Korean J. Chem. Eng., 34(5), 1435-1443 (2017)
DOI: 10.1007/s11814-017-0028-y

pISSN: 0256-1115
eISSN: 1975-7220

Solubility of celecoxib in N-methyl-2-pyrrolidone + water mixtures at various temperatures: Experimental data and thermodynamic analysis

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(*Received 22 November 2016 • accepted 6 February 2017*)

Abstract−Solubility is one of the most significant physicochemical properties of drugs, and improving the solubility of drugs is still a challenging subject in pharmaceutical sciences due to requirements of enhancing their bioavailability. Celecoxib, according to the biopharmaceutics classification system (BCS), is a class 2 drug, possessing low water solubility (<5 $\mu g \cdot mL^{-1}$) and high permeability. Increasing the solubility of this group can lead to improved bioavailability, dose reduction and subsequently, increased efficiency and reduced side effects. In this study, celecoxib solubility was determined in binary mixtures of N-methyl-2-pyrrolidone (NMP)+water at 293.2, 298.2, 303.2, 308.2 and 313.2 K. The solubility of celecoxib is increased with the addition of NMP to the aqueous solutions and reaches a maximum value in neat NMP. In addition, increased temperature leads to enhanced solubility of celecoxib in a given solvent composition. The solubility data of celecoxib in NMP+water at different temperatures were correlated using different mathematical models including, the Jouyban-Acree model and a combination of the Jouyban-Acree and van't Hoff models. Thermodynamic parameters, Gibbs energy, enthalpy and entropy of dissolution processes were performed based on Gibbs and van't Hoff equations. Thermodynamic analysis allowed observing two main entropy or enthalpy-driven dissolution mechanisms, varying according to the composition of aqueous mixtures. Moreover, preferential solvation of celecoxib by water is observed in water-rich mixtures but preferential solvation by NMP was seen in mixtures with similar composition and also in NMP-rich mixtures.

Keywords: Celecoxib, Solubility Profiles, Solubility Mathematical Model, Enthalpy-entropy Compensation, Thermodynamic Parameters

INTRODUCTION

Solubility plays a significant role in pharmaceutical sciences. Oral formulations are the most popular and preferred way of medicine intake. Due to very low aqueous solubility of approximately 40% of currently marketed compounds in pharmaceutical industry, solubility enhancement, utilizing divers methods, is one of the most challenging debates among pharmaceutical chemists [1,2]. Among the numerous approaches employed to enhance the solubility, cosolvency is one of the exceptionally effective methods. Solubility enhancement by solvent mixing is used for both pharmaceutically [3] or chemically [4] interested solute. The pharmaceutical cosolvents are used in the formulation of drugs including parenteral [5,6], oral and topical dosage forms [7,8]. In addition, solvent mixing can influence the mechanism of drug transportation from different drug formulations [9], crystal engineering [10] and extraction of drugs from different samples [11,12].

N-Methyl-2-pyrrolidone (NMP) is a slightly yellow, clear liquid with low volatility and low flammability. It is a powerful solvent for solubilizing chemicals and pharmaceuticals [13]. This solvent has low toxicity, orally and parenterally [14]. NMP improves drug solubility by simultaneously acting as a cosolvent and a complexing agent [15,16].

Celecoxib (Systematic IUPAC name: 4-[5-(4-Methylphenyl)-3-(trifluoromethyl)pyrazol-1-yl]benzenesulfonamide, CAS number: 169590-42-5, molar mass: 381.373 $g \cdot mol^{-1}$, Fig. 1), a white to pale yellow crystalline powder, is a cyclooxygenase (COX) inhibitor that shows comparative *in vitro* and *ex vivo* selectivity for COX-2 over COX-1. It is used to treat pain or inflammation caused by many conditions such as arthritis, ankylosing spondylitis, and menstrual pain, and juvenile rheumatoid arthritis in children who are at least 2 years old [17]. It is the first COX-2 particular inhibitor approved for use in osteoarthritis and rheumatoid arthritis [18]. According to biopharmaceutics classification system (BCS), celecoxib is a class

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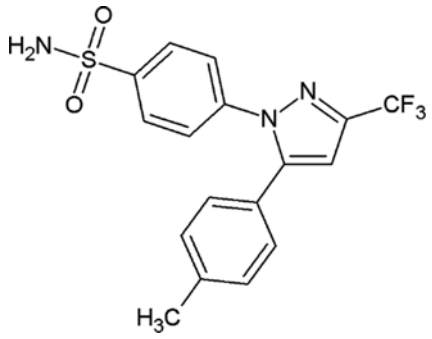

Fig. 1. Molecular structure of celecoxib.

2 drug (low water solubility (<5 μg·mL^{-1}) and high permeability). Increasing the solubility of this group can lead to increased bioavailability, dose reduction and, subsequently, increased efficiency and reduced side effects. The solubility of celecoxib in mixed solvents is not investigated systematically and the only reported paper dealing with the solubility of etoricoxib in a number of cosolvents+water at 298.2 K has been published by our group [19].

