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Solution thermodynamics and solubilization behavior of diclofenac sodium in binary mixture of Transcutol-HP and water

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Solution thermodynamics and solubilization behavior of diclofenac sodium (DS) in binary mixture of Transcutol-HP and water is not reported in the literature so far. Therefore, the aim of the present study was to investigate the solution thermodynamics and solubilization behavior of DS in mono-solvents and various Transcutol-water mixtures at 298.15–333.15 K. The mole fraction solubility of DS was determined by shake flask method and thermodynamic parameters (enthalpies and entropies) were calculated with the help of the modified Apelblat model. The experimental solubility data of DS in all sample matrices was found to be correlated well with the modified Apelblat model with correlation coefficients of 0.9950–0.9990. Absolute relative deviation was found to be less than 3% in most of the Transcutol-water mixtures at each temperature studied. The mole fraction solubility of DS was observed to be highest in pure Transcutol (0.139 at 298.15 K) as compared to pure water and other Transcutol-water mixtures. The enthalpies and entropies for DS dissolution were observed as positive values for all cosolvent mixtures which indicated that the dissolution of DS is endothermic and an entropy-driven process. Based on solubility data, DS was considered as sparingly soluble in pure water and freely soluble in Transcutol. These results indicated that Transcutol could be used as an alternate of ethanol, propylene glycol and polyethylene glycol to enhance aqueous solubility of DS. These preliminary studies could be useful in formulation development of DS especially in terms of liquid dosage forms and injectable formulations.

1. Introduction

Diclofenac sodium (DS) is the sodium salt of [*o*-(2,6-dichloroaniline) phenyl] acetate (Fig. 1). It is the most commonly prescribed analgesic and anti-inflammatory drug which is available commercially in various dosage forms such as tablets, capsules, gels, creams, and injections (Bustamante et al. 1998; Llinas et al. 2007; Zilnik et al. 2007). According to the biopharmaceutical classification system (BCS) of drugs, it is poorly soluble and highly permeable (BCS class II drug) which is the main obstacle for the formulation development of DS especially in terms of liquid dosage forms (Wu and Benet 2005; Chuasuwan et al. 2009). Thermodynamics parameters (enthalpies and entropies) of drugs/pharmaceuticals are important properties which can be used for their characterization (Craig and Newton 1991; Chadha et al. 2003). These thermodynamic parameters have been successfully used to investigate the extent of crystallinity in drugs/pharmaceuticals as well as solubility and dissolution rate of drugs (Fini et al. 1995; Llyod et al. 1999; Chadha et al. 2003). Many cosolvents such as acetone, ethyl acetate, dimethyl sulfoxide, methanol, ethanol and 2-propanol have been used to enhance the solubility of DS either at room temperature or various temperature ranges (Zilnik et al. 2007; Saei et al. 2008). The solubility/solubility parameter of DS in water, various aqueous buffers and organic solvents have also been investigated (Fini et al. 1995; Bustamante et al. 1998; O'Connor and Corrigan 2001; Kincl et al. 2004; Llinas et al. 2007; Zilnik et al. 2007). Cosolvents are usually used for solubilization and stabilization of drugs/pharmaceuticals in aqueous solutions (Shakeel et al. 2013b; Soleymani et al al. 2013). Temperature dependent solubility data of drugs in cosolvent mixtures had significant importance because of its applications in drug crystallization, drug purification, drug dissolution/permeation, preformulation studies and formulation development such as creams, gels and injections etc (Jimenez and Martinez 2006; Shakeel et al. 2013a, 2013b). Hence, temperature dependent solubility data of drugs must be determined to get complete information regarding physicochemical parameters of drugs

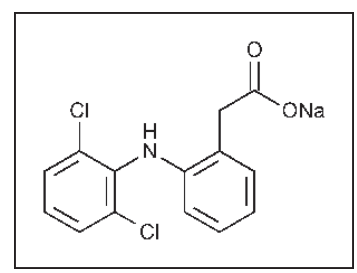

Fig. 1: Molecular structure of diclofenac sodium.

