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Solubilisation of griseofulvin and rutin in aqueous micellar solutions of gemini and heterogemini surfactants and their mixtures

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ABSTRACT

The solubilisation of two natural compounds, griseofulvin and rutin, in micellar solutions of mixtures of gemini (*N*,*N*′-didecyl-*N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diyldiammonium dibromide) and heterogemini (decyl 2-[decyl(dimethyl)ammonio]ethylphosphate) surfactants has been studied. The highest solubilisation capacities were found for mixtures with a molar fraction of heterogemini surfactant equal or greater than the molar fraction of gemini surfactant. The relationship between synergism in surface properties of mixtures of surfactants and their solubilisation properties was also investigated.

1. Introduction

Poor solubility of some natural compounds in non-toxic solvents can often hamper their pharmacological testing. Some co-solvents as ethanol or dimethyl sulfoxide can improve the solubility of compounds. Other alternative is in using micellar solubilisation of sparingly soluble substances in water employing surfactants. Surfactants are capable of forming colloidal-sized clusters in solutions, known as micelles (Mall et al., 1996). Micelles have an anisotropic distribution of water within their structure. The water concentration decreases from the surface towards the core of the micelle and the spatial position of a solubilised substance in a micelle will depend on its polarity. Hydrophilic drugs can be adsorbed on the surface of the micelle; drugs with intermediate hydrophilic properties are located in the palisade layer between the hydrophilic groups and the first few carbon atoms of the non-polar groups; and hydrophobic drugs are situated in the inner core of the micelle (Rangel-Yagui et al., 2005). Different types of surfactants, cationic (Devínsky et al., 1991; Veselovská et al., 1978), anionic (Mall et al., 1996), or non-ionic (Arida et al., 2007), can be used in solubilisation of sparingly soluble compounds. Surfactants with two polar head groups and two hydrophobic groups are known as gemini surfactants. According to polar groups, they can be divided into true geminis, which are symmetrical compounds containing identical polar head groups and identical hydrophobic tails, and heterogemini surfactants with different types of polar head groups. Geminis and heterogemini surfactants are a relatively new group of amphiphilic compounds which posses interesting physico-chemical properties (Devínsky and Lacko, 1990; Menger and Keiper, 2000; Menger and Peresypkin, 2001, 2003; Pisárčik et al., 2009; Zana, 2004).

Rutin is one of the most common flavonoids. It is a polyphenolic compound, constituent of many plants, e.g., *Ruta graveolens* (Kostova et al., 1999), family *Marantaceae* (Abdullah et al., 2008) or *Sophora japonica* (Kim and Yun-Choi, 2008). Rutin possesses antioxidant, antithrombotic or antineoplastic activities. Topical administration of flavonoids also inhibits ultraviolet radiation-induced cutaneous oxidative stress and inflammation (Saja et al., 1998; Röpke et al., 2002; Casagrande et al., 2007).

Griseofulvin is an antifungal agent isolated from *Penicillium nigricans*. It inhibits fungal mitosis. It interacts with polymerised microtubules and causes disrupting the mitotic spindle (Gull and Trinci, 1973). Griseofulvin can be used in treatment of diseases caused by fungi *Microsporum*, *Epidermophyton* or *Trichophyton* (Chadeganipour et al., 2004).

As an extension our previous work (Devínsky et al., 1991; Lukáč et al., 2009) the physico-chemical properties of gemini and heterogemini surfactants and their solubilisation properties were investigated. Bisammonium salt and dialkylphosphocholine (Scheme 2) were chosen as representative dimeric surfactants. Mutual interactions of amphiphilic compounds were studied by surface tension measurements. Rutin and griseofulvin (Scheme 1) represented the compounds sparingly soluble in water. The solubilisation capacities of micellar solutions of surfactants and their mixtures in relation to investigated natural compounds were followed and compared. Griseofulvin and rutin were chosen as model compounds which are solubilised in the hydrophobic micelle core (Crothers et al., 2005) or in the palisade layer of micelle (Chat et al., 2011), respectively.

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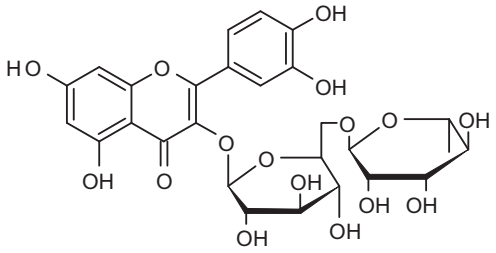
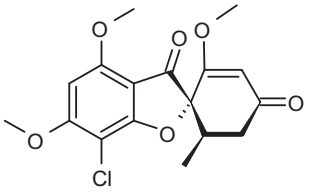
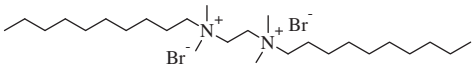


rutin

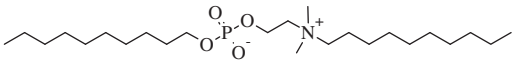


griseofulvin

Scheme 1. Structures of solubilised compounds.