The cosolvency models presented from 1960 to 2007 were reviewed in an article and their accuracies for correlating and/or predicting the solubility of drugs in cosolvent+water mixtures were discussed [20]. The cosolvency models could be divided into theoretical [21-24], semi-empirical [25,26] and empirical [27,28] models. One of the most accurate cosolvency model in terms of its ability to describe the experimental solubility in mixed solvents at various temperatures, is the Jouyban-Acree model, which provides acceptable prediction to be used in pharmaceutical industry according to the computational results [29]. The accuracy of the model was checked in several different articles [30-32]. The model can predict the solubility in various solubility units and requires the experimental solubility of a solute in the mono-solvent systems. The proposed model enables the researchers to predict the solubility of drugs in solvent mixtures at various temperatures and reduces the number of required experimental data points [32].

The Jouyban-Acree model was derived from a thermodynamic mixing model that includes contributions from both two-body and three-body interactions [21]. The model was presented for solubility calculations in mixed solvents at various temperatures and was expressed as:

$$\log X_{m,T} = m_1 \log X_{1,T} + m_2 \log X_{2,T} + m_1 m_2 \sum_{i=0}^{2} \frac{J_i}{T} (m_1 - m_2)^i \quad (1)$$

where m_1 and m_2 are the fractions of solvents 1 and 2 in the absence of the solute, $X_{1,T}$ and $X_{2,T}$ are the solubilities of the solutes in the mono-solvents 1 and 2, T is temperature (Kelvin), and J_i are the constants of the model computed by a no intercept regression analysis [33]. Briefly, one could regress the numerical values of ($\log X_{m,T} - m_1 \log X_{1,T} - m_2 \log X_{2,T}$) against m_1m_2/T, $m_1m_2(m_1-m_2)/T$ and $m_1m_2(m_1-m_2)^2/T$ terms using an available statistical software like SPSS or Excel.

In addition, the solubility data in a given solvent composition at different temperatures could be correlated by the van't Hoff equation [34]:

$$\log X_T = A + \frac{B}{T} \quad (2)$$

where A and B are the constants of the model. The A and B terms could be calculated by employing only two solubility data of the solute for each solvent at two temperatures (e.g. the minimum and maximum temperatures). This equation is established for providing accurate predictions of a solute dissolved in a solvent at a limited temperature range [35].

Moreover, a combination of the Jouyban-Acree model and van't Hoff equation has been proposed to correlate the solubility of drugs in solvent mixtures at different temperatures [36] as:

$$\log X_{m,T} = m_1\left(A_1 + \frac{B_1}{T}\right) + m_2\left(A_2 + \frac{B_2}{T}\right) + m_1 m_2 \sum_{i=0}^{2} \frac{J_i}{T} (m_1 - m_2)^i \quad (3)$$

in which the constants of the model could be either replaced from the corresponding values from Eqs. (1) and (2) or computed from regressing of $\log X_{m,T}$ against m_1, m_1/T, m_2, m_2/T, m_1m_2/T, $m_1m_2(m_1-m_2)/T$ and $m_1m_2(m_1-m_2)^2/T$ using a no intercept least square analysis.

The main advantage of Eq. (3) over Eq. (1) is that it does not require any experimental data for predicting the solute solubility at other solvent compositions or temperatures whereas the solubility data in the mono-solvents at the temperatures of interest is required for Eq. (1).

MATERIAL AND METHODS

1. Materials

Celecoxib (0.990 mass fraction purity) was purchased from Arastoo pharmaceutical company (Tehran, Iran). NMP (0.995 mass fraction purity) was purchased from Scharlau (Spain). Distillated water was used for preparation of the solutions and ethanol (0.935 mass fraction) from Jahan Alcohol Teb (Arak, Iran) was used for dilution of the samples prior to spectrophotometric analysis.

2. Experimental Method

Binary NMP+water mixtures as mass fractions ranging from 0.00 to 1.00 with 0.10 intervals were prepared by mixing appropriate masses of the solvents. Various methods were reviewed for determination of the solubility of drugs in a recent work [37]. The solubility of celecoxib in binary mixtures was determined using the saturation shake-flask method of Higuchi and Connors [38]. Concisely, to ensure the saturation of the prepared solutions, excess amounts of celecoxib was added to the solvents and then were placed on a shaker (Behdad, Tehran, Iran), which was placed in an incubator equipped with a temperature-controlling system (uncertainty of 0.2 K, Kimia Idea Pardaz Azarbayjan (KIPA) Co., Tabriz, Iran).

A period of two days (48 h) was needed for saturation of solutions to achieve equilibrium at the deliberated temperature. The considered amount of solutions was filtered using hydrophilic Durapore filters (0.45 μm), then diluted by ethanol (96% v/v or 0.935 in mass fraction). The absorbance was recorded at 254.5 nm using a UV-Vis spectrophotometer (Biotech-Ultraspec 2000, England), and the molar concentrations of diluted solutions were calculated using UV absorbance calibration curves. Each solubility datum is an average of at least three independent measurements on different equilibrated samples. The relative standard deviation (RSD) of three re-

petitive trials was under 10% with the overall RSD of 5.5%. Densities of saturated solutions were determined using a 5 mL pycnometer, with the uncertainty of 0.001 g·cm^{-3}.

3. Computational Method

The solubility of celecoxib in binary solvent mixtures at different temperatures was mathematically represented by Eqs. (1) and (3), employing whole or minimum number of data points as training set. The constants of the models were calculated using regression analysis [33] and the mean percentage deviation (MPD) was calculated as an error criterion of different numerical analyses:

$$\mathrm{MPD} = \frac{100}{\mathrm{N}} \sum \left[\frac{\mathrm{X}_{m,T}^{calculated} - \mathrm{X}_{m,T}^{observed}}{\mathrm{X}_{m,T}^{observed}} \right] \quad (4)$$

where N is the number of data points in each set.

