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ORIGINAL ARTICLE

Mathematical modeling of pH-surfactant-mediated solubilization of nimesulide

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Abstract

Aim: The equilibrium-based mathematical model was used to describe the pH-surfactant-mediated solubilization of weakly acidic electrolyte, nimesulide, in buffer solutions. This model assumed that the total drug solubility could be expressed as a sum of the solubilities of four different species: unionized and ionized form in solution and their corresponding micellar forms. Sucrose-laurate, new synthetic surfactant, and polysorbate 80 were investigated for their benefits in the testing of poorly soluble acidic model drug. *Method*: Two sets of solubility data, determined at pH values 4.5 and 9.0 in media containing different surfactant concentrations, were used to calculate solubilization slopes and corresponding micellar equilibrium constants for the unionized (K_n) and ionized (K_i) drug. These values were used to estimate drug solubilization in media considered to represent physiologically relevant conditions. *Results*: Predicted solubility values were in good agreement with the experimental data, suggesting that the impact of pH and surfactant on nimesulide solubility could be well characterized by the equilibrium model described in this article. *Conclusions*: Obtained results indicated that the extent of solubilization was significantly dependent on the surfactant used.

Key words: *Nimesulide; pH effect; polysorbate 80; solubilization; sucrose-laurate; surfactant*

Introduction

In vitro dissolution testing has been generally accepted as a valuable tool for solid dosage forms evaluation. It became an integral part of pharmaceutical product development and quality evaluation. In addition, drug release test could be used to reflect the in vivo situation (i.e., kinetics of drug dissolution after oral administration). Recent trends in dissolution testing point out the necessity of developing a relevant dissolution methodology for poorly water-soluble drugs (BCS Class II drugs according to Biopharmaceutics Classification System)[1,2]. For these drugs, in vivo solubilization and dissolution are key factors influencing drug's absorption. To overcome the in vitro solubility problems, different approaches have been suggested, mainly concerning the choice of test media. Some of them, such as the use of large volume media[3] and hydroalcoholic media[4] or the introduction of organic cosolvents into the media composition[5] have no relevance to physiological conditions and should be discouraged[6]. A number of physiological determinants, such as pH, bile salts, ionic strength, buffer capacity, gastrointestinal motility, food intake, and viscosity can influence drug's solubility and dissolution[7,8].

As both pH and surfactants can significantly influence dissolution, especially in the case of ionizable poorly water-soluble drugs, a number of studies accessing combined effect of pH and surfactant have been reported so far[9–11]. To further rationalize the use of pH-surfactant media, mathematical models describing the process have been extensively studied[12–15]. The choice of an appropriate surfactant may depend on the nature of the particular drug substance, as well as the purpose of the dissolution testing (i.e., quality control, formulation screening, establishment of in vitro–in vivo correlation).

Suitable surfactant should be efficient regarding its solubilization capacity, compatible with the drug substance and other components of the dissolution media, cost-effective, and should not interfere with analytical procedures employed. So far, sodium lauryl-sulfate (SLS)

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has been the most widely used surfactant in dissolution media composition although it was shown not to be ideal for all sparingly soluble drugs[6,16]. Park and Choi[17] investigated the effects of the type of surfactant on the solubility and dissolution of poorly water-soluble drugs using, besides SLS, cetyltrimethylammonium bromide (CTAB) and polysorbate 80. Shah et al.[6] described the use of sodium oleate, Brij 35 (polyoxyethylene lauryl ether), and sodium bistridecyl sulfosuccinate. Naturally occurring surfactants such as bile salts and lecithin have been used in the 'physiologically based media' designed by Galia et al.[18] There were also attempts to use mixed micellar systems such as Tween 40/Tween 20, Tween 40/Span 80[19,20]. Recently, there is a growing interest in the applicability of sugar esters as the surfactants with potential advantages[21]. Sucrose esters are nonionic, nontoxic, biodegradable surface-active agents that are widely used in cosmetic products and as food additives and increasingly evaluated as pharmaceutical excipients[22,23]. Sucrose-laurate is characterized with high HLB (hydrophilic-lipophilic balance) value (HLB 16) indicating its potential to solubilize lipophilic substances.

