Thermodynamic Study of Partitioning and Solvation of (+)-Naproxen in Some Organic Solvent/Buffer and Liposome Systems

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Naproxen (NAP) partitioning thermodynamics was studied in different solvent/buffer systems such as cyclohexane (CH/W), octanol (ROH/W), isopropyl myristate (IPM/W), and chloroform (CLF/W), as well as in dimyristoyl phosphatidylcholine (DMPC) and dipalmitoyl phosphatidylcholine (DPPC) liposome systems. In all cases, the mole fraction partition coefficients ($K^X_{o/w}$) were greater than unity; therefore, the standard Gibbs energies of transfer were negative indicating a high affinity of NAP for all the organic media. $K^X_{o/w}$ values were approximately 1000-fold higher in the ROH/W system with respect to the CH/W system, thus indicating a high degree of hydrogen-bonding contribution to partitioning, whereas in the case of the IPM/W and CLF/W systems, the $K^X_{o/w}$ values were approximately only 2-fold or 5-fold lower than those observed in ROH/W. On the other hand, $K^X_{o/w}$ values were approximately 55-fold or 39-fold higher in the liposomes compared to the ROH/W system, for DMPC and DPPC, respectively, thus indicating a high degree of bilayer immobilization and/or an electrostatic contribution to partitioning. In almost all cases, standard enthalpies of transfer of NAP from water to organic solvents were negative (except for CH), whereas the standard entropies of transfer were positive (except for IPM). For liposomes, the standard enthalpies and entropies of transfer were positive. These results indicate some degree of participation of the hydrophobic hydration on the NAP partitioning processes. By using the reported data for solvation of NAP in water, the associated thermodynamic functions for NAP solvation in all tested organic phases were also calculated. Finally, all the results obtained for NAP were compared with those presented previously for ketoprofen.

Introduction

Naproxen (NAP) as well as ketoprofen (KTP) are nonsteroidal anti-inflammatory drugs (NSAIDs) widely used in the treatment of several inflammatory and painful events.[1] Although NAP is widely used nowadays in therapeutics, physicochemical information about transfer processes of this drug, like other NSAIDs, is not complete at present. As useful information in pharmaceutical and medicinal chemistry, the thermodynamics of transfer of drug compounds can be studied by measuring the mole fraction partition coefficient as a function of temperature by means of the van't Hoff method. Such data can be used for the prediction of absorption, membrane permeability, and in vivo drug distribution.[2]

According to Leo et al.,[3] semi-polar solvents have been found to yield better correlations with the partitioning of solutes obtained in model membranes compared to nonpolar solvents such as cyclohexane (CH), which interacts only by nonspecific forces (London interactions). In particular, octanol (ROH) has been found to be a useful solvent as the reference for extrathermodynamic studies in a variety of systems.[4] Isopropyl myristate (IPM) has also been used acting as a hydrogen acceptor as well, and it has been used especially for determining drug hydrophobic constants because it simulates most closely the corneum stratum/water partition. IPM is best related to skin/transdermal absorption because its polar/nonpolar balance simulates the complex nature (polar/nonpolar matrix) of the skin.[5−7] On the other hand, chloroform (CLF) has also been used in these kind of studies because it acts mainly as a hydrogen donor for establishing hydrogen bonds with Lewis basic solutes.[8] Thus, the effect of hydrogen bonding on partitioning would be studied completely.

However, the octanol/water system has proven to be a poor model system for several drug transport processes as well as for correlating some pharmacokinetic parameters. Otherwise, when analyzing the behavior of several drugs, the liposome systems have shown to discriminate branched solutes regarding bulk systems such as oil/water. This behavior has been found especially in the case of some phenols,[9,10] phenotiazines,[11,12] beta-blockers,[13] and some NSAIDs.[2] In addition, dipyridamole partitioning was higher in liposomes than in ROH[14] and higher for mefloquine, quinine, and other antimalarial drugs[15,16] and for some sulfonamides,[17] benzocaine,[18] and KTP.[19] For these reasons, different liposome types have been used combined to organic solvents for partitioning experiments to develop quantitative structure−activity relationships (QSAR studies).

As a contribution to the generation and systematization of physicochemical information about NSAIDs' transfer properties, the main goal of this study was to compare the partitioning and solvation behavior of NAP in different organic medium/buffer systems, namely, cyclohexane (CH/W), octanol (ROH/W), isopropyl myristate (IPM/W), chloroform (CLF/W), and dimyristoyl phosphatidylcholine (DMPC/W) as well as dipalmitoyl phosphatidylcholine (DPPC/W) liposome systems, by employing a thermodynamic approach based on the mole fraction partitioning variation with respect to temperature. From the obtained values of the corresponding transfer thermodynamic functions, an interpretation based on solute−solvent interactions was developed. Therefore, the present study is a continuation of those

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previously presented for KTP,[19] which is another NSAID structurally related to NAP.

Theoretical

The apparent partition coefficient expressed in molality ($K_{o/w}^{m-app}$: distribution coefficient) for any solute between organic and aqueous phases (at any pH value, which would imply drug dissociation) is calculated by means of

$$K_{o/w}^{m-app} = W_w \frac{C_1 - C_2}{C_2 W_o} \quad (1)$$

where W_w and W_o are the masses (usually in grams) of aqueous and organic phases, respectively, and C_1 and C_2 are the solute aqueous concentrations of solute (usually in micrograms per milliliter) before and after the transfer from the aqueous phase to the organic medium, respectively.[20] To obtain the real molal partition coefficients ($K_{o/w}^{m}$), the following equation is commonly used[19]

$$K_{o/w}^{m} = K_{o/w}^{m-app}(1 + 10^{pH-pK_a}) \quad (2)$$

Sometimes eq 2 is written as $P = D(1 + 10^{pH-pK_a})$, where P is the real partition coefficient and D is the distribution coefficient, respectively. In turn, the mole fraction partition coefficients ($K_{o/w}^{X}$) are calculated from $K_{o/w}^{m}$ values as

$$K_{o/w}^{X} = K_{o/w}^{m}(M_o/M_w) \quad (3)$$

where M_o and M_w are the molar masses of the organic and aqueous phases, respectively.[19]

The definition of $K_{o/w}^{m}$ and $K_{o/w}^{X}$ implies that no drug association or dissociation takes place in any of the respective phases; that is, the partitioning obeys the Nernst limit law.

