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Gas antisolvent crystallization of organic salts from aqueous solutions

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Abstract

The selection of process conditions for the crystallization of an organic salt for pharmaceutical applications is studied in the present work. The crystallization process is carried out using the gas anti-solvent (GAS) technique to obtain particles with specific size and size distribution. The application of this process to organic salt aqueous solutions requires the use of cosolvents to increase the solubility of the antisolvent gas in the aqueous phase. The solubility of lobenzarit has been measured in water, methanol and water + methanol mixtures. The low solubility of lobenzarit in organic solvents is taken into account in the selection of the process scheme. Favorable operating conditions are found on the basis of a group contribution with association equation of state coupled with a non-linear optimizer. The feasibility of the proposed scheme and operating conditions are confirmed by experimental studies in a high pressure crystallizer, using CO_2 as the antisolvent agent. The particles morphology is found to be strongly dependent on the feed capillary diameter.

Keywords: Supercritical fluids; Antisolvent; Crystallization; Aqueous mixtures; Lobenzarit; Solubility; Methanol

1. Introduction

Supercritical fluids have been proposed as agents to obtain solids with specific size and size distribution properties. One of the first techniques proposed for this purpose was the rapid expansion of supercritical solutions (RESS). A comprehensive review of this procedure has been presented by Tom and Debenedetti [1]. However this versatile technique for particle formation is limited by the low solubility of the solids in the supercritical fluids. This is the case in the present work, in which the solute to be crystallized is an organic salt. Another technique that has been proposed is the gas antisolvent crystallization process (GAS) [2]. This process is based on the supersaturation of a liquid solution, by the dissolution of a near critical or supercritical fluid. The dissolved gas creates an antisolvent effect, which results in the precipitation of the solid solute. A

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recent review of RESS and GAS is given by Knutson et al. [3]. This process offers the possibility of obtaining small crystals with an adequate size distribution for pharmaceutical applications [4]. In the present work, the selection of conditions for the crystallization by GAS of the lobenzarit salt is studied. Lobenzarit ($C_{14}H_8ClNNa_2O_4$, disodium -4-chloro -2,2′-iminodibenzoate)[1] is a powerful antiarthritic agent. This salt is moderately soluble in water, slightly soluble in methanol and almost insoluble in most organic solvents. The addition of a water soluble organic antisolvent is the usual way to precipitate the lobenzarit from a saturated aqueous solution. However the particles obtained are agglomerates of irregular shape, mainly square and it is difficult to control the particle average size and size distribution. The antisolvent gases considered in this study are CO_2 and ethane, and the initial feed is an aqueous solution of lobenzarit. The solubility of these gases in the lobenzarit aqueous solution is very small, even at high pressures. Therefore no antisolvent effect can be expected under these conditions. The application of the gas antisolvent process requires the proper selection of a cosolvent or cosolvent mixtures to achieve the desired gas antisolvent effect. Furthermore, the pressure, temperature and process scheme, to achieve a high loading of the organic salt in the feed and at the same time complete miscibility with the near critical fluid, should be investigated. Many pharmaceutical drugs are in the form of salts, with relatively high solubility in water and very low solubility in organic solvents. Therefore, the development of feasible conditions for the gas antisolvent crystallization process of these compounds is of considerable interest. The use of a non-polar antisolvent gas reduces the electrostatic forces between the particles and the particles and the solvent, decreasing the agglomeration effect and leading to the precipitation of single crystals of regular shape. The use of a cosolvent together with the gas antisolvent mixtures resembles the emulsion solvent diffusion (ESD) process proposed by Kawashima [5]. This process is based on generating an emulsion of the drug solution into a non-solvent liquid, where the solvent and the non-solvent are miscible. The ESD process has been proposed for crystallization of spherical particles of pharmaceutical drugs: an example of this application is given by Espitalier et al. [6].

Another important feature in the crystallization process is to avoid the separation of an aqueous phase in the crystallization vessel. This phenomena will reduce the recovery of the solute and damage the quality of the solid particles. Therefore, the solubility of water in the near critical phase should be controlled to keep the gas, the cosolvent and the water in a single phase. Three main properties that should be considered in the selection of process conditions and operating procedure are:

1. complete miscibility of the gas (antisolvent)-cosolvent-water mixture,
2. good solubility of water in the near critical phase, and
3. high solubility of lobenzarit in the feed.

