range and the system studied. It would be interesting to note the effect of additives, especially other sugar moieties, upon the solubility of various solutes.

Whether the dielectric concept, or activity concept mechanisms, or a combination of these are strictly involved cannot be completely delineated in this work. Although the fair correlation given for theophylline has some basis in dielectric constants, no sweeping involvement of dielectric constants for all their systems is apparent. In addition, the observations made may eventually show a very strong solute nature and solvent system dependence. Studies attendant to these points are being carried out in these laboratories and will be the subject of future communications.

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Solubilizing Properties of Bile Salt Solutions II

Effect of Inorganic Electrolyte, Lipids, and a Mixed Bile Salt System on Solubilization of Glutethimide, Griseofulvin, and Hexestrol

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Studies of the influence of inorganic electrolyte on the solubilization of griseofulvin, glutethimide, and hexestrol in four individual bile salt solutions at 37° showed that sodium chloride had little effect on the solubility of the former two drugs but significantly increased the solubility of hexestrol. Based on these findings the possible location of the drug molecules within the micelle is considered. A mixed bile salt system was found to possess a significantly lower critical micelle concentration (CMC) than any of the individual bile salts previously studied. However, the affinities of this mixed micellar system for the drugs were comparable with those obtained with individual bile salts. The addition of lipids to the mixed bile salt system resulted in a decrease in hexestrol solubility but had little effect on griseofulvin and glutethimide solubility. The biological implications of the results obtained in the present communication are explored, and a mechanism for the role of dietary lipids and bile salts in the absorption of drugs is proposed.

BORGSTRÖM (1) has proposed a theory for the fate of ingested triglycerides prior to absorption. According to this theory, the breakdown products of pancreatic lipolysis (*i.e.*, 1- and 2-monoglycerides and fatty acids) are solubilized by bile salt micelles, present in the upper segment of the small intestine, prior to their absorption across the intestinal mucosa. In connection with this theory of fat absorption, several *in vitro* investigations have appeared in the literature demonstrating the marked micellar solubilizing properties of conjugated bile salts for fatty acids and monoglycerides (2–5). There has also been *in vivo* and *in vitro* evidence that the intestinal mucosa is capable of uptaking fatty acids and monoglycerides from a mixed micellar solution composed of these substances and conjugated bile salts (6–8).

In a previous communication (9) the effects of bile salt concentration and type, and temperature on the micellar solubilizing properties of bile salt solutions for the relatively water-insoluble drugs, griseofulvin, glutethimide, and hexestrol were reported. This report proposed that bile salts play a role in the dissolution step of the intestinal absorption mechanism for water-insoluble drugs.

In the present communication the results of findings on the influence of a mixed bile salt system, inorganic electrolyte concentration, and pancreatic lipolytic products and bile components on the degree of micellar solubilization of griseofulvin, glutethimide, and hexestrol are presented.

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EXPERIMENTAL

Materials.—Hexestrol,[1] griseofulvin,[2] and glutethimide[3] were used as received. The pure bile salts, sodium cholate,[4] sodium desoxycholate,[4] sodium taurocholate,[5] sodium glycochenodesoxycholate,[6] sodium glycodesoxycholate,[6] sodium taurochenodesoxycholate,[6] and sodium taurodesoxycholate[6] were dried *in vacuo* for 36 hr. prior to use. The first four bile salts were used individually to study the effect of inorganic electrolyte concentration on the degree of micellar solubilization of the three drugs, whereas, the latter six conjugated bile salts, representing those found in the human intestinal bile content, were used as a mixture to examine their influence on solubilization, alone and in the presence of lipid additives.

Reagent grade (Fisher Scientific Co.) sodium chloride, anhydrous sodium phosphate, and sodium biphosphate were used as received.

The lipid additives chosen for this study were those which are normal components of human bile or the end products resulting from the enzymatic action of pancreatic lipase during the process of digestion of ingested dietary triglycerides. The former compounds are represented by cholesterol,[7] and lecithin,[7] and the latter by lauric acid,[8] myristic acid,[8] palmitic acid,[8] 1-monolaurin,[9] 1-monomyristin,[9] and 1-monostearin.[9]

Effect of Inorganic Electrolyte on Solubilization.—Solutions of 0.04 *M* sodium cholate, sodium desoxycholate, sodium glycocholate, and sodium taurocholate were prepared and adjusted to 0.06, 0.08, or 0.16 *M* total sodium ion concentration by the addition of sodium chloride.

