Self-Emulsifying Drug Delivery Systems: Formulation and Biopharmaceutic Evaluation of an Investigational Lipophilic Compound

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Self-emulsifying drug delivery systems (SEDDSs) represent a possible alternative to traditional oral formulations of lipophilic compounds. In the present study, a lipophilic compound, WIN 54954, was formulated in a medium chain triglyceride oil/nonionic surfactant mixture which exhibited self-emulsification under conditions of gentle agitation in an aqueous medium. The efficiency of emulsification was studied using a laser diffraction sizer to determine particle size distributions of the resultant emulsions. An optimized formulation which consisted of 25% (w/w) surfactant, 40% (w/w) oil, and 35% (w/w) WIN 54954 emulsified rapidly with gentle agitation in 0.1 *N* HCl (37°C), producing dispersions with mean droplet diameters of less than 3 μm. The self-emulsifying preparation was compared to a polyethylene glycol 600 (PEG 600) solution formulation by administering each as prefilled soft gelatin capsules to fasted beagle dogs in a parallel crossover study. Pharmacokinetic parameters were determined and the absolute bioavailability of the drug was calculated by comparison to an i.v. injection. The SEDDS 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}). There was no significant difference in the absolute bioavailability of WIN 54954 from either the SEDDS or the PEG formulations.

KEY WORDS: self-emulsification; oral delivery system; formulation; soft gelatin capsule; lipophilic drug.

INTRODUCTION

Self-emulsifying systems are isotropic mixtures of oil and surfactant which form fine oil-in-water emulsions when introduced into aqueous phases under conditions of gentle agitation. Such mixtures have been used extensively by the chemical industry for the transport of concentrated herbicides and pesticides (1,2). Recently, self-emulsifying systems have been formulated using medium-chain triglyceride oils and nonionic surfactants which, being acceptable for oral ingestion, could form the basis of self-emulsifying drug delivery systems (SEDDSs) (3–10). These preparations may be formulated in soft gelatin capsules to produce precise and convenient unit dosage systems.

Self-emulsifying drug delivery systems represent a possible alternative to the more traditional oral formulations for lipophilic compounds. The delivery system is expected to self-emulsify rapidly in the aqueous contents of the stomach, thereby presenting the drug in solution in small droplets of oil (<5 μm). Fine oil droplets should empty rapidly from the stomach and promote wide distribution of the drug throughout the gastrointestinal tract (GI) tract, thereby minimizing irritation frequently encountered with extended contact between bulk drug substances and the gut wall. An additional advantage of SEDDSs over simple oily solutions is that they provide a large interfacial area for partitioning of the drug between oil and water. For drugs subject to dissolution rate-limited absorption, SEDDSs may offer an improvement in both the rate and extent of absorption and the reproducibility of plasma concentration profiles.

In the present investigation, a medium-chain triglyceride oil, Neobee M5, and a nonionic surfactant, Tagat TO, were used to formulate a SEDDS for an investigational lipophilic compound, WIN 54954 (11). Equilibrium phase studies were conducted and phase boundaries determined for the oil/surfactant system with and without the compound. The efficiency of self-emulsification, used as an indication of formulation optimization, was evaluated under conditions of varying composition (oil, surfactant, and compound) and was assessed by measuring the droplet diameter using a laser diffraction sizer.

The self-emulsifying formulation of WIN 54954 was compared to a more traditional polyethylene glycol 600 (PEG) solution formulation by administering each preparation as prefilled soft gelatin capsules to fasted beagle dogs in a parallel crossover study. Pharmacokinetic parameters for WIN 54954 were determined for each formulation relative to an i.v. standard.

