since when sodium was completely replaced by potassium in the bathing buffer solutions, only a 1.08 value was obtained for the ratio of permeability coefficients for salicylate ion.

5. It would appear that the virtual pH hypothesis of Hogben *et al.* (4) is inoperative when considering *in vitro* intestinal transport.

6. If the presently accepted hypotheses concerning the *in vivo* intestinal absorption of ionizable drugs are valid, it would appear that *in vitro* intestinal transport studies could lead to erroneous conclusions concerning the degree of absorption of ionizable drugs *in vivo*.

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Parameters Affecting Absorption of Griseofulvin in a Human Subject Using Urinary Metabolite Excretion Data

PETER KABASAKALIAN, MICAELA KATZ, BERNARD ROSENKRANTZ, and EDWARD TOWNLEY

Abstract □ Using the urinary excretion of 6-demethylgriseofulvin as the index of absorption, the effects of three previously studied parameters (high-fat breakfast, particle size, and dissolution rate) on the absorption of griseofulvin in a single subject are compared with published blood level data derived from many subjects. The results of the effects of three new parameters (time of dose administration, low-dose level, and gastrointestinal transit time) are also reported.

Keyphrases □ Physiological availability—griseofulvin, man □ Griseofulvin absorption parameters—urinary excretion data, man □ 6-Demethylgriseofulvin metabolite—griseofulvin absorption parameters, man □ Trimethylsilyl ether derivative—6-demethylgriseofulvin, griseofulvin metabolite □ GLC—analysis

The factors (1–12) affecting the absorption of orally administered griseofulvin in man have been studied by measuring (using a fluorometric chemical analytical procedure) the level of griseofulvin in blood at various times after drug administration. The calculation of the degree of absorption is based on the assumption that the physiological availability of the drug is proportional to the area (usually determined by the trapezoidal rule) under the blood level–time curve (3, 5, 13–15).

The factors affecting absorption were found to be a function of the diet (high-fat meal) (1, 2), the dosage formulation [particle size (3–7), dissolution rate (8, 9), solubility (7, 10), and presence of surfactants (4, 7)], and the dosage regimen [dosage level (3, 11, 12) and repetitive dosage schedule (6, 7, 9, 11)].

The nonlinear (logarithmic) relationship (3, 11, 12) between the dose ingested and the area under the blood level–time curve has raised questions concerning the validity of the model on which this method of calculating absorption is based. Atkinson *et al.* (11) suggested

the existence of a linear relationship between the half-life and logarithm of the ingested dose. This dependence of half-life on the amount of drug in the blood is unusual if elimination was following a simple model containing first-order rate constants. Riegelman has shown that one basic assumption of the model, the constancy of the apparent volume of distribution, is invalid for griseofulvin in the rabbit (16). He has also questioned the single-compartment basis of the model in man (17). However, Riegelman has recently shown that, although a multicompartment model is necessary for calculating absorption, the plasma level–time curve for man (18) was proportional to the dose administered.

A further complication relating to the use of blood data has been the fact that most investigations have used a single-dosage regimen. Marvel *et al.* (7) have shown that in the case of griseofulvin, a factor (surfactant in formulation) which enhanced absorption of griseofulvin under a single-dosage regimen did not do so under a multiple-dosage regimen for which this drug is intended.

Besides the use of blood level data, physiological availability can be estimated from urinary excretion data (19, 20). A significant amount of drug must be excreted unchanged in the urine if questions of valid use of this method are not to be raised (21). Unfortunately, the amount of free griseofulvin excreted in the urine is only about 0.1% of the ingested dose (22). Fortunately, the urinary excretion of the reported metabolite (23) (6-demethylgriseofulvin) of griseofulvin can be used for this purpose. Absorbed griseofulvin is reported to be completely excreted as 6-demethylgriseofulvin (10).

This investigation was undertaken to determine whether urinary metabolite excretion data as first used by Riegelman (10) can be used to study the parameters that affect the absorption of griseofulvin in man, but which may not conveniently be studied by the blood level method.

