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Solid dispersions of oxazepam

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Summary

The dissolution profiles of oxazepam from solid dispersion systems with PEG 6000 and Gelita Collagel have been investigated. The best results were obtained with spray-dried oxazepam-Collagel. X-ray diffractometry was applied to explain the changes in dissolution characteristics of oxazepam in the studied samples.

Key words: Oxazepam, Polyoxyethylene glycol 6000; Gelita Collagel; Solid dispersion

Introduction

Solid dispersion systems have been investigated in considerable detail. The methods of their preparation gave good results with very slightly water soluble drugs (Yakou et al., 1984; Francés et al., 1991; Rabasco et al., 1991). Many substances have been extensively studied with respect to carrier properties (Bogdanova et al., 1983; Ibrahim and Shawky, 1983; Craig and Newton, 1992). Water-soluble polymers such as PEG and PVP have been found to be the best carriers and are therefore most commonly used for preparation of solid dispersions.

The purpose of this investigation was to apply a solid dispersion technique to promote the dissolution rate of oxazepam poorly water soluble drug.

Oxazepam is a member of the 1,4 benzodiazepines, an active metabolite of diazepam which is one of the most frequently prescribed drugs in the treatment of anxiety and insomnia. In the present study, two types of substances were chosen as carriers to prepare solid dispersions systems with oxazepam: polyethylene glycol (PEG 6000) and Gelita Collagel an enzymatically produced collagen hydrolysate in the form of a spray-dried powder (Mol. Wt 18300; light diffusion method), widely used as a pharmaceutical adjuvant in tablet formulations (Nörnberg and Schenk 1988; Nörnberg and Kutz (1989).

The present work describes the preparation of oxazepam-Gelita Collagel and oxazepam-PEG 6000 solid dispersion, their characterization by X-ray diffractometry and dissolution analysis of oxazepam in the studied forms.

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Experimental

Materials

The materials used were as follows: oxazepam (Pharmaceutical Works, Tarchomin Polfa), polyoxyethylene glycol (PEG 6000) (Laborche-

mikalien, Carl Roth OHG) and Gelita Collagen (Deutsche Gelatine Fabriken Stoess and Co. GmbH, Eberbach).

Procedure

The test samples of solid dispersions and physical mixtures were prepared in the same (w/w) ratios of 1:10 drug to carrier.

Preparation of solid dispersion systems

The melting method was used for samples with PEG 6000 as previously described (Jachowicz, 1987). The final solid mass was crushed, pulverized and sieved through screens (200 μm)

Spray-drying: A given amount of oxazepam and PEG 6000 was dissolved in ethanol 95°, oxazepam and Collagel in ethanol 70°. The samples were spray-dried using a Büchie 190 mini spray-dryer apparatus. The temperature inlet was at 67°C, the outlet at 46°C for the samples with PEG 6000 and 134 and 77°C for Collagel.

Dissolution studies

Dissolution rate studies were conducted using the paddle method. Apparatus No. 2 for dissolution testing (USP XXI) was applied. A certain amount of powder samples, equivalent to 20 mg of oxazepam, was put into small tea bags and jointed to the paddle in 1000 ml of water at 37°C. The paddle rotation speed was 50 rpm. 10-ml samples of the solution were removed at measured intervals and the volume was kept constant by adding the same amount of dissolution medium at the same temperature. Samples were suitable diluted in 0.1 N HCl and assayed spectrophotometrically. The test was performed in triplicate.

The concentration of oxazepam in samples was calculated as the percent dissolved vs time t (Fig. 1).

Assay procedure

Oxazepam was assayed spectrophotometrically in a Unicam SP 500 spectrophotometer at $\lambda = 236$ nm.

X-ray diffraction studies

Powder X-ray diffractometry was carried out with a Philips Röntger powder diffractometer by using monochromatic Cu-Kα radiation (λ = 1.5418 Å).

