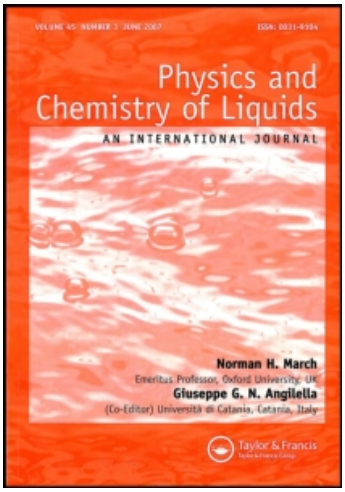

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Solution thermodynamics of naproxen in some volatile organic solvents

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Solution thermodynamics of naproxen in some volatile organic solvents

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The thermodynamic functions Gibbs energy, enthalpy and entropy for the solution processes of naproxen (NAP) in four volatile organic solvents were calculated from solubility values obtained at the temperature interval from 293.15 to 313.15 K. NAP solubility was determined in ethyl acetate, acetone, dichloromethane and acetonitrile, as pure solvents. The respective thermodynamic functions for mixing and solvation processes and the activity coefficients for the solute were also calculated. The NAP solubility decreases in the order, Acetone > AcOEt > DCM > AcNit. In addition, the thermodynamic quantities relative to the transfer process of this drug from cyclohexane to the organic solvents were also calculated in order to estimate the contributions due to hydrogen-bonding or other dipolar interactions. The results were discussed in terms of solute–solvent interactions.

Keywords: naproxen; solubility; transfer; solution thermodynamics; organic solvents

1. Introduction

Naproxen (NAP) is a non-steroidal anti-inflammatory drug. NAP has also analgesic and antipyretic actions without producing addiction [1]. This drug is widely used in current therapeutics and it is administered mainly by oral route as tablets, capsules and suspensions. On the other hand, this drug is also available as gel intended for topic use and injectable solution intended for intramuscular administration [2].

Recently, hydrophobic drugs delivery systems based on techniques of micro-encapsulation became a viable strategy. Microparticles systems are often prepared by emulsion techniques that include aqueous and organic phases; the drug solubility in each phase is an important value that needs to be determined for every microencapsulation study. Most of microencapsulation techniques of hydrophobic drugs employ volatile organic solvent to dissolve the matrix polymer and, if it is possible, the drug as well. Therefore, it is essential to determine the drug solubility in solvents, like ethyl acetate (AcOEt), acetone, dichloromethane (DCM) and acetonitrile (AcNit). The results of the solubility studies will form the basis of most considerations of choosing the appropriate microencapsulation technique [3].

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As a first stage towards a more thorough understanding of the molecular forces involved, the present work studied the thermodynamics of the solubility of NAP in four different volatile organic solvents used for microencapsulation processes. This research was made with the basic purpose to present more complete and systematic information about the properties of dissolution and transfer for this drug. The solubility at several temperatures was determined in AcOEt, acetone, DCM and AcNit, as pure solvents, and the respective dissolution thermodynamic analysis was made by using the van't Hoff and Gibbs equations. These four solvents were chosen because they act in solution mainly as Lewis bases in order to establish hydrogen bonds with several solutes, and on the other hand, because they are widely used in drug microencapsulation processes. Otherwise, by using the values reported for the NAP fusion and sublimation processes the contributions due to the mixing and solvation processes towards the overall dissolution were also analysed [4,5].

2. Experimental

2.1. *Materials*

Naproxen USP [6]; ethyl acetate A.R. (AcOEt) Merck; acetone A.R. Merck; dichloromethane A.R. (DCM) Merck; acetonitrile A.R. (AcNit) Merck; Millex®-13 mm filters, Millipore Corp.

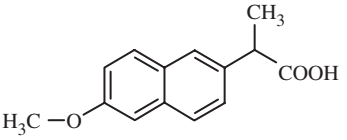
2.2. *Solubility determinations*

An excess of NAP was added to 20 cm^3 of each organic solvent evaluated in stoppered glass flasks. Solid–liquid mixtures were placed on a thermostatic mechanical shaker (Julabo SW23) kept at 313.15 ± 0.05 K at least three days to reach solution equilibrium (equilibrium time was established by quantifying the drug concentration up to obtain a constant value). Once at equilibrium, supernatant solutions were filtered (at isothermal conditions) to remove insoluble particles before composition analysis. Drug concentrations were determined by mass balance by weighing a specified quantity of the respective saturated solution and allowing the solvent evaporation up to constant mass. After the procedures already described the temperature was decreased by 5.0 K and therefore, it was stabilised at 308.15 K over at least 2 days allowing the precipitation of the drug dissolved in excess and quantifying the drug concentration in equilibrium. This procedure was repeated by decreasing the temperature in 5.0 K steps to reach 293.15 K. All experiments were made at least three times and averaged.

