Development and Characterization of a Biocompatible Soybean Oil-Based Microemulsion for the Delivery of Poorly Water-Soluble Drugs

CAROLINA ALOISIO,[1,2] MARCELA R. LONGHI,[1] ANSELMO GOMES DE OLIVEIRA[2]

[1]Unidad de Investigación y Desarrollo en Ciencia y Tecnología Farmacéutica (UNITEFA-CONICET), Departamento de Farmacia, Facultad de Ciencias Químicas-Universidad Nacional de Córdoba, Ciudad Universitaria, Córdoba X5000HUA, Argentina
[2]UNESP-Universidade Estadual Paulista, Faculdade de Ciências Farmacêuticas, Araraquara, São Paulo 14801-902, Brazil

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ABSTRACT: The aim of this work was the development and characterization of a biocompatible microemulsion (ME) containing soybean oil (O), phosphatidylcholine/sodium oleate/Eumulgin®HRE40 as the surfactant mixture (S) and water or buffer solution as the aqueous phase (W), for oral delivery of the poorly water-soluble drugs sulfamerazine (SMR) and indomethacin (INM). A wide range of combinations to obtain clear oil-in-water (o/w) ME was observed from pseudo-ternary phase diagrams, which was greater after the incorporation of both drugs, suggesting that they acted as stabilizers. Drug partition studies indicated a lower affinity of the drugs for the oil domain when they were ionized and with increased temperature, explained by the fact that both drugs were introduced inside the oil domain, determined by nuclear magnetic resonance. High concentrations of SMR and INM were able to be incorporated (22.0 and 62.3 mg/mL, respectively). The ME obtained presented an average droplet size of 100 nm and a negative surface charge. A significant increase in the release of SMR was observed with the ME with the highest percentage of O, because of the solubilizing properties of the ME. Also, a small retention effect was observed for INM, which may be explained by the differences in the partitioning properties of the drugs. © 2015 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 104:3535–3543, 2015

Keywords: microemulsions; solubility; sulfamerazine; indomethacin; surfactants; sulfonamides; NMR spectroscopy; drug release

INTRODUCTION

Microemulsions (ME) are isotropic, optically clear nanostructured and thermodynamically stable dispersions, composed of two nonmiscible liquids such as an aqueous phase and an oily phase, stabilized by an interfacial film of surfactants often associated with a cosurfactant.[1–5] The formation of water-in-oil (w/o) or oil-in-water (o/w) ME is dependent on the properties of the surfactant mixture, the oil–surfactant ratio and the temperature.[6] It has also been reported that the ME structure plays an important role in drug release.[7–10]

Over the last decade, a large number of studies on the ME systems available for pharmaceutical application has been published.[4,5,7,11–15] These systems involve the use of biocompatible components with the ability to improve the solubility of sparing soluble drugs.[8,9,16–18] Soy phosphatidylcholine (SPC) is a widely used biocompatible surfactant of natural origin from a component of cell membranes and is a known pharmaceutical ingredient that can be used for all administration routes including i.v.[1,19,20] In addition, monounsaturated fatty acids, such as oleic acid, have received increasing attention as penetration enhancers.[10] A typical analysis of pure soybean oil indicates that the main composition is palmitic acid (9%–13%), stearic acid (3%–6%), linoleic acid (50%–57%), oleic acid (17%–26%), and linolenic acid (5%–10%). Interest in using nonionic surfactants associated with a cosurfactant is growing in ME composition, mainly because of the high stability, low toxicity, and biodegradability of these compounds. Polyoxyethylenglycerol (PEG)-40 hydrogenated castor oil is a nonionic surfactant for pharmaceutical use[21,22] that provides adequate conditions to stabilize w/o ME when used in surfactant mixtures.[12,23,24]

The effect of ME on drug delivery has been well described in the literature and reveals a favorable influence on the modification of the bioavailability of many drugs, such as the antimicrobial activity of glycerol monolaurate by using o/w ME;[5] tween-based MEs has been developed for the delivery of a fixed-dose combination of three first-line antitubercular drugs;[11] and other MEs have been produced for the solubilization of many drugs such as azithromicin,[25] chloramphenicol,[4] and several water-soluble peptides of different molecular structures, sizes, and charges in w/o MEs containing long- or medium-chain triglycerides.[6] In addition, several recent studies have suggested that MEs have the potential to increase transdermal drug delivery of both hydrophilic and lipophilic drugs, such as naproxen,[26] testosterone,[10] curcumin,[2] T4,[27] ketoprofen, lidocaine, and caffeine.[28]

The main purpose of this work was the development of a biocompatible ME for the oral delivery of sparingly water-soluble acid/ionic drugs, using sulfamerazine (SMR) and indomethacin (INM) as model drugs. Experimental approaches applied to these drugs can also provide information for other poorly water-soluble drugs with similar physicochemical properties. The obtained systems were characterized using pseudo-ternary phase diagrams (PTPD), polarizing light microscopy, ^{1}H nuclear magnetic resonance (NMR) spectroscopy, conductivity, and particle size and zeta potential measurements. In addition, the incorporation of the drugs related to the system composition and the *in vitro* release from selected ME were also analyzed.

