

# Drug Solubility and Dissolution Thermodynamic Approach in Various Solvents at Different Temperatures: A Review

Ravibhai Bhola <sup>1</sup> , Hasit Vaghani <sup>1,\*</sup> , Keyur Bhatt <sup>1,\*</sup> , Rizwan Ghumara <sup>2</sup> 

<sup>1</sup> Department of Chemistry, Ganpat University, Gujarat-384012, India

<sup>2</sup> Department of Chemistry, Kadi Sarva Vishvavidyalaya, Gujarat-382024, India

\* Correspondence: hvv01@ganpatuniversity.ac.in (H.V.);

Scopus Author ID 53980703900

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**Abstract:** In chemical science, pharmaceutical, food science, petrochemicals, and material science, the solubility parameter is one of the most important factors. The studies of solubility and thermodynamics properties are directly used in crystallization-recrystallization, purification of yields, low toxicity of solvent or green solvent, modification, and many more. The experimental mole fraction solubility of compounds may be determined by various methods such as static gravity, laser dynamic, isothermal equilibrium, shake flask, and a number of other ways. The present review is focusing on the shake flask method. Further, the experimental mole fraction solubility was correlated with a theoretical model such as the Appellate and Buchowski equations. With the help of model correlation such as the Relative Average Deviation (RAD), Absolute Relative Deviation (ARD), and Root Mean Square Deviation (RMSD) for prediction of the best model fitting in theoretical approach. The Van't Hoff equation is most effective in the prediction of the dissolution thermodynamic factors such as  $\Delta H^\circ$  (mixing enthalpy change),  $\Delta G^\circ$  (mixing Gibbs energy change), and  $\Delta S^\circ$  (mixing entropy change). It had been given consequence details about endothermic or exothermic and entropy drive, which was directly applied in industrial production and purification of the drug.

**Keywords:** solubility; shake flask method; Apelblat and Buchowski equation; dissolution thermodynamic.

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## 1. Introduction

Solubility is the most important term in chemical science, physics, pharmaceutical, food science, petrochemicals, and material science. The solubility and related dissolution thermodynamics parameters ( $\Delta G^\circ$ ,  $\Delta H^\circ$ ,  $\Delta S^\circ$ ) are effective in the modification and design or separation process in pharmaceutical, chemical, food industry, and many more [1-3]. The solubility has been given particular statics data of solute solubility in solvents is asserted in the process of crystallization-recrystallization and improve the yield of products [4, 5]. The process of crystallization-recrystallization effect on the nature of solute and solvents and interaction of solute and solvent and other factors affected [6].

The solubility may be delineated as the most extent of solute that can be completely dissolved in a given proportion of solution at a certain temperature. The solubility of a compound may be described in various units, and each unit, which showed in Table 1, represents the quantity of solute dissolved in solvents at a specified temperature [7].

