

Solubility and Dissolution Thermodynamic Data of Mefenamic Acid Crystals in Different Classes of Organic Solvents

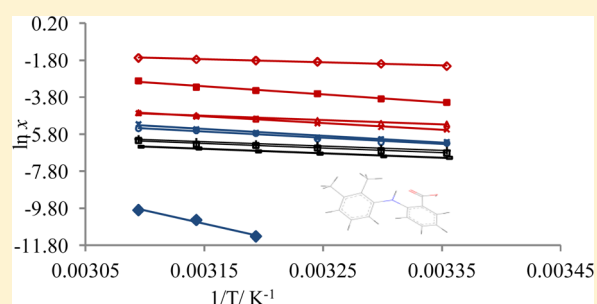
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ABSTRACT: Different classes of solvents provide different polarity values, which influence the solubility of pharmaceutical solids. In this article, the solubility of mefenamic acid in different classes of organic solvents, including polar protic, dipolar aprotic, and apolar aprotics at a range of temperatures from (298 to 323) K are reported. It has been found that mefenamic acid shows high solubility in dipolar aprotic solvents (*N,N*-dimethylacetamide, *N,N*-dimethylformamide, ethyl acetate, and propanone), moderate solubility in polar protic solvents (ethanol and propan-2-ol), and poor solubility in apolar aprotic solvents (hexane, heptane, and cyclohexane) and water.



INTRODUCTION

2-[(2,3-Dimethylphenyl)amino]benzoic acid ($C_{15}H_{15}NO_2$, mefenamic acid) is a widely used nonsteroidal anti-inflammatory and analgesic agent for the treatment of pain caused by menstrual disorders.^{1,2} The compound has been known to exist in two polymorphic forms: Form I and Form II.^{1–5} An additional polymorph, Form III, has recently been reported.⁶ Form I is relatively stable at ambient conditions as compared to Forms II and III. The order of stability is $I > II > III$ at ambient conditions. However, above 175 °C, the order of stability becomes $II > I > III$ due to the enantiotropic relationship of the polymorphs.⁶ Form II is expected to be more pharmaceutically active than Form I because of its higher solubility.⁷ Although the solubility value for Form III is yet to be reported, it can be inferred that Form III is the most pharmaceutically active due to its lowest value of lattice energy, as compared to Forms I and II.⁶ However, due to the metastable characteristic of Forms II and Form III, the use of Form I in the pharmaceutical formulations is more practical.^{3,6}

It has been shown that polymorphs of mefenamic acid can be recrystallized from different solvents.^{1–6} In order to determine the best solvent and suitable crystallization methods for producing different polymorphs of mefenamic acid, it is very important to have the solubility data of the compound in various solvents.⁸ Currently, the availability of such data in the literature is very limited.^{5,7,9,10} The solubility data can be obtained experimentally using a technique known as the isothermal method.¹¹ The technique basically involves the determination of a maximum amount of solute that can dissolve in a solvent at a constant temperature with agitation for a time period between 4 to 24 h. The analysis for the solute can be either done

gravimetrically¹² or using spectroscopy.¹³ Some variations of the technique are also available, which are described in detailed elsewhere.^{11,14} Another experimental technique for the solubility determination involves heating up a suspension of solid and solvent to dissolution and detecting the clear point, which is taken as the solubility point, visually or using optical probes.¹⁵ In the present work, the solubility of mefenamic acid in different classes of organic solvents, which are dipolar aprotic, polar protic, and apolar aprotic are measured using the isothermal method at temperatures ranging from (298 to 323) K. The solvents are *N,N*-dimethylacetamide (DMA), *N,N*-dimethylformamide (DMF), ethyl acetate (EA) and propanone, ethanol, propan-2-ol (IPA), hexane, heptane, cyclohexane, and water. The solubility data of mefenamic acid in ethyl acetate obtained in this work are compared with the literature.^{5,7} The enthalpy of dissolution and Gibbs free energy are computed from the experimental data using the modified van't Hoff equation.