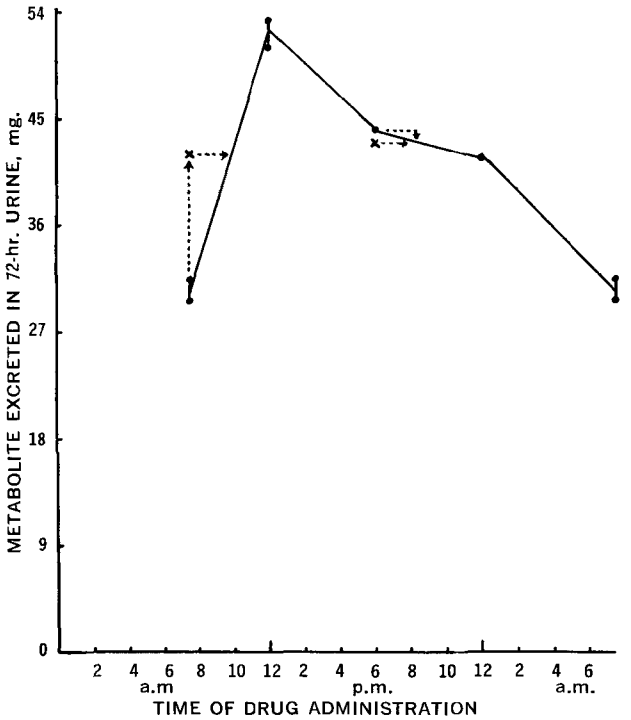

Figure 1—*Plot of metabolite yield after the subject has taken a single dose of 250-mg. microsize griseofulvin experimental Product A at various times during the day: ●, with a nonfat meal; and ×, with a fat meal.*

Table I—Urinary Excretion of Metabolite[a]

Time of Administration	Diet, Meal	Time after Drug Administration, days	Metabolite: In 24-hr. Urine, mg.	Metabolite: In 72-hr. Urine, mg.
7:30 a.m.	Nonfat	1.0	23.1	—
		2.0	5.7	—
		3.0	0.9	29.7
7:30 a.m. repeat[b]	Nonfat	1.0	20.9	—
		2.0	8.7	—
		3.0	1.9	31.5
7:30 a.m.	Fat	1.0	28.1	—
		2.0	10.4	—
		3.0	3.5	42.0
12:00 noon	Nonfat	1.0	37.6	—
		2.0	13.0	—
		3.0	2.8	53.4
12:00 noon repeat[b]	Nonfat	1.0	36.6	—
		2.0	11.5	—
		3.0	3.0	51.1
6:00 p.m.	Nonfat	1.0	29.2	—
		2.0	11.7	—
		3.0	3.3	44.2
6:00 p.m.	Fat	1.0	25.0	—
		2.0	13.9	—
		3.0	4.1	43.0
12:00 midnight	Nonfat	1.0	31.3	—
		2.0	9.4	—
		3.0	1.1	41.8

[a] By subject receiving a single dose of 250 mg. of microsize griseofulvin experimental Product A at various times of drug administration and with or without a fat meal.
[b] Repeat run 1 month later.

EXPERIMENTAL[1]

Material—Commercially available 250-mg. regular size and microsize griseofulvin formulations of three manufacturers, together with one 500-mg. regular size and one 250-mg. and seven 125-mg. microsize experimental griseofulvin formulations, were used in this study.

***In Vitro* Dissolution Test**—Katchen's (8, 24) modified oscillatory tube method was used with simulated intestinal fluid.

Subject—A single healthy ambulatory subject was used in this study. During the experimental period, there were no dietary restrictions except for fat intake during the time of dosage administration and high-fat meal experiments. The normal diet was bland. During the gastrointestinal transit time study, the diet was altered as noted in Table V.

Dosage Regimen—A single-dosage regimen was used. The dose was administered at 7:30 a.m., 12:00 noon, 6:00 p.m., or 12:00 midnight as noted in the time of dose administration study immediately prior to the three regular daily meals; no meals were skipped. After this study, 12:00 noon was chosen as a fixed parameter for the rest of the studies.

Urine Collection—The urine was collected normally for 3 days subsequent to drug administration and combined into 24-hr. samples. The urine volume and pH were noted. The urine was analyzed right after collection. No change in metabolite concentration was observed over several months on repeated assays.