**Table 1.** The units described the amount of pure solute dissolved in a pure solvent at a specified temperature.

Sr.No.	Term	Definition	Equation	Application
1	Solution	If the supreme amount of solute is dissolved in a given solvent at a particular temperature is known as a saturated solution. If the solute concentration is lesser than the saturated solution at a given temperature is called an unsaturated solution. Under specific conditions, a metastable solution can be prepared, known as a supersaturated solution.	S= solvent + solute	<ul style="list-style-type: none"> <li>It is used in pharmaceuticals</li> <li>In food science</li> <li>Most important in</li> <li>Chemical science</li> </ul>
2	Molarity	The molarity of the solution is denominated by the M symbol. The number of moles of solute per liter solution.	$M = \frac{n}{V}$ $\frac{\text{mole}}{\text{litter}} \text{ or } \frac{\text{mole}}{\text{dm}^3}$	<ul style="list-style-type: none"> <li>In petrochemicals</li> <li>It is widely used in material science and many more.</li> </ul>
3	Mole	The moles are shown by the n symbol, and the weight of an individual compound upon the molecular weight of the compound is known as a mole of that particular compound.	$n = \frac{W_1}{M.W.}$	
4	Normality	The normality is shown by N. The normality of the solution is expressed by the number of the equivalent of solute dissolved in a liter of solution. The equivalent is equal to the number of grams upon its equivalent weight.	$N = \frac{W_1}{E_1} \times V$ $\frac{\text{eq.}}{\text{L}} \text{ or } \frac{\text{eq.}}{\text{dm}^3}$	
5	Molality	The molality is expressed by the m symbol. The whole number of mole of solute per kilogram ( $10^{-3}$ ) solvent.	$m = \frac{n}{S_1}$	
6	Mole fraction	The correspondence ratio of the number of mole of singular component upon total moles. The total mole of all compounds present is always equal to 1 in the solution.	$X_a = \frac{n_a}{n_a + n_b}$ $X_b = \frac{n_b}{n_a + n_b}$ $n_a + n_b = 1$	
7	Weight percentage	It is express by % $W/W$ symbol. The numbers of a gram of solute dissolved in 100 grams of solution.	$\% W/W = \frac{w_2}{w_3}$	
8	Volume percentage	It is express by % $V/V$ symbol. The numbers of a millilitre of solute dissolved in 100 millilitres of solution.	$\% V/V = \frac{v_2}{v_3}$	
9	Weight-volume percentage	It is express by % $W/V$ symbol. The numbers of grams of solute dissolved in 100 millilitres of solution.	$\% W/V = \frac{w_2}{v_3}$	
10	Ppm	The parts pert per million is signify by Ppm. It may be revealed as the total amount of the solute dissolved in $10^6$ equal units of solution.	$\text{Ppm} = \% W/V \times 10000 \text{ or } \% V/V \times 10000 \text{ or } \% W/W \times 10000$	

Here, n = the numbers of the moles of solute, M. W. = molecular weight of – the solute,  $E_1$  = equivalent weight of the solute,  $S_1$  = weight of the solvent in the kilogram,  $X_a$  = mole fraction of solute,  $X_b$  = mole fraction of the solvent,  $n_a$  = the numbers of the moles of solute,  $n_b$  = the numbers of the moles of solvent,  $w_1$  = weight of the solute, V = volume of the solution in a litter.

## 2. Materials and Methods

### 2.1. Measurement of solubility.

#### 2.1.1. The shake flask method.

Solubilities were determined by a shake-flask method [6, 8-14] along with spectrophotometric analysis. The approximate amount of compound (i.e. 20 to 50 gm) is added to each pure or binary solvent mixture in stoppered glass flasks. These flasks were put down into the ultrasonic bath or thermostat to maintain the specific temperature for at least (2 to 5 days) to achieve the solid-liquid equilibrium in solute and solvent. After the saturation or equilibrium, the solutions had been filtered at the isothermal conditions. Before sampling, it was ensured that the solution is free of solvent or other particles of matter. Then compound or drug concentrations were investigated using UV spectrophotometry titration with NaOH (0.10 N) at a specified wavelength. Above all, the solubility investigations were carried out a minimum of three times. Then the increase in temperature difference is taken as 5 Kelvin in thermostat, followed by similar steps referred as above.

The mathematical representation of the experimental mole fraction solubility ( $x$ ) of a compound in each pure solvent can be expressed by using equation number (1).

$$x = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2 + \dots + \sum_n^i m_i/M_i} \quad (1)$$

where,  $m_1$  is the mass of solute,  $m_2$  is the solvent's mass and  $M_1, M_2$  are the molar masses of solute and solvent, respectively.

Table 2 depicts the measurement of experiment mole fraction solubility in various solvent systems and at different temperatures by various researchers.

**Table 2.** Measurement of experimental mole fraction solubility in the various solvent system and different temperatures.

