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Measurement, correlation and thermodynamics of solubility of metronidazole in 2-(2-ethoxyethoxy)ethanol + water cosolvent mixtures at (298.15 to 333.15) K

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ABSTRACT

The aim of present study was to measure and correlate the solubility of metronidazole (MTZ) in various 2-(2-ethoxyethoxy)ethanol + water mixtures from (2981.5 to 333.15) K using the shake flask method. The experimental solubilities of MTZ were correlated with Apelblat equation and Yalkowsky model. The percent of root mean square deviations (% RMSD) was obtained as (0.80 to 4.51)% for Apelblat equation and (1.42 to 11.57)% for Yalkowsky model. The mole fraction solubility of MTZ was observed to be the highest in pure 2-(2-ethoxyethoxy)ethanol (2.07×10^{-2} at 298.15 K). The MTZ dissolution was observed as endothermic and *spontaneous* in all cosolvent mixtures. Based on current solubility data, MTZ has been considered as slightly soluble in pure water and soluble in pure 2-(2-ethoxyethoxy)ethanol.

1. Introduction

The IUPAC name of metronidazole (MTZ) is 2-(2-methyl-5-nitro-1*H*-imidazol-1-yl) ethanol and its molecular structure is presented in Fig. 1 (molecular formula—$C_6H_9N_3O_3$, *molar mass*—171.15 $g \cdot mol^{-1}$, CAS registry number—443-48-1) [1,2]. It is a powerful antiprotozoal and antibacterial agent which is clinically effective in the treatment of amoebic colitis, giardiasis and trichomoniasis [2,3]. It is a slightly soluble drug in water (equilibrium solubility 10 $mg \cdot mL^{-1}$ at 20 °C and 10.5 $mg \cdot mL^{-1}$ at 25 °C) which is the main barrier for the formulation development of MTZ [3,4]. Thermodynamic parameters in terms of enthalpies and entropies of drugs/pharmaceuticals have shown important thermal properties which can be used for thermal characterization of these drugs/pharmaceuticals [5,6]. These thermal parameters have also been used to characterize crystalline/amorphous nature of drugs/pharmaceuticals along with their solubility and dissolution rate [6–10]. Some cosolvents such as ethanol, N,N-dimethylacetamide, propylene glycol (PG) and solketal have been used to enhance the aqueous solubility of MTZ [11]. Cosolvent technique has been reported error free technique for the solubilization and stabilization of drugs/pharmaceuticals in aqueous solutions [12–16]. Temperature dependent solubility data of poorly water-soluble compounds in cosolvent mixtures had significant importance because of its wide range of applications in pharmaceutical and chemical industries [9,10,12,17]. Ethanol, PG and polyethylene glycol-400 (PEG-400) have been reported as commonly used cosolvents for formulation development and solubilization of poorly water-soluble compounds [12–17]. Recently, 2-(2-ethoxyethoxy)ethanol (Transcutol) has also been investigated as an efficient and alternative cosolvent of ethanol, PG and PEG-400 in solubilization of various poorly water-soluble drugs such as paracetamol, diclofenac sodium, glibenclamide, risperidone, tadalafil, thiosemicarbazones and isoniazid analogs [9,12,18–23]. To the best of our knowledge, the temperature dependent solubility data of MTZ in 2-(2-ethoxyethoxy)ethanol + water cosolvent mixtures has not been reported in any pharmacopeia/encyclopedia/literature. Therefore, the aim of this study was to investigate the temperature dependent solubility data of MTZ in various 2-(2-ethoxyethoxy)ethanol + water cosolvent mixtures at temperature range from (298.15 to 333.15) K using the shake flask method. The obtained experimental data was also correlated with Apelblat equation and Yalkowsky model. These preliminary studies would be useful for pharmaceutical/chemical industries in drug purification, dissolution studies, preformulation studies and formulation development of MTZ.

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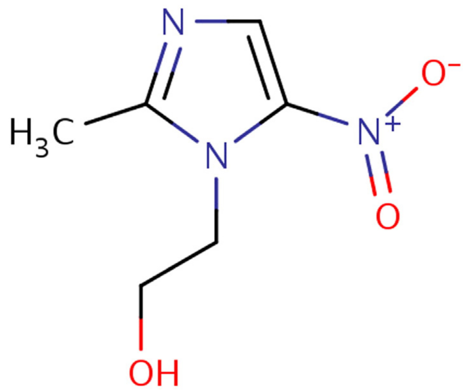

Fig. 1. Molecular structure of MTZ.

