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Processing of carbamazepine–PEG 4000 solid dispersions with supercritical carbon dioxide: preparation, characterisation, and in vitro dissolution

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Abstract

The purpose of this study was to apply the attractive technique of the supercritical fluid to the preparation of solvent-free solid dispersions. In particular, the gas antisolvent crystallisation technique (GAS), using supercritical carbon dioxide as processing medium, has been considered to prepare an enhanced release dosage form for of the poorly soluble carbamazepine, employing PEG 4000 as a hydrophilic carrier. The physical characterisation of the systems using laser granulometer, powder X-ray diffraction, thermal analyses, and scanning electron microscopy was carried out in order to understand the influence of this technological process on the physical status of the drug. The results of the physical characterisation attested a substantial correspondence of the solid state of the drug before and after treatment with GAS technique, whereas a pronounced change in size and morphology of the drug crystals was noticed. The dramatic reduction of the dimensions and the better crystal shape, together with the presence of the hydrophilic polymer determined a remarkable enhancement of the in vitro drug dissolution rate.

Keywords: Gas antisolvent crystallisation; Supercritical fluids; Solid dispersions; Carbamazepine; PEG 4000; Physico-chemical characterisation

1. Introduction

For poorly soluble orally administered drugs, the rate of absorption is often controlled by the rate of dissolution of the drug in the gastrointestinal tract. Many technological methods of enhancing the dissolution characteristics of slightly water-soluble drugs have been reported in literature, such as micronisation, formation of solvates, adsorbates, complexes, microspheres, or more often, solid dispersions. However, besides the tremendous potential of solid dispersions systems

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of improving drug dissolution, the methods traditionally used to prepared these systems determine serious limitations on their applicability in the market, often implying physical instabilities of the solid dispersions on storage, problems of grinding or difficult removal of the solvent (Bloch and Speiser, 1987; Greenhalgh et al., 1999; Serajuddin, 1999). To overcome these problems a technology using supercritical fluids (SCFs) has been proposed to prepare solvent-free solid dispersions systems having reduced dimensions without the need of a grinding procedure. Only a few researchers have successfully used this technology in this sense (Sencar-Bozic et al., 1997; Kerc et al., 1999), even though SCFs have demonstrated to be promising extraction media for the formation of microparticles of drugs and biodegradable polymers (McHugh and Krukonis, 1994; Subramaniam et al., 1997; Steckel et al., 1997; Thies and Müller, 1998; Ghaderi et al., 2000; York, 2000). Compared to the above mentioned investigations focused on the preparation of solid dispersions where the particles were generated from gas saturated solutions (PGSS), in this research the gas antisolvent crystallisation technique (GAS) using supercritical carbon dioxide as a processing medium has been considered.

Carbon dioxide (CO_2) was chosen among the supercritical fluids because is nontoxic, nonflammable, inexpensive and it has a relatively high dissolving power and in consideration of its relatively low critical parameters ($T_c = 31.1$ °C, $P_c = 73.8$ bar). The properties make CO_2 particularly attractive for processing heat-sensitive pharmaceuticals (McHugh and Krukonis, 1994).

The gas antisolvent crystallization (GAS) was described by Gallagher et al. (1989). The relatively low solubilities of pharmaceutical compounds in unmodified CO_2 are exploited in this process wherein the solute of interest (typically a drug, polymer or both) is dissolved in a conventional solvent to form a solution. When the supercritical gas is added, the liquid phase expands and the solubility of solute decreases until the solute precipitates to form particles. Advantages include higher solute throughput and flexibility of solvent choice. GAS technique is of interest in the formation of fine peptide and protein powders and polymer microspheres (Subramaniam et al., 1997; Reverchon, 1998, 1999).

The aim of this research was to apply this technique to develop a solid delivery system able to improve the rate and extent of the dissolution of carbamazepine (CBZ). This anticonvulsant drug is practically insoluble in water (about 170 mg/l at 25 °C) and its absorption after oral administration is very slow and irregular because of limited dissolution rate (Levy et al., 1975). There are many reports in the literature concerning the polymorphic transformations of this drug (Krahn and Mielck, 1987; Lowes et al., 1987; Roberts and Rowe, 1996; Rustichelli et al., 2000).

