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Apparent Absorption Kinetics of Micronized Griseofulvin after Its Oral Administration on Single- and Multiple-Dose Regimens to Rats as a Corn Oil-in-Water Emulsion and Aqueous Suspension

THEODORE R. BATES ˣ and PHILIP J. CARRIGAN

Abstract □ This investigation was designed to quantitate and compare in the rat the oral absorption characteristics of micronized griseofulvin from a corn oil-in-water emulsion dosage form containing suspended drug and a control aqueous suspension after single-dose (50 mg/kg) and multiple-dose (50 mg/kg every 12 hr for five doses) administrations. The time course of intact drug in the plasma of all animals was best described by a one-compartment open model with apparent zero-order absorption. In contrast to that observed with the aqueous suspension, the onset of drug absorption after single-dose administration of the corn oil emulsion was significantly delayed. This difference disappeared upon multiple dosing of the two dosage forms, with the mean onset being quite rapid in both cases. Administration of a single dose of the antibiotic as the corn oil emulsion resulted in considerable increases in the maximum plasma levels of griseofulvin and in the duration, relative extent, and uniformity of drug absorption compared to those observed after administration of the control aqueous suspension. The potentiating effects of the lipid on drug absorption persisted on multiple dosing but at a somewhat reduced level.

Keyphrases □ Griseofulvin, micronized, absorption kinetics—corn oil-in-water emulsion compared to aqueous suspension, single and multiple doses, rats □ Absorption kinetics, micronized griseofulvin—corn oil-in-water emulsion compared to aqueous suspension, single and multiple doses, rats □ Corn oil-in-water emulsion, micronized griseofulvin—absorption kinetics compared to aqueous suspension, single and multiple doses, rats

Several investigators (1–3) suggested that 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 the most common reasons for clinical failure with griseofulvin therapy. In a previous report (4), it was demonstrated, using the rat as an animal model, that the maximum plasma levels, the bioavailability, and, of considerable importance, the uniformity of absorption of micronized griseofulvin were markedly enhanced after oral administration of a single dose of the antibiotic dispersed in a corn oil-in-water emulsion dosage form vehicle.

These findings were recently confirmed in a study conducted in humans in which the absorption characteristics of micronized griseofulvin from the same corn oil-in-water emulsion were compared with those from an aqueous suspension and two different commercial tablet dosage forms (5). The results of this study provided evidence that the maximum plasma levels and bioavailability of micronized griseofulvin can be increased approximately three- to fourfold and twofold, respectively, by administering the drug as a corn oil-in-water emulsion.

It is not without precedence for absorption differences, which appear after *single-dose* drug administration, to diminish or even to disappear upon *multiple* oral dosing of a drug or drug product (6). Hence, the purposes of the present investigation were to assess and to compare the absorption profiles of micronized griseofulvin from a corn oil-in-water emulsion and a control aqueous suspension dosage form after single and repetitive administrations to rats. The resultant plasma antibiotic level–time data were subjected to pharmacokinetic analysis with the intent of developing a mechanistic explanation for the

enhanced absorption of micronized griseofulvin from lipid-in-water emulsion dosage forms.

EXPERIMENTAL

Dosage Forms—The corn oil-in-water emulsion and control aqueous suspension dosage forms employed in these studies were identical in composition and method of preparation to those previously described (4). Both dosage forms contained suspended micronized griseofulvin[1] (specific surface area of 1.32 m^2/g) and the same quantity of the nonionic surfactant polysorbate 60. Prior to use, they were assayed in triplicate for drug content by the spectrophotometric procedure described earlier (4).

Absorption Studies—Adult male Sprague–Dawley rats[2], 250–325 g, were used. All experiments were initiated between 8:00 and 9:00 am.

Single-Dose Oral Studies (Fasting Animals)—The animals were fasted for 20–24 hr prior to, and during, the absorption experiments, but they were allowed free access to water. The aqueous suspension and corn oil-in-water emulsion dosage forms were administered by oral intubation to 11 or 12 lightly anesthetized (ether) rats at a griseofulvin dosage level of 50 mg/kg and a dosing volume of 5.0 ml/kg. After dosing, the animals were placed in restraining cages.

Approximately 0.5-ml blood samples were collected from the tail artery of each rat into heparinized tubes immediately prior to drug administration and at 1, 2, 4, 6, 8, and 12 hr postadministration. Twenty-four-hour samples were obtained *via* decapitation. The blood samples were then centrifuged, and a 0.2–0.3-ml aliquot of the plasma was accurately measured directly into a culture tube extraction vessel. A 2.0-ml plasma sample was obtained at the 24-hr time period. All plasma samples were immediately frozen solid and assayed for griseofulvin within 48 hr of collection.

Single-Dose Oral Studies (Nonfasting Animals)—The *in vivo* protocol employed in studies designed to establish the effect of food on the oral absorption characteristics of griseofulvin from the corn oil-in-water emulsion was similar to that used for fasting animals. The sole exception was that the animals were allowed free access to food[3] prior to, and during, the absorption experiment.

