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SOLUBILITY STUDY OF ANTI-DIABETIC DRUG- ROSIGLITAZONE MALEATE USING COSOLVENCY APPROACH

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ABSTRACT

The present investigation constitutes the models for predicting solubility of drugs in solvent mixtures have an important practical application. Solubility behavior of rosiglitazone maleate in solvent blends ranging from non-polar to highly polar is essential. So the present investigation deals with study of rosiglitazone maleate in binary solvent systems. The solubility of rosiglitazone maleate in various dimethylsulfoxide-water mixtures was analyzed in terms of solute-solvent interactions using modified Hildebrand-Scatchard treatment. The solubility of rosiglitazone maleate in dimethylsulfoxide-water shows a curve with solubility maxima well above the ideal solubility of the drug. The discrepancy between the results using the original Hildebrand-Scatchard equation and experimental points demonstrates that regular solution theory cannot be used to predict drug solubility in dimethylsulfoxide-water binary systems. This behavior has been dealt with the theoretical replacement of mean geometric solubility parameters (δ1δ2) term with the interaction energy term (W). This is attributed to solvation of drug with the dimethylsulfoxide-water mixture, and indicates that the solute-solvent interaction energy (W) is larger than the geometric mean (δ1δ2).The new approach provides an accurate prediction of solubility once the interaction energy 'W' is obtained. In this case, the energy term is regressed against a polynomial in δ1 of the binary solvent mixture. Quadratic, cubic, and quartic expressions were utilized for predicting the solubility of rosiglitazone maleate in dimethylsulfoxide-water mixtures. But a quartic expression of 'W' in terms of solvent solubility parameter was found appropriate for predicting the mole fraction solubility and yields an error ~27.68%, a value approximating that of the experimentally determined solubility. Extended Hildebrand Solubility Approach was successfully applied to reproduce the solubility behavior of rosiglitazone maleate in dimethylsulfoxide-water binary mixtures within the accuracy. The method has potential usefulness in preformulation and formulation studies during which solubility prediction is important for drug design.

AIM: The present investigation was carried out with the aim to: Selection of various cosolvents, determination of solubility of rosiglitazone maleate, solubility of drug in individual solvents, Preparation of binary mixture, solubility behavior of rosiglitazone maleate in binary system, solubility parameter of rosiglitazone maleate, prediction of solubility behaviors using Extended Hildebrand Solubility Approach (EHSA), determination of the best fit approach for solubility.

KEYWORDS: Extended Hildebrand solubility approach, N, N-dimethylsulfoxide, rosiglitazone maleate, regular solution theory, solubility parameter.

1. INTRODUCTION

Solubility is defined in quantitative terms as the concentration of solute in a saturated solution at a certain temperature, and in a qualitative way, it can be a defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion. Practically the solubility of a solute in a solvent at a particular temperature is the number of grams of the solute necessary to saturate 100 gm of the solvent at that temperature. Understanding solubility properties will provide a basis for understanding the golden rule of solubility- "Like dissolves like".

A saturated solution is one in which the solute is in equilibrium with the solid phase (solute). An unsaturated or subsaturated solution is one containing the dissolved solute in a concentration below that necessary for complete saturation at a definite temperature. A supersaturated solution is one that contains more of dissolved solute than it would normally contain at a definite temperature, where the undissolved solute is also present.[1] When aqueous solubility of drug candidate is inadequate to permit solution formulation, cosolvents are often employed to improve solubility.[2]

1.1. Solubility Expression

The solubility of a drug can be expressed quantitatively in number of ways like in terms of molarity, morality, percentage, mole fraction and parts per million etc.[3,4]

Table 1: Expressions for approximate solubility

Terms	Parts of Solvent Required for One Part of Solute
Very Soluble	Less than 1 part
Freely Soluble	1 to 10 parts
Soluble	10 to 30 parts
Sparingly Soluble	30 to 100 parts
Slightly Soluble	100 to 1,000 parts
Very Slightly Soluble	1,000 to 10,000 parts
Practically Insoluble or Insoluble	More than 10,000 parts

1.2. Importance of Solubility

Solubility of a solute in a solvent is an important phenomenon as pharmaceutical point of view because it permits the pharmacist to choose best solvent medium for a drug or combination of drugs, helps in overcoming certain difficulties that arise in the preparation of pharmaceutical solutions.

