DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 14(9), 1185-1202 (1988)

DISSOLUTION RATE OF GRISEOFULVIN FROM SOLID DISPERSIONS WITH POLY(VINYLMETHYLETHER/ MALEIC ANHYDRIDE)

Cristina Flego, Mara Lovrecich and Fulvio Rubessa

Institute of Pharmaceutical Chemistry, University of Trieste, Trieste (Italy)

ABSTRACT

A solid dispersion technique with poly(vinylmethylether/ maleic anhydride) (PVM/MA) and its half esters has been used to enhance griseofulvin dissolution.

A marked increase of the dissolution rate and solubility of griseofulvin contained in these solid dispersions was observed compared with that of drug alone and that of physical mixture with the carrier.

Differences in dissolution rates resulted from the molecular weight and the chemical structure of the carrier.

X-Ray powder diffractometry, differential scanning calorimetry (DSC) and wettability tests were employed to investigate the nature of the studied forms.

INTRODUCTION

Griseofulvin, a poorly water-soluble antifungal antibiotic,has been shown to be incompletely and irregularly absorbed after oral administration because of its slow dissolution rate in the gastrointestinal tract (1-3). Attempts has been made to modify its physical properties and success has been achieved by the formation of solid dispersion systems.

Several carriers have been used in the preparations of these systems. The most successful include polyethylene glycol (4-9), and polyvinylpyrrolidone (10,11).Other carriers have been employed to a lesser extent: citric acid (4) , succinic acid (12-14), pentaerythritol (4),pentaerythrityl tetraacetate (4), polyoxyethylen and polyoxypropylen copolymer (15),polyoxyethylene stearate (8,9), hydroxypropylmethylcellulose phthalate (16), cellulose acetate phthalate (16), carboxymethyl-ethylcellulose (16), methacrylic acid/methacrylyc acid methylester copolymer (16), and phospholipids (17).

On this regard no particular attention has been given to poly(vinylmethylether/maleic anhydride) (PVM/MA) and its alkyl half esters. However these polymers have been proposed as film coating for tablets (18-22), in compressed and cast polymeric matrices (23-27) and microcapsules (28).

The purpose of this study is to evaluate the release kinetics of griseofulvin from PVM/MA and its half esters solid dispersion systems prepared by a solvent technique and to determine the parameters of the loaded systems which enhance the solubility pattern of the drug.

EXPERIMENTAL

MATERIALS

The PVM/MA polymers,marketed GAN 119 and 169, were obtained commercially from GAF (Milano,Italy) and used as received. Their average molecular weight was 20000 and 67000 respectively. The ethyl half ester of PVM/MA (GAN ES 225) and nonylphenoxypoly-(ethylenoxy) ethanol (Antarox CO 630) were also supplied by GAF. Griseofulvin was received from Farmitalia Carlo Erba (Milano, Italy). Solvents and buffers were analytical grade.

METHODS

Partial esterification of PVM/MA with nonylphenoxypoly(ethylen-oxy) ethanol (GAAN).

15 g of PVM/MA 67000 were dissolved in 500 mL of 2-butanone and added with 3 g of the alcohol. The mixture was refluxed for 9h ,the ongoing of the reaction was investigated using infrared spectroscopy. The decrease of the anhydride peak (1780 cm^{-1}) and the increase of the ester peak (1725 cm^{-1}) were followed until no longer changed. The volume of the solution was reduced and by pouring it into cold petroleum ether a precipitate was obtained. The crude solid was washed three times in n-hexane, dried and pulverized. The degree of esterification was 5% assessed by titration in an ethanolic solution with 0.01N NaOH.

Preparation of the solid dispersions with the solvent method.

The required amounts of polymer and drug were weighed, dissolved in 2-butanone, then the solvent was evaporated under reduced pressure. Further drying was carried out in a dessicator

over anhydrous calcium sulphate. All samples were pulverized and sieved with a 250 μm sieve.

Each batch of the prepared dispersions was tested for content of the drug. This was done by dissolving a weighed amount of the dispersion in methanol and the drug present was determined spectrophotometrically at 294 nm.

Preparation of the physical mixture

Physical mixtures were prepared by simple mixing of the two products, recrystallized from 2-butanone and possessing the same particle size range (200-250 μm),in various proportions.

Differential scanning calorimetry (DSC)

Samples were placed in aluminum pans and analyzed using a differential scanning calorimeter (Mettler DSC 20,TA 3000) with indium as a calibration standard under nitrogen flow and a heating rate of 10°C/min.

X-Ray diffractometry

The solid was exposed to Cu-Kα radiation in a wide angle diffractometer (Philips, PW 1050/70) over a range of 2ϑ angles from 4 to 35 degrees.

Wettability test

Solid-water contact angles were measured with a wettability tester (Lorentzen-Wettre, Sweden). Small drops of distilled water were placed on the surface compact by a microsiringe. The contact angle values were derived from the height and length of the drop image. At least six replications were carried out.

Solubility measurements

The solubility of griseofulvin dispersed in the polymer was measured by placing an excess amount of the system in a cell

containing 50 mL of pH 7.50 phosphate buffer solution at 37°C under constant stirring. The solution was filtered and pumped directly to a spectrophotometer cell.

