



THERMODYNAMICS OF ALLOXAN SOLUBILITY IN VARIOUS SOLVENTS AT DIFFERENT TEMPERATURES

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The solubility of Alloxan in methanol, ethanol, ethane-1, 2-diol, water, acetone, and tetrahydrofuran was measured by gravimetric method over a temperature range (293.15 to 323.15) K at atmospheric pressure. The solubility increases non-linearly with temperature in all the studied solvents. Further, in protic solvents, solubility is maximum in methanol and minimum in ethane-1, 2 diol whereas in the selected nonprotic solvents, solubility is greater in tetrahydrofuran than in acetone. The experimental data were correlated with modified Apelblat and Buchowski-Ksiazczak equations. The calculated results show good agreement with the experimental data. Some thermodynamic parameters such as dissolution enthalpy, Gibb's free energy, and entropy of mixing have also been calculated. The evaluated thermodynamic parameters are found to be positive. The positive enthalpy and Gibb's free energy indicate endothermic and spontaneous dissolution of compounds. The positive entropy suggests entropy-driving dissolution process.

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Introduction

Diabetes mellitus has been considered as one of the major health concerns all around the world today.^{1,2} One of the most potent methods to induce experimental diabetes mellitus is chemical induction by alloxan which is a well known diabetogenic agent.³⁻⁶

Alloxan is an oxygenated pyrimidine derivative, and its IUPAC name is 2,4,5,6-pyrimidinetetrone. Figure 1 shows the structure of alloxan.

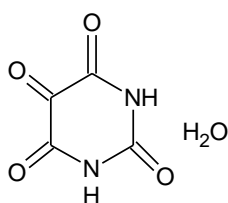


Figure 1. The structure of alloxan

It causes selective necrosis of the β -cells of pancreatic islets. In pharmaceutical industries, the crystallization process is a critical method for both drug intermediates and final drugs. The solubility data is essential for the selection of the proper solvent for the crystallization process and in pre-formulation studies.⁷ Further, phenomenological treatment of drug delivery, transport and distribution are dependent on knowledge of solubility.⁸ The transportation through membranes and the topical activity of drugs can also be predicted by solubility data.⁹

Various workers have reported solubility of drugs and other compounds in different solvents.¹⁰⁻¹² Thus, in the present work, the solubilities of alloxan have been

determined in various solvents; methanol, ethanol, ethane-1,2-diol, water, tetrahydrofuran and acetone over a temperature range 293.15 K to 323.15 K by a gravimetric method. The experimental solubility data were correlated with modified Apelblat and Buchowski-Ksiazczak models. Further, some thermodynamic parameters such as enthalpy of dissolution, Gibb's energy, and entropy of solutions have been evaluated.

Experimental

Materials

Alloxan was purchased from Loba Chemie Pvt. Ltd. The polymorph used in this study was monohydrate. The melting point of alloxan was determined measured by Differential Scanning Calorimeter (Shimadzu-DSC-60) and was found to be 254 °C. All of the solvents used for the present study were of analytical grade and supplied by Loba Chemie Pvt. Ltd. These solvents were purified by drying over anhydrous sodium sulfate and were fractionally distilled. The solvents were stored over molecular sieves. The purities of the solvents were confirmed by GC-MS (SHIMADZU-Model No.-QP-2010) equipped with column (DB-5MS, 25 m in length, 0.20 mm internal diameter and 0.33 μ m film) and were found to be greater than 99.8 %.

Solubility measurement

The solubility of alloxan was determined by the gravimetric method. For each measurement, an excess mass of drug was added to a known mass of solvent. The equilibrium cell was heated to a constant temperature with continuous stirring for about 5 hours (the temperature of the water bath approached the constant value, and then the actual value of the temperature was recorded). After 5 hours, stirring was stopped, and the solution was kept for 2 hours to approach equilibrium. The equilibrium time of 2 hours is optimized by checking the concentration of solution at

different intervals of time. After 2 hours, the change in concentration was less than 1 %, so the saturated solution was assumed to be equilibrium. The upper portion of this clear solution was filtered through a membrane (0.22 μm) and was kept in a weighed vial. The vial with the solution was quickly weighed to determine the mass of the sample. When the mass of the residue reached constant value, the final mass was recorded. All of the masses were taken using an electronic balance (Mettler Toledo AB204-S, Switzerland) with an uncertainty of ± 0.0001 g. At each temperature, the measurement was conducted three times, and an average value was used to determine the mole fraction solubility. The saturated mole fraction solubility (x_i) of the drug in each solvent can be calculated by using equation (1).

$$x_i = \frac{\frac{m_2}{M_2}}{\frac{m_1}{M_2} + \frac{m_2}{M_2}} \quad (1)$$

where

M_1 is the molar mass of solvent and

M_2 is the molar mass of alloxan.

m_1 and m_2 are the mass of the solvent and solute (alloxan), respectively.