Table 1: Experimental (X_e) and calculated mole fraction solubility (X_{mAc}) data of diclofenac sodium in various mass fraction of Transcutol (w) at 298.15 to 333.15 K

w	$10^3 X_e$								$10^3 X_{mAc}$							
	298.15	303.15	308.15	313.15	318.15	323.15	328.15	333.15	298.15	303.15	308.15	313.15	318.15	323.15	328.15	333.15
0.0	0.800	0.984	1.204	1.475	1.759	2.109	2.545	3.060	0.785	0.958	1.166	1.415	1.712	2.065	2.483	2.977
0.1	2.569	2.919	3.364	3.837	4.354	4.880	5.540	6.195	2.581	2.947	3.357	3.817	4.330	4.903	5.542	6.251
0.2	8.570	8.966	9.407	9.899	10.325	10.905	11.434	12.053	8.501	8.946	9.406	9.883	10.375	10.883	11.408	11.950
0.3	15.582	15.982	16.410	16.929	17.467	18.060	18.658	19.357	15.433	15.949	16.474	17.008	17.549	18.099	18.658	19.224
0.4	22.528	23.064	23.525	24.095	24.698	25.247	26.030	26.743	22.315	22.894	23.478	24.068	24.662	25.261	25.866	26.475
0.5	29.666	30.214	30.849	31.546	32.193	32.949	33.798	34.665	29.409	30.130	30.801	31.503	32.210	32.922	33.637	34.358
0.6	35.263	35.903	36.861	37.564	38.428	39.332	40.298	41.343	34.961	35.804	36.652	37.506	38.365	39.231	40.103	40.980
0.7	43.473	44.290	45.447	46.435	47.402	48.579	49.745	51.082	43.168	44.221	45.281	46.348	47.424	48.507	49.597	50.695
0.8	56.177	57.375	58.973	60.113	61.566	62.938	64.846	66.294	55.785	57.187	58.601	60.027	61.463	62.911	64.370	65.840
0.9	78.696	80.500	82.616	84.487	86.257	88.195	90.628	92.628	78.592	80.529	82.481	84.448	86.429	88.425	90.435	92.460
1.0	139.831	143.148	146.208	149.897	153.899	157.467	161.981	166.116	139.040	142.682	146.359	150.068	153.810	157.586	161.393	165.233

Mass fraction of Transcutol in cosolvent mixtures (w), experimental solubility of diclofenac sodium (X_e), mole fraction solubility of diclofenac sodium calculated by the modified Apelblat model (X_{mAc}), relative absolute deviation between experimental and calculated solubility was observed as 0.009–4.037 %.

(Jimenez and Martinez 2006). Transcutol-HP has been evaluated extensively as a cosurfactant in formulation development of various nano-sized lipid-based carriers such as nanoemulsions, microemulsions, self-nanoemulsifying drug delivery systems (SNEDDS) and self-microemulsifying drug delivery systems (SMEDDS) which are known to enhance solubility/dissolution and *in vivo* bioavailability of poorly soluble drugs (Shafiq et al. 2007; Shakeel et al. 2013a, 2013c, 2013d). Nevertheless, it has not been used as a cosolvent to enhance the solubility of DS in water-cosolvent mixtures in literature so far. The solubility of DS in various cosolvent mixtures such as methanol-water, ethanol-water, and 2-propanol-water, various oils and microemulsion have been investigated (Fanun 2007; Saei et al. 2008; Nayak 2010). However, its solution thermodynamics and solubilization behavior in Transcutol-water mixtures has not been presented in the literature so far. Therefore, the aim of present study was to evaluate solution thermodynamics and solubilization behavior of DS in mono-solvents (pure water and pure Transcutol) as well as in various Transcutol-water mixtures at a temperature range from 298.15 to 333.15 K. The obtained experimental solubility data were correlated with the modified Apelblat model at each temperature range. These preliminary studies could be useful for pharmaceutical/chemical industries in drug dissolution studies, purification, preformulation studies and formulation development of DS. These studies could also be useful in the development of various nanosized lipid based carriers of DS such as nanoemulsions/microemulsions, SNEDDS/SMEDDS and injectable formulations.

