ELSEVIER

International Journal of Pharmaceutics 143 (1996) 247–253

international journal of pharmaceutics

Thermal investigation of crystallization of polyethylene glycols in solid dispersions containing oxazepam

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Received 31 May 1996; accepted 18 August 1996

Abstract

A critical issue in the processing of solid dispersions is to elucidate the microstructure of the resulting product. Morphological features such as crystallinity degree of both carrier and drug, and particle size of the latter, have a deep effect on the properties of the drug dissolution. In the present paper, Hot Stage Microscopy (HSM) has been employed to investigate the crystallization of polyethylene glycols (PEG) of different molecular weights used in the processing of a benzodiazepine (oxazepam). The results have shown that the crystalline morphology and the radial growth rate were dependent on the polymer molecular weight, crystallization temperature, and also on the molecular state of the drug incorporated into the polymer, forming a solid dispersion and strongly influencing the drug dissolution rate.

Keywords: Crystallization; HSM; Oxazepam; Polyethylene glycols; Solid dispersions

1. Introduction

The polyethylene glycols (PEG) are a series of water soluble synthetic polymers obtained by catalytic condensation of ethylene oxide and water. The general formula of these compounds belongs to:

$$HO-CH_2-CH_2-[O-CH_2-CH_2]_n-OH$$

where n represents the average number of oxyethylene groups ($-OCH_2CH_2-$), i.e. the degree of polymerization (Seymour and Carraher, 1988).

These polymers have a wide range of applications in the pharmaceutical field. Although

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PII S0378-5173(96)04702-3

around thirty different materials—including polymers—have been proposed as carriers for the elaboration of solid dispersions, in particular PEG based polymers have been extensively used with advantages due to their favourable solution properties, low toxicity and low cost (Draguet-Brughmans et al., 1984; Ginés et al., 1990; Singla and Vijan, 1990). Moreover, they are the carriers of election in the preparation of solidified melts, because they display a low melting point and their molecular size favours the formation of interstitial solid solutions with drugs. Besides this, the high viscous nature of the melt tends to entrap the drug in a molecular state or to form microparticles.

The term 'solid dispersion' refers to the dispersion of one or more active ingredients in an inert carrier or matrix at a solid state. In the field of pharmaceutical technology, they are commonly employed for solving problems related to poor water solubility and poor bioavailability of active ingredients, instability, dosing problems and others (Alonso et al., 1988; Gupta et al., 1991). The selection of the carrier and the method of preparation presents an important influence on the properties of the resulting solid dispersion. These systems are usually manufactured by heating a physical mixture of the drug and the polymer until the fluid state is reached and next, the melt is cooled. However, the conditions used for the fusion and solidification process are frequently unstated, despite their influence. Two conditions for cooling are generally employed: slow cooling at room temperature and fast cooling in an ice bath. The carriers reported in the literature are numerous, but according to previous studies in this field, one can justify the universality of PEG polymers as fast release carriers for poorly soluble or insoluble drugs (Craig and Newton, 1991a,b; Ginés et al., 1990).

It is well known that the temperature of solidification plays an important influence over the drug dissolution rate. However, little information has been reported on the effect of crystallization temperature on the microstructure of the obtained solid dispersion (Mihailov et al., 1978; Prud'homme, 1982). Thus, the solidification rate of the melt may play an important role in controlling the dissolution rate of the obtained product. For instance, a short crystallization time may lead to the production of small crystals, and hence, high dissolution rates, whereas a longer crystallization period favours large crystals with low dissolution rates.

Although the techniques employed in the field of physicochemical characterization of solid dispersions are numerous, including spectroscopic, microscopic and thermal ones, only a few of them are employed to characterize the crystallization process. In this paper, we have make use of Hot Stage Microscopy (HSM) to investigate the crystallization of pure PEG of different molecular weights. We proceed further to the examination of the effect of the incorporation of oxazepam at low percentages (5% w/w) on the crystallization of PEG 4000 after its elaboration as a solid dispersion.

