FORMATION OF FINE PARTICLES - A COMPARISON OF PCA AND RESS PROCESS

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In this contribution an experimental and theoretical comparison between the RESS and PCA process will be given. The differences of both processes regarding the level of supersaturation and the supersaturation creating rate were shown so that the large differences in particle size can be explained. Experiments with cholesterol were carried out and it was found that the mean size of the RESS processed particles was more than 10 times smaller than the size of the PCA processed particles. On the other hand the production rate was up to 100 times higher using the PCA process.

1. INTRODUCTION

Many product properties that are relevant in the industrial use can be adjusted by changing the particle size and particle size distribution of the powder. This statement is valid in several fields ranging from polymers to pharmaceutical and inorganic powders.
Generally, micronization is mostly carried out in industrial production by two commonly used techniques: recrystallization from solution and comminution. However, these two methods have some drawbacks such as wide particle size distribution, high thermal and mechanical stress, and environmental pollution problems associated with the use of large amounts of organic solvents.
Therefore it is desirable to explore alternative methods, which at least partially overcome those problems. As an alternative to the traditional techniques, various supercritical fluid based precipitation processes have recently been proposed [1]. The characteristics of compressed gases allow to vary the morphology of solid particles in a wide range. Two different processes are the RESS (Rapid Expansion of Supercritical Solutions) and PCA (Precipitation with a Compressed Fluid Antisolvent) technique which complement one another and have their analogous in the spray and salting-out crystallization, respectively.
In the RESS process, the substance to micronize is dissolved in the supercritical fluid and precipitated by depressurization of this solution through a nozzle. In the PCA process, the solute is first dissolved in a liquid organic solvent, and this solution is sprayed into a supercritical antisolvent which has a low affinity for the solute and a high affinity for the solvent.
Nevertheless, it is interesting to process a substance with both processes and to compare the results.

2. MATERIALS AND APPARATUS

Carbon dioxide was used as the supercritical fluid in the RESS process as well as in the PCA process. It was purchased from Linde (99.9 % purity). Acetone and toluene (Fluka, 99.5 % purity) were used as solvents for cholesterol (Merck, purity: 98 %). All three solvents were completely miscible with the CO_2 at all process conditions.
The experimental work was carried out in a high pressure pilot plant made by Sitec (Switzerland) that was described elsewhere in detail [2, 3].

3. RESULTS

3.1 The RESS process

Cholesterol as a model substance for pharmaceuticals was micronized in the Fraunhofer ICT using the RESS process. The raw material ($x_{50,3}$ = 20 µm) was put in the extractor and treated by supercritical carbon dioxide at different extraction conditions. The extraction pressure p_{Extr} varied in these experiments between 15 MPa and 30 MPa, the extraction temperature ϑ_{Extr} was between 35 °C und 70 °C. The temperature before the nozzle ϑ_0 was held constant at 100 °C, the pre-expansion pressure p_0 was the same as the extraction pressure.

In Figure 1 the median value of the volume distribution of the system cholesterol/carbon dioxide is shown as a function of extraction pressure. The extraction temperature was constant at 45 °C and the expansion of the solution was achieved by discharging through a nozzle (Laval nozzle with a minimum diameter of 100 µm) into an expansion chamber, which was held at ambient conditions (0.1 MPa, 25 °C).