Analytical Method—The urine was analyzed for 6-demethylgriseofulvin[2] by gas-liquid chromatography. Twenty-five milliliters of urine was acidified to pH 1 and extracted with 25 ml. of chloroform.

[1] All gas chromatograms were obtained on a F and M model 400 gas chromatograph with a flame-ionization detector and a Minneapolis Honeywell recorder.
[2] β-Glucuronidase and sulfatase hydrolysis did not indicate the presence of any conjugated metabolite.

Table II—Urinary Excretion of Metabolite[a]

Dose, mg.	Time after Drug Administered, days	Urine ml.	Urine pH	Metabolite In 24-hr. Urine, mg.	Metabolite In 72-hr. Urine, mg.	Metabolite/Dose Ratio in 72-hr. Urine
500	1.0	1860	6.4	35.2	—	—
	2.0	1220	5.6	6.7	—	—
	3.0	1080	5.7	2.0	43.9	0.088
250	1.0	1750	6.3	15.2	—	—
	2.0	960	5.7	6.1	—	—
	3.0	1630	6.4	2.9	24.2	0.097
125	1.0	1650	6.5	9.3	—	—
	2.0	1150	6.6	3.3	—	—
	3.0	1100	6.2	0.7	13.3	0.106
45	1.0	790	6.6	3.3	—	—
	2.0	700	6.0	1.3	—	—
	3.0	1120	6.2	0.2	4.8	0.107
15	1.0	860	5.7	1.02	—	—
	2.0	1620	6.8	0.28	—	—
	3.0	810	6.3	0.11	1.41	0.094
5	1.0	1180	6.2	0.46	—	—
	2.0	1820	6.3	0.00	—	—
	3.0	1700	6.6	0.00	0.46	0.092

[a] By subject receiving at 12:00 noon a single dose or fractions of 500 mg. of regular size griseofulvin Product B.

A 10-ml. aliquot of the chloroform extract was evaporated to a residue on a steam bath under a nitrogen atmosphere. The residue was dried in a draft oven at 60° for 10 min. The trimethylsilyl ether derivative was formed according to the procedure of Horning *et al.* (25), using 100 μl. of B.S.A. reagent,[3] mixing, and heating for 10 min. at 60°. After the addition of 100 μl. of pyridine, a 5-μl. sample was injected into a diatomaceous earth[4] column containing 1% OV-17[4] (a phenylmethyl siloxane polymer) as liquid phase. A 1.22-m. (4.0-ft.) column exhibited at 225° a retention time of 12.4 min. and 1300 theoretical plates for 6-demethylgriseofulvin.

RESULTS AND DISCUSSION

Time of Dosage Administration—The amount of metabolite excreted in the urine in a 3-day period after the administration of an experimental 250-mg. microsize griseofulvin product, A, is recorded in Table I. While the subject's diet was kept low in fats, the time of dosage administration was varied. The results of these experiments are also displayed in the form of a graph in Fig. 1.

The absorption as indicated by the amount of metabolite yield is a function of the time of drug administration. The absorption is lowest early in the morning after a night of fasting. In all the previous (1–12) studies of absorption of griseofulvin in man, the drug was administered early in the morning, *i.e.*, at breakfast time. The absorption reached a maximum when the drug was administered at noon. Griseofulvin administered at supper time or at midnight yielded intermediate absorption values.

The effect of time of griseofulvin administration has not previously been reported. It is not evident why there should be a maximum and minimum absorption when the drug is administered at noon and breakfast time, respectively. That this is not a spurious response but very real was revealed by the fact that the amount of metabolite excreted when the drug was again administered at noon and breakfast time after a lapse of a month was nearly identical to the initial values as shown in Table I.

Perhaps a circadian rhythm (26) involved in the drug absorption [such as intestinal motility or the 24-hr. bile cycle (27)] is responsible for this phenomenon.

High-Fat Meal—Using the experimental Product A, the effect of a high-fat meal at breakfast and supper time just prior to drug administration yielded the results shown in Table I. It should be noted that the high-fat meal followed by drug administration at breakfast increased drug absorption. There was no similar effect when the high-fat meal before drug administration was at supper time.