Effect of a Simulated Intestinal Bile Salt Mixture on Solubilization.—A stock bile salt solution, reported to approximate the human intestinal bile content (10) was prepared. It contained, per liter of final solution: sodium glycocholate, 0.030 mole; sodium glycochenodesoxycholate, 0.030 mole; sodium glycodesoxycholate, 0.015 mole; sodium taurocholate, 0.010 mole; sodium taurochenodesoxycholate, 0.010 mole; sodium taurodesoxycholate, 0.005 mole; and sodium chloride, 0.05 mole. The final stock solution was thus 0.1 *M* with respect to total bile salt concentration and 0.15 *M* with respect to sodium ion concentration. This solution was kept refrigerated when not in use.

A pH 6.4 phosphate buffer solution was prepared by mixing the following solutions in appropriate volumes to give the desired pH. A 0.3 *M* NaH_2PO_4 solution and a 0.15 *M* Na_2HPO_4 solution were mixed in a ratio of 55 parts of the former solution to 45 parts of the latter solution. The resulting solution was thus 0.3 *M* with respect to sodium ion concentration. This stock buffer solution was diluted 1:1 (v/v) with distilled water immediately before use.

The concentration of the simulated intestinal bile salt mixture was varied from 0–0.06 *M* by volumetrically mixing the 0.1 *M* stock solution with the appropriate volume of diluted pH 6.4 buffer. The pH of a 0.06 *M* solution prepared in this manner was approximately 6.48.

Preliminary experiments with this mixture showed that it supported the growth of bacteria under the conditions posed by the solubility experiments. Therefore, all solutions containing this mixture were sterilized by means of Millipore filtration (0.45 μ pore size) in the presence of ultraviolet light. Solutions sterilized in this manner showed no evidence of bacterial growth during the time required for the samples to reach equilibrium.

Effect of Lipid Additives on Solubilization.—In these experiments the simulated bile salt mixture (0.04 *M*), adjusted to the pH (about 6.4), and total sodium ion concentration (0.15 *M*) of the intestinal contents was employed. Predetermined amounts of the lipid additives were rotated for 1 to 2 hr., at 37°, in measured quantities of the bile salt mixture until solution was effected. The resulting clear solutions were then subjected to sterile filtration, and an excess quantity of drug added. These solutions were rotated at 37° until equilibrium was established.

The lipid additives, and the concentration in which they were employed are as follows: (*a*) 1-monolaurin, 0.40%; (*b*) 1-monomyristin, 0.20%; (*c*) 1-monostearin,[10] about 0.025%; (*d*) lauric acid, 0.40%; (*e*) myristic acid, 0.20%; (*f*) palmitic acid,[10] about 0.05%; (*g*) lecithin, 0.20%; (*h*) cholesterol,[10] about 0.025%.

The percentages of lipid additives selected were such that the mixed bile salt micelles were nearly saturated with these compounds. This condition is quite similar to *in vivo* conditions during fat digestion where the bile salt micelles are saturated with the digestive products (*i.e.*, fatty acids and monoglycerides).

A concentration of 0.04 *M* bile salt approximates the molarity of total bile salts present in the small intestine within 30 min. after the administration of a test meal containing corn oil (10).

Equilibration.—In each of the above experiments an excess amount of drug was added to bile salt solution contained in suitably sealed tubes. For those experiments in which the simulated intestinal bile salt mixture was employed, the drug was added under sterile conditions. The tubes were then placed in a shaker-incubator[11] and equilibrated for periods usually not less than 1 week's duration. Equilibrium was determined by repetitive sampling.

Assay Procedure.—The procedure employed for sampling and determining the amount of solubilized drug has been previously reported (9). Sodium chloride and all of the lipid additives, with the exception of lecithin, had no effect on the Beer's law curves for

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[1] Obtained from Gallard-Schlesinger Chemical Mfg. Co., New York, N. Y.

