IBUPROFEN MICRONIZATION BY CAPILLARY RESS

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Ibuprofen (a chiral nonsteroidal anti-inflammatory drug) is micronized by the expansion of the supercritical Ibufrofen/carbon-dioxide solution in a RESS apparatus equipped with a capillary tube. The effects of extraction pressure (130-170 bar), pre-expansion temperature (76-104 ^{o}C), capillary length (8-12 mm), spraying distance (20-60 mm), and collision angle (45^{o} and 90^{o}) on the size and morphology of the precipitated Ibuprofen particles are investigated. The characterization (size, morphology and crystallinity) of the particles is carried out using scanning electron microscopy (SEM), and X-ray diffraction (XRD) measurements. The average particle sizes of Ibuprofen samples obtained after micronization by the RESS process were in the range of 2.85-7.48 µm, depending upon the experimental conditions used. While the average particle size of the original material was 45 µm. The degree of crystallinity of Ibuprofen is slightly reduced after processing with the RESS, as compared to the original material. No clear dependence of the particle size on the extraction pressure is observed, whereas an increase in the spraying distance caused particle size increase. However increases in the pre-expansion temperature, capillary length, and collision angle reduce the average size of Ibuprofen particles obtained.

INTRODUCTION

A large number of drugs are insoluble or poorly soluble in water. Bioavalibility is the percentage of the drug absorbed by the body to reach the general blood circulation in the body compared to its initial dosage. The bioavailability and the dissolution rate of the available dosage forms of these kind of drugs are limited by this insolubility and can be improved by reduction in their particle size (increase in surface area per unit weight).

Ibuprofen is a nonsteroidal antiinflammatory drug, exhibiting poor solubility in water, and its dissolution rate can be enhanced by reducing the particle size of the drug. The dissolution rate of drugs in the gastrointestinal fluids is generally the rate-determining step in the absorption of poorly water soluble drugs. The dissolution rate is a function of the surface area of particles and their solubility. Most drugs intended for oral administration require formulation with excipients to facilitate manufacturing of the product to increase the stability of the formulation, for the aesthetic reasons or for identification. The manufacture of tablets by the direct compression requires uniform mixing between the excipients and the drug to attain good content uniformity. Smaller particles in the formulation will allow better content uniformity during the final manufacturing process.

Charoenchaitrakool *et al*. [1] studied the effect of pre-expansion pressure, spraying distance and the nozzle length on the size and the morphology of the resultant particles. They found that the pre-expansion pressure and nozzle length had no effect on the particle size and morphology, whereas the particle size was decreased with an increase in the spraying distance.

In this present study, the effects of extraction pressure, capillary length, spraying distance, as well as the effect of collision angle, and pre-expansion temperature on the size and morphology of the precipitated Ibuprofen particles were investigated.

I - MATERIALS AND METHODS

In this study, Ibuprofen was used as the solute, and supplied by Atabay İlaç Sanayi A.Ş., (İstanbul, Turkey). Carbon dioxide (99.7% pure), in cylinders equipped with dip tubes, was supplied by Habaş A.Ş., (İstanbul, Turkey), and used as the solvent. Ibuprofen particles precipitated by the RESS process were characterized by scanning electron microscopy (SEM, Jeol 6400), and X-ray diffraction (Shimadzu XRD-6000). Prior to the SEM examination the particles, subjected to three minutes of sonication, were coated with a gold-palladium alloy with a sputter coater (Fisons Instrument, Polaron SC502).

