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Self-emulsifying drug delivery systems (SEDDS) with polyglycolyzed glycerides for improving in vitro dissolution and oral absorption of lipophilic drugs

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Abstract

The ability of polyglycolyzed glycerides (PGG) with varying fatty acid and polyethylene glycol (PEG) chain lengths to produce the self-emulsification of oil in water has been investigated. The quality of the resulting emulsions depends on the oil and emulsifier pair selected. These self-emulsifying drug delivery systems (SEDDS) were prepared using various concentrations of PGG as emulsifiers. Two oils, a medium-chain triglyceride (Neobee M5) and Peanut Oil, were chosen as the vehicle for the drug. A lipophilic drug with excellent oil solubility was selected for this study. The droplet size distribution, the release rate of the drug and the oil/water partition coefficient ($PC_{o/w}$) of the drug in these systems were evaluated for the SEDDS obtained. The results indicate that PGG are effective emulsifiers for SEDDS. Droplet particle size in combination with droplet polarity in the emulsion are prerequisites for efficient SEDDS. The $PC_{o/w}$ of the drug from these SEDDS is helpful in evaluating these properties. A phase diagram was used to obtain the optimum concentrations of drug, oil and emulsifying agent. The results obtained with PGG were compared with previously reported SEDDS for the efficiency of drug release (Bachynsky et al., (1989) AAPS Annual Meeting). In vitro dissolution and in vivo absorption of a lipophilic drug from SEDDS are compared with those properties of other dosage forms.

Key words: Self-emulsification; Polyglycolyzed glyceride; Nonionic surfactant

1. Introduction

Self-emulsifying drug delivery systems (SEDDS) are isotropic mixtures of an oil and a non-ionic emulsifier. One feature of these mixtures is their ability to form fine oil-in-water emulsions with only gentle agitation when exposed to aqueous media. This property makes SEDDS good candidates for the oral delivery of hydrophobic drugs with adequate oil solubility. After oral administration of soft gelatin capsules containing SEDDS, readily disperse in the stomach to form a fine emulsion; in this case, the digestive motility of the stomach and the intestine can provide the agitation necessary for self-emulsification (Groves and De Galindez, 1976; McClintic., 1976). At a given temperature, self-

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emulsification occurs when the entropy change that favors dispersion is greater than the energy required to increase the surface area of the dispersion (Reiss, 1975). The performance of SEDDS is dependent upon two main factors: (1) the ability of the self-emulsifying mixture to form an emulsion of fine particles (i.e., $< 5\ \mu m$) with a uniform size distribution; and (2) the polarity of the resulting oil droplets to promote a fast rate of release of the drug into the aqueous phase. The efficiency of emulsifiers in SEDDS is commonly related to their ability to form fine droplet size of the emulsion on exposure to water, having polarity favoring faster rate of the drug release (Groves and De Galindez, 1976; Pouton, 1985; Charman et al., 1992). For drugs subject to dissolution rate limited absorption, SEDDS may offer improvement in the rate and extent of absorption, as well as in the reproducibility of the blood level-time profile (Pouton, 1985; Charman et al., 1992). SEDDS containing medium-chain monoglycerides (Capmul MCM90) and PEG-25 trioleate (Tagat TO) have been reported to form small (submicron) droplet oil-in-water emulsions (Bachynsky et al., 1989; Shah et al., 1990; Charman et al., 1992).

In the present study, PGG were evaluated as potential emulsifiers for SEDDS. A comparison was made between PGG, Capmul MCM90 and Tagat TO for their efficiency as emulsifier in the SEDDS. Finally, in order to check the potential utility of SEDDS for improving the absorption of poorly water soluble drugs, in vitro dissolution and in vivo absorption studies were conducted for various dosage forms.

2. Theoretical considerations

The efficiency of SEDDS depends on two main factors: (1) uniform fine particle size of oil droplets on exposure to aqueous media; and (2) the polarity of the resulting oil droplets. Both properties control the rate of release of the drug from the oil to the aqueous phase.

Once exposed to the aqueous phase, SEDDS form oil-in-water (o/w) emulsions. The resulting o/w emulsions produced spontaneously because SEDDS are thermodynamically stable, as opposed to the regular emulsions, which are thermodynamically unstable. There are two factors that favor emulsion stability in the case of SEDDS: (1) relatively small volume of the dispersed oil phase; and (2) narrow range of droplet size distribution. For a given combination of components, emulsions with small, uniform droplet size will take longer to break. Larger droplets are less stable than smaller droplets due to their larger area to volume ratio, and so will tend to grow at the expense of the smaller droplets (Shaw, 1980). The smaller droplets will have a larger interfacial surface area per unit volume. The diffusion path for a drug will decrease with the reduction of the radius of the droplets.

