Micronization by Rapid Expansion of Supercritical Solutions to Enhance the Dissolution Rates of Poorly Water-Soluble Pharmaceuticals

M. Charoenchaitrakool, F. Dehghani, and N. R. Foster*

School of Chemical Engineering and Industrial Chemistry, The University of New South Wales, Sydney, Australia, 2052

H. K. Chan

Faculty of Pharmacy, The University of Sydney, Sydney, Australia, 2006

The dissolution of a drug into the biological environment can be enhanced by reducing the particle size of the drug. In this study the rapid expansion of supercritical solutions (RESS) process was employed to micronize racemic ibuprofen, and the dissolution rate of the micronized product in a buffered solution was examined. The chiral nonsteroidal antiinflammatory, racemic ibuprofen, was used as a model drug because its dissolution rate is limited by its poor solubility in water. The phase behavior of the ibuprofen−CO_2 binary system was investigated prior to the solubility measurements being undertaken. The solubility of racemic ibuprofen in supercritical CO_2 was measured using a dynamic apparatus at pressures between 80 and 220 bar and temperatures of 35, 40, and 45 °C. The solubility data was modeled using the Peng−Robinson equation of state with van der Waals mixing rules. The ratio of R and S isomers in the extract was found to be the same as that in the original material. The solubility of pure optical isomers of ibuprofen, namely, (S)-ibuprofen and (R)-ibuprofen, were also determined at 35 °C within the pressure range of 80−200 bar. It was found that (S)-ibuprofen exhibited solubility in CO_2 similar to (R)-ibuprofen, and the solubility of the pure isomers was at least 60% higher than that of the racemic ibuprofen at all pressures. The RESS experiments involved studying the effect of spraying distance, the pre-expansion pressure, and nozzle length on the particle size. The median particle size of ibuprofen precipitated by RESS was less than 2.5 μm. Although the particles obtained were aggregated, they were easily dispersed by ultrasonication in water. The pre-expansion pressure and nozzle length had no effect on the particle size and morphology within the range of operating conditions studied. An increase in spraying distance resulted in a slight decrease in particle size and degree of aggregation. The powder dissolution rate of racemic ibuprofen was enhanced as the particle size decreased. The degree of crystallinity of the processed ibuprofen was slightly decreased; as a result, the micronized product exhibited a higher disk intrinsic dissolution rate. The increase in dissolution rate of ibuprofen was hence due to both the reduction in particle size and the degree of crystallinity.

Introduction

Many drugs exhibit poor solubility in water, and their absorptions in the gastrointestinal tract are limited by their dissolution rates. In the pharmaceutical industry, micronization techniques are used to improve dissolution rates of drugs into the biological environment. Several conventional techniques have been utilized for particle size reduction. These include mechanical comminution (crushing, grinding, and milling), spray-drying, freeze-drying, and recrystallization of the solute particles from solutions using liquid antisolvents. The disadvantages of using these conventional techniques are thermal and chemical degradation of products, large amounts of solvent use and associated disposal problems, broad particle size distributions, and solvent residues.[1]

A novel technique, the rapid expansion of supercritical solutions (RESS), was recently developed for micronization of particles. In the RESS process, solutes are dissolved in a supercritical fluid, resulting in a solute-laden supercritical phase. By reduction of the pressure across an expansion device, fine particles with a narrow size distribution can be obtained. One advantage of micronization by the RESS process is the ability to produce solvent-free product without the need for additional solvents or surfactants to induce precipitation. Low critical temperature solvents such as CO_2 (T_c = 31.1 °C) can be used for the precipitation of thermally labile materials without the risk of degradation. The application of RESS can also be extended to the processing of shock and chemically sensitive substances, for the formation of thin films and fibers, for microencapsulation, and for mixing of powders.[2]

Ibuprofen is a chiral nonsteroidal antiinflammatory drug (NSAID) of which the (S)-(+)-enantiomer exhibits higher antiinflammatory activity than the (R)-(−) enantiomer.[3] It is most often prescribed to treat arthritis, fever, menstrual symptoms, and pain. The required intakes of ibuprofen can be minimized by improving its effectiveness in terms of increasing the dissolution rate in the biological environment.

* To whom correspondence should be addressed. Phone: 61-2-9385-4341. Fax: 61-2-9385-5966. E-mail: N.Foster@unsw.edu.au.

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It is well recognized that the dissolution rate of drugs in the gastrointestinal fluids is generally the rate-determining step in the absorption of drugs rather than their diffusion rates across the gut wall. However, the in vivo dissolution rate and the availability of a drug for gastrointestinal absorption from solid dosage forms are difficult to determine. In vitro dissolution rate experiments are generally performed instead.[4]

In this study, the feasibility of the RESS technique for the micronization of poorly water-soluble ibuprofen was investigated. Prior to the RESS experiments, an investigation of ibuprofen solubility in supercritical CO_2 (SC CO_2) was required. The solubility of racemic ibuprofen in SC CO_2 was measured using a dynamic apparatus for pressures between 80 and 220 bar and temperatures of 35, 40, and 45 °C. The solubility data was modeled using the Peng−Robinson equation of state with van der Waals mixing rules. The solubilities of (S)-ibuprofen and (R)-ibuprofen were also determined at 35 °C within the pressure range of 80−200 bar. The RESS experiments involved an investigation of the effects of the pre-expansion pressure, spraying distance, and nozzle length on the size and morphology of the particles. The dissolution kinetics of the particles in a phosphate buffered solution were also determined. Two different dissolution tests, powder dissolution and disk intrinsic dissolution, were employed to investigate the effect of size reduction and degree of crystallinity on the dissolution kinetics of ibuprofen.