MATERIALS AND METHODS

Materials

Self-emulsifying drug delivery systems were prepared comprising a medium chain triglyceride oil (Neobee M5, Stepan Co., Maywood, NJ), ethoxylated glyceryl trioleate nonionic surfactant (Tagat TO, Goldschmidt Chemical Corp., Hopewell, VA), and an investigational lipophilic compound, WIN 54954. WIN 54954 (5-[5-[2,6-dichloro-4-(dihydro-2-oxazolyl)phenoxy]pentyl]-3-methylisoxazole) is a low-melting (40–42°C), lipophilic compound (log octanol/water partition coefficient, 5.3; vegetable oil solubility, >200 mg/ml) having a pK_a of 2.1 for the oxazoline nitrogen and limited aqueous solubility in the range suitable for pharmaceutical formulations (<1 μg/ml, pH 4 to 9.5). Sample soft gelatin capsules were supplied by R. P. Scherer, Clearwater, FL. Polyethylene glycol 600 (Union Carbide, Danbury, CT) and Tween 80 (ICI, Wilmington, DE) were USP N.F. grade and were used as received. Liposyn II lipid emulsion was

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used for the i.v. formulation and was obtained from Abbot Laboratories, North Chicago, IL.

Equilibrium Phase Studies

Formulation components (oil, surfactant, and WIN 54954) were accurately weighed into screw-capped glass tubes with water-tight closures. The mixtures were sequentially diluted by the weighed addition of distilled water and heated to approximately 60°C to facilitate mixing using a vortex apparatus. Mixtures were equilibrated to the temperature of interest using a thermostatted water bath. Equilibrium mixtures were prepared both with and without WIN 54954. Care was taken during the equilibrium process to mix the contents of each tube regularly to ensure uniformity as the equilibrium temperature was approached. Each mixture was left for a period of 1–2 hr during which they were visually inspected using a polarizing viewer. Mixtures did not change considerably during this 2-hr period, which was found to be adequate for comparison of the phase behavior of formulations with and without drug. In this study, emphasis was placed on approximate identification of the phase boundary for solubilization of water in the oil–surfactant–WIN 54954 mixtures and the presence of liquid crystalline phases within the mixtures.

Self-Emulsification

Mixtures of oil, surfactant, and WIN 54954 were prepared by accurately weighing ingredients into glass tubes with PTFE-lined closures followed by vortex mixing. One of two methods was used to prepare emulsions under conditions of gentle agitation at a controlled temperature. In Method A, SEDDSs (0.3 ml) were introduced into 400 ml of 0.1 *N* HCl in a 1-liter glass beaker held at 37°C in a thermostated water bath. Agitation was provided by gentle shaking on a mechanical shaker at 50 oscillations per min and an amplitude of 3 in. Samples were removed after 10 min for particle sizing. In Method B, SEDDSs (0.3 ml) were emulsified in 400 ml of 0.1 *N* HCl in a 1-liter glass vessel under the action of a standard Teflon-coated dissolution paddle mounted immediately below the meniscus of the aqueous phase and rotating at 100 rpm. The temperature was held at 37°C by placing the vessel in a thermostated water bath. Samples were removed after 10 min for particle sizing.

Particle Sizing

Mean emulsion droplet diameters (MEDDs) were determined (with appropriate dilution) using a Malvern 2600c Laser Fraunhofer Diffraction Sizer (Malvern, UK). Experiments were performed in duplicate and the size distributions of the resultant emulsions were compared using the apparent volume-average diameters of the 50 and 90 percentiles, $D(v,0.5)$ and $D(v,0.9)$, respectively. Efficient emulsification was arbitrarily defined as a system which produced MEDD values of $D(v,0.5) < 3$ μm and/or $(v,0.9) < 7$ μm.

Investigational Drug Formulations

Soft gelatin capsules were filled with the formulation using a syringe and sealed with hot gelatin. The optimized self-emulsifying formulation contained 35% (w/w) WIN 54954, 40% (w/w) Neobee M5, and 25% (w/w) Tagat TO. The PEG solution formulation comprised 20% (w/w) WIN 54954, 76% (w/w) PEG 600, and 4% (w/w) Tween 80. Each capsule was filled to contain 200 mg of WIN 54954 in either the SEDDS or the PEG solution formulation.