2. Experimental

2.1. Materials

PEG with nominal molecular weights of 1500, 4000 and 6000 were supplied by Acofar (Barcelona, Spain). PEG samples ranging from 15 000 to 200 000 were provided from Serva Laboratories (Barcelona, Spain) and used without further purification. The nominal molecular weight values of this set of PEG samples is accurately guaranteed by the suppliers and all of them were of pharmaceutical purity grade. Oxazepam, a 3-hydroxybenzodiazepine, was purchased from Boehringer-Ingelheim (Barcelona, Spain).

2.2. Preparation of solid dispersions

Oxazepam-PEG 4000 solid dispersions were prepared by the melting carrier method at 1:20% w/w ratio. The PEG samples were gradually heated at 100 and 150°C. When the carrier was completely molten at this temperature, the drug was added. After the obtained mixture was found to be homogeneous, the molten mixture was cooled and rapidly solidified. A previous investigation carried out by the authors indicated that

oxazepam particles mixed with PEG 4000 after heating at 100°C remain unaltered, whereas, in contrast, at 150°C the drug particles dissolved well into the molten carrier (Ginés et al., 1994b).

2.3. Hot stage microscopy (HSM)

In order to characterize the systems under study, samples crystallized at identical conditions were subjected to a HSM study. The procedure carried out in different samples was as follows: approximately 1 mg of each commercial PEG sample or of the solid dispersions were placed over glass slides with coverglass and heated up to 100°C and 150°C using the furnace provided by the HSM equipment (Mettler FP82 HT) at the rate of 10°C/min. After this thermal treatment, all the samples were quenched at different conditions (room temperature or ice bath). The study of the crystallization process was carried out using an Olympus BH-2 microscope with polarized light.

2.4. Dissolution rate studies

The dissolution rate studies were carried according to the USP XXII rotating basket method. The samples, corresponding to 10 mg oxazepam, were previously placed into hard gelatin capsules. Dissolution medium was artificial gastric medium prepared under the specifications of USP XXII. The stirring speed was 50 rpm and the temperature 37 ± 0.5°C. The aliquots (3 ml) were withdrawn at various time intervals using a syringe and analyzed spectrophotometrically at 230 nm using a Hitachi U-2000 spectrophotometer.

3. Results and discussion

3.1. Thermal study of pure vehicles

It is clear from the literature that the mobility of the macromolecules of which each polymer is composed, determines the tendency and degree of crystallinity. For this reason, the molecular weight and cooling rate may influence the morphology of the obtained solid. Different crystalline morphologies have been observed for PEG after crystallization, namely spherulites, spherulitoids, hedrites and ovals (Mihailov et al., 1978).

Fig. 1 shows selected micrographs corresponding to PEG 4000 and PEG 6000 after cooling under an ice bath. The results indicated that the obtained morphology is PEG molecular weight dependent. The melt of low molecular weight PEG (Fig. 1) crystallizes to give aggregates named spherulites. These are spherical or disc-shaped formations in which, generally, needle-shape crystals are arranged regularly about a centre. These structures consist of chain-folded lamellae radiating from a central point. Branching causes the spherulite to become spherical in shape after plenty of growth. Under polarized light, they can be recognized by the typical black Maltese cross.

Fig. 1. HSM microphotograph corresponding to (a) PEG 4000 and (b) PEG 6000, both samples after cooling under an ice bath. Polarized light, × 400.