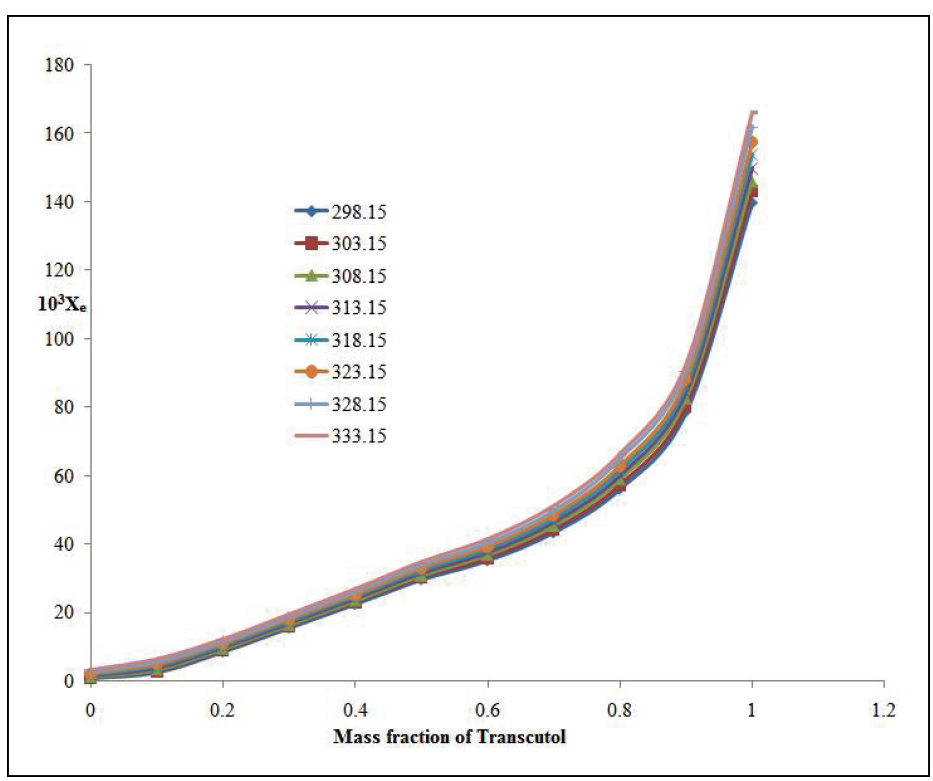

Fig. 2: Effects of mass fraction of Transcutol on mole fraction solubility (Xe) of diclofenac sodium at various temperatures (298.15–333.15 K).

2. Investigations, results and discussion

2.1. Solubility data of DS

The mole fraction solubility data of DS in mono-solvents (Transcutol and water) and various cosolvent mixtures at various temperatures are listed in Table 1. It was observed that the mole fraction solubility of DS increased exponentially with increase in temperature and mass fraction of Transcutol in all sample matrices. The experimental solubility of DS was observed highest and lowest in pure Transcutol and pure water, respectively at each temperature studied (Table 1). The mole fraction solubility of DS in pure Transcutol was observed as 139.831×10^{-3} at 298.15 K as compared to 0.800×10^{-3} in pure water (Table 1) which was significantly higher in pure Transcutol than its aqueous solubility. Around 175 fold enhancement in solubility was observed in pure Transcutol as compared to pure water. The effect of mass fraction of Transcutol on mole fraction solubility of DS at various temperatures is presented in Fig. 2. It was observed that the solubility of DS was found to be increased with increase in mass fraction of Transcutol at each temperature studied. It is very well known that water is a much more polar solvent than organic solvents/cosolvents such as Transcutol (Faraji et al. 2009). Hence, the lowest solubility of DS in pure water was due to its highest polarity/dielectric constant (Mali et al. 2007). The solubility of DS in cosolvent mixtures was enhanced rapidly by increasing the mass fraction of Transcutol in cosolvent mixtures that was probably due to reduced polarities/dielectric constants in cosolvent mixtures (Chen et al. 2005; Faraji et al. 2009). The results of the present study on DS solubility were in agreement with previous report of polarities. The highest solubility of DS in pure Transcutol was probably due to the lower polarity of Transcutol. The mole fraction solubility of DS in pure water was found to be 0.802×10^{-3} at 298.15 K (Kincl et al. 2004). However, in the present study the mole fraction solubility of DS in pure water was observed as 0.800×10^{-3} at the same temperature (298.15 K) which was very close to reported values. However, the mole fraction solubility of DS in pure Transcutol or Transcutol-water mixtures is not reported in the literature so far. Based on present solubility data, DS was considered as freely soluble in pure Transcutol and sparingly soluble in pure water. Hence, Transcutol could be utilized as a physiologically compatible cosolvent in preformulation studies and formulation development especially in terms of liquid dosage form and injectable formulations of DS. Because DS was found to be freely soluble in Transcutol, it can also be used as a cosurfactant in the development of lipid based formulations