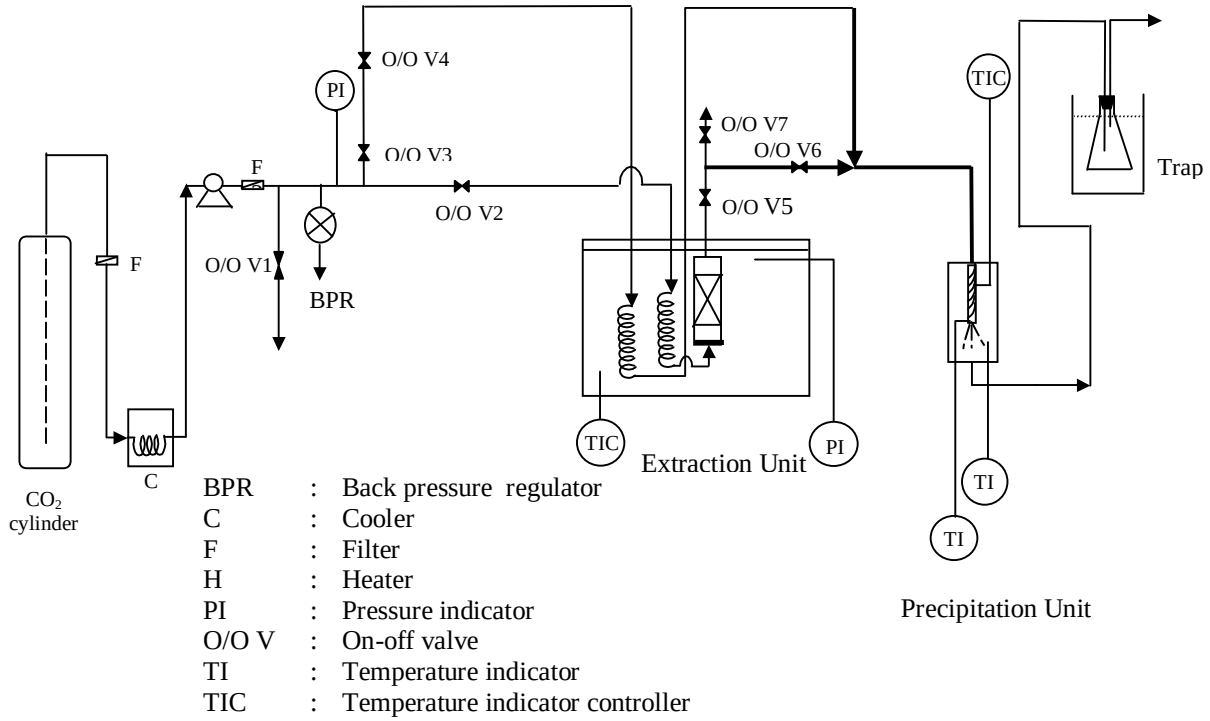


Figure 1: The experimental set-up for the RESS process

Figure 1 shows the experimental set-up used for the RESS process. The set-up mainly consists of two units: The extraction and the precipitation units. The extraction vessel, mounted in a constant temperature bath, has an internal diameter of 45 mm and a depth of 200 mm. The precipitation unit consists of a precipitation cell, an expansion device, and a collection device. The most important part of the set-up is the expansion device. The

supercritical solution prior to expansion is heated by a tube resistance, which is shown in Figure 2. The supercritical solution is expanded through a PEEK capillary having a diameter of 180 µm.