Multiple-Dose Oral Studies—Six animals were fasted for 20–24 hr prior to oral administration of the first 50-mg/kg dose of griseofulvin as the aqueous suspension or corn oil-in-water emulsion. The animals were then allowed free access to food until 20–24 hr prior to the final dose, at which time they were again fasted for the duration of the absorption experiment. Five 50-mg/kg doses of griseofulvin were administered at a constant dosing interval of 12 hr. Blood samples were collected from the tail artery of each animal immediately prior to, and at 1, 2, 4, 6, 8, and 12 hr after, the administration of the last drug dose.

Plasma samples were assayed for intact griseofulvin content by the spectrofluorometric procedure described earlier (4).

RESULTS AND DISCUSSION

Pharmacokinetic Analysis—Previous studies indicated that the plasma levels of griseofulvin decline in a monoexponential fashion with time after intracardiac (i.c.) administration to rats of a single 5- or 10-mg/kg dose of the antibiotic as a solution in polyethylene glycol 400 (7). There was no evidence of a dose dependency in the disposition kinetics of the drug, and the plasma levels attained in the intracardiac studies were comparable to those observed in the present 50-mg/kg dose oral studies.

Therefore, all plasma griseofulvin concentration–time data obtained following single- or multiple-dose oral administration of the dosage forms were fitted to an appropriate linear pharmacokinetic model, using the digital computer, nonlinear regression analysis program (NONLIN) of Metzler (8), and equal weighting of the data points. The goodness of fit of the data to a one-compartment open model with either apparent first-order (Scheme I and Eqs. 1 and 2) or apparent zero-order (Scheme II and Eqs. 3*a*, 3*c*, 4*a*, and 4*c*) absorption was tested (8–10).

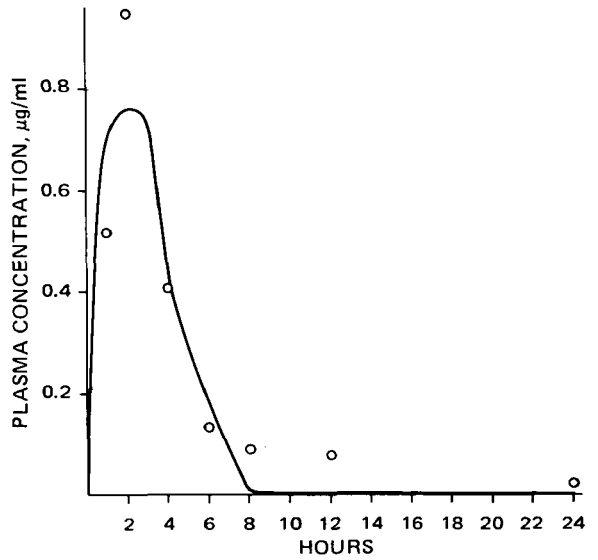

Figure 1—*Plasma concentrations of griseofulvin as a function of time following the oral administration of a 50-mg/kg single dose of micronized griseofulvin as an aqueous suspension to Rat 51. Key:* o, *actual experimental points; and* —, *obtained by computer, nonlinear least-squares regression according to Eq. 1 (CORR = 0.934).*

One-Compartment Open Model with First-Order Absorption—Scheme I shows the simplified model where A_A is the amount of griseofulvin in solution at the absorption site at any time t, k is the apparent first-order absorption rate constant, and K' is the apparent elimination rate constant.

$$A_A \xrightarrow{k} A_B \xrightarrow{K'} A_E$$

Scheme I

For single-dose administration, griseofulvin plasma concentrations (C) at any time t following oral drug administration are given by:

$$C = \left(\frac{FD}{V}\right)\left(\frac{k}{k - K'}\right)[\exp[-K'(t - t_0)] - \exp[-k(t - t_0)]] \quad \text{(Eq. 1)}$$

where F is the fraction of the oral dose absorbed, D is the oral dose, V is the volume of distribution, and t_0 is the lag time before absorption commences or the onset of absorption.

For multiple-dose administration, the plasma concentration of griseofulvin at any time t' following the oral administration of the nth dose (C_n) is given by:

$$C_n = \left(\frac{FD}{V}\right)\left(\frac{k}{k - K'}\right)\left[\left(\frac{1 - \exp - (nK'\tau)}{1 - \exp - (K'\tau)}\right) \times \exp[-K'(t' - t_0)] - \left(\frac{1 - \exp - (nk\tau)}{1 - \exp - (k\tau)}\right) \times \exp[-k(t' - t_0)]\right] \quad \text{(Eq. 2)}$$

where $t' = t - (n - 1)\tau$, n is the number of fixed doses administered, τ is the constant time interval between doses, and C_n is the plasma concentration of griseofulvin at any time t' after the nth dose.

One-Compartment Open Model with Apparent Zero-Order Absorption—Scheme II shows the simplified model where k_0 is the apparent zero-order absorption rate constant.

$$A_A \xrightarrow{k_0} A_B \xrightarrow{K'} A_E$$

Scheme II

[1] Supplied by the Schering Corp., Bloomfield, N.J.
[2] Obtained from Blue Spruce Farms, Altamont, NY 12009
[3] Charles River Rat Formula (low in fat content), Country Foods, Syracuse, N.Y.