An i.v. formulation was prepared as a lipid emulsion utilizing a commercially available intravenous lipid emulsion, Liposyn II. Drug was incorporated into the emulsion according to the method of El-Sayed and Repta (12) and the final formulation contained 1% (w/w) WIN 54954 in 10% (v/v) Liposyn II to provide a final drug concentration of 10 mg/ml. The stability of the i.v. and oral formulations was demonstrated prior to and during the course of the study by validated HPLC methodology.

In Vivo Study Design and Biological Sampling

The *in vivo* study was a parallel (PEG solution vs SEDDS) crossover (i.v. Liposyn II emulsion vs oral formulation) design conducted in fasted male beagle dogs. Each animal received (i) the i.v. formulation (10 mg/kg dose) administered as a 10-min infusion and (ii) either the PEG solution or the SEDDS oral formulation (each a 200-mg dose). The order of administration was randomized and each administration was separated by 1 week.

Venous blood samples were obtained prior to medication (−10 min) and at 0 (end of infusion), 5, 10, 15, 30, 45, and 60 min and 1.5, 2, 3, 4, 6, 8, and 10 hr postmedication for the i.v. administration and at −10 min and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 10 hr postmedication for the oral preparations.

Pharmacokinetic parameters were calculated from the plasma concentrations of the parent compound following each administration in individual animals. Parameters included the area under the plasma concentration vs time curve from −10 min (start of infusion) to infinity ($AUC^{-10\rightarrow\infty}$) for the i.v. administration and from 0 to infinity ($AUC^{0\rightarrow\infty}$) for the oral administrations, the maximum plasma concentration (C_{max}), the time to reach the maximum plasma concentration (t_{max}), and the terminal elimination half-life ($t_{1/2}$). The $AUC^{-10\rightarrow\infty}$ and $AUC^{0\rightarrow\infty}$ were calculated using the standard trapezoidal rule from time −10 min or 0, respectively, to the last measured concentration and adding to that the extrapolated area calculated by dividing the last measured concentration by the terminal rate constant. The absolute bioavailability (BA) of WIN 54954 administered in the oral formulations was calculated from AUC data relative to that for the i.v. administration (correcting for the difference in dose) according to standard pharmacokinetic procedures (13).

Quantitation of WIN 54954 in Plasma Samples

Venous blood samples were collected in tubes containing anticoagulant and centrifuged to separate the plasma, which was stored at −4°C prior to analysis. To 1 ml of plasma, 50 μl of internal standard (a compound structurally related to WIN 54954) at a concentration of 10 μg/ml was added along with 0.5 ml of 0.2 *M* borate buffer (pH 9.0). The samples were mixed, followed by the addition of 6.0 ml hexane. The samples were vortexed, placed on a rotary shaker for 10 min, and then centrifuged. The hexane layer was

transfered to a silanized conical tube and evaporated to dryness at 60°C under a stream of nitrogen. Seventy-five microliters of hexane was added to redissolve the residue and 1 μl was injected into the gas chromatograph.

A gas chromatography method was used for the quantitation of WIN 54954 in plasma following oral and i.v. administration. The gas chromatography method utilized a Hewlett Packard 5710A gas chromatograph (Avondale, PA) equipped with a Ni-63 electron capture detector. The glass column used was 2 ft × 2 mm, i.d., packed with 3% OV-25 on Gas Chrom Q (100/120 mesh). The carrier gas was argon:methane (90:10) at a flow rate of 30 ml/min. The injector, oven, and detector temperatures were 300, 260, and 300°C, respectively. Data were collected using a Hewlett Packard 3357 lab automation system (Palo Alto, CA).

RESULTS AND DISCUSSION

Equilibrium Phase Behavior

Although self-emulsification is a dynamic nonequilibrium process involving interfacial phenomena, information can be obtained about the mechanism of self-emulsification using investigations of equilibrium phase behavior. The efficiency of emulsification of oil–surfactant systems in the absence of drug has been characterized in some detail and has been correlated with equilibrium phase diagrams (6–9). There appears to be a correlation between emulsification efficiency (as determined from particle size measurements) and (i) a region of enhanced water solubilization typical of nonionic surfactant systems and thought to be a phase inversion region and (ii) the formation of a lamellar liquid crystalline dispersion phase on further incorporation of water (6,7). There have been only preliminary reports, however, of the *in vitro* characteristics of self-emulsifying systems formulated to include drugs.

