

## ORIGINAL ARTICLE

## Thermodynamics-based mathematical model for solubility prediction of glibenclamide in ethanol–water mixtures

Faiyaz Shakeel<sup>1,2</sup>, Fars K. Alanazi<sup>2,3</sup>, Ibrahim A. Alsarra<sup>1,2</sup>, and Nazrul Haq<sup>1,2</sup><sup>1</sup>Center of Excellence in Biotechnology Research, <sup>2</sup>Department of Pharmaceutics, College of Pharmacy, and <sup>3</sup>Kayyali Chair for Pharmaceutical Industry, Department of Pharmaceutics, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia

## Abstract

Temperature-dependent solubility data of glibenclamide (GBN) in various ethanol–water mixtures is not reported in literature so far. Therefore, the aim of this study was to determine the mole fraction solubility of GBN in various ethanol–water mixtures at the temperature range of 293.15 to 318.15 K. The solubility of GBN was determined by reported shake flask method and the experimental data was fitted in thermodynamics-based modified Apelblat model. The solubility of GBN was found to be increased with increase in temperature and mass fraction of ethanol in ethanol–water mixtures. The experimental data of GBN was well correlated with the modified Apelblat model at each temperature range with correlation coefficient of 0.9940–1.0000. The relative absolute deviation (AD) was found to be less than 0.1% except in pure ethanol and water. The positive values of enthalpies and entropies for GBN dissolution indicated that its dissolution is endothermic and an entropy-driven process.

## Introduction

Glibenclamide (GBN), also known as glyburide (molecular formula- $C_{23}H_{28}ClN_3O_5S$ , molecular weight-494 g/mol and CAS registry Number-10238-21-8), is an oral hypoglycemic agent which has been recommended for the management and treatment of type II non-insulin-dependent diabetes mellitus<sup>1</sup>. Physicochemical characterization of this drug indicates that it has very poor aqueous solubility but shows very good permeability through gastrointestinal mucosa<sup>2,3</sup>. The poor solubility is the main barrier for the drug development process of GBN especially in terms of liquid dosage forms where high amount of GBN is required to be solubilized in relatively small amounts of the solvents<sup>1–5</sup>. A thorough literature survey revealed that several thermodynamics-based mathematical models are used for prediction of solubility of various drugs/pharmaceuticals in various mixtures of solvents/cosolvents<sup>4–10</sup>. Nevertheless, all these mathematical models do not consider the impact of temperature on solubility data of these drugs/pharmaceuticals due to certain limitations of each model<sup>4,5</sup>. Therefore, it is very important to measure temperature-dependent solubility data of such poorly soluble drugs in order to maintain complete information about the physicochemical parameters of such drugs<sup>4</sup>. The most recent research works on temperature-dependent solubility data of some pharmaceuticals such as 2,4-dichlorophenoxyacetic acid, 4-acetylbenzoic acid, daidzein and succinic anhydride have shown that the modified Apelblat model is the most accurate and commonly employed thermodynamics-based mathematical model for both polar as well as for nonpolar systems to predict temperature-dependent solubility data<sup>11–14</sup>. Although, saturated

## Keywords

Dissolution, ethanol, glibenclamide, mole fraction solubility, thermodynamics

## History

Received 17 April 2013

Revised 5 June 2013

Accepted 22 June 2013

Published online 9 August 2013

equilibrium solubility of GBN in water (0.024 mg/ml – practically insoluble) and ethanol (5 mg/ml – slightly soluble) at room temperature (298.15 K) has been reported in several pharmacopeias but temperature-dependent mole fraction solubility data of GBN in various ethanol–water mixtures has not been reported in literature or any pharmacopeia so far<sup>1–3</sup>. Therefore, the attempts were made in the present study for measurement of the mole fraction solubility of GBN in various ethanol–water mixtures by shake flask method to correlate experimental solubility data with the modified Apelblat model at the temperature range from 293.15 to 318.15 K. These preliminary studies could be useful in generating temperature-dependent solubility data of various poorly soluble drugs as well as in preformulation studies and formulation development of GBN.

## Materials and methods

## Materials

Glyburide (Figure 1; purity 99.0%) was obtained as a gift sample from Alfa Aesar (Ward Hill, MA). Ethanol (purity 96.0%) was purchased from Sigma Aldrich (St. Louis, MO). Distilled water was obtained from distillation unit in the laboratory. Various ethanol–water mixtures were prepared at mass fraction of 0–1.0 with the help of density of ethanol and water. All these chemicals were used without further purification and their general properties are listed in Table 1.