Another important factor for the performance of SEDDS is the polarity of the oil droplets. The polarity of the oil droplets is governed by the hydrophile-lipophile balance (HLB), the chain length and degree of unsaturation of the fatty acid, the molecular weight of the hydrophilic portion and the concentration of the emulsifier. The combination of small droplets together with the appropriate polarity (lower $PC_{o/w}$ of the drug) of the droplets will permit an acceptable rate of release of the drug. Polarity of the oil droplets is also estimated by the oil/water partition coefficient ($PC_{o/w}$) of the lipophilic drug.

A schematic representation of the drug release from emulsion is shown in Fig. 1. The amount of

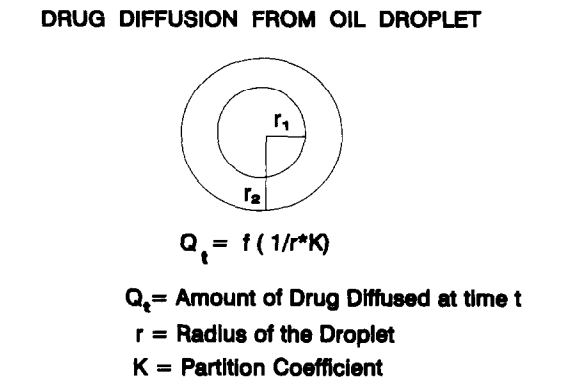

Fig. 1. Schematic of drug diffusion from oil droplet. r_1 and r_2 are the 'ending and starting' droplet size as release is taking place.

drug diffused at time t, Q_t, from the oil droplet to the aqueous environment is primarily a function of the radius of the droplet, r, which is a reflection of the surface area, and the partition coefficient, K (polarity), which reflects the affinity of the drug for oil and/or water and the type of forces formed. A picture of an ideal SEDDS indicating its maximum efficiency on exposure to water is shown in Fig. 2.

3. Experimental

3.1. Materials

All the following materials were used as received:

Lipophilic model drug: Ro 15-0778, a naphthalene derivative, with low water solubility, < 0.01 mg/ml, and high peanut oil solubility, 95 mg/ml.

Vegetable oils: Peanut Oil (Ruger, Irvington, NJ and Croda, New York, NY), Neobee M5 (Stepan Co., Maywood, NJ).

Table 1
Polyglycolyzed glycerides

Emulsifier PEG glyceride	Oil/main fatty acid in glyceride	Mol. Wt of PEG in glyceride	HLB
Labrafil M 2125 CS	corn oil/ linoleic acid, $C_{18:2}$	300	3–4
Labrafil M 1944 CSD	apricot kernel oil/oleic acid, $C_{18:1}$	300	3–4
Labrafac Hydro	MCT/ caprylic and capric	200	4–5
Labrafac CM 6 BM 290	MCT/ caprylic and capric	200	6
Labrafil WL 2609 BS	corn oil/ linoleic acid, 18:2	400	6–7
Labrafac CM 8 BM 284	MCT/ caprylic and capric	400	8
Labrafac CM 10 BM 287	MCT/ caprylic and capric	400	10
Labrafil M 10 BM 355	corn oil/ linoleic acid, 18:2	600	10
Labrafil NA 10 BM 369	apricot kernel oil/oleic acid, 18:1	600	10
Labrasol	MCT/ caprylic and capric	400	14

MCT, medium chain (C_8–C_{10}) triglycerides from coconut oil.