3. Results and discussion

The molecular structure of NAP and some of their physicochemical properties are summarised in Table 1. The melting point, the enthalpy of fusion and the enthalpy of sublimation were reported by Perlovich et al. [4]. This drug acts in solution mainly as a Lewis acid in order to establish hydrogen bonds with proton-acceptor functional groups in the solvents (oxygen in –O– or O=C< and nitrogen in NC–). On the other hand, NAP could also act as a proton-acceptor compound by means of its carbonyl, hydroxyl and methoxyl moieties [5].

Table 1. Some physicochemical properties of NAP.

Molecular structure[a]	M(g mol^{-1})[a]	ΔH_{fus} (kJ mol^{-1})[b]	T_{fus}(K)[b]
	230.26	31.5	427.6

Notes: [a]Ref. [7], [b]Ref. [4].

Table 2. NAP experimental solubility in four volatile organic solvents expressed in mole fraction and ideal solubility at several temperatures.

	Temperature				
Solvent	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
AcOEt	0.02370 (0.00005)	0.02633 (0.00012)	0.02958 (0.00006)	0.03234 (0.00003)	0.03620 (0.00015)
Acetone	0.0441 (0.0006)	0.0504 (0.0004)	0.0565 (0.0004)	0.0644 (0.0003)	0.0729 (0.0006)
DCM	0.01145 (0.00010)	0.01564 (0.00012)	0.01963 (0.00009)	0.02531 (0.00015)	0.03197 (0.00013)
AcNit	0.00491 (0.00002)	0.00642 (0.00003)	0.00829 (0.00008)	0.01051 (0.00001)	0.01286 (0.00007)
Ideal	0.03527	0.04098	0.04748	0.05489	0.06330

3.1. *Ideal and experimental solubility of NAP*

In a first approach, the ideal solubility of a crystalline solute in a liquid solvent can be calculated by Equation (1):

$$\ln X_2^{id} = -\frac{\Delta H_{fus}(T_{fus} - T)}{RT_{fus}T} + \left(\frac{\Delta S_{fus}}{R}\right)\left[\frac{(T_{fus} - T)}{T} + \ln\left(\frac{T}{T_{fus}}\right)\right], \quad (1)$$

where X_2^{id} is the ideal solubility of the solute in mole fraction, ΔH_{fus} and ΔS_{fus} are the molar enthalpy and entropy of fusion of the pure solute (at the melting point), T_{fus} is the absolute melting point, T is the absolute solution temperature and R is the gas constant [5].

Table 2 summarises the experimental solubilities of NAP, expressed in mole fraction, in addition to the ideal solubilities calculated by means of Equation (1) from ΔH_{fus}, and T_{fus} presented in Table 1. In almost all cases the coefficients of variation for experimental solubility were smaller than 1.0%.

It may be observed that the highest solubility value in mole fraction for NAP was obtained in AcOEt at 313.15 K, while the lowest value was found in AcNit at 293.15 K. On the other hand, at 303.15 K the order obtained was: Acetone > AcOEt > DCM > AcNit. However, no reports about solubility values

for this drug in these solvents are available, and therefore no direct comparison is possible. It is interesting to note that NAP solubility in acetone was greater than ideal solubility at all temperatures tested.

3.2. *Naproxen solubility analysis in terms of solubility parameters*

Although experimental solubility is a complex phenomenon, several equations have been proposed in order to explain this important physicochemical property of drugs. One of them was proposed by Hildebrand et al. [8] in terms of the solubility parameter, δ, which is defined as the root square of cohesive energy density, and it is calculated according to Equation (2):

$$\delta = \left(\frac{\Delta H_{\text{vap}} - RT}{V}\right), \tag{2}$$

where, ΔH_{vap} is the vapourisation enthalpy and V is the molar volume. Hildebrand solubility parameters were initially proposed for non-polar compounds interacting among them by dispersion forces (London forces); nevertheless, NAP and almost all the solvents investigated interact by London forces and also by other more energetic forces, namely, dipolar forces and hydrogen-bonding. In this context, Hansen split the general δ values in three partial parameters considering the respective contributions by dispersive forces δ_d, dipolar forces δ_p, and hydrogen-bonding δ_h [9]. These subparameters are related to total solubility parameter δ_T, according to:

$$\delta_T^2 = \delta_d^2 + \delta_p^2 + \delta_h^2. \tag{3}$$

The experimental determination of partial solubility parameters is not easy and therefore some calculus methods based on the contribution of groups have been described. The methods more used are those proposed by Fedors and van Krevelen [10]. In this context, Table 3 summarises the NAP solubility parameters reported by Aragon et al. [11], where it can be seen that the London forces are the most relevant for this compound, which could be attributed mainly to naphthyl and methyl moieties. Thus, based on the δ_T value (21.1 $MPa^{1/2}$), NAP could be considered as semipolar compound. On the other hand, according to Martin and Bustamante [12], the greatest drug solubility value should be found in solvents with similar δ values. For this reason, Table 3 also summarises the δ values for the organic solvents tested [10,13].

Table 3. Molar volume and partial and total solubility parameters at 298.15 K for NAP[a] and the solvents tested[b].

Compound	V($cm^3\,mol^{-1}$)	δ_d($MPa^{1/2}$)	δ_p($MPa^{1/2}$)	δ_h($MPa^{1/2}$)	δ_T($MPa^{1/2}$)
NAP	166.7	20.0	3.5	8.8	22.1
AcOEt	98.5	15.8	5.3	7.2	18.1
Acetone	74.0	15.5	10.4	7.0	20.0
DCM	63.9	18.2	6.3	6.1	20.3
AcNit	52.6	15.3	18.0	6.1	24.4

Notes: [a]Ref. [11], [b]Ref. [10].

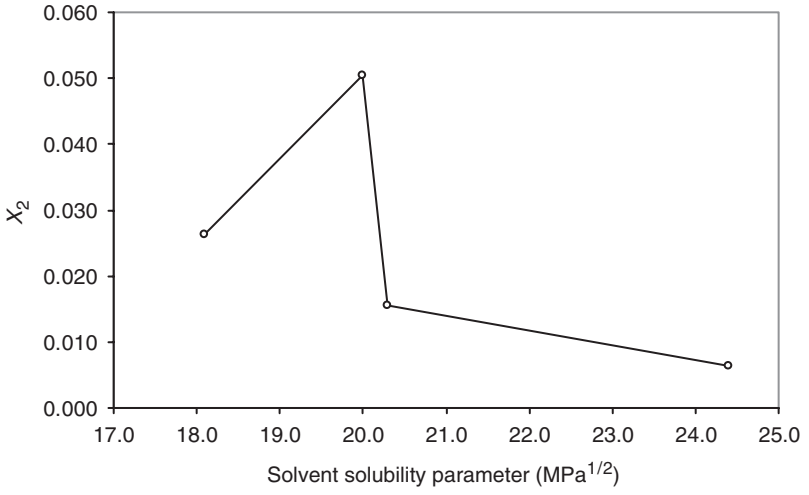


Figure 1. NAP equilibrium solubility as a function of Hildebrand solubility parameters of tested organic solvents.

Table 4. NAP activity coefficients in four volatile organic solvents at several temperatures.

	Temperature				
Solvent	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
AcOEt	1.49	1.56	1.61	1.70	1.75
Acetone	0.80	0.81	0.84	0.85	0.87
DCM	3.08	2.62	2.42	2.17	1.98
AcNit	7.18	6.39	5.73	5.22	4.92

Apparently, no similarity in all δ values is observed by comparing NAP in all the solvents tested (Table 3) when they are related to the equilibrium solubilities (Table 2). This fact demonstrates that the solubility of a certain drug compound is a more complex phenomenon than that exclusively described by solubility parameters and without considering other properties. In the same way, Figure 1 clearly shows that no simple relation between NAP equilibrium solubility and solvents δ values is found.

3.3. *NAP activity coefficients*

The solute activity coefficient in the solution (γ_2) is calculated as X_2^{id}/X_2 and is an indication of the deviation presented by NAP from its ideal behaviour [5]. Table 4 shows activity coefficients as a function of temperature. It is interesting to note that γ_2 values in acetone are lower than unit, in contrast with the other solvents, and these values increase for this solvent as the temperature increases. Otherwise, for DCM and AcNit γ_2 values diminish as the temperature increases indicating apparently more ideal behaviour with temperature rise, whereas the behaviour observed for AcOEt is opposite, although the main reason for these results is unclear.

