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Polymorphic properties of micronized carbamazepine produced by RESS

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Abstract

Carbamazepine microparticles were produced by the rapid expansion of supercritical carbon dioxide solutions (RESS) method. The characteristics of the resulting particles were studied by X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), scanning electron microscopy (SEM) and image analysis. X-ray diffractograms and SEM photomicrographs revealed that the crystalline nature of the produced carbamazepine microparticles depended on operating pressure and temperature conditions. Different polymorphs were obtained under various operating conditions. Under certain temperature (below 40 °C) and pressure (below 240 bar) conditions, it was possible to form primarily the carbamazepine polymorph stipulated by US Pharmacopeia. A significant reduction was observed in the particle size and size distribution range of carbamazepine produced by RESS. The processed particles had a mean diameter smaller than 3 μm and a size distribution range between 0.5 and 2.5 μm compared to unprocessed starting material with a mean diameter of approximately 85 μm and a size distribution range between 15 and 336 μm. Thus, this study demonstrates that the polymorphic characteristics of carbamazepine microparticles produced by the RESS method can be controlled by varying operating pressure and temperature parameters.

Keywords: Supercritical; Carbon dioxide; Polymorphism; Carbamazepine; Micronization

1. Introduction

Many substances have the ability to crystallize in more than one crystalline form. This polymorphism reflects the existence of different crystal structures which, although chemically identical, can differ significantly in their physicochemical properties. Different polymorphic forms of a drug may influence the important pharmaceutical qualities, such as tableting characteristics, dissolution profile as well as chemical and physical stability during storage (Krahn and Mielck, 1989; Kobayashi et al., 2000; Roberts et al., 2000). Targeting of pure crystalline forms often requires expensive and time-consuming operations, such as repeated re-crystallization commonly carried out from organic solvents. Thus, the investigation of alternative methods, which permit the isolation of a particular crystalline form meeting flowability, compactability, solubility and bioavailability requirements, is of primary importance for the pharmaceutical industry (Bettini et al., 2001). Solution-enhanced dispersion with supercritical fluids (SEDS^{TM}), a particle formation process using supercritical fluids as antisolvent, has proven to be efficient in producing pure

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polymorphs of sulfathiazole, salmeterol xinafoate and carbamazepine (Edwards et al., 2001; Kordikowski et al., 2001; Tong et al., 2001).

Rapid expansion of supercritical solutions (RESS) is another supercritical-based method that has been developed to obtain micronized drug particles (Turk, 1999; Charoenchaitrakool et al., 2000; Helfgen et al., 2000). In this process, supercritical carbon dioxide can be used as solvent if the molecule of interest shows sufficient solubility, and thus organic solvents can be avoided. Reasons for avoiding organic solvents include residual solvents, possibility of chemical reactivity and environmental considerations. The aim of this study is to examine the possibility of applying the RESS method to control the polymorphic properties of drugs and to obtain significant size reduction of drug particles.

Carbamazepine, an anticonvulsant, has been chosen as the model drug since four polymorphs (I–IV) and one dihydrate form have been reported in the literature (Krahn and Mielck, 1987; Matsuda et al., 1994; Rustichelli et al., 2000). In addition, control of the polymorphic properties of this drug is an important issue as USP stipulates the use of polymorph III (β-form) in pharmaceutical formulations (USP XXIV, 1999). Polymorph I is less documented in the literature compared to the other carbamazepine polymorphs. Its crystal type has not yet been identified. Polymorph II is a triclinic crystal with prismatic morphology (Ceolin et al., 1997). On the other hand, polymorphs III and IV are fully described in the literature. The International Centre for Diffraction Data (ICDD) has reported that polymorph III has a monoclinic crystal structure. This form also shows a prismatic morphology and is the most stable polymorph at room temperature (Matsuda et al., 1994). Polymorph IV, or α-carbamazepine, presents a needle-shape morphology. It crystallizes at high temperature as trigonal crystal (Lowes et al., 1987). The melting points of these four polymorphs have been reported to be in the 175–190 °C range (Behme and Brooke, 1991; ICDD, 1995a,b). Carbamazepine can also exist in a dihydrate form and crystallize in the orthorhombic system (Dugue et al., 1991; McMahon et al., 1996). This paper details the carbamazepine particles produced by the RESS method and characterized by X-ray powder diffraction, differential scanning calorimetry, scanning electron microscopy and image analysis.