EXPERIMENTAL SECTION

Materials. Table 1 shows the description of materials used in this work. Results of powder X-ray diffraction (PXRD) analysis for mefenamic acid illustrated in Figure 1 show that the received mefenamic acid is Form I. The characteristics of solvents, such as dielectric constant (ϵ), molecule dipole moment (DM), polarity index (PI), cohesive energy density (E), summation of hydrogen donor propensity ($\sum H_d$), and summation of hydrogen acceptor propensity ($\sum H_a$) are shown in Table 2.

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Table 1. Description of Materials Used

chemical name	source	initial mass fraction purity	purification method	analysis method
mefenamic acid	Baoji Tianxin Pharmaceutical Co. Ltd., China	0.9800	none	HPLC ^a
ethanol	Fisher Scientific	0.9990	none	GC ^b
propan-2-ol	Fisher Scientific	0.9999	none	GC ^b
N,N-dimethyl acetamide	Fisher Scientific	0.9900	none	GC ^b
N,N-dimethyl formamide	Fisher Scientific	0.9900	none	GC ^b
propanone	Fisher Scientific	0.9950	none	GC ^b
ethyl acetate	Fisher Scientific	0.9950	none	GC ^b
hexane	Fisher Scientific	0.9990	none	GC ^b
heptane	Fisher Scientific	0.9900	none	GC ^b
cyclohexane	Fisher Scientific	0.9900	none	GC ^b

^aHigh-performance liquid chromatography. ^bGas-liquid chromatography.

Solubility Measurement. The isothermal method¹¹ was used to determine the solubility of mefenamic acid in various solvents listed in Table 2. An excess of mefenamic acid was added into glass vials containing two (2) mL of solvent and shaken in a temperature controlled block (Eppendorf Thermomixer Shaker) at a range of temperatures between (298 and 323) K. All samples were maintained at the selected temperatures for a period of 24 h to reach equilibrium. After that, the supernatant solutions were separated at isothermal conditions by filtration using a 0.45 μm PTFE membrane syringe filter. The supernatant was transferred into an evaporating dish, which was initially weighed to determine its empty weight. After the transfer, the evaporating dish was weighed again to determine the wet weight.

Assay of the supernatants was conducted using the gravimetric method¹² that involves evaporation overnight, i.e., approximately a few hours at room temperature initially and then increased to 60 °C. The evaporating dish was repeatedly weighed and dried until constant weights were obtained (dry weight). The information on dry, wet, and empty weights was used to calculate the solubility of the solute in the solvent and construct the solubility curve. All of the experimental results were the average of three replicated experiments. The solubility,

S of solute in the solvents at a particular temperature was calculated as follows:

$$S = \frac{w_d - w_o}{w_w - w_d} \quad (1)$$

where w_o is the empty weight, w_w is the wet weight, w_d is the dry weight, and $w_d - w_o$ is the weight of the solute. In eq 2, m_1 is in grams, while $w_w - w_d$ is the weight of solvent, and m_2 is in grams. An average value was used to calculate the mole fraction solubility, x_1 based on the following equation:

$$x_1 = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2} \quad (2)$$

where M_1 and M_2 are the molecular weights of the solute and the solvent, respectively.¹⁶

RESULTS AND DISCUSSION

Solubility. The solubilities of mefenamic acid in ethanol, IPA, water, DMA, DMF, EA, propanone, hexane, heptane, and cyclohexane in mole fraction measured from (298 to 323) K with their uncertainties are tabulated in Table 3. On the basis of the extensive literature review, this is the first time the solubility data of mefenamic acid in hexane, heptane, and cyclohexane have been reported. These solubility data are used to construct linearized van't Hoff plots as presented in Figure 2. The R^2 values of the van't Hoff plots are between 0.97 and 0.99 and thus signify the reliability of the experimental solubility data. The result on the solubility of mefenamic acid in EA obtained in this work was compared with those in the literature and are shown in Figure 3. As can be seen, the data show a satisfactory agreement with that of Park and co-workers.⁷ The solubility data in this work deviate less than 10 % with those in the literature as shown in Table 4. The solubility value of mefenamic acid in ethanol and ethyl acetate at 298 K were reported by Romero et al.⁵ in mole fractions as 0.0018 and 0.0038, respectively. These values only deviate less than 5 % than those reported in this work, which was 0.0019 and 0.0039 mol fractions in ethanol and ethyl acetate, respectively.