Otherwise, the enthalpy change for the transfer of solutes from aqueous phases to organic systems may be obtained directly by thermometric titration microcalorimetry or, in the case of liquid/liquid systems, indirectly as the difference of the respective heats of solution (or dilution) in each one of the phases, which may be obtained by solution calorimetry.[21] As was said previously, a method widely used in the physicochemical study of pharmaceutical compounds is by means of the analysis of the temperature-dependence for partitioning. It is well-known that the making of weighted graphs based on the logarithm of partition coefficients as a function of the reciprocal of the absolute temperature permits the enthalpic change of transfer from aqueous media to organic systems ($\Delta H_{w\rightarrow o}^{0X}$) to be obtained by means of the classical van't Hoff equation (eq 4). It is important to note that an excellent precision is required in $K_{o/w}^{X}$ values to enable the calculation of meaningful enthalpy values from them.

$$\left(\frac{\partial \ln K_{o/w}^{X}}{\partial(1/T)}\right)_p = -\frac{\Delta H_{w\rightarrow o}^{0X}}{R} \quad (4)$$

Nevertheless, in more recent treatments, some modifications have been introduced to eq 4 to reduce the propagation of errors and, therefore, to separate the chemical effects from those due only to statistical treatments used in enthalpy−entropy compensation plots, as will be seen below. For this reason, the mean harmonic temperature (T_{hm}) is used in the van't Hoff analysis. T_{hm} is calculated as[22]

$$T_{hm} = \frac{n}{\sum_i^n (1/T)} \quad (5)$$

where n is the number of tested temperatures. When temperature intervals, from 293.15 K to 313.15 K (varying in 5.00 K) are evaluated, the T_{hm} value obtained is just 303 K. The modified expression more widely used at 303 K can be written as follows

$$\left(\frac{\partial \ln K_{o/w}^{X}}{\partial(1/T - 1/303)}\right)_p = -\frac{\Delta H_{w\rightarrow o}^{0X}}{R} \quad (6)$$

The standard Gibbs energy change for the transfer process ($\Delta G_{w\rightarrow o}^{0X}$) has been traditionally calculated in the literature as[8−21]

$$\Delta G_{w\rightarrow o}^{0} = -RT \ln K_{o/w}^{0X} \quad (7)$$

Nevertheless, considering the approach proposed by Krug et al.[22] at 303 K, this property is more appropriately calculated by means of

$$\Delta G_{w\rightarrow o}^{0X} = -R\cdot 303\cdot \text{intercept} \quad (8)$$

in which the intercept used is the one obtained from $\ln K_{o/w}^{0X}$ vs $1/T - 1/303$ plots (eq 6). Although the enthalpy obtained by using eq 6 is the same as that obtained by means of eq 4, the $\Delta G_{w\rightarrow o}^{0X}$ value obtained by using eq 8 is slightly different with respect to that calculated by means of eq 7 at 303.15 K because in the former case this property depends on all the partitioning data, whereas in the traditional form it depends solely on the value obtained at the specified temperature.

The standard entropic change for the transfer process ($\Delta S_{w\rightarrow o}^{0X}$) at 303 K is obtained from the respective $\Delta H_{w\rightarrow o}^{0X}$ and $\Delta G_{w\rightarrow o}^{0X}$ values, by using

$$\Delta S_{w\rightarrow o}^{0X} = \frac{\Delta H_{w\rightarrow o}^{0X} - \Delta G_{w\rightarrow o}^{0X}}{303} \quad (9)$$

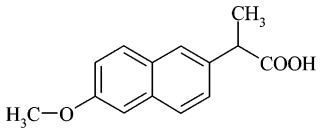
The thermodynamic functions $\Delta H_{w\rightarrow o}^{0X}$ and $\Delta S_{w\rightarrow o}^{0X}$ represent the standard changes in enthalpy and entropy, respectively, when one mole of drug is transferred from the aqueous medium to the organic system at infinite dilution expressed in the mole fraction scale.[2,20]

Experimental

Chemicals. In this investigation, the following chemicals were used: naproxen USP;[23] cyclohexane A.R. (Merck); octanol extra pure grade (Merck); *i*-propyl myristate for synthesis (Merck); chloroform A.R. (Mallinckrodt); DMPC (ref P-7331) and DPPC (ref P-5911) (Sigma Chemical Co.); potassium chloride A.R. (Merck); hydrochloric acid A.R. (Merck); sodium mono- and dihydrogen phosphates A.R. (Merck); distilled water (conductivity < 2 μS·cm^{-1}).

Organic Solvent/Buffer Partitioning. Both the aqueous and organic solvents were mutually saturated before performing the experiments. Solutions of NAP at known concentrations were prepared in aqueous buffers adjusted to pH 1.2 and 7.4 at ionic strength (I) equal to 0.15 mol·L^{-1}.[24] Then, in glass flasks, specific volumes of organic solvents were added to specific volumes of the aqueous NAP solutions. The employed volumes were as follows: for CH/W, 10 mL of CH and 10 mL of (10 μg·mL^{-1}) NAP aqueous solution at pH 1.2; for ROH/W, 10

Table 1. Some Physical and Chemical Properties of NAP

molecular structure	M/g·mol^{-1}	pK_a	λ_{max}/nm
	254.28	4.1[a]	229[b] 262[c]

[a] From Betageri et al.[2] at $I = 0$ mol·L^{-1} and corrected at $I = 0.15$ mol·L^{-1} by means of the extended Debye−Hückel equation.[29] [b] In water at pH 1.2 and $I = 0.15$ mol·L^{-1}. [c] In water at pH 7.4 and $I = 0.15$ mol·L^{-1}.

mL of ROH and 10 mL of (50 μg·mL^{-1}) NAP aqueous solution at pH 7.4; for IPM/W, 20 mL of IPM and 5 mL of (40 μg·mL^{-1}) NAP drug aqueous solution at pH 7.4; for CHL/W, 20 mL of CHL and 10 mL of (40 μg·mL^{-1}) NAP aqueous solution at pH 7.4. All aliquots were weighed on a digital analytical balance (Mettler AE 160) whose sensitivity was ± 0.1 mg.