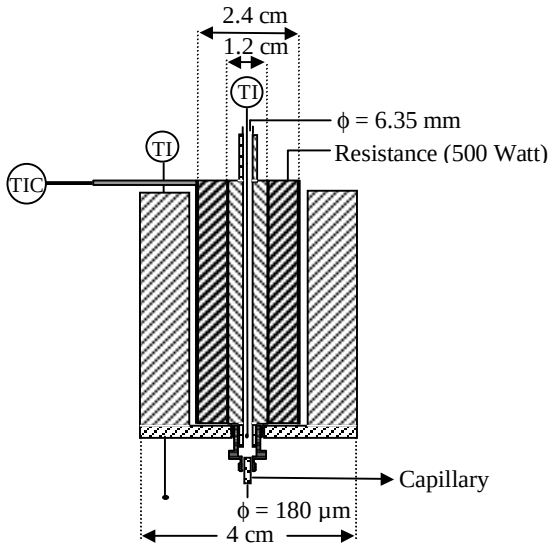


Figure 2: Heated expansion device used in the RESS set-up

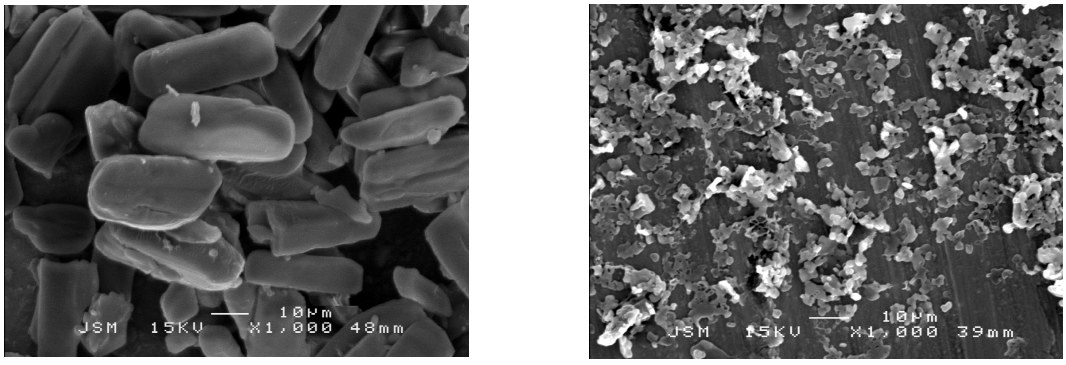
In each experiment, four grams of Ibuprofen was placed in the cylindrical wire netting packed with glass wool in the extraction cell. Before beginning a run, the on-off valves V1, V3, V4, V6, V7 were all kept closed. After obtaining the desired temperatures throughout the system, the extraction unit was filled with CO_2 through the on-off valve V2. The diaphragm pump was then turned on to bring the system to the desired pressure. After the desired pressure and temperature were achieved in the extraction unit, the diaphragm pump was turned off, and the on-off valve V2 was closed, the tube resistance of the nozzle was turned on and set to the run temperature, and the heating tapes wrapped around the line from the extraction unit to the precipitation unit were activated. The supercritical solution in the extraction unit was left at the extraction temperature and pressure for an hour to attain the equilibrium conditions. After the equilibrium conditions were reached, the pump was again turned on, V3 and V4 were opened to bring the system to the extraction pressure. To start the carbon dioxide flow through the expansion device V3 and V4 were opened. Supercritical carbon dioxide at the extraction pressure was passed through the capillary (by-passing the extractor) for ten minutes to stabilize the temperature prior to expansion. Then, valves V3 and V4 were closed, and immediately valves V2, V5, and V6 were opened, letting flow of the supercritical solution in the extraction unit through the expansion device. Samples were collected for ten minutes on a glass slide placed in the precipitation unit.

II - RESULTS AND DISCUSSION

The SEM images of the samples obtained by RESS revealed that the particles were highly aggregated. Water was chosen as the dispersion medium, since the Ibuprofen is poorly soluble in water. The samples were subject to the ultrasonication in water for three minutes. Figure 3 shows the SEM images of the unprocessed Ibuprofen particles, and the RESS processed particles at the extraction pressure, extraction temperature, pre-expansion temperature, capillary length, spraying distance, and the collision angle of 150 bar, 35 ^{o}C, 93 ^{o}C, 8 mm, 60 mm, and 90^{o}, respectively. The particle sizes were measured from SEM images, and particle size distributions were obtained. Figure 4 presents the particle size distribution of the original material and one of the samples obtained from the RESS process at the conditions specified in the figure caption. The effects of RESS parameters were discussed according to the means of particles size distributions. The particle size of the original Ibuprofen particles was as high as 95 µm, and the average particle size of the original particles were found to be 45 µm, whereas the average particle sizes of the RESS processed Ibuprofen particles were

