EFFECT OF THE PHASE BEHAVIOUR OF SOLVENT-ANTISOLVENT SYSTEMS IN GAS-ANTISOLVENT CRYSTALLISATION

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Crystallisation processes using supercritical CO_2 as an antisolvent have been shown to be feasible for medium and large scale applications in the past years. However, the development of concrete applications still requires a lot of experimental and theoretical work based on detailed experience in the field. Here we discuss some effects based on ternary phase equilibria aimed at crystallising paracetamol. A calculation method for the proper choice of the solvent is proposed, based on a global phase diagram method.

INTRODUCTION

Gas-Antisolvent Crystallisation (GAS) was introduced in the 1980's as a laboratory-scale method and has gained a lot of interest in the context with the production of crystalline solids having adjustable morphological properties [1]. The principle of this technique is based upon the pressurisation of a liquid solution with a gas, which dissolves in the liquid phase thus causing the precipitation of the solute from the solution. In recent years, results of pilot-scale applications have shown that this process is readily applicable also on a larger scale. The development of applications, however, still requires a lot of experimental work and theoretical analysis in order to obtain the required process data.

First comparative studies of gas antisolvent crystallisation were initiated by Kordikowski et al. They measured the volume expansion of liquid solvents as a result of the uptake of the antisolvent for different solvent-antisolvent systems and deduced a close relationship with solute solubilities [2]. The studies of de la Fuente Badilla et al. lead to a more descriptive expression of the volume behaviour of the liquid phase based on a thermodynamic description [3,4] capable of predicting an optimum pressure range for the crystallisation. An even more thorough analysis has been carried out by Kikic et al. on well determined systems containing naphthalene and phenanthrene dissolved in toluene and carbon dioxide [5,6]. The proposed model is capable of predicting solubility curves of the solutes with good accuracy and can be applied either for S-L-V or S-L1-L2-V phase behaviour occurring at different system temperatures.

In practice, it would be favourable to derive a method to predict the phase behaviour as well as the solid solubility of a less known ternary system without running great numbers of experiments in order to find suitable solvents or either solvent mixtures.

METHODS

Ternary phase equilibrium calculation

The phase equilibrium between solvent and antisolvent is one key factor to influence the gas antisolvent crystallization process since it fixes the maximum attainable supersaturation by the equilibrium concentration of each of the components of the system. It can be described by cubic equations of state and depicted in phase diagrams. Within this work, the Peng-Robinson equation (1) was used for modelling the phase behaviour of the investigated substances [7].

$$p = \frac{RT}{V_\mathrm{m} - b} - \frac{a(T)}{V_\mathrm{m}(V_\mathrm{m} + b) - b(V_\mathrm{m} - b)} \tag{1}$$

Here, V_m is the molar volume, R is the gas constant, T the temperature and p the pressure. The parameters a and b are specific parameters of the substance which can be calculated from the critical data T_c and p_c. For mixtures of substances, the binary attraction parameters were calculated by the Lorentz-Berthelot combining rules.

$$a = \sum_i \sum_j x_i x_j \sqrt{a_{ii} a_{jj}} \left(1 - k_{ij}\right) \tag{2}$$

$$b = \sum_i \sum_j x_i x_j b_{ii} b_{jj} \left(1 - l_{ij}\right) \tag{3}$$

The Peng-Robinson equation is not able to describe the fugacity of solid components. Hence, the fugacity of a virtual sub-cooled liquid state is calculated for the solid phase and corrected by means of a Clapeyron-type approach.

$$\ln f^\mathrm{s} = \ln f^\mathrm{l} + \frac{\Delta H_\mathrm{tr}}{\mathrm{R}} \left(\frac{1}{T_\mathrm{tr}} - \frac{1}{T} \right) \tag{4}$$

Here f^s is the fugacity of the solid, ΔH_tr the enthalpy of fusion at the triple point and T_tr the triple point temperature. Accepting a small deviation, the normal melting point temperature T_m and heat of fusion ΔH_m can be used instead of the values at the triple point.