Release studies

900 mL of a phosphate buffer (38.8mM) at pH 7.50 were placed in a USP XXI rotating paddle apparatus (Erweka,mod.DT-1,West Germany) at 150 rpm and maintained at 37°C. A powdered sample equivalent to 4.5 mg griseofulvin was poured on the surface of the buffer solution. The aqueous medium was filtered and continuosly pumped to a flow cell in a spectrophotometer and absorbance values were recorded at 294 nm. The presence of the polymer did not interfere with the analysis of griseofulvin. The results are average of triplicate experiments and variation of the mean was within 5 percent.

Dissolution of the polymers was studied using the same method. The polymer concentration was measured spectrophotometrically at 216 nm.

RESULTS AND DISCUSSION

-Physicochemical properties of griseofulvin in the solid dispersions.

The physical state of griseofulvin, dispersed in PVM/MA 20000 and 67000 and esters (GAN ES 225 and GAAN), was assessed by differential scanning calorimetry and X-ray powder diffractometry.

The measured values of the endothermic energy of the solid dispersions with PVM/MA 67000 are listed in Table 1. The percentage of cristallinity of the drug increases with the percentage of the dispersed griseofulvin. The intercept of the

TABLE 1

Measured endothermic heats for griseofulvin-PVM/MA 67000 solid dispersion.

percentage of griseofulvin	weight ratio drug:polymer	ΔH J/g
100		120.7
75	3:1	93.5
50	1:1	71.9
33	1:2	37.1
17	1:5	13.5
9	1:10	-*

*Unable to discern endotherm of significant value

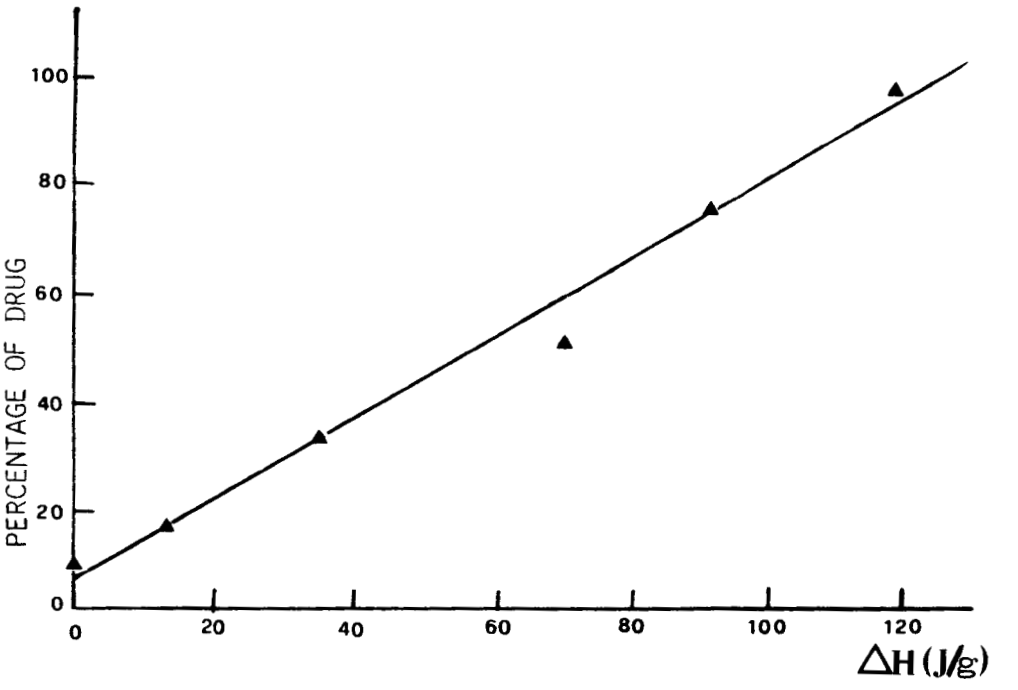


FIGURE 1

Plot of percentage of drug in dispersion with PVM/MA 67000 versus the measured endothermic energy.

