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Preparation, characterization and dissolution of ciprofloxacin/PEG 6000 binary systems

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Summary

Thermomicroscopy and DSC were employed to study ciprofloxacin/PEG 6000 binary systems in the form of solid dispersions and physical mixtures. The dissolution processes of ciprofloxacin from the binary systems and pure ciprofloxacin were also studied.

Introduction

Ciprofloxacin (1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazin-1-ylquinoline-3-carboxylic acid) is an antimicrobial agent with an antibacterial spectrum similar to that of norfloxacin, but greater activity (Martindale, 1989). Due to its molecular structure it is poorly water soluble and to avoid this problem it is commonly used as a lactate or hydrochloride.

Solid dispersion systems may provide a means of decreasing the dissolution time and improving the bioavailability of drugs that are poorly water soluble (Chiou and Riegelman, 1970). A solid dispersion is a binary system in a solid state formed by a water-soluble, pharmacologically inert carrier or matrix, into which a very hydrophobic drug is dispersed. Solid dispersions can be prepared by several methods: (a) fusion (Corrigan and Timoney, 1976), (b) dissolution (Geneide et al., 1978) and (c) fusion-dissolution (Veiga et al., 1988). These methods may cause some problems when the transposition to an industrial scale is made.

To use the fusion method, since both components must be melted, much energy is required and, although carriers such as PEG 6000 and PEG 1500 have low melting points, numerous drugs have melting points close to 200 °C or higher. This involves high costs and difficulty in handling of the molten material. An additional drawback appears when one of the substances, drug or carrier, decomposes while melting.

The dissolution method may cause problems, since finding a common solvent is sometimes difficult, or high proportions of solvent are required.

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In this method also, as in fusion-dissolution, residues of the solvent may be entrapped within the solid dispersion which renders the system impure, thereby modifying drug-carrier interactions.

The aim of this paper is to obtain and describe solid dispersions of ciprofloxacin/PEG 6000 by using a method that overcomes the above-mentioned obstacles.

These systems will be characterised using thermal analysis techniques, namely, differential scanning calorimetry (DSC) and hot-stage microscopy (HSM). Finally, dissolution profiles study will reveal whether drug dissolution times have been shortened and to what extent.

Materials and Methods

Materials

Ciprofloxacin was kindly supplied by Química Farmacéutica Bayer, Barcelona (Spain), in form of the hydrochloride. PEG 6000 was supplied by Panreac S.A., Madrid (Spain), and was employed without further purification.

Methods

Isolation of ciprofloxacin as a base

A solution of ciprofloxacin hydrochloride in distilled water was treated with a solution of 1 N NaOH. Phenolphtalein was used as an indicator. Once the ciprofloxacin base had precipitated, it was isolated by filtration. The solid obtained was washed with water until no chloride was detected in the filtrate (using $AgNO_3 + HNO_3$). The final product was desiccated to constant weight, then sieved, and the particle size fraction below 100 μm collected for use in further studies.

Preparation of the binary systems

Solid dispersions of ciprofloxacin in PEG 6000 were prepared as follows: the carrier (PEG 6000) was melted using a water bath at 70 °C, the drug was added in solid state, and the mixture was stirred to facilitate interposition. Once a homogeneous mixture had been obtained, it was cooled to room temperature until solidification occurred, ground with a mortar and the particle size fraction smaller than 100 μm was selected by sieving.

By this method, three types of solid dispersions were obtained, differing in the proportions of the two components of the system, viz., 10, 30 and 50% ciprofloxacin in PEG 6000. Solid dispersions containing higher proportions of ciprofloxacin could not be prepared this way, since the final product was not homogeneous.

In addition, three ciprofloxacin/PEG 6000 physical mixtures were prepared in the same proportions as in the solid dispersions (10, 30 and 50% ciprofloxacin with PEG 6000). The carrier was previously sieved and the particle size range below 100 μm was selected. Ciprofloxacin (particle size range < 100 μm) and PEG 6000 were thoroughly mixed until a homogeneous mixture was obtained.

Characterization of the binary systems

Two thermal analysis techniques, hot-stage microscopy (HSM) and differential scanning calorimetry (DSC), were used to characterize the binary systems obtained.

All the samples, situated on a Kofler stage, were observed between 20 and 270 °C. The heating rate was the same in every case. Examination was carried out using a Reichert microscope/Kofler stage.

