Bioavailability of Micronized Griseofulvin from Corn Oil-in-Water Emulsion, Aqueous Suspension, and Commercial Tablet Dosage Forms in Humans

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Abstract □ The purposes of this investigation were to determine and to compare the oral absorption characteristics of micronized griseofulvin (500 mg) after its administration to humans in the form of a corn oil-in-water emulsion containing dispersed drug, an aqueous suspension, and two different commercial tablets (A and B). The four dosage forms were administered in a random crossover fashion to five fasting subjects, and drug absorption was assessed from urinary excretion data for the major metabolite of the antibiotic (6-desmethylgriseofulvin). The drug was most rapidly, uniformly, and completely absorbed from the corn oil-in-water emulsion. As compared to either the aqueous suspension, Tablet A, or Tablet B, three- to fourfold increases in the maximum body levels and a twofold enhancement in the bioavailability of the antibiotic were observed after administration of the emulsion dosage form. A mechanism based on the ability of the linoleic and oleic acids liberated during the digestion of corn oil to inhibit GI motility and stimulate gallbladder evacuation may explain the marked enhancing effect of emulsified corn oil on griseofulvin absorption in humans. This new lipid-in-water emulsion dosage form of micronized griseofulvin appears to offer several clinical advantages in the treatment of fungal infections.

Keyphrases □ Griseofulvin, micronized—bioavailability from corn oil-in-water emulsion, aqueous suspension, and commercial tablet dosage forms, humans □ Emulsions, corn oil-in-water—bioavailability of micronized griseofulvin, humans □ Bioavailability—griseofulvin, emulsion, suspension, and tablet dosage forms, humans □ Dosage forms—micronized griseofulvin, bioavailability from corn oil-in-water emulsion, aqueous suspension, and commercial tablets, humans

Griseofulvin [7-chloro-2′,4,6-trimethoxy-6′β-methylspiro[benzofuran - 2(3*H*),1′ - [2] - cyclohexene]-3,4′-dione], a chemically neutral systemic antifungal antibiotic, is commonly used in the treatment of dermatophyte infections in humans (1, 2). As a result of its low aqueous solubility (~15 mg/liter at 37°), the drug is slowly, erratically, and incompletely absorbed from the GI tract of humans (3–6). Although oral administration of the micronized form of griseofulvin alone (7–9), with meals high in fat content (7, 9), or as a 1:9 (w/w) drug–polyethylene glycol 6000 solid dispersion (10) considerably enhances the bioavailability of the drug, its absorption from commercial tablet (11) and methylcellulose suspension (12) dosage forms is poor and quite variable.

An average of 52.7% of a 500-mg dose of micronized griseofulvin as a commercial tablet was slowly absorbed for as long as 30 hr after its oral administration to five fasting subjects (range of 38.5–52.3% of dose; coefficient of variation = 19.5%) (11). One to two months later, the absorption study was repeated in four of the five subjects and an average of 49.3% of the dose was absorbed (range of 27.0–72.5%; coefficient of variation = 40.6%). Similar results were also obtained after administration of a methylcellulose suspension of micronized griseofulvin to five fasting subjects (12). In this study, the average amount of drug absorbed was 50% of the dose (range of 31.0–63.0%; coefficient of variation = 23.2%).

As suggested by several investigators (5, 7, 8), the slow rate and low extent of absorption, as well as the appreciable intersubject differences in the amount of micronized griseofulvin absorbed from conventional dosage forms, are undoubtedly the most common reasons for subtherapeutic blood levels in some patients and, thus, for clinical failure with griseofulvin therapy. Therefore, a convenient, acceptable, and improved dosage form of micronized griseofulvin is needed from which the drug is uniformly, rapidly, and maximally absorbed in humans. Such a dosage form should assure that therapeutic blood levels of the antibiotic would be consistently attained in all patients.