The previous (1, 2) reported effects of a high-fat meal were determined at breakfast time.

Gastric-emptying time (28) is affected by the fat content of the meal. Since griseofulvin is reported to be absorbed (29) mainly in the intestines, the effect of the high-fat meal would be equivalent to taking the drug at a later time.

Using the graph in Fig. 1, the metabolite yield when a high-fat breakfast was consumed by the subject, and assuming a linear relationship to be in existence between the maximum and minimum absorption points, one can calculate a delay of about 2.5 hr. A similar equivalent delay at supper time would cause no increase in absorption (Fig. 1).

Dose Level—A single dose or fractions of the regular size 500-mg. griseofulvin Product B was administered at noon. The metabolite yields are listed in Table II. The results of these experiments are also displayed in the form of a graph in Fig. 2 using the metabolite-to-griseofulvin dose ratio as an indicator. The urine pH and volumes are also presented and show no effect.

As the dose level of the griseofulvin increased 100-fold, the amount of metabolite excreted increased proportionately, as indicated by the constancy of the metabolite-to-griseofulvin ratio. It is apparent that the percentage of the drug absorbed is independent of the dose level. The constancy of this metabolite yield-to-dose ratio served as an internal calibration of absorption, even though the metabolite yield was low in this individual. In previous (3, 11, 12) studies in man, the logarithm of the dose and blood level have been linearly correlated. Atkinson *et al.* (3, 11) have used dose levels of 250 mg. to 1.0 g., while Grin and Denic (12) have used dose levels of approximately 250 mg. to 8.0 g. A plot of logarithm of dose administered and amount of metabolite excreted is shown in Fig. 3. There appears to be no linear relationship as with the blood level data.

These results cannot be compared with blood level data since no experimental data with low griseofulvin levels have been previously reported.

The absorption of drugs from the gastrointestinal tract are generally assumed to undergo two steps as shown in Eq. 1:

$$A_{\text{solid}} \rightarrow A_{\text{solution}} \rightarrow A_{\text{body}} \qquad \text{(Eq. 1)}$$

The first is the dissolution of the solid dosage and the second is the transport of the drug in solution in the gastrointestinal lumen through a lipoidal permeable membrane into the blood.

Although the extremely low water solubility of griseofulvin probably makes the dissolution step the rate-limiting step in the absorption process, one might have expected that the water solubility would not be self-limiting any longer at the lower doses and that at least the regular size griseofulvin would approach the microsize griseofulvin in its yield of metabolite (a metabolite-to-griseofulvin dose ratio of 0.10 *vs.* 0.21 from the time of dose administration study). Instead, the regular size griseofulvin acted as if it obeyed the cube root law of dissolution of Hixson and Crowell (30).

Hixson and Crowell derived an equation for the dissolution of a single particle in which the surface area was allowed to change with time while its shape factor (ratio of dimensions) remained constant. Niebergall and Goyan (31) extended the equation for use

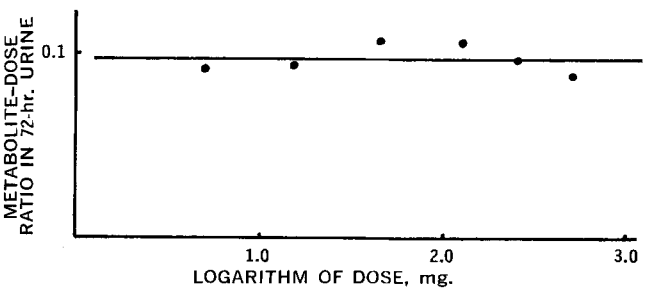

Figure 2—*Plot of metabolite-dose ratio* vs. *logarithm of dose for subject receiving at 12:00 noon a single dose or fraction of 500-mg. regular size griseofulvin Product B.*

[3] B.S.A. reagent (bistrimethylsilyl acetamide) is available from Mann Research, New York, N. Y.