Mixtures were then stirred on a mechanical shaker (Wrist Action Burrel model 75) for 1 h. Samples were placed on water baths (Magni Whirl Blue M. Electric Company) at (293.15, 298.15, 303.15, 308.15, and 313.15) K (± 0.05 K) for at least 48 h with sporadic stirring to achieve the partitioning equilibrium, as it was made studying other compounds.[8,17−19] After this time period, the aqueous phases were removed followed by determination of the drug concentration by means of UV absorbance measurement and interpolation on previously constructed calibration curves for NAP in buffer at pH 1.2 or 7.4 (Unicam UV2-100 spectrophotometer) according to validated methodologies.[25]

The $K_{o/w}^{m-app}$ values were then calculated by using eq 1 and converted into $K_{o/w}^{m}$ values by means of eq 2, in which the parenthesis term on the right side is equal to 1996 because the pH is 7.4 and the pK_a of NAP corrected to an I value of 0.15 mol·L^{-1} is 4.1 (Table 1). In the case of the CH/W system, the value obtained by means of eq 1 is considered directly as real because at pH 1.2 the NAP is present mainly as a nondissociated compound, and thus, the same species is partitioned. From $K_{o/w}^{m}$ values, the mole fraction partition coefficients ($K_{o/w}^{X}$) were calculated from eq 3 employing the following molar masses:[19,26] 99.47 g·mol^{-1} for water-saturated ROH; 263.72 g·mol^{-1} for water-saturated IPM; 113.89 g·mol^{-1} for water-saturated CLF; 84.16 g·mol^{-1} for water-saturated CH; 18.16 g·mol^{-1} for (ROH, IPM, or CH) organic solvent-saturated buffers; and 18.29 g·mol^{-1} for CLF-saturated buffers.[27]

Liposome/Buffer Partitioning. Liposomes were prepared by a modified Bangham method,[28] as it was made studying other compounds.[2,17−19] Thin films of 25 mg of DMPC or DPPC were formed on the walls of 50 mL round-bottomed flasks after rotary evaporation (Buchler Instr.) of 2.5 mL aliquots of lecithin chloroformic solutions (10 mg·mL^{-1}). Then all flasks were placed in an oven at 313.15 K for 1 h. Thereafter, the films were dispersed in 2.5 mL of NAP aqueous solution (200 μg·mL^{-1}, pH 7.4, and I value 0.15 mol·L^{-1}) and then were heated at 298.15 K (for DMPC) or 318.15 K (for DPPC) and vortex-mixed (Mistral Mixer, model 1192, Lab-Line Instr.) until the whole film was removed from the flasks' walls. These temperatures were above their respective values for gel−liquid crystal transitions for both liposomes. This procedure resulted in formation of multilamellar vesicles (MLVs).

Aliquots of 1.2 mL of the liposomal dispersions were transferred to 2.0 mL microtubes and placed on water baths (Magni Whirl Blue M. Electric Company) at (293.15, 298.15, 303.15, 308.15, 313.15, and 318.15) K (± 0.05 K) for at least 48 h with sporadic stirring to achieve the partitioning equilibrium, as it was performed studying other compounds.[17−19] After this time period, the aqueous phases were removed by centrifugation (25000g for 45 min) at the specified temperature followed by determination of the drug concentrations by means of UV absorbance measurement and interpolation on a previously constructed calibration curve for NAP in buffer at pH 7.4 (Unicam UV2-100 spectrophotometer) according to a validated methodology.[25]

The apparent and true partition coefficients were calculated by using the same equations as in organic solvent/buffer partitioning. The molar masses for lecithins are 677.90 g·mol^{-1} for DMPC and 734.05 g·mol^{-1} for DPPC. All partitioning experiments were repeated at least three times, and the produced data were averaged.

Results and Discussion

Physical and Chemical Properties of NAP. The molecular structure and some physicochemical properties of NAP are summarized in Table 1. The pK_a value was corrected to an I value of 0.15 mol·L^{-1} (similar to that of the gastrointestinal tract and blood)[24] by means of the extended Debye-Hückel equation.[29] The partitioning was determined at pH 7.4 (resembling the blood physiological value) except for the CH/W system (studied at pH 1.2). Such pH values were regulated with phosphate buffer or KCl/HCl buffer having β capacities of 0.01 calculated by the Koppel−Spiro−Van Slyke equation,[29] using pK_a values corrected to an I value of 0.15 mol·L^{-1}. At pH 7.4, the NAP has a lower apparent partition coefficient value because the dissociated compound form predominates, thus having more affinity for water. For this reason, it is necessary to use eq 3 to obtain the true values of partitioning that would follow the Nernst law, which implies no association or dissociation of the drug, in the organic or aqueous phases,[4] as was already said.

Partition Coefficients of NAP. The temperature dependence of the mole fraction partition coefficients for the NAP in all tested partitioning systems is summarized in Table 2. In all cases, the $K_{o/w}^{X}$ values are greater than unity and increased with rising temperature for the CH/W and liposome systems, whereas they diminished for the ROH/W, IPM/W, and CLF/W systems. Partitioning diminishes at 298.15 K in the order DMPC/W > DPPC/W > ROH/W > IPM/W > CLF/W > CH/W, which is similar to data found for other drugs.[18,19] For NAP, the partitioning was greater in IPM/W than in CLF/W, in contrast to KTP behavior.[19] The data found are in agreement that NAP displays a lipophilic semi-polar behavior which is similar to that obtained for KTP.[19] In all cases, in the liquid systems, the $K_{o/w}^{X}$ values are higher for NAP with respect to KTP, except for CH/W, whereas in the liposome systems, the results obtained are very similar for both drugs.