Previous studies from these laboratories (13) indicated that one can markedly enhance the bioavailability and uniformity of absorption of micronized griseofulvin in rats by orally administering the drug dispersed in a corn oil-in-water emulsion vehicle as compared to administration in either an aqueous or corn oil vehicle. If similar results occur in humans, then an emulsion dosage form would offer obvious advantages in the treatment of fungal infections. The purposes of the present investigation were to determine and to compare the oral absorption characteristics of micronized griseofulvin after its administration to fasting subjects as a corn oil-in-water emulsion, as two different commercial tablets, and as a control aqueous suspension.

EXPERIMENTAL

Dosage Forms—Four dosage forms containing micronized griseofulvin (specific surface area of 1.32 m^2/g) were subjected to bioavailability testing in humans. The corn oil-in-water emulsion and control aqueous suspension dosage forms were prepared as described previously (13). Both preparations contained 300 mg of polysorbate 60[1] and 500 mg of suspended griseofulvin/30 g. The other two dosage forms were commercial tablets containing 500 mg of micronized griseofulvin (Tablets A[2] and B[3]). All dosage forms were assayed in triplicate for drug content by the spectrophotometric method described earlier (13).

Absorption Studies in Humans—Five healthy, nonobese, male subjects, 23–29 years old and weighing 61–82 kg (mean 69 kg), participated in this study. They were instructed not to consume any drug product or alcoholic beverage for 7 days prior to, and for 4 days following, griseofulvin administration. A single 500-mg oral

[1] Tween 60.
[2] Grifulvin V, Control No. SJ2901, McNeil Laboratories.
[3] Fulvicin-U/F, Control No. OAUG17P35531, Schering Corp.

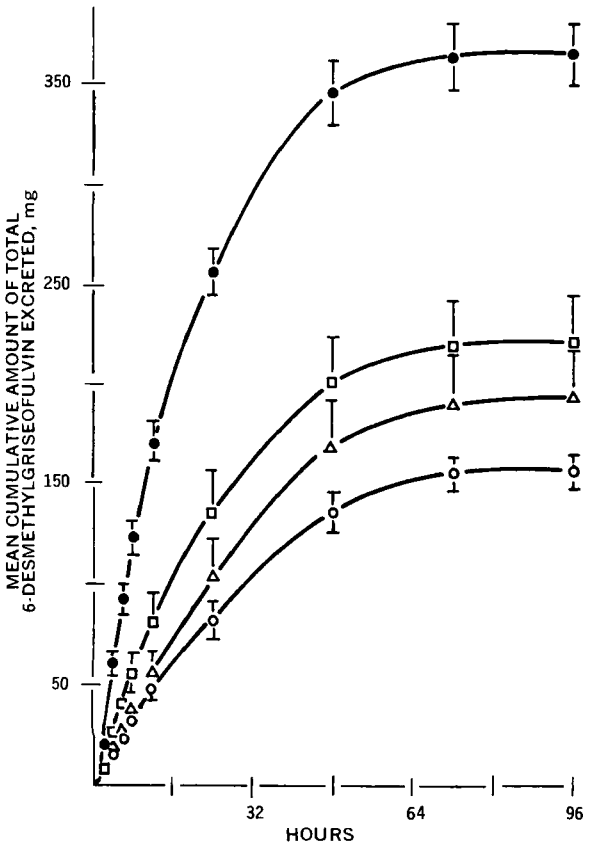

Figure 1—*Cumulative excretion of total 6-desmethylgriseofulvin as a function of time after a 500-mg oral dose of micronized griseofulvin as an aqueous suspension* (○), *as Tablet A* (△), *as Tablet B* (□), *and as a corn oil-in-water emulsion, 30 g* (●). *Each point represents the mean of five fasting subjects. Bars denote standard errors of the mean.*

dose of micronized griseofulvin in the form of the corn oil-in-water emulsion (30 g), aqueous suspension (30 g), and commercial Tablets A and B was administered at 8:00 am in a random crossover fashion to each subject after an overnight fast (at least 8 hr). At least 1 week was allowed between drug administrations.