[2] Marketed as Fulvicin by the Schering Corp., Bloomfield, N. J.

[3] Marketed as Doriden by the Ciba Pharmaceutical Co., Summit, N. J.

[4] Obtained from Mann Research Laboratories, Inc., New York, N. Y.; special enzyme grade; reported to be > 99% pure.

[5] Obtained from Southeastern Biochemicals, Morristown, Tenn. Reported to be 98–99% pure by thin-layer chromatography.

[6] Obtained from Gallard-Schlesinger Chemical Mfg. Co., New York, N. Y. These bile salts were reported to be not less than 98% pure. Synthesized by T. J. Sas & Son, Ltd., London, England.

[7] Cholesterol S.C.W. (standard for clinical work) and the vegetable lecithin (95% pure) were obtained from Nutritional Biochemical Co., Cleveland, Ohio.

[8] Obtained from Mann Research Laboratories, Inc., New York, N. Y. Reported to be >99% pure.

[9] Supplied by the Distillation Products Industries, Rochester, N. Y., in 99.5% purity.

[10] Due to the very low solubility of these compounds in the bile salt mixture these percentages are approximate and essentially represent their saturation solubility.

[11] Gyratory incubator shaker, model G-25, New Brunswick Scientific Co., New Brunswick, N. J.

TABLE I.—EFFECT OF INORGANIC ELECTROLYTE (NaCl) ON THE MICELLAR SOLUBILIZING PROPERTIES OF 0.04 *M* BILE SALT SOLUTIONS ON GRISEOFULVIN, HEXESTROL, AND GLUTETHIMIDE AT 37°

Drug	Solubilizer	Total Sodium Ion Concn. 0.04 *M*	0.06 *M*	0.08 *M*	0.16 *M*
Griseofulvin[a]	Sod. cholate	6.9	6.3	6.8	6.5
	Sod. desoxycholate	9.1	8.3	9.2	8.7
	Sod. taurocholate	6.8	7.2	6.7	6.5
	Sod. glycocholate	7.0	6.5	7.2	6.8
	Water	...	...	...	0.7
Hexestrol[a]	Sod. cholate	122.0	127.6	136.2	175.6
	Sod. desoxycholate	139.4	142.5	152.0	...
	Sod. taurocholate	148.0	166.9	178.0	196.0
	Sod. glycocholate	143.0	164.6	170.9	192.1
	Water	...	...	...	0.8
Glutethimide	Sod. cholate	1.98	2.04	2.04	2.00
	Sod. desoxycholate	2.51	2.45	2.41	2.42
	Sod. taurocholate	1.90	1.93	1.93	1.86
	Sod. glycocholate	1.82	1.77	1.75	1.69
	Water	...	...	...	1.08

[a] Solubilities expressed as mg./100 ml. [b] Solubility expressed as mg./ml.

the three drugs, in the concentrations present in the solutions subjected to spectrophotometric analysis. In the case of lecithin, which does absorb, a blank solution containing the same concentration of lecithin and simulated intestinal bile salt mixture as the sample being analyzed was employed.

RESULTS AND DISCUSSION

Effect of Inorganic Electrolyte on the Degree of Solubilization.—The effects of total sodium ion concentration on the solubility of griseofulvin, hexestrol, and glutethimide in 0.04 *M* concentrations of the four individual bile salts at 37° are presented in Table I. As can be seen from this table, the solubility of griseofulvin and glutethimide, in all of the individual bile salts, is essentially constant over the entire sodium ion concentration range (0.04–0.16 *M*) studied. However, the solubility of hexestrol significantly increased with increasing total sodium ion concentration, in each of the bile salt solutions examined. Sodium chloride, in itself, has no solubilizing potential. For example, the solubility of each of the drugs in water and 0.16 *M* sodium chloride solution, respectively, at 37°, are: griseofulvin (1.4 mg./100 ml., 0.7 mg./100 ml.), glutethimide (1.20 mg./ml., 1.08 mg./ml.), and hexestrol (1.0 mg./100 ml., 0.8 mg./100 ml.).

