PARACETAMOL MICRONIZATION BY PRECIPITATION WITH THE SAS / SEDS PROCESS: INFLUENCE OF PROCESS PARAMETERS

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Supercritical Antisolvent (SAS) and Solution Enhanced Dispersion by Supercritical fluids (SEDS) was used for the crystallization of Paracetamol from Ethanol solution using supercritical CO_2 as the dispersing and extracting solvent. Pressures up to 250 bar and temperatures between 40 and 80 ^{0}C were used. Various concentrations of the Paracetamol/ Ethanol mixture were studied. The temperature and pressure effects on the size and morphology of the particles were examined systematically at the supercritical region and at high CO_2 content. The particle size and morphology were studied using Scanning Electron Microscopy. Two different crystal morphologies were observed as a function of the system pressure (hence the density of the supercritical CO_2), at constant temperature and solute concentration. A coaxial nozzle was used for the introduction of the supercritical CO_2 and the solution of the pharmaceutical compound. Coaxial introduction lead to a faster and thorough mixing of the organic solvent and the supercritical antisolvent, resulting in smaller microparticles. FT-IR and XRD were also employed for the characterization of the microparticles.

INTRODUCTION

Supercritical fluids offer considerable advantages as solvents or antisolvents for crystallization and precipitation processes. Micronization for industrial purposes is mostly carried out by two techniques: recrystallization from solution and comminution. However, these two methods have several drawbacks such as, wide size distribution, high thermal and mechanical stress, environmental pollution, large quantities of residual organic solvent, and multi stage processes [1]. These drawbacks are the main reasons for the increasing interest in alternative methods of precipitation. In this respect the role of supercritical fluids has been up scaled and their use as solvents and antisolvents is now in the center of attention. In the sensitive area of pharmaceuticals processing, various requirements need to be fulfilled [2]. Supercritical fluid processes fulfill all these requirements and moreover present numerous other advantages.

Paracetamol, as a model drug, has attracted much attention recently as regards its micronization via supercritical fluids [2,3]. The object of this work was to micronize paracetamol via the SEDS method [2] and evaluate the effect of temperature, pressure, and solution concentration on the particle characteristics. The effect of temperature and pressure was monitored over a wide range and was correlated to the morphology, the mean size and the size distribution of the particles.

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MATERIALS AND METHODS

Materials

Paracetamol ($C_8H_9NO_2$, M=151.2, 99.5 % purity) was supplied from Boehriner Ingelheim (Germany). Analytical grade analysis Ethyl Alcohol (EtOH, M=46.07 g/mol, 99.8 % purity) was purchased from Riedel-deHaen (Germany). Instrument grade carbon dioxide (purity 99.99 %) was supplied from Air Liquide Mediterranée (Vitrolles, France).

Apparatus

Micronization was done on a home – made apparatus that consists of the precipitation chamber which is equipped with sapphire windows to allow for optical observations, two high pressure pumps (Milton Roy) delivering the organic solution and the supercritical fluid, and a coaxial nozzle through which the two flows are introduced into the chamber. Two filters are used for the collection of the precipitated powder and a low pressure vessel, collects the organic solvent. The chamber is located in an air bath for temperature control.

The produced powder after micronization was characterized by a number of analytical techniques. Samples were observed with a scanning electron microscope (JEOL, model JSM-840A). Prior to the analysis, the samples were coated with graphite to avoid charging under the electron beam. Fourier Transform-Infrared (FT-IR) spectra were acquired using a Perkin-Elmer Spectrum GX FT-IR spectrometer. In each spectrum, 64 consecutive scans with 4 cm^{-1} resolution were co added. X Ray Diffraction (XRD) analysis was performed using an XRD 3003 TT Seifert apparatus.

RESULTS AND DISCUSSION

Effect of Pressure

The morphologies of the Paracetamol crystals, before and after their processing, are shown in Figure 1. From these SEM micrographs the size distributions, shown in Figure 4, were obtained. The processing of the organic solution results in a reduction of the mean size of the particles. At 100 bar, coalesced sphere-like particles are produced. These particles, although of a much smaller mean size, are rather agglomerated and appear to have a spherical morphology with no distinct edges. At 150 bar the formed particles appear to be agglomerated to a smaller extent while distinct edges start to form. At 200 and 250 bar, there is no apparent agglomeration and the formed microparticles are well defined, faceted and prismatic.

