J. Chem. Thermodynamics 178 (2023) 106955

Contents lists available at ScienceDirect

The Journal of Chemical Thermodynamics

journal homepage: www.journals.elsevier.com/the-journal-of-chemical-thermodynamics

On the diffusion of ketoprofen and ibuprofen in water: An experimental and theoretical approach

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ARTICLE INFO

Keywords:
Non-steroidal anti-inflammatory drugs
Diffusion coefficients
Taylor dispersion method
Molecular dynamics

ABSTRACT

In view of its importance for the development of dispersion and distribution models in the environment and also for the design of removal methods from wastewaters, the mobility and solute-solvent interaction in aqueous solutions of two non-steroidal anti-inflammatory drugs (ketoprofen and ibuprofen) were studied by measuring mutual diffusion coefficients of each pharmaceutical in water at infinitesimal concentration as a function of temperature, using the Taylor dispersion method. Intra-diffusion coefficients of the same solutes in water at the same temperature range were also calculated by Molecular Dynamics simulations. The analysis of the simulation trajectories allowed the study of the structure of the solvent molecules around the solute and their mutual interaction, which was also addressed by quantum mechanical (DFT) calculations. Ibuprofen presents a higher mutual diffusion coefficient in water than ketoprofen and molecular dynamics simulations are able to predict the experimental values for two solutes. Besides the solute molecular weight and molecular dimensions, the diffusion coefficients of these two pharmaceuticals are influenced by the solute-solvent interactions, which seem to be stronger in the case of ketoprofen. The solvation free energy obtained via DFT calculations confirms that hypothesis.

1. Introduction

Pharmaceuticals are probably the most important chemical substances in use in the everyday life. They contribute to the collective welfare of the population and have been the most responsible for the increase of the average life expectancy in the last century. There are thousands of pharmaceuticals available, belonging to hundreds of therapeutic categories. The consumption of pharmaceuticals has been growing steadily worldwide over the last decades, causing a significant growth of the market of these substances, whose total revenue raised from €3.63 × 10^8 in 2001 to €1.18 × 10^9 in 2020 [1,2].

The intensive and extensive use of pharmaceuticals also implies that huge amounts of these substances are everyday discharged into the wastewater systems, both in their parent form and in the form of metabolites produced by the organism. These discharges include those that are done by the final consumers (by natural excretion or bad management of the medicine leftovers) in an urban context, the effluents of the producers in industrial context and the disposal of veterinary pharmaceutical drugs in rural and periurban areas. Most of the wastewater treatment plants (WWTP) are designed to remove mainly the bulk pollutants, being the pharmaceuticals removed with wide variable efficiencies, ranging from 2 to 100 % depending on their chemical structure and the type of the treatment employed [3]. It means that a considerable number of pharmaceuticals discharged in the sewage systems are not efficiently removed by the WWTP, having the potential to contaminate the water receptor media [4].

Notwithstanding their proven beneficial effects, pharmaceutical drugs resulting from WWTP effluents can rapidly become harmful pollutants for aquatic fauna and flora as accidental xenobiotics and ultimately for human beings through bioaccumulation, which provides additional deleterious doses for the human body [5].

Following the disposal of any pollutant into the environment, it is important to know its fate and transport characteristics, as well as its distribution between all the environmental compartments. The recourse

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https://doi.org/10.1016/j.jct.2022.106955
Received 7 July 2022; Received in revised form 16 October 2022; Accepted 12 November 2022
Available online 17 November 2022

Table 1
Data for substances used in this work. Purities were provided by the suppliers.

Chemical Name	Source	Initial mole fraction purity	Purification method
Ketoprofen	Sigma-Aldrich	0.98	None
Ibuprofen	TCI	0.98	None
Acetaminophen	Cayman Chemical	0.98	None
1-propanol	Prolabo-VWR	0.998	None
Chemical Name	**Source**	**Final resistivity / MΩ.cm**	**Purification method**
Water	Distilled water	18.2	Filtration and ion exchange

of dispersion, transport and distribution models has become a very useful strategy and many different models have been proposed in the last decades, since the seminal work of MacKay and co-workers [6–8]. In the case of pharmaceutical drugs, the discharges are usually done on surface waters and the models designed to follow and predict their fate and dispersion have to take into account, not only the physical phenomena related to the dispersion (mass transport within the solution, sorption on soils, sediments, colloids and biota, evaporation from water or soil to air, etc), but also the chemical phenomena (photo-degradation, biodegradation and hydrolysis) that may transform the original compounds into new ones with different properties [3,9,10].

The development and the application of these models implies knowing some key physical and chemical properties of the substances involved, such as, for the physical phenomena, Henry's constant, sediment/water partition constant, octanol/water partition constant and the diffusion coefficient of the pharmaceutical both in bulk aqueous solution and in confined media inside sediments and colloids. Once obtained, the diffusion coefficient of pharmaceuticals in liquid media is thus an important input to predict their dispersion when discharged in surface natural waters.

On the other hand, the removal of this kind of pollutants very often requires the use of non-conventional treatment methods, which can be divided in three categories [11]: phase changing, advanced oxidation and biological treatment methods. In the case of the phase changing methods, the most used processes have been liquid-liquid extraction and especially sorption methods based on activated carbon and other porous materials such as biochar, nanomaterials or clay materials. In order to model and design such processes, some thermophysical parameters are needed for the molecules to be removed, including their mutual diffusion coefficients in water. This property is also essential for the design of drug delivery systems based on membrane pockets or gels/aerogels [12].

Ibuprofen and ketoprofen are nonsteroidal anti-inflammatory drugs with analgesic and antipyretic effects that have been widely used in clinical treatment, being ibuprofen one of the most consumed pharmaceuticals worldwide. They have quite similar chemical structures based on a phenyl propionic acid, being the group attached to phenyl radical the difference between them: a benzoyl group for ketoprofen and a *tert*-butyl group in the case of ibuprofen.

Both ketoprofen and ibuprofen have already been detected in effluents from WWTP [4], being two compounds whose environmental fate is worth to study and predict and to which some key physical properties (such as mutual diffusion coefficients in water) have to be rigorously known. In fact, in most cases, when this property is needed for the dispersion models, using estimations and correlations has been the most common strategy.

Chi *et al* [13] experimentally evaluated the rate of release of ketoprofen from a polaxamer-based gel, studying several process variables, such as the polymer and solvent (ethanol) concentration, the initial concentration of the drug, temperature and pH. The mutual diffusion coefficient of ketoprofen in the gel was obtained as a function of ethanol concentration.

A study of the adsorption of ketoprofen and ibuprofen inside ZnAl/biochar composite by three dimensional mass transport modeling, was done by Moreno-Pérez *et al* [14], which enable the authors to obtain surface diffusion coefficients on the composites. The aqueous mutual diffusion coefficients needed for the calculation were estimated using the Wilke and Chang correlation [15].

Also, Cao *et al* [16] developed a mathematical model to investigate the ibuprofen adsorption from pharmaceutical wastewater, in this case, into activated carbon and sonicated activated carbon. The diffusion coefficient of the solute in solution was one of the parameters evaluated and a series of tentative values (from 1×10^{-10} to 10×10^{-10} m^2/s) were considered.