According to the theory proposed for micellar solubilization by typical ionic surfactants, inorganic electrolytes function to shrink effectively the double layer surrounding the like-charged polar head groups of the surfactant molecules comprising the micelle. As a result, the electrical repulsions existing between adjacent charged surfactant molecules are reduced and the surfactant molecules are able to approach one another more closely in the micelle. This condition would, in effect, allow more surfactant molecules to enter the micelle with the result that the size of the micelle and therefore the volume of the hydrocarbon center of the micelle would increase. As a consequence of the increased volume, the solubility of a material which is solubilized by a mechanism involving incorporation into this region of the micelle (*i.e.*, nonspecific solubilization) should be enhanced. The enhancement noted in the solubilization of hexestrol, in the four individual bile salts, upon the addition of sodium chloride, is consistent with this theory (Table I). This suggests that hexestrol is solubilized by a "nonspecific" mechanism. A concomitant effect of inorganic electrolytes is to increase the degree of packing of the surfactant molecules in the micelle and thereby effectively reduce the volume in the palisade layers of the micelle. Consequently, the solubility of a compound which is solubilized by a mechanism involving incorporation into the palisade layers of the micelle (*i.e.*, specific solubilization) would either remain the same as in the absence of added electrolyte or decrease, depending on the concentration of electrolyte added to the surfactant system. The data given in Table I showing the effect of total sodium ion concentration on the solubility of griseofulvin and glutethimide in the four individual bile salts are consistent with the premise that these solubilizate molecules are solubilized by a mechanism in which they are more closely associated with the palisade layers of the bile salt micelle. This hypothesis, however, is not in agreement with tentative conclusions based solely on relative saturation ratio data (9, 11, 12).

Effect of a Simulated Intestinal Bile Salt Mixture on Solubilization.—The solubilization curves for griseofulvin, hexestrol, and glutethimide, in varying concentrations of the simulated intestinal bile salt mixture, at 37° are shown in Figs. 1–3, respectively. The CMC values for this mixture as determined from the solubilization of griseofulvin and hexestrol at 37° are 0.004 and 0.003 *M*, respectively. These values are in excellent agreement with that determined by Hofmann from the solubilization of azobenzene (5). This investigator obtained, under the same experimental conditions of pH, temperature, and total sodium ion concentration, a CMC value of 0.0035 *M* for this simulated intestinal mixture.

The CMC values obtained for the conjugated bile salt mixture are considerably lower than those previously obtained for the individual, conjugated bile salts, sodium glycocholate and sodium taurocholate at 37° (9). The lower CMC can be attributed to the effect of sodium ion concentration, the presence of more than one surfactant in the system, and the pH on the process of micelle formation. Inorganic electrolytes have been shown to

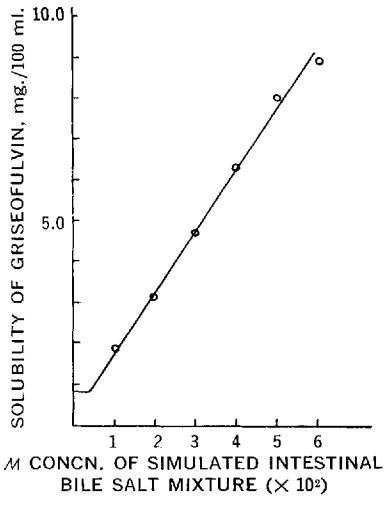

Fig. 1.—Solubility of griseofulvin as a function of simulated intestinal bile salt mixture concentration at 37°.

