GUIDELINES FOR THE DESIGN OF AN OPTIMUM GAS PROCESS: MEASUREMENTS, MODELING AND THERMODYNAMIC INTERPRETATION

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Abstract
This contribution comprises the various results of a long-term research programme to study the fundamental thermodynamic aspects of the gas anti-solvent process. For this purpose, the phenomenon of volume expansion, the phase behavior of a number of relevant ternary systems, the development of optimum thermodynamic guidelines for the gas anti-solvent process, and the verification of the proposed guidelines have been received attention.

Introduction
Supercritical fluids are being increasingly used as the media for producing fine particles, in particular micronized pharmaceuticals. Among the most important techniques for micronizing pharmaceuticals, are the rapid expansion of supercritical solutions (RESS) [1-3] and the gas anti-solvent (GAS) [4-8] processes. In the RESS process, a solid is dissolved in a supercritical fluid at a certain temperature and pressure, followed by the expansion of the solution to some lower pressure level, causing precipitation of the solids. The RESS process can be used to produce fine particles with narrow size distributions at relatively low temperatures. However, a major limitation of this process is that the solubilities of most chemicals, especially pharmaceuticals, are usually very low in supercritical fluids.

To overcome this shortcoming of the RESS process, the GAS process was introduced. In the GAS process, a high-pressure gas or a supercritical fluid acts as an anti-solvent for recrystallization or precipitation of a solid dissolved in an organic solvent. In this process, the anti-solvent gas is highly soluble in the liquid solvent, which causes a volume expansion of the liquid solvent and thus reduces the solvent power of the organic solvent. As a result, precipitation of the dissolved solute occurs and fine particles with narrow size distribution can be obtained. The use of gases or supercritical fluids as anti-solvents for fine particle formation is a rapidly developing field of research. The possibility of obtaining solvent-free micro- or even nano-particles with a narrow size distribution makes this technology very attractive, especially in the pharmaceutical industry.

Most of the publications on the GAS process are focused on the effects of operational conditions such as temperature, pressure, and rate of addition of anti-solvent on the size and size distribution of the particles, as well as its morphology. But in order to evaluate the feasibility of such a process and to optimize the choice of operative variables, it is important to understand the thermodynamic fundamentals of the GAS process.

Recently, de la Fuente Badilla et al. [9] noticed that the classical definition of volume expansion of the solution in the GAS process [8,10] is not able to distinguish the differences of the liquid-phase volume expansivities of different solvents expanded by the same anti-solvent. Therefore, a new definition was proposed for the volume expansion of the solvent-solute solution caused by the anti-solvent. This new definition allowed the selection of the optimum solvent + anti-solvent combination for a given solute, and the determination of the optimum process conditions as well. De la Fuente Badilla et al. [9,11] did demonstrate the validity of this definition of volume expansion for the systems carbon dioxide + toluene + naphthalene and carbon dioxide + toluene + phenanthrene.

The aim of this work is to further investigate the approach proposed by de la Fuente Badilla et al. [9,11] by applying it to newly obtained simulation results for some gas + organic solvent + model pharmaceutical systems. The following systems have been studied:

- Carbon dioxide + 1-propanol + salicylic acid
- Carbon dioxide + acetone + benzoic acid
- Ethene + acetone + benzoic acid

In addition, an algorithm has been proposed for selecting the best combination of solvent + anti-solvent for a given solute.

Experiments

Unfortunately, there is a serious lack in literature of experimental data on the phase behavior of the systems of interest in the GAS process. Shariati and Peters [12] studied the phase behavior of the ternary system carbon dioxide + 1-propanol + salicylic acid experimentally. Details of the apparatus, the experimental procedures, and the experimental data obtained have previously been reported by Shariati and Peters [12].

