International Journal of Pharmaceutics, 89 (1993) 119–124

IJP 02920

Thermal behaviour of drugs from binary and ternary systems

M.D. Veiga, M.J. Bernad and C. Escobar

Departamento de Farmacia y Tecnología Farmaceutica, Facultad de Farmacia, Universidad Complutense de Madrid, Ciudad Universitaria, 28040 Madrid (Spain)

(Received 13 April 1992)
(Accepted 9 May 1992)

Key words: Binary system; Ternary system; Oxodipin/PEG 6000/Tween 20; Griseofulvin/PEG 6000/Tween 20; Thermal analysis; DSC; Hot-stage microscopy

Summary

Thermomicroscopy and differential scanning calorimetry were employed to characterize oxodipin and griseofulvin from binary and ternary systems with PEG 6000 and Tween 20. The interaction resulting between drug and PEG 6000 during heating allowed the preparation of solid dispersions. An oxodipin/PEG 6000 10:90 (w/w) solid dispersion was formed exclusively by mixed crystals of PEG 6000 and drug which were detected by thermomicroscopy. The rest of the solid dispersions prepared (with or without surfactant agent) were formed by mixed crystals and particles of pure drug. The presence of Tween 20 does not appear to affect the thermal behaviour between drugs and PEG 6000.

Introduction

Poorly water-soluble drugs can frequently cause bioavailability problems when they are included in solid oral dosage forms. The formation of solid dispersions with hydrosoluble carriers such as PEG 6000 has successfully been used to minimize these drawbacks (Badwan et al., 1991; Dordunoo et al., 1991; Nakagami, 1991; Craig and Newton, 1992).

On the other hand, appropriate dissolution media have been developed in order to determine the aqueous dissolution of drugs that are practically water insoluble. These dissolution media can include surfactants such as sodium lauryl sulfate, bile salts and Tween 20. In this way, the results obtained have improved upon those in the case where organic solvents were added to the dissolution media (Shah et al., 1989).

Techniques such as differential scanning calorimetry (DSC) and X-ray diffraction have been used to characterize solid dispersions (Doherty and York, 1989; Fujii et al., 1990), however, the results obtained have not consistently been useful for the elucidation of the kind of interaction occurring between the carrier and the drug.

The aim of this paper is the characterization of solid dispersions by studying the thermal behaviour of drugs included in those systems prepared with PEG 6000 as carrier, and also to observe the influence that one surfactant can have over the interaction drug-carrier.

Correspondence to: M.D. Veiga, Departamento de Farmacia y Tecnología Farmaceutica, Facultad de Farmacia, Universidad Complutense de Madrid, Ciudad Universitaria, 28040 Madrid, Spain.

The drugs studied were oxodipin and griseofulvin. They have different chemical structures: oxidipin, 1,4-dihydro-2,6-dimethyl-4-(2′,3′-methylenedioxyphenyl)pyridin-3,5-dicarboxylic acid, methyl ethyl ester; griseofulvin, 7-chloro-4,6-dimethoxycoumaran-3-one-2-spiro-1′-(2′-methoxy-6′-methylcyclohex-2′-en-4′-one).

They also exert different therapeutic actions; griseofulvin is an antifungicidal drug whilst oxodipin is a new drug with calcium channel blocking properties. Nevertheless, both have one common characteristic: their marked hydrophobia that has led us to study them together.

Materials and Methods

Materials

Oxodipin was kindly supplied by the Instituto para el Desarrollo Químico Biológico, Madrid (Spain). Griseofulvin and Tween 20 were purchased from Sigma, St. Louis, MO (U.S.A.). Polyethylene glycol 6000 was purchased from Panreac, Madrid (Spain). All materials were used without further purification.

Methods

Preparation of the binary and ternary systems

Four sorts of binary systems were prepared: oxodipin/PEG 6000 physical mixtures, oxodipin/PEG 6000 solid dispersions, griseofulvin/PEG 6000 physical mixtures and griseofulvin/PEG 6000 solid dispersions.

To prepare physical mixtures the drugs and the carrier were previously sieved and the particle size range below 100 μm was selected, then the materials were mixed thoroughly.

The solid dispersions were prepared as follows: the carrier was melted at 70°C, the drug (particle size smaller than 100 μm) was added in the solid state and mixed until a homogeneous system was obtained. It was then left to solidify at room temperature. The systems obtained were ground and sieved. The fraction with size smaller than 100 μm was collected to carry out later studies.

The four sorts of binary systems were prepared at different proportions drug/carrier: 10:90, 20:80, 30:70, 40:60 and 50:50 (w/w).