At 40 ^{0}C there is a sharp rise in the density of CO_2 between 70 and 150 bar [4]. Thus, above 150 bar, coagulation and agglomeration phenomena seem to disappear as the increased density of CO_2 results in a better and more rapid expansion of the organic solvent. This way, separate well defined microparticles precipitate at elevated pressures. The particle size distribution of the microparticles produced at 250 bar is shown in Figure 4.

The majority of the microparticles precipitated at 250 bar have a particle size between 2 and 6 μm. In contrast, the unprocessed Paracetamol consists of needle-like particles that range from 20 to 60 μm and in some cases even longer. In addition, the size distribution of the original material is much wider, between 20 to 100 μm, while the processed Paracetamol has a size distribution between 2 to 10 μm. It should be mentioned at this point that the range 2 – 5 μm is considered to be the most suitable for pulmonary delivery of the drugs [5]. The particle size distribution is equally if not more important to the mean particle size. A narrow size distribution means uniform and well controlled characteristics of the precipitated material

and, due to the dissolution kinetics, better control of drug concentration in recipient's organism [2].

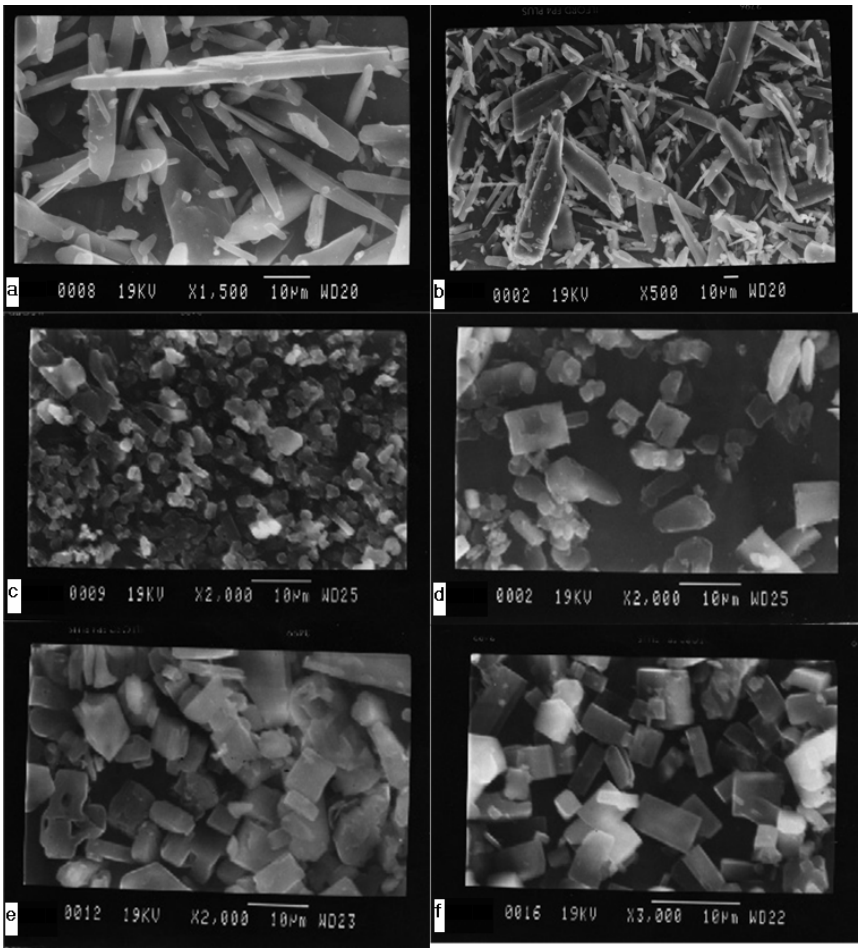

Figure 1. SEM images of unprocessed Paracetamol particles a), b) and processed Paracetamol particles at 40 ^{0}C at c)100 bar, d)150 bar, e)200 bar and f)250 bar

The mean particle size of Paracetamol particles that precipitated at 200 and 250 bar is 7.7 and 5.4 μm, respectively. A reduction in the mean size is thus noted with increase in pressure. A larger ratio of supersaturation is achieved as a result of the increased miscibility of Ethanol and CO_2 and the increased diffusion rate. Consequently, a larger number of nuclei are formed during the nucleation leading to smaller mean sizes.