The chemical structure of mefenamic acid, which consists of carboxylic, amine, aromatic, and methyl groups, is shown in Figure 4. The presence of carboxylic and amine group in its chemical structure demonstrates polar protic characteristics,

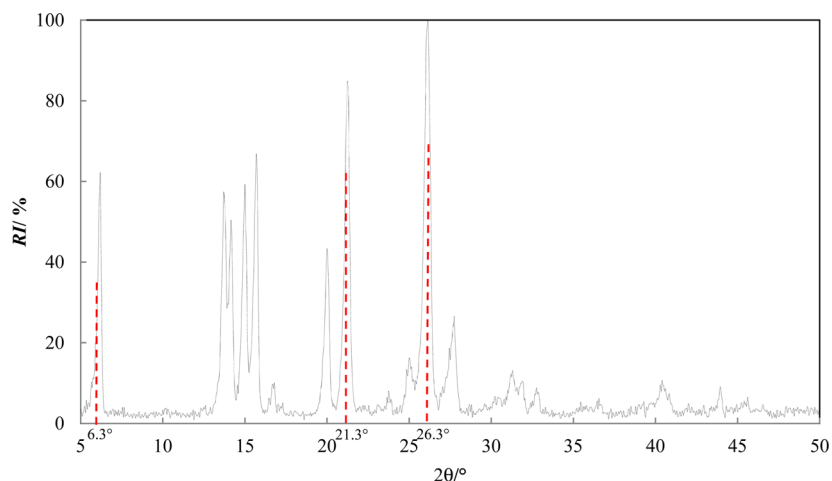


Figure 1. Comparison of PXRD patterns of mefenamic acid powder (raw material) in this work with that of major peaks obtained by Kato and co-workers.³ Solid line, this work; and dashed line, Kato and co-workers.³ RI stands for relative intensities.

Table 2. Characteristics of Polar Protic, Dipolar Aprotic and Apolar Aprotic Solvents^a

solvents	ϵ^{18}	DM^{19}	PI^{18}	E^{20}	$\sum H_d^{21,22}$	$\sum H_a^{21,22}$
Polar Protic						
ethanol	24.55	1.69	5.01	618.87	0.37	0.48
IPA	19.92	1.56	4.57	489.11	0.33	0.56
water	78.36 ²³	1.87	10.2	2095.93	1.17	0.47
Dipolar Aprotic						
DMA	37.78	3.70	5.21	439.94		0.78
DMF	36.71	3.82	5.34	463.96		0.74
propanone	20.70	2.88	4.61	362.07	0.04	0.49
EA	6.70	1.78	4.17	300.64		0.45
Apolar Aprotic						
hexane	1.88	0.00	0.35	200.76		
heptane	1.92	0.00	0.39	200.08		
cyclohexane	2.00	0.00	1.02	254.59		

^a ϵ is the dielectric constant; DM is the molecule dipole moment; PI is the polarity index; E is the cohesive energy density; $\sum H_d$ is the summation of hydrogen donor propensity; and $\sum H_a$ is the summation of hydrogen acceptor propensity.

Table 3. Saturated Mole Fraction Solubility x of Mefenamic Acid in Different Organic Solvents at Experimental Pressure (0.1 MPa) and Temperatures T from (298 to 323) K^a