RESULTS AND DISCUSSION

1. Experimental Solubility

Celecoxib solubility was determined in binary mixtures of NMP+water at five different temperatures, the obtained experimental molar and mole fraction solubility data along with the density of saturated solutions are reported in Table 1. The minimum solubility of celecoxib, among the investigated solvent systems in this work is observed in neat water at 293.2 K. The solubility of celecoxib increases by increasing NMP fraction in the solvent mixtures and reaches a maximum value in neat NMP. In addition, increased temperature leads to enhanced solubility of celecoxib, as expected from past observations regarding the solubility of crystalline solutes. As a result, the maximum solubility of drug was observed at 313.2 K in neat NMP. This pattern for solubility of drugs in NMP+water mixtures was also observed for the solubility of clonazepam, diazepam, lamotrigine [39], acetaminophen [40], amiodarone HCl [35] and glibenclamide [41]. However, in a number of systems, maximum values were observed in the mixed solvent, as for phenobarbital at 0.90 of NMP [39] and pioglitazone HCl at 0.90 of NMP

Table 1. Celecoxib solubility in NMP+water mixtures at different temperatures (T), m_1 is mass fraction of NMP, $C_{m,T}$ is solubility in molar concentration unit, RSD is relative standard deviation, the mole fraction solubility ($X_{m,T}$) and ρ (g·cm^{-3}) is density of the saturated solutions

m_1	$C_{m,T}$	RSD	$X_{m,T}$	ρ
		293.2 K		
0.00	4.10×10^{-6}	5.2	7.36×10^{-8}	0.997
0.10	1.95×10^{-5}	6.1	5.10×10^{-7}	1.001
0.20	3.99×10^{-5}	3.2	1.35×10^{-6}	1.011
0.30	1.28×10^{-4}	7.9	5.35×10^{-6}	1.018
0.40	2.55×10^{-4}	7.4	1.25×10^{-5}	1.029
0.50	8.83×10^{-4}	7.1	5.01×10^{-5}	1.034
0.60	2.43×10^{-3}	8.2	1.55×10^{-4}	1.043
0.70	7.78×10^{-3}	3.8	5.57×10^{-4}	1.047
0.80	8.12×10^{-2}	5.2	6.57×10^{-3}	1.049
0.90	0.312	4.6	2.89×10^{-2}	1.075
1.00	0.563	9.1	5.93×10^{-2}	1.099
		298.2 K		
0.00	4.40×10^{-6}	3.1	8.01×10^{-8}	0.998
0.10	2.25×10^{-5}	9.1	5.88×10^{-7}	1.003
0.20	5.67×10^{-5}	9.3	1.92×10^{-6}	1.011
0.30	1.61×10^{-4}	10.4	6.68×10^{-6}	1.019
0.40	2.97×10^{-4}	3.4	1.46×10^{-5}	1.027
0.50	1.07×10^{-3}	2.1	6.08×10^{-5}	1.036
0.60	2.80×10^{-3}	2.7	1.79×10^{-4}	1.044
0.70	1.56×10^{-2}	4.4	1.12×10^{-3}	1.048
0.80	0.100	3.9	8.13×10^{-3}	1.054
0.90	0.366	1.2	3.42×10^{-2}	1.078
1.00	0.623	6.6	6.72×10^{-2}	1.095
		303.2 K		
0.00	5.00×10^{-6}	4.6	9.16×10^{-8}	0.999
0.10	2.97×10^{-5}	6.6	7.79×10^{-7}	1.001
0.20	6.77×10^{-5}	3.4	2.31×10^{-6}	1.008
0.30	2.18×10^{-4}	8.0	9.19×10^{-6}	1.007
0.40	4.20×10^{-4}	2.1	2.07×10^{-5}	1.026
0.50	1.44×10^{-3}	4.9	8.16×10^{-5}	1.034
0.60	3.97×10^{-3}	2.6	2.55×10^{-4}	1.040
0.70	2.11×10^{-2}	9.7	1.52×10^{-3}	1.045
0.80	0.135	7.0	1.11×10^{-2}	1.053
0.90	0.414	6.6	4.01×10^{-2}	1.061
1.00	0.709	6.8	7.76×10^{-2}	1.107
		308.2 K		
0.00	7.00×10^{-6}	9.0	1.27×10^{-7}	0.995
0.10	4.54×10^{-5}	2.7	1.19×10^{-6}	1.000
0.20	1.61×10^{-4}	7.3	5.51×10^{-6}	1.006
0.30	2.29×10^{-4}	7.6	9.56×10^{-6}	1.016
0.40	5.58×10^{-4}	7.2	2.76×10^{-5}	1.023
0.50	1.95×10^{-3}	4.6	1.11×10^{-4}	1.034
0.60	5.41×10^{-3}	9.0	3.48×10^{-4}	1.040
0.70	2.50×10^{-2}	8.1	1.80×10^{-3}	1.044
0.80	0.137	2.9	1.13×10^{-2}	1.052
0.90	0.425	2.5	4.04×10^{-2}	1.083
1.00	0.725	7.5	7.99×10^{-2}	1.104
		313.2 K		
0.00	7.90×10^{-6}	7.2	1.44×10^{-7}	0.998
0.10	5.19×10^{-5}	1.5	1.36×10^{-6}	1.000
0.20	2.01×10^{-4}	4.5	6.84×10^{-6}	1.007
0.30	3.51×10^{-4}	2.5	1.46×10^{-5}	1.016
0.40	7.81×10^{-4}	2.1	3.86×10^{-5}	1.023
0.50	2.48×10^{-3}	1.2	1.41×10^{-4}	1.034
0.60	6.50×10^{-3}	7.7	4.18×10^{-4}	1.041
0.70	3.09×10^{-2}	9.0	2.23×10^{-3}	1.046
0.80	0.172	4.9	1.42×10^{-2}	1.054
0.90	0.515	7.7	5.01×10^{-2}	1.084
1.00	0.812	4.5	9.17×10^{-2}	1.108