From the γ_2 values presented in Table 4 an approximate estimation of solute–solvent intermolecular interactions can be made by considering the following expression:

$$\ln \gamma_2 = (w_{11} + w_{22} - 2w_{12}) \frac{V_2 \phi_1^2}{RT}, \tag{4}$$

where w_{11}, w_{22} and w_{12} represent the solvent–solvent, solute–solute and solvent–solute interaction energies, respectively; V_2 is the molar volume of the supercooled liquid solute, and finally, ϕ_1 is the volume fraction of the solvent. In a first approach the term $(V_2\phi_1^2/RT)$ may be considered approximately constant at the same temperature, and then γ_2 depends almost exclusively on w_{11}, w_{22} and w_{12} [14]. While the term w_{12} favours the solution process, both w_{11} and w_{22} terms are unfavourable for solubility. The contribution of w_{22} represents the work necessary to transfer drug molecules from the solid to the vapour state and, therefore, it is constant in all organic solvents.

Tested solvents are volatile and have low solubility parameters, which imply low w_{11} values, whereas w_{22} value is relatively large, based on ΔH_{fus} and T_{fus} values (Table 1). For these reasons, in order to obtain γ_2 values near to unit, large w_{12} values would be required for this solute in these solvents.

3.4. *Thermodynamic functions of solution*

According to van't Hoff analysis, the apparent standard enthalpy change of solution is obtained from the slope of $\ln X_2$ *versus* $1/T$ plot. Nevertheless, in recent thermodynamic treatments some modifications have been introduced in the van't Hoff equation in order to diminish the propagation of errors and consequently to separate the chemical effects from those due to statistical treatments used when enthalpy–entropy compensation plots are developed. For this reason, the mean harmonic temperature (T_{hm}) is used in the van't Hoff analysis. T_{hm} is calculated as $n/\sum_{i=1}^{n}(1/T_i)$, where n is the number of temperatures studied [15]. In the present case the T_{hm} value obtained is just 303 K. The modified expression more widely used is the following [16]:

$$\left(\frac{\partial \ln X_2}{\partial(1/T - 1/T_{\text{hm}})}\right)_P = -\frac{\Delta H_{\text{soln}}^{0\text{app}}}{R}. \tag{5}$$

The modified van't Hoff plot for NAP in all the solvents tested is presented in Figure 2. In general, linear regression models with good determination coefficients were obtained in all cases studied.

The apparent standard free energy change for the solution process ($\Delta G_{\text{soln}}^{0\text{app}}$), considering the approach proposed by Krug et al. [15] is calculated by means of:

$$\Delta G_{\text{soln}}^{0\text{app}} = -RT_{hm} \times \text{intercept} \tag{6}$$

in which, the intercept used is the one obtained in the analysis by treatment of $\ln X_2$ as a function of $1/T - 1/T_{\text{hm}}$. Finally, the standard entropic change for the

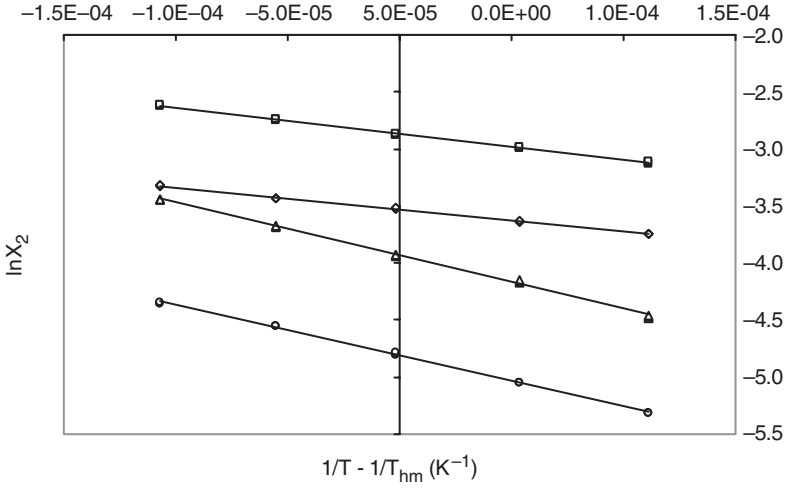


Figure 2. van't Hoff plot for NAP solubility in AcOEt (◇), Acetone (□), DCM (Δ), and AcNit (○).