In the present investigation, the effects of drug inclusion on the efficiency of emulsification were studied using equilibrium phase diagrams. In the phase diagrams, described in Figs. 1A, B, and C, aqueous-based liquids are denoted L_1, oil-based liquids L_2, and liquid crystalline phases LC. Multiphasic mixtures were clearly distinguished by their turbidity and the presence of significant quantities of liquid crystalline material was easily established by strong birefringent patterns observed using the polarizing viewer. No attempt was made to quantify the composition or volume fraction of the phases present in the multiphasic mixtures. Such studies are extremely tedious and were not necessary for the purpose of this work. Turbid mixtures, which tended to separate on storage into a water-rich phase and an oil-rich phase, were designated (L_1 + L_2) or (L_1 + L_2 + LC) when LC material was clearly present. Two types of LC phases were identified. The LC phase was viscous and exhibited "white" birefringence. In contrast, the transparent liquid crystalline dispersion phase, denoted LC_a, differed from the LC phase in that it exhibited low viscosity and "multicolored" birefringence, typical of lamellar liquid crystalline phases.

Figure 1A displays the partial phase diagram for a self-emulsifying vehicle containing 30% (w/w) Tagat TO and 70% (w/w) Neobee M5 diluted with distilled water. The phase behavior and presence of the LC_a phase correlated with efficient emulsification determined for the system by particle size analysis. Figure 1B displays the partial phase diagram for a mixture of 5% (w/w) WIN 54954, 30% (w/w) Tagat TO, and 65% (w/w) Neobee M5 and the phase behavior of this system was very similar to that seen in the absence of drug.

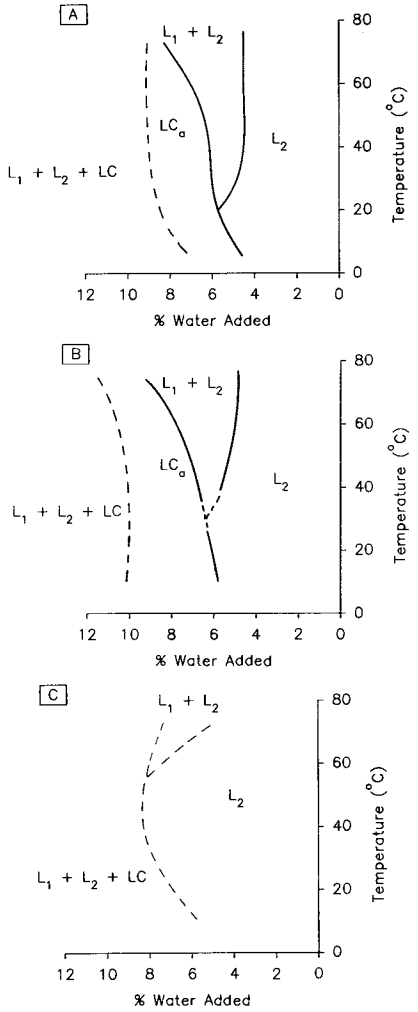

Fig. 1. Partial equilibrium phase diagrams for a mixtures of Tagat TO, Neobee M5, and WIN 54954 diluted with distilled water. (A) 30% (w/w) Tagat TO, 70% (w/w) Neobee M5. (B) 5% (w/w) WIN 54954, 30% (w/w) Tagat TO, and 65% (w/w) Neobee M5. (C) 30% (w/w) WIN 54954, 30% (w/w) Tagat TO, and 40% (w/w) Neobee M5. Aqueous-based liquids are designated L_1, oil-based liquids, L_2; liquid crystal phases ("white" birefringence), LC; and liquid crystal phases ("multicolored" birefringence), LC_a (see text).