Polyethylene glycol 4000 has been chosen as carrier for its well known favourable solution properties. Previous data have shown that this low-meltable polymer in solid dispersions is able to increase the dissolution rate of low water soluble drugs, included carbamazepine (Craig, 1990; Doshi et al., 1997).

The binary systems prepared with several carrier contents, were characterised with laser granulometer, powder X-ray diffraction (PXRD), thermal analyses (DSC and hot-stage microscopy) and scanning electron microscopy (SEM), in order to understand the influence of the technological process on the physical, morphological and dissolution properties of the drug.

2. Materials and methods

2.1. Materials

Crystalline carbamazepine, with a melting point of 192 °C (DSC method) and a geometric mean diameter by weigh of 284 μm (95% 184–433 μm), was kindly donated by Zanchetta (Montecarlo-Lucca, Italy). The carrier was PEG 4000 with a melting point of 60 °C, purchased from ACEF (Fiorenzuola D'Arda-Piacenza, Italy). The chemicals were of reagent-grade. All the solvents used were of analytical grade.

2.2. Coprecipitate preparation

The detailed experimental equipment has been already presented by Kikic et al., (1998).

A precipitation vessel with a nominal capacity of 50 ml was loaded with a 7 ml solution of pure drug or CBZ:PEG in acetone. The supercritical CO_2 was added from the bottom of the chamber and when the liquid phase expanded, the formed particles were retained in the vessel by a suitable filter. During the coprecipitate formation, the pressure was fixed at 70 bar and the temperature at 40 °C.

The following CBZ: PEG weight ratios were used to prepare binary systems: 5:1 (A), 1:15 (B) and 1:11 (C)%.

2.3. Assay of the total drug content

Known amounts of the prepared samples were dissolved in ethanol and then the drug content was evaluated spectrophotometrically at 285 nm (Mod. 552, Perkin Elmer, Padova, Italy).

2.4. Particle size

Particle size analysis and dynamic shape characterisation of the coprecipitates were determined using a laser diffractometer Galai Mod.CIS-100 (Tecno Galenica s.r.l., Cernusco S/N, Milano, Italy)

The samples were suspended by magnetic stirring and ultrasonic treatment in a 1:1 w/w paraffin oil–*n*-heptane mixture containing a dispersing agent (0.1% dioctyl sulphosuccinate sodium salt).

2.5. Powder X-ray diffraction studies (PXRD)

Samples were studied by means of PXRD technique using a STOE D500 diffractometer with Cu Kα radiation, monochromatised by a secondary flat graphite crystal. The scanning angle ranges from 5 to 35 ° of 2θ, steps were of 0.1° of 2θ, and the counting time was of 1 s/step. The current used was 20 mA and the voltage 40 kV.

2.6. Differential scanning calorimetry (DSC)

Calorimetric analyses were performed with a DSC mod. TA 4000 (Mettler, UK), equipped with a measuring cell DSC 20. Samples, containing about 2 mg of carbamazepine were placed in pierced aluminium pans and heated at a scanning rate of 10 °C per min from 30 to 200 °C.

2.7. Hot-stage microscopy (HSM)

Physical changes in the samples on heating were monitored performing hot stage microscopy studies. A hot plate (FP 52 Mettler, Greifensee, Switzerland), connected to a temperature controller (FP 5 Mettler) was used. A little amount of each sample was placed on a glass slide with a cover glass and heated at 10 °C/min in the temperature range of 30–200 °C. The changes in the samples were observed via an optical microscope (Reichert Biovar, Wien, Austria; magnification 10 ×).

2.8. Scanning electron microscopy analyses (SEM)

The shape and surface characteristics of pure components and binary systems were observed by SEM. Samples were sputter-coated with Au/Pd using a vacuum evaporator (Edwards, Milano, Italy) and examined using a scanning electron microscope (model 500, Philips, Eindhoven, The Netherlands) at 10 kV accelerating voltage using the secondary electron technique.

2.9. Determination of drug dissolution

Carbamazepine release profiles were obtained according to the USP XXIII paddle method: 100 rpm, 900 ml of water as dissolution medium, $T = 37 \pm 0.1$ °C, sink conditions ($C < 0.2C_s$). The aqueous solution was filtered and continuously pumped to a flow cell in a spectrophotometer and absorbances were recorded at 285 nm. PEG 4000 did not interfere with the UV analysis. Experimental points were the average of at least three replicates, and standard deviations did not exceed 3% of mean value. Dissolution profiles were com-

pared to that of the pure carbamazepine, at the same experimental conditions.