## Measurement of GBN solubility by shake flask method

The solubility of GBN in various ethanol–water mixtures was measured by shake flask method reported by Higuchi et al. (1979) at the temperature range<sup>15</sup> from 293.15 to 318.15 K. An excess amount of solid GBN was carefully added in 25 ml of each ethanol–water mixture in 50 ml capacity stoppered conical flasks. Each solid–liquid mixture was mixed thoroughly and transferred

Address for correspondence: Dr Faiyaz Shakeel, Center of Excellence in Biotechnology Research, King Saud University, Riyadh, Kingdom of Saudi Arabia (KSA). Tel: +966-537507318. E-mail: faiyazs@fastmail.fm

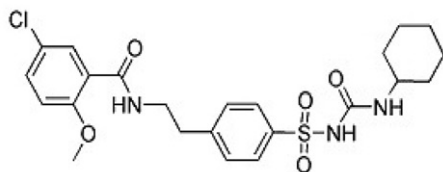


Figure 1. Molecular structure of glibenclamide.

Table 1. General properties of glibenclamide, ethanol and water.

Materials	Molecular formula	M.W. (g/mol)	D (g/ml)	Purity (%)	CAS No.
Glibenclamide	C <sub>23</sub> H <sub>28</sub> ClN <sub>3</sub> O <sub>5</sub> S	494.000	1.360	99.00	10238-21-8
Ethanol	C <sub>2</sub> H <sub>5</sub> OH	46.069	0.789	96.00	64-17-5
Water	H <sub>2</sub> O	18.015	1.000	100	7732-18-5

Table 2. Experimental ( $X_e$ ) and calculated mole fraction solubility ( $X_{mAc}$ ) data of glibenclamide in various ethanol–water mixtures (293.15 to 318.15 K).

T/K	$10^3 X_e$	$10^3 X_{mAc}$	AD (%)	K at 298.15 K
Ethanol + W ( $w=0.0$ )				
293.15	0.0042	0.0042	-0.563	
298.15	0.0050	0.0051	-2.059	
303.15	0.0062	0.0061	2.065	78.360
308.15	0.0074	0.0072	2.494	
313.15	0.0088	0.0086	2.218	
318.15	0.0099	0.0102	-3.353	
Ethanol + W ( $w=0.1$ )				
293.15	2.1774	2.1773	0.003	
298.15	2.1800	2.1804	-0.018	
303.15	2.1829	2.1834	-0.019	72.954
308.15	2.1859	2.1863	-0.018	
313.15	2.1893	2.1892	0.004	
318.15	2.1919	2.1921	-0.010	
Ethanol + W ( $w=0.2$ )				
293.15	4.3498	4.3492	0.014	
298.15	4.3528	4.3528	-0.001	67.548
303.15	4.3560	4.3563	-0.005	
308.15	4.3594	4.3597	-0.007	
313.15	4.3632	4.3631	0.001	
318.15	4.3670	4.3664	0.012	
Ethanol + W ( $w=0.3$ )				
293.15	6.5233	6.5227	0.0009	
298.15	6.5276	6.5276	-0.000	
303.15	6.5319	6.5325	-0.008	62.142
308.15	6.5368	6.5373	-0.007	
313.15	6.5422	6.5420	0.003	
318.15	6.5471	6.5466	0.006	
Ethanol + W ( $w=0.4$ )				
293.15	8.6983	8.6982	0.000	
298.15	8.7027	8.7041	-0.016	56.736
303.15	8.7083	8.7099	-0.018	
308.15	8.7140	8.7156	-0.018	
313.15	8.7203	8.7212	-0.011	
318.15	8.7265	8.7268	-0.002	
Ethanol + W ( $w=0.5$ )				
293.15	10.8772	10.8781	-0.008	
298.15	10.8832	10.8846	-0.012	51.330
303.15	10.8892	10.8910	-0.016	
308.15	10.8952	10.8973	-0.018	
313.15	10.9020	10.9034	-0.013	
318.15	10.9087	10.9095	-0.007	
Ethanol + W ( $w=0.6$ )				
293.15	13.0910	13.0938	-0.021	
298.15	13.1059	13.1107	-0.036	