Correspondence to: Marcela R. Longhi (Telephone: +54-351-5353865; E-mail: mrlcor@fcq.unc.edu.ar)

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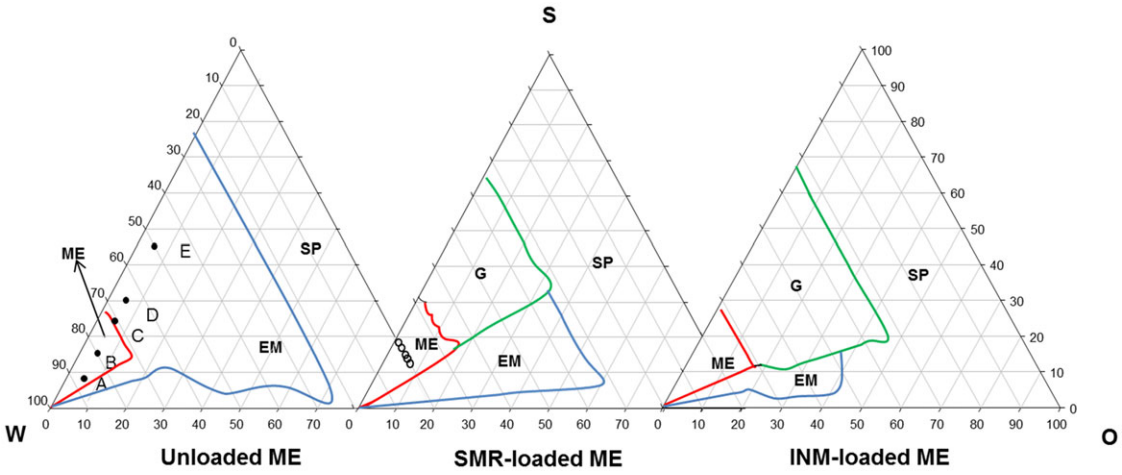

Figure 1. Pseudo-ternary phase diagram of: unloaded, SMR-loaded, and INM-loaded ME. (a–e) Selected formulations for polarized light microscopy study. Selected MEs for incorporation studies. ME, microemulsion; EM, emulsion; G, gel; SP, separation of phases.

MATERIALS AND METHODS

Materials

The MEs used in this work were chosen according to a previous study.[12] SPC was purchased from Degussa Texturants Systems Deutshland GmbH and Company (Hamburg, Germany); (PEG)-40 hydrogenated castor oil (Eumulgin® HRE 40) (EU) (CAS number 61788-85-0) was purchased from Pharma Special (São Paulo, Brazil); soybean oil (Liza®) (O), SMR, and INM were obtained from Parafarm® (Buenos Aires, Argentina); sodium oleate (SO) was obtained from the stoichiometric reaction of oleic acid with 1 M NaOH solution for 30 min. The precipitate was filtered and washed with three portions of 100 mL of acetone. All the other materials and solvents were of analytical grade or better. Purified water was obtained from a Millipore Milli-Q Water Purification System.

Methods

Pseudo-Ternary Phase Diagram

Pseudo-ternary phase diagrams were obtained from previous studies of our research group, utilizing hydrophilic–lipophilic balance (HLB) values for the same surfactant system used in this study.[12] The surfactant system containing an SPC–EU–SO (35:35:30) mixture with an HLB value of 12 was used to define the phase diagrams. Semisolid mixtures of oil–surfactant (O–S) (1.0 g) with weights ranging from 1:9 to 9:1 ratios were titred with aqueous phase under ultrasonic stirring using a Ultrasonic Liquid Processor, Heat System XL 2020 apparatus. The whole study was carried out at room temperature. The transitions from semisolid mixture to opaque dispersion (emulsion), and from emulsion to optically clear ME or phase separation (PS), were sharp and reproducible with 0.1 mL of precision. For the drug-loaded ME, 0.021 or 0.0071 g, the SMR or INM were added, respectively, to the S–O mixture before titration with the aqueous phase, and the procedure was followed as described above for drug-free ME.

Polarizing Light Microscopy

Drug-loaded and drug-unloaded ME, with constant 5% content of oil phase selected from the PTPD, were analyzed by polarized light microscopy (Jenamed 2; Carl Zeiss®, Jena, Thuringia, Germany). to differentiate MEs (nonbirefringent) from liquid crystalline structures (birefringent). The O–S–W percent composition of samples analyzed were: A = 5:8:87; B = 5:15:80; C = 5:24:71; D = 5:71:65; and E = 5:65:50 (see Fig. 1 for phase diagram illustration). A digital camera (Nikon CoolPix 990, Tokyo, Japan) was attached to the microscope for capturing the images.

Conductivity (σ)

The conductivity (σ) was measured for both unloaded and drug-loaded ME as a function of the O–S ratio or drug content using a Digimed® DM-32 conductivity meter with a Digimed® DMC 010 M electrode with a cell. The conductivity meter was calibrated using a standard solution of 1413 μS/cm before testing. The selected composition for all studies are presented in Table 1. All measurements were carried out in triplicate at 25 ± 1°C.

Determination of Partition Coefficients

In order to estimate the partition behavior of the drugs in ME systems, studies between the used aqueous phases and soybean oil were performed. The drug partition coefficients were calculated according to the concentrations of SMR or INM remaining in the phases after separation of 1:1 water–oil systems.

To carry this out, 3 mL of water, 10 mM potassium phosphate buffer solution (PBS) of pH 7.4 or 8 and soybean oil, were added to 5 or 10 mg of SMR or INM, respectively. These mixtures were maintained at 25 or 37 ± 1°C with constant agitation of 200 rpm for 72 h using a Shaker Ferca® (Santa Fe, Argentina), before being centrifuged for 30 min at 700 g for PS using a Rolco® (Buenos Aires, Argentina) centrifugator. The concentration of the substrates was calculated by measuring the absorbance using a Cary 60, Agilent Technologies® (Santa Clara, CA, USA) UV–Visible spectrometer.

The oil/water partition coefficients were calculated using the following equation:

$$\log P = C_{oil}/C_{water}$$

where C_{oil} and C_{water} are the concentrations of drug in oil and in water, respectively.