The aim of this article was to investigate the effect of pH combined with surfactant on the solubility of nimesulide (NIM) in an in vitro environment. The equilibrium-based mathematical model was used to describe the pH-surfactant-mediated solubilization of NIM. New synthetic surfactant, sucrose-laurate, was used as a surfactant in this study. For comparison purposes, polysorbate 80, nonionic surfactant, recommended for dissolution testing of poorly soluble drugs[24], was used as a reference.

NIM, a nonsteroidal anti-inflammatory agent with analgesic and antipyretic activity, was chosen as a model drug (Figure 1). It is weakly acidic, pK_a 6.5[25], highly permeable, and poorly soluble drug (BCS Class II) with no dissolution test requirements in the United States Pharmacopeia (USP) or other regulatory documents.

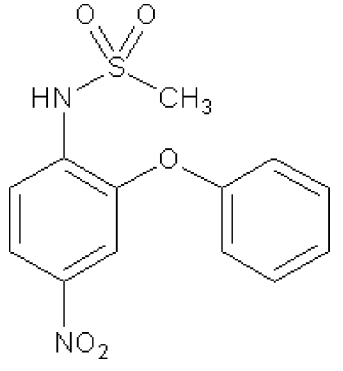

Figure 1. Chemical structure of nimesulide.

Materials and methods

Theoretical basis

The equilibrium model proposed by Rippie et al.[12] and Jinno et al.[13] was employed to describe the combined effect of pH and surfactant on the equilibrium solubility of weakly acidic electrolyte in buffer solutions.

According to Henderson–Hasselbalch equation, concentration of ionized drug as a result of solution pH can be written as:

$$C_i = C_0 \times 10^{pH-pK_a}, \tag{1}$$

where pK_a and pH are negative logarithms of drug dissociation constant (K_a) and hydrogen ion concentration ($[H^+]$), respectively, and C_0 and C_i are the concentrations of unionized and ionized drug.

According to the proposed model, both unionized and ionized drugs can migrate into the micelles [Equations (2) and (3)] resulting in four different species establishing equilibrium: unionized drug (C_0), ionized drug (C_i), unionized drug in micelles ($C_{0(micelle)}$), and ionized drug in micelles ($C_{i(micelle)}$).

$$K_n = \frac{C_{0(micelle)}}{C_0 \times C_m} \tag{2}$$

$$K_i = \frac{C_{i(micelle)}}{C_i \times C_m}, \tag{3}$$

where K_n and K_i are the micellar solubilization coefficients for unionized and ionized drug, respectively, and C_m is concentration of the micelles, which can further be expressed as

$$C_m = [S] - cmc. \tag{4}$$

In Equation (4), [S] is the apparent surfactant concentration and cmc is its critical micellar concentration.

For a weak electrolyte, the total drug solubility in pH-surfactant environment can be expressed as a sum of the solubilities of four different species: unionized and ionized form in solution and their corresponding micellar forms:

$$C_{tot} = C_0 + C_i + C_{0(micelle)} + C_{i(micelle)}. \tag{5}$$

After combining with Equations (1)–(3), Equation (5) can be rearranged into Equation (6):

$$C_{tot} = C_0 \times \left[1 + 10^{pH-pK_a} + C_m \times (K_n + K_i \times 10^{pH-pK_a})\right]. \quad (6)$$

Accordingly, total drug solubility is a function of C_0, pK_a, K_n, K_i, pH, and C_m. Here, only pH and C_m may be considered as variables while other parameters remain constant. With this regards, a new parameter, dimensionless solubility number, solubilization power (C_{sp}) can be introduced to characterize the ability of a given surfactant to solubilize the drug at the particular pH value:

$$C_{sp} = \frac{C_{tot}}{C_0}. \quad (7)$$

Using Equation (6), Equation (7) can further be expressed in a following form:

$$C_{sp} = (K_n + K_i \times 10^{pH-pK_a}) \times C_m + (1 + 10^{pH-pK_a}). \quad (8)$$

This demonstrates that, at a given pH value, C_{sp} is a linear function of C_m, described by the corresponding slope $(K_n + K_i \times 10^{pH-pK_a})$ and the intercept $(1+10^{pH-pK_a})$. Although the value of the intercept is determined only by the pH of the solution, solubilization slope depends both on pH and on surfactant concentration. Although it is expected for the elevated pH and/or addition of surfactant to improve solubility of weak acid, the proposed equation reveals mathematical explanation of this phenomenon. Further, Equation (8) could be used to calculate solubilization slopes and corresponding micellar equilibrium constants K_n and K_i, which could latter be utilized to mathematically predict the drug solubilization at any pH-surfactant concentration.

