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Intestinal Absorption of Griseofulvin from a Triolein Digestion Mixture in Rats

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Abstract □ The intestinal absorption rate of dissolved griseofulvin was determined from: (*a*) an aqueous phase, (*b*) an aqueous phase containing a micellar phase composed of taurodeoxycholate, monoolein, and oleic acid, and (*c*) an aqueous phase containing the micellar phase and emulsified triolein. The triolein digestion mixtures were recirculated through 20-cm segments of *in situ* rat jejunum. Lipid concentrations were maintained constant by infusing the lipids into the digestion mixture at the same rate as they disappeared. Griseofulvin distribution among the aqueous, micellar, and oil phases was determined by solubility and equilibrium dialysis experiments. Analysis with a linear kinetic model indicated that griseofulvin absorption from the micellar and oil phases was negligible compared to its absorption from the aqueous phase.

Keyphrases □ Griseofulvin—GI absorption from aqueous phase and aqueous phases containing triolein digestion mixture, rats □ Triolein digestion mixture—in aqueous phase containing griseofulvin, GI absorption in rats □ Absorption, GI—griseofulvin from aqueous phase and aqueous phases containing triolein digestion mixture, rats □ Lipids—triolein digestion mixture, GI absorption of griseofulvin, rats □ Antifungal agents—griseofulvin, GI absorption from aqueous phase and aqueous phases containing triolein digestion mixture, rats

The literature is replete with examples of the effects of lipids on the oral bioavailability of lipophilic, poorly water-soluble drugs. For example, griseofulvin bioavailability increased with the amount of lipid in the diet of humans (1) and was greater in the rat when coadministered with corn oil (2) or corn oil emulsion (3) than when administered in water. Sulfisoxazole acetyl had greater bioavailability after oral administration in a vegetable oil-in-water emulsion than in water in rats and humans (4) and, compared to water, triolein increased the extent of sulfisoxazole acetyl and dicumarol absorption in rats (5).

Examples of lipids that decreased the bioavailability of lipophilic substances also were reported. Compared to its administration in an aqueous vehicle, chlorophenothane (DDT) absorption appeared to increase when it was administered in corn or olive oil but decreased when given in mineral oil (6). Similarly, sucrose polyester, a nonabsorbable lipid, decreased the absorption of cholesterol from a triolein vehicle when it was included in the triolein as a mixed oil phase. The decrease was linear as the fraction of sucrose polyester in the vehicle increased up to 50% (7).

Consideration of the potential effects of lipids on the absorption of lipophilic substances requires an understanding of the behavior of lipids in the GI tract. Dietary lipids, mainly triglycerides of long chain fatty acids, are emulsified in the gut lumen and hydrolyzed by pancreatic lipase to 2-monoglycerides and fatty acids (8). The 2-monoglycerides may isomerize to 1-monoglycerides (9). The water-insoluble fatty acids and monoglycerides combine with bile salts to form "mixed micelles" (10); they move in this form to the intestinal epithelium where they are absorbed (11). As the fatty acids and monoglycerides are absorbed from the mixed micelle, the bile salts either remain in the lumen to solubilize and transport lipid digestion products (12) or are absorbed, primarily in the ileum by an active transport process (13), and returned to the bile.

Consequently, the lipid digestion mixture of the intestinal lumen can be viewed as a three-phase system: an oil phase consisting primarily of triglycerides; a micellar phase composed of bile salts, fatty acids, and monoglycerides; and an aqueous phase. In this system, lipophilic drugs would probably concentrate in the oil and micellar phases; for example, cholesterol partitions extensively into these phases (14). This study developed and tested a model that describes the absorption of a lipophilic drug from a lipid digestion mixture.