Figure 1C illustrates the partial phase diagram for the dilution of a mixture of 30% (w/w) WIN 54954, 30% (w/w) Tagat TO, and 40% (w/w) Neobee M5. In contrast to the vehicle alone, the LC_a phase was not formed upon dilution with water. Instead, a turbid mixture (thought to be L_1 + L_2 + LC) formed which included a considerable amount of liquid crystalline material. This behavior is interesting in view of the fact that a 35% (w/w) WIN 54954 system was still able to self-emulsify as determined by particle size measurements. In a separate group of experiments (unpublished data), mixtures of 30% (w/w) Tagat TO formed LC_a phases upon dilution with water for all concentrations of WIN 54954

up to 25% (w/w). Between 30 and 40% (w/w) WIN 54954, the first phase change resulted in the turbid (L_1 + L_2 + LC). While self-emulsification was poor at 40% WIN 54954, it was acceptable at 35% WIN 54954, indicating that the change from good to poor behavior was not predicted directly from the phase diagrams.

It is not clear how different the turbid (L_1 + L_2 + LC) phase is from the typical LC_a phase generally associated with self-emulsification. The nature of the LC_a phase has been studied previously (6,7) and is thought to consist of a dispersion of lamellar liquid crystal in the L_2 phase. Typically LC_a is optically clear and shows no tendency to separate even after storage for several months. However, ultracentrifugation has some effect on the distribution of colored birefringence in samples of LC_a, suggesting that a liquid crystal-rich phase can be separated under the influence of considerable centrifugal force. The LC_a phase is probably best regarded as a biphasic (L_2 + LC) mixture, both phases of which have similar densities and refractive indices. The difficulty in classifying the LC_a mixtures arises because it appears at first sight to be monophasic as the phase is transparent. It is possible that the turbid (L_1 + L_2 + LC) mixture which forms when the 30% (w/w) WIN 54954 system is diluted with water (Fig. 1C) is actually very similar to LC_a even though its visual appearance may be misleading. This could be caused by the high density of WIN 54954, which may promote separation of LC and L_2 phases.

Particle Size Determinations

In comparison to other methods of particle sizing, such as centrifugal photosedimentometry, the laser diffraction sizer used in the present investigation offers a rapid and flexible means of assessing particle sizes ranging from 0.5 to 50 μm. A notable advantage of laser diffraction sizing over centrifugal photosedimentometry is that measurement of the droplet density is not required. This aspect is particularly relevant for emulsions containing a high surfactant content, for which it is difficult to measure droplet density.

Previous studies conducted using binary systems comprising medium-chain triglyceride oil and Tagat TO have indicated that the MEDD (determined using a laser diffraction sizer) in water sharply decreases as the surfactant concentration is increased to 30% (w/w) (6,7). Binary systems containing between 30 and 65% (w/w) Tagat TO have been found to self-emulsify rapidly in water (6,7). Therefore, an oil–surfactant system containing 30% (w/w) Tagat TO was chosen as the starting point for the present formulation, as it contained a low surfactant content and produced fine emulsions.

A series of SEDDSs was prepared consisting of WIN 54954, medium-chain triglyceride oil, and a constant Tagat TO concentration of 30% (w/w). These systems were allowed to self-emulsify in 0.1 *N* HCl at 37°C to simulate the conditions present in the stomach. Mean effective droplet diameters for these preparations are presented in Table IA. Duplicate experiments produced very similar emulsions and MEDDs. Up to 40% (w/w) WIN 54954 could be included without loss of efficiency of emulsification. Loss of emulsification efficiency was immediate when the compound content was increased to 45% (w/w), as the emulsion became coarse and polydisperse.