1.3. Importance of Solubility Prediction

Solubility prediction is important in formulation of liquid pharmaceuticals. Solubility predictions are valuable for obtaining the optimum concentration of the cosolvent in liquid dosage form of a drug especially in preformulation studies where a small amount of drug is available. Solubility prediction or approaches used for predicting the solubility of drug save experiments that are expensive and time consuming in drug formulation and other experimentations. Predicted solubility data is used for correlation with physical properties of drug as linear free energy relationship which in turn is applicable to quantitative structure activity relationship. These data also used for correlation between biological activities and various physical properties of drug.[7]

1.4. Types of Interactions in Solution

Solids (and liquid) molecules are held together by a certain amount of intermolecular forces. The intermolecular forces include[8,9]

1. Vander Waals Forces
2. Dipole-Dipole Interactions
3. Dipole Induced-Dipole Interactions
4. Induced Dipole-Induced Dipole Interactions
5. Hydrogen Bonding

For a solution to occur, the solvent molecules must overcome these intermolecular forces in the solute and find their way between and around the solute molecules. At the same time, the solvent molecules themselves must be separated from each other by the molecules of the solute.

1.5. Different Approaches for Solubilization of Drug

Various approaches are used for solubilization of drug molecule in various range of solubility enhancement.[10] Table 2- presents a comparison of the magnitudes of increases in solubility that can be expected from commonly used methods of drug solubilization.

Table 2: Comparison of drug solubilization techniques

Sr. No.	Methods	Approximate range of solubility increase
1.	Surfactant	1-50X
2.	Complexation	1-100X
3.	Salt formation	1-1000X
4.	Prodrug formation	1-1000X
5.	Cosolvency	1-1000X

Table 3: List of commonly used cosolvents in formulation[22,23]

Ethanol	Propylene Glycol	N-Methyl-2-Pyrrolidone
Polyethylene Glycol	Glycerin	γ-Butyrolactone
N,N-Dimethyl Acetamide	Dioxolanes	N,N-Dimethyl Formamide
Triglyme	Triacetin	N-(β-hydroxyethyl)-lactamide
Dimethyl Isosorbide	Diacetin	Benzyl Alcohol
1,2-Butylene Glycol	Glycerol Formal	Ethyl Lactate
Transcutol	Labrasol	Acetyl Triethyl Citrate

1.6. Theoretical Methods of Solubility Prediction

Following methods are used for solubility predictions-

1. Solubility prediction on the basis of dielectric constant
2. Solubility prediction in an ideal solution
3. Hildebrand solubility approach/ Regular solution theory/ Solubility prediction in non-ideal solution
4. Extended hildebrand solubility approach (E.H.S.A)
5. Yalkowsky solubility approach/ Partition coefficient approach/ Log-linear model

1.6.4. Extended Hildebrand Solubility Approach (E.H.S.A.)

Extended Hildebrand Solubility Approach is applied to predict the solubility of rosiglitazone maleate in mixtures of water and N, N-dimethylsulfoxide (DMSO). DMSO is a very interesting cosolvent to study the interrelation between drug solubility and medium polarity because it is aprotic and completely miscible with water[1]. Water-DMSO mixtures are strongly non ideal and can act in the solute-solvation process via hydrophobic interactions and preferential solvation. In terms of polarity, water-DMSO mixtures cover a wide range of Hildebrand solubility parameters from 13 (pure DMSO) to 23.4 (pure water).