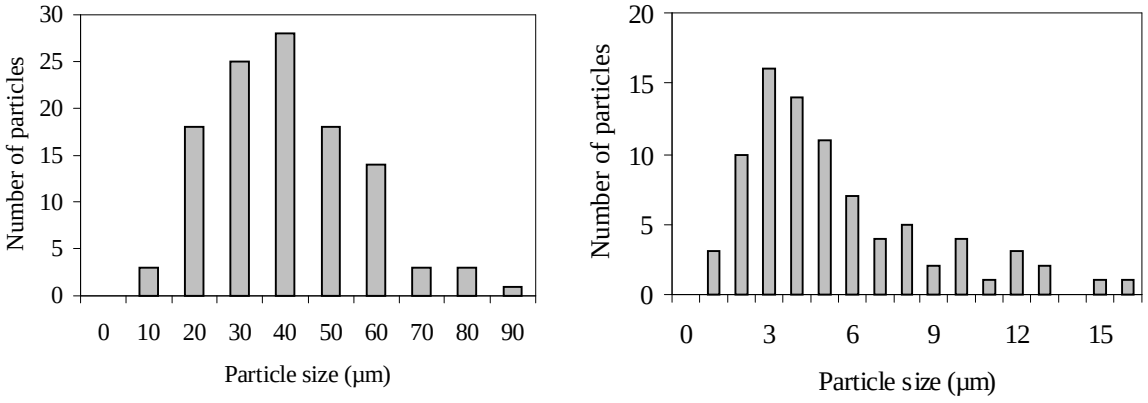
below 8 µm for all the conditions tested. SEM images shown in Figure 3 reveal the significant size reduction of the particles processed by RESS. The original material had a defined shape (rectangular), whereas the processed particles had irregular shapes. During expansion, the solution exposed to the sudden changes in temperature and pressure. The stresses applied on the particle during the process can cause defects in their crystal structure. Figure 5 shows the difference between the XRD patterns of the original material, and the RESS processed particles at the extraction pressure, extraction temperature, pre-expansion temperature, capillary length, spraying distance, and the collision angle of 150 bar, 35 ^{o}C, 82 ^{o}C, 12 mm, 60 mm, and 90^{o}, respectively. The intensities of the peaks seemed to be lowered, which shows the decrease in the degree of crystallinity.

The average particle size of the RESS produced particles was slightly decreased, as the pre-expansion temperature was increased approximately 10 ^{o}C out of the retrograde region. When the supercritical solution is heated, an unsaturated solution is obtained. The unsaturated solution prevents the particle formation in the capillary, and allows shorter nucleation and growth time. The decrease in the particle size with an increase in the pre-expansion temperature in this study may be attributable to this fact.



(a) (b)

Figure 3: SEM photographs of original Ibuprofen and Ibuprofen precipitates obtained by RESS (a) original material; (b) RESS produced particles with 3 minutes of sonication



(a) (b)

Figure 4: Particle size distributions of (a) original material; (b) sample obtained from RESS process (extraction P = 150 bar, extraction T = 35 ^{o}C, pre-expansion T =76 ^{o}C, capillary length = 8 mm, spraying distance = 35 mm, spraying angle = 45^{o})

