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A PARTIALLY ORGANIC DISSOLUTION MEDIUM FOR GRISEOFULVIN DOSAGE FORMS

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ABSTRACT

Forty percent alcohol in simulated gastric fluid was used as a dissolution medium for two griseofulvin dosage forms. Rank-order correlation of dissolution profiles with plasma levels was obtained.

The use of this partially organic dissolution medium for griseofulvin dosage forms is suggested as a convenient alternative to entirely aqueous media employed in large volumes (18 to 72 liters per dosage form).

INTRODUCTION

Griseofulvin is a neutral and practically insoluble antifungal agent. The water solubility at 37° is 15

mcg/ml (1). This low solubility has presented problems in the development of aqueous dissolution tests. For example, Katchen and Symchowicz (1,2) obtained good correlations for dissolution with absorption in man. However, they had to employ 18 liter volumes of simulated intestinal fluid and were limited to 125 mg dosage forms or fractions of dosage forms. Chiou and Riegelman (3) also used 18 liter volumes of simulated intestinal fluid for 125 mg dosage forms in obtaining correlations of dissolution with absorption in dogs.

Other investigators (4,5) have employed 1 liter volumes of aqueous media to obtain rank-order correlations of dissolution with absorption in man. However, their correlations were based upon data generated with griseofulvin dissolving under non-sink (6) conditions.

Though the use of large volumes of aqueous dissolution media or incomplete dissolution in small volumes of aqueous dissolution media have produced successful correlations, there are difficulties in handling large volumes of liquids, regulatory restrictions on testing fractions of dosage forms and risks in evaluating formulations when drug solubility under non-sink conditions is the determining factor. By using a partially organic dissolution medium, a convenient volume of dissolution fluid can be used, intact dosage forms can be tested and formulations can be compared without concern for non-sink effects.

The use of partially organic dissolution media is less desirable than entirely aqueous media because it is a

further departure from physiologic conditions. However, if a partially organic system permits a dissolution-bioavailability correlation, then the partially organic system can be offered as a convenient alternative to an all aqueous system. This communication describes the use of a partially organic dissolution medium for griseofulvin dosage forms and the rank-order correlation of the dissolution data to bioavailability in man.

EXPERIMENTAL

Materials - Production batches of microsize griseofulvin[1] tablets, 500 mg, and microsize griseofulvin[1] suspension, 125 mg/5 ml were used.

Dissolution - After studying the solubility of griseofulvin in several organic solvent-aqueous media blends, 40% alcohol, USP, in simulated gastric fluid, TS, USP without pepsin, was selected to be the dissolution medium for griseofulvin. The ambient temperature solubility of griseofulvin in this medium was 0.689 mg/ml. Thus, there was ample griseofulvin solubility to permit the dissolution of 500 mg in 1900 ml at 37.5°.

The equivalent of 500 mg of griseofulvin was added to 1900 ml of 40% alcohol in simulated gastric fluid without pepsin contained in a 2 liter round bottom flask. The

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[1]Grifulvin®-V, McNeil Laboratories, Inc., Fort Washington, PA 19034

system was maintained at 37.5° ± 0.5. Agitation was provided by a semi-circular paddle[2] positioned 5 cm above the bottom of the flask and rotated at 150 rpm.

Four ml samples were withdrawn after 5, 10, 15, 30, 60 and 120 minutes of testing. The samples were filtered through 0.6 mμ Polyvic®[3] filters.

Two ml of filtered samples are diluted to 50 ml with methanol. The diluted samples are assayed spectrophotometrically at ∿292 nm in a 1 cm cell versus the same blank employed in the sample assay.

The dissolution test was performed in triplicate and the means of three determinations for all sampling times were reported.

Bioavailability - Twenty-four, normal, healthy, male volunteers were used in the study. The subjects had a mean age of 28 years and a range of 22-46 years, a mean weight of 76 kg and a range of 65-89 kg, and a mean height of 177 cm and a range of 170-185 cm. The subjects were free of any recognizable medical or surgical disease and had not received any drugs for a period of two weeks prior to the start of the study. The subjects fasted overnight (at least 12 hours) and did not consume any food or liquids, except water, until four hours after administration of the drug. A standard, light meal was consumed four hours post-dosing.

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[2]No. 9510T-104, Lab Glass, Inc., Vineland, NJ 08360.

[3]No. BDWP 04700, Millipore Corp., Bedford, MA 01730.

The composition of the meal was equivalent on both weeks of treatment. The treatment schedule was as follows:

Treatment A was one 500 mg tablet of microsize griseofulvin and Treatment B was 20 ml of a 125 mg/5 ml suspension of microsize griseofulvin according to the following schedule.

	Treatment	
Subjects	Week 1	Week 2
2, 4, 5, 6, 8, 12, 13, 17, 19, 20, 22, 24	A	B
1, 3, 7, 9, 10, 11, 14, 15, 16, 18, 21, 23	B	A

The doses were given with 250 ml of water with portions of the water being used to rinse the container for the suspension dose.

