SUPERCRITICAL ANTI SOLVENT MICRONIZATION OF MANDELIC ACID: MATHEMATICAL MODELING AND SCALE-UP

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The micronization of mandelic acid from ethyl acetate solutions has been performed in a semicontinuous Supercritical Anti Solvent (SAS) pilot plant. The effect of the main operating parameters (pressure, temperature, flowrate, nozzle and vessel design) on the particle size and the yield of the precipitation has been analyzed. The results have been interpreted with the aid of a detailed mathematical model of the process. This model takes the main physical phenomena involved in this process into account, including jet hydrodynamics, mass transfer, phase equilibrium, as well as nucleation and crystal growth kinetics. For the application of this model, a detailed knowledge of the phase equilibrium of the system is required. For this reason, the solubility of mandelic acid in mixtures of SC-CO_2 and ethyl acetate has been measured using a variable volume visual cell. The mathematical model has also been used to study the scale-up of the process.

INTRODUCTION

The production of micron and sub-micron particles using a supercritical fluid as anti solvent has been extensively studied in the last years, with applications as pharmaceuticals, natural substances, explosives or food additives [1]. One of the main challenges in the development and optimization of a Supercritical Anti Solvent (SAS) process is the simultaneous influence of the operating parameters on different process steps, such as the hydrodynamics, mass transfer and particle formation and growth. This makes difficult to relate changes in the process conditions with changes in product characteristics, or to predict the effect of a certain variation in the operating parameters. Likewise, when a SAS process is scaled-up, it is difficult to predict the effects of the variations in the process design in its performance, and particularly in its hydrodynamic and mass transfer behavior.

In a previous work [2], a mathematical model of the SAS process was developed. This model considers the main steps of the SAS process, including the fluid mechanics, the mass transfer, and the kinetics of particle nucleation and growth. One of the main applications of this model is the possibility to gain an insight into the interactions between the process steps, and the way in which a variation in the operating conditions affect each of them. The combination of this knowledge with an experimental study of the process can provide the basis for a rational optimization and scale-up of the process.

In this work, this approach has been applied to the development, optimization and scale-up of the Supercritical Anti Solvent precipitation of mandelic acid, a hydrocarboxylic acid with several applications in the pharmaceutical and cosmetic industries [3]. With this objective, the effect of the operating parameters on product characteristics, including particle size and morphology, and precipitation yield, has been studied experimentally and analyzed with the aid of the mathematical model. This information has been used to select the optimum operating parameters for this process. Finally, the scale-up of the process has been studied with the aid of the model, and the proposed scaled-up design has been tested experimentally.

MATERIALS AND METHODS

DL-Mandelic acid with a minimum purity of 99% was purchased from Fluka. Ethyl Acetate with a minimum purity of 99.5% was purchased from Panreac Química (Spain).CO_2 at 99,95% was delivered by Carburos Metálicos S.A. (Spain).

A schematic diagram of the pilot plant used for the semicontinuos SAS process is presented in Figure 1. The equipment used are two diaphragm pumps (Dosapro, Spain), one for the CO_2 (L - 210), and the other for the solution (L - 230); an isolated and jacketed AISI 316 stainless steel precipitator (H – 110) with 1.5 L volume and with a porous metallic frit at the exit; an external stainless steel filter (H - 310) from Headline Filters (UK), which has a screen size of 1 μm; two back pressure regulator valves (K300 A/B) placed in parallel for safety reasons; and a separation flask (H - 320) to achieve the separation of solvent and CO_2 after pressure release. Other elements are the heat exchangers required to cool CO_2 before pumping it (E-220) and for achieving the operating conditions (E-120), safety devices (safety valve and rupture disc), and instrumentation. A Pt - 100 thermoresistance with an accuracy of ±0,1 K is placed inside the precipitation vessel. The inlet temperatures of SC - CO_2 and solution are also measured. For the pressure a DESIN TPR - 10 digital pressure meter (DESIN Instruments, Spain), with an accuracy of ±0,05 MPa, is used. The CO_2 mass flow is controlled with a coriolis flow meter (Sensor MICRO Motion Elite CMF010 NB, Transmitter MICRO Motion Elite RFT91), with an accuracy ±0,01 Kg/h. The solution flowrate is determined by the decrease of feed volume with time.