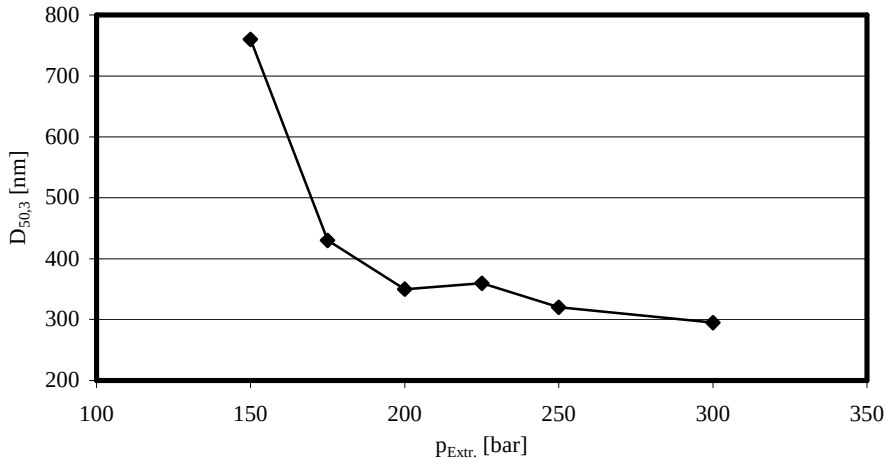

Fig. 1: Mean diameter of micronized cholesterol at different extraction pressures ($\vartheta_{Extr.}$ = 45 °C, ϑ_N = 100 °C, D_N = 100 µm)

From the figure it is seen that particles in the submicron range can be processed by the RESS process. An increase of the extraction pressure results in a decreasing particle size. The pressure has an influence on the solubility of cholesterol in CO_2 as well as on the mass flow rate of CO_2 through the nozzle. Both is increased if pressure is enlarged. If the solubility increases the concentration of cholesterol in the supercritical solution before the nozzle is higher and a higher supersaturation is achieved during the expansion which results in a higher nucleation rate and therefore smaller particles are produced. The higher mass flow rate leads to a dilution in the spray jet behind the nozzle so that the particle number density decreases and coagulation processes are reduced and the mean particle size decreases. This dilution effect can also be obtained if nitrogen is mixed into the jet [4].

The influence of the extraction temperature and of the nozzle diameter is presented in Figure 2. The nozzle temperature was constant at 100 °C and the extraction pressure was 20 MPa. Two different Laval nozzles with an inner diameter of 100 µm and 150 µm were used, respectively.

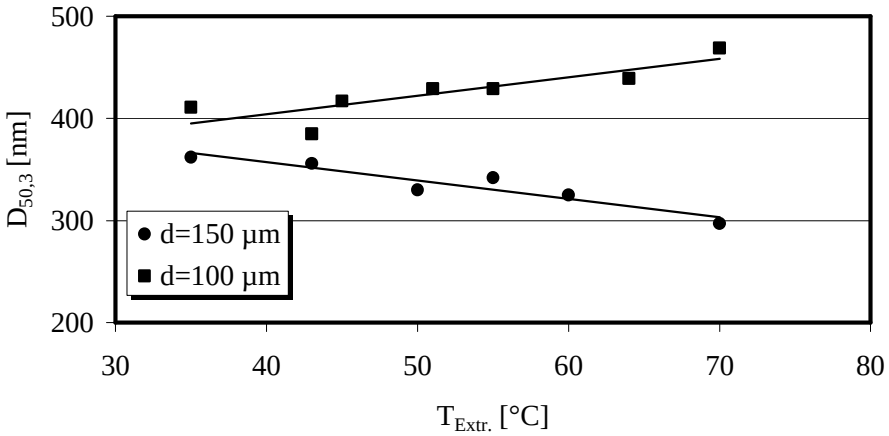

Fig. 2: Mean particle size of cholesterol at different extraction temperatures (ϑ_N = 100 °C, p_N = p_{Extr} = 20 MPa)

It is shown that the extraction temperature has only a very small effect on the particle size. From the phase diagram of the system cholesterol/CO_2 [5] it becomes clear that the solubility is only slightly increased at elevated temperatures. The influence of the nozzle diameter can be explained by the enhanced mass flow rate through the larger nozzle and the resulting dilution of the jet in the expansion chamber.

