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Bioavailability of griseofulvin from a novel capsule formulation

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The *in vivo* availability of griseofulvin from a novel formulation has been compared with the micronized powder. The formulation technique involves the conversion of the hydrophobic surface of the drug to a hydrophilic one by treatment with a film forming polymer. This enhances the wettability of the power, and increases its dissolution rate. The results of the *in vivo* study show the formulation technique has increased the rate and extent of bioavailability of griseofulvin when compared with the non-treated powder.

Drugs that are poorly wetted may be among those compounds whose absorption is dissolution rate limited. The small 'effective' surface area presented by such drugs to the dissolution medium will give rise to low dissolution rates. The aim of formulation is to increase dissolution. Particle size reduction will increase the true surface area, but with hydrophobic drugs this increase may have a smaller effect than anticipated because of problems of wetting.

A technique has been described (Lerk, Lagas & others, 1978) in which the large surface area of a hydrophobic drug having a small particle size, is more effectively used for dissolution, by the creation of a hydrophilic surface on the drug particles. It seemed appropriate to investigate the usefulness of this technique *in vivo*.

Griseofulvin is a poorly water soluble drug, which is slowly, erratically and incompletely absorbed from the gastrointestinal tract in man. Various techniques and formulations have been devised to overcome this (Chiou & Riegelman, 1971; Yamamoto, Nakano & others, 1974; Bates & Sequeira, 1975). In the course of investigations on griseofulvin, its hydrophobicity was mentioned (Elworthy & Lipscomb, 1968; Chiou & Riegelman, 1971) and because of this and the availability of pharmacokinetic data for comparison, griseofulvin was chosen to evaluate the technique of Lerk & others (1978) on *in vivo* availability.

MATERIALS AND METHODS

Materials

Griseofulvin (ICI Pharmaceuticals Ltd.) was used as received. It had a mean particle size of 4 μm based on air permeability determinations. Hydroxypropyl cellulose (Klucel, L. F., Hercules Powder Co. Ltd., London) which is soluble in both water and some organic solvents, and forms films on drying, was used in solution as the material for treating the drug. A sample of 6-demethylgriseofulvin was kindly supplied by the Schering Corporation, U.S.A.

Methods

Treatment of griseofulvin. This was carried out in a small high speed mixer (Moulinex, Type 241). 25 g of griseofulvin was placed in the mixer and 2·5 ml of a 10% ethanolic solution of hydroxypropyl cellulose added. The mixer was run for 30 s, stopped, and the material mixed with a spatula to remove any dead spots. This process was repeated four times. The quantities of materials and the conditions of mixing were determined from empirical observations. The powder was dried in an oven at 50° for 2 h and screened through a 250 μm sieve.

Capsule filling. No. 4 hard gelatin capsules (Parke Davis Ltd., Hounslow) were hand filled with 120 mg of either griseofulvin or the treated griseofulvin. No excipients were employed.

Dissolution testing of capsules. Dissolution rate testing was carried out in a manner similar to that described by Newton & Rowley (1970). The capsules were held in a spiral (3 coils per 2 cm) located at the centre of a flat bottomed 5 litre beaker. The dissolution fluid was 4 litres of 0·1 M hydrochloric acid maintained at 37° and stirred with a three bladed stirrer rotating at 80 rev min^{-1}. Samples were taken at appropriate times, filtered through a sintered glass filter (porosity 3) and the griseofulvin concentration determined spectrophotometrically at 291 nm.

Bioavailability study

The study was carried out in five healthy male volunteers. After an overnight fast, the participants

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had a standard breakfast before 8.30 a.m. Two 120 mg capsules of either griseofulvin or treated griseofulvin were taken at 11 a.m. together with 100 ml of water. A standard, non-fat lunch was eaten at 1.30 p.m. Complete urine collections were made for the time intervals 0–2, 2–4, 4–6, 6–8, 8–12, 12–24, 24–36, 36–48 and 48–72 h. The study was repeated with the alternative product one week after the last urine collection. The volume and pH of the urine were recorded, and aliquots stored at −25°. The samples were analysed for total 6-demethylgriseofulvin by the method of Rowland & Riegelman (1973).

RESULTS AND DISCUSSION

Dissolution testing

The mechanisms involved in the increase in dissolution rate of another hydrophobic drug, hexobarbitone, treated in a similar manner to that described have been fully discussed by Lerk & others (1978). In the present work, there is no evidence to suggest that mechanisms other than those described by Lerk and his colleagues, namely the creation of a hydrophilic surface, are involved in the increased dissolution rate obtained and shown in Fig. 1. The solubilities of the drug in 0·1 M hydrochloric acid, and in 0·1 M hydrochloric acid containing the maximum possible concentration of dissolved hydroxypropyl cellulose are not significantly different. Intrinsic dissolution rates measured from non-disintegrating discs of the two materials were also not significantly different. It may therefore be concluded that the process is creating a hydrophilic surface on the particles allowing more rapid penetration of the dissolution fluid leading to a faster dissolution rate. The high speed mixing limits agglomeration and the high surface area of the drug is more effectively used.

