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RESEARCH ARTICLES

Effects of Lipids on Bioavailability of Sulfisoxazole Acetyl, Dicumarol, and Griseofulvin in Rats

DUANE C. BLOEDOW * and WILLIAM L. HAYTON *

Abstract □ The effects of hexadecane, oleyl alcohol, polysorbate 80, trioctanoin, and triolein on the bioavailability of sulfisoxazole N^1-acetyl, dicumarol, and griseofulvin were investigated. Compared to administration of the drugs in water, the rate of absorption of the drugs was either decreased or not changed by the lipids. The extent of absorption of sulfisoxazole acetyl and dicumarol was significantly increased by polysorbate 80 and triolein and not affected by hexadecane or oleyl alcohol. Trioctanoin increased the extent of absorption of sulfisoxazole acetyl but had no effect on the absorption of dicumarol. Compared to the aqueous vehicle, the extent of absorption of griseofulvin was decreased by hexadecane, oleyl alcohol, and triolein, increased by polysorbate 80, and not affected by trioctanoin. The extent of absorption of sulfisoxazole acetyl was not affected by the amount of triolein in which it was administered nor by emulsification of triolein prior to administration.

Keyphrases □ Bioavailability—sulfisoxazole acetyl, dicumarol, griseofulvin, effect of lipids, rats □ Sulfisoxazole acetyl—effect of lipids on bioavailability, rats □ Dicumarol—effect of lipids on bioavailability, rats □ Griseofulvin—effect of lipids on bioavailability, rats □ Lipids—effect on bioavailability of sulfisoxazole acetyl, dicumarol, and griseofulvin, rats

The bioavailability of orally administered drugs having low aqueous solubility may be incomplete due primarily to slow dissolution in the lumen of the GI tract. Several reports indicate that the bioavailability of poorly water-soluble drugs, particularly drugs that are also lipophilic, can be improved by coadministration of a lipid, which apparently increases the rate of dissolution of such drugs. For example, the bioavailability of indoxole in humans is increased following oral administration of the drug in a lipid emulsion compared to administration as an aqueous suspension (1). Similar results in rats were reported following the oral administration of indoxole dissolved or suspended in cottonseed oil or dissolved in polysorbate 80 (2).

The bioavailability of griseofulvin in humans increases with the amount of lipid in the diet (3) and is greater following oral administration with corn oil (4) or corn oil emulsion (5) than with water. The therapeutic effect of N^1-acyl derivatives of sulfanilamide in mice is increased following oral administration of suspensions of the drugs in olive oil compared to administration in water (6). In rats and humans, the bioavailability of sulfisoxazole N^1-acetyl is greater following oral administration of the drug in a vegetable oil-in-water emulsion than it is when administered in water (7).

While bioavailability may be improved by lipids, there are also examples of lipids decreasing the bioavailability of lipophilic substances. The absorption of chlorophenothane (DDT), as reflected by LD_{50} values, is increased when it is administered in corn oil or olive oil but decreased when given in mineral oil compared to its administration in an aqueous vehicle (8). And ingestion of potato chips containing small amounts of methyl polysiloxane, a lipid-like agent that enhances crispness, apparently significantly reduced the absorption of warfarin and phenindione in patients taking these drugs (9).

The purpose of this study was to examine physicochemical and physiological properties of lipids that may alter the bioavailability of lipophilic, poorly water-soluble drugs. The drugs used and their aqueous solubilities in milligrams per liter were: sulfisoxazole acetyl, 70 (10); dicumarol, 0.5 at low pH (11); and griseofulvin, 8.8 (12). The bioavailabilities of the drugs were determined following their oral administration in selected lipid vehicles and water.

The lipid vehicles (Table I) were selected on the basis of their diverse physicochemical and physiological properties. Because the environment of the GI lumen is aqueous, the primary physicochemical prop-

Table I—Lipids Used in This Investigation

Lipid	Characteristics
Hexadecane	Nonpolar, nondigestible
Oleyl alcohol	Polar, Class I, nondigestible
Polysorbate 80	Polar, Class III, digestible[a]
Trioctanoin	Polar, Class I, digestible
Triolein	Polar, Class I, digestible; forms chylomicrons

[a] Following hydrolysis in the gut, the oleic acid moiety is absorbed and the polyoxyethylene sorbitan portion is eliminated in the feces (33).

erty considered was polarity as it relates to the interaction of lipids with water (13). Thus, lipids are classified as *nonpolar* (no interaction with water) or *polar*. Polar lipids interact with water and, depending on the interaction, are placed in one of three groups: Class I, spread on water to form a stable monolayer; Class II, form a stable monolayer on water and water dissolves in them; or Class III, form no stable monolayer but dissolve in water and form micelles. The physiological properties considered in selecting the lipids are digestibility and, for digestible lipids, chylomicron formation.

EXPERIMENTAL

Materials—Sulfisoxazole N^1-acetyl[1] (mp 192°), dicumarol[2] (mp 260°), and griseofulvin[3] (mp 222°) were used as received. Dicumarol-^{14}C-methylene[4] was mixed with unlabeled dicumarol, and the radiochemical purity was determined by TLC on silica gel G developed with 1-propanol–ammonium hydroxide (7:3). Dicumarol was visualized with UV light, consecutive 1-cm^2 scrapings of silica gel were removed from the chromatogram, and the radioactivity in each scraping was determined by liquid scintillation counting[5]. Dicumarol and radioactivity moved as a single spot, with 97% of the radioactivity associated with the visualized spot.

