Drug Development and Industrial Pharmacy, 23(8), 809-816 (1997)

RESEARCH PAPER

Factors Affecting the Efficiency of a Self-Emulsifying Oral Delivery System

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ABSTRACT

Dosage forms containing a self-emulsifying system have shown significant promise in improving the in vitro dissolution rate and oral absorption of lipophilic drugs. In such a system, a surfactant, or a surfactant plus medium chain monoglyceride (co-emulsifier), is added to a lipophilic vehicle (oil) containing dissolved drug. In the present study, surfactants with different hydrophile-lipophile balance (HLB), fatty acid glycerides (co-emulsifiers) with varying fatty acid (C_8–C_{18}) chain length, and lipophilic vehicles (oils) containing different fatty acid (C_8–C_{18}) compositions were evaluated for their effectiveness in producing self-emulsifying systems. This investigation showed that the HLB of the surfactant, as well as the fatty acid chain length of the monoglyceride have a significant effect on the performance of the self-emulsifying system; a surfactant with an HLB in the range of 10–15 and a monoglyceride of medium chain fatty acid (C_8–C_{10}) were most effective. Also, there are certain critical concentrations of surfactant and monoglyceride necessary for preparing an optimum self-emulsifying oral drug delivery system.

INTRODUCTION

Lipophilic drugs, having extremely poor solubility in aqueous media, are potential candidates for problems associated with poor absorption from the gastrointestinal tract. When formulated in a conventional tablet or capsule, the drug particles may not be wetted by the hydrophilic contents of the gastrointestinal tract. The hydrophobic drug may dissolve very slowly resulting in incomplete absorption.

A self-emulsifying system (SES) has been reported as a possible alternative to solid dosage formulations for delivering lipophilic drugs by the oral route (1,2). By definition, the self-emulsifying system is a mixture of oil and

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surfactant which, when mixed with an aqueous system under mild agitation, forms a fine emulsion. For example, when a lipophilic drug is dissolved in oil, a surfactant added, and mixed with the gastric contents of the stomach, fine oil droplets containing solubilized drug are formed. The drug, in solution from the fine oil droplets, diffuses out and is readily available for absorption. Thus, such a system provides a more rapid and uniform delivery of drug to the absorption site than does undissolved drug in either tablet or capsule form. In the latter cases, the drug has to be dissolved first before it can be transported across absorptive membranes.

In a good self-emulsifying system, small emulsion droplets containing dissolved drug are formed on contact with gastrointestinal fluid. The drug in the fine emulsion droplets is exposed to a large interfacial area thus allowing for greater diffusion through the membrane to take place.

It has been reported that at least 30% surfactant is needed for easy self-emulsification when fractionated coconut oil (Miglyol 812) and Tween 85, or ethoxylated glycerol trioleate were used (3,4). In a later report, most of the surfactant was replaced with a mono (90%)-diglyceride of medium chain fatty acids (caprylic and capric) (Capmul MCM 90) and only 5% of surfactant was used in preparing the self-emulsifying formulation (5,6,7).

The purpose of this study was to evaluate the surfactants with different hydrophile-lipophile balance (HLB) values and determine the optimum concentration of the most effective surfactant in a self emulsifying system. In addition, the co-emulsifier with varying fatty acid (C_8–C_{18}) chain length was evaluated and the best performer was identified with respect to its optimum concentration. Finally several lipophilic vehicles were tested. A lipophilic model drug, practically insoluble arotinoid, was used in this investigation. The self emulsifying system was physically evaluated by dissolution testing and particle size analysis.

