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Solution thermodynamics and solubility of indomethacin in ethanol-water mixtures in the temperature range from 293.15 to 318.15 K

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The aim of this study was to correlate the solubility of indomethacin (IND) in pure solvents and various ethanol-water mixtures in the temperature range from 293.15 to 318.15 K. The solubility of IND was determined by the shake flask method and resulting data correlated with the modified Apelblat equation. The experimental data of IND were found to correlate well with the modified Apelblat model. The solubility of IND was found to increase with increasing temperature in pure solvents, as well as in ethanol-water mixtures. The mole fraction solubility of IND was highest in pure ethanol (2.50×10^{-3} at 298.15 K) as compared to pure water (4.48×10^{-8} at 298.15 K) at each temperature. The values of enthalpy and entropy indicated that the dissolution of IND is an endothermic and entropy-driven process.

Keywords: Ethanol, indomethacin, mole fraction solubility, thermodynamics, modified Apelblat model.

INTRODUCTION

Indomethacin (IND) is an indole derivative: 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-3-indoleacetic acid and its molecular structure is presented in Figure 1 (molecular formula $C_{19}H_{16}ClNO_4$, molecular weight 357.79 g/mol, CAS registry number 53-86-1) [1].

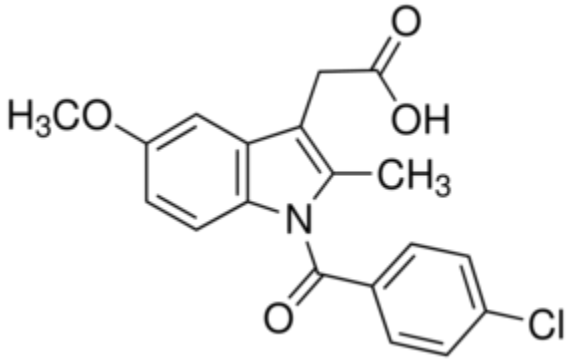

Fig. 1. Molecular structure of indomethacin

It has several pharmacological activities such as anti-inflammatory, analgesic & antipyretic and is commercially available in the form of tablets/capsules, gels and injections [1-4]. It is considered as a practically insoluble drug according to several pharmacopoeias, which is the main obstacle for the formulation development of IND especially for parenteral/liquid dosage forms [1-10]. Therefore, physicochemical data of drugs such as solubility, partition coefficient, dissolution, volume of solvents and other components in the solution are very important for facilitating formulation/drug development processes [4-7]. The solubility data of drugs in water-cosolvent mixtures have significant importance because they are frequently used in drug release/dissolution studies, drug permeation studies, drug purification, drug crystallization, preformulation studies and formulation/drug development [10-13]. Although various mathematical models/equations have been reported in the literature for calculation of solubility of drugs, no temperature dependent solubility data of drugs could be obtained using all these models [3-19]. Therefore, it is important to determine temperature dependent solubility data of drugs in order to get complete information about their physicochemical data [7]. Ethanol is a commonly used cosolvent in preformulation studies and formulation development process of several poorly soluble drugs due to its nontoxicity, good solubilizing capacity, cost effectiveness, etc. [20]. The modified Apelblat model is the most accurate one and is applied for both polar and nonpolar systems to make correlation between experimental and calculated solubility data [21]. Therefore, the aim of this study was to determine the mole fraction solubility of IND in pure solvents (distilled water and ethanol), as well as in ethanol-water mixtures in order to make correlation between experimental data and the modified Apelblat model in the temperature range from 293.15 to 318.15 K. These preliminary studies on IND solubility could be useful in drug dissolution/permeation studies, purification, preformulation studies and formulation development of IND.

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Table 1 General properties of the materials used in the experiment

Materials	Molecular formula	M.W. (g/mol)	D (g/ml)	Purity (%)	CAS No.
Indomethacin	$C_{19}H_{16}ClNO_4$	357.790	1.320	99.20	53-86-1
Ethanol	C_2H_5OH	46.068	0.789	99.90	64-17-5
Water	H_2O	18.015	1.000	100	7732-18-5

EXPERIMENTAL

Materials

IND (purity 99.20%) was obtained as a gift sample from Alfa Aesar (Ward Hill, MA). Ethanol (purity 99.9%) was purchased from Sigma Aldrich (St. Louis, MO). Distilled water was obtained from a distillation unit. All other chemicals and reagents used were of analytical reagent (AR) grade. The general properties of all materials used in the present study are listed in Table 1.