Solubilization power is correlated to the solubilization capacity, which can be calculated by the following equation:

$$\chi = \frac{C_{tot} - C_w}{[S] - cmc}, \quad (9)$$

where C_{tot} is the total drug solubility, C_w is the drug solubility in media without surfactant and [S] is the molar concentration of surfactant in solution[26]. This value was additionally calculated to characterize the ability of a particular surfactant to solubilize the drug at a given pH value.

Materials

NIM was kindly donated by Zdravlje Actavis, Leskovac (Serbia). Sucrose-laurate (Surfhope® SE Pharma, D1216) was a generous gift from Mitsubishi-Kagaku Foods Corporation (Tokyo, Japan). Polysorbate 80 (Sorbital T 80 PH, T80) was purchased from Eigenmann &Veronelli SPA (Milano, Italy). All other chemicals used were of analytical grade. Double distilled water was prepared *in house* and used for all experiments.

Solubility determination

Equilibrium solubility was determined by a 'shake-flask' method using 0.2 M KH_2PO_4/0.2 M NaOH buffers (pH 4.5, 7.4, and 9.0) with/without the addition of 0.5% and 1% T80 or 1% and 2% D1216. An excess amount of NIM powder (100–500 mg) was placed into the vials, each containing 40 mL of previously described media, and shaken at 250 rpm for 3 hours at ambient temperature (25°C ± 2°C). Withdrawn samples were centrifuged at 3000 rpm for 15 minutes and filtered using CST Membrane Filter with 0.2 μm pore size. After appropriate dilution, drug concentration was assayed UV spectrophotometrically (Cary 50; Varian, Mulgrave, VIC, Australia). To encounter the pH-induced shift in the UV absorption spectra, separate calibration curves recorded at the wavelengths of the relative spectral maxima (in the range of 300–399 nm) were used for NIM quantification in different media. All measurements were performed in triplicate.

Results and discussion

Solubility

To calculate micellar solubilization coefficients for unionized (K_n) and ionized (K_i) form, the equilibrium solubility of NIM was determined in buffers, pH 4.5 and 9.0 (pH values at which the drug is present mostly in one form, i.e., unionized or ionized), containing different concentrations of D1216 or T80. The obtained data are presented in Table 1.

Using the intrinsic solubility of NIM (determined at pH 4.5), the corresponding solubilization power values were calculated and presented graphically (Figure 2).

The slopes of the regression lines obtained from the C_{sp} data at pH 4.5 and 9.0 were used to calculate K_n and K_i constants [Equation (8)]. The obtained results are given in Table 2. Both in the case of D1216 and T80, the obtained results showed that NIM solubility increased

Table 1. Equilibrium solubility of nimesulide (μg/mL ± SD) in various pH/surfactant systems (25 ± 2°C).

	Solubility (μg/mL ± SD)	
	pH	
Surfactant concentration	4.5	9.0
0%	7.07 ± 0.05	280.22 ± 12.18
1% (w/v) D1216	29.47 ± 0.04	389.30 ± 12.82
2% (w/v) D1216	57.94 ± 0.25	456.19 ± 2.22
0.5% (w/v) T80	30.53 ± 1.19	572.06 ± 6.50
1% (w/v) T80	74.04 ± 2.08	713.88 ± 19.89

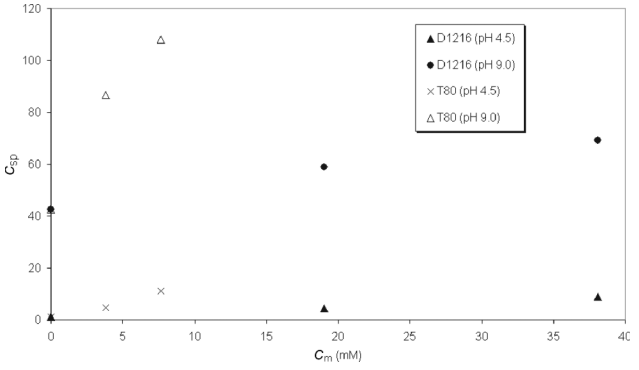

Figure 2. Solubilization power versus surfactant concentration at different pH values.