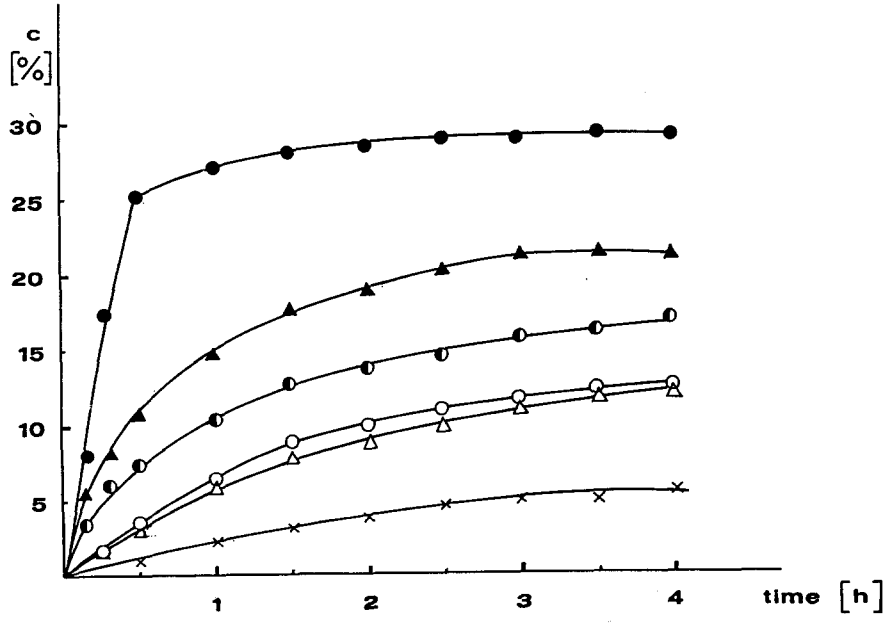

Fig. 1. Dissolution profiles of oxazepam from physical mixtures (Ph. M) and solid dispersions (S.D): (●——●) oxazepam-Collagel (S.D.); (○——○) oxazepam-Collagel (Ph.M); (▲——▲) oxazepam-PEG 6000 (S.D) melt; (△——△) oxazepam-PEG 6000 (Ph.M) (◐——◐) oxazepam-PEG 6000 (spray-dried); (×——×) oxazepam alone.

Results and Discussion

The dissolution profiles of oxazepam solid dispersions demonstrated the fastest dissolution rates of spray-dried oxazepam-Collagel in samples of 1 : 10 w/w ratio (Fig .1). After 30 min the amount of dissolved drug rose gradually and remained constant up to 2 h. After 4 h the amount of oxazepam dissolved was about 1.4-times greater than that from the melt of oxazepam in PEG 6000 and 1.8-fold greater than that from spray-dried oxazepam-PEG 6000. The lower dissolution rate of the spray-dried oxazepam-PEG 6000 product was due to the presence of crystalline oxazepam, of which the existence was demonstrated by the X-ray diffraction pattern shown in Fig. 2.

Dissolution rate studies of oxazepam from solid dispersions were carried out in comparison with the corresponding physical mixture and oxazepam alone.

Oxazepam dissolution from all solid dispersions is the most rapid. The amount of oxazepam dissolved from the spray-dried sample with Collagel is about 6-fold greater than that of drug alone, while from the melt and the sample spray-dried with PEG 6000 4- and 3-times greater amounts were measured as compared to drug alone. Similar investigations with physical mixtures showed an approx. 2-fold greater amount of drug dissolved, which can be explained on the basis of the wetting and solubilizing effect of the carriers.

The X-ray diffraction technique was used to determine the observed changes in dissolution characteristics of oxazepam in the studied samples. Major X-ray diffraction peaks of oxazepam at 7 and 19° are present in samples of the physical mixtures of oxazepam with PEG 6000 and in oxazepam-PEG 6000 spray-dried samples (Figs 2 and 3). The diffraction peaks of oxazepam are lower than that of the pure drug and only intense diffraction peaks of PEG 6000 are present. All samples above contained only 10% of oxazepam, thus explaining why the peaks are smaller.

In spray-dried oxazepam-Collagel samples, the characteristic peaks attributed to oxazepam crystals are absent and only a halo was observed in the X-ray diffraction pattern (Fig. 2). These results indicate that an amorphous form is adopted during the spray-drying process with Collagel.

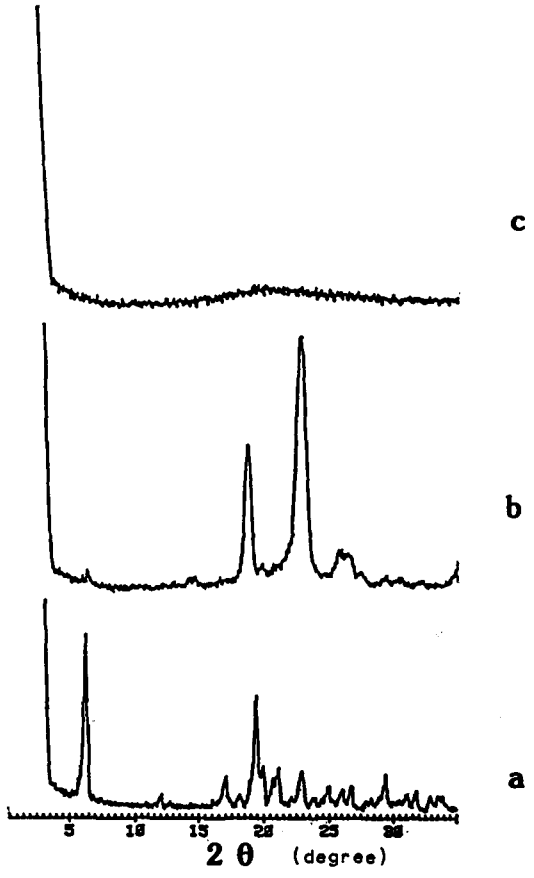

Fig. 2. X-ray diffraction spectra: (a) pure oxazepam, (b) spray-dired oxazepam-PEG 6000, (c) spray-dried oxazepam-Collagel.