solvent	T	x	solvent	T	x
	K			K	
ethanol	298	0.0019	IPA	298	0.0020
	303	0.0020		303	0.0024
	308	0.0024		308	0.0026
	313	0.0032		313	0.0033
	318	0.0037		318	0.0040
	323	0.0042		323	0.0053
water	298	0.0000	DMA	298	0.1219
	303	0.0000		303	0.1377
	308	0.0000		308	0.1535
	313	0.00001		313	0.1648
	318	0.00003		318	0.1753
	323	0.00005		323	0.1901
DMF	298	0.0171	EA	298	0.0039
	303	0.0208		303	0.0045
	308	0.0275		308	0.0055
	313	0.0327		313	0.0071
	318	0.0391		318	0.0079
	323	0.0551		323	0.0096
propanone	298	0.0054	hexane	298	0.0013
	303	0.0055		303	0.0014
	308	0.0065		308	0.0016
	313	0.0070		313	0.0018
	318	0.0084		318	0.0020
	323	0.0098		323	0.0024
heptane	298	0.0011	cyclohexane	298	0.0009
	303	0.0013		303	0.0009
	308	0.0015		308	0.0011
	313	0.0017		313	0.0012
	318	0.0018		318	0.0014
	323	0.0022		323	0.0016

^aThe standard uncertainty u is $u(T) = 1$ K; the relative standard uncertainty, $u_r(x) = 0.05$.

while the aromatic and methyl groups are nonpolar. During the dissolution process, the carboxylic group of mefenamic acid, which is more electronegative than the amine group, will donate a hydrogen atom and form a hydrogen bond with either

Table 4. Deviation D of Experimental Mefenamic Acid Solubility S in Ethyl Acetate at Various Temperatures from Literature Data

T	$S_{\text{Experimental}}$	$S_{\text{Literature}}^7$	D^a
K	100 w	100 w	
298	1.0664	1.00	6.64
303	1.2294	1.18	4.63
308	1.4948	1.45	3.09
313	1.9316	1.80	7.31
318	2.1391	2.20	2.77
323	2.6257	2.70	2.75

^a $D = |(S_{\text{Experimental}} - S_{\text{Literature}})/S_{\text{Literature}}| \times 100$.

Table 5. Calculated Dissolution Enthalpy ΔH_{diss} and Gibbs Free Energy Change ΔG_{diss} of Mefenamic Acid in Various Solvents

solvent	ΔH_{diss}	ΔG_{diss} at 298 K	ΔG_{diss} at 308 K	ΔG_{diss} at 318 K	ΔG_{diss} at 328 K
	$\text{kJ}\cdot\text{mol}^{-1}$	$\text{kJ}\cdot\text{mol}^{-1}$	$\text{kJ}\cdot\text{mol}^{-1}$	$\text{kJ}\cdot\text{mol}^{-1}$	$\text{kJ}\cdot\text{mol}^{-1}$
ethanol	27.9025	15.49	15.08	14.66	14.45
IPA	30.3718	15.53	15.03	14.53	14.28
water	119.0427	33.64	30.77	27.91	26.47
DMA	13.8515	5.16	4.87	4.58	4.44
DMF	36.1335	10.17	9.30	8.43	7.99
EA	29.3541	13.80	13.28	12.75	12.49
propanone	18.2663	13.13	12.96	12.78	12.70
hexane	19.3555	16.56	16.47	16.37	16.33
heptane	21.0266	16.87	16.73	16.59	16.52
cyclohexane	20.0705	17.55	17.47	17.38	17.34

polar or dipolar aprotic solvents in the solution. Prior to the formation of the hydrogen bond between mefenamic acid molecules and solvents, the solvent–solvent interactions in the solution need to be broken. As shown in Figure 2, the solubilities of mefenamic acid are high in dipolar aprotic solvents studied in the order of DMA, DMF, propanone, EA. However, the solubilities are moderate in polar protic solvents, which are IPA and ethanol. The solubilities are low in the apolar aprotic solvents studied, which are hexane, heptane, and cyclohexane. Although water is a polar protic solute, mefenamic acid shows very low solubility in it. In terms of the temperature