[4] Gas-Chrom Q, Applied Science Laboratories, Inc., State College, PA 16801

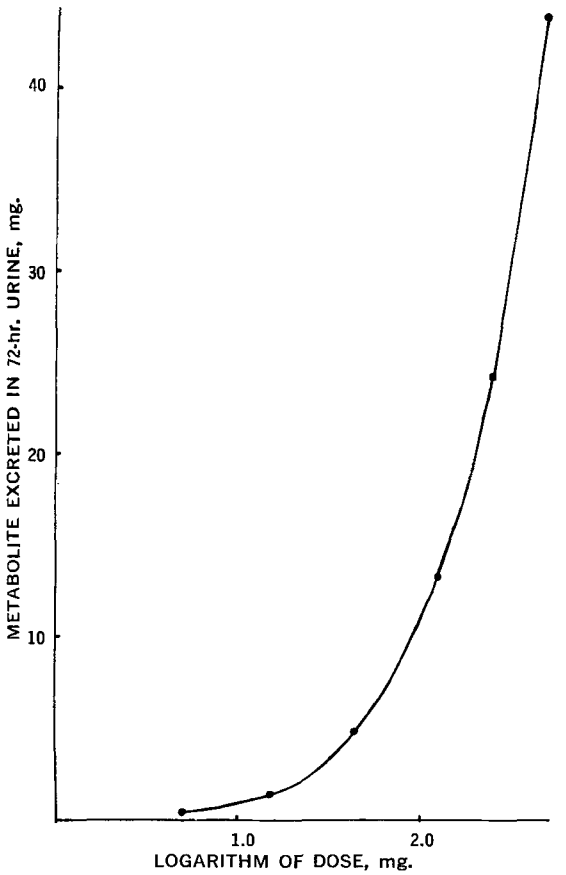

Figure 3—*Plot of metabolite yield* vs. *logarithm of dose for subject receiving at 12:00 noon a single dose or fraction of 500-mg. regular size griseofulvin Product B.*

in multiparticulate systems by assuming N equal-size particles. When the amount of solute needed to saturate a given volume of solvent is much greater than the concentration of material in solution, the integrated form becomes

$$N^{1/3}(w_0^{1/3} - w^{1/3}) = N^{1/3}(Kt) \qquad \text{(Eq. 2)}$$

where N is the number of particles, w_0 is the initial weight of each particle, w is the weight of the particle at time t, and K is the product of the intrinsic dissolution rate constant, solubility, density, and shape factor for the solute.

Therefore, no matter what the total number of particles is, the cube-root law indicates that all particles of identical size obey the fundamental relationship. A graphic presentation of this law using the fraction dissolved, $(w_0 - w)/w_0$, is shown in Fig. 4. A consequence of this relationship is that if the gastrointestinal transit time is constant, the percentage absorption of the drug will be independent of the amount of drug administered.

Particle Size—Table III contains the results of six commercially available 250-mg. griseofulvin products. Three products, C, D, and E, were manufactured with microsize griseofulvin; three products, F, G, and H, were produced with regular size griseofulvin. These drugs were administered at noon time.

The microsize griseofulvin products yielded about twice as much metabolite as the regular size griseofulvin products.

Although the results within each group appeared to differ from each other, these differences are not considered significant since they include formulation content and analytical variations. The mean amount of metabolite obtained from the use of the microsize griseofulvin products was found to be 50.7 mg., while the corresponding value from the regular size griseofulvin products was found to be 26.6 mg. This indicates that the regular size griseofulvin is equivalent to about one-half the microsize griseofulvin.

This equivalency was difficult to determine when blood level data were used because of the nonlinear response of blood level to dose administered. However, blood level data (3–7) did yield this information when dosages of microsize and regular size griseofulvin were compared at identical blood levels.

Table III—Urinary Excretion of Metabolite[a]

Product	Griseofulvin	Time after Drug Administered, days	Metabolite: In 24-hr. Urine, mg.	Metabolite: In 72-hr. Urine, mg.
C	Microsize	1.0	37.1	—
		2.0	12.3	—
		3.0	2.9	52.3
D	Microsize	1.0	30.4	—
		2.0	16.9	—
		3.0	4.1	51.4
E	Microsize	1.0	37.9	—
		2.0	9.4	—
		3.0	1.1	48.4
F	Regular	1.0	17.1	—
		2.0	7.4	—
		3.0	1.5	26.0
G	Regular	1.0	15.2	—
		2.0	8.3	—
		3.0	2.4	25.9
H	Regular	1.0	19.8	—
		2.0	6.7	—
		3.0	1.5	28.0

[a] By subject receiving a single dose of commercially available 250-mg. griseofulvin products administered at 12:00 noon.