Measurement of IND solubility

The saturated solubility of IND in pure solvents (distilled water and ethanol) and ethanol-water mixtures (mass fraction [w] from 0.1 to 0.9) was determined by a previously reported shake flask method at atmospheric pressure in the temperature range from 293.15 to 318.15 K [4]. An excess amount of IND was added to 25 g of distilled water, ethanol and ethanol-water mixtures in 50 ml capacity conical flasks in triplicate. Each solid-liquid mixture after proper mixing was kept in an isothermal mechanical shaker bath (Julabo, PA) at a shaking speed of 100 rpm for 72 h to reach equilibrium (shorter and longer time studies were performed and optimum time was observed to be 72 h to reach equilibrium). After 72 h, all samples were removed from the shaker and allowed to settle the drug particles for 2 h at the bottom of conical flasks. The samples were filtered through 0.45 μm filter paper, the supernatant from each sample was taken and properly diluted with the respective solvent and subjected for analysis of the IND content
spectrophotometrically at 318 nm [2]. The standard uncertainty for the temperatures u(T) was found to be ± 0.20 K. However, the standard uncertainty in solubilities $u_r(x_e)$ was 1.52 %. The experimental mole fraction solubility (x_e) of IND in each sample was calculated using the reported equation 1 [22]:

$$x_e = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2 + m_3/M_3} \quad \text{.....(1)}$$

where m_1 is the mass of IND (solute) and m_2 and m_3 are the masses of ethanol and distilled water, respectively. M_1 represents the molecular mass of IND; M_2 and M_3 represent the molecular masses of ethanol and distilled water, respectively.

RESULTS AND DISCUSSION

Solubility data of IND

The mole fraction solubility data of IND in neat solvents (distilled water and ethanol) and ethanol-water mixtures in the temperature range from 293.15 to 318.15 K are listed in Table 2.

Table 2 Mole fraction solubility (x_e) of indomethacin in various ethanol-water mixtures in the temperature range from 298.15 to 318.15 K[a]

w	10^3 x_e					
	293.15	298.15	303.15	308.15	313.15	318.15
0.0	4.48×10^{-5}	4.73×10^{-5}	5.04×10^{-5}	5.29×10^{-5}	4.54×10^{-5}	5.84×10^{-5}
0.1	6.43×10^{-4}	8.58×10^{-4}	1.12×10^{-3}	1.44×10^{-3}	1.87×10^{-3}	2.35×10^{-3}
0.2	2.06×10^{-3}	2.40×10^{-3}	2.98×10^{-3}	3.61×10^{-3}	4.35×10^{-3}	5.10×10^{-3}
0.3	7.39×10^{-3}	8.00×10^{-3}	8.74×10^{-3}	9.48×10^{-3}	1.02×10^{-2}	1.10×10^{-2}
0.4	7.65×10^{-2}	8.65×10^{-2}	9.98×10^{-2}	0.11	0.12	0.13
0.5	0.18	0.21	0.26	0.31	0.36	0.42
0.6	0.26	0.33	0.42	0.53	0.63	0.75
0.7	0.42	0.49	0.56	0.64	0.74	0.85
0.8	0.82	0.88	0.98	1.07	1.17	1.27
0.9	1.66	2.05	2.55	3.11	3.66	4.32
1.0	2.50	3.32	4.26	5.50	6.96	8.87

[a]The relative standard uncertainty for temperature was ± 0.20 K, the uncertainty for solubility was 1.52 % and measurements were recorded at a pressure of 0.1 MPa, mass fraction of ethanol in cosolvent mixtures (w), experimental solubility of indomethacin (x_e), relative deviation between experimental and calculated solubility using Apelblat equation was 0.01-5.57 %.