THEORETICAL

The distribution of a poorly water-soluble lipophilic drug among the three phases of a lipid digestion mixture and the potential absorption of drug from each phase is illustrated in Scheme I. Absorption of the drug from all three phases represents the general case; if the case of no absorption is excluded, seven subcases exist for absorption from a single phase or from a combination of phases. The passive transport of drug

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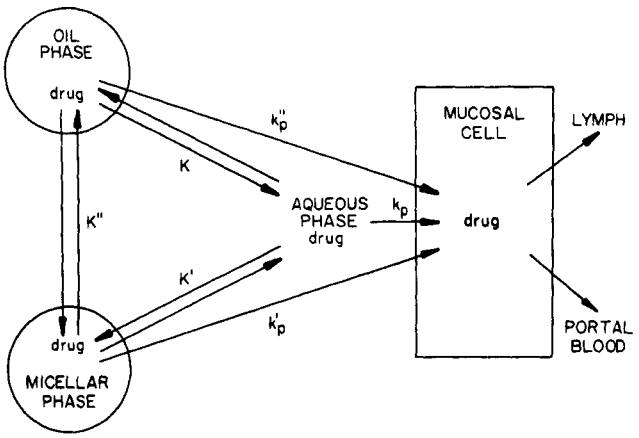

Scheme I—Distribution of a lipophilic drug among the three phases of a lipid digestion mixture with the potential for absorption from each phase. The K, K′, *and* K″ *are apparent partition coefficients for drug between oil and aqueous phases, micellar and aqueous phases, and micellar and oil phases, respectively;* k_p, k_p', *and* k_p'' *are clearance constants for absorption of the drug from the aqueous, micellar, and oil phases, respectively.*

molecules from a single phase across a biological membrane in the direction of a concentration gradient can be described by (15):

$$\frac{dX}{dt} = \frac{-D_m K_m A(C_M - C_S)}{h} \quad \text{(Eq. 1)}$$

where dX/dt is the disappearance rate of drug X from the intestinal lumen (mass/time), D_m is the diffusion coefficient of the drug in the membrane (length^2/time), K_m is the partition coefficient between the membrane and the phase transferring drug X to the membrane, A is the cross-sectional area of the membrane (length^2), and $(C_M - C_S)/h$ is the concentration gradient of the drug across the intestinal mucosa (mass/length^4) at any time.

If it is assumed that the drug is constantly carried from the serosal side of the membrane such that $C_M \gg C_S$ and that A and h are constant throughout the experiment, then:

$$\frac{dX}{dt} = -k_c C_M \quad \text{(Eq. 2)}$$

where k_c is equal to $D_m K_m (A/h)$ and is a clearance constant with the units of flow (length^3/time).

By analogy, the disappearance rate of a lipophilic drug from the intestinal lumen according to the model shown in Scheme I can be described by:

$$\frac{dX}{dt} = (-k_p C_w) - (k_p' C_m) - (k_p'' C_o) \quad \text{(Eq. 3)}$$

where C_w, C_m, and C_o are the drug concentrations in the aqueous, micellar, and oil phases, respectively; and k_p, k_p', and k_p'' are the respective clearance constants. Each clearance constant is a function of four parameters:

$$k_p^i = \frac{D_m K_m^i A^i}{h} \quad \text{(Eq. 4)}$$

Two parameters, D_m and h, are the same for all three clearance constants. The membrane–luminal phase distribution coefficient, K_m^i, and the area of absorbing surface in contact with each luminal phase, A^i, are different for each phase, and they largely determine the relative values of the clearance constants.

The drug concentration in the micellar and oil phases can be related to the aqueous phase concentration by the micellar–aqueous and oil–aqueous partition coefficients:

$$C_m = K' C_w \quad \text{(Eq. 5)}$$

$$C_o = K C_w \quad \text{(Eq. 6)}$$

Substitution of Eqs. 5 and 6 into Eq. 3 and combination of terms give:

$$\frac{dX}{dt} = -[k_p + (k_p' K') + (k_p'' K)] C_w \quad \text{(Eq. 7)}$$

Each phase may be expressed as a fraction, f, of the total volume, V_T:

$$f_w = \frac{V_w}{V_T} \quad \text{(Eq. 8)}$$

$$f_m = \frac{V_m}{V_T} \quad \text{(Eq. 9)}$$

$$f_o = \frac{V_o}{V_T} \quad \text{(Eq. 10)}$$

where V_w, V_m, and V_o are the volumes of the aqueous, micellar, and oil phases, respectively. The total drug concentration, C_T, is then:

$$C_T = (f_w C_w) + (f_m C_m) + (f_o C_o) \quad \text{(Eq. 11)}$$

Substitution of Eqs. 5 and 6 into Eq. 11 gives:

$$C_T = (f_w C_w) + (f_m K' C_w) + (f_o K C_w) \quad \text{(Eq. 12)}$$

and, by rearrangement:

$$C_w = \frac{C_T}{f_w + (f_m K') + (f_o K)} \quad \text{(Eq. 13)}$$

Substitution of Eq. 13 into Eq. 7 for C_w yields:

$$\frac{dX}{dt} = \frac{-[k_p + (k_p' K') + (k_p'' K)] C_T}{f_w + (f_m K') + (f_o K)} \quad \text{(Eq. 14)}$$

Finally, substitution of Eqs. 8–10 for the fractions f_w, f_m, and f_o in Eq. 14 and division by V_T give:

$$\frac{dC_T}{dt} = \frac{-[k_p + (k_p' K') + (k_p'' K)] C_T}{V_w + (V_m K') + (V_o K)} \quad \text{(Eq. 15)}$$

Equation 15 predicts that, in the general case of absorption from all three phases, the rate of decline of the concentration of a lipophilic drug in the intestinal lumen would follow apparent first-order kinetics. A plot of log C_T *versus* time would be linear, and an apparent first-order rate constant could be determined from the slope. It would be a function of the clearance constants, partition coefficients, and phase volumes:

$$k_{app} = \frac{k_p + (k_p' K') + (k_p'' K)}{V_w + (V_m K') + (V_o K)} \quad \text{(Eq. 16)}$$

Less complex models can be developed if absorption occurs from only one or two phases. Some evidence suggests that absorption of lipophilic substances occurs primarily from the micellar or aqueous phase and may not occur directly from the oil phase. For example, salicylamide was absorbed from the aqueous phase after release to that phase from the oil phase in the rat colon (16, 17). Another study indicated that vitamin A acetate was released from the micellar phase, adsorbed to the mucosa of the rat intestine, and then absorbed; oil droplets adsorbed to the mucosa interfered with this process (18). This study also reported that, unlike vitamin A acetate, phenylbutazone was absorbed primarily from the aqueous phase when the vehicle was a three-phase system of oil, micelles, and water. If a drug is not absorbed from a given phase, one subcase of the general model would be appropriate to describe its absorption.

The work described here involved perfusion of a segment of the *in situ* rat small intestine with triolein digestion mixtures containing griseofulvin. The apparent absorption rate constant, k_{app}, for griseofulvin was measured along with the partition coefficients K and K'. These experimentally determined values were used to estimate clearance constants for the intestinal absorption of griseofulvin from the aqueous, micellar, and oil phases.

EXPERIMENTAL

Materials—Oleic acid[1], monoolein[2], triolein[3], sodium taurodeoxycholate[4], and griseofulvin[4] were used as received. All other reagents and solvents were reagent grade.

Intestinal Absorption—Male Sprague–Dawley rats, 180–300 g, were fasted 12–20 hr and then anesthetized with urethan, 1.3 mg/g ip. They were prepared for study of the intestinal absorption of griseofulvin as described previously (19). The abdomen of each rat was opened by a midline incision; a small cannula[5] was inserted into the jejunum, 10 cm

[1] Merck and Co., Rahway, N.J.
[2] Eastman Organic Chemicals, Rochester, N.Y.
[3] Pfaltz and Bauer, Flushing, N.Y.
[4] Sigma Chemical Co., St. Louis, Mo.
[5] Intramedic polyethylene tubing, PE160, 1.14 mm i.d.