On the other hand, Gao *et al* [17] have developed a diffusion-theory-based model from Noyes–Whitney equation to simulate the dissolution kinetics of ibuprofen in water. Since the application of such a model implies knowing mutual diffusion coefficient of ibuprofen in water, it was obtained recurring to six estimation methods.

Finally, Kashihara *et al* [18] succeeded in experimentally determining the intra-diffusion coefficient of ketoprofen and some radicalar products of its photo-degradation in methanol.

In this work, a twofold (both experimental and theoretical) approach to the study of mobility and solute-solvent interaction of ketoprofen and ibuprofen in water is attempted, by experimentally determining the mutual diffusion coefficient at infinitesimal concentration at three different temperatures and estimating this property by molecular dynamics simulations (via solute intra-diffusion coefficient calculation). Additional analysis of simulation trajectories from the structural point of view and DFT calculations allowed correlating the values of diffusion coefficients with fine details of the solute-solvent interaction.

2. Experimental section

2.1. Materials

Ketoprofen [(RS)-2-(3-benzoylphenyl) propanoic acid, 0.98 purity) and ibuprofen [(RS)-2-(4-(2-methylpropyl)phenyl) propanoic acid, 0.98 purity] were supplied by Sigma-Aldrich and TCI respectively and used as received. In both cases, a racemic mixture of the two enantiomers was used. Water was purified in a Millipore filtration and ion exchange system to a final resistivity of 18.2 MΩ.cm and boiled prior to use. Solutions were prepared by weight in stoppered glass bottles in order to incorporate the smallest possible amount of air. The details of the studied compounds are given in Table 1.

2.2. Experimental methods

The mutual diffusion coefficients of each solute in water were determined by the Taylor dispersion method [19] using differential refractometry as the detection means. In this method, a solution (a solute in a solvent) with a known concentration is set to flow, with a previously selected flow rate, through a long cylindrical tube helically wound around a metal cylinder. At one of the tube ends, a very small volume of a solution composed by the same solute and solvent but with a slightly different concentration (usually with a higher solute concentration) is injected by a six-port valve, producing a pulse of different concentration as similar as possible to a delta function, which is carried away by the flowing solution. As it travels through the tube, this pulse of different composition is gradually broadened by the combined action of the parabolic flow velocity profile and the diffusion, provided that the flow is laminar. At the other end of the tube, the detector measures the refractive index difference between the flowing solution after the introduction of the pulse and the initial solution, being the results recorded as a function of time.

The passage of the pulse through the detector produces a signal that, if represented over time, has a shape of a Gaussian curve, whose first two

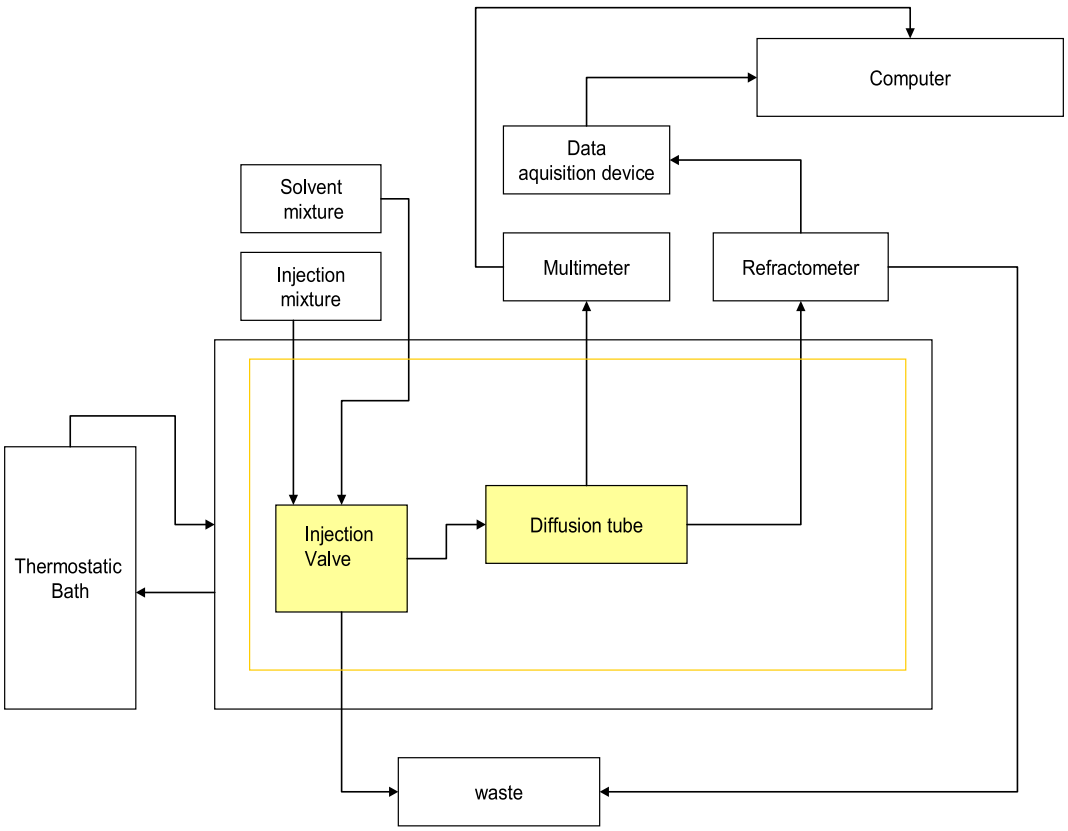


Figure 1. Flow scheme of the Taylor dispersion measuring apparatus.

Table 2
Dimensional parameters of the apparatus for the determination of mutual diffusion coefficients.

Parameter	Value
Tube winding radius (m)	0.11
Diffusion tube length (m)	13.216
Diffusion tube radius (m)	4.01×810^{-4}
Injection volume (m^3)	2.0×10^{-8}
Detector cell volume (m^3)	8×10^{-9}
Radius of the connection tube to detector (m)	1.14×10^{-4}

moments (retention time, $\bar{t}$, and variance, σ^2) are used to calculate the mutual diffusion coefficient. The procedure used in this work for the calculation of the mutual diffusion coefficient was based on the treatment of Alizadeh *et al* [20], through Eq. (1):

$$D_{12} = \frac{a_0^2}{24\bar{t}} \left\{ \frac{\left(1 + 4\frac{\sigma^2}{\bar{t}^2}\right)^{1/2} + 3}{\left(1 + 4\frac{\sigma^2}{\bar{t}^2}\right)^{1/2} + \frac{2\sigma^2}{\bar{t}^2} - 1} \right\} \left\{ \frac{1}{2} + \frac{1}{2}(1 - \delta_a)^{1/2} \right\} \tag{1}$$

where a_0 is the radius of the diffusion tube and δ_a is given by:

$$\delta_a = (768)^2 K \zeta_0 \tag{2}$$

where $K = 2.1701\ldots x10^{-5}$ and ζ_0 is given by:

$$\zeta_0 = \frac{2\sigma^2 - \bar{t}^2 + (\bar{t}^4 + 4\bar{t}^2\sigma^2)^{1/2}}{8\bar{t}^2 - 8\sigma^2} \tag{3}$$

Both the retention time and the variance obtained directly by the experience must be corrected to be used in the above equations. These corrections are due to the deviations between the real characteristics of the equipment and those considered ideal in the context of the Taylor dispersion method theory. The helicoidal arrangement of the diffusion tube (instead of linear), the finite volume of injection solution and the concentration monitor (instead of infinitesimal) and the existence of a tube segment connecting the diffusion tube and the detector cell constitute the main deviations from ideal arrangement.