Rosiglitazone is an oral hypoglycemic agent used in the treatment of type II diabetes which acts by decreasing insulin resistance. Rosiglitazone freebase and its maleate salt have very low aqueous solubility's, and the maleate salt is used in the pharmaceutical formulations. Rosiglitazone maleate is (RS)-5-{p-[2-(methyl-2-pyridylamino) ethoxy] benzyl1} -2,4-thiazolidine dione maleate(1:1). It is official in IP 2010 till date. Though the molecule is found to be effective, its therapeutic efficacy is hindered due to its poor aqueous solubility. The drugs with low aqueous solubility usually suffer oral bioavailability problems because of limited gastrointestinal transit time of the undissolved drug particles and limited solubility at the absorption site. The poor aqueous solubility and wettability of rosiglitazone maleate give rise to difficulties in pharmaceutical formulations meant for oral or parenteral use, which may lead to variation in bioavailability.

As such, no solubility reports are found for its estimation and prediction by any of the method till date. Hence, the aim of this communication is to report the solubility behavior of rosiglitazone maleate in individual solvents (water and DMSO) and different concentrations of water-DMSO mixtures, predict it theoretically by applying the Extended Hildebrand Solubility Approach.

1.6.5. Yalkowsky Solubility Approach/ Partition Coefficient Approach/ Log-Linear Model

Yalkowsky solubility approach is known as partition coefficient approach or log-linear approach. Solubility and partitioning relationship between aqueous solubility and Octanol-Water partition coefficient are given by Yalkowsky and Valvani.[53,54] Hansch et al. also observed a relationship between aqueous solubilities of nonelectrolytes and partitioning.

1.6.6. Similarity between Extended Hildebrand Solubility Approach and Yalkowsky Approach

1. Yalkowsky approach is based on partition coefficient of solute and E. H. S. approach is based on solubility parameter with solubility of drug. But in both approaches partition coefficient and solubility parameter of solvent blends are related to the activity coefficient of solute which in turn determines forces existing in the molecules in the solution.
2. Both the approaches doesn‟t follow geometric mean rule.
3. Both approaches require only the knowledge of melting point of solute and entropy of fusion.

UV/V is spectrophotometer, Jasco model V-503 with spectral bandwidth of 2 nm, wavelength accuracy ±0.5 nm and a pair of 10 mm matched quartz cells were used to measure absorbance of the resulting solutions. Citizen balance, CX-100, was used for weighing of rosiglitazone maleate. Differential Scanning Calorimeter, Shimadzu TA-60 WS, was used for determination of melting point and heat of fusion of rosiglitazone maleate.

2. MATERIALS SPECIFICATION

Rosiglitazone maleate, obtained as gift sample from Lupin Pharmaceuticals, Ltd., Indore, India. N, N-Dimethylsulfoxide was purchased from Research Lab Fine Chemical Industry, Islampur, India. Throughout the study double distilled water was used for experimental purpose. All chemicals and reagents used in the study were of analytical grade and used as such. Double beam

2.1 Procurement of Drug and Cosolvent

Table 4: List of chemicals/reagents

Name of Chemical/reagent	Company name
Rosiglitazone maleate	Lupin Ltd., Indore
1,4-dioxane	
N-methyl-2 pyrrolidone	
Dimethyl acetamide	
Dimethyl formamide	

Propylene glycol PEG-200 PEG-400 PEG-600 1,4-butanediol Glycerine Dimethyl sulphoxide Methanol Ethanol	Research Lab Fine Chemical Industry, Islampur Jiangsu Huaxi International, China

2.2 Instruments Specification

Table 5: List of instruments/equipments

Sr. No.	Name of instruments/ equipments	Make/Model
1	UV Spectrophotometer	Jasco V-503
2	Differential Scanning Calorimeter	Shimatzu TA-60 WS
3	IR Spectrometer	Jasco FT-IR PS-4000
4	Refractometer	Abbe‟s
5	Ultrasonicator	Chief Scientific Industries
6	Weighing Balance	Citizen
7	Hot Air Oven	Universal Hot Air Oven