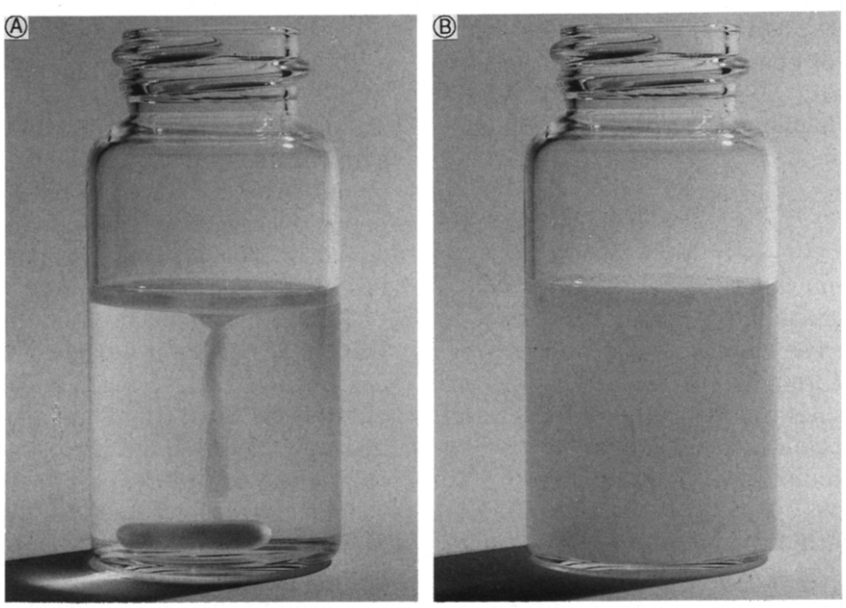

Fig. 2. Photograph of an ideal SEDDS in water. (A) t = 0 min, (B) t = 2 min.

Table 2
Formulation of SEDDS

Ingredients	I (% w/w)	II (% w/w)	III (% w/w)
Lipophilic drug (Ro 15-0778)	5	5	5
Polyglycolyzed glycerides	5–60	–	–
Medium-chain mono- and diglycerides (Capmul MCM90)	–	17	–
PEG-25 glyceryl trioleate	–	–	30–60
Polysorbate 80	–	5	–
Peanut oil/Neobee oil, q.s.	100	100	100

Non-ionic emulsifiers: (A) glyceryl monocaprylate/caprate (Capmul MCM90, 90% monoglycerides of medium-chain fatty acids, C_8–C_{10}) (Karlshamns U.S.A., Inc., Columbus, OH) and (B) polyglycolyzed glycerides (see Table 1) (Gattefossé, s.a.).

Non-ionic surfactants: (A) Polysorbate 80 (ICI Corp., Wilmington, DE) and (B) PEG-25 glyceryl trioleate (Tagat TO) (Goldschmidt Chemical Corp., Hopewell, VA).

Formulation for SEDDS

The formulation of oil solution for SEDDS is shown in Table 2. A 500 mg formulation was filled manually with a syringe in a soft gelatin capsule and the resulting hole was sealed with heat. The composition of the capsule is gelatin (54.20%), glycerin (38.73%), purified water (6.80%), methylparaben (0.22%) and propylparaben (0.05%).

3.2. Methods

Release rate determination

USP XXII, Dissolution Apparatus 2 (Van-Kel Industries, Inc.) was employed to obtain the release of the drug from the oil to aqueous systems. Soft gelatin capsules containing the SEDDS were placed in copper coils to keep them at the bottom of the dissolution vessel, which was filled with 900 ml of 5% aqueous solution of Alkamuls EL-719 (HLB = 16, polyoxyethylated (40) castor oil, non-ionic surfactant from Rhône-Poulenc) at 37°C. Alkamuls EL-719 was used to provide sink conditions and permit quantitation of the drug release from SEDDS. A fine emulsion is formed by gentle agitation provided by the Teflon-coated dissolution paddle, rotating at 50 rpm. The emulsion was filtered through a 0.2 μm Millipore filter and analyzed by UV at 298 nm (UV DU®-65 Spectrophotometer).

Emulsion particle size measurement

The particle size of the emulsions obtained were determined using a Malvern Particle Size Analyzer (Model No. 2600, 63 mm lens; Malvern, U.K.). The particle size distributions of the resultant emulsions were compared with the apparent volume-average diameters of 50 percentile $D(v,0.5)$. Efficient emulsification was arbitrarily defined (in the same fashion as Charman et al., 1992) as a system which produced mean emulsion droplet diameters (MEDD) values of $D(v,0.5) < 5$ μm.

Partition coefficient

Equal amounts of formulation and aqueous solution of 5% Alkamuls EL-719 were mixed for 1 h on a Glas-Col Laboratory Rotator, speed 4, centrifuged and each phase diluted appropriately and analyzed for drug content by UV spectrophotometry at 298 nm.