MATERIALS

Materials used in this study were: a) an investigational arotinoid drug with solubility in water and simulated gastric fluid less than 0.01 mg/mL, (1,2,3,4-tetrahydro-1,1,4,4-tetramethyl-6-[(E)-alpha-methylstyryl] naphthalene, (Hoffmann-La Roche, Inc., Nutley, N.J.); b) sorbitan fatty acid esters and polyoxyethylene sorbitan fatty acid esters (ICI Americas, Wilmington, DE): sorbitan monolaurate (Span 20), sorbitan monooleate (Span 80), polyoxyethylene (20) sorbitan monolaurate (Tween 20), polyoxyethylene (20) sorbitan monopalmitate (Tween 40), polyoxyethylene (20) sorbitan monooleate (Tween 80), polyoxyethylene (5) sorbitan monooleate (Tween 81), polyoxyethylene (20) sorbitan trioleate (Tween 85); c) glycerol esters: monoglyceride of caprylic-capric acid (C_8–C_{10}) 90% (Capmul MCM90, ABITEC, Columbus, OH), glycerol monolaurate (C_{12}) (Stepan Co., Maywood, NJ), glycerol monostearate (C_{18}) (Stepan Co., Maywood, NJ); d) vegetable oils: peanut oil (Ruger, Inc., Irvington, NJ), soybean oil (Croda, Inc., Parsippany, NJ), safflower oil (Croda, Inc., Parsippany, NJ); e) surfactant in dissolution medium: Emulphor 719 (Rhône-Poulenc, Cranbury, NJ).

METHODS

Formulations

The formulations were prepared by dissolving drug in the oleaginous vehicle, the emulsifiers added, and mixed with a lightnin stirrer at medium speed until uniformly distributed. 500 mg of the product were incorporated into an air filled soft gelatin capsule with a syringe and needle. The resulting pinhole was resealed with heat.

In Vitro Dissolution Testing

Dissolution testing using USP 23-NF 18, Apparatus 2, Paddles, at 50 rpm and 37°C (Van-Kel Ind. Inc., Chatham, NJ), was performed on the formulation in the soft gelatin capsule containing 25 mg of the lipophilic drug. The dissolution medium was 900 mL of Distilled Water containing 5% Emulphor 719. Spectrophotometric determinations were made at 288 nm through an optical path of 1 cm. An automated system was used in which sample readings were recorded every 2.5 min for up to 1 hr using a Beckman DU-65 Spectrophotometer.

Droplet Size Analysis

The Malvern Particle Size Analyzer, Model No. 2600 (Malvern Inst., Southborough, MA), with a 63 mm lens was used to measure emulsion droplet size. The average droplet size is indicated as d[0.5]. The instrument is based on the principle of laser diffraction. The system inherently measures the integral light scattering from all particles present in the beam. As material flows through the beam, the measured light scattering is continuously changing to give the instantaneous

integral of the material illuminated by the analyzer beam. Approximately 0.002% of emulsion concentration in water was incorporated into a 15 mL volume cell, and under slow agitation, the scattered light intensity was measured.

RESULTS AND DISCUSSION

Surfactant Study

The basic self-emulsifying formulation (Table 1) with surfactants of variable hydrophile-lipophile balance (HLB) (Table 2) gave different dissolution release profiles as seen in Figure 1. A range of surfactants was selected beginning with the more lipophilic affinities (HLB 4.3 and 8.6) followed by increasingly more hydrophilic ones with higher HLB numbers. The initial lag time in the dissolution was attributed to the capsule shell dissolution.

The results indicate that optimum dissolution occurred in the HLB range of 11–15 (Tween 85 and Tween 80) with 100% release within 60 min. Slower releases were obtained with more lipophilic surfactants (Span 80, Span 20, Tween 81) and slowest release with more pronounced hydrophilic surfactants (Tween 40 and Tween 20). Span 80, a very lipophilic surfactant whose HLB is 4.3, dissolved only 67% in 60 min. On the other extreme, Tween 20, a very hydrophilic surfactant whose HLB is 16.7, dissolved 45% in 60 min. With very hydrophilic surfactants, the drug may be entrapped in the formed micelles, causing slower release in the dissolution medium.

Table 1

Basic Self-Emulsifying Formulation

Ingredients	% W/W*	mg/cap*
Lipophilic Drug	5	25
Surfactant	5	25
Glycerol Ester	17	85
Vegetable Oil	73	365
Total	100	500

*Concentration used unless otherwise indicated in experimental design.