2. EXPERIMENTAL METHODS

Solubility measurements

Solubilities of rosiglitazone maleate (δ2 = 11.34) were determined in mixed solvent consisting of DMSO (δDMSO = 13) and water (δW = 23.4). Solvent blends were made covering 0-100% DMSO (v/v). About 25 ml of DMSO, water, or mixed solvents were placed into screw-capped vials (Thermostated at 250 and under continuous magnetic stirring) containing an excess amount of rosiglitazone maleate and agitation was maintained at 150 rpm for 24 h in a constant temperature bath. Preliminary studies showed that this time period was sufficient to ensure saturation at 250. After equilibration, the solution was microfiltered (0.45 µm) and the filtrate was then diluted with double distilled water to carry out the spectrophotometric determination at the maximum wavelength of absorption of the rosiglitazone maleate (λmax-248.5 nm). Calibration graphs of rosiglitazone maleate in each solvent blend were previously established with correlation coefficients greater than 0.9973. The working concentration range was from 10 to 60 µg/ml rosiglitazone maleate. The densities of the blends as well as the filtrates of saturated solutions were determined by using 25-ml specific gravity bottle at 250. Once the densities of solutions are known, the solubilities can be expressed in mole fraction scale.

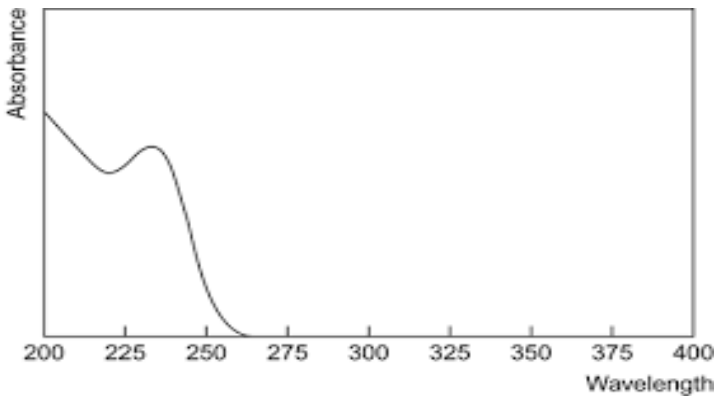

Figure 1: UV spectrum of rosiglitazone maleate

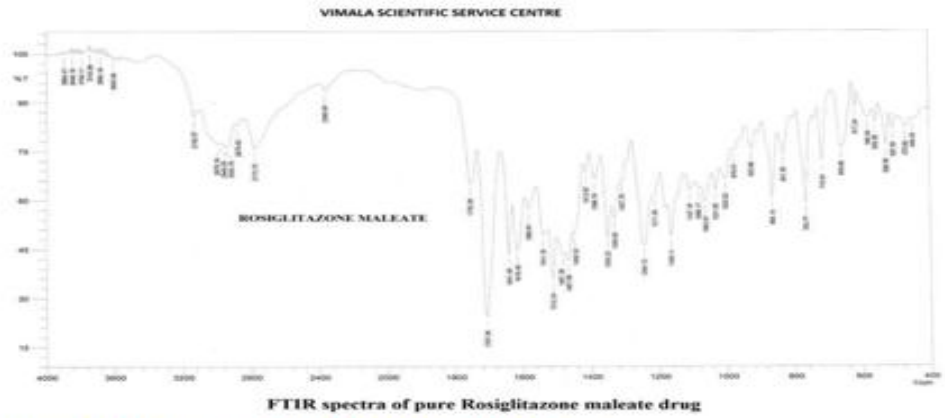

Figure. 4. FTIR spectra of Rosiglitazone maleate drug

3.1 Determination of partition coefficient of rosiglitazone maleate.

Partition Coefficient in Octanol-Water system was determined by equilibrating small amount of rosiglitazone maleate (not exceeding the aqueous solubility of drug) for 24 hours in the mixture of Octanol-Water system (1:1). After attaining the equilibrium, the two phases were separated and the partitioned amount of drug in each phase was determined. The separated phases were analyzed after appropriate dilution on UV Spectrophotometer. Partition Coefficient was determined in duplicate and the content was recorded in Table 06.