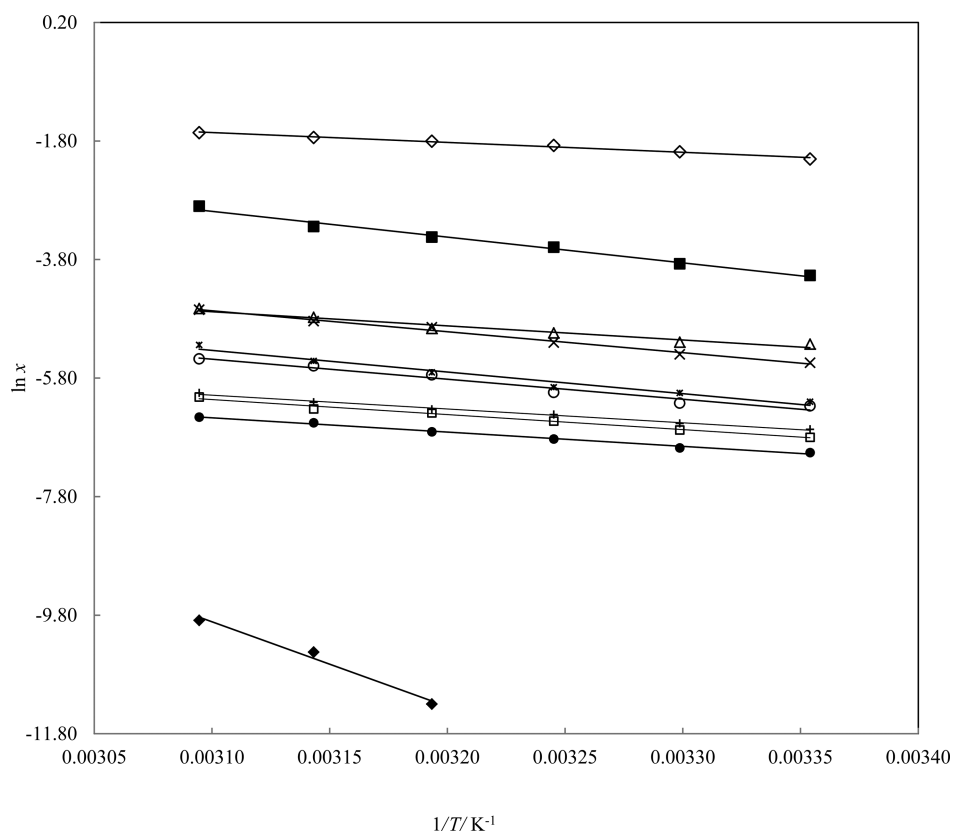


Figure 2. van't Hoff plot of the saturated mole fraction solubility of mefenamic acid x and reciprocal temperature in different organic solvents: \diamond , DMA; \blacksquare , DMF; Δ , propanone; \times , ethyl acetate; $*$, IPA; o , ethanol; $+$, hexane; \square , heptane; \bullet , cyclohexane; \blacklozenge , water.

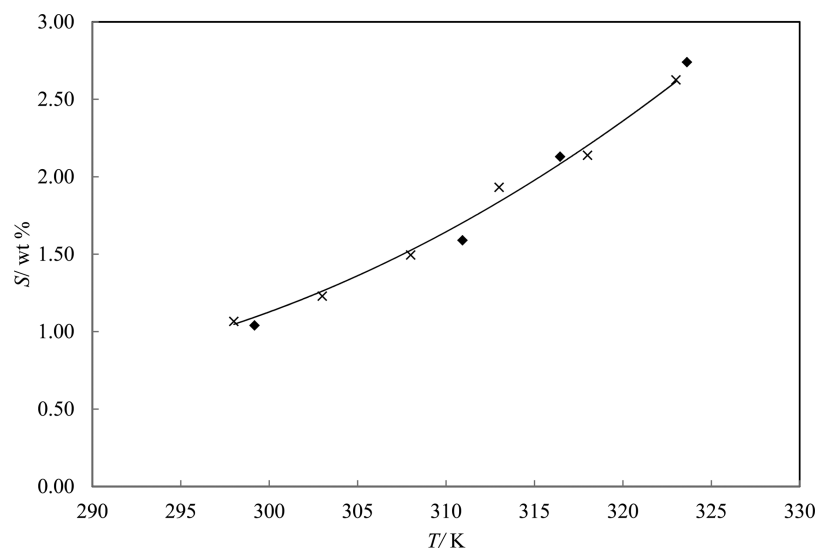


Figure 3. Comparison of mass fraction solubility data S of mefenamic acid in ethyl acetate at different temperatures obtained in this work (\times) and in the work by Park and co-workers (\blacklozenge).⁷

effect, the solubility of mefenamic acid is increased with the increase of temperature for all of the solvents studied. These findings are in agreement with Mullin.¹⁷