A time zero urine specimen was collected immediately prior to drug administration. The dosage forms were ingested with 100 ml of water, and urine specimens were collected at 2, 4, 6, 8, 12, 24, 48, 72, and 96 hr after drug administration. The pH and volume of each specimen were recorded, and an aliquot was stored in the frozen state until assayed in duplicate for 6-desmethylgriseofulvin content. No food was permitted until 4 hr after drug administration.

By using the same protocol, the effects of the amount of emulsified corn oil administered and of the anticholinergic agent propantheline (a potent inhibitor of GI motility) on the absorption of micronized griseofulvin were assessed in Subject JAS. In the former preliminary studies, a 500-mg dose of the drug was administered in 7.5, 15, or 30 g of corn oil-in-water emulsion. These amounts correspond to 3, 6, and 12 g of emulsified corn oil, respectively. The volume of water ingested with the dose was appropriately adjusted so as to maintain the total fluid intake constant. In the latter studies, a single 30-mg oral dose of propantheline bromide[4] was administered 30 min prior to a 500-mg dose of the drug as the aqueous suspension dosage form. Drug absorption was also evaluated in the same subject after oral administration of a corn oil suspension dosage form (13). The dose of this suspension was such that the subject received 500 mg of micronized griseofulvin and 12 g of unemulsified lipid.

Free 6-desmethylgriseofulvin in the urine was determined by the double-extraction, differential spectrophotometric method of Rowland and Riegelman (14). Total 6-desmethylgriseofulvin (free and the glucuronide conjugate) was assayed by the same procedure after incubating an aliquot of the urine specimens with 500 units of β-glucuronidase[5] for 2 hr at pH 6.8 and 37°. Blank urine specimens collected over the previously mentioned time period after administration of the aqueous suspension and corn oil-in-water emulsion vehicles yielded zero absorbance readings when treated by this assay procedure. Only minor amounts of intact griseofulvin and its 4-desmethyl metabolite are excreted in human urine (12). However, they were found not to interfere with the determination of 6-desmethylgriseofulvin.

Differences among more than two mean values were statistically evaluated by an analysis of variance (15), and differences between any two means were compared using Tukey's multiple-range test (15).

RESULTS AND DISCUSSION

The urinary excretion rate of free and total 6-desmethylgriseofulvin in humans has been shown to be proportional to plasma griseofulvin levels (10, 12). A proportionality also exists between the amount of 6-desmethylgriseofulvin excreted and both the oral dose of griseofulvin (9) and the area under the griseofulvin plasma concentration–time curve (16). Therefore, the urinary excretion of 6-desmethylgriseofulvin may be used to assess the absorption characteristics of orally administered griseofulvin (9, 16). However, 6-desmethylgriseofulvin is a weakly acidic metabolite (pKa 4.27) and its elimination may be affected by changes in urinary pH and/