3.2 The PCA process

The model substance cholesterol was dissolved in acetone and toluene, respectively and micronized by the PCA process using carbon dioxide as the antisolvent. In pure CO_2 the solubility of cholesterol at 40 °C is about 0.2-0.5 mg/ml in the 10-20 MPa pressure range. However, cholesterol solubility in the pure organic solvent is up to 400 times higher so that it seems advantageous to precipitate cholesterol from organic solutions rather than from CO_2 solutions.

Figure 3 shows the results from PCA experiments from acetone solutions at different precipitation pressures. The temperature in the precipitation chamber was 40 °C, the nozzle diameter 100 µm. The mass flow rate of the CO_2 was 12 kg/h and the flow rate of the solution was 10 ml/min.

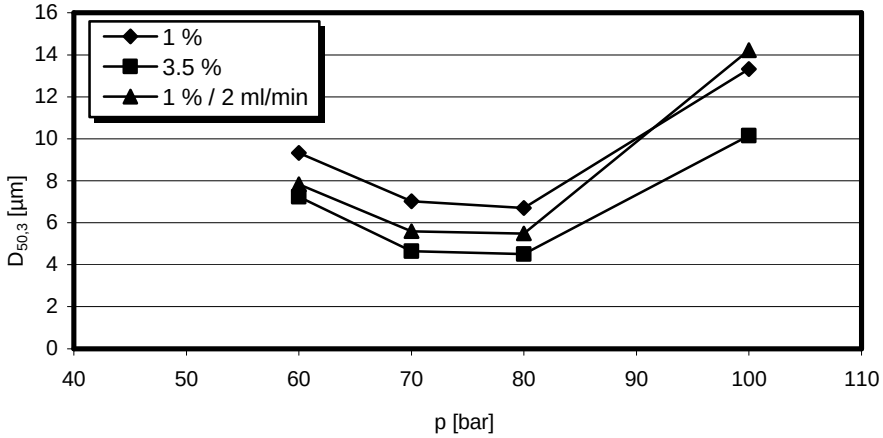

Fig. 3: Mean particle size of cholesterol micronized by PCA from acetone solution at different precipitation pressures (D_N = 100 µm, ϑ = 40 °C, m_{CO2} = 12 kg/h, V_{sol} = 10 ml/min)

The first point which can be seen from these experiments is that a micronization of cholesterol by PCA is possible although cholesterol is not insoluble in supercritical CO_2. The particle size is in the range of 15 to 4 µm which is about 25 times larger than the particles micronized by RESS. An increase of pressure from sub- to supercritical state results in a decrease of mean particle size. A further increase does not affect the particle size until a sharp increase of particle size can be observed. Simultaneously with this particle enlargement the yield decreased from above 90 % to below 40 %. With this information it becomes clear that the precipitation in the high pressure CO_2 is going worse and the large particles are formed during the depressurization step at the end of the experiment. At pressures higher than 10 MPa no precipitation occurs due to the higher solubility of cholesterol in the CO_2-solvent mixture. Large amounts of cholesterol were found in the separator where the solvent is separated from the CO_2 by depressurization.
Both, a higher concentrated initial solution and a higher dilution (larger mass ratio between antisolvent and solution) result in smaller particles. The first effect can be explained by the higher supersaturation and higher nucleation rate. Due to the higher dilution the antisolvent excess improves the kinetic of the mass transfer of the CO_2 into the droplets in the spray which results to a faster creation of the supersaturation and a higher nucleation rate and smaller particles.
Figure 4 presents the results of the PCA experiments from toluene solutions at different precipitation pressures. The temperature in the precipitation chamber was 40 °C, the nozzle diameter 100 µm. The mass flow rate of the CO_2 was 12 kg/h and the flow rate of the solution was 10 ml/min.

