Colloids and Surfaces A: Physicochem. Eng. Aspects 442 (2014) 80–87

Contents lists available at ScienceDirect

Colloids and Surfaces A: Physicochemical and Engineering Aspects

journal homepage: www.elsevier.com/locate/colsurfa

Surfactant-rich biocompatible microemulsions as effective carriers of methylxanthine drugs

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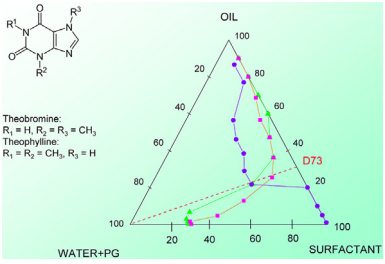
HIGHLIGHTS

- Surfactant-rich biocompatible microemulsions were prepared and structurally studied.
- Controlled release of methylxanthine drugs from the microemulsions was observed.
- Drug permeation was not affected by the membrane flexibility or the polarity of the surfactant's monolayer.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 19 November 2012
Received in revised form 7 March 2013
Accepted 15 May 2013
Available online 23 May 2013

Keywords:
Microemulsions
Drug carrier
Dynamic light scattering
Electron paramagnetic resonance spectroscopy
Theophylline
Theobromine

ABSTRACT

Under the perspective of their potential pharmaceutical applications, new surfactant-rich biocompatible microemulsions were prepared and structurally characterized to be used as novel carriers of theophylline and theobromine. The existence of single phase regions was investigated in pseudo-ternary phase diagrams of three different microemulsion systems: (1) isopropyl palmitate/Triton X-100/water + propylene glycol, (2) Miglyol 818/Triton X-100/water + propylene glycol and (3) isopropyl palmitate/Triton X-100 + Span 20/water + propylene glycol. Electrical conductivity measurements indicated the formation of water-in-oil (w/o) structures. Interfacial properties of the microemulsions were studied by electron paramagnetic resonance (EPR) spectroscopy employing the nitroxide spin probe 5-doxylstearic acid (5-DSA). The determined order parameter and wobbling angle showed that the system composition influences the membrane flexibility whereas drug incorporation resulted in more flexible membranes. Particle size measurements were performed using dynamic light scattering (DLS) showing that addition of the drugs resulted in the formulation of larger aqueous droplets. To evaluate the ability of the proposed microemulsions to serve as carriers of bioactive compounds for topical administration, *in vitro* permeation studies were carried out using the Franz type diffusion cells and a model membrane. The nature of the oil and the surfactant used for the construction of the microemulsions affected the phase behavior, the size and also the interfacial properties of both free and loaded systems. Drug permeation studies revealed the effectiveness of the proposed formulations as carriers of theophylline and theobromine.

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1. Introduction

In recent years the potential of using skin as an alternative route for administering systemically active drugs has received considerable interest. Transdermal drug delivery offers many advantages over other routes of administration such as avoidance of the hepatic first pass metabolism, ease of administration, control over the rate

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http://dx.doi.org/10.1016/j.colsurfa.2013.05.055

of drug delivery and the possibility of immediate removal of the treatment if required [1,2].

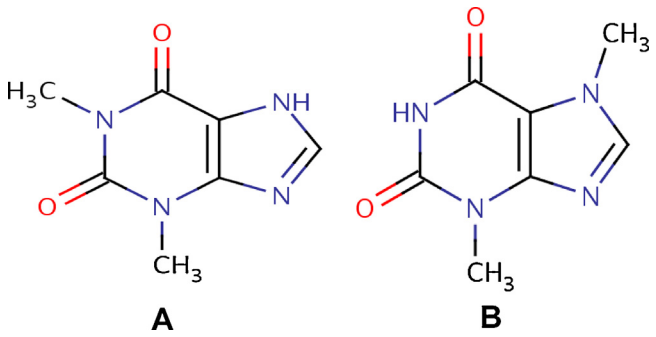
With transdermal delivery becoming more popular, research has focused on improving the absorption of specific drugs, as delivery rates are limited by the skin barrier and also the physicochemical properties of the drug in the formulation. In this sense only very potent drugs that are also compatible with the formulation matrix could be possible candidates for transdermal administration. In this respect, the design and development of new drug delivery systems with the intention of enhancing the efficacy of existing drugs without irritating or sensitizing the skin itself, is an ongoing process in pharmaceutical research. In particular, the potential of using stable nanosized liquid dispersions as effective carriers of bioactive molecules was investigated [3,4].

In the present study, microemulsions based on safe and pharmaceutically acceptable materials were preferably selected among other types of liquid nanodispersions, mainly due to their unique physicochemical properties [5–7]. Microemulsions are thermodynamically stable, easy to prepare systems that can be formulated with at least three components: a polar solvent (usually water), a nonpolar solvent (oil) and a surfactant (amphiphile). In some cases cosurfactants and/or cosolvents are added to lower interfacial tension, to improve oil solubilization or reduce the polarity of the aqueous phase. Depending on the relative ratios of their constituent components, microemulsions are classified into three types: oil-in-water, bicontinuous, and water-in-oil. The coexistence of distinct domains of opposite polarity offers the unique possibility to solubilize both hydrophilic and lipophilic substances in a macroscopically homogeneous solution [8,9].