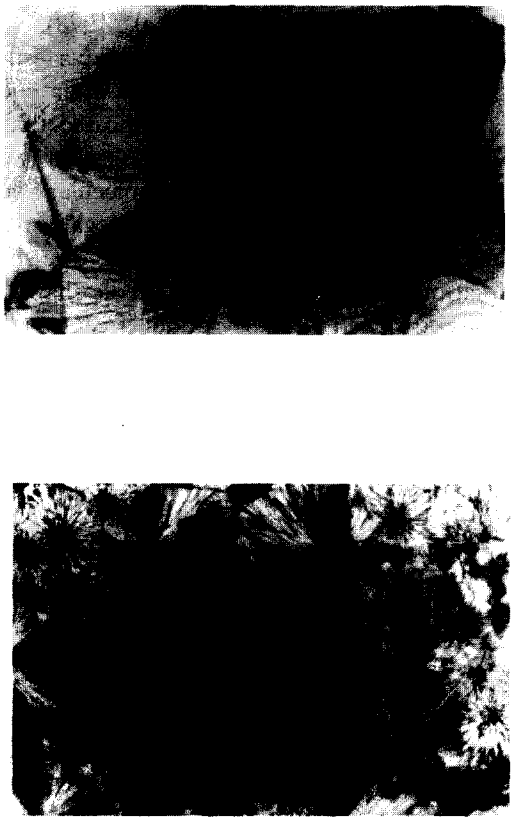

Fig. 2. HSM microphotograph corresponding to (a) PEG 20 000 and (b) PEG 40 000, both samples after cooling under an ice bath. Polarized light, × 400.

For PEG presenting intermediate molecular weights, ranging from 20 000 to 40 000, the spherulites are incompletly formed (Fig. 2). A transition state between spherulite and hedrite can be observed, characterized by the gradual disappearance of the Maltese cross, while the concentric stacking of platelets is retained. These structures are spherulitoids. In their morphology, the spherulitoids combine some features of hedrites as well as of the spherulites (Allen and Mandelkern, 1982). The surface has a fibrilar character that is typical of the spherulites. Probably the growth mechanism of these structures is a combination of the hedrites and spherulites, i.e. a combination of a screw dislocation growth or large horizontal lamellae and two dimensional nucleation of a lot of little lamellae on defective small areas of their surface, as proposed in the literature (Mihailov et al., 1978). The study of the optical properties of these structures permitted us to establish one important difference between them and the typical hedrites. The spherulitoids show a weak positive birefringence. In some cases a weak Maltese cross is observed (Fig. 2b)

PEG of molecular weight above 40 000 (Fig. 3) show a different morphology, constituted by hedrites. The hedrites are thus characterized by extinguished birefringence of the Maltese cross. Some birefringence, as well as a fibrous appearance, can be found in worst developed hedrites. For this PEG the thickness of the melt increases and the fibrous character of the surface of the resulting structures becomes more evident. Similar results were obtained with different fractions of polyethylene oxide (Mihailov et al., 1978).

It is clear that one factor which significantly participates in the crystallization is the temperature. The outcome indicates that the size of spherulites depends upon the cooling rate. For a fixed PEG molecular weight (e.g. 4000), the microphotographs show evidence that a slow cooling rate (room temperature) produced large spherulites (Fig. 4), while fast cooling (ice bath) provides smaller spherulites (Fig. 1). Clearly, the size of spherulites is also crystallization-temperature dependent. The spherulites have different radii according to the different crystallization conditions, indicating that the growth rate of the crystals in the solidification of the melt increases under conditions of fast cooling. These results

Fig. 3. HSM microphotograph corresponding to PEG 200 000 after cooling under an ice bath. Polarized light, × 400.

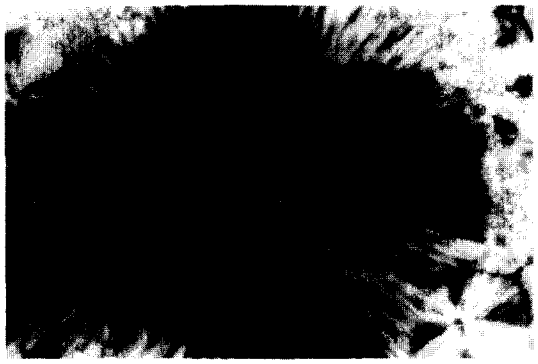

Fig. 4. HSM microphotograph corresponding to PEG 4000 after slow cooling at room temperature (see the differences with the micrograph presented in Fig. 1a). Polarized light, × 400.

could be explained on the basis of their different viscosites in the molten state. Thus, fast cooling conditions produce the simultaneous formation of several crystallization nuclei, producing smaller spherulites, as shown in Fig. 1.

