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Characterization of Carbamazepine in systems containing a dissolution rate enhancer

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Abstract

Carbamazepine is an important anti-convulsant drug, characterized by a low water solubility. In order to improve its dissolution rate, drug:polymer systems were prepared using cross-linked polyvinylpyrrolidone (Polyplasdone XL®-10) as dissolution rate enhancer. The systems were obtained by mixing, milling and solvent evaporation.

The systems, characterized by improved drug dissolution rate, were studied by: Scanning Electron Microscopy (SEM), X-Ray Diffraction Powder (XRD), and Differential Scanning Calorimetry (DSC).

Keywords: Carbamazepine; Cross-linked polyvinylpyrrolidone; Dissolution test; Polymorphism; Physico-chemical characterization

1. Introduction

In the last years, many technological approaches such as micronization, drug loading on the surface of a carrier (Bettinetti and Mura, 1994), preparation of solid dispersions (Chiou, 1977), have been developped in order to improve the dissolution characteristics of drugs with low solubility in water. However, these methods can influence some physical characteristics of the drug such as crystallinity, which can be affected by changes in the crystal structure, as amorphization, or polymorphic transformation (York, 1983). Thus, an important step during preformulation studies is the characterization of starting materials and their mixtures in order to detect possible incompatibilities that could influence the formulation.

The effect of polymorphism on solubility, dissolution rate, bioavailability and formulation quality of poorly soluble drugs, have been earlier described (Bouché and Draguet-Brughmans, 1985).

In order to improve the dissolution rate of a low water soluble drug, and evaluate the physical characteristics of the starting materials and preliminary systems, carbamazepine was chosen as model drug.

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Carbamazepine was developed in the early 1950s and it is used for epilepsy and trigeminal neuralgia treatment. It is very slightly soluble in water, and its absorption from the gastro-intestinal tract is slow and irregular (Bertilsson and Tomson, 1986). There are many reports in the literature concerning the polymorphic transformation of this drug (Pölmann et al., 1975; Kala et al., 1986; Lowes et al., 1987) and the influence of these forms on: dissolution behaviour (Lowes et al., 1987; Lovrecich et al., 1994), pharmacokinetics (Kahela et al., 1983), grinding and compression (Lefebvre et al., 1986), formulations (Lefebvre et al., 1987), photostability (Matsuda et al., 1994). However, these numerous papers are heterogeneous with regards to the number of the polymorphic modifications and their characterization.

Previous studies have been carrried out in our laboratory regarding the use of swellable polymers as enhancers for the improvement of the dissolution rate (Sangalli et al., 1989; Giunchedi et al., 1990). These polymers are hydrophilic and water insoluble. In this work, cross-linked polyvinylpyrrolidone, an insoluble swellable homopolymer of N-vinyl-2-pyrrolidone, was used.

Drug:polymer systems were prepared by mixing, milling and solvent evaporation techniques to improve the dissolution rate of carbamazepine.

The aim of this work is the physical characterization of the systems using Scanning Electron Microscopy, X-Ray Analysis and Differential Scanning Calorimetry in order to understand the influence of the technological process used in the physical characteristics of the drug.

2. Materials and methods

2.1. Materials

Carbamazepine (CB) was supplied by Recordati Industria Chimica Farmaceutica SpA, Milano, Italy; melting range: 174–176°C; solubility in water: 130 mg/L at 24°C, dvs = 11.72 μm (Coulter Counter model TA II, Coulter Electronics Ltd, Luton, UK) (experimental data).

Cross-linked polyvinylpyrrolidone: Polyplasdone XL®10 (Pxl) particle size: 70-85% less than 37 μm and 95% less than 75 μm, 4.76% H_2O (Karl Fischer) was obtained from ISP Corporation, Wayne, New Jersey, USA.

2.2. System preparations

The compositions of the systems prepared, their weight ratios and the procedures to obtain them are reported in Table 1.

The procedures were performed as follows:

2.2.1. Mixing technique (mix)

Systems were prepared by mixing drug and polymer (Turbula apparatus, type T2A, W.A. Bachofen, Basel, CH), for 2 h (at the speed of 26 rpm)

2.2.2. Milling technique (mill)

Drug and polymer were milled for 2 h in a ball milling (at the speed of 26 rpm).