Betageri et al.[2] previously reported data regarding this drug partitioning in the ROH/W and DMPC/W systems at pH 7.0 and expressed on the molal scale. Nevertheless, the results presented in Table 2 for both systems are not in agreement with those presented in the literature when they were converted to mole fraction. For the ROH/W system, according to Betageri et al.[2] the NAP partitioning increases as the temperature increases, which is opposite to the data presented in Table 2; besides, the individual values are lower compared with those presented in the same table. Otherwise, for the DMPC/W system, according to the same authors,[2] smaller $K_{o/w}^{X}$ values were found when increasing the working temperature, which is again opposite to the data presented in the present study. On the other hand, according to graphical results presented in the same reference,[2] apparently the NAP molal partition is similar

Table 2. Mole Fraction Partition Coefficient of NAP in Different Partitioning Systems as a Function of Temperature (± 0.05 K)[a]

	$K^X_{o/w}$					
system	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K	318.15 K
CH/W	20.13 (0.17)	20.99 (0.05)	21.89 (0.04)	22.82 (0.12)	23.6 (0.4)	–
ROH/W	2.297 (0.017)·10^4	2.177 (0.019)·10^4	2.059 (0.009)·10^4	1.950 (0.030)·10^4	1.829 (0.021)·10^4	–
IPM/W	1.162 (0.011)·10^4	9.73 (0.18)·10^3	8.19 (0.09)·10^3	7.09 (0.06)·10^3	5.75 (0.08)·10^3	–
CLF/W	5.11 (0.05)·10^3	4.456 (0.011)·10^3	3.828 (0.018)·10^3	3.432 (0.016)·10^3	2.959 (0.015)· 10^3	–
DMPC/W	5.00 (0.14)·10^5	1.211 (0.017)·10^6	1.478 (0.023)·10^6	1.81 (0.04)·10^6	2.170 (0.030)·10^6	2.51 (0.06)·10^6
DPPC/W	6.41 (0.08)·10^5	8.45 (0.21)·10^5	1.003 (0.026)·10^6	1.270 (0.018)·10^6	1.630 (0.020)·10^6	3.82 (0.04)·10^6

[a] Values in parentheses are standard deviations.

in both ROH/W and DMPC/W systems, which is not in agreement with Table 2 data even if partition coefficients are converted to molality.[30] In a similar way, opposite results were also found for KTP behavior between Betageri et al.[2] and Lozano and Martínez.[19] The reasons for these disagreements are unclear.

According to Table 2, the partitioning in DMPC is almost 55-fold greater than the respective partitioning in ROH/W at 298.15 K. When comparing the results obtained for all organic solvents, a higher preference of NAP for ROH with respect to the other tested solvents, in particular regarding CH, can be deduced. This behavior is very similar to that obtained for KTP.[19] As has been previously described in the literature, the ROH has a microheterogeneous structure on water saturation.[4,26] This structure is conformed by two water molecules hydrogen bonded between them, and in turn, each one of the water molecules is bonded to three octanol molecules, also by hydrogen bonding; the result is a tendency to form small inverted-like micelle regions. For this reason, ROH interacts with NAP by hydrogen bonding through methoxyl and carboxyl groups present in this drug and by weak interactions, such as London dispersion forces, which conduce to structural immobilization of drug molecules near the alkyl moieties of ROH.

As was already indicated, the phospholipidic vesicles have been investigated as a model for studying drug distribution in membranes because liposomes resemble the ordered structures present in biological membranes. As shown in Table 2, the NAP partitioning is higher in these systems compared to ROH/W. This fact demonstrates a high contribution to partitioning by the drug immobilization inside the bilayers or by means of electrostatic interactions with the polar head of phospholipids located at the bilayer interfaces, as has been described in the literature.[12−14] In addition, the vesicles can partition the drug in the aqueous spaces available within the vesicles increasing the NAP solubilization. On the other hand, some surface phenomena due to the possible amphiphilic nature of NAP (such as changes in the membrane flexibility) would also be considered because the nature of the bilayer interfaces could be modified. This consideration has been done recently by studying the behavior of ibuprofen (another NSAID compound structurally related to NAP and KTP) in micellar solutions of ionic and non-ionic surfactants.[31]

Comparing the results obtained in the liposome systems, the partitioning is higher in DMPC/W with respect to DPPC/W ranging from (298.15 to 313.15) K. Such behavior could be explained in terms of the liposomes' flexibility according to the states of liposomes, that is, fluid or rigid. In this temperature interval, the DMPC liposomes are in a fluid state (liquid crystal) while DPPC liposomes are in a rigid state (gel) because the transition gel−liquid crystal temperatures (T_C) for these compounds are (296.8 and 314.5) K, respectively.[32] Therefore, the liposomes' flexibility and permeability is greater in a fluid state than in a rigid state, i.e., at temperatures higher than T_C.

On the other hand, when partitioning is compared for liposomes present in the same state, the NAP partitioning is higher for DPPC/W with respect to DMPC/W; i.e., at 293.15 K, both liposome systems are in a gel state (rigid), whereas at 318.15 K, both liposome systems are in a liquid crystal state (flexible). In particular, this result could be considered as an additional demonstration about the lipophilic nature of this drug because DPPC has two additional methylene groups in each hydrocarbon moiety with respect to DMPC. Nevertheless, certainly NAP, as well as KTP, is not a hydrophobic drug because the CH/W partitioning is relatively low when it is compared to partitioning obtained in the other organic solvents (Table 2).

Seiler and Other Analogue Parameters. As was described previously,[19] Seiler[33] proposed an equation analogous to eq 10 to compare partition coefficients of drugs in the ROH/W and CH/W systems, with the basic purpose of obtaining information related to the contribution of hydrogen bonding for partitioning of solutes. In a more complete treatment, other considerations such as molecular geometry and steric effects of solutes and solvents should be considered for such an aim. However, in a first approach, eq 10 is a good attempt for identifying the main solute−solvent interactions affecting the solute transfer

$$\Delta \log K^X_{ROH/CH} = \log K^X_{ROH/W} - \log K^X_{CH/W} \qquad (10)$$

The above equation may also be written as a quotient relationship in the form $\Delta \log K^X_{ROH/CH} = \log(K^X_{ROH/W}/K^X_{CH/W})$ showing the hydrogen-bonding nature of the interactions between the drug and ROH with respect to CH. If $\Delta \log K^X_{ROH/CH}$ is greater than 0, then this result indicates some contribution of hydrogen bonding to the partitioning of drugs. Table 3 presents the values of the parameters of Seiler and other analogous parameters for NAP at 298.15 K, calculated from the different rational partition coefficients shown in Table 2 (which are presented in Table 3 as decimal logarithms).