Table 5. Apparent thermodynamic functions relative to solution process of NAP in four volatile organic solvents including ideal process at 303 K.

Solvent	ΔG^0_{soln} (kJ mol^{-1})	ΔH^0_{soln} (kJ mol^{-1})	ΔS^0_{soln} (J mol^{-1} K^{-1})	$T\Delta S^0_{soln}$ (kJ mol^{-1})	$\%\zeta_H$[a]	$\%\zeta_{TS}$[a]
AcOEt	8.89 (0.01)	16.1 (0.2)	23.7 (0.3)	7.17 (0.08)	69.1	30.9
Acetone	7.23 (0.01)	19.1 (0.3)	39.2 (0.5)	11.86 (0.16)	61.7	38.3
DCM	9.91 (0.01)	38.7 (0.5)	95.1 (1.2)	28.80 (0.35)	57.3	42.7
AcNit	12.12 (0.01)	37.0 (0.4)	82.0 (0.8)	24.84 (0.25)	59.8	40.2
Ideal	7.7	22.3	48.3	14.6	60.4	39.6

Notes: [a]$\%\zeta_H$ and $\%\zeta_{TS}$ are the relative contributions by enthalpy and entropy towards free energy of solution. These values were calculated by means of Equations (8) and (9), respectively.

solution process (ΔS^0_{soln}) is obtained from the respective ΔH^0_{soln} and ΔG^0_{soln} values by using:

$$\Delta S^0_{soln} = \frac{\left(\Delta H^0_{soln} - \Delta G^0_{soln}\right)}{T_{hm}}. \quad (7)$$

Table 5 summarises the apparent standard thermodynamic functions for the experimental solution process of NAP in all the organic solvents investigated, including those functions for the ideal process. In order to calculate the thermodynamic magnitudes of experimental solution some methods to calculate the propagation of errors were used [17]. It is found that the standard free energy of solution is positive in all cases; i.e. the solution process apparently is not spontaneous, which may be explained in terms of the concentration scale used (mole fraction), where the reference state is the ideal solution having the unit as concentration of NAP (the solid pure solute).

With the aim to compare the relative contributions by enthalpy ($\%\zeta_H$) and by entropy ($\%\zeta_{TS}$) towards the solution process, Equations (8) and (9) were employed, respectively [4]:

$$\%\zeta_H = 100\frac{\left|\Delta H^0_{\text{soln}}\right|}{\left|\Delta H^0_{\text{soln}}\right| + \left|T\Delta S^0_{\text{soln}}\right|}. \tag{8}$$

$$\%\zeta_{TS} = 100\frac{\left|T\Delta S^0_{\text{soln}}\right|}{\left|\Delta H^0_{\text{soln}}\right| + \left|T\Delta S^0_{\text{soln}}\right|}. \tag{9}$$

From Table 5 it follows that in all cases the solution enthalpy contributes in greater proportion to Gibbs energy of the NAP solution processes, than the solution entropy. It is interesting to note that enthalpy and entropy contributions for AcOEt and acetone are almost equal to those obtained for the ideal solution process.

3.5. *Thermodynamic functions of mixing*

The solution process may be represented by the following hypothetical stages [18]:

$$\text{Solute}_{(\text{Solid})} \rightarrow \text{Solute}_{(\text{Liquid})} \rightarrow \text{Solute}_{(\text{Solution})},$$

where the respective partial processes towards the drug dissolution are solute fusion and mixing at the same temperature (303 K), which permits calculation of the partial thermodynamic contributions to the overall solution process by means of Equations (10) and (11), respectively.

$$\Delta H^0_{\text{soln}} = \Delta H^{303}_{\text{fus}} + \Delta H^0_{\text{mix}}. \tag{10}$$

$$\Delta S^0_{\text{soln}} = \Delta S^{303}_{\text{fus}} + \Delta S^0_{\text{mix}}, \tag{11}$$

where $\Delta H^{303}_{\text{fus}}$ and $\Delta S^{303}_{\text{fus}}$ represent the thermodynamic functions of the fusion process at the harmonic temperature (303 K). Nevertheless, for practical purposes, $\Delta H^{0\text{id}}_{\text{soln}}$ and $\Delta S^{0\text{id}}_{\text{soln}}$ values (Table 5) were used instead of $\Delta H^{303}_{\text{fus}}$ and $\Delta S^{303}_{\text{fus}}$ as has been done previously in other researches [5,18,19]. In Table 6 the thermodynamic functions of mixing of NAP are summarised.