The reference solute concentration ($C_{1,Ref}$) for which the mutual diffusion coefficient is determined is given by [20]:

$$C_{1,Ref} = C_{1,F} + \frac{N_1\left(\frac{5}{16} - \frac{1}{8\sqrt{\pi}}\right)}{\pi a_0^2 (2\zeta_0 \bar{t})^{1/2}} \tag{4}$$

where $C_{1,F}$ is the concentration of the solute in the flow solution and N_1 is the number of moles of the solute (1) in the sample in excess of those present in the same volume of the flowing stream. The reference concentration (in $moldm^{-3}$) was then converted to solute mole fraction ($x_{1,Ref}$). In the case of this work, $C_{1,F}$ used was zero for both solutes at all the temperatures.

A flow scheme of the measuring apparatus is shown in Figure 1 and its main dimensions and parameters presented in Table 2. As said above, the detector is a differential refractometer (Hitachi, L-2490) with a sensitivity of 2.5×10^{-10} RIU/V at full scale, whose analog tension signal is digitized by an analog-digital converter (National Instruments, USB-6210, 16-bit) prior his acquisition by a specific software. The diffusion tube and the injection valve were placed in a thermostatic bath, whose temperature is controlled by a circulating thermostat/cryostat (VWR, 1157P) and a PID controller (Hart Scientific, 2100) and measured by two platinum resistance probes through a 6 ½ digital multimeter (Keithley, 2000) in a four-wire arrangement (with a uncertainty of 0.01 K). The flowing solution is set to flow by an infusion pump (Harvard, 22) and the injection solution is inserted in the flowing stream via a six-port valve (Rheodyne, 7010, 20 μL).

The mutual diffusion coefficients were measured for ketoprofen and ibuprofen in water at infinitesimal concentration and three different

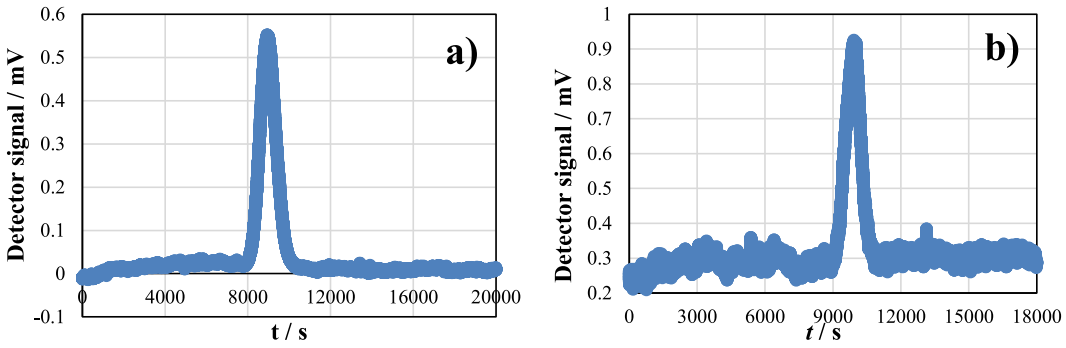


Figure 2. Typical response curves of the IR detector (signal *vs* time) for the systems (ketoprofen + water) (a) and (ibuprofen + water) (b).

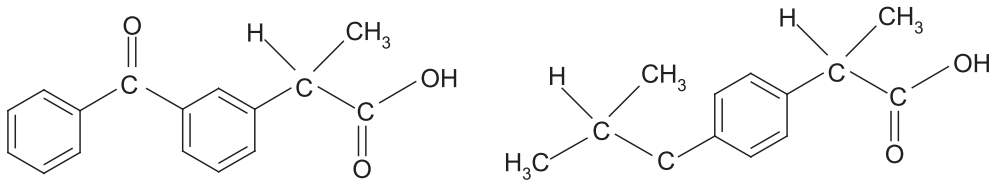


Figure 3. Molecular structures of ketoprofen (1) and ibuprofen (2).

Table 3
Water solubility (in mole fraction scale, x) of ibuprofen [26] and ketoprofen [27] at three different temperatures.

T/K	x (ketoprofen) × 10^5	x (ibuprofen) × 10^5
298.15	0.773	1.36
308.15	1.17	1.90
313.15	1.37	–
318.15	–	2.24

Table 4
Mutual diffusion coefficients (D_{12}) of 1-propanol (1) in liquid water (2) and their standard uncertainties (u) as a function of solute mole fraction at 298.15 K and p = *0.1 MPa* determined by the Taylor dispersion method [a,b,c]. $x_{1,ref}$ are the solute mole fractions at which the determinations have been done (solute reference mole fractions). This system were studied in order to test the experimental apparatus.

$x_{1,\ ref}$	$D_{12}.10^9$ (m^2/s)	$u(D_{12}).10^9$ (m^2/s)
2.1×10^{-5}	1.00	0.01
4.2×10^{-5}	1.00	0.02
1.0×10^{-4}	1.02	0.04
5.9×10^{-4}	1.04	0.01
1.2×10^{-3}	1.01	0.03
3.1×10^{-3}	0.99	0.01
5.2×10^{-3}	0.98	0.02
1.0×10^{-2}	0.88	0.03

[a] Standard uncertainty for temperature: u(T) = 0.01 K.
[b] Relative standard uncertainty for reference mole fractions: $u_r(x_{1,ref})$ = 0.01 %.
[c] Standard uncertainty for pressure: $u(p)$ = 2.5x10^{-3} MPa.

temperatures (298.15, 308.15 and 318.15 K). The first temperature was chosen for general comparison means, being the others chosen using two criteria: 1) should be higher than 298.15 K, otherwise unpredictable and undesired reductions of water solubility could occur; 2) three equally spaced temperatures constitute the minimal temperature set to estimate the diffusion activation energy in a limited temperature range. Given the very limited solubility of both pharmaceuticals in water, the flowing solution was always composed by pure solvent with no addition of any

Table 5
Mutual diffusion coefficients (D_{12}) of acetaminophen (1) in liquid water (2) and their standard uncertainties (u) as a function solute mole fraction at 298.15 K and p = *0.1 MPa* determined by the Taylor dispersion method [a,b,c]. $x_{1,ref}$ are the solute mole fractions at which the determinations have been done (solute reference mole fractions). This system were studied in order to test the experimental apparatus.