For single-dose administration, the plasma concentration of griseofulvin at any time during its absorption over T hours is given by:

$$C = \frac{k_0}{VK'}[1 - \exp[-K'(t - t_0)]] \qquad \text{(Eq. 3a)}$$

with the condition that $t_0 \leq t \leq T$ and where $k_0 = FD/T$, T is the duration of the absorption process, and t is any time after oral administration of griseofulvin.

At the end of the absorption process, the maximum plasma concentration of griseofulvin ($C_{\max,T}$) can be described by the relationship:

$$C_{\max,T} = \frac{k_0}{VK'}[1 - \exp[-K'(T - t_0)]] \qquad \text{(Eq. 3b)}$$

when $t = T$.

After absorption has ceased, the plasma levels of griseofulvin decline monoexponentially with time in accordance with:

$$C = (C_{\max,T})\exp[-K'(t - T)] \qquad \text{(Eq. 3c)}$$

when $t \geq T$.

For multiple-dose administration, at any time t' during the absorption of the nth dose, the plasma levels of griseofulvin are given by:

$$C_n = \frac{k_0}{VK'}\Bigg[1 - \exp - [K'(t' - t_0)] - \left(\frac{1 - \exp - [(n-1)K'\tau]}{1 - \exp - (K'\tau)}\right)(\exp[-K'(t' - t_0 + \tau)] - \exp[-K'(t' - t_0 + \tau - T)])\Bigg] \qquad \text{(Eq. 4a)}$$

with the condition that $t_0 \leq t' \leq T$ and where $t' = t - (n-1)\tau$ = time elapsed after oral administration of the nth dose.

The maximum plasma concentration attained after the nth dose ($C_{n,\max,T}$) is:

$$C_{n,\max,T} = \frac{k_0}{VK'}\Bigg[1 - \exp - [K'(T - t_0)] - \left(\frac{1 - \exp -[(n-1)K'\tau]}{1 - \exp - (K'\tau)}\right) \times (\exp[-K'(T - t_0 + \tau)] - \exp[-K'(\tau - t_0)])\Bigg] \qquad \text{(Eq. 4b)}$$

when $t' = T$.

After the nth dose is absorbed, the plasma concentration decreases with time in accordance with:

$$C_n = (C_{n,\max,T})\exp[-K'(t' - T)] \qquad \text{(Eq. 4c)}$$

when $t' \geq T$.

As can be seen from the representative computer-predicted curves, the use of the apparent first-order absorption model (Scheme I and Eqs. 1 and 2) consistently resulted in poor agreement between the predicted and experimental plasma level–time data obtained from both single- (Figs. 1 and 2) and multiple- (Fig. 3) dose absorption studies. However, when the same experimental data were analyzed by the apparent zero-order absorption model (Scheme II and Eqs. 3a, 3c, 4a, and 4c), excellent computer fits were realized (Figs. 4–6). Therefore, this model was used to interpret the results of all *in vivo* absorption studies performed with griseofulvin.

It is important to note that griseofulvin is *apparently* absorbed in a zero-order fashion from the *test dosage forms* whereas the drug is probably absorbed from *solution* by an apparent first-order process (11, 12). The observed, apparent zero-order absorption profile of griseofulvin can be explained on the basis that a slow, rate-determining dissolution step precedes the true absorption process (13–15). The assumption that the rate-limiting dissolution process is kinetically zero-order appears to be consistent with the unusually low aqueous solubility of griseofulvin (about 15 mg/liter at 37°) and the limited volume of GI fluids available for drug dissolution relative to the oral dose administered to the animals (*i.e.*, 50 mg/kg or approximately 15 mg/animal). A similar hypothesis was proposed (16) to account for the *apparent* zero-order absorption profile of sulfisoxazole from tablet dosage forms in humans.

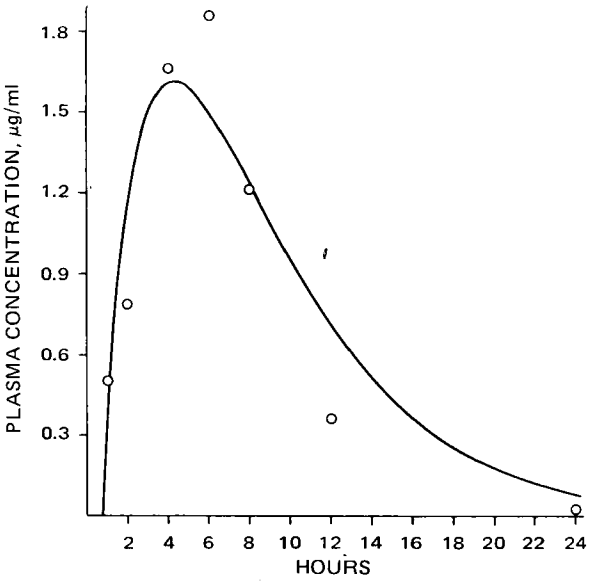

Figure 2—*Plasma concentrations of griseofulvin as a function of time following the oral administration of a 50-mg/kg single dose of micronized griseofulvin as a corn oil-in-water emulsion to Rat 42. Key: O, actual experimental points; and —, obtained by computer, nonlinear least-squares regression according to Eq. 1 (CORR = 0.941).*