Two types of ternary systems were prepared: oxodipin/PEG 6000/Tween 20 solid dispersion and griseofulvin/PEG 6000/Tween 20 solid dispersion. The method of preparation consisted of fusion of PEG 6000 at 70°C, addition and mixing of Tween 20. Then the drug (oxodipin or griseofulvin) was incorporated (with a size of less than 100 μm). The system obtained was left to solidify at room temperature and we proceeded as in binary systems. The two types of ternary systems were prepared in different proportions of drug/carrier/surfactant: 10:90:10, 20:80:10, 30:70:10, 40:60:10 and 50:50:10 (by wt).

Characterization of the binary and ternary systems

Two thermal analysis techniques, differential scanning calorimetry (DSC) and hot-stage microscopy (HSM), were used as tools to evaluate the systems prepared.

DSC was performed using a Mettler modular system with an FP-80 HT control unit and an FP-85 furnace. The sample size was about 10 mg, and the scanning rate used 10°C/min between 30 and 300°C.

A Reichert microscope with Kofler stage was used to carry out the thermomicroscopic study. Sample behaviour was observed between 30 and 250°C. The heating rate was the same in every case.

Results and Discussion

Preparation of binary and ternary systems

The method used to prepare solid dispersions allows us to differentiate the interaction that exists between carrier and drug according to drug characteristics.

When the solid dispersion oxodipin/PEG 6000 10:90 was prepared, this appeared as a homogeneous system (transparent at 70°C, as pure melted PEG 6000), the same happening with the solid dispersion oxodipin/PEG 6000/Tween 20 10:90:10. This shows that the drug is dissolved in PEG 6000 or in the PEG 6000/Tween 20

mixture at 70°C. The rest of the solid dispersions of oxodipin, with or without Tween 20, did not give rise to homogeneous systems during their preparation and we attribute this to an excess of drug in the system.

Solid dispersions of griseofulvin/PEG 6000 and griseofulvin/PEG 6000/Tween 20 behaved during their preparation as a suspension. To mix griseofulvin in a melted carrier, with or without surfactant agent, we created a system in which the drug did not disappear by dissolution in any of the prepared dispersions, independently of the proportion in which it was found and because of this, these systems were not transparent at 70°C.

Thermal studies

Fig. 1 shows the DSC curves for PEG 6000, oxodipin and the binary and ternary systems prepared. PEG 6000 shows an endothermic peak at 58–60°C (melting point), and oxodipin exhibits also a unique endothermic peak (167°C) that corresponds to its fusion. The DSC curves for the physical mixtures are similar to those which belong to solid dispersions (with or without Tween 20) with the same proportions of drug/carrier.

All the systems which have drug in low proportions display DSC with only one peak that shows PEG 6000 fusion, and drug or surfactant are not detected in those curves. Only the binary systems with drug/carrier ratios of 40:60 and 50:50, or the ternary systems where the proportions of drug/ carrier/ surfactant are 40 : 60 : 10 and 50:50:10 display in their DSC curves two endothermic peaks: one at the fusion temperature of PEG 6000 and the other at the fusion temperature of oxodipin. However, the peaks corresponding to fusion of the drug seem very small as compared with the peak exhibited by the pure oxodipin DSC curve.

Fig. 2 shows DSC curves for PEG 6000, griseofulvin and the binary and ternary systems prepared with those materials. The behaviour is similar to that displayed by oxodipin systems. Here also only DSC curves of systems with a high proportion of drug exhibit two endothermic peaks: fusion of PEG 6000 (60°C) and griseofulvin fusion (220°C). Also, as in previous systems the peak that corresponds to drug fusion is very small compared with the fusion peak of pure griseofulvin.