$x_{1,\ ref}$	$D_{12}.10^9$ (m^2/s)	$u(D_{12}).10^9$ (m^2/s)
5.7×10^{-7}	0.69	0.01
5.1×10^{-5}	0.67	0.03
1.0×10^{-4}	0.65	0.01
2.0×10^{-4}	0.68	0.04
5.0×10^{-4}	0.69	0.01
1.0×10^{-3}	0.64	0.04

[a] Standard uncertainty for temperature: u(T) = 0.01 K.
[b] Relative standard uncertainty for reference mole fractions: $u_r(x_{1,ref})$ = 0.02 %.
[c] Standard uncertainty for pressure: $u(p)$ = 2.5x10^{-3} MPa.

buffer solution. The solute mole fractions of injection solutions were 7.3 × 10^{-6} and 3 × 10^{-6} for ketoprofen and ibuprofen respectively, which has resulted in very low reference mole fractions (Table 4), allowing to be considered as infinitesimal concentrations. Each value of mutual diffusion coefficient reported (for each system and temperature) is the result of between 8 and 13 independent measurements. In Figure 2 typical response (unfitted) curves of the detector are shown, one for each solute. The chemical structures of both solutes are shown in Figure 3 and their water solubility (in the neutral form) at three different temperatures is presented in Table 3.

Prior to the experimental study here reported, the apparatus was tested by measuring mutual diffusion coefficients of 1-propanol in water in a dilute concentration range and at 298.15 K. The results deviate between 0.2 and 5 % from data obtained by Hao and Leaist [21] in a solute mole fraction range between 2 × 10^{-5} and 0.01. In much more limited mole fraction ranges, our results deviate 3 % from those by Harris *et al* [22], 2 % from those by Pratt and Wakeham [23] and 4 % from those obtained by Rehfeldt and Stichlmair [24]. The results are shown in Table 4. Furthermore, in the sequence of the ongoing project of our group on the mobility of pharmaceuticals in water, mutual diffusion

Table 6
Mutual diffusion coefficients (D_{12}) of ketoprofen or ibuprofen (1) in liquid water (2) and their standard uncertainties (u) at infinitesimal concentration as a function temperature (T) at $p = 0.1$ *MPa* determined by the Taylor dispersion method [a,b,c]. $x_{1,ref}$ are the solute mole fractions at which the determinations have been done (solute reference mole fractions).

ketoprofen (1) in water (2)			
T/K	$x_{1,\ ref}$	$D_{12}.10^9$ (m^2/s)	$u(D_{12}).10^9$ (m^2/s)
298.15	1.2×10^{-7}	0.44	0.03
308.15	1.4×10^{-7}	0.58	0.01
318.15	1.6×10^{-7}	0.71	0.04
ibuprofen (1) in water (2)			
T/K	$x_{1,\ ref}$	$D_{12}.10^9$ (m^2/s)	$u(D_{12}).10^9$ (m^2/s)
298.15	6.1×10^{-8}	0.50	0.02
308.15	6.4×10^{-8}	0.60	0.02
318.15	6.4×10^{-8}	0.76	0.03

[a] Standard uncertainty for temperature: $u(T) = 0.01$ K.
[b] Relative standard uncertainty for reference mole fractions: $u_r(x_{1,ref}) = 0.2$ %.
[c] Standard uncertainty for pressure: $u(p) = 2.5x10^{-3}$ MPa.

coefficients of acetaminophen in water, also in a dilute concentration range and 298.15 K, were obtained, which compares favorably with the results from Ribeiro *et al* [25] (deviations between 0.1 and 10 % in the 0–0.001 solute mole fraction range). The results, which will be object of a future publication, are shown in Table 5, in advance.

3. Simulation details

3.1. Models

The optimized potentials for liquid simulations all-atom (OPLS-AA) force-field [28] framework was used to model the solutes. This force-field models each atom as an interaction site and the potential energy is written as the sum of contributions due to bond stretching, bond angle bending, dihedral angle torsion and non-bonded interactions (van der Waals plus electrostatic interactions). Water was modelled by the TIP4P/2005 force field developed by Abascal and Vega [29], which is a four-center rigid model based on TIP4P from Jorgensen *et al.* [30]. The atomic charges of ketoprofen and ibuprofen were evaluated by quantum mechanical calculations at the MP2/aug-cc-pVTZ//B3LYP/6–31 + G(d, p) level of theory, with the partial charges obtained by the CHelpG procedure [31]. Similar theory level and basis sets has been shown to yield reliable partial charges for use with the OPLS-AA force field in previous studies [32]. All quantum calculations were performed using the Gaussian 16 package [33]. Geometry optimizations were performed without symmetry constrains, using the tight convergence criteria and an ultrafine grid was used for the integration of the electronic density.

Following the OPLS-AA parameterization, geometrical combining rules were used to compute the non-bonded Lennard-Jones interactions between sites of different types:

$$\varepsilon_{ij} = \sqrt{\varepsilon_{ii}\varepsilon_{jj}} \tag{5}$$

$$\sigma_{ij} = \sqrt{\sigma_{ii}\sigma_{jj}} \tag{6}$$

For non-bonded interactions between sites in the same molecule, only sites separated by three or more bonds are considered. Non-bonded interactions between sites separated by three bonds are scaled by a factor of 0.5. In this work, all bonds involving hydrogen were treated as rigid, with the respective length fixed at the equilibrium distance, and the LINCS [34] algorithm was used to constrain them.

3.2. Methods

Molecular Dynamics simulations were performed using the GROMACS package [35,36] (version 4.5.5), with systems of 5000 total molecules (one solute molecule and 4999 or 4998 water molecules), to which periodic boundary conditions were applied in three directions. The initial liquid box sizes were established according to the experimental densities. For each system, the following simulation protocol was applied: an initial *NpT* equilibration run of 4 ns followed by a 10 ns long *NpT* production run from which the density of the system could be calculated; then a 4 ns *NVT* equilibration run followed by a 20 ns *NVT* production run, whose trajectories were used to compute the intra-diffusion coefficients of solutes in water. Before doing the *NVT* simulations, the box volume was adjusted to the average value of the *NpT* production run. The equations of motion were solved using the leapfrog integration algorithm, with a time step of 1 fs and the positions, velocities and forces were stored every 1000 steps, except for the *NVT* production run, where they were stored every 500 steps. The temperature was controlled using the Nosé-Hoover thermostat [37,38] and pressure (in *NpT* ensembles) was controlled by the Parrinello-Rahman barostat [39,40], using coupling constants of 0.1 ps and 2.0 ps respectively for temperature and pressure and compressibilities of 4.673×10^{-5}, 4.444×10^{-5} and 4.418×10^{-5} bar^{-1} for 298.15, 308.15 and 318.15 K respectively. An initial velocity obtained from a Maxwell distribution at the desired initial temperature has been assigned to all atoms.

In all simulations a neighbor list, with a radius of 1.4 nm, was used and updated every 5 time steps. Both non-bonded Lennard-Jones and electrostatic potential were truncated by using cut-offs of 1.6 nm and 1.4 nm respectively and analytical tail corrections to dispersion terms were added both for energy and pressure calculation. The long-range electrostatic (coulombic) interactions beyond the cutoff were calculated using the particle-mesh Ewald method with a fourth-order spline interpolation and a Fourier grid spacing of 0.13 nm. Before the molecular dynamics runs, the boxes were subjected to energy minimization by the steepest descent method to a maximum force of 10 $kJmol^{-1}nm^{-1}$, with a maximum number of steps of 1×10^5.