4. Results and discussion

Polyglycolyzed glycerides (PGG) were investigated for their utility in SEDDS. A comparison of the efficiency of PGG in SEDDS was made with previously investigated SEDDS containing medium-chain monoglyceride (Capmul MCM90) and PEG (25) trioleate (Tagat TO).

The formulations used in the evaluation of PGG in SEDDS over a range of PGG content are described in Table 2. Fig. 3 and 4 show the effect of fatty acid chain length and the effect of molecular weight of PEG and viscosity in the glyceride, respectively, on the release of the drug. A long chain length of fatty acid in the glyceride (Labrafil WL 2609 BS) leads to a more lipophilic environment, whereas a medium chain length of the fatty acid in the glyceride (Labrafac CM 10 BM 287 or simply Labrafac CM 10) offers a less

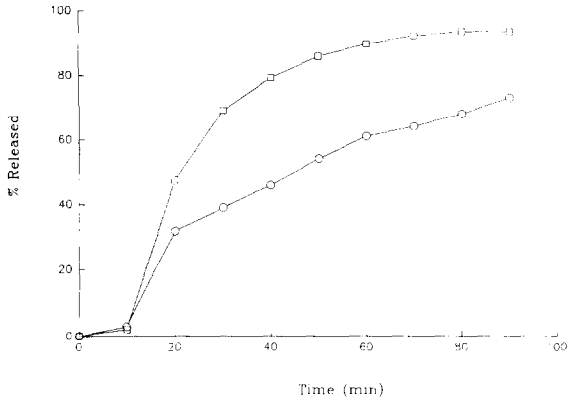

Fig. 3. Effect of fatty acid chain length in polyglycolyzed glycerides on the release of Ro 15-0778. (○) Labrafil WL 2609 BS ($C_{18:2}$); (□) Labrafac CM 10 BM 287 (C_8–C_{10}).

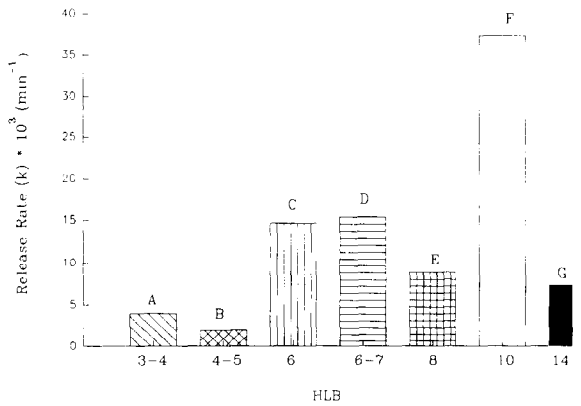

Fig. 5. Comparison of different HLB on the release rate of Ro 15-0778 at 60% of emulsifier. (A) Labrafil M 2125 CS; (B) Labrafac Hydro; (C) Labrafac CM 6 BM 290; (D) Labrafil WL 2609 BS; (E) Labrafac CM 8 BM 284; (F) Labrafac CM 10 BM 287; (G) Labrasol.

lipophilic system. The arrangement of the lipophilic portion of the PGG with the oil phase and the polar heads with water gives an energetically more favorable situation than complete solution in either phase, and therefore, tends to be more efficient in releasing the drug. Also, within the same fatty acid chain length but with different molecular weights of PEG, e.g., Labrafil M 10 ($C_{18:2}$, PEG 600) and Labrafil WL 2609 BS ($C_{18:2}$, PEG 400) were less lipophilic than Labrafil M 2125 CS ($C_{18:2}$, PEG 300) resulting in a different rate of drug release. The molecular weight of PEG plays an important role in the glycerides,

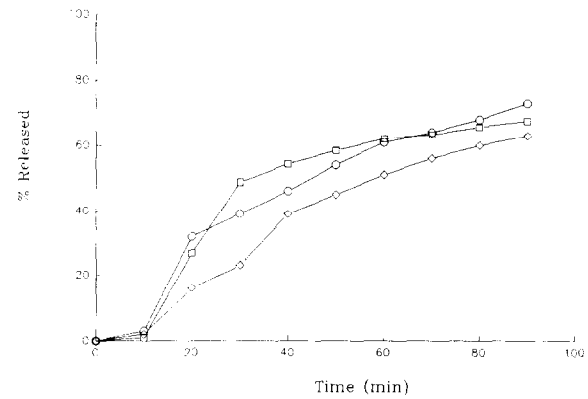

Fig. 4. Effect of molecular weight of PEG in polyglycolyzed glycerides on the release of Ro 15-0778. (○) Labrafil WL 2609 BS ($C_{18:2}$, PEG 400); (◇) Labrafil M 2125 CS ($C_{18:2}$, PEG 300); (□) Labrafil M 10 BM 355 ($C_{18:2}$, PEG 600).