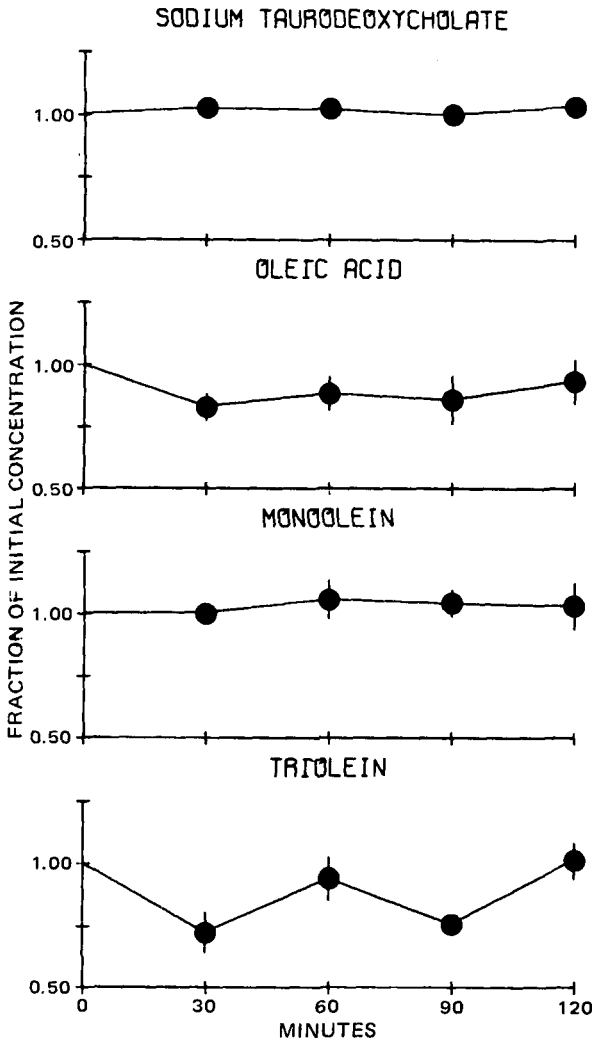

Figure 1—*Fractions of the initial concentration of sodium taurodeoxycholate (8 mM), oleic acid (6 mM), monoolein (3 mM), and triolein (2 g/100 ml) remaining in the intestinal solution as a function of time. Each point represents the mean from six experiments; bars indicate ±1* SE.

distal to the stomach, and tied in place with a silk suture. A second cannula[6] was placed 20 cm distal to the first cannula.

The intestinal segment was washed twice (20) with 10-ml volumes of irrigating solution (21) and then twice with 3-ml volumes of perfusion solution containing all components of the ensuing experiment.

The cephaled cannula was connected to the outlet of a perfusion pump[7] with polyethylene tubing[8], and the caudad cannula was connected to a well-stirred reservoir[9]. The external reservoir was filled with perfusion solution containing griseofulvin (23 μM) in 68 mM sodium phosphate buffer; the buffer, at pH 6.2, was made isotonic with 87 mM sodium chloride. The drug solution was recirculated at 6.5 ml/min through the intestinal segment for approximately 3 min before the zero-time sample was obtained from the reservoir. The experiments were continued for 60–120 min, and samples were withdrawn periodically from the reservoir and subsequently analyzed for griseofulvin.

Throughout the perfusion experiments, the rectal temperature of each rat was maintained at 37 ± 1° by warming the rat on a heating pad when necessary. The volume of the perfusate was held constant by intermittently adding buffer to the reservoir from a buret. The volume tended to decline, because samples were removed and water was absorbed by the intestine. After each experiment, the length of intestine perfused and the volume of buffer added to the reservoir were determined.

[6] Intramedic, PE320, 2.7 mm i.d.
[7] Peristaltic pump model 1201, Harvard Apparatus Co.
[8] Intramedic, PE60, 0.76 mm i.d.
[9] The reservoir was constructed from a 5-ml volumetric flask by adding four 1.5-cm pieces of 3-mm o.d. glass tubing at equally spaced distances around the body of the flask.