Table 6: Partition coefficient of rosiglitazone maleate

Sr. No.	Partition coefficient	Log p	Average Log p
1	0.8881	-0.0515	-0.0367
2	0.9949	-0.0022	

3.2 Determination of aqueous solubility of rosiglitazone maleate

Solubility of rosiglitazone maleate in distilled water was determined in triplicate by adding excess amount of drug in screw capped vials containing fixed quantity of distilled water. Then the vials were subjected to ultrasonication for 30 minutes and then allowed to stand at room temperature (□30°C) for 24 hrs without disturbance to attain saturation equilibrium. The solutions were filtered through Whatmann filter paper (no.41) and analyzed spectrophotometrically at 248.8 nm after appropriate dilutions with distilled water. The absorbances of the samples were measured on UV spectrophotometer and content was recorded in Table 07.

Table 7: Aqueous solubility of rosiglitazone maleate

Set No.	Absorbance	Solubility (mg/ml)
1	0.5253	0.0529
2	0.5362	0.0654
3	0.5288	0.0721
Average	**0.5301**	**0.0635**

3.3 Determination of solubility of rosiglitazone maleate in buffer systems

Solubility of rosiglitazone maleate in phosphate buffer pH 6.8, acetate buffer pH 4 and acid phthalate buffer pH 3.4 were determined in duplicate by adding excess amount of drug in screw capped vials containing fixed quantity of buffer. Then the vials were subjected to ultrasonication for 30 minutes and then allowed to stand at room temperature (□30°C) for 24 hrs without disturbance to attain saturation equilibrium. The solutions were filtered through Whatmann filter paper (no.41) and analyzed spectrophotometrically at 248.8 nm after appropriate dilutions with respective buffer. The absorbances of the samples were measured on UV spectrophotometer and content was recorded in Table 8.

Table 8: Solubility of rosiglitazone maleate in (mg/ml) in buffer systems

Buffer	Series I	Series II	Average
Phosphate buffer pH 6.8	0.00824	0.00729	0.00776
Acetate buffer pH 4	0.01285	0.01562	0.01424
Acid phthalate buffer pH 3.4	0.00452	0.00822	0.00637

3.4 Determination of solubility of rosiglitazone maleate in binary solvent systems

Different binary solvent systems were prepared by using cosolvent and water, ranging from 0-100% respectively, in screw capped vials. The final volume of each binary system was kept constant at 2 ml. A slight excess of rosiglitazone maleate was introduced into these vials. These solutions were ultrasonicated for 30 minutes and then allowed to stand at room temperature (□30°C) for 24 hrs without disturbance to attain saturation equilibrium. These saturated systems were carefully filtered through Whatmann filter paper (no.41) and were analyzed spectrophotometrically at 269 nm after appropriate dilutions with distilled water on UV-Visible Spectrophotometer. These experiments were conducted in sets of three. Experimental data of solubility (G/ml) of rosiglitazone maleate in binary solvent systems were shown in Table 9 to Table 11.

Table 9: Solubility of rosiglitazone maleate (gm/ml) in Glycerin-water blend

% of cosolvent	Series I	Series II	Series III	Average	SD
0	0.000022	0.000022	0.000023	0.000022	5.40637E-07
10	0.000028	0.000029	0.000028	0.000028	5.08003E-07
20	0.000029	0.000032	0.000031	0.000031	2.66625E-07
30	0.000047	0.000045	0.000046	0.000046	1.12039E-06
40	0.000044	0.000043	0.000045	0.000044	1.64384E-07
50	0.000069	0.000070	0.000071	0.000070	5.79272E-07
60	0.000088	0.000106	0.000105	0.000099	8.93545E-06
70	0.000284	0.000285	0.000277	0.000282	2.41431E-06
80	0.000466	0.000495	0.000429	0.000463	9.92382E-06
90	0.000665	0.000782	0.000618	0.000688	1.48721E-05
100	0.000565	0.000522	0.000577	0.000554	1.10284E-05