Hexadecane[6], oleyl alcohol[6], polysorbate 80[7], polyethylene glycol 400 USP[8], trioctanoin[9], triolein[2], and methylcellulose 4000[8] were used as received. Anhydrous analytical reagent grade ether[10] was distilled immediately prior to use.

Solubility—A sufficient quantity of sulfisoxazole acetyl, dicumarol, or griseofulvin was placed in each of a series of 10-ml glass ampuls to assure saturation of the solvent with the drug. Approximately 5 ml of lipid was added to each ampul, which was sealed by flame. The ampuls were rotated for 72 hr in a 37 ± 0.5° water bath and then placed upright for several hours to allow suspended particles to settle. A sample of the supernate was removed and filtered[11], and the concentration of the drug was determined. Preliminary experiments showed that the lipids were saturated with drug prior to 72 hr.

Bioavailability—Male Sprague–Dawley rats[12], 225–350 g, were fasted 16 hr prior to and 12 hr following drug administration. Access to water was allowed *ad libitum* throughout the experiments, and all studies were initiated at the same time of day to eliminate the effects of circadian variation.

Sulfisoxazole acetyl (100 mg/kg), dicumarol (10 mg/kg), and griseofulvin (50 mg/kg) were administered orally as suspensions in 5 ml/kg of each lipid and 0.5% aqueous methylcellulose. The animals were anesthetized lightly with ether to facilitate drug administration. The particle-size distributions of the drugs, determined from scanning electron micrographs of the powders (14), were log normal. The geometric mean diameter and standard deviation in micrometers were: sulfisoxazole acetyl, 1.8 (2.3); dicumarol, 1.3 (2.5); and griseofulvin, 0.43 (1.5).

Table II—Percent of Drug Dissolved in the Suspension Dosage Forms

Vehicle	Percent Dissolved[a]		
	Sulfisoxazole Acetyl	Dicumarol	Griseofulvin
Hexadecane	<0.01	1.4	<0.01
Oleyl alcohol	1.7	12	3.6
Polysorbate 80	100[b]	100[b]	94
Trioctanoin	6.8	19	13
Triolein	3.1	13	3.4

[a] Calculated from solubilities. [b] Solutions.

All suspensions were agitated at room temperature for 72 hr before administration to ensure that the vehicles were saturated with drug. The amount of drug dissolved in the suspensions is shown in Table II. Dicumarol was also administered in solution at a dose of 1.0 mg/kg in all vehicles except hexadecane, where the dose was 0.1 mg/kg due to low solubility. The specific activity of ^{14}C-dicumarol in all solutions and suspensions was approximately 1 × 10^6 dpm/ml.

The drugs were administered orally with a 2- or 5-ml syringe attached to a No. 8 French rubber catheter having a blunt tip and a hole in the side 5 mm from the tip. Each syringe and catheter was calibrated to determine the amount of drug delivered to the stomach of each animal. Solutions of the drugs in polyethylene glycol 400 containing 10% water were administered intravenously *via* the dorsal penile vein. The dose of drug was the same as that given orally, and the volume injected was 2–3 ml/kg.

Following the administration of sulfisoxazole acetyl and dicumarol, the animals were placed in individual metabolism cages[13]. Urine was collected at 12 and 24 hr and at 24-hr intervals until drug was no longer excreted. All urine samples were frozen and stored at −20° until assayed. After administration of griseofulvin, each animal was placed in a separate cage and 0.4-ml samples of blood were collected from the tail into heparinized micro blood collecting tubes (15).

Blood was collected at approximately 1, 2, 4, 6, 8, and 12 hr postadministration, except for the oleyl alcohol vehicle where the times of collection were 2, 4, 6, 8, 11, and 14 hr. Blood samples were obtained at 24 hr by cardiac puncture. Plasma was separated from the blood samples and stored frozen in 10-ml centrifuge tubes with screw caps[14] until assayed for griseofulvin.

The bioavailability of dicumarol was based on the urinary excretion of radioactivity following administration of ^{14}C-dicumarol. Since dicumarol and its metabolites were measured together, bioavailability refers to the rate and extent of absorption of dicumarol, provided the drug is not altered in the lumen of the GI tract. The bioavailabilities of sulfisoxazole acetyl and griseofulvin were based on urinary excretion and blood plasma concentration of intact drug and, therefore, reflect the relative amount of drug that reached the general circulation.

Analytical Methods—In the solubility studies, sulfisoxazole acetyl, dicumarol, and griseofulvin were determined by UV spectrophotometry[15] after dilution with chloroform. The appropriate lipid containing no drug was diluted with chloroform, and its absorbance was used for the blank. A colorimetric method (16) was used to determine free (non-N^4-conjugated) sulfisoxazole in urine samples. No sulfisoxazole acetyl was detected on thin-layer chromatograms of the 0–96-hr urine collected following oral or intravenous administration of 100 mg/kg of sulfisoxazole acetyl.