Table 2. Continued

T/K	$10^3 X_e$	$10^3 X_{mAc}$	AD (%)	K at 298.15 K
308.15	13.1395	13.1439	-0.033	45.924
313.15	13.1562	13.1601	-0.029	
318.15	13.1730	13.1761	-0.023	
Ethanol + W ( $w=0.7$ )				
293.15	15.3033	15.3059	-0.016	
298.15	15.3256	15.3281	-0.016	
303.15	15.3478	15.3501	-0.014	40.518
308.15	15.3676	15.3717	-0.026	
313.15	15.3898	15.3930	-0.020	
318.15	15.4121	15.4140	-0.012	
Ethanol + W ( $w=0.8$ )				
293.15	17.5606	17.5593	0.007	
298.15	17.5938	17.5929	0.005	
303.15	17.6270	17.6260	0.005	35.112
308.15	17.6602	17.6587	0.008	
313.15	17.6934	17.6908	0.014	
318.15	17.7229	17.7226	0.001	
Ethanol + W ( $w=0.9$ )				
293.15	20.1959	20.1985	-0.012	
298.15	20.3426	20.3480	0.026	29.707
303.15	20.4893	20.4960	0.032	
308.15	20.6360	20.6427	0.032	
313.15	20.7826	20.7880	0.025	
318.15	20.9293	20.9321	0.013	
Ethanol + W ( $w=1.0$ )				
293.15	0.3441	0.3409	0.930	
298.15	0.3728	0.3726	0.051	
303.15	0.4109	0.4066	1.039	24.300
308.15	0.4413	0.4431	-0.417	
313.15	0.4784	0.4823	-0.814	
318.15	0.5335	0.5241	1.763	

Distilled water (W), experimental mole fraction solubility of glibenclamide ( $X_e$ ), mole fraction solubility of glibenclamide calculated by the modified Apelbalt equation ( $X_{mAc}$ ), relative absolute deviation between experimental and calculated solubility (AD), dielectric constant at 298.15 K ( $K$ ).

to an isothermal shaker bath (Julabo, PA) for the period of 24 h to reach equilibrium. After 24 h (enough time to reach equilibrium)<sup>14</sup>, each solid–liquid mixture was removed from shaker bath and allowed to settle drug particles for the period of 2 h (it is reported time for complete settling of solute particles)<sup>12</sup> at the bottom of flasks. The uncertainties in temperature and mole fraction solubility were observed as 0.65 and 0.74%, respectively. All the samples were filtered through 0.45  $\mu$ m membrane filters, diluted suitably with respective solvent and subjected for analysis of GBN content using UV-Visible spectrophotometer at the wavelength<sup>16,17</sup> of 245 nm. Experimental mole fraction solubility ( $x_e$ ) of GBN was calculated using Equation (1)<sup>12–14</sup>:

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

where,  $m_1$  is the mass of GBN (solute), and  $m_2$  and  $m_3$  are the mass of ethanol and distilled water, respectively.  $M_1$  represents the molecular weight of GBN (g/mol) and  $M_2$  and  $M_3$  represents the molecular weight (g/mol) of ethanol and distilled water, respectively.

## Results and discussion

### Solubility data of GBN

Figure 2. Experimental mole fraction solubility ( $X_e$ ) of glibenclamide in various ethanol–water mixtures against temperature.