2.2.3. Solvent evaporation technique (rv)

Polymer was suspended into a solution of carbamazepine 1% w/v (ethanol 95°: acetone) (3:1 v/v) and stirred for 15 min. The solvent was removed with a rotary evaporator (Rotavapor Büchi R110, Flawil, CH) at about 50°C, on a water bath. The residual product was kept under vacuum at room temperature for 24 h. Subsequently, it was deagregated using a 200 mesh sieve (75 μm).

Table 1
Composition of drug:polymer systems

Code	Drug:polymer weight ratio	Procedure
CB:Pxl (mix)	1:2	Mixing technique
CB:Pxl (mill)	1:2	Milling technique
CB:Pxl (rv)	1:2	Solvent evaporation

CB: carbamazepine; Pxl: cross-linked polyvinylpyrrolidone.

2.3. In vitro dissolution test

Dissolution profiles were obtained for each system and for the powder Carbamazepine alone in triplicate (mean values with standard deviations are reported). A modified USP XXIII no. 2 apparatus was used. In order to carry out the studies "in sink" conditions, samples containing 30 mg of Carbamazepine were placed directly into 5000 mL of 37°C distilled water.

The analyses were conduced spectrophotometrically at 285 nm (Spectracomp 602, Advanced Products, Milano, Italy).

2.4. Physical characterization

2.4.1. Scanning electron microscopy (S.E.M.)

The morphology of the materials used and systems prepared were studied by scanning electron microphotographs (JSM 35C, Japan Electron Optical Laboratory, Tokyo, Japan).

2.4.2. X-ray analyses (XRD)

Samples were analyzed through X-ray Powder Diffraction, for the charaterization of the crystalline phases (Philips PW1800/10 diffractometer, equipped with a Digital Microvax 2000, with a specific sofware APD 1700). The main characteristics and setting parameters of the diffractometer were: Wavelengths (λ): $K\alpha_1 = 1.54060Å$, $K\alpha_2 = 1{,}54439Å$. High voltage: 50kV. Tube current: 30mA. Automatic divergence slits (ADS). Goniometer: scan range: 2°–50° 2θ and scan speed: 0.02°/second. Monochromator: graphite crystal.

2.4.3. Differential scanning calorimetry (DSC)

A thermal analyzer (Mettler TA 4000, Greifensee, CH) equipped with a 25 mod DSC cell, was used to record trasition temperatures and heats. A 10°C/min heating rate was employed. The analysis was conducted on 2–7 mg samples in aluminun pans under a dry nitrogen atmosphere (30 mL/min)

3. Results and discussion

The dissolution profiles of the systems are shown in Fig. 1 and are compared with the dissolution profile of CB alone.

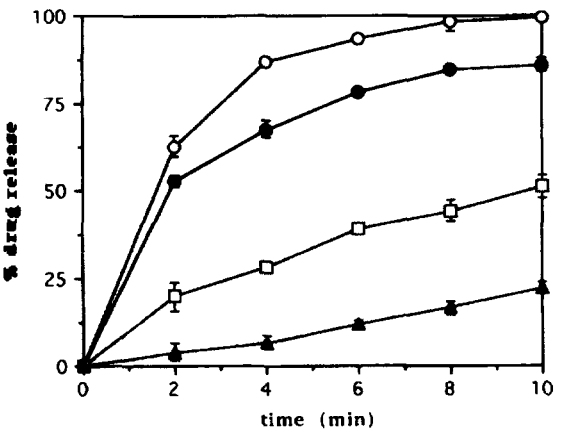

Fig. 1. In vitro dissolution profiles of: ▲ carbamazepine; □ rv system (1:2); ● mix system (1:2); ○ mill system (1:2).

All the systems show an improvement of drug dissolution rates compared with the pure CB. However, solvent evaporation system (rv) presents a lower improvement in comparison with the mix and mill systems.