2. Phase equilibria and process selection

The complete miscibility of CO_2 or ethane with water can be achieved by the use of a cosolvent. This cosolvent has to be completely miscible in both water and CO_2 (or ethane) in order to get operating conditions outside the heterogeneous region. In this way, the liquid-liquid or liquid-supercritical fluid diagram will be of type I, which exhibits a continous region of complete miscibility above the binodal curve (Fig. 1).

The operation of a gas antisolvent process crystallization can be carried out in two different ways, when operating in a semi-batch mode:

1. The cosolvent is added to the lobenzarit aqueous solution. Afterwards, this solution is fed to the crystallization vessel already charged with the near critical or supercritical gas.
2. The lobenzarit aqueous solution is fed directly to the crystallizer, already charged with a mixture of the cosolvent and the near critical gas.

The selection of the more convenient operating condition depends strongly on the effect of the cosolvent over the solubility of the organic salt in

[1] Register number supplied by author: C14H8ClNNa204, 64808-48-6.

the water-cosolvent mixture. Therefore, this problem is studied first.

2.1. Solubility of lobenzarit in water, organic solvents and aqueous-organic solutions

Lobenzarit is moderately soluble in water (40 mg/cc at pH 7), slightly soluble in methanol (0.58 mg/cc) and with even lower solubility in ethanol, acetone, diethyl ether and chloroform at room temperature. Experimental values of solubilities of lobenzarit in water, methanol and in water + methanol mixtures were obtained at different temperatures. The crystallizers used in the solubility studies were 30-cc flasks with stirrer and a reflux condenser, to avoid losses of the liquid solvent. The temperature was controlled within ± 0.1°C. The salt was added to the liquid phase until no further dissolution was achieved. Then, the solution was stirred during 2 or 3 days and after stirring was stopped, the clear solution was sampled with a Hamilton syringe and filtered through a Millipore membrane of 0.45-μm pore diameter. The concentration of lobenzarit in the saturated liquid phase was measured by UV spectrophotometry.

The solubilities of lobenzarit in water and in methanol as a function of temperature are shown in Fig. 2 and Table 1. The temperature range is typical for crystallization conditions and the maximum temperature is limited by the boiling point of methanol (337.7 K). The solubility of lobenzarit in water increases with temperature, but remains constant in methanol. The solubility in methanol, the second best solvent for lobenzarit, is almost 50 times smaller than in water. This result points to the need for looking for water-cosolvent mixtures that will offer greater lobenzarit solubility, and at the same time good solubility of the near critical or supercritical gas. The solubility