Solubility data are essential for an accurate experimental design and for calculation of the concentration of supercritical solutions at different RESS operating conditions. Solubility data for ibuprofen in SC CO_2 at 50 °C has been reported by Estevez and Suleiman.[5] However, no information regarding the phase behavior of ibuprofen in CO_2 nor solubility data at other isotherms were reported.

McHugh and Krukonis[6] found that some solid organics may exhibit melting-point (or freezing-point) depressions when compressed in the presence of a supercritical fluid (SCF). As the pressure increases, the solubility of the SCF in the solute phase increases, resulting in lower temperatures being required to freeze the solute. The degree of melting-point depression is dependent on the solubility of the SCF in the solute phase. If the solubility of the SCF is large, the melting-point depression will be significant. Melting-point depression has been observed in several binary systems, such as CO_2−naphthalene and CO_2−octacosane.[7] In this study, the phase behavior of racemic ibuprofen and its enantiomers was examined prior to the solubility measurements being conducted.

Modeling of Solubility Data

The solubility of a solid in a SCF can be expressed as a function of operating pressure and temperature as shown in eq 1[8]

$$y_2 = \frac{P_2^{SAT}(T)\exp\left(\frac{v_2^s(P - P_2^{SAT}(T))}{RT}\right)}{\Phi_2 P} \qquad (1)$$

where y_2 is the equilibrium mole fraction of solid in the SCF phase, $P_2^{SAT}(T)$ is the solid-saturated vapor pressure at temperature T, R is the universal gas constant, P is the operating pressure, Φ_2 is the solute fugacity coefficient, and v_2^s is the solute molar volume.

The Peng−Robinson equation of state (PR EOS) is commonly used to evaluate the fugacity coefficient at high pressure.[9] The objective of this modeling was to provide a mathematical description of the measured data, which can be used to interpolate the solubility at other conditions.

Solute physical properties, such as critical temperature (T_c), critical pressure (P_c), and acentric factor (ω), for high molecular weight compounds are not commonly available. The group contribution techniques such as Joback, Ambrose, and Lydersen[10,11] have been employed to estimate solute physical properties. The vapor pressure of ibuprofen and its molar volume were estimated by the methods presented by Lyman et al.[11] The interaction parameter (k_{ij}) was assumed to be a function of temperature and was varied to obtain the best fit of the experimental data. A PASCAL program was written to optimize k_{ij} by minimizing the average absolute relative deviation (AARD) using the golden search method.[12] The AARD that was used as an objective function was calculated by the following equation,

$$\text{AARD} = \frac{1}{N}\Sigma\left|\frac{y_{pred} - y_{expt}}{y_{expt}}\right| \qquad (2)$$

where N is the number of experimental data, y_{pred} is the solubility predicted by the model, and y_{expt} is the experimental data.

Materials and Methods

Materials. Racemic ibuprofen (Sigma, 99.8% purity), (S)-(+)-ibuprofen (Aldrich, 99% purity), (R)-(−)-ibuprofen (RBI, 99% purity) were used as received. Carbon dioxide (BOC Gases, 99.95%) was used as the solvent. Phosphate buffer (Sigma, 8.3 mmol/L, pH 7.2) was used for preparing the mobile phase for HPLC analysis.

Potassium phosphate monobasic (Sigma, 99% purity) and sodium hydroxide (Sigma, minimum 98% purity) were used to prepare phosphate buffer solution for the dissolution studies.

Melting-Point Depression Studies. A study of the melting-point depression of racemic ibuprofen and its enantiomers was carried out using a static technique. A glass tube (i.d. = 5 8 mm) loaded with the solute was placed inside the view cell (Jerguson sight gauge series No. 32). The system was placed in the constant temperature water bath. Carbon dioxide was gradually fed into the view cell at 3 bar increments. The system was isolated and equilibrated for at least 10 min after each pressurization. The melting point was determined by visual observation when the first droplet of the liquid was formed in the system, and the pressure at which ibuprofen started to melt was recorded. The system was pressurized up to 220 bar if no melting was observed.

Solubility Measurements. The solubility of solid solute in CO_2 was measured using a dynamic solubility measurement technique described previously by Alessi et al.[13] In summary, an equilibrium cell was packed with the solute and placed in the constant temperature water bath. The temperature of the system was controlled by a thermostat heater (Thermoline unistat 130), and pressure was monitored by a pressure transducer (Druck, DPI 260). Liquid CO_2 was fed to a syringe pump (ISCO model 260D) and delivered through a preheating

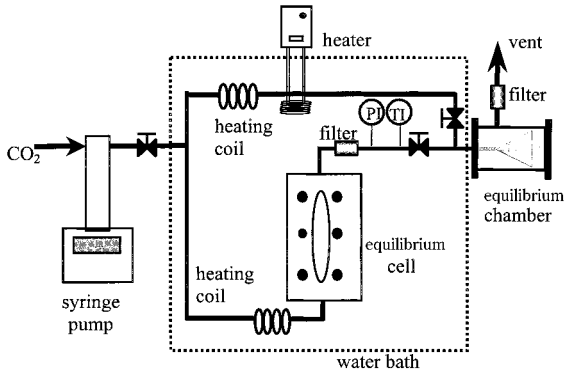

Figure 1. Schematic diagram of the RESS apparatus.

coil, which was immersed in the water bath. The SC CO_2 at the desired extraction pressure and temperature was then fed into the equilibrium cell. A 0.5-μm filter was installed after the equilibrium cell to prevent physical entrainment of solute. The solute-laden CO_2 was then flashed to atmospheric pressure via a metering valve, causing the dissolved solute to precipitate out of the fluid phase. The released CO_2 was passed through a water saturator and a wet gas meter (Alexander Wright & Co., type DM3A).