Volume Expansion

The classical definition of the volume expansion of the liquid phase commonly used in the GAS process [8,10] is given by the following equation:

$$\frac{\Delta V}{V} = \frac{V(T,P) - V_0(T,P_0)}{V_0(T,P_0)} \qquad (1)$$

where $V(T,P)$ is the total volume of the liquid phase at the temperature T and pressure P of the system, and $V_0(T,P_0)$ represents the total volume of the pure solvent at the same temperature and a reference pressure P_0 which is normally the atmospheric pressure. Recently, De la Fuente Badilla et al. [9] noticed that different solvents show almost the same volume expansion behavior for a given anti-solvent using the classical definition of the volume expansion (Eq. 1). Indeed, when one mole of an anti-solvent is added to a liquid phase, the total volume of the system always increases because of the increasing system mass, regardless of volume effects due to non-ideal mixing. But, if the molar volume of the system is considered, the results are different. Since total volume is an extensive thermodynamic property, it depends on the quantities of material involved, i.e., it is apparent that the classical definition of volume expansion is not able to distinguish between different solvents in their liquid phase expansivity by the same anti-solvent. Figures 1 and 2 illustrate this feature for the different solvents suggested by Kordikowski et al. [10] having been expanded by carbon dioxide and ethene, respectively.

In order to be able to discriminate between the volume expansion behavior of all combinations of anti-solvent + solvent in the GAS process, the following definition of volume expansion was proposed by de la Fuente Badilla et al. [9]:

$$\frac{\Delta V}{V} = \frac{\tilde{V}(T,P) - \tilde{V}_0(T,P_0)}{\tilde{V}_0(T,P_0)} \tag{2}$$

where $\tilde{V}(T,P)$ is the molar volume of the liquid phase at the temperature and the pressure of the system, and $\tilde{V}_0(T,P_0)$ is the molar volume of the pure solvent at the system temperature and a reference pressure P_0, usually taken as atmospheric pressure.
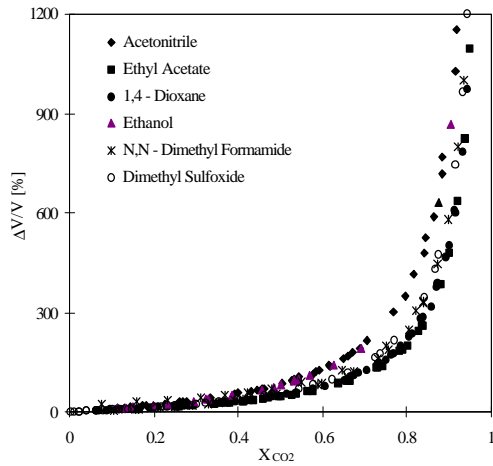

Figure 1. Relative total volume expansions of several organic solvents, expanded by carbon dioxide at 298.15 K. The experimental data are from Ref. [10].
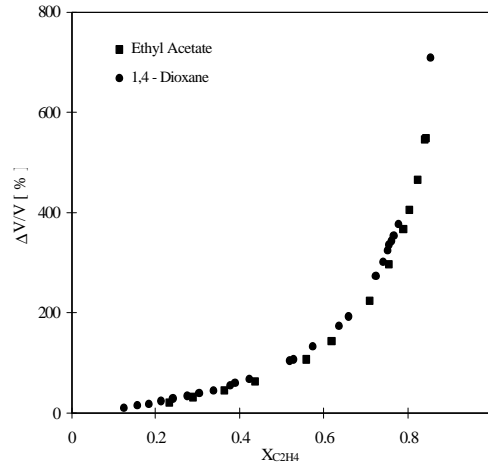

Figure 2. Relative total volume expansions of several organic solvents, expanded by ethene at 298.15 K. The experimental data are from Ref. [10].

Using the new definition of volume expansion, Figures 3 and 4 show the volume expansion of the same systems presented in Figures 1 and 2. Both these figures show that not only the volume does not expand; in all cases it even contracts. These figures also show that in some cases at sufficiently high concentrations of the anti-solvent, volume contraction will change into volume expansion. It is also evident that with this new definition of volume expansion, the curves of different expanded solvents are clearly distinguishable from each other.