The main aim of the present study was to formulate and structurally characterize surfactant-rich microemulsions to be used as carriers of methylxanthine drugs. Up to now, the vast majority of research interest and consequently most of published work on the domain of microemulsions has been focused on systems containing low concentrations of surfactants. The main reason for this preference was the high cost and the eventual toxicity of the surfactants used to formulate the microemulsions. Regarding the latter, it should not be an issue if the proposed surfactant molecules were biocompatible, considering also the fact that the external application on the skin is quite short and can be easily stopped.

It was of particular interest, thus, to investigate the area of the surfactant-rich microemulsions and shed light on their special structural characteristics. Furthermore the ability of these systems to incorporate and release the drugs under investigation was also elucidated. The procedure followed comprised the construction of phase diagrams by using a titration technique under controlled temperature. The use of safe nonionic surfactants (propylene glycol tert-octylphenyl ether and sorbitan monolaurate) and different biocompatible oils (isopropyl palmitate and caprylic/capric/linoleic triglyceride) was suggested. Once the phase diagrams were completed, two drugs having different water solubilities, namely theophylline and theobromine were incorporated in the system.

Theophylline and theobromine (Scheme 1) are methylxanthine drugs having a large number of effects, some of which are clinically important. Methylxanthines act as bronchodilators by relaxing bronchial smooth muscle and help the constricted airways to dilate. In addition to bronchodilation, they have immunomodulatory, anti-inflammatory, cardiac stimulant and bronchoprotective effects. They induce lipolysis at the cell level acting on the membrane. They enhance local blood circulation and contribute to the skin metabolism. Theophylline had been widely used for the treatment of asthma, bronchitis and other chronic obstructive pulmonary disease by oral or intravenous route clinically [10,11]. In recent years, derivatives of xanthines have received increasing attention as components of transdermal patches, energy drinks and dietary supplements.



Scheme 1. Chemical structures of (A) theophylline and (B) theobromine.

Structural characterization of the microemulsions in the presence and in the absence of the drugs was carried out. Some of the major methods relevant to the characterization of the microemulsions include electrical conductivity, electron paramagnetic resonance spectroscopy (EPR) and dynamic light scattering (DLS). Electrical conductivity can be used to differentiate types of microemulsions [12–14]. Interfacial properties of the surfactants monolayer can be studied by electron paramagnetic resonance (EPR) spectroscopy and the spin-probing technique [15,16]. Dynamic light scattering (DLS) can provide valuable information on the size and size distribution of the dispersed domains both in the absence and in the presence of active ingredients [17].

Finally the ability of the proposed surfactant-rich microemulsions to release the enclosed active ingredients in an aqueous environment was studied through diffusion-like tests using a Franz cell apparatus and a model membrane [18,19].

2. Materials and methods

2.1. Materials

Isopropyl palmitate (IPP) (~90%) was from Fluka, Switzerland. Triton X-100 (propylene glycol tert-octylphenyl ether) (~99%) and Span 20 (sorbitan monolaurate) (>99%) were from Sigma–Aldrich, Germany. Miglyol 818 (caprylic/capric/linoleic triglyceride) (~95%) was from Sasol Germany GmbH. Miglyol 818 is composed of caproic acid (C6:0) maximum 2 wt%, caprylic acid (C8:0) 45–65 wt%, capric acid (C10:0) 30–45 wt%, lauric acid (C12:0) maximum 3 wt%, myristic acid (C14:0) maximum 1 wt% and linoleic acid (C18:2) maximum 2–5 wt%. 1,2-Propandiol (propylene glycol, PG) (98+ %) was purchased from Alfa Aesar. 5-Doxyl stearic acid [5-(1-oxyl-2,2-dimethyl-oxazolidin) stearic acid] was obtained from Sigma–Aldrich, Germany. Theophylline (1,3-dimethylxanthine) anhydrous and theobromine (3,7-dimethylxanthine) were from Sigma–Aldrich, Germany.

2.2. Methods

2.2.1. Construction of phase diagrams

A series of microemulsions were prepared for each of the three systems presented in Table 1, with varying weight percentages of oil, surfactant and aqueous phase (water and propylene glycol at fixed weight ratio 2:1) at constant temperature 25 °C. These microemulsions were described with pseudo-ternary phase diagrams prepared as follows. Mixtures of oil and surfactants with varying mass ratios, from 1:9 to 9:1 were prepared by weighting the appropriate amount of each component in screw-capped glass vials and let equilibrate in a water bath. Then, a mixture of water and propylene glycol (2:1) was added drop wise until solubilization

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