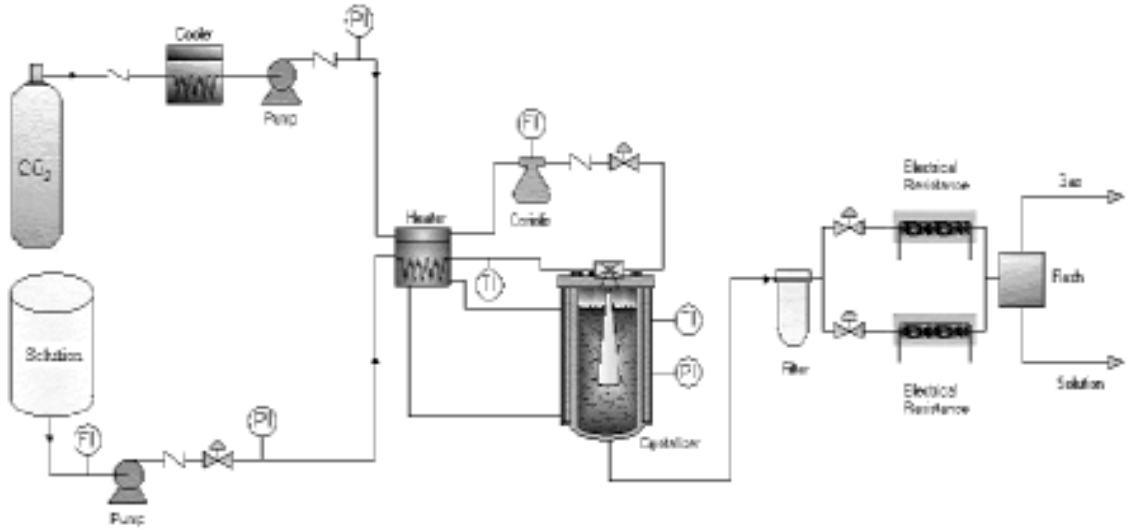

Figure 1: Schematic diagram of the SAS pilot plant

A standard experiment is as follows: the experiment starts by pumping pure CO_2 into the precipitator. When the desired operating conditions (temperature, pressure and flow rate) are achieved and remain stable, the solution is fed to the precipitator. When the desired amount of solution has been injected (aprox. 400 mL), the liquid pump is stopped and only pure CO_2 is pumped. The flow of CO_2 is maintained during a period long enough for the complete removal of solvent from the precipitator. The minimum amount of CO_2 required for this step was determined experimentally, and an amount of 1 kg (roughly equivalent to 1.5 times the volume of the precipitator) was used in the experiments. After the decompression, a sample of the particles retained in the frit is collected analysis. Samples of the feed and the liquid effluent collected after the depressurization step, are also taken for analysis.

Pictures of the particles collected were taken by means of a Nikon OPTIPHOT-2 optic microscope. The mean particle size was measured with the ZEISS image analysis software. As all the particles obtained in this work have needle-like morphology, the values of particle size presented correspond to the length of the needles. For the determination of the yield of the precipitation, the amount of mandelic acid precipitated is calculated as the difference between the amount of mandelic acid in the feed, and the amount collected in the liquid effluent.

RESULTS AND DISCUSSION

Several series of experiments with variations in different operating parameters, including pressure, temperature, initial concentration, and flowrates, have been carried out. The objective of these experiments is to study the effect of these parameters on particle size and precipitation yield. The effect of other parameters relevant for the scale-up of the process, such as the design of the nozzle, the residence time in the precipitator and the drying time, has also been studied.

Influence of the operating parameters

Several experiments with different operating pressure, temperature, initial concentration and flowrates have been performed in order to study the effect of these parameters on product characteristics. A summary of all the experiments is presented in Table 1. Figure 2 shows pictures of the particles collected in some of the experiments, obtained with the optic microscope. It can be seen that in most experiments, needle-like particles with crystalline structure have been obtained.