The solubility of IND was found to increase exponentially with the increase in temperature in pure solvents, as well as in ethanol-water mixtures. The mole fraction solubility of IND was highest in pure ethanol (w = 1.0) and lowest in distilled water (w = 0.0) at each temperature studied. The mole fraction solubility of IND in pure ethanol was 2.50 × 10^{-3} at 298.15 K as compared to 4.48 × 10^{-8} in distilled water (Table 2), i.e., it was significantly higher in ethanol than in water. The effect of mass fraction of ethanol on the mole fraction solubility in the temperature range from 293.15 to 318.15 K is presented in Figure 2.

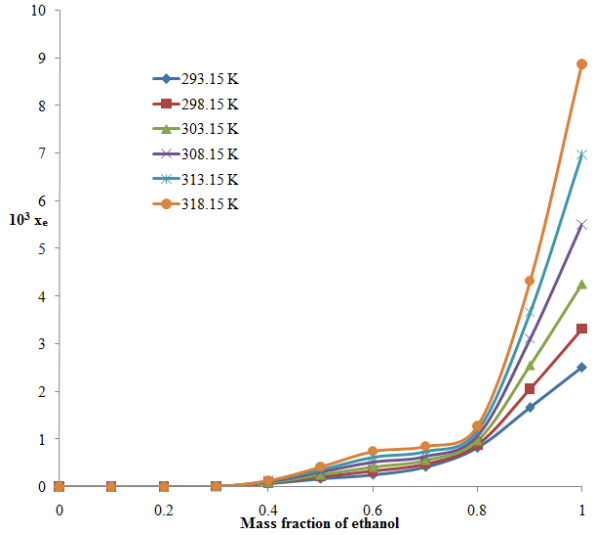


Fig. 2. Impact of mass fraction of ethanol on experimental mole fraction solubility (x_e) of indomethacin at 293.15 - 318.15 K

The mole fraction solubility of IND was found to increase with the increase in mass fraction of ethanol at each temperature studied. It is well known that water is of higher polarity than ethanol because the dielectric constant of water at 298.15 K is 78.36 as compared to 24.30 of ethanol [23]. It has also been reported that the solubility of the solute could be increased by decreasing the polarity of solvents or solvent mixtures [24, 25]. Our results were in good agreement with previous reports of polarities. Moreover, the solubility of IND in ethanol-water mixtures increased by increasing the mass fraction of ethanol that could be due to reduced polarity of the ethanol-water mixtures [23-25]. Therefore, we can conclude that the mole fraction solubility could depend on several factors such as dielectric constant, molecular structure and molecular masses of the solutes and solvents. These results were in agreement with recently published temperature dependent solubility data of paracetamol and risperidone in Transcutol-water cosolvent mixtures [26, 27]. Based on these results, IND could be considered as soluble in ethanol and practically insoluble in distilled water. In the literature, IND has also been reported as practically insoluble in water and soluble in ethanol [3, 4]. The results of the current study are in agreement with previously published solubility reports [4]. Therefore, ethanol could be utilized as a physiologically compatible cosolvent in preformulation studies and formulation development of IND.

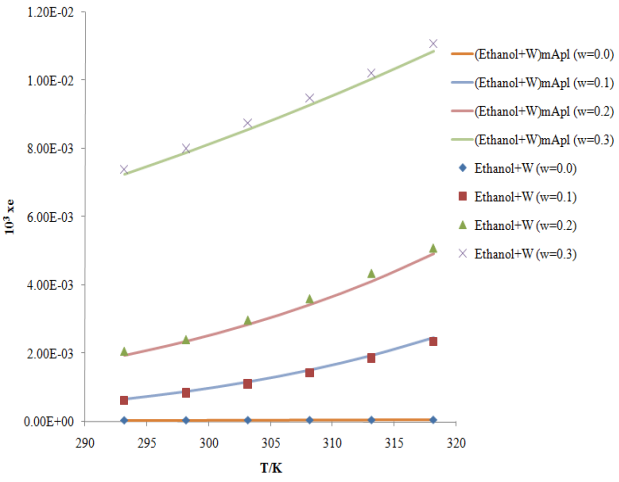
Thermodynamic modeling of IND solubility