[1] Donated by Hoffmann-La Roche, Nutley, N.J.
[2] Pfaltz and Bauer, Flushing, N.Y.
[3] Sigma Chemical Co., St. Louis, Mo.
[4] Activity of 8.4 mCi/mmole, New England Nuclear, Boston, Mass.
[5] Packard Tri-Carb model 3320, Packard Instrument Co., Downers Grove, Ill.
[6] Eastman Organic Chemicals, Rochester, N.Y.
[7] Atlas Chemical Industries, Wilmington, Del.
[8] Ruger Chemical Co., Irvington, N.J.
[9] J. T. Baker, Phillipsburg, N.J.
[10] Mallinckrodt Chemical Works, St. Louis, Mo.
[11] Millipore filter, type UG, 0.25-μm pore size, Millipore Corp., Bedford, Mass.
[12] Hilltop Lab Animals, Chatsworth, Calif.
[13] Model HB-11M with HB-66 food tunnel, Hoeltge, Inc., Cincinnati, Ohio.
[14] Lined with Teflon.
[15] Beckman DU, Beckman Instruments, Inc., Fullerton, Calif., with Gilford model 2000 multiple sample absorbance recorder, Gilford Instrument Laboratories, Oberlin, Ohio.

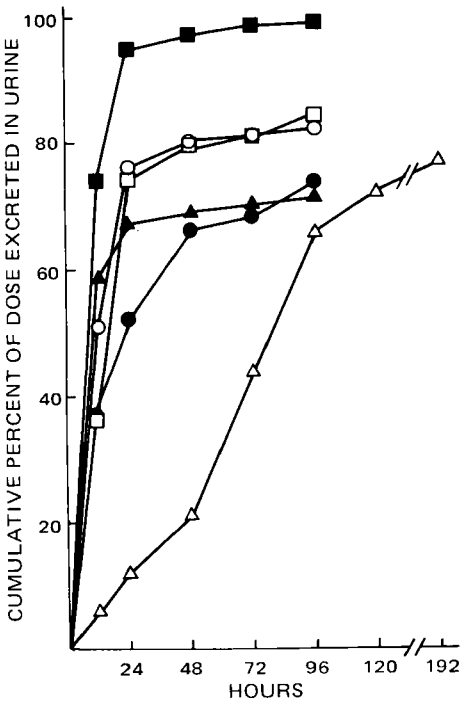

Figure 1—*Cumulative urinary excretion of free sulfisoxazole (expressed as a percent of the administered dose on a molar basis) following oral administration of 100 mg/kg of sulfisoxazole acetyl suspended in lipid vehicles and water. Each point represents the mean of six animals. Key: ●, hexadecane; △, oleyl alcohol; ■, polysorbate 80 (solution); □, trioctanoin; ○, triolein; and ▲, water (with 0.5% methylcellulose).*

Chromatograms were prepared by extracting the urine, diluted to 500 ml and adjusted to pH 5, with chloroform, reducing the volume of the extract by evaporation, and spotting the concentrated extract on silica gel-coated plates. The chromatograms were developed with chloroform–methanol (95:5) and visualized with *p*-dimethylaminobenzaldehyde (17). When using this method, less than 1% of the administered dose could be detected. These results agree with other reports indicating that sulfisoxazole acetyl is not present in the urine following its oral administration (18, 19).

The amounts of sulfisoxazole determined in the urine were converted on a molar basis to sulfisoxazole acetyl for comparison with the amount of sulfisoxazole acetyl administered. The mean assay blank, determined for each animal from urine collected for 24 hr prior to drug administration, was equivalent to 0.86 mg/24 hr of apparent sulfisoxazole acetyl. The oral administration of 5.0 ml/kg of the vehicles without drug did not affect the assay blank. In addition, oral administration of the vehicles did not affect the urinary excretion kinetics of sulfisoxazole following the simultaneous intravenous administration of 100 mg/kg of sulfisoxazole acetyl (20).

Table III—Plasma Concentration–Time Parameters[a] following Oral Administration of 50 mg/kg of Griseofulvin in Various Vehicles

Vehicle	Peak Plasma Concentration, μg/ml	t_{max}[b], min	Area under Plasma Concentration–Time Curve[c], μg hr/ml
Water (with 0.5% methylcellulose)	0.95 ± 0.60	281 ± 64	9.43 ± 4.61
Oleyl alcohol	0.36 ± 0.17[d]	576 ± 97[d]	3.16 ± 1.06[d]
Triolein	0.33 ± 0.04[d]	269 ± 83	3.36 ± 1.38[d]
Hexadecane	0.46 ± 0.15	317 ± 166	4.50 ± 0.92[d]
Trioctanoin	0.42 ± 0.16	277 ± 101	5.11 ± 1.55
Polysorbate 80	1.53 ± 0.28	422 ± 96[d]	15.77 ± 3.34[d]

[a] Average of six animals ± *SD* for each vehicle. [b] Time of occurrence of peak plasma concentration. [c] Determined by using Simpson's method (34). [d] Significantly different from water as determined by the Student *t* test ($p < 0.05$).