Table 1: Analysis of the effect of the operating parameters, experiments performed

Experiment	P (MPa)	T (K)	c_0 (g/L)	F_{CO2} (kg/h)	F_{SOL} (kg/h)	d_{50} (µm)	Y (wt%)
1	9	323	40	2	0.3	115	59
2	9	323	40	2	0.3	130	61
3	9	308	40	2	0.3	210	51
4	9	313	40	2	0.3	157	48
5	9	333	40	2	0.3	45	65
6	8	308	40	2	0.3	80	59
7	10	308	40	2	0.3	210	71
8	11	308	40	2	0.3	190	77
9	9	323	30	2	0.3	100	37
10	9	323	50	2	0.3	145	68
11	9	323	75	2	0.3	140	81
12	9	323	40	1	0.3	160	65
13	9	323	40	2.5	0.3	150	38
14	9	323	40	3	0.3	125	21
15	9	323	40	2.5	0.4	110	65
16	9	323	40	1.5	0.25	140	68

The analysis of the experimental results allows to identify the following trends of variation with the operating conditions:

-Intial concentration (Experiments 1, 9-11): an increase in the concentration causes a slight increase in the particle size, and a large increase in the precipitation yield,

-Temperature (Experiments 1-5): When temperature is increased, a systematic decrease in particle size) and an increase in the precipitation yield are observed.

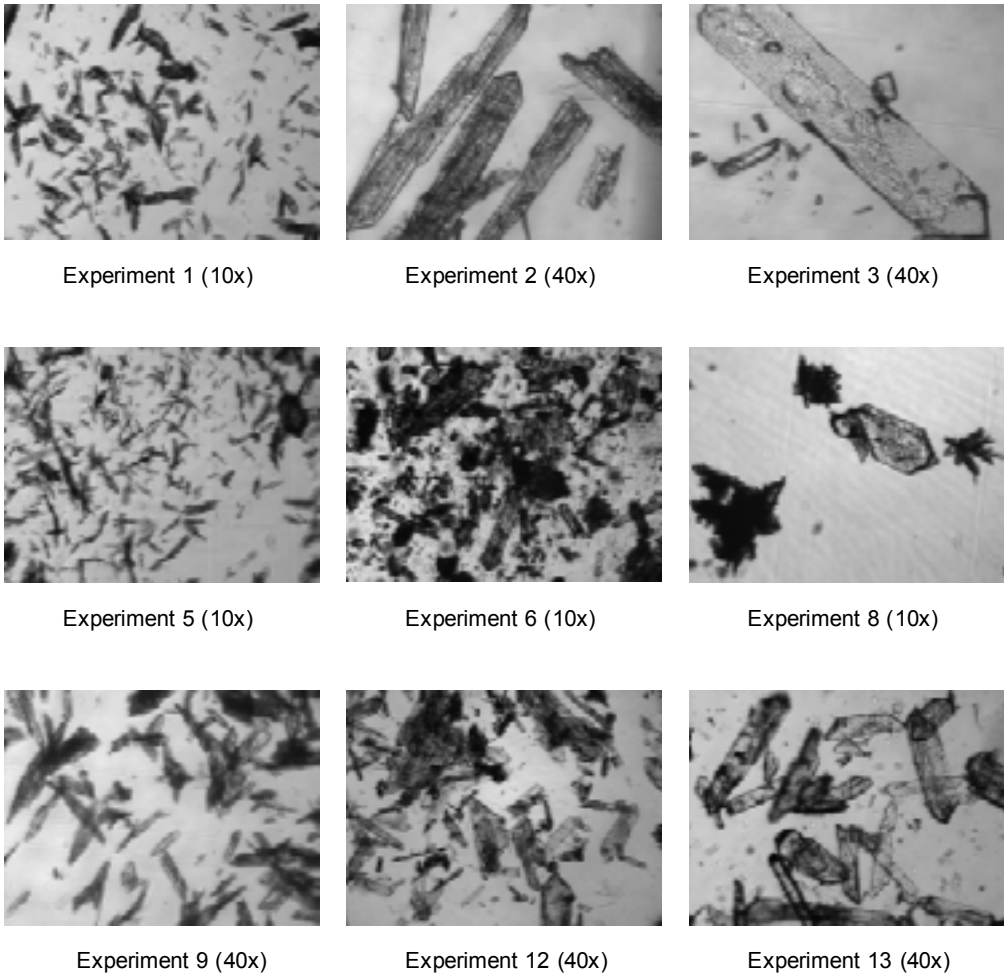

Figure 2: Pictures of the particles collected in some of the experiments of Table 1

