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Phase behaviour, microstructure and ibuprofen solubilization capacity of pseudo-ternary nonionic microemulsions

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ABSTRACT

This study investigated phase behaviour, microstructure and solubilization capacity of pseudo-ternary surfactant/cosurfactant/isopropyl myristate/water systems employing complex mixtures of nonionic surfactants for formation of single-phase microemulsions. The surfactant was PEG-8 caprylic/capric glycerides (Labrasol®). A well defined mixture of octoxynol-12 and polysorbate 20 and/or PEG-40 hydrogenated castor oil, available as commercial nonionic surfactants Solubilisant gamma® 2421, Solubilisant gamma® 2429 and Cremophor® RH 40, respectively, were evaluated as cosurfactants. Surfactant + cosurfactant mixtures were treated as a single component (pseudo-component), since a surfactant-to-cosurfactant weight ratio (Km 50:50) was constant through the study. Phase behaviour study revealed enlargement of single-phase microemulsion area as surfactant + cosurfactant-to-oil weight ratio (SCoS/O) increases. The formation of fully dilutable microemulsions containing the maximum of water incorporation in the surfactant/cosurfactant/oil preconcentrates of $W_{max} \geq 80\%$ w/w, was achieved at SCoS/O 90:10. Microemulsions formed along the single-phase sequence at SCoS/O 90:10 in the presence of different cosurfactants, were characterized using polarized light microscopy, photon correlation spectroscopy (PCS), and rheological measurements. Different performances of complex mixtures of nonionic surfactants in stabilization of single-phase microemulsions were observed only in highly diluted oil-in-water microemulsions area. Investigation of solubilization capacity for poorly soluble drug ibuprofen revealed the critical importance of water-to-surfactant + cosurfactant ratio and penetration of oil at the interface.

1. Introduction

It is well known that two immiscible liquids (i.e. water and oil) can be brought into a thermodynamically stable, macroscopically homogeneous, optically transparent and isotropic phase by addition of a sufficient amount of an appropriate surfactant or a mixture of surfactant and cosurfactant. This unique class of colloidal dispersions, known as *single-phase microemulsions* or *one-phase microemulsions* is of great importance from both academic and technological viewpoints. These systems have attracted attention as promising pharmaceutical formulations because of their high capacity to solubilize guest substances [1–3]. Solubilization of poorly soluble drugs by microemulsions can be a useful approach for overcoming solubility problems [4–8]. Solubilization capacity of microemulsion systems is governed by both the physicochemical properties of the employed constituents and the type of microstructure formed by a particular oil/water/amphiphile(s) combination and it can hardly be predicted [9,10].

A single surfactant is often not sufficient to form a single-phase microemulsion and a suitable combination of surfactant and cosurfactant is required for the formation of an optimal microemulsion-forming region. The term cosurfactant can describe any component that affects the efficiency of the surfactant in microemulsion formation. Development of microemulsions employing the mixtures of nonionic surfactants is of special interest from a pharmaceutical formulation viewpoint, due to generally low toxicity and irritancy of nonionic surfactants [11]. Interest in using nonionic surfactants as cosurfactants (so-called non-alcohol cosurfactants) is useful for elimination of toxic or irritating hydrophilic cosolvents, and thus for improvement of the biocompatibility of microemulsions. By using the mixtures of the nonionic surfactants, the concentrations of individual surfactants are lowered compared to the required concentration when they are used as single surfactants, what makes the suitable conception to increase biocompatibility of the microemulsion formulations. Overmore, the mixtures of two surfactants at the well balanced weight ratio can demonstrate the enhanced performances in stabilization of microemulsions, over their individual components, providing the large microemulsion area as well as the formation of microemulsions containing a decreased content of the surfactants [12–15]. Recently, commercial mixtures of nonionic surfactants octoxynol-12 and

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polysorbate 20 with or without addition of PEG-40 hydrogenated castor oil (Solubilisant gamma® 2421 and Solubilisant gamma® 2429, respectively) were introduced as cosurfactants for nonionic surfactant Labrasol® (PEG-8 caprylic/capric glycerides) [17]. Well defined mixtures of different nonionic surfactants, available as commercial products, can be treated as a single component (i.e., a pseudo-component) in the microemulsion system [16]. The efficiency of complex mixtures of nonionic surfactants in simultaneous solubilization of oil, water and drug molecules is scarcely investigated. The evaluation of drug delivery potential of Labrasol®-based microemulsions was the subject of numerous studies during the past decade [18–29]. Recent studies have investigated the phase behaviour of the mixtures of Labrasol® with Solubilisant gamma® 2421 (octoxynol-12 + polysorbate 20) or Solubilisant gamma® 2429 (octoxynol-12 + polysorbate 20 + PEG-40 hydrogenated castor oil) [17]. However, microstructure and drug solubilization capacity of Labrasol®-based microemulsions are poorly characterized.

This study aims to evaluate the stability of Labrasol®/cosurfactant/oil/water single-phase microemulsions as well as to characterize their microstructure and capacity for solubilization of a poorly soluble drug in a wide composition range. The cosurfactants were Solubilisant gamma® 2421, Solubilisant gamma® 2429 or Cremophor® RH 40 (PEG-40 hydrogenated castor oil). The oil phase was isopropyl myristate. As a model drug was employed nonsteroidal anti-inflammatory drug (NSAID) ibuprofen, in therapeutic concentration for transdermal application (5% w/w).

