THERMODYNAMIC PARAMETERS OF SOLUTIONS OF SILDENAFIL CITRATE IN SOME ORGANIC SOLVENTS AT DIFFERENT TEMPERATURES

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ABSTRACT

The solubility of Sildenafil citrate in some organic solvents; hexane, toluene,1-butanol and 1,2 dichloroethane has been determined using gravimetric method over different temperature range (298.15 K to 328.15 K) at one atmospheric pressure. The modified Apelblat and Buchowski-Ksiazczak h equations were used to correlate the experimental solubility data. Further, various thermodynamic parameters have been evaluated from these solubility data.

Key Words: Solubility, Organic solvents, Sildenafil citrate, Thermodynamic parameters

1.   INTRODUCTION:

 Sildenafil citrate 1-[4-ethoxy-3-(6,7-dihydro-1-methyl- 7-oxo-3-propyl-1*H*-pyrazolo[4,3-*d*] pyrimidin-5-yl) phenylsulfonyl]-4-methylpiperazine is a drug which has been used to treat erectile dysfunction and pulmonary arterial hypertension [1]. It relaxes the arterial wall, leading to decreased pulmonary arterial resistance and pressure. It was developed and is being marketed by the pharmaceutical company Pfizer. It is well known by the name Viagra. It is metabolised by liver enzymes and excreted by both the liver and kidneys. Further, it is a selective inhibitor of cyclic guanosine monophosphate-specific phosphodiesterase [2]. Professional athletes also use this drug to enhance their performance [3].

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Due to its important applications, it was thought of interest to study its solubility in different solvents which may help its use in other fields. Thus, in the present study, the solubility of Sildenafil citrate was determined in hexane, toluene, 1-butanol and 1,2 dichloroethane at different temperatures (298.15 K to 328.15 K) by a gravimetric method. Further, various thermodynamic parameters were evaluated from the solubility data.

2.   EXPERIMENTAL SECTION

- *Materials:*

Sildenafil citrate [Fig. 1], with mass purity of 0.99 was purchased from Ami Life Sciences Pvt. Ltd. Vadodara (India). The solvents; hexane, toluene,1-butanol and 1,2 dichloroethane were analytical grade reagents, which were purified by fractional distillation. The purity was determined by using Shimadzu gas chromatography/mass spectrometry (Model No QP-2010) and was found to be greater than 99.5%.
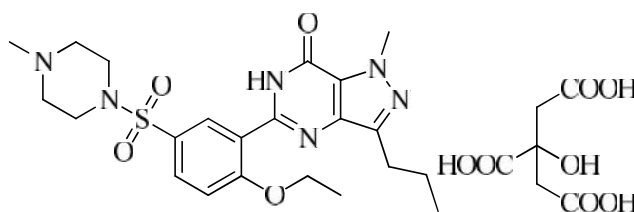

Fig.1. Chemical structure of Sildenafil citrate

- *Solubility measurement*

The gravimetric method was used to study the solubility. For each measurement, an excess mass of Sidnafil citrate was added to a known mass of solvent. Then equilibrium cell was heated to a constant temperature with continuous stirring. After, at least 3.5 h, the stirring was stopped and the solution was kept at a constant temperature for 2 h. The equilibrium time of 2 h is optimized by checking the concentration of the solution at different intervals of time. After 2 h, the change in concentration was less than 1 %, so saturated solution was assumed to be in equilibrium. Upper portion of this clear solution was filtered by a membrane (0.45 μm) and kept in a weighed vial. The vial with solution was quickly weighed to determine the mass of the sample and placed in vacuum oven at 313.15 K to fully evaporate solvents. When the mass of the residue reached at 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 of solute (*x*) in solvents by using equation (1) and given in Table 2.

$$x = \frac{m_2/M_2}{m_2/M_2 + m_1/M_1} \tag{1}$$

where M_1 and M_2 is the molar mass of solvent and drug respectively. m_1 and m_2 are weights of solvent and drug in the solution respectively.