2. Materials and methods

2.1. Preparation of micronized carbamazepine particles

Carbamazepine microparticles were produced by the RESS method using a custom-made laboratory scale experimental apparatus shown schematically in Fig. 1. Carbon dioxide (Praxair, UN 1013, supercritical grade 99.9997%) was the solvent of choice. The extraction unit, an empty chromatographic column with an internal diameter of 1 cm and a length of 30 cm, was loaded with 1–2 g of the carbamazepine powder (Sigma, St. Louis, MO, lot DU05104DR) mixed with glass beads to obtain a non-compressible homogeneous bed, which was placed in a thermostated oven (Hewlett-Packard 5890A oven for gas chromatography). A high performance liquid chromatography (HPLC) pump (Varian 8500) operating in the constant-pressure mode was used for the flow control of supercritical solutions. The expansion unit was composed of a 20 μm diameter nozzle fixed to a block heater. The temperature of the expansion unit was set at or above the temperature of the extraction unit.

Carbon dioxide was brought to the desired operating pressure and temperature conditions (above its critical point of 31 °C and 73 bar) by controlling oven temperature and the pump flow rate. The supercritical carbon dioxide was then allowed to pass through the extraction unit to dissolve bulk carbamazepine and

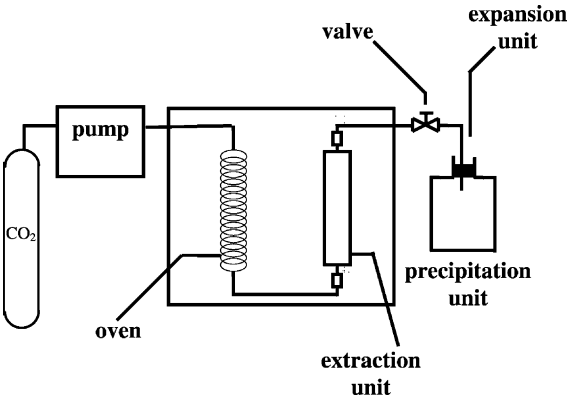

Fig. 1. Diagram of the rapid expansion of supercritical solutions (RESS) experimental apparatus.

form a supercritical solution. Particles were formed by precipitation, due to the rapid reduction of solvent density during the expansion of supercritical solution across the 20 μm opening to atmospheric conditions. Finally, carbamazepine microparticles were recovered in a glass container. Extraction temperature varied from 35 to 100 °C, expansion temperature from 75 to 130 °C, and pressure from 170 to 240 bar. The influence of extraction temperature, expansion temperature and pressure on particle characteristics was studied. Experimental runs were conducted in triplicate under each processing condition.

2.2. Characterization of carbamazepine microparticles

The crystal properties, morphology, particle size and size distribution of carbamazepine microparticles produced under different operating pressure and temperature conditions were studied.