In order to determine whether there is any relationship between the new definition of volume expansion and the optimum operating conditions of the GAS process, it is necessary to know the phase behavior of the system of interest.
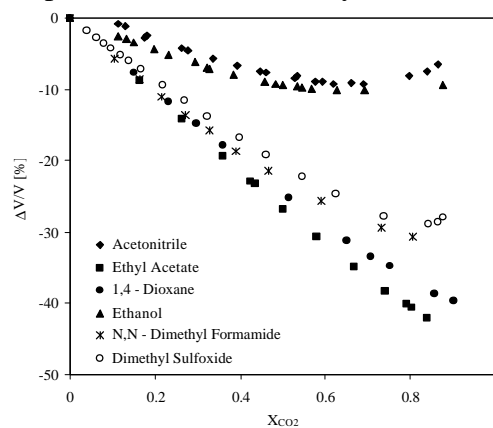

Figure 3. Relative molar volume expansions of several organic solvents, expanded by carbon dioxide at 298.15 K. The experimental data are from Ref. [10]
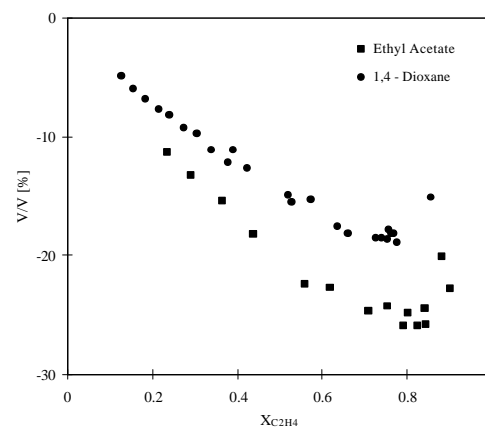

Figure 4. Relative molar volume expansions of several organic solvents, expanded by ethene at 298.15 K. The experimental data are from Ref. [10].

Thermodynamic Modeling

The modelling approach applied in this study is based on the works of de la Fuente Badilla et al. [9,11] and Shariati and Peters [12].

Results and Discussions

The systems carbon dioxide + 1-propanol + salicyclic acid, carbon dioxide + acetone + benzoic acid, and ethene + acetone + benzoic acid were studied in this work. Both the solute mole fractions in the expanded liquid phases, and the volume expansions of the liquid phases were calculated using the Peng-Robinson EOS [9]. Figure 5 shows the computational results for the system carbon dioxide + 1-propanol + salicyclic acid. At a temperature of 288 K, there is a sharp decrease of the salicyclic acid concentration in the liquid phase within a narrow pressure range of about 4.60 to 4.75 MPa. This modeling result has already been validated using the experimental data reported by Shariati and Peters [12]. However, when the temperature is increased to 313 K, which is above the critical point of the anti-solvent (CO_2), such a sharp decrease in the concentration of salicyclic acid is no longer observed. Looking at the volume expansion curve of this system, also at 288 K, it is evident that there is a minimum in this curve in exactly the same pressure range as the curve showing a sharp decrease in the salicyclic acid concentration, i.e., where almost all the solute is precipitated. Such a phenomenon cannot be seen in the volume expansion curve of this system at 313 K.
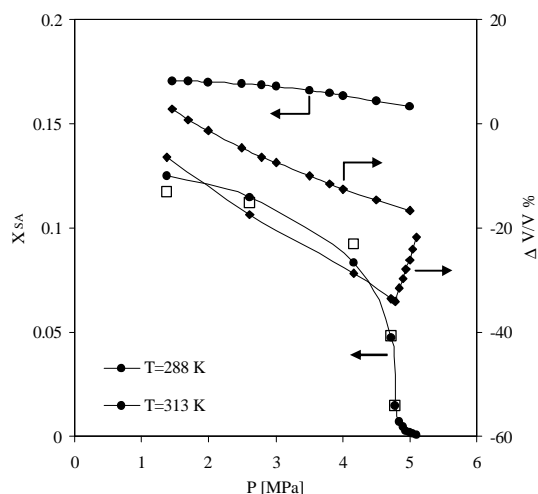