Table I. Droplet Diameters (50 and 90 Percentiles) for Emulsions Produced by SEDDSs Consisting of WIN 54954, Neobee M5, and Tagat TO[a]

Mixture composition (%, w/w)			Droplet diameter (μm)	
WIN 54954	Tagat TO	Neobee M5	*D*(*v*, 0.5)	*D*(*v*, 0.9)
		A. Constant Tagat TO[b]		
0	30	70	2.2, 2.4	4.6, 4.8
5	30	65	2.2, 1.7	4.3, 4.0
10	30	60	2.4, 1.9	4.4, 4.1
15	30	55	2.5, 2.2	5.1, 7.4
20	30	50	2.2, 2.3	4.3, 4.7
25	30	45	2.4, 2.4	6.3, 6.2
30	30	40	1.7, 1.4	4.0, 3.6
35	30	35	3.0, 0.8	8.1, 2.3
40	30	30	2.8, 2.9	6.3, 6.9
45	30	25	19.6, 8.1	47.8, 22.9
		B. Constant WIN 54954[c]		
30	15	55	38.3, 34.7	81.2, 74.6
30	20	50	3.1, 1.9	7.5, 3.1
30	25	45	1.9, 2.0	3.0, 3.6
30	30	40	0.8 0.7	1.7, 1.3
30	35	35	1.4, 1.3	4.8, 3.7
30	40	30	3.4, 3.5	4.0, 8.3
30	45	25	3.8, 4.5	17.4, 18.9
30	50	20	3.8, 3.6	9.3, 8.3
30	55	15	7.8, 8.7	32.7, 26.8
		C. Constant Neobee M5[c]		
30	30	40	0.8, 0.7	1.7, 1.3
35	25	40	0.8, 0.8	1.6, 1.7
40	20	40	3.6, 3.3	9.7, 10.4
45	15	40	28.1, 31.8	68.3, 73.2
		D. Mixed systems[c]		
30	30	40	0.8, 0.7	1.7, 1.3
35	35	30	3.3, 2.5	8.3, 4.4
37.5	37.5	25	3.5, 3.2	13.3, 8.2
40	40	20	4.2, 18.6	18.2, 37.9
42.5	42.5	15	18.6, 16.5	57.8, 54.5

[a] Emulsification was carried out in 0.1 *N* HCl at 37°C.
[b] Emulsification using method A described in the text.
[c] Emulsification using method B described in the text.

Further studies were conducted to establish the influence of each component on the efficiency of emulsification and to provide data which would indicate the optimum formulation (i.e., maximum compound load, minimum surfactant content, small droplet diameter). Figure 2 represents a ternary diagram of the three components. The region of efficient emulsification is bound by the dashed line. Filled circles represent compositions which were found to emulsify efficiently, whereas open circles indicate neighboring compositions which were comparatively poor SEDDSs (i.e., systems producing MEDDs of $D(v,0.5) > 3$ μm and/or $D(v,0.9) > 7$ μm). The data collated in Table IA (constant Tagat TO concentration of 30%, w/w) represent a traverse between

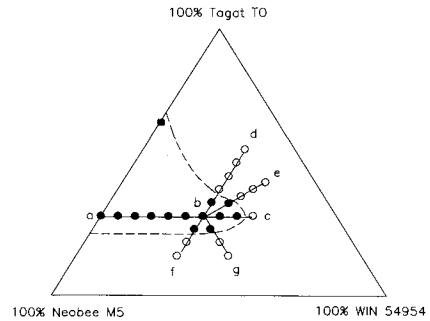

Fig. 2. Ternary diagram of Neobee M5/Tagat TO/WIN 54954 systems indicating a region of efficient emulsification bound by the dashed line for the compositions of SEDDSs studied. The open circles represent systems which were relatively poor self-emulsifiers, whereas the filled circles denote efficient self-emulsifying systems [MEDDs of $D(v,0.5) < 3$ μm or $D(v,0.9) < 7$ μm; see text]. The filled square is taken from previous investigations (see Refs. 6 and 7). Traverses are defined in the text.

point a and point c in Fig. 2. Tables IB and C list the MEDD values for a series of related mixtures which were allowed to self-emulsify in 0.1 *N* HCl at 37°C. The traverse f to d in Fig. 2 (data in Table IB) represents systems containing a constant 30% (w/w) WIN 54954. The finest emulsions were produced by the system containing 30% (w/w) Tagat TO. Traverse b to g in Fig. 2 (data in Table IC) displays a constant oil content of 40% (w/w) and indicates that 25% (w/w) Tagat TO could be regarded as the minimum surfactant concentration required for efficient self-emulsification. Traverse b to e in Fig. 2 (data in Table ID) illustrates that, when WIN 54954 is present, there is no advantage gained by increasing the Tagat TO concentration beyond 35% (w/w).