The apparatus was modified for measuring the liquid solute solubility in CO_2. A ball valve was installed before the equilibrium cell to isolate the system and prevent backflow of the liquid solute. (S)-(+)-ibuprofen or (R)-(−)-ibuprofen was loaded into the equilibrium cell without any glass wool. Carbon dioxide was delivered by a syringe pump and bubbled through the liquid solute using a sparger (0.5-μm porous metal filter). The system was maintained at the desired extraction pressure and temperature for at least 2 h before the sample was collected. In this study, only the vapor-phase composition was determined. Flow rate studies were carried out so that a suitable flow rate could be applied when sampling. A low flow rate, typically 0.6 L of CO_2/h, was used during sampling to ensure saturation, and to maintain the equilibrium. A cryogenic solute trap was connected after the filter to ensure that all the solute was collected.

The solubility of solute was calculated by a gravimetric technique using the mass of the precipitates collected in the metering valve and the filter and the volume of CO_2 determined from the wet gas meter. Each solubility data point was repeated at least three times, and the average value with a relative standard deviation (RSD) of <5% was determined. The reliability of the experimental setup and of the experimental technique was examined by measuring the solubility of *o*-hydroxybenzoic acid in supercritical CO_2 at various conditions. The results agreed within 5% of previously published data.[14]

The ratios of optical isomers in the original racemic ibuprofen and the extracted product were obtained using HPLC (Shimadzu, C-R4A). A chiral AGP column (Chrom Tech, 100 × 4.0 mm, particle size 5 μm) was used to analyze the (R)- and (S)-ibuprofen isomers. The compounds were detected at 225 nm (ISCO V^4 Absorbance detector). Phosphate buffer solution with 0.6 vol % phosphoric acid (1.5 M) was used as a mobile phase. The flow rate in the column was set to 0.9 mL/min.

RESS Experiments. The apparatus for the RESS process shown in Figure 1 was a modification of the solubility measurement apparatus. A 50-μm capillary nozzle (1 or 2 cm in length) was used as an expansion device. In this study, the effects of the pre-expansion pressure, spraying distance, and nozzle length on the size and morphology of the particles were studied. The pre-expansion temperature was maintained at the same temperature as the extraction cell. The effect of pre-expansion temperature was not investigated in this study because high temperature in the pre-expansion section may adversely affect the crystallinity of ibuprofen and also because of complications related to the substantial melting-point depression characteristics. The particles were precipitated inside the expansion chamber at atmospheric conditions.

Particle Characterization. The crystallinity and melting point of the original material and precipitates were tested by X-ray diffraction (XRD) (Rigaku) and differential scanning calorimetry (DSC) (2010 TA Instruments). The morphology of particles precipitated directly on aluminum stubs placed inside the expansion chamber at different distances from the nozzle was analyzed by scanning electron microscopy (SEM) (Hitachi S4500). Specific surface areas of the precipitated powders and original material were measured by nitrogen gas adsorption (BET method) using an ASAP 2000 instrument.

Difficulties were experienced in selecting a suitable dispersion medium for the particle size distribution (PSD) analysis. An attempt to determine the PSD profile using a Malvern Mastersizer with water as a dispersing medium was unsuccessful. The obscuration level (the concentration of the sample added to the dispersant) did not remain constant after the sample was added into the magnetic stirred cell. This observation indicated that the micronized ibuprofen dissolved in water, and hence water is not a suitable dispersing medium for this analysis. Various alternative dispersing mediums such as 0.1 M HCl solution, water saturated with ibuprofen, were also examined. However, the micronized ibuprofen dissolved in all of these dispersants.

Particle size distribution was subsequently determined by counting at least 500 particles from the SEM images. The SEM images were prepared by dispersing the ibuprofen precipitates in water and drying the samples in the vacuum oven. The sample was sonicated for 60 s to maximize the dispersion of the aggregated particles and minimize the ibuprofen solvation in water.

Dissolution Kinetics Studies. The effect of particle size and degree of crystallinity of racemic ibuprofen on the dissolution kinetics were assessed by means of powder dissolution and disk intrinsic dissolution, respectively.

Powder dissolution studies were performed using the USP paddle method in 1 L of phosphate buffer solution at pH 6.3, 37 °C, and 50 rpm. Accurately weighed samples were introduced into the dissolution medium. Aliquots (≈4 mL) were withdrawn in certain time intervals and passed through a 0.45-μm filter. The amount of ibuprofen in the withdrawn samples was determined by measuring the absorbance at $\lambda = 221$ nm using spectrophotometry.