Table I—Infusion Rates that Maintain Constant Concentrations of Lipids in the Intestinal Perfusate

Lipid	Infusion Rate[a], μg/min	Intestinal Clearance[b], μl/min/cm
Monoolein, 3 mM	61.0	2.35
Oleic acid, 6 mM	96.4	2.34
Triolein, 2 g/100 ml	778.5	1.45
Sodium taurodeoxycholate, 8 mM	116.2	0.89

[a] Includes replacement of losses due to sampling. Samples of 0.3 ml were removed at 30-min intervals. [b] Calculated by infusion = clearance × concentration in the perfusate. Corrected for removal of samples.

When the lipids were included in the perfusates, they were monoolein (3 mM), oleic acid (6 mM), sodium taurodeoxycholate (8 mM), and triolein (2 g/100 ml). The lipids were infused[10] into the reservoir at a rate equal to their removal rate in samples and the absorption rate by the intestine. By using the infusion rates of the lipids that were determined empirically by preliminary experiments (Table I), it was possible to maintain the concentration of the lipids in the perfusates relatively constant (Fig. 1). The bile salt concentration was sufficient to solubilize the monoglyceride and free fatty acid (22).

Semilogarithmic plots of the fraction of initial griseofulvin concentration *versus* time gave straight lines (Fig. 2) when fitted by the method of least squares. The initial point was omitted from the fit to ensure stationary-state conditions. The absorption rate constants of griseofulvin were determined from the slopes of the fitted lines and were converted to clearance per centimeter of intestine by multiplying the rate constant by the volume of perfusate, correcting for drug removed as samples, and dividing by the length of the intestine.

Triolein–Aqueous Phase Partition Coefficient (K)—Centrifuge tubes were prepared to contain 20 ml of a pH 6.2 aqueous phase containing griseofulvin (23 μM), sodium phosphate buffer (68 mM), sodium taurodeoxycholate (1.2 mM), and sodium chloride (87 mM) and 5 ml of triolein in which griseofulvin (0.58 mM) was dissolved. The mixtures were allowed to equilibrate for 48 hr in an environmental shaker[11] operated at 200 rpm. The tubes were centrifuged[12] at 2500×g for 15 min; the phases were separated, and aliquots of both phases were analyzed for griseofulvin.

Micellar Phase–Aqueous Phase Partition Coefficient (K')—A

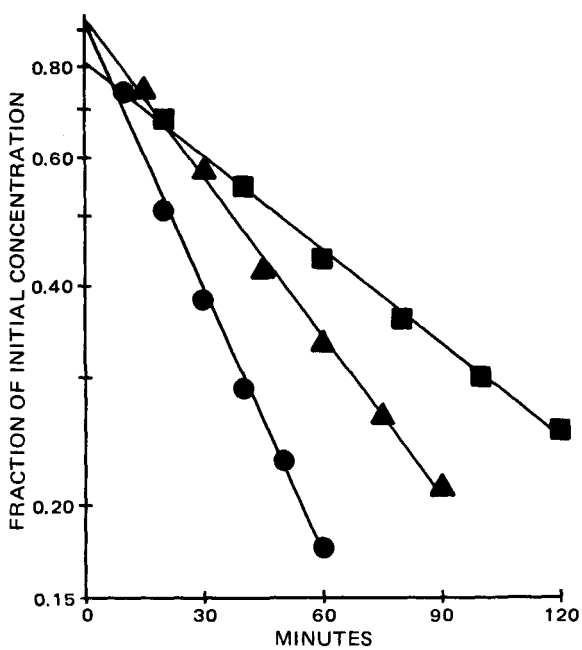

Figure 2—*Disappearance of griseofulvin from perfusate composed of aqueous phase (●), aqueous and micellar phases (▲), or aqueous, micellar, and oil phases (■). Each point represents the mean from six animals.*

[10] Syringe pump model 940, Harvard Apparatus Co.
[11] Model G24, New Brunswick Scientific Co., New Brunswick, N.J.
[12] Model CRU-5000, Damon/IEC Division, Needham Heights, Mass.