The area under the plasma griseofulvin concentration–time curve from time zero to infinity after a single dose of the drug

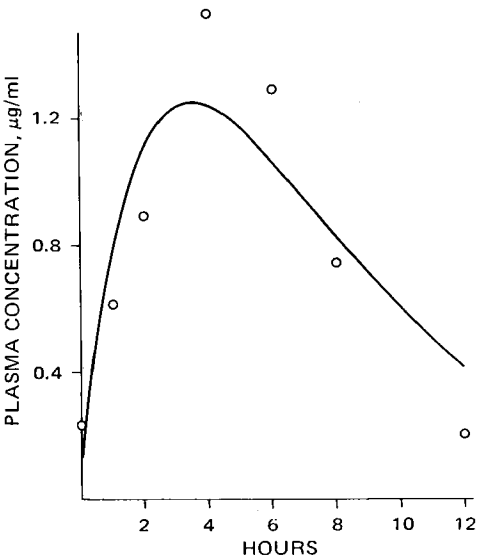

Figure 3—*Plasma concentrations of griseofulvin as a function of time following the oral administration of the fifth 50-mg/kg dose of micronized griseofulvin as a corn oil-in-water emulsion to Rat 38. Key: O, actual experimental points; and —, obtained by computer, nonlinear least-squares regression according to Eq. 2 (CORR = 0.915).*

Table I—Plasma Concentrations of Griseofulvin following Its Oral Administration as a Single 50-mg/kg Dose as an Aqueous Suspension (AS) or a Corn Oil-in-Water Emulsion (COE) to Rats

Hour	Plasma Concentration, μg/ml		
	AS[a] (Fasting Animals, n = 12)	COE[a] (Fasting Animals, n = 11)	COE[a] (Nonfasting Animals, n = 6)
1.0	0.418 (0.06)[b]	0.362 (0.03)	0.279 (0.06)
	0.162–0.822[c]	0.205–0.502	0.164–0.549
2.0	0.715 (0.10)	0.805 (0.07)	0.885 (0.17)
	0.271–1.31	0.606–1.39	0.509–1.58
4.0	0.748 (0.14)	1.76 (0.19)	1.63 (0.20)[d]
	0.154–1.08	0.931–2.96	1.26–2.16
5.0	—	—	2.50[e]
	—	—	1.94; 2.56[f]
6.0	0.400 (0.09)	1.81 (0.20)	1.36 (0.16)[d]
	0.053–0.941	0.756–3.11	1.04–1.65
8.0	0.259 (0.06)	1.29 (0.17)	1.47 (0.56)
	0.056–0.661	0.733–2.60	0.412–1.54
12.0	0.186 (0.04)	0.524 (0.11)	0.307 (0.07)
	0–0.450	0.236–1.40	0.112–0.589
24.0	0.051 (0.01)	0.050 (0.01)	0.025 (0.02)
	0–0.112	0.016–0.100	0.003–0.101

[a] Micronized griseofulvin was in suspension in dosage form. [b] Mean (*SE*). [c] Range. [d] Mean (*SE*) for four animals. [e] Average for two animals. [f] Individual values for two animals.

($AUC_{0-\infty}$) and during the dosing interval after the fifth oral dose (AUC_τ) was determined using the trapezoidal rule (10).

***In Vivo* Absorption Studies**—*Single-Dose Oral Studies (Fasting Animals)*—The mean[4] time course of griseofulvin in the plasma of fasting rats after oral administration of a single 50-mg/kg dose of micronized griseofulvin as the control aqueous suspension or corn oil-in-water emulsion dosage form is presented in Table I. All plasma level–time data were pharmacokinetically interpreted according to a one-compartment open model with apparent zero-order absorption (Eqs. 3*a* and 3*c* and Figs. 4 and 5).

The computer-generated nonlinear least-squares regression estimates of the model parameters[4] are summarized in Table II, together with indications of the goodness of fit of the experimental data to the proposed model. Statistical comparisons of the mean model parameters are presented in Table III. An examination of the mean t_0 values (Table II) reveals that the onset of absorption of griseofulvin from the corn oil emulsion is slightly, but significantly (Table III), delayed relative to that observed from the control aqueous suspension. No statistical difference was noted between the dosage forms with respect to either the relative rate of drug absorption or the apparent elimination rate constant (Table III). However, the duration of absorption of griseofulvin, as reflect-