For calculating the solid-liquid-gas equilibrium of a three-component system containing a solid, a liquid and a gaseous substance, a set of nonlinear equations has to be solved simultaneously as described in more detail elsewhere [8, 9] or deduced by other authors [5, 10].

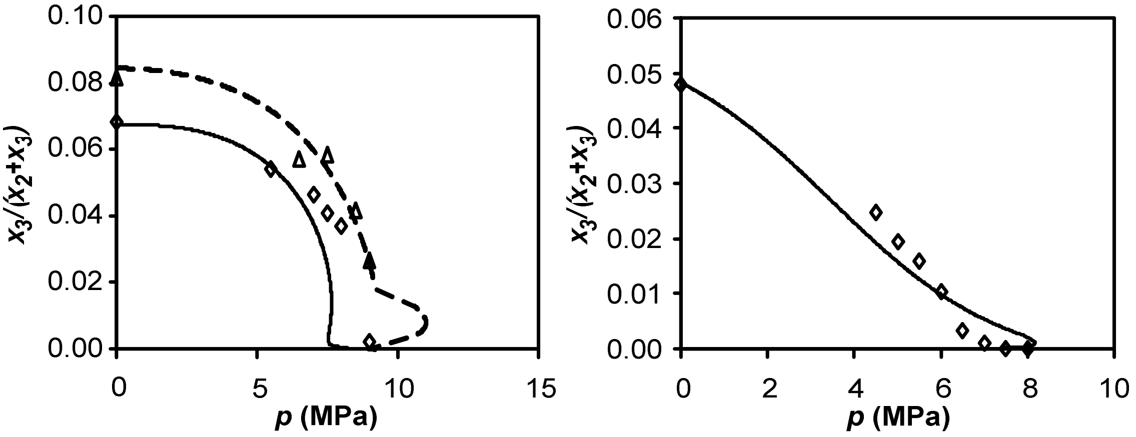
In order to be able to predict the properties with the model, all available substance-related parameters have been taken from literature data. Since critical parameters and acentric factors are just available for a few solid substances only, they had to be determined by group contribution methods [11].

The interaction parameters k_{ij} and l_{ij} in the mixing rules were also taken from published data of binary systems [12,13,14]. The interaction parameters between solids and solvents were determined from the solubility at ambient conditions. Hence the only parameter left to fit measured solubility data was the interaction parameter between solid and gas. For paracetamol T_m is 441.2 K and ΔH_m has a value of 27.1 kJ/mol [15,16]. The solubility data was measured on a dynamic solubility setup described in detail elsewhere [8]. Viewcell experiments were carried out on a viewcell with variable volume (NWA Lörrach, Germany).

In addition to the analysis of the phase behaviour based on *px*-diagrams the global phase diagram method can be employed to estimate the usefulness of a specific solvent-antisolvent mixture for the GAS process. In global phase diagrams ratios of the molecular interaction parameters such as the van der Waals attraction parameter a_{ij} are plotted rather than thermodynamic variables. In such diagrams the regions of different type of phase behaviour are separated by thermodynamic boundary curves. The boundary curve of interest in the context of this work is the tricritical curve. It separates phase diagram types with and without a liquid-liquid-gas three phase coexistence usually located close to the critical point of the more volatile substance, which is here the antisolvent CO_2.