Table II—Apparent Partition Coefficients for Griseofulvin

Phases	Apparent Partition Coefficient
Triolein–aqueous[a] (K)	87.7 (9.0)[c]
Micellar[b]–aqueous (K')	65.5[d]
Triolein–micellar (K'')	1.3 (0.1)[c]

[a] Sodium taurodeoxycholate (1.2 mM) in sodium phosphate (68 mM) and sodium chloride (87 mM), pH 6.2. [b] "Mixed micelles" composed of monoolein, oleic acid, and sodium taurodeoxycholate above the CMC. [c] Mean from eight determinations; standard deviation in parentheses. [d] Each point in the line describing the solubility of griseofulvin as a function of the micellar phase fraction (Fig. 3) was the mean from eight determinations.

series of centrifuge tubes was prepared to contain griseofulvin in excess of its solubility and increasing amounts of the micellar phase in an aqueous solution of 68 mM sodium phosphate and 87 mM sodium chloride at pH 6.2. The tubes were equilibrated for 48 hr in an environmental shaker at 200 rpm. They were centrifuged at 2500×g for 15 min, and aliquots of the supernate were analyzed for griseofulvin.

The amount of the micellar phase in an aliquot was calculated by summing the amounts of monoolein, oleic acid, and sodium taurodeoxycholate in the aliquot and subtracting the amount of sodium taurodeoxycholate present as a true solution. The amount of sodium taurodeoxycholate as a true solution was calculated from the reported (23) critical micelle concentration (CMC) of 1.2 mM at 40° in isotonic sodium chloride. It was assumed that the CMC of sodium taurodeoxycholate was not appreciably affected by the inclusion of monoolein and oleic acid in the mixed micellar phase.

In each tube, the ratio of the amount of monoolein, oleic acid, and sodium taurodeoxycholate in the micellar phase was the same. For example, the intestinal perfusates contained 3 mM monoolein, 6 mM oleic acid, and 8 mM sodium taurodeoxycholate; the ratio in the micellar phase was 3:6:6.8. A solution that contained twice the concentration of the micellar phase would be 6 mM monoolein, 12 mM oleic acid, and 14.8 mM sodium taurodeoxycholate, and the ratio in the micellar phase would be 6:12:13.6.

The solubility of griseofulvin in a mixture containing micelles is the sum of the solubilities in the individual phases:

$$S = (S_w f_w) + (S_m f_m) \qquad \text{(Eq. 17)}$$

where S is the solubility in the mixture, S_w and S_m are the respective solubilities in the aqueous and micellar phases, and f_w and f_m are the fractions of the solution as the aqueous and micellar phases, respectively. With the relationships:

$$S_m = S_w K' \qquad \text{(Eq. 18)}$$

$$f_w + f_m = 1 \qquad \text{(Eq. 19)}$$

Equation 17 can be rearranged to:

$$\frac{S}{S_w} = (K' - 1) f_m + 1 \qquad \text{(Eq. 20)}$$

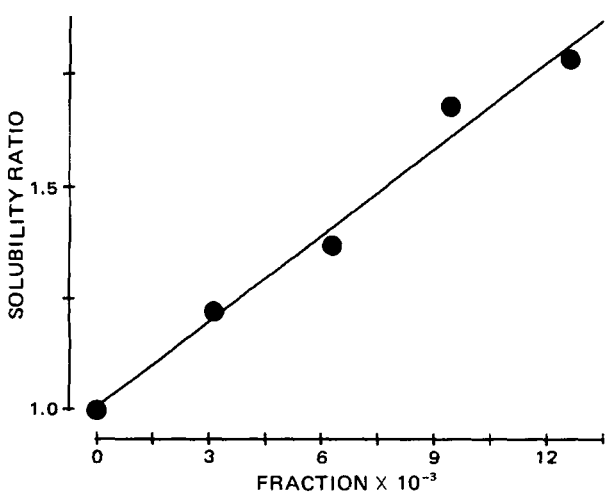

Figure 3—*Apparent solubility of griseofulvin in a mixture containing micelles as a function of the fraction (0–1.2%) of the mixture as the micellar phase. Apparent solubility is expressed as a ratio relative to the solubility of griseofulvin in the aqueous phase.*