2.2. Thermodynamic modeling of DS solubility

The modified Apelblat model is the most commonly applied mathematical model for both polar as well as for nonpolar systems, hence it was applied in the present study in order to correlate the experimental solubility with the calculated one (Cantillo et al. 2013; Wang et al. 2013; Wang and Lv 2013). According to the modified Apelblat model, the temperature-dependent solubility of DS can be represented by Eq. (1) at the equilibrium (Apelblat and Manzurola 1999):

$$\ln x_e = A + \frac{B}{T} + C \ln(T) \quad (1)$$

where, x_e and T represent the experimental mole fraction solubility and absolute temperature (K), respectively. Parameters A, B and C are adjustable model parameters. These parameters were determined by the regression analysis of the experimental solubility data using Eq. (1). The calculated or the modified Apelblat solubilities (x_{mAc}) were calculated with the help of model parameters A, B and C. The experimental solubilities of DS were correlated with the modified Apelblat solubilities and the percentage of absolute relative deviation (% AD) was calculated with the help of Eq. (2).

$$AD(\%) = \frac{(x_e - x_c)}{x_s} \times 100 \quad (2)$$

where, x_e and x_c represent the experimental and calculated mole fraction solubility of DS, respectively. The data of experimental mole fraction solubility and modified apelblat solubility in mono-solvents and cosolvent mixtures are listed in Table 1.
The % AD was found to be less than 3% in most of the cosolvent mixtures and pure Transcutol at 298.15–318.15 K. However, the % AD was found to be 1.866–4.037 in pure water. The values of regressed parameters A, B and C in pure water (w = 0.0), pure Transcutol (w = 1.0) and cosolvent mixtures (w = 0.1–0.9) are listed in Table 2. The values of correlation coefficients (R^2) for DS in pure water and pure Transcutol were observed as 0.9990 and 0.9970, respectively (Table 2). However, R^2 values for DS in various cosovent mixtures were observed in the range of 0.9950–0.9990 which indicated the good fitting of the experimental data in mono-solvents as well as in various cosolvent mixtures.

Table 2: The modified Apelblat parameters (A, B and C) for diclofenac sodium in various Transcutol-water mixtures

Sample	Modified Aplelblat model			
	A	B	C	R^2
Transcutol + W (w = 0.0)	−68.8419	54.2000	12.0100	0.9990
Transcutol + W (w = 0.1)	−44.5667	36.8000	7.9680	0.9990
Transcutol + W (w = 0.2)	−15.4235	22.8000	3.0680	0.9980
Transcutol + W (w = 0.3)	−8.5903	16.2000	1.9790	0.9960
Transcutol + W (w = 0.4)	−5.5159	14.8000	1.5400	0.9960
Transcutol + W (w = 0.5)	−4.6368	11.3000	1.4010	0.9950
Transcutol + W (w = 0.6)	−4.6421	13.6000	1.4310	0.9970
Transcutol + W (w = 0.7)	−4.5306	14.4000	1.4480	0.9970
Transcutol + W (w = 0.8)	−4.5329	15.1000	1.4930	0.9970
Transcutol + W (w = 0.9)	−4.0274	15.9000	1.4640	0.9990
Transcutol + W (w = 1.0)	−3.9782	1.8000	1.5550	0.9970