2.2.1. Crystal properties

Polymorphic composition and degree of crystallinity were evaluated by X-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC). A DSC system (Seiko RDC 220) was used at scanning speeds of 1, 5, 10, 20, 30 and 40 °C/min in the temperature range from 30 to 235 °C to analyze 10 ± 1 mg of powder samples in sealed aluminium pans. The DSC system was calibrated for temperature and heat flow with gallium, indium and tin. X-ray powder diffraction experiments were carried out using a Siemens D-5000 X-ray diffractometer with Co Kα radiation ($\lambda = 1.7890$ Å) at a scanning speed of $0.005^\circ\ s^{-1}$ 2θ over a range of 3–40°. Silicon served as the internal standard. Diffrac AT software was used to display the X-ray diffraction patterns. Quantitative analysis of different carbamazepine polymorphs (processed drug) was possible, as the intensity of a characteristic diffraction peak of a polymorph is proportional to its weight fraction in a mixture of polymorphs of the same molecule (Klugh and Alexander, 1974; Suryanarayanan, 1995; Fagel et al., 2001). Previous studies have shown a linear relationship between the relative intensity of a characteristic peak and the amount of carbamazepine polymorphs (III, IV and the dihydrate form) in a ternary mixture (Suryanarayanan, 1989; Iyengar et al., 2001). Same relationship has been assumed in this work as well. Characteristic major peaks for each of the four carbamazepine polymorphs and the dihydrate form were chosen from the pure crystalline structure data for quantitative analysis. They were 4.47 Å at 23.32° 2θ, 6.32 Å at 16.30° 2θ, 5.82 Å at 17.57° 2θ, 17.5 Å at 5.82° 2θ and 9.97 Å at 8.90° 2θ for carbamazepine polymorphs I–IV and the dihydrate form, respectively (Lefebvre et al., 1987; ICDD, 1995a,b; Rustichelli et al., 2000).

The degree of crystallinity or fraction of crystalline material was assessed by comparing the integrated area of the diffracted peaks (crystalline structures) with the integrated intensity of the background peaks (amorphous structures) (Jenkins, 2000). The amorphous substances showed more background noise as they led to wider peaks with less intensity (Suryanarayanan and Mitchell, 1985). Therefore, the degree of crystallinity was calculated from the ratio of the total area under the curve after subtracting the background noise on the total area. This method permitted rank ordering of the varying degrees of crystallinity of the samples, independently of polymorphic composition.

2.2.2. Particle morphology

The microparticles were evaluated morphologically by scanning electron microscopy (SEM, Jeol JSM-820). They were attached to the specimen holder with double-coated adhesive tape and were gold-coated with an Edwards Auto 306 sputter coater for 2 min at 10 kV/20 mA. Pictures were taken at 5.0 kV and magnifications of 75× and 5000×.

2.2.3. Particle size and size distribution measurements

Particle size and size distribution range were determined by image analysis of photomicrographs. Fifty particles were selected and analyzed by Grafter Ultimage X-1.41 software. Particle size was determined by Waddel disk diameter, which is the diameter of a circle of the same area as the particle.

3. Results and discussion

3.1. Crystal properties

Fig. 2 is selected diffractograms of unprocessed carbamazepine particles and of those produced by the