It is well-known that CH is an aprotic solvent unable to form hydrogen bonds as a donor or acceptor and therefore acts only through nonspecific interactions (London forces). However, the hydroxyl group of ROH can be an acceptor and/or a donor of protons, and moreover, as was already expressed, its alkyl moieties allow the structural immobilization of solutes due to the tetrahedral microstructure adopted in saturation by this solvent in contrast to the CH behavior.[4,26] Therefore, $\Delta \log K^X_{ROH/CH}$ includes contributions by hydrogen bonding and by structural immobilization to the partitioning (in this analysis it is considered that the nonspecific interactions are similar for all organic solvents and drugs).

Otherwise, $\Delta \log K^X_{IPM/CH}$ allows estimation of the contribution of the organic solvent as a hydrogen-bonding acceptor in IPM/W rational partitioning. By comparison of the Seiler parameter ($\Delta \log K^X_{ROH/CH}$) with $\Delta \log K^X_{IPM/CH}$, it is shown that the ROH, besides contributing to the drug partitioning as an

Table 3. Seiler and Other Analogue Parameters of NAP at (298.15 ± 0.05) K

parameter	system 1	system 2	$\log K^X_{o/w}$(syst.1)	$\log K^X_{o/w}$(syst.2)	$\Delta \log K^X_{o1/o2}$ [a]
$\Delta \log K^X_{ROH/CH}$	ROH/W	CH/W	4.338	1.322	3.016
$\Delta \log K^X_{IPM/CH}$	IPM/W	CH/W	3.988	1.322	2.666
$\Delta \log K^X_{CLF/CH}$	CLF/W	CH/W	3.649	1.322	2.327
$\Delta \log K^{X\alpha}_{ROH/IPM}$	ROH/W	IPM/W	4.338	3.988	0.350
$\Delta \log K^{X\beta}_{ROH/CLF}$	ROH/W	CLF/W	4.338	3.649	0.689
$\Delta \log K^X_{DMPC/ROH}$	DMPC/W	ROH/W	6.083	4.338	1.745
$\Delta \log K^X_{DPPC/ROH}$	DPPC/W	ROH/W	5.927	4.338	1.589

[a] $\Delta \log K^X_{o1/o2} = \log K^X_{o/w}(\text{syst.1}) - \log K^X_{o/w}(\text{syst.2})$.

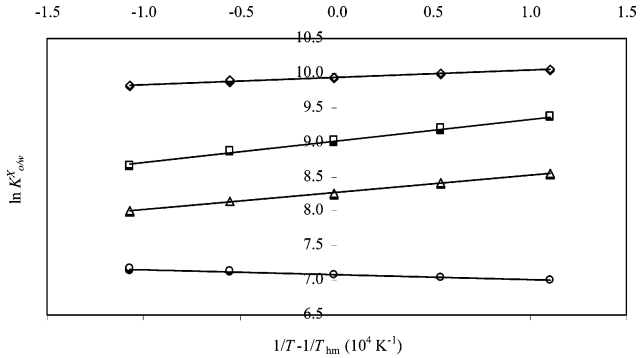


Figure 1. Modified van't Hoff plot for the NAP partitioning in the organic solvent/buffer systems. ◇, ROH/W; □, IPM/W; △, CLF/W; ○, CH/W (expressed as $\ln K^X_{o/w} + 4$).

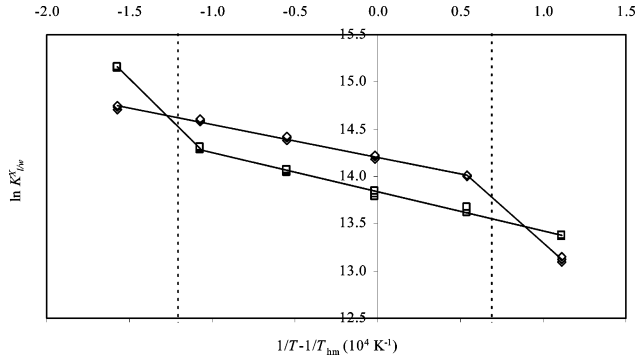


Figure 2. Modified van't Hoff plot for the NAP partitioning in the DMPC (◇) and DPPC (□) liposome systems. Vertical discontinued lines are the phase transition temperatures for liposomes: (296.8 and 314.5) K, for DMPC and DPPC, respectively.[32]

acceptor of hydrogen, may also contribute as a hydrogen donor; therefore, the $\Delta \log K^X_{IPM/CH}$ value is smaller than the Seiler parameter (Table 3).

A third parameter, namely, $\Delta \log K^{X\alpha}_{ROH/IPM}$, was calculated by comparing the ROH/W and IPM/W partition coefficients to establish the contribution of the organic solvent as a hydrogen donor to the partitioning. As was already said, CLF acts mainly as a hydrogen donor, and therefore, the other two parameters were calculated to analyze the contribution of this kind of interaction on the partitioning of NAP. $\Delta \log K^X_{CLF/CH}$ permits one to observe the possible contribution of CLF as a hydrogen donor, whereas $\Delta \log K^{X\beta}_{ROH/CLF}$ (obtained from ROH/W and CLF/W partitioning values) permits one to evaluate the behavior of ROH as a hydrogen acceptor.