Frequently, in fast-cooled crystals solidified between the slide and the cover-slip, occurs contraction of the fissures. They are caused by volume changes which can form characteristic patterns. Fig. 2a displays polarized optical microphotographs corresponding to the spherulitic crystallization of PEG 20 000, where concentrical deformations can be appreciated.

3.2. Thermal study of solid dispersions

The microscopical examination during the elaboration of solid dispersions by the fusion carrier method (see experimental section) revealed that the PEG 4000 molten at 150°C is able to dissolve the amount of 5% w/w oxazepam, while in the solid dispersion elaborated at 100°C, crystalline particles of this drug remain unaltered.

It is recognized that the crystallization of a polymer from the melt is a two stage process. First, a nucleation process must occur, followed by crystal growth. Two types of nucleation have been distinguished. Homogeneous nucleation occurs as a result of random order fluctuations in supercooled phase, while heterogeneous nucleation is induced by foreing surfaces, e.g. small particles acting as impurities. This last crystallization type must occur into the solification of solid dispersion. If the drug remains as isolated particles, i.e. not dissolved into the molten carrier, the drug particles can act as a nucleating agent. In fact, the solid dispersions incorporating 5% w/w oxazepam (Fig. 5) elaborated at 100°C showed similar crystallization (spherulites). The presence of drug crystals did not modify the crystallization of the polymer as compared with the microphotographs included in Figs. 1 and 4.

Note that Fig. 5 shows how the drug particles act as nucleating agents and how they are always found at the center of the spherulites. In the same sense, these spherulites containing drug particles showed the larger size. This evidence suggests that these spherulites are formed in the first stages of crystallization. This fact was observed under careful microscopical examination by HSM and strongly supports the above assumption. In contrast, examination under polarized light—after crystallization of solid dispersions—demonstrated that the drug particles, after the dissolution process in the molten carrier at 150°C, remain in an amorphous state in the final solid dispersion obtained after the process of solidification. In this case, the drug shows no recrystallization, but its presence modifies the crystallization of the polymer. Thus, the microstructure obtained in the solid dispersion prepared at 150°C (Fig. 6) showed different morphology as compared with

Fig. 5. HSM microphotograph of PEG 4000-5% w/w oxazepam solid dispersion prepared at 100°C, after slow cooling at room temperature. The crystallized drug particles are indicated by arrows. Polarized light, × 400.

Fig. 6. HSM microphotograph of PEG 4000-5% w/w oxazepam solid dispersion prepared at 150°C, after cooling under an ice bath. Polarized light, × 400.

the pure PEG 4000 (Fig. 4). Consequently, a conversion from spherulite to hedrite can be appreciated.

3.3. Dissolution study

The dissolution data for samples prepared in capsules containing pure drug and the 5% w/w oxazepam-PEG 4000 physical mixture and solid dispersions are presented in Fig. 7. The capsules required a latency period of 2 min for their own dissolution, afterwards, the samples commenced the dissolution process.

When comparing the dissolution profiles of the three binary systems with pure oxazepam, we can appreciate that, in all cases, the addition of PEG 4000 lead to faster drug dissolution rates. The increase in the dissolution rate of oxazepam in the physical mixture is attributed to a local solubilization effect, produced by the polymer in the diffusion layer immediately surrounding the drug particles.