PEG 400 provided a better environment for the drug release than PEG 300. However, PEG 600 in the glyceride does not follow the trend, and the results of PEG 400 and PEG 600 overlap. This could be due to the fact that Labrafil M 10 ($C_{18:2}$, PEG 600) possesses higher viscosity than Labrafil WL 2609 BS ($C_{18:2}$, PEG 400), 105 cps vs 70 cps. Therefore, due the higher viscosity, the diffusion path of the drug is slightly impeded and the advantage of a glyceride containing higher molecular weight (PEG 600), and higher HLB = 10 is compromised.

The achievement of 'adequate' polarity of the resulting oil droplets permits an acceptable rate of release of the drug. Fig. 5 illustrates the polarity in terms of HLB; PGG with an HLB of about 10 gives the best results in terms of drug release. However, an HLB around 10 (Fig. 6) needs to meet some qualifications, i.e., it should be obtained by appropriate combination of fatty acid and PEG (Table 4). Labrafac CM 10 provides a faster drug release than either Labrafil M 10 or Labrafil NA 10 due to the medium chain length (C_8–C_{10}) of the fatty acid present in its composition. Drug release was slightly faster with Labrafil M 10 than with Labrafil NA 10. This can be explained by the degree of unsaturation present in the fatty acid chain length between Labrafil M 10 ($C_{18:2}$) and Labrafil NA 10 ($C_{18:1}$). Unsatura-

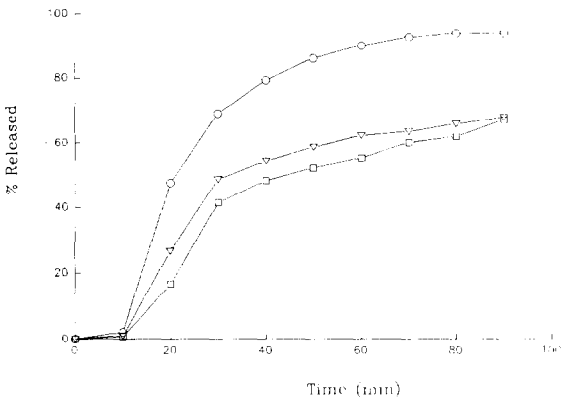

Fig. 6. Effect of fatty acid chain length and saturation of fatty acid present in the glyceride, on the drug release, at 60% emulsifier concentration and HLB of 10. (○) Labrafac CM 10 BM 287 (C_8–C_{10}); (▽) Labrafil M 10 BM 355 ($C_{18:2}$); (□) Labrafil NA 10 BM 369 ($C_{18:1}$).

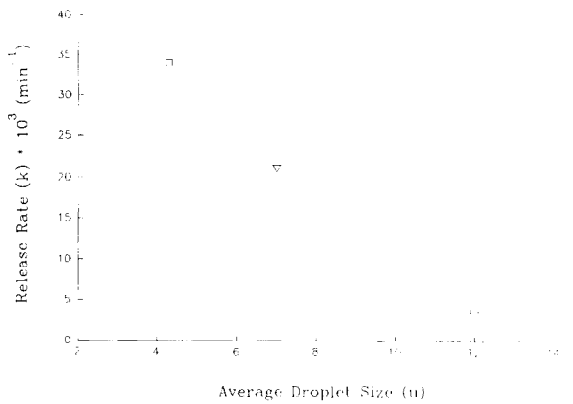

Fig. 7. The influence of emulsifier concentration in SEDDS containing Labrafac CM 10 BM 287 on the release rate of Ro 15-0778 and droplet size of the emulsifier. (□) 60%; (▽) 40%; (○) 20%.

tion present in the fatty acid molecule is predisposed to be more polarizable.

Fig. 7 illustrates the role of the emulsifier (Labrafac CM 10) concentration for efficient SEDDS. The higher the concentration of the emulsifier the smaller is the droplet size of the emulsion and the faster the release rate of the drug. Fig. 8 shows the relationship of partition coefficient with release rate as a function of the emulsifier Labrafac CM 10 concentration. The results indicate that the formation of a fine particle size emulsion together with the lower partition coefficient ($PC_{o/w}$) of the drug from these oil droplets are the prerequisites for the optimum efficiency of SEDDS in terms of drug release.