Table 2
Apelblat parameters (A, B and C), correlation coefficients (R^2), root mean square deviations (RMSD) and standard errors (SE) for MTZ in various 2-(2-ethoxyethoxy) ethanol + water co-solvent mixtures (m).

m	A	B	C	R^2	RMSD (%)	SE
0.0	−65.56	1560.76	9.39	0.999	2.62	0.002
0.1	13.53	−2047.87	−2.32	0.995	1.59	0.012
0.2	−135.44	4638.20	19.93	0.997	2.17	0.001
0.3	7.10	−1753.41	−1.27	0.997	0.80	0.009
0.4	10.92	−2236.24	−1.59	0.994	2.32	0.017
0.5	−31.63	−79.78	4.65	0.998	4.57	0.009
0.6	−2.05	−1425.42	0.31	0.997	3.20	0.010
0.7	111.45	−6719.39	−16.43	0.994	4.09	0.002
0.8	−77.38	2127.65	11.55	0.997	0.91	0.010
0.9	−29.44	−110.49	4.51	0.999	1.30	0.006
1.0	−81.64	2338.92	12.27	0.998	2.12	0.008

2. Experimental

2.1. Materials

MTZ (mass fraction purity of 0.992) was procured from Sigma Aldrich (St. Louis, MO). Transcutol [IUPAC name: 2-(2-ethoxyethoxy)ethanol and mass fraction purity of 0.999] was obtained as a kind gift sample from Gattefosse (Lyon, France). Distilled water was collected from distillation unit.

2.2. Measurement of MTZ solubility

The solubility of MTZ against mass fraction of 2-(2-ethoxyethoxy)ethanol (m = 0.0 to 1.0) in various 2-(2-ethoxyethoxy)ethanol + water cosolvent mixtures was measured by shake flask method at atmospheric pressure and temperature range of (298.15 to 333.15) K [24]. The excess amount of MTZ was added in 5 g of each cosolvent mixture in 10 mL capacity flasks. Each solid–liquid mixture was then kept in an isothermal water shaker bath (Julabo, PA) with the shaking speed of 100 rpm for 72 h. After 72 h, all the solid–liquid mixtures were removed from the shaker bath and allowed to settle the drug particles for the period of 2 h at the bottom of each flask [10]. After complete settling of drug particles, the supernatants from each sample were taken, diluted and subjected for the quantification of MTZ using UV–Visible spectrophotometer (SP1900, Axiom, Germany) at the wavelength of 320 nm [25]. The proposed spectrophotometric method was observed linear in the concentration range of (2 to 20) $\mu g \cdot g^{-1}$ with correlation coefficient of 0.999. The standard uncertainty in temperatures $u(T)$ was recorded as ±0.20 K. However, the relative standard uncertainty in solubility $u_r(x_e)$ for MTZ was recorded as 0.94%. The experimental mole fraction solubilities (x_e) of MTZ were then calculated as reported in literature [9,10,12].

3. Results and discussion

3.1. Solubility data of MTZ

The solubility data of MTZ against mass fraction of 2-(2-ethoxyethoxy)ethanol in various 2-(2-ethoxyethoxy)ethanol + water cosolvent mixtures is listed in Table 1. The mole fraction solubility of MTZ in pure water has been reported as 1.05×10^{-3} and 1.10×10^{-3} at 293.15 K and 298.15 K, respectively [3,4]. However, in the present study the mole fraction solubility of MTZ in pure water was observed as 1.11×10^{-3} at 298.15 K which was very close to the reported value of MTZ at 298.15 K (1.10×10^{-3}). The mole fraction solubility data of MTZ in pure 2-(2-ethoxyethoxy)ethanol or 2-(2-ethoxyethoxy)ethanol + water cosolvent mixtures is not reported in literature. Our results were in good agreement with the reported solubility of MTZ in water. In general, the mole fraction solubility of MTZ was found to be increased exponentially with increase in temperature and mass fraction of 2-(2-ethoxyethoxy)ethanol in 2-(2-ethoxyethoxy) ethanol + water cosolvent mixtures from (298.15 to 333.15) K. The experimental solubility of MTZ was observed to be the highest in pure 2-(2-ethoxyethoxy)ethanol (m = 1.0) (2.07×10^{-2} at 298.15 K) at each temperature studied (Table 1). However, the lowest one was observed in pure water (m = 0.0) (1.11×10^{-3} at 298.15 K). The lowest mole fraction solubility of MTZ in pure water was probably due to its high polarity/dielectric constant as compared to pure 2-(2-ethoxyethoxy)ethanol and other cosolvent mixtures [19,20]. These results were in agreement with recently published solubility data of various poorly water-soluble drugs in 2-(2-ethoxyethoxy)ethanol + water cosolvent mixtures [18–23].