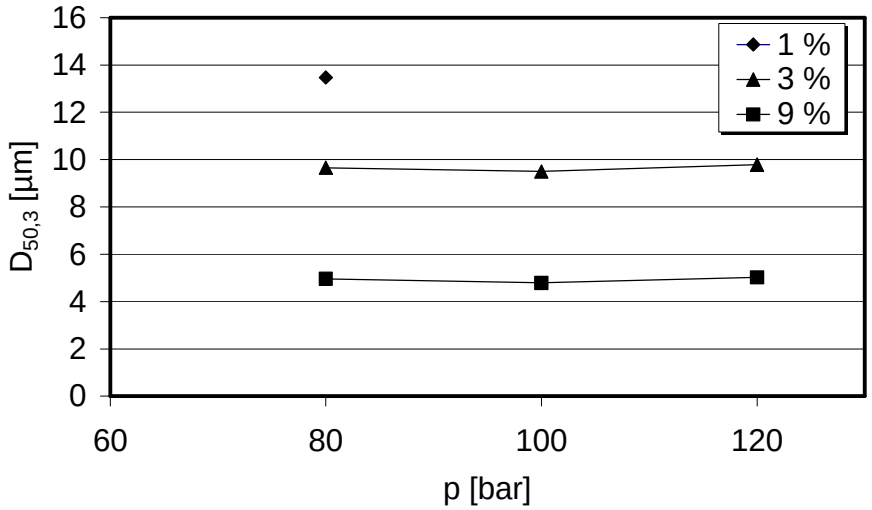

Fig. 4: Mean particle size of cholesterol micronized by PCA from toluene solution at different precipitation pressures (D_N = 100 µm, ϑ = 40 °C, m_{CO2} = 12 kg/h, V_{sol} = 10 ml/min)

In the cholesterol-toluene-CO_2-system no precipitation occurred in the subcritical region and at pressures higher 12 MPa. In the region between 8 and 12 MPa no pressure effect was found. An increase of initial solute concentration from 1 to 9 wt.-% results in a decrease of particle size from 14 µm to 5 µm.

4. DISCUSSION

Particles with large differences in scale were obtained according to the process which was used. With RESS particles in the range between 300 and 600 nm were processed and with

PCA 4 to 12 µm particles were micronized. The reason for those large differences is the much higher supersaturation and the faster creation rate of the supersaturation which is achieved in the RESS process. In contrast to the PCA process no mass transfer across a phase boundary is necessary to supersaturate the system. Therefore no diffusion limitation is possible and the process is faster. In the PCA process the diffusion of the antisolvent into the solution droplet and the evaporation of the solvent out of the droplets limit the supersaturation. Although the droplets are much smaller than expected (atomization in compressed gases is enhanced compared to the atomization into atmospheric environment [5]) it means a mass transfer boundary and therefore a limitation.
Nevertheless, it can make sense to produce cholesterol by the PCA process because the production rate is about 100 times larger than in the RESS process due to the much higher solubility of cholesterol in organic solvents compared to the solubility in supercritical carbon dioxide. A second point is the limitation of particle size in the RESS process; it is not possible to micronize cholesterol in the micron range by RESS. Both processes complement one another regarding to the compounds as well as to the particle size which can be obtained.

5. SUMMARY

A CO_2-soluble compound (cholesterol) was micronized by the RESS as well as the PCA process. The micronization by the PCA process was only successful provided that the process is carefully controlled to limit losses of material due to solubilization in the CO_2-solvent mixture.
Large differences in particle size were observed. The particle size in the PCA experiments were about 25 times larger than the particle size in the RESS experiments. This is due to the very different scales of supersaturation and the time in which supersaturation is achieved.
In the RESS process the processes behind the nozzle in the precipitation chamber predominate over the nucleation and crystal growth so that coagulation is the most important step and influences the particle size more than solubility.
In the PCA process diffusion and crystallization kinetics (and atomization) affect the particle size. Which process predominates depends on the process conditions. Moreover, the phase behaviour of the ternary system (solute-solvent-antisolvent) is important for the product quality and to optimize the complex process. Unfortunately, data for most systems are not available and the measurement is difficult and time-consuming.

6. REFERENCES

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