Table 6. Thermodynamic functions relative to mixing process of NAP in four volatile organic solvents at 303 K.

Solvent	ΔG^0_{mix} (kJ mol^{-1})	ΔH^0_{mix} (kJ mol^{-1})	ΔS^0_{mix} (J mol^{-1} K^{-1})	$T\Delta S^0_{\text{mix}}$ (kJ mol^{-1})	$\%\zeta_H$[a]	$\%\zeta_{TS}$[a]
AcOEt	1.21	−6.2	−24.6	−7.5	45.6	54.4
Acetone	−0.45	−3.2	−9.1	−2.8	53.7	46.3
DCM	2.23	16.4	46.8	14.2	53.7	46.3
AcNit	4.44	14.7	33.7	10.2	58.9	41.1

Notes: [a]$\%\zeta_H$ and $\%\zeta_{TS}$ are the relative contributions by enthalpy and entropy towards Free energy of mixing. These values were calculated by means of equations analogous to Equations (8) and (9), respectively.

The partial contributions by ideal solution (related to solute fusion process) and mixing processes to the enthalpy and entropy of drug solution, shows that ΔH^{0id}_{soln} and ΔS^{0id}_{soln} are positive (Table 5), while the contribution of the thermodynamic functions relative to the mixing process towards the solution process is variable, that is, ΔH^{0}_{mix} and ΔS^{0}_{mix} are positive for DCM and AcNit and negative for AcOEt and acetone. It can be concluded that the solution process of this drug in the former two solvents is mainly driven by the entropy of mixing, whereas for the last two solvents the process is driven by the enthalpy of mixing (based on the negative values presented in Table 6).

The net variation in ΔH^{0}_{mix} values results from the contribution of several kinds of interactions. The enthalpy of cavity formation (required for solute accommodation) is endothermic because energy must be supplied against the cohesive forces of the solvent. This process decreases solubility. On the other hand, the enthalpy of solute–solvent interaction is exothermic and results are mainly from van der Waals and Lewis acid–base interactions. On this way, the negative values obtained in enthalpy and entropy of mixing for NAP in AcOEt and acetone could indicate that the hydrogen bonds established between NAP and these solvents are so much greater than the solvent–solvent intermolecular interactions, which leads to energy release upon the mixing processes.

3.6. *Thermodynamic functions of solvation*

In addition to the hypothetic fusion-mixing stages previously exposed, the solution process may also be represented by the following hypothetic stages [18]:

$$\text{Solute}_{(\text{Solid})} \rightarrow \text{Solute}_{(\text{Vapor})} \rightarrow \text{Solute}_{(\text{Solution})},$$

where the respective partial processes towards the solution process are, in this case, sublimation and solvation. This treatment allows calculating the partial thermodynamic contributions to solution process by means of Equations (12) and (13), respectively, while the Gibbs energy of solvation is calculated by means of Equation (14):

$$\Delta H^{0}_{soln} = \Delta H^{0}_{subl} + \Delta H^{0}_{solv} \tag{12}$$

$$\Delta S^{0}_{soln} = \Delta S^{0}_{subl} + \Delta S^{0}_{solv} \tag{13}$$

$$\Delta G^{0}_{soln} = \Delta G^{0}_{subl} + \Delta G^{0}_{solv}, \tag{14}$$

where $\Delta H^{0}_{subl} = 128.3\,\text{kJ mol}^{-1}$ was taken from Perlovich et al. [4] and therefore, the function ΔH^{0}_{solv} was calculated from ΔH^{0}_{soln} values presented in Table 5. The respective Gibbs energy ($\Delta G^{0}_{subl} = 57.32\,\text{kJ mol}^{-1}$) and entropy of sublimation ($\Delta S^{0}_{subl} = 234.3\,\text{J mol}^{-1}\,\text{K}^{-1}$) at 303 K were taken from Mora and Martínez [5]. In Table 7 the thermodynamic functions of solvation are presented, while on the other hand, with the aim to compare the relative contributions by enthalpy ($\%\zeta_H$) and entropy ($\%\zeta_{TS}$) towards the solvation process, two equations analogous to Equations (8) and (9) were employed.