[42]. In separate reports the solubilities of drugs were investigated in some of NMP+water mixtures whereby increasing pattern was observed [16,44]; however, the studies did not report the NMP-rich areas, so it is not possible to detect the maximum solubility values in neat NMP or the binary mixtures. Another paper reported the solubility of terephthalic acid in NMP-rich area of NMP+water mixtures at various temperatures where the maximum solubility was observed in neat NMP [45].

2. Solubility Correlation

The generated solubility data points were correlated using various cosolvency models. The obtained models after including statistically significant constants are:

$$\log X_{m,T} = m_1 \log X_{1,T} + m_2 \log X_{2,T} - \frac{125.485 m_1 m_2}{T} - \frac{129.88 m_1 m_2 (m_1 - m_2)}{T} + \frac{1815.955 m_1 m_2 (m_1 - m_2)^2}{T} \quad (5)$$

and

$$\log X_{m,T} = m_1\left(3.566 - \frac{1417.796}{T}\right) + m_2\left(1.337 - \frac{2528.848}{T}\right) - \frac{128.962 m_1 m_2}{T} - \frac{154.198 m_1 m_2 (m_1 - m_2)}{T} + \frac{1807.264 m_1 m_2 (m_1 - m_2)^2}{T} \quad (6)$$

Eqs. (5) and (6) could be used to calculate the solubility of celecoxib in NMP+water mixtures at various temperatures and the obtained MPD values for these equations are 15.9 and 13.6, respectively. Careful examination of individual percentage deviations (IPDs) shows that the solubility data in NMP+water of m_1=0.7 at 293.2 K produced very high correlation errors (117 and 77%) using Eqs. (5) and (6). Such datum could be obtained due to any error in experimental determination procedure. One of the characteristics of a good cosolvency is its capability for detecting such data points. This data point is reported in this work as it was obtained from experimental findings to show the capability of the Jouyban-Acree model in detection of outliers which usually produces large IPD values. When the aforementioned data point was excluded from the computations, slightly modified model constants were obtained and the MPD values are reduced to 14.0 and 12.4%, respectively, for Eqs. (1) and (3).

Cosolvents enhance the solubility during different actions including, decreasing the polarity of the bulk solvents to a level that more closely reflects the polarity of nonpolar solute with the property of being less polar than water; increasing the aqueous solubility of poorly water soluble drugs by disordering the intermolecular hydrogen bonding networks that aqueous system includes; increasing the drug solubility according to the principle of "like dissolve like" by decreasing the polarity of the solvent and the formation of a situation with physicochemical properties more similar to the solute; the small nonpolar hydrocarbon area in the cosolvent can decrease the capability of the aqueous system to squeeze out nonpolar solutes [2,46].

Experimental solubility of celecoxib in binary solvent mixtures at different temperatures shows a non-linear profile (Fig. 2) with a maximum solubility in neat cosolvent. The well-established cosolvency model for solubility prediction is the log-linear model proposed by Yalkowsky [47]. However, it is not able to predict non-linear profile and maximum solubility in solvent mixtures (instead of neat solvent) with good accuracy. The main reason for these deviations from the log-linear model is that most of the assumptions made in the derivation of the log-linear model are not applicable to most solubility profiles in cosolvent+water mixtures. The Jouyban-Acree model combined with van't Hoff model could predict the non-linear solubility profile in solvent mixtures at different temperatures with good accuracy. The Jouyban-Acree model needs the solubility of solute in the mono-solvents at each temperature [48]. The required experimental solubility data in mono-solvents at each temperature could be considered as a limitation for these predictions, which could be solved by combining the Jouyban-Acree model with the van't Hoff equation, and predicting the

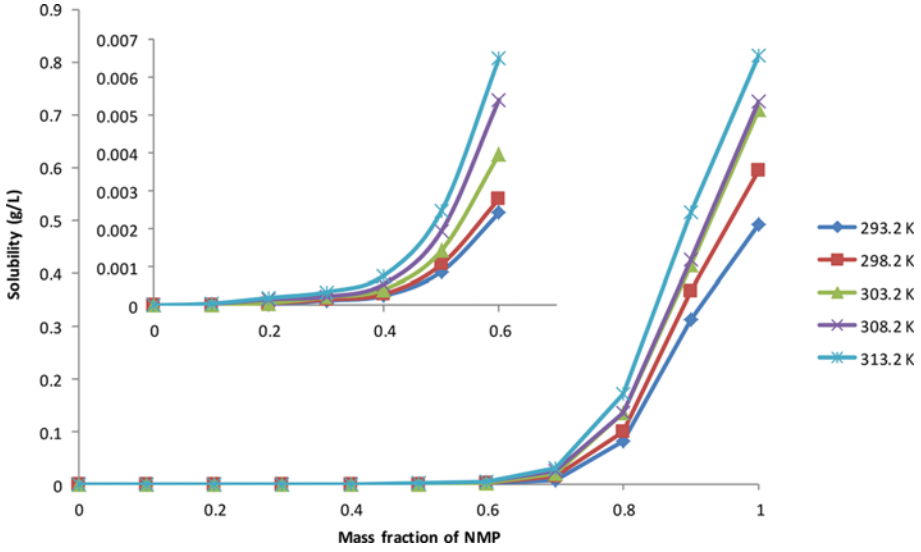

Fig. 2. Experimental solubility profile of celecoxib in binary solvent mixture of NMP+water at different temperatures.