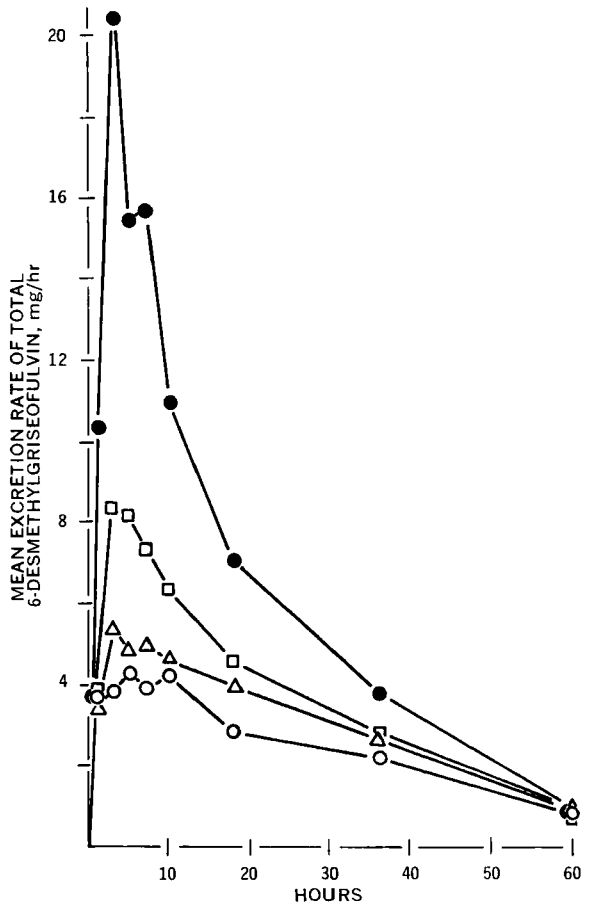

Figure 2—*Excretion rate of total 6-desmethylgriseofulvin as a function of time after a 500-mg oral dose of micronized griseofulvin as an aqueous suspension* (○), *as Tablet A* (△), *as Tablet B* (□), *and as a corn oil-in-water emulsion, 30 g* (●). *Each point represents the mean of five fasting subjects.*

[4] Two 15-mg Pro-Banthine tablets, Searle Co., Chicago, Ill.

[5] Bacterial-type II, Sigma Chemical Co., St. Louis, Mo.

Table I—Maximum Excretion Rate of Total 6-Desmethylgriseofulvin after Oral Administration of a 500-mg Dose of Micronized Griseofulvin in Four Dosage Forms

Subject	Maximum Excretion Rate of Total 6-Desmethylgriseofulvin, mg/hr				Ratio		
	Aqueous Suspension (AS)	Commercial Tablet A (CT-A)	Commercial Tablet B (CT-B)	Corn Oil-in-Water Emulsion (COE)	COE:AS	COE:CT-A	COE:CT-B
SIF	4.27	3.06	3.70	18.61	4.36	6.08	5.03
JPL	6.85	6.96	8.07	23.60	3.45	3.39	2.92
PJC	5.98	8.77	12.30	24.49	4.10	2.79	1.99
AVT	3.17	7.50	6.10	19.01	6.00	2.53	3.12
JAS	4.89	3.97	14.49	20.19	4.13	5.09	1.40
Mean	5.03	6.05	8.93	21.18	4.41	3.98	2.89
SE[a]	0.64	1.09	1.98	1.21	0.43	0.69	0.62
CV, %[b]	28.58	40.14	49.57	12.74	—	—	—

Statistical Comparisons

Differences among four dosage forms: $p < 0.001$ ($F^c = 31.8$; $df = 3,16$) (analysis of variance)
Difference between any two dosage forms [Tukey's allowable difference ($p = 0.05$; $df = 4,16$) = 5.35]:
COE − AS = 16.15; significant[d] AS − CT-A = 1.02; not significant
COE − CT-A = 15.13; significant[d] AS − CT-B = 3.90; not significant
COE − CT-B = 12.25; significant[d] CT-A − CT-B = 2.88; not significant

[a] Standard error of the mean. [b] Coefficient of variation. [c] Critical *F* value for 3 and 16 *df* at the 0.1% level is 9.00. [d] Also significant at 1% level.

or urine flow rate. Analysis of variance tests indicated that at the collection periods examined, neither urinary pH nor urine volume was significantly altered by the nature of the dosage form orally administered. Consequently, differences noted in the amounts of total 6-desmethylgriseofulvin excreted in the urine accurately reflect differences in the absorption profile of griseofulvin from the four dosage forms employed in this investigation.