Table 2

Surfactant Hydrophile-Lipophile (HLB) Values

Surfactant	HLB
Span 80	4.3
Span 20	8.6
Tween 81	10.0
Tween 85	11.0
Tween 80	15.0
Tween 40	15.6
Tween 20	16.7

The emulsion droplet size formation of formulations containing Tween 20, Tween 80, and Span 80 in water were measured by the Malvern Particle Size Analyzer. The results correspond to the effectiveness of the emulsifier system in the formulations (Figure 2).

The best formulation in terms of dissolution (Tween 80) produced the smallest emulsion droplet size (6 microns) with 70% of the droplet size being below 10.5 microns. The lipophilic Span 80 had a seven-fold increase in particle size, an average particle size of 40 microns, with 98% of emulsion droplets being 10.5 to 100 microns in size. Thus a coarser emulsion resulted in greater interfacial tension, and a longer diffusion path resulting in slower dissolution. Slowest dissolution occurred with Tween 20, but yet the average particle size was smaller (16 microns) than that shown with Span 80. Because of increased hydrophilicity (HLB) as compared to Span 80, Tween 20 was efficient in reducing the particle size of the oil; however, the drug could have been contained within the micelles resulting in slower dissolution.

In a second set of experiments, varying concentrations of Tween 80 were used in the basic self-emulsifying formulation. The levels ranged from 1% to 5% to 10%, with a corresponding adjustment in peanut oil concentration. The dissolution profile is shown in Figure 3 and the particle size distribution is given in Figure 4.

The optimum level is 5% Tween 80 with an average particle size range of 6 microns and 100% release in 40 min. Decreasing Tween 80 concentration to 1% resulted in a coarser emulsion with 88% of particles being in a size range of 10.5 to 55 microns (average particle size 25 microns). Ten percent Tween 80 resulted in a finer emulsion than 1% Tween 80, but however the dissolution rate was greatly reduced. In 60 min, only 38% of drug was released with 10% Tween 80, whereas with 1% Tween 80, 73% of drug dissoluted in the same time period. The phenomenon again may be explained that efficient emulsification occurred with 1% Tween 80, and micellar solubilization and entrapment occurred at 10% level.

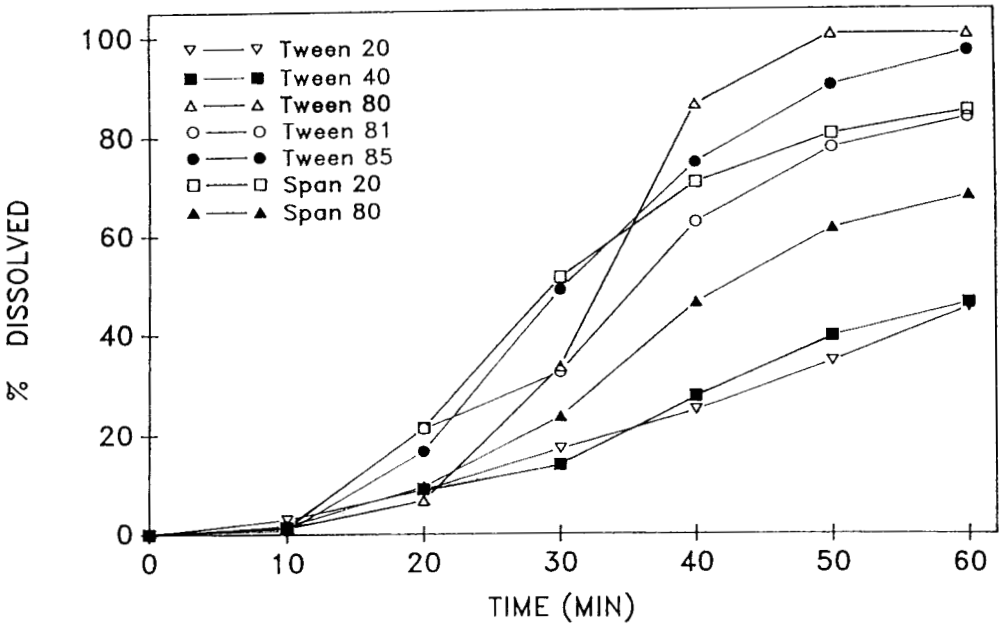

Figure 1. Dissolution profile of arotinoid (25 mg) capsules with surfactants of variable HLB.