solubility of celecoxib by van't Hoff model using solubility data only at 20 °C and 40 °C. The solubility prediction in solvent mixtures at different temperatures by employing only solubility data in mono-solvents at two temperatures (solubility data in minimum and maximum temperatures are used in this study); as a result, the advantage of this model is predicting solubility in solvent mixture by using less experimental data, and the mean percentage deviation is almost equal with the trained models using whole data points. The MPD for the predicted solubility of celecoxib dissolved in binary solvents at different temperatures using Eqs. (1) and (3) trained by a minimum number of data points are 20.0 and 21.0%, respectively. Although the MPD values are doubled, this is preferred in the pharmaceutical/chemical industries since the predictions are based on minimum experimental efforts.

3. Thermodynamic Quantities of Dissolution

The apparent standard enthalpy change of dissolution of celecoxib is obtained from Eq. (7) by using the mean harmonic temperature (T_{hm}=303.0 K) [49,50]:

$$\left(\frac{\partial \ln X_{m,T}}{\partial(1/T-1/T_{hm})}\right)_P = -\frac{\Delta_{soln}H^o}{R} \tag{7}$$

The apparent standard Gibbs energy change for the dissolution process ($\Delta_{soln}G^o$) of this drug is calculated at T_{hm} by means of [49,50]:

$$\Delta_{soln}G^o = -RT_{hm}\cdot\text{intercept} \tag{8}$$

in which the intercept used is the one obtained in the regression analysis of ln x_3 (Table 1) (as y-axis) as a function of $1/T-1/T_{hm}$ (as x-axis) for each cosolvent composition, when x-axis is equal to zero. Finally, the respective standard apparent entropic change for the dissolution process ($\Delta_{soln}S^o$) is calculated by using [49,50]:

$$\Delta_{soln}S^o = \frac{(\Delta_{soln}H^o - \Delta_{soln}G^o)}{T_{hm}} \tag{9}$$

Table 2 reports the apparent standard molar thermodynamic functions for dissolution of celecoxib (3) in all the NMP (1)+water (2) solvent mixtures and the neat solvents [12]. It is important to note that the following solubility values were not considered in van't Hoff regression analyses: m_1=0.20 and 0.30 at 308.2 K and m_1=0.70 at 293.2 K, because they deviate notoriously from the normal linear behavior.

As expected, the standard Gibbs energies of dissolution of this drug are positive in every case, as also are the standard enthalpies and entropies of dissolution (except $\Delta_{soln}S^o$ in neat water). Thus, the global dissolution processes are almost always endothermic and entropy-driven. The relative contributions by enthalpy (ζ_H) and entropy (ζ_{TS}) toward all the dissolution processes are given by the following equations [51]:

$$\zeta_H = \frac{|\Delta_{soln}H^o|}{|\Delta_{soln}H^o| + |T\Delta_{soln}H^o|} \tag{10}$$

$$\zeta_{TS} = \frac{|T\Delta_{soln}S^o|}{|\Delta_{soln}H^o| + |T\Delta_{soln}S^o|} \tag{11}$$

In all cases, the main contributor to the positive standard molar Gibbs energies of dissolution of this drug is the positive enthalpy (ζ_H>0.62), indicating the energetic predominance of celecoxib on the dissolution processes in all these aqueous mixtures.

4. Enthalpy-entropy Compensation Analysis

The pharmaceutical and chemical literature reports several cases where non-enthalpy-entropy compensation was observed when studying the solubility of some drugs in binary mixtures [52-54]. These analyses have been used to identify the mechanism of action of the dissolving cosolvent. Weighted plots of $\Delta_{soln}H^o$ vs. $\Delta_{soln}G^o$ at the harmonic mean temperature permit such an analysis. Thus, Fig. 3 shows that celecoxib presents a non-linear $\Delta_{soln}H^o$ vs. $\Delta_{soln}G^o$ trend with a negative but variable slope in compositions of mixtures $0.00<x_1$ (mole fraction of NMP in the absence of celecoxib) <0.20, whereas in other compositions ($0.20<x_1<1.00$) a positive slope is observed. Accordingly, in the former mixtures the driving mechanism is the entropy, probably due to hydrophobic hydration around the non-polar groups of this drug; whereas, in other mixtures the driving mechanism is the enthalpy, probably owing to better solvation of celecoxib by the NMP molecules, as aforementioned.