The mean cumulative amount of total 6-desmethylgriseofulvin excreted in the urine as a function of time after oral administration of 30 g of the corn oil-in-water emulsion, 30 g of the aqueous suspension, and the two commercial tablets to the five fasting subjects is shown in Fig. 1. In all cases, a plateau value was reached in 72–96 hr, indicating that the experimental time period selected was adequate to assess completely the excretion and, thereby, the absorption characteristics of micronized griseofulvin.

The mean excretion rate profiles depicted in Fig. 2 indicate that micronized griseofulvin was absorbed at a considerably faster rate from the corn oil-in-water emulsion than from the aqueous suspension, Tablet A, or Tablet B. In addition, it is evident from an examination of the data presented in Table I that the maximum excretion rate of total 6-desmethylgriseofulvin, which is proportional to the maximum body level of griseofulvin, was substantially higher and less variable after administration of the corn oil-in-water emulsion (30 g) as compared to that observed after oral administration of any one of the other three dosage forms. The three- to fourfold increases experienced with the emulsion dosage form are highly significant, as determined by the method of Tukey (Table I). No significant differences in the mean maximum excretion rates of total 6-desmethylgriseofulvin exist between the control aqueous suspension and either tablet dosage form or between the two tablet formulations (Table I).

Analysis of the representative semilogarithmic excretion rate plots for total 6-desmethylgriseofulvin (Fig. 3) reveals that micronized griseofulvin was absorbed at a rapid rate during the first 3–7 hr after oral administration of the four dosage forms to Subject JPL and was then slowly absorbed over an additional period of approximately 29–33 hr. Subsequently, the drug was eliminated from the body in a monoexponential fashion. The terminal linear segments of the four plots are parallel, indicating that no significant absorption occurred after 40 hr irrespective of the dosage form orally administered to the subject. Similar prolonged absorption profiles were also observed in the other four subjects and are consistent with the results first reported by Rowland *et al.* (11) and later confirmed by Chiou and Riegelman (10) for micronized griseofulvin in humans.

The cumulative amounts of total 6-desmethylgriseofulvin ultimately excreted in the urine for each subject after each dosage form, expressed as percent of the oral dose of griseofulvin, are listed in Table II. The mean data indicate that the extent of absorption (bioavailability) of micronized griseofulvin from the corn oil-in-water emulsion (30 g) was, on the average, significantly and markedly enhanced by 134, 100, and 70% as compared to that observed with the control aqueous suspension, commercial Tablet A, and commercial Tablet B dosage forms, respectively. No statistical

Table II—Bioavailability of Micronized Griseofulvin after Oral Administration of a 500-mg Dose in Four Dosage Forms

Subject	Cumulative Amount of Total 6-Desmethylgriseofulvin Excreted in 96 hr, % of Dose				Ratio		
	Aqueous Suspension (AS)	Commercial Tablet A (CT-A)	Commercial Tablet B (CT-B)	Corn Oil-in-Water Emulsion (COE)	COE:AS	COE:CT-A	COE:CT-B
SIF	30.03	28.08	31.69	66.84	2.23	2.38	2.11
JPL	34.96	45.30	51.43	78.24	2.24	1.73	1.52
PJC	33.61	57.00	57.15	80.93	2.41	1.42	1.42
AVT	27.47	30.98	39.40	72.99	2.66	2.36	1.85
JAS	30.64	30.91	40.76	65.97	2.15	2.13	1.62
Mean	31.33	38.45	44.09	72.99	2.34	2.00	1.70
SE[a]	1.33	5.53	4.53	2.98	0.09	0.19	0.12
CV, %[b]	9.50	32.15	23.00	9.13	—	—	—

Statistical Comparisons

Differences among four dosage forms: $p < 0.001$ ($F^c = 21.6$; $df = 3,16$) (analysis of variance)
Differences between any two dosage forms [Tukey's allowable difference ($p = 0.05$; $df = 4,16$) = 15.92]:
COE − AS = 41.66; significant[d] AS − CT-A = 7.12; not significant
COE − CT-A = 34.54; significant[d] AS − CT-B = 12.76; not significant
COE − CT-B = 28.90; significant[d] CT-A − CT-B = 5.64; not significant

[a] Standard error of the mean. [b] Coefficient of variation. [c] Critical *F* value for 3 and 16 *df* at the 0.1% level is 9.00. [d] Also significant at 1% level.