Besides agglomeration phenomena, another difference between the samples is noted. Above 150 bar, the morphology of the particles changes: At low pressures the particles are sphere-like with no distinct edges, while at elevated pressures a transition is noted to prismatic well facetted crystalline forms. A similar behavior has been reported by Shekunov et al. [6].

Effect of Temperature

The SEM microphotographs of the produced samples are shown in Figure 2. The morphology of the sample taken at 150 bar and 60 ^{0}C (Figure 2a) is that of elongated, needle-like crystals. The length of the crystals in one direction exhibits an increase by a factor of 10 compared to the unprocessed particles of Paracetamol. Similar behavior has been reported by other authors [7]. The reason for this shift in the particle morphology is attributed to the

increased solubility of Paracetamol in the modified supercritical CO_2/Ethanol system [2]. At 150 bar and 80 ^{0}C, however, a shift in behavior is noted. As shown in Figure 2b, the produced powder is in an amorphous state. The material seems to have solidified rather than precipitated. It appears that at the higher temperature of 80 ^{0}C the miscibility between Ethanol and CO_2 decreases to such a degree that separate particles do not form. At 250 bar, however, the behavior of the system at both temperatures is similar to that at 150 bar and 60 ^{0}C. Figures 2c and 2d show the morphology of the produced samples at 60 and 80 ^{0}C, respectively. Once again the typical morphology of the crystals is needle-like. The mean size of the particles at 60 ^{0}C and at 150 and 250 bar is 362 and 367 μm, respectively.

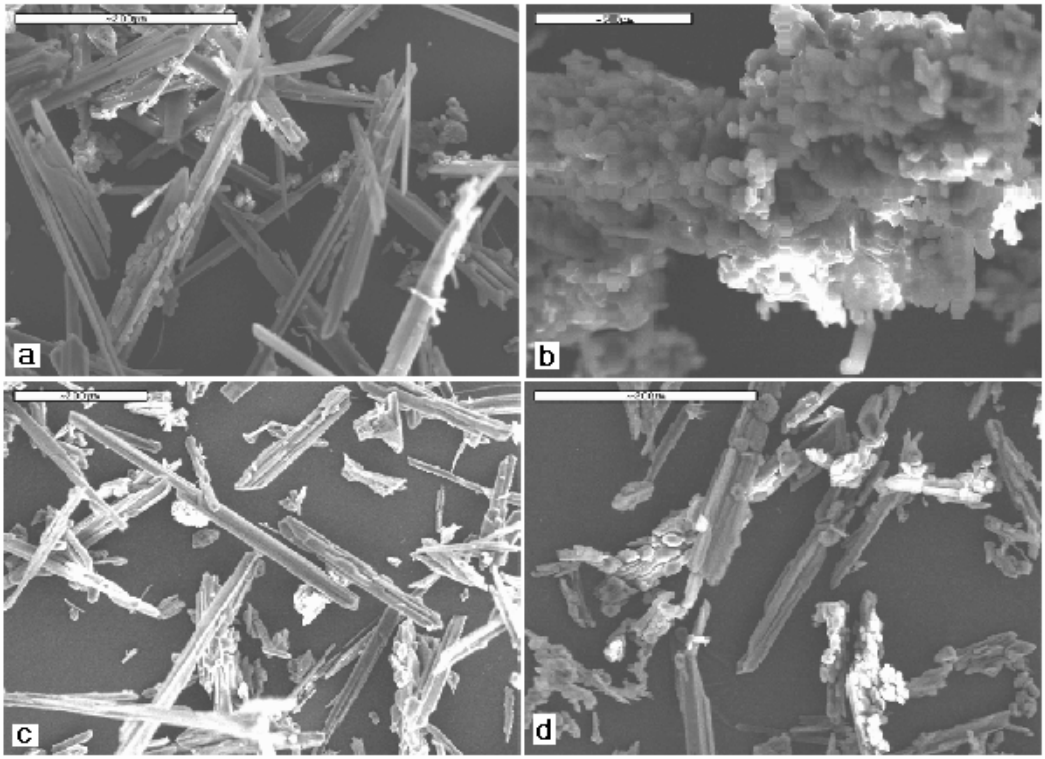

Figure 2. SEM images of processed Paracetamol particles at a)150 bar and 60 ^{0}C, b)150 bar and 80 ^{0}C, c)250 bar and 60 ^{0}C, d)250 bar and 80 ^{0}C