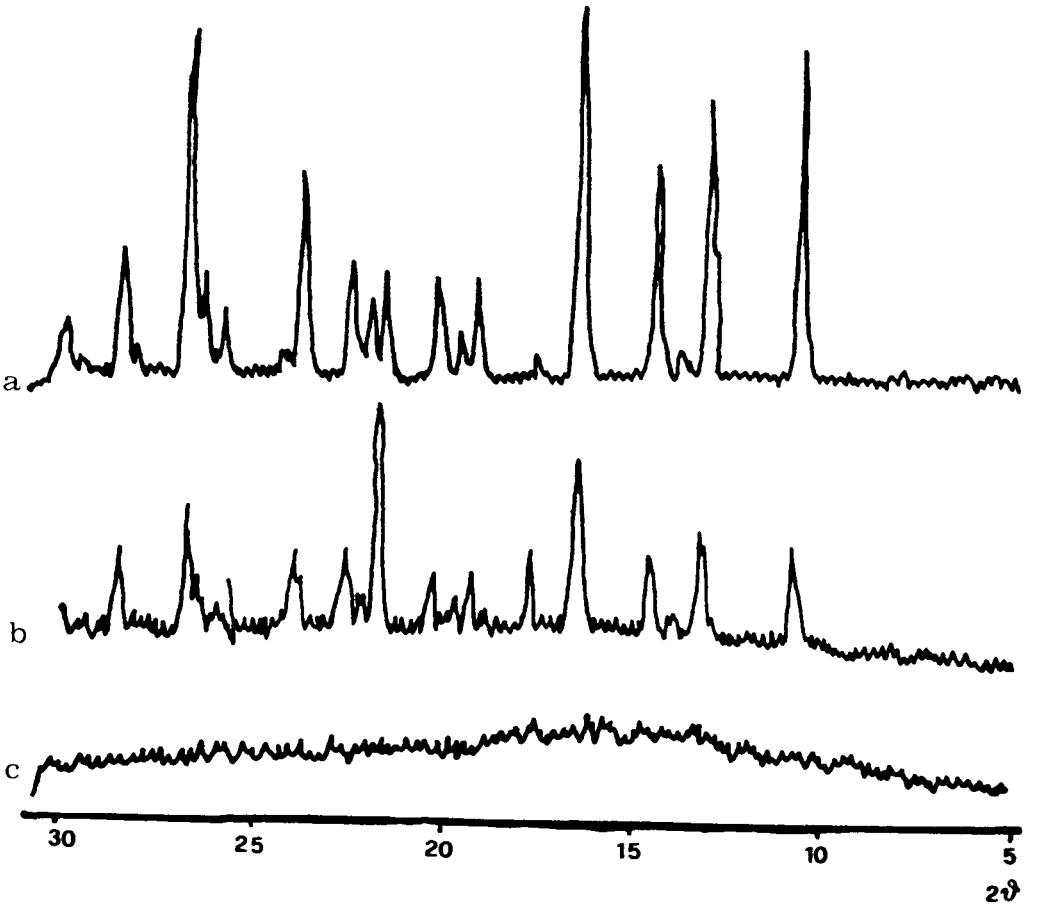


FIGURE 2

X-Ray diffraction spectra. a) recrystallized griseofulvin; b)1:10 griseofulvin-PVM/MA 67000, physical mixture; c) 1:10 griseofulvin-PVM/MA 67000, solid dispersion.

plot of the percentage of drug in dispersion versus the endothermic energy is the apparent dispersibility of griseofulvin in the polymer (10) (Figure 1).

A value of 5.9% of drug in the solid dispersion is obtained which is in agreement with the finding that griseofulvin is completely amorphous in a 9% system (1:10 drug/polymer ratio).

TABLE 2

Chemical structure and contact angle values of the studied polymers

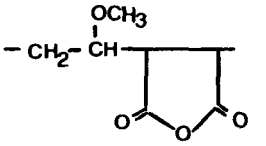
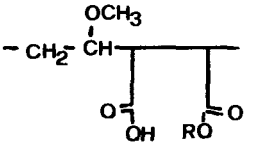
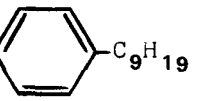
Polymer	monomer	δ (degrees)
PVM/MA 20000		0
PVM/MA 67000		0
		
GAN ES 225	R=-C_2H_5	30
GAAN	R=-CH_2-CH_2-$(OCH_2CH_2)_8$-O-  -C_9H_{19}	53

TABLE 3

Contact angle values of coprecipitates with different loading percentages of griseofulvin in PVM/MA 67000.

percentage of drug	weight ratio	δ(degrees)
9	1:10	22
17	1:5	41
33	1:2	45
pure drug		57

X-Ray diffractograms confirmed that a sample lacked cristallinity when no endotherm peak was observed. On the other hand physical mixture, made with the same proportions of materials, exhibited characteristic crystalline diffraction patterns (Figure 2).

The solid dispersions with the other studied polymers show same behavior; the griseofulvin is present in an amorphous or in a ultrafine crystalline state, depending on its percentage of loading.

The wettability of the four studied polymers depends on the chemical structure of the monomer (Table 2). The anhydrides are completely hydrophilic while esters are partially hydrophobic and this property is associated to the lenght of the ester chain (24).

The hydrophilicity of the polymer enhances the wettability of the prepared solid dispersions. Furthermore as expected, a dispersion with a lower percentage of the loaded drug possesses a higher wettability (Table 3).

-Solubility behavior

Griseofulvin is practically insoluble in water, a concentration of 11.8 μg/mL was determined at 37°C, while its solubility increased in all studied solid dispersions.