Although the *Federal Register* (32) classifies griseofulvin into large particles (regular size) and microsize material, there isn't as large a difference between the material as their names imply. The specification of the specific surface area for the large particle griseofulvin is that it should not be less than 0.35 and not more than 0.65 m.²/g., while that for the microsize griseofulvin is that it should not be less than 1.3 and not more than 1.7 m.²/g. The ratio of the average of these limits is 1:3 with respect to surface area.

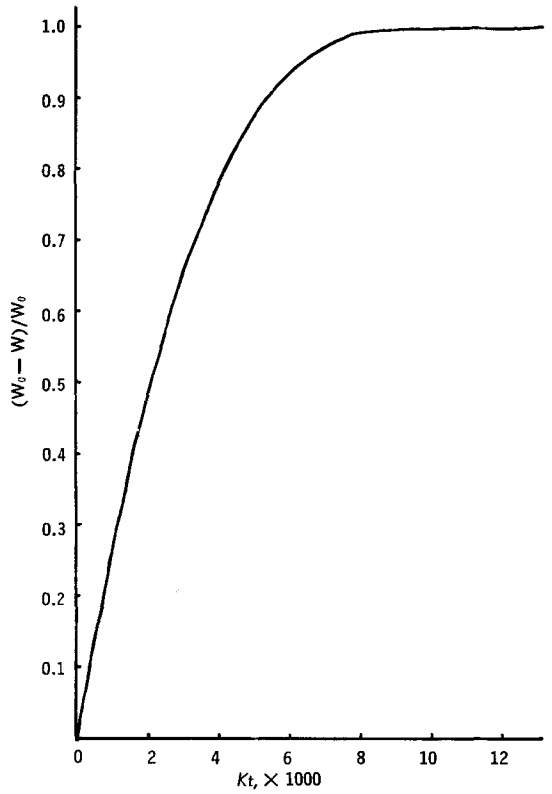

Figure 4—*Plot of the cube-root law of dissolution of Hixson and Crowell in terms of the fraction of solute,* $(W_0 - W)/W_0$, *dissolved* vs. Kt.

Table IV—Urinary Excretion of Metabolite[a]

Product	Dissolution Rates Time, min.	% Dissolved	Time after Drug Administered, days	Metabolite In 24-hr. Urine, mg.	Metabolite In 72-hr. Urine, mg.
I	30	88	1.0	18.2	—
	60	93	2.0	6.1	—
	120	95	3.0	2.0	26.3
J	30	60	1.0	13.8	—
	60	80	2.0	7.1	—
	120	91	3.0	1.9	23.1
K	30	34	1.0	15.9	—
	60	54	2.0	4.6	—
	120	76	3.0	1.4	21.9
L	30	19	1.0	18.9	—
	60	39	2.0	6.1	—
	120	59	3.0	1.7	26.7
M	30	8	1.0	18.4	—
	60	16	2.0	5.9	—
	120	32	3.0	2.1	26.4
N	30	2	1.0	8.8	—
	60	5	2.0	2.5	—
	120	9	3.0	0.8	12.1

[a] By subject receiving at 12:00 noon a single dose of 125 mg. of microsize griseofulvin products having different dissolution rates.

Matthews and Rhodes (33) reported surface area of 0.38 m.²/g. of regular size griseofulvin and 1.32 m.²/g. of microsize griseofulvin. The ratio of surface area of regular size to microsize griseofulvin in this case is 1:3.5.

