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Improving Ibuprofen solubility by surfactant-facilitated self-assembly into mixed micelles

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ABSTRACT

Ibuprofen is a poorly water-soluble drug, characterized by dissolution-limited oral bioavailability. One approach to improve its water solubility and bioavailability is by solubilizing it in micellar surfactant solutions. Here we investigate the effect of the surfactant type and the mechanism of solubility enhancement of Ibuprofen in surfactant solutions. The equilibrium Ibuprofen solubility in solutions of six surfactants was determined by HPLC. The nonionic surfactant polysorbate 80 (Tween 80), and the anionic surfactants sodium dodecyl sulfate (SDS) and sodium lauryl ethoxy (3) sulfate (SLES-3EO) improve the Ibuprofen solubility by a factor of 200, as compared to the solubility in water. The highest Ibuprofen solubility is observed in SDS and SLES-3EO solutions, containing 0.6 M NaCl. The mole fraction of Ibuprofen in the micelles and the transfer energy of Ibuprofen molecules from the aqueous phase into the micelle environment were determined by thermodynamic analysis of the solubility data. The maximum Ibuprofen mole fraction in the micelles of all studied surfactants is exceptionally high (between 0.4 and 0.6). Thus we can conclude that the main mechanism of Ibuprofen solubility enhancement is self-assembly within mixed micelles with the main surfactant. The energy of co-micellization is estimated to be around 14 *kT* per Ibuprofen molecule.

1. Introduction

More than 40% of the new chemical entities that emerge from modern drug discovery programs are characterized by poor water solubility [1]. The slow and incomplete dissolution of such drugs in the gastro-intestinal fluids limits their oral bioavailability and presents a significant problem in drug development. One of the classical approaches to improve the water solubility of hydrophobic drugs, which is still being used in the pharmaceutical industry, is to use appropriate surfactants [2–5].

Surfactants are a large group of pharmaceutical excipients, which are used in a variety of drug delivery vehicles as solubilizers, emulsifiers, foamers, wetting agents, etc. [6]. Above the critical micelle concentration (CMC) the surfactant molecules form micelles [7]: molecular aggregates which have a hydrophobic core and a hydrophilic surface. The hydrophobic interior of the micelles provides a suitable environment for hydrophobic molecules, which leads to the solubilization phenomenon [6–8], namely, a significant increase of the solubility of poorly water-soluble molecules in the micellar solutions, due to their incorporation in the surfactant micelles. On the other hand, amphiphilic drugs like nortriptyline hydrochloride and promazine hydrochloride can form mixed micelles with the classical surfactants [9,10] which also leads to a strong enhancement of their solubility.

In the current article we investigate the effect of surfactants on the solubility of the non-steroidal anti-inflammatory drug Ibuprofen (IBP), which is used to relieve pain, fever and inflammation. IBP is a weak acid with pKa ≈ 4.4, solubility in water of around 11 μg/mL, and high membrane permeability [11]. Since the IBP molecule can be ionized, its solubility depends strongly on the solution pH. Thus, IBP is poorly soluble in the stomach, where pH ranges between 2 and 3 [12], whereas its solubility increases significantly in the small intestine (pH between 4.5 and 7.5 [13]). For example, IBP solubility at pH 5 and 7.5 is 140 and 2300 μg/mL, respectively [14].

However, the drug solubility in water *per se* does not provide direct information whether the drug will be sufficiently soluble in the gastro-intestinal tract. The orally administered drug dose differs strongly, depending on the drug type and the therapeutical

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application. The Biopharmaceutical Classification System (BCS), introduced by Amidon et al. [15], defines the so-called "dose number" (Do), which takes into account both the drug dose per given volume and the equilibrium drug solubility. Thus, drugs for which Do $\leq$ 1 are classified as highly soluble, whereas all others have poor water solubility [16].

The maximum single dose of IBP is relatively high (800 mg) and for this reason IBP's Do is always bigger than one: Do = 290 at pH = 2 (approximate conditions in the stomach) and Do = 1.4 at pH = 7.5 (maximum pH value in the small intestine). Thus we see that the IBP concentration in the stomach fluids, after oral administration of 800 mg IBP, is 290 times higher than the equilibrium IBP solubility under these conditions. As a result, IBP is characterized by poor water solubility and is classified as Class II drug according to BCS [17].

There are different approaches for enhancing IBP delivery: controlled-release formulations [18–20], lipid-based drug delivery systems [21–23], nano-particles [24,25], vesicles [26] or solubilization by surfactants [27–29].

Surfactants are reported to increase significantly IBP solubility [27–29] and are thus expected to improve its oral bioavailability. The effect of sodium dodecyl sulfate (SDS), dodecyl octa(ethylene oxide) (C12E8) and dodecyltrimethyl-ammonium bromide (DTAB) on IBP solubilization at pH 7.4 was studied by Stephenson et al. [27]. These authors found that the aqueous solubility of IBP increases linearly with concentration for these surfactants. The highest solubilization was observed upon the addition of DTAB, followed by $C_{12}E_8$ and SDS. A molecular-thermodynamic modelling approach was developed to predict theoretically the solubilization behavior of these systems. The obtained theoretical results on the IBP solubility in SDS and $C_{12}E_8$ solutions were in a good agreement with the experimental data.