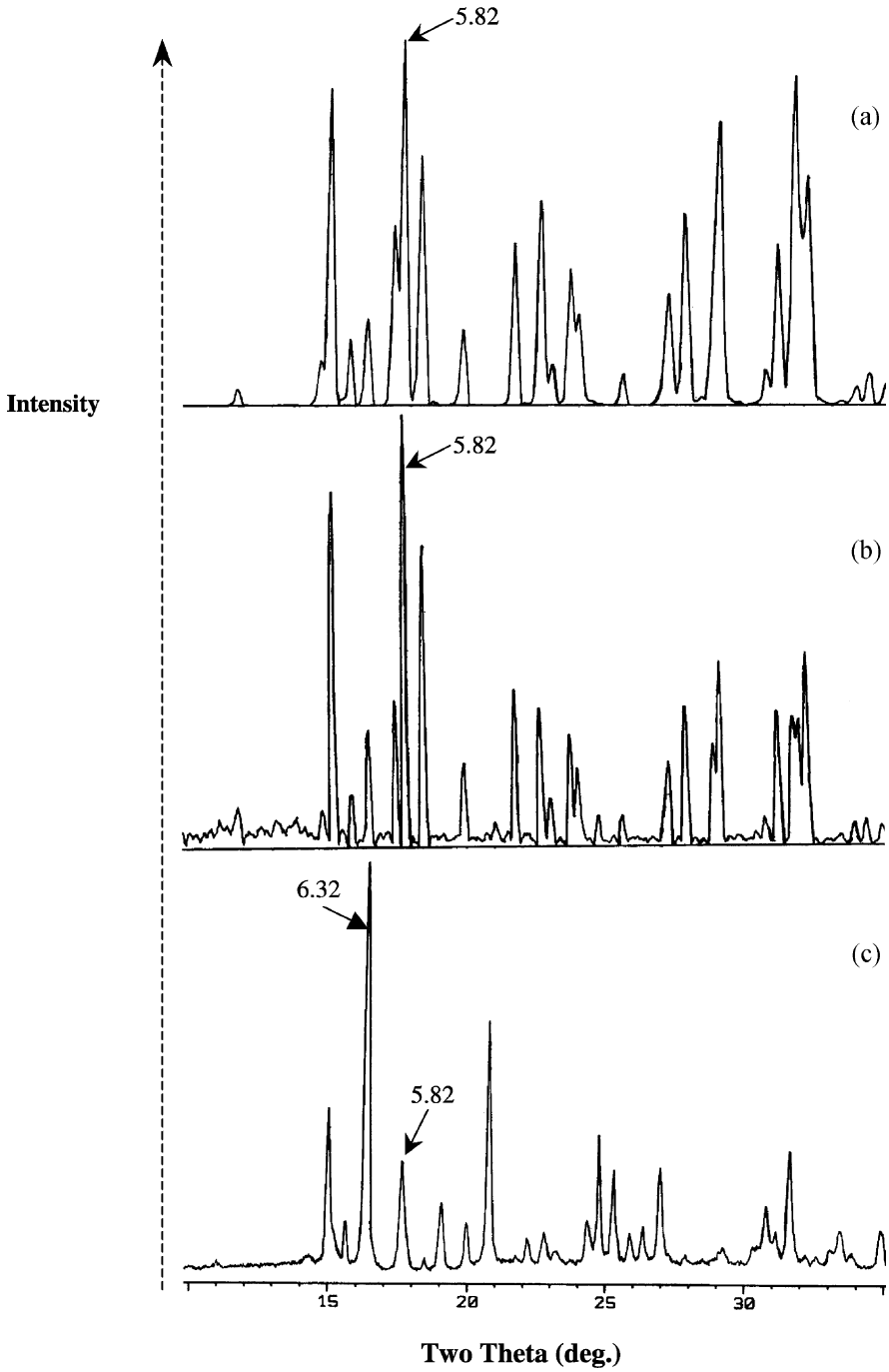

Fig. 2. X-ray powder diffractogram of (a) USP β-carbamazepine unprocessed starting material (polymorph III), (b) USP β-carbamazepine particles prepared by the RESS method under operating condition 2 of 170 bar at an extraction temperature of 35 °C and an expansion temperature of 75 °C (polymorph III) and (c) carbamazepine prepared by the RESS method under operating condition 3 of 170 bar at an extraction temperature of 55 °C and an expansion temperature of 75 °C (mixture of polymorphs II and III).

Table 1
Crystal properties, degree of crystallinity, size and size distribution of carbamazepine particles produced by the rapid expansion of supercritical solutions method under different operating conditions of pressure (bar), extraction temperature (°C) and expansion temperature (°C)