It can be noted that griseofulvin, dispersed in PVM/MA 20000, has a maximum solubility ,46 μg/mL and 41 μg/mL for loading weight ratios of 1:2 and 1:10 respectively,observed after 1.5 minutes (Fig. 3). On the other hand in the PVM/MA 67000 solid dispersion the maximum solubility, 36 μg/mL and 30 μg/mL for 1:2

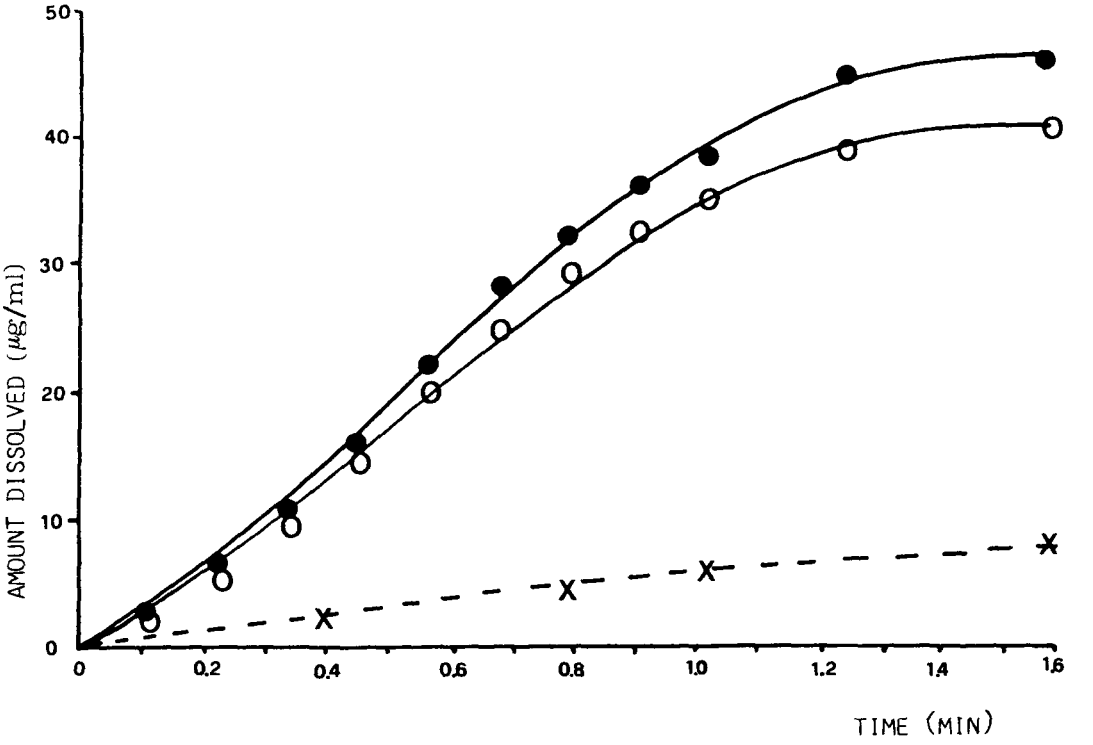


FIGURE 3
Solubility of griseofulvin from solid dispersions with PVM/MA 20000 in water at 37°C;—●— 1:2 weight ratio;—○— 1:10 weight ratio;-x- - - recrystallized griseofulvin.

and 1:10 drug/ polymer ratio, was noticed after 6 minutes. There was no significant difference in the solubility patterns in these two systems even if griseofulvin is amorphous in 1:10 coprecipitate while is partially crystalline, as determined by DSC, in the 1:2 system (Fig. 4).

Slightly lower solubility values are obtained from solid dispersions with esters (GAN ES 225 and GAAN) (Fig. 5).