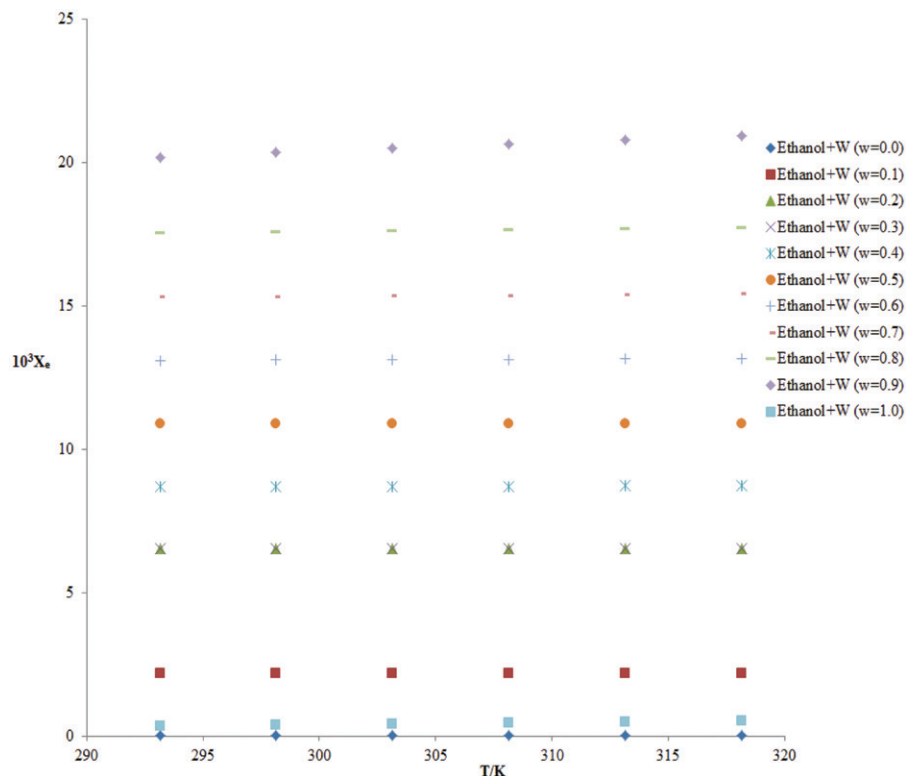
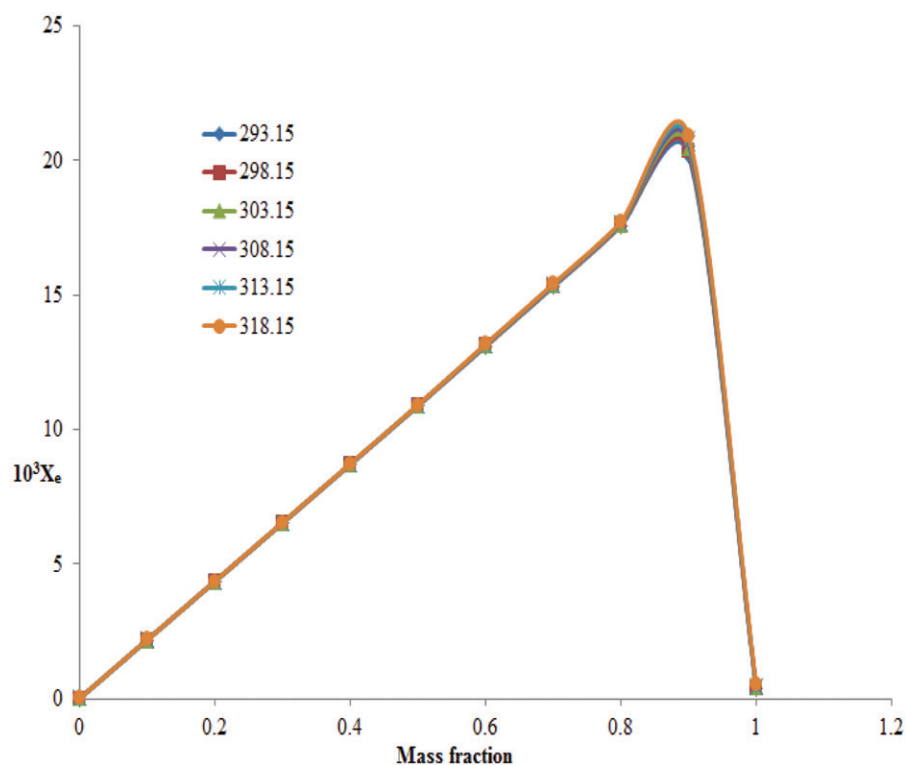


Figure 3. Experimental mole fraction solubility ( $X_e$ ) of glibenclamide against mass fraction of (0–1.0) of ethanol–water mixtures at various temperatures (293.15 to 318.15 K).