Table 7. Thermodynamic functions relative to solvation process of NAP in four volatile organic solvents at 303 K.

Solvent	ΔG^0_{solv} (kJ mol^{-1})	ΔH^0_{solv} (kJ mol^{-1})	ΔS^0_{solv} (J mol^{-1} K^{-1})	$T\Delta S^0_{solv}$ (kJ mol^{-1})	$\%\zeta_H$[a]	$\%\zeta_{TS}$[a]	$\%\varepsilon_H$[b]	$\%\varepsilon_S$[b]
AcOEt	−48.4	−112.2	−210.6	−63.8	63.7	36.3	58.5	78.8
Acetone	−50.1	−109.2	−195.1	−59.1	64.9	35.1	54.3	64.9
DCM	−47.4	−89.6	−139.2	−42.2	68.0	32.0	26.5	14.7
AcNit	−45.2	−91.3	−152.3	−46.1	66.4	33.6	29.0	26.5

Notes: [a]$\%\zeta_H$ and $\%\zeta_{TS}$ are the relative contributions by enthalpy and entropy towards free energy of solvation. These values were calculated by means of equations analogous to Equations (8) and (9), respectively.
[b]$\%\varepsilon_H$ and $\%\varepsilon_S$ are the relative ratio of specific and non-specific solute-solvent interactions expressed in terms of enthalpy and entropy. These values were calculated by means of Equations (15) and (16), respectively.

From the values of $\%\zeta_H$ and $\%\zeta_{TS}$ presented in Table 7 it follows that the main contributing force to standard Gibbs energy of the solvation process of NAP in all volatile solvents tested is the enthalpy ($\%\zeta_H$ are greater than 63%).

Because not only the main driving force of solvation process of drug compounds is important, but also the balance between specific and non-specific solute–solvent interactions as well, some parameters which describe the relative ratio of specific and non-specific solute–solvent interaction in terms of enthalpies ($\%\varepsilon_H$) and in terms of entropies ($\%\varepsilon_S$), were used according to the following definitions introduced by Perlovich et al. [4]:

$$\%\varepsilon_H = 100\left|\frac{\Delta H^0_{spec}}{\Delta H^0_{non\text{-}spec}}\right| \tag{15}$$

$$\%\varepsilon_S = 100\left|\frac{\Delta S^0_{spec}}{\Delta S^0_{non\text{-}spec}}\right|, \tag{16}$$

where $\Delta H^0_{spec} = \Delta H^0_{soln(W)} - \Delta H^0_{soln(CH)} = \Delta H^0_{soln(CH\rightarrow W)}$, $\Delta H^0_{(non\text{-}spec)} =$, $\Delta H^0_{soln(CH)} - \Delta H^0_{sub1} = \Delta H^0_{solv(CH)}$, $\Delta S^0_{spec} = \Delta S^0_{soln(W)} - \Delta S^0_{soln(CH)} = \Delta S^0_{soln(CH\rightarrow W)}$, and finally, $\Delta S^0_{(non\text{-}spec)} = \Delta S^0_{soln(CH)}$.

Cyclohexane (CH) was chosen as an 'inert' solvent, which interacts with drug molecules solely by non-specific interactions (dispersion forces), while the volatile solvents tested interact with NAP by specific interactions such as hydrogen bonding or other dipole–dipole forces. Solution thermodynamic quantities of NAP in cyclohexane at 303 K are $\Delta G^0_{soln(CH)} = 23.75$ kJ mol^{-1}, $\Delta H^0_{soln(CH)} = 57.5$ kJ mol^{-1} and $\Delta S^0_{soln(CH)} = 111.5$ kJ mol^{-1} [20].

The $\%\varepsilon_H$ and $\%\varepsilon_S$ values for NAP solvation are also presented in Table 7. These values indicate that during dissolution of NAP in all the solvents studied, the specific solute–solvent interactions (hydrogen bonding, mainly) affect the entropic term of Gibbs energy with respect to non-specific interactions, in particular in AcOEt and acetone ($\%\varepsilon_S > 64\%$), whereas this effect is less significant in DCM and AcNit ($\%\varepsilon_S < 27\%$). With regard to the enthalpic term the non-specific solute–solvent

interactions dominate in all solvents because it is lower than 59%. The results obtained in AcOEt and acetone, are similar in magnitude to those obtained for this drug in other organic solvents with different hydrogen bonding capability [20].