3. RESULTS AND DISCUSSION

The experimental solubility data of drug in hexane, toluene, 1-butanol and 1,2 dichloroethane are summarized in Table 1 at different temperatures. It is observed that solubility increases with temperature in all the solvents. The variation of solubility as a function of temperature is also shown in Fig. 2. It is observed that over all, solubility is maximum in toluene and minimum in dichloroethane. The solubility of drug in these solvents is compared with dielectric constant and dipole moments of the solvents (Table 2). Both hexane and toluene have lower dielectric constants and dipole moments as compared to those for 1-butanol and dichloroethane. This is reverse of solubility results. This suggests the solubility of studied drug is reverse of dielectric constants and dipole moments. However, among hexane and toluene, solubility is higher in toluene (having higher dielectric constant and dipole moment) whereas among 1-butanol and DCE, solubility is higher in -butanol (having higher dielectric constant and dipole moment). This indicates that other factors also contribute to dissolution of a substance in a solvent.

Table 1. Experimental mole fraction solubilities (*x),* calculated mole fraction solubilities ($x^{a/b}_c$) and relative deviation (*RD*) of Sildenafil citrate in studied solvents.

T/K	$x \times 10^4$	$x^a_c \times 10^4$	100RD	$x^b_c \times 10^4$	100RD
			Hexane		
298.15	4.00	4.15	-3.70	3.46	13.54
303.15	4.80	4.35	9.34	4.42	7.99
308.15	4.70	4.93	-4.97	5.60	-19.04
313.15	6.10	6.01	1.41	7.04	-15.33
318.15	7.50	7.85	-4.62	8.78	-17.10
323.15	11.50	10.91	5.12	10.89	5.32
328.15	16.00	16.10	-0.65	13.41	16.18
			Toluene		
298.15	3.00	2.60	13.32	2.97	1.04
303.15	5.00	5.73	-14.59	5.69	-13.81
308.15	9.00	11.63	-29.25	10.68	-18.66
313.15	26.00	21.87	15.88	19.64	24.45
318.15	44.00	38.25	13.07	35.44	19.45
323.15	64.00	62.48	2.38	62.80	1.88
328.15	87.00	95.69	-9.99	109.34	-25.68
			n-Butanol		
298.15	0.40	0.396	0.89	0.46	-16.01
303.15	0.60	0.635	-5.87	0.63	-5.37
308.15	1.00	0.939	6.09	0.85	14.72
313.15	1.30	1.287	0.99	1.14	12.36
318.15	1.60	1.643	-2.69	1.51	5.73
323.15	1.90	1.962	-3.26	1.98	-4.20
328.15	2.25	2.200	2.23	2.58	-14.53
			DCE		
298.15	0.25	0.281	-12.30	0.34	-37.22
303.15	0.60	0.495	17.44	0.49	18.08
308.15	0.80	0.789	1.36	0.70	12.98
313.15	1.05	1.142	-8.77	0.97	7.14
318.15	1.45	1.510	-4.17	1.35	6.82
323.15	1.80	1.835	-1.95	1.85	-2.98
328.15	2.15	2.059	4.25	2.52	-17.15

Table 2. Dielectric constants and dipole moments of the solvents at 293.15 K.

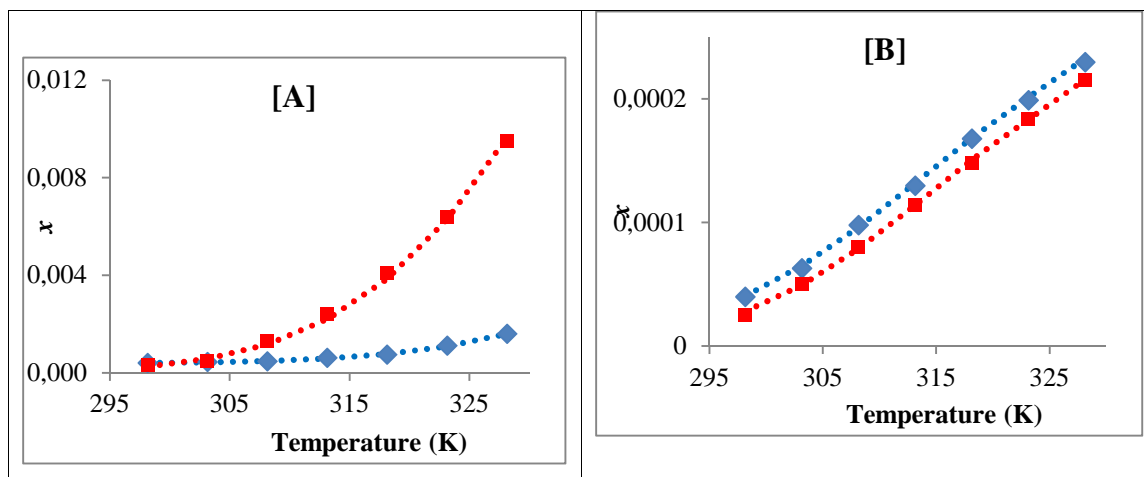|	*Hexane*	*Toluene*	*1-butanol*	*DCE*
Dielectric constant	1.89 (20)	2.38(25)	17.50(25)	10.35(25)
Dipole moments	0.08(25)	0.375(25)	1.66(20)	1.20(30)