3. Results and discussion

The analyses of drug content confirmed the theoretical values of the formulations.

The dissolution profiles of the binary systems are shown in Fig. 1, compared with the dissolution profiles of CBZ treated and untreated with supercritical CO_2. The results presented here demonstrated that the use of PEG as solid dispersion carrier increased the rate and extent of dissolution of CBZ. Furthermore, a direct correlation between the increase of polymer content and dissolution enhancement was observed. This phenomenon could be ascribed to the solubilising effect of PEG (Doshi et al., 1997).

The comparison between CBZ treated with GAS and untreated gave the following results: the first one exhibited 50 and 90% of dissolution in 5 and 12 min, respectively (D_{50} and D_{90}); whereas commercial sample provided a D_{50} of 30 min and D_{90} of 120 min. These great differences among the two dissolution rates were due to the GAS micronising effect (5,7,10). In fact, from granulometric analyses, the particle size of the pure drug was reduced from 284 to 31 μm.

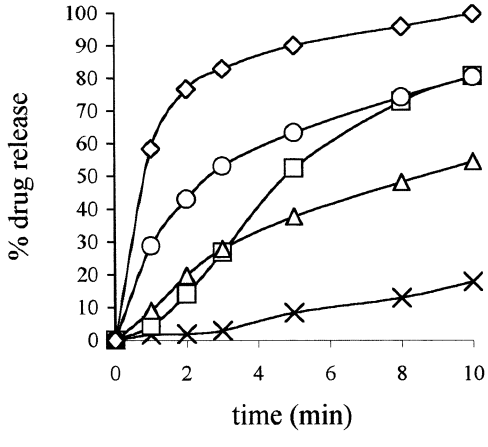

Fig. 1. Dissolution profiles of untreated CBZ (×); treated CBZ (△); 5:1 system (□); 1:1.5 system (○); 1:11 system (◇).

In Fig. 2a,b the SEM pictures of CBZ samples before and after GAS process are presented.

Photomicrographs illustrate that the GAS method changed the appearance of the size and crystal morphologies among the two samples. In fact, besides the particle size reduction, the untreated CBZ were mainly characterised by well-defined prisms (Fig. 2a) while crystals with predominantly needle-like structures were present in CBZ treated (Fig. 2b). This sample was a light voluminous powder, quite similar to supercritical CO_2 precipitates of griseofulvin previously obtained by Reverchon et al. (1995) and, more recently, by Sarkary et al. (2000). The needle-like structures of the treated crystals were also evident from the results of image analysis, as shown in Fig. 3a. It is reasonable that this better crystal shape of the treated CBZ favoured the dissolution process, as previously reported by Giunchedi et al. (1990).

SEM analyses of binary systems are showed in Fig. 2d–f.

In the 5:1 sample, discrete needle shape particles of CBZ could be easily recognised together with a few porous PEG agglomerates. In the 1:1.5 system, a certain degree of adhesion between different crystals of CBZ and the polymer was observed. A further increase of the polymer content determined the formation of large agglomerates and the particles of the drug could not be recognised. This phenomenon could be ascribed to the fusion of the polymer during the process. In fact, other authors observed a reduction of its melting point, due to the CO_2 solubility into this polymer (Daneshvar et al., 1990; Weidner et al., 1997; Wiesmet et al., 2000).

These findings were in complete agreement with the results of image analysis of the performed binary systems (Fig. 3c–e).

The morphological structure of the polymer after treatment has been observed with SEM, showing the presence of agglomerates with a porous surface (Fig. 2c).

In order to study the solid state of the drug and to check whether the changes in the crystal morphology corresponded to a polymorphic transition, X-ray powder diffraction analysis were conducted. The PXRD patterns of CBZ before and after GAS process are shown in Fig. 4a,b.