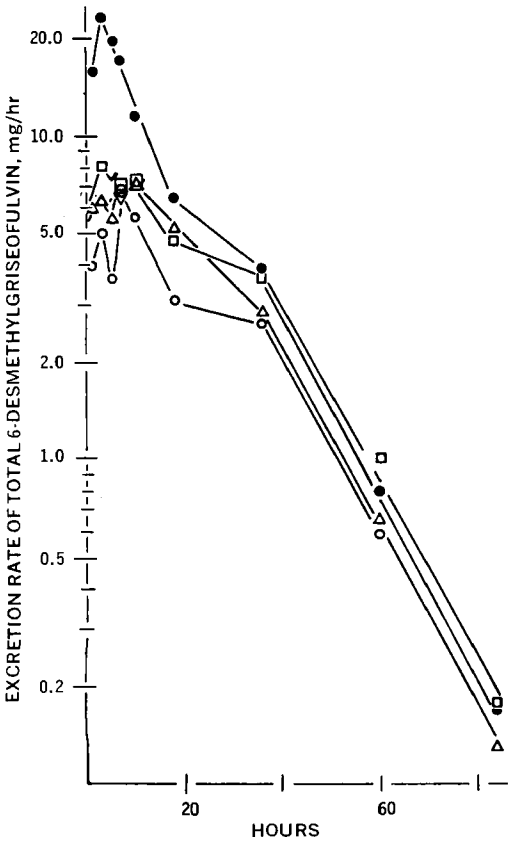

Figure 3—*Excretion rate of total 6-desmethylgriseofulvin as a function of time after administration of a 500-mg oral dose of micronized griseofulvin to Subject JPL as an aqueous suspension* (○), *as Tablet A* (△), *as Tablet B* (□), *and as a corn oil-in-water emulsion, 30 g* (●).

difference in bioavailability was found to exist between the aqueous suspension and either commercial tablet or between the two commercial tablets (Table II).

Chiou and Riegelman (10) reported that 65.3% of an intravenous dose of griseofulvin was ultimately excreted in the urine by one of their subjects as total 6-desmethylgriseofulvin, and Lin *et al.* (12) showed that total 6-desmethylgriseofulvin represented 84% (mean of five subjects) of the total radioactivity excreted in the urine after an oral dose of ^{14}C-griseofulvin. Based on these values and the mean 96-hr cumulative excretion data obtained in this investigation (Table II), it would appear that the oral dose of micronized griseofulvin was almost completely absorbed after administration as a corn oil-in-water emulsion.

Of considerable clinical importance is the fact that large intersubject variations were observed in the amount of micronized griseofulvin absorbed from the two commercial tablet dosage forms, as reflected by the high coefficients of variation listed in Table II. Similar variations in drug absorption from tablet formulations were reported by other investigators (11, 16). On the other hand, administration of the drug in the corn oil-in-water emulsion vehicle substantially reduced the degree of intersubject variability (Table II). In addition, the presence of emulsified corn oil in the body caused no appreciable change in the ratio of the amount of free to conjugated 6-desmethylgriseofulvin ultimately excreted in the urine (Table III). The mean ratios calculated from the corn oil-in-water emulsion and aqueous suspension data were quite similar (Table III) and were comparable to literature values of 1.24–1.86 (10, 12). The slightly, yet statistically significant, greater amount of 6-desmethylgriseofulvin glucuronide excreted by all subjects after administration of the corn oil-in-water emulsion is probably of no clinical significance but is worthy of additional study.