DSC was performed using a Mettler TA 3000 system with a differential scanning calorimeter (model DSC 20), using aluminium sample pans and lids. All samples weighted 10 mg, and the scanning rate used was 10 °C min^{-1} between 30 and 300 °C. Calibration of the instrument was checked periodically with standard samples of indium.

Dissolution study

Dissolution of the three types of solid dispersions and physical mixtures was investigated, and the results compared with those obtained in the study of the dissolution process of pure ciprofloxacin in order to determine the influence the proportion of PEG 6000 and of the method employed to prepare the solid dispersions on

ciprofloxacin dissolution. In all cases, samples with particle size below 100 μm were used.

The dissolution assembly consisted of 500 ml of distilled water in a water-jacketed beaker maintained at 37 ± 0.5 °C. The dissolution medium was stirred with a glass paddle, placed at the center and maintained at a rate of 250 rpm by an overhead motor. All samples, containing an amount equivalent to approx. 50 mg of pure ciprofloxacin, were added to the medium in a powdered form.

At measured time intervals, samples were withdrawn and filtered with porous filters of 0.45 μm pore diameter. Following dilution, samples were assayed spectrophotometrically in a Shimadzu spectrophotometer at 272 nm. The results were computed with a standard calibration curve of the drug.

Statistical analysis

To determine whether the differences between the dissolution profiles obtained were significant, Student's *t*-test was applied to the experimental values. Pairs of drug concentration average values and their respective standard deviations were compared for each sampling time. A significance level of $p = 0.01$ was chosen.

Results and Discussion

Thermal studies of the binary systems

Hot-stage microscopy has proven to be a very useful technique in the study of binary systems, since it allows the observation of sample behaviour during the heating process, as well as the differentiation of pure substances from impurities, and of amorphous materials from crystalline forms (Vera et al., 1991). However, the main disadvantage of hot stage microscopy is that exact definition of the substance's melting point is not possible, nevertheless, DSC provides this parameter exactly.

Inspection by microscopy of the different samples (pure ciprofloxacin, PEG 6000 and the six binary systems prepared) revealed that they were all crystalline and homogeneous, except in physical mixtures where two types of crystals (corresponding to pure ciprofloxacin and PEG 6000) could be observed. Particles of solid dispersions were constituted by ciprofloxacin crystals included in PEG 6000 crystals. The difference between the 10, 30 and 50% solid dispersions was that the amount of ciprofloxacin crystals included in PEG 6000 particles was greatest in the 50% solid dispersion and lowest in that of 10%.

TABLE 1

Results of the thermomicroscopy study

Composition	Temperature (°C)	Change of state
Pure ciprofloxacin	250	fusion
PEG 6000	60	fusion
10% S.D. and P.M.	60	PEG fusion
	60–180	ciprofloxacin dissolution
30% S.D. and P.M.	60	PEG fusion
	60–200	ciprofloxacin dissolution
	250	excess ciprofloxacin fusion
50% S.D. and P.M.	60	PEG fusion
	60–200	ciprofloxacin dissolution
	250	excess ciprofloxacin fusion

P.M., physical mixture; S.D., solid dispersion.

Table 1 lists the results of the thermomicroscopy study. Pure products (ciprofloxacin and PEG 6000) show only a single change of state during the test, corresponding to fusion (250 and 60 °C, respectively).

On heating, the 10% solid dispersion remains unchanged until 60 °C is reached. At this temperature, all the 10% solid dispersion particles melt, and inside the PEG 6000 droplets, ciprofloxacin microcrystals can be seen. The amount of these microcrystals gradually decreases with rising temperature, none remaining when 200 °C is reached. The 10% physical mixture shows thermal behaviour basically similar to that of the 10% solid dispersion. The difference between these two binary systems of identical drug-carrier ratio is that in the 10% physical mixture, when PEG 6000 melts (60 °C), the ciprofloxacin crystals remain on the surface and between the PEG 6000 droplets, rather than within the droplets as occurs in the 10% solid dispersion. At temperatures

above 60 °C, the viscosity of PEG 6000 decreases gradually with increasing temperature; this is the reason why PEG 6000 droplets extend and entrap ciprofloxacin crystals. Once entrapment has taken place, the amount of ciprofloxacin crystals decreases gradually with increasing temperature, until all of the drug crystals have disappeared by the time 200 °C is reached.

The gradual and total disappearance of ciprofloxacin crystals before reaching the melting point in both systems is attributed to the dissolution of ciprofloxacin in PEG 6000.