Fig.2. Variation of mole fraction solubilities (*x*) with temperature (*T*) for Sildenafil citrate in different studied solvents. **[A]** in Hexane   and Toluene   ; [B] in 1-butanol   and dichloroethane   . Corresponding dotted lines are for solubilities calculated by eq 2.

The temperature dependence of solubility in a solvent is described by the modified Apelblat equation [4, 5].

$$ln\ x = A + B/T + C\ ln(T) \qquad (2)$$

where *x* is the mole fraction solubility of drug at temperature *T*. *A*, *B* and *C* are parameters determined by least square analysis from the correlation of the experimental data and values of these parameters are given in Table 3. Using these parameters, mole fraction solubilities (x^a_{ci}) for drug were evaluated and are given in Table1.

The Buchowski–Ksiazczak   h equation [6, 7] describes the solid-liquid equilibrium behavior by only two adjustable parameters   and h.

$$\ln\left(\boldsymbol{1} + \frac{\}(\boldsymbol{1} - \chi^{b}_{ci})}{\chi^{b}_{ci}}\right) = \}h\left[\frac{\boldsymbol{1}}{(T/K)} - \frac{\boldsymbol{1}}{(T_m/K)}\right] \qquad (3)$$

where *T* and T_m represents the experimental and melting temperatures of drug in Kelvin.   and *h* are the model adjustable parameters, which are given in Tables 4.

Table 3. Parameters A, B and C of eq (2), ARD of eq (5) and RMSD of eq (6) of Sildenafil citrate in studied solvents.

Solvent	A	B	C	RMSD	100 AAD
Hexane	-1987.23	88006.01	295.61	3.56576E-05	0.369
Toluene	1444.82	-77278.22	-209.54	4.75E-04	-1.31
1-butanol	1653.66	-81833.01	-243.84	4.71532E-06	-0.23
DCE	2123.65	-104399.48	-313.11	7.49607E-06	-0.59

Table 4. Parameters   and h of eq (3), ARD of eq (5) and RMSD of eq (6) of Sildenafil citrate in studied solvents

Solvent		h	RMSD	100 AAD
Hexane	0.066	4421	1.34E-04	-3.5174
Toluene	356.71	11763	9.39E-04	2.0493
1-butanol	0.0360	5592	1.57E-05	1.0327
DCE	0.0787	6503	1.63E-05	0.6884

Using these parameters, mole fraction solubility ($x^b{}_{ci}$) for drug in different solvents at different temperatures was evaluated and was compared with experimental mole fraction solubility and are given in Table 1. The relative deviation (RD) between experimental and calculated solubility values is calculated by the following equation (4) and is listed in Table 1.

$$RD = \frac{\left(x_i - x_{ci}^{a/b}\right)}{x_i} \tag{4}$$

where x_i is experimental solubility and $x_{ci}^{a/b}$ is calculated solubility. For Apelblat eq. (2), calculated solubility is x_{ci}^{a} whereas for Buchowski–Ksiazczak eq. (3), it is x_{ci}^{b}.

The, average relative deviations (ARD) and root-mean-square deviations (RMSD) were also calculated for modified Apelblat and   h relations using equations (5) and (6) and are listed in Tables 3 and 4.

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

$$RMSD = \left[\sum_{i=1}^{N} \frac{(x_{ci}^{a/b} - x_i)^2}{N-1} \right]^{1/2} \tag{6}$$

where N is the number of experimental points.