-Pressure (Experiments 1 , 6-8): Two different trends can be observed in this figure: in the pressure range 9 – 11 MPa, particle size shows almost no variations with pressure, while the yield increases with pressure from 51% at 9 MPa to 77% at 11 MPa. However, when pressure is decreased from 9 MPa to 8 MPa, a decrease in particle size and an increase in the precipitation yield is observed.
-CO_2/solution flow ratio (Experiments 1, 12-14): there is not a clear trend of variation of particle size with the flowrate. With higher CO_2 flowrates, a large decrease in the precipitation yield is observed.
-CO_2 and solution flowrates (Experiments 1, 15-16): When the flowrates are increased, the mean particle size decreases slightly, while the precipitation yield remains approximately constant

Influence of other parameters
The effect of other parameters such as the drying time, the design of the nozzle, and the residence time in the precipitator, has been studied. The optimization of these parameters is of interest for the scale-up of the process.
- Amount of CO_2 requiered for drying: A minimum amount of CO_2 equal to1.1 – 1.2 times the capacity of the precipitator is required for the complete removal of the organic solvent

prior to the depressurization. This result indicates that the low model in the precipitator during the drying is similar to plug flow.
- Residence time: The residence time in the precipitator has been varied by placing the filter at different heights. A reduction in the volume of the precipitator from 1.5 L to 0.7 L did not cause a significant variation in the results, indicating that the precipitator is oversized.
- Mixer design: Different nozzles for the mixing of CO_2 and solution were tested. It was found that when the CO_2 and the solution are introduced in the precipitator through different connections instead of with a mixing nozzle, an increase in particle size is observed, thus indicating that a poor design of the nozzle can cause a bad performance of the process.

Modeling
The mathematical model presented in [2] has been applied to the precipitation of mandelic acid. This requires knowledge of the phase behavior of the ternary system CO_2 – ethyl acetate – mandelic acid. For this reason, the solubility of mandelic acid in CO_2, and in mixtures of CO_2 and ethyl acetate with different concentrations of organic solvent, has been measured with a variable volume view cell according to the synthetic method. The measurements in pure CO_2 agree well with literature data [4] (Figure 3), while the measurements in mixtures of CO_2 and ethyl acetate are new data.

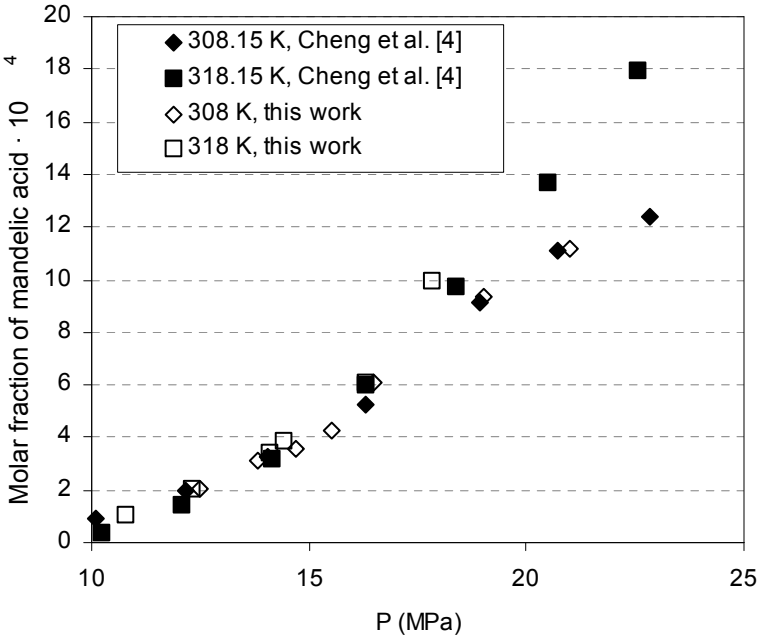

Figure 3: Solubility of mandelic acid in SC-CO_2, literature data [4] and results from this work.