No.	Operating conditions			Polymorphic forms (%)				Degree of crystallinity (%)	Diameter (μm)	
	Pressure (bar)	Extraction temperature (°C)	Expansion temperature (°C)	I	II	III	IV		Mean	Size distribution
1	Unprocessed starting material			–	–	100	–	89.1	84.64	[15.12–336.11]
2	170	35	75	–	–	100	–	68.6	0.97	[0.60–1.83]
3	170	55	75	–	71	29	–	57.9	1.21	[0.73–1.82]
4	170	75	75	2	71	24	3	75.4	1.51	[0.83–2.20]
5	200	35	75	–	–	100	–	64.4	1.14	[0.68–1.85]
6	240	35	75	12	18	70	–	58.6	1.27	[0.49–2.47]
7	240	40	85	6	74	20	–	44.9	0.91	[0.49–1.28]
8	240	60	85	4	76	20	–	42.1	0.80	[0.41–1.99]
9	240	100	135	9	59	17	15	57.4	0.85	[0.26–2.60]

RESS method at different pressures (P), extraction temperatures (T) and expansion temperatures (T_{exp}). The polymorphic composition and degree of crystallinity are listed in Table 1.

3.1.1. Polymorphic composition

Depending on the operating parameters, processed carbamazepine particles presented different diffraction patterns. Fig. 2(a) illustrates the XRPD pattern of unprocessed carbamazepine, which corresponds to USP β-carbamazepine (polymorph III), and Fig. 2(b) shows the XRPD pattern of particles produced under condition 2 where pure USP β-carbamazepine (polymorph III) was formed. The peak assignation on Fig. 2(a) and (b) was identical as they represented samples constituted of the same polymorph. For this polymorph, the peak with maximum intensity was found at 17.57° 2θ. Similar XRPD patterns of powder were obtained under conditions 5 and 6, where polymorph III was also primarily produced. Fig. 2(c) reveals the XRPD pattern of particles produced under condition 3, which are primarily constituted of polymorph II. Similar XRPD patterns of powder were obtained under conditions 4, 7–9 where polymorph II was also primarily produced. In these cases, the peaks showing maximum intensities were found at 16.30° 2θ.

Characteristic peaks of all the four polymorphs of carbamazepine were found under some operating conditions (conditions 4 and 9). However, the dihydrate form was not detected in the pressures and temperatures range employed in this study, which is not surprising as there was no water involvement in the RESS method. The most important result of our work is that under certain operating conditions (2 and 5), the specific crystal form required by USP for pharmaceutical applications (polymorph III) could be produced.

It appears that pressures below 200 bar combined with extraction temperature of 35 °C and expansion temperature of 75 °C led to the crystallization of pure β-carbamazepine (polymorph III). Under pressure at 240 bar and extraction temperature at 35 °C, USP carbamazepine was still produced primarily but with small quantities of polymorphs I and II. Those results seem to indicate that the primary factor leading to the formation of pure or mixtures of polymorphs may be the temperature. Indeed, polymorph III was produced only at the lower conditions of temperature (conditions 2, 5 and 6). Crystallization temperatures near room temperature led to the formation of this crystal type, which shows higher thermodynamic stability in this range. With increasing temperature (extraction and expansion) and pressure, other polymorphs appeared in varying proportions. At elevated extraction and expansion temperatures, polymorph II was produced. This demonstrates that extraction temperatures higher than 35 °C and expansion temperatures higher than 75 °C mostly led to the formation of polymorph II and is independent of the pressure conditions. Polymorphs I and IV were obtained only in traces under the conditions studied. Polymorph I was produced at high pressure (240 bar) as well as at high extraction temperature (75 °C) combined with low pressure (170 bar). Polymorph IV was generated only under extraction temperatures higher than 75 °C.

3.1.2. Degree of crystallinity

As listed in Table 1, the RESS process leads to amorphous materials when compared to the unprocessed starting material. This can also be seen in comparing Fig. 2(a) (unprocessed material XRPD) and Fig. 2(b) (processed particles XRPD). Indeed, processed particles, even composed of the same crystal type as starting material, showed more background (characteristic to amorphous materials) in diffraction patterns. The starting material had 89% degree of crystallinity and particles produced by RESS method have 42–75% crystallinity, depending on the operating conditions. Increasing pressure seemed to lead to less crystalline materials for samples that were composed of polymorph III. Samples comprised of polymorph II were the most amorphous materials produced during this study and increasing pressure and temperature seem to result in less crystalline materials. It has been observed that the presence of polymorph IV resulted in a significant increase in the degree of crystallinity.