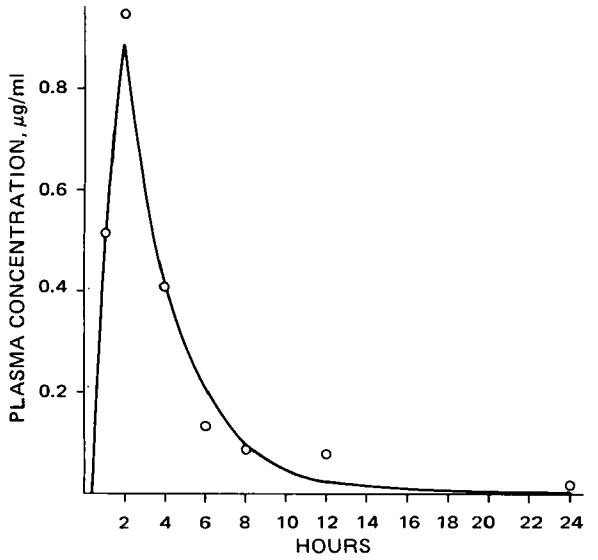

Figure 4—*Plasma concentrations of griseofulvin as a function of time following the oral administration of a 50-mg/kg single dose of micronized griseofulvin as an aqueous suspension to Rat 51. Key: O, actual experimental points; and —, obtained by computer, nonlinear least-squares regression according to Eqs. 3a and 3c (CORR = 0.991).*

[4] Data for each animal are available upon request.

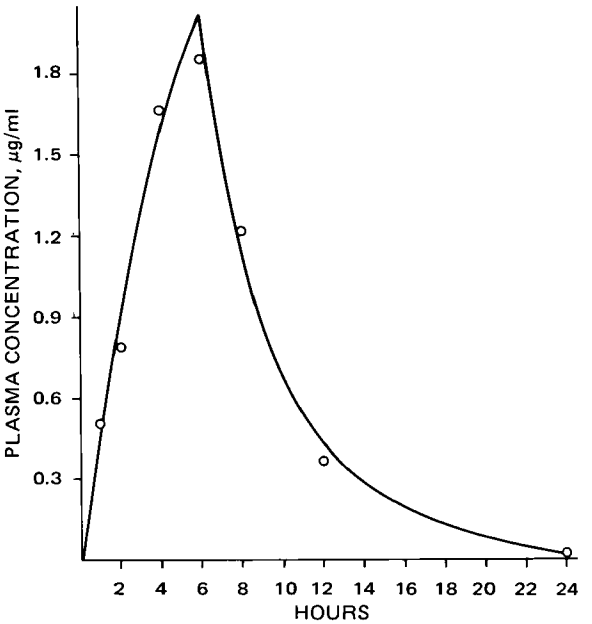

Figure 5—*Plasma concentrations of griseofulvin as a function of time following the oral administration of a 50-mg/kg single dose of micronized griseofulvin as a corn oil-in-water emulsion to Rat 42. Key: O, actual experimental points; and —, obtained by computer, nonlinear least-squares regression according to Eqs. 3a and 3c (CORR = 0.994).*

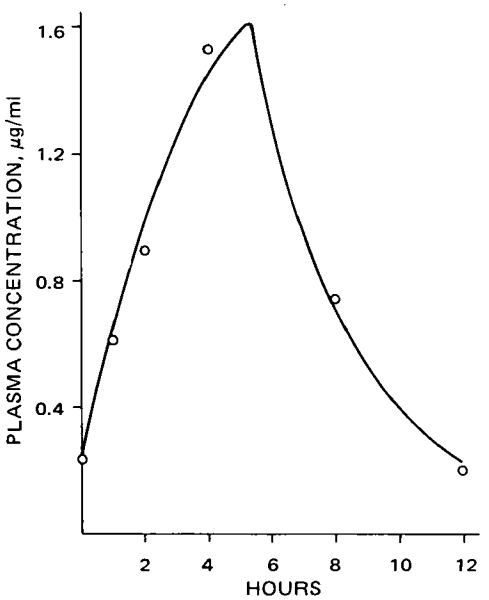

Figure 6—*Plasma concentrations of griseofulvin as a function of time following the oral administration of the fifth 50-mg/kg dose of micronized griseofulvin as a corn oil-in-water emulsion to Rat 38. Key: O, actual experimental points; and —, obtained by computer, nonlinear least-squares regression according to Eqs. 4a and 4c (CORR = 0.994).*

Table II—Pharmacokinetic Parameters Estimated from Plasma Griseofulvin Concentrations following Oral Administration of a Single 50-mg/kg Dose of Micronized Griseofulvin as an Aqueous Suspension (AS) or a Corn Oil-in-Water Emulsion (COE) to Rats