Sr. No.	Name	Name of Compound	Use of Solvent	Temperature range in Kelvin	Observation	Reference
1	Fleming M. <i>et al.</i>	meloxicam	(formamide+ water),(N-methylformamide+water),(N,N-dimethylformamide+water) binary mixture use	293.15 to 313.15	Solubility was risen up as temperature, and co-solvent amount part arises. Maximum solubility was obtained in (N,N-dimethylformamide +water) binary solvent system.	[8]
2	Fleming M. <i>et al.</i>	Sulfadiazine	(Ethylene glycol+ water) binary solvent system use	278.15 to 318.15	Solubility in mole fraction was increased in order to increase in temperature. It is also found that ethylene glycol proportion is enhanced as solubility increased.	[9]
3	Hongkum <i>et al.</i>	2-Amino-6-chlorobenzoic acid	Ethylene glycol(EG),N-methyl pyrrolidone(NMP),acetonitrile,n-propanol,n-heptanol,isobutanol,water,toluene,ethanol,isopropanol, cyclohexane,ethyl acetate,1-octanol pure solvents use	278.15 to 323.15	The solubility was increased along with an increase in temperature, and the mole fraction of the solubility was maximum and minimum in NMP and cyclohexane, respectively	[6]
4	Hongkum <i>et al.</i>	5,7-dibromo-8-hydroxyquinoline	Methanol, ethane, isopropanol, n-propanol, N,N-dimethyl amide, n-butanol, acetone, toluene, ethyl acetate,1,4-dioxane,1-methyl-2-pyrrolidinone, 2-butanol pure solvents use	288.15 to 328.15	Solubility increases as the temperature increase, as well as the highest and lowest solubility in pure 1-methyl-2-pyrrolidinone and pure methanol, respectively.	[10]

Sr. No.	Name	Name of Compound	Use of Solvent	Temperature range in Kelvin	Observation	Reference
5	Faiyaz S. <i>et al.</i>	Glipizide	Water, methanol, transcitol-HP ethanol, 2-butanol, isopropanol, ethylene glycol, poly(ethylene glycol)-400, ethyl acetate, dimethyl sulfoxide, 1-butanol, propylene glycol, pure solvent use	298.2 to 318.2	The solubility was recorded maximum in dimethyl sulfoxide ( $281 \times 10^{-4}$ ) at 318.2 Kelvin temperature among all of the pure solvents and also noticed that solubility rise up with a rise in temperature.	[11]
6	S.Alvani-Alamdari <i>et al.</i>	mesalazine	Ethanol and water binary solvent system use	293.2 to 313.2	The solubility had been increased in order to rise in temperature and become greater in ethanol, having a mass fraction of 0.5 ( $1.15 \times 10^{-2}$ ) at 313.2 Kelvin.	[12]
7	Daniel R.D. <i>et al.</i>	sulphadiazine	(acetonitrile+water)binary solvents (acetonitrile+methanole)	293.15 to 313.15	The solubility in the mole fraction was raised when temperature increased and increased with increased acetonitrile proportion.	[13]
8	Abolghasem Jouyban <i>et al.</i>	acetaminophen	Two binary solvent systems use	293.2 to 313.2	The solubility was increased in order to increase in temperature at a constant solvent mixture.	[14]

## 2.2. The solubility correlation.

### 2.2.1. The Apelblat equation.

Apelblat equation is the explanation of solid solubility in non-polar as well as polar solution behavior [15]. The semi-empirical mathematical equation is demonstrated in equation number (2),

$$\ln x = A + \frac{B}{T} + C \ln T \quad (2)$$

In eq. 2, The variables A, B, and C are the empirical model variables calculated using Origin software, and T refers to the absolute temperature.

### 2.2.2. $\lambda h$ equation.

The  $\lambda h$  equation [16] explained the dissolution behavior of solid in liquid which is mathematically represented as given in (3),

$$\ln \left[ 1 + \frac{\lambda(1-x_1^{cal})}{x_1^{cal}} \right] = \lambda h \left( \frac{1}{T} - \frac{1}{T_m} \right) \quad (3)$$

where the absolute temperature was indicated as T, and the melting temperature was  $T_m$ . The empirical model parameters such as  $\lambda$  and h can be obtained using Origin software. *cal* is the calculated mole fraction solubility.

Baozeng Ren *et al.*[17-21], Kui Wu *et al.*[22], Hongwei Shi *et al.*[23], Bing Li *et al.*[24], Piotr Cysewski *et al.*[25] and Satish G. *et al.*[26] have predicted the theoretical mole fraction solubility by Apelblat and Buchowski equation, compared the experimental mole fraction solubility values, and concluded that both models fit best.