Co-Emulsifier Study

Besides the primary emulsifier, an auxiliary co-emulsifier and coupling agent for the oil-in-water system at a concentration of 17% was added to reduce the amount of the primary emulsifier. Three glyceryl esters with varying fatty acid chain lengths were tested: caprylic/capric (C_8–C_{10}) 90% monoglyceride (Capmul MCM90); monolaurate (C_{12}) GML; and monostearate (C_{18}) GMS. As the fatty acid ester chain length increased, the dis-

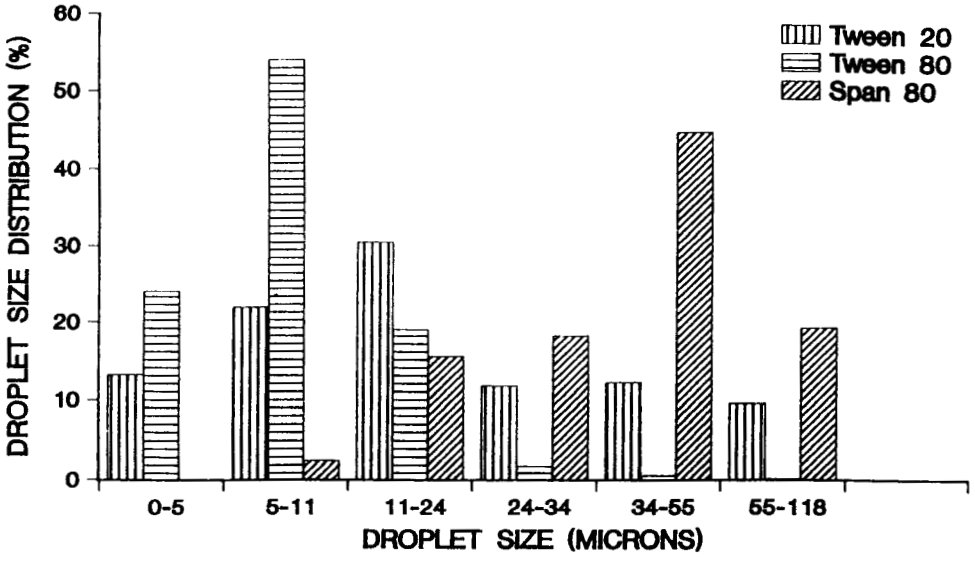

Figure 2. Effect of surfactant HLB on emulsion droplet size.

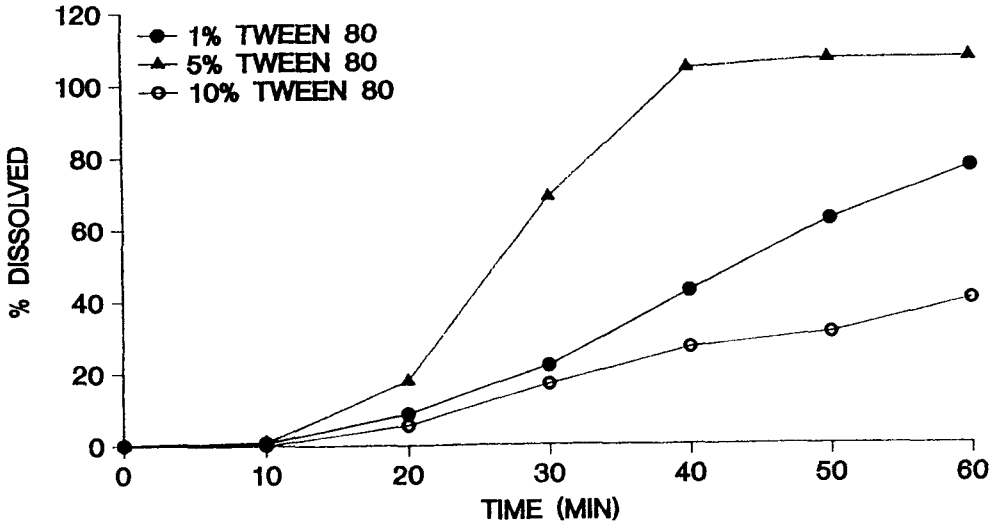

Figure 3. Dissolution profile of arotinoid (25 mg) capsules with differing Tween 80 concentrations.

solution rate decreased and emulsion droplet size increased (Figures 5 and 6).