Fig. 2 shows the scanning electron photomicrographs of CB starting material, with an irregular shape (Fig. 2a), and the characteristic pop-corn form of cross-linked polyvinylpyrrolidone (Fig. 2b)

The morphological structures (Fig. 3) illustrate the differences among the systems. Mix and mill systems (Fig. 3a and b) show both the crystal of starting CB and Pxl particles. A heterogeneous particle size of carbamazepine in the mix system is shown in comparison with a more homogeneous particle size in the mill system. A morphological change of CB in the rv system occurs (Fig. 3c), and it is featured predominantly by needle-like structures and small sticks.

Photomicrograph of polymer previously evaporated in the same solvent mixture as the preparation of rv system but without drug (Fig. 2c) shows more or less the same morphological structure as the starting Pxl (Fig. 2b).

Powder X-ray diffraction analysis of starting CB shows an identical pattern (Fig. 4a) to beta carbamazepine reference by the JCPDS card Patent No. 33-1565 and the USP Carbamazepine Reference Standard.

Although all patterns of the systems show an enhancement of the background due to presence of the polymer (Fig. 4b), patterns of mix and

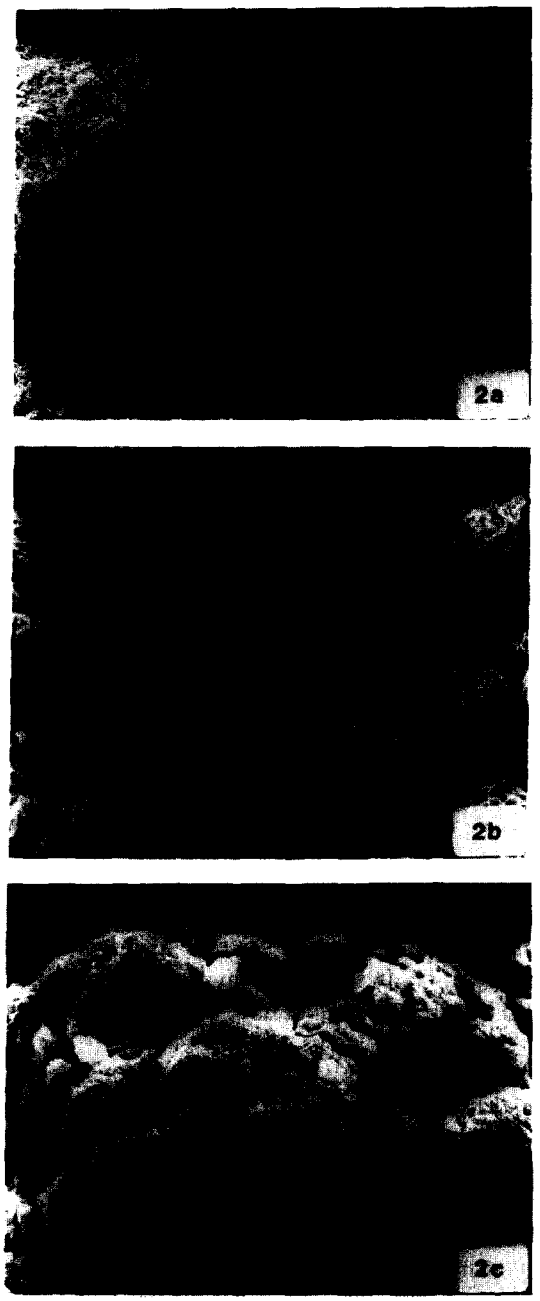

Fig. 2. Photomicrographs (SEM) of: (a) Carbamazepine; (b) Polyplasdone XL®-10; (c) Polyplasdone XL®-10 after treatment.