Distilled water (W), mass fraction of Transcutol in cosolvent mixtures (w)

2.3. Thermodynamic parameters for DS dissolution

According to the modified Apelblat model, the dissolution of DS into a liquid can be expressed as (Apelblat and Manzurola 1999): Solid + liquid = solid-liquid at the equilibrium.
The molar enthalpies (ΔH^0) and entropies (ΔS^0) of DS dissolution were calculated using Eqs. (3) and (4), respectively:

$$\Delta H^0 = RT(C - \frac{B}{T}) \quad (3)$$

Table 3: Thermodynamic parameters (ΔH^0 and ΔS^0) for dissolution of diclofenac sodium in various Transcutol-water mixtures

Sample	T/K							
	298.15	303.15	308.15	313.15	318.15	323.15	328.15	333.15
THP + W (w = 0.0)								
ΔH^0 (kJmol^{-1})	29.321	29.820	30.320	30.819	31.318	31.818	32.317	32.816
ΔS^0 (Jmol^{-1}K^{-1})	98.345	98.370	98.394	98.417	98.440	98.462	98.483	98.504
THP + W (w = 0.1)								
ΔH^0 (kJmol^{-1})	19.446	19.777	20.108	20.440	20.771	21.102	21.433	21.765
ΔS^0 (Jmol^{-1}K^{-1})	65.223	65.240	65.256	65.272	65.287	65.302	65.317	65.331
THP + W (w = 0.2)								
ΔH^0 (kJmol^{-1})	7.415	7.543	7.660	7.798	7.926	8.053	8.181	8.308
ΔS^0 (Jmol^{-1}K^{-1})	24.872	24.883	24.893	24.903	24.912	24.922	24.931	24.939
THP + W (w = 0.3)								
ΔH^0 (kJmol^{-1})	4.771	4.853	4.935	5.017	5.100	5.182	5.264	5.347
ΔS^0 (Jmol^{-1}K^{-1})	16.002	16.010	16.017	16.024	16.030	16.037	16.043	16.050
THP + W (w = 0.4)								
ΔH^0 (kJmol^{-1})	3.694	3.758	3.822	3.886	3.950	4.014	4.078	4.142
ΔS^0 (Jmol^{-1}K^{-1})	12.391	12.398	12.404	12.411	12.417	12.423	12.429	12.434
THP + W (w = 0.5)								
ΔH^0 (kJmol^{-1})	3.379	3.437	3.495	3.553	3.612	3.670	3.728	3.786
ΔS^0 (Jmol^{-1}K^{-1})	11.333	11.338	11.343	11.348	11.353	11.357	11.362	11.366
THP + W (w = 0.6)								
ΔH^0 (kJmol^{-1})	3.434	3.493	3.553	3.612	3.672	3.731	3.791	3.850
ΔS^0 (Jmol^{-1}K^{-1})	11.518	11.524	11.531	11.536	11.542	11.548	11.553	11.558
THP + W (w = 0.7)								
ΔH^0 (kJmol^{-1})	3.469	3.529	3.590	3.650	3.710	3.770	3.830	3.891
ΔS^0 (Jmol^{-1}K^{-1})	11.637	11.644	11.650	11.657	11.663	11.668	11.674	11.679
THP + W (w = 0.8)								
ΔH^0 (kJmol^{-1})	3.575	3.637	3.699	3.761	3.823	3.885	3.947	4.010
ΔS^0 (Jmol^{-1}K^{-1})	11.992	11.999	12.006	12.012	12.018	12.024	12.030	12.036
THP + W (w = 0.9)								
ΔH^0 (kJmol^{-1})	3.496	3.557	3.618	3.679	3.740	3.801	3.862	3.923
ΔS^0 (Jmol^{-1}K^{-1})	11.728	11.736	11.743	11.750	11.756	11.763	11.769	11.775
THP + W (w = 1.0)								
ΔH^0 (kJmol^{-1})	3.715	3.779	3.844	3.909	3.973	4.038	4.102	4.167
ΔS^0 (Jmol^{-1}K^{-1})	12.460	12.468	12.475	12.482	12.489	12.496	12.503	12.509