Parameter[a]	AS (Fasting Rats, n = 12)	COE (Fasting Rats, n = 11)	COE (Nonfasting Rats, n = 5)
Apparent onset of absorption (t_0), hr	0.183 (0.05)[b] 0.002–0.431[c] 99[d]	0.516 (0.07) 0.235–0.900 45	0.378 (0.13) 0.071–0.792 78
Apparent duration of absorption (T), hr	2.66 (0.30) 1.23–4.24 39	5.33 (0.37) 3.15–7.16 23	4.90 (0.55) 3.26–6.48 25
Apparent rate of absorption (k_0/V), mg/hr-liter	0.577 (0.09) 0.218–1.41 56	0.769 (0.11) 0.458–1.52 49	0.745 (0.12) 0.457–1.13 36
Apparent elimination rate constant (K'), hr^{-1}	0.255 (0.03) 0.104–0.437 37	0.220 (0.03) 0.106–0.442 50	0.241 (0.02) 0.174–0.287 18
Estimated maximum concentration ($C_{max,T}$)[e], μg/ml	0.944 (0.13) 0.392–1.89 49	2.12 (0.21) 1.11–3.44 32	1.96 (0.28) 1.23–2.70 32
Observed C_{max}, μg/ml	0.875 (0.14) 0.324–2.04 55	1.92 (0.21) 0.931–3.11 36	1.88 (0.18)[f] 1.26–2.56 24
Estimated area under plasma level–time curve [$(AUC)_{0-\infty}$][g], mg-hr/liter	5.72 (1.1) 1.39–14.3 65	17.2 (1.5) 9.82–26.1 29	13.9 (2.2) 8.23–19.9 36
Observed $(AUC)_{0-\infty}$[h], mg-hr/liter	6.42 (1.2) 1.49–14.5 63	17.7 (1.6) 12.0–27.7 30	13.4 (1.9)[f] 8.00–20.8 34
Correlation parameters			
(r^2)[i]	0.990 0.978–0.999	0.990 0.978–0.999	0.985 0.965–0.999
(CORR)[j]	0.987 0.960–0.998	0.985 0.969–0.999	0.988 0.971–0.999

[a] Nonlinear least-squares regression parameters calculated using Eqs. 3*a* and 3*c*. [b] Mean (*SE*). [c] Range. [d] Coefficient of variation, percent. [e] Calculated using Eq. 3*b* and nonlinear least-squares parameters. [f] Mean (*SE*) for six animals. [g] Calculated using the following equation, $(AUC)_{0-\infty} = (k_0/V)(T/K')$, and nonlinear least-squares parameters. [h] Calculated using actual plasma level–time data and the trapezoidal rule. [i] Coefficient of determination. [j] Correlation of observed *versus* predicted plasma levels.

ed by the magnitude of the mean T values listed in Table II, was significantly increased by 2.7 hr (Table III) when the drug was administered to the fasting animals as a suspension in the emulsified corn oil vehicle as compared to the aqueous suspension.

The maximum plasma levels attained following oral administration of griseofulvin in the two dosage forms to fasting animals were calculated with Eq. 3*b* and the computer-generated model parameters; the mean values are listed in Table II. The estimated values compare favorably with those actually observed (Table II). The mean data show that the maximum plasma level of the antibiotic from the corn oil emulsion was approximately two times higher and less variable (lower coefficient of variation) than from the control aqueous suspension. This difference was highly significant (Table III).

The mean estimated and observed areas under the plasma griseofulvin level–time curves for both dosage forms are also listed in Table II, and excellent agreement exists. A statistical comparison of the mean areas (Table III) reveals that there was a highly significant, threefold increase in the amount of drug absorbed from the corn oil emulsion relative to that absorbed from the control aqueous suspension. As reflected by the magnitude of the coefficients of variation associated with this parameter (Table II), the absorption of micronized griseofulvin appears to be more uniform from the corn oil-in-water emulsion.

Multiple-Dose Oral Studies—It was considered important to determine whether the marked improvement in griseofulvin bioavailability observed with the corn oil emulsion dosage form after single-dose administration also occurred upon multiple dosing. Therefore, animals received orally a 50-mg/kg dose of micronized griseofulvin as the control aqueous suspension or corn oil-in-water emulsion dosage form every 12 hr for a total of five doses. The dosing interval employed was designed to yield an average plasma level at steady state (17) of approximately 1 μg/ml and minimal drug accumulation after repetitive oral dosing with the emulsion dosage form.

The mean[4] plasma griseofulvin concentration–time data fol-

Table III—Statistical Comparisons[a] of the Mean Pharmacokinetic Parameters Associated with the Absorption of a Single 50-mg/kg Dose of Micronized Griseofulvin from an Aqueous Suspension (AS) or a Corn Oil-in-Water Emulsion (COE)

Parameter	AS (n = 12) *versus* COE (n = 11), Fasting Animals		COE (Fasting Animals, n = 11) *versus* COE (Nonfasting Animals, n = 5)	
	Student t Value	Level of Significance (p)	Student t Value	Level of Significance (p)
t_0	3.84	<0.001	1.01	>0.3 (N.S.)[b]
T	5.69	<0.001	0.658	>0.5 (N.S.)
k_0/V	1.31	>0.2 (N.S.)[b]	0.129	>0.8 (N.S.)
K'	0.821	>0.4 (N.S.)	0.400	>0.6 (N.S.)
Estimated $C_{max,T}$	4.89	<0.001	0.437	>0.6 (N.S.)
Observed C_{max}	4.24	<0.001	0.120[c]	>0.9 (N.S.)
Estimated $(AUC)_{0-\infty}$	6.33	<0.001	1.22	>0.2 (N.S.)
Observed $(AUC)_{0-\infty}$	5.74	<0.001	1.65[c]	>0.1 (N.S.)

