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Lecithin-linker formulations for self-emulsifying delivery of nutraceuticals

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ABSTRACT

Lecithin-linker microemulsions are formulations produced with soybean lecithin in combination with a highly lipophilic (lipophilic linker) and highly hydrophilic (hydrophilic linkers) surfactant-like additives. In this work, lecithin-linker systems were formulated to produce self-emulsifying delivery systems for β-carotene and β-sitosterol. The concentration of the lipophilic linker, sorbitan monooleate, was adjusted to minimize the formation of liquid crystals. The concentration of hydrophilic linkers, decaglyceryl caprylate/caprate and PEG-6-caprylic/capric glycerides, was gradually increased (scanned) until single phase clear microemulsions were obtained. For these scans, the oil (ethyl caprate) to water ratio was set to 1. The single phase, clear microemulsions were diluted with fed-state simulated intestinal fluid (FeSSIF) and produced stable emulsions, with drop sizes close to 200 nm. Using pseudo-ternary phase diagrams to evaluate the process of dilution of microemulsion preconcentrates (mixtures of oil, lecithin and linkers with little or no water) with FeSSIF, it was determined that self-emulsifying systems are obtained when the early stages of the dilution produce single phase microemulsions. If liquid crystals or multiple phase systems are obtained during those early stages, then the emulsification yields unstable emulsions with large drop sizes. An *in vitro* permeability study conducted using a Flow-Thru Dialyzer revealed that stable emulsions with drop sizes of 150–300 nm produce large and irreversible permeation of β-carotene to sheep intestine. On the other hand, unstable emulsions produced without the linker combination separated in the dialyzer chamber.

1. Introduction

Microemulsions are one type of nano-sized oral delivery vehicles capable of enhancing the bioavailability of poorly soluble drugs (Lawrence and Rees, 2012). These systems enhance the bioavailability of hydrophobic drugs by reducing drop size, increasing the solubilization of the active ingredient, and increasing the residence time of the drug in the intestine (Acosta et al., 2011a; McClements, 2012). Microemulsions have oil and/or water nano-domains that exist in thermodynamic equilibrium due to the adsorption of surfactants at the oil/water interface. Microemulsion can be composed of oil nano-domains solubilized in micelles (water continuous); or water nano-domains solubilized in reverse micelles (oil continuous); or they can be composed of coexisting oil and water nano-domains in bicontinuous systems (Kesisoglou et al., 2007; Rosen, 2004; Huang et al., 2010; McClements, 2012). Winsor used the terms Type I, II and III to identify oil-in-water, water-in-oil, and bicontinuous "saturated" microemulsions, respectively, that coexisted with an excess phase (oil for Type I, water for Type II, and oil and water for Type III) (Salager et al., 2005). The transition from oil to water continuous microemulsions can be accomplished by changing the formulation conditions, for example, increasing the hydrophilicity of the surfactant or surfactant mixture (Salager et al., 2005). One characteristic property of saturated microemulsions near or at the phase inversion point is that the interfacial tension with the excess phase is ultralow (10^{-2}–10^{-5} mN/m) (Salager et al., 2005). For single phase microemulsions (no excess phases), the transition from oil to water continuity can also be accomplished by increasing the water/oil ratio. For these unsaturated microemulsions, the phase inversion is captured by

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changes in electrical conductivity, self-diffusion coefficients (NMR techniques), and micelle/reserve micelle morphology (neutron or X-ray scattering) (Garti et al., 2004; Datema et al., 1992; Fisher et al., 2013).

Self-emulsifying delivery systems (SEDS) represent a form of delivery systems that are related to microemulsion systems. SEDS are ideally isotropic, water-free mixtures of oils, surfactants, or co-solvents/surfactants that emulsify to form fine oil in water emulsions or microemulsions (SMEDS) upon aqueous dilution and gentle agitation (Pouton, 1997; Gursoy and Benita, 2004). These systems have been used to enhance the absorption of lipophilic drugs (Narang et al., 2007; Pouton, 2000; Acosta, 2009).

In addition to sufficient drug absorption, oral delivery formulations should be safe for consumption. Despite the limited selection of food-grade ingredients (Acosta, 2009; Garti and Yuli-Amar, 2008; Calderon et al., 2010), biocompatible microemulsions have been developed using triglycerides, terpenes, and ethyl esters of fatty acids as the oil phase (Gupta et al., 2006; Von Corswant et al., 1997; Gupta and Moulik, 2008; Torchilln, 2008). The use of phospholipids (lecithin mainly) as the main surface active material is also desirable due to lecithin's GRAS status (21 CFR 184.14), and its long alkyl tail (C16–C18) that provides greater oil solubilization capacity (Acosta et al., 2005). Unfortunately, lecithin tends to produce liquid crystals that promote the formation of undesirable gels and emulsions. This limitation has been overcome with the introduction of linker molecules in lecithin microemulsions. Fig. 1 shows a schematic of the surfactant and linker assembly at the oil/aqueous interface (Acosta et al., 2005).

