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Experimental determination of Naproxen solubility in organic solvents and aqueous binary mixtures: Interactions and thermodynamic parameters relating to the solvation process

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ABSTRACT

The experimental solubility of Nap in fifteen pure solvents and in eight aqueous–organic cosolvent mixtures was determined. The results obtained indicate that the π^* parameter which describes the polarity/polarizability of the solvent, and the Hildebrand's solubility parameter, which accounts for the cohesive forces of the solvent, have a greater influence on the solubility of Nap. This drug has a lower solubility ($T = 300.0 \pm 0.3$ K) in water ($3.02\ 10^{-4}$ M) and a greater solubility in DMS (1.56 M) and DMF (1.48 M). In all the cosolvent mixtures analyzed, the solute was preferentially solvated by the organic cosolvent. For the aqueous binary mixtures formed by ethanol, ethylene glycol and propylene glycol, the apparent enthalpy, entropic and Gibbs free energy changes involved with the solvation process were determined. In the three systems analyzed, it can be seen that the process is always entropically favorable and endothermic or unfavorable; hence, solute–solute and/or solvent–solvent interactions predominate. The solution process is driven by the enthalpy term. The contributions of enthalpy and therefore entropy do not change when modifying the composition of the mixture of cosolvents.

1. Introduction

Naproxen [Nap; (S)-(+)-2-(6-methoxy-2-naphthyl) propionic acid; Fig. 1] is a non-steroidal antiinflammatory drug (NSAIDs) derived from propionic acid. Nap is widely used in current therapeutics as analgesic and antipyretic although it is also used for relief of symptoms of rheumatoid arthritis and osteoarthritis in addition to treatment of dysmenorrheal, among other indications [1,2].

Considering the widespread use of Nap, it is fundamental to know its physicochemical properties such as solubility in different solvents, in solvent mixtures, and their interaction, since this understanding facilitates the design process of liquid pharmaceutical dosage forms (LPDF) [3]. It is further known that the solubility behavior of drugs in pure solvents and mixtures of cosolvents is useful to establish the physicochemical parameters that have a more significant contribution to the process of solubilization. These variables are frequently used in purification methods, in preformulation studies and in the design of LPDF, among other applications [4–6]. Thus, it is very important to determine systematically the solubility of drugs, in order to obtain complete information about physicochemical characteristics for pharmaceutical systems. This information facilitates the work of pharmacists who research and develop new products in the pharmaceutical industry [7].

On the other hand, the dependence of the solubility with temperature allows the thermodynamic analysis which gives us information about the mechanisms involved in the dissolution process [8,9].

In this paper, which refers to the prediction of properties of liquid systems, we present a physicochemical study of solubility of Nap in fifteen organic solvents and the influence of the composition of the cosolvent on the solubility of Nap in eight binary aqueous mixtures. Similarly, we determined the thermodynamic parameters involved in the process of solubility.

2. Materials and methods

2.1. Experimental details

Pure solvents and binary mixtures of w(water)–o (organic cosolvent) (from $X_w = 0.00$ to $X_w = 1.00$) were maintained in closed containers with continuous agitation by a shaking incubator Jeio Tech SI-300 R at constant temperature (300 ± 0.3 K) for at least 48 h after saturation with Nap. The concentration of saturated systems was determined using a UV–VIS spectrophotometer, after suitable dilutions to the wavelength of maximum absorbance of Nap (231 nm; $\varepsilon = 73{,}271$ Lmol^{-1} cm^{-1}) in methanolic medium. With the aim of ensuring

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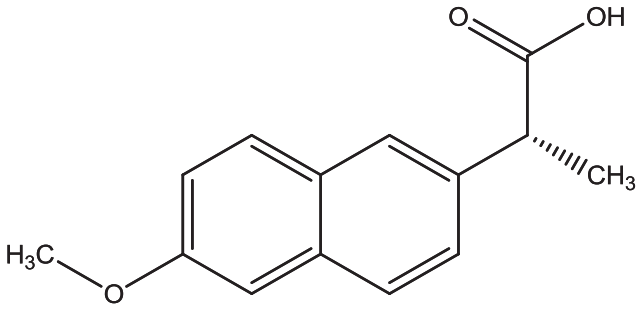

Fig. 1. Scheme of Naproxen.

the reproducibility and saturation of the solutions, all dilutions and solubility measurements were performed in triplicate and experimental results reported are the average of three measurements. Absorbance readings were performed with a Shimadzu double beam UV 160A fitted thermostatic cell holder. In order to perform the determinations of thermodynamic parameters, we proceeded in the same way for water–organic solvent (ethanol, ethylene glycol and propylene glycol or glycerol) mixtures, varying the working temperature (291.0–307.0 ± 0.3 K). Nap (CAS 22204-53-1; MW 230.26) was purchased from Sigma Aldrich ≥99.8%. The organic solvents that are of spectroscopic grade were obtained from Merck and Sigma Aldrich. Ethylene glycol, propylene glycol and i-butanol, ACS grade, were obtained from Sintorgan. All reagents used were purchased without any purification process. Bidistilled water was purified by using a Super Q Millipore System, with conductivity lower than 1.8 μS cm^{-1}.

2.2. Data analysis

The data processing and fittings of all equations were carried out using the scientist program Origin v 8.0. For equation fitting, linear regression was performed by minimal squares. The statistical analysis was performed with IBM SPSS Statistics v 19 program.

3. Theory

3.1. Analysis in pure solvents

Solvents have different chemical properties, closely related to the different processes in solution, such as solubility, distribution between two liquids, retention in chromatography, rates of reactions, free energy and enthalpy of equilibrium, among others. At constant temperature, the solubility process depends on the chemical properties of solvent as well as the solute–solute, solute–solvent and solvent–solvent interactions. When the solubility of a solute in a solvent or a solvent mixture is considerable, then solute–solvent interactions are significant and must be taken into account in any interpretation of solubility data. In order to study the role played by different modes of interaction on solubility, a multiple linear regression analysis (MLRA) involving various solvent parameters was used. Of the many expressions that have been proposed for the description of linear free energy relationships (LSER), one that was found to be widely used is the Kamlet–Taft expression [10,11], in which XYZ is a property linearly related to Gibbs energy:

$$\mathrm{XYZ} = \mathrm{XYZ}_0 + \text{cavity formation energy} + \sum \text{solute}-\text{solvent interaction energy}. \quad (1)$$

In the above equation, XYZ_0 is a constant that depends only on the solute, the cavity term is related to solvent, and the sum includes all modes of solute–solvent interaction.

Now we can write [12]:

$$\mathrm{XYZ} = \mathrm{XYZ}_0 + m\delta_H^2 + p\pi^* + a\alpha + b\beta. \quad (2)$$

In this expression δ_H is Hildebrand's solubility parameter of the solvent, which represents their self cohesiveness, and the solvatochromic parameter π^* describes a combination of properties, the polarity and the polarizability of the solvent. The quantities α and β are the solvatochromic properties of the solvent, α is the hydrogen bond donation (HBD) ability and β is the hydrogen bond acceptance (HBA) ability or electron pair donation ability to form a coordinative bond. They are determined primarily by the energies of the longer wavelength absorption peaks of certain carefully selected probe solutes in the solvents in question, after subtraction of the effect that non-HBD and/or non-HBA solvents would have on the probe, determined in separate experiments. They have been designed and given numerical values so that ideally they describe exclusively the HBD and HBA properties of the solvents, not being affected by their other properties, such as polarity, polarizability or tightness of cohesion [13]. For some processes, any of the coefficients XYZ_0, *m*, *p*, *a* and/or *b* may be negligible, so the corresponding terms do not play a role in the characterization of the solvent effects for these processes.

3.2. Analysis in water–organic solvents mixtures

The solubility of solutes in mixed solvents is of great practical importance, since in industrial processes such as in laboratory procedures it is used by default. The reasons for preferring the use of solvent mixtures are numerous, including the improvement of both, certain physical properties, such as the density, volatility, viscosity, and their chemical properties, such as stability and their ability to dissolve some substances. Moreover, the study of the drug solubility in cosolvent systems is very useful, in particular for formulations intended for parenteral administration, because it allows us to define the most suitable cosolvent compositions that ensure the physical stability of the formulations.

It is known that the solubility (log S) is related to the standard molar Gibbs energy of solvation. In an ideal solvation, the standard Gibbs energy in a mixture of cosolvents is given by the average of molar fraction, and the solubility in a mixture binary solvent, log S_{wo} is a linear function of molar fraction. The deviation from linearity expresses the existence of a non-ideal process of solvation. For all the mixtures analyzed, data point for log S_{wo} can be fitted satisfactorily with a polynomial cubic in X_w according to the following equation [14]:

$$\log S_{wo} = A + BX_w + CX_w^2 + DX_w^3. \quad (3)$$

In the above equation, A represents the value of log S in the organic solvent pure. The representation of Eq. (3) allows the classification of solubility profiles in cosolvent systems in two groups [15]: the solubility profiles without any maximum and those with a maximum. For the former class of profiles, the nonlinear variation of log S_{wo} with mole fraction should be attributed to the preferential solvation of the solute through one of the two components of the mixture [16].

The δ parameter representing the excess or deficiency of a component (water or organic solvent) of the mixture of cosolvents in the local region can be calculated from:

$$\delta_w = [\log S_{wo} - (X_w \log S_w + X_o \log S_o)]/[\log S_w - \log S_o]. \quad (4)$$

This parameter allows the comparison of performance of different binary solvent mixtures. The variation of δ_w with X_w responds to a cubic polynomial that can be expressed by:

$$\delta_w = \text{Intercept} + B_1X_w + B_2X_w^2 + B_3X_w^3. \quad (5)$$