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Dissolution behaviour of drugs from binary and ternary systems

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Summary

Dissolution profiles of oxodipine and griseofulvin were obtained from binary and ternary systems prepared with PEG 6000 and PEG 6000/Tween 20, respectively. The improvement obtained in drug dissolution from physical mixtures prepared in several proportions with PEG 6000 is due to the disaggregant action of the hydrophilic carrier. This agent reduces the electrostatic forces that maintain the drug particles united together. During the preparation of solid dispersions an interaction between the two components is produced; this phenomenon explains the enhancement in the dissolution profile of the incorporated drug. Also, an increase in drug dissolution rate is observed to increase the proportion of carrier in these binary systems, since it also increases the amount of drug that interacts with PEG 6000 during preparation. The dissolution of drugs (oxodipine or griseofulvin) from ternary systems, drug/PEG 6000/Tween 20, is better than that obtained from the respective binary systems, since in the former the wetting action of surfactant agent and the solubilizing effect of PEG 6000 over drug are additive.

Introduction

The dissolution of a substance in a solvent depends on its structural characteristics, which condition the solute-solvent interaction forces. Poorly water soluble substances do not interact adequately with water molecules, and therefore only a very small number of drug molecules can be dissolved in the aqueous medium. For many drugs their dissolution in the biological fluids of the gastrointestinal tract is the limiting step in their absorption; if the drug is sparingly water soluble its absorption can be decreased or even abolished. For this reason, research in this field is directed towards enhancing the solubility and dissolution rate of poorly water soluble drugs.

To improve the interaction between a solute and a solvent it is possible to use a third substance. The combination of hydrophobic drugs with hydrophilic carriers allows the preparation of solid dispersions that enhance the dissolution processes in aqueous media of several and very different drugs such as ciprofloxacin (Francés et al., 1991), benzodiazepines (Fujii et al., 1991) or paracetamol (Tasic et al., 1992).

On the other hand, the presence of a biosur-

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factant can enhance the solubility and dissolution of drugs such as indomethacin and phenylbutazone (Tripathi et al.,, 1992), and it is usual to add surfactants to the dissolution media to achieve consistent results during the dissolution of poorly water soluble drugs (Uekama et al., 1992).

Therefore, other researchers have shown interest in the use of surfactants to increase the dissolution rate of drugs included in solid dispersions (Fernández et al., 1989; Serajuddin et al., 1990; Sjökvist et al., 1991).

The aim of this study is to investigate the dissolution processes of two drugs; oxodipine and griseofulvin from binary and ternary systems prepared with PEG 6000 and with PEG 6000/Tween 20, respectively. We have previously characterized these systems by thermomicroscopy and differential scanning calorimetry (Veiga et al., 1992) and the conclusions obtained can be useful to explain their dissolution behaviour.

Materials and Methods

Materials

Oxodipine was kindly supplied by the Instituto de Investigación y Desarrollo Químico Biológico, Madrid (Spain) and griseofulvin was purchased from Sigma, St. Louis, MO (U.S.A.), These materials were used without further purification. Also, binary systems (physical mixtures and solid dispersions) with each drug and PEG 6000, and ternary systems (solid dispersions) with each drug, PEG 6000 and Tween 20 were used. The proportions of drug/carrier or drug/carrier/surfactant are listed in Table 1. The method of fusion (70°C) has been used to prepare all solid dispersions.

Methods

Dissolution of each pure drug and its binary and ternary systems was studied to investigate the influence of PEG 6000 and the combination of PEG 6000 and Tween 20 on the dissolution of two poorly water soluble drugs. A Sotax AT-7 dissolution apparatus with paddles was used. The experimental conditions used were as follows: rate of rotation, 100 rpm; dissolution medium, 1000 ml of distilled water; temperature, 37 ± 0.1°C. All samples containing an amount equivalent to 15 mg of drug were added to the medium in a powdered form (size < 100 μm). The duration of assay was 3 h and at measured time intervals, samples were withdrawn and filtered with a porous filter of 0.45 μm pore diameter. Samples were assayed spectrophotometrically at 233 nm (for oxodipine) or 291 nm (for griseofulvin). The results were computed with the standard calibration curve of each drug.

TABLE 1

Composition of binary and ternary systems used to study their dissolution process

	Binary systems (drug/PEG 6000) (w/w)	Ternary systems (drug/PEG 6000/ Tween 20) (w/w)
Solid dispersions	10:90	10:90:10
	20:80	20:80:10
	30:70	30:70:10
	40:60	40:60:10
	50:50	50:50:10
Physical mixtures	10:90	
	20:80	
	30:70	
	40:60	
	50:50	

Results and Discussion

Fig. 1 shows the dissolution profiles of oxodipine from physical mixtures with PEG 6000. Also, the dissolution curve of pure oxodipine can be seen. In the physical mixtures only a superficial interaction exists between drug particles and carrier particles, and the dissolution enhancement with regard to pure drug is slight, although it can be noted that with increasing carrier proportion in the systems the dissolution rate of oxodipine also increases. Clearly, PEG 6000 acts as a disaggregant in these systems; the electrostatic charges that keep drug particles united together are reduced and oxodipine can dissolve in the dissolution medium.