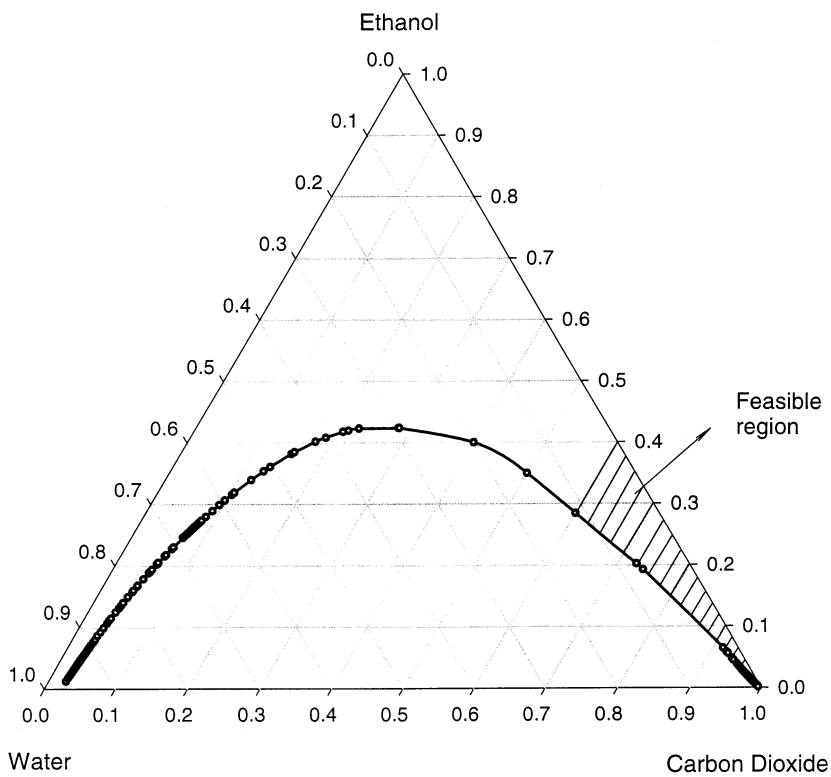

Fig. 1. The feasible region for gas antisolvent crystallization (GCA-EOS prediction of the binodal curve for water-CO_2-ethanol at 298 K and 90 bar).

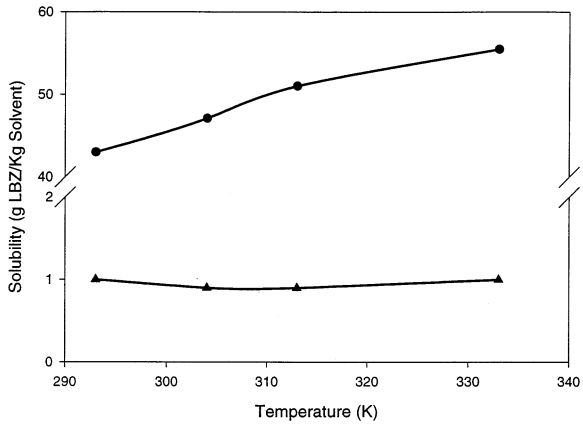

Fig. 2. Solubilities of lobenzarit disodium in water (■) and methanol (▲).

Table 1
Solubilities of lobenzarit disodium in water and methanol

Temperature (K)	Solvent: water	Solvent: methanol
	$W^*_{LBZ}\left(\frac{\text{g of LBZ}}{\text{kg of water}}\right)$	$W^*_{LBZ}\left(\frac{\text{g of LBZ}}{\text{kg of MeOH}}\right)$
293	43	1.1
304	47.13	0.9
313	51.04	0.9
333	55.51	1.1

of the ternary mixture water-methanol-lobenzarit disodium was investigated at two temperatures: 293 and 333 K. The data are shown in Table 2 and Fig. 3. The results indicate a significant decrease of solubility with alcohol concentration. For instance, at a concentration of methanol of 90% in weight, required to achieve complete miscibility with CO_2, the solubility of lobenzarit is ten times lower than in water, at the same temperature.

2.2. Selection of process conditions for gas antisolvent crystallization

The amount of water introduced into the crystallizer per unit mass of precipitated salt is a key property for the process capacity. The results of the solubilities of lobenzarit in water-alcohol mixtures indicate that the mass ratio of water/lobenzarit varies with the alcohol concentration. There is a maximum ratio of 30:1 when the alcohol concentration is ~87.7%, and 24 and 18 for zero alcohol concentration at 298 and 333 K, respectively. The amount of gas antisolvent mixture required per unit of mass of precipitated salt is directly proportional to this ratio. This is due to the fact that the amount of water determines the quantity of gas antisolvent mixture required, to avoid the formation of an aqueous phase in the crystallizer. The selection of cosolvent and operating conditions can be studied over a wide range of

Table 2
Solubilities of lobenzarit disodium in methanol-water mixtures

$\left(\frac{\text{Ra g water}}{\text{g water+g MeOH}}\right)$	C^* solubility of LBZ $\left(\frac{\text{g of LBZ}}{\text{kg water+kg MeOH}}\right)$	
	$T=293$ K	$T=333$ K
0	1.1	1.1
0.0623	2.6	–
0.12303	4.1	6.1
0.23992	8.1	9.5
0.35112	9.9	14.3
0.558	14	26
0.6544	17	38
0.8347	25	42
0.9191	32	54
1	43	55.51

