Characterization of Prototype Self-Nanoemulsifying Formulations of Lipophilic Compounds

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ABSTRACT: This study describes the evaluation and characterization of a self-nanoemulsifying drug delivery system (SNEDDS) consisting of a nonionic surfactant (Cremophor RH40), a mixture of long chain mono-, di-, and triacylglycerides (Maisine 35-1 and Sesame oil) and ethanol. Compositions containing 10% (w/w) ethanol, 40%–60% (w/w) lipid content, and 30%–50% (w/w) Cremophor RH40 were identified as pharmaceutically relevant, robust, and self-nanoemulsifying when dispersed in aqueous media. The influence of adding three different lipophilic model drug compounds (danazol, halofantrine, and probucol) to the SNEDDS was evaluated. While danazol precipitated from the SNEDDS after dispersion in aqueous media, halofantrine and procubol remained solubilized. Halofantrine- and procubol-loaded SNEDDS were evaluated in both saline and in media simulating fasted and fed-state intestinal fluid (FaSSIF and FeSSIF) using dynamic light scattering and small-angle X-ray scattering (SAXS) techniques. Stable nanoemulsions with droplet sizes in the range of 20–50 nm were formed in all media and with and without drugs. The mean size of the droplets was neither affected significantly by being dispersed into the media simulating gastro intestinal fluid, nor by addition of the drug.
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Keywords: emulsion/microemulsion; formulation vehicle; surfactants; light scattering (dynamic); self-emulsifying drug delivery system (SEDDS); small-angle X-ray scattering (SAXS)

INTRODUCTION

The high-throughput screening approach in drug discovery within the pharmaceutical industry has lead to drug candidates with increasing lipophilicity.[1] A typical characteristic for these compounds is low and variable oral bioavailability from solid dosage forms due to their poor water solubility. One increasingly popular approach to overcome this problem, is the use of a self-emulsifying drug delivery system (SEDDS).[2–4] The bioavailability enhancing properties of SEDDS compared to solid dosage forms has

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primarily been attributed to the ability of the vehicles to keep the compound in solution in the gastro intestinal (GI) tract and thereby maintaining a maximal free drug concentration and omitting a rate determining dissolution step.[5,6] However, the parameters differentiating the absorption from different SEDDS compositions is not well understood. The most common parameters put forward in order to explain the difference in absorption are rate of dispersion, particle size of the resultant dispersion,[7] the rate of digestion for formulations susceptible to digestion[8] and possibly also the solubilization capacity of the digested formulation.[9]

A prerequisite for the use of SEDDS, for oral administration, is that the dose of the compound is soluble in the SEDDS preconcentrate and stay solubilized in the vehicle after dispersion. Solubility in the preconcentrate is the limiting factor for a number of poorly water-soluble compounds, which are also poorly soluble in lipids. Therefore SEDDS, as a rule of thumb, is primarily considered relevant for oral delivery of potent compounds (low dose) and compounds with a log p-value above 4.[10] However, a better indication for the applicability of SEDDS is a good solubility of the compound in surfactant and lipid excipients. This is exemplified by cyclosporine, which has low log p value of 3.0[11] but high-oil solubility.

SEDDS can be formulated using a combination of surface-active excipients, lipids and polar cosolvents,[4] though SEDDS has also been formulated without the use of a polar cosolvent.[10] The typical polar cosolvent is ethanol which is well known, recognized as a safe pharmaceutical excipient and also known to facilitate the self-dispersion of SEDDS.[12]

Some attempts have been made to categorize SEDDS and predict the behavior of the systems based on type and content of surfactant, lipid phase and cosolvent.[10] So far the strategy for the evaluation and characterization of SEDDS has primarily been based on applying basic concepts from equilibrium phase behavior studies of systems mixed with water[5] and evaluation of the self-emulsification with respect to rate of emulsification and the particle size and distribution of the resultant emulsion.[13] As an example, Khoo et al.[14] described a visual grading system where the emulsification rate and resultant emulsion are qualitatively characterized. Emulsification rate and particle size have also been assessed by measurement of turbidity as a function of time.[15] The increase in turbidity was used to monitor emulsification rate and the final turbidity were correlated to mean particle size.[13,16]

Particle size measurements of self-emulsifying systems are often performed after dispersion in water or other simple aqueous media.[17–19] However, in the GI tract the formulation will encounter a more complex environment containing endogenous surfactants as bile salt (BS) and phospholipid (PL). This may impact the particle size of the resulting SEDDS aggregates.

The purpose of the present work was to evaluate and characterize a system known to produce self-nanoemulsifying drug delivery system (SNEDDS) with special emphasis on: (1) the solubility in SNEDDS and solubilization capacity after dispersion; (2) the influence of selected model drug compounds on dispersion properties and particle size of the identified SNEDDS; and (3) investigate whether media simulating the BS/PL rich environment in the gastrointestinal tract would have any effect on the particle size of the identified SNEDDS and if this was dependent on drug load. The selected system, known to produce SNEDDS, consisted of a nonionic surfactant (Cremophor RH40), a mixture of long chain mono-, di-, and triacylglycerides (Maisine 35-1 and Sesame oil) and ethanol. Evaluation of self-emulsifying properties and screening for SNEDDS were evaluated when dispersed in saline using visual inspection and turbidity measurements. Three different lipophilic model drug compounds (danazol, halofantrine, and probucol) were selected on the basis of different physicochemical properties to represent a range of lipophilic compounds. Their solubility was determined in the preconcentrate and precipitation was evaluated after dispersion. Particle size of the identified SNEDDS with and without drug load was evaluated using laser diffraction analysis, dynamic light scattering, and small-angle X-ray scattering (SAXS).

MATERIALS AND METHODS

Materials

Cremophor® RH40 (Cr RH40) (polyethoxylated hydrogenated castor oil obtained by ethoxylating hydrogenated castor oil with 40 mol ethylenoxide per mol) was obtained from BASF-BASIS Kemi, Copenhagen, Denmark and Maisine® 35-1 (obtained by partial alcoholysis of maize oil and contains a mixture of monoacylglycerides (MAG), diacylglycerides (DAG), and triacylglycerides (TAG)