Table 10: Solubility of rosiglitazone maleate (gm/ml) in DMSO-water blend

% of cosolvent	Series I	Series II	Series III	Average	SD
0	0.000033	0.000031	0.000032	0.000032	1.00187E-06
10	0.000205	0.000189	0.000200	0.000198	1.67225E-06
20	0.000365	0.000321	0.000357	0.000347	2.84716E-06
30	0.001095	0.001045	0.001010	0.001050	1.29422E-05
40	0.001298	0.001312	0.001391	0.001333	6.94765E-06
50	0.002455	0.002416	0.001955	0.002275	2.26082E-05
60	0.005486	0.005222	0.005483	0.005397	2.31459E-05
70	0.026545	0.026352	0.021593	0.024830	2.09208E-04
80	0.165545	0.178253	0.164258	0.169352	9.25653E-04
90	0.264217	0.227144	0.229674	0.240345	2.10458E-03
100	0.273425	0.309124	0.274124	0.285557	1.31989E-02

Table 11: Solubility of rosiglitazone maleate (gm/ml) in Ethanol-water blend

% of cosolvent	Series I	Series II	Series III	Average	SD
0	0.000047	0.000048	0.000049	0.000048	9.25465E-07
10	0.000365	0.000394	0.000322	0.000360	9.45761E-06
20	0.000391	0.000399	0.000398	0.000396	5.41983E-06
30	0.000452	0.000502	0.000511	0.000488	6.81150E-06
40	0.001125	0.001325	0.001555	0.001335	1.54342E-05
50	0.002625	0.002741	0.002369	0.002578	2.50051E-05
60	0.010882	0.013014	0.010826	0.011574	6.84412E-05
70	0.039613	0.035470	0.037043	0.037375	3.82341E-04
80	0.063466	0.064337	0.063635	0.063812	4.78832E-04
90	0.074552	0.076884	0.076638	0.076024	1.00373E-03
100	0.032283	0.033550	0.034774	0.033535	8.40412E-04

4. RESULTS AND DISCUSSION

4.1 Yalkowsky Approach

Yalkowsky approach involves the transformation of solubility data of a solute into a suitable form which can give a linear plot of solubility as a function of cosolvents contribution in the binary solvent system employing the equation

$$Log\,(S_f / S_w) \square \square . f_c$$

The linearity of curve is an indicator of solute-solvent interaction, which depends on concentration of

cosolvent. Tables 31-43 are compilation of solubility data in the form of logarithm of ratio of solubility of rosiglitazone maleate in cosolvent to its solubility in water {log (Sf/Sw)} and volume fraction of cosolvent (fc). A visual representation of these data is displayed in Yalkowsky plot (log Sf/Sw Vs fc) as shown in Figures 5-17.The review of Yalkowsky plot reveals the linear trend in drug solubility even up to 100 % of cosolvent in case of DMA, DMF, DMSO, NMP, PG and PEG-400. With other solvents linear trend is observed till varied cosolvent concentrations. The solvents 1,4-Butanediol, 1,4-Dioxane, Ethanol, Methanol, Glycerin, PEG-200 and PEG-600 exhibited linear trend in drug solubility with respect to cosolvent concentration up to 90%. The linearity is satisfactory with correlation coefficient values above 0.90 for all the cosolvents studied however DMA and PG shows 0.84 and 0.89 respectively.

Table 12: Yalkowsky Approach for handling solubility data of rosiglitazone maleate in 1, 4-Butanediol-water system

Volume fraction	Log (S_f/S_w)			
(f_c)	Series I	Series II	Series III	Average
0	0.000000	0.000000	0.000000	0.000000
0.1	0.542541	0.553047	0.557811	0.550895
0.2	0.747243	0.760200	0.797905	0.767985
0.3	0.982865	1.001445	1.034612	1.005839
0.4	1.302223	1.367102	1.402078	1.357300
0.5	1.601303	1.642836	1.682355	1.641920
0.6	1.853792	1.838624	1.864637	1.852191
0.7	2.132252	2.155893	2.172507	2.153124
0.8	2.309155	2.327806	2.362359	2.332641
0.9	2.584593	2.620833	2.655164	2.619841
1.0	2.525593	2.598698	2.614255	2.579694
Slope	**2.7554**	**2.7743**	**2.7983**	**2.7758**
Intercept	**0.1657**	**0.1783**	**0.1937**	**0.1791**
Correlation	**0.9916**	**0.9901**	**0.9891**	**0.9905**