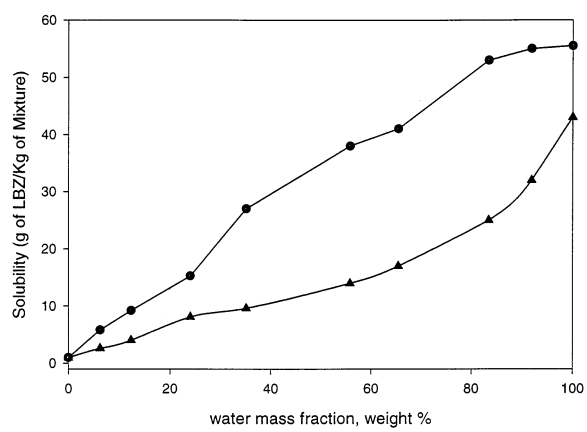

Fig. 3. Solubilities of lobenzarit disodium in methanol + water mixtures: ▲, 293 K; ●, 323 K.

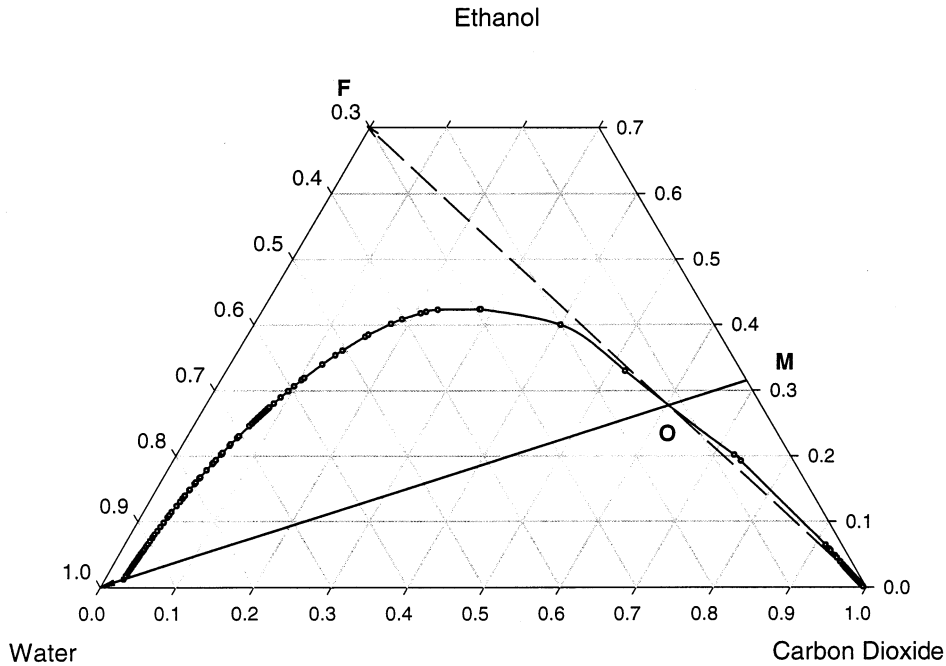

Fig. 4. Schemes of operation of the gas-antisolvent crystallization process.

temperatures, pressures and compositions, with the help of a suitable thermodynamic model for predictions of phase equilibria in mixtures of alcohol-water-CO_2. The GC-EOS model was proposed by Skjold-Jorgensen [7] to study gas solubilities in non-ideal mixtures at high pressures, and was applied for the prediction and correlation of solubilities of solvents in supercritical fluids by Brignole et al. [8]. However, the original model takes into account only repulsive and dispersive interactions. Gros et al. [9] have extended the capability of this model to treat associating mixtures (GCA-EOS). With the help of the GCA-EOS model, the binodal curves of different water-alcohol-near critical fluid (CO_2 or ethane) mixtures were investigated, at different pressures and temperatures. The criteria to determine the optimum operating conditions is based on the maximum solubility of water in the crystallizer under the process conditions. The maximization procedure is carried out subject to the following constraints:

1. the process conditions should be outside the heterogeneous region, limited by the binodal curve;
2. the concentration of the near critical fluid in molar fraction is chosen to be greater than 60% in molar fraction, to ensure a strong gas antisolvent effect and to avoid agglomeration of the crystals obtained.