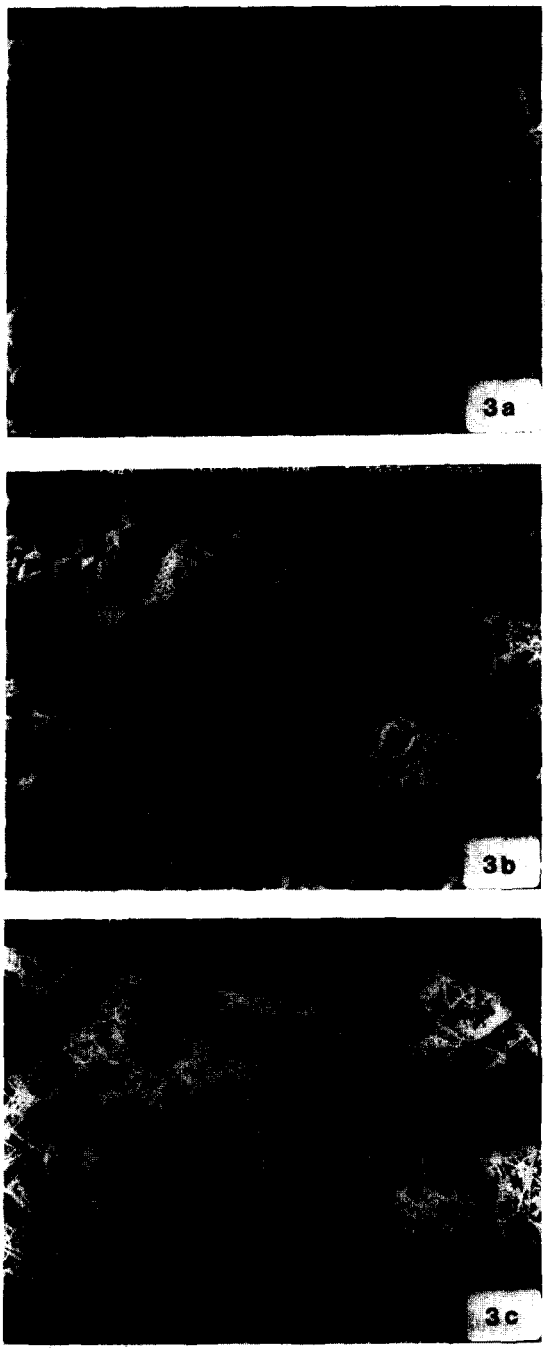

Fig. 3. Photomicrographs (SEM) of: (a) mix system; (b) mill system; (c) rv system; weight ratio: (1:2).

mill systems (Fig. 5a and b) are very similar to the pattern present in Fig. 4a; these results indicate that mill and mix techniques did not induce any polymorphic transformation.

Measurements of full width at half maximum intensity (FWHM) of all the peaks from 5 to 25 2θ of CB pattern have been carried out both in the case of the drug alone and in the cases of the mix and mill systems; this measurement should be proportional to the crystallinity degree of the drug. In fact, a lowering in the crystallinity leads to a widing of the peak. However, the experimental measurements did not show any difference in the crystallinity degree between the pure drug and the drug present in the mix and mill systems.

The pattern of rv system exhibits a different crystalline form of CB (Fig. 5c). The powder pattern of this polymorph closely resembles alfa-

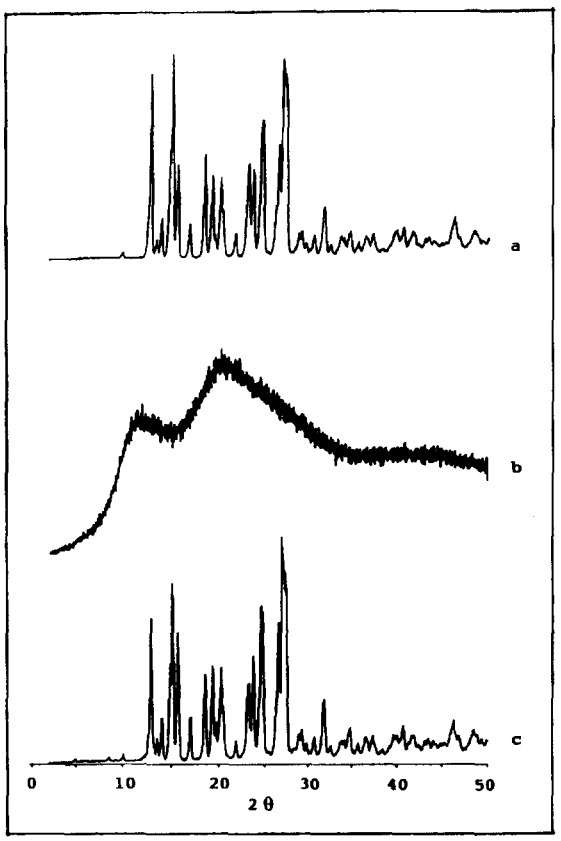

Fig. 4. Patterns (XRD) of: (a) Carbamazepine; (b) Polyplasdone XL®-10; (c) Carbamazepine after treatment.