The optimum formulation containing Capmul MCM-90 had a droplet size of 6 microns compared to 23 and 26 microns for the other two fatty acid chain lengths. The dissolution rate with these two latter fatty acid esters did not exceed 20% in 60 min.

An upper concentration level of 17% of Capmul MCM90 as co-emulsifier is needed for satisfactory release of the arotinoid drug, from the self-emulsifying system. Lower concentrations of Capmul MCM90 resulted in inferior self-emulsifying systems, producing coarser emulsion droplets with slower release of drug in in-vitro studies (Figures 7 and 8).

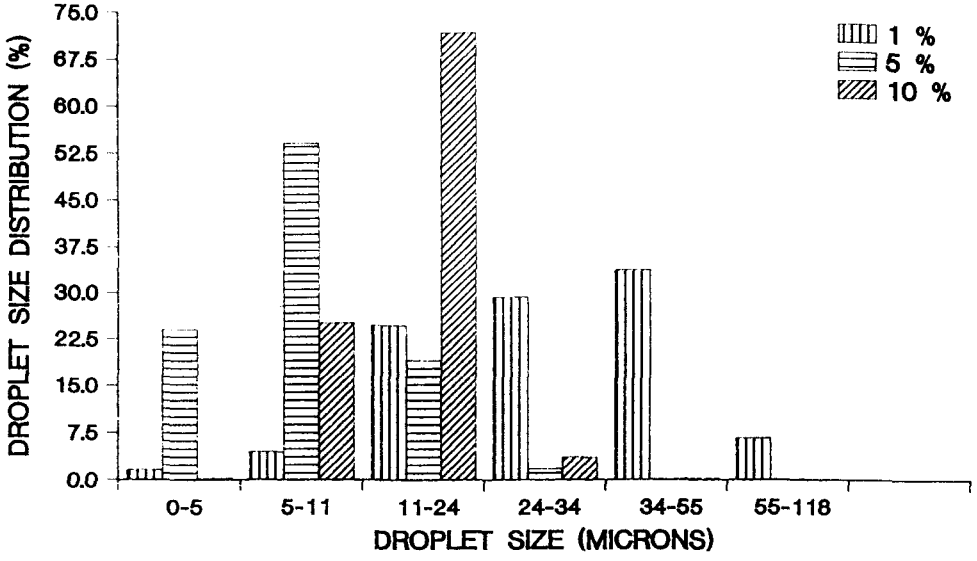

Figure 4. Effect of Tween 80 concentration on emulsion droplet size.

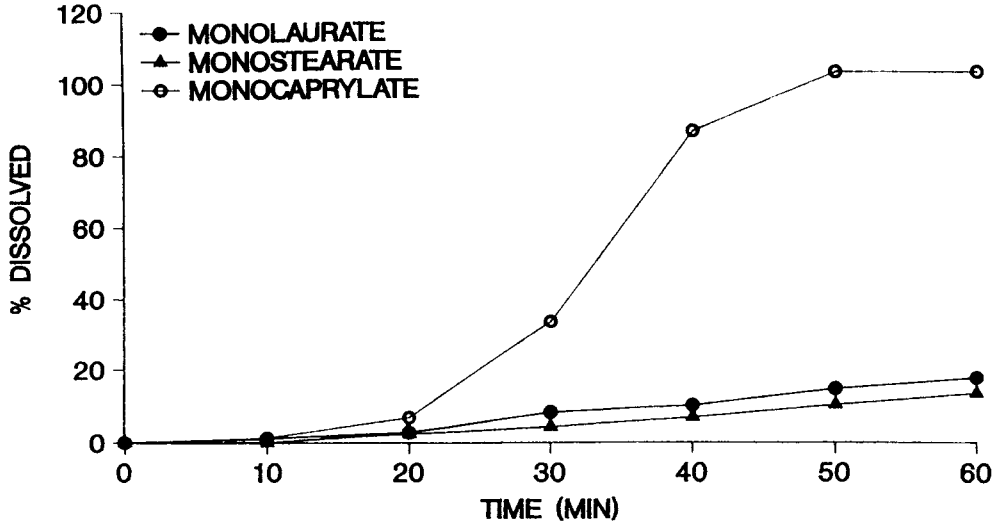

Figure 5. Dissolution profile of arotinoid (25 mg) capsules containing co-emulsifiers of varying fatty acid chain length.