The computations are based on the assumption that the presence of the salt will not change the phase equilibria conditions of the ternary water + alcohol + near critical fluid mixture, because its solubility is extremely low in the near critical fluid phase.

Fig. 4 shows two possible schemes of operation:

1. The cosolvent is added to the lobenzarit aqueous solution.
2. The cosolvent is added to the near critical gas in the crystallizer.

In case a) the cosolvent + water + lobenzarit mixture is fed to the crystallizer already charged with CO_2. This process is indicated in Fig. 4 by the operating line that starts at the pure CO_2 corner and is directed towards point F, that corresponds to the water-cosolvent (ethanol) feed mixture on the alcohol-water side of the diagram. The change in conditions, during the feed addition to

the crystallizer is given by the segment that links the CO_2 corner with point O. In this case it is clearly seen from Fig. 4 that the conditions inside the vessel are in the two phase region, with the separation of an aqueous phase. In case b) the operation starts with the crystallizer filled up with a given cosolvent + CO_2 mixture (point M) and the operating line starts at point M and is directed towards the pure water corner during the process of addition of the aqueous solution of lobenzarit. The feasible operation line is given by the MO segment. Point O is on the intersection of this operating line with the binodal curve, at which the mixture in the vessel becomes saturated with water. Therefore if the operation goes beyond this point an aqueous phase again will appear in the crystallizer.

For the crystallization process carried out as described (semi-batch mode), we have seen that different compositional paths are followed by the fluid inside the crystallizer, depending of the scheme of operation. During the crystallization process it is required that the compositional path does not cross the heterogeneous region. This is clearly the situation for case b) because the initial charge to the crystallizer is a mixture of alcohol with CO_2 or ethane. In this case the addition of feed moves the mixture initial conditions, from point M towards the binodal curve. The final operating point should be chosen close to the binodal curve. If the vessel is charged initially with pure CO_2 (case a), the mixture conditions in the crystallizer move away from the pure CO_2 corner. In this case the heterogeneous region is crossed, even though the final condition is again in the complete miscibility region, just outside the binodal curve. Therefore, scheme b) is preferred. Another advantage of this type of operation is that the selection of the cosolvent is independent of the solvent power of the cosolvent for the organic salt, because the feed is a salt aqueous solution. The selection of the cosolvent is therefore solely based on its properties to give complete miscibility of the gas-water-cosolvent mixture and on the magnitude of the solubility of water in this mixture. Ethanol, 2-propanol, acetone and methanol have been investigated as cosolvents in the present work.

The optimization of operating conditions (maximum water solubility criteria) as a function of mixture composition and temperature, for different gas-cosolvent combinations was obtained with a non-linear programming optimization code [10]. The operating pressure, in all cases, was well above the critical pressure of CO_2 or ethane. In this way, the appearance of three phase formation is avoided. This phenomena has been reported, in aqueous mixtures of these cosolvents with CO_2 or ethane in the vicinity of the critical point. For a recent discussion on this subject the reader is referred to Ref. [11]. Suitable process conditions are reported in Table 3. The results from Table 3 indicate that CO_2 is better than ethane as an antisolvent gas. The hydrophobic effect of ethane reduces the amount of water in the organic phase. The three alcohols studied as cosolvents have similar properties, with regard to the amount of water concentration at saturation.

Table 3
Optimum conditions for different cosolvent-gas combinations

Antisolvent, X1	Solvent, X2	Cosolvent, X3	Temperature (K)	*P* (bar)	X1 (molar)	X2 (molar)	X3 (molar)
CO_2	Water	Methanol	322.6	170	60	13.39	26.61
CO_2	Water	Ethanol	333.12	170	60	15.3	24.7
CO_2	Water	2-Propanol	353.0	170	60	16.95	23.05
CO_2[a]	Water	Acetone	283.0	170	60	9.2	30.8
Ethane[a]	Water	Methanol	353.0	170	92.13	2.44	5.43
Ethane[a]	Water	Ethanol	301.13	170	80.44	1.00	18.56
Ethane[a]	Water	2 Propanol	353.0	170	60.0	2.61	37.43
Ethane[a]	Water	Acetone	353.0	170	73.31	2.16	24.53

[a] Predictions using the GC-EOS model [7].