Kokot & Zmidzinska [28] studied the IBP solubilization in unbuffered SDS, Brij 35 and Tween 60 surfactant solutions. They reported a significant increase of IBP solubility and no specific effect of the surfactant type.

Park et al. studied the saturation solubility of IBP [29] and showed that at pH = 1.2, highest solubility is obtained with solutions of cetyltrimethylammonium bromide (CTAB), compared to much lower solubility for Tween 80 and SDS. The better IBP solubilization in CTAB, compared to SDS solutions, was explained by attractive electrostatic interactions, without accounting for the longer hydrophobic chain length of CTAB. The authors reported also a higher dissolution rate of IBP tablets in surfactant solutions, relative to pure water.

None of the above studies has provided mechanistic explanation for the observed very strong effects of surfactants on IBP solubility. Therefore, the aim of the current article is to clarify (1) the mechanism of IBP solubility enhancement in surfactant solutions and (2) the effect of the surfactant type. To achieve this aim we determined experimentally the effect of four nonionic (Tween 20, 40, 60 and 80) and two anionic (SDS and SLES-3EO) surfactants on the IBP solubility. The mechanism of improved IBP solubility and the strength of the drug-surfactant interactions are analyzed using a thermodynamic treatment of the solubility data.

2. Materials and methods

2.1. Materials

2.1.1. Drug and surfactants

We used IBP (see Fig. 1), product of Sigma Aldrich (M_W = 206.29 g/mol, purity 99%, cat. no. I4883). To increase the drug solubility, we used several nonionic and anionic surfactants. Table 1 provides information about all studied surfactants: type, trade name/abbreviation used in the text, purity, molecular weight, chemical formula, producer, and critical micelle concentration (CMC). The molecular structures of the studied surfactants are presented in Fig. 2.

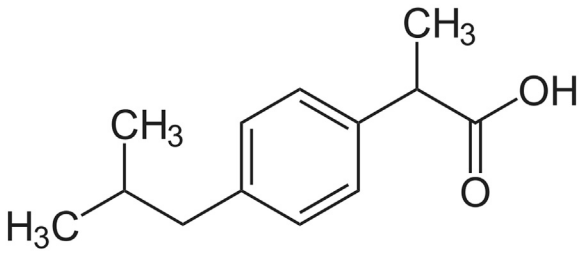

Fig. 1. Molecular structure of IBP.

2.1.2. Buffer solutions, solvents for HPLC and water

To prepare the buffer solutions we used H_3PO_4 (85%, Merck, cat. no. 100563), NaH_2PO_4 (99%, Fluka Analytical, cat. no. 71504), $Na_2HPO_4.7H_2O$ (99%, Riedel de Haën, cat. no. 30413), CH_3COOH (100%, Merck, cat. no. 100056) and $CH_3COONa.3H_2O$ (99%, Merck, cat. no. 106267).

The mobile phase solvents for HPLC analysis include acetonitrile (HPLC grade, 99%) and 20 mM aqueous solutions of CH_3COOH and CH_3COONa. All aqueous solutions and buffers were prepared using deionized water from water-purification system Elix 3 (Millipore, USA).

2.2. Methods

2.2.1. Determination of equilibrium solubility of IBP

We determined the effect of the pH on the IBP solubility in aqueous medium using the following procedure: we weighed 20 mg IBP in a 20 mL bottle and then added 10 mL buffer solution with a pH value in the range between 3.5 and 6. The mixture was then stirred on a magnetic stirrer for 24 h, at 400 rpm and 37 °C.

The effect of surfactants was studied at a constant concentration of 0.5 wt%. We first prepared 10 mL of 4 wt% surfactant solution; then, we weighed 20 mg IBP in another bottle of 20 mL and added 1.25 mL of the respective 4 wt% surfactant solution and 8.75 mL water. For the experiments in the presence of 600 mM NaCl we dissolved the surfactant in a freshly prepared 600 mM NaCl solution which was used also for dilution in the mixtures of surfactant and IBP. We prepared similarly the solutions for the experiments performed in the presence of buffer.

All mixtures were stirred for 24 h with a magnetic stirrer at 400 rpm and 37 °C. After incubation, the obtained IBP suspension was filtered through 200 nm NYLON syringe filter (thermostated at 37 °C) to eliminate the undissolved particles. Finally, the concentration of the dissolved drug in the obtained clear filtrate was determined by HPLC. The samples temperature was maintained at 37 °C during all stages of this procedure.

2.2.2. HPLC analysis

The HPLC analysis was carried out on a Shimadzu apparatus, equipped with two high-pressure mixing binary gradient pumps (LC-20AD), autosampler (SIL-10ADvp), four-line membrane degasser (DGU-14A), wide temperature range column oven (CTO-10ASvp) and a dual-wave length UV-VIS detector (SPD-10Avp).

We modified an analytical procedure, described in the United States Pharmacopoeia (USP). We used an XBridge C18 column (100 × 4.6 mm^2, 3.5 μm particle size) and an isocratic elution for 10 min with total flow of 1 mL/min, with a mobile phase of acetic