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Oil type effect on diclofenac solubilization in mixed nonionic surfactants microemulsions

Monzer Fanun*

Colloids and Surfaces Research Laboratory, Faculty of Science and Technology, Al-Quds University, P.O. Box 51000 East-Jerusalem, Palestine

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ABSTRACT

Diclofenac solubilization capacity and the associated structural transitions U-type microemulsions characterized by a large continuous isotropic region were studied. The microemulsions were composed from biocompatible components that are water/sucrose laurate/ethoxylated mono-di-glyceride/oil + ethanol. The oil was R(+)-limonene or isopropylmyristate. The mixing ratios (w/w) of sucrose laurate/ethoxylated mono-di-glyceride and that of ethanol/oil equal unity. The systems were studied along the dilution line N60 (weight ratio of mixed surfactants/oil/ethanol phase equals 6/2/2) at 25 °C. Solubilization capacity of the drug was dependent on the oil type and microstructure of the microemulsion. The solubilization capacity of the drug in the reverse micelles and microemulsions was very much higher than its solubility in R(+)-limonene or isopropylmyristate. The structural transition from the water-in-oil to bicontinuous and to oil-in-water microemulsions were identified by small angle X-ray scattering and nuclear magnetic resonance measurements. Diclofenac affects the curvatures of the microstructures and consequently the limits of the structural transitions. Dilutable microemulsions are promising new diclofenac vehicles for oral intake.

1. Introduction

Diclofenac is a nonsteroidal compound with analgesic, anti-inflammatory and antipyretic properties. Different colloidal systems were used as delivery vehicles of diclofenac in order to improve its bioavailability [1–15]. These systems include liquid crystals [1], emulsions [2], multiple emulsions [3], nanoemulsions [4], microemulsions [5–10], solid-in-oil suspensions [11,12], nanoparticles [13], gelatine microspheres [14], vesicles [15]. The adsorption of drug using microemulsions system is influenced by the particle size, the partition coefficient of the drug between the two immiscible phases, the presence of the drug in the interface, the site or path of absorption microemulsion components that can act as absorption enhancers and the drug solubility in microemulsion components. Microemulsions were found [5,16,17] to be effective vehicles of the solubilization of certain drugs since they provide all the possible requirements of a liquid system including thermodynamic stability, ease of preparation, low viscosity, high surface area, and very small droplet size. Solubilization capacity of microemulsions can be influenced by many factors, e.g., geometrical parameters [18,19], structural variations [20] and thermodynamic aspects [21], so many attempts have been undertaken in the literature to rationalize behavior of surfactants, cosurfactants and oils at the interfaces in relation to their hydrophile–lipophile balance [22,23], effective packing parameter [24] as well as hydrophilic-lipophilic deviation [25–27]. The small droplets have better chance to adhere to membranes and to transport bioactive molecules in a more controlled fashion. Microemulsions can be envisaged as protecting medium for the entrapped of drugs from degradation, hydrolysis, and oxidation. These systems can also provide prolonged release of the drug and prevent irritation despite the toxicity of the drug. Microemulsions can be introduced into the body orally, topically on the skin, or nasally, as an aerosol for direct entry into the lungs. The characterization of microemulsions used as drug delivery systems is necessary to determine the locus of the drug in the loaded microemulsion. Properties of drug loaded microemulsions can reveal the presence of molecular interactions between the loaded drug and the microemulsion. These properties include electrical conductivity [28,29], viscosity [30,31], periodicity, correlation length [32,33], diffusion [34–38], droplet size [18,39,40] and others [41–43]. The microstructure of the microemulsion (water-in-oil, bicontinuous, or oil-in-water) influence the loci of the solubilized molecules, resulting in changes in its solubilization capacity, and in the ability of the interface to protect the solubilized drug from environmental oxidative interactions and the release patterns [44,45]. It is essential to fully investigate the structural transitions of microemulsions upon water dilution in the presence of loaded drugs and try to form U-type microemulsions. Pharmaceutically acceptable microemulsions systems should be prepared using generally recognized and ideally

* Tel.: +972 522 40 60 61; fax: +972 22 79 69 60.
E-mail addresses: fanunm@gmail.com, mfanun@science.alquds.edu.

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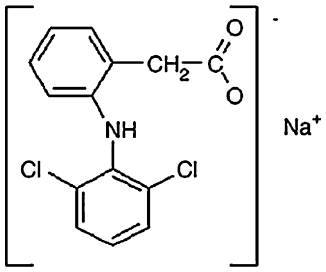

Fig. 1. Chemical structure of diclofenac sodium.

pharmaceutical grade ingredients, i.e., ones already approved by regulatory bodies for pharmaceutical use and are devoid of undesirable effects. The choice of ingredients is challenging, as most of the oils, surfactants and cosurfactants utilised in fundamental research are not suitable due to bioincompatibility issues. Amongst the pharmaceutically acceptable oils are isopropylmyristate (IPM) [8,44,46] and R(+)-limonene (LIM) [47–49]. Amongst the nonionic surfactants are sucrose esters [36–38,50–53], polyoxyethylene alkyl ethers and amongst the cosurfactants are ethanol medium chain mono and diglycerides [54–57], 1,2-alkanediols alkyl monoglucosides [57]. The objectives of this study are: firstly, to evaluate the solubilization of sodium diclofenac in U-type fully dilutable microemulsions based on mixed nonionic surfactants, biocompatible oils and ethanol as the cosurfactant, secondly, to evaluate the influence of the solubilized drug on the structural and diffusion properties of the drug loaded microemulsions.