It was observed that drug release from formulations containing peanut oil or Neobee M5 was

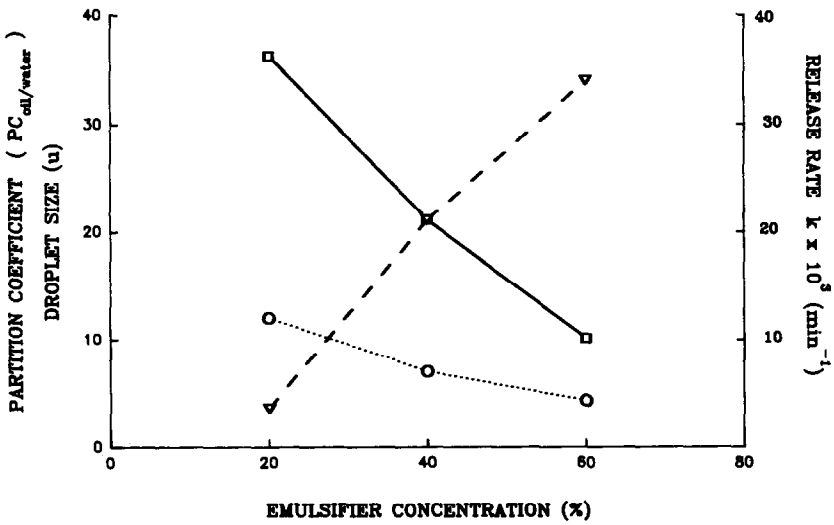

Fig. 8. Effect of concentrations of emulsifier, Labrafac CM 10 BM 287, on partition coefficient (□) droplet size (○) and the release rate (▽) of Ro 15-0778.

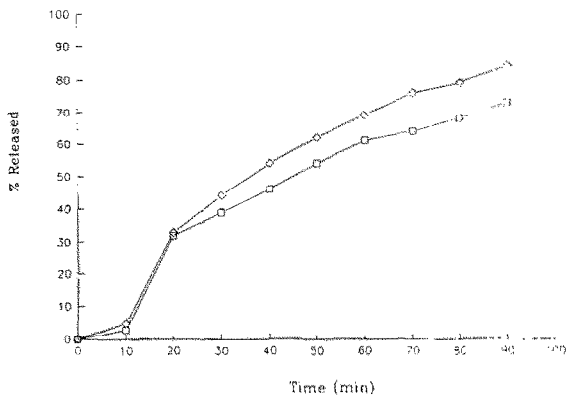

Fig. 9. Effect of lipophilic vehicle on the release of Ro 15-0778. (◇) Neobee oil; (□) peanut oil.

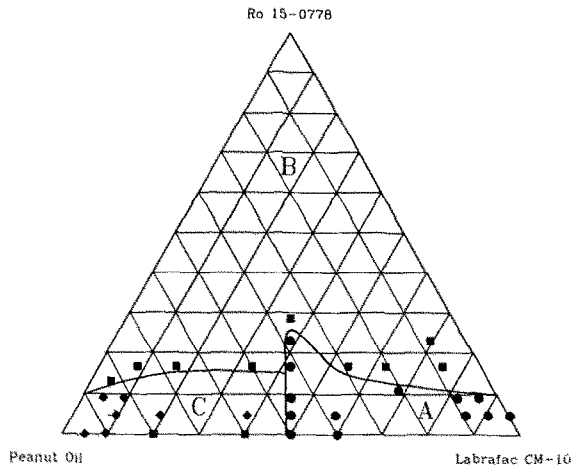

Fig. 10. Phase diagram for peanut oil/emulsifier, Labrafac CM-10 BM 287/Ro 15-0778 system. (●) Region A: good and efficient self-emulsifying systems; (■) region B: poor self-emulsifying systems; (◆) region C: intermediate self-emulsifying systems.

slightly different (Fig. 9). This difference is explained in terms of the compositions of the two oils: peanut oil contains saturated and unsaturated C_{18} fatty acids, whereas Neobee M5 contains medium-chain saturated C_8–C_{10} fatty acids.