Table IV—Bioavailability of Orally Administered Sulfisoxazole Acetyl, Dicumarol, and Griseofulvin in Various Lipids and Water

Vehicle	Bioavailability, %			
	Sulfisoxazole Acetyl[a] Suspension (100 mg/kg)	Dicumarol[b]		Griseofulvin[c] Suspension (50 mg/kg)
		Solution (1 mg/kg)	Suspension (10 mg/kg)	
Hexadecane	78	114	102	6
Oleyl alcohol	81	105	115	4
Polysorbate 80	104	157	121	19
Trioctanoin	90	112	90	6
Triolein	87	125	111	4
Water[d]	77	105	95	12

[a] Bioavailability determined by comparing cumulative urinary recovery of free drug at 96 hr (for oleyl alcohol, 192 hr) following oral administration with that following intravenous administration. [b] Bioavailability determined by comparing cumulative urinary recovery of radioactivity at 288 hr following oral administration of ^{14}C-dicumarol with that following intravenous administration. [c] Bioavailability determined by comparing area under the plasma concentration–time curve following oral administration with that following intravenous administration. [d] Water with 0.5% methylcellulose for all suspensions and 0.01 *M* pH 8 tromethamine buffer for the dicumarol solution.

Radioactivity, representing dicumarol and its metabolites, in urine was determined by liquid scintillation counting[5]. Urine samples of 0.5–2.0 ml were mixed with 15 ml of scintillation fluid[16]. The efficiency of the counting system was approximately 80%; quench corrections were made for each sample, using ^{14}C-toluene as an internal standard. Griseofulvin was determined in blood plasma samples by a modification (5) of a fluorometric[17] procedure (21).

RESULTS AND DISCUSSION

The effects of the lipids on the absorption of sulfisoxazole acetyl, dicumarol, and griseofulvin are apparent in the urinary excretion and plasma concentration–time data in Figs. 1–4 and Table III. The effects of the lipids on the bioavailabilities of the drugs relative to a standard administered intravenously are shown in Table IV; changes induced by the lipids in the rate and extent of absorption of the drugs with reference to an aqueous vehicle are shown in Tables V and VI.

Absorption Rate—Compared to the aqueous vehicle, the lipids either reduced or did not change the rate of absorption of the drugs (Table V). The digestible lipids polysorbate 80, trioctanoin, and triolein generally had no detectable effect on absorption rate while hexadecane and oleyl alcohol tended to reduce the rate of absorption of the drugs.

To measure the rate of drug release from the lipids, suspensions of the drugs in the lipids were added to a 4-liter bottle, 15-cm diameter by 25 cm, containing 1 liter of water. The bottle was rotated horizontally around the long axis at 1 rpm at room temperature, and the concentration of drug in filtered samples of the aqueous phase was measured periodically. In all cases except polysorbate 80, the solid drug remained in the lipid phase, which floated as a lens on the surface of the aqueous phase. The results for all drugs were similar to those obtained for griseofulvin (Fig. 5).

The relatively slow release of drug from oleyl alcohol *in vitro* (Fig. 5) suggests that this lipid reduces the absorption rate of the drugs *in vivo* by reducing the rate of drug release to the fluids of the GI tract. However, in addition to slowing the rate of release of the drugs, oleyl alcohol also appears to reduce markedly GI motility. For example, the absorption of sulfisoxazole acetyl appears to continue for 2–3 days following its administration in oleyl alcohol (Fig. 1); this period is well beyond the normal GI transit time of

[16] PCS Solubilizer, Amersham/Searle Corp., Arlington Heights, Ill.
[17] Aminco-Bowman spectrofluorometer, American Instrument Co., Silver Spring, Md.

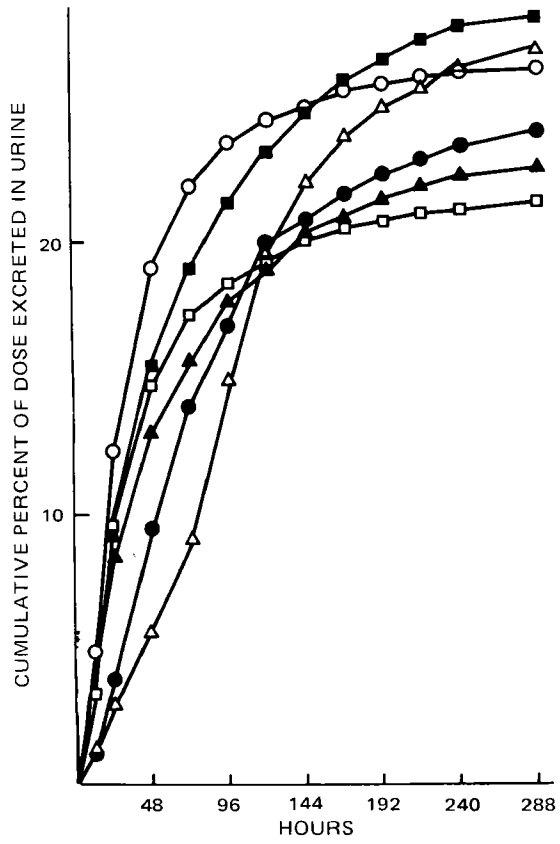

Figure 2—*Cumulative urinary excretion of radioactivity (expressed as a percent of the administered dose) following oral administration of 10 mg/kg of ^{14}C-dicumarol suspended in lipid vehicles and water. Each point represents the mean of six animals. Key: see Fig. 1.*