Blood was collected in heparinized tubes at the following times: 0, 2, 4, 8, 24, 48 and 72 hours. The plasma was isolated by centrifugation and stored frozen.

The samples were assayed using a fluorometric technique (7). The assay procedure is as follows. To one ml of plasma, one ml of water and 10 ml of ethyl ether were added. The samples were shaken vigorously for one minute, centrifuged (2500 rpm x 10 minutes), cooled to -80° in dry ice/acetone (30 seconds). The ether was decanted and evaporated using nitrogen. The residues were dissolved in 5 ml of 1:1 methanol-

water and 5 ml of hexane were added. After shaking and centrifuging the samples, the fluorescence of the aqueous-alcoholic layers were determined on a fluorimeter at the following instrumental settings:

excitation wave length:	300 nm
excitation slit opening:	6
emission wave length:	420 nm
emission slit opening:	12
meter sensitivity:	3

A standard curve was obtained using 0.2, 0.5, 1.0, 1.3, 1.5, 1.75, 2.0 and 2.5 µg/ml of griseofulvin in water and in plasma as shown in Figure 1. Standard samples were run with each set of plasma samples.

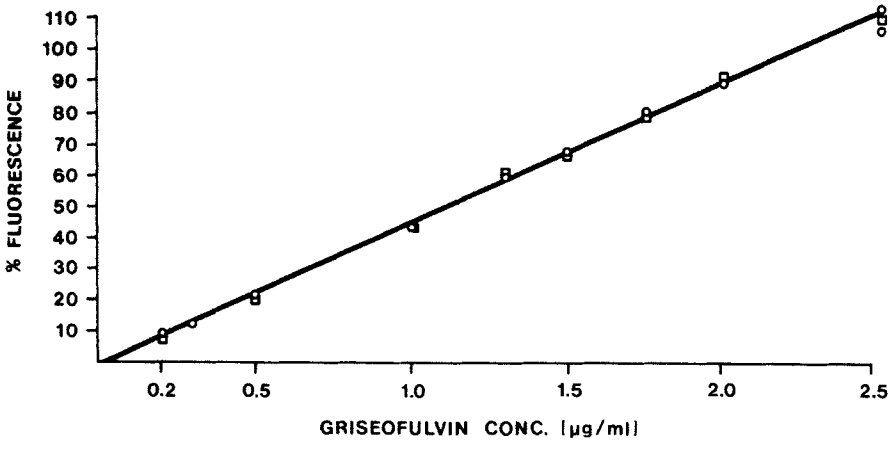

Fig. 1. Typical griseofulvin standard curve prepared from solutions in water (—O—) and solutions in plasma (—□—).

The plasma concentration data for the two dosage forms were statistically compared using analysis of variance for a crossover experimental design.

RESULTS AND DISCUSSION

The dissolution data are reported in Figure 2. The data show a readily observable difference between the suspension and the tablet dosage forms.

The mean plasma levels of griseofulvin obtained through the two treatments are reported in Table I and Figure 3. The observed and derived pharmacokinetic parameters from these data are also reported in Table I.

Significant differences in the mean plasma level concentrations of the tablets and suspension are obtained 2, 4, 8 and 24 hours after their administration. There are also significant differences between the peak plasma concentrations and the area under the plasma concentration-time curve from 0 to 72 hours.

A comparison of the dissolution curves in Figure 2 to the plasma level curves in Figure 3 clearly shows a rank-order correlation between dissolution and plasma levels. Of particular consequence is the large difference in the first 30 minutes of the dissolution processes and the reflection of that difference in the first 24 hours of the plasma concentrations.

An attempt to mathematically relate a dissolution parameter to a bioavailability parameter was not undertaken

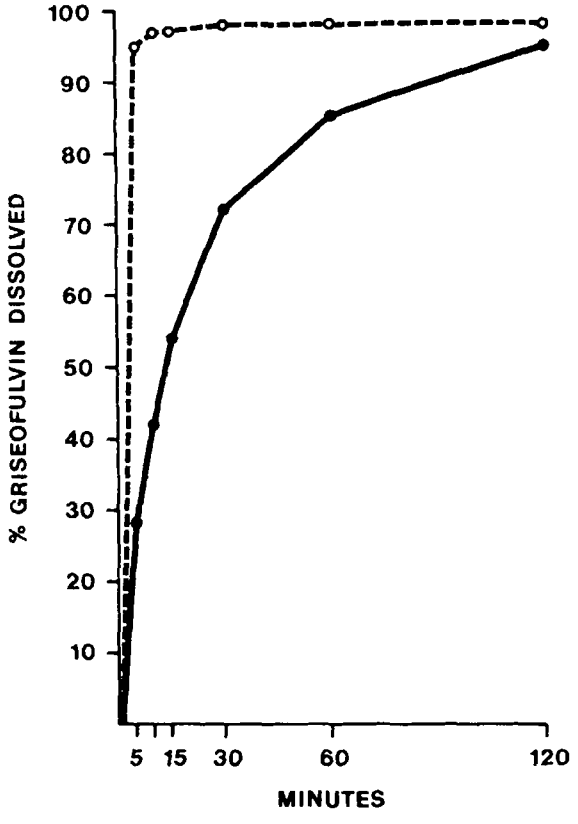

Fig. 2. Mean griseofulvin dissolution profiles in 3 flasks which contained 500 mg of microsize griseofulvin as a suspension (—○—) or as tablets (—●—) per 1900 ml of 40% alcohol in simulated gastric fluid without pepsin.

since at least 3 dosage forms would had to have been evaluated in order to make such a relationship relevant.