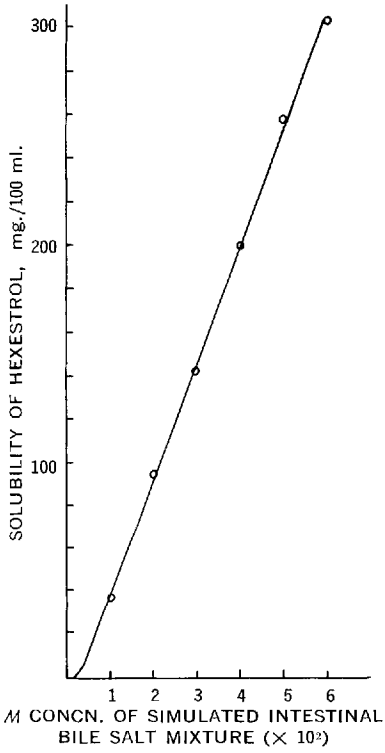

Fig. 2.—Solubility of hexestrol as a function of simulated intestinal bile salt mixture concentration at 37°.

decrease the CMC of ionic surfactants by decreasing the repulsive forces existing between adjacent charged surfactant molecules in the micelle (11, 12). The effect of mixtures of ionic surfactants on the CMC has a twofold effect (11, 12). First, at low concentrations the surfactants that have the lesser tendency to form micelles act as though they were salts to lower the CMC of the other surfactants. Second, at higher concentrations, the surfactants that have the lesser tendency to form micelles become important constituents of the micelle because they themselves are solubilized (12). The presence of these surfactants within the palisade layers of the micelle acts to stabilize the resulting mixed micelle through the formation of intermolecular van der Waal and hydrogen bonding. This stabilization also results in a decrease in the CMC. Normally, the effect of reducing the CMC is to increase micellar solubilization since at a given concentration of surfactant the number of micelles available are increased.

In the case of ionic surfactants the extent of ionization will be influenced by pH. The pH of an aqueous solution of the six conjugated bile salts, in water, is approximately 7.2. Since they are anionic in nature a decrease in the pH to 6.4 will significantly reduce the extent of ionization of some of the bile salts. In the micelle, those bile salts which are least ionized act to screen the repulsive forces between the bile salts which are ionized to a greater extent at this pH. The charge density on the micelle is also reduced. Thus, the over-all effect of pH is to increase the stability of the resultant mixed micelle and thereby lower the CMC.

The saturation ratios for griseofulvin, hexestrol, and glutethimide are included in Table II. For

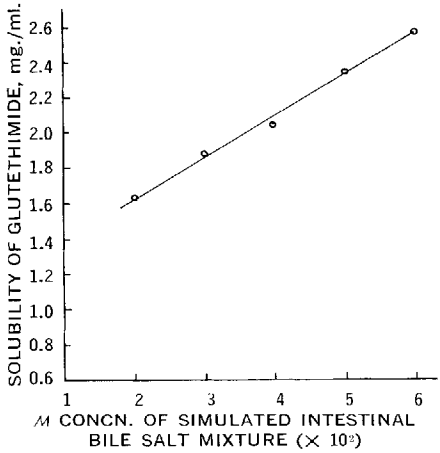

Fig. 3.—Solubility of glutethimide as a function of simulated intestinal bile salt mixture concentration at 37°.

TABLE II.—MAXIMUM SOLUBILIZING POWER OF BILE SALTS FOR GRISEOFULVIN, HEXESTROL, AND GLUTETHIMIDE AT 37°

Solubilizer	Saturation Ratio[a] × 10³ (moles of Drug/mole of Solubilizer) Griseofulvin	Hexestrol	Glutethimide
Sodium cholate[b]	6.18	195	104
Sodium desoxycholate[b]	6.18	167	163
Sodium taurocholate[b]	4.90	225	108
Sodium glycocholate[b]	5.13	231	71.8
Simulated intestinal mixture	4.22	197	108

[a] Slope of linear portion of solubilization curve, above the CMC, determined by the method of least squares. [b] Values obtained from *Reference 9*.