A compacted disk dissolution apparatus was used to study the intrinsic dissolution kinetics.[15] The dissolution cell consisted of a Perspex cylinder, lid, and a stainless steel compact holder. Powder samples (unsieved, ≈50 mg) were compressed directly by a hydraulic press (1 metric ton, 60 s, Press H30-IMK.2 series No. 0241) to form a 1-cm diameter disk. The sample holder with the

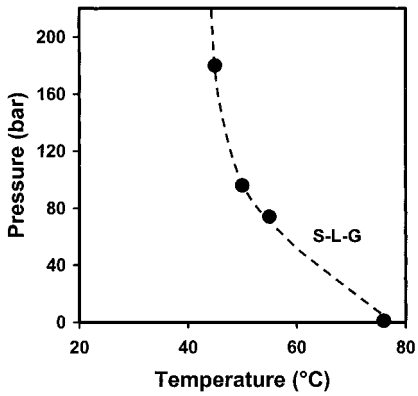

Figure 2. Pressure−temperature trace of the three-phase S−L−G line for the racemic ibuprofen−carbon dioxide system.

in situ disk was screwed into the base of the cylinder, thus allowing the sample surface to be exposed to the dissolution medium. Phosphate buffer solution (1 L), pH 6.3, was pre-equilibrated at 37 °C and used as the dissolution medium. The solution was stirred at 50 rpm using a stirrer driven by a synchronous motor. Samples (4 mL) were taken at fixed time intervals for 150 min and filtered before analysis by UV spectrophotometry at $\lambda = 221$ nm.

Results and Discussion

Melting-Point Depression Studies. The normal melting point of racemic ibuprofen was verified using differential scanning calorimetry (DSC) and was found to be 76 °C. The melting point of racemic ibuprofen was depressed to 55, 50, and 45 °C when the solute was present in SC CO_2 at 74, 96, and 180 bar, respectively. However, no melting-point depression of racemic ibuprofen was observed for 35 and 40 °C isotherms for pressures <220 bar. The pressure−temperature trace of the three-phase solid−liquid−gas (S−L−G) line for the racemic ibuprofen−carbon dioxide system is plotted in Figure 2.

The normal melting points of (S)-(+)-ibuprofen and (R)-(−)-ibuprofen were verified to be 51 and 52 °C, respectively. (S)-ibuprofen started to melt at 24 °C when the system was pressurized with CO_2 to 46 bar. Similarly, the melting point of R-(−)-ibuprofen was depressed to 24 °C at 47 bar.

Solubility Measurements. The solubility of racemic ibuprofen was measured at pressures in the range of 80−220 bar, temperatures of 35 and 40 °C, and up to 170 bar for 45 °C. The solubility data for racemic ibuprofen are generally in the range from 10^{-5} to 10^{-3} mole fraction, as shown in Table 1. The effect of pressure on the solubility is illustrated in Figure 3, and it can be seen that the solubility increased as the pressure was increased. As pressure is increased, carbon dioxide density increases and the intermolecular mean distance of carbon dioxide molecules decreases; therefore, the specific interaction between the solute and solvent molecules is increased.[14] The crossover region for the ibuprofen−CO_2 system is in the range of pressures between 125 and 132 bar.

The solubility data for racemic ibuprofen in CO_2 obtained in this study represented solid solubility because, within the experimental conditions, no melting of ibuprofen was observed. On the basis of the assumption that the supercritical fluid does not dissolve into a solid solute, the solubility was correlated using the PR EOS with van der Waals mixing rules. The estimated physical properties of ibuprofen using various group contribution methods are shown in Table 2.

Table 1. Solubility Data for the Racemic Ibuprofen and Its Enantiomers in Carbon Dioxide

temperature (°C)	pressure (bar)	solubility (mole fraction × 10^3)
	Racemic Ibuprofen	
35	80	0.053
35	85	0.543
35	90	0.995
35	100	1.35
35	110	1.81
35	120	2.13
35	130	2.50
35	140	2.43
35	150	2.68
35	160	3.23
35	170	3.82
35	180	3.78
35	200	4.23
35	210	4.23
35	220	4.41
40	95	0.585
40	120	2.32
40	140	3.18
40	170	4.67
40	200	6.80
40	220	6.49
45	85	0.030
45	90	0.040
45	95	0.113
45	100	0.302
45	110	1.29
45	120	2.00
45	140	3.74
45	170	5.84
	(S)-Ibuprofen	
35	80	0.211
35	90	1.58
35	100	2.34
35	120	4.16
35	150	5.57
35	170	8.37
35	200	11.23
	(R)-Ibuprofen	
35	80	0.165
35	90	1.74
35	100	2.83
35	120	3.49
35	150	7.36
35	170	8.60
35	200	10.96

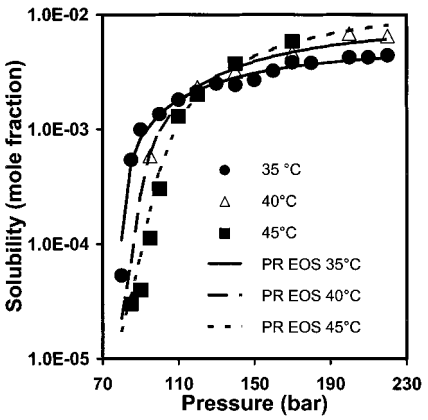

Figure 3. Comparison between the measured solubility of racemic ibuprofen in CO_2 and the calculated solubility from the PR EOS using the Lydersen group contribution method.