RESULTS

Based upon the above assumptions, systems like paracetamol/ethanol/CO_2 and ascorbic acid/ethanol/CO_2 could be described reasonably well, despite these systems contain polar substances. It was possible to keep constant values for the interaction parameters over the regarded temperature range. Furthermore, the model was able to predict a phase split of the system paracetamol/ethanol/CO_2, which could be verified in view cell experiments. Figure 1a) shows the solubility of paracetamol in the ternary system depending on the CO_2 pressure. While at 313K the solubility curve is not an unambiguous function for pressures above 7.5 MPa, the bump at 323 K and above 10 MPa clearly indicates a liquid-liquid immiscibility region. The behaviour of the system becomes clearer by looking at the densities of the corresponding phases. Figure 2 shows an enlarged plot of the solubility curve at 313K above 7.0 MPa and the calculated density of the fluid phases. The discontinuity of the density function for the liquid phase acknowledges a phase split at a pressure above 7.5 MPa. The corresponding phases can be regarded as liquid, due to their densities between 800 and 900 g/dm^3 at the designated temperature and pressure, and show a different solubility of paracetamol. Gas-phase and l_2-phase meet in a binary critical point at a pressure of 8.2 MPa showing a density of 450 g/dm^3. The phase behaviour of this ternary system resembles the type IV behaviour of a corresponding quasi-binary system.



a) b)

Figure 1: Solubility curves of paracetamol in ethanol/CO2 at 313K (solid line) and 323K (broken line) (a), in acetone/CO_2 at 313 K (b).

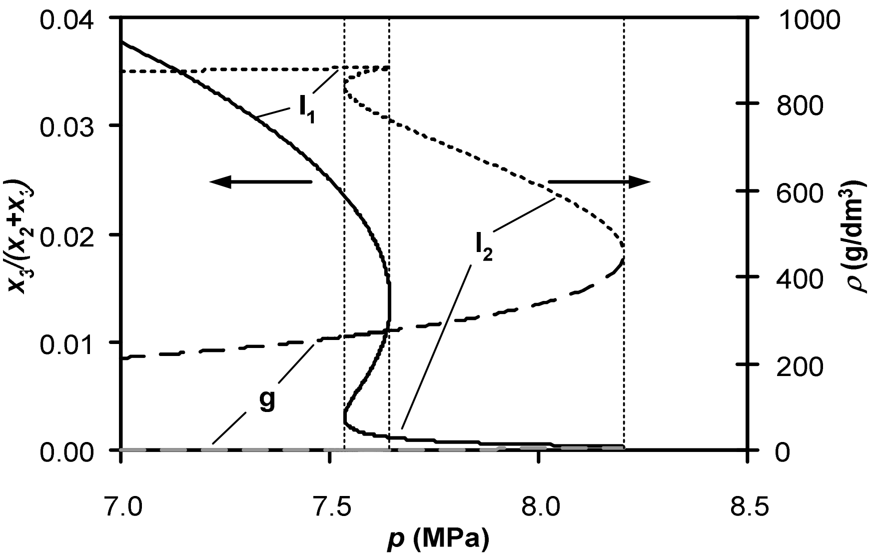


Figure 2: Enlarged plot of the solubility curve of paracetamol in ethanol/CO_2 at 313K including the calculated densities of the different fluid phases. The solid black curve denotes the solubility in the liquid phases, the broken grey curve shows the solubility in the compressed gas phase. The dotted curves denote the liquid density, the broken black curve the "gas"-density.

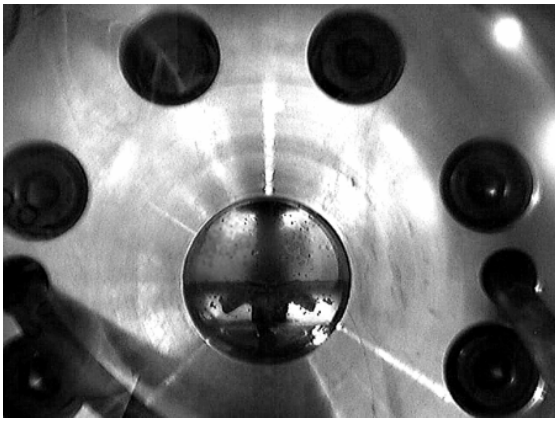


Figure 3: Liquid-liquid demixing of a paracetamol solution in ethanol when it is pressurised with CO_2. Crystallisation only takes place in the upper, CO_2-rich liquid phase.

The splitting of the liquid phase leads to undesired effects in practical crystallization as described by Reverchon et al. and makes it impossible to attain safe processing conditions [18]. Hence, an alternative solvent for paracetamol was sought using model calculations. The system paracetamol/acetone/CO_2 showed a more balanced solubility curve and no phase split at even much higher temperatures (Figure 1b).