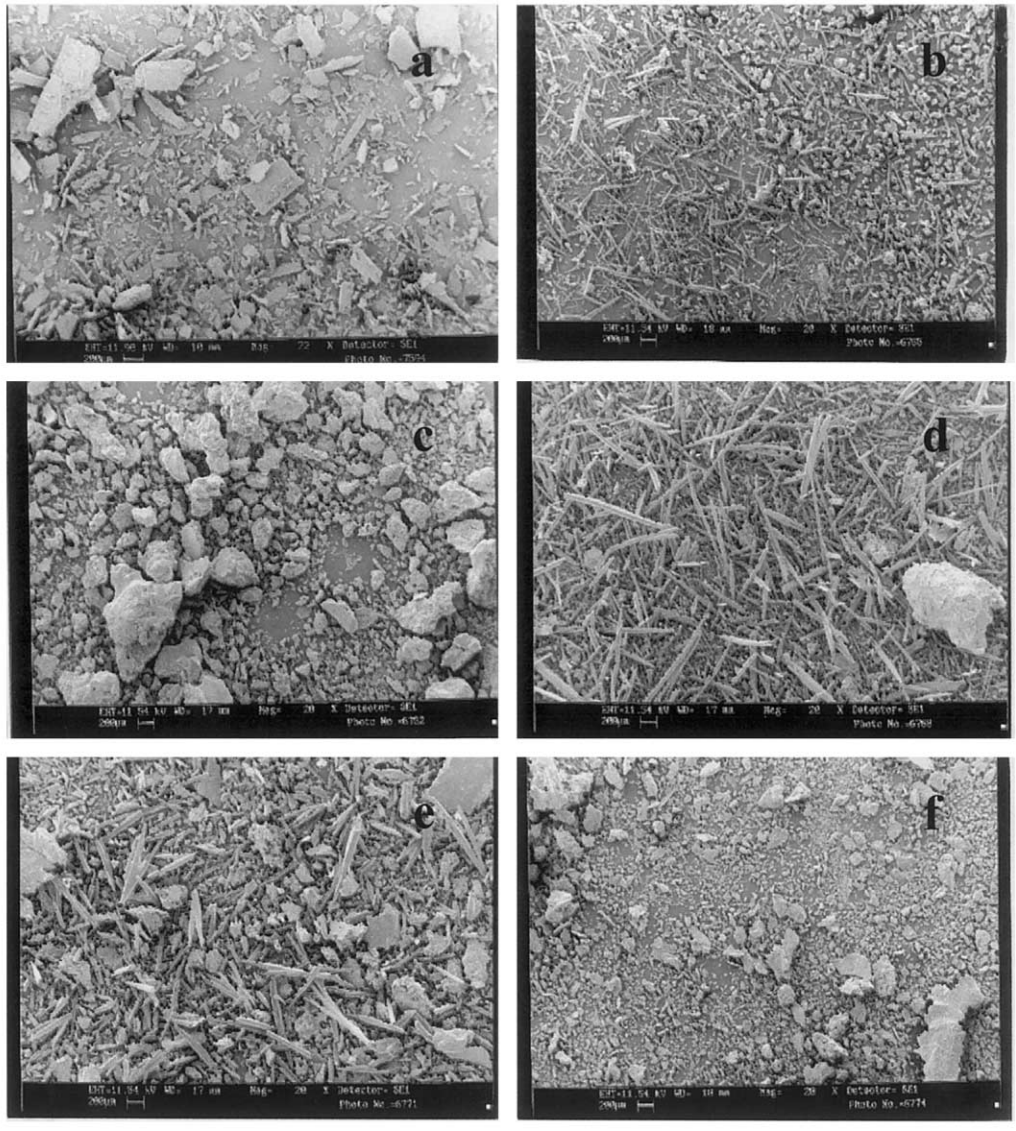

Fig. 2. SEM pictures of (a) untreated CBZ; (b) treated CBZ; (c) treated PEG; (d) 5:1 system; (e) 1:1.5 system; (f) 1:11 system.

The analysis of starting CBZ clearly showed that the sample was a mixture of β and α forms. The peaks at values lower than 10° of 2θ, having low intensities, were attributable to the trigonal form (Lowes et al., 1987). On the other hand, several signals corresponded to β carbamazepine USP reference standard and to the form reported by the International Centre for Diffraction Data. In the X-ray diffraction patterns of CBZ treated by supercritical fluid the presence of a mixtures of the two polymorphic forms was reconfirmed, and an increase of intensity of the peak at 9° of 2θ, typical of the α form, was noticed. Hence, no evidence of significant structural changes into the solid state of the treated drug could be attested.