Additional experiments were conducted to corroborate the influence of each component on the efficiency of SEDDS and to provide information indicating the best formulation (small droplet size, maximum in vitro dissolution). A phase diagram can be used to establish the optimum concentrations of the drug, oil and emulsifying agent (Fig. 10). In region A, good self-emulsification occurs; this area represents an isotropic mixture. Good emulsification is related to the mutual solubility existing between the oil in water and vice versa. Region C is especially dependent on the emulsifier, since polyglycolyzed glycerides are predisposed to form liquid crystal dispersions with the oil. This leads to more difficult penetration of the water into this system, and hence, the efficiency of SEDDS is diminished. In region B, poor SEDDS are expected because the drug concentration exceeds its solubility.

Fig. 11 shows that glyceryl monoesters appear to be comparable to polyglycolyzed glycerides (PGG) as effective emulsifiers for SEDDS when an auxiliary surfactant, for the formation of efficient SEDDS, is added. The presence of an auxiliary nonionic surfactant Polysorbate 80 was necessary to assist Capmul MCM90 in enhancing the release of the lipophilic drug from SEDDS. Capmul MCM90 alone, even at higher concentrations, does not provide for efficient SEDDS. In contrast, the addition of an auxiliary surfactant was not required for Labrafac CM 10 or Tagat TO. This behavior could be attributed to the fact that Capmul MCM90 is a less hydrophilic emulsifier (HLB about 5) consisting of only 1 mole of glycerol and saturated fatty acid. When Polysorbate 80 [polyoxyethylene (20) sorbitan mono-

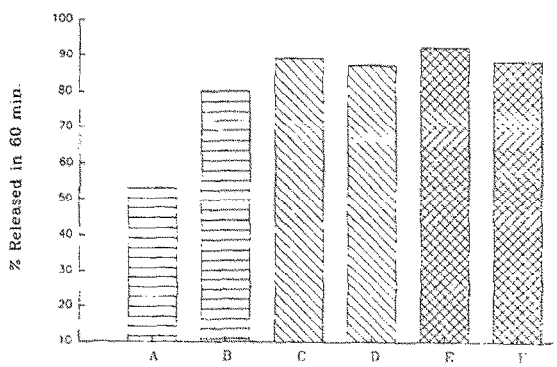

Fig. 11. Effect on drug release after the addition of 5% of Polysorbate 80 to the emulsifier. (A) Capmul MCM90 (17%); (B) Capmul MCM90 (17%) + Polysorbate 80; (C) Labrafac CM 10 (60%); (D) Labrafac CM 10 (60%) + Polysorbate 80; (E) Tagat TO (60%), (F) Tagat TO (60%) + Polysorbate 80.

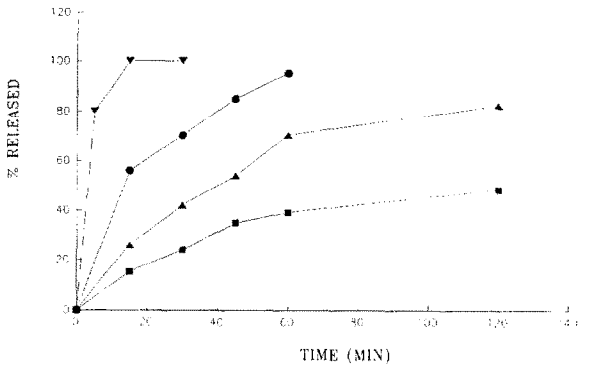

Fig. 12. In vitro dissolution drug profile from different formulations. (●) SEDDS; (▼) 1.2% PEG 400; (▲) wet milled spray dried powder; (■) micronized drug.

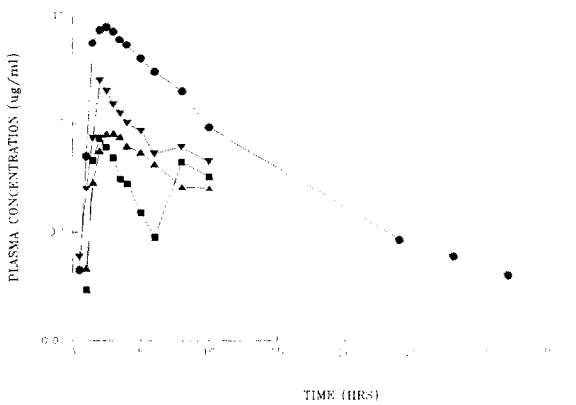

Fig. 13. Mean plasma concentration of Ro 15-0778 in non-fasted dogs, after oral administration of four different formulations. (●) SEDDS; (▼) 1.2% PEG 400; (▲) wet milled spray dried powder; (■) micronized drug.

oleate] is added, a more hydrophilic environment is attained resulting in a reduction of the interfacial surface tension between the oil and water, and adequate polarity. In the case of Labrafac CM 10 and Tagat TO, the presence of a satisfactory chain length of PEG in the molecule provides adequate hydrophile-lipophile balance (Table 4).