As mentioned in the introduction, many equations/models have been used to correlate experimental solubility data with theoretical mole fraction solubility. The modified Apelblat model is the most accurate one and is applied for both polar and nonpolar systems; therefore it was selected in our study to correlate experimental data with calculated solubility data [21, 22, 28]. The temperature-dependent mole fraction solubility of IND can be represented by equation 2 to describe the solid-liquid equilibrium according to the modified Apelblat equation [29]:

$$\ln x_e = A + \frac{B}{T} + C\ln(T) \quad \text{.....(2)}$$

where, x_e is the experimental mole fraction solubility, T is the absolute temperature (K), parameters A, B and C are adjustable equation parameters. Parameters A, B and C were determined by multivariate regression analysis of the experimental data using equation 2. The modified Apelblat solubilities (x_{mAc}) were calculated using the equation parameters A, B and C. The modified Apelblat solubilities were correlated with experimental solubilities of IND and the percentage of absolute relative deviation (% AD) was calculated using equation 3. The correlations between experimental and calculated solubility of IND in various ethanol-water mixtures are presented in Figure 3.

$$AD\ (\%) = \frac{(x_e - x_c)}{x_e} \times 100 \quad \text{.....(3)}$$



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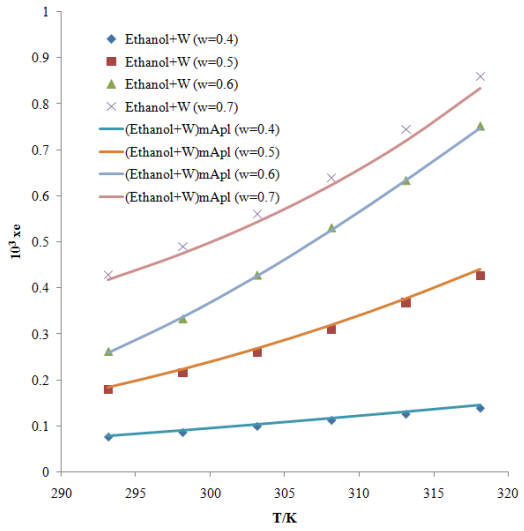

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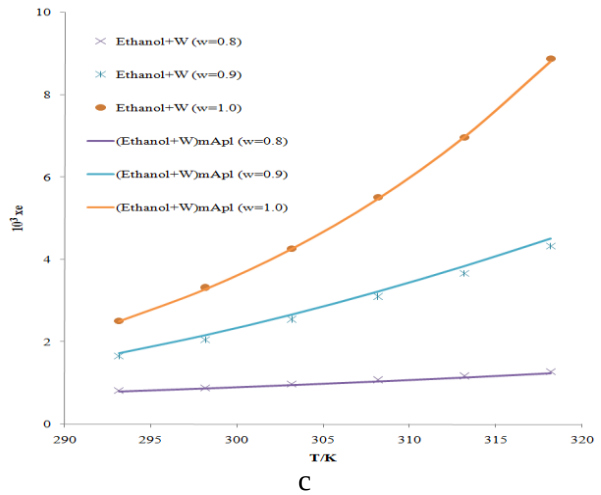

c

Fig. 3 Correlation and curve fitting of experimental mole fraction solubilities (x_e) with the modified Apelblat solubilities (m_{Apl}) for indometacin in various ethanol + water mixtures from 293.15 to 318.15 K [a-lower solubility curves, b-low solubility curves and c-high solubility curves]

where, x_e is the experimental mole fraction solubility and x_c is the calculated solubility of IND. The lowest % AD was found in pure ethanol (0.1 to 0.98) at all temperatures studied. However, % AD in the range of 0.03 to 5.57 % was observed in other cosolvent mixtures. The values of regressed parameters A, B and C in distilled water, ethanol and ethanol-water mixtures are listed in Table 3. The values of R^2 for IND in distilled water and ethanol were 0.998 and 0.999, respectively (Table 3).

The R^2 values for IND in various ethanol-water mixtures were in the range from 0.995 to 0.999, indicating a good fit in pure solvents, as well as in cosolvent mixtures.