An inspection of Fig. 4 indicates that the rate of dissolution is essentially constant up to the time when about 40% of the solute has dissolved. Therefore, the ratio of percentage absorptions of microsize and regular size griseofulvin can be calculated by the use of a form of the Noyes-Whitney (34) equation, Eq. 3 (where S is the surface area, V the volume of solvent, K_1 the rate constant, and w_s the weight of solute needed to saturate the solution), when the total absorption is below 40% and the amount of solute in solution is very much less than that required to saturate the solution.

$$V(dw/dt) = -K_1S(w_s) \qquad \text{(Eq. 3)}$$

$$\frac{[N_1(dw_1/dt)]}{[N_2(dw_2/dt)]} = \frac{N_1S_1}{N_2S_2} \qquad \text{(Eq. 4)}$$

Substituting the reported (33) surface areas of 1.32 and 0.38 m.²/g. of microsize and regular size griseofulvin, respectively, yields the following ratio:

$$(N_1S_1)/(N_2S_2) = 1.32/0.38 = 3.5 \qquad \text{(Eq. 5)}$$

The ratio of metabolite yield actually found was 2. This may be due to the fact that the griseofulvin has a hydrophobic surface which has not been completely converted to a hydrophilic surface by granulation (35, 36), and/or that there is significant absorption of air on its surface (37), and/or the particles do not regain their surface area on disintegration of the dosage formulation due to particle aggregation.

Of course, the model used may be incorrect because of the nonuniformity of particle size and/or departure from the concept of retention of constant shape factor during the course of the dissolution process.

Dissolution Rate—Comparison of the amount of metabolite excreted after the ingestion of six experimental microsize griseofulvin formulations, having different dissolution rates (Table IV), did not reveal any relationship between the logarithm of the dissolution rate (Fig. 5) and absorption (except for the slowest dissoluting Product N). These observations appear to differ from those of Katchen and Symchowicz (8, 9). They reported a positive correlation between the logarithm of dissolution rate (amount dissolved in 30 min.) in simulated intestinal fluid and the 24-hr. mean griseofulvin plasma level. However, a closer scrutiny of Katchen and Symchowicz's papers indicates that under the single-dosage regimen there is a large intersubject variation in the effect of dissolution rates. In fact, two (Subjects 4 and 8) out of their 18 subjects show

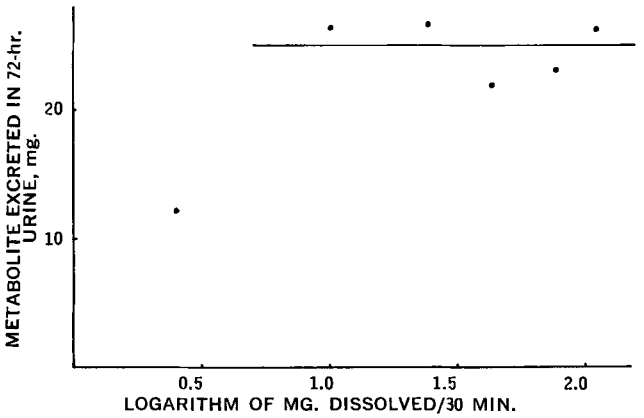

Figure 5—*Plot of metabolite yield* vs. *logarithm of dissolution rate (mg. dissolved/30 min.) for subject receiving at 12:00 noon a single dose of 125 mg. of microsize griseofulvin experimental products having different dissolution rates.*

no correlation between dissolution rate and drug absorption. The subject used in this investigation evidently falls into this minority group.

Recently there has been a flurry of investigations to increase the dissolution rate of griseofulvin and thus supposedly of increasing gastrointestinal absorption. Goldberg *et al.* (38) have reported a eutectic mixture with considerable solid solubility of griseofulvin in succinic acid having dissolution rates about seven times faster than the pure material. Mayersohn and Gibaldi (39) have published a new method of solid-state dispersion of griseofulvin in polyvinylpyrrolidone. The resultant product is reported as having greatly increased dissolution rates over micronized griseofulvin. A recent patent (40) reports that higher griseofulvin blood levels in the rat can be obtained by the use of an intimate mixture of griseofulvin and isogriseofulvin. The success of all these approaches has yet to be proven in man.