## 2.3. The solubility model correlation.

The RAD (Relative Average Deviation), A.D. (Absolute relative Deviation), and RMSD (Root Mean Square Deviation) equations were the prediction of the difference between experimented and calculated solubility data values, and it's evaluated the best fitting model.

### 2.3.1. Relative Average Deviation (RAD).

The Relative Average Deviation [27-29] was used to predict the result, which is more fitting in the model. The equation of RAD is,

$$RAD = \frac{1}{N} \sum \left( \frac{|x_i^c - x_i^e|}{x_i^e} \right) \quad (4)$$

where the observation reading is denominated by the N symbol and  $x_i^c$  = theoretical solubility points or  $x_i^e$  = *practical solubility points*.

### 2.3.2. Absolute Relative Deviation (A.D.).

The Absolute relative Deviation [30, 31] evaluate the fitting effect of the experiment and calculate solubility data value; the equation of A.D. is,

$$A.D. = \frac{|x_i^e - x_i^c|}{x_i^e} \quad \text{or} \quad A.D. (\%) = \frac{|x_i^e - x_i^c|}{x_i^e} \times 100 \quad (5)$$

where,  $x_i^c$  is calculated solubility data and  $x_i^e$  is indicated as practical solubility data.

### 2.3.3 Root mean square deviation (RMSD).

The Root Mean Square Deviation (RMSD) (eq.7) [32, 33] was used to predict the difference between experimental and calculated solubility data values,

$$RMSD = \sqrt{\frac{\sum_{i=1}^N (x_i^c - x_i^e)^2}{N}} \quad \text{or} \quad RMSD (\%) = 100 \times \sqrt{\frac{\sum_{i=1}^N (x_i^c - x_i^e)^2}{N}} \quad (6)$$

where, the experiment data point value is shown by N and  $x_i^c$  and  $x_i^e$  are the calculated and practical solubility data values, respectively.

## 2.4. Dissolution thermodynamics.

Thermodynamic properties like  $\Delta S^\circ$ ,  $\Delta G^\circ$ ,  $\Delta H^\circ$  (entropy change, Gibbs energy change, and enthalpy change, respectively) are the most important parameters thadescribing a solid-liquid's dissolution processes and mechanism system equilibrium.

All the apparent thermodynamic quantities of dissolution were predicted in terms of the  $T_{hm}$ (mean harmonic temperature) [34, 35] which can be obtained by using equation number (7),

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

where the total numbers of temperature range that were taken for the observation are represented with the symbol n.

When a solid solute is dissolved in a liquid solvent, the dissolution process is investigated by an important equation such as a Van't Hoff.

With the help of the modified Van't Hoff equation, the calculations of  $\Delta H^\circ_{soln}$  and  $\Delta G^\circ_{soln}$  (apparent standard enthalpy changes of dissolution [36, 37] and the standard Gibbs energy of the dissolution [38, 39]) using Van't Hoff plot between slope and intercept of solubility curves vs  $\left[ \frac{1}{T} \text{ or } \frac{1}{T_{hm}} \right]$  as mentioned below in equations (8) and (9),

$$\left(\frac{\partial \ln x}{\partial\left(\frac{1}{T}-\frac{1}{T_{hm}}\right)}\right)_p = -\frac{\Delta H_{soln}^\circ}{R} \quad (8)$$

$$\Delta G_{soln}^\circ = -RT \times \ln x \text{ (intercept)} \quad (9)$$

The standard entropy change of solution [40, 41] is obtained by using the value of the Gibbs energy and enthalpy of the dissolution, which was mentioned here in equation 10,

$$\Delta S_{soln}^\circ = \frac{(\Delta H_{soln}^\circ - \Delta G_{soln}^\circ)}{T_{hm}} \quad (10)$$

The relative enthalpy and entropy of the solution [42, 43] are predicted by using equations (11) and (12) as mentioned below,

$$\zeta H = \frac{|\Delta H_{soln}^\circ|}{|\Delta H_{soln}^\circ| + |T\Delta S_{soln}^\circ|} \quad (11)$$

$$\zeta S = \frac{|\Delta S_{soln}^\circ|}{|\Delta H_{soln}^\circ| + |T\Delta S_{soln}^\circ|} \quad (12)$$

Observations from different researchers on dissolution thermodynamics properties on various drugs have been shown in Table 3.