Table 2. Surfactant-mediated solubilization of nimesulide at different pH values: solubilization slopes and micellar equilibrium constants.

	pH	Solubilization slope (r^*)	K_n (L/mol)	K_i (L/mol)
D1216	4.5	187.96 (0.998)	187.95	1.46
	9.0	650.58 (0.990)		
T80	4.5	1234.08 (0.985)	1233.87	21.38
	9.0	7995.24 (0.981)		

*Coefficient of correlation.

with surfactant concentration at pH 4.5 and 9.0, as theoretically expected, although it was evident that equilibrium solubility was much higher at pH 9.0 where the drug was completely ionized. This demonstrated that pH had greater effect on the total solubility enhancement than the presence of surfactant, as illustrated in Figure 2. Addition of surfactant enhanced solubility by solubilizing both the unionized and the ionized drug, especially at higher surfactant concentration. The degree of ionization and the contribution of unionized and ionized drug forms to the total solubility depended on both the pH and the surfactant type and concentration. At low pH, higher K_n value relative to K_i indicated that solubility contribution from the unionized drug and its micelles was greater than from the ionized drug. However, according to this model, in the case of weekly acidic drugs, it was expected for the solubility contribution from the micellar ionized form to become more significant at higher pH values.

On the other hand, the obtained results indicated that the extent of solubilization of NIM was significantly dependent on the type of surfactant used. Although solubility was enhanced by both surfactants, T80 showed higher ability to solubilize NIM at both pH values as expressed in its higher solubilizing capacity (calculated values for both surfactant at pH 4.5 and 9.0 are shown in Figure 3). Possible explanation of this phenomenon is that fairly nonpolar NIM molecules (log P 2.60[27]) have greater affinity for longer hydrocarbon tails of T80 (C18) in comparison to D1216 (C12) and, thus, greater solubility in T80 solutions.

Model evaluation

The above data were used to estimate NIM solubility at pH 7.4 in the presence of 1% D1216 or T80 (Table 3). Because of the low solubility of NIM at lower pH values (pK_a 6.5), it might be assumed that under in vivo conditions, drug will be mostly solubilized and absorbed in the pH 7.4 intestinal region. The addition of surfactant would have a role to mimic the presence of naturally occurring bile salts.

The model has underpredicted the solubility of NIM both in the cases of D1216 and T80 containing pH 7.4 media by a factor of 1.18 and 1.05, respectively. Still, according to Li and Zhao[14], this can be considered as a reasonable estimate for NIM solubility in media contain-

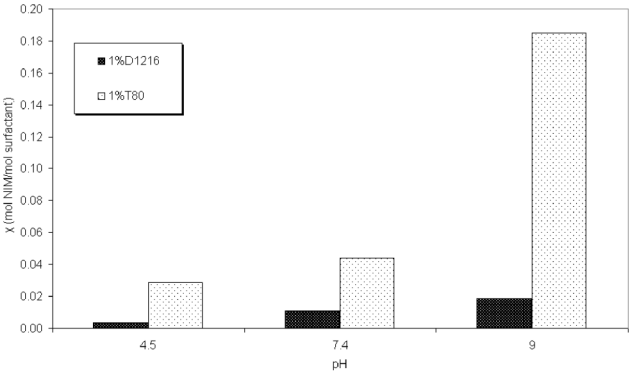

Figure 3. Solubilizing capacities of 1% D1216 and 1% T80 at different pH values.

Table 3. Solubility of nimesulide at pH 7.4 and 1% D1216 or T80: experimental versus predicted.

		Solubility (μg/mL)	
pH	Surfactant concentration	Experimental	Predicted
7.4	1% (w/v) D1216	107.15 ± 1.72	90.49
7.4	1% (w/v) T80	146.28 ± 1.17	139.63

ing surfactants. The model yielded good estimation for some drugs previously reported by other authors[13–15], providing a reliable expectation that it could be useful in the cases of other weakly acidic drugs also.

Conclusion

The equilibrium model used in this study may be applied to NIM with relative success. Considering the pH-dependent solubility of weak electrolytes throughout the GIT, the proposed model could be used to facilitate an attempt to find appropriate, physiologically relevant pH-surfactant combination for the in vitro dissolution testing of BCS Class II drugs.

Although T80 showed higher solubilization capacity, both surfactants used in low amounts (≤1%) enhanced NIM solubility, indicating that they could eventually be used as solubility improving agents in the routine in vitro dissolution testing.

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Declaration of interest: The authors report no conflicts of interest.

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