Vegetable Oil Study

In the last series of experiments, three vegetable oils at 73% concentration were incorporated into the basic formulation as the lipophilic vehicles and solubilizers for the drug. Release of drug from the formulations containing peanut oil and soybean oil were similar and more rapid than the release from safflower oil (Figure 9). A 30% decrease in dissolution was noted with the safflower oil as compared to peanut and soybean oils after 60 min. The main difference in compositions between the three oils is in the amount of saturated and unsaturated C_{18} fatty acid. Safflower oil has the greatest percentage of linoleic acid and the lowest concentration of oleic acid of the three oils.

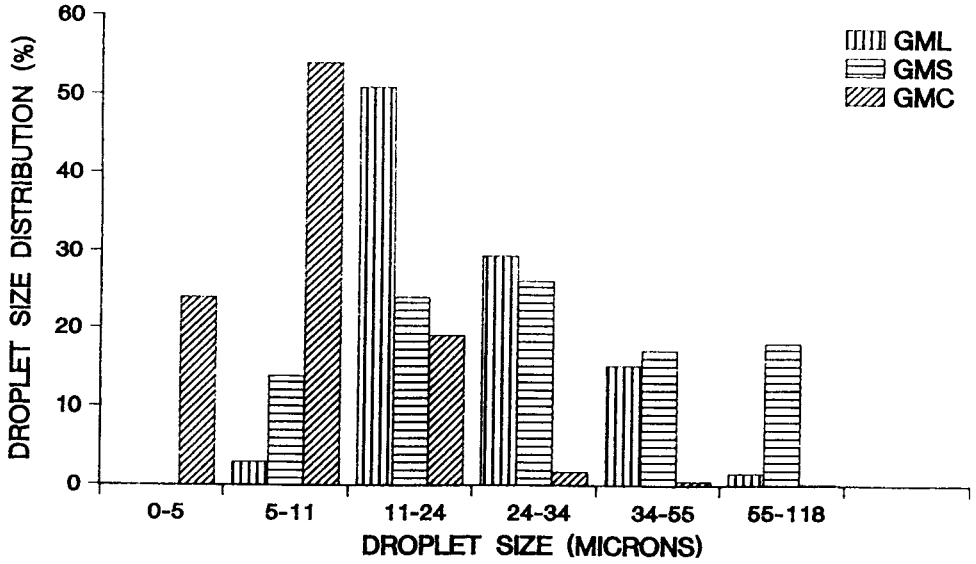

Figure 6. Effect of fatty acid chain length (as co-emulsifier) on emulsion droplet size.