**Table 3.** The dissolution thermodynamics properties of various drugs.

Sr.No.	Researcher	Observation	Reference
1	F.Martinez <i>et al.</i>	The dissolution thermodynamics parameters of meloxicam in three binary and pure solvent systems and observed that $\Delta G^\circ$ (the standard Gibbs energy of dissolution) and $\Delta H^\circ$ (enthalpy of dissolution) were positive values. The entropy of dissolution was negative in most cases, except in the mixture of $0.30 \leq x_1 \leq 0.50$ of the (N-methyl formamide+ water) system was found to be positive. The global dissolution process was endothermic, and it was also concluded that the dissolution mechanism was free from enthalpy or entropy drive except in $0.30 \leq x_1 \leq 0.50$ of the (N-methyl form amide+ water) system.	[8]
2	F. Martinez <i>et al.</i>	The dissolution thermodynamics parameters of sulfadiazine in ethylene glycol+ water mixture was an endothermic process which demonstrated the standard Gibbs energy and enthalpy were positive in each case. The entropies of dissolution was positive in all cases (except in mixture $w_1 = 0.90$ and $0.95$ in pure ethylene glycol positive entropy obtained)	[9]
3	F.Martinez <i>et al.</i>	The global dissolution processes of meloxicam in (carbitol+water) mixture was always endothermic, which observed the standard Gibbs energy and enthalpy were positive in every case. The dissolution process is also without entropy or enthalpy drive except in $x_1 = 0.10$ where positive entropy found.	[44]
4	F.Martinez <i>et al.</i>	The global dissolution processes of meloxicam in (acetonitrile+water) mixture was always endothermic and without entropy or enthalpy drive except in the mixture of $0.00 \leq x_1 \leq 0.20$ negative entropy observed. The Gibbs energy is positive in all cases with respect to the enthalpy of the dissolution process.	[45]
5	Guoquan <i>et al.</i>	The dissolution process of chloroquine diphosphate in a neat and mixture of organic solvents was discovered; results indicated that the dissolution mechanism was spontaneous and endothermic. It was also noted that entropy-driven was found in every case. The value of Gibbs energy was small, signifying that the solubility increases and is more suitable for dissolution.	[46]
6	Kamal <i>et al.</i>	The dissolution process of the cefixime trihydrate in an aqueous deep eutectic system was non-spontaneous and endothermic and also found that the thermal effect was more acted than entropy.	[47]
7	Demian Han and co-worker	The global dissolution process was endothermic and entropy-driven in every system. It was also established that the value of $\Delta G^\circ$ (standard Gibbs energy) as well as of $\Delta H^\circ$ and $\Delta S^\circ$ (standard enthalpy and entropy) was also positive obtained in every single case.	[48]

### 3. Conclusions

Solubility is one of the most important parameters of physicochemical properties. The solubility and dissolution thermodynamics properties of various compounds or drugs have key roles in chemical science, physics, pharmaceutical, food science, petrochemicals, material science, and many more. With the help of the shake flask method, the prediction of experimental mole fraction solubility of drugs determined in various pure or mixed solvent systems at different temperature ranges and using Apelblat and Buchowski equation the theoretical solubility was assumed. Further, the comparison of experimental and theoretical mole fraction solubility of the drug was made. The dissolution thermodynamics parameters such as the Standard Gibbs energy of dissolution, the standard enthalpy of dissolution, and the entropy of dissolution described the global dissolution processes such as endothermic or exothermic without or with enthalpy or entropy-driven. This information can be useful in industries for modification of drugs or compounds and crystallization and recrystallization.

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### Conflicts of Interest

The authors declare no conflict of interest.

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