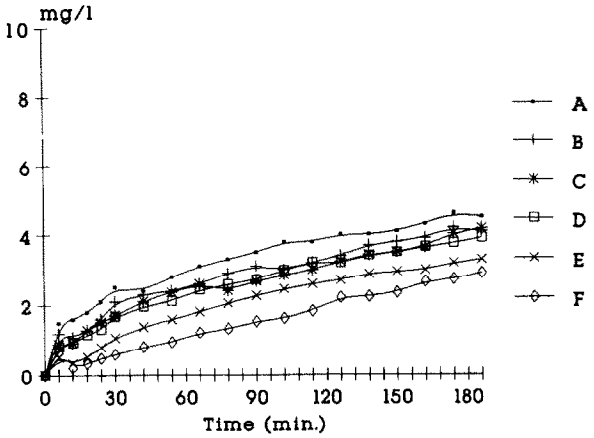

Fig. 1. Dissolution profiles of oxodipine from physical mixtures and pure oxodipine. (A) Oxodipine/PEG 6000 10:90 w/w; (B) oxodipine/PEG 6000 20:80 w/w; (C) oxodipine/PEG 6000 30:70 w/w; (D) oxodipine/PEG 6000 40:60 w/w; (E) oxodipine/PEG 6000 50:50 w/w; (F) pure oxodipine.

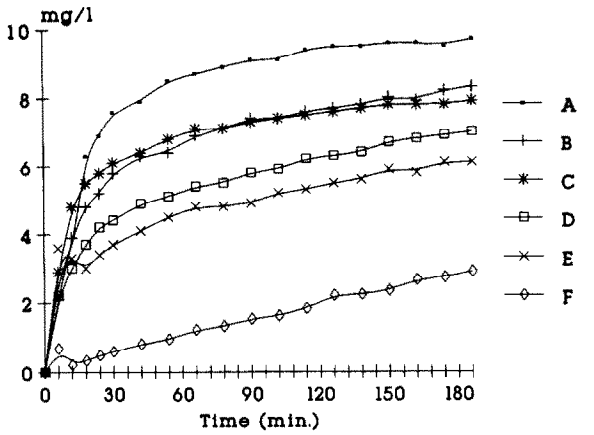

Fig. 3. Dissolution profiles of oxodipine from solid dispersions and pure oxodipine. (A) Oxodipine/PEG 6000 10:90 w/w; (B) oxodipine/PEG 6000 20:80 w/w; (C) oxodipine/PEG 6000 30:70 w/w; (D) oxodipine/PEG 6000 40:60 w/w; (E) oxodipine/PEG 6000 50:50 w/w; (F) pure oxodipine.

The time courses for evolution of dissolved griseofulvin from physical mixtures of griseofulvin/PEG 6000 and pure griseofulvin are plotted in Fig. 2. Here we also can observe the disaggregant action of PEG 6000 on griseofulvin particles. On comparison of the dissolution curves of pure oxodipine and pure griseofulvin, one observes that they have clearly different kinetics, however,

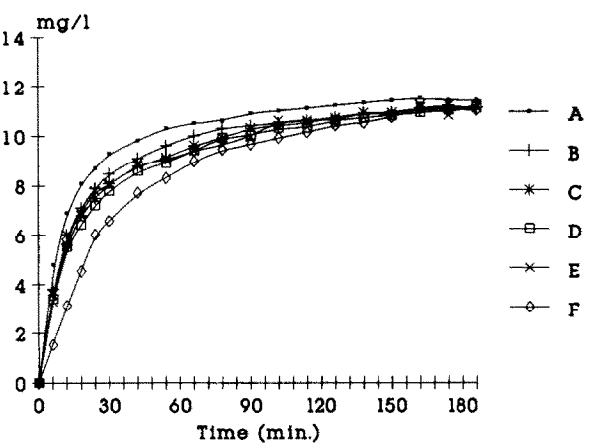

Fig. 2. Dissolution profiles of griseofulvin from physical mixtures and pure griseofulvin. (A) Griseofulvin/PEG 6000 10:90 w/w; B, griseofulvin/PEG 6000 20:80 w/w; (C) griseofulvin/PEG 6000 30:70 w/w; (D) griseofulvin/PEG 6000 40:60 w/w; (E) griseofulvin/PEG 6000 50:50 w/w; (F) pure griseofulvin.

the PEG 6000 in physical mixtures does not modify their kinetics, and only induces a steady increase in the amount of dissolved drug with regard to pure drug over the same time intervals (Figs 1 and 2), since here the hydrophilic carrier acts solely on the surface of particles.