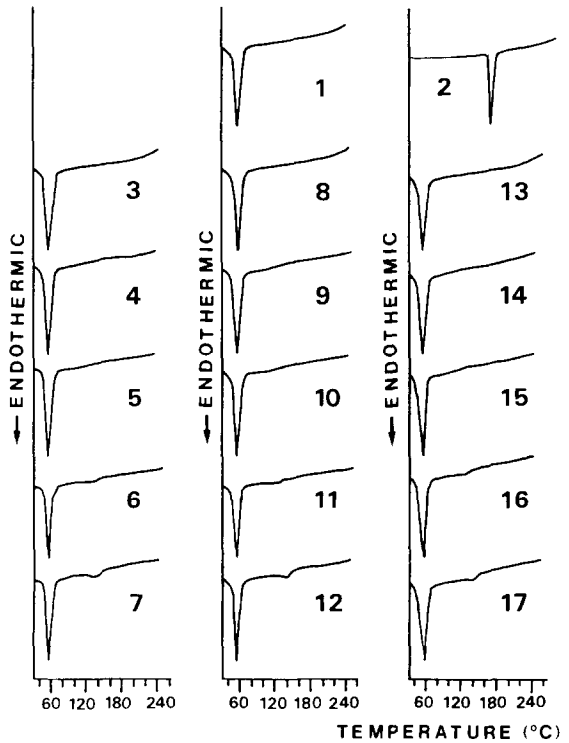

Fig. 1. DSC curves from binary and ternary systems of oxodipin: (1) PEG 6000, (2) pure oxodipin, (3) 10:90 P.M., (4) 20:80 P.M., (5) 30:70 P.M., (6) 40:60 P.M., (7) 50:50 P.M., (8) 10:90 S.D., (9) 20:80 S.D., (10) 30:70 S.D., (11) 40:60 S.D., (12) 50:50 S.D., (13) 10:90:10 S.D. with T., (14) 20:80:10 S.D. with T., (15) 30:70:10 S.D. with T., (16) 40:60:10 S.D. with T., and (17) 50:50:10 S.D. with T. P.M., physical mixture (oxodipin/PEG 6000); S.D., solid dispersion (oxodipin/PEG 6000). S.D. with T., solid dispersion with Tween 20 (oxodipin/PEG 6000/Tween 20).

On comparison of DSC curves from binary systems with those which belong to ternary systems, differences cannot be seen, which demonstrates that surfactant is not detected with DSC.

The results obtained from study with HSM technique are detailed in Tables 1 and 2.

Table 1 lists all the changes of state that occur in the systems prepared with oxodipin. The pure materials show only one change of state: solid to liquid (fusion). However, fusion and interaction between components is observed in binary and ternary systems when the temperature increases.

The behaviour of all physical mixtures of oxodipin/PEG 6000 is similar. At 58–60°C carrier fusion is observed and subsequently dissolution of oxodipin into melted carrier. Only the oxodipin particles near to melted PEG 6000 are dissolved, the rest of the oxodipin remaining unchanged until its fusion (160°C).

The solid dispersions of oxodipin/PEG 6000 with or without Tween 20 behave in different ways from their respective physical mixtures, because in these systems an intimate union between the components was produced during the process of preparation. When the solid dispersion of oxodipin/PEG 6000 10:90 reached 58–60°C, we observed the fusion of carrier and instantaneous dissolution of all of the drug, which was forming mixed crystals with PEG 6000.

Solid dispersions of oxodipin/PEG 6000 with ratios of drug/carrier of 20:80 and 30:70 show two changes at different temperatures: the first one corresponds to fusion (PEG 6000) and dissolution (oxodipin) in the range 58–60°C, and the second one represents the dissolution of oxodipin particles not before dissolving, this process happening at temperatures below oxodipin's melting point.

The solid dispersions with excess of oxodipin (40:60 and 50:50) show the following processes: first fusion and dissolution, followed by dissolution of particles of oxodipin not previously dissolved and finally fusion of the remaining oxodipin.

The behaviour of oxodipin/PEG 6000 solid dispersions observed with HSM is comparable to that of a solute that dissolves in a solvent. If the amount of solute is much less than the maximum permissible amount, the dissolution rate is high (instantaneous dissolution), but increasing the quantity of solute to dissolve reduces the speed of dissolution until the solubility parameter is reached; the rest of the solute remains undissolved in the solid state.

Table 2 lists the thermomicroscopic results obtained from griseofulvin binary and ternary systems. Pure griseofulvin shows fusion at 220°C. All the physical mixtures of griseofulvin/PEG 6000 display similar behaviour when observed under the microscope. To begin heating, the fusion of PEG 6000 is carried out firstly and thereafter, the dissolution of griseofulvin particles nearby slowly begins. The rest of the particles remain unaltered until its fusion (220°C). We also noted that in-

TABLE 1

Thermomicroscopic results of binary and ternary systems with oxodipin

Composition	Temperature (°C)	Change of state
Oxodipin	160	fusion
PEG 6000	60	fusion
10:90 P.M. 20:80 P.M. 30:70 P.M. 40:60 P.M. 50:50 P.M.	58–60 160	PEG fusion and OXD dissolution OXD fusion
10:90 S.D. 10:90:10 S.D. with T.	58–60	PEG fusion and OXD dissolution
20:80 S.D. 30:70 S.D. 20:80:10 S.D. with T. 30:70:10 S.D. with T.	58–60 60–140	PEG fusion and OXD dissolution OXD dissolution
40:60 S.D. 50:50 S.D. 40:60:10 S.D. with T. 50:50:10 S.D. with T.	58–60 60–140 150–160	PEG fusion and OXD dissolution OXD dissolution OXD fusion

P.M., physical mixture; S.D., solid dispersion; S.D. with T., solid dispersion with Tween 20; PEG, PEG 6000 and OXD, oxodipin.

creasing the drug proportion in these systems simultaneously increases the proportion of particles that remain undissolved in the melted carrier.