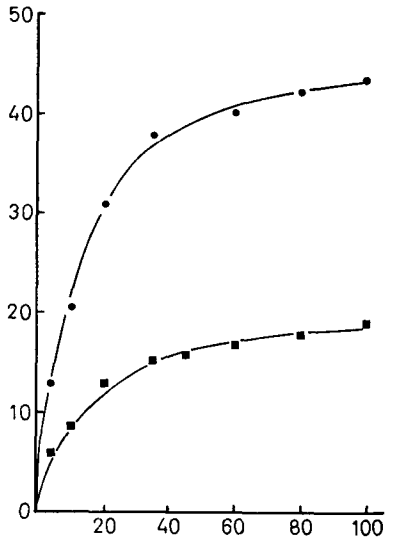

FIG. 1. The dissolution rates of the griseofulvin powders in 0·1 M HCl. ■ = non-treated powder. ● = treated powder. Ordinate: Amount released (mg). Abscissa: Time (min).

Bioavailability study

The rate of excretion of total 6-demethylgriseofulvin (6-DMG) after oral administration of griseofulvin is proportional to the plasma concentration of griseofulvin and the total amount of 6-DMG excreted is proportional to the amount of griseofulvin absorbed (Chiou & Riegelman, 1971). Generally, collection of urine for five to six half lives is sufficient to assess the total amount of drug excreted in urine. The elimination half life of griseofulvin for each subject was in the range of 10 to 13 h as determined from log amount remaining to be excreted *vs* time plots. Therefore the amount of 6-DMG excreted in the 72 h urine could be used to assess the relative bioavailability of griseofulvin from the two formulations.

The cumulative amounts of total 6-DMG excreted in the urine up to 24 h and up to 72 h for each subject and for each dose are given in Table 1, and the mean cumulative urinary excretion against time profiles for total 6-DMG after oral administration of each dose form are given in Fig. 2. The mean value for amount of 6-DMG excreted in 72 h after taking the treated formulation, Table 1, is 33% higher than the mean value of 6-DMG excreted up to 72 h after administration of the non-treated formulation. In three subjects the percent of dose excreted as 6-DMG, 80, 74 and 75% respectively, suggests complete absorption of griseofulvin from the treated formulation, since the reported fraction of dose excreted as 6-DMG after intravenous administration of griseofulvin is 0·65 (Chiou

Table 1. *Cumulative amounts of total 6-DMG (mg) excreted in 24 and 72 h in individual subjects after taking 240 mg of the treated and non-treated formulations.*

	Treated powder		Non-treated powder	
Subject	24 h	72 h	24 h	72 h
I	92	139	30	124
II	122	177	86	131
III	141	180	68	—
IV	76	153	52	112
V	170	192	114	141
mean + s.e.	120±17	168±10	70±14	127±6

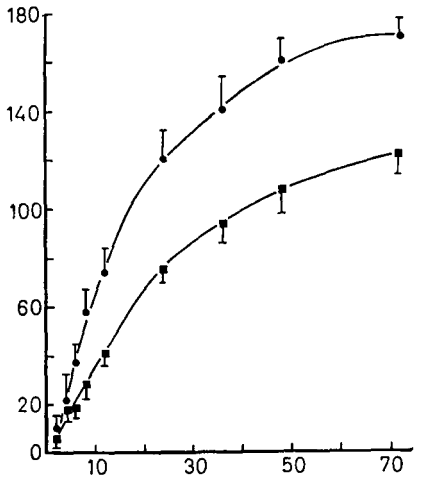

FIG. 2. Mean cumulative urinary excretion of total 6-DMG in five subjects after oral administration of 240 mg of griseofulvin. Symbols as in Fig. 1. Ordinate: Cumulative amount excreted (mg). Abscissa: Time (h). Bars indicate the s.e.m.

& Riegelman, 1971) and 0·85 (Lin, Magat & others, 1973). Therefore, these results show that the treatment of the micronized griseofulvin with hydroxypropyl cellulose significantly increased ($P = 0{\cdot}05$) the amount of griseofulvin absorbed.