Thermodynamic parameters for IND dissolution

The dissolution of IND into a liquid can be expressed as [15-17]:

Solid + liquid = solid-liquid at an equilibrium

The molar enthalpy ($\Delta_{sol}H$) and entropy ($\Delta_{sol}S$) of IND dissolution can be calculated using equations 4 and 5, respectively:

$$\Delta_{sol}H = RT\left(C - \frac{B}{T}\right) \quad \text{.....(4)}$$

$$\Delta_{sol}S = R\left(C - \frac{B}{T}\right) \quad \text{.....(5)}$$

where B and C are the adjustable parameters calculated by the modified Apelblat equation. R and T are the universal gas constant and the absolute temperature, respectively. $\Delta_{sol}H$ and $\Delta_{sol}S$ for IND dissolution were calculated using equations 4 and 5, respectively at various temperatures. The $\Delta_{sol}H$ of IND dissolution in distilled water and ethanol at various temperatures ranged from 7.97 to 8.40 kJmol^{-1} and from 38.54 to 39.34 kJmol^{-1}, respectively. However, the $\Delta_{sol}H$ of IND dissolution in various ethanol-water mixtures ranged from 12.19 to 41.91 kJmol^{-1} in the same temperature range. These results indicated that IND dissolution in distilled water, ethanol and various ethanol-water mixtures was endothermic because the values of $\Delta_{sol}H$ were positive in each case. It was considered that the solute is solid and energy is required for the hypothetical melting process before mixing with the solvent. Hence, the positive values of $\Delta_{sol}H$ were probably due to the formation of new bond energy of attraction between IND molecules and the solvent molecules. The $\Delta_{sol}S$ values of IND dissolution in distilled water, ethanol and various ethanol-water mixtures were also positive at each temperature studied which also indicated that IND dissolution is an endothermic and an entropy-driven process.

Table 3 Modified Apelblat model parameters for indomethacin in various ethanol-water mixtures

w	Apelblat parameters			
	A	B	C	R^2
0.0	0.47	-162.68	-2.08	0.998
0.1	110.41	-9755.55	-16.08	0.999
0.2	-62.45	-684.46	9.09	0.998
0.3	-32.15	-356.24	3.79	0.999
0.4	128.20	-8175.47	-19.32	0.997
0.5	86.25	-7036.76	-12.47	0.999
0.6	437.59	-23588.50	-64.32	0.995
0.7	-231.08	7957.44	34.53	0.998
0.8	-53.33	685.40	7.72	0.997
0.9	252.03	-14746.20	-36.63	0.997
1.0	36.01	-5866.89	-3.87	0.999

Mass fraction of ethanol in cosolvent mixtures (w), correlation coefficient (R^2)

CONCLUSION

In the present study, the mole fraction solubility of IND in distilled water, ethanol and various ethanol-water mixtures in the temperature range from 293.15 to 318.15 K was measured. The solubilities of IND were found to increase with the increase in temperature in distilled water, ethanol and various ethanol-water mixtures. The solubility of IND in pure ethanol was found to be significantly higher than that in pure distilled water. The solubility data of IND in distilled water, ethanol and various ethanol-water mixtures correlates well with the modified Apelblat equation. Based on solubility data, IND is considered as soluble in ethanol and practically insoluble in distilled water. These preliminary studies indicate that ethanol could be utilized as a green cosolvent in preformulation studies and formulation development of IND.

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ТЕРМОДИНАМИКА И РАЗТВОРИМОСТ НА ИНДОМЕТАЦИН В ВОДНО-ЕТАНОЛОВИ СМЕСИ В ТЕМПЕРАТУРНИЯ ИНТЕРВАЛ ОТ 293.15 ДО 318.15 K

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(Резюме)

Цел на работата е да се намери корелация между разтворимостта на индометацин (IND)в чисти разтворители и във водно-етанолови смеси в температурния интервал от 293.15 до 318.15) K. Ратворимостите са определяни след разбъркване на клатачна машина, а получените данни са корелирани с модифицираното уравнение на Apelblat. Установено е, че разтворимостта на IND нараства с температурата в чисти разтворители, както и във водно-алкохолните смеси. Моларната разтворимост на IND е най-висока в чист етанол (2.50 x 10^{-3} при 298.15 K) в сравнение с тази в чиста вода (4.48 x 10^{-8} при 298.15 K) за всяка изследвана температура. Резултатите за енталпиите и ентропиите показват, че разтварянето на IND е ендотермичен и ентропийно обусловен процес.