Solid dispersions of griseofulvin with or without Tween 20 are practically identical in thermal behaviour. When they contain a low proportion of drug, 10:90, 10:90:10, 20:80, 20:80:10, 30:70 and 30:70:10, they show two changes of state: fusion of carrier and subsequently slow dissolution of griseofulvin in melted PEG 6000. However, the process of dissolution of griseofulvin is strongly influenced by the proportion in which it is present in the system. In this way, in systems 10:90 or 10:90:10, in order to dissolve

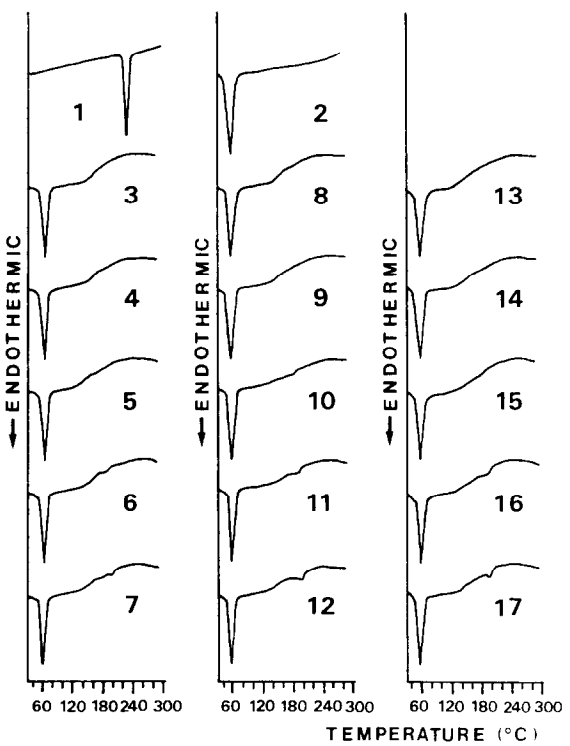

Fig. 2. DSC curves from binary and ternary systems of griseofulvin: (1) pure griseofulvin, (2) PEG 6000, (3) 10:90 P.M., (4) 20:80 P.M., (5) 30:70 P.M., (6) 40:60 P.M., (7) 50:50 P.M., (8) 10:90 S.D., (9) 20:80 S.D., (10) 30:70 S.D., (11) 40:60 S.D., (12) 50:50 S.D., (13) 10:90:10 S.D. with T., (14) 20:80:10 S.D. with T., (15) 30:70:10 S.D. with T., (16) 40:60:10 S.D. with T., and (17) 50:50:10 S.D. with T. P.M., physical mixture (griseofulvin/PEG 6000); S.D., solid dispersion (griseofulvin/PEG 6000); S.D. with T., solid dispersion with Tween 20 (griseofulvin/PEG 6000/Tween 20).

TABLE 2

Thermomicroscopic results of binary and ternary systems with griseofulvin

Composition	Temperature (°C)	Change of state
Griseofulvin	220	fusion
10:90 P.M.	58–60	PEG fusion
20:80 P.M.	58–60	PEG fusion
30:70 P.M.	60–200	GRV dissolution
40:60 P.M.	220	GRV fusion
50:50 P.M.	220	GRV fusion
10:90 S.D.	58–60	PEG fusion
10:90:10 S.D. with T.	60–150	GRV dissolution
20:80 S.D.	58–60	PEG fusion
20:80:10 S.D. with T.	60–175	GRV dissolution
30:70 S.D.	58–60	PEG fusion
30:70:10 S.D. with T.	60–185	GRV dissolution
40:60 S.D.	58–60	PEG fusion
50:50 S.D.	60–210	GRV dissolution
40:60:10 S.D. with T.	210–220	GRV fusion
50:50:10 S.D. with T.	210–220	GRV fusion

P.M., physical mixture; S.D., solid dispersion; S.D. with T., solid dispersion with Tween 20; PEG, PEG 6000 and GRV, griseofulvin.

griseofulvin the temperature must be 150°C, and in those with proportions 30:70 or 30:70:10 the temperature must be 185°C.

In solid dispersions with high proportions of griseofulvin (40:60, 40:60:10, 50:50 and 50:50:10) one can observe three changes of state, PEG 6000 fusion, griseofulvin dissolution and griseofulvin fusion. The processes of griseofulvin dissolution and fusion overlap.