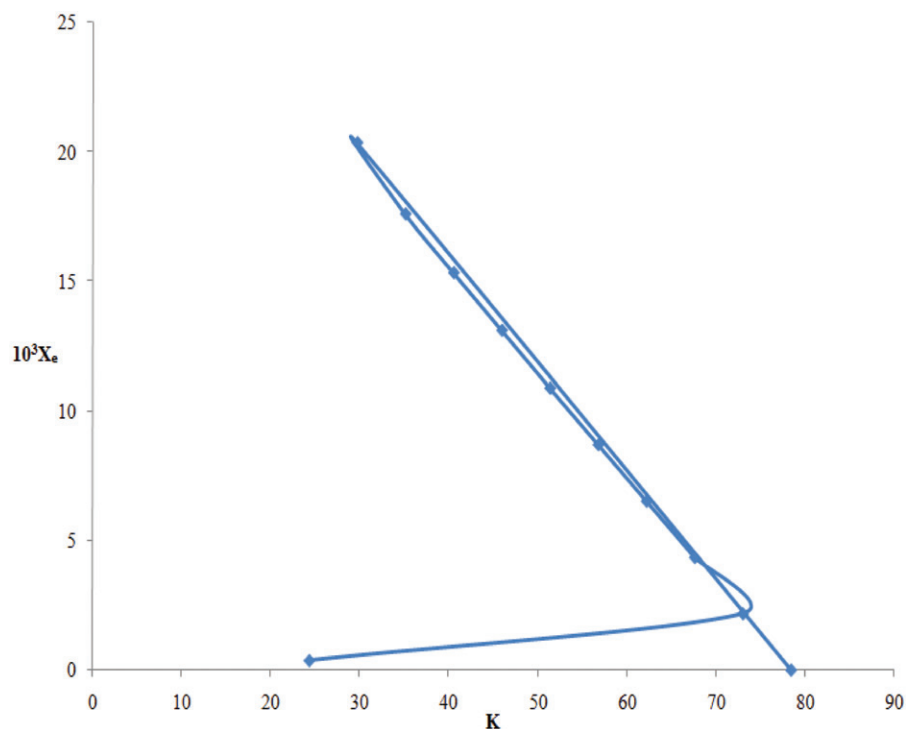
298.15 K are also listed in Table 2 for each cosolvent mixture. The value of  $K$  was calculated using Equation (2):

$$K = \frac{k_1 \times w_1 + k_2 \times w_2}{100} \quad (2)$$

where,  $k_1$  and  $k_2$  represent the dielectric constant of ethanol and

It was observed that the mole fraction solubility of GBN was found to be increased exponentially with increase in temperature in each mixture of ethanol and water. The mole fraction solubility of GBN was found to be highest and lowest in ethanol–water mixture ( $w=0.9$ ) and distilled water, respectively at each temperature studied (Figure 2). Mole fraction solubility of GBN

Figure 4. Impact of dielectric constant ( $K$ ) on experimental mole fraction solubility ( $X_e$ ) of glibenclamide at room temperature (298.15 K).



distilled water (Table 2). The effect of mass fraction of ethanol on mole fraction solubility of GBN at various temperatures is depicted in Figure 3. It was observed that the mole fraction solubility of GBN was found to be increased with increase in mass fraction of ethanol (up to 0.9 in ethanol–water mixtures) and started to decrease at mass fraction of 1.0 (pure ethanol) at each temperature studied (Figure 3). The highest value of mole fraction solubility was obtained at mass fraction of 0.9 at each temperature studied. The results of mole fraction solubility of GBN have also been correlated with dielectric constant/polarity and molecular weight of cosolvents. The effect of dielectric constant/polarity of various ethanol–water mixtures on mole fraction solubility of GBN is presented in Figure 4. It has been reported in literature that the dielectric constant ( $K$ ) of pure water (78.36) is much higher than pure ethanol<sup>18</sup> (24.30) at 298.15 K. Therefore, the lowest mole fraction solubility of GBN in distilled water was probably due to its highest polarity<sup>19</sup>. It has also been reported in literature that the solubility of solutes could be increased by decreasing the dielectric constants of solvents or cosolvent mixtures<sup>20</sup>. The solubility of GBN in ethanol–water mixtures was increased significantly by increasing the mass fraction of ethanol in cosolvent mixtures (except in case of pure ethanol) that could be due to reduced polarities in ethanol–water mixtures<sup>18–20</sup>. As stated previously that the mole fraction solubility of GBN was found to be highest at mass fraction 0.9 of ethanol in ethanol–water mixtures (Figure 3). The dielectric constant of mass fraction 0.9 was observed as 29.707 (Table 2) which was greater than pure ethanol (24.30). Therefore, we can conclude that mole fraction solubility could depend not only on polarity/dielectric constant but also on molecular structure and molecular weight of the solutes and solvents. The highest mole fraction solubility of GBN at 0.9 mass fraction of ethanol in ethanol–water mixture was probably due to the lower molecular weight of ethanol (46.069) because it is inversely proportional to the molecular weight of cosolvents. Based on the solubility data of GBN in pure distilled water and pure ethanol, it was considered as practically insoluble

as a green and environmentally benign cosolvent in preformulation studies and formulation development especially for liquid dosage forms of GBN.