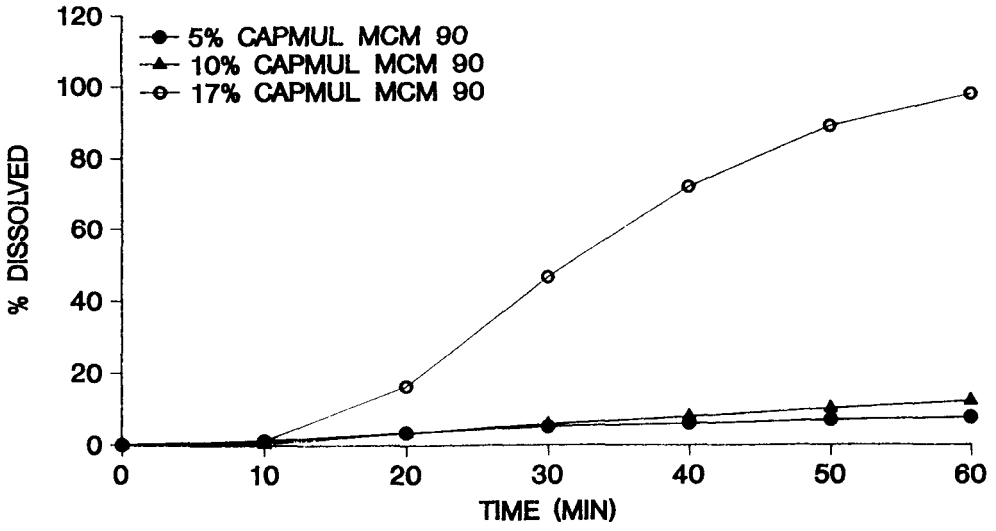

Figure 7. Dissolution profile of arotinoid (25 mg) capsules with differing levels of C_8–C_{10} (Capmul MCM90) co-emulsifier.

CONCLUSION

A lipophilic model drug, an arotenoid, was incorporated into a self-emulsifying formulation containing drug, glycerol ester, surfactant, and vegetable oil. Surfactants containing differing hydrophile lipophile ratios (HLB values) affected the efficiency of the SES system. Surfactants with HLB values in the range of 11–15 and at a concentration of 5% produced the best self-emulsifying system which released 100% of a lipophilic drug in an aqueous dissolution medium. This system also produced emulsion droplet particles of the smallest size (6 microns).

In testing the effectiveness and concentration of the glycerol ester as co-emulsifier, the caprylic/capric (C_8–C_{10}) fatty acid ester was superior to either the glyceryl

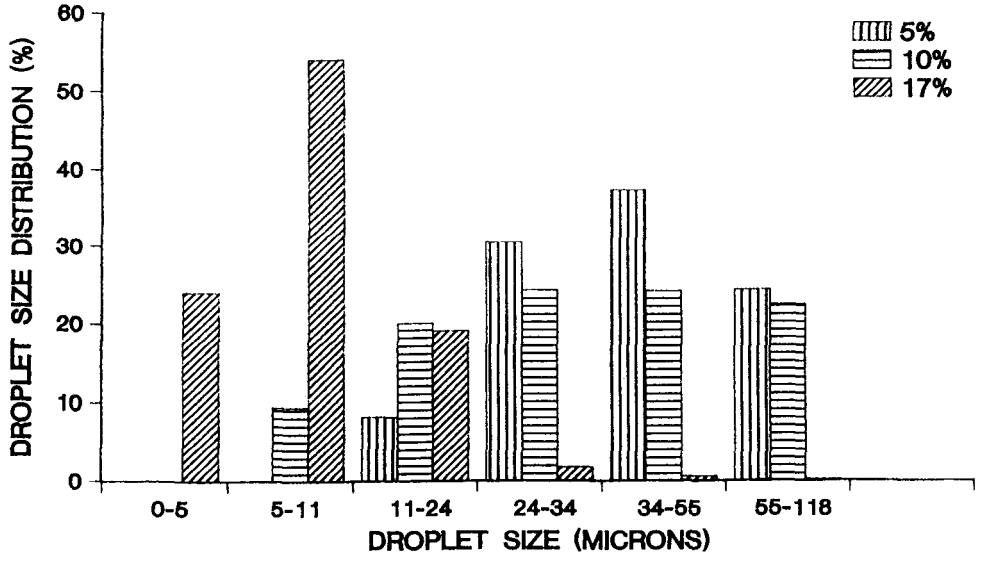

Figure 8. Effect of co-emulsifier (Capmul MCM90) concentration on emulsion droplet size.