For each state point and system, a total of 20 independent simulation sequences were performed, each one starting from a different initial configuration. The final value of intra-diffusion coefficient was calculated as the average of the 20 values obtained independently for each state point.

3.3. Calculations

The intra-diffusion coefficients of the solutes in water (D_1) were calculated from the linear part of the mean square displacement of the center of mass of the solute molecule according to the Einstein equation:

$$D_1 = \frac{1}{6N}\lim_{t\to\infty}\frac{d}{dt}\sum_{i=1}^{N}\left\langle\left[\vec{r}_i(t) - \vec{r}_i(0)\right]^2\right\rangle \tag{7}$$

where $\left[\vec{r}_i(t) - \vec{r}_i(0)\right]^2$ is the mean square displacement of the solute and the $\langle\rangle$ brackets stand for average over time.

In order to compare the simulated with experimental results, the known relationship between self-diffusion coefficients and mutual diffusion coefficients (Darken equation) should be taking into account:

$$D_{12} = \left(1 + \frac{\partial \ln\gamma_1}{\partial \ln x_1}\right)(x_2 D_1 + x_1 D_2) \tag{8}$$

where x_1, D_1 and x_2, D_2 are mole fraction and self-diffusion coefficients of the solute and the solvent respectively, and γ_1 is the activity coefficient of the solute. For the systems studied in this work, since the solutes are always at infinitesimal concentration, mutual diffusion coefficients of solute in the solvent are approximately equal to the self-diffusion coefficients of the solutes and these are considered to be equivalent to intra-diffusion coefficients.

Since the diffusion coefficient calculation depends on the box dimensions, simulations with a box volume doubled were carried out for both solutes and the diffusion coefficients obtained didn't differ appreciably from the original values.

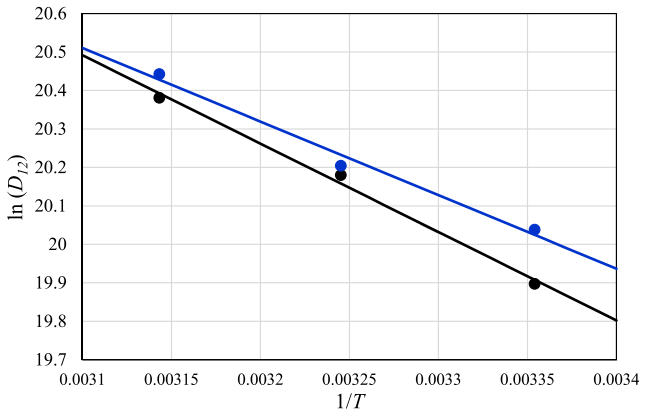


Figure 4. Natural logarithm of mutual diffusion coefficients of ketoprofen (black) or ibuprofen (blue) in water as a function of the inverse of the temperature, determined by the Taylor dispersion method. Symbols: experimental results; lines: Arrhenius law linear fitting.

Table 7
Estimated diffusion (E_D) activation energies and diffusion pre-exponential factor (A_D) of ketoprofen and ibuprofen in liquid water and their standard uncertainties (u) at infinitesimal concentration in the 298.15–318.15 K temperature range, at $p = 0.1$ MPa, determined from the results of diffusion coefficients experimentally obtained.

System	E_D / Jmol^{-1}	u (E_D) / Jmol^{-1}	A_D.10^7 / m^{2}s^{-1}	u (A_D).10^7 / m^{2}s^{-1}
ketoprofen in water	19,114	1511	10	6
ibuprofen in water	15,906	1929	3	2

Table 8
Estimated ratios of hydrodynamic and gyration radius (R_h) between ketoprofen and ibuprofen as solutes in water.

T/K	$\frac{R_h(ketoprofen)}{R_h(ketoprofen)}$	$\frac{R_g(ketoprofen)}{R_g(ketoprofen)}$
298.15	1.152	1.051
308.15	1.025	1.051
318.15	1.063	1.051

Both systems addressed in this work (ketoprofen and ibuprofen in water) have been studied by MD at infinitesimal concentration and at 298.15, 308.15 and 318.15 K. Since both solutes are weak acids, which means that in pure water they can be in neutral and also in deprotonated (ionized) form, we performed two series of simulations (for three temperatures studied), one using a solute molecule in the protonated (neutral) form and the other using its deprotonated or ionized (negative) form. The atomic charges of the deprotonated solutes have been calculated using the same quantum mechanical method at the same level of the theory as the neutral compounds.

4. Results and discussion

4.1. Experimental mutual diffusion coefficients

The experimental mutual diffusion coefficients of ketoprofen and ibuprofen in water at infinitesimal concentration as a function of temperature are presented in Table 6 and shown in Figure 4. In this figure, the representation of ln(D_{12}) *vs* $1/T$ suggests an Arrhenius-like behavior with respect to the temperature dependence of mutual diffusion coefficients, from which the diffusion activation energies for both systems were obtained and presented in Table 7 (along with pre-exponential factors).

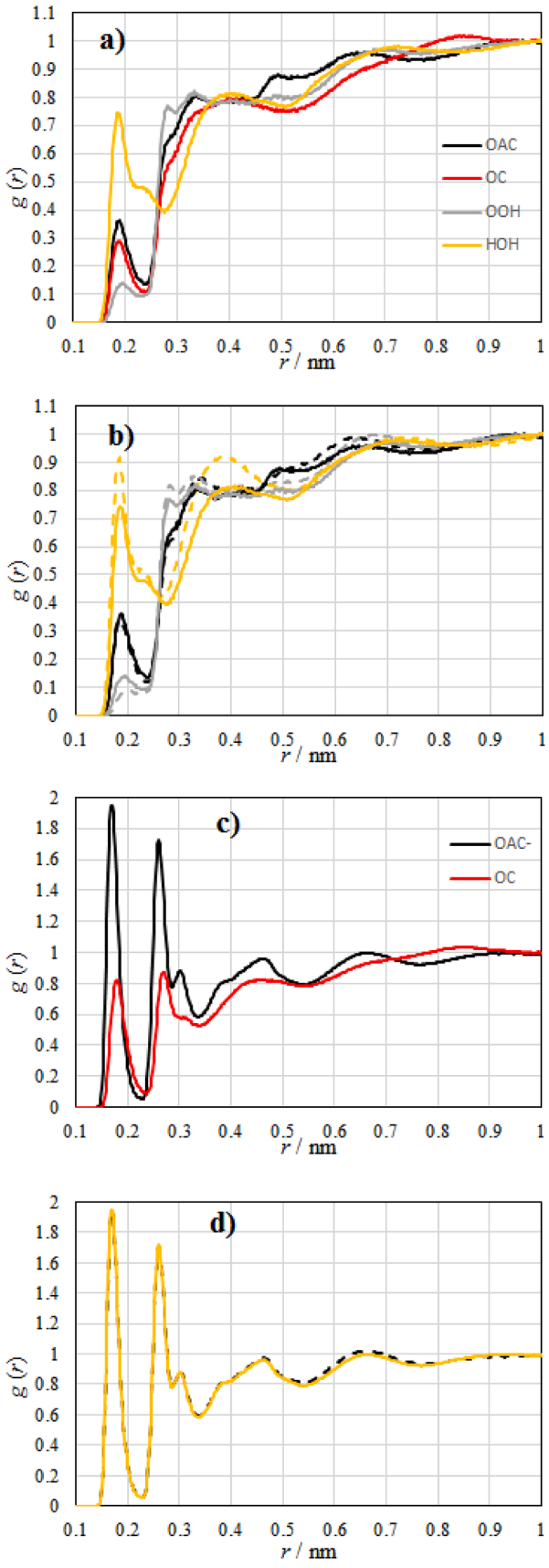
The mutual diffusion coefficients of ibuprofen in water are higher than those of ketoprofen at all the temperatures studied, following the inverse order of molecular weights and molecular dimensions. According to hydrodynamic theory, the diffusion coefficient of a large spherical solute 1 in a structureless solvent 2 at infinitesimal concentration can be estimated by the Stokes-Einstein equation:

$$D_{12}^0 = \frac{kT}{6\pi\eta_2 R_{h,1}} \tag{9}$$

where k is the Boltzmann constant, T is the temperature, η_2 is the solvent viscosity and $R_{h,1}$ is the hydrodynamic radius of the solute. If we apply this equation to our systems, where the solvent is for both the same (water), the ratio $\frac{D_{12}^0(ibuprofen)}{D_{12}^0(ketoprofen)}$ is equal to the ratio $\frac{R_h(ketoprofen)}{R_h(ibuprofen)}$ provided that the temperature is fixed. The estimated ratios of hydrodynamic radius between ketoprofen and ibuprofen for each temperature are presented in Table 8. Using simulation results (detailed in section 4.2), the gyration radius (R_g) of each solute was calculated, being the ratio (ketoprofen/ibuprofen) also presented in Table 8. As can be seen, the ratio of hydrodynamic radius is higher than the ratio of gyration radius for each temperature, except for 308.15 K. Usually, it is considered that the main difference between R_h and R_g for a solute in a solvent is the fact that the former includes the solvent coordination sphere around the solute and the latter is due to only the molecular dimensions of the solute. So we can conclude that ketoprofen tends to form a larger coordination sphere of solvent than ibuprofen, which may indicate a more intense solute–solvent interaction in the case of ketoprofen,

Table 9
Intra-diffusion coefficients (D_1) of ketoprofen or ibuprofen (1) in water (2) and their standard uncertainties (u) at infinitesimal concentration as a function temperature determined by molecular dynamics simulation using both neutral and ionized solute. Deviations from experimental diffusion coefficients are also presented [(D_{siuml} – D_{exp})/D_{exp}].

ketoprofen (1) in water (2)						
	neutral solute			*ionized solute*		
T/K	D_1.10^9 (m^2/s)	$u(D_1)$.10^9 (m^2/s)	$\frac{D_{simul} - D_{exp}}{D_{exp}} \times 100$	D_1.10^9 (m^2/s)	$u(D_1)$.10^9 (m^2/s)	$\frac{D_{simul} - D_{exp}}{D_{exp}} \times 100$
298.15	0.51	0.05	17	0.43	0.02	−0.72
308.15	0.58	0.06	−0.37	0.53	0.05	−9.4
318.15	0.83	0.07	16	0.78	0.05	9.8
ibuprofen (1) in water (2)						
	neutral solute			*ionized solute*		
T/K	D_1.10^9 (m^2/s)	$u(D_1)$.10^9 (m^2/s)	$\frac{D_{simul} - D_{exp}}{D_{exp}} \times 100$	D_1.10^9 (m^2/s)	$u(D_1)$.10^9 (m^2/s)	$\frac{D_{simul} - D_{exp}}{D_{exp}} \times 100$
298.15	0.50	0.04	−1.4	0.47	0.02	−6.8
308.15	0.67	0.05	12	0.59	0.03	−1.7
318.15	0.83	0.09	9.9	0.73	0.07	−2.8



(caption on next column)

Figure 5. Radial distribution functions of water (center of mass) around selected atoms from ketoprofen [a) and c)] and comparison with ibuprofen [b) and d), ibuprofen in dashed lines, ketoprofen in solid lines]. a) and b) is for neutral solutes; c) and d) for ionized species. Solute atom code: OAC: oxygen from carbonyl belonging to carboxyl group; OC: oxygen from carbonyl belonging to benzoyl group; OOH: oxygen from hydroxyl belonging to carboxyl group; HOH: hydrogen from hydroxyl belonging to carboxyl group; OAC-: oxygen for carboxylate in ionized solutes. In d), *rdf* water/OAC- for ketoprofen is shown in yellow; for the rest, the color code in the legends are valid.

Being both solutes essentially hydrophobic owing to the alkylic and/or aromatic moieties present in their structures, the carboxylic group (also present in both solutes), should allow a more direct interaction with the solvent by hydrogen bonding. In the case of ketoprofen, the carbonyl group can provide an additional way of interaction with water, restricting the solute mobility.

Both ketoprofen and ibuprofen are weak acids, which implies that, in pure water, they have to be partially dissociated. Using averages obtained by several literature values, we estimated that pK_a at 298.15 K is 4.305 [41] for ketoprofen and 4.419 for ibuprofen [41]. Considering the reference concentration of each solute for the diffusion coefficient determination, we conclude that, at 298.15 K, ketoprofen presents a dissociation degree (α) of 0.89 while ibuprofen presents a α value of 0.92, which means that: 1) both solutes are predominantly dissociated; 2) ibuprofen is more dissociated than ketoprofen. In principle, the ionized form of the solute is more prone to interact with water than the neutral one, following the solubility trends encountered for instance in carboxylic acids/carboxylate salts series, despite the fact that the ionized form of the solute has lost hydrogen bonding donor capacity. So, the higher dissociation degree presented by ibuprofen should enhance the interactions with water but it seems to be insufficient to overcome the effect of the extra carbonyl group of the ketoprofen molecule.

On the other hand, the diffusion activation energy for ketoprofen in water is larger than that of ibuprofen, revealing a higher mobility hindrance for the former and a greater need of thermal agitation to the diffusion process.

The value of the mutual diffusion coefficient of ibuprofen in water at 298.15 K obtained in this work is considerably different from that reported by Ye *et al* [42] (7.13×10^{-10} $m^2 s^{-1}$). However, that value was obtained for a saturated ibuprofen solution instead of infinitesimal concentration conditions. It seems logical to consider that, at a higher concentration, the dissociation degree of ibuprofen is lower (for a saturated solution we estimate a α value of 0.20 compared with 0.92 for our conditions) and, with the predominance of the neutral form of the solute, the overall mutual diffusion coefficient should be higher.

4.2. Simulation results

In order to elucidate some molecular/interaction aspects of these systems, molecular dynamics simulations of each solute studied (ketoprofen and ibuprofen) at infinitesimal concentration and for three temperatures (298.15, 308.15 and 318.15 K) were carried out. Given the weak acid character of the pharmaceuticals, both neutral and ionized species were studied as solutes in water.