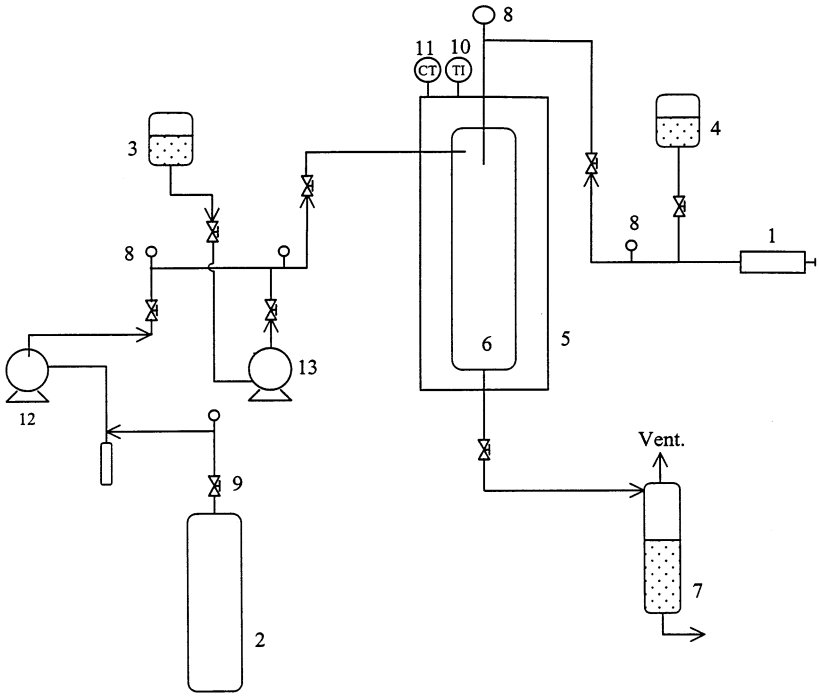

Fig. 5. Gas-antisolvent crystallization apparatus: 1, pressure generator; 2, gas cylinder; 3, alcohol vessel; 4, aqueous solution vessel; 5, thermometer; 6, filter; 7, depressurizing tank; 8, manometers; 9, valves; 10, thermometer; 11, temperature controller; 12, high pressure compressor; 13, high pressure pump.

2.3. GAS crystallization experiments

The crystallization experiments using CO_2 + cosolvent mixtures were designed on the basis of the results of Table 3. Mixtures of 2-propanol and ethanol with CO_2 were selected for the preliminary crystallization studies. These experiments were carried out at sub- and supercritical temperatures. The crystallization apparatus is similar to that described by Schmitt and Reid [12]. The crystallizer is a 2.54-cm inside diameter, stainless steel vertical tube, 30.5 cm long. High pressure CO_2 is supplied to the crystallizer by means of a diaphragm compressor. The actual system pressure in the autoclave is controlled by a hand pressure generator. The pressure is measured with a Bourdon type Heise digital manometer, with a range of 0–400 bar. The crystallizer is surrounded by a 20-mm thick aluminum jacket, externally heated by electrical resistances connected to a temperature controller. The temperature range covered was from 278 to 333 K. At temperatures below ambient the cell is placed within an air box maintained at 268 K. The temperature is measured with copper constantan thermocouples connected to a digital indicator. The cell serves as mixing, precipitation and filtration chamber. The experimental set-up is shown in Fig. 5. A double head high pressure metering pump (Eldex model 460) is used to inject the organic cosolvent and a pressure generator is used to feed the lobenzarit aqueous solution. The lobenzarit aqueous feed concentration was kept at 33 mg/cm^3 in all the experiments. This solution was filtered through a 0.45-μm membrane. The experimental procedure is similar to that reported by Winters et al. [13], for protein crystallization. A collection plate was specially constructed to recover the solid precipitated in the column. The bottom of the cell is a removable 0.45-μm Millipore membrane that separates the solid product from the CO_2 + cosolvent + water mixture. After a crystallization run