There are basically two types of drugs (41), those in which the sequence of drug concentration in the body and pharmacologic activity coincides and those in which there is a considerable delay. In the former case, rapid onset of pharmacological activity is desired; therefore, a dosage form which permits the drug to be

Table V—Urinary Excretion of Metabolite[a]

Irritating Diet Component	Time after Drug Administered, days	Metabolite In 24-hr. Urine, mg.	Metabolite In 72-hr. Urine, mg.
None	1.0	16.6	—
	2.0	6.6	—
	3.0	2.0	25.2
Red pepper	1.0	20.2	—
	2.0	5.9	—
	3.0	1.8	27.9
Milk	1.0	21.8	—
	2.0	3.8	—
	3.0	1.2	26.8
Pepperoni	1.0	20.6	—
	2.0	6.1	—
	3.0	2.0	28.7
Greasy fried food	1.0	24.2	—
	2.0	5.8	—
	3.0	1.5	31.5
Alcohol	1.0	20.2	—
	2.0	2.8	—
	3.0	4.7	27.7
Nuts	1.0	24.4	—
	2.0	6.7	—
	3.0	1.6	32.7
None	1.0	18.5	—
	2.0	5.0	—
	3.0	1.4	24.9

[a] By subject receiving at 12:00 noon a single dose of 125 mg. of microsize griseofulvin Product O followed by alterations in diet.

absorbed rapidly is required. These drugs are usually taken in a *single-dosage regimen* and may be considered to belong to the fast-action "aspirin" type drugs.

In the second case, where there is considerable delay in pharmacologic response, there is little advantage in rapid drug release from the dosage form as long as release is not delayed to the point of reducing drug absorption. The drugs in this category are usually taken in a *multiple-dosage regimen*. Griseofulvin fits into this category. The usually recommended treatment with griseofulvin is a multiple-dosage regimen lasting from 4 to 6 weeks.

Gastrointestinal Transit Time—The results of the attempt to vary the gastrointestinal transit time by the use of alterations in diet (red peppers, excess milk, pepperoncini, greasy fried foods, nuts, and alcohol) for the noon meal immediately after ingestion of 125-mg. microsize griseofulvin experimental Product O are shown in Table V. These variant components of the diet were used independently. Red peppers, excess milk, and pepperoni had a diarrheic effect; excess nuts had a constipating effect; the greasy fried food had a nauseating and a sense-of-fullness effect; and the alcohol had a relaxing effect on the subject.

Product O had a dissolution rate which was slightly faster than that for Product N whose absorption appeared to be impaired by its low-dissolution rate. The percentages dissolved in 30, 60, and 120 min. were 3, 6, and 13%, respectively.

Although these diets may have varied the transit time through the whole gastrointestinal tract, there is little evidence that the transit time through the absorption site was affected much (except in the cases of greasy fried food and nuts), as evidenced by the relatively constant metabolite yield which was comparable to that obtained when the subject had his normal meal. The absorption increased significantly when the irritating diet components were greasy fried foods and nuts.

SUMMARY AND CONCLUSIONS

The effects of six parameters on the physiological availability of orally administered griseofulvin formulations were studied by the use of urinary metabolite excretion data from a single subject. The first parameter, time of dosage administration, had an effect on griseofulvin absorption in the manner of a circadian rhythm, the absorption being least in the morning and the most at noon time. The second parameter, high-fat meal, appeared to be equivalent to a delay in time of dosage administration and subsequently had its effect dependent on the previous factor. The third parameter, dose level, indicated that the percentage absorption of drug was independent of the amount of drug administered. The fourth parameter, particle size, showed that microsize griseofulvin was absorbed about twice as much as regular size griseofulvin. The fifth parameter, dissolution rate of the griseofulvin formulation, had little effect on absorption of griseofulvin as long as the dissolution rate was above that for Product N. The sixth parameter, gastrointestinal transit time, could not be varied enough by dietary means (except in the cases of greasy fried foods and nuts) to affect significantly the residence time of the griseofulvin at the absorption sites.

Obviously, these effects cannot be considered representative of the general population. The urinary metabolite excretion data were in agreement with published blood level data estimation of physiological availability of griseofulvin in formulations for the effect of particle size, high-fat breakfast, and dissolution rate (minority subjects). No published blood level data exist for the time of dosage administration, gastrointestinal transit time, and low-level dose factors. It is inconvenient or impracticable to study these parameters by the blood level method.

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