2. Experimental

2.1. Materials

The sucrose laurate (L1695) was obtained from Mitsubishi-Kasei Food Corp., (Mie, Japan). The purity of combined Lauric acid equals 95%, the esters compositions are 80% monoester and 20% di, tri and polyester, HLB equals 16. Ethoxylated mono-di-glyceride (EMDG) (MAZOL 80 MG KOSHER), HLB equals 13.5 was obtained from BASF Corporation (Gurnee, Illinois, USA). R(+)-limonene (LIM)45 (98%), isopropylmyristate (IPM), and sodium diclofenac (DIC) (see Fig. 1) were purchased from Sigma Chemicals Co. (St. Louis, USA). All of the components were used as supplied without further purification. Triple distilled water was used.

2.2. Methods

2.2.1. Pseudoternary phase diagrams at constant temperature

The phase behavior of a system consisting of water, oil, a mixture of surfactants and cosurfactant were reported elsewhere [51,58].

2.2.2. Small angle X-ray scattering (SAXS)

The scattering experiments of the systems studied in this work were reported elsewhere [51,59].

2.2.3. Pulsed gradient spin echo-nuclear magnetic resonance (PGSE-NMR)

NMR measurements of the systems studied in this work were reported elsewhere [51].

2.2.4. Solubilization evaluation of pharmaceutical active ingredient

Diclofenac was solubilized in transparent microemulsions samples. The mixture is heated to 50 °C for 30 min and then stored at 25 °C. Samples that remained transparent for at least 10 days were loaded step-wise with additional diclofenac to its maximum solubilization. The appearance of turbidity, or a precipitate, indicates that the microemulsions were drug saturated (or supersaturated). No further drug loading in such samples was done.

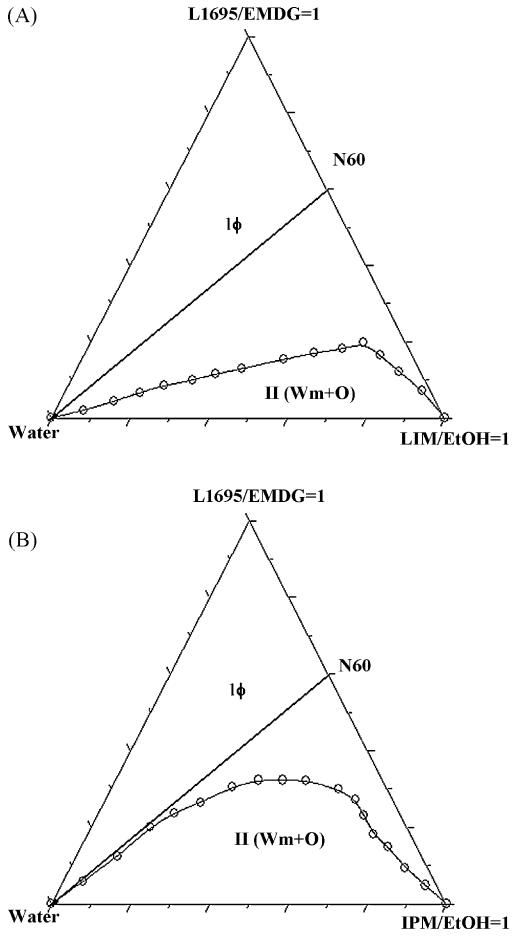

Fig. 2. Pseudoternary phase behavior of the water/sucrose laurate/ethoxylated mono-di-glyceride/oil + ethanol system at 25 °C. The oils were [A] R(+)-limonene and [B] isopropylmyristate. The mixing ratios (w/w) of ethoxylated mono-di-glyceride/sucrose laurate and that of ethanol/oil equal unity. The one phase region is designated by 1ϕ, and the two phase region consisted of water continuous micellar solution with excess oil is designated by (Wm+O). N60 is the water dilution line where the weight ratios of sucrose laurate/ethoxylated mono-di-glyceride/oil/ethanol equal to 3/3/2/2.

3. Results and discussion

3.1. Diclofenac solubilization evaluations

We examined the solubilization capacity of diclofenac in the formulated U-type microemulsions composed of water/sucrose laurate/ethoxylated mono-di-glyceride/oil + ethanol at 25 °C for the solubilization of sodium diclofenac along the N60 dilution line. The oils were R(+)-limonene and isopropylmyristate. The mixing ratios (w/w) of sucrose laurate/ethoxylated mono-di-glyceride and that of ethanol/oil equal unity [8,51,59]. The phase diagrams of these systems are presented in Fig. 2. We have shown [8,51,59] that in U-type phase diagrams, mixtures of oil and surfactant phases spontaneously self-assemble into reverse micelles. Dilution with aqueous phase causes progressive deformation of the water-in-oil swollen micelles and the droplets become bicontinuous structured domains. Upon further dilution full inversion occurs and oil-in-water nanodroplets are formed. The solubilization capacity (SC) is defined as the amount (ppm) of solubilized diclofenac within the total formulation. We determined the maximum solubilization