Drug Development and Industrial Pharmacy, 27(4), 267–276 (2001)

REVIEW ARTICLE

Formulation and Physiological and Biopharmaceutical Issues in the Development of Oral Lipid-Based Drug Delivery Systems

Kishor M. Wasan*

Division of Pharmaceutics and Biopharmaceutics, Faculty of Pharmaceutical Sciences, University of British Columbia, 2146 East Mall, Vancouver, BC, Canada V6T 1Z3

ABSTRACT

The rapidly increasing availability of drug receptor structural characteristics has permitted the receptor-guided synthesis of potential new drug molecules. This synthesis strategy frequently results in the creation of polycyclic and highly hydrophobic compounds, with attendant poor oral bioavailability resulting from low solubility and slow dissolution rate in the primarily aqueous contents of the gastrointestinal (GI) tract. In an attempt to improve the solubility-limited bioavailability associated with these compounds, formulators have turned to the use of lipid excipients in which the compounds can be solubilized prior to oral administration. This new class of excipients presents the pharmaceutical scientist with a number of new challenges at all stages of the formulation development process, beginning with the excipient selection and stability assessment of the prototype formulation, up to and including scale-up and mass production of the final market-image product. The interaction of lipid-based formulations with the gastrointestinal system and associated digestive processes presents additional challenges and opportunities that will be understood more fully as we begin to unravel the intricacies of the GI processing of lipid excipients. For example, an increasing body of evidence has shown that certain lipids are capable of inhibiting both presystemic drug metabolism and drug efflux by the gut wall mediated by p-glycoprotein (PGP). And, it is well known that lipids are capable of enhancing lymphatic transport of hydrophobic drugs, thereby reducing drug clearance resulting from hepatic first-pass metabolism. This review addresses the

* Fax: 604-822-3035; E-mail: Kwasan@interchange.ubc.ca

current state of knowledge regarding oral lipid-based formulation development and scale-up issues and the physiological and biopharmaceutical aspects pertinent to the development of an orally bioavailable and efficacious dosage form.
KEY WORDS: *Gastrointestinal drug metabolism; P-Glycoproteins; Lipid excipients; Lipid-based drug delivery; Lymphatic drug transport; MDR proteins.*

INTRODUCTION

The primary roles of traditional excipients were to bind and provide bulk to the dosage form, to facilitate or control drug release from the excipient matrix, and to facilitate product manufacturing on high-speed, automated production equipment. However, lipid excipients, unlike their traditional counterparts, have the ability to solubilize hydrophobic drugs within the dosage form matrix. This often results in improved drug absorption, which is primarily mediated by a reduction in the barriers of poor aqueous solubility and slow drug dissolution rate in the gastrointestinal (GI) fluids. Some of these excipients also have desirable self-emulsifying properties, readily forming fine dispersions of lipid-solubilized drug in the aqueous contents of the GI tract and creating optimal conditions for absorption.

The pivotal activities involved in the development of any oral dosage form (a conventional solid or lipid-based formulation) include (1) physiochemical and biopharmaceutical understanding of the drug substance, which would guide initial excipient selection and subsequent design of a prototype dosage form; (2) product stability and dissolution testing, which demonstrates physical and chemical stability of the drug substance during the shelf life of the product; (3) formulation scale-up to production size batches; (4) development of a discriminating dissolution test method to provide assurance of product quality and batch-to-batch consistency; and (5) justification of the formulation rationale to regulatory agencies. However, while the pivotal activities associated with the development of a lipid-based formulation are similar to those for a conventional oral solid, the manner in which pharmaceutical scientists achieve those goals will be different. The ability of pharmaceutical scientists in redefining these pivotal development activities for lipid-based oral formulations in fact may determine the future success of this technology.

A number of important questions will need to be addressed more fully to provide pharmaceutical scientist formulators with consistent guidelines for the development of oral lipid-based formulations. For example, what role will dissolution testing play in the development and evaluation of liquid and semisolid lipid-based dosage forms? Should dissolution testing be performed at all? If so, what parameters are important, and how will the data be interpreted? How is stressed stability testing performed on semisolid dosage forms, which melt at elevated temperatures? Will the physical state of drugs in matrices change on aging, and how might this have an impact on drug delivery? What types of chemical incompatibilities are peculiar to lipid excipients? How will these excipients affect the integrity of gelatin capsules?

The availability of a wide variety of pharmaceutical-grade lipid excipients has coincided with a recent advance in encapsulation technology, which now allows hard gelatin encapsulation of both liquid and semisolid formulations. This advance, along with the fact that nearly half of all new chemical entities fit the category of ''poorly water soluble'' has created a window of opportunity for the rapid introduction of oral lipid-based drug formulations into the marketplace.

As we begin to unravel the intricacies of the GI processing of lipid excipients, further improvements in the performance of lipid-based delivery systems can be expected. For example, an increasing body of evidence has shown that certain lipids are capable of inhibiting both presystemic drug metabolism and p-glycoprotein-mediated (PGP-mediated) drug efflux by the gut wall (1–5). And, it is well known that lipids are capable of enhancing lymphatic transport of hydrophobic drugs, thereby reducing drug clearance resulting from hepatic first-pass metabolism (6–26). This article not only addresses formulation issues, but also addresses these physiological and biopharmaceutical aspects of oral lipid-based drug delivery.

PRINCIPLES OF LIPID DIGESTION AND ABSORPTION

To understand fully how different lipid-based excipients modulate drug oral absorption, a general understanding of GI digestion and absorption of lipids is required. A number of excellent reviews by Tso and coauthors have been written on the digestion and absorption of dietary lipids (27–30).

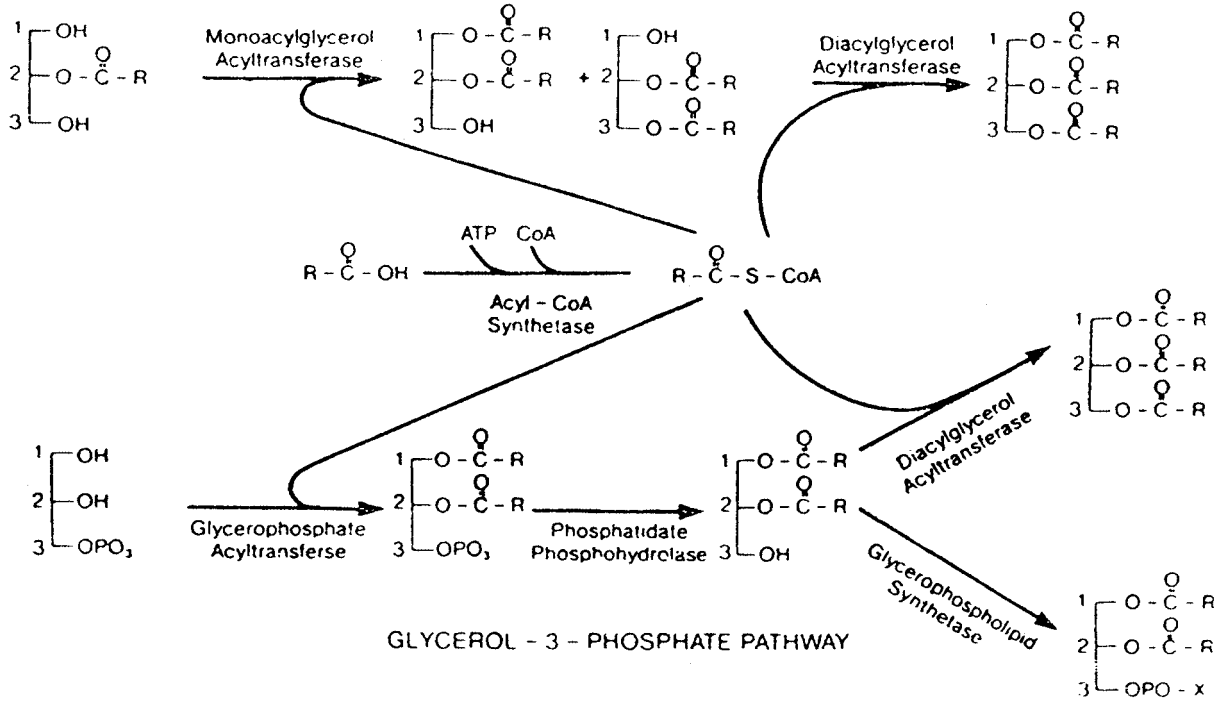

Figure 1. Pathways of triacylglyerol biosynthesis in the rat and hamster intestinal mucosa. (Reprinted from P. Tso and K. Fujimoto, The adsorption and transport of lipids by the small intestine, Brain Res. Bull., 27, 477–482, 1991, with permission from Elsevier Science.)

Triacylglycerol (TG) is the major form of dietary fat in human beings, and each glycerol backbone is esterified with predominantly three long-chain fatty acids (FAs) (Fig. 1). The human small intestine is also presented daily with both dietary and endogenous phospholipids and sterols (27–31). Of all the luminal phospholipids present, phosphatidylcholine (PC) is the most important. Luminal PC can be derived from both the diet and from bile, but the biliary contribution is significantly more than the dietary (27–31) (Table 1). The predominant sterol, particularly in Western diets, is cholesterol. However, plant sterols account for 20%–25% of the total dietary sterol.

Digestion of Dietary Lipids

The majority of TG digestion occurs in the duodenum of the small intestine (27,31). Through the action of pancreatic lipase, TG is hydrolyzed to form predominantly 2-monoglyceride (MG) and FA (31) (Fig. 1). Most dietary lipids are present in the human duodenum as emulsified droplets that range from 1 to 50 μm in size, and little additional emulsification of the dietary lipids occurs in the duodenum. The lipolytic action of lipase on the lipid emulsion containing TG and bile salts occurs slowly, resulting from the inhibition caused by bile salts at concentrations above the critical micellar concentration. However, overcoming this inhibition and achieving complete digestion of dietary TG in the intestinal lumen requires another protein, called colipase, in the pancreatic juice.

Table 1

Class Distribution of Phospholipids

	Percentage Distribution	
Phospholipid Class	Prechylomicrons	Chylomicrons
Phosphatidylcholine	50	80
Phosphatidylethanolamine	12	4.4
Lysophosphatidylcholine	11	—
Sphingomyelin	6	4.5
Phosphatidic acid	11	6.6
Phosphatidylinositol	7	4

Source: Adapted from P. Tso and K. Fujimoto, The adsorption and transport of lipids by the small intestines, Brain Res. Bull., 27, 477–482, 1991.

Luminal PC is digested in the presence of pancreatic phospholipase A2 to form lysophosphatidylcholine (LPC) and FA (27,31). Traditionally, it had been believed that dietary cholesteryl ester hydrolysis by cholesterol esterase into the free cholesterol form was required for cholesterol to be absorbed (via the enterocytes) by the small intestine (31). However, recent studies have been published that suggest that cholesterol GI absorption may be controlled genetically and supports a protein-mediated mechanism for cholesterol uptake into the intestinal mucosal cell (32).

Uptake of Lipid Digestion Products by the Enterocyte

For many years, it was generally hypothesized that FA and MG are absorbed by the enterocytes through simple diffusion. However, FA and MG have to overcome the diffusion barrier afforded by the ''unstirred water layer.'' This is achieved by the micellar solubilization of MG and FA by bile salts. Through micellar solubilization, the concentration of FA and MG next to the enterocyte membrane increases markedly, thus facilitating the entry of these lipids, as monomers, into the enterocytes. However, recent direct and indirect evidence supports not only the presence of an FA-binding protein associated with the brush-border membrane, but also a large family of FA transport proteins (FATPs), expressed at high levels on the apical side of mature enterocytes in the small intestine. One specific carrier-mediated transporter, FATP4, facilitates the enterocyte uptake of FA (27–30).

The uptake of LPC is believed to be by passive diffusion. However, studies by Stremmel and colleagues suggest that the brush-border membrane FA-binding protein also has the capacity to bind and transport LPC, thus raising the possibility that LPC transport may also be carrier mediated (33).

The uptake of cholesterol by enterocytes appears to be specific since β-sitosterol (a plant sterol), a molecule that bears considerable resemblance to cholesterol, is poorly absorbed. This specificity requires energy as the deprivation of blood supply results in free permeability of different sterols. Hauser et al. recently identified that a scavenger receptor class B, type I is present in the small intestine brush-border membrane, where it facilitates the uptake of dietary cholesterol from either bile salt micelles or phospholipid vesicles (32). This receptor can also function as a port for several additional classes of lipids, including cholesteryl esters, triacylglycerols, and phospholipids.

FORMULATION ISSUES

Selection of Compounds for Lipid-Based Delivery Systems

Compounds for which improvement in bioavailability has been most dramatic and most easily recognized as being due to lipid excipients have been those possessing high membrane permeability and low aqueous solubility (Biopharmaceutical Classification System [BCS] Class II), as well as good solubility in a digestible lipid. The BCS can serve as a useful preliminary guide for the selection of candidates for lipid-based delivery (Table 2) (74). Further elucidation of the physiological aspects of lipid excipients (e.g., inhibition of gut wall efflux mediated by multidrug resistant [MDR] PGP and presystemic metabolism by cytochrome P450 3A4 [CYP 3A4] bound to the gut wall) can be expected to define further candidate selection based on the BCS.

Dissolution Testing of Lipid-Based Dosage Forms

Dissolution testing of liquid, solid, and semisolid oral dosage forms plays an important role in establishing therapeutic performance, as well as providing a means for ensuring product quality and batch-to-batch consistency (75). However, considerable controversy surrounds dissolution testing of lipid-based formulations intended for oral administration. For instance, thermal and textural properties, as well as viscosity and consistency of the

Table 2

Biopharmaceutical Classification System (BCS) and Potential Advantage of Lipid-Based Systems

BCS Class	Aqueous Solubility	Membrane Permeability	Potential Advantage of Lipid-Based Systems
I	High	High	Enzymatic degradation Gut wall efflux
II	Low	High	Solubilization Bioavailability
III	High	Low	Enzymatic degradation Gut wall efflux Bioavailability
IV	Low	Low	Solubilization Enzymatic degradation Gut wall efflux Bioavailability

dosage form, can influence drug release from lipid-based formulations (76). Proponents of dissolution testing argue that it serves as an effective means of verifying batch-to-batch product consistency, as well as provides a means of identifying formulation-dependent extremes of release rate prior to in vivo testing, while potentially allowing for the establishment of an in vitro–in vivo correlation (75). Those against the use of dissolution testing argue that it is impossible to reproduce faithfully the complex GI environment in vitro (76). In addition, it has been shown that changes in dissolution rate on aging do not always correlate with changes in bioavailability from lipid-based formulations (77). Furthermore, dissolution test results are not meaningful for microemulsion formulations, which have a dependence that is closely related to the droplet size of the dispersed formulation (77), a parameter that is not assessed by dissolution testing.

Crison et al. studied dissolution media for in vitro testing of water-insoluble drugs by determining the effect of surfactant purity and electrolyte on in vitro dissolution of carbamazepine in aqueous solutions of sodium lauryl sulfate (SLS) (34). They found that their results illustrated the sensitivity of the micelle to impurities and electrolytes with regard to size and loading capacity and the effect these changes have on the solubility and dissolution rate. Thus, they concluded that, when using surfactants in dissolution media for in vitro testing of dosage forms, consideration must be given to the level of impurities present so that the results are consistent and reliable. Abrahamsson and colleagues studied the drug release of a water-insoluble compound, felodipine, using SLS, polyoxyethylene 20 sorbitan monooleate (Tween), or cetyltrimethylammonium bromide in test medium as solubilizers (35). They observed that all three solubilizers substantially enhanced the drug solubility, and sink conditions were obtained. In addition, the choice of solubilizer affected the drug release rate due to the physicochemical interactions between the gel-forming agent and the solubilizers. In both studies, solubilizers were used in the dissolution testing of these water-insoluble compounds, which begs the question: Was drug release a function of the compound formulation characteristics or a function of the type of solubilizer used? Further development is required in this area.

Stability Testing of Lipid-Based Dosage Forms

Stability testing of oral lipid-based formulations is an area currently under development. Stability testing peculiar to formulations incorporating lipid excipients includes monitoring the stability of the excipient, as well as the active ingredient, since lipids are capable of undergoing degradative changes, particularly oxidative changes or formation of peroxides, over time. Particularly, polyglycolyzed glycerides and surfactants are known to contain or form peroxides on aging. The interaction of peroxides with the gelatin capsule can result in gelatin cross-linking and an associated, slower dissolution rate (78). Results from accelerated stability testing at elevated temperatures may yield results that are not easily extrapolated to ambient temperatures due to the increased existence of temperature-dependent degradation mechanisms. This scenario is particularly true for semisolid dosage forms, which may melt at the testing temperature. In addition, the oxygen permeability of gelatin capsules increases at temperatures greater than approximately 40°C–50°C, further promoting oxidative degradation, to which many lipids are particularly sensitive (79).

However, to date, few studies have been done to evaluate the stability testing methodologies employed for lipid-based products. Yoon and Burgess utilized interfacial properties as stability predictors of lecithin-stabilized perfluorocarbon emulsions (36). The purpose of their study was to determine whether the addition of small quantities of minor lecithin components (i.e., phosphatidylinositol, phosphatidic acid, lysophosphatidylethanolamine, and cholesterol) and Pluronic F68 to lecithin could improve the stability of lecithin-stabilized perfluorocarbon emulsions. Attempts were made to correlate emulsion stability with interfacial properties (i.e., tension and charge). Dynamic interfacial tension was determined using a Teflon Wilhelmy plate method as previously described (37). Microelectrophoresis was used to measure emulsion droplet charge, and photon correlation spectroscopy and Coulter analysis were used to determine emulsion stability as a function of droplet size. They found that small quantities of additives altered emulsion stability, and these data were correlated with interfacial properties and initial droplet diameters. The addition of cholesterol to lecithin resulted in the most stable perfluorocarbon emulsion.

Opawale and Burgess further studied the influence of interfacial rheological properties of mixed emulsifier films on the stability of water-in-oil-in-water emulsions (38). They found a positive correlation between the interfacial elasticity and emulsion stability data. It was concluded that mixed emulsifiers that give higher film strength, as quantified by interfacial elasticity measurements, resulted in more stable water-in-oil-in-water emulsions. Additional studies and evaluation of stability

testing pertaining to oral lipid-based dosage forms are still required.

The Effect of Lipid Excipients on Formulation Integrity

Very little research has been completed that evaluates the effects of lipid excipients on formulation integrity. Rabiskova and Valaskova investigated the influence of hydrophilic-lipophilic balance (HLB) on the incorporation of oils by complex coacervation (39). They found that, when surfactants with HLB values from 1.8 to 6.7 were used, the amount of incorporated oil was high (65%–85%). A significant decrease of the oil content in the microcapsules was found when Tween 61 with HLB = 9.6 had been added to the mixture. No oil was found inside the microcapsules from the coacervate emulsion mixture containing Tween 81 (HLB = 10) and Tween 80 (HLB = 15).

Ratsimbazafy and colleagues studied the rheological behavior of drug suspensions in Gelucire mixtures and proxyphylline release from matrix hard gelatin capsules (40). They found greater release of proxyphylline from matrix hard gelatin capsules formulated with Gelucire than with gelatin capsules not formulated with Gelucire.

PHYSIOLOGICAL AND BIOPHARMACEUTICAL ISSUES

The Role of P-Glycoprotein and Multidrug-Resistant Protein

MDR cells are thought to maintain a low intracellular therapeutic drug concentration through the active efflux of drugs across the cell membrane (41–43). It is presently believed that PGP and MDR proteins mediate this energy-dependent drug efflux by interacting directly with various lipophilic compounds (44,45). In addition, recently an increasing body of evidence has shown that certain lipids and lipid- and polymer-based excipients are capable of inhibiting both presystemic drug metabolism and PGP-mediated drug efflux by the gut wall (46–50).

Initial work demonstrated that nonionic detergents such as Triton X-100 and Nonidet P-40 at very low concentrations reverse the MDR phenotype by inhibiting PGP drug binding, while fatty acid ester surfactants (i.e., Cremophor EL and Solutol HS 15) were modulators of MDR resistance (51). Pluronic P85 block copolymer has been shown to inhibit PGP and increase apical-to-basolateral permeability in Caco-2 monolayers with respect to a broad panel of structurally diverse compounds previously shown to be affected by PGP and/or MDR-associated protein efflux systems (52).

Regev and coworkers have recently reported that the anesthetics benzyl alcohol, the nonaromatic chloroform, and diethyl ether abolish PGP ATPase activity by membrane fluidization (53). Broad specificity of the lipid and copolymer effects with respect to drugs and efflux systems appear to be valuable properties in view of developing pharmaceutical formulations to increase drug accumulation in selected organs and to overcome both acquired and intrinsic drug resistance that limits the effectiveness of many chemotherapeutic agents.

The Role of Cytochrome P-450s

CYP 3A4 is the major phase I drug-metabolizing enzyme in humans; it accounts for approximately 30% of all hepatic cytochrome P450s and greater than 70% of all small intestinal cytochrome P450s (54–56). Along with the MDR gene product PGP, CYP 3A4 is present at high concentrations in villus tip enterocytes of the small intestine and shares a significant overlap in substrate specificity with PGP (57). Many studies have established metabolism by intestinal CYP 3A4 as a major determinant of the systemic bioavailability of orally administered drugs (58–60). However, to date, there is relatively little or no data regarding the effects of lipid-based drugs and/or the lipid excipients that compose these formulations on intestinal cytochrome P450s, particularly CYP 3A4. The only evidence that lipid-type excipients may effect cytochrome P450 expression and activity comes indirectly from literature on nutrition.

Yoo et al. reported that levels of cytochrome P450s in rat liver and lung could be modulated by dietary lipid (61). When male Sprague-Dawley rats were fed 20% corn oil for 4 days following 2 days of fasting, the hepatic P450s 1A2, 2B2, 2E1, and 3A were regulated positively, but the level of pulmonary P450 2B1 was suppressed by dietary lipid compared to control rats fed a fat-free diet. Shavila et al. observed that an high-fat diet alone increased ferret liver microsomal 7-ethoxyresorufin *O*-deethylase activity by 90%, but had no effect on 7-methoxy-, 7-pentoxy-, or 7-benzyloxy-resorufin *O*-dealkylase activities compared to animals fed a fat-free diet (4).

In the mid-1970s, Hietanen and colleagues observed that lipid diets consisting of cholesterol, cocoa butter and/or olive oil diets decreased the activities of drug hydroxylation and glucuronidation in the duodenal mucosa (62). They reported 12 years later that dietary cholesterol can modulate total monooxygenase activities primarily in

the intestine, change P-450 isozyme composition in both the liver and the intestine, and modify isozyme composition without changing the overall enzyme activity (63).

On the contrary, Caderni reported that the fat content of a lipid-enriched diet containing olive or corn oil did not affect small intestine and colon monooxygenase activities (3). Smith-Barbaro et al. observed that rats fed a high-fat diet had a significantly elevated small intestinal enzyme activity compared to controls (1). Van Veld et al. reported that dietary fat (primarily TG) inhibits the intestinal metabolism of the carcinogen benzo[a]pyrene (BP) in fish (2). Following the intestinal absorption of BP by fish, this compound becomes incorporated along with dietary TG into membrane-bound fat vacuoles within the intestinal epithelial cell (2). These vacuoles, arising from the smooth endoplasmic reticulum, are important transient structures involved in both the uptake and metabolism of BP. It appears that TG-solubilized BP is capable of diffusion from fat vacuoles to microsomal enzymes. However, increases in the concentration of fat vacuoles (via a fat-enriched diet) decrease the availability of BP to microsomal BP hydroxylase, resulting in less BP being metabolized within the intestine. No studies have been published that investigate if lipid excipients (let alone dietary lipids) affect intestinal cytochrome P450 expression or activity (i.e., CYP 3A4), thus in turn modulating drug bioavailability.

The Role of Lymphatic Transport

The lymphatic system is an elaborate network of specialized vessels distributed throughout the vascular regions of the body (7). The primary and well-recognized function of the lymphatics is to drain the capillary beds and return extracellular fluid to the systemic circulation, thus maintaining the body's water balance. However, the structure and function of the lymphatics throughout the body are not uniform, and in specific areas, the lymphatics perform a specialized role (64–66). For example, the intestinal lymphatic system is responsible for the transport of dietary fat (67) and lipid-soluble vitamins to the systemic circulation (64–66).

Contribution of Lymphatic Transport

Charman et al. have published extensively on the contribution of lymphatic transport to the increased absorption of water-insoluble drugs into the systemic circulation by suggesting that the majority of orally administered drugs gain access to the systemic circulation by direct absorption into the portal blood (6,7). However, for some water-insoluble compounds, transport by way of the intestinal lymphatic system may provide an additional route of access to the systemic circulation (68). Exogenous compounds absorbed via the intestinal lymph appear to be transported generally in association with the lipid core of intestinal lipoproteins (predominantly triglyceride-rich chylomicrons), thereby requiring coadministered lipid to stimulate lipoprotein formation. Delivery into the bloodstream by way of the intestinal lymphatics has been suspected to contribute to the overall absorption of a number of highly lipophilic compounds (7–14).

Lymph from the intestinal lymphatic system (as well as hepatic and lumbar lymph) drains through the thoracic lymph duct into the left internal jugular vein and then to the systemic circulation (15). Thus, the transport of drug by way of the intestinal lymphatic system may increase the percentage of drug that can gain access to the systemic circulation. In addition, the process of intestinal lymphatic drug transport often continues over time periods longer than typically observed for drug absorption through the portal vein. Consequently, drug transport through the lymph may be utilized to prolong the time course of drug delivery to the systemic circulation.

Evaluation and Assessment of Intestinal Lymphatic Transport

A number of animal models have been described for the assessment of intestinal lymphatic drug transport (6,7). Lymphatic transport studies are commonly first conducted in the laboratory rat, with larger, more complicated models (i.e., dog or pig) subsequently investigated (6,7). However, the utility of lymph fistulation in large animals is limited by considerable logistic and economic constraints. Ideally, sampling strategies for lymphatic transport studies should provide the capacity to estimate both the extent of lymphatic transport and the extent of portal blood absorption to estimate the overall bioavailability of the drug/formulation. This strategy enables the unambiguous determination of the extent of lymphatic transport relative to absorption via the portal blood and the total bioavailability of the drug/formulation. As lymphatic transport can be affected by experimental factors such as the site of lymphatic cannulation and the period of fasting prior to dosing (6–10), it is important to standardize procedures when comparing between studies.

The triple-cannulated anesthetized rat model (in which the mesenteric lymph duct, jugular vein, and duodenum are accessed) has been used for the assessment of lymphatic transport. General anesthesia precludes oral dosing in the anesthetized model; consequently, drug and lipid

formulations are administered intraduodenally (6,7). This limitation thus circumvents the inherent emulsifying action of the stomach and the potential effects of lipids on gastric emptying. Recently, Hauss et al. described a conscious, minimally restrained rat model that enables the simultaneous collection of mesenteric lymph and peripheral venous blood from conscious rats (80). This model has been successfully applied to the study of several lipid-based drug delivery systems (81,82).

Proposed Mechanisms That Govern the Lymphatic Transport of Water-Insoluble Drugs

Although the mechanisms by which drugs gain access into the intestinal lymphatic system through the enterocyte are not fully elucidated, there is growing evidence that supports our hypothesis that the majority of drugs transported by the lymphatics are associated with the triglyceride core of chylomicrons (69–71). In addition, two important factors, which appear to be prerequisites for the lymphatic transport of water-insoluble drugs, are the diffusion/partition behavior and lipid solubility of the drug.

Diffusion and Partition Behavior of Water-Insoluble Drugs

The extent of a drug's partitioning between the portal blood and intestinal lymph may be estimated from a comparison of the relative rates of drug mass transfer by each route. In this regard, the rate of fluid flow in the intestinal lymphatic system is approximately 500-fold less than that in the portal blood (72,73), and during peak lipid transport, the lipid content of the lymph is only of the order of 1%–2% (w/v). Thus, the effective mass ratio between lymph lipid and the portal blood is of the order of 1: 50,000. Consequently, the selective lymphatic transport of low molecular weight water-soluble drugs is unlikely if the route of absorption (portal blood versus lymph) is governed by the relative rates of fluid flow. However, this ratio suggests that, for similar extents of absorption and transport by the portal blood and intestinal lymph (not taking into account metabolic conversion, chemical stability, and/or bioavailability considerations), a candidate molecule should have a log octanol/water partition coefficient log P in the region of 5 (highly water insoluble).

Lipid Solubility of Water-Insoluble Drugs

In addition to a high partition coefficient being a prerequisite for lymphatic transport, lipid solubility is a further important parameter to consider. Charman and Stella reported the relationship between lipid solubility and lymphatic transport of two highly water-insoluble compounds (DDT and hexachlorobenzene [HCB]), which have similar octanol/water partition coefficients yet different solubilities (15). Both compounds would be regarded as highly lipophilic, as evidenced by their high octanol/water partition coefficients (6.2 for DDT vs. 6.5 for HCB); however, the 13-fold higher triglyceride solubility of DDT compared with HCB (solubility of 9.75 ± 0.15 for DDT vs. 0.75 ± 0.05 for HCB in peanut oil [g solute/100 ml]) is reflected in the 14.6-fold increase in the extent of intestinal lymph transport reported in an anesthetized rat model (15).

FUTURE DIRECTIONS

A number of years ago, we were confronted with the daunting task of formulating highly water-insoluble compounds into a viable oral dosage form. Available to us at that time was a meager handful of ''approved'' lipid excipients, none of which was capable of producing an acceptable, orally bioavailable formulation. Furthermore, little was known about the physiological and biopharmaceutical aspects of these lipid excipients. In this review article, I tried to address the major formulation, physiological, and biopharmaceutical issues in developing an oral lipid-based drug delivery system. Although much has been learned in the past 10 years about these dosage forms, it is apparent a number of areas still need to be addressed. These include procedures used in the selection and testing of viable lipid-based excipients and how these excipients influence biopharmaceutical aspects such as MDR, drug metabolism, and drug delivery.

ACKNOWLEDGMENT

I would like to acknowledge the lively discussions with and contributions of Drs. David Hauss and Bill Charman about this subject matter.

REFERENCES

1. Smith-Barbaro, P.; Hanson, D.; Reddy, B. S. Lipids, **1981**, *16*, 183–188.
2. Van Veld, P. A.; Vetter, R. D.; Lee, R. F.; Patton, J. S. J. Lipid Res. **1987**, *28*, 810–817.
3. Caderni, G.; Bianchini, F.; Dolara, P.; Lodovici, M.; Quattrucci, E. Nutr. Cancer **1990**, *13*, 111–117.

4. Shavila, J.; Ioannides, C.; King, L. J.; Parke, D. V. Xenobiotica **1994**, *24*, 1063–1076.
5. Mueller, E. A.; Kovarik, J. M.; Uresin, Y.; Preisig-Fluckiger, S. S.; Hensel, S.; Lucker, P. W.; Holt, B. J. Clin. Pharmacol. **1997**, *37*, 1001–1008.
6. Pouton, C. W.; Charman, W. N. Adv. Drug Delivery Rev. **1997**, *25*, 1–2.
7. Porter, C. H. J.; Charman, W. N. Adv. Drug Delivery Rev. **1997**, *25*, 71–89.
8. Charman, W. N.; Porter, C. H. J. Adv. Drug Delivery Rev. **1996**, *19*, 149–169.
9. Ueda, C. T.; Lemaire, M.; Gsell, G.; Nussbaumer, K. Biopharm. Drug Dispos. **1983**, *4*, 113–124.
10. Grimus, R. C.; Schuster, I. Xenobiotica **1984**, *14*, 287–294.
11. Porter, C. J. H.; Charman, S. A.; Charman, W. N. J. Pharm. Sci. **1996**, *85*, 351–356.
12. Humberstone, A. J.; Porter, C. J. H.; Charman, W. N. J. Pharm. Sci. **1996**, *85*, 525–529.
13. Hauss, D. J.; Fogal, S. E.; Ficorilli, J. V.; Price, C. A.; Roy, T.; Jayaraj, A. A.; Keirns, J. J. J. Pharm. Sci. **1998**, *87*, 165–169.
14. Sieber, S. M. Pharmacology **1976**, *14*, 443–454.
15. Charman, W. N.; Stella, V. J. Int. J. Pharm. **1986**, *34*, 175–178.
16. Tucker, G. Lancet **1993**, *341*, 1314–1315.
17. Horst, H. J.; Holte, W. J.; Dennis, M.; Coert, A.; Geelen, J.; Voigt, K. D. Klin. Wschr. **1976**, *54*, 875–879.
18. Gallo-Torres, H. E. Int. J. Vitam. Nutr. Res. **1970**, *40*, 505–514.
19. Ichihashi, T.; Kinoshita, H.; Takagishi, Y.; Yamada, H. J. Pharm. Pharmacol. **1992**, *44*, 560–564.
20. Ichihashi, T.; Kinoshita, H.; Takagishi, Y.; Yamada, H. Pharm. Res. **1991**, *8*, 1302–1306.
21. Sugihara, J.; Furuuchi, S.; Ando, H.; Takashima, K.; Harigaya, S. J. Pharmacobio.-Dyn. **1988**, *11*, 555–562.
22. Sugihara, J.; Furuuchi, S. J. Pharmacobio.-Dyn. **1988**, *11*, 121–130.
23. Muranishi, S. Adv. Drug Res. **1991**, *21*, 1–38.
24. Adachi, I.; Liu, H.; Horkoshi, I.; Ueno, M. Yakugaku Zasshi **1993**, *113*, 256–263.
25. Liu, H.-X.; Adachi, I.; Horkoshi, I.; Ueno, M. Int. J. Pharm. **1995**, *118*, 55–64.
26. Hauss, D. J.; Mehta, S.; Radebaugh, G. W. Int. J. Pharm. **1994**, *108*, 85–93.
27. Tso, P. Intestinal lipid absorption. In *Physiology of the Gastrointestinal Tract*; Johnson, L. R., Chief Ed.; Raven Press: New York, 1994; 1867–1908.
28. Tso, P.; Karlstad, M. D.; Bistrian, B. R.; DeMichele, S. J. Am. J. Physiol. **1994**, *268*, G568–G577.
29. Tso, P.; Balint, J. A. Am. J. Physiol. **1986**, *250*, G715–G725.
30. Tso, P.; Lee, T.; Demichele, S. J. Am. J. Physiol. **1999**, *277*, G333–340.
31. Davis, R. A.; Vance, J. E. Structure, assembly and secretion of lipoproteins. In *Biochemistry of Lipids, Lipoproteins and Membranes*; Vance, D. E., Vance, J. E., Eds.; Elsevier: New York, 1996; 473–493.
32. Hauser, H.; Dyer, J. H.; et al. Biochemistry **1998**, *37*, 17843–17850.
33. Stremmel, W.; Lotz, G.; Strohmeyer, G.; Berk, P. D. J. Clin. Invest. **1985**, *75*, 1068–1076.
34. Crison, J. R.; Weiner, N. D.; Amidon, G. L. J. Pharm. Sci. **1997**, *86*, 384–388.
35. Abrahamsson, B.; Johansson, D.; Torstensson, A.; Wingstrand, D. Pharm. Res. **1994**, *11*, 1093–1097.
36. Yoon, J. K.; Burgess, D. J. Pharm. Dev. Technol. **1996**, *1* (4), 333–341.
37. Kim, Y. H.; Koczo, K.; Wasan, D. T. J. Colloid Interface Sci. **1997**, *187* (1), 29–44.
38. Opawale, F. O.; Burgess, D. J. J. Pharm. Pharmacol. **1998**, *50*, 965–973.
39. Rabiskova, M.; Valaskova, J. J. Microencapsul. **1998**, *15*, 747–751.
40. Ratsimbazafy, V.; Bourret, E.; Duclos, R.; Brossard, C. Eur. J. Pharm. Biopharm. **1999**, *48*, 247–252.
41. Roepe, P. D. Curr. Pharm. Des. **2000**, *6*, 241–260.
42. Sugiyama, Y.; Kusuhara, H.; Suzuki, H. J. Controlled Release **1999**, *62*, 179–186.
43. Ouar, Z.; Lacave, R.; Bens, M.; Vandewalle, A. Cell Biol. Toxicol. **1999**, *15*, 91–100.
44. Orlowski, S.; Garrigos, M. Anticancer Res. **1999**, *19*, 3109–3123.
45. Nielsen, D.; Skovsgaard, T. Biochim. Biophys. Acta **1992**, *1139*, 169–183.
46. Komarov, P. G.; Shtil, A. A.; Buckingham, L. E.; Balasubramanian, M.; Piraner, O.; Emanuele, R. M; Roninson, I. B.; Coon, J. S. Int. J. Cancer **1996**, *68*, 245–250.
47. Lo, Y. L.; Huang, J. D. Biochem. Pharmacol. **2000**, *59*, 665–672.
48. Ruetz, S.; Gros, P. J. Biol. Chem. **1995**, *270*, 25388–25395.
49. Batrakova, E.; Lee, S.; Li, S.; Venne, A.; Alakhov, V.; Kabanov, A. Pharm. Res. **1999**, *16*, 1373–1379.
50. Miller, D. W.; Batrakova, E. V.; Kabanov, A. V. Pharm. Res. **1999**, *16*, 396–401.
51. Zordan-Nudo, T.; Ling, V.; Liu, Z.; Georges, E. Cancer Res. **1993**, *53*, 5994–6000.
52. Batrakova, E. V.; Li, S.; Miller, D. W.; Kabanov, A. V. Pharm. Res. **1999**, *16*, 1366–1372.
53. Regev, R.; Assaraf, Y. G.; Eytan, G. D. Eur. J. Biochem. **1999**, *259*, 18–24.
54. Wacher, V. J.; Silverman, J. A.; Zhang, Y.; Benet, L. Z. J. Pharm. Sci. **1998**, *87*, 1322–1330.
55. Shimada, T.; Yamazaki, H.; Mimura, M.; Inul, Y.; Guengerich, F. P. J. Pharmacol. Exp. Ther. **1994**, *270*, 414–423.
56. Watkins, P. B.; Wrighton, S. A.; Schuetz, E. G.; Molowa, D. T.; Guzellan, P. S. J. Clin. Invest. **1987**, *80*, 1029–1036.
57. Kaminsky, L. S.; Fasco, M. J. Crit. Rev. Toxicol. **1991**, *21*, 407–422.

58. Wacher, V. J.; Wu, C.-Y.; Benet, L. Z. Mol. Carcinog. **1995**, *13*, 129–134.
59. Wacher, V. J.; Salphati, L.; Benet, L. Z. Adv. Drug Delivery Rev. **1996**, *20*, 99–112.
60. Parkinson, A. Toxicol. Pathol. **1996**, *24*, 45–57.
61. Yoo, J. S.; Smith, T. J.; Ning, S. M.; Lee, M. J.; Thomas, P. E.; Yang, C. S. Biochem. Pharmacol. **1992**, *43*, 2535–2542.
62. Hietanen, E.; Laitinen, M.; Vainio, H.; Hanninen, O. Lipids **1975**, *10*, 467–472.
63. Hietanen, E.; Ahotupa, M.; Bereziat, J. C.; Park, S. S.; Gelboin, H. V.; Bartsch, H. Biochem. Pharmacol. **1987**, *36*, 3973–3980.
64. Davidson, N. O. Cellular and molecular mechanisms of small intestinal lipid transport. In *Physiology of the Gastrointestinal Tract*, 3rd Ed.; Johnson, L. R., Ed.; Raven Press: New York, 1994; 1909–1934.
65. Johnson, J. M. Triglyceride biosynthesis in the intestinal mucosa. In *Lipid Absorption: Biochemical and Clinical Aspects*; Rommel, K., Goebell, H., Bohmer, R., Eds.; MTP Press: Lancaster, PA, 1976; 85–94.
66. Zilversmit, D. B. J. Clin. Invest. **1965**, *44*, 1610–1622.
67. McDonald, G. B.; Weidman, M. Q. J. Exp. Physiol. **1987**, *72*, 153–159.
68. Hofmann, A. F.; Borgstrom, B. Physico-chemical state of lipids in intestinal content during their digestion and absorption. Feb. Proc. *21*, 43–50.
69. White, D. G.; Story, M. J.; Barnwell, S. G. Int. J. Pharm. **1991**, *69*, 169–174.
70. McDonald, G. B.; Saunders, D. R.; Weidman, M.; Fisher, L. Am. J. Physiol. **1980**, *239*, G141–G150.
71. Bugaut, M.; Carlier, H. Role of intestinal hydrolases, endogenous substrates and chyloportal partition in fat absorption. In *Fat Absorption*; Kuksis, A., Ed.; CRC Press: Boca Raton, FL, 1987; Vol. 1, 197–232.
72. Bollman, J. L.; Cava, J. C.; Grindley, J. H. J. Lab. Clin. Med. **1948**, *33*, 1349–1352.
73. Reininger, E. J.; Saperstein, L. A. Science **1957**, *126*, 1176.
74. Lobenberg, R.; Amidon, G. L. Eur. J. Pharm. Biopharm. **2000**, *50*, 3.
75. Dressman, J. B.; Amidon, G. L.; Reppas, C.; Shah, V. P. Pharm. Res. **1998**, *15*, 11.
76. Brockmeier, D.; Dengler, H. J.; Voegele, D. Eur. J. Clin. Pharmacol. **1985**, *28*, 291.
77. von Corswant, C.; Thoren, P.; Engstrom, S. J. Pharm. Sci. **1998**, *87*, 200.
78. Chen, G. L.; Hao, W. H. Drug Dev. Ind. Pharm. **1998**, *24*, 557.
79. Itabe, H. Prog. Lipid Res. **1998**, *37*, 181.
80. Hauss, D. J.; Fogal, S. E.; Ficorilli, J. V. Contemp. Top. Lab. Anim. Sci. **1998**, *37*, 56.
81. Hauss, D. J.; Fogal, S. E.; Ficorilli, J. V.; Price, C. A.; Roy, T.; Jayaraj, A. A.; Keirns, J. J. J. Pharm. Sci. **1998**, *87*, 165.
82. Charman, S. A.; Charman, W. N.; Porter, C. J. H. J. Pharm. Sci. **2000**, *89*, 1073.