#### Thermodynamic modeling of GBN solubility

According to the modified Apelblat model, the mole fraction solubility of solutes/drugs depends mainly on absolute temperature ( $T$ )<sup>11–14</sup>. At an equilibrium, the temperature-dependent mole fraction solubility ( $x_e$ ) of GBN can be represented by Equation (3) (modified Apelblat equation)<sup>12</sup>:

$$\ln x_e = A + \frac{B}{T} + C \ln(T) \quad (3)$$

where,  $A$ ,  $B$  and  $C$  are adjustable parameters of the modified Apelblat equation. In the present study, these adjustable parameters were determined by regression analysis of the experimental solubility data. The modified Apelblat/calculated solubility ( $x_{mAc}$ ) at each temperature was calculated using equation parameters  $A$ ,  $B$  and  $C$ . The modified Apelblat solubility was correlated with experimental solubility of GBN (Figure 5). The percent of absolute relative deviation (%AD) was also calculated using Equation (4) to evaluate the differences between experimental ( $x_e$ ) and calculated ( $x_c$ ) solubility of GBN. The data of all these parameters is listed in Table 2.

$$AD(\%) = \frac{(x_e - x_c)}{x_e} \times 100 \quad (4)$$

It was observed that the %AD was found to be less than 0.1% in most of the ethanol–water mixtures at each temperature studied (Table 2). The values of equation parameters  $A$ ,  $B$  and  $C$  in various ethanol–water mixtures are listed in Table 3. The correlation between the experimental and modified Apelblat solubility data in various ethanol–water mixtures is presented in Figure 5. The values of correlation coefficient ( $R^2$ ) for GBN in pure water ( $w = 0.0$ ) and pure ethanol ( $w = 1.0$ ) were found to be 0.9916 and 0.9966, respectively (Table 3). The  $R^2$  values for

Figure 5. The correlation of experimental mole fraction solubilities ( $X_e$ ) with the modified Apelblat model for glibenclamide in various ethanol–water mixtures at temperature range from 293.15 to 318.15 K (mApl denotes the modified Apelblat solubilities).

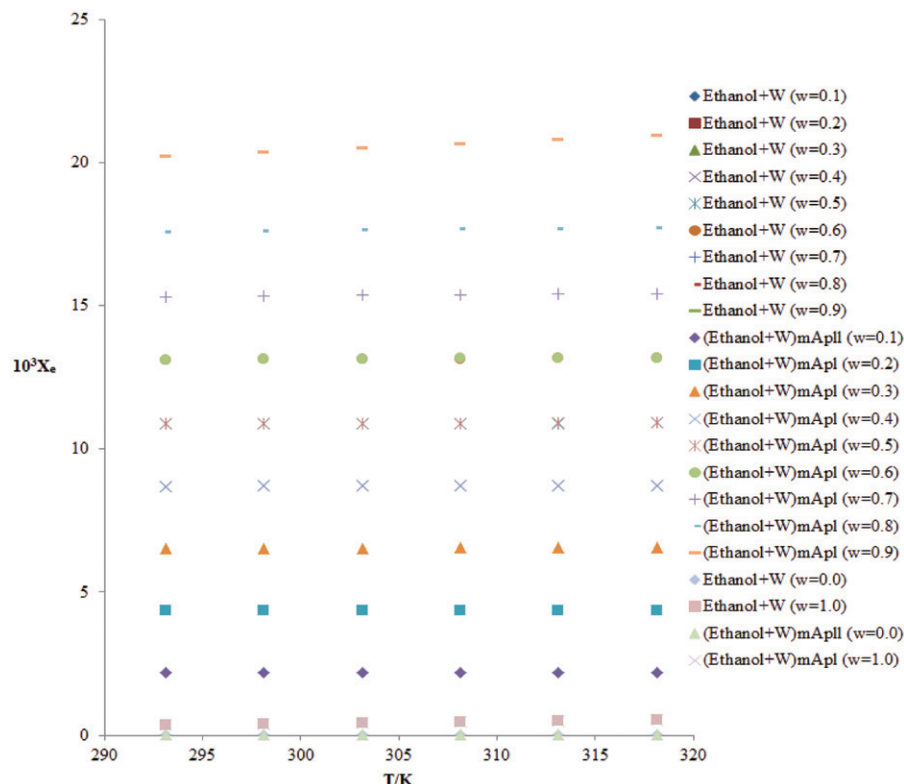


Table 3. The modified Apelblat model parameters ( $A$ ,  $B$  and  $C$ ) for glibenclamide in various ethanol–water mixtures.