3.1.3. Differential scanning calorimetry (DSC) analysis

DSC is usually combined with XRPD to determine polymorphic composition of pharmaceutical powders, when the polymorphs present different melting points. Fig. 3 shows a DSC curve of the starting material, which was composed of pure USP carbamazepine. It was obtained from analysis performed at a heat rate of 1 °C/min that is typical for non-conductive material such as pharmaceutical powder. The graph shows a unique melting point at 190 °C and an enthalpy of fusion of 109 J/g, which correspond to thermodynamic data of polymorph IV. In fact, it was observed that any crystal type of carbamazepine was transformed into polymorph IV as the temperature was increasing during DSC analysis, especially at slow heating

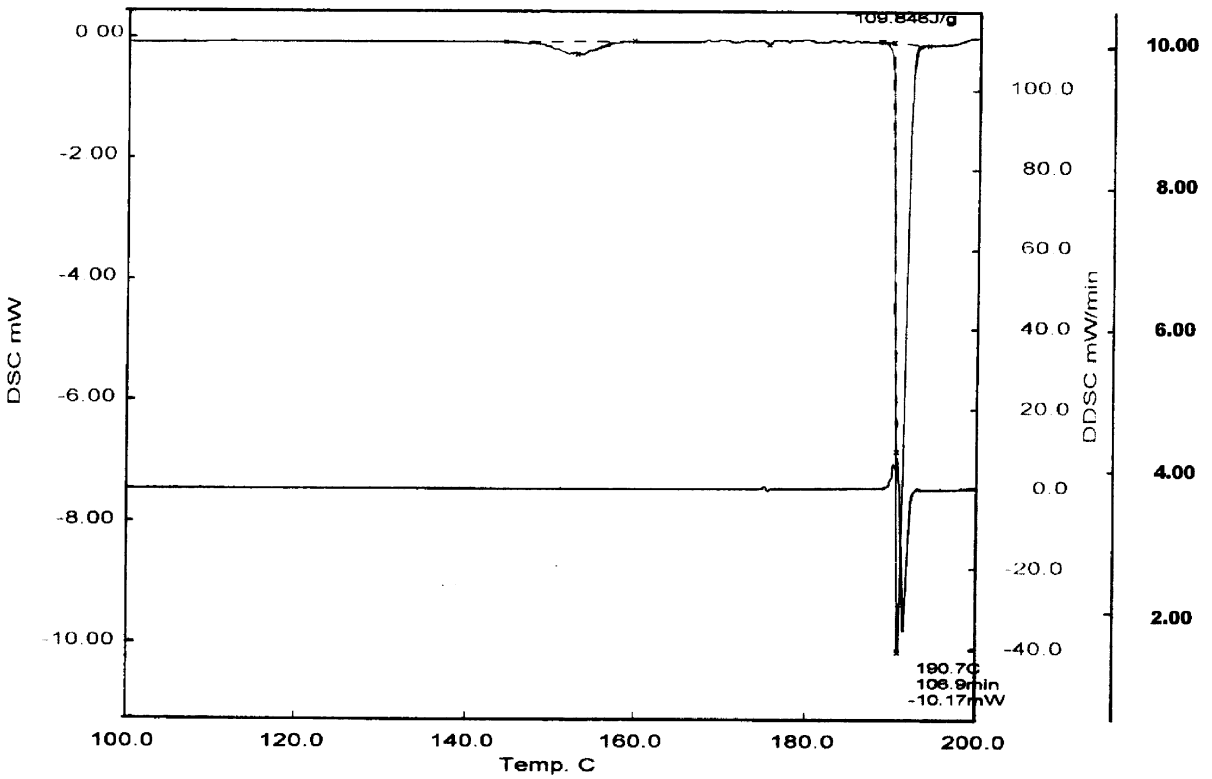

Fig. 3. Differential scanning calorimetry curve of USP β-carbamazepine unprocessed starting material (polymorph III). The USP form was transformed to polymorph IV (melting point of 190 °C) during the analysis.

rates. This phenomenon also appears at heating rates as high as 40 °C/min. As DSC is a dynamic method, the heating rate impeded possible quantitative analysis of polymorphic composition of carbamazepine particles because phase transitions occurred during analysis.