Table 2. Estimated Properties of Ibuprofen

property	method of estimation	value
T_c (K)	Joback	891.2
T_c (K)	Lydersen	749.7
T_c (K)	Ambrose	753.6
P_c (bar)	Joback	22.5
P_c (bar)	Lydersen	23.0
P_c (bar)	Ambrose	21.8
ω	Joback	0.788
ω	Lydersen	0.819
ω	Ambrose	0.749
P^{SAT} at 35 °C (bar)	Lyman et al.	4.95×10^{-7}
P^{SAT} at 40 °C (bar)	Lyman et al.	8.97×10^{-7}
P^{SAT} at 45 °C (bar)	Lyman et al.	1.60×10^{-6}
molar volume (cm^3/mol)	Immirzi and Perini	182.1

Table 3. Optimized Interaction Parameters for the Modeling of Ibuprofen Solubility in CO_2 with the PR EOS and the van der Waals Mixing Rules

temperature (°C)	method of estimation	k_{ij} ($\times 10^2$)	% AARD
35	Lydersen	8.5	12.6
35	Ambrose	7.7	17.4
35	Joback	21.1	27.3
40	Lydersen	7.72	6.2
40	Ambrose	7.0	12.8
40	Joback	20.5	19.2
45	Lydersen	7.12	32.0
45	Ambrose	8.62	36.5
45	Joback	22.9	43.6

The optimized interaction parameters, k_{ij}, that gave the best fit between the experimental data and the modeling with PR EOS and van der Waals mixing rules using different group contribution methods are presented in Table 3. It was found that among the three group contribution methods employed in the modeling, the Lydersen method yielded the best correlation between the modeling results and the experimental data for all solubility isotherms. The least successful correlation was generated by the Joback method. The poor correlation results obtained with the Joback technique may be due to a high predicted value of the critical temperature of ibuprofen.

The comparison between the experimental data and the results using the PR EOS with the Lydersen group contribution method is shown in Figure 3. The correlation may be improved by using different models or mixing rules that are not dependent on the estimated solute critical properties and are suitable for large polar molecules such as ibuprofen. Macnaughton and Foster[16] reported that an improvement in the correlation of the solubility data of 2,4-D in CO_2 was achieved when the modified PR EOS was used. In their study, the energy and size parameters of the solute were left as adjustable parameters rather than estimating them from the solute critical properties.

The ratio of the optical isomers (R-to-S ratio), defined by peak areas from the HPLC chromatogram, in the extracted ibuprofen was found to be 0.95, which was similar to that of the original material (R/S = 0.96). These results indicate that both enantiomers in the racemic ibuprofen were extracted with CO_2 to the same extent.[17]

The solubility data for (S)-ibuprofen and (R)-ibuprofen are also shown in Table 1. It was found that (S)-ibuprofen exhibits solubility in CO_2 similar to (R)-ibuprofen consistent with the similar melting points and phase behaviors in the presence of CO_2. In general, the solubility of the pure optical isomers of ibuprofen are

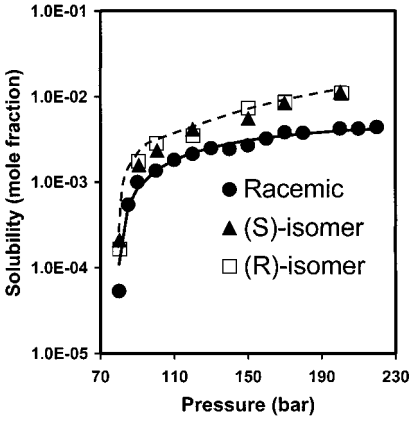

Figure 4. Comparison between the solubility of racemic ibuprofen and the solubility of its enantiomers at 35 °C.

in the range from 10^{-4} to 10^{-2} mole fraction. The measured solubility data for these isomers have not been correlated with the PR EOS because they existed as a liquid under the conditions of study, and hence the assumption that SC CO_2 does not dissolve in the solute phase is not valid.

A comparison between the solubility data for racemic ibuprofen and its enantiomers at 35 °C is illustrated in Figure 4. It was clearly shown that the solubility of (S)-ibuprofen and (R)-ibuprofen were significantly higher than that of the racemic ibuprofen at all pressures. This was due to the lower melting points of the pure isomers and thus higher vapor pressures of the solutes. From the solubility studies, it is confirmed that racemic ibuprofen is not simply a mixture of S and R isomers, but is a racemic compound. Dwivedi and co-workers[18] also found that the powder X-ray diffraction patterns of the ibuprofen enantiomers were identical, but different from those of racemic ibuprofen.

RESS Experiments. The particle size of the original racemic ibuprofen as received from Sigma was as high as 250 μm, as shown in Figure 5. Ibuprofen particles precipitated by the RESS process were significantly smaller than the original material. The SEM images of processed particles as illustrated in Figure 5b−d reveal that particles were irregular in shape and were aggregated.

The effect of spraying distance, pre-expansion pressure, and nozzle length on the nature of the micronized product was then investigated.

Spraying distances of 7 and 11 cm measured from the tip of the nozzle to the surface of the stub were used. The SEM images of particles obtained are shown in Figure 5b and c. An increase in spraying distance resulted in a slight decrease in both particle size and the degree of aggregation. This may be due to the fact that as the distance increased, the jet had more time to break up and allow the formation of discrete particles. Reverchon and co-workers[19] also found that crystal networking of precipitated salicylic acid decreased as the spraying distance increased.