Fig. 4e–g reports the X-ray diffraction patterns of the binary systems: the diffractograms showed that the drug was still present in a microcrys-

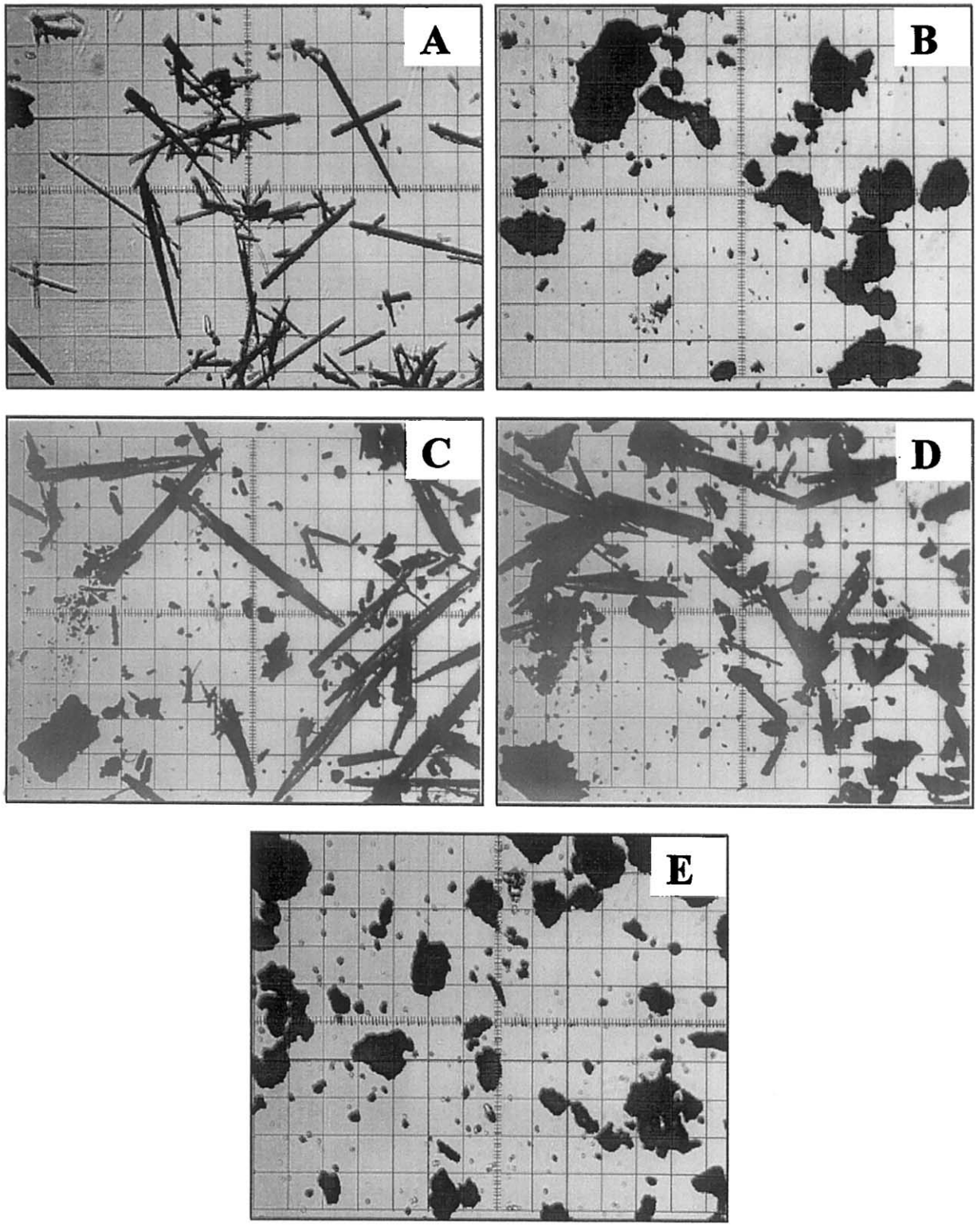

Fig. 3. Image analyses of (a) treated CBZ; (b) treated PEG; (c) 5:1 system; (d) 1:1.5 system; (e) 1:11 system.

talline in all the drug to polymer ratios. Furthermore, the peaks attributable to the drug completely corresponded to the patterns of the treated CBZ.