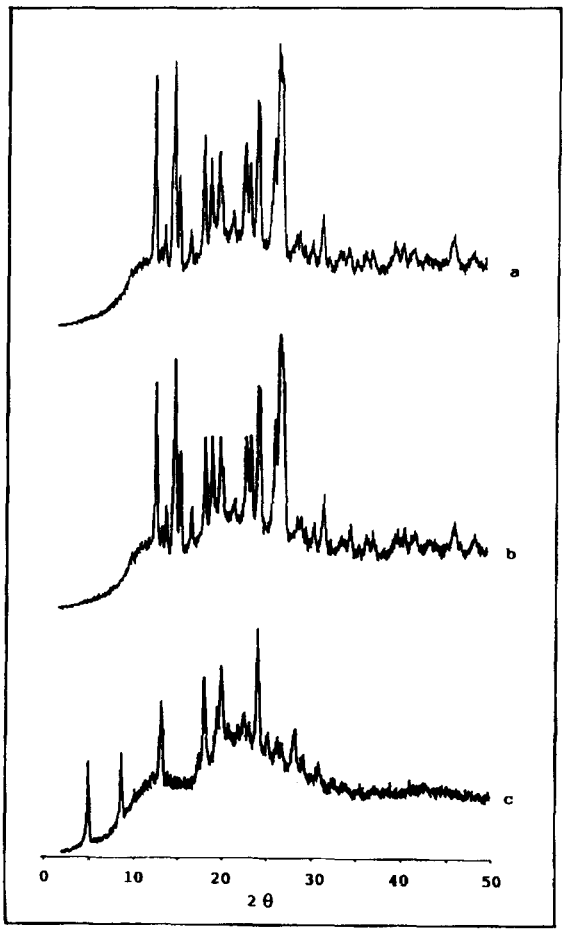

Fig. 5. Patterns (XRD) of: (a) mix system; (b) mill system; (c) rv system; weight ratio: (1:2).

CB reference by JCPDS card no. 33-1566 and by earlier publications (Pölmann et al., 1975; Kala et al., 1986; Lowes et al., 1987).

Starting material of CB was treated at the same conditions used for the preparation of rv system but without polymer, and a very similar pattern of beta-form was obtained (Fig. 4c). This result confirms that the presence of the polymer suspended in the drug solution with a subsequent evaporation of the solvent is necessary to achieve the polymorphic transformation.

Thermal analyses confirm the results of powder X-ray diffractions (XRD). Thermal behaviour of pure CB shows a thermogram corresponding to beta polymorph (m.p. about 175.6°C) (Fig. 6a) as

earlier published (Lowes et al., 1987; Behme et al, 1991)

The thermogram of Pxl shows a dehydration profile typical for a hygroscopic amorphous material (Fig. 6b).

Thermograms of mix and mill systems (Fig. 6c and d) show a single endothermic peak at 175.8 and 175.2°C, respectively; this peak represents the melting of beta polymorph. Whereas, the thermogram of rv system exhibits one endothermic peak at 190.5°C (Fig. 6e).

All thermogram systems show a large endotherm between 50 and 120°C approximately,

