The Effects of Bile Salts and Lipids on the Physicochemical Behavior of Gemfibrozil[1]

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Physicochemical effects caused by intestinal fluids on drugs in the gastrointestinal (GI) tract can be a contributing factor in food induced changes in bioavailability. To identify physicochemical properties of gemfibrozil that may be altered by endogenous and dietary lipids, in vitro studies were conducted in model systems approximating the conditions of the upper GI tract. Factors examined include pH, solubility in bile salt micellar and mixed micellar systems with monoolein and lecithin, effect of fatty acids, dissolution, wetting, and partitioning in triglyceride dispersions. Gemfibrozil was solubilized by glycocholate solutions in a manner typical of other lipids and a three-fold increase in solubility was observed over physiologic concentrations. Addition of increasing amounts of swelling amphiphiles (monoolein, lecithin) to glycocholate solutions resulted in a linear increase in solubility. Fatty acid salts had no effect on gemfibrozil solubilization by micellar solutions. The dissolution rate of gemfibrozil increased slightly in the presence of glycocholate relative to buffer, however, addition of monoolein increased the dissolution rate three-fold. In triglyceride dispersions of mixtures of lipids, monoolein increased the fraction of drug in the micellar subphase, whereas fatty acid reduced it. The results indicate that in the conditions of the fed state gemfibrozil solubility and dissolution could be substantially increased relative to the conditions in the fasted state.

KEY WORDS: gemfibrozil; bile salts; dietary lipids; solubility; dissolution rate; partitioning.

INTRODUCTION

Understanding and evaluating the effects of food and dosing regimens on drug absorption are important considerations in the development of oral dosage forms because the intake of food can substantially influence the bioavailability of drugs (1). There are considerable differences in the composition of the intestinal milieu between the fed and fasted states and variety of substances are present in the GI tract during digestion that can affect drug absorption (2). Of particular interest with regard to formulation development are physicochemical effects of the intestinal milieu on drug dissolution/release in the fed or fasted state that can influence drug absorption.

Because lipophilic drugs have a tendency to be affected by the presence of food, particularly lipids, a key area of interest is the lipid digestion process (3). The main chemical components associated with lipid digestion that are most likely to have physicochemical effects on drugs are bile salts, fatty acids, di- and triglycerides, monoglycerides and lecithin. Bile salts and other digestive components, such as fatty acids, monoglycerides, and lecithin dissolved in bile salt solutions have been examined in detail because of their effects on solubilization and dissolution (4–8). Also, during fat digestion the intestinal contents are similar to an oil/water emulsion in equilibrium with a micellar solution and lipids partition between these phases (9). Drug partitioning between oil and micellar/aqueous phases of lipid digestion mixtures has also been investigated as a potential mechanism affecting drug absorption (10).

The purpose of this study was to examine a broad range of physicochemical properties of a drug in model systems, approximating both fed and fasted states conditions in the upper GI tract, and develop a clearer understanding of how the components of the intraluminal phase of fat digestion (3) affect it. Gemfibrozil, a lipid lowering agent indicated for Types IV, V, and in some cases Type IIb hyperlipidemia, was chosen as a model drug because it is a weak acid ($pK_a \approx 5$, octanol/water log $P \approx 2.8$) with low aqueous solubility and as such has properties similar to fatty acids. Because of structural similarities, gemfibrozil would likely be influenced by the same processes that affect dietary lipids. The factors examined include: drug solubility and the effects of micellar solubilization, the effect of fat digestion products, pH, dissolution, wetting, and drug partitioning between oil and aqueous phases. The influence of these factors are assessed in terms of the differences observed in simulated fed and fasted state conditions. Only the processes occurring in the lumen up to the movement of drug to the intestinal membrane are considered and membrane absorption effects are not addressed.

MATERIALS AND METHODS

A single lot of gemfibrozil was used for all experiments except for the pH-solubility profile experiments. Sodium glycocholate (a representative bile salt), monoolein (a model monoglyceride and lipolytic product), sodium oleate (a fatty acid salt), and olive oil (a model triglyceride) were all obtained from Sigma (St. Louis, MO; 99+% pure). Lecithin was obtained from ICN Chemicals (Costa Mesa, CA; 90–96% phosphatidylcholine) and oleic acid was obtained from Fisher Scientific (Springfield, NJ; class IIIB). An estimated molecular weight of 787 g/mol for lecithin was used in calculations. Other materials used were reagent grade and all samples were filtered using 0.45 μm Millex HV filters (Millipore, Milford, MA) unless otherwise specified. All studies, with the exception of the pH-solubility profile, were done in 0.12 M pH 5.9 sodium phosphate buffer (see Results and Discussion section) with an ionic strength of 0.15, approximating that in the upper GI tract. All studies were conducted at 37°C, unless otherwise specified.

Solubility Studies

For the bile salt solubility studies, 10 ml of sodium glycocholate solutions in the concentration range of 0–20 mM

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were added to excess gemfibrozil and equilibrated with agitation for at least 48 hours. Samples were subsequently filtered and assayed for gemfibrozil by an HPLC method described below. The solutions for studies done in the presence of monoolein or lecithin in the range of 0 to 10 mM were similarly prepared except monoolein and/or lecithin was first dispersed in glycocholate solution and allowed to dissolve. The pH-solubility experiments were performed in a similar manner using buffers covering the pH range 1 to 8 (0.1 N HCl, 0.05 M citrate, 0.10 M phosphate buffer systems). Preliminary studies indicated that equilibrium was achieved in 48 hours in buffer or glycocholate solutions.

Dissolution

The dissolution rate of gemfibrozil was determined using a rotating disk apparatus. Approximately 0.5 g of gemfibrozil were compressed in a specially made stainless steel punch and die using a Carver Press (Model M, Menomonee Falls, WI) at 3000 lbs force (30 sec dwell time). The die assemblies (disk area was 0.6 cm^2) were attached to shafts which fit into a USP dissolution apparatus (Vankel 6000RC, Edison, NJ). Dissolution media (pH 5.9 phosphate buffer, 10 mM glycocholate and 10 mM glycocholate with 6.15 mM monoolein) were prepared as in the solubility studies. Volumes of 350 and 300 ml (for glycocholate + monoolein only) were used in USP dissolution vessels and the rotational speed was 200 rpm. Samples were taken over 1–2 hr and gemfibrozil was assayed by HPLC; concentrations were corrected for sample removal.

Contact Angle and Surface Tension Measurements

The contact angles of the solutions used for the dissolution experiments were measured on gemfibrozil compacts with a Rame-Hart Contact Angle Goniometer (Mountain Lakes, NJ) in an enclosed, humidified, chamber thermostated at 25°C. One gram of gemfibrozil was compressed between two polished flat faced punches in a circular die (19 mm diameter) using a Carver Press at 3000 lbs force (30 sec dwell time). A 10 μl drop was placed on the compact with a micrometer syringe and the contact angle was measured initially (within the first min) and at 5 min on at least 7 drops on a minimum of 3 compacts for each solution; deviations were 2–3°. For the glycocholate/monoolein solution a 5 min reading was not possible because the drop was absorbed into the compact, so for analysis purposes the initial data was utilized. The 5 min contact angles for the buffer and glycocholate solutions were 4° less than the initial contact angle. The surface tensions of the solutions used in the contact angle studies were measured by the Wilhelmy plate method using a Roller-Smith Precision Balance (Laboratory Products, Boston, MA).

Partitioning Studies

Stock solutions of gemfibrozil in buffer, glycocholate, or glycocholate + monoolein solutions were prepared at concentrations of about 80 μg/ml. The gemfibrozil concentration was kept below solubility at ambient temperature to prevent precipitation of the drug upon cooling during or after ultracentrifugation. Olive oil was used for the triglyceride phase and oleic acid was used as a typical fatty acid. Varying amounts of olive oil and oleic acid were weighed directly into vials and buffer or micellar gemfibrozil solutions were added; the aqueous volumes were all 10 ml. The samples were shaken by hand for 15 sec, placed in a sonicator bath for 5 min and then equilibrated with agitation for 48 hours. Buffer/olive oil dispersions were centrifuged for 1 hr at 30,000 rpm (≈80,000 × *g*; Beckman L5-50E Ultracentrifuge, Palo Alto, CA). Dispersions containing glycocholate and glycocholate/monoolein required 4 hr of centrifugation. The clear infranatant was carefully aspirated from the bottom of the tube and was assayed by HPLC with the method used for the dissolution experiments.

HPLC Assays

For the solubility studies a Supelcosil LC-18-DB, 5 cm × 4.6 mm, 5 μm column (Supelco Inc. Bellefonte, PA) was used with a mobile phase of methanol:water:acetic acid in a 80:19:1 ratio. The flow rate was 1 ml/min with 10 μl injection volumes and the absorbance of gemfibrozil was measured at 276 nm. For the dissolution and partitioning studies a more sensitive assay was needed. In this case a longer column was used (15 cm) and the injection volume was increased to 100 μl. Assays were performed using a Hewlett-Packard 1050 HPLC with Chemstation (Rockville, MD).

RESULTS AND DISCUSSION

pH-Solubility Effects

For an ionizable drug, changes in the pH in the upper GI tract due to the presence of food can greatly influence drug solubility. Figure 1a shows chemical structure of gemfibrozil and its pH-solubility profile is shown in Fig. 1b. The solubility value remains below 0.03 mg/ml until the pH is increased beyond a value of approximately 5.5. A recent study showed that the median duodenal pH was 6.1 during fasting, 6.3 during a meal, and 5.4 at 30 minutes postprandial and that the stomach pH rises from a median fasted pH of 1.7 to 5.0 during a meal (11). Application of these pH estimates to the

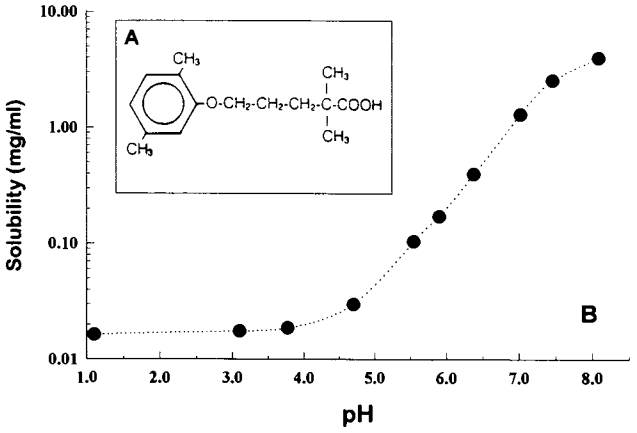

Fig. 1. (A) Chemical structure of gemfibrozil (5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoic acid). The molecular weight is 250.4 (B) Gemfibrozil pH-solubility profile, 37°C. Each data point represents the mean (n = 3) and SD is within the symbols.

pH-solubility profile for gemfibrozil shows that solubility in the stomach may be enhanced in the presence of food, but in the upper GI tract food should not substantially increase solubility due to pH. Based on this information, solutions were buffered to a pH value of 5.9 in all subsequent experiments because the main region of interest in these studies was the duodenum. This value represents a good approximation of duodenal pH with or without the presence of food.

Effects of Bile Salts and Swelling Amphiphiles

The concentrations of bile salts and lipids used were patterned after those determined from the micellar phase of human postprandial duodenal contents. The mean concentrations, in mM, were reported by Hernell et al. as: 13.1 (±10.8) for bile salts, 9.3(±7.4) for fatty acids, 2.8(±2.9) for monoglycerides, 0.06(±0.2) for triglycerides, and 3.2(±2.5) for phospholipids (12). Duodenal bile salt concentrations for fasting, and 30 min and 60 min postprandial of 5 mM, 15 mM, and 8 mM, respectively (13), were also used as guidelines in establishing concentration ranges. Glycocholate was chosen as a model bile salt because it comprises about 25–30% of the bile salt pool. The solubilization of gemfibrozil by glycocholate is shown in Fig. 2a. The curve is similar to those of fatty acids and other compounds solubilized by bile salt solutions (4,14); the curve becomes linear once the apparent critical micellar concentration of the bile salt is surpassed (in the range of 10 mM in Fig. 2a). The lack of a sharp inflection in the curve is probably due to the stepwise aggregation of the bile salt molecules (15) and this behavior is prevalent with glycocholate (4,14,16). The saturation ratio for gemfibrozil, calculated from the slope of the linear portion of the curve (14) over the 8 to 20 mM range, is 0.13 mol/mol glycocholate. A significant increase in solubility is only achieved when the bile salt concentration is substantially above 10 mM.

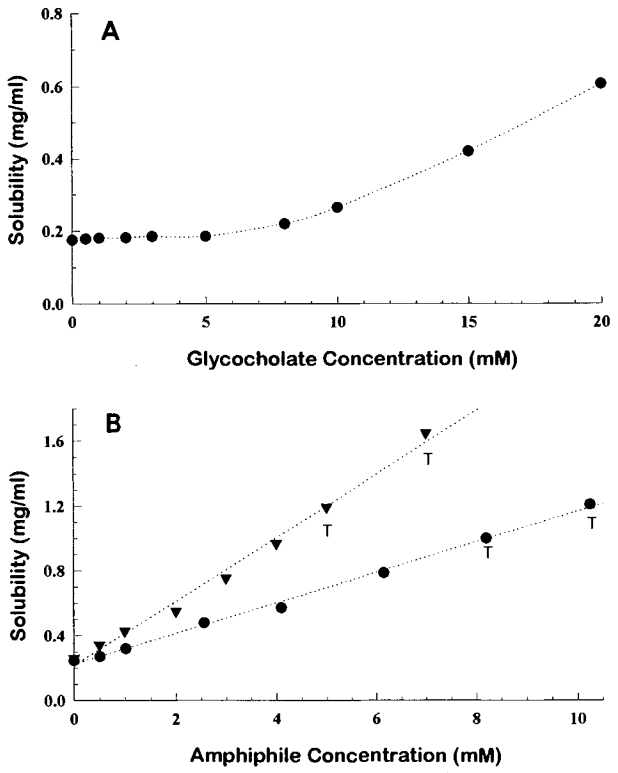

Fig. 2. (A) Solubility of gemfibrozil in pH 5.9 phosphate buffer as a function of glycocholate concentration at 37°C. Each data point represents the mean (n = 4) and SD is within the symbols. (B) Solubility of gemfibrozil in 10 mM glycocholate, pH 5.9 phosphate buffer, 37°C, as a function of monoolein (●) and lecithin (▼). [T] indicates turbidity was present in the filtrate. The lines correspond to the linear regression parameters. Each data point represents the mean (n = 2 for monoolein; n = 4 for lecithin), and SD is within the symbols for lecithin.

The saturation ratio for gemfibrozil falls in range observed for fatty acids of 0.07 to 1.9 (16). It is also comparable to that of indomethacin and mefenamic acid which have values of 0.21 and 0.24, respectively (17,6). In general, the saturation ratio can be used to categorize the solubility behavior of a drug molecule to better predict how bile salts in the GI tract might influence solubility. The solubility of drugs with high saturation ratios can be greatly increased by the presence of bile salts in both the fed and fasted states. However, because of the nature of the interaction of lipids with bile salts, a low saturation ratio does not preclude significant solubilization when bile salts are present with other lipids, as is the case with fatty acids. This is also exemplified by the large difference in the values for griseofulvin with a ratio of 5.13 (5), versus diazepam with a ratio of 0.03 (7). Absorption of both drugs is enhanced in the presence of food (1), but the low saturation ratio for diazepam is not indicative of a bile salt solubilization effect.

Dietary fatty acids, monoglycerides and free fatty acids formed from lipolysis of triglycerides during digestion are abundant in the aqueous phase of the contents of the lumen (12,18). Monoolein and lecithin, insoluble swelling amphiphiles, enhance solubilization of solutes in bile salt solutions (19). To study the effect of swelling amphiphiles, the glycocholate concentration was held fixed and solubility evaluated as a function of amphiphile concentration. A concentration of 10 mM glycocholate was used because it is in the range of the apparent critical micellar concentration and is a good estimate of postprandial duodenal bile salt concentration. Figure 2b shows the gemfibrozil solubility results for monoolein and lecithin. The linear profiles are similar to those for other lipophilic molecules solubilized by expanded bile salt micellar systems (14,16).

The amphiphilic index, calculated from the slope of the solubilization curves (16) in Fig. 2b, quantitatively defines the effectiveness of an amphiphile to enhance the solubility of a solute under a fixed set of conditions. The values for gemfibrozil are 0.39 and 0.78 mol per mol of amphiphile for monoolein (0–10 mM) and lecithin (0–7 mM) respectively. The larger value for lecithin indicates that it is a more powerful solubilizing agent than monoolein. The presence of lecithin in the micelle probably results in a more favorable environment for solubilizing gemfibrozil than does monoolein. These values are in the range observed for fatty acids with other bile salts under slightly different conditions (16). A large amphiphilic index indicates a substantial increase in solubility in the presence of bile salts and amphiphiles relative to bile salts alone and suggests that solubility may be increased in the presence of lipid digestion products.

Because lipids combine during digestion to form mixed-

lipid micelles with bile salts, it was important to determine how monoolein and lecithin together affected gemfibrozil solubility. Sodium oleate was also included because fatty acids formed from triglyceride digestion can also expand bile salt micelles (16,19). Table I compares the solubility of gemfibrozil as a function of different combinations of lipid additives. The addition of monoolein to the glycocholate/lecithin system produced an increase in solubility that falls between the estimated solubilities in the glycocholate/monoolein or glycocholate/lecithin systems at an equivalent molar concentration of additive (4.55 mM). These results also indicate specific interactions in the micelle can significantly modify the affinity of the micelle for the drug. The addition of oleate to the glycocholate/lecithin/monoolein system produced no further increase in solubility. These types of solubility studies under physiologically relevant conditions can be used to assess surfactant concentrations that yield similar solubilities for use in dissolution testing to develop in vitro/in vivo correlations.

The effect of the jejunal environment on solubility and its potential to influence drug absorption can also be assessed by evaluating the dose-to-solubility (D/S) ratio under conditions approximating those found in the fed and fasted states. The D/S ratio is a volume which is compared to the volume of the intestinal region (250 to 1000 ml) and is a rough indicator of dissolution rate limited absorption. Table I shows the calculated D/S ratio values for gemfibrozil. Although the water solubility of gemfibrozil is high enough that dissolution would occur relatively rapidly, the D/S ratio provides an indication of the in vivo capacity for additional solubilization. Unless the bile salt concentration is very high, amphiphiles are needed as well to achieve substantial reductions in the D/S ratio. Because the D/S ratios in fed state conditions are lower than those in the fasted state it is likely that dissolution in vivo may be accelerated in the fed state.

Fatty acids are formed from the enzymatic breakdown of triglycerides in the GI tract and are abundant in food. Because of structural and chemical similarities between gemfibrozil and fatty acids and because fatty acids have been shown to compete for micellar solubilization (19), the influence of several fatty acids salts on gemfibrozil in the micellar phase was also examined. Experiments conducted in solutions of 10 mM glycocholate, with or without 2.55 mM monoolein, which were saturated with either sodium laurate or sodium stearate showed no effect on gemfibrozil concentration. Therefore, fatty acids would not be expected to have a significant influence on gemfibrozil solubility in the micellar phase of intestinal contents in vivo.

Wetting and Dissolution

The wetting is an important factor influencing drug dissolution because it is the first step in the dissolution process. Also, the surface tension of the fluid in the GI tract can be substantially reduced, relative to water, by bile salts, endogenous amphiphiles and dietary components. This can potentially result in differences in wetting depending on which components are present. The contact angles and cosθ values for solutions approximating physiologic concentrations in the postprandial jejunum on gemfibrozil compacts are shown in Table II. The addition of the bile salt to the buffer solution lowered the contact angle by only 3° despite a 23 mN/m decrease in surface tension, but incorporation of monoolein greatly reduced the contact angle, indicating increased wettability. The much lower contact angle in the glycocholate/monoolein system indicates that the presence of bile salts with amphiphiles in the fed state may result increased wetting of the drug compared to that in the fasted state. Comparison of the trend in the adhesion tensions (a measure of immersional wetting) in Table II indicates that dewetting may be occurring because the value for the glycocholate solution is lower than that for water. These results indicate that there is greater overall adsorption in the glycocholate + monoolein solutions and also suggest that specific adsorption effects may contribute to wetting/dewetting depending on the combination of amphiphiles present. The addition of monoolein caused an additional 19.4 mN/m reduction in surface tension, much below that which can be achieved with only glycocholate. These results point out that amphiphiles should be considered in addition to bile salts when preparing physiologically relevant dissolution media for screening dosage form performance.

The dissolution rate studies for gemfibrozil using the

Table I. Solubility of Gemfibrozil in Combinations of Lipids and Calculated Dose-to-Solubility Ratios in pH 5.9 Buffer, 37°C

Lipids	Lipid concentrations (mM)	Gemfibrozil solubility (mg/ml)	Dose-to-solubility ratio ≈D/S[a]
none	0.0	0.17	3530
Glycocholate (fasted state concentration range)	5.0	0.19	3160
Glycocholate (postprandial concentration range, median)	10.0	0.27	2220
Glycocholate (postprandial concentration range, high)	20.0	0.61	980
Glycocholate/Monoolein	10/2.55	0.50	1200
Glycocholate/Lecithin	10/2.0	0.55	1090
Glycocholate/Lecithin/Monoolein	10/2.0/2.55	0.71	850
Glycocholate/Lecithin/Monoolein/Oleate	10/2.0/2.55/0.5	0.71	850
Glycocholate/Monolein	10/4.55	0.66[b]	910
Glycocholate/Lecithin	10/4.55	1.11[b]	540

[a] The dose is 600 mg.
[b] Estimated solubilities based on amphiphilic indexes (see text).

Table II. Wetting and Dissolution Parameters for Gemfibrozil

Solution	Surface tension[a] γ mN/m	Contact angle[a] ° degrees	Cosθ	Adhesion tension γcosθ mN/m	Dissolution rate[b] D_r mg/cm²/hr	Solubility[c] S mg/ml
buffer, pH 5.9	73.6	70	0.34	25.17	1.23	0.17
10 mM Glycocholate	50.3	67	0.39	19.65	1.69	0.27
10 mM Glycocholate + 6.15 mM Monoolein	30.9	24	0.91	28.23	3.71	0.79

[a] Determined at 25°C.
[b] Determined at 37°C and 200 rpm. The slopes of the amount dissolved vs. time profiles were all significantly different from each other.
[c] Determined at 37°C.

rotating disk method were conducted in the media employed in the wetting experiments shown in Table II. The dissolution rates were calculated from the slopes obtained from linear least-squares analysis of the data (normalized to surface area) and are summarized in Table II. The dissolution rate with monoolein was two times greater than in glycocholate solutions alone. In the presence of both bile salts and amphiphiles, as occurs in the fed state, the dissolution of gemfibrozil might be increased with respect to the fasted state, in which bile salts are predominantly present. Based on these data it is difficult to evaluate the relative contribution of solubility and wetting effects to the dissolution rate. Additional contributing factors may be the diffusion coefficient of gemfibrozil in the micellar phases and the diffusion of the micelles to and from the drug surface (20).

Partitioning

During digestion the chyme is essentially an oil/water emulsion in equilibrium with a micellar solution and lipids partition between the micellar and oil phases (9,19). Also, the presence of oil phases can have a significant influence on drug absorption (10,21). Hence, a primary physicochemical difference between the fed and fasted state intestinal contents is the presence of a triglyceride/oil phase in the fed state. Studies of mixtures of intestinal lipids were conducted to determine how digestion components influence the distribution of gemfibrozil.

The amount of triglyceride (olive oil) present has a strong influence on the drug partitioning in an olive oil/buffer system, as shown in Fig. 3a. Addition of a small amount of triglyceride results in a large shift in partitioning into the oil phase and this suggests that when large quantities of triglyceride are present, the availability of gemfibrozil in the aqueous phase may be less than that when triglyceride is absent. Figure 3b compares the distribution of gemfibrozil in several different dispersions. The amounts of lipids used were based on postprandial total lipid concentrations in unfractionated duodenal contents, in mg/ml, of 5.5(±5.1), 1.5(±1.5), and 1.5(±1.6) for fatty acids, monoglycerides and triglycerides, respectively (18). Monoolein enhances partitioning into the micellar solution presumably by expanding the bile salt micelles and creating a lipophilic core that is more thermodynamically favorable for gemfibrozil. Oleic acid shifts partitioning to the oil phase. Although some oleic acid may be solubilized in the micellar phase, the majority apparently combines with olive oil, effectively increasing the mass of the oil phase, resulting in greater partitioning into that phase. In the four component mixtures of intestinal lipids simulating physiologic conditions (glycocholate/olive oil/oleic acid/monoolein) only about 40% of the gemfibrozil remained in the micellar solution. These results show that individual lipid

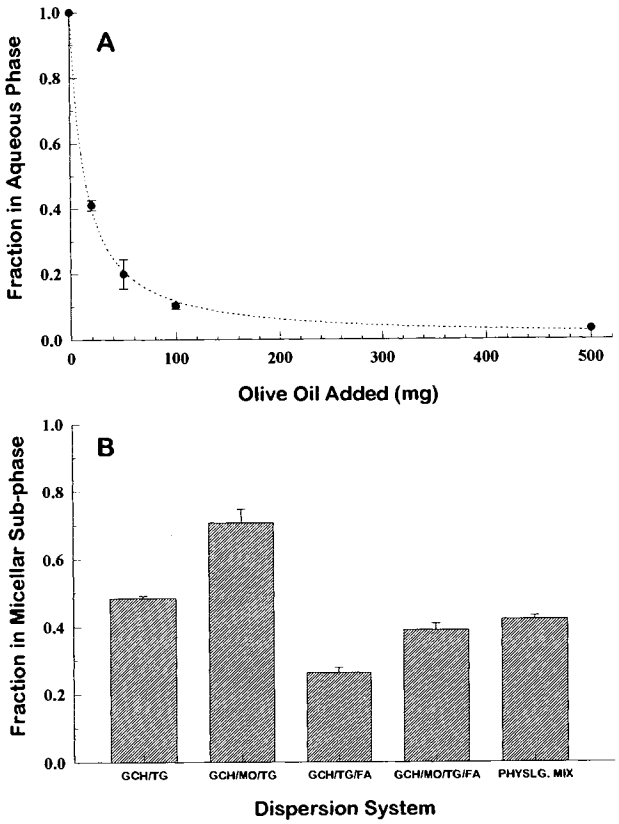

Fig. 3. (A) Effect of triglyceride (olive oil) on the partitioning of gemfibrozil between phases. The initial gemfibrozil concentration was approximately 78 μg/ml in 10 ml of pH 5.9 phosphate buffer, 37°C. Each point represents the mean (±SD) of 3 to 5 replicates. (B) Partitioning of gemfibrozil in dispersions of bile salts, lipids and pH 5.9 phosphate buffer at 37°C. The initial gemfibrozil concentration was approximately 80 μg/ml. The concentrations for glycocholate (GCH), olive oil (TG), monoolein (MO), and oleic acid (FA) were 10 mM, 2 mg/ml, 2 mg/ml, and 2.2 mg/ml, respectively, in 10 ml of buffer. The physiologic mixture contained 1.3 mg/ml olive oil, 1.5 mg/ml monoolein and 3.6 mg/ml oleic acid. Each point represents the mean of 2 to 4 replicates. Error bars represent ±SD except for the physiologic mixture where it corresponds to the range.

components can have a significant effect on drug partitioning, even when the drug is mostly ionized and soluble in the aqueous phase. The presence of an oil phase may also enhance drug solubility and dissolution. The kinetics of partitioning, emulsification, and lipid absorption will also play a significant roles; however, due to the necessity of separating the phases for assay and the time scale involved, the analysis of these aspects cannot be done using the methods employed in these studies.

In conclusion, in vitro lipid systems patterned after pre- and postprandial duodenal contents are useful in examining the relative influence endogenous and exogenous lipids have on the physicochemical behavior of a drug or dosage form. The results for gemfibrozil suggest that solubility, wetting and dissolution of the drug in the fed state will be greater than in the fasted state and these factors could potentially influence gemfibrozil absorption. These types of studies can be used as a screening tool to indicate which factors may need to be considered in more detail when designing dosage forms or clinical studies that involve the presence of food and the fat digestion process. Additionally, solubility data from mixed lipid systems can be applied to formulation of physiologically relevant dissolution media.

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