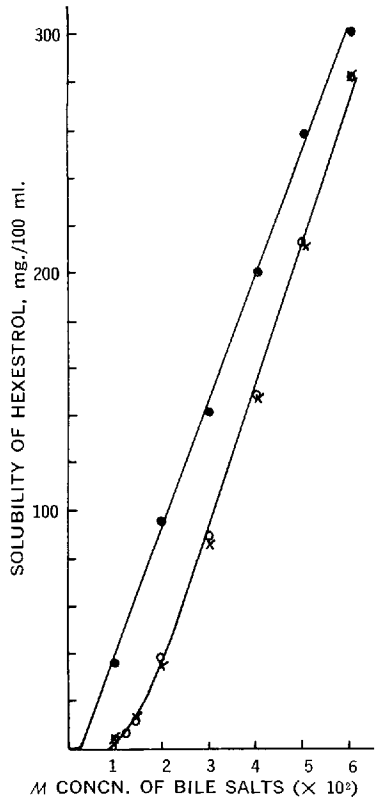

Fig. 4.—Solubility of hexestrol as a function of sodium taurocholate, sodium glycocholate, and simulated intestinal bile salt mixture concentration at 37°. Key: ●, simulated intestinal bile salt mixture; ○, sodium taurocholate; ×, sodium glycocholate.

griseofulvin, a comparison of the saturation ratios of all of the bile salts listed in Table II shows that at 37° the simulated intestinal mixture has the lowest saturation ratio, even though its CMC is the lowest. For hexestrol the simulated intestinal mixture has a saturation ratio lower than that for the conjugated bile salts, sodium taurocholate and sodium glycocholate, even though its CMC is considerably lower. In the case of glutethimide, the presence of the mixed bile salt system had little effect on the maximum solubilizing power (*i.e.*, saturation ratio).

As noted, the presence of more than one surfactant in the system should result in a decrease in the CMC of the system. As a result of the lowering of the CMC, solubilization should begin at a concentration lower than that for a system containing one surfactant. The results of this investigation are consistent with this theory. In addition, as predicted by theory, the amount of hexestrol solubilized at any one simulated intestinal bile salt mixture concentration is higher than that at the same concentration of sodium taurocholate or sodium glycocholate (Fig. 4). However, the increased degree of solubilization based on individual solubilities at a particular surfactant concentration should not be construed as indicating that the simulated intestinal bile salt mixture is a more efficient solubilizer than is sodium taurocholate or sodium glycocholate. As may be noted in Table II the saturation ratio, for hexestrol, obtained with the simulated intestinal bile salt mixture is significantly lower than that obtained with either conjugated bile salt, both of which are components of the mixture. This is indicative of a reduced affinity of the micelle for the solubilizate molecules. The same situation exists in the case of griseofulvin (Table II).

The formation of a mixed surfactant micelle is usually accompanied by a closer degree of packing of the surfactant molecules in the micelle. It is quite possible that this increased packing reduces the maximum solubilizing ability (*i.e.*, saturation ratio) of the simulated intestinal mixture as compared to a system containing one surfactant. The inclusion of surfactant molecules within the palisade layer of the micelle may preclude the effective penetration of solubilizate molecules.

Effect of Lipid Additives on Solubilization at 37°.—The effects of saturated fatty acids, 1-monoglycerides, lecithin, and cholesterol on the solubilization of griseofulvin, glutethimide, and hexestrol in 0.04 *M* simulated intestinal bile salt mixture at 37° are manifest in the data presented in Table III.

Nonpolar additives which are solubilized in the hydrocarbon center of the micelle would, according to theory, "swell" the micelle and effectively increase the volume available in the palisade layers of the micelle for the solubilizate molecules. Consequently, the solubility of a material normally solubilized by a "specific" process, should be enhanced. Whereas solubilizate molecules, normally solubilized by a "nonspecific" mechanism, should show a decrease in solubility upon the addition of nonpolar additives to the system. This results from a competition existing between the solubilizate and nonpolar additive for the space available in the hydrocarbon center of the micelle.

Amphiphilic additives (*i.e.*, compounds which are believed to be solubilized by a "specific" mechanism) act on the surfactant molecules comprising the micelle in a manner similar to inorganic electrolytes and would therefore essentially have the same effect on the solubility of solubilizate molecules. The nature of the effect would depend on the region of the micelle in which the solubilizate molecule normally resides (*i.e.*, specific or nonspecific solubilization).