[a] Student t test (20). [b] N.S. = not significant. [c] Value based on the mean of 11 fasting animals and the mean of six nonfasting animals.

Table IV—Plasma Concentrations of Griseofulvin following the Fifth Oral Dose Administered as an Aqueous Suspension (AS) or a Corn Oil-in-Water Emulsion (COE) to Rats (Multiple-Dose Regimen: 50 mg/kg every 12 hr)

Time after Fifth Oral Dose, t', hr	Plasma Concentration, μg/ml	
	AS[a] (n = 6)	COE[a] (n = 6)
0.0	0.207 (0.05)[b]	0.200 (0.02)
	0.106–0.411[c]	0.114–0.264
1.0	0.896 (0.10)	1.13 (0.16)
	0.471–1.15	0.615–1.57
2.0	1.19 (0.15)	1.38 (0.21)
	0.534–1.69	0.895–2.17
4.0	1.14 (0.20)	1.89 (0.13)
	0.541–1.82	1.53–2.36
6.0	0.507 (0.08)	1.38 (0.10)
	0.301–0.805	0.992–1.68
8.0	0.222 (0.05)	0.736 (0.08)
	0.087–0.475	0.559–1.00
12.0	0.106 (0.03)	0.224 (0.03)
	0.022–0.204	0.127–0.378

[a] Micronized griseofulvin was in suspension in dosage form. [b] Mean (SE). [c] Range.

lowing the fifth oral dose of the antibiotic appear in Table IV, and a representative computer fit of the data to Eqs. 4a and 4c is shown in Fig. 6. A statistical comparison of the nonlinear least-squares estimates of the pharmacokinetic parameters associated with the absorption of griseofulvin from the two dosage forms (Tables V and VI) reveals no significant differences in onset and relative rate of drug absorption or in the apparent elimination rate constant of griseofulvin.

Table V—Pharmacokinetic Parameters Estimated from Plasma Griseofulvin Concentrations following the Fifth Oral Dose of Micronized Griseofulvin Administered as an Aqueous Suspension (AS) or a Corn Oil-in-Water Emulsion (COE) to Rats (Multiple-Dose Regimen: 50 mg/kg every 12 hr)

Parameter[a]	AS (n = 6)	COE (n = 6)
Apparent onset of absorption (t_0), hr	0.034 (0.01)[b]	0.025 (0.01)
	0.001–0.070[c]	0.001–0.053
	91[d]	99
Apparent duration of absorption (T), hr	2.81 (0.44)	4.58 (0.40)
	1.54–4.36	3.21–5.31
	39	22
Apparent rate of absorption (k_0/V), mg/hr-liter	0.992 (0.17)	0.945 (0.14)
	0.332–1.53	0.576–1.50
	44	36
Apparent elimination rate constant (K'), hr^{-1}	0.370 (0.09)	0.320 (0.04)
	0.180–0.813	0.236–0.490
	62	28
Estimated maximum concentration ($C_{max,T}$)[e], μg/ml	1.55 (0.09)	2.20 (0.08)
	0.743–2.09	1.62–2.82
	14	8.8
Observed C_{max}, μg/ml	1.32 (0.19)	1.89 (0.13)
	0.541–1.82	1.53–2.36
	35	17
Estimated area under plasma level–time curve, $[(AUC)_T]f$, mg-hr/liter	7.33 (0.81)	12.9 (0.74)
	4.19–9.28	10.6–15.6
	27	14
Observed $[(AUC)_T]f$, mg-hr/liter	6.97 (0.88)	12.5 (0.85)
	3.81–9.01	10.3–16.1
	31	17
Correlation parameters		
$(r^2)g$	0.984	0.982
	0.965–0.999	0.959–0.996
(CORR)[h]	0.978	0.970
	0.934–0.999	0.910–0.994

[a] Nonlinear least-squares regression parameters calculated using Eqs. 4a and 4c. [b] Mean (SE). [c] Range. [d] Coefficient of variation, percent. [e] Calculated using Eq. 4b and nonlinear least-squares parameters. [f] Area under plasma concentration–time curve from t' = 0 to t' = 12 hr as determined with the aid of the trapezoidal rule and computer-generated (estimated value) or actual (observed value) plasma level–time data. [g] Coefficient of determination. [h] Correlation of observed *versus* predicted plasma levels.

Table VI—Statistical Comparison[a] of the Mean Pharmacokinetic Parameters Associated with the Absorption of the Fifth Dose of Micronized Griseofulvin Administered as an Aqueous Suspension or a Corn Oil-in-Water Emulsion (Multiple-Dose Regimen: 50 mg/kg every 12 hr)

Parameter	Student t Value	Level of Significance (p)
t_0	0.567	>0.5 (N.S.)[b]
T	2.94	<0.02
k_0/V	0.206	>0.8 (N.S.)
K'	0.502	>0.6 (N.S.)
Estimated $C_{max,T}$	2.48	<0.05
Observed C_{max}	2.49	<0.05
Estimated $(AUC)_T$	5.03	<0.001
Observed $(AUC)_T$	4.50	<0.005

[a] Student t test (20). [b] N.S. = not significant.