Table III—Apparent Intestinal Clearance of Griseofulvin from a Perfusate Containing Various Phases of a Triolein Digestion Mixture[a]

Phase	Intestinal Clearance, µl/min/cm	Intestinal Clearance, % of Aqueous	Gut Length, cm	Water Flux, µl/min/cm
Aqueous[b]	9.72 (1.43)	100.0	19.8 (1.03)	0.46 (0.35)
Aqueous and micellar[c]	5.84 (1.09)[e]	60.1	20.1 (0.86)	0.54 (0.25)
Aqueous, micellar, and oil[d]	3.14 (0.70)[e,f]	32.3	19.9 (0.86)	0.21 (0.21)

[a] Mean from six experiments; standard deviation in parentheses. [b] Sodium taurodeoxycholate (1.2 mM) in sodium phosphate (68 mM) and sodium chloride (87 mM), pH 6.2. [c] Monoolein (3 mM), oleic acid (6 mM), and sodium taurodeoxycholate (8 mM) in sodium phosphate (68 mM) and sodium chloride (87 mM), pH 6.2. [d] Emulsified triolein (2 g/100 ml), monoolein (3 mM), oleic acid (6 mM), and sodium taurodeoxycholate (8 mM) in sodium phosphate. [e] Significantly different from the mean griseofulvin clearance from the aqueous perfusate alone ($p < 0.001$). [f] Significantly different from the mean griseofulvin clearance from perfusate containing the micellar phase ($p < 0.001$).

A plot of the solubility ratio, S/S_w, *versus* the micellar fraction of the mixture yielded a straight line (Fig. 3). The slope of the line gave the micellar phase–aqueous phase partition coefficient.

Triolein–Micellar Phase Partition Coefficient (K'')—A diffusion cell[13] was assembled with a cellulose dialysis membrane and filled with 5 ml of micellar solution and excess griseofulvin on one side (suspension compartment). The other side (emulsion compartment) contained 5 ml of micellar solution with 2% triolein. The membrane allowed passage of griseofulvin but not of triolein. At equilibrium, assay of the contents of the suspension compartment showed that triolein had not crossed the dialysis membrane.

The diffusion cell was equilibrated at 37° in an environmental incubator shaker for 48 hr at 200 rpm. The contents of the suspension compartment were centrifuged at 2500×g for 15 min. Aliquots from both compartments were analyzed for griseofulvin. The griseofulvin solubility attributable to triolein was determined as the difference between the concentration of dissolved griseofulvin in the two compartments. The griseofulvin concentration in triolein divided by the micellar phase concentration (calculated from the total concentration in the suspension compartment and the micellar phase–aqueous phase partition coefficient) gave the triolein–micellar phase partition coefficient.

Analytical Methods—Griseofulvin was determined in the aqueous samples by a spectrofluorometric[14] method (3, 24), which involved extraction of the drug with freshly distilled ether, evaporation of an aliquot of ether to dryness, and reconstitution of the residue with methanol–water (1:1). The methanol–water mixture was washed with hexane, and the fluorescence was determined at activation and emission wavelengths of 298 and 420 nm (uncorrected), respectively. The samples were quenched with 4 drops of concentrated sulfuric acid, and the background fluorescence was determined. The sample fluorescence minus the background fluorescence gave the griseofulvin fluorescence.