All of the lipids listed in Table III, with the exception of lecithin and 1-monolaurin, have been shown to function as nonpolar additives in a system containing one bile salt at 37° (2–4). The decrease in the solubility of hexestrol in their presence can therefore be attributed to a competition between hexestrol and the nonpolar additives for the space available in the hydrocarbon center of the micelle. Although lecithin and 1-monolaurin have been reported to function as amphiphiles in a system containing a single bile salt (4, 5), it is conceivable that in a mixed surfactant system they are functioning as nonpolar additives. In the case of glutethimide and griseofulvin the addition of these lipids to the simulated intestinal bile salt system had little or no effect on the solubility of the drugs. However, a sufficient quantity of nonelectrolytes were present in the system such that they nearly saturated the mixed bile salt micelles. Under these saturated

TABLE III.—EFFECT OF LIPID ADDITIVES ON THE SOLUBILIZATION OF GRISEOFULVIN, HEXESTROL, AND GLUTETHIMIDE IN 0.04 *M* SIMULATED INTESTINAL BILE SALT MIXTURE (SIM) AT 37° (pH 6.4 [Na^+] TOTAL 0.15 *M*)

Solvent	Drug— Griseofulvin, mg./100 ml.	Hexestrol, mg./100 ml.	Glutethimide, mg./ml.
pH 6.4 buffer, Na^+ total 0.15 *M*	0.8	1.1	1.08
SIM, alone	6.3	200.0	2.04
SIM plus the fatty acids:			
Lauric acid, 0.40%	6.7	144.9	2.29
Myristic acid, 0.20%	6.3	160.6	1.94
Palmitic acid, 0.05%	5.5	176.4	1.84
SIM plus the 1-monoglycerides:			
Monolaurin, 0.40%	6.3	184.3	2.29
Monomyristin, 0.20%	5.9	178.7	2.21
Monostearin, 0.025%	5.5	192.1	1.88
SIM plus cholesterol (0.025%)	6.3	204.7	2.04
SIM plus lecithin (0.20%)	5.5	182.6	2.04

conditions it is highly probable that these nonpolar, lipid compounds, which are normally solubilized by a nonspecific mechanism, also penetrate into the palisade layers of the micelle. If such penetration occurs then competition with the griseofulvin and glutethimide solubilizate molecules would be expected. As a result, the increase in the solubility of these solubilizates which would normally occur in the presence of nonpolar additives, is counterbalanced by the decrease in solubility resulting from the competition between the solubilizate molecules and the nonpolar additives. It is conceivable that the solubilities of griseofulvin and glutethimide reported in Table III represent the net effect of these two opposing factors.

BIOLOGICAL IMPLICATIONS

The significantly high micellar phase to nonmicellar phase (*i.e.*, pH 6.4 buffer) partition coefficients found at 37° for hexestrol, griseofulvin, and glutethimide, (*viz.*, 2.69×10^5, 1.03×10^4, and 1.2×10^3, respectively) indicates that these relatively water-insoluble drugs are preferentially partitioned to the simulated intestinal bile salt micelle, in agreement with the theory proposed for the physical state of the pancreatic lipolytic products during fat digestion and absorption. Based on this similarity, it is quite reasonable to predict that bile salts play a role in the intestinal absorption of water-insoluble drugs.

The absorption and serum levels of griseofulvin have been shown to be enhanced, in humans, when the drug was administered in conjunction with high fat meals (13). A similar effect was observed in rats when griseofulvin was administered in corn oil (14). The present studies conducted to examine the influence of fatty acids, 1-monoglycerides, lecithin, and cholesterol have shown that these lipid substances have no critical effect on the solubilization of griseofulvin and glutethimide, but a decreasing effect on hexestrol solubility. Even though the solubility of hexestrol decreased in the presence of added lipid, its solubility is still significantly higher than that in the absence of bile salts and lipids (*i.e.*, 132–182 times its solubility in pH 6.4 buffer).

The present findings suggest a mechanism to explain the reported enhancement of drug absorption following the administration of a high fat meal. It is well known that triglycerides and other fatty material stimulate the flow of bile into the small intestine. The elevated bile salt concentration then serves to solubilize the drug to a degree far greater than its water solubility. From the limited observations with three different drug molecules it would appear that the concurrent solubilization of fatty material does not preclude significant solubilization of the drug molecules. The increased solubility results in an increased rate of dissolution (15) and, in turn, an increased absorption rate for any compound which manifests a dissolution rate-limited absorption process.

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