At each temperature, the measurement was conducted three times. By using the average value, mole fraction solubility of alloxan in selected solvents was calculated.

Results and discussion

The mole fraction solubilities x_i of alloxan in the selected solvents are presented in Table 1 at different temperatures (293.15 to 323.15 K) with an uncertainty of ± 0.1 K and more visually given in Fig. 2. It is observed that the solubility of alloxan increases nonlinearly with temperature. Further, in protic solvents, solubility is maximum in methanol and minimum in ethane-1,2-diol. The order of solubility is: methanol > water > ethanol > ethane-1,2 diol. In the selected nonprotic solvents, solubility is greater in tetrahydrofuran than in acetone. The results are compared with dielectric constants and dipole moments of the solvents, which was given in Table 2. For protic solvents, solubility was maximum in methanol and minimum in ethane-1,2-diol which is of reverse order of dipole moment. The dipole moment of ethane-1,2-diol is highest among studied protic solvents whereas that of methanol is lowest. In nonprotic solvents, solubility was found to be in higher in tetrahydrofuran (THF) than in acetone. The dipole moment of acetone is higher than that of THF. So, the solubility of alloxan was increasing with decreasing of dipole moment.

The temperature dependence of alloxan solubility in pure solvents was described by the modified Apelblat model.¹³

$$\ln x_{ci}^a = A + \frac{B}{T} + C \ln T \quad (2)$$

Table 1. Experimental and calculated mole fraction solubilities (x_i) of alloxan in different studied solvents at different temperatures.

T/K	x_i	x_{cal}^a	x_{cal}^b
Methanol			
293.15	0.1054	0.1055	0.1061
298.15	0.1172	0.1172	0.1170
303.15	0.1291	0.1294	0.1287
308.15	0.1420	0.1420	0.1410
313.15	0.1550	0.1549	0.1541
318.15	0.1681	0.1681	0.1680
323.15	0.1813	0.1815	0.1826
Ethanol			
293.15	0.0856	0.0856	0.0865
298.15	0.0962	0.0962	0.0963
303.15	0.1069	0.1073	0.1068
308.15	0.1190	0.1189	0.1181
313.15	0.1310	0.1307	0.1301
318.15	0.1426	0.1427	0.1429
323.15	0.1546	0.1548	0.1565
Ethane-1,2 diol			
293.15	0.0113	0.0114	0.0116
298.15	0.0143	0.0141	0.0141
303.15	0.0172	0.0172	0.0169
308.15	0.0206	0.0206	0.0202
313.15	0.0240	0.0240	0.0240
318.15	0.0283	0.0283	0.0283
323.15	0.0327	0.0327	0.0333
Water			
293.15	0.0377	0.0378	0.0378
298.15	0.0403	0.0403	0.0404
303.15	0.0429	0.0429	0.0429
308.15	0.0456	0.0455	0.0456
313.15	0.0482	0.0482	0.0483
318.15	0.0510	0.0511	0.0511
323.15	0.0539	0.0539	0.0540
THF			
293.15	0.0460	0.0461	0.0469
298.15	0.0549	0.0546	0.0546
303.15	0.0638	0.0638	0.0632
308.15	0.0739	0.0739	0.0729
313.15	0.0840	0.0840	0.0836
318.15	0.0954	0.0954	0.0955
323.15	0.1068	0.1067	0.1086
Acetone			
293.15	0.0128	0.0129	0.0128
298.15	0.0132	0.0132	0.0132
303.15	0.0136	0.0136	0.0135
308.15	0.0140	0.0139	0.0139
313.15	0.0143	0.0143	0.0143
318.15	0.0146	0.0146	0.0146
323.15	0.0150	0.0150	0.0150

^aApelblat equation, ^bBuchowski-Ksiazczak equation.

The values of parameters A , B and C were evaluated by nonregression method and are given in Table 3.