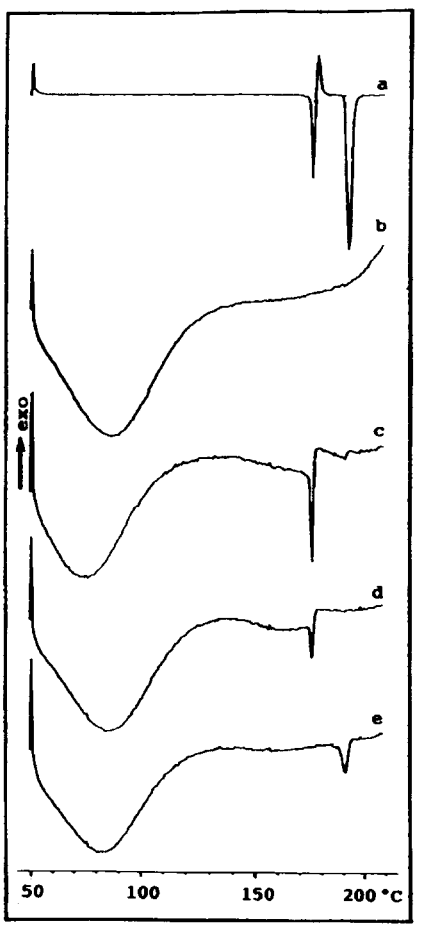

Fig. 6. Thermograms (DSC) of: (a) Carbamazepine; (b) Polyplasdone XL®-10; (c) mix system; (d) mill system; (e) rv system; weight ratio: (1:2).

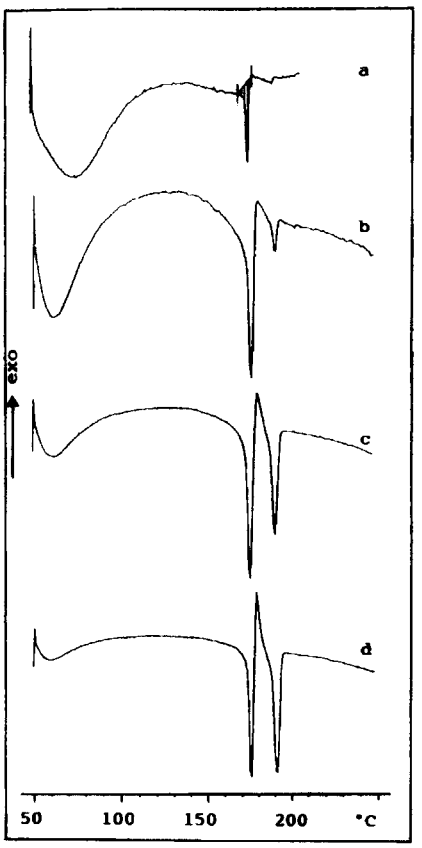

Fig. 7. Thermograms (DSC) of mix systems with different CB:Pxl weight ratios: (a) 1:2; (b) 1:1; (c) 2:1; (d) 3:1.

due to the loosing of water from the polymer, which does not allow the accurate calculation of the heats of fusion (ΔH_f) of the beta-polymorph present in the systems.

Thermograms of mix and mill systems do not exhibit the second endothermic peak, and this suggests an interaction between the polymer and the crystalline drug. In order to study this phenomenon, drug:polymer systems with different weight ratios were prepared by mixing technique. While drug:polymer system weight ratio (1:2) does not exhibit the second endothermic peak (about 191°C), thermograms of the other systems with less polymer concentration show the presence of this peak (Fig. 7). In fact, a decrease of polymer concentration causes an increase of the second peak area.

4. Conclusions

Mixing and milling techniques led to a remarkable improvement of the dissolution rate of CB from the systems with respect to the pure drug.

The system prepared by solvent evaporation is less effective in achieving the enhacement of the drug dissolution rate. This result could be due to polymorphic transformation (from beta to alpha form) of the drug loaded on the polymeric structure of Pxl. The recrystallization of the drug obtained in the same solvent mixture used for the preparation of the rv system does not lead to any structural change of the crystallinity of the drug (beta form was mantained), which indicates that the loading of CB on the surface of Pxl induces a polymorphic transformation.

The mix and mill systems did not produce any lowering in the crystallinity of the CB. This result was confirmed by the measurements of full width at half maximum intensity (FWHM) from the patterns of the systems and the drug alone.

The thermal behaviour of the mix and mill systems shows an interaction between CB and Pxl, this interaction takes place in a ratio of 1:2 drug:polymer; while this weight ratio does not exibit any peak at about 190°C, an increase of CB concentration produces the appearance of the second peak. The area (fusion heat, ΔH_f) of this peak is proportional to the concentration of CB in the systems. However, it is necessary subsequent studies to determinate the interaction between CB and Pxl.

For all these reasons, the preparation of CB:Pxl systems by dry techniques (mix and mill) which do not involve the use of any organic solvent can be used as a first formulation step for achieving extended release dosage forms, in which the dissolution rate is not any more a limiting factor of the drug release from the dosage form.

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