3.7. *Apparent thermodynamic functions of NAP transfer from cyclohexane to other organic solvents*

In order to contribute with the generation and systematisation of thermodynamic quantities of transfer, useful in QSAR studies and novel pharmaceutical dosage forms design, these values were calculated for the transfer of NAP from CH to the volatile organic solvents.

In Table 8 the Gibbs energy, enthalpy and entropy of transfer are shown including the respective $\%\zeta_H$ and $\%\zeta_{TS}$ values. The thermodynamic quantities were calculated as the difference between the solution functions in the organic solvents (Table 5) and those for CH presented in the literature [20]. According to Table 8, the transfer process of this drug from CH to all volatile organic solvents is spontaneous ($\Delta G^0_{CH\rightarrow org} < 0$) and driven by enthalpy ($\Delta H^0_{CH\rightarrow org} < 0$). On the other hand, the enthalpy is the main contributor to the transfer process in all cases ($\%\zeta_H > 60\%$), whereas for IPM and ROH the contributions are similar.

In the net drug transfer process between hydrocarbons and organic solvents with hydrogen-bonding capability as donors or acceptors or other dipole–dipole interactions, the enthalpic and entropic changes imply, respectively, the energetic requirements and the molecular randomness (increase or decrease in the molecular disorder). In general terms, the behaviour presented in each phase should be considered independently, before and after the transfer process.

Since hypothetically the solute is initially present only in the hydrocarbon phase, hence, the generation of a cavity in the dipolar organic medium in order to accommodate the solute after the transfer process is required. This is an endothermic phenomenon, since an energy supply is necessary to overcome the solvent–solvent interaction of dipolar organic solvent molecules. When the solute molecules are accommodated in the dipolar organic phase an amount of energy is released, mainly due to formation of hydrogen bonds (or other dipolar interactions) between the molecules of the drug and the solvent.

Table 8. Thermodynamic functions of NAP transfer from cyclohexane to four volatile organic solvents at 303 K[a].

Solvent	$\Delta G^0_{CH\rightarrow Org}$ (kJ mol^{-1})	$\Delta H^0_{CH\rightarrow Org}$ (kJ mol^{-1})	$\Delta S^0_{CH\rightarrow Org}$ (J mol^{-1} K^{-1})	$T\Delta S^0_{CH\rightarrow Org}$ (kJ mol^{-1})	$\%\zeta_H$[b]	$\%\zeta_{TS}$[b]
AcOEt	−14.86	−41.4	−87.8	−26.61	60.9	39.1
Acetone	−16.52	−38.4	−72.3	−21.92	63.7	36.3
DCM	−13.84	−18.8	−16.4	−4.98	79.0	21.0
AcNit	−11.63	−20.5	−29.5	−8.94	69.7	30.3

Notes: [a]These quantities were calculated as $\Delta\Psi^0_{1\rightarrow 2} = \Delta\Psi^0_{soln-(Organic)} - \Delta\Psi^0_{soln-(CH)}$, where Ψ is G, H or S.

[b]$\%\zeta_H$ and $\%\zeta_{TS}$ are the relative contributions by enthalpy and entropy towards Free energy of transfer. These values were calculated by means of equations analogous to Equations (8) and (9), respectively.

On the other hand, after a certain number of solute molecules have migrated from the hydrocarbon to the organic phase to reach the hypothetical equilibrium, the original cavities occupied by the drug in the hydrocarbon phase have been now occupied by CH molecules. This event produces an energy release due to CH–CH interactions. Thus, the negative enthalpy values of transfer obtained could be explained as the strong interactions due to hydrogen-bonding (or other dipolar interactions) among NAP and the dipolar solvents, which, on the other hand, diminishes the entropy by drug immobilisation inside these solvents.

From all topics discussed previously it can be concluded that the solution process of NAP in the volatile organic solvents studied is complex depending on the solvent nature. Thus, these solution processes are not adequately described in terms of Hildebrand or Hansen solubility parameters. Otherwise, large values for the solute–solvent interaction terms would be present in these solution processes because the drug activity coefficients are near to unit. On the other hand, the solution process of this drug in DCM and AcNit is mainly driven by the entropy of mixing, whereas, the process in AcOEt and acetone is driven by the enthalpy of mixing, although the main reasons for this behaviour are unclear. Finally, it can be said that the data presented in this report amply the physicochemical information about the equilibrium solubility for the extensively used anti-inflammatory drug.

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