However, in contrast to what was observed after repetitive administration of the aqueous suspension, the presence of emulsified corn oil in the GI tract produced approximately a 1.8-hr increase in the duration of the absorption process, a 1.4-fold increase in the maximum plasma levels attained, and a 1.8-fold increase in the bioavailability of griseofulvin (Table V). All of these differences were highly significant (Table VI).

In addition, the drug was more uniformly absorbed from the emulsion dosage form (*i.e.*, the coefficients of variation were lower, Table V) and plasma levels exceeding 1 μg/ml, the minimum effective level in humans (18) and dogs (15), were maintained for appreciably longer periods (Table IV). The fact that the absorption of micronized griseofulvin from the corn oil emulsion is considerably enhanced after both single and repetitive oral administration demonstrates that the effect of emulsified lipid on griseofulvin absorption is not transient.

Effect of Food on Absorption of a Single Dose of Micronized Griseofulvin from a Corn Oil-in-Water Emulsion—In general, food has an inhibitory effect on the GI absorption of most drugs from pharmaceutical dosage forms (19). To determine whether the presence of food in the GI tract could affect the absorption of griseofulvin from the corn oil-in-water emulsion, a single 50-mg/kg dose of this dosage form was administered orally to another group of rats who had been allowed free access to food both before and after drug administration (nonfasting animals). The mean[4] time course of griseofulvin in the plasma of each nonfasting rat is presented in Table I. The pharmacokinetic analysis of the plasma level data is summarized in Table II.

A statistical comparison of the parameters obtained after oral administration of the corn oil emulsion to nonfasting animals with those obtained in fasting animals (Table II) indicated that food did not affect the apparent onset, duration, or rate of drug absorption from the corn oil emulsion (Table III). In addition, the presence of food did not significantly alter the maximum plasma levels, the bioavailability, or the apparent elimination rate constant of the antibiotic from the corn oil emulsion (Table III).

The mechanism underlying the enhanced absorption of micronized griseofulvin after single- and multiple-dose administration to rats as a lipid-in-water emulsion will be the subject of a subsequent report.

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Succinylsulfathiazole Crystal Forms II: Effect of Additives on Kinetics of Interconversion

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Abstract □ The effect of various additives on the rate of transformation of the metastable anhydrous succinylsulfathiazole Form I to the water-stable dihydrate Form II in aqueous suspensions was studied. Some structurally related compounds, viscosity-imparting agents, surfactants, and coloring agents were used as possible transformation retardants. The effect of including seeds of Form II in the presence and absence of additives is also discussed. Some additives, *e.g.*, methylcellulose and phthalylsulfathiazole, showed significant transformation-retarding effects. Other additives, *e.g.*, sulfanilamide and glycerin, increased the rate of transformation. Coloring agents had only slight effects. Utilization of the results in the formulation of physically stable aqueous suspensions of succinylsulfathiazole is discussed.

Keyphrases □ Succinylsulfathiazole—crystal forms, interconversion, effect of structurally related compounds, viscosity-imparting agents, surfactants, and coloring agents □ Crystal forms—succinylsulfathiazole, effect of additives on interconversion

Succinylsulfathiazole crystal forms, their preparation, characterization, interconversion, and kinetics of transformation under standard conditions, were previously described (1). It was concluded (1) that the formulation of physically stable aqueous suspensions of succinylsulfathiazole may be achieved in one of two ways. The first involves the use of Form II (the water-stable dihydrate), which does not undergo further transformation in suspension and, consequently, does not change in shape or size distribution, thus producing a stable suspension. The second involves the anhydrous Form I (frequently available commercially), provided that adequate measures are taken to prevent the transformation to Form II which results in physical instability. Stabilization of the metastable form (Form I) in aqueous suspension by the use of some formulation additives is the subject of the present report.

The use of various additives to stabilize drug polymorphs has already been reported (2–6). These additives included structurally related compounds, viscosity-imparting materials (hydrocolloids), surfactants, and coloring agents. The present study is concerned with effects of representative examples of these additives, the suspension concentration of Form I, and seeding with Form II on the rate of transformation of the anhydrous succinylsulfathiazole Form I to the dihydrate Form II in aqueous suspension.

EXPERIMENTAL

Materials and Apparatus—Succinylsulfathiazole[1] Forms I and II were obtained as micronized commercial samples. Sulfanilamide, sulfathiazole, phthalylsulfathiazole, methylcellulose, acacia, glycerin, syrup, polysorbate 80, fluorescein sodium, and amaranth, all of USP, BP, or BPC grade, were used. Yellow No. 4[2] and Bordeaux B (BPC 1949) were also used.

IR measurements were made with a double-beam grating spectrophotometer[3].

[1] Courtesy of Chemical Industries Development, Guiza, Egypt.
[2] Lebensmittel, D.F.G., Germany.
[3] Perkin-Elmer model 237-B.