Generally, in contrast to KTP behavior,[19] the results show lower $\Delta \log K^X_{o1/o2}$ values when NAP acts as a hydrogen acceptor ($\Delta \log K^X_{CLF/CH}$ and $\Delta \log K^{X\alpha}_{ROH/IPM}$) with respect to those obtained when this drug acts as a hydrogen donor ($\Delta \log K^X_{IPM/CH}$ and $\Delta \log K^{X\beta}_{ROH/CLF}$). The acid hydrogen present in this drug is the one present in its carboxylic group, whereas the basic groups (hydrogen acceptor) in NAP are the methoxyl group present in the naphthyl ring and the carbonyl moiety in the carboxyl group, although the hydroxyl moiety would also be a proton acceptor. At this point, it is convenient to restate that in the previously made analyses we were considering only the effect of hydrogen bonding without considering the other kinds of interactions or geometric parameters, such as differences in molecular sizes.

More recently, eq 11 has been exposed to obtain information about the higher distribution of drugs inside liposome bilayers compared to that obtained in ROH.[18,19]

$$\Delta \log K^X_{DMPC/ROH} = \log K^X_{DMPC/W} - \log K^X_{ROH/W} \qquad (11)$$

The $\Delta \log K^X_{DMPC/ROH}$ parameter allows a rough estimate of the contribution to NAP partitioning by structural immobilization and by solute−lipid electrostatic effects (in addition to the aqueous spaces within the vesicles), which would be present depending on the phospholipid employed for the preparation of liposomes.[12−14] Table 3 shows that the effect due to immobilization is higher in DMPC liposomes with respect to DPPC liposomes ($\Delta \log K^X_{DMPC/ROH} > \Delta \log K^X_{DPPC/ROH}$), which is also similar to that obtained for KTP.[19] This behavior can be explained in terms of the liposome aggregation state according to the temperature evaluated. As was already exposed, in the studied range, the DMPC liposomes are in a liquid crystal state (fluid), which are more flexible and permeable, whereas the DPPC liposomes are in a gel state (rigid). According to the data presented in Table 3, the contribution by structural immobilization of NAP inside the liposomes apparently would be more important than the respective contribution by hydrogen bonding on the overall partition processes because $\Delta \log K^X_{DMPC/ROH}$ is greater than $\Delta \log K^X_{ROH/CH}$.

Thermodynamics of Partitioning for NAP. Modified van't Hoff plots for CH/W, ROH/W, IMP/W, and CLF/W partitioning of NAP are shown in Figure 1. In all cases, linear regression models with good determination coefficients, r^2, were obtained (0.981 for CH/W, 0.986 for ROH/W, 0.995 for IPM/W, and 0.998 for CLF/W). This behavior is different with respect to that obtained for KTP,[19] where nonlinear models were obtained for the same systems, except for CH/W, where a linear behavior was obtained.

Figure 2 shows the modified van't Hoff plot for NAP partitioning in DMPC and DPPC liposomes. In both cases, the results were adjusted to linear regression models considering the temperature intervals for which the liposomes are in the same state. The r^2 values were 0.995 and 0.993, for DMPC and DPPC, respectively. As was already indicated, transition temperatures for DMPC and DPPC liposomes are (296.8 and 314.5) K, respectively.[32] Therefore, the temperature intervals considered were from (298.15 to 318.15) K for DMPC (fluid

Table 4. Standard Gibbs Energy ($\Delta G^{0X}_{w\to o}$), Enthalpy ($\Delta H^{0X}_{w\to o}$), and Entropy ($\Delta S^{0X}_{w\to o}$) of NAP Transfer from Water to Different Organic Systems and Relative Contributions of Enthalpy (% ζ_H) and Entropy (% ζ_{TS}) toward Transfer Processes at 303 K[a]

system	$\Delta G^{0X}_{w\to o}$ kJ·mol^{-1}	$\Delta H^{0X}_{w\to o}$ kJ·mol^{-1}	$\Delta S^{0X}_{w\to o}$ J·mol^{-1}·K^{-1}	$T\Delta S^{0X}_{w\to o}$ kJ·mol^{-1}	% ζ_H	% ζ_{TS}
CH/W	−7.77	6.15	45.9	13.9	30.6	69.4
	(0.01)	(0.24)	(1.8)	(0.5)		
ROH/W	−25.02	−8.66	54.0	16.4	34.6	65.4
	(0.01)	(0.28)	(1.8)	(0.5)		
IPM/W	−22.71	−26.3	−11.75	−3.56	88.1	11.9
	(0.01)	(0.5)	(0.24)	(0.07)		
CLF/W	−20.82	−20.65	0.54	0.165	99.2	0.8
	(0.01)	(0.28)	(0.01)	(0.002)		
DMPC/W	−35.78	29.0	214	64.8	30.9	69.1
	(0.02)	(0.6)	(4)	(1.3)		
DPPC/W	−34.86	34.6	229	69.5	33.3	66.7
	(0.02)	(1.5)	(5)	(1.6)		

[a] Values in parentheses are standard deviations.

state) and from (293.15 to 313.15) K for DPPC (rigid state). Although the T_{hm} value for the former temperature interval is not properly 303 K, this value was also employed for DMPC liposomes, to compare directly the respective thermodynamic functions between all partitioning systems.

From the estimated slopes in the modified van't Hoff plots, the respective standard enthalpic changes for transfer were calculated by means of eq 6 using the respective method of errors propagation.[34] Then, the transfer enthalpies ($\Delta H^{0X}_{w\to o}$) were calculated as the product of slopes multiplied by $-R$ (that is, -8.314 J·mol^{-1}·K^{-1}). The obtained values for this thermodynamic function are summarized in Table 4, in addition to the standard Gibbs energy for transfer ($\Delta G^{0X}_{w\to o}$) of NAP from water to different organic systems (expressed in mole fraction at 303 K). The $\Delta G^{0X}_{w\to o}$ values were calculated by means of eq 7, based on all the partitioning data presented in Table 2 using the respective method of errors propagation.[34] In all cases, $\Delta G^{0X}_{w\to o}$ was negative indicating the preference of this drug for organic media. The NAP behavior in this thermodynamic function is similar to that obtained for KTP.[19]