Distilled water (W), Transcutol-HP (THP), mass fraction of Transcutol-HP in cosolvent mixtures (w)

$$\Delta S^0 = R(C - \frac{B}{T}) \quad (4)$$

where, R represents the universal gas constant and other parameters are already defined. The ΔH^0 and ΔS^0 for DS dissolution were calculated with the help of Eqs. (3) and (4), respectively at 298.15–333.15 K. The results of these thermodynamic parameters in mono-solvents (pure water and pure Transcutol) and various cosolvent mixtures at 298.15–333.15 K are listed in Table 3. The ΔH^0 values of DS dissolution in pure water and pure Transcutol were observed in the range of 29.321–32.816 and 3.715–4.167 kJmol^{-1}, respectively at 298.15–333.15 K (Table 3). However, the ΔH^0 values for DS dissolution in various cosolvent mixtures were observed in the range of 3.434–21.765 kJmol^{-1} at 298.15–333.15 K (Table 3). It was observed that the ΔH^0 values for DS dissolution in pure Transcutol and various cosolvent mixtures were significantly reduced as compared to pure water. This clearly indicated that very low energies are required for solubilization of DS in pure Transcutol as well as in various cosolvent mixtures. The rapid decline in the ΔH^0 values was observed in cosolvent mixtures up to mass fraction of 0.4 after that only slight changes were observed. Moreover, the values of ΔH^0 were found to be positive in all sample matrices which indicated that DS dissolution was endothermic. The positive values of ΔH^0 were probably due to the molecular forces of attraction between solute (DS) molecules and the molecules of solvents (Sunsandee et al. 2013). The ΔS^0 values for DS dissolution were also observed as positive values in all samples (11.333–98.504 Jmol^{-1}K^{-1}) at (298.15 to 333.15) K which also indicated that the dissolution of DS is an endothermic and an entropy-driven process.

2.4. Conclusion

The present studies were undertaken to investigate solution thermodynamics and solubilization behavior of diclofenac sodium in pure water, pure Transcutol and various cosolvent mixtures at 298.15–333.15 K. The solubility of diclofenac sodium was found to be increased exponentially with temperature in all sample matrices investigated. The solubility of diclofenac sodium in pure Transcutol was found to be significantly higher than its aqueous solubility. The experimental solubility data of diclofenac sodium was correlated well with the modified Apelblat model with the correlation coefficients in the range of 0.9950–0.9990. Based on solubility data of the present study, diclofenac sodium is considered as freely soluble in pure Transcutol and sparingly/poorly soluble in water. Overall, these studies indicated that Transcutol could be used as a physiologically compatible cosolvent in preformulation studies and formulation development of diclofenac sodium. Various lipid

based and injectable formulations of diclofenac sodium could also be developed using current solubility data in order to enhance its solubility and bioavailability.

3. Experimental

3.1. Materials

Diclofenac sodium (purity 99.40%) was purchased from Sigma Aldrich (St. Louis, MO). Highly purified diethylene glycol monoethyl ether (Tarnscutol-HP, purity 99.98%) was procured as a kind gift sample from Gattefosse (Cedex, France). Distilled water was obtained from distillation unit in the laboratory. All other chemicals used were of analytical grade.