However, the rank order correlation is important in that it demonstrates the utility of a partially organic dissolution media in evaluating griseofulvin dosage forms. The rank-order correlation coupled with the general use-

TABLE I

SUMMARY OF OBSERVED AND DERIVED PHARMACOKINETIC PARAMETERS FOR GRISEOFULVIN OBTAINED FROM THE STUDY COMPARING BIOAVAILABILITY OF 500 MG OF MICROSIZE GRISEOFULVIN ADMINISTERED AS A TABLET OR A SUSPENSION.

Parameter	Tablet Mean (CV%*)	Suspension Mean (CV%*)	Result of ANOVA**
Plasma Concentration at time (ng/ml)			
2 hours	0.37 (38.4)	0.46 (32.7)	Sig. (F = 6.82, p = 0.02)
4 hours	0.40 (41.0)	0.55 (23.3)	Sig. (F = 12.45, p = 0.002)
8 hours	0.40 (40.5)	0.49 (31.9)	Sig. (F = 6.60, p = 0.02)
24 hours	0.38 (31.0)	0.42 (24.3)	Sig. (F = 4.57, p = 0.04)
48 hours	0.22 (46.1)	0.26 (47.2)	NS
72 hours	0.14 (80.2)	0.12 (62.2)	NS
Peak Plasma Concentration (µg/ml)	0.50 (30.7)	0.61 (20.2)	Sig. (F = 10.61, p = 0.004)
Time of Occurrence of Peak Plasma Concentration (minutes)	800 (112)	500 (123)	NS
Area Under Plasma Concentration-Time Curve AUC^{0-72} Hours (µg X min/ml)	1235 (23.7)	1409 (23.5)	Sig. (F = 12.27, p = 0.002)

* Coefficient of variation.

** Test of treatment mean square in the analysis of variance for crossover experimental design.

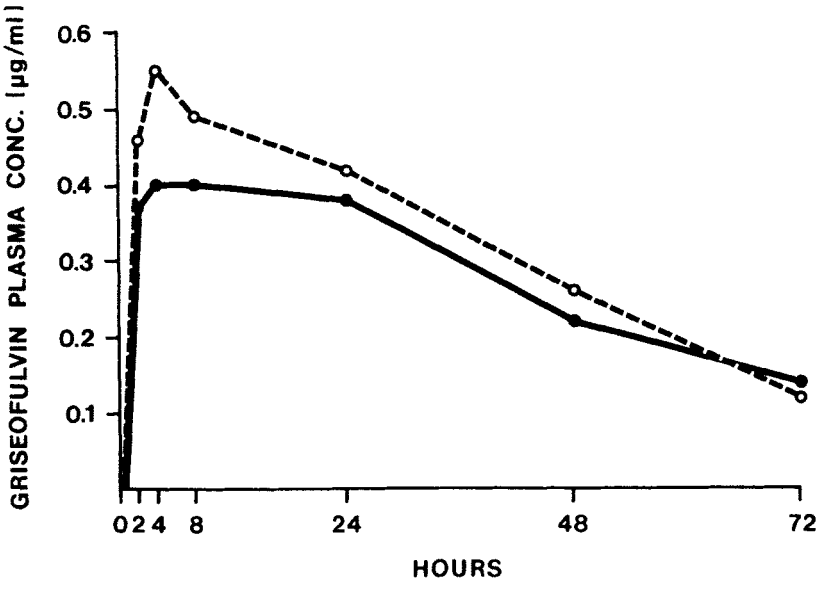

Fig. 3. Mean griseofulvin plasma levels in 24 human subjects who received 500 mg of microsize griseofulvin as a suspension (—○—) or as tablets (—●—).

fulness of being able to use small volumes of dissolution media along with being able to use intact dosage forms of up to 500 mg makes partially organic dissolution media convenient alternatives to be investigated for the evaluation of griseofulvin products.

Other griseofulvin dosage forms such as hard gelatin capsules, soft gelatin capsules or dosage forms prepared from solid dispersions have not been evaluated in these laboratories. In order to obtain a proper correlation of dissolution data from these dosage forms to plasma data, it may be necessary to adjust the dissolution test variables - e.g., alcohol content, paddle size, paddle speed, etc.

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