The most plausible major mechanism underlying the marked enhancement noted in the absorption of micronized griseofulvin following its oral administration to humans as a corn oil-in-water emulsion is similar to that established in these laboratories in the rat (13, 17). The inhibitory effect of lipid (emulsified corn oil) on the gastric emptying process (17–19) could have allowed only small amounts of undissolved drug to be emptied into the small intestine, as compared to the rapid emptying and, therefore, significantly larger amounts of drug emptied when administered in nonlipid-containing dosage forms (*i.e.*, the aqueous suspension and commercial tablets). The smaller amounts of drug present in the upper region of the small intestine at any particular time after oral administration of the corn oil emulsion, coupled with the inhibitory effect of lipid on proximal small intestinal motility (17, 18), allows the drug more time to dissolve in, and be absorbed from, the region of the intestinal tract where absorption is optimal (20).

It is also possible that the presence of emulsified corn oil in the intestinal tract stimulated bile secretion (21–24) which, because of the presence of increased micellar concentrations of physiological surfactants (bile salts and lysolecithin) in the intestinal fluids (22, 23, 25), increased the rate of dissolution (26, 27) and, thereby, the rate of absorption and bioavailability of this poorly soluble antibiotic. Additional support for this hypothesis was obtained from preliminary studies conducted in Subject JAS, which clearly demonstrate, apparently for the first time, the significant effect of GI motility on the absorption of micronized griseofulvin in humans. When a 30-mg oral dose of propantheline bromide, a potent inhibitor of GI motility, was administered 30 min prior to a 500-mg oral dose of the antibiotic in aqueous suspension, the time of occurrence and the magnitude of the maximum excretion rate of total 6-desmethylgriseofulvin were increased by 9 hr and by 165%, respectively (Table IV). The anticholinergic agent also caused a 1.53-fold increase in the amount of antibiotic absorbed from the aqueous suspension dosage form (Table IV). However, the absorption-enhancing effect of propantheline was less than that experienced with 30 g of the corn oil-in-water emulsion (Table IV).

In another series of experiments, the effect of varying the amount of emulsified corn oil administered to Subject JAS on the absorption of a 500-mg dose of micronized griseofulvin from the corn oil-in-water emulsion was examined (Table IV). As the amount of emulsified corn oil administered was increased from zero (aqueous suspension) to 12 g (equivalent to 30 g of corn oil-in-water emulsion), there was a progressive increase in both the maximum excretion rate and the cumulative 96-hr excretion of total 6-desmethylgriseofulvin, with both parameters reaching plateau values after 6 g of emulsified corn oil had been administered. Similar types of dose–response relationships also exist between the amount of fat or long chain fatty acid ingested and its effect on both GI motility (18, 28) and gallbladder evacuation (24) in humans. The doses of emulsified corn oil employed in this portion of the investigation are comparable to those necessary for initiation of the reflexes that result in decreases in GI motility and increases in gallbladder contraction.

In this connection, Card (18) reported that the minimum inhibitory effect of fat (arachis oil) on gastric motility can be rapidly (within 1–4 min) achieved in humans after administration of a 4-g

Table III—Ratio of the Amount of Free 6-Desmethylgriseofulvin to 6-Desmethylgriseofulvin Glucuronide Ultimately Excreted in the Urine after Oral Administration of a 500-mg Dose of Micronized Griseofulvin as an Aqueous Suspension and Corn Oil-in-Water Emulsion to Fasting Subjects

Subject	Aqueous Suspension	Corn Oil-in-Water Emulsion (30 g)
JPL	2.03	1.81
SIF	0.99	0.81
PJC	1.49	1.36
AVT	1.51	1.13
JAS	2.35	1.62
Mean	1.67	1.35
SE[a]	0.24	0.18
CV, %[b]	31.57	29.27
Statistical significance[c]	$p < 0.05$	

[a] Standard error of the mean. [b] Coefficient of variation. [c] Determined by paired *t* test.