Linker molecules can be described as unbalanced surfactants that segregate or adsorb at the oil/water interface, however, their primary interaction is with either the oil phase (lipophilic linkers) or the aqueous phase (hydrophilic linkers) (Acosta et al., 2003, 2004, 2005, 2011b; Sabatini et al., 2003). A lipophilic linker has a long (C10+) hydrophobe (tail) and a weak hydrophile such as an alcohol (R—OH) group or one or two ethylene oxide groups. A hydrophilic linker has a short hydrophobe (typically C6–C9) but a conventional surfactant hydrophile such as carboxylates, sulfonates, polyethylene glycol (more than 3 ethylene oxide groups), poly-glucoside, poly-glycerols, etc. (Sabatini et al., 2003). Although most of the literature does not differentiate between surfactants and linkers, it has been shown that combination of hydrophilic and lipophilic linkers alone cannot produce microemulsions because they do not associate with each other. The linkers associate with a balanced surfactant (lecithin in this case), producing a "zipper"-like self-assembly of hydrophilic and lipophilic linkers (Acosta et al., 2004).

In this work, we hypothesize that linker-based lecithin microemulsions can be formulated as oral drug delivery vehicles for hydrophobic drugs using food and pharmaceutical grade ingredients, using the lecithin-linker formulations of Yuan and Acosta (2009), Yuan et al. (2010) as starting point. The transdermal formula of Yuan consisted of lecithin, isopropyl myristate as the oil, sorbitan monooleate as lipophilic linker, and caprylic acid and sodium caprylate as hydrophilic linkers. In order to avoid pH sensitivity, the caprylic acid and its salt were substituted with decaglyceryl caprylate/caprate (food additive) and PEG-6-caprylic/capric glycerides (pharmaceutical grade). A similar mixture of non-ionic hydrophilic linkers was used by Xuan et al., 2012. Isopropyl myristate (IPM) was replaced with ethyl caprate, a food-grade oil.

To evaluate the linker-based SEDS as oral delivery vehicles, β-sitosterol and β-carotene, both lipophilic nutraceuticals, were selected as model drugs. Their chemical structures are shown in Fig. 2. β-Sitosterol is a plant sterol that has low water solubility, and that slows or inhibits the incorporation of dietary and biliary cholesterol (Rozner et al., 2007; Rozner and Garti, 2006). β-Carotene
is a carotenoid (yellow-orange color) insoluble in water that has antioxidant properties and is affirmed as GRAS for use as a nutrient (21 CFR 184.1245) by the FDA. β-Carotene was also used as a lipophilic marker in the *in vitro* permeability tests. Pseudo-ternary phase diagrams of the lecithin-linker mixture, fed state simulated intestinal fluid (FeSSIF), and ethyl caprate with and without β-sitosterol were developed to guide the formulation of self-emulsifying delivery systems (SEDS). An *in vitro* method was used to assess active ingredient permeability by outfitting a Flow-Thru Dialyzer (Xuan et al., 2012; Yan and Gemeinhart, 2005), with excised lamb intestine.

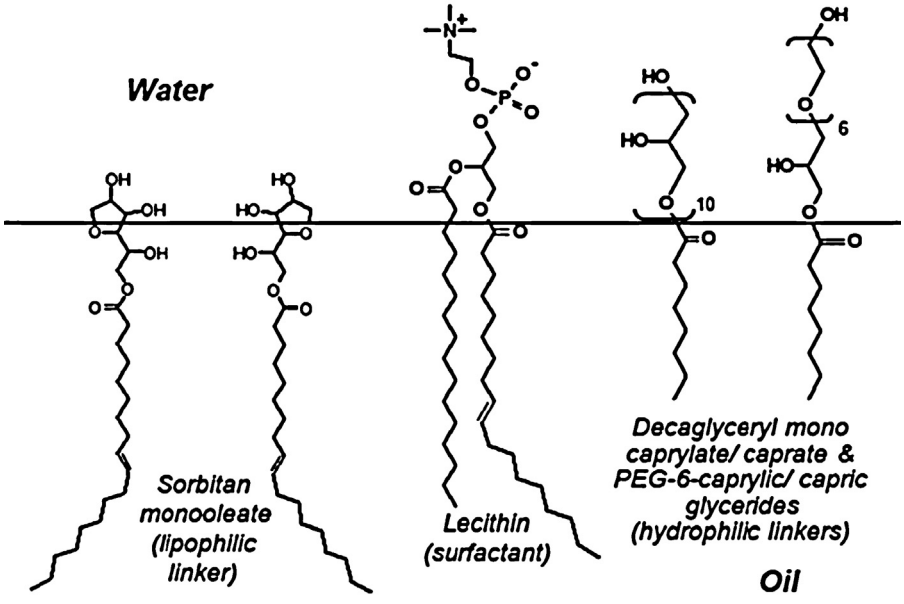

Fig. 1. Schematic of the linker effect at the oil/water interface.