Intra-diffusion coefficients of the solutes (neutral and deprotonated) in water for the temperatures studied are presented in Table 9. As stated above, these values are very close to the mutual diffusion coefficients, making the comparison between these two properties legitimate.

From the values of this table some conclusions can be drawn. First of all, the agreement between experimental and simulated results are remarkable for both solutes, especially considering the inherent difficulty to obtain transport properties by computer simulation. In general, the results for ionized solutes are closer to the experimental ones than those for neutral solutes, which agrees with the fact that, in such conditions, the solutes are predominantly dissociated and the model used seems to be sensitive to this structural detail. With some exceptions, the

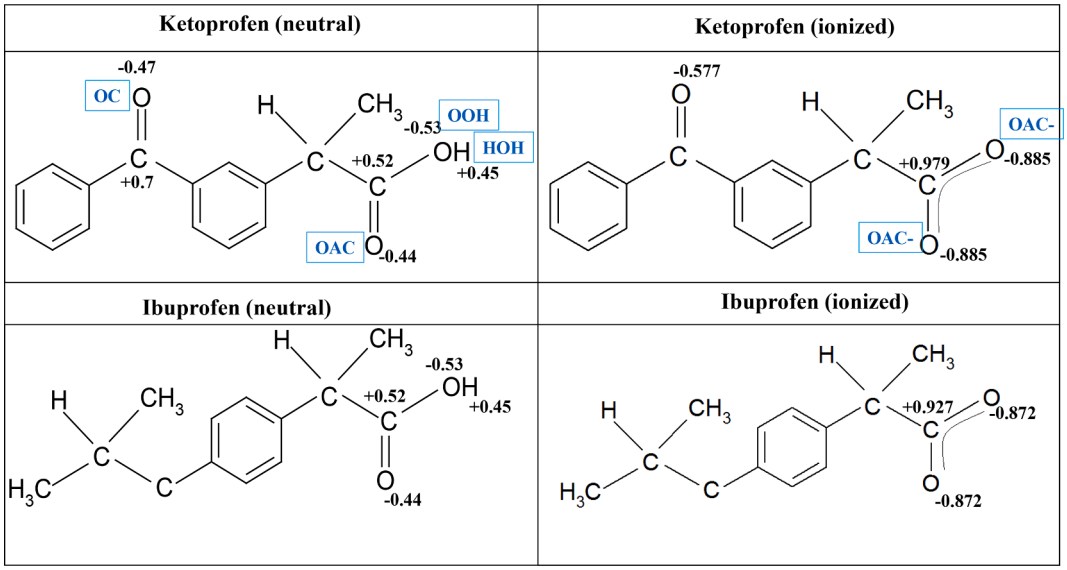


Figure 6. Atomic charges of some relevant atoms for ketoprofen and ibuprofen (both in neutral and ionized forms) used in the MD simulations.

simulation results also exhibit the tendency of ibuprofen presenting higher diffusion coefficients than ketoprofen.

From the production simulation trajectories, radial distribution functions (*RDF*) between the most relevant atoms from the solute and the center of mass of water were obtained at 298.15 K. The average values of five trajectories were used for the calculations and, in view of the anticipated affinities, *RDF* of water molecules around carbonyl oxygens [both belonging to benzoyl (OC) and to carboxyl (OAC) groups], oxygen (OOH) and hydrogen (HOH) from hydroxyl group and the oxygen atoms from carboxylate group (OAC-, for ionized forms) have been obtained.

The results of the calculation of radial distribution functions are presented in Figure 5 [a) and b) for neutral species and c) and d) for ionized ones] and, in Figure 6, atomic charges along with the codes of solute's relevant atoms are shown. As can be seen, the *RDF* for neutral and ionized solutes are quite different from each other. In the case of neutral solutes, the first peaks of all the interactions studied have intensities below 1, which can be explained by the fact that the solutes are hydrophobic as a whole and the local density of water around any point of the solute is below its bulk density. However, for both solutes, the most intense interaction seems to be that of water around hydrogen from hydroxyl group (the center of mass of water is very close to oxygen atom) and, for ketoprofen, the interaction between water and the carbonyl belonging to carboxyl group seems to be more intense than that between water and carbonyl from benzoyl group. For comparable groups, the peaks involving ketoprofen are more intense than those involving ibuprofen, even though the atomic charges are similar for both solutes (Figure 6), except for the interaction between water and hydroxyl hydrogen, which seems to indicate a stronger water-solute overall interaction in the case of the former compared to the latter.

The *RDF* for ionized solutes are more structured, all the peaks are more intense than for neutral species and the ones involving carboxylate oxygen atoms present maxima above 1. This can be explained by the fact that the atomic charges of the atoms involved had become more negative for the ionized species, including the oxygen from benzoyl group in ketoprofen (as can be seen in Figure 6). Moreover, we can see in Figure 5 d) that the first two peaks of water-carboxylate *RDF* are slightly more intense for ketoprofen than for ibuprofen in line with oxygen atomic charge difference.

Also from production simulation trajectories, the number of hydrogen bonds per group (carboxyl CO and OH and benzoyl carbonyl) between each solute and water has been obtained. For a hydrogen bonding scheme D-H….A (where A is an acceptor and D is a donor) a hydrogen bond is considered to occur when the atoms D and A are at a distance less than 0.35 nm and the angle between D-H and D…A are less than 30°.

The average numbers of hydrogen bonds per group/type between water and each solute as a function of temperature are shown in Figure 7. As can be seen, ketoprofen presents a higher average number of solute-water hydrogen bonds than ibuprofen both in neutral and ionized forms. This result can be explained in part by the fact that ketoprofen possesses an extra acceptor group (an isolated carbonyl group) in comparison with ibuprofen. However, it is interesting to note that the average number of hydrogen bonds involving the other (common) groups (and in the case of carboxyl OH, both acting as acceptor and donor) are in general higher for ketoprofen than for ibuprofen, being this trend more apparent for neutral solutes and despite de fact that it was the water-HOH *RDF* that was more intense for ibuprofen than ketoprofen. Thus, the simulated results seem to indicate a more intense solute-water interaction for ketoprofen in comparison with ibuprofen. That enhanced interaction can be viewed as an explanation for the less intrinsic mobility of ketoprofen in water.

The figure also shows that the number of hydrogen bonds involving the ionized forms of both solutes and water is more than double that those with the neutral forms, which can be explained by the extra lone electronic pair in the ionized solute molecule and the overall negative charge of the molecule with special incidence in oxygen atoms (Figure 6). Also as expected, in general, the total average number of hydrogen bonds between each solute and water decreases with the increasing temperature, which is explained by the interaction breaking effect of the thermal agitation. In some cases however, the differences are negligible and the number of hydrogen bonds is practically independent of temperature.