Based upon the partial phase diagrams and particle size determinations, a formulation comprising 35% (w/w) WIN 54954, 25% (w/w) Tagat TO, and 40% (w/w) medium-chain triglyceride oil was chosen for biopharmaceutic evaluation. The system contained a relatively high load of drug along with a low surfactant concentration. The MEDD obtained for the mixture in 0.1 *N* HCl at 37°C was $D(v,0.9)$ of 1.7 μm, which is within the arbitrary range of efficient self-emulsification described in previous studies (6,7).

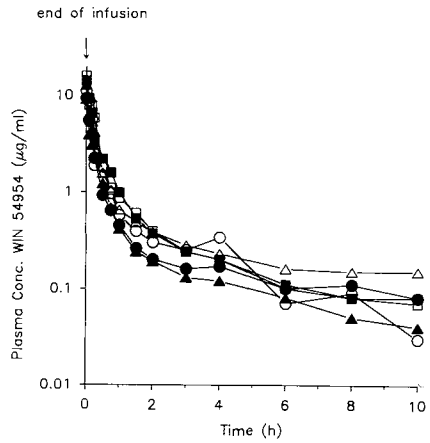

Fig. 3. Plasma concentration vs time profile for WIN 54954 administered as an i.v. lipid emulsion (10 mg/kg) to fasted beagle dogs. Symbols represent data for individual animals. Animal number 1, ○, 2, ●, 3, △; 4, ▲; 5, □; 6, ■.

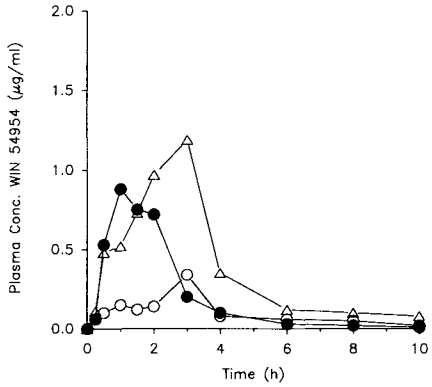

Fig. 4. Plasma concentration vs time profiles for WIN 54954 administered orally as a PEG 600 solution (200 mg dose) to fasted beagle dogs. Symbols represent data for individual animals. Animal number 1, ○; 2, ●; 3, △.

Biopharmaceutic Evaluation of SEDDSs

Plasma concentration vs time profiles for WIN 54954 administered to fasted beagle dogs as an i.v. formulation, a PEG solution soft gelatin capsule, and the self-emulsifying soft gelatin capsule are presented graphically in Figs. 3, 4, and 5, respectively. Pharmacokinetic parameters (AUC, C_{max}, t_{max}, BA) for each administration in individual animals are given in Table II.

Plasma profiles for WIN 54954 following i.v. administration were highly reproducible (Fig. 3). The mean AUC, $t_{1/2}$, and C_{max} data are presented in Table II. The pharmacokinetic parameters following i.v. administration were consistent between all animals, suggesting that the clearance of the compound did not differ significantly between animals at the administered dose.

Following oral administration of the PEG solution formulation for WIN 54954, the plasma profiles were erratic and inconsistent as shown in Fig. 4. The t_{max} ranged from 1 to 3 hr, the maximum plasma concentration varied from 0.34 to 1.19 μg/ml, and the absolute bioavailability ranged be-

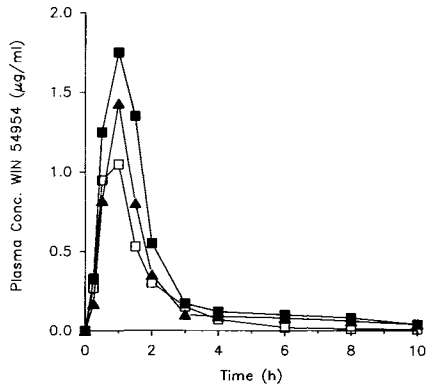

Fig. 5. Plasma concentration vs time profiles for WIN 54954 administered orally as a SEDDS (200 mg dose) to fasted beagle dogs. Symbols represent data for individual animals. Animal number 4, ▲; 5, □; 6, ■.