The enhancement in the drug dissolution rate considering the solid dispersion elaborated at 100°C is probably due to an increase in the surface area of the drug exposed to the dissolution medium. This increase in the surface area is caused by the smaller particle size reached for the oxazepam into the solid dispersion. Undoubtedly, other factors such as wettability and reduced aggregation, have also contributed to the dissolution enhancement to some extent. Anyway, it is difficult to separate these different contributions.

The difference in the dissolution profiles obtained for solid dispersions incorporating oxazepam at 100 and 150°C was probably caused by the different physicochemical state of the drug particles in the two formulations. While oxazepam appeared in a crystalline form in the solid dispersion elaborated at 100°C, it was forming a solid solution in the solid dispersion prepared at 150°C, as demonstrated by the HSM study. In this latter case, the oxazepam is molecularly solubilized into the solid PEG 4000 (solid solution) and their solubilization into the dissolution medium is produced simultaneously with that of the polymer. Moreover, the different crystalline structure of the PEG 4000 in the two samples, may influence the dissolution characteristics of the drug, spherulite into the solid dispersion elaborated at 100°C and hedrite into the solid dispersion elaborated at 150°C.

On the other hand, the dissolution behaviour of solid dispersions can be altered in storage due to

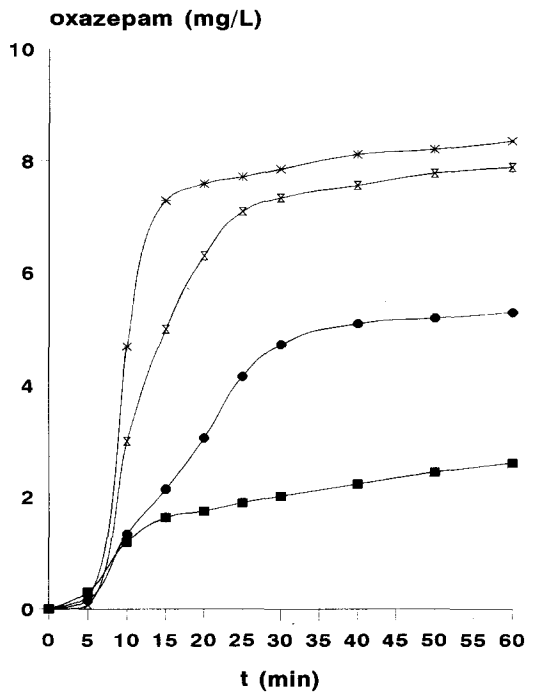

Fig. 7. Dissolution profiles of different samples: ■ oxazepam; ● physical mixture oxazepam-PEG 4000; ⋈ solid dispersion oxazepam-PEG 4000 elaborated at 100°C; * solid dispersion oxazepam-PEG 4000 elaborated at 150°C.

changes in the physicochemical characteristics of the drug, the carrier, or both. Thus, the solid dispersions containing amorphous or molecularly dispersed drugs, can be metastable systems. Often, the drug in molecular form may precipitate, due to supersaturation. This process, when it occurs, produces a decrease in the dissolution efficiency of the drug. In this case, the dissolution efficiencies of the solid dispersions stored at room temperature for 6 months showed unchanged dissolution profiles. Similar results have been reported in the literature for various drugs dispersed in PEG of different molecular weight (Duclos et al., 1990; Ginés et al., 1994a). These results are in good agreement with those obtained from the HSM study, because no visual modification of the samples were appreciated during storage. From these results, it can be concluded that the solid dispersion prepared at 150°C constitutes a stable system, and this solid solution remains unaltered after 6 months, resulting in the same dissolution rate. This fact may be explained because of the low concentration of the solute in the solid dispersion (5% w/w), which does not exceed its equilibrium solubility and does not produce further precipitation of the drug in the system.

Taking into account these results, further research on solid dispersions using PEG of different molecular weights and other drugs are now in progress to examine their influence on drug dissolution rates. They will be matter of future reports.