the filtrate (CO_2 + cosolvent + water) is removed from the bottom of the autoclave. Before each experimental run the crystallizer was purged with CO_2 to remove any presence of air. The cystallizer was then pressurized at the operating pressure with CO_2. Two different capillary diameters were used to carry out experimental crystallization studies (0.6- and 0.1-mm internal diameter). The morphology, size and size distribution of the crystals was determined using a JEOL 100 CX electron transmission microscope and a JEOL 35 CF scanning electron microscope (SEM).

3. Crystallization results

3.1. Effect of temperature at constant pressure

The results at three temperatures, using a mixture of CO_2 with ethanol as a cosolvent, are reported in Table 4. The phase composition reported is that at the end of the crystallization process. The experimental results show that better crystallization results were obtained working at subcritical temperatures. This may be due to a decrease in water solubility in the CO_2 phase at near critical temperatures, giving rise to the segregation of an aqueous phase at the experimental conditions studied. The effect of capillary diameter is shown for experiments using 2-propanol as a cosolvent in Table 5. Even though the particle size decreases with capillary diameter, the morphology of the particles is completely different. The particles obtained with the smaller capillary diameter are made of a conglomerate of nanocrystals, that seems to originate from a single very small drop. With the 0.6-mm capillary diameter the crystals were obtained as individual needles without the presence of agglomeration. Figs. 6 and 7a,b show, characteristics of the original lobenzarit crystals obtained by addition of ethanol to a saturated aqueous solution of lobenzarit, and the results of the gas antisolvent recrystallization process, using a mixture of CO_2 and ethanol working with different capillary diameters. The crystal morphology indicates a predominance of a nucleation mechanism, due to high supersaturation of the droplets, followed by agglomeration for the 0.1-mm internal diameter capillary tube. This capillary tube produced a fine mist of droplets. The results of experiments working with the larger capillary tube diameter, sug-

Table 4
Effect of temperature at constant pressure for the crystallization of lobenzarit disodium from an aqueous solutions using CO_2 with ethanol as cosolvent[a]

T (K)	P (Bar)	ρ (CO_2) (g/ml)	X (CO_2) (molar)	X (EtOH) (molar)	X (H_2O) (molar)	Particle size (μm)	Yield, %
283	120	0.93688	80	14.52	5.48	0.24 ± 0.14	75 ± 5
298	120	0.84726	64.7	25	10.3	0.21 ± 0.14	97 ± 3
303	120	0.80312	60	29.6	10.4	0.63 ± 0.29	10 ± 4
323	120	0.58548	60	26.4	13	NF	NF

[a] NF, not feasible.

Table 5
Effect of capillary diameter on the crystallization of lobenzarit di sodium from aqueous solutions using CO_2 with isopropanol alcohol (IPA) as cosolvent

T (K)	P (bar)	ρ (CO_2) (g/ml)	Capillary diameter (mm)	X (CO_2) (molar)	X (IPA) (molar)	X (H_2O) (molar)	Particle size (μm)	Yield, %
298	80	0.84623	0.1	60	32.52	7.51	1.8 ± 0.5	82 ± 5
298	80	0.84623	0.6	60	32.52	7.51	0.31 ± 0.17	75 ± 5