The effect of the treatment on the rate of absorption of griseofulvin can be seen by comparison of the average rate of excretion of total 6-DMG against time plots given in Fig. 3. The treated formulation

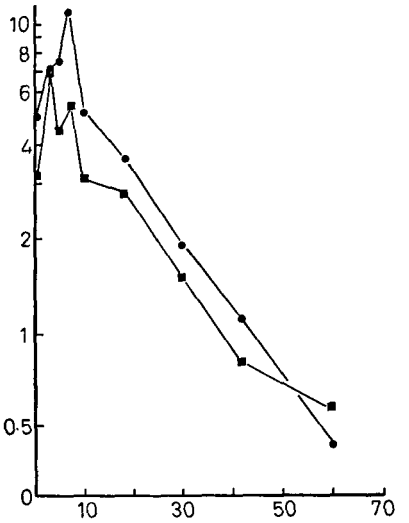

FIG. 3. Mean rate of excretion of 6-DMG in five subjects after oral administration of 240 mg of griseofulvin. Symbols as in Fig. 1. Ordinate: Excretion rate (mg h^{-1}). Abscissa: Time (h).

was found to give much higher initial rates of excretion, indicating faster absorption of griseofulvin from this formulation than from the untreated preparation. Similarly, comparison of the ratio of 6-DMG excreted after administration of the two formulations at 24 h and at 72 h of 1·9 and 1·3 (treated/non-treated) support the suggestion of the treatment having an effect on the rate of absorption as well as the extent of absorption. Although the average rate plot, Fig. 3, indicates complete absorption in 10 h for the treated formulation compared with 30 h for the non-treated formulation, examination of the individual rate plots showed two cases, given in Fig. 4, of prolonged absorption with the treated formulation.

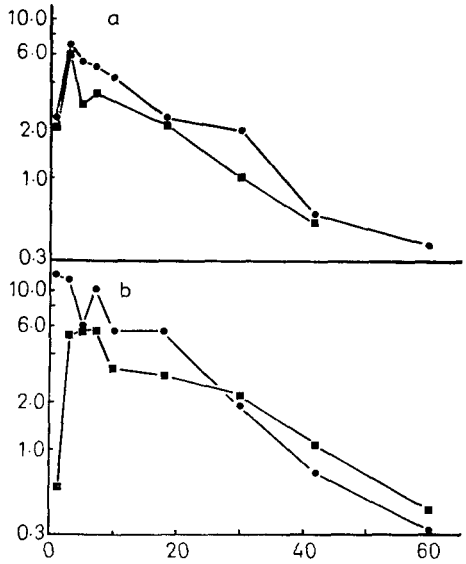

FIG. 4. Log excretion rate of 6-DMG *vs* time plots for subject III (a) and II (b) after oral administration of 240 mg of griseofulvin. Symbols as in Fig. 1. Ordinate: Excretion rate (mg h^{-1}). Abscissa: Time (h).

The treated formulation therefore increases the rate and extent of availability of micronized griseofulvin. It does not always lead to complete absorption from the upper intestine as has been reported for an alternative method of increasing absorption of griseofulvin, that is formation of a solid disperse system with polyethyleneglycol 6000 (Chiou & Riegelman, 1971). The latter method is reported to act by formation of microfine crystals or a colloidal solution, the enhanced surface area leading to increased dissolution rates. The similarity of the results of Chiou & Riegelman (1971) to those reported in this paper suggest a similar mechanism,

that is the treated micronized griseofulvin has a much larger 'effective' surface area available for dissolution than the non-treated micronized griseofulvin. A further factor suggested by Chiou & Riegelman, namely the formation of a super saturated solution of griseofulvin on dissolution of the solid dispersion, is unlikely to be applicable in the method described. This results in faster and more complete absorption. It probably does not increase the surface area available for dissolution as much as the solid disperse system since this method resulted in a more rapid completion of absorption. However, in a bioavailability study of a polyethyleneglycol griseofulvin formulation (Barrett & Hanigan, 1975) it was found that only 52% of the griseofulvin dose was excreted as 6-DMG during one dose interval at steady state. Therefore the coating technique could be equally as effective as the formation of the solid dispersed system in increasing the bioavailability of griseofulvin.

Improvement in bioavailability of griseofulvin has also been found when the griseofulvin is formulated as a suspension in corn oil (Bates & Sequeira, 1975). The increase in this instance is thought to be caused by the oil decreasing intestinal tract motility and therefore allowing greater time for dissolution. The amount of hydroxypropyl cellulose present in the treated formulation is considered insufficient to have a similar effect on gut motility.

Therefore this novel formulation method was found to increase the *in vitro* dissolution rate and *in vivo* bioavailability of griseofulvin. It is a simple and rapid technique that could possibly be applied to other hydrophobic drugs.

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