Table 13: Yalkowsky Approach for handling solubility data of rosiglitazone maleate in DMSO-water system

Volume fraction	Log (S_f/S_w)			
(f_c)	Series I	Series II	Series III	Average
0	0.000000	0.000000	0.000000	0.000000
0.1	0.825669	0.803001	0.798943	0.803583
0.2	1.049658	1.026180	1.022770	1.027249
0.3	1.550755	1.526960	1.519959	1.526955
0.4	1.644485	1.621413	1.621440	1.623483
0.5	1.911559	1.897250	1.903433	1.898463
0.6	2.254540	2.239535	2.240848	2.239342
0.7	2.891953	2.863985	2.867331	2.868805
0.8	3.631726	3.610025	3.606257	3.610378
0.9	3.867690	3.854473	3.859849	3.855054
1.0	3.960152	3.982304	3.939490	3.955477
Slope	**3.9098**	**3.9237**	**3.9096**	**3.9120**
Intercept	**0.1895**	**0.1677**	**0.1707**	**0.1721**
Correlation	**0.9752**	**0.9767**	**0.9765**	**0.9763**

4.2 Interpretation of Solvent Power (ζ)

The solvent power of a cosolvent can be predicted on Yalkowsky approach. The slope of the Yalkowsky plot is the measure of the solvent power Table 44. The high value of slope of the plot is indicative of high solvent power of the cosolvent. The slopes values more than one for Yalkowsky plot indicate a satisfactory solvent power of the cosolvent for the solute and its usefulness in solubility enhancement. Among the solvents studied, 1, 4-Butanediol, DMA, PEG-400 and Glycerin appeared to be poor cosolvents in combination of water (The slopes are 2.7757, 2.5398, 1.9448, 1.6814 respectively). The cosolvents like 1, 4-Dioxane, DMF, NMP, PG, Methanol and DMSO emerged as the cosolvents of choice for rosiglitazone maleate with best solvent power. According to the slope values, the solvent power of these cosolvents can be put in order as 1, 4-Dioxane>DMF>NMP>PG>Methanol>DMSO. The rank classifications of slopes according to the solvent power of cosolvents are shown in Table 45. Figure 18 is the plot of solvent power of various cosolvents. The solvent power can be used to estimate hypothetical partition coefficient in between cosolvent and octanol blend by the equation

□ □ log $PC_{(o/w)}$ □ log $PC_{(o/c)}$

It was found that, as the solvent power of cosolvent increased, its partition coefficient in cosolvent-octanol decreased. This relationship can be observed in the graph of solvent power and partition coefficients Vs solubility of the solute in individual cosolvent as shown in Figure 3 and Figure 4 respectively.