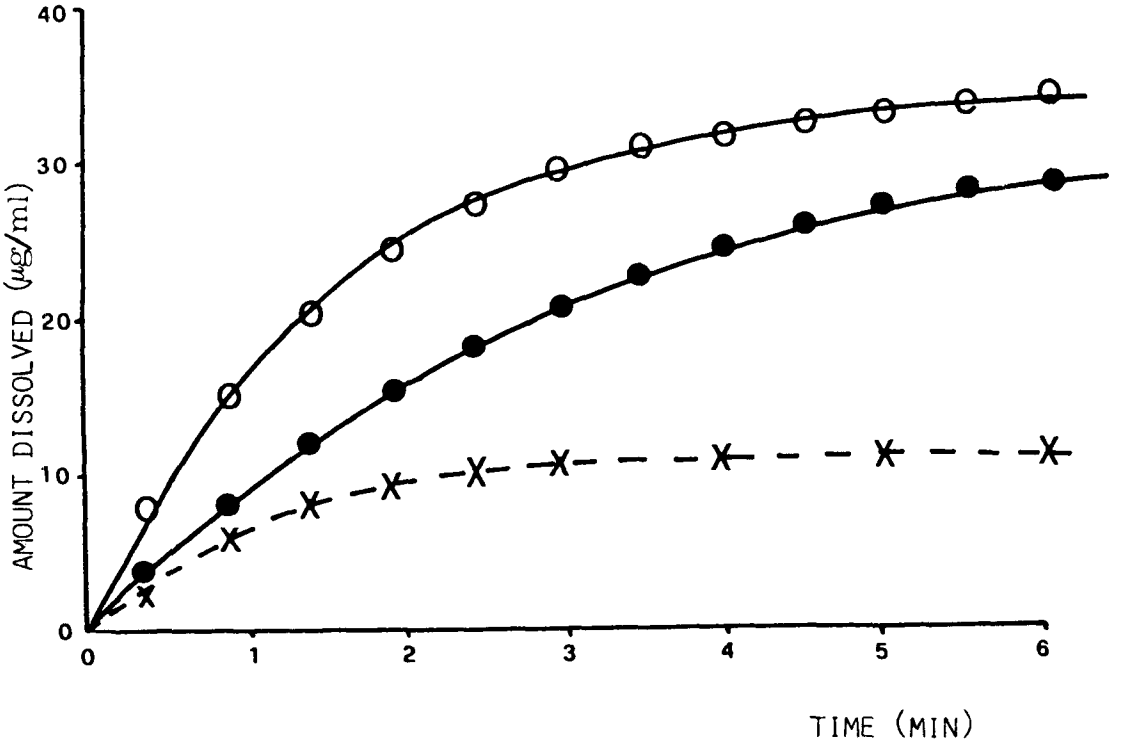


FIGURE 4

Solubility of griseofulvin from solid dispersions with PVM/MA 67000 in water at 37°C; —○— 1:2 weight ratio; —●— 1:10 weight ratio; -x- - recrystallized griseofulvin.

-Release Rates

The release rate of griseofulvin from all studied solid dispersions increased markedly from those of the physical mixture and the drug alone.

The dissolution of griseofulvin, solvated with 2-butanone, is shown for comparison and is essentially the same as micronized griseofulvin. Finally no significant change in the dissolution pattern from physical mixture and drug alone was noticed.

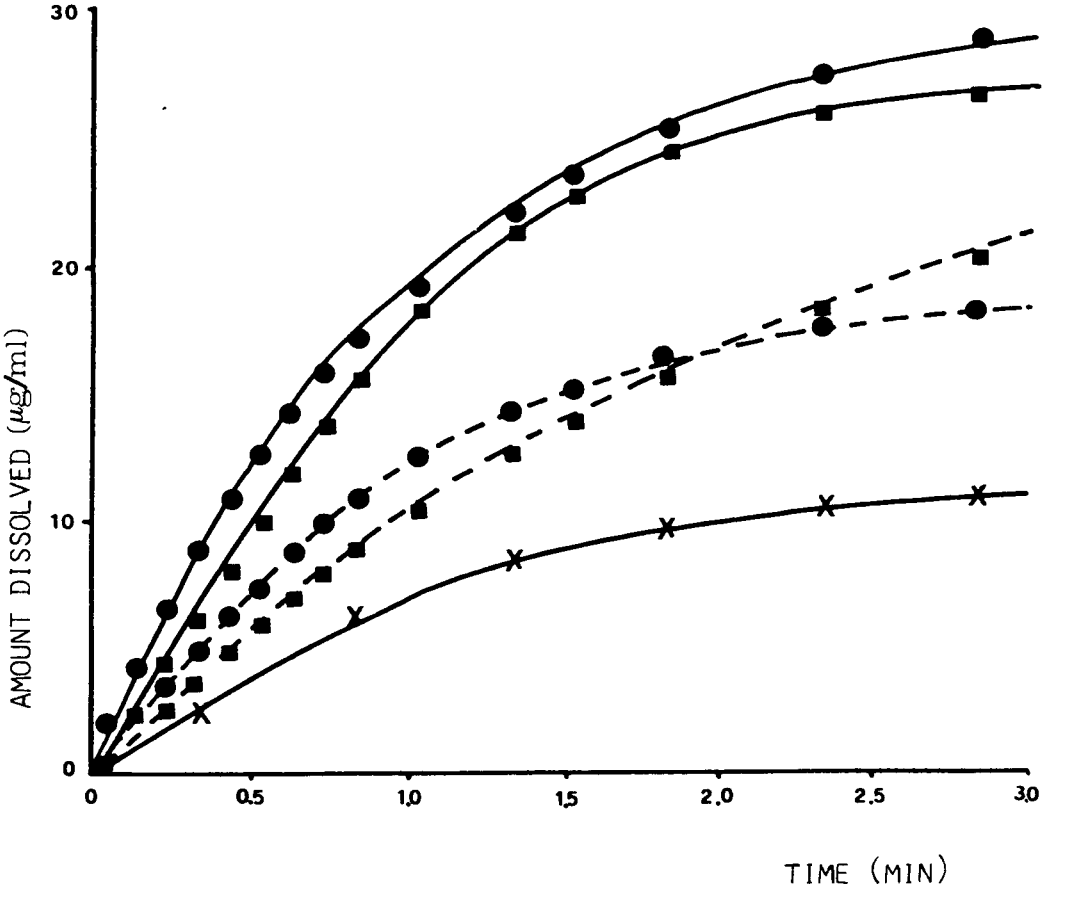


FIGURE 5

Solubility of griseofulvin from solid dispersions with half esters in water at 37°C. —x— recrystallized griseofulvin
GAN ES 225: —●— 1:2 weight ratio; -●- - - 1:10 weight ratio
GAAN : —■— 1:2 weight ratio; -■- - - 1:10 weight ratio