The effect of liquid-liquid demixing can also be observed in high-pressure viewcell experiments. A saturated solution of paracetamol in ethanol (c=150 kg/m^3) splits into two liquid phases when pressurised with CO_2 at pressures above 7.6 MPa (Figure 2). The same experiment with a saturated solution of paracetamol in acetone (c=75 kg/m^3) does not show any liquid-liquid demixing.

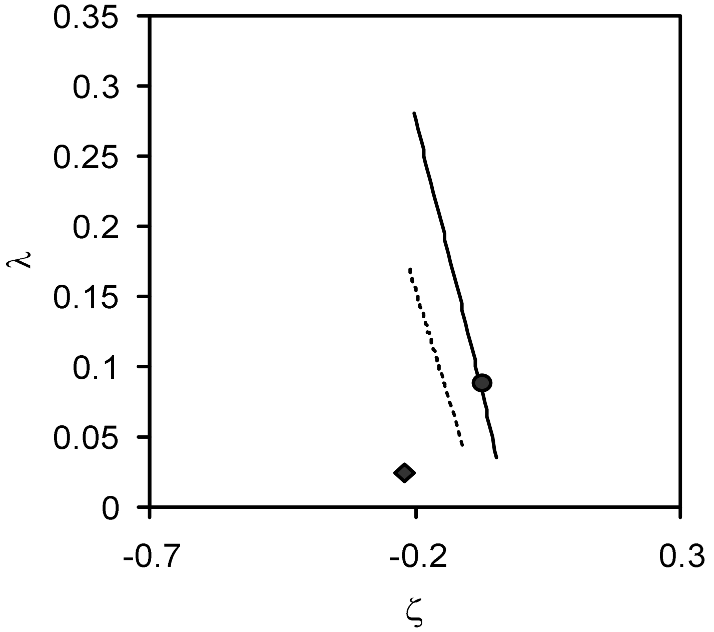


Figure 4: Part of the global phase diagram for CO_2/ethanol (bullet) and CO_2/acetone (diamond). The solid line is the tricritical line for the co-volume ratio of the CO_2/ethanol system. The dashed line is the tricritical line for the co-volume ratio of the CO_2/ acetone. The axes are defined as $l \propto -a_{12}$, which is related to the cross-attraction, and $V \propto a_{22} - a_{11}$ which is a reduced difference between the interaction parameters of the pure components.

Global Phase Diagram calculations

Figure 4 shows the location of the two CO_2/solvent systems in a global phase diagram. One can see that the CO_2/ethanol system is very close to the tricritical boundary which means that it can change its phase behaviour by small perturbations leading to a liquid-liquid immiscibility. The CO_2/acetone system, however, is in significant distance to the tricritical boundary. Therefore, it is unlikely that the addition of a solute will affect the type of phase behaviour and furthermore liquid-liquid immiscibility is not expected. Such systems are suitable for the GAS process.

CONCLUSIONS

The phase behaviour of a ternary gas-antisolvent system has been modelled based on the cubic Peng-Robinson equation of state supplemented by a Clapeyron-type approach for the solid phase. The results show that for certain systems a liquid-liquid phase split appears after adding a solid substance to the solvent-antisolvent system. For further analysis we calculated the tricritical boundary for each binary solvent system, which limits the appearance of the liquid-liquid phase split interfering with the solute precipitation. As a criterion for the suitability of a solvent-antisolvent system for the gas antisolvent process, the distance to the corresponding tricritical curve has been analysed. This criterion goes beyond a possible inspection of a pressure-mole fraction phase diagram and gives more reliable estimates of the solvent suitability for GAS. The closer a solvent-antisolvent system is located to a tricritical boundary the more likely the quasibinary system is moved across this boundary by adding the solute. In case of sufficient distance to the tricritical curve the addition of the solute less likely leads to a change in phase behaviour.

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