Figure 5. The solubility of salicyclic acid in the liquid phase expanded by the anti-solvent and the relative molar volume expansion of the liquid phase for the ternary system carbon dioxide + 1-propanol + salicyclic acid. Open squares denote experimental data reported by Shariati and Peters [12].

Assuming that the relative expansion of the solvent is not strongly affected by the solute since its concentration in the liquid phase is usually low, it is possible to find the best combination of solvent + anti-solvent by using the volume expansion curves of different solvents having been expanded by the same anti-solvent (like Figures 3 and 4). The best combination of the solvent + anti-solvent is when the minimum in the volume expansion curve occurs at lower pressures. However, it is obvious that other factors such as low solubility of the solute in the anti-solvent and a reasonable solubility of the solute in the organic solvent, should also be considered for the optimum choice solvent + anti-solvent combination. Another result of this phenomenon is that the optimum operating pressure for each GAS process has to be chosen in such a way that the volume expansion of the solvent + anti-solvent mixture shows a minimum value. In addition, the results indicate that the thermodynamically suitable operating temperature of the GAS process should be close but below the critical temperature of the anti-solvent. In order to further evaluate the above conclusions, the carbon dioxide + acetone + benzoic acid, and ethene + acetone + benzoic acid systems were studied. The results of these two systems are presented in Figures 6 and 7, respectively. Again, it can be seen that at

operating temperatures below the critical temperature of the anti-solvents, there are sharp drops in the solute concentrations in a narrow pressure range. But at temperatures higher than the critical temperatures of the anti-solvents, this phenomenon does not occur. Also, the minima in the volume expansion curves almost exactly coincide with the optimum pressures for precipitating the solute.
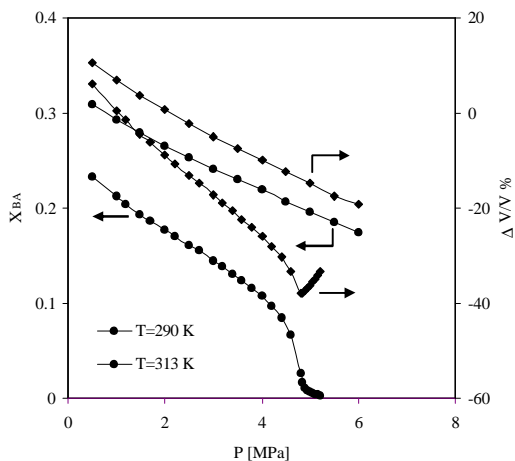

Figure 6. The solubility of benzoic acid in the liquid phase expanded by the anti-solvent and the relative molar volume expansion of the liquid phase for the ternary system carbon dioxide + acetone + benzoic acid.
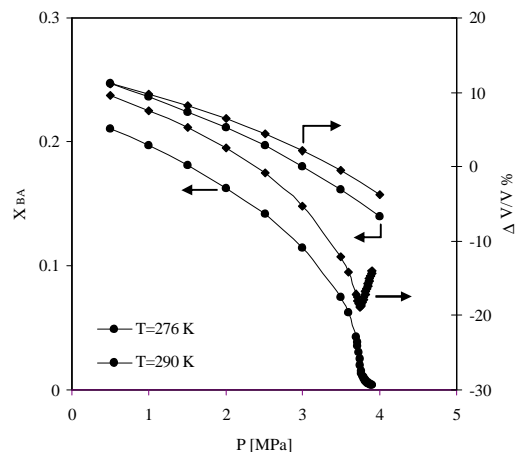
Figure 7. The solubility of benzoic acid in the liquid phase expanded by the anti-solvent and the relative molar volume expansion of the liquid phase for the ternary system ethene + acetone + benzoic acid.