The effect of pre-expansion pressure on precipitates was investigated for pressures between 130 and 190 bar. No significant change in size or morphology was observed. This could be due to an insignificant change in the concentration of ibuprofen in CO_2 as the pressure increased from 130 to 190 bar. The effect of pre-expansion pressure on the size and shape of the precipitates was also found to be inconclusive in the studies of griseofulvin in SC CHF_3,[20] naphthalene in CO_2,[21] and

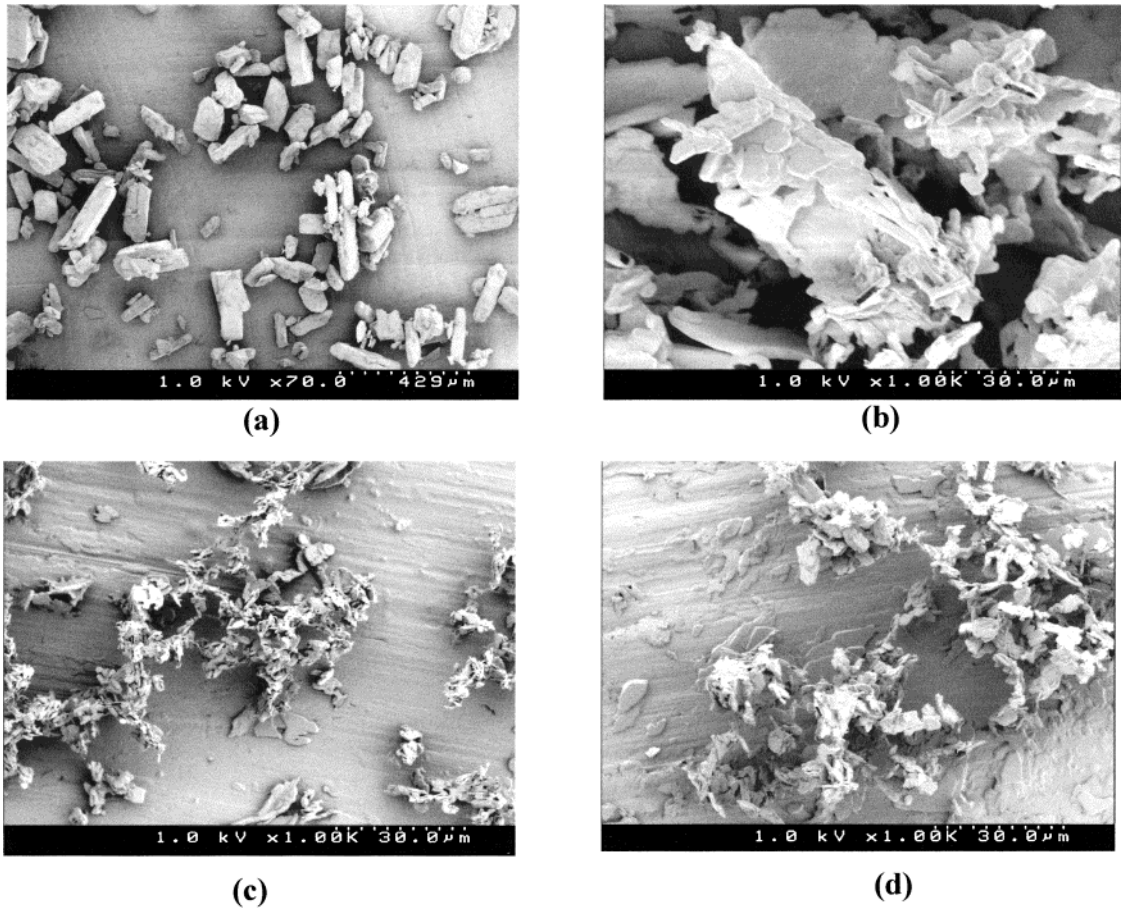

Figure 5. SEM photographs of original ibuprofen and the precipitates obtained by RESS at T_{expt} = 35 °C and P_{expt} = 130 bar: (a) original material; (b) RESS with spraying distance = 7 cm and nozzle length =1 cm; (c) RESS with spraying distance = 11 cm and nozzle length = 1 cm; (d) RESS with spraying distance = 11 cm and nozzle length = 2 cm.

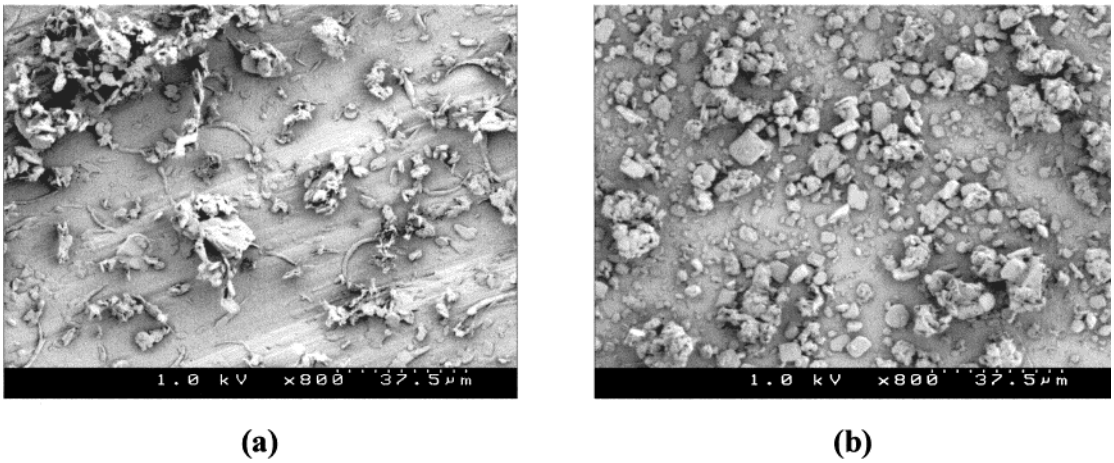

Figure 6. SEM photographs of the precipitates obtained by RESS at T_{expt} = 35 °C and P_{expt} = 190 bar: (a) without sonication; (b) with 60 s of sonication in water.

benzoic acid in SC CO_2.[22] Changing the nozzle length from 1 to 2 cm also did not significantly affect the size of ibuprofen precipitated by RESS.