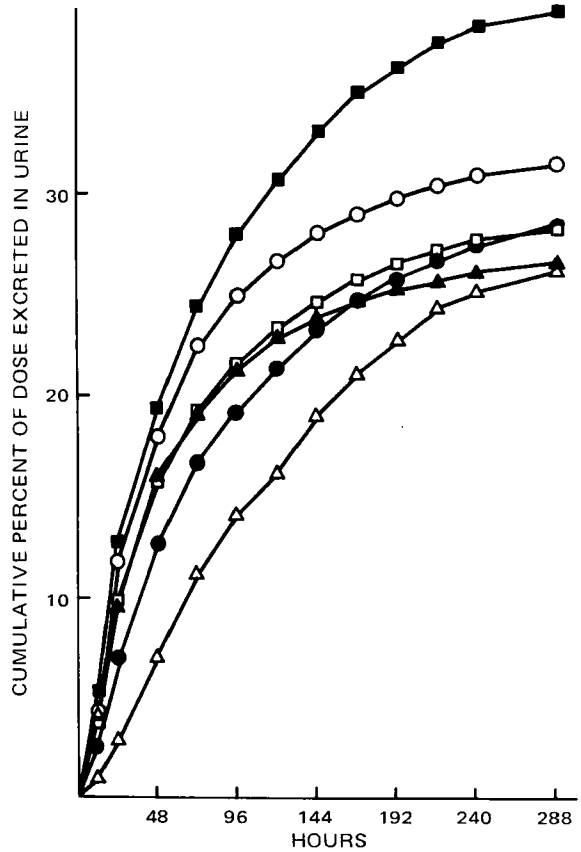

Figure 3—*Cumulative urinary excretion of radioactivity (expressed as a percent of the administered dose) following oral administration of 1 mg/kg (0.1 mg/kg for hexadecane) of ^{14}C-dicumarol dissolved in lipid vehicles and 0.01 M pH 8 aqueous tromethamine buffer. Each point represents the mean of six animals. Key: see Fig. 1.*

16–24 hr in the rat (22). Thus, the rate of gastric emptying, an important determinant of the rate of absorption of many drugs (23), may be slowed by oleyl alcohol.

Since hexadecane does not appear to slow significantly the rate of drug release *in vitro*, its effect *in vivo* may also be to reduce the rate of gastric emptying. Although the digestible lipids are also known inhibitors of gastric emptying, they apparently did not slow emptying enough to reduce significantly the rate of drug absorption in this study.

A statistically significant ($p < 0.05$) correlation was found between the rate of release of griseofulvin *in vitro* and both its bioavailability (Fig. 6) and peak plasma concentration (not shown). Such correlations indicate that the absorption of griseofulvin was dissolution rate limited, in agreement with results reported previously (24, 25). No significant correlation was established between the *in vitro* rate of release of sulfisoxazole acetyl and dicumarol and their *in vivo* rates of absorption. When considering the low aqueous solubilities of dicumarol and sulfisoxazole acetyl, it is likely that their absorption is limited by their rate of release from the lipids *in vivo*. The lack of *in vitro–in vivo* correlation indicates that drug release *in vitro* did not simulate drug release in the complex digestion mixture present in the intestinal lumen following administration of the digestible lipids (26).

More sophisticated *in vitro* release rate studies will be required to identify factors that control the rate of drug release from lipids *in vivo*. Examples of factors that may be important are the lipid

Table V—Comparison[a] between the Effects of Lipids and Water on the Apparent Rate of Absorption of Sulfisoxazole Acetyl, Dicumarol, and Griseofulvin

Vehicle	Sulfisoxazole Acetyl[b]	Dicumarol[c]		Griseofulvin[d]
		Solution	Suspension	
Hexadecane	—	0	—	0
Oleyl alcohol	—	—	—	—
Polysorbate 80	0	0	0	—
Trioctanoin	—	0	0	0
Triolein	0	0	0	0

[a] The (–) indicates a statistically significant ($p < 0.05$, Student t test) negative effect on the rate of absorption of the drug from the lipid vehicle as compared to the water vehicle, and the (0) indicates no significant difference. [b] Rate of absorption based on amounts of sulfisoxazole excreted in the urine at 12 hr after dosing. [c] Rate of absorption based on amounts of radioactivity excreted in the urine at 12 hr after dosing. [d] Rate of absorption based on time of occurrence of peak plasma concentrations of griseofulvin.

Table VI—Comparison[a] between the Effects of Lipid and Water on the Bioavailability of Sulfisoxazole Acetyl, Dicumarol, and Griseofulvin

Vehicle	Sulfisoxazole Acetyl[b]	Dicumarol[c]		Griseofulvin[d]
		Solution	Suspension	
Hexadecane	0	0	0	—
Oleyl alcohol	0	0	0	—
Polysorbate 80	+	+	+	+
Trioctanoin	+	0	0	0
Triolein	+	+	+	–

[a] The (+) and ( ) indicate a significant ($p < 0.05$) increase or decrease, respectively, in bioavailability compared to the aqueous vehicle; the (0) indicates no significant difference. [b] Based on amounts of sulfisoxazole excreted in urine at 96 hr (192 hr for oleyl alcohol). [c] Based on amounts of radioactivity excreted in urine at 288 hr. [d] Based on area under the plasma concentration–time curve from 0–24 hr.