Effect of Concentration

The 1 w/v % solution of Paracetamol did not produce particles. At pressures 150 and 200 bar, coagulation is evident and precipitation results in agglomerated particles. It is clear that the production of Paracetamol microparticles from diluted solutions is only possible at high pressures (250 bar). However, even at this elevated pressure, the produced particles are much larger than those produced by a 2 w/v % solution. This is due to the low concentration of the solution which leads to a decreased ratio of supersaturation.

In Figure 3 the morphology of the produced particles for a 4 w/v % solution of Paracetamol and at pressures 100, 150, 200, and 250 bar, respectively is shown. At 100 bar large amorphous agglomerates are clearly visible (Figure 3a). The behavior of the system changes, however, at 150 bar. Figure 3b is characteristic of the morphology of the produced material at this pressure. Although agglomeration phenomena are still visible, the bulk of the sample shifts to a more crystal-like morphology. Production of distinct microparticles is successful at 200 and 250 bar as shown in Figure 3c and 3d respectively. At this pressure, the

CO_2 has a solvent strength enabling it to produce supersaturation ratios large enough for the production of microparticles to be observed. The particle size distribution at 200 and 250 bar are shown in Figure 4, respectively.

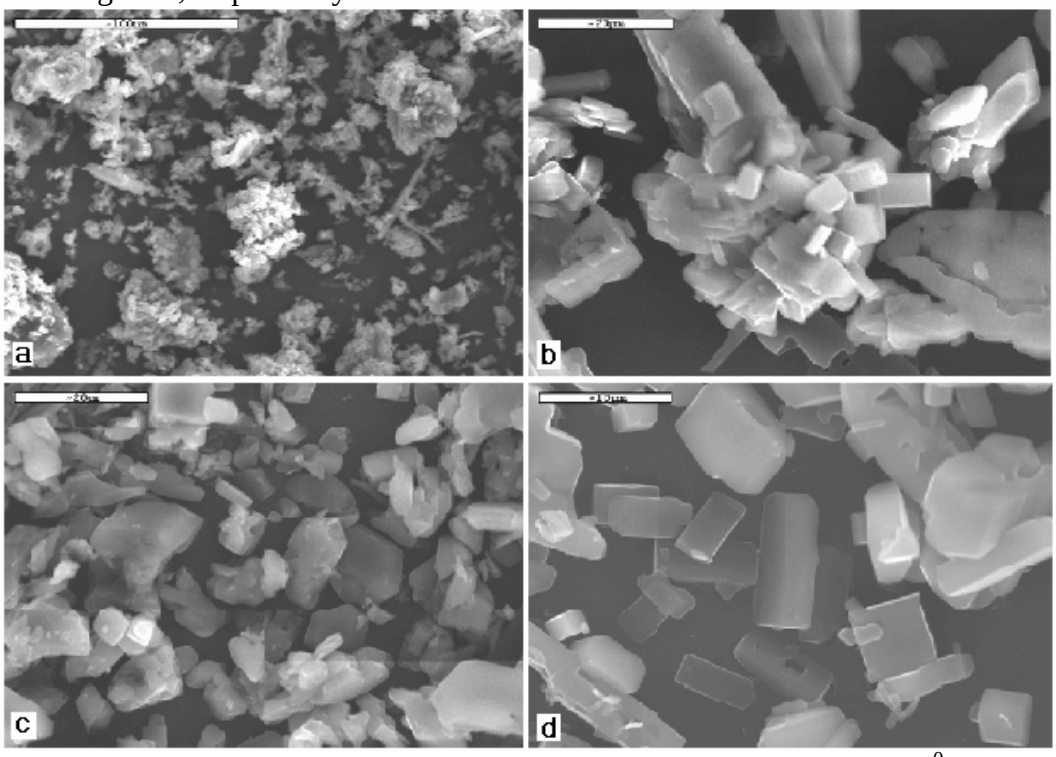

Figure 3. SEM microphotographs of Paracetamol particles processed at 40 ^{0}C, 4 w/v % concentration and at a)100 bar, b)150 bar, c)200 bar, d)250 bar