The treatment of PEG 4000 with GAS technique did not alter the PXRD pattern from that of the original material (Fig. 4c and d). In fact, the two major reflections at 2θ angle of 19.2 and 23.4° and some multiplets with lower intensity, typical of pure PEG 4000 (Lin and Cham, 1995; Martínez-Oharríz et al., 1999), were also detected in the spectrum of PEG with supercritical CO_2. If anything could be said, a small reduction of the intensity of the main PEG peaks was noticed, suggesting a possible decrease in its crystallinity.

DSC thermograms of drug and polymer before and after CO_2-treatment, are shown in Fig. 5. The DSC traces of pure (Fig. 5d) and treated drug (Fig. 5c) only showed a melting endotherm at about 192 °C with a heat of fusion of 103.5 J/g. In order to understand whether a polymorphic transition happened during the process, the same analyses were performed using a different scanning rate, as previously suggested by Rustichelli et al. (2000). In fact, the DSC traces, as well as the melting point values, depend on the analytical heating rate, and it is possible to observe very different curves owing to differences in the rate of transformation CBZ β form → α form: a low scan rate causes the solid-solid transition into form α around 155 °C and hence, the thermogram shows only the correspondent peak of fusion at about 190 °C. Hence, the DSC analyses of treated and starting CBZ were repeated performing the analysis at 40 °C/min and the corresponding DSC traces are reported in Fig. 5a and b. In this case, two endotherms of fusion are present: the first peak corresponded to the melting of β form (m.p. about 175 °C), followed by crystallisation and melting of α form (m.p. about 190 °C). No differences were found between treated and untreated CBZ, reconfirming the findings of the PXRD analysis.

In Fig. 5e and f the DSC traces (performed at 10 °C/min) of starting and treated polymer are depicted. The analysis of the untreated PEG 4000 trace shows a melting peak at 62.3 °C with a fusion enthalpy of 190.3 J/g. After GAS process the melting peak shifted to 60.6 °C and a decrease of the fusion enthalpy was noticed ($\Delta H =$

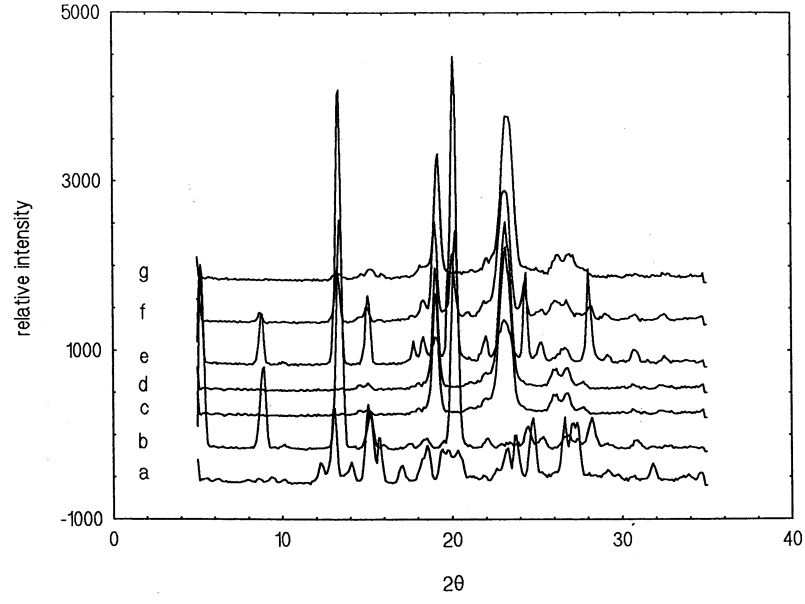

Fig. 4. XRD patterns (a) untreated CBZ; (b) treated CBZ; (c) untreated PEG; (d) treated PEG; (e) 5:1 system; (f) 1:1.5 system; (g) 1:11 system.

162.1 J/g), with a crystallinity loss of 15%. Moreover, the treated polymer exhibited a more pronounced pretransition, that may be attributed to the melting of the polymer folded chains as previously underlined by Kovacs and Gonthier (1972). A weak exothermal inflection in the baseline of the polymer was then detected at about 150 °C, attesting its instability on heating. Similar effects have been reported by Dordunoo et al. (1991). The decomposition of the polymer also occurred in the 1:11 solid dispersion and it was probably responsible for the masking of the CBZ peak, which was absent in the thermogram of this system (Fig. 5i). In fact, increasing the amount of drug (1:1.5 system) three events were recognisable into the DSC trace: the melting of the polymer, its decomposition and finally the melting of the drug, corresponding to the broad endotherm appearing at about 180 °C (Fig. 5h). These three events were even better recognised in the 5:1 system (Fig. 5g).