It is widely known that the protic solute is more soluble in dipolar aprotic solvents followed by polar protic and apolar aprotic solvents.¹⁷ This is probably due to the formation of the higher strength of the hydrogen bonds between the protic solute and the dipolar aprotic solvents during the dissolution process compared to that in polar protic solvents. In apolar aprotic

solvents, no hydrogen bonds are formed. The low solubility values in apolar aprotic solvents might be due to the weak van der Waals interaction between the molecules. In water, the protic atoms of mefenamic acid, which are COO^- and N^+ , have a tendency to provide hydrogen atoms to water molecules and may form hydrogen bonds with water. However, the presence of aromatic and methyl groups in the mefenamic acid chemical structure is more dominant and influences the structure of the surrounding water molecules and thus leads to poor solubility.

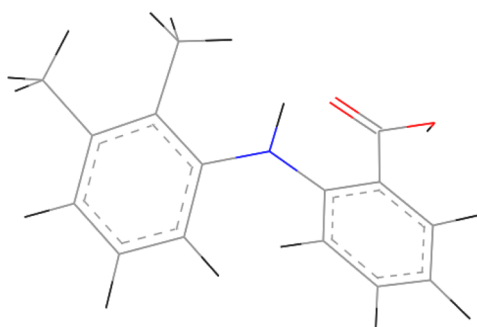


Figure 4. Chemical structure of mefenamic acid Form I. Color representation: gray, carbon; black, hydrogen; blue, nitrogen; and red, oxygen.

Heat of Dissolution and Gibbs Free Energy Change.

Heat of dissolution and Gibbs free energy change during the dissolution process are important parameters, which are associated with the solubility behavior of the targeted compound. The higher energy changes during the dissolution process indicate high stability in solid phase and lower solubility values.²⁴ Using the linear fitting of the van't Hoff plot in Figure 2, the dissolution enthalpy and entropy in respective solvents were determined. The value of enthalpy of dissolution, ΔH_{diss} in $\text{J}\cdot\text{mol}^{-1}$, calculated from the graph's slope in Figure 2, indicated the amount of heat adsorbed or released during disaggregation and diffusion of mefenamic acid in each solvent used. The

entropy of dissolution, ΔS_{diss} in $\text{J}\cdot(\text{mol}\cdot\text{K})^{-1}$ obtained from the y -intercept describes the disorder of the dissolution process. The relationship between ΔH_{diss} and ΔS_{diss} with the changes of Gibbs free energy, ΔG_{diss} in different solvents is shown by the Gibbs–Helmholtz equation:²⁵

$$\Delta G_{\text{diss}} = \Delta H_{\text{diss}} - T\Delta S_{\text{diss}} \quad (3)$$

The calculated values of heat of dissolution, ΔH_{diss} and change in Gibbs free energy are tabulated in Table 5. From this table, it is clear that the values of ΔH_{diss} and ΔG_{diss} are positive in all solvents studied. These values indicate that the dissolution process of mefenamic acid in the solvents is endothermic but not a spontaneous process. The highest values of ΔH_{diss} and ΔG_{diss} were obtained during the dissolution of mefenamic acid in water, which indicates low solubility or poor solute–solvent interactions. However, the values of ΔH_{diss} and ΔG_{diss} were the lowest ones in DMA, which indicate high solubility or good solute–solvent interactions.

The plot of Gibbs free energy change (ΔG_{diss}) studied for each solvent as a function of temperature is shown in Figure 5. The decrease of ΔG_{diss} values with the decrease in the solution temperature indicates less energy is required to initiate the dissolution of mefenamic acid in the respective solvents. Therefore, high solubility or good solute–solvent interactions are obtained at higher temperature.