4. Conclusions

In solid dispersions elaborated by the fusion carrier method at 100°C, oxazepam was present in crystalline form and PEG 4000 in spherulite form. In opposition, oxazepam is presented at the molecular state (solid solution) in the solid dispersions elaborated at 150°C. In this case, the crystalline structure of the polymer is modified, appearing as hedritic forms. These results are consistent with the different dissolution rates obtained for the two solid dispersions in artificial gastric medium.

References

Allen, R.C. and Mandelkern, L., *J. Polym. Sci.: Polym. Phys. Ed.*, 20 (1982) 1465–1484.

Alonso, M.J., Maincent, P., García-Arias, T. and Vila-Jato, J.L., A comparative biopharmaceutical study of fresh and ageing tolbutamide-polyethyleneglycols solid dispersions. *Int. J. Pharm.*, 42 (1988) 27–33.

Craig, D.Q.M. and Newton, J.M., Characterization of polyethylene glycols using differential scanning calorimetry. *Int. J. Pharm.*, 74 (1991a) 33–41.

Craig, D.Q.M. and Newton, J.M., Characterization of polyethylene glycol solid dispersions using differential scanning calorimetry and solution calorimetry. *Int. J. Pharm.*, 76 (1991b) 17–24.

Draguet-Brughmans, M., Lefebvre, C., Guyot-Hermann, A.M. and Bouche, R., Etude physique de dispersions solides de laurylsulfate de papavérine dans le polyoxyéthylène glycol 4000. *Pharm. Acta Helv.*, 59 (1984) 310–315.

Duclos, R., Grenet, J., Saiter, J.M., Besançon, P. and Orecchioni, A.M., Effect of ageing on progesterone polyoxyethylene glycol 6000 dispersions. X-ray study. *Drug Dev. Ind. Pharm.*, 16 (1990) 255–265.

Ginés, J.M., Sánchez-Soto, P.J., Justo, A., Vela, M.T. and Rabasco, A.M., Elaboration and characterization of the diazepam-polyethyleneglycol 6000 solid dispersions. *Drug Dev. Ind. Pharm.*, 16 (1990) 2283–2301.

Ginés, J.M., Arias, M.J., Holgado, M.A., Fernández-Arévalo, M. and Rabasco, A.M., Dissolution rate study of fresh and aging triamterene-urea solid dispersions. *Drug Dev. Ind. Pharm.*, 20 (1994a) 2729–2740.

Ginés, J.M., Arias, M.J., Moyano, J.R., Pérez-Barrales, M., Rabasco, A.M. and Sánchez-Soto, P.J., Application of hot stage microscopy to the thermal study of oxazepam-PEG 4000 binary system. *Proc. 13th Int. Congr. on Electron Microscopy, Section: Biomaterials*, Paris, 1994b, pp. 83–84.

Gupta, R.L., Kumar, R. and Singla, A.K., Enhanced dissolution and absorption of trimethoprim from coprecipitates with polyethylene glycols and polyvinylpyrrolidone. *Drug Dev. Ind. Pharm.*, 17 (1991) 463–468.

Mihailov, M., Nedkov, E. and Goshev, I., Temperature dependence of morphology of supermolecular structures growing in the thin layer melt of fractions of poly(ethylene oxide). *J. Macromol. Sci. Phys.*, 15 (1978) 313–328.

Prud'homme, R.E., Fractionation in mixtures of polyethylene oxide fractions during crystallization. *J. Polym. Sci.*, 20 (1982) 307–316.

Seymour, R.B. and Carraher, C.E., *Polymer Chemistry: an introduction*, 2nd edn, Dekker, New York, 1988, p. 644.

Singla, A.K. and Vijan, T., Dissolution of sulphamethoxazole from polyethylene glycols and polyvinylpyrrolidone solid dispersions. *Drug Dev. Ind. Pharm.*, 16 (1990) 875–882.