Choice of Nonionic Surfactant Used to Formulate Type IIIA Self-Emulsifying Drug Delivery Systems and the Physicochemical Properties of the Drug Have a Pronounced Influence on the Degree of Drug Supersaturation that Develops During *In Vitro* Digestion

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ABSTRACT: The performance of self-emulsifying drug delivery systems (SEDDS) is influenced by their tendency to generate supersaturated systems during dispersion and digestion in the gastrointestinal tract. This study investigated the effect of drug loading on supersaturation during digestion of fenofibrate or danazol SEDDS, each formulated using long-chain lipids and a range of nonionic surfactants. Supersaturation was described by the maximum supersaturation ratio (SR^M) produced by *in vitro* digestion. This parameter was calculated as the ratio of the total concentration of drug present in the digestion vessel versus the drug solubility in the colloidal phases formed by digestion of the SEDDS. SR^M proved to be a remarkable indicator of performance across a range of lipid-based formulations. SEDDS containing danazol showed little evidence of precipitation on digestion, even at drug loads approaching saturation in the formulation. In contrast, fenofibrate crystallized extensively on digestion of the corresponding series of SEDDS, depending on the drug loading. The difference was explained by the generation of higher SR^M values by fenofibrate formulations. A threshold SR^M of 2.5–2.6 was identified in six of the seven SEDDS. This is not a definitive threshold for precipitation, but in general when SR^M is greater than 3, fenofibrate supersaturation could not be maintained. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:1050–1063, 2014
Keywords: supersaturation; precipitation; SEDDS; poorly water-soluble drugs; LFCS; lipids; surfactants; in vitro models; SR^M

INTRODUCTION

Examples of lipid-based formulations commonly used in oral drug delivery include simple oil solutions, self-emulsifying drug delivery systems (SEDDS), and cosolvent/surfactant mixtures, each of which have been used to improve the oral absorption of poorly water-soluble drugs (PWSDs).[1–4] SEDDS, consisting of a mixture of drug, oil(s), surfactant(s), and sometimes cosolvent, are perhaps the most widely used type of lipid formulation; Neoral® (the Novartis SEDDS formulation of cyclosporine) is a well-known commercial example. SEDDS are designed to emulsify spontaneously on addition to an aqueous phase, generating colloidal oil-in-water dispersions. The size of the colloidal oil droplets is dependent on the composition of the formulation, particularly the lipid–surfactant ratio and the type of surfactant used.[5–8] Although the average particle size of these systems immediately following dispersion is often determined by formulators,[3,9] the reality is that oil droplet size and the overall structure and composition of the colloids is continually changing during gastrointestinal transit, as the formulation encounters the digestive system, and as individual components are absorbed. In recent years, other, more robust measures of SEDDS performance have been sought. Methods for assessment of the fate of the drug during either *in vitro* dispersion or *in vitro* digestion are increasingly being used to predict the *in vivo* performance of lipid-based systems.[6,10–13] The rationale for such *in vitro* tests stems from the knowledge that SEDDS and other types of lipid formulations may suffer a loss of solubilization capacity following dispersion in the aqueous fluids in the gastrointestinal tract[3,14,15] or following digestion of lipids and/or surfactants in the intestine.[6,13,16,17] Dependent on drug loading, loss of solubilization capacity can lead to drug supersaturation, and the risk of drug precipitation.

The Lipid Formulation Classification System (LFCS), proposed by Pouton,[15,18] provides some initial guidance on SEDDS performance during dispersion and digestion. The LFCS describes four different classes of lipid formulations. Depending on the excipients used, SEDDS fall into either Type II or Type III according to the LFCS. Type II formulations consist of oils and water-insoluble surfactant(s), and form turbid dispersions of oil droplets that typically range from 0.25 to 2 μm in diameter. Because of the lack of water-soluble components, Type II formulations typically result in minimal loss of solubilization capacity on dispersion.[15–17] Type III formulations consist of oils mixed with water-soluble (high HLB) surfactant(s) and sometimes also a water-miscible cosolvent. Type III formulations are therefore more hydrophilic. They may form ultrafine dispersions (<100 nm) but typically lose solvent capacity on dispersion and digestion. Type III A/B subclasses have also been introduced to better differentiate between Type III formulations showing high (IIIA) or low (IIIB) lipid contents. The high

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lipid content (>40%) in Type IIIA formulations is often able to prevent rapid and extensive precipitation on dispersion,[10,16,17] unless the formulation contains high drug loadings and/or cosolvent,[6,13] However, oils present in SEDDS (both Types II and IIIA/B) are likely to be readily digested by pancreatic lipases in the small intestine,[19,20] causing the physicochemical nature of the SEDDS to change dramatically. More specifically, at the molecular level, digestion involves the enzymatic hydrolysis of esters in triglyceride and diglyceride molecules and the formation of less lipophilic monoglyceride and fatty acid molecules. This process at a formulation level causes a progressive depletion of an oil droplet phase and the enrichment of bile salt/phospholipid-mixed micellar phase(s) that include the digestion products. Digestion has the effect of "forcing" drug to partition from the oil reservoir, which is rapidly decreasing in volume, into the micellar phase. As lipophilic drugs typically have lower affinity toward the more hydrated micellar phases, the transfer of drug from an oil-rich phase by digestion is associated with a decrease in drug solubility. This is analogous to other events that are known to create supersaturation by shifting the position of equilibrium, such as solvent-shift phenomena.[21,22]