Table 2. Thermodynamic quantities relative to solution processes of celecoxib (3) in NMP (1)+water (2) mixtures at 303.0 K

m_1[a,b]	$\Delta_{soln}G^o$/kJ·mol^{-1}[b]	$\Delta_{soln}H^o$/kJ·mol^{-1}[b]	$\Delta_{soln}S^o$/J·mol^{-1}·K^{-1}[b]	$T\Delta_{soln}S^o$/kJ·mol^{-1}[b]	ζ_H	ζ_{TS}
0.00	40.6	27.4	−43.5	−13.2	0.675	0.325
0.10	35.3	40.8	18.0	5.5	0.882	0.118
0.20	32.2	61.2	95.8	29.0	0.678	0.322
0.30	29.3	39.1	32.4	9.8	0.800	0.200
0.40	27.1	44.0	55.6	16.8	0.723	0.277
0.50	23.7	40.7	56.1	17.0	0.705	0.295
0.60	20.9	40.3	64.3	19.5	0.674	0.326
0.70	16.5	34.9	60.6	18.4	0.655	0.345
0.80	11.6	28.7	56.2	17.0	0.627	0.373
0.90	8.2	19.4	36.8	11.1	0.635	0.365
1.00	6.6	16.0	31.1	9.4	0.629	0.371

[a] m_1 is the mass fraction of NMP (1) in the NMP (1)+water (2) mixtures free of celecoxib (3)

[b] Standard uncertainties are u(T)=0.10 K, u(p)=2.5 kPa, u(m_1)=0.0010. Average relative standard uncertainties in thermodynamic quantities are as follows: $u_r(\Delta_{soln}G^o)$=0.06 or 6.0%, $u_r(\Delta_{soln}H^o)$=0.09 or 9.0%, and $u_r(\Delta_{soln}S^o)$=0.12 or 12%

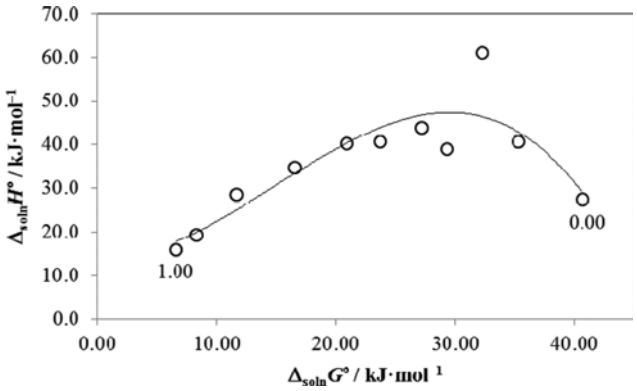

Fig. 3. $\Delta_{soln}H^o$ vs. $\Delta_{soln}G^o$ enthalpy-entropy compensation plot for dissolution process of celecoxib (3) in NMP (1)+water (2) mixtures at 303.0 K.

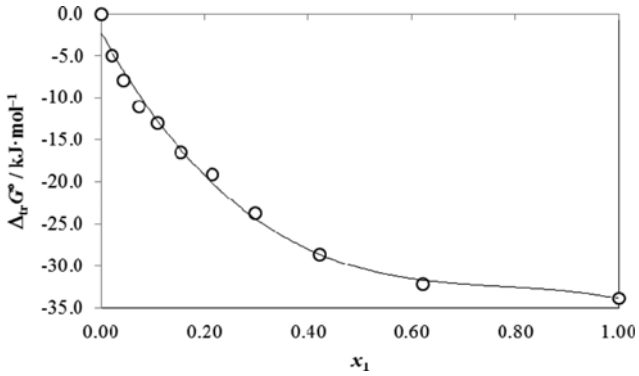

Fig. 4. Gibbs energy of transfer of celecoxib (3) from neat water (2) to NMP (1)+water (2) mixtures at 298.2 K.

5. Preferential Solvation

The preferential solvation parameter of celecoxib (compound 3) by NMP (compound 1) in NMP (1)+water (2) mixtures is defined as [55,56]:

$$\delta x_{1,3}=x^{L}_{1,3}-x_1=-\delta x_{2,3} \quad (12)$$

where $x^{L}_{1,3}$ is the local mole fraction of NMP (1) in the environment near to celecoxib (3). If $\delta x_{1,3}>0$ then the drug is preferentially solvated by NMP; however, if this parameter is <0, the drug is preferentially solvated by water. Values of $\delta x_{1,3}$ are obtainable from the inverse Kirkwood-Buff integrals for the individual solvent components analyzed in terms of some thermodynamic quantities as shown in the following equations [55,56]:

$$\delta x_{1,3}=\frac{x_1x_2(G_{1,3}-G_{2,3})}{x_1G_{1,3}+x_2G_{2,3}+V_{cor}} \quad (13)$$

With,

$$G_{1,3}=RT\kappa_T-V_3+x_2V_2D/Q \quad (14)$$

$$G_{2,3}=RT\kappa_T-V_3+x_1V_1D/Q \quad (15)$$

$$V_{cor}=2522.5(r_3+0.1363(x^{L}_{1,3}V_1+x^{L}_{2,3}V_2)^{1/3}-0.085)^3 \quad (16)$$

Here κ_T is the isothermal compressibility of the NMP (1)+water (2) solvent mixtures (in GPa^{-1}), V_1 and V_2 are the partial molar vol-