Dissolution curves of oxodipine from oxodipine/PEG 6000 solid dispersions are shown in Fig. 3. A considerable improvement compared with the physical mixtures is observed when oxodipine is formulated as a solid dispersion. When the proportion of PEG 6000 in the solid dispersion is increased, the rate of oxodipine dissolution also increases, the greatest value corresponding to the oxodipine/PEG 6000 10:90 w/w solid dispersion. The explanation is that this solid dispersion was a true dissolution of oxodipine in melted PEG 6000, at 70°C, during the preparation of the system and, to solidify, mixed crystals between the drug and carrier are produced (Veiga et al., 1993). Van der Waals interaction forces between drug molecules are decreased in these mixed crystals, and as a consequence the dissolution of oxodipine from this solid dispersion is faster than from physical mixtures prepared in the same proportion, or pure oxodipine. The rest of the oxodipine/PEG 6000 solid dispersions is constituted of mixed crystals and an excess of pure

oxodipine crystals. The larger the proportion of oxodipine in the system, the greater is the proportion of oxodipine which does not form mixed crystals with PEG 6000. The amount of dissolved oxodipine from these systems depends on two simultaneous processes: dissolution from mixed crystals and dissolution from pure oxodipine crystals. As the dissolution rate of pure oxodipine is lower than that of oxodipine from mixed crystals, to increase the proportion of pure oxodipine crystals in the solid dispersions, the dissolved amount of oxodipine is reduced over the same time intervals.

The dissolution profiles of griseofulvin from griseofulvin/PEG 6000 solid dispersions are plotted in Fig. 4. On comparison of these curves with those of the physical mixtures (Fig. 2), it is evident that practically all the dissolution curves from solid dispersions are above those from the physical mixtures, however, the differences are not as marked as those shown by oxodipine binary systems, since the interaction resulting between griseofulvin and PEG 6000 during the preparation of solid dispersions does not reach completion, due to total dissolution of griseofulvin in melted PEG 6000 in any system being attained, as could be observed during the preparation of these systems.

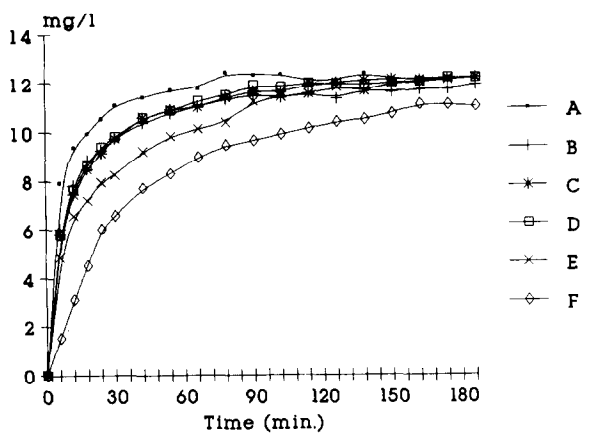

Fig. 4. Dissolution profiles of griseofulvin from solid dispersions and pure griseofulvin. (A) Griseofulvin/PEG 6000 10:90 w/w; (B) griseofulvin/PEG 6000 20:80 w/w; (C) griseofulvin/PEG 6000 30:70 w/w; (D) griseofulvin/PEG 6000 40:60 w/w; (E) griseofulvin/PEG 6000 50:50 w/w; (F) pure griseofulvin.

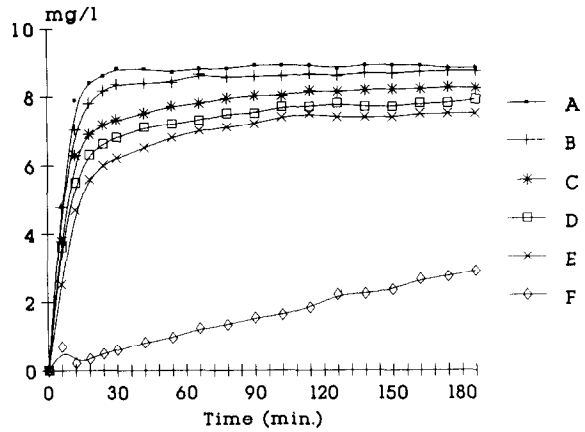

Fig. 5. Dissolution profiles of oxodipine from ternary systems and pure oxodipine. (A) Oxodipine/PEG 6000/Tween 20 10:90:10 w/w; (B) oxodipine/PEG 6000/Tween 20 20:80:10 w/w; (C) oxodipine/PEG 6000/Tween 20 30:70:10 w/w; (D) oxodipine/PEG 6000/Tween 20 40:60:10 w/w; (E) oxodipine/PEG 6000/Tween 20 50:50:10 w/w; (F) pure oxodipine.