The thermomicroscopic examination of the commercial carbamazepine revealed the presence of prismatic and needle-shape particle with various dimensions, confirming the results of SEM and image analysis. These findings were also in agreement with the results of the PXRD studies, attesting the presence of both β and α form, having habit prismatic and needle, respectively (Roberts and Rowe, 1996). After dynamic heating, around 177 °C the drug underwent a phase transition from β to α-polymorph, and only appeared as needle-shape particles. The drug subsequently melted at 190 °C, according to the endothermic event registered by DSC. The treated carbamazepine mainly appeared as needle particles, even if few prismatic crystals could also be found. It must be pointed out that CBZ only existed as little particles.

In the solid dispersions 1:11, in the range of temperature from 30 to 60 °C the identification of drug particle was not possible by optical microscopy. After heating to 65 °C the PEG melted and CBZ could be easily recognised as dispersed particles surrounded by the molten base. In the binary systems with an higher CBZ content, the drug particles were detectable since the beginning of the analysis. In the 1:1.5 system the drug particles were mostly arranged into little agglomerates made of few crystals, subsequently disinte-

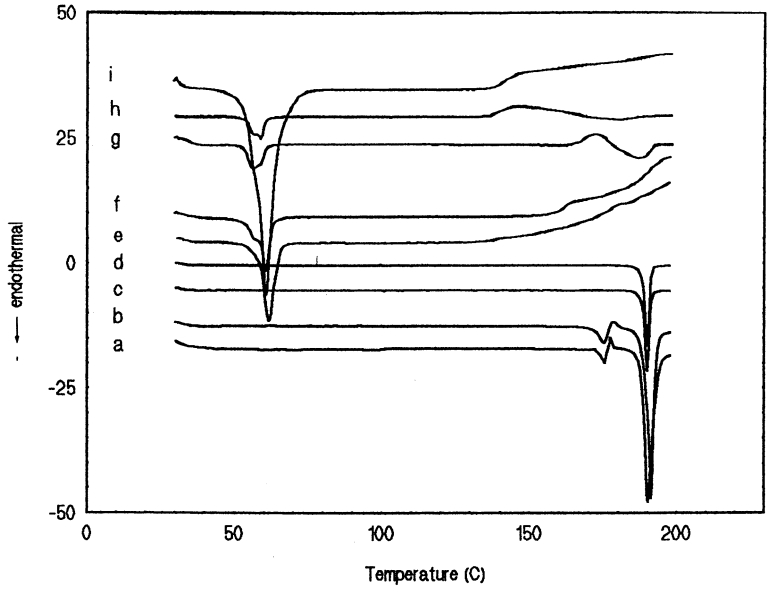

Fig. 5. DSC traces of (a) treated CBZ (scanning rate of 40° min^{-1}); (b) untreated CBZ (scanning rate 40° min^{-1}); (c) treated CBZ; (d) untreated CBZ; (e) untreated PEG; (f)treated PEG; (g) 5:1 system; (h) 1:1.5 system; (i) 1:11 system.

grating after the fusion of the carrier in single crystals of CBZ. The fusion of the drug occurred at about 180 °C in the 1:1.5 system, and at about 185 °C in the 5:1 solid dispersion, according to DSC data previously obtained.

4. Conclusions

In this study, the gas antisolvent crystallisation (GAS) technique has been applied to the preparation of solid dispersions. In particular, this technique has been proved to be a viable and alternative means of preparing solvent-free binary systems. These coprecipitates, prepared with PEG 4000 as carrier, were able to increase remarkably the dissolution characteristics of the poorly soluble carbamazepine. The physical characterisation of the systems attested a substantial correspondence between the solid state of the drug before and after treatment. Furthermore, crystalline drug was still detectable in all the binary systems prepared with GAS process. However, it must be pointed out that the analysis of the morphology and the size of the drug showed a dramatic change into the crystals after treatment with supercritical fluids, indicating the formation of a light voluminous powder made of little particles mostly having habit needle. The improved dissolution of the drug was attributable to the reduction of its particle size, to the better shape of the crystals and to the increased wettability when the polymer was dissolved.

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