Table 3. Some properties associated to preferential solvation of celecoxib (3) in NMP (1)+water (2) mixtures at 298.15 K

x_1[a]	D/ kJ·mol^{-1}	Q/ kJ·mol^{-1}	RT κ_T/ cm^3·mol^{-1}	V_1/ cm^3·mol^{-1}	V_2/ cm^3·mol^{-1}	$G_{1,3}$/ cm^3·mol^{-1}	$G_{2,3}$/ cm^3·mol^{-1}	V_{cor}/ cm^3·mol^{-1}	100 $\delta x_{1,3}$
0.00	−109.84	2.479	1.133	89.90	18.09	−1034.5	−232.8	963	0.00
0.05	−96.56	2.263	1.153	90.89	18.07	−965.3	−426.7	964	−5.01
0.10	−84.16	2.252	1.173	91.77	18.00	−838.1	−575.7	1053	−5.24
0.15	−72.65	2.357	1.193	92.55	17.89	−701.3	−660.6	1213	−0.95
0.20	−62.03	2.513	1.214	93.25	17.74	−583.0	−693.1	1353	2.58
0.25	−52.29	2.670	1.234	93.85	17.56	−490.6	−692.1	1464	4.59
0.30	−43.43	2.800	1.254	94.38	17.37	−421.2	−671.7	1556	5.49
0.35	−35.46	2.887	1.274	94.82	17.15	−369.6	−640.3	1635	5.66
0.40	−28.38	2.925	1.295	95.20	16.92	−331.1	−602.1	1706	5.37
0.45	−22.17	2.919	1.315	95.52	16.69	−302.3	−559.1	1771	4.79
0.50	−16.86	2.881	1.335	95.78	16.46	−280.7	−512.8	1834	4.04
0.55	−12.43	2.826	1.355	95.98	16.23	−264.7	−464.7	1894	3.22
0.60	−8.88	2.769	1.375	96.14	16.01	−253.1	−417.6	1955	2.41
0.65	−6.22	2.725	1.396	96.26	15.82	−245.1	−375.4	2016	1.72
0.70	−4.45	2.704	1.416	96.35	15.64	−240.2	−343.4	2079	1.20
0.75	−3.56	2.710	1.436	96.40	15.49	−237.5	−327.3	2144	0.89
0.80	−3.55	2.737	1.456	96.44	15.38	−236.4	−332.5	2211	0.79
0.85	−4.43	2.769	1.476	96.45	15.31	−236.1	−363.6	2279	0.80
0.90	−6.19	2.773	1.497	96.46	15.29	−235.8	−426.3	2346	0.82
0.95	−8.84	2.699	1.517	96.45	15.32	−234.9	−532.6	2411	0.65
1.00	−12.38	2.479	1.537	96.45	15.40	−232.4	−713.9	2468	0.00

[a]x_1 is the mole fraction of NMP (1) in the NMP (1)+water (2) mixtures free of celecoxib (3)

umes of the solvents in the mixtures (in $cm^3 \cdot mol^{-1}$), similarly, V_3 is the partial molar volume of celecoxib (3) in these mixtures (in $cm^3 \cdot mol^{-1}$). The function D (Eq. (17)) is the derivative of the standard molar Gibbs energies of transfer of celecoxib (3) from neat water (1) to NMP (1)+water (2) mixtures with respect to the solvent composition (in $kJ \cdot mol^{-1}$, as also is RT). The function Q (Eq. (18)) involves the second derivative of the excess molar Gibbs energy of mixing of the two solvents (G^{Exc}_{1+2}) with respect to the water proportion in the mixtures (also in $kJ \cdot mol^{-1}$) [55,56]. V_{cor} is the correlation volume and r_3 is the molecular radius of the solute (in nm) calculated by means of Eq. (19) with N_{Av} as Avogadro's number.

$$D = \left(\frac{\partial \Delta_{tr} G^{o}_{3,\,2\rightarrow 1+2}}{\partial x_1}\right)_{T,\,p} \tag{17}$$

$$Q = RT + x_1 x_2 \left(\frac{\partial^2 G^{Exc}_{1+2}}{\partial x_2^2}\right)_{T,\,p} \tag{18}$$

$$r_3 = \left(\frac{3 \cdot 10^{21} V_3}{4\pi N_{Av}}\right)^{1/3} \tag{19}$$

Note that the definitive correlation volume requires iteration, because it depends on the local mole fractions. This iteration is done by replacing $\delta x_{1,3}$ in Eq. (12) to calculate $x^{L}_{1,3}$ until a non-variant value of V_{cor} is obtained.

Fig. 4 shows the Gibbs energy of transfer behavior of celecoxib (3) from neat water (2) to NMP (1)+water (2) mixtures at 298.15 K. These values were calculated from the mole fraction drug solubility data reported in Table 1 by using the following expression:

$$\Delta_{tr} G^{o}_{3,\,2\rightarrow 1+2} = RT \ln\left(\frac{x_{3,\,2}}{x_{3,\,1+2}}\right) \tag{20}$$

$\Delta_{tr} G^{o}_{3,2\rightarrow 1+2}$ values were correlated according to polynomial presented as Eq. (21), with r^2=0.9916.

$$\Delta_{tr} G^{o}_{3,2\rightarrow 1+2} = -2.28 - 109.84 x_1 + 137.23 x_1^2 - 59.00 x_1^3 \tag{21}$$