- ***Thermodynamic functions of dissolution***

The dissolution of a substance in a solvent is associated with changes in thermodynamic functions such as standard Gibb's energy (G_{sol}), standard enthalpy (ΔH_{sol}) and standard entropy (ΔS_{sol}) of solution which are calculated from experimental solubility data. The changes that occur in the solute during dissolution process can be explained by these thermodynamic functions.

According to the Krug et al. [8] approach, the following modified van't Hoff expression [9] was used to determine the enthalpy of solution (ΔH_{sol}).

$$\left(\frac{\partial \ln x}{\partial \left(\frac{1}{T} - \frac{1}{T_{hm}} \right)} \right)_P = -\frac{\Delta H_{sol}}{R} \qquad (7)$$

where H_{sol} is the standard enthalpy energy charge for the solution process and T_{hm} is the harmonic mean of the experimental temperatures, which is evaluated by following equation.

$$T_{hm} = \frac{n}{\sum_{1}^{n} \left(\frac{1}{T} \right)} \qquad (8)$$

where n is the number of experimental temperatures [10]. In the present case, T_{hm} value is 312.83 K. The value of ΔH_{sol} was obtained from the slope of the plot of *ln x* versus (*1/T-1/312.83*). The standard Gibbs energy change for the solution process (G_{sol}), considering the approach proposed by Krug et al., is calculated at T_{hm} by following equation.

$$G_{sol} = -R \cdot T_{hm} \cdot Intercept \qquad (9)$$

in which, the intercept was obtained from the plot of *ln x* versus (*1/T-1/T_{hm}*).

Finally, from these evaluated ΔH_{sol} and ΔG_{sol} values, the entropies of solutions (ΔS_{sol}) were obtained from equation [8, 11]

$$\Delta S_{sol} = \frac{\Delta H_{sol} - \Delta G_{sol}}{T_{hm}} \qquad (10)$$

Table 5. Thermodynamic parameters of dissolution of drug in studied solvents.

Parameters	*Hexane*	*Toluene*	*1-Butanol*	*DCE*
G/kJ.mol^{-1}	18.92	16.31	23.67	24.08
H/kJ.mol^{-1}	36.76	97.79	46.49	54.06
S/J.mol^{-1}.K^{-1}	57.01	260.48	72.94	95.85

Table 5 summarizes these evaluated thermodynamic parameters. It is found that enthalpy of dissolution *(ꓴHsol)* is positive for all the solvents suggesting thereby endothermic dissolution of drug. This indicates that the interactions between drug and solvent molecules are more powerful than those between the solvent molecules. Thus, 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 [12, 13]. The Gibbs energy of dissolution *(ꓴGsol)* is also positive for the studied solvents suggesting that the dissolution process is spontaneous [14]. Further, comparison of solubility and ꓴGsol trend for different solvents shows that the order of ꓴGsol is reverse of solubility data. The higher positive ꓴGsol decreases the solubility in all studied solvents. The entropy of dissolution *(ꓴSsol)* is also positive, which indicates favorable entropy of solubilisation for drug in studied solvents [15]. This may be due to different molecular structures and space conformations between solute and solvent molecules. As Sildenafil citrate molecules contain groups of different nature like –N-, C=-O, -NH, SO_2, the dissolution of this drug in various solvents may cause various interactions such as dipole-dipole, hydrogen bonding, hydrophobic interactions, stereoscopic effects, etc. [16]. Due to these interactions, may be the drug disrupts the alignment of solvent molecules which increases entropy.

4.   CONCLUSION

The solubility of Sildenafil citrate is higher in toluene and decreases with increase in dielectric constant and dipole moment. The solubility is found to increase with temperature and dissolution of this drug is spontaneous and endothermic phenomenon.

Nomenclature

m = weight

M= molar mass

x= Mole fraction

A, B and C = Parameter for Apelblet equation

T/K= Absolute temperature in Kelvin

R = Gas Constant

T$_{hm}$= Harmonic mean of the experimental temperatures

G_{sol}= Standard Gibb's energy *(kJ.mol^{-1})*

ꓴH$_{sol}$= Standard enthalpy *(kJ.mol^{-1})*

US_{sol}= Standard entropy $(J.mol^{-1}.K^{-1})$

H_{sol} = Standard enthalpy energy charge for the solution process

$, h =$ Parameters for Buchowski–Ksiazczak equation

Superscripts

RD = Relative deviations

ARD = Average relative deviations

RMSD = Root-mean-square deviations

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