Micronized ibuprofen precipitated at 190 bar and 35 °C was used as a representative sample for particle size distribution (PSD) analysis and the specific surface area measurement. The SEM images of the micronized ibuprofen before and after sonication in water were shown in Figure 6 a and b, respectively. The SEM images reveal that the degree of aggregation was reduced after sonication.

As is illustrated in Figure 7, the PSD profile of the micronized ibuprofen showed that 90% of the counted particles were <5 μm. On the basis of the number distribution, the median particle size was found to be <2.5 μm. To compare the particle size distribution results, the PSD of the unprocessed ibuprofen was also performed using the same technique. As shown in Figure 8, 90% of the unprocessed material was <120 μm, and no particle <7 μm was observed. The median particle size was found to be 42 μm, which was 17 times higher than that of the micronized ibuprofen.

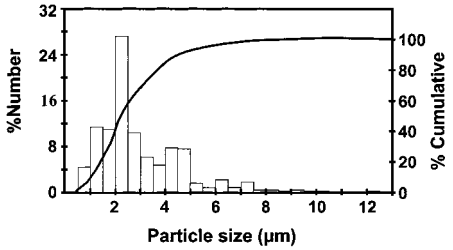

Figure 7. Particle size distribution of the micronized ibuprofen (P_{expt} = 190 bar, T_{expt} = 35 °C) after 60 s of sonication in water.

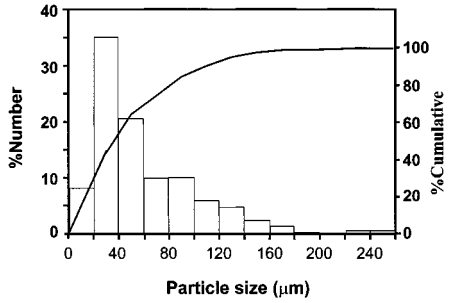

Figure 8. Particle size distribution of the unprocessed ibuprofen after 60 s of sonication in water.

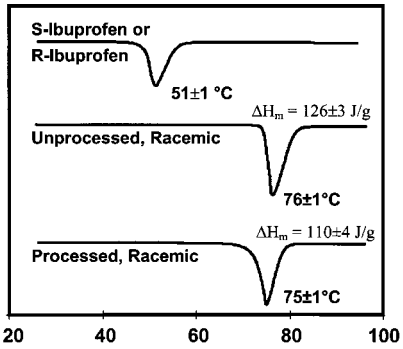

Figure 9. DSC results of ibuprofen enantiomers and racemic ibuprofen before and after RESS processing.

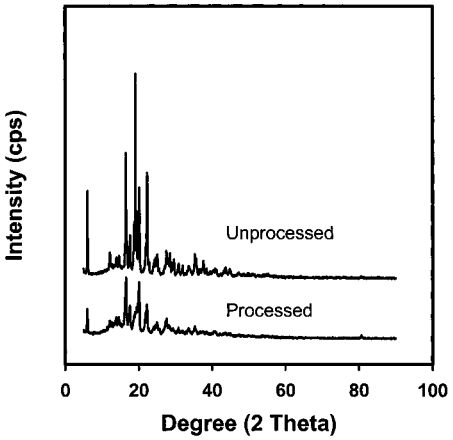

Figure 10. XRD patterns of racemic ibuprofen before and after RESS processing.

The BET surface area of the micronized ibuprofen was found to be 3.48 m^2/g, which was ≈16 times higher than that of the original material (0.22 m^2/g). The BET surface area results also confirmed that ibuprofen was micronized successfully by the RESS process.

As is illustrated in Figures 9 and 10, similar melting points and X-ray diffraction patterns were observed for the original material and the precipitates obtained by RESS. On the basis of the previous HPLC analysis, the melting point, and XRD investigations, it was confirmed that the processed ibuprofen is still a racemic compound with the retention of crystalline structure retained.

However, the heat of melting (ΔH_m) obtained from DSC analysis and the intensity of the XRD peaks of the processed ibuprofen were slightly lower compared with the original material. These results indicated a slight reduction in the degree of crystallinity of ibuprofen after processing with RESS.

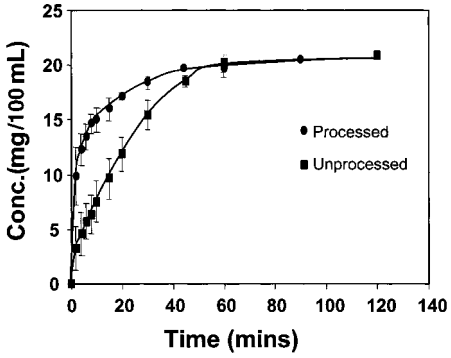

Figure 11. Dissolution profiles (in phosphate buffer solution at 37 °C, pH 6.3) of racemic ibuprofen before and after RESS processing.

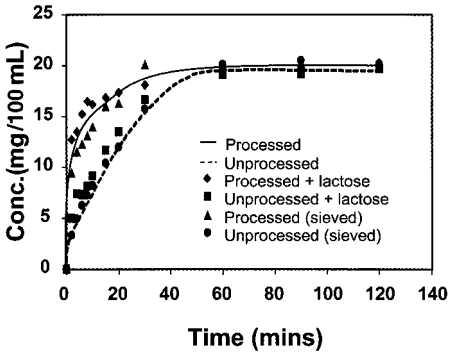

Figure 12. Effects of lactose and preconditioning of ibuprofen powders on the dissolution profiles.