Thus, D values reported in Table 3 were calculated from the first derivative of the polynomial model, solved according to the composition of cosolvent mixtures. The values of Q were calculated from excess Gibbs energies which were in turn calculated at 298.15 K, as described by Marcus [57]. $RT\kappa_T$ values were calculated by assuming additive mixing with the reported κ_T values for NMP ($0.620\ GPa^{-1}$) and water ($0.457\ GPa^{-1}$) at 298.15 K [58]. In a similar way, the partial molar volumes of both solvents were calculated from reported excess molar volumes and density values of NMP (1)+water (2) mixtures at 298.15 K [57,59]. Moreover, molar volume of celecoxib (3) was calculated as $233.9\ cm^3 \cdot mol^{-1}$ by means of the Fedors' method as shown in Table 4 [60]. $G_{1,3}$ and $G_{2,3}$ values shown in Table 3 are negative in all cases, indicating that celecoxib exhibits affinity for both solvents in the mixtures. Solute radius value (r_3) was calculated as 0.453 nm. The correlation volume was iterated three times by using Eqs. (12), (13) and (16) to obtain the values reported in Table 3. This table also shows the preferential solvation parameters of celecoxib by NMP (1), $\delta x_{1,3}$.

Fig. 5 shows that the values of $\delta x_{1,3}$ vary non-linearly with the NMP proportion in the aqueous mixtures. Addition of NMP causes the $\delta x_{1,3}$ values of celecoxib from the pure water to be negative, up to x_1=0.16, reaching a minimum value in the mixture x_1=0.10 ($\delta x_{1,3} = -5.24 \times 10^{-2}$). Possibly the hydrophobic hydration around the non-polar groups of celecoxib contributes to lowering the net $\delta x_{1,3}$ to negative values in these water-rich mixtures [61,62].

Table 4. Application of the Fedors' method to estimate internal energy, molar volume, and Hildebrand solubility parameter of celecoxib (3)

Group	Group number	$\Delta U^o/kJ \cdot mol^{-1}$	$V/cm^3 \cdot mol^{-1}$
$-CH_3$	1	4.71	33.5
>C<	1	1.47	−19.2
=CH-	1	4.31	13.5
=C<	2	2×4.31=8.62	2×−5.5=−11.0
Phenylene	2	2×31.90=63.80	2×52.4=104.8
$-NH_2$	1	12.60	19.2
-N<	1	4.20	−9.0
-N=	1	11.70	5.0
$-SO_2-$	1	25.55	19.5
-F (trisubstituted)	3	3×2.30=6.90	3×22.0=66.0
Ring closure-5	1	1.05	16.0
Conjugate bond	2	2×1.67=3.34	2×−2.2=−4.4
		$\Sigma\ \Delta U^o$=148.25	Σ V=233.9
			$\delta_3=(148{,}250/233.9)^{1/2}=25.2\ MPa^{1/2}$

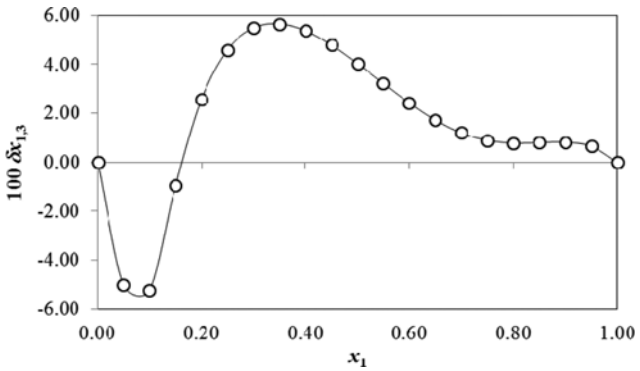

Fig. 5. $\delta x_{1,3}$ values of celecoxib (3) in NMP (1)+water (2) mixtures at 298.2 K.

In the mixtures with composition $0.16<x_1<1.00$, the $\delta x_{1,3}$ values are positive, indicating preferential solvation of celecoxib by NMP. In this way, the cosolvent action to increase the celecoxib solubility may be related to the breaking of the ordered structure of water (hydrogen bonds) around the non-polar moieties of the solute, as was already mentioned, which increases the solvation of celecoxib and exhibits a maximum value in x_1=0.35 ($\delta x_{1,3} = 5.66 \times 10^{-2}$). It is conjecturable that in $0.16<x_1<1.00$ region celecoxib is acting as Lewis acid with NMP molecules because this cosolvent is more basic than water, as described by their respective Kamlet-Taft hydrogen bond acceptor parameters, i.e. β=0.77 for NMP and 0.47 for water [58].

CONCLUSION

The solubility profile of celecoxib in NMP+water mixtures shows

a nonlinear pattern with maximum solubility in neat NMP. Cosolvency method with increasing temperature leads to a significant solubility enhancement of celecoxib. Two cosolvency models, Jouyban-Acree model and the combination of this model with van't Hoff equation, were applied to correlate solubility data of celecoxib in binary solvent mixtures and to measure significance parameters with a reasonable accuracy. The models also provided reasonably accurate predictions after training by a minimum number of experimental data points. Thermodynamic analysis shows two main entropy or enthalpy driven dissolution mechanisms according to the composition of mixtures. Finally, preferential solvation of celecoxib by water is observed in water-rich mixtures but preferential solvation by NMP can be spotted in mixtures with similar composition and in NMP-rich mixtures.

ACKNOWLEDGEMENTS

This report is a part of the results of S. Nozohouri's Pharm.D. thesis submitted to the Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran.

DISCLOSURE STATEMENT

No potential conflict of interest was reported by the author.

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