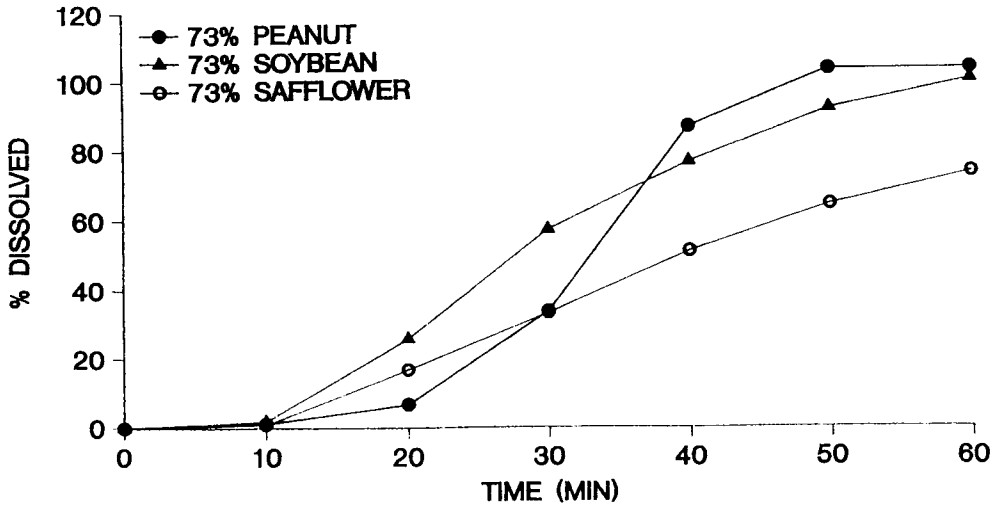

Figure 9. Dissolution profile of arotinoid (25 mg) capsules in lipophilic vehicles with differing fatty acid compositions.

monolaurate or glyceryl monostearate. At least 17% of the co-emulsifier (C_8–C_{10}) is needed for a good emulsifying system. The lipophilic vehicle has a lesser effect upon the efficiency of the SES system than the surfactant or co-emulsifier, as expected. Variations in the unsaturation of the C_{18} fatty acid compositions affected the drug dissolution pattern in one of three vegetable oils.

In summary, it is the appropriate choice of surfactant and its concentration, together with the proper choice of co-emulsifier and its concentration, which provides an optimum formulation with self-emulsifying properties, and maximum in vitro dissolution characteristics.

The best emulsifiers and their concentration are those which produce fine emulsion droplets without significant solubilization and entrapment of the drug in the micellar phase.

Our studies indicate that a surfactant with an HLB in the range of 11–15 at 5% concentration and a co-emulsifier consisting of a monoglyceride of caprylic/capric at 17% concentration were most effective in a formulation having good self-emulsifying properties and satisfactory dissolution characteristics.

REFERENCES

1. C. W. Pouton. Self-Emulsifying Drug Delivery Systems: Assessment of the Efficiency of Emulsification, Inter. J. Pharm., 27: 335, 1985.
2. N. H. Shah, M. T. Carvajal, C. I. Patel, M. H. Infeld, and A. W. Malick. Self-Emulsifying Delivery System with Polyglycolysed Glycerides for Improving In Vitro Dissolution and Oral Absorption of Lipophilic Drugs, Int. J. Pharm., 106, 15–23, 1994.
3. S. A. Stout, C. W. Pouton, M. C. Rogge, and W. N. O. Charman. Biopharmaceutic Evaluation of a Lipophilic Compound Administered as a Self-Emulsifying Formulation, Contributing Paper Abstract #PD 880, Pharm. Res., 5: (10) S-92, 1988.
4. C. W. Pouton, M. G. Wakerly, and B. J. Meakin. Self-Emulsifying Systems for Oral Delivery of Drugs, Proceed. Intern. Symp. Control. Rel. Bioact. Mater. 14: 1987, Controlled Release Society, Inc.
5. M. O. Bachynsky, N. H. Shah, M. H. Infeld, R. J. Margolis, A. W. Malick, D. H. Palmer. Oral Delivery of a Lipophilic Drug in a Self-Emulsifying Liquid Formulation, Internal Report (unpublished data), February 23, 1990.
6. D. Hane, A. Dockery, R. Rusignuolo, and J. Cannizzaro. Acute Toxicity of Ro 15-0778/000 (Arotinoid) in Mice, Rats, and Rabbits, Internal Report (unpublished data), February 27, 1984.
7. N. J. Greenberger, and T. G. Skillman. Medium-Chain Triglycerides, N. Engl. J. Med., 280: 1045, May 8, 1969.