Based on thermodynamic fundamentals, it is possible to summarize all our findings for selecting the best combination of solvent + anti-solvent for a given solute in Figure 8. According to Figure 8, a solvent is selected among a set of solvents in which the solute has the highest solubility. Based on the selected solvent, an anti-solvent is chosen which has the highest solubility in the solution. Indeed, when the anti-solvent has the highest solubility in the solution, then the operating pressure is the lowest. After selection of the anti-solvent, the temperature should be set close to, but below the critical temperature of the anti-solvent. Then it has to be checked if the relative molar volume expansion-pressure curve has a minimum or not. If there is a minimum, then the solvent + anti-solvent pair is the best choice, and, if not, the procedure should be repeated for the anti-solvent which has the second highest solubility in the same solvent + solute solution.
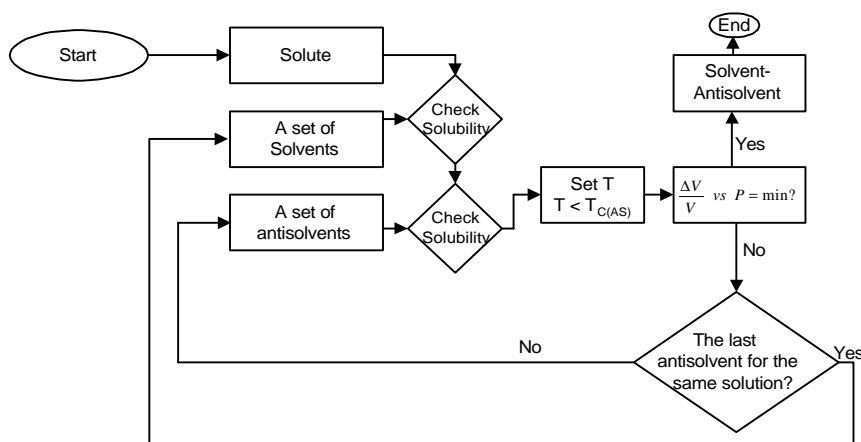

Figure 8. A systematic method for selecting the best combination of solvent + anti-solvent.

This method should be continued until a proper set of solvent + anti-solvent is obtained. In case that none of the anti-solvents in the set of anti-solvents satisfies the condition of having a minimum in the relative molar volume expansion-pressure curve for the considered solution, the procedure should be repeated for the solvent which is the second highest in the solvent power for the solute and then the anti-solvent which has the highest solubility in the newly selected solution, is chosen. This systematic method should be continued until the best set of solvent + anti-solvent is obtained.

Conclusions

In this work, the new definition of volume expansion proposed by de la Fuente Badilla et al. [9] has been further investigated by applying it to some gas + organic solvent + model pharmaceutical systems. It is shown that the new definition of volume expansion can be used as one of the thermodynamic criteria for selecting the optimum combination of the solvent + anti-solvent and also for selecting the optimum operating conditions for the GAS process. At the optimum operating pressure, almost all the solid is precipitated. A comparison of the position of the optimum pressure on the solubility curve of the solute to the pressure where the volume expansion curve reaches a minimum value showed that these two pressures coincide with each other. To model the solubility curve of the solute in the GAS process, the model proposed by de la Fuente Badilla et al. [9,11] and Shariati and Peters [12] was used. It is observed that when the operating temperature of the system is close but below the critical temperature of the anti-solvent, there is a sharp drop in the solute concentration in the liquid phase. This phenomenon is desirable in the GAS process. Such a behavior does not occur at temperatures higher than the critical temperature of the anti-solvent. In addition, a systematic method has been proposed for selecting the appropriate combination of solvent + anti-solvent.

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