Monoolein, oleic acid, and triolein were determined in the rat gut perfusate by a slightly modified spectrophotometric[15] method (25). The lipids were extracted with chloroform and spotted on thin-layer plates[16] 0.25 mm thick. The plates were developed with petroleum ether (bp 30–60°)–ether–methanol–acetic acid (90:7:4:0.5). The lipid spots were visualized with iodine vapor, scraped into tubes, and carbonized in concentrated sulfuric acid at 200° for 45 min. The absorbance of the sulfuric acid was measured at 375 nm.

Sodium taurodeoxycholate was estimated in intestinal perfusate using a crude preparation of the enzyme 3α-hydroxysteroid dehydrogenase (EC 1.1.1.50), obtained from *Pseudomonas testosteroni* (26, 27). The reaction is NAD coupled, and the increase in absorbance at 340 nm was followed spectrophotometrically to completion. The change in absorbance was linearly related to the concentration of sodium taurodeoxycholate over the 0–2 mM range.

[13] Plexiglas; each compartment had a capacity of 10 ml which was exposed to 10 cm² of membrane.

[14] Aminco-Bowman spectrophotofluorometer, American Instrument Co., Silver Spring, Md.

[15] Beckman DU (Beckman Instruments, Fullerton, Calif.) with a Gilford model 2000 multiple-sample recorder (Gilford Instrument Laboratories, Oberlin, Ohio).

[16] Analtech, Newark, Del.

Table IV—Individual Clearance Constants for the Intestinal Absorption of Griseofulvin from Triolein Digestion Mixture

Phase	Clearance, μl/min/cm	Percent of Aqueous Phase
Aqueous	9.72	100
Micellar	-2.31×10^{-2}	−0.24
Oil	1.89×10^{-2}	0.19

RESULTS AND DISCUSSION

Griseofulvin has a slightly greater affinity for triolein than for the micellar phase (Table II). The triolein–micellar partition coefficient (K'') was 1.3 whether measured directly by dialysis or calculated as the ratio of K to K'.

The disappearance of griseofulvin from lipid digestion mixtures composed of one, two, and three phases followed apparent first-order kinetics as predicted by Eq. 15 (Fig. 2). The presence of the micellar and triolein phases reduced significantly the overall clearance of griseofulvin (Table III). The reduced clearance could not be attributed to differences in the length of intestine perfused nor to differences in the rate of water absorption from the perfusate (Table III).

The clearance constants in Table III and the partition coefficients in Table II were used with Eq. 16 to estimate the individual clearance constants for absorption from the micellar and oil phases. Since the volume of the micellar phase was not known, it was approximated by its weight. These calculations suggest that the clearance of griseofulvin from the micellar and oil phases was negligible compared to its clearance from the aqueous phase (Table IV).

For the experimental system studied, the individual clearance constants reflect the area of absorbing surface that each phase contacts and the partitioning of griseofulvin between the absorbing membrane and each phase (Eq. 4). The irregular nature of the surface, covered with villi and microvilli, makes an estimation of the effective area of the surface impossible. Furthermore, it is not possible to estimate the areas of surface contacted by the micellar and oil phases. Thus, whether the lack of absorption from the micellar and oil phases is due to negligible phase and membrane contact or to a small membrane–phase distribution coefficient is not known.

If it is arbitrarily assumed that the area each phase contacts is proportional to its phase volume ratio, the clearances from the micellar and oil phases can be calculated to be −3.70 and 0.95 μl/min/cm, respectively. These clearance values would be observed if the entire perfusate were composed solely of micelles or of oil. The large negative clearance from the micellar phase is, of course, unrealistic. It may be an artifact that results from one or more components of the micellar phase inhibiting the clearance of griseofulvin from the aqueous phase.

In summary, the oral bioavailability of griseofulvin increases when it is administered with triglycerides (1–3). This study shows that the absorption of dissolved griseofulvin by the intestine is slowed in the presence of triglyceride digestion products. The drug concentrates in the micellar and oil phases, and there is negligible absorption from these phases. Thus, the ability of triglycerides to enhance the oral absorption of griseofulvin apparently is due solely to enhanced dissolution (28) and not to enhanced absorption of dissolved drug.

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