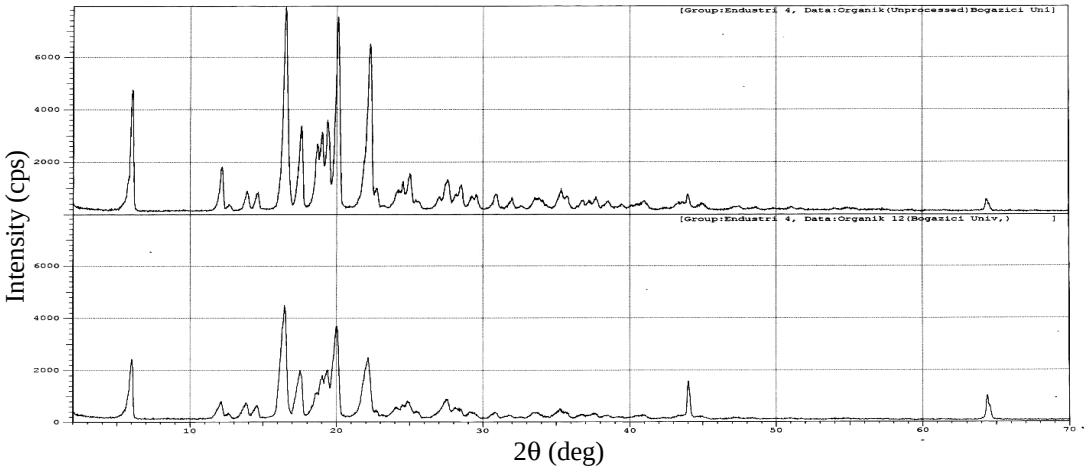


Figure 5: XRD patterns of (a) Ibuprofen (as obtained); (b) powders produced by RESS process

Extraction pressure modifies the solute concentration in the supercritical solution. As the solute concentration increases with increasing extraction pressure, higher nucleation rates can be attained during the process, thus leading to the formation of smaller particles. In this study, three different extraction pressures were tested. The system was pressurized to 130 bar, 150 bar, and 170 bar at an extraction temperature of 35 ^{o}C. The solubility of Ibuprofen in carbon dioxide at 35 ^{o}C and in between 130-170 bar does not change significantly, therefore no clear dependence of the average particle size was obtained on extraction pressure.

A change in the spraying distance from 20 mm to 35 mm and 60 mm resulted in an increase in the average particle sizes obtained. When the spraying distance is short, the time that the particles stay in the growth region is also short. As particles have shorter times to spend in the expansion region before colliding with the collection surface, particle growth is hindered. The same result was obtained by Subra *et al.* [2] for caffeine particles, whereas Reverchon *et al*. [3] and Charoenchaitrakool *et al*. [1] obtained an opposite effect of spraying distance for salicylic acid and Ibuprofen particles, respectively. In the present study, the collection surface was held at two different angles of 45^{o} and 90^{o} to the direction of flow. Smaller particles were obtained with a collision angle of 90^{o} as compared to 45^{o}.

In the experiments performed two capillary lengths of 8 mm and 12 mm were used, both having the same, i.e.180 µm, diameter. This variation resulted in two different capillary L/D ratios of 44.4 and 66.6 to investigate the effect of the capillary geometry on the characteristics of the particles obtained. When the capillary is smaller, pressure reduction starts earlier in the expansion device, even in the upstream of the capillary. A more gradual decrease of the pressure is expected with an earlier start of pressure reduction in the shorter capillaries. A more gradual pressure reduction means lower supersaturation and nucleation rates, which give rise to the formation of larger particles. The experimental results showed that larger particles are produced from the shorter capillaries due to the reason mentioned above.

CONCLUSIONS

The average particle sizes of the RESS precipitated Ibuprofen were in the range of 2.85-7.48 μm (originally 45 μm) for the different conditions tested in the experiments, representing a minimum of nearly 6 fold decrease in particle size. The X-ray diffraction pattern observations indicated a reduction in the crystallinity of the Ibuprofen after processing with RESS.

No clear dependence of particle size on the extraction pressure could be determined, since the solubility of Ibuprofen in carbon dioxide does not significantly change between 130 bar and 170 bar. A slight increase in the particle size was observed with increasing pre-expansion temperature. When the capillary length is increased from 8 mm to 12 mm, smaller particles were produced. As the spraying distance was increased from 2 cm to 6 cm, the average particle size also increased. On the other hand, as the collision angle was increased from 45^{o} to 90^{o}, the particle size decreased. A three minute sonification period was found necessary and sufficient for the RESS processing of Ibuprofen.

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