Table II. Pharmacokinetic Parameters Determined for WIN 54954 in Fasted Beagle Dogs Following i.v. Administration and Oral Administration of a PEG 600 Solution and a SEDDS

	Animal No.	AUC (μg · hr/ml)	$t_{1/2}$ (hr)	C_{max} (μg/ml)	t_{max} (hr)	Absolute BA (%)
i.v. (10 mg/kg)	1	5.41	1.4	11.10	—	—
	2	4.28	1.8	9.33	—	—
	3	6.08	1.9	9.43	—	—
	4	4.17	1.5	12.83	—	—
	5	7.06	1.4	16.05	—	—
	6	6.68	1.5	14.18	—	—
PEG solution (200 mg)	1	1.04	1.8	0.34	3.0	8.7
	2	2.06	1.8	0.88	1.0	24.6
	3	4.03	2.0	1.19	3.0	33.9
SEDDS (200 mg)	4	2.34	1.0	1.43	1.0	27.9
	5	1.77	0.7	1.05	1.0	12.5
	6	3.36	1.7	1.75	1.0	25.2

tween 8.7 and 33.9%. This difference in absolute bioavailability could be attributed to interanimal differences in either the absorption of the compound from the GI tract or the presystemic clearance of molecule.

The plasma profiles for WIN 54954 administered as a SEDDS (Fig. 5) were more reproducible than those observed following administration of the PEG solution. Following administration of the SEDDS, the t_{max} was 1 hr in all three animals, the C_{max} ranged from 1.05 to 1.75 μg/ml, and the absolute bioavailability was between 12.5 and 27.9%. While the two dosage systems represent different types of vehicles (SEDDS being lipid based and the PEG being water miscible), the plasma profiles of WIN 54954 from the SEDDS appeared to be more consistent between animals than that following administration of the PEG solution.

The improvement in the plasma profiles of WIN 54954 following administration of the SEDDS is most likely a function of solubilization and dispersion of the drug in the GI tract. The effect of the SEDDS formulation on the absorption profile is not likely to be a function of lipid-based promotion of intestinal lymphatic transport, as the administered lipid was a medium-chain triglyceride which does not promote lipoprotein formation (14). Following administration of the water-miscible PEG-based formulation, PEG 600 would be expected to diffuse from the dosage form upon release into the aqueous environment of the GI tract, which may lead to precipitation of the lipophilic compound and subsequent erratic absorption characteristics.

In a separate study, plasma profiles for WIN 54954 following administration to fasted dogs at the same dose in a soybean oil base were also found to be inconsistent and erratic (unpublished results). This further supports the hypothesis that the improvement in the plasma profiles seen following administration of the SEDDS is most likely a manifestation of the solubilizing and dispersing properties of the self-emulsifying system, and not simply a function of the lipid component present in the formulation. The presence of surfactant in the system could result in changes in membrane permeability, however, such changes would be expected to affect the bioavailability of the compound and this was not observed.

In conclusion, the present exploratory investigation illustrates the potential utility of SEDDSs for the delivery of lipophilic compounds. Through use of equilibrium phase diagrams and particle size measurements, a self-emulsifying formulation for an investigational lipophilic compound was developed which produced a fine emulsion with a mean droplet diameter of less than 3 μm under conditions of gentle agitation. When administered orally to animals, the self-emulsifying formulation resulted in improved absorption characteristics relative to a water miscible PEG based formulation. For drugs which undergo dissolution rate-limited absorption, significant improvements in reproducibility and bioavailability may be realized with self-emulsifying formulations. Fine oil droplets would be expected to empty rapidly from the stomach, distribute throughout the GI tract, and provide a large surface area for drug partitioning. Further investigations are necessary to characterize fully the biopharmaceutical performance of these delivery systems.

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