According to our previous statements, we can deduce that the nature of the drug governs its interactions with the carrier, and as a consequence the characteristics of the systems obtained. Oxodipin in low proportions is dissolved instantaneously in melted PEG 6000, displaying true dissolution at 70°C. However, on allowing the system to cool, the PEG 6000 crystallizes as well as oxodipin, creating mixed crystals, as detected by thermomicroscopy. Dispersions with higher proportions of oxodipin are suspensions at the temperature of preparation: one part of the drug is dissolved in melted carrier and the re-

mainder is suspended. When the system cools, it creates mixed crystals formed by PEG 6000 and oxodipin which appear in a mixture with oxodipin particles which did not dissolve at the moment of preparation. The larger the proportion of total oxodipin present in the system, the greater is the proportion of oxodipin which does not form mixed crystals with PEG 6000.

Adding griseofulvin over melted PEG 6000 at 70°C, we did not observe total dissolution of the drug in any of the solid dispersions prepared. Therefore, at the moment of preparation, these systems were suspensions of griseofulvin in PEG 6000. There will be a very small quantity of dissolved griseofulvin and the rest will be in the solid state. On cooling the system mixed crystals of griseofulvin and PEG 6000 will be formed, but the largest proportion of drug will be as particles of pure griseofulvin in a mixture with mixed crystals.

The presence of Tween 20 does not appear to affect the interactions between drug and carrier, since the thermal behaviour of systems in which it is present coincides with that of systems prepared without a surfactant.

As in a previous work (Frances et al., 1991), the DSC technique is not enough to explain the interaction between drug and carrier in solid dispersions, since the processes of dissolution that occur between drug and melted carrier take place with very low energetic changes and are not detected with this technique. Neither is it useful to differentiate physical mixtures from solid dispersions. On the other hand, curves drawn in which two fusion peaks appear (carrier and drug) can induce error, since as stated above, the peak that appears is very small, and this is due to the fact that in those systems most of the drug is dissolved at that temperature and the peak area is a function of the amount of sample melted.

The results obtained have allowed us to reach the following conclusions:

The interaction of oxodipin with PEG 6000 is more extensive than that of griseofulvin with PEG 6000, according to the results obtained by thermomicroscopy.

The solid dispersion of oxodipin/PEG 6000 10:90 is formed exclusively by mixed crystals of two components; it is hoped that it will present the best dissolution profile of all the solid dispersions prepared.

The rest of the solid dispersions prepared with oxodipin or griseofulvin are formed by mixed crystals and particles of pure drugs.

In ternary systems Tween 20 does not affect the interaction that occurs between the other components of the systems when the temperature increases.

References

Badwan, A.A., Abu-Malooh, A., Owais, I., Sheikh Salem, M., Alkaysi, H.N. and Arafat, T.A., Some formulations aspects of terfenadine solid dispersions. *Eur. J. Pharm. Biopharm.*, 37 (1991) 166–170.

Craig, D.Q.M. and Newton, J.M., The dissolution of nortriptyline HCl from polyethylene glycol solid dispersions. *Int. J. Pharm.*, 78 (1992) 175–182.

Doherty, C. and York, P., Accelerated stability of an X-ray amorphous frusemide-polyvinylpyrrolidone solid dispersion. *Drug Dev. Ind. Pharm.*, 15 (1989) 1969–1987.

Dordunoo, S.K., Ford, J.L. and Rubinstein, M.H., Preformulation studies on solid dispersions containing triamterene or temazepan in polyethylene glycols or gelucire 44/14 for liquid filling of hard gelatin capsules. *Drug. Dev. Ind. Pharm.*, 17 (1991) 1685–1713.

Frances, C., Veiga, M.D., Español, O.M. and Cadorniga, R., Preparation, characterization and dissolution of ciprofloxacin/PEG 6000 binary systems. *Int. J. Pharm.*, 77 (1991) 193–198.

Fujii, M., Harada, K. and Matsumoto, M., Physicochemical properties of phenobarbital solid dispersion with phosphatidylcholine. *Chem. Pharm. Bull.*, 38 (1990) 2237–2241.

Nakagami, H., Solid dispersions of indomethacin and griseofulvin in non porous fumed silicon dioxide, prepared by melting. *Chem. Pharm. Bull.*, 39 (1991) 2417–2421.

Shah, U.P., Koneeny, J.J., Everett, R.L., McCullough, B., Noorizadeh, A.C. and Skelly, J.P., In vitro dissolution profile of water-insoluble drug dosage forms in the presence of surfactants. *Pharm. Res.*, 6 (1989) 612–618.