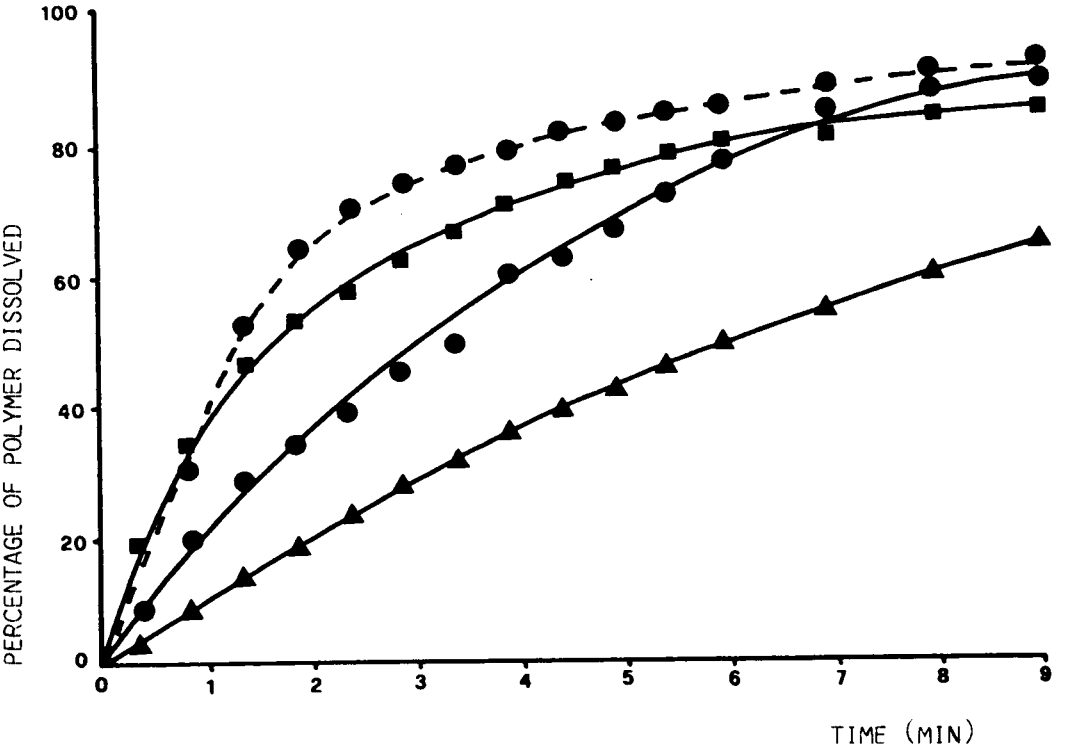


FIGURE 6

Dissolution rates of the polymers.-- ●- - - PVM/MA 20000, ●— PVM/MA 67000, ■— GAN ES 225, ▲— GAAN.

The fast release of the drug from the coprecipitates may be attributed to the rapid erosion kinetics of the polymer in the aqueous medium (Fig. 6) and subsequent dissolution of the amorphous or highly dispersed microcrystalline griseofulvin entrapped in the system.

Differences in dissolution rates resulted from the molecular weight and the nature of the carrier. The degree of enhancement of dissolution rate achieved by PVM/MA polymers showed some decrease as the molecular mass increased. The amount of dissolved

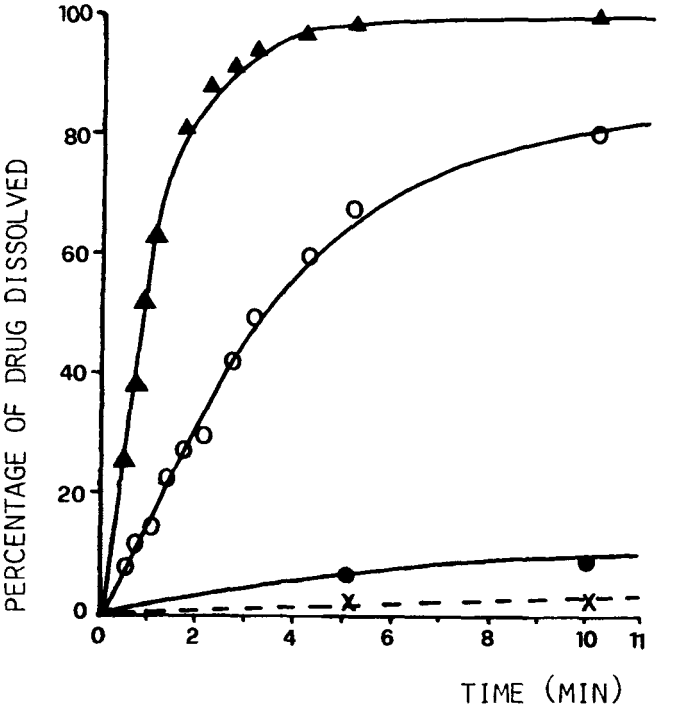


FIGURE 7

Dissolution rates of griseofulvin from solid dispersions with PVM/MA 20000 in water at 37°C;—○— 1:2 weight ratio; —▲— 1:10 weight ratio;—●— 1:10 physical mixture;– ✱ – – recrystallized griseofulvin.

griseofulvin from solid dispersions with PVM/MA 20000 was 81.1% and 97.8% for 1:2 and 1:10 solid dispersion systems after 10 minutes while approximately the same values are obtained only within 45 minutes using PVM/MA 67000 (Fig.7,8). Furthermore in solid dispersions with PVM/MA the loading ratio affects the dissolution rate of griseofulvin while no differences are noticed for various coprecipitates prepared with half esters.