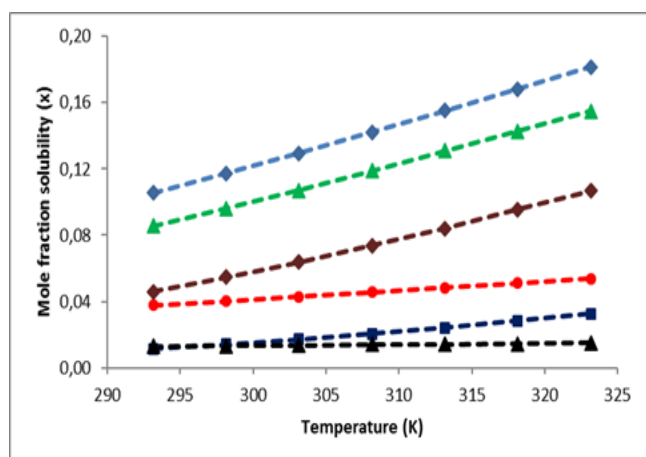


Figure 2. Variation of mole fraction solubilities (x_i) with temperature (T) for alloxan in different studied solvents. Methanol (\blacklozenge), ethanol (\blacktriangle), water (\bullet), ethane-1,2-diol (\blacksquare), THF (\blacklozenge), acetone (\blacktriangle). Dashed lines represent calculated mole fraction solubility by Apelblat equation

Using these parameters, mole fraction solubility (x_{ci}^a) was evaluated. These calculated solubilities (x_{ci}^a) are also plotted against temperature along with experimental mole fraction solubility (x_i) as shown in Figure 2. It is observed that these are good agreement between the experimental and calculated solubility values.

The Buchowski-Ksiazczak (λh) equation was first introduced by Buchowski *et al.* to describe solid-liquid equilibrium. In the present study, solubility data was also correlated with temperature by the following Buchowski-Ksiazczak (λh) model.¹⁴

$$\ln \left(1 + \frac{\lambda(1 - x_{ci}^b)}{x_{ci}^b} \right) = \lambda h \left[\frac{1}{T} - \frac{1}{T_m} \right] \quad (3)$$

where

T and T_m are the experimental and melting temperature of alloxan

λ and h are two adjustable parameters.

Table 2. Dipole moments and Dielectric constants of the studied solvents

Solvent	Dipole moment	Dielectric constant
Methanol	1.70	32.70
Ethanol	1.69	24.55
Ethane-1,2 diol	2.28	38.66
Water	1.80	80.00
THF	1.55	5.61
Acetone	2.88	20.70

The values of λ and h are evaluated using experimental solubility data and are reported in Table 4. Using these values of adjustable parameters, solubility (x_{ci}^b) is calculated using equation (3). These values are also plotted against temperature along with experimental mole fraction solubility (x_i) as shown in Figure 3. It is observed that the calculated solubilities by Buchowski-Ksiazczak (λh) model are in good agreement with experimental solubility in all the solvents.

The root-mean-square deviations (RMSD) and average relative deviations (ARD) are also calculated for both Apelblat and Buchowski-Ksiazczak models using following equations:

$$RMSD = \left[\frac{\sum_{i=1}^N (x_{ci}^{a/b} - x_i)^2}{N-1} \right]^{1/2} \quad (4)$$

$$ARD = \frac{1}{N} \sum_i \frac{x_i - x_{ci}^{a/b}}{x_i} \quad (5)$$

where N is the number of experimental points.

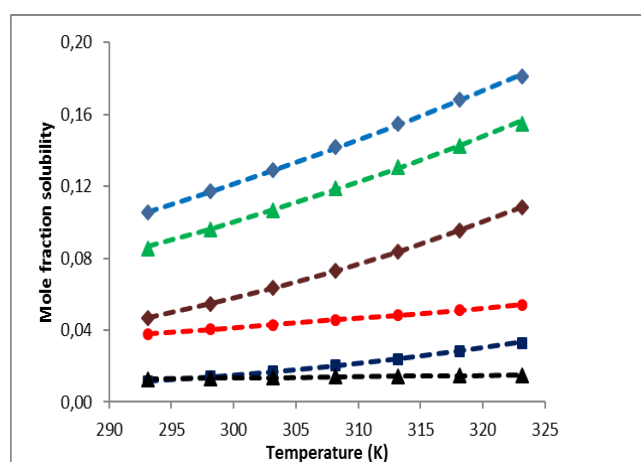


Figure 3. Variation of mole fraction solubilities (x_i) with temperature (T) for alloxan in different studied solvents. Methanol (\blacklozenge), ethanol (\blacktriangle), water (\bullet), ethane-1,2-diol (\blacksquare), THF (\blacklozenge), acetone (\blacktriangle). Dashed lines represent calculated mole fraction solubilities by Buchowski-Ksiazczak equation

These values are listed in Tables 3 and 4 for Apelblat and Buchowski-Ksiazczak models respectively.

From these solubility data, some thermodynamic parameters such as enthalpies of solution (ΔH_{sol}), Gibb's energy of dissolution (ΔG_{sol}) and entropy of solutions (ΔS_{sol}) have also been evaluated. The enthalpies of solution (ΔH_{sol}) was calculated by modified van't Hoff equation, i.e., from the slope of the plot of $\ln x$ versus $(1/T - 1/T_{hm})$.