Table IV—Factors Affecting Absorption of a 500-mg Oral Dose of Micronized Griseofulvin from Corn Oil-in-Water Emulsion and Aqueous Suspension Dosage Forms (Subject JAS, Fasting State)

Regimen	Maximum Excretion Rate of Total 6-Desmethylgriseofulvin, mg/hr	Cumulative Amount of Total 6-Desmethylgriseofulvin Excreted in 96 hr, % of Dose
Aqueous suspension	4.89 (1)[a]	30.64
Aqueous suspension, 30 min after a 30-mg oral dose of propantheline	13.01 (10)	46.96
Corn oil-in-water emulsion		
7.5 g (equivalent to 3 g of lipid)	15.39 (3)	50.17
15.0 g (equivalent to 6 g of lipid)	21.30 (3)	63.97
30.0 g (equivalent to 12 g of lipid)	20.19 (3)	65.97
Corn oil suspension		
13.1 g (equivalent to 12 g of lipid)	10.11 (3)	48.57

[a] Time of occurrence of maximum excretion rate (hours) in parentheses.

dose of unemulsified fat or after only a 2-g dose of fat emulsified with bile salts. Also, considerable emptying of the gallbladder of its bile content can occur in humans within 30–60 min after an oral dose of approximately 5 g of lipid (one egg yolk), with complete emptying occurring after a 25-g dose of lipid (five egg yolks) (24).

The total 6-desmethylgriseofulvin excretion patterns observed after oral administration of micronized griseofulvin (500 mg) to Subject JAS with 12 g of unemulsified corn oil (as a 13.1-g dose of corn oil suspension) and 12 g of emulsified corn oil (as a 30-g dose of corn oil-in-water emulsion) are compared with the excretion pattern for the control aqueous suspension in Table IV. An analysis of these data revealed that although the presence of 12 g of unemulsified lipid in the GI tract caused an appreciable increase in the rate and extent of absorption and maximum body levels of the antibiotic, an even greater enhancement in drug absorption was realized with the same amount of lipid in an emulsified form. In fact, the potentiating effect of 12 g of unemulsified corn oil on griseofulvin absorption is comparable to that observed with only 3 g of emulsified corn oil (Table IV).

These results, which are similar to those previously observed in the rat with the same dosage forms (13), are consistent with the fact that to stimulate the fat-sensitive receptors in the duodenum, which cause inhibition of gastric emptying in humans, the fat must be digested (29); the rapidity and efficiency of the digestion process are increased by increasing, through emulsification, the effective surface area of triglyceride exposed to the hydrolytic action of pancreatic lipase (30, 31). It has also been reported that some fat digestion must take place prior to the appearance of any significant effect on gallbladder evacuation and that the latter process is fat digestion rate limited (24).

The results obtained from this investigation suggest that to maximize the rate, extent, and, perhaps most importantly, uniformity of absorption of micronized griseofulvin, it should be administered in a lipid-in-water emulsion dosage form to patients with fungal infections for which the drug is indicated. The emulsion dosage form is also advantageous from the standpoint that only relatively small amounts (6–12 g) of emulsified, unsaturated lipid need be administered to the patient as compared to the considerably larger amounts (>60 g) needed when unemulsified lipid from dietary sources is used to enhance the absorption of micronized griseofulvin in humans (5, 9). Since the enhanced bioavailability of the antibiotic from the corn oil-in-water emulsion appears to be solely dependent on the effect of emulsified corn oil and/or its digestion products (oleic and linoleic acids) on the physiological processes of GI motility and gallbladder evacuation, it is not unreasonable to expect similar increases in drug absorption if a comparable amount of any vegetable oil containing long chain (C_{14}–C_{18}) saturated or unsaturated fatty acids is substituted for corn oil in the emulsion formulation. The applicability of the lipid-in-water emulsion as a dosage form vehicle for potentiating the bioavailability in humans of other poorly absorbed drugs is currently being ascertained in these laboratories.

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