Based on solubility data of MTZ, it has been considered as soluble in pure 2-(2-ethoxyethoxy)ethanol and slightly soluble in water.

Table 1
Experimental mole fraction solubilities (x_e) of MTZ against mass fraction of 2-(2-ethoxyethoxy)ethanol (m) in various 2-(2-ethoxyethoxy)ethanol + water co-solvent mixtures in the absence of solute at temperatures T = (298.15 to 333.15) K and pressure p = 0.1 MPa.[a]

m	x_e							
	T = 298.15	T = 303.15	T = 308.15	T = 313.15	T = 318.15	T = 323.15	T = 328.15	T = 333.15
0.0	1.11×10^{-3}	1.19×10^{-3}	1.28×10^{-3}	1.37×10^{-3}	1.47×10^{-3}	1.59×10^{-3}	1.70×10^{-3}	1.82×10^{-3}
0.1	1.39×10^{-3}	1.53×10^{-3}	1.62×10^{-3}	1.72×10^{-3}	1.83×10^{-3}	2.01×10^{-3}	2.09×10^{-3}	2.22×10^{-3}
0.2	1.82×10^{-3}	1.96×10^{-3}	2.11×10^{-3}	2.29×10^{-3}	2.49×10^{-3}	2.72×10^{-3}	2.97×10^{-3}	3.24×10^{-3}
0.3	2.43×10^{-3}	2.59×10^{-3}	2.84×10^{-3}	3.05×10^{-3}	3.23×10^{-3}	3.42×10^{-3}	3.66×10^{-3}	3.94×10^{-3}
0.4	3.54×10^{-3}	3.79×10^{-3}	4.15×10^{-3}	4.64×10^{-3}	5.03×10^{-3}	5.59×10^{-3}	6.01×10^{-3}	6.32×10^{-3}
0.5	4.68×10^{-3}	5.12×10^{-3}	5.54×10^{-3}	6.06×10^{-3}	6.47×10^{-3}	6.92×10^{-3}	7.46×10^{-3}	8.20×10^{-3}
0.6	6.50×10^{-3}	7.12×10^{-3}	7.64×10^{-3}	8.27×10^{-3}	9.09×10^{-3}	9.75×10^{-3}	1.02×10^{-2}	1.11×10^{-2}
0.7	8.73×10^{-3}	9.68×10^{-3}	1.05×10^{-2}	1.14×10^{-2}	1.24×10^{-2}	1.33×10^{-2}	1.42×10^{-2}	1.50×10^{-2}
0.8	1.17×10^{-2}	1.27×10^{-2}	1.37×10^{-2}	1.48×10^{-2}	1.60×10^{-2}	1.71×10^{-2}	1.83×10^{-2}	2.03×10^{-2}
0.9	1.64×10^{-2}	1.80×10^{-2}	1.94×10^{-2}	2.09×10^{-2}	2.27×10^{-2}	2.42×10^{-2}	2.63×10^{-2}	2.85×10^{-2}
1.0	2.07×10^{-2}	2.27×10^{-2}	2.44×10^{-2}	2.63×10^{-2}	2.83×10^{-2}	3.03×10^{-2}	3.30×10^{-2}	3.61×10^{-2}

[a] The standard uncertainty in temperatures $u(T)$ is ±0.20 K, the relative standard uncertainty in solubility $u_r(x_e)$ for MTZ is 0.94%.

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