The 30 and 50% solid dispersions behave similarly to that of 10%: in these two cases, after reaching 200 °C, undissolved ciprofloxacin microcrystals still remain that do not change until the melting point of ciprofloxacin has been reached. The undissolved microcrystals are present in greater amounts in the 50% solid dispersion than in that of 30% and undergo melting on reaching the melting point of ciprofloxacin (250 °C).

The behaviour of the 30 and 50% physical mixtures during the heating process is similar to that of solid dispersions containing the same amount of drug, since in these systems, a certain amount of drug is also dissolved in melted PEG 6000, the excess ciprofloxacin remaining present in a solid state until melting at 250 °C.

The DSC curve for pure ciprofloxacin exhibits two endothermic peaks (110 and 270 °C), which represent water loss and melting of the sample, respectively. The DSC curve for pure PEG 6000 shows only one endothermic peak (62 °C), corresponding to fusion. The 10% solid dispersion and physical mixture have similar DSC curves with only one endothermic peak (62 °C), which also corresponds to PEG 6000 fusion. The 30% and 50% solid dispersions and physical mixtures exhibit similar DSC curves with two endothermic peaks. The first, at 62 °C, corresponds to PEG 6000 melting, the second (260 °C) being attributed to fusion of ciprofloxacin (Fig. 1).

The results obtained by employing hot-stage microscopy and DSC to ciprofloxacin/PEG 6000 binary systems indicate that the former technique provides more information than DSC about the thermal behaviour of such systems. The reason for this is that the dissolution of ciprofloxacin in

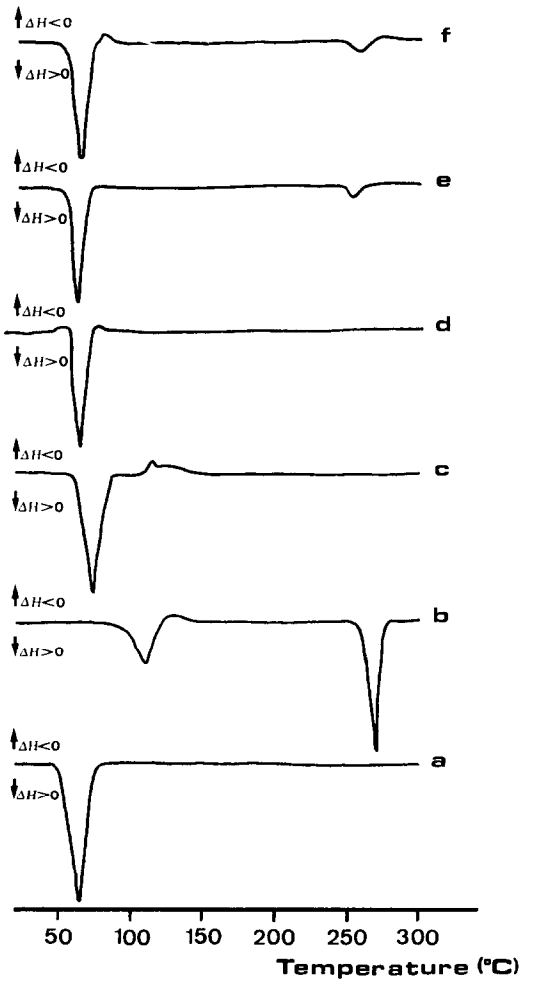

Fig. 1. DSC curves: (a) PEG 6000, (b) pure ciprofloxacin, (c) 10% solid dispersion, (d) 10% physical mixture, (e) 30% solid dispersion and (f) 30% physical mixture.

melted PEG 6000, when the temperature is above 70 °C and below the melting point of ciprofloxacin, is not shown on the DSC curves but may be clearly defined in hot-stage microscopy. The baselines of DSC curves remain unchanged when ciprofloxacin dissolves in PEG 6000, perhaps because this process takes place with low energy modifications, due to the implication of Van der Waals forces in the solute-solvent interaction.