Fig. 3 also shows the diffraction peaks of samples containing melted oxazepam in PEG 6000. The characteristic peak of oxazepam at 7° 2θ is of very weak intensity and peaks at 18 and 23° 2θ identified as being due to PEG 6000 are visible but of lower intensity than pure PEG 6000. Polarizing microscopy analysis indicated the presence of anisotropic crystals in this sample. Observation of the behaviour of samples during the heating process provided additional information. The particles began to melt at a temperature of 60°C (corresponding to the melting temperature of PEG 6000) and very small crystals of oxazepam

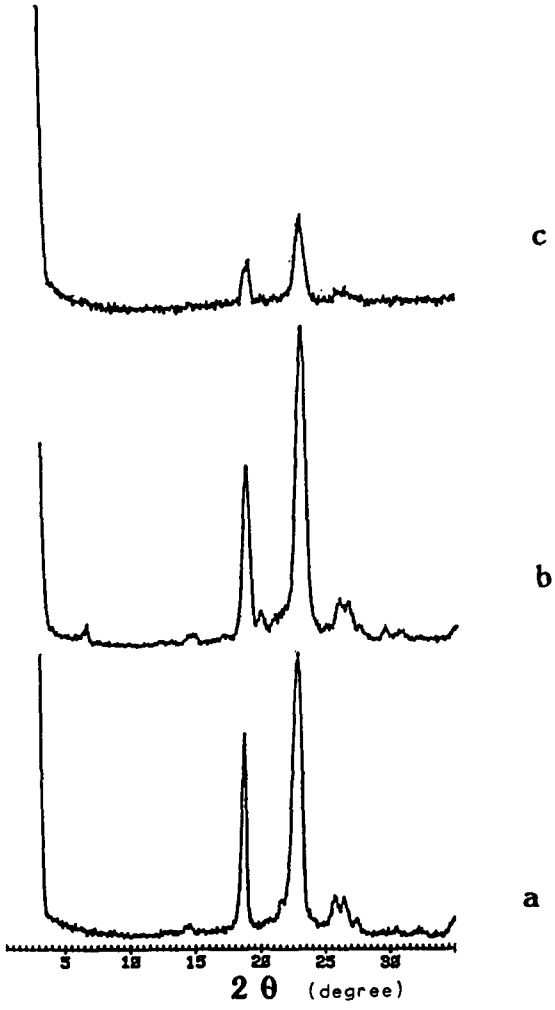

Fig. 3. X-ray diffraction spectra: (a) pure PEG 6000, (b) oxazepam-PEG 6000 physical mixture (c) oxazepam-PEG 6000 solid dispersion.

inside melted PEG 6000 droplets were observed. Their size decreased with increasing temperature up to 142°C before reaching the melting temperature of pure oxazepam (204°C). At 142°C all the crystals were dissolved in PEG 6000. The thermal behaviour of spray-dried oxazepam-PEG 6000 was similar, but at 60°C only part of the oxazepam crystals had been included in PEG 6000 droplets. Other crystals remained between droplets, however, all had disappeared (at 148°C) by the time the temperature of 204°C had been attained. In physical mixtures, only small crystals could be observed in melted PEG. After reaching 145°C, undissolved crystals remained unchanged and melted at 204°C. All the samples studied were anisotropic except for spray-dried oxazepam-Collagel which was isotropic. These results confirm the existing X-ray regarding amorphous oxazepam in Collagel.

It has been assumed that the observed changes in dissolution characteristics of oxazepam do not depend on the solubilization effect of carriers, but rather depend on the drug particles characteristics. The greatest dissolution rate was shown in samples containing oxazepam in the amorphous form which was prepared by spray-drying of oxazepam with Collagel. The same method of preparation but with PEG 6000 as a carrier did not produce the same results. In the latter case, oxazepam existed in crystalline form and had a slower dissolution rate. The better results obtained by using the melting method for oxazepam-PEG 6000 were due to the formation of a solid solution of oxazepam in the melt.

It can be concluded that for the enhancement of the dissolution rate of oxazepam, the spray-drying method with Collagel as carrier is recommended. Future investigations dealing with the stability of oxazepam in prepared samples are planned in order to establish in which form, amorphous or crystalline, oxazepam exists after storage.

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