Table VII—Urinary Recovery[a] of Radioactivity following Intravenous Administration of ^{14}C-Dicumarol

Dose, mg/kg	Cumulative Percent of Dose Recovered at 288 hr
1	25.3 ± 0.91
10	23.8 ± 1.62

[a] Average of six animals ± *SD* for each dose.

viscosity, the lipid–water partition coefficient of the drug, the micellar phase–lipid partition coefficient of the drug (27), and the possible wetting of the solid drug by the aqueous phase. The latter factor is determined by the relative interfacial tensions between lipid and water, lipid and drug, and water and drug (28) and could be very sensitive to the presence of surface-active agents.

Bioavailability—Compared to the aqueous vehicle, the lipids either increased or did not change the bioavailability of sulfisoxazole acetyl or dicumarol (Table VI). The bioavailability of griseofulvin was decreased by hexadecane, oleyl alcohol, and triolein and increased only by polysorbate 80. The negative effect of triolein on the bioavailability of griseofulvin does not agree with the positive effects of digestible triglycerides on griseofulvin absorption reported previously (4, 5). Differences in the strain of rat (4), use of corn oil rather than triolein (4, 5), volume of lipid administered (4, 5), and particle size of the drug (5) may explain the different effects observed.

In general, the extent of drug absorption from the lipids increased with the polarity of the lipid. There is a perfect rank-order correlation between the bioavailability of sulfisoxazole acetyl and lipid polarity and, while not correlated perfectly, there is a tendency for the bioavailability of griseofulvin and dicumarol to increase with the polarity of the lipid. The solubility of the drugs in the lipids also increases with the polarity of the lipids (Table II), and the correlation between bioavailability and polarity may simply reflect the fraction of the dose in solution at the time of administration. However, when dicumarol was administered as a solution, the lipids affected its rate of absorption and bioavailability the same as when the drug was given as a suspension (Tables V and VI), indicating that the extent of dissolution of the drugs at the time of administration was not an important factor in this study.

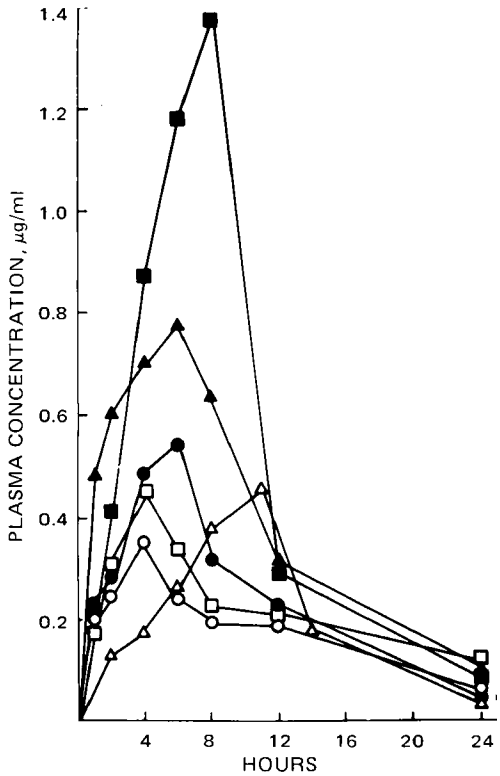

Figure 4—*Representative plasma concentrations of griseofulvin following oral administration of 50 mg/kg of griseofulvin suspended in lipid vehicles and water. Each curve, representing data from one animal, has a peak plasma concentration and t_{max} closest to the mean values for each group as reported in Table III. Key: see Fig. 1.*

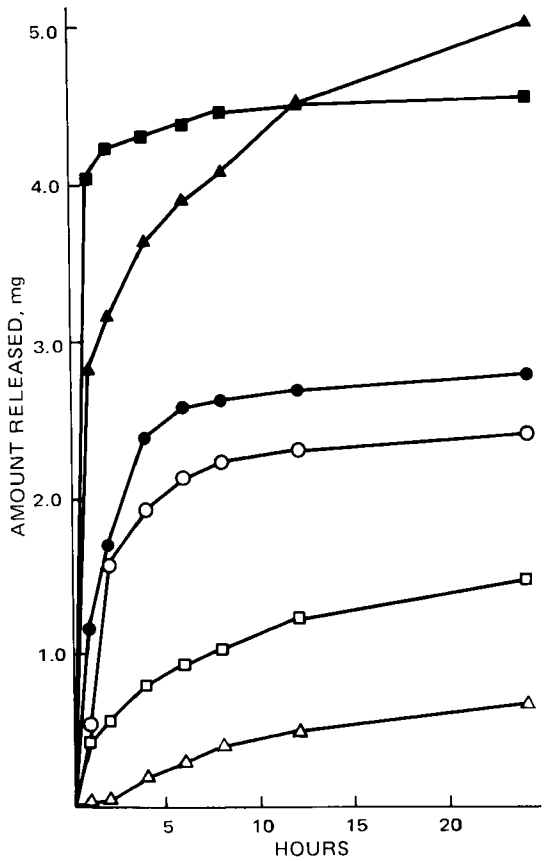

Figure 5—*Release of griseofulvin into water from suspensions containing 5 mg of drug in lipid and water. Each point represents the mean of three experiments. Key: see Fig. 1.*