Dissolution study

Fig. 2 illustrates the dissolution profiles plotted from the experimental values. Student's *t*-test

TABLE 2

Results obtained by Student's t-test analysis of dissolution profiles for binary systems and pure ciprofloxacin

Pairs studied	Differences obtained
(A) 30% P.M.-50% S.D.	non-significant
(B) 30% P.M.-10% P.M.	non-significant until 50 min significant from 60 to 180 min
(C) 10% P.M.-50% S.D.	non-significant until 150 min
(D) 50% P.M.-pure ciprofloxacin	non-significant
(E) 30% P.M.-pure ciprofloxacin	significant
(F) 10% P.M.-pure ciprofloxacin	significant until 110 min non-significant from 120 until 180 min
(G) 50% S.D.-pure ciprofloxacin	significant
(H) 50% P.M.-50% S.D.	significant
(I) 50% P.M.-30% P.M.	significant
(J) 50% P.M.-10% P.M.	significant

P.M., physical mixture; S.D., solid dispersion.

was used to assess the statistical significance of the results obtained on the amount of ciprofloxacin dissolved at the same time for four binary systems and pure ciprofloxacin; the results are shown in Table 2. In Fig. 2 three groups of curves can be distinguished. The dissolution profiles of ciprofloxacin from 10 and 30% solid dispersions exhibit instantaneous dissolution, the whole sample being dissolved within 5 min. The second group of curves includes the dissolution profiles of ciprofloxacin from the 50% solid dispersion, and the 10 and 30% physical mixtures. No significant differences among these three systems were observed, at least during the first 150 min (Table 2). These binary systems gave rise to longer dissolution times than those achieved with the 10 and 30% solid dispersions, however, faster dissolution rates were achieved than with pure ciprofloxacin.

Pure ciprofloxacin and its 50% physical mixture, that show similar dissolution profiles, have been included in the third group of curves. Among these profiles no significant differences in the amount of ciprofloxacin dissolved at the same times were observed (see Table 2).

Conclusions

The most suitable binary systems for enhancing the rate of ciprofloxacin dissolution are the solid dispersions, particularly the 10 and 30% solid dispersions which were almost equally effective.

This behaviour is explained by:

(a) the high proportion of PEG 6000 in the system, because of the carrier-solubilizing action

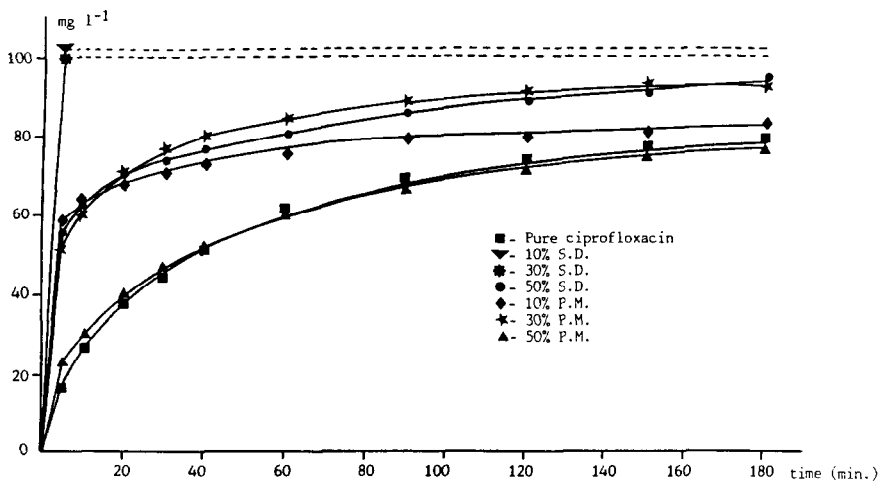

Fig. 2. Dissolution profiles of ciprofloxacin from binary systems and pure ciprofloxacin.

on ciprofloxacin, demonstrated using hot-stage microscopy.

(b) the technological process used in the preparation of the solid dispersions. This is the underlying cause of the different dissolution behaviour shown by two binary systems having the same drug/PEG 6000 ratio but differing preparation procedures, for example, 10% solid dispersion and physical mixture, 30% solid dispersion and physical mixture and 50% solid dispersion and physical mixture. The differences between the 10% physical mixture and solid dispersion, and the 30% physical mixture and solid dispersion are evident in Fig. 2. Comparison of the 50% physical mixture and solid dispersion by statistical analysis also demonstrated significant differences between them (Table 2).

We believe that during the preparation of solid dispersions, a high degree of interposition between PEG 6000 and the drug was achieved. From the thermal studies, we have determined that at temperatures above the melting point of PEG 6000, ciprofloxacin dissolves in the melted carrier, the extent of dissolution depending upon the proportion of drug in the system. We can assume that in melted PEG 6000 at 70 °C (temperature at which the solid dispersions were prepared), the intermolecular forces for ciprofloxacin are at least weakened and that a certain proportion of the drug may be close to being in the molecular state, which is consistent with the dissolution profiles obtained.

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