Table 3. Parameters A, B and C of Apelblat model in studied solvents

Parameters	A	B	C	10 ² RMSD	10 ² ARD
Methanol	76.1403	-5030.5957	-10.7785	0.0146	-0.0533
Ethanol	106.5523	-6563.97	-15.2482	0.0233	-0.0003
Ethane-1,2-diol	241.2325	-14029.2250	-34.8287	0.0085	0.0734
Water	-2.2895	-992.8372	0.4225	0.0065	-0.0346
THF	180.4289	-10624.1830	-25.9236	0.0125	0.0604
Acetone	-3.4772	-450.6254	0.1161	0.0053	-0.0096

*ARD=average relative deviation, RMSD=root mean square deviation

Table 4. Parameters of Buchowski-Ksiazczak λh equation in the studied solvents

Parameters	λ	h	10 ² RMSD	10 ² ARD
Methanol	1.4234	1204.997	0.0762	-0.0084
Ethanol	1.4710	1272.619	0.0955	-0.0017
Ethane-1,2 diol	1.7522	1890.145	0.0326	-0.0562
Water	0.2071	5423.384	0.0115	-0.2255
THF	2.5826	1025.290	0.0897	-0.0345
Acetone	0.0270	18197.910	0.0039	-0.0929

*ARD=average relative deviation, RMSD=root mean square deviation

$$\left[\frac{\partial \ln x_i}{\partial \left[\frac{1}{T} - \frac{1}{T_m} \right]} \right]_p = - \frac{\Delta H_{sol}}{R} \quad (6)$$

where

T is the experimental temperature, and

R is gas constant.

T_{hm} is the mean harmonic temperature

T_{hm} is given as

$$T_{hm} = \frac{n}{\sum_{i=1}^n \frac{1}{T}} \quad (7)$$

where n is the number of experimental temperatures.

In the present case, the T_{hm} value obtained is only 307.83 K. From the intercepts of these plots, Gibbs energy change (ΔG_{sol}) for the solubility process was evaluated by the following relation:

$$\Delta G_{sol} = -RT_{hm} \text{ intercept} \quad (8)$$

Using these evaluated ΔH_{sol} and ΔG_{sol} values, the entropies of solutions (ΔS_{sol}) were obtained from the following equation:

$$\Delta S_{sol} = \frac{(\Delta H_{sol} - \Delta G_{sol})}{T_{hm}} \quad (9)$$

Table 5 summarizes these thermodynamic parameters. It is found that enthalpy of dissolution (ΔH_{sol}) is positive for all the solvents indicating the thereby endothermic behavior of dissolution.

Table 5. Thermodynamic parameters: Enthalpy of dissolution (ΔH_{sol}), Gibbs's Energy (ΔG_{sol}) and Entropy (ΔS_{sol}) of dissolution of alloxan in different studied solvents

Solvent	ΔH_{sol} kJ mol ⁻¹	ΔG_{sol} kJ mol ⁻¹	ΔS_{sol} J mol ⁻¹ K ⁻¹
Methanol	14.2502	5.0260	29.9640
Ethanol	15.5638	9.8789	47.3505
Ethane-1,2 diol	27.5526	10.0150	56.9030
Water	9.3283	7.9160	4.5880
THF	22.0155	6.7260	49.6690
Acetone	4.0431	10.9410	22.4080

This suggests that there may be strong interactions between drug and solvent molecules that those between the solvent molecules and the newly formed bond energy between drug and solvent molecule is not powerful enough to compensate the energy needed for breaking the original association bond in various solvents.¹⁵ The Gibbs energy of dissolution (ΔG_{sol}) is positive for the studied solvents suggesting that the dissolution process is spontaneous. Further, the order of ΔG_{sol} values is the reverse of solubility data. The Gibbs energy of dissolution is minimum for methanol and maximum for acetone whereas solubility is maximum for methanol and minimum for acetone. Further, the entropy of dissolution (ΔS_{sol}) is found to be positive in all the solvents. The positive entropy change indicates that the entropy of solubilization is unfavorable for the solute in solution.¹⁴ The entropy depends on the functional groups present in the drug as well as in the solvent. Owing to the Alloxan molecule containing groups of different nature like -NH-, -C=O, there may exist various forces such as electrostatic force, hydrogen bond, hydrophobic interaction and stereoscopic effect in the dissolving process.

Conclusion

In protic solvents, solubility is maximum in methanol and minimum in ethane-1,2-diol. The order of solubility is: methanol > ethanol > water > ethane-1,2-diol. In the selected nonprotic solvents, solubility is greater in THF than in acetone. The positive Gibbs energy and enthalpy of dissolution suggest dissolution process be endothermic and spontaneous.

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