We and others have shown that digestion of Type IIIA SEDDS can dramatically lower their solubilization capacity for hydrophobic drugs to a point where drug precipitation occurs.[5,11,13,16,17] The effect of precipitation on drug absorption is dependent on the physical form of the drug in the precipitate. The emergence of a crystalline solid with a slow rate of redissolution (often the case for PWSD) is likely to be associated with decreased bioavailability.[1,6,13] Rational lipid formulation design therefore requires an awareness of the factors that may contribute to drug precipitation, the critical factor being the extent of supersaturation generated by a loss of solubilization upon dispersion and digestion.

In our previous study,[17] the performance of a Type IIIA SEDDS consisting of long-chain lipids (soybean oil and Maisine™ 35-1), the surfactant Tween® 80, and a high loading (~85 mg/g) of the PWSD fenofibrate, was examined *in vitro*. Precipitation of fenofibrate during dispersion was moderate (<25% over 24 H). However, during 30 min of digestion, because of exposure to pancreatin and bile, more than 85% of the drug crystallized from solution. The substantial increase in precipitation observed during digestion tests was attributed to a marked increase in the degree of supersaturation caused by digestion of the SEDDS, which decreased the solubilization capacity.[17] The present study was designed to extend our understanding of the performance of Type IIIA SEDDS during *in vitro* digestion testing, by further exploring whether the degree of supersaturation attained during digestion could explain differences in drug precipitation. Model drugs were chosen with high (fenofibrate) or lower (danazol) solubility in anhydrous SEDDS, which allowed a wide range of drug loadings to be evaluated. In this study, we explored the influence of the choice of surfactant. Each SEDDS consisted of long-chain lipids combined with one of seven different nonionic surfactants. The surfactants included various digestible materials[6] [Cremophor® EL, Cremophor® RH40, Tween® 80 and Solutol® HS-15, D-α-tocopherol polyethylene glycol (TPGS) 1000 succinate] and nondigestible materials (Brij® 97 and Brij® 98). The focus on the choice of surfactant is timely, given that recent studies have suggested that the digestibility of the surfactant in SEDDS can dramatically influence the performance *in vitro* and *in vivo*.[6,23,24] Other recent studies have compared various nonionic surfactants and reported their differential capacity to affect the activity of intestinal digestion enzymes,[6,25] the interfacial properties at the oil–water interface,[26–28] and cytochrome-mediated drug metabolism in the gastrointestinal tract.[29–31] These studies all reiterate the need for the judicious selection of formulation surfactant in SEDDS. The studies presented herein aimed to investigate the extent of precipitation of two drugs, fenofibrate and danazol, from a range of formulations that differed only in the identity of the surfactant used to form Type IIIA lipid-based delivery systems. The emphasis of the study was to evaluate precipitation as an unbiased measure of performance, and to ask whether there was any relationship between the extent of precipitation and the degree of supersaturation generated during digestion of the formulations.

MATERIALS AND METHODS

Materials

Details of the nonionic surfactants used in the study are presented in Table 1. Fenofibrate, soybean oil (a long-chain triglyceride), sodium taurodeoxycholate (>95%, NaTDC), porcine pancreatin extract (P7545, 8× USP specifications activity), calcium chloride dehydrate ($CaCl_2 \cdot 2H_2O$), Tris–maleate, and the lipid digestion inhibitor 4-bromophenylboronic acid (4-BPB) were purchased from Sigma–Aldrich Company (St. Louis, Missouri). Danazol was kindly supplied by Sterling Pharmaceuticals (Sydney, New South Wales, Australia). Maisine™ 35-1 (a blend of long-chain mono-, di-, and some tri-glyceride) was supplied

Table 1. Details of the Nonionic Surfactants Used in the Type IIIA SEDDS

Surfactant	Chemical Name	Quoted HLB Value/Range
Brij® 97[a]	Polyoxyethylene (10) oleyl ether	~12
Brij® 98[a]	Polyoxyethylene (20) oleyl ether	15
Cremophor® EL[b]	Polyethylene glycol (35)-glycerol ricinooleate	12–14
Cremophor® RH40[b]	Polyethylene glycol (40)-glycerol hydroxystearate	14–16
Solutol® HS-15[b]	Polyethylene glycol (15)-hydroxy stearate	14–16
Tween® 80[a]	Polyoxyethylene (20) sorbitan monooleate	15
TPGS[a]	D-α-tocopherol polyethylene glycol (23) succinate	~13

The oxyethylene content of each material is quoted using a common nomenclature, not necessarily used by the manufacturers, where the number in brackets represents the approximate number of $–CH_2CH_2O–$groups per molecule. However, the materials are not synthesized by common methods. The oxyethylene chains are a varied chain length because of their polymeric nature and the materials, particularly the esters, may contain complex mixtures of molecules.

[a] Obtained from Sigma–Aldrich, St. Louis, Missouri.

[b] Obtained from BASF, Washington, New Jersey.

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