3.2. Particle morphology

Fig. 4 presents a photomicrograph of the prismatic morphology of unprocessed starting material composed of large particles of USP carbamazepine (polymorph III). Fig. 5 is a photomicrograph of processed carbamazepine under operating pressure and temperature conditions (2) where USP carbamazepine was primarily produced. It had a prismatic morphology as the starting material, but a significant size reduction of particles can be seen compared to the starting material. Microparticles obtained under operating conditions 5 and 6 of 200 and 240 bar, respectively, at the same extraction (35 °C) and expansion (75 °C) temperatures, showed prismatic morphology similar to that found under operating condition 2. Fig. 6 reveals a photomicrograph of processed carbamazepine under operating temperature and pressure conditions (3) where polymorph II was primarily produced. It also had a prismatic morphology, although different from that of USP carbamazepine. Indeed, single particles of polymorph II are more elongated than particles of USP carbamazepine. Similarly, operating conditions 4, 7–9 resulted in microparticles rich in polymorph II with elongated prismatic morphology. Fig. 7 out lines the needle-shape of polymorph IV crystals, which

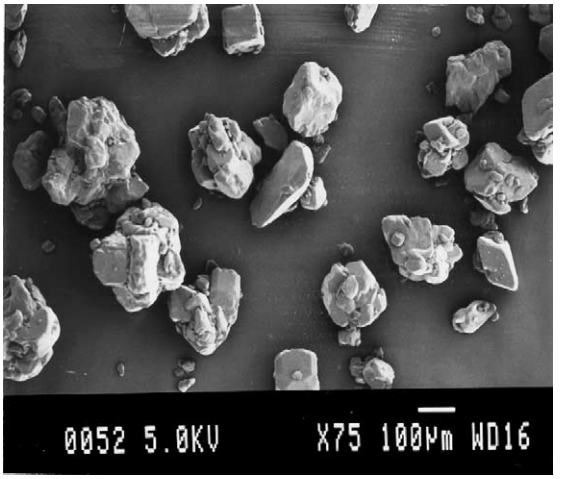

Fig. 4. Photomicrograph produced by scanning electron microscopy showing the prismatic morphology of carbamazepine unprocessed starting material at 5.0 kV (75×).

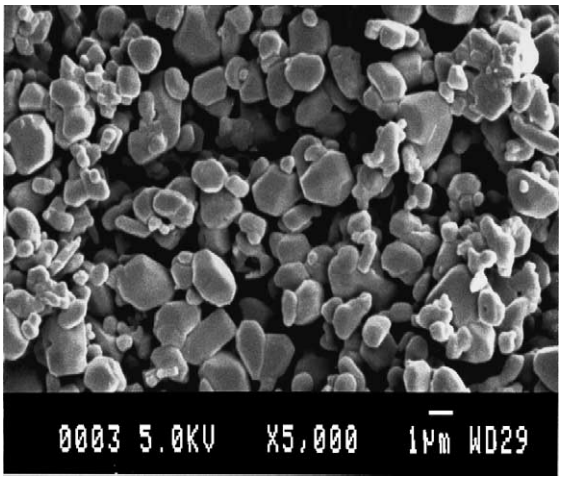

Fig. 5. Photomicrograph produced by scanning electron microscopy showing the prismatic morphology and the small size of USP β-carbamazepine particles prepared by the RESS method under operating condition 2 of 170 bar at an extraction temperature of 35 °C and an expansion temperature of 75 °C (5000×).