2. Material and methods

2.1. Material

Labrasol® (PEG-8 caprylic/capric glycerides) was used as a surfactant. Solubilisant gamma® 2421 (octoxynol-12 and polysorbate 20), Solubilisant gamma® 2429 (octoxynol-12 (and) polysorbate 20 (and) PEG-40 hydrogenated castor oil) and Cremophor® RH 40 (PEG-40 hydrogenated castor oil) were used as cosurfactants. Labrasol®, Solubilisant gamma® 2421 and Solubilisant gamma® 2429 were kindly donated by Gattefosse, France. Cremophor® RH 40 was a gift from BASF, Germany. The oil phase was isopropyl myristate (Crodamol® IPM, Croda Chemicals Europe, England). All of the components were used as supplied without further purification. The aqueous phase of microemulsions was double-distilled water.

2.2. Phase behaviour investigations

The previous study [17] has demonstrated the maximum efficiency of the mixture of Labrasol® and polyoxyethylene surfactants for simultaneous solubilization of isopropyl myristate and water at surfactant-to-cosurfactant weight ratio (Km) 50:50 (expressed as the weight percentages of the surfactant and a cosurfactant in the mixture). The present paper extends this earlier study with the examination of the effect of the surfactant + cosurfactant-to-oil weight ratio (SCoS/O) on the single-phase microemulsion area. Phase behaviour of the Labrasol®/cosurfactant/oil/water systems was investigated by the construction of pseudo-ternary phase diagrams at room temperature. Labrasol® and the cosurfactant were mixed to give Km 50:50, and it was kept constant through the phase behaviour investigations. The Labrasol® + cosurfactant mixture was treated as a pseudo-component. The obtained surfactant + cosurfactant mixtures were mixed with the oil at SCoS/O ratios: 10:90, 20:80, 30:70, 40:60, 50:50, 60:40, 70:30, 80:20, and 90:10 (expressed as the weight percentages of the surfactant + cosurfactant mixture and the oil, respectively). The Labrasol®/cosurfactant/oil mixtures were titrated dropwise with water (so-called water-dilution lines), under moderate magnetic stirring, until the mixture changed from transparent to turbid or milky. Clear, isotropic, single-phase systems were designated as microemulsions. In the present study, no distinction has been made between a microemulsion and a dispersion of micelles. The loss of the transparency was interpreted as the breakdown of the microemulsion.

The maximum percentage of water incorporated (W_{max}) was calculated from the Eq. (1):

$$W_{max}(\%w/w) = (m_w / (m_w + m_o + m_s + m_{cos})) \times 100 \quad (1)$$

where m_w, m_o, m_s, and m_{cos} are the water, oil, surfactant, and cosurfactant amounts, respectively, in the mixture at the microemulsification failure point.

2.3. Physico-chemical characterization of microemulsions

Numerous potential microemulsion vehicles at the SCoS/O ratio selected in accordance with the results of the phase behaviour investigations, were readily prepared by stirring the required quantities of the components until forming a transparent liquid, at room temperature. Solubilization of ibuprofen in the vehicles was examined by dissolving the model drug into the preweight vehicle, under magnetic stirring, at room temperature. The microemulsions with and without ibuprofen were stored at room temperature for 48 h before characterization. Stable systems were identified as those free of any physical change (e.g. blurriness, precipitate). The homogeneity and optical isotropy of microemulsions were verified by a cross-polarizer. Microemulsions were characterized by applying photon correlation spectroscopy, rheological measurements and pH value measurements.

2.3.1. Polarized light microscopy

Optical isotropy of the transparent samples was examined using cross-polarized light microscopy (Leitz Wetzlar 307–083.103 514652, Germany). A drop of sample was placed between a coverslip and a glass slide and then examined under cross-polarized light. Polarizing light microscopy can be used to differentiate microemulsions and liquid crystals, since optically isotropic materials which have no birefringence, such as microemulsions, do not interfere with the polarized light and the field of view remains dark [30].

2.3.2. Photon correlation spectroscopy

The droplet size of microemulsions was characterized by photon correlation spectroscopy (PCS), which analyses the random intensity fluctuations in light scattering due to Brownian motion of the particles [31]. The droplet size was determined in accordance with ISO 13321 [32], using the apparatus Nano ZS90 (Malvern Instruments, U.K.) equipped with a He–Ne laser at 633 nm. The size measurements were carried out at fixed angle of 90° after external standardization with spherical polystyrene beads (63 nm).The autocorrelator of the instrument creates an exponentially decaying correlation function from intensity *vs.* time profile. This function is related to characteristic decay times which are related to diffusion coefficient (D) that can be converted into the radius of the non-interacting spherical droplet (r) using the Stokes–Einstein equation [33]:

$$D = (k_B T) / (6\pi\eta r) \quad (2)$$

where k_B is the Boltzmann's constant, T is the absolute temperature, and η is viscosity. The measurements were performed at 20 °C. The predetermined viscosity of microemulsions was incorporated into the associated computer software which performs statistical analysis of data and calculates the average droplet size (Z-Ave) and polydispersity index (PDI) from intensity distribution. The results are the mean and standard deviation (S.D.) of three consecutive measurements for each sample.