Dissolution Kinetics Studies. Micronized ibuprofen precipitated at 190 bar and 35 °C was used as a representative sample for the RESS product in the dissolution kinetics studies. As a basis for comparison, the dissolution rate coefficient (K_w) is defined as the reciprocal of the time after which 63.2% of the original amount of drug has dissolved.[23]

The dissolution profiles of the original material and the processed ibuprofen are shown in Figure 11. The dissolution rate coefficient of the micronized ibuprofen was found to be 0.25 min^{-1}, which is 5 times higher than that of the original material. The enhanced dissolution rate of ibuprofen was attributed to the reduction in the particle size.

Because of the hydrophobic nature of ibuprofen, aggregation of ibuprofen powders was observed during the dissolution testing. Passing the ibuprofen powder through a 250-μm sieve or mixing with lactose (1:1 ratio) prior to the test did not improve the dispersion of ibuprofen powders in the dissolution medium. The dissolution profiles of preconditioned ibuprofen are depicted in Figure 12.

The effect of adding a surfactant on the dissolution rate of ibuprofen powders was also examined. In this study, 100 mg of sodium lauryl sulfate (SLS) was dissolved in 1 L of the dissolution medium. As can be

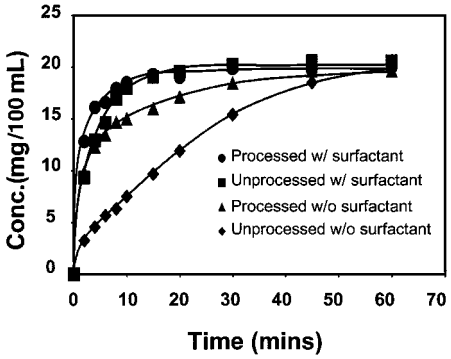

Figure 13. Effect of surfactant on the dissolution profiles of racemic ibuprofen.

Table 4. Dissolution Rate Coefficients (K_w) of Racemic Ibuprofen Powders at Various Conditions

	dissolution rate coefficient, K_w (min^{-1})	
conditions	processed	unprocessed
pure	0.25	0.05
mixed with lactose	0.35	0.06
passed through sieve	0.16	0.05
surfactant-treated medium	0.79	0.31

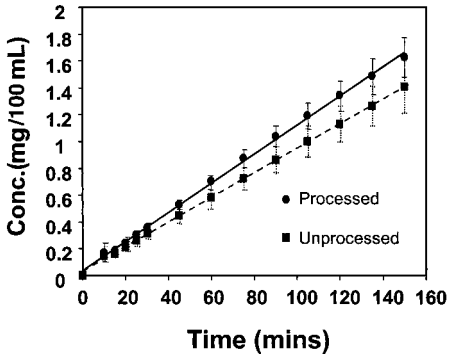

Figure 14. Dissolution profiles of compacted disks of racemic ibuprofen before and after RESS processing.

seen from Figure 13, the dissolution rates of RESS product and original material were both enhanced in the surfactant-treated medium. The dissolution rate coefficients of the micronized ibuprofen and the original material in the surfactant-treated solution, shown in Table 4, were found to be 0.79 and 0.31 min^{-1}, respectively. These enhanced dissolution rates indicated more efficient wetting and improved powder dispersion.

It was also found that the micronized ibuprofen exhibited a similar dissolution rate to that obtained for the original material combined with surfactant. This result demonstrates that the use of surfactant in the drug formulation can be eliminated when the micronized ibuprofen is used.

The effect of the degree of crystallinity on the dissolution rate was investigated by measuring the disc intrinsic dissolution rate (disc-IDR). Upon compression of a drug to form a compact disk of constant surface area, the surface area of the individual crystals is eliminated. As is illustrated in Figure 14, the disc-IDR of the processed ibuprofen was slightly higher than that of the original material. Between 45 and 120 min, it was found that the disc-IDR between the RESS product and the original material is significantly different at a 95% confidence limit. However, at other time intervals, there is no significant difference at 95% confidence limits because of large deviations of each data point. The higher disc-IDR of the processed ibuprofen resulted from the reduction in the degree of crystallinity.

The results obtained from the powder dissolution and disc intrinsic dissolution suggested that the enhanced dissolution rate of micronized ibuprofen was due to the reduction in particle size and the degree of crystallinity after the RESS process.

Conclusions

The solubility of racemic ibuprofen and its enantiomers in CO_2 were measured using a dynamic solubility measurement technique. The solubility data for racemic ibuprofen were correlated successfully using the PR EOS with van der Waals mixing rules. (S)-ibuprofen exhibited solubility in CO_2 similar to (R)-ibuprofen, and the solubility of the pure isomers was significantly higher than that of the racemic ibuprofen at the same operating conditions. Micronization of ibuprofen was successfully performed by RESS using CO_2 as a supercritical solvent. Increasing the spraying distance reduced the particle size. Although the particles obtained were aggregated, they were easily dispersed by ultrasonication in water. The powder dissolution rate of micronized ibuprofen in phosphate buffered solution was 5 times greater than that of the original material. The enhanced dissolution rate of ibuprofen was due to the reduction in both the particle size and the degree of crystallinity.

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