The efficiency of SEDDS for in vitro dissolution and in vivo absorption was compared to three other dosage forms: (i) a 1.2% drug solution in PEG 400; (ii) a tablet of the micronized drug; and (iii) a capsule of 55% wet-milled spray dried powder at a 200 mg dose level. In vitro dissolution profiles of these dosage forms and SEDDS are shown in Fig. 12. A single oral dose of 200 mg of each formulation was administered to non-fasted male beagle dogs. The plasma concentration vs time profiles are shown in Fig. 13.

Table 3
Pharmacokinetic parameters of Ro 15-0778 from different formulations in non-fasting dogs

Formulation	C_{max} (μg/ml)	t_{max} (h)	AUC (μg h ml^{-1})	% relative bioavailability
Self-emulsified 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 form. of wet-milled spray dried powder	0.78	3.00	2.69	35.3
Tablet form. of micronized drug	0.58	2.00	1.32	17.2

Table 4
Different emulsifiers, same HLB = 10 and concentration = 60%

Emulsifier	Main fatty acid	PEG	$C_{fatty\ acid}$/C_{PEG} ratio C = carbon units	Droplet size (μm)	% release at t = 60 min
Labrafac CM 10	C_8–C_{10}	8	1:1 or 1.25:1	4.3	91
Labrafac M 10	$C_{18:2}$	12	1.5:1	4.0	62
Labrafac NA 10	$C_{18:1}$	12	1.5:1	3.5	55
Tagat TO	$C_{18:1}$	25	1:1.4	2.7	93

The superior performance of SEDDS compared to the other dosage forms is clearly apparent. In vivo absorption data showed at least 3-fold greater C_{max} and AUC with SEDDS than with the other dosage forms (Table 3). Even though the in vitro dissolution rate from PEG 400 solution was faster than that of SEDDS, in vivo absorption data showed greater C_{max} and AUC with SEDDS. Drug in solution in PEG 400 could possibly have precipitated out during in vivo administration. During in vitro dissolution studies, precipitation was not observed due to the presence of surfactant in the dissolution medium. These data clearly demonstrated the utility of SEDDS in improving oral absorption of lipophilic drugs.

5. Conclusions

Polyglycolyzed glycerides (PGG) with varying fatty acid and polyethylene glycol (PEG) chain lengths have shown their ability to produce the self-emulsification of oil in water. The performance of self-emulsifying drug delivery systems (SEDDS) is governed by two main factors: (1) the ability of the self-emulsifying mixture to form an emulsion with uniform fine particle size droplets (i.e., $< 5\ \mu m$); and (2) the polarity of the resulting oil droplets which permits a faster rate of release of the drug into the aqueous phase.

The chain length and unsaturation of the fatty acid, as well as the molecular weight and concentration of PEG in the emulsifier, influence the droplet particle size and droplet polarity in the emulsion and thus the drug release. An HLB of the emulsifier, around 10, gives the best results in terms of drug release, for this particular study. However, this HLB needs to meet some qualifications, i.e., it should be obtained by an appropriate combination of fatty acid(s) and PEG.

In addition to the above factors, small particle size and drug release rate, the partition coefficient was found to be an important parameter to be considered for the evaluation of the efficiency of SEDDS. The smaller the particle size of the oil droplets and the lower the $PC_{o/w}$, the more efficient will be the SEDDS.

SEDDS containing PGG, such as Labrafac CM 10, were comparable to those with Capmul MCM90 plus Polysorbate 80, and PEG-25 glyceryl trioleate (Tagat TO) for their efficiency and stability.

In in vivo absorption studies in dogs for a lipophilic drug, SEDDS gave at least a 3-fold greater C_{max} and AUC than either the drug in solution, a tablet of micronized drug or a capsule of wet-milled spray dried powder.

The data presented have shown that SEDDS provide a most efficient way of improving the oral absorption of a lipophilic drug.

6. Acknowledgments

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