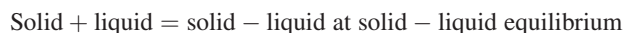
Sample	Modified Apelblat model			$R^2$
	$A$	$B$	$C$	
Ethanol + W ( $w=0.0$ )	-66.64	35.30	10.7510	0.9940
Ethanol + W ( $w=0.1$ )	0.302	2.00	0.0826	0.9980
Ethanol + W ( $w=0.2$ )	1.190	1.68	0.0482	0.9961
Ethanol + W ( $w=0.3$ )	1.615	1.62	0.0448	0.9972
Ethanol + W ( $w=0.4$ )	1.907	1.58	0.0400	0.9954
Ethanol + W ( $w=0.5$ )	2.181	1.55	0.0352	0.9983
Ethanol + W ( $w=0.6$ )	2.130	1.96	0.0766	0.9992
Ethanol + W ( $w=0.7$ )	2.232	2.20	0.0860	0.9996
Ethanol + W ( $w=0.8$ )	2.215	2.36	0.1131	0.9999
Ethanol + W ( $w=0.9$ )	0.5117	5.40	0.4359	1.0000
Ethanol + W ( $w=1.0$ )	-31.53	68.90	5.2550	0.9963

Distilled water (W), mass fraction of ethanol in cosolvent mixtures ( $w$ ).

%AD and higher values of  $R^2$  clearly indicated a good fitting of the experimental data with the modified Apelblat model.

### Thermodynamic parameters for GBN dissolution

According to thermodynamics principles, the process of GBN dissolution into a liquid or cosolvent mixtures can be expressed as:



The molar enthalpy ( $\Delta\text{solH}$ ) and entropy ( $\Delta\text{solS}$ ) for GBN dissolution can be calculated with the help of Equations (5) and (6), respectively<sup>21–23</sup>:

$$\Delta\text{solH} = RT \left( C - \frac{B}{T} \right) \quad (5)$$

The results of these thermodynamic parameters in various ethanol–water mixtures at the temperature range of 293.15 to 318.15 K are listed in Table 4. The  $\Delta\text{solH}$  for GBN dissolution in pure water and pure ethanol ranged from 25.910–28.145 and 12.235–13.327 kJ mol<sup>-1</sup>, respectively at various temperatures. However, the  $\Delta\text{solH}$  for GBN dissolution in various ethanol–water mixtures ranged from 0.072–3.483 kJ mol<sup>-1</sup> at same temperature range which was significantly lower than pure solvents (Table 4). The  $\Delta\text{solH}$  for GBN dissolution in pure water was observed as highest as compared to pure ethanol and various ethanol–water mixtures which clearly indicated that high input of energy is required for complete dissolution/solubilization of GBN in pure water as compared to pure ethanol and various ethanol–water mixtures. However, the lower values of  $\Delta\text{solH}$  for GBN dissolution in pure ethanol and various ethanol–water mixtures indicated that relatively low input of energy is required for complete dissolution/solubilization of GBN in pure ethanol and various ethanol–water mixtures. Overall, the positive values of  $\Delta\text{solH}$  in pure water, pure ethanol and various ethanol–water mixtures indicated that the dissolution process of GBN is endothermic in each case<sup>12</sup>. The  $\Delta\text{solS}$  values for GBN dissolution in pure water, pure ethanol and various ethanol–water mixtures were also observed as positive values at each temperature studied which also indicated the possibility of GBN dissolution as an endothermic and an entropy-driven process (Table 4).

### Conclusions

In the present study, the mole fraction solubility of GBN in various ethanol–water mixtures was measured by shake flask method at various temperatures. The solubility data of GBN was found to be temperature-dependent in all ethanol–water mixtures (solubility was found to be increased exponentially with increase

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

## LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

## FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

## E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.