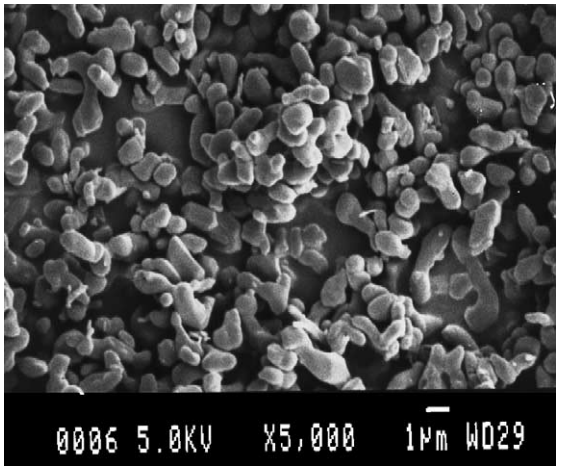

Fig. 6. Photomicrograph produced by scanning electron microscopy showing the elongated prismatic morphology of polymorph II particles of carbamazepine prepared by the RESS method under operating condition 3 of 170 bar at an extraction temperature of 55 °C and an expansion temperature of 75 °C (5000×).

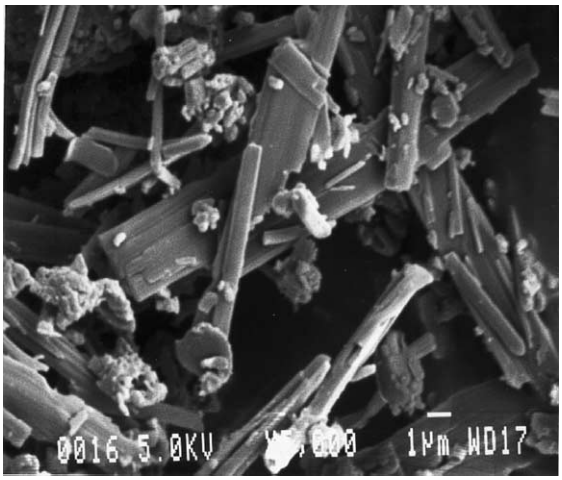

Fig. 7. Photomicrograph produced by scanning electron microscopy showing the needle-shaped morphology of polymorph IV particles of carbamazepine prepared by the RESS method under operating condition 9 of 240 bar at an extraction temperature of 100 °C and an expansion temperature of 135 °C (5000×).

comprised 15% of the sample obtained at condition 9. The majority of particles produced under condition 9 still presented a prismatic morphology.

3.3. Particle size and size distribution measurements

Particle size and the size distribution range of carbamazepine were significantly reduced by the RESS method, as shown in Table 1. Carbamazepine particles used as the starting material had a mean diameter of approximately 85 μm with a wide size distribution range between 15 and 336 μm. Under the different operating pressure and temperature conditions, processed particles were similar in size and size distribution range. They had a mean diameter smaller than 3 μm and a narrower size distribution range between 0.5 and 2.5 μm. The rapid nucleation that occurs because of the enormous pressure gradient between the expansion unit (170–240 bar) and atmospheric conditions (1 bar) caused the formation of micronized particles with narrow size distribution. Even though several crystal types were produced with different operating conditions, no correlation between the particle size and size distribution is noticed for carbamazepine in this study.

4. Conclusion

This study demonstrates that the RESS method could be potentially used to control the crystal structure of drug particles by varying pressure and temperature conditions. In addition, it could significantly reduce the particle size and size distribution of bulk drug in the same one step process. For carbamazepine, depending on the operating parameters, different diffraction patterns were observed. All four polymorphs of carbamazepine were produced under particular operating conditions. The most significant result of this study is that we were able to demonstrate that, for the anticonvulsant drug carbamazepine, the specific crystal form required by the USP for pharmaceutical formulations can be obtained by the RESS method.

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