4.3. DFT results

From DFT combined with a continuum solvent model calculations, an estimation of the solvation free energy of each solute in water was obtained. The free energy of solvation was calculated as

$$\Delta G^{*}_{sol} = G_S - G_g \tag{10}$$

where G_s and G_g represent the free energy of the species calculated in solution and the gas phase respectively [43,44]. Geometry optimizations of the species were performed both for the gas and solvent phases by

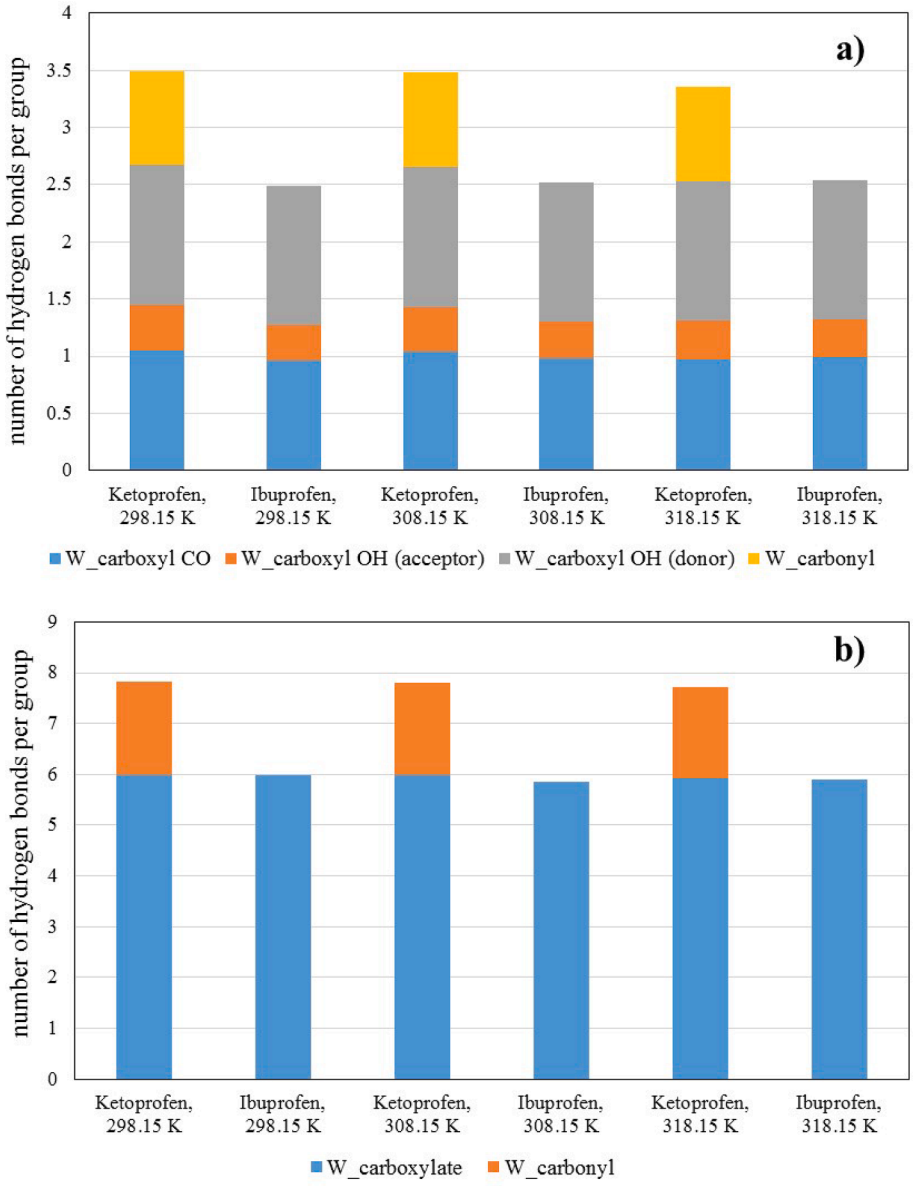


Figure 7. Average number of hydrogen bonds between each solute and water per acceptor/donor group for ketoprofen and ibuprofen at three different temperatures (results from MD simulations). a) neutral forms of the solutes; b) ionized forms of the solutes.

Table 10
Solvation energies of ketoprofen or ibuprofen in water obtained by DFT calculations.

Solute	Solvation free energy /kJmol^{-1}
Ketoprofen (neutral form)	−49.67
Ketoprofen (ionized form)	−280.72
Ibuprofen (neutral form)	−28.86
Ibuprofen (ionized form)	−275.95

using the hybrid *meta*-GGA exchange–correlation M06-2X [45] functional together with the aug-cc-pVDZ basis set in SMD solvation continuum [46], with the recommended solvation parameters for water and in the gas phase. The SMD, one of the most employed continuum solvent models, was developed to be applied to charged or neutral solutes and has been extensively used in the calculation of properties like solvation free energies, *LogP* and *pKa* [43,44,47,48,49]. The conjugation of the SMD solvation model with the M06-2X functional presented very good performance in previous studies [50–52], in particular for main group chemistry.

As for computer simulations, both neutral and ionized forms of solutes were considered and the results are presented in Table 10. Two main conclusions can be drawn from the table: as expected, the solvation free energy is much more negative for ionized species than for neutral ones, which can be easily explained by the additional affinity to water conferred by the negative charges on carboxylate a group. On the other hand, ketoprofen presents solvation free energies more negative than ibuprofen (both in neutral and ionized form), which corroborates the hypothesis of a more intense interaction between ketoprofen and water when compared to ibuprofen. The difference between the solutes is however more apparent for neutral forms than for ionized ones, since in the latter case, the carboxylate charge (common to both solutes) becomes so important that is able to almost supersede the other structural details.

5. Conclusions

Mutual diffusion coefficients of ketoprofen and ibuprofen in water

were experimentally measured at infinitesimal concentration and three different temperatures (298.15, 308.15 and 318.15 K) by Taylor dispersion method. Ibuprofen presents a higher mutual diffusion coefficient than ketoprofen in water, which cannot be completely explained by the difference in the molecular weights and molecular dimensions between the two pharmaceuticals. Intra-diffusion coefficients of the same solutes in water at the same temperature range were also obtained by Molecular Dynamics simulations. The agreement between experimental and simulated results of diffusion coefficients (at the studied conditions, intra-diffusion and mutual diffusion coefficients are comparable) are remarkable, especially if ionized forms of the drugs are considered in the simulations (taking into account that both ketoprofen and ibuprofen are weak acids). The analysis of the simulation trajectories allowed the study of the structure of the solvent molecules around the solute and their mutual interaction. The number of hydrogen bonds per molecule indicates a stronger solute-solvent interaction for ketoprofen in comparison with ibuprofen and this is confirmed by the results of the solvation free energy obtained by DFT calculations.

CRediT authorship contribution statement

Felisberto S. Mendes: Investigation, Data curation. **Carlos E.M. Cruz:** Investigation. **Rafaela N. Martins:** Methodology, Formal analysis, Writing – review & editing. **João P. Prates Ramalho:** Software, Writing – review & editing, Formal analysis, Validation. **Luís F.G. Martins:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Validation, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgements

The work was supported through the project UIDB/50006/2020 | UIDP/50006/2020, funded by FCT/MCTES through national funds. We acknowledge ICT (Évota pole) for providing computational facilities. FSM acknowledges to Instituto Camões the award of a scholarship.

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