In several instances, the bioavailability of dicumarol was significantly greater than 100% (Table IV), particularly with the 1-mg/kg dose. When 1 and 10 mg/kg of the drug were given intravenously, the same fraction of the administered radioactivity was excreted in the urine (Table VII). Differences in the mode of metabolism of dicumarol following intravenous and oral administration to rats have been reported (29), and the abnormally high bioavailability of orally administered dicumarol compared to the intravenously ad-

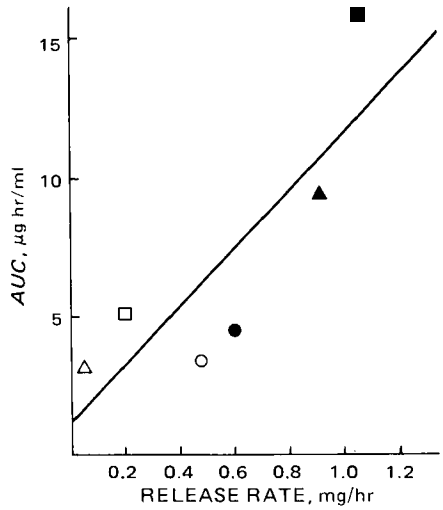

Figure 6—*Correlation of the area under the plasma concentration–time curve* (AUC) *with the average 0–4-hr rate of release of griseofulvin* in vitro. *Key: see Fig. 1.*

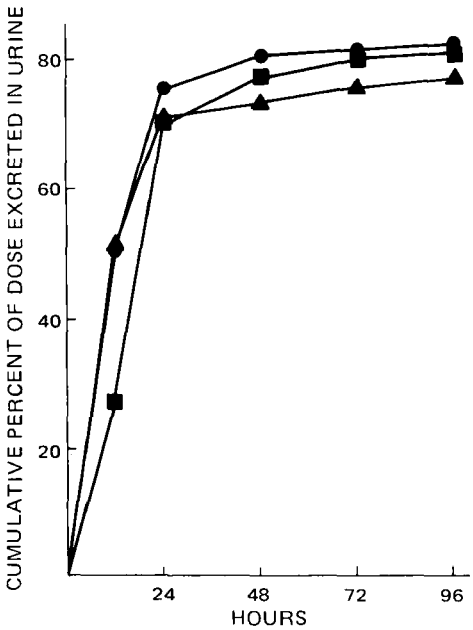

Figure 7—*Effect of the volume of triolein administered on the cumulative urinary excretion of free sulfisoxazole (expressed as a percent of the administered dose on a molar basis) following oral administration of 100 mg/kg of sulfisoxazole acetyl. Each point represents the mean of six animals. Key: ▲, 2.0 ml/kg; ●, 5.0 ml/kg; and ■, 10.0 ml/kg.*

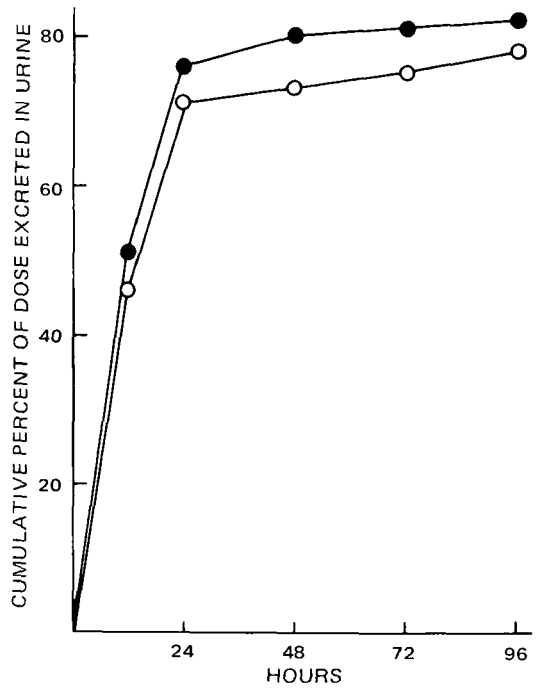

Figure 8—*Effect of emulsification of triolein on the cumulative urinary excretion of free sulfisoxazole (expressed as a percent of the administered dose on a molar basis) following oral administration of 100 mg/kg of sulfisoxazole acetyl. Each point represents the mean of six animals. Key: ○, emulsion; and ●, suspension.*

ministered standard may be due to such differences. Polysorbate 80, trioctanoin, and triolein were the only lipids that promoted bioavailability (Table VI); therefore, digestibility may be an important characteristic of lipids for enhancement of bioavailability. Since the digestible lipids were also the most polar, it is not possible to establish the relative importance of polarity and digestibility.