3.2. Measurement of DS solubility

The equilibrium solubility of DS in mono-solvents and various cosolvent mixtures was determined by the shake flask method at 298.15–333.15 K (Shakeel et al. 2013a, 2013b). DS in an excess amount was added in 5 mL of mono-solvents or cosolvent mixtures in 10 mL capacity flasks in triplicate. The mixtures were then tightly closed with the cap and each solid-liquid mixture was kept in an isothermal water shaker bath (Julabo, PA) at 100 rpm for 72 h to reach the equilibrium. After 72 h, all the solid-liquid mixtures were taken out from the shaker bath and allowed to settle solute (drug) particles for 2 h at the bottom of the flasks (Sunsandee et al. 2013). All the samples were then filtered using 0.45 μm filter paper, diluted suitably with respective solvent/cosolvent mixture and supernatant from each sample was subjected for analysis of DS content using UV-Visible spectrophotometer (SP1900, Axiom, Germany) at 276 nm (Fini et al. 1995; Kincl et al. 2004). The proposed analytical method was found to be linear in the range of 2–20 $\mu g.mL^{-1}$ with correlation coefficient of 0.999. The uncertainties in the experiment were observed in the range of 0.54–0.87 %. The experimental mole fraction solubilities (x_e) of DS were calculated using Eq. (5) (Shakeel et al. 2013a, 2013b):

$$x_e = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2 + m_3/M_3} \quad (5)$$

where, m_1 represents the mass of DS (solute) and m_2 & m_3 represent the mass of Transcutol and water, respectively. However, M_1 represents the molecular mass of DS and M_2 & M_3 represent the molecular mass of Transcutol and water, respectively.

Conflict of interest: The authors report no declaration of interest. The authors alone are responsible for the content and writing of the paper.

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References

Apelblat A, Manzurola E (1999) Solubilities of o-acetylsalicylic, 4-aminosalicylic, 3,5-dinitrosalicylic and p-toluic acid and magnesium-DL-aspartate in water from T = (278 to 348) K. J Chem Thermodyn 31: 85–91.

Bustamante P, Pena MA, Barra J (1998) Partial solubility of parameters of naproxen and sodium diclofenac. J Pharm Pharmacol 50: 975–982.

Cantillo EA, Delgado DR, Martinez F (2013) Solution thermodynamics of indomethacin in ethanol + propylene glycol mixtures. J Mol Liq 181: 62–67.

Chadha R, Kashid N, Jain DVS (2003) Microcalorimetric studies to determine the enthalpy of solution of diclofenac sodium, paracetamol and their binary mixtures at 310.15 K. J Pharm Biomed Anal 30: 1515–1522.

Chen J, Spear SK, Huddleston JG, Rogers RD (2005) Polyethylene glycol and solutions of polyethylene glycol as green reaction media. Green Chem 7: 64–82.

Chuasuwan B, Binjesoh V, Polli JE, Zhang H, Amidon GL, Junginger HE, Midha KK, Shah VP, Stavchansky S, Dressman JB, Barends DM (2009) Biowaiver monographs for immediate release solid oral dosage forms: diclofenac sodium and diclofenac potassium. J Pharm Sci 98: 1206–1219.

Craig DQM, Newton JM (1991) Characterisation of polyethylene glycols using solution calorimetry. Int J Pharm 74: 43–48.

Fanun M (2007) Conductivity, viscosity, NMR and diclofenac solubilization capacity studies of mixed nonionic surfactants microemulsions. J Mol Liq 135: 5–13.

Faraji M, Farajtabar A, Gharib F (2009) Determination of water-ethanol mixtures autoprotolysis constants and solvent effect. J Appl Chem Res 9: 7–12.

Fini A, Fazio G, Feroci G (1995) Solubility and solubilization properties of non-steroidal anti-inflammatory drugs. Int J Pharm 126: 95–102.

Jimenez JA, Martinez F (2006) Thermodynamic study of the solubility of acetaminophen in propylene glycol + water cosolvent mixtures. J Braz Chem Soc 17: 125–134.

Kincl M, Meleh M, Veber M, Vrecer F (2004) Study of physicochemical parameters affecting the release of diclofenac sodium from lipophilic matrix tablets. Acta Chim Slov 51: 409–425.