The release rate of griseofulvin from half esters can be compared to solid dispersions with PVM/MA 67000 at the initial time period but after 7 hours an incomplete release was observed.

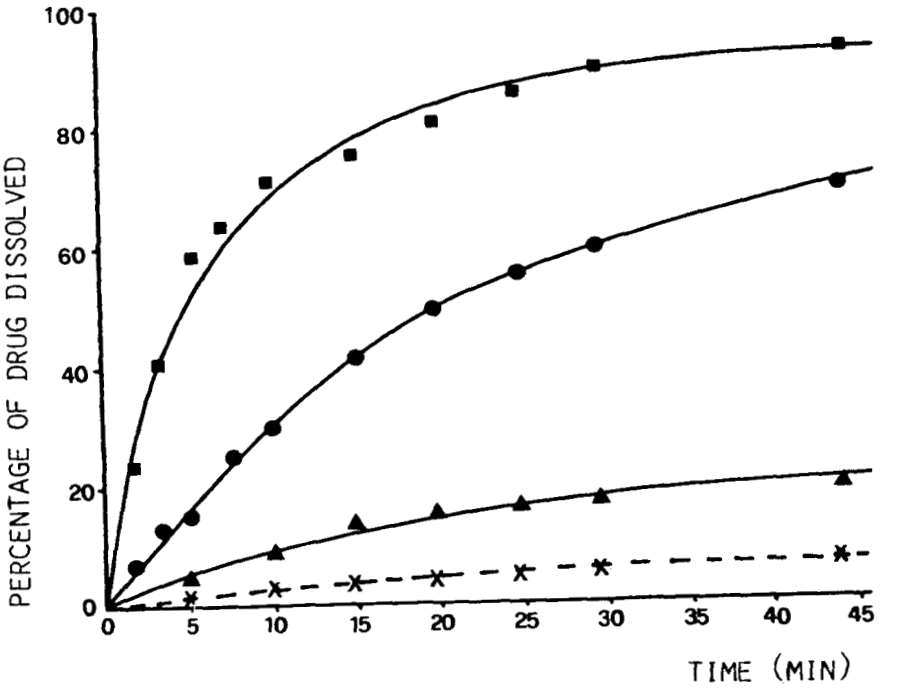


FIGURE 8

Dissolution rates of griseofulvin from solid dispersions with PVM/MA 67000 in water at 37°C; —■— 1:2 weight ratio; —●— 1:10 weight ratio; —▲— 1:10 physical mixture; —x— recrystallized griseofulvin.

This fact can be attributed to the absorption of same griseofulvin on the hydrophobic surface of the polymer (Fig. 9).

CONCLUSIONS

The molecular mass of the two anhydride polymers influences the solubility and dissolution rate of griseofulvin from their solid dispersions; PVM/MA 20000 gave better results than PVM/MA 67000.

The loading ratio of the drug in the anhydride polymers affects the solubility and the dissolution rate while with half