The mathematical model allows to study different parameters of the process, such as the fluid velocities, solvent and solute concentrations, supersaturation, or particle formation and growth rate. For example, Figure 4 presents the density and the supersaturation profiles for the conditions of Experiment 8. For these conditions, the model predicts a mean particle size of 15 μm, although it must be considered that the model can only yield approximate values of particle size, and with spherical morphology instead of the needle-like shape found in the experiments.

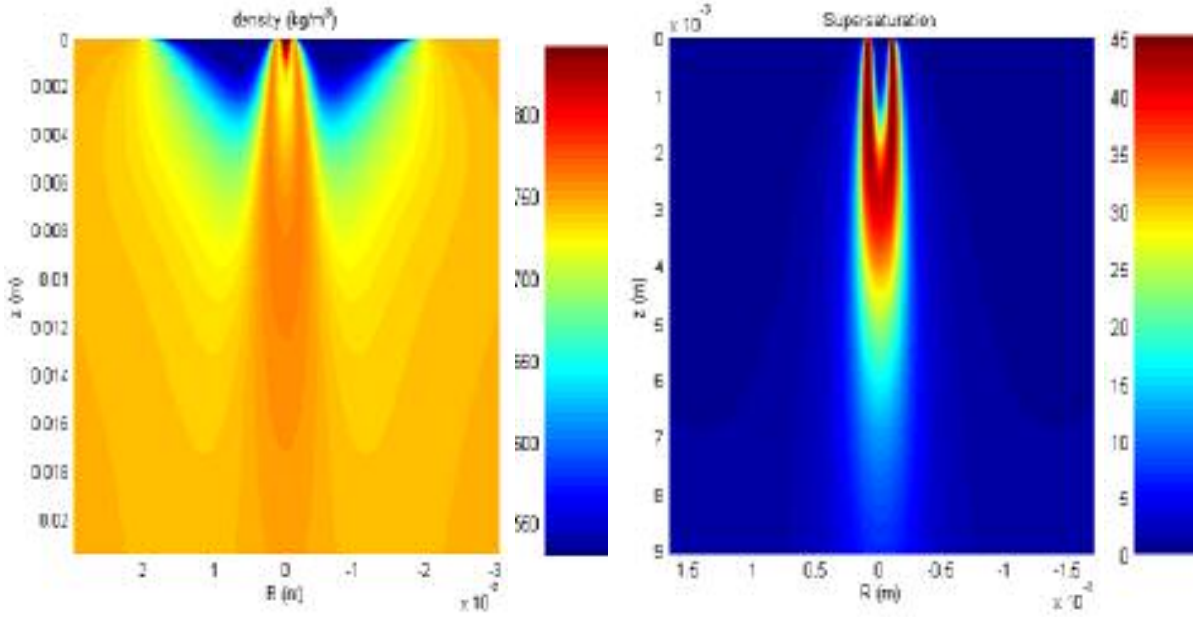

Figure 4: Density and supersaturation profiles, model results

Optimization and Scale-up

The analysis of the process has led to the selection of the following optimum operating conditions: 333 K, 9 MPa, initial concentration of mandelic acid in the ethyl acetate solution of 90 g/L, and CO_2/solution flow ratio of 6 kg/kg.

For the study of the scale-up of the process, a five-fold increase in the flowrates has been tested. This scale-up has allowed the processing of 0.3 kg of mandelic acid, with similar results as in the lower scale experiments.

CONCLUSIONS

A detailed study of the precipitation of mandelic acid with the Supercritical Anti Solvent (SAS) process has been performed. The influence of different operating parameters, including temperature, pressure, initial concentration and flowrates, has been studied. Other parameters of relevance for the scale-up of the process, such as the drying time, the precipitator volume and the nozzle design, have been studied. A detailed mathematical model has also been used to study the process, For the application of this model, the phase equilibrium in the ternary system CO_2 – ethyl acetate - mandelic acid has been measured with the synthetic method. The study of the process has led to the selection of the optimum operating conditions. A five-fold scale-up of the process has been experimentally tested.

ACKNOWLEDGMENTS

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