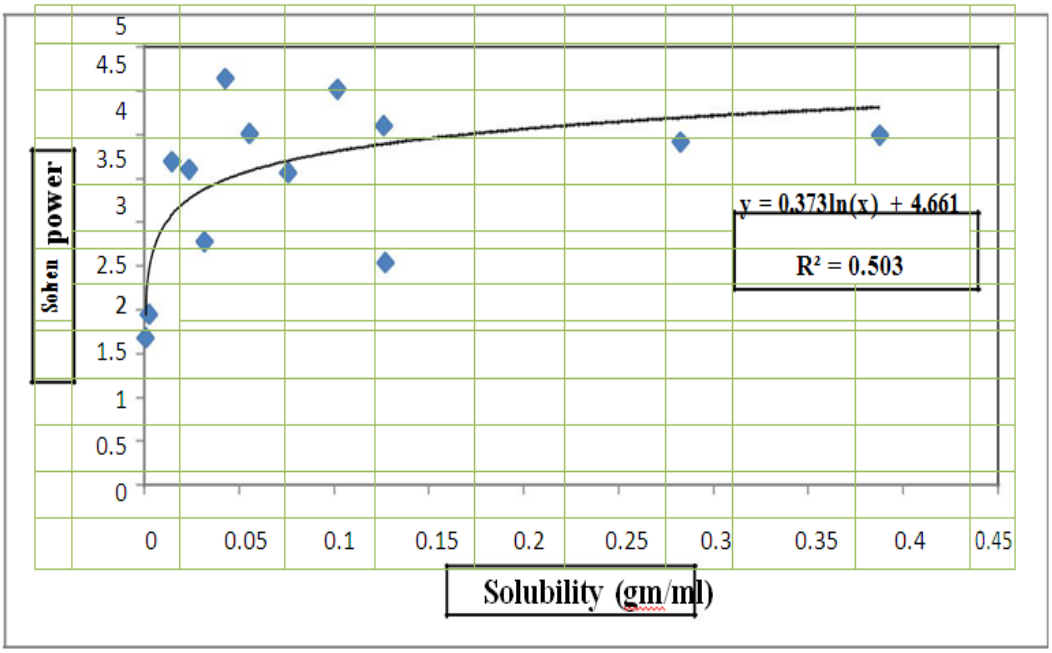

Figure 03: Plot of solvent power vs. solubility (gm/ml) for rosiglitazone maleate in various cosolvents

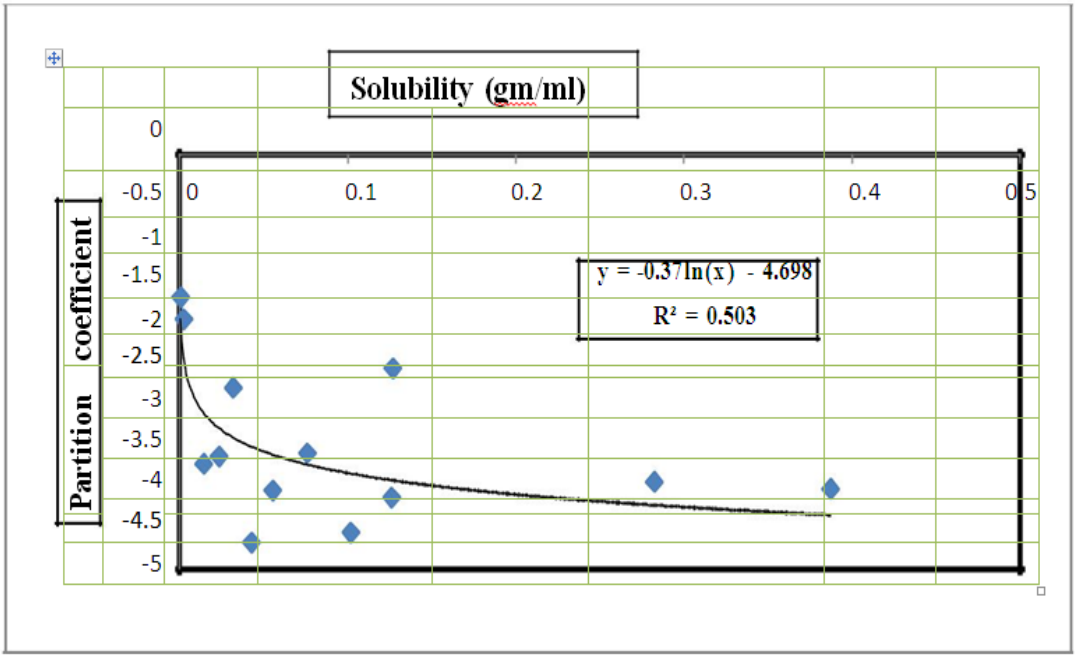

Figure 4: Plot of partition coefficient vs. solubility (gm/ml) for rosiglitazone maleate in various cosolvents

4.3 Ideal Mole Fraction Solubility (X_2^i)

When ideal solution of solid in liquid is formed, energy is necessary to solubilize the solute. The process of solubