Pharmaceutical Research, Vol. 12, No. 11, 1995

Review

Lipid Microemulsions for Improving Drug Dissolution and Oral Absorption: Physical and Biopharmaceutical Aspects

Panayiotis P. Constantinides[1,2]

Received March 7, 1995; accepted June 20, 1995

Purpose. This review highlights the state-of-the-art in pharmaceutical microemulsions with emphasis on self-emulsifying systems, from both a physical and biopharmaceutical perspective. Although these systems have several pharmaceutical applications, this review is primarily focused on their potential for oral drug delivery and intestinal absorption improvement.
Methods. Physicochemical characteristics and formulation design based on drug solubility and membrane permeability are discussed.
Results. Case studies in which lipid microemulsions have successfully been used to improve drug solubilization/dissolution and/or intestinal absorption of poorly absorbed drugs/peptides are presented.
Conclusions. Drug development issues such as commercial viability, mechanisms involved, range of applicability, safety, scale-up and manufacture are outlined, and future research and development efforts to address these issues are discussed.

KEY WORDS: self-emulsifying systems; microemulsions; drug dissolution; membrane permeability; intestinal absorption; medium-chain glycerides; enhancer; peptide delivery.

INTRODUCTION

Much attention has been given recently to the use of lipid microemulsions in drug delivery, and excellent reviews can be found in the literature that described both physical properties and pharmaceutical applications (1-3) of these novel lipid-based drug carriers. The purpose of this review is not to give a comprehensive overview of the literature on microemulsions, but instead to focus and critically discuss the potential of self-emulsifying microemulsion systems as a novel oral dosage form for drug solubilization and intestinal absorption enhancement.

Microemulsions are thermodynamically stable, isotropically clear dispersions of two immiscible liquids, such as oil and water, stabilized by an interfacial film of surfactant molecules (1). The surfactant may be pure, a mixture, or combined with other additives. In the absence of water, mixtures of oil(s) and non-ionic surfactant(s) form clear and transparent isotropic solutions that are known as self-emulsifying drug delivery systems (SEDDS) and are recently being used for improving lipophilic drug dissolution and absorption (4-6). One characteristic of these systems is their ability to form fine oil-in-water emulsions upon mild agitation when exposed to aqueous media. Thus, SEDDS represent an efficient vehicle for the *in vivo* administration of emulsions. It is for this reason that they are considered for oral delivery of lipophilic drugs, provided however, that the drug has adequate solubility in the oil or oil/surfactant blend. Microemulsions are superior to simple micellar solutions in terms of solubilization potential and their thermodynamic stability offers advantages over unstable dispersions, such as emulsions and suspensions, since they can be manufactured with little energy input (heat, mixing) and have a long shelf-life. However, the design of effective self-emulsifying microemulsion formulations of drugs, using well-defined and pharmaceutically acceptable excipients is still in its infancy. Few microemulsion systems in marketed products or clinical evaluation have been identified, as in the case of Cyclosporin A with Sandimmune (7) and Sandimmune Neoral (8) soft gelatin formulations although the former formulation is rather a crude emulsion and not a microemulsion. Thus, the full drug delivery potential of lipid microemulsions has yet to be realized, particularly with water-soluble drugs. Oil-soluble drugs can be formulated in oil-in-water (o/w) microemulsions whereas, water-soluble ones are better suited for water-in-oil (w/o) systems. Phase inversion of microemulsions (9,10) upon addition of excess of the dispersed phase or in response to temperature is an interesting property of these systems that can affect drug release both *in vitro* and *in vivo* (1,2).

An increasing number of reports in the literature suggest that lipid-based microemulsions (o/w and w/o) can be used to enhance the oral bioavailability of drugs, including peptides (3,11,12). Drug delivery advantages offered by microemulsions include improved drug solubilization and protection

[1] Pharmaceutical Development, UW 2921 Pharmaceutical Technologies, SmithKline Beecham Pharmaceuticals, P.O. Box 1539, King of Prussia, Pennsylvania, 19406.
[2] To whom correspondence should be addressed.

Abbreviations: AUC, area under the plasma concentration-time curve; F, absolute bioavailability; GI, gastrointestinal; HLB, hydrophile-lipophile balance; i.d., intraduodenal; i.v., intravenous; MCG, medium-chain glycerides; MCM, medium-chain monoglycerides; O/W, oil-in-water; PEG, polyethylene glycol; PGG, polyglycolyzed glycerides; p.o., peroral; SEDDS, self-emulsifying drug delivery systems; W/O, water-in-Oil.

0724-8741/95/1100-1561$07.50/0

against enzymatic hydrolysis, as well as the potential for enhanced absorption afforded by surfactant-induced membrane fluidity and thus permeability changes (13).

In this review, the structure, formulation and physical properties of microemulsions for oral drug delivery are considered first, followed by case studies where lipid microemulsions have been used successfully to improve drug dissolution and/or absorption. In this section, SEDDS together with o/w and w/o microemulsions for lipophilic and hydrophilic drug/peptide delivery, respectively, will be discussed and key factors will be identified that are considered to contribute to the improved absorption from these lipid formulations. Finally, drug development issues and approaches to address these issues are discussed with the hope that this review will stimulate further interest in this important area of drug delivery.

FORMULATION DESIGN/DEVELOPMENT CONSIDERATIONS

Excipient Selection

Although several microemulsion systems have been described in the literature, the challenge for the pharmaceutical formulator is to predict which oil(s) and surfactant(s) to select for a particular application, taking into consideration their acceptability due to potential toxicity (13). The formation of w/o and o/w microemulsions usually involves a combination of three to five basic components, namely, oil, water, surfactant, cosurfactant and electrolyte. However, the use of cosurfactant in microemulsions is not mandatory and alcohol-free self-emulsifying microemulsion systems have been described in the literature (14,15). The tendency toward a w/o or an o/w microemulsion is dependent on the properties of both the oil and surfactant and the oil-to-water ratios. The hydrophile-lipophile balance (HLB) is an empirical formula that is used to select surfactants for microemulsions (1,2). For both non-ionic and ionic surfactants, the HLB value generally varies from 1-45, with the range being 1-20 for non-ionics. Non-ionic or zwitterionic surfactants are often considered for pharmaceutical applications and microemulsion formulation since are less toxic (13,14) and less affected by pH and ionic strength changes (15). Water-in-oil microemulsions are formed using emulsifiers within the HLB range of 3 to 8 while o/w microemulsions are formed within the range of 8-18. The choice of emulsifiers is determined by the average HLB requirement of the proposed microemulsion. Some of the oils and surfactants used to formulate microemulsions for oral drug delivery along with their HLB values and manufacturer's name are listed in Table 1. In most cases, it is the right blend of a low and high HLB surfactant that leads to the formation of a stable microemulsion in the absence of a cosurfactant (14,15).

Medium-chain glycerides derived from coconut oil are particularly attractive for formulating orally active microemulsions since, a) they are stable food grade products and generally recognized as safe by the Food and Drug Administration agency (US FDA Code of Federal Regulations, Title 21, Sections 172 and 184, Interpharm Press, 1989), b) microemulsions incorporating these excipients can be formulated at ambient temperature over a wide range of compositions (15), c) medium-chain glycerides (mono-, di-, and triglycerides) are reported to improve the intestinal absorption of co-formulated drugs (3,5,6,8,11-13,16-18) and, d)

Table 1. Some of the Common Excipients Used to Formulate Lipid Microemulsions for Oral Drug Delivery

Excipient (HLB)	Chemical Definition	Manufacturer
Arlacel 80 (4.3)	sorbitan oleate	ICI Americas (Wilmington, DE)
Arlacel 186 (2.8)	monoolein: propylene glycol (90:10)	ICI Americas (Wilmington, DE)
Capmul MCM (5.5-6.0)	C_8/C_{10} mono-/diglycerides from coconut oil	Abitec (Columbus, OH)
Captex 200 (oil)	C_8/C_{10} diesters of propylene glycol from coconut oil	Abitec (Columbus, OH)
Captex 355 (oil)	C_8/C_{10} triglycerides from coconut oil	Abitec (Columbus, OH)
Centrophase 31 (4.0)	Liquid Lecithin	Central Soya (Fort Wayne, IN)
Cremophor EL (13.5)	polyoxyethylene glycerol triricinoleate 35 DAC	BASF (Parsippany, NJ)
Labrafac CM 10 (10)	C_8/C_{10} polyglycolyzed glycerides from coconut oil	Gattefosse (Westwood, NJ)
Labrafil M 1944 CSD (3-4)	primarily oleic acid ($C_{18:1}$) polyglycolysed glycerides from apricot kernel oil	Gattefosse (Westwood, NJ)
Labrafil M 2125 CS (3-4)	primarily linoleic acid ($C_{18:2}$) polyglycolyzed glycerides from corn oil	Gattefosse (Westwood, NJ)
Labrasol (14)	C_8/C_{10} polyglycolyzed glycerides from coconut oil	Gattefosse (Westwood, NJ)
Miglyol 812 (oil)	C_8/C_{10} triglycerides from coconut oil	Huls, America (Piscataway, NJ)
Myvacet (oil)	distilled acetylated monoglycerides	Eastman Chemicals (Kingsport, TN)
Myverol 18-92 (3.7)	distilled sunflower oil monoglyceride (90% glyceryl linoleate)	Eastman Chemicals (Kingsport, TN)
Soybean Oil	primarily oleic (25%) and linoleic (54%) triglycerides	Croda (Mill Hall, PA)
Tagat TO (11.3)	polyoxyethylene (25) glycerol trioleate	Goldschmidt Chem. (Hopewell, VA)
Tween 80 (15.0)	polyoxyethylene (20) sorbitan oleate	BASF (Parsippany, NJ)

Miglyol 812, a mixture of C_8/C_{10} triglycerides (Table 1), is present in a marketed soft gelatin capsule of Vitamin D_3 (19).

Recently polyglycolyzed glycerides (PGG) with varying fatty acid and polyethylene glycol (PEG) chain lengths and thus varying HLB, in combination with vegetable oils have been used to solubilize poorly water-soluble drugs and improve their bioavailability (6). According to the manufacturer, these products are derived from selected, high purity, food grade vegetable oils which are reacted with pharmaceutical grade PEG and therefore expected to be well tolerated by the body. The work by Shah et al. (6) where factors controlling lipophilic drug release and absorption from SEDDS with polyglycolyzed glycerides have been thoroughly investigated, should serve as a useful reference in properly selecting polyglycolyzed glycerides for similar drug delivery applications.

Lecithin-based microemulsions, both o/w and w/o, are recently being considered as alternative drug delivery system that avoids problems of toxicity associated with some of the non-ionic surfactants (2). However, since lecithin is too lipophilic (HLB = 4.0) and has a tendency to form lamellar liquid crystalline phases, short-chain alcohols are often included to alter the HLB and aid emulsification by destabilizing the liquid-crystalline phases (20). Thus far, phospholipid microemulsions have primarily been used for topical drug delivery (2) and their potential for oral drug delivery needs to be determined.

Microemulsion Formulation and Drug Incorporation

Phase Diagrams

Microemulsion existence fields can be identified from ternary phase diagrams of systems containing oil-surfactant-water. Fig. 1 shows a hypothetical pseudo-ternary phase diagram that represents schematically conventional micelles (L1 Phase), reverse micelles or w/o microemulsions (L2 Phase), o/w microemulsions and coarse emulsions. In the absence of water, oil-surfactant mixtures can be either clear and isotropic solutions (SEDDS) or oily dispersions (Fig. 1) depending on the nature of the oil and surfactant and their mixing ratio. Since water-in-oil microemulsions are also known as reverse micelles or L2 phase, these two phases are represented by the same field on the phase diagram (Fig. 1). Coarse emulsions which are thermodynamically unstable two-phase dispersions are represented on the right side of the phase diagram and along the oil-water line (Fig. 1). In mixtures of oil, water and surfactant several other association structures are formed, such as lamellar, hexagonal and cubic phases and detailed phase diagrams describing these phases can be found in the literature (1,2). These phases, however, although of interest to drug delivery, are beyond the scope of this review article. In terms of their microstructure, o/w and w/o microemulsions are very complex and dynamic systems with intermediate bicontinuous structures being present between the o/w and w/o regions (Fig. 1). These phases are also referred to as type I, II or III Winsor microemulsions and represent microemulsions in equilibrium with excess water, excess oil or both (1). Much of the interest in multiphase microemulsion systems is focused on

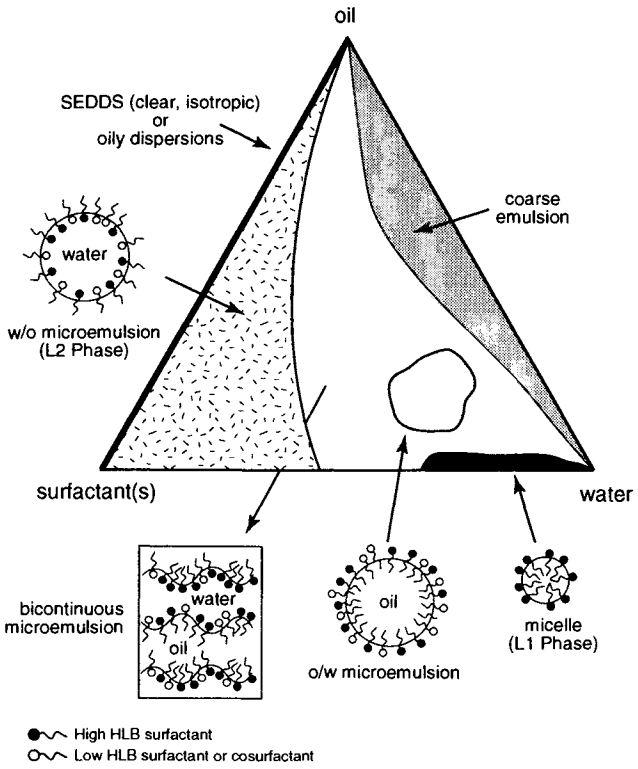

Fig. 1. A hypothetical pseudo-ternary phase diagram of an oil/surfactant/water system with emphasis on microemulsion and emulsion phases. Within the phase diagram, existence fields are shown where conventional micelles (L1 phase), reverse micelles or w/o microemulsions (L2 phase) and o/w microemulsions are formed, along with the bicontinuous microemulsion and coarse emulsion phases. Outside the phase diagram, surfactant microstructures in various phases are schematically indicated. In the absence of water, oil-surfactant blends can be either clear isotropic solutions (SEDDS) or oily dispersions depending on the nature of the oil and surfactant and the oil-to-surfactant ratio.

their applications in enhanced oil recovery and biotechnology (1).

SEDDS are formulated in the absence of water by mixing an oil with a non-ionic surfactant or polyglycolyzed glyceride (4-6) and a lipid-soluble drug to form an isotropic oily solution. Upon dilution or *in vivo* administration they formed fine o/w emulsions. In order to formulate self-emulsifying o/w and w/o microemulsions, however, an oil, a blend of two surfactants and an aqueous phase (water or saline) is used, that is, a total of four basic components. These systems can best be described by pseudo-ternary phase diagrams where, a constant ratio of two of the components is used, and the other two are varied (1,2,15). For example, the mixture of the oil and the oil-soluble low HLB surfactant can be held fixed and titrated with known amounts of the high HLB surfactant and water (11,15). Since the formation of the microemulsion is thermodynamically favored, the order of addition of the components should not have any effect on the final size and stability of the particle.

For preparing microemulsions incorporating long-chain glycerides, such as soybean oil and monoolein, the various components are added and mixed at temperatures between 40-60 °C in order to reduce viscosity. For components which

are solid at room temperature, such as monolein, premelting at the appropriate temperature is necessary before mixing with the oil and other surfactants. For these systems, further equilibration of the resulting microemulsion at 40-50°C for about 24 hrs was found to improve stability (15). Microemulsions incorporating medium-chain glycerides can be formed spontaneously at room temperature over a wide range of compositions (11,15) when their components are brought into contact, that is without the application of high energy or the inclusion of short-chain alcohols that are known to cause tissue irritation (14). Formulation at ambient temperature is particularly advantageous for thermolabile drugs, particularly peptides. The formation and stability of microemulsions consisting of non-ionic components (oil plus surfactants) is not affected by the pH and/or ionic strength of the aqueous phase in the pH range between 3 and 10. This property can be beneficial for drugs and other molecules exhibiting higher solubility and/or stability at low or high pH.

Drug Incorporation into Microemulsions

In properly selecting a suitable microemulsion system for drug solubilization and delivery it is important to have some pre-formulation data, particularly aqueous and/or oil solubility or even better oil/water partition coefficients (11,17) along with *in vitro* membrane permeability data across different regions of intestinal tissues (21). The drug classification by Amidon et al. (22) based on drug solubility and intestinal permeability best described some of the factors controlling the drug dissolution and absorption process. This new biopharmaceutical drug classification is adapted in Table 2 of this review article along with the recommended microemulsion systems to address drug dissolution and absorption for each of the four drug classes (22). It should be emphasized, however, that in order to design efficient microemulsion system(s) to address specific drug delivery needs, computational modelling along with physicochemical studies of both the drug and the microemulsion system(s) are necessary to better understand drug structure/microemulsion composition/permeability correlations.

For SEDDS and o/w microemulsions the drug is solubilized in the oil or the oil/surfactant blend whereas, for w/o microemulsions the drug is preferably solubilized in the aqueous phase followed by the addition of oil/surfactants. The amount of drug incorporated into a given microemulsion is dependent on its relative solubility in the various components of the system, particularly on its oil/water partition coefficient. Preformulation data that includes aqueous solubility, as well as solubility in selected microemulsion excipients (Table 1) is useful and it should preceed any microemulsion formulation work. In addition, it is necessary to investigate what effect the drug has on the formation and stability of the microemulsion particle using some of the physicochemical methods that are described in the next section. Phase diagrams should be constructed in the presence of a particular drug, particularly if the drug is surface active and thus expected to significantly affect the microemulsion region.

Physical Characterization of Microemulsions

Once the construction of the phase diagram is complete and the microemulsion existence field has been identified, simple tests, such as dye solubilization, dilutability by the excess of the dispersed phase and conductance measurement (23) are employed to identify the structure of water-containing microemulsions. Oil-in-water microemulsions where the external phase is water are highly conducting, whereas w/o are not, since water is the internal or dispersed phase. Likewise, o/w microemulsions are dilutable with water, whereas w/o are not and undergo a phase inversion into o/w micro-emulsions (9,10) a property that may have *in vivo* implications. Finally, a water-soluble dye is solubilized within the aqueous phase of the w/o particle but is dispersable in the o/w particle. Non-aqueous microemulsions (SEDDS) can easily be identified as clear and transparent oil-surfactant blends in the absence and presence of a lipophilic drug. Further physical characterization of microemulsions involves measurement of the interfacial tension (1), determination of density, refractive index and viscosity (11,15,24) and particle size (2,10,25). A thorough review by Kahlweit et al. (26) is focused on different experimental techniques used to study microemulsions and it should serve as useful reference for those interested in obtaining further insight into the dymamics of microemulsion structure. Table 3 summarizes some of the physical properties of representative w/o microemulsions incorporating long- vs medium-chain glycerides and saline as the aqueous phase (15). Major

Table 2. Potential Microemulsion Systems for Oral Drug Delivery Based on Aqueous Solubility and Membrane Permeability Considerations[a]

Aqueous Solubility	Membrane Permeability	Potential Microemulsion System	Anticipated Drug Delivery Benefits
High	High	W/O	stabilization and protection against chemical and enzymatic hydrolysis
High	Low	W/O	stabilization and protection against chemical and enzymatic hydrolysis, increased bioavailability[b]
Low	High	SEDDS, O/W	improved solubilization and dissolution, increased bioavailability[b]
Low	Low	SEDDS, O/W	improved solubilization and dissolution, increased bioavailability[b]

[a] Adapted from ref. 22.
[b] Increased rate and/or extent of absorption.

Table 3. Comparison of the Physical Properties of Self-Emulsifying Water-in-Oil Microemulsions Incorporating Long- vs Medium-Chain Glycerides (ref. 15)

Physical Property[a]	Long-Chain[b]	Medium-Chain[c]
Density (gr/cm^3)	0.9010	0.9677
Refractive Index	1.471	1.449
Viscosity (cP)	125.1	56.7
Conductance (μmhos/cm)[d]	0.177	0.540
Droplet Diameter[e] (nm) (mean ± sd)	10.3 ± 2.5	15.2 ± 4.1
Polydispersity[e]	0.114	0.153

[a] Determined at room temperature.
[b] Soybean oil/Arlacel 186/Tween 80/Saline (65/22/10/3, % w/w).
[c] Captex 355/Capmul MCM/Tween 80/Saline (65/22/10/3, % w/w).
[d] The conductance of saline alone was 13,400 μmhos/cm.
[e] Both expressed as particle number results; a polystyrene beads standard of 63 nm produced a particle with a mean droplet diameter of 64.2 ± 15.1 nm and a polydispersity of 0.031.

differences in density, refractive index and viscosity can be seen whereas, similar conductance and particle size were obtained. The extremely low conductance and particle size of these microemulsions is characteristic of a thermodynamically stable w/o particle. Interestingly, saline alone had a conductance of 13,400 μmhos/cm (Table 3).

ORAL DRUG DELIVERY APPLICATIONS OF MICROEMULSION SYSTEMS/CASE STUDIES

SEDDS and O/W Microemulsions

Early work by Pouton (4) on the physical chemistry of SEDDS was very useful and has led to the establishment of these systems for the oral administration of lipophilic drugs that are subject to dissolution rate limited absorption. An efficient SEDDS should, a) be able to form a fine emulsion having particle size of less that 5 μm upon dilution with aqueous media under mild agitation (4-6), and, b) produce oil droplets of appropriate polarity which permit a faster drug release to the aqueous phase (6). In a subsequent study, Charman et al. (5) showed that a self-emulsifying formulation of a lipophilic drug WIN 54954 (5-[5-[2,6-dichloro-4-(dihydro-2-oxazolyl) phenoxy]pentyl]-3-methylisoxazole) that consisted of a medium-chain triglyceride (Neobee M5)/non-ionic surfactant (Tagat TO)/drug (40/25/35, % w/w), can be emulsified rapidly upon gentle agitation in 0.1 N HCl at 37 °C producing emulsions with mean droplet diameter of less than 3 μm. When the absolute bioavailability of the drug in fasted dogs from a soft gelatin capsule of the self-emulsifying formulation was compared to that produced from a PEG 600 solution in a capsule, no significant differences in bioavailability from these two formulations were observed (5). The SEDDS however, improved the reproducibility of the plasma profile in terms of the maximum plasma concentration (C_{max}) and the time to reach the maximum concentration (t_{max}).

Although several non-ionic surfactants can be used in combination with vegetable oils to produce SEDDS, polyglycolyzed glycerides (Table 1) are effective emulsifiers. It has been shown (6) that the molecular weight of PEG in glyceride, the fatty acid chain length and degree of unsaturation, as well as, the concentration of glyceride in the SEDDS play a crucial role in optimizing the performance of the SEDDS (6). Monitoring the release of a lipophilic drug, Ro 15-0778, which is a naphthalene derivative (6), from several SEDDS using different polyglycolyzed emulsifiers, it has been found that Labrafac CM 10 with an HLB of 10 (Table 1) produced the highest release rate. Furthermore, both the dissolution of Ro 15-0778 and pharmacokinetic parameters upon oral administration to non-fasted dogs from a) SEDDS, b) drug solution in PEG 400, (control) c) capsule formulation of wet-milled spray dried powder, and d) tablet formulation of micronized drug, were determined and compared and Fig. 2 and Table 4 summarize these data (6). As can be seen from Fig. 2 and Table 4, the use of the SEDDS resulted in both improved dissolution and absorption (increased C_{max} and AUC) as compared to the other oral dosage forms.

Self-emulsifying formulations of new lipophilic benzodiazepine compounds which can be filled into hard or soft gelatin capsules for oral administration have been recently patented (27). These formulations contain propylene glycol, polyglycolyzed glycerides, such as, Labrafil M 2125 CS or M 1944 CS or Labrasol in combination with Tween 80 (Table 1) and are claimed to be useful for the treatment of pain, panic or anxiety.

Improved dissolution and oral absorption of Indomethacin in the rat from a self-microemulsifying drug delivery system (SMEDDS) incorporating polyglycolyzed glycerides as compared to an aqueous suspension of the drug has also been recently reported (28). This SMEDDS is similar to SEDDS and consists of an oil, surfactant and co-surfactant mixture which emulsifies spontaneously when diluted with water under gentle stirring (28). Its applicability to other lipophilic drugs/peptides need to be determined.

The use of o/w microemulsions, for oral drug delivery has centered around lipophilic peptide delivery, particularly of Cyclosporine. Two oral dosage forms of Cyclosporine are available commercially, which are marketed by the name Sandimmune, an olive oil-based solution that also contains

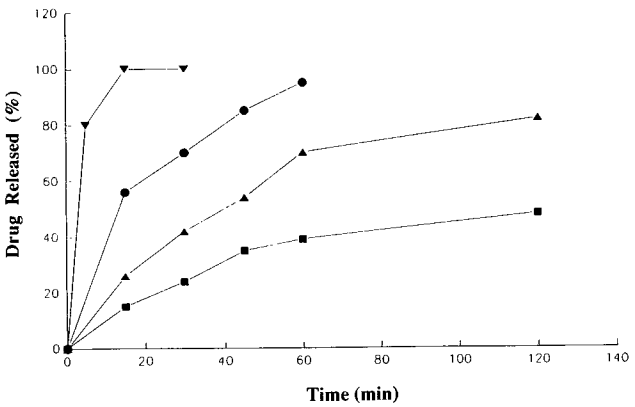

Fig. 2. In vitro dissolution profile of Ro 15-0778 from different formulations. (●) SEDDS; (▼) 1.2 % PEG 400; (▲) wet milled spray dried powder; (■) micronized drug. (Source: ref. 6 with permission)

ethanol and Labrafil M 1944 CS (Table 1) and a soft gelatin formulation that contains, corn oil, gelatin, glycerol, dehydrated ethanol and Labrafil M 2125 CS (Table 1). The extent and rate of absorption of the drug, however, from this formation varies widely, both within-patient and between patient populations, with the oral bioavailability being in the range from about 7-90% and the time to reach peak plasma concentration between 1.5 to 22 hrs (7). Therefore, there has been a need to develop an orally effective formulation of Cyclosporine with more consistent absorption characteristics and several investigators began exploring this possibility using different microemulsion systems.

In a systematic study, Ritschel (3,29,30) reported on the gastrointestinal absorption of Cyclosporin A using a number of o/w microemulsion systems. Three different physical forms of microemulsions were employed: a) a liquid microemulsion for *in situ* studies using the isolated segment rat model to determine absorption site, b) a microemulsion gel formed by the addition of silicon dioxide for rectal bioavailability studies, and c) a microemulsion gel encapsulated into hard gelatin capsules for peroral administration to dogs. Results from a) and b) indicated that the absorption of cyclosporin A followed the order: small intestine > rectum > large intestine ≥ stomach. The results from c) in dogs (29) showed no difference in both the absolute and relative bioavailability between the commercially available Sandimmune solution and an o/w microemulsion formulation (3,29). Similar experiments were carried out in rats (3,30) where the standard Sandimmune p.o. solution and two different microemulsion formulations were administered perorally by intragastric feeding tube and the results are shown in Table 5 (3,30). An approximately 3-fold increase in absolute bioavailability was observed with one of the microemulsions compared to the Sandimmune solution (Table 5). However, a similar microemulsion formulation in which branched chain fatty acid esters were substituted for long-chain fatty acid esters gave no significant improvement in bioavailability over the standard oral solution (Table 5). Although the smaller droplet size in the microemulsion as compared to that of coarse emulsion plays a role in improving absorption, certainly other factors need to be considered, such as, the type of the lipid phase and surfactants in the microemulsion and the digestibility of the lipid used (3). A working model based on a hypothesized mechanism utilizing lipid absorption pathways by which peptides are being absorbed from microemulsions given perorally has been proposed by Ritschel (3). However, caution should be exercised in proposing lipid absorption pathways for the uptake of micellar lipid-based carriers (31), such as mixed micelles and microemulsions, since only monomeric lipid molecules are known to permeate intestinal epithelial cells (32).

A new cyclosporine formulation (Sandimmune Neoral) has recently been developed by Sandoz (33) and is now a marketed product in Europe and in clinical studies elsewhere. This new formulation is a microemulsion preconcentrate that is similar to the earlier discussed SEDDS and it contains cyclosporin A, along with a surfactant, a hydrophilic cosolvent and a blend of lipophilic and hydrophilic solvents (33). Due to compositional differences in the oil and surfactant between the original Sandimmune and Sandimmune Neoral, the later formulation forms an o/w microemulsion upon *in vivo* self-emulsification (33) whereas the former formulation forms a crude emulsion. In clinical studies, Sandimmune Neoral, has shown to produce reduced inter- and intrapatient variability in cyclosporine pharmacokinetics when compared to the marketed original Sandimmune (8). Representative data comparing the pharmacokinetics of these two cyclosporine formulations in stable renal transplant patients is given in Table 6 (33). As can be seen from these data, this new oral formulation of cyclosporin A offers substantial advantages over the currently marketed Sandimmune formulation with respect to the consistency and extent of absorption. It exhibits, reduced t_{max}, increased C_{max} and AUC and thus improved oral bioavailability with less variability (Table 6). In addition, the cyclosporine pharmacokinetics with the Neoral formulation was less affected by the presence of food (Table 6). Independent studies (34) have demonstrated improved dose linearity of cyclosporine pharmacokinetics from the latter formulation. It is very likely, that the differences between these two soft gelatin oral formulations of cyclosporine and the advantages seen with the Sandimmune neoral may be due, at least in part, to the microemulsion structure and composition of this formulation.

W/O Microemulsions

Water-in-oil microemulsions have been rationally designed to overcome metabolic and physical barriers to water-soluble drug molecules, particularly peptides and proteins. Recent reports and patent literature describe self-emulsifying water-in-oil microemulsions (11,12,15,35-37) which are particularly attractive for peptide delivery since they do not require high temperature and/or homogenization for their preparation a condition which is undesirable for labile peptides and proteins. What has contributed to the rapid growth of w/o microemulsions as an oral drug delivery vehicle over

Table 4. Pharmacokinetic Parameters of Ro 15-0778 from Different Formulations in Non-fasting Dogs[a]

Formulation	C_{max} (μg/ml)	t_{max} (h)	AUC (μg h ml^{-1})	Relative Bioavailability (%)
Self-emulsifying solution (SEDDS)	5.57	2.50	29.77	389.0
Drug solution in PEG 400 (control)	1.44	2.00	7.64	100.0
Capsule formulation of wet-milled spray dried powder	0.78	3.00	2.69	35.3
Tablet of micronized drug	0.58	2.00	1.32	17.2

[a] Source: ref. 6, with permission.

Table 5. Pharmacokinetic Parameters of Cyclosporin A Absorption in the Rat after Peroral Administration in Sandimmune Solution and Two Microemulsion Formulations

Parameters[a]	Sandimmune Solution	Microemulsion ME 11[b]	Microemulsion ME 14[c]
Absolute Bioavailability (%F)	11.8 ± 2.8	41.4 ± 18.1	15.0 ± 3.3
Relative Bioavailability (% EBA)	100 (standard)	447.1 ± 287.6[d]	147.2 ± 26.5
C_{max} (μg/ml)	1.95 ± 0.03	4.36 ± 1.65[d]	3.72 ± 1.35
t_{max} (h)	4.35 ± 0.59	9.00 ± 3.47	4.25 ± 0.50

[a] Average ± SD.
[b] Containing Cetiol A (lauric acid hexylester) as the oil phase, a blend of Brij 35 (polyoxyethylene lauryl ether) and Arlacel 186 (Table 1) as surfactants, isopropanol as a cosurfactant and distilled water.
[c] Same as in M11 except that Cetiol A was replaced with Purcellin (branced fatty acids with 13 molecules of ethyleneoxide).
[d] Significantly different from p.o. solutions ($p < 0.05$).
Source: ref 3, with permission.

the last five years or so, however, was the early report (38) that the absorption of insulin, calcitonin and growth hormone can be enhanced upon formulation in a complex water-in-oil microemulsion, a chylomicron-type particle, which is prepared by homogenization at high temperature (38). However, it has later appeared that this system, besides its complexity for processing and manufacture, requires further verification and appropriate controls.

Using w/o microemulsions incorporating long-chain fatty acid esters, surfactants and co-surfactants (isopropanol), Ritschel and co-workers (3) showed that absorption of vasopressin in rats from ligated small intestinal segments was increased by about two-fold when the peptide was formulated in the microemulsion as compared to an aqueous solution (3). In similar studies with insulin (3,39) it was found that the optimal site for absorption of insulin from a microemulsion was the small intestine. They observed significantly higher pharmacologic availability of insulin in the colon of dogs when formulated in a colon-released capsule encapsulating a gel microemulsion (3). As in their studies with cyclosporin A (3,29,30) they found that the composition of the microemulsion strongly influenced absorption of both vasopressin and insulin based on pharmacologic availability (3).

Water-in-oil microemulsions encapsulating water-soluble biologically-active materials, such as peptides, have been reported by Owen et al. (35). These "convertible", w/o microemulsions upon addition of an aqueous fluid are converted to an o/w microemulsion releasing the encapsulated water-soluble molecule. Microemulsions incorporating medium-chain glycerides are claimed to improve the room temperature stability of encapsulated proteins and depending on their composition they can significantly improve the oral and rectal absorption of calcitonin in the rat based on calcium and phosphate serum level reduction (35).

Using several w/o microemulsions (11,12,35,36) of different composition and particle size we have demonstrated significant bioavailability enhancement of a highly water-soluble and poorly absorbed RGD peptide, SK&F 106760 (40) upon intraduodenal administration to rats. This cyclic tetrapeptide [cyclo(S,S)-(2-mercapto)benzoyl-(Nα-methyl)-Arg-Gly-Asp-(2-mercapto)-phenylamide] has a MW of 634 (acetate salt), and is zwitterionic in the physiological pH range (40). Its equilibrium solubility at 25 °C in 0.010 M Tris buffer pH 7.4 is 54 mg/ml (12) and in physiological saline or dilute acetic acid exceeds 100 mg/ml (12). Using a 1:1 (v/v) mixture of Capmul MCM and Ringer's buffer, its oil/buffer partitioning at 37 °C was found to be 13/87 (12). Thus, as expected from its high aqueous solubility, SK&F 106760 partitions primarily in the aqueous phase of this two-phase system and this is likely its distribution between the oil and aqueous phase in a w/o microemulsion. In addition, this peptide is enzymatically stable towards hydrolysis by intestinal enzymes and has low membrane permeability (unpublished

Table 6. Mean (CV%) Pharmacokinetic Parameters Following Twice-Daily Dosing with Sandimmune (SIM) or Sandimmune Neoral (SIMN) by Eleven Stable Renal Transplant Patients

Parameter	SIM Fasting	SIM Non-fasting	SIMN Fasting	SIMN Non-fasting
t_{max} (h)	2.1 (33.3)	2.6 (76.9)	1.5 (33.3)	1.2 (33.3)
C_{max} (μg/L)	663 (34.5)	528 (40.5)	997 (20.0)	892 (35.8)
C_{min} (μg/L)	78 (30.8)	92 (29.3)	94 (22.3)	100 (23.0)
AUC (μg.h/L)	2645 (25.7)	2432 (24.3)	3454 (17.6)	3028 (19.7)
PTF %	261 (23.4)	212 (36.8)	317 (18.0)	309 (31.1)

All concentrations measured in whole blood at steady state. AUC was measured over a dosing interval.
PTF % = percentage peak-trough fluctuation.
Source: ref. 33, with permission.

data). Due to its poor membrane permeability, the observed oral bioavailability of this peptide from a solution is low (Table 7) thus making it a good candidate for absorption enhancement evaluation from w/o microemulsions.

The composition of the evaluated microemulsions along with their droplet size and the bioavailability data are summarized in Table 7. The intraduodenal bioavailability of this peptide from a saline solution is less than 1% but increases up to 29% from the various microemulsion formulations (Table 7). Consistent with other findings (Table 5 and ref. 3,35), enhanced absorption was found to be dependent on the lipid composition of microemulsions, particularly lipids containing medium-chain fatty acids. There was no correlation between the particle size of microemulsion and the increased bioavailability of the aqueous soluble SK&F 106760 (Table 7). In contrast, for lipophilic drugs/peptides, where absorption is dissolution rate limited, a strong correlation was found between the particle size of the emulsion and bioavailability (41,42). A w/o microemulsion formulation of SK&F 106760 with lipid composition similar to that of ME1 and ME2 of Table 7, administered intraduodenally to dogs, (n = 4) resulted in about a 10-fold bioavailability enhancement when compared to a saline formulation of the peptide (unpublished data).

We have also evaluated the approach of enhancing intestinal absorption from w/o microemulsions using Calcein [5(6) carboxyfluorescein, MW = 623] a water-soluble marker molecule. Interestingly, although Calcein and the structurally unrelated RGD peptide have very similar size (MW of about 650), unlike the zwitterionic RGD peptide, Calcein is negatively charged at physiological pH. The solubility of Calcein at 25 °C and pH 7.4 exceeds 100 mg/ml and its oil/buffer partitioning in the Capmul MCM/Ringer's buffer (1:1) system at 37 °C was found to be 7/93 (11). That is, as the RGD peptide, Calcein can be found primarily in the aqueous phase in an oil/water system. From intestinal absorption enhancement perspective, the intraduodenal bioavailability of Calcein in the rat can be enhanced from about 2 % in isotonic 10 mM Tris, pH 7.4 to about 45 % in the ME2 microemulsion of Table 7 where the aqueous phase of the microemulsion (saline) was replaced by isotonic 10 mM Tris, pH 7.4 (11).

DEVELOPMENT ISSUES WITH ORAL MICROEMULSION FORMULATIONS

Commercial Viability

Oil-based soft gelatin capsule formulations of drugs have been on the market as oral medications since early times. However, while considerable progress has been made towards understanding bioavailability of solids from tablets or capsules, there is still not sufficient information in the literature, on the effects of oil(s)/lipid(s) on the absorption of drugs presented in soft gelatin capsules, particularly with lipid microemulsion formulations. For pharmaceutical purposes, each gelatin capsule for oral administration can contain between approximately 0.1 and 1.0 gr of formulated liquid or semi-solid. Therefore, for a commercially viable soft gel capsule formulation that is intended for human use, the dose volume is restricted to about 0.5 ml/capsule or 0.010 ml/kg (for a 70 kg human). Most of the experimental work with animals, however, reported improved bioavailability at much higher administration volume of oils/lipids, thus making any comparisons with human dose difficult. An early

Table 7. Intraduodenal Bioavailabilities of an RGD Peptide (SK&F 106760) in the Rat from W/O Microemulsions of Different Composition and Particle Size (ref. 11,12)

ME	Composition[a] (%, w/w)	Droplet Diameter[b] (mean ± sd)	% F[c] (mean ± sd) n = 3
ME1	Captex 200/Capmul MCM/Centrophase 31/Cremophor EL/Saline (68.3/8.3/1.6/16.5/5.3)	26.4 ± 11.0	29.1 ± 7.1
ME2	Captex 355/Capmul MCM/Tween 80/Saline (65/22/10/3)	15.2 ± 4.2	27.4 ± 8.9
ME3	Captex 200/Centrophase 31/Cremophor EL/Saline (76.5/1.6/16.6/5.3)	585.2 ± 303.7	19.4 ± 11.8
ME4	Captex 200/Capmul MCM/Myverol 18-92/Cremophor EL/Saline (76.5/9.3/1.0/10.0/3.2)	29.5 ± 10.1	14.4 ± 4.4
ME5	Captex 200/Capmul MCM/Centrophase 31/Tween 80/Saline (76.6/9.3/2.1/8.7/3.3)	18.3 ± 4.8	7.4[d]
ME6	Myvacet/Capmul MCM/Myverol 18-92/Cremophor EL/Saline (76.9/9.1/1.0/9.8/3.2)	16.5 ± 4.0	5.4 ± 2.2
ME7	Captex 200/Dicaprin/Centrophase 31/Cremophor EL/Saline (76.5/9.3/1.0/10.0/3.4)	760.1 ± 296.7	2.5 ± 1.9
ME1-C[e]	same as in ME1	same as in ME1	5.3 ± 3.6
Saline	NA	NA	0.5 ± 0.3

[a] The chemical names of the excipients are given in Table 1.

[b] Based on particle number distributions (peptide-free microemulsions).

[c] $F = (AUC_{id}/AUC_{iv}) \times (Dose_{iv}/Dose_{id}) \times 100$; where, AUC is the area under the plasma concentration-time curve in mg.min/ml; the administered dose of the peptide (mg/kg) was 6.5 for ME1 and ME3, 8.4 for ME2 and 10 for saline and the rest of the microemulsions; the administered microemulsion volume was 3.3 ml/kg.

[d] n = 1.

[e] Administration of ME1 (peptide-free) first, followed in 15 min with 10 mg/kg of the peptide in saline.

report in the literature (43) has demonstrated indeed that the oral absorption of an anti-iflammatory lipophilic drug using oily solutions or suspensions incorporating long- or medium-chain glycerides, was strongly dependent on the dose volume of the lipid vehicle in the more clinically relevant range of 0.020-0.100 ml/kg. Gastric emptying in the rat was found to be directly related to the administered lipid vehicle volume, i.e. the higher the volume ($\geq$0.100 ml/kg) the slower the gastric emptying (43). In addition, the fluidity and digestibility of the employed oil were found to affect drug absorption with greater effects being observed with more fluid i.e., less viscous digestible oils, such as medium-chain triglycerides (43). Calcein bioavailability from a w/o microemulsion administered intraduodenally to rats was found to be independent of the dose volume in the range between 0.25 and 2.5 ml/kg (44). These administered formulation volumes/kg, however, are still at least an order of magnitude above the desired formulation volume per body weight or surface area in a clinical dose of a given drug. The administered lipid vehicle volume is expected to have not only physiological effects on the intestine but also physical and structural effects on the intestinal mucosa and this issue is discussed in the next section.

Mechanism(s) of Absorption Enhancement

As discussed earlier, in the case of lipophilic drug absorption from SEDDS or o/w microemulsions improved drug dissolution appear to be the predominant mechanism by which these systems improve oral absorption although for lipophilic peptides, prevention of metabolism is another factor to consider. Very little is known, however, on the mechanism(s) by which w/o microemulsions enhance the oral bioavailability of water-soluble drugs/peptides. Although mechanisms implicating lipid absorption pathways have been proposed (3,38), such mechanisms are not supported by what is known in terms of lipid uptake into the intestinal mucosa (31,32) *In vivo,* w/o microemulsions undergo phase inversion releasing the encapsulated drug (10,35). The exact nature of the *in vivo* particle, however, as well as the site of drug release are largely unknown. One of the proposed mechanisms is based on enhancer (medium-chain glycerides)-induced structural and fluidity changes in the mucosal membrane thus resulting in significant permeability changes. Supporting this mechanism is the fact that several *in vitro* studies have shown that medium-chain glycerides markedly affect the permeability of paracellular markers (13,45,46).

Using medium-chain glyceride formulations of β-lactam antibiotics (16) site-specific absorption enhancement has been obtained with larger effects being observed in the lower than in the upper intestine. In those studies (16) fasted dogs (n = 4) were dosed with 300 mg of cefmetazole sodium in a) enteric coated capsules filled with 2 g of medium-chain glycerides, b) uncoated capsules filled with 2 g of medium-chain glycerides, and c) enteric coated capsules filed with cefmetazole sodium powder. The obtained absolute bioavailabities were, a) 64.8 ± 11.0, b) 20.8 ± 3.8, and c) 5.6 ± 1.7 (16). These results are straightforward and emphasize the suitability of enteric coated capsules in inducing a strong absorption enhancement effect by medium-chain glycerides and are consistent with those of other studies using microemulsion formulations of peptides (3). In addition, *in vitro* studies (46) indicated that Capmul MCM (Table 1) affected electrical and permeability properties of rabbit intestinal epithelium with the distal colon being more sensitive than the ileum. Although there exist structural/compositional differences between upper and lower gastrointestinal mucosal membranes (3,13,45), there is probably a common mechanism by which medium-chain glycerides enhance absorption throughout the gastrointestinal tract and it may involve villus cells in the ileum and surface cells in the distal colon (13,46). Clearly a better understanding of the biophysical characteristics of the epithelial membranes and enhancer-membrane interactions, is necessary in order to elucidate the mechanism by which certain drugs/peptides cross mucosal membranes from microemulsion and other formulations incorporating absorption enhancers.

Toxicity/Safety

There are several points to consider when using absorption enhancers in a dosage form and several review articles can be found in the literature that describe both absorption enhancement technologies and mechanisms (13,45,47). Some of these points include: a) whether the enhancer causes irritation and tissue damage, b) whether the action is reversible, c) the effects of repeated administration, d) whether the enhancer maintains the structural integrity of the mucosa or potentially interacts with mucosal proteins and lipids, e) whether there is any selectivity in the action of the enhancer, that is, it promotes the permeation of the drug only and not of any other formulation components/excipients and/or contents of the intestine, f) how the enhancer is being metabolized and, g) the overall safety of the enhancer. It is obvious that these effects may have serious toxicological implications and must be carefully evaluated when considering absorption enhancers for product development.

In some of the oral drug delivery studies in animals (rats) using microemulsion formulations at different dosing volumes, tissue irritation is usually evaluated by gross examination of the entire gastrointestinal tract at the conclusion of the absorption studies (11,12). Absence of any lesions is, in general, indicative of no tissue damage (11,12). However, a more definitive histological examination is required in order to assess acute local toxicity and mucosal damage as described by Swenson et al. (13,48). Using a single pass rat intestinal perfusion system (48) they ranked different surfactants (bile salts, Tween 80 and sodium dodecyl sulfate) for their absorption enhancing ability using phenol red as a model compound. The observed absorption enhancement effect was then correlated to biochemical and morphological effects of these surfactants on the intestine. Release of enzymes, such as LDH, and lipid phosphate accompanied some of the surfactants employed (48) and suggested some intestinal wall damage by these surfactants. Further histological examination demonstrated, at least qualitatively, that the release of the aforementioned cellular markers was associated with tissue damage and it was not only due to increased mucosal permeability (48). Interestingly, upon removal of the surfactant both biochemical and histological markers returned to their normal levels, suggesting revers-

ibility in the action of the enhancer and ability of the epithelial cells to rapidly repair the damage (48). Although encouraging, it should be emphasized that these studies, as well as others (13,45), only address short-term effects of absorption enhancers/surfactants and there is a need for chronic oral toxicity studies of each enhancer-containing formulation, preferably in a gelatin capsule using a suitable animal model. Results from these studies would allow a therapeutically useful window to be identified between the absorption enhancing and toxic dose of a particular surfactant. A versatile absorption enhancer, perhaps by a combination of a synthetic and a naturally occurring biopolymer that exhibits the ideal toxicological and bioavailability profile will be a dream come through for pharmaceutical development.

Range of Applicability

It is difficult to predict the *in vivo* behavior of drug formulations using lipid microemulsions both non-aqueous and emulsified ones. This can be ascribed to several factors, both physical and physiological, that may affect drug absorption from these systems. These factors include: 1) whether the drug is formulated in an oil or emulsified form and in the later form how it is being distributed between the two phases, 2) the absorption pathway of the drug, 3) the nature and particle size of the *in vivo* emulsion, 4) the role of surfactants/enhancers, 5) the metabolic pathway of the oil (triglyceride), and 6) the tendency of the formulation to slow gastric motility and to promote emptying of the gall bladder.

Not surprising, reports in the literature have shown that the absorption of drugs from oral dosage forms containing oil(s)/lipid(s) is sometimes increased by the presence of a lipophilic solvent and sometimes is unaffected or even decreased if the oil is non-digestible (49). It is therefore apparent that any prediction of possible effects of lipid(s) on drug absorption is dependent on the particular combination of the drug and lipid involved, and this in turn has implications in the formulation of lipid-based dosage forms. A useful approach frequently used to predict effects of lipids on absorption are *in vitro* drug release studies from lipid-base dosage forms, particularly under simulated gastrointestinal conditions. The nature of the drug and the lipid, as well as the aqueous and lipid solubility of the drug are crucial factors that control drug release/absorption from lipid-based dosage formulations (49).

For SEDDS it has been shown (4-6) that the oil/water partition coefficient of the drug and droplet size can modulate drug release. Droplet size upon dilution with aqueous media is primarily controlled by the nature and concentration of the emulsifier, and phase diagrams of the oil/non-ionic surfactant/drug can be constructed to identify regions where maximum self-emulsification occurs (4-6). The higher the concentration of the emulsifier, the smaller the droplet size of the resulting emulsion and the faster the drug release (4-6). The combination of small droplets along with a low oil/water partition coefficient will allow for an optimum drug release from SEDDS (6).

Likewise, drug release from microemulsions (o/w and w/o), depends on a number of different process parameters, such as oil/aqueous phase ratio, the droplet size, the distribution of the drug in the phases of the microemulsion system and its diffusion rate in both phases (50). For water-soluble dyes, such as methylene, bromophenol and sudan blue, using aqueous or medium-chain glyceride solutions, a good correlation between their solubility in the medium-chain glyceride and rectal absorption in the rat was observed (17). The higher the aqueous solubility or the lower the solubility in the medium-chain glycerides that is, the higher the water/oil partition coefficient, the higher the bioavailability (17). It is therefore not surprising that not all water-soluble drugs can be formulated in water-in-oil microemulsions with a concomitant improvement of their intestinal absorption. Though direct determination of drug distribution between the aqueous and oil phases of a microemulsion is difficult, water/oil partitioning studies using the aqueous and oil phases of the corresponding microemulsion (11,12,17) should be conducted and correlated to the observed oral bioavailability and/or *in vitro* permeability (11,46).

Scale-up and Manufacture

Some of the general issues with the scale-up of liquid and semisolid disperse systems, such as compositional changes, scale-up equipment, in-process controls and finished product specifications have recently been addressed by the joint AAPS/FDA/USP Workshop III (51). In the case of emulsions/suspensions, in-process controls such as the rate, intensity and duration of agitation/mixing, emulsification conditions (time, rate and temperature), order of addition, heat gain/loss and particle size reduction need to be considered (51). One of the advantages of self-emulsifying microemulsions over emulsions or suspensions, in relation to scale-up and manufacture is that, they form spontaneously upon mixing their components under mild agitation and they are thermodynamically stable. That is, microemulsion preparation requires only the availability of the most basic mixing equipment. Furthermore, their manufacture is to a lesser extent dependent on the careful control of manufacturing process as, for example, during the preparation of emulsions. However, batch-to-batch variability of the excipients which are natural products of varying degrees of purity, as well as, chemical instabilities need to be addressed and evaluated as part of the formulation work. In addition drug stability, potency and release from oral dosage forms (gelatin capsule) using microemulsion formulations need to be considered.

Liquid fill soft or hard gelatin capsules will continue to be an attractive oral dosage form for microemulsion formulations. In order to develop a product, however, using a soft or hard gelatin drug formulation of a realistic size, the selection of the vehicle where the drug has maximum solubility becomes an important issue to consider. In addition, issues as the hygroscopicity of the contents inducing dehydration of the gelatin shell or solute migration into the shell must also be considered. It is important that these dynamic changes are thoroughly investigated during the preformulation stage in the development of a particular soft or hard gel product. These studies should also include solubility characteristics of the drug to be encapsulated particularly in relation to temperature and moisture effects. This information can then be used to design fill liquid formulations which give optimum conditions for drug solubility, physical stability and enhanced bioavailability.

CONCLUSION

Specific examples of improved drug delivery characteristics from microemulsion formulations, such as, increased dissolution and oral bioavailability compared to more conventional dosage forms have been discussed in the preceeding sections. Unlike SEDDS and o/w microemulsions, however, where specific pharmacokinetic requirements have been met with drugs/peptides already on the market i.e. cyclosporin A, the commercial potential of w/o microemulsions has yet to be proven and most of the work to date has been focused on a very productive pre-clinical research, particularly during the last five years or so. SEDDS are likely to have increasing applications in the future as oral dosage forms for lipid-soluble drugs/peptides. Selecting, however, the most suitable system for a particular drug is always challenging and requires a better understanding of their drug release and absorption characteristics. Further research and development is necessary, taking into consideration the aforementioned drug development issues, in order to establish a database on drug structure/microemulsion composition/ absorption relationships and rationally use this information to design orally active dosage forms.

ACKNOWLEDGMENTS

I like to thank my colleagues at SmithKline Beecham Pharmaceuticals, Drs. Choon Oh and Doris Wall, as well as Drs. Albert J. Owen and Seang H. Yiv of IBAH Inc. Bio-Pharm Drug Delivery Services for their useful comments upon reading the manuscript. I am grateful to Dr. David W. Holt of St. George's Hospital Medical School (London, UK), Dr. Wolfgang A. Ritschel of the University of Cincinnati College of Pharmacy and Dr. Navnit H. Shah of Hoffmann-La Roche, for permission to include some of their published data in this review article.

REFERENCES

1. G. M. Eccleston. Microemulsions. In: J. Swarbrick and J. C. Boylan (eds). *Encyclopedia of Pharmaceutical Technology*. Marcel Dekker, New York, 1992, Vol. 9, pp. 375-421.
2. D. Attwood. Microemulsions. In: J. Kreuter (ed). *Colloidal Drug Delivery Systems*. Marcel Dekker, New York, 1994, pp. 31-71.
3. W. A. Ritschel. Microemulsions for improved peptide absorption from the gastrointestinal tract. *Meth. Find. Exp. Clin. Pharmacol.* 13: 205-220 (1993).
4. C. W. Pouton. Self-emulsifying drug delivery systems: assessment of the efficiency of emulsification. *Int. J. Pharm.* 27: 335-348 (1985).
5. S. A. Charman, W. N. Charman, M. C. Rogge, T. D. Wilson, F. J. Dutko and C. W. Pouton. Self-emulsifying drug delivery systems: formulation and biopharmaceutical evaluation of an investigational lipophilic compound. *Pharm. Res.* 9: 87-93, (1992).
6. N. H. Shah, M. T. Carvajal, C. I. Patel, M. H. Infeld and A. W. Malick, Self-emulsifying drug delivery systems with polyglycolyzed glycerides for improving *in vitro* dissolution and oral absorption of lipophilic drugs. *Int. J. Pharm.* 106: 15-23 (1994).
7. R. J. Ptachcinsky, R. Venkataramanan, and G. J. Burckart, Clinical pharmacokinetics of Cyclosporin. *Clin. Pharmacokinet.* 11: 107-132 (1986).
8. J.M. Kovarik, E. A. Mueller, J. B. van Bree, W. Tetzloff and K. Kutz, Reduced inter- and intraindividual variability in Cyclosporine pharmacokinetics from a microemulsion formulation. *J. Pharm. Sci.* 83: 444-446 (1994).
9. Greiner, R. W. and D. F. Evans, Spontaneous formation of a water-continuous emulsion from water-in-oil microemulsion. *Langmuir* 6: 1793-1796 (1990).
10. P. P. Constantinides and S. H. Yiv. Particle size of phase inverted water-in-oil microemulsions under different dilution and storage conditions. *Int. J. Pharm.* 115: 225-234 (1995).
11. P. P. Constantinides, J.P. Scalart, C. Lancaster, J. Marcello, G. Marks, H. Ellens and P. L. Smith. Formulation and intestinal absorption enhancement evaluation of water-in-oil microemulsions incorporating medium-chain glycerides. *Pharm. Res.* 11: 1385-1390 (1994).
12. P. P. Constantinides, C. M. Lancaster, J. Marcello, D. Chiossone, D. Orner, I. Hidalgo, P. L. Smith, A. B. Sarkahian, S. H. Yiv and A. J. Owen. Enhanced intestinal absorption of an RGD peptide from water-in-oil microemulsions of different composition and particle size. *J. Control. Rel.* 34: 109-116 (1995).
13. E. C. Swenson and W. J. Curatolo. Intestinal permeability enhancement for proteins, peptides and other polar drugs: mechanisms and potential toxicity. *Adv. Drug Deliv. Rev.* 8: 39-92, (1992).
14. D. W. Osborne, C. A. Middleton, and R. L. Rogers. Alcohol-free microemulsions. *J. Dispersion Sci. Technol.* 9: 415-423 (1988).
15. P. P. Constantinides and J-P. Scalart. Self-emulsifying water-in-oil microemulsions in drug delivery: Formulation and physical characterization. *Particul. and Process. Sci. Technol.: An Int. Journal* 1 (1): in press (1995).
16. M. Sekine, H. Terashima, K. Sasahara, K. Nishimura, R. Okada and S. Awazu. Improvement of bioavailability of poorly absorbed drugs II. Effect of medium-chain glyceride base on the intestinal absorption of cefmetazole sodium in rats and dogs. *J. Pharmacobio-Dyn.* 8: 286-295 (1985).
17. M. Sekine, K. Sasahara, R. Okada and S. Awazu. Improvement of bioavailability of poorly absorbed drugs. IV. Mechanism of the promoting effect of medium-chain glyceride on the rectal absorption of water soluble drugs. *J. Pharmacobio-Dyn.* 8: 645-652 (1985).
18. G. Beskid, J. Unowsky, C. R. Behl, J. Siebelist, J. L. Tossounian, C. M. McGarry, N. H. Shah and R. Cleeland. Enteral, oral and rectal absorption of Ceftriaxone using glyceride enhancers. *Chemother.* 34: 77-84 (1988).
19. I. Holmberg, L. Aksnes, T. Berlin, B. Lindback, J. Zemgals and B. Lindeke. Absorption of a pharmacological dose of vitamin D3 from two different lipid vehicles in man: comparison of peanut oil and a medium-chain triglyceride. *Biopharm. Drug Disposition* 11: 807-815 (1990).
20. K. Shinoda, M. Araki, A. Sadaghiani, A. Khan, and B. Lindman. Lecithin-based microemulsions: Phase behavior and microstructure. *J. Phys. Chem.* 95: 989-993 (1991)
21. N. Jezyk, W. Rubans and G. M. Grass. Permeability characteristics of various intestinal regions of rabbit, dog and monkey. *Pharm. Res.* 9: 1580-1586 (1993).
22. G. L. Amidon, H. Lennernas, V. P. Shah and J. R. Crison. A theoretical basis for a biopharmaceutic drug classification: The correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. *Pharm. Res.* 12: 413-420 (1995).
23. B. Latreille and P. Paquin. Evaluation of emulsion stability by centrifugation and conductivity measurements. *J. Food Sci.* 55: 1666-1672, (1990).
24. G. Ktistis. A viscosity study on oil-in-water microemulsions. *Int. J. Pharm.* 61: 213-218 (1990).
25. A. M. Cabazat, D. Langevin, and A. Pouchelon. Light scattering study of water-in-oil microemulsions. *J. Colloid Interface Sci.* 73: 1-11 (1980).
26. M. Kahlweit, R. Strey, D. Haase, H. Kunieda, T. Schmeling, B. Faulhaber, M. Borkovec, H.-F. Eicke, G. Busse, F. Eggers, T.H. Funck, H. Richmann, L. Magid, O. Soderman, P. Stilbs, J. Winkler, A. Dittrich and W. Jahn. How to study microemulsions. *J. Colloid Interface Sci.* 118: 436-453 (1987).
27. Lievens, Hildegard S. R. Pharmaceutical formulations of benzodiazepines. *European Patent Application* EP 0 517 412 A1, 26 May, 1992.
28. N. Farah, J. P. Laforet and J. Denis. Self-microemulsifying drug

delivery systems for improving dissolution of drugs: *in vitro/in vivo* evaluation. *Pharm. Res.* **11**: S-202 (1994).
29. W. A. Ritschel, G. B. Ritschel, A. Sabouni, D. Wolochuk and T. Schroeder. Study on the peroral absorption of the endekapeptide cyclosporin A. *Meth. Find. Exp. Clin. Pharmacol.* **11**: 281-287 (1989).
30. W. A. Ritschel, S. Adolph, G. B. Ritschel and T. Schroeder. Improvement of peroral absorption of cyclosporin A by microemulsions. *Meth. Find. Exp. Clin. Pharmacol.* **12**: 127-134 (1990)
31. P. L. Smith, D. A. Wall and G. Wilson. Drug carriers for the oral administration and transport of peptide drugs across the gastrointestinal epithelium. In: A. Rolland (ed). *Pharmaceutical Particulate Carriers: Therapeutic Applications*. Marcel Dekker, New York, 1993, pp. 109-166.
32. H. Westergaard and J. M. Dietschy. The uptake of lipids into the intestinal mucosa. In: T.E. Andreoli, J. F. Hoffman, D. D. Fanestil and S. G. Schultz, (eds). Membrane Transport Processes in Organized Systems. Plenum, New York, 1987, pp. 213-224.
33. D. W. Holt, E. A. Mueller, J. M. Kovarik, J. B. van Bree and K. Kutz. The pharmacokinetics of Sandimmune Neoral: A new oral formulation of cyclosporine. *Transplant. Proc.* **26**: 2935-2939 (1994).
34. E. A. Mueller, J. M. Kovarik, J. B. van Bree, W. Tetzloff, J. Grevel and K. Kutz. Improved dose linearity of cyclosporine pharmacokinetics from a microemulsion formulation. *Pharm. Res.* **11**: 301-304 (1994).
35. A. J. Owen, S. H. Yiv and Ani Sarkahian. Convertible microemulsion formulations. *PCT Patent Application* WO 92/18147, 29 October 1992.
36. P. P. Constantinides. Water-in-oil microemulsions. *PCT Patent Application* WO 93/02664, 18 February 1993
37. P. P. Constantinides and S. H. Yiv. Pharmaceutical emulsion compositions. *PCT Patent Application* WO 94/08610, 28 April 1994.
38. Y. W. Cho. Pharmaceutical Compositions. *U.S Patent* 4, 849, 227, 18 July 1989.
39. W. A. Ritschel, G. B. Ritschel and G. Sathyan. Insulin drug delivery systems: rectal gels. *Res. Commun. Chem. Pathol. Pharmacol.* **62**: 103-112 (1988).
40. J. Samanen, F. Ali, T. Romoff, R. Calvo, E. Sorenson, J. Vasko, B. Storer, D. Berry, D. Bennett, M. Strohsacker, D. Powers, J. Stadel and A. Nichols. Development of a small RGD peptide fibrinogen receptor antagonist with potent antiaggregatory activity *in vitro*. *Med. Chem.* 34: 3114-3125 (1991).
41. R. A. Myers and V. J. Stella, Systemic bioavailability of penclomedine (NSC-338720) from oil-in-water emulsions administered intraduodenally to rats. *Int. J. Pharm.* 78: 217-226 (1992).
42. T. T. Kararli, T. E. Needham, M. Griffin, G. Schoenhard, L. J. Ferro and L. Alcorn, Oral delivery of a renin inhibitor compound using emulsion formulations. *Pharm. Res.* **9**: 888-893 (1992).
43. Y. Yamahira, T. Noguchi, H. Takenaka and T. Maeda. Biopharmaceutical studies of lipid-containing oral dosage forms: Relationship between drug absorption and gastric emptying of lipid formulations. *J. Pharmacobio Dyn.* **1**: 160-167 (1978).
44. S. T. Nielsen, S. H. Yiv, P. Dentinger, A. Dickason and A. Owen. Microemulsion-based drug delivery system: Characterization of pharmacokinetic parameters of calcein absorption in the rat. *Pharm. Res.* **10**: S 293 (1993).
45. V.H.L.Lee, A. Yamamoto and U. B. Kompella. Mucosal penetration enhancers for facilitation of peptide and protein drug absorption. *Crit. Rev. Ther. Drug Carrier Syst.* 8: 91-192 (1991).
46. P.-Y. Yeh, P. L. Smith and H. Ellens. Effect of medium-chain glycerides on physiological properties of rabbitt intestinal epithelium *in vitro*. *Pharm. Res.* **11**: 1148-1154 (1994).
47. D. S. Hsieh. Understanding permeation enhancement technologies. In: D. S. Hsieh (ed). *Drug permeation enhancement: Theory and applications*. Marcel Dekker, New York, 1994, pp. 3-17.
48. E. S. Swenson, W. B. Milisen and W. Curatolo. Intestinal permeability enhancement: efficacy, acute local toxicity and reversibility. *Pharm. Res.* **11**: 1132-1142 (1994).
49. N. A. Armstrong and K. C. James. Drug release from lipid-based dosage forms. II. *Int. J. Pharm.* **6**: 195-204 (1980).
50. M. Ttotta, M. R. Gasco and S. Morel. Release of drugs from oil-in-water microemulsions. *J. Control. Rel.* **10**: 237-243 (1989).
51. G. A. van Burskirk, V. P. Shah, D. Adair, H. M. Arbit, S. V. Dighe, M. Fawzi, T. Feldman, G. L. Flynn, M. A. Gonzalez, V. A. Gray, R. H. Guy, A. K. Herd, S. L. Hem, C. Hoiberg, R. Jerussi, A. S. Kaplan, L. J. Lesko, H. M. Malinowski, N.M. Meltzer, R. L. Nedich, D. M. Pearce, G. Peck, A. Rudman, D. Savello, J. B. Schwartz, P. Schwartz, J. P. Skelly, R. K. Vanderlaan, J. C. T. Wang, N. Weiner, D. R. Winkel and J. L. Zatz. Workshop III Report: Scale-up of liquid and semisolid disperse systems. *Eur. J. Pharm. Biopharm.* 40: 251-254 (1994).