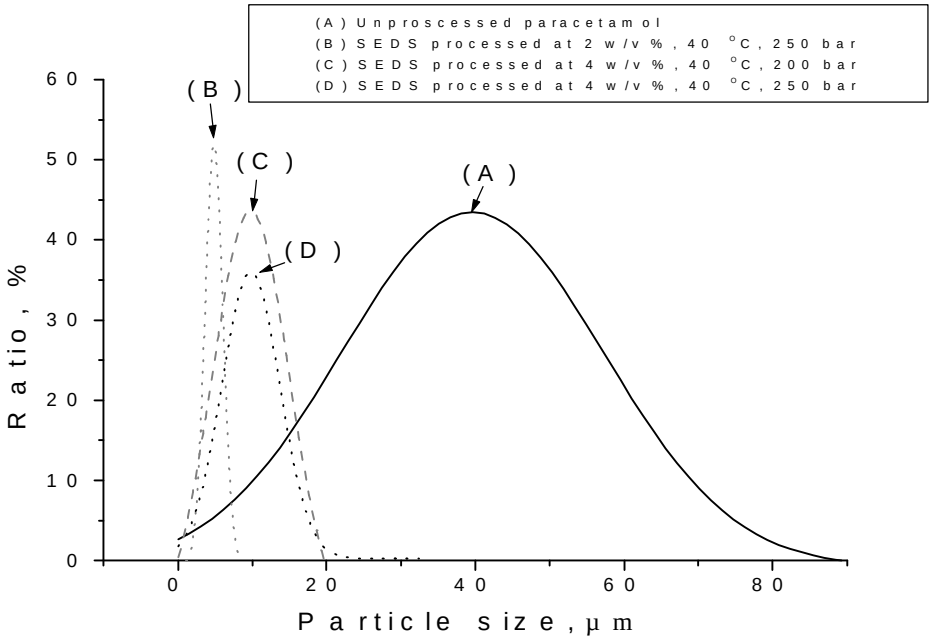

Figure 4. Particle size distribution of unprocessed Paracetamol (A) and SEDS processed at: 2 w/v %, 40 ^{0}C , 250 bar (B); 4 w/v %, 40 ^{0}C , 200 bar (C); 4 w/v %, 40 ^{0}C , 250 bar(D).

As observed in Figure 4, although microparticles are formed, their mean size and size distribution are larger and broader than those produced by a 2 w/v % solution. Similar observations have been made by Reverchon et al. [8]. A shift towards smaller sizes and a narrower size distribution are noted compared to the precipitate at 200 bar for the 250 bar experiment.

Analysis of Paracetamol Powder

FT-IR analysis was performed on the produced microparticles. No residual solvent was detected by this technique. Moreover, the FT-IR analysis was used to determine whether variations in the composition of the material were introduced or not. No variations in the compositions between the untreated and treated material are observed. The comparison of XRD patterns shows that Paracetamol is crystalline before processing and after SEDS. This result confirms the observations made from the SEM images in which highly crystalline forms were observed. Moreover, no variations in the composition are noticed.

CONCLUSIONS

Paracetamol microparticles were successfully precipitated from Ethanol solutions using CO_2 as an antisolvent. During the SEDS process the mean particle size of Paracetamol was reduced by an order of magnitude and the particle size distribution was narrowed significantly. Most importantly, at 2 w/v %, 40 ^{0}C and 250 bar, the size of the bulk of Paracetamol crystals was in or near the range of 2-5 μm, a range appropriate for the pulmonary delivery of pharmaceutical substances. The main parameters of the SEDS method such as pressure, temperature, solution concentration, and their effect on particle size, size distribution and morphology were studied. High pressures increase the miscibility of Ethanol with CO_2 leading to the production of smaller particles with narrow size distributions. On the contrary, an increase in temperature leads to a decrease of the solvent power of supercritical CO_2 and, thus, results in the production of elongated needles or large amorphous coagulates. The more dilute solutions (1 w/v %) proved unsuitable for the production of distinct particles. Precipitation was successful from more concentrated solutions (2 and 4 w/v %).

Acknowledgements

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