Fig. 5 shows the dissolution profiles of oxodipine from ternary systems. The differences between the curves in Figs 3 and 5 are that the former show oxodipine dissolution from binary systems and the latter from ternary systems. The presence of a new substance (Tween 20) in the system can modify some of the dissolution profiles. The surfactant does not mix with PEG 6000 or oxodipine during the preparation of the ternary system, as observed on examination by thermomicroscopy (Veiga et al., 1993). Therefore, in the dissolution process of ternary systems, Tween 20 acts as a wetting agent, explaining the observed improvement in all dissolution profiles of oxodipine/PEG 6000 solid dispersions. Tween 20 does not act as a solubilizing agent, since in dissolution assays the amount of ternary system added never contains a surfactant quantity exceeding its critical micelle concentration which has been reported to be 0.060 g/l (Wan and Lee, 1974). The influence of Tween 20 on oxodipine dissolution is stronger in those systems which contain higher proportions of the drug since, as stated above, these systems possess greater proportions of pure oxodipine crystals and the wetting action of Tween 20 is more extensive in these crystals.

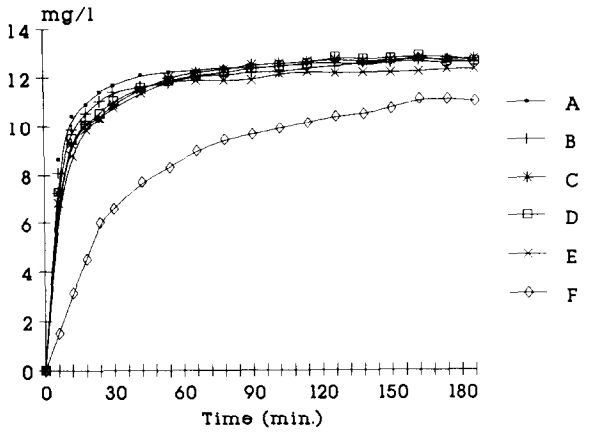

Fig. 6. Dissolution profiles of griseofulvin from ternary systems and pure griseofulvin. (A) Griseofulvin/PEG 6000/Tween 20 10:90:10 w/w; (B) griseofulvin/PEG 6000/Tween 20 20:80:10 w/w; (C) griseofulvin/PEG 6000/Tween 20 30:70:10 w/w; (D) griseofulvin/PEG 6000/Tween 20 40:60:10 w/w; (E) griseofulvin/PEG 6000/Tween 20 50:50:10 w/w; (F) pure griseofulvin.

The dissolution profiles of griseofulvin from ternary systems are plotted in Fig. 6. The profiles curves from all systems assayed show superposition. On comparison of the curves in Figs 4 and 6, one can observe that the presence of a surfactant in the griseofulvin solid dispersion with PEG serves to equalize all disssolution profiles from ternary systems and to exceed the levels obtained from any binary system, even those which contain a smaller proportion of drug (griseofulvin/PEG 6000 10:90 solid dispersion). Moreover, in this case, the explanation lies in the interaction taking place between griseofulvin and PEG 6000 during heating, since melted PEG 6000 dissolves practically no griseofulvin, and therefore, the improvement obtained in griseofulvin dissolution from solid dispersions with PEG 6000 is not very pronounced. As a consequence, the wetting action of Tween 20 is more marked in solid dispersions of griseofulvin than of oxodipine. In the griseofulvin/PEG 6000/Tween 20 ternary systems, the surfactant does not mix with PEG 6000, and during the dissolution of the system, Tween 20 decreases the interfacial tension between the medium and the griseofulvin particles, thus facilitating wetting and dissolution of the pure drug particles by the medium. As the proportion of pure drug particles is larger in systems with griseofulvin compared to those with oxodipine, the action of surfactant is more marked on the dissolution of systems with griseofulvin.

Conclusion

This study has demonstrated the formulation of two poorly water soluble drugs in solid dispersions with PEG 6000 as a means of enhancing drug dissolution rate. The explanation for the enhancement lies in the method of preparation.

If, during the preparation of a solid dispersion, molecular interaction between drug and carrier occurs (oxodipine and PEG 6000), this solid dispersion will enhance the drug dissolution. If there is no drug-carrier molecular interaction during the preparation of the solid dispersion, or if it is insignificant (griseofulvin and PEG 6000), the carrier will act only as a disaggregant in drug dissolution. In the latter case, the addition of a surfactant to the solid dispersion during preparation will decrease the interfacial tension between drug particles and the dissolution medium, and enhance the dissolution rate of the drug from the ternary system. The characterization of solid dispersions by thermal analysis allows one to explain the differences resulting in dissolution processes.

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