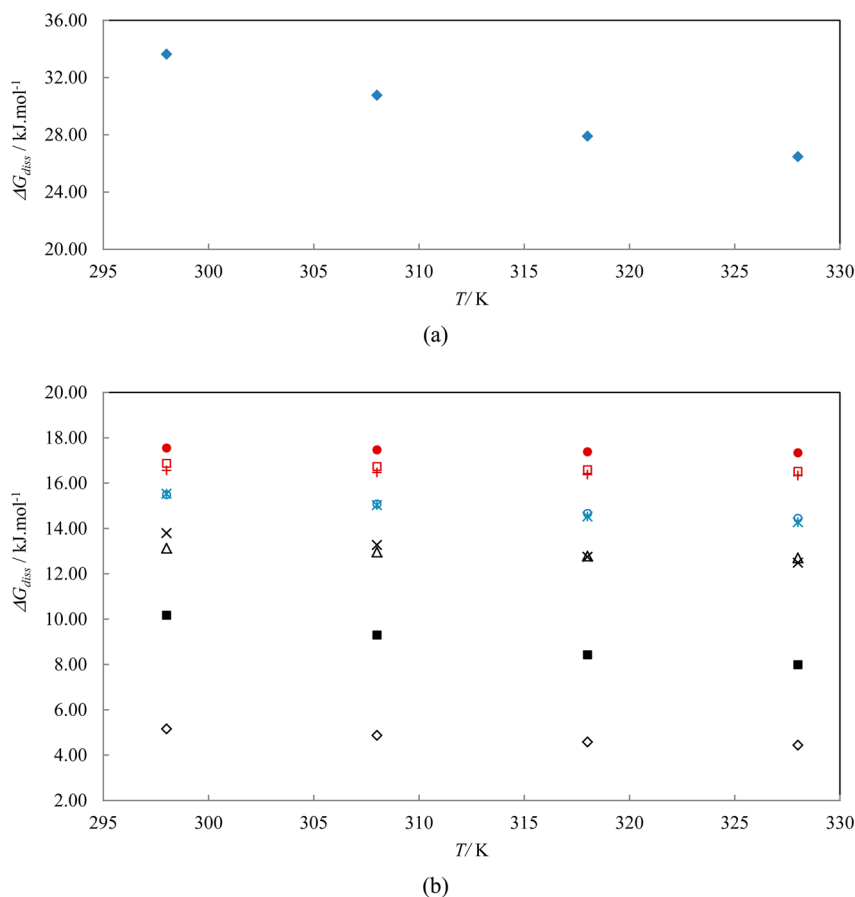


Figure 5. Gibbs free energy change of dissolution ΔG_{diss} as a function of temperature T in (a) water and (b) organic solvents: \diamond , DMA; \blacksquare , DMF; Δ , propanone; \times , ethyl acetate; blue asterisk, IPA; blue circle, ethanol; red +, hexane; red open square, heptane; and red circle, cyclohexane. Color representation: black, dipolar aprotic solvents; blue, polar protic solvents; and red, apolar aprotic solvents.

CONCLUSIONS

The solubility of mefenamic acid in three different classes of organic solvents from (298 to 323) K was determined using isothermal and gravimetric methods. It was found that the solubility values increased with temperatures for all of the solvents tested in this work. Mefenamic acid demonstrates high solubility values in the dipolar aprotic solvents studied in the order of DMA, DMF, propanone, and EA, followed by polar protic solvents, which are IPA and ethanol. The solubilities are low in the apolar aprotic solvents studied, which are hexane, heptane, and cyclohexane. Water, which is a polar protic solvent, however, is not a suitable solvent for the dissolution of mefenamic acid. Different hydrogen bonding propensities in the solvents have contributed to different solubility values. The calculated values of enthalpy and Gibbs free energy change of dissolution of mefenamic acid in solvents are consistent with the experimental solubility data.

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Notes

The authors declare no competing financial interest.

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