From $\Delta G^{0X}_{w\to o}$ and $\Delta H^{0X}_{w\to o}$ values, the respective standard entropic changes of transfer ($\Delta S^{0X}_{w\to o}$) in mole fraction were calculated from eq 8. These values are also presented in Table 4. The $\Delta H^{0X}_{w\to o}$ and $\Delta S^{0X}_{w\to o}$ values obtained for NAP in liquid/liquid systems are very different with respect to those obtained previously for KTP.[19] The enthalpies of transfer of NAP were negative, except for CH/W, whereas for KTP, these values were all positive. On the other hand, the respective entropies of transfer of NAP were positive (except for IPM/W), whereas for KTP, these values were positive in all cases.[19]

Otherwise, Burgot and Burgot determined the enthalpy of transfer of NAP from water to ROH by means of thermometric titration calorimetry,[35] obtaining the value -13.33 kJ·mol^{-1}, which is significantly different in magnitude with respect to that presented in Table 4 (-8.66 kJ·mol^{-1}). Although this difference could be expected because an indirect method was used here, the calorimetry is a direct measure of the heat evolved.

The enthalpic and entropic changes imply, respectively, all the energetic requirements and the molecular randomness (increase or decrease in the molecular disorder) involved in the net transfer of the drug from water to different organic media. In general terms, it should be considered independently of the behavior presented in each phase, before and after the partitioning process.

Because initially the NAP is present only in water, it is necessary to create a cavity in the organic medium to accommodate the solute after the transfer process. This is an endothermic event because an energy supply is necessary to separate the organic solvent molecules (to overcome the cohesive forces). When the solute molecules are accommodated into the organic phase, an amount of energy is released due to solute−organic solvent interactions. This event would imply an entropy increase in this medium due to the mixing process.

In turn, after a certain number of solute molecules have migrated from the aqueous phase to the organic medium to reach the partitioning equilibrium, the original cavities occupied by the drug molecules in the aqueous phase have been now occupied by water molecules. This event produces an energy release due to water−water interactions. However, depending on the solute's molecular structure, it is also necessary to keep in mind the possible disruption of the water structure, that is, the water molecules organized as "icebergs" around the alkyl or aromatic groups of the drug (namely, hydrophobic effect or hydrophobic hydration). This event in particular implies an intake of energy in addition to a local entropy increase by separation of some water molecules which originally were associated among them by hydrogen bonding.[36]

From Table 4, it can be observed that for all cases the NAP transfer processes from water to organic media were exothermic, except for CH/W. In principle, it could be said for the CH/W system that the obtained values in enthalpy and entropy are due mainly to disruption of water icebergs present around the hydrocarbon groups of this drug (one naphthyl and two methyl groups) and, on the other hand, to the creation of a cavity in the cyclohexane to accommodate the solute. Both events, as was already said, imply an energy intake and a disorder increase at the molecular level.

In the case of the ROH/W system, the enthalpy of transfer is negative and relatively low, whereas the entropy of transfer has a value comparable with the corresponding value for the CH/W system. These values could be explained in terms of a possible organization in the water-saturated octanol due to the replacement of an octanol molecule by a drug molecule. This replacement would be present in some centers conformed by two water molecules and six octanol molecules, inside the microheterogeneous structure of this water-saturated organic solvent.[4,26] The previous event releases energy and compensates the molecular disorder produced by the drug−organic solvent mixing process and the energy intake required in the aqueous media to separate the water molecules present around the nonpolar groups of NAP.

For the IPM/W and CLF/W systems, the negative enthalpies of transfer are relatively high compared with the ROH/W system, whereas the entropies of transfer (almost isentropic for CLF/W and negative for IPM/W) are very different from those obtained for CH/W and ROH/W systems. These results indicate a noncommon behavior of NAP in these organic media implying more ordered systems. Unfortunately, no information about the structural properties for these water-saturated organic solvents is available at the moment, and therefore, it is not possible to explain these interesting results at the molecular level.

On the other hand, in the case of liposomes, where the enthalpies and entropies of transfer were positive (Table 4), besides that previously described for the aqueous media in the CH/W system, because of the highly organized structure of phospholipidic bilayers, the energy requirement for separation of the lipid bilayers and/or disruption of the head groups packing (to accommodate the solute molecules) implies a relatively high

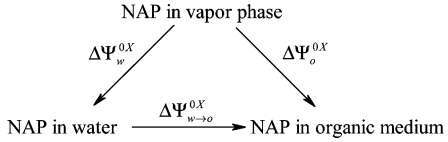


Figure 3. Transfer processes of NAP between water, an organic medium, and the vapor phase.

enthalpy of transfer. The same event implies a high increment in the entropy of the systems by the disorder generated inside the vesicle bilayers.

By comparing the values obtained for both thermodynamic properties, it follows that they are higher for DPPC liposomes (rigid state) than those for DMPC liposomes (fluid state). This result could be explained in terms of the lower flexibility of DPPC liposomes with respect to DMPC liposomes and, therefore, the higher energy requirements for accommodating the solute inside the DPPC vesicles. This behavior is similar to that presented by the liposome partitioning of any other drugs, such as sulfonamides,[17] benzocaine,[18] and KTP.[19]

Equations 12 and 13 were used to evaluate the respective contributions in absolute values by enthalpy and entropy toward the standard Gibbs energy of transfer and indeed to identify the dominant effect on transfer, that is, energy changes or molecular organization changes. These equations have been introduced by Perlovich et al.[37] studying the NAP solubility in several solvents, and they have been used previously to evaluate the partitioning behavior of some acetanilide derivatives[38] and KTP.[19] The respective contributions for all the partitioning systems evaluated are also presented in Table 4.

$$\%\ \zeta_H = 100\frac{|\Delta H_{w\rightarrow o}^{0X}|}{|\Delta H_{w\rightarrow o}^{0X}| + |T\Delta S_{w\rightarrow o}^{0X}|} \quad (12)$$

$$\%\ \zeta_{TS} = 100\frac{|T\Delta S_{w\rightarrow o}^{0X}|}{|\Delta H_{w\rightarrow o}^{0X}| + |T\Delta S_{w\rightarrow o}^{0X}|} \quad (13)$$