Llinas A, Burley JC, Box KJ, Glen RC, Goodman JM (2007) Diclofenac sodium: independent determination of the intrinsic solubility of three crystal forms. J Med Chem 50: 979–983.

Lloyd GR, Craig DQM, Smith A (1999) A calorimetric investigation into the interaction between paracetamol and polyethylene glycol 4000 in physical mixes and solid dispersions. Eur J Pharm Biopharm 48: 59–65.

Mali CS, Chavan SD, Kanse KS, Kumbharkhane AC, Mehrotra SC (2007) Dielectric relaxation of poly ethylene glycol-water mixtures using time domain technique. Ind J Pure Appl Phys 45: 476–481.

Nayak AK (2010) Thermodynamic study of the diclofenac sodium solubility in various oils. Chem 19: 121–128.

O'Connor KM, Corrigan OI (2001) Comparison of the physicochemical properties of the N-(2-hydroxyethyl) pyrrolidine, diethylamine and sodium salt forms of diclofenac. Int J Pharm 222: 281–293.

Saei AA, Jabbaribar F, Fakhree MAA, Acree Jr WE, Jouyban A (2008) Solubility of sodium diclofenac in binary water + alcohol solvent mixtures at 25 °C. J Drug Deliv Sci Technol 18: 149–151.

Shafiq S, Shakeel F, Talegaonkar S, Ahmad FJ, Khar RK, Ali M (2007) Development and bioavailability assessment of ramipril nanoemulsion formulation. Eur J Pharm Biopharm 66: 227–243.

Shakeel F, Haq N, Alanazi FK, Alsarra IA (2013a) Thermodynamic modeling for solubility prediction of indomethacin in self-nanoemulsifying drug delivery system (SNEDDS) and its individual components. Drug Develop Ind Pharm doi: 10.3109/03639045.2013.814063.

Shakeel F, Alanazi FK, Alsarra IA, Haq N (2013b) Thermodynamics-based mathematical model for solubility prediction of glibenclamide in ethanol-water mixtures. Pharm Develop Technol doi: 10.3109/10837450.2013.823992.

Shakeel F, Haq N, Elbadry M, Alanazi FK, Alsarra IA (2013c) Ultra fine super self-nanoemulsifying drug delivery system (SNEDDS) enhanced solubility and dissolution of indomethacin. J Mol Liq 180: 89–94.

Shakeel F, Haq N, Alanazi FK, Alsarra IA (2013d) Impact of various non-ionic surfactants on self-nanoemulsification efficiency of two grades of Capryol (Capryol-90 and Capryol-PGMC). J Mol Liq 182: 57–63.

Soleymani J, Djozan D, Martinez M, Jouyban A (2013) Solubility of ranitidine hydrochloride in solvent mixtures of PEG 200, PEG 400, ethanol and propylene glycol at 25 °C. J Mol Liq 182: 91–94.

Sunsandee N, Hronec M, Stolcova M, Leepipatpiboon N, Pancharoen U (2013) Thermodynamics of the solubility of 4-acetyl benzoic acid in different solvents from 303.15 to 373.15 K. J Mol Liq 180: 252–259.

Wang L, Lv TT (2013) Determination and modeling of the solubility and prediction of the dissolution properties of 2, 4-dichlorophenoxyacetic acid in toluene, tetrachloromethane and the binary solvent mixtures of (cyclohexane + ethyl acetate). J Mol Liq 181: 29–33.

Wang Q, Chen Y, Deng L, Tang J, Zhang Z (2013) Determination of the solubility parameter of ionic liquid 1-allyl-3-methylimidazolium chloride by inverse gas chromatography. J Mol Liq 180: 135–138.

Wu C, Benet LZ (2005) Predicting drug disposition via application of BCS: transport/absorption/elimination interplay and development of a biopharmaceutics drug disposition classification system. Pharm Res 22: 11–23.

Zilnik LF, Jazbinsek A, Hvala A, Vrecer F, Klamt A (2007) Solubility of sodium diclofenac in different solvents. Fluid Phase Equilib 261: 140–145.