N,*N*′-didecyl-*N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diyldiammonium dibromide (***N***)



decyl [2-decyl(dimethyl)ammonio]ethylphosphate (***P***)

Scheme 2. Structures of surfactants used for solubilisation.

2. Materials and methods

2.1. Materials

Decyl 2-[decyl(dimethyl)ammonio]ethylphosphate (***P***) and *N*,*N*′-didecyl-*N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diyldiammonium dibromide (***N***) were prepared according to the procedure described by Lukáč et al. (2009). Griseofulvin was purchased from Acros Organics. Rutin was obtained from Lachema.

2.2. Measurements

2.2.1. Equilibrium surface tension

The surface tension measurements were made according to the modified procedure described by Lukáč et al. (2010a). The solvent surface tension values were measured by the Wilhelmy plate technique using a Kruss 100 MK2 tensiometer. Deionised water or NaBr solution in deionised water (c = 0.01 mol dm^{-3}) was used in the preparation of all samples. The temperature of the measurements was kept at 25 ± 0.1 °C. Measurements of equilibrium surface tension were taken repeatedly (every 6 min) until the change in surface tension was less than 0.05 mN m^{-1}. The critical micelle concentration (cmc) and surface tension at the cmc (γ_{cmc}) were determined from the break point of the surface tension vs. log(c) curve. Surface tension data points used for the cmc determination were taken from the linear part of the surface tension vs. log(surfactant concentration) curve in the premicellar region close to the cmc point and were fitted by a straight line. From the surface tension data, the surface excess Γ_{cmc} (mol m^2) is calculated utilizing the Gibbs adsorption isotherm (Rosen, 2004)

$$\Gamma_{cmc} = -[d\gamma/d\log c]_T/(2.303iRT) \quad (1)$$

where γ is the surface tension (mN m^{-1}), c is the surfactant concentration (mol dm^{-3}), T is the absolute temperature, R the gas constant and i is the prefactor (***N*** in water, i = 3; ***P*** and ***N*** in NaBr solution, i = 1). The prefactor depends on the ionization of surfactants. Bisammonium salts are ionized into 3 ions, one organic and two bromide anion, therefore the prefactor is 3. Ionized molecules of zwitterionic surfactants create only one ion (zwitterion) therefore i = 1 (Zana, 2004). Surface excess may be determined from the slope below the cmc in the surface tension vs. log(c) plots. The surface excess Γ_{cmc} is the number of molecules participating in the Gibbs monolayer per unit area and is obtained by integrating the excess concentration (with respect to the bulk one) over the entire solution (Diamant and Andelman, 2004). Surface area at the surface saturation per head group (A_{cmc}) is obtained from the equation (Rosen, 2004)

$$A_{cmc} = 10^16/N_A\Gamma_{cmc} \quad (2)$$

where N_A is the Avogadro constant.

2.2.2. ^{31}P NMR spectroscopy

Measurement of aggregation of ***P*** in water by ^{31}P NMR spectroscopy was performed according to the described procedure (Lukáč et al., 2010b). The sample was prepared in an NMR tube. Deionised water (100 μl) were added to 50 mg of ***P***. The mixture was homogenised by several cycles of heating to about 50 °C and cooling to −18 °C. ^{31}P NMR spectrum was measured on the prepared sample at 25 °C. ^{31}P NMR spectra were recorded on a Varian Gemini 2000 spectrometer operating at 121.5 MHz.

2.2.3. Solubilisation

Saturated drug solutions were prepared in glass vessels by mixing excess powdered drug (5 mg) with 2.5 ml of deionised water or surfactant solution with a concentration c = 0.01 mol dm^{-3} and stirring (250 rpm) at a constant temperature t = 25 ± 1 °C for 72 h before filtering (Millipore, 0.22 μm) to remove any unsolubilised material. The extent of dissolution was determined by UV-spectroscopy. The filtered solution (1 ml) was diluted quantitatively with methanol in a 25 ml volumetric flask. Absorbance was measured at the optimum wavelength (griseofulvin 292 nm, rutin 358 nm), which was then compared with the appropriate Beer's law plot for the drug in methanol. Water content in the measured solution was low enough to allow the calibration with methanol solutions to be used without correction. Measurements were performed in triplicate and the results were averaged. Standard deviations were also calculated; considering all sources of error, we estimate a maximum uncertainty in s of ±10%.

3. Results and discussion

3.1. Surface properties of gemini and heterogemini surfactants, and their mixtures

The critical micelle concentration is one of the most important values, which describes the properties of amphiphilic compounds. The measurement of surface tension at different surfactant concentrations is a method often used in its determination. The plots of surface tension vs. log concentration of surfactants (Fig. 1) gave the values of cmc, γ_{cmc}, A_{cmc}, which are summarised in Table 1. The cmc obtained for ***P*** and ***N*** in deionised water are in good agreement with literature values (Devínsky et al., 1991; Peresypkin and Menger, 1999). Addition of NaBr to the measured solution caused