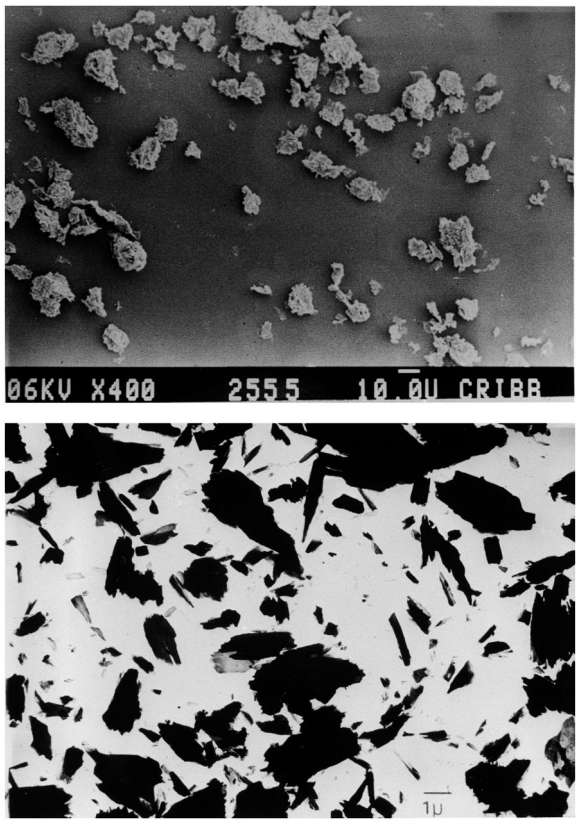

Fig. 6. Original crystals of lobenzarit.

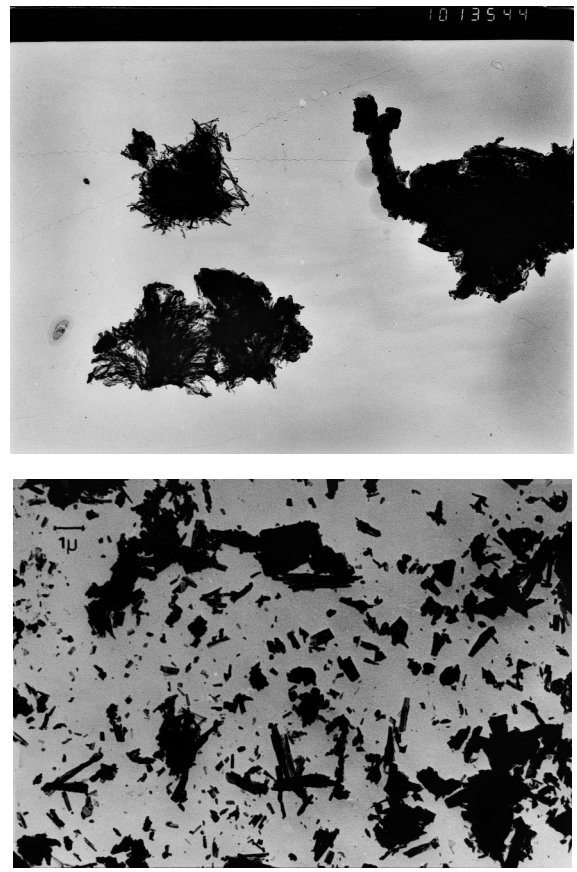

Fig. 7. (a) Crystals obtained by gas-antisolvent crystallization: capillary diameter 0.1 mm. (b) Crystals obtained by gas-antisolvent crystallization: capillary diameter 0.6 mm.

gest the predominance of condensation mechanism, indicating in this case that the supersaturation was controlled by the diffusion of the gas antisolvent mixture into the aqueous drops. This is a likely explanation of the differences in morphology because with the larger capillary size, small individual droplets, instead of a mist, were discharged from the capillary tube. These results show the advantage of the gas antisolvent technique in controlling the degree of supersaturation and the morphology of the particles. The precipitation of the crystals from a rich CO_2 solution is facilitated by the solution low viscosity. Another advantage of the GAS crystallization process is the ready removal of the solvents from the precipitate by pressure reduction.

4. Conclusions

The solubility of lobenzarit in organic cosolvents and in cosolvent + water mixtures is very low if complete miscibility of the feed with the gas antisolvent is desired. A process scheme where the water solution is added directly to the gas antisolvent-cosolvent mixture is shown to be the best operating scheme for a semi-batch crystallizer.

The optimization of the process conditions is based on the maximum solubility of water at saturation in the ternary water + gas-antisolvent + cosolvent mixture. Experimental studies confirmed the feasibility of the proposed scheme and process conditions. It is shown that the size distribution and morphology can be controlled using different capillary diameters. In this way it

is possible to obtain individual crystals without agglomeration.

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