Chylomicrons are important for the transport of some lipophilic substances, such as cholesterol (30) and octadecanol (31), from the intestinal mucosa, and it might be anticipated that chylomicron generation would be an important characteristic of lipids for enhancing the bioavailability of lipophilic drugs. The bioavailability of sulfisoxazole acetyl and griseofulvin was not increased when the drugs were administered in triolein compared to trioctanoin (Table IV), indicating that chylomicrons are not important for absorption of these drugs. However, the bioavailability of dicumarol is greater from triolein than from trioctanoin and the generation of chylomicrons by triolein may explain the increased bioavailability.

The effect on bioavailability of the amount of triolein administered with sulfisoxazole acetyl was investigated. The results (Fig. 7) indicate that over the range studied the extent of absorption of the drug is not affected by the amount of lipid administered. However, the highest dose of lipid reduced the initial rate of absorption of sulfisoxazole acetyl, probably by reducing the rate of drug emptying from the stomach.

To investigate the effect of emulsification of the lipid vehicle on the bioavailability of sulfisoxazole acetyl, an oil-in-water emulsion containing 0.5 ml of triolein, 125 mg of acacia, and 10 mg of sulfisoxazole acetyl/ml was prepared. The emulsion was mixed by the dry-gum method (32), passed three times through a hand homogenizer[18], and agitated for 72 hr prior to administration of 10 ml/kg. The particle-size distribution of the triolein was determined by a photomicrographic method to be log normal (14). The geometric mean diameter and standard deviation were 1.5 and 2.2 μm, respectively. Neither the rate nor the extent of bioavailability of sulfisoxazole acetyl was affected significantly by emulsifying the triolein (Fig. 8).

The results of this study indicate that polar, digestible lipids increase the bioavailability of lipophilic, poorly water-soluble drugs without increasing their rate of absorption. The nonpolar, nondigestible lipids generally do not affect the bioavailability of lipophilic, poorly water-soluble drugs, but they do appear to reduce the rate of absorption of such drugs. Neither the amount of lipid administered nor emulsification of the lipid affected bioavailability significantly.

[18] Aloe Scientific Division, St. Louis, Mo.

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Saturable First-Pass Metabolism of Sulfisoxazole N^1-Acetyl in Rats

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Abstract □ Saturable metabolism of sulfisoxazole N^1-acetyl in the rat during the initial pass of the drug from the intestinal lumen through the liver following oral administration of the drug (saturable first-pass metabolism) was investigated. The fraction of the total amount of drug recovered from the urine as the N^4-conjugate decreased as the dose of orally administered sulfisoxazole acetyl was increased. No dose dependency of the N^4-conjugated fraction was apparent following the intravenous administration of sulfisoxazole acetyl or the oral administration of sulfisoxazole at the same dose levels.

Keyphrases □ Sulfisoxazole acetyl—saturable first-pass metabolism, rats □ Metabolism, saturable first pass—sulfisoxazole acetyl, rats

Evidence of saturable metabolism of drugs in humans during the initial pass of the drug from the intestinal lumen through the liver following oral administration (saturable first-pass metabolism) has been reported for various drugs including propranolol (1), levodopa (2), lidocaine (3), and aspirin (4). Recent studies indicate that the aromatic amino group of certain drugs may undergo first-pass conjugation. For example, aminosalicylic acid is more extensively acetylated following oral administration than following intravenous administration, and the extent of acetylation following oral administration is dose dependent (5, 6).

This type of dose dependency may have great clinical implications, since small changes in the dose given, or in the rate or extent of absorption, may result in large, unexpected changes in the systemic availability of the drug. This study investigated the saturable first-pass conjugation of the aromatic amino group of sulfisoxazole N^1-acetyl (sulfisoxazole acetyl) and sulfisoxazole over a dose range where the extent of conjugation following intravenous administration of sulfisoxazole acetyl is constant.

EXPERIMENTAL

Materials—Sulfisoxazole N^1-acetyl[1], sulfisoxazole[2], propantheline bromide[3], polysorbate 80[4], polyethylene glycol 400 USP[5], ammonium sulfamate[6], reagent grade sodium nitrite[7], and N-(1-naphthyl)ethylenediamine dihydrochloride[8] were used as received. All other reagents were reagent grade.

Dosage Forms—Solutions for oral administration contained 2, 5, or 20 mg of sulfisoxazole acetyl or sulfisoxazole/ml of polysorbate 80. Solutions for intravenous administration contained 5, 12.5, or 50 mg of sulfisoxazole acetyl/ml of polyethylene glycol 400 containing 10% water. A solution of propantheline bromide for intraperitoneal administration contained 2.5 mg of the drug/ml of water.

***In Vivo* Urinary Excretion**—Male Sprague–Dawley rats[9], 200–350 g, were fasted 16 hr prior to and 12 hr following the initia-

[1] Donated by Hoffmann–La Roche, Nutley, N.J.
[2] Sigma Chemical Co., St. Louis, Mo.
[3] Pfaltz and Bauer, Flushing, N.Y.
[4] Atlas Chemical Industries, Wilmington, Del.
[5] Ruger Chemical Co., Irvington, N.J.
[6] MCB Manufacturing Chemists, Norwood, Ohio.
[7] J. T. Baker, Phillipsburg, N.J.
[8] Eastman Organic Chemicals, Rochester, N.Y.
[9] Hilltop Lab Animals, Chatsworth, Calif.