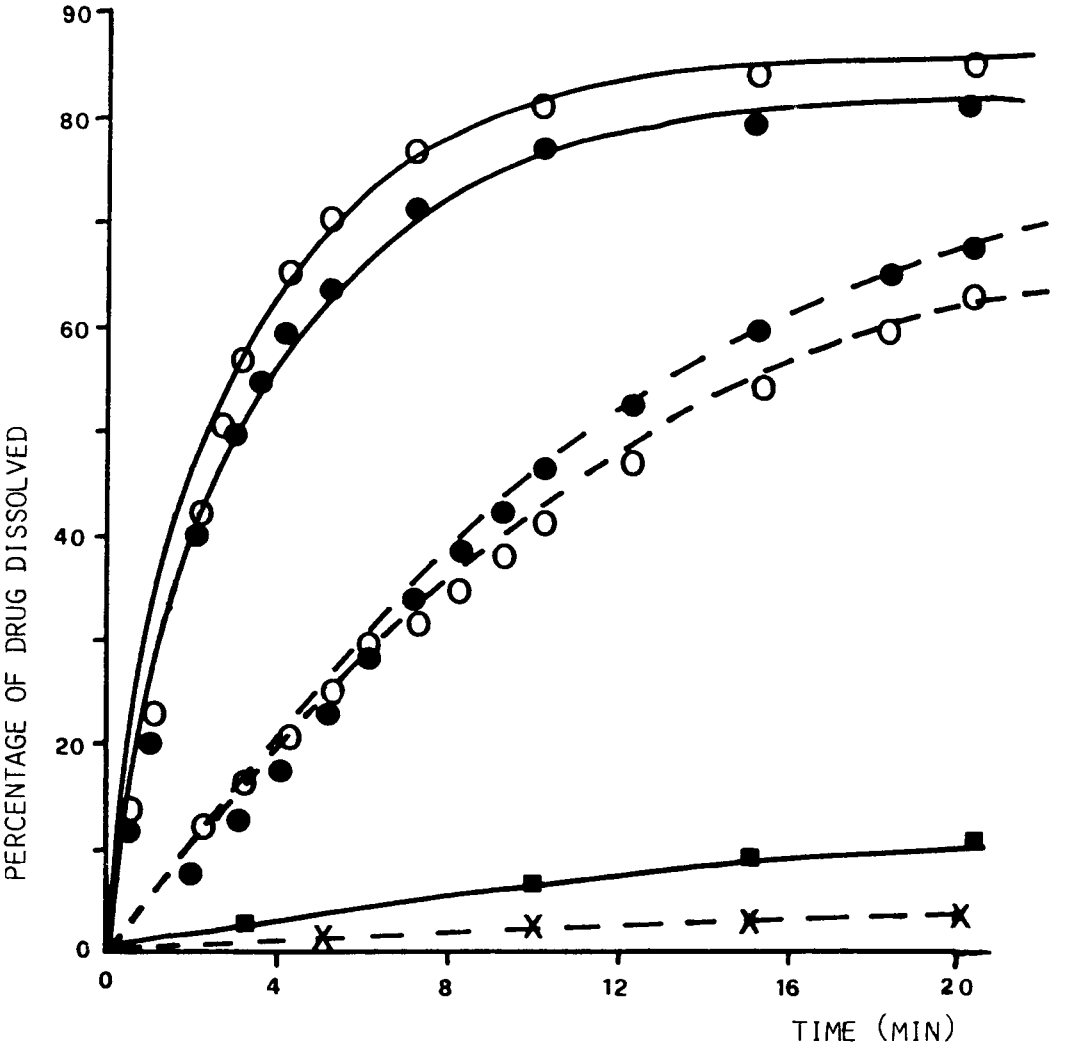


FIGURE 9

Dissolution rates of griseofulvin from solid dispersions with half esters. GAN ES 225:—●— 1:2 weight ratio;—○— 1:10 weight ratio;—■— 1:10 physical mixture. GAAN:-●- -1:2 weight ratio; - - - ○- - 1:10 weight ratio,- -x- - recrystallized griseofulvin.

esters polymers this parameter influences only the maximum solubility of griseofulvin.

Similar solubility patterns are observed with coprecipitates with half esters polymers while the more hydrophobic ester produces a slower dissolution rate of griseofulvin.

REFERENCES

1. R.M. Atkinson,C. Bedford, K.J. Child, and E.G. Tomich, Antibiot. Chemother. 12, 225 (1962)
2. B.Katchen and S.Symchowiz, J. Pharm. Sci.,56, 1108 (1967)
3. M. Rowland, S. Riegelman, and W.L. Epstein, J. Pharm. Sci.,57,984 (1968)
4. W.L. Chiou and S. Riegelman, J. Pharm. Sci.,58, 1505 (1969)
5. W.L. Chiou and S. Riegelman, J. Pharm. Sci.,59, 937 (1970)
6. W.L. Chiou and S. Riegelman, J. Pharm. Sci.,60, 1281 (1971)
7. J.L. Dubois and J.L. Ford, J. Pharm. Pharmacol.,37,494 (1985)
8. R. Kaur, D.J.W.Grant, and T. Eaves, J. Pharm. Sci.,69,1317 (1980)
9. R. Kaur, D.J.W. Grant, and T. Eaves, J. Pharm. Sci.,69,1321 (1980)
10. E. Shefter and K.C. Cheng, Int. J. Pharm., 6,179 (1980)
11. F. Carli, I. Colombo, L. Magarotto, A. Motta, and C.Torricelli, Int. J. Pharm., 33,115 (1986)
12. A.H. Goldberg,M.Gibaldi, and J.L. Kanig, J. Pharm.Sci., 55, 487 (1966)
13. W.L. Chiou and S. Niazi, J. Pharm. Sci.,62, 498 (1973)
14. W.L. Chiou and S. Niazi, J. Pharm. Sci.,65, 1212 (1976)
15. K.H. Fromming, K. Heyer, and R.Hosemann, Deutsche Apoth. Zeit., 121, 2276 (1981)

16. A. Hasegawa, R. Kawamura, H. Nagasawa, and I. Sugimoto, Chem. Pharm. Bull., 33, 3429 (1985)

17. S. Venkataram and J.A.Rogers, Drug Dev. Ind. Pharm., 11,223 (1985)

18. L.C. Lappas and W. McKeeham, J. Pharm. Sci., 51, 808 (1962)

19. L.C. Lappas and W. McKeeham, J. Pharm. Sci., 54,176 (1965)

20. L.C. Lappas and W. McKeeham, J. Pharm. Sci., 56, 1257 (1967)

21. E. Chalboub, H.A.M. ElShibini, N.A. Daabis, Pharm. Ind., 38, 844 (1976)

22. E. Chalboub, H.A.M. ElShibini, and N.A. Daabis, Pharm. Ind.,38, 1020 (1976)

23. C.W. Woodruff, G.E. Peck,and G.S. Banker, J. Pharm. Sci.,61, 1916 (1972)

24. J. Heller, R.W. Baker, R.M. Gale, and J.O. Rodin, J. Appl. Polym. Sci., 22, 1991 (1978)

25. J. Heller and P.V. Trescony, J. Pharm. Sci., 68, 919 (1979)

26. A. Urrti, Int. J. Pharm., 26,45 (1985)

27. A. Urrti, L. Salminen and O. Miinalainen, Int. J. Pharm.,23, 147 (1985)

28. S.A. Mortada, Pharmazie,36, 420 (1981)