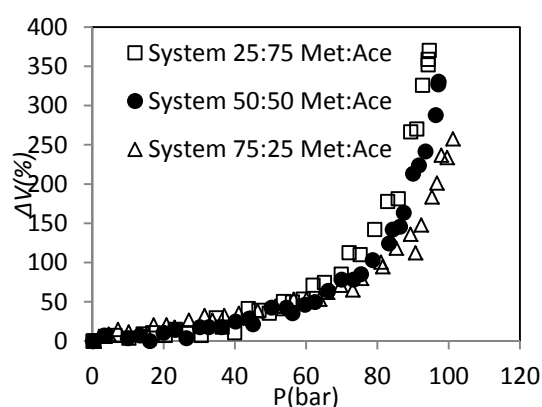


Figure 14: Percent volume change vs pressure of CO_2 for methanol : acetone system at 60 °C.

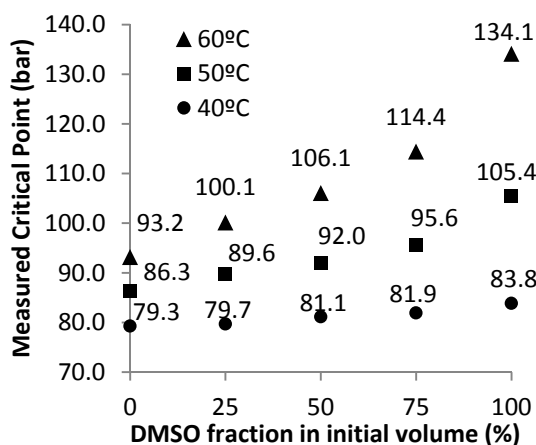


Figure 15: Measured critical points vs DMSO fraction for carbon dioxide / acetone / DMSO system at various temperatures: 40 °C, 50 °C, 60 °C.

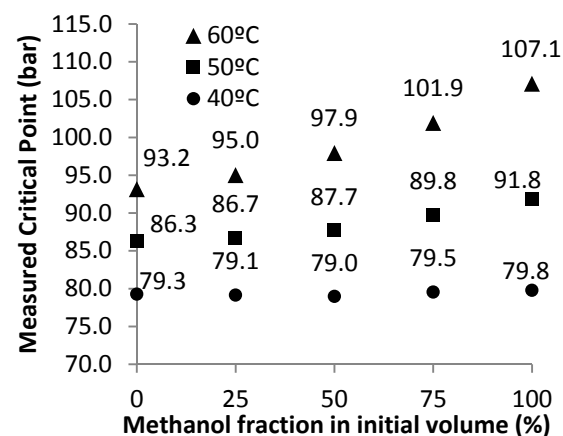


Figure 16: Measured critical points vs methanol fraction for carbon dioxide / acetone / methanol system at various temperatures: 40 °C, 50 °C, 60 °C.

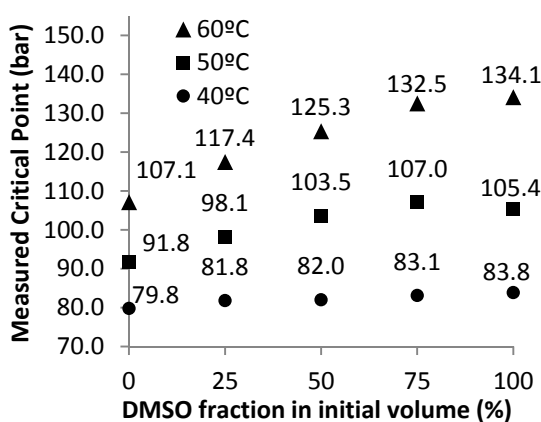


Figure 17: Measured critical points vs DMSO fraction for carbon dioxide / methanol / DMSO system at various temperatures: 40 °C, 50 °C, 60 °C.

Methanol and DMSO both have low solubility in carbon dioxide either due to large dipole moment or to hydrogen bonding (Kordikowski et al. 1995). Their ternary system CO₂/methanol/DMSO (Figures 9-11) had a volume expansion for the tested compositions, temperatures and pressures considerably below linear behavior, especially for higher concentrations of methanol (75:25 and 50:50 methanol:DMSO % v/v). Methanol and its hydrogen bonding interaction with DMSO, that can interact accepting hydrogen bonds, are suspected to be the main reason for the decreased solubility of carbon dioxide in this system.

For the ternary system CO₂/acetone/methanol (Figures 12-14) the volume expansion behaved mostly linearly with the changes in composition for conditions tested. This means that intermolecular interactions do not strongly affect this system. However, there was a slight preference for lower than linear volume expansion. This also might be related to the fact that acetone can receive hydrogen bonds from methanol.

Figures 15-17 show the mixture critical points measured for different conditions. The relationship of the critical points is not linear with temperature nor it is with the volume ratio used for each system. Generally the value of the critical pressure follow the trend of the initial composition of the binary organic mixture, however there were some exceptions, such as the system CO₂/methanol/DMSO at 50 °C, that presents a different behavior: the critical point for the 25:75 methanol:DMSO (v/v) ratio (Figure 17) is higher than for other ratios tested. Also, for the system CO₂/acetone/DMSO the critical point considerably decreases from pure DMSO to 25:75 acetone:DMSO composition.

4. Conclusion

Precipitation techniques are dependent on the volume expansion of organic solvents by dense gases and on the mixture critical points. In this study, new volume expansion and mixture critical points data were experimentally determined for binary and ternary systems of organic solvents and CO₂ at different temperatures and pressures. The behavior of ternary systems near critical conditions was observed and the results covered a significant number of conditions. Some organic solvents like methanol and DMSO that expand in a similar way at lower temperatures, showed significant different behaviors at higher temperatures. It was observed that the mixture critical point of the ternary systems depends on the composition of the starting solvent mixture. This can be used to allow better control over the precipitation stage in dense gas antisolvent processes, for example the acetone can be used in small ratios (below 25%) to considerably bring down the critical point of a mixture with either methanol or DMSO.

Acknowledgments

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