On the basis of data for % ζ_H and % ζ_{TS} from Table 4, it follows that transfer of NAP from water to organic systems is driven mainly by organizational changes, except for IPM/W and CLF/W. This result confirms that previously observed for the signs of entropies of transfer, which are positive in almost all cases, except for IPM/W, whereas the process is almost isentropic for CLF/W. Thus, the partitioning is only entropy driven for CH/W, DMPC/W, and DPPC/W, only enthalpy driven for IPM/W, and enthalpy and entropy driven for ROH/W and CLF/W. In the case of CLF/W, practically no contribution by entropy toward the transfer process is presented. The CH/W system has the higher entropy contribution toward transfer followed by liposomes and the ROH/W system. As has been already said, the dominant effect of entropy on the Gibbs free energy of transfer from water to ROH would be due to a disorder increase presented in the microheterogeneous structure of water-saturated octanol by the solute accommodation.[4,26]

Thermodynamics of Solvation for NAP. As was described previously,[19] according to Katz and Diamond,[39] the values of thermodynamic functions of partitioning, $\Delta G_{w\rightarrow o}^{0X}$, $\Delta H_{w\rightarrow o}^{0X}$, and $\Delta S_{w\rightarrow o}^{0X}$, depend both upon interactions between drug and water and upon interactions between drug and an organic medium. To obtain quantities that can be discussed solely in terms of drug−organic medium interactions, the contributions of drug−water must be removed. This can be accomplished by referring to hypothetical processes presented in Figure 3, in which Ψ^{0X} stands for any thermodynamic function whose change can be measured when one mole of NAP is transferred between water, an organic medium, and the vapor phase. The term $\Delta\Psi_w^{0X}$ represents the standard Gibbs energy, enthalpy, or entropy of solvation of NAP in water, and the term $\Delta\Psi_o^{0X}$ represents correspondingly the standard Gibbs energy, enthalpy, or entropy of solvation of NAP in the organic medium. From this scheme, the following equations can be stated

$$\Delta\Psi_{w\rightarrow o}^{0X} = \Psi_o^{0X} - \Psi_w^{0X} \quad (14)$$

$$\Delta\Psi_o^{0X} = \Psi_o^{0X} - \Psi_v^{0X} \quad (15)$$

$$\Delta\Psi_w^{0X} = \Psi_w^{0X} - \Psi_v^{0X} \quad (16)$$

where Ψ_v^{0X} is the respective thermodynamic value of the function in the vapor phase. The $\Delta\Psi_{w\rightarrow o}^{0X}$ values for NAP obtained from partitioning experiments are presented in Table 4. On the other hand, the $\Delta\Psi_w^{0X}$ values of solvation of this drug in water have been presented by Mora and Martínez,[40] which were obtained by using some aqueous solubility values and the thermodynamic quantities of sublimation presented by Perlovich et al.[37] From these values, the $\Delta\Psi_o^{0X}$ values were calculated by means of

$$\Delta\Psi_o^{0X} = \Delta\Psi_{w\rightarrow o}^{0X} + \Delta\Psi_w^{0X} \quad (17)$$

Table 5. Standard Gibbs Energy (ΔG_{solv}^0), Enthalpy (ΔH_{solv}^0), and Entropy for Solvation (ΔS_{solv}^0) of NAP in Water and Several Organic Systems and Relative Contributions of Enthalpy (% ζ_H) and Entropy (% ζ_{TS}) toward Solvation Processes at 303 K

system	ΔG_{solv}^0 kJ·mol^{-1}	ΔH_{solv}^0 kJ·mol^{-1}	ΔS_{solv}^0 J·mol^{-1}·K^{-1}	$T\Delta S_{solv}^0$ kJ·mol^{-1}	% ζ_H	% ζ_{TS}
W[a]	−24.0	−98.3	−245.2	−74.3	56.9	43.1
CH	−31.7	−92.1	−199.3	−60.4	60.4	39.6
ROH	−49.0	−106.9	−191.2	−57.9	64.9	35.1
IPM	−46.7	−124.5	−257.0	−77.9	61.5	38.5
CLF	−44.8	−118.9	−244.7	−74.1	61.6	38.4
DMPC	−59.7	−69.3	−31	−10	87.9	12.1
DPPC	−58.8	−63.6	−16	−5	93.0	7.0

[a] From Mora and Martínez.[40]

Table 5 shows the standard thermodynamic functions of solvation of this drug in all organic phases studied, including the respective contributions by enthalpy and entropy toward solvation in each medium (calculated by means of expressions analogous to eqs 12 and 13). In all cases, the ΔG_{solv}^{0X}, ΔH_{solv}^{0X}, and ΔS_{solv}^{0X} values are negative. These results indicate the preference of NAP by organic media with respect to its vapor phase and also indicate that all the solvation processes are enthalpy driven. Because ΔS_{solv}^{0X} is negative in all cases, there is a diminishing in the molecular randomness by passing of drug molecules from the vapor state to liquid or liposomal systems. According to % ζ_H and % ζ_{TS} values, the enthalpy is the main property contributing to the solvation process of NAP in all media, including the aqueous phase. This result is particularly relevant for the DPPC/W and DMPC/W systems.

Finally, to clarify and understand the specific interactions presented between NAP (and/or KTP) and DMPC or DPPC liposomes, it would be important to dispose information about UV, IR, and NMR spectral data and DSC calorimetry, among others. These instrumental techniques have been used in some studies about the partition of any other drugs in liposomal systems. Some properties of pharmaceutical compounds studied have been the interaction of propranolol with liposomes,[41] the

interaction of phenylbutazone in DMPC and DPPC liposomes,[42] and the interaction of paclitaxel with DPPC liposomes,[43] among several others.

Conclusions

From the previously exposed analyses, in general terms, it could be concluded that NAPs, as well as KTP, have mainly semipolar lipophilic behavior, although these drugs are not certainly hydrophobic compounds because their $K^X_{o/w}$ values in the CH/W system are the lowest among all systems tested. On the other hand, these drugs possess a greater affinity by liposomes with respect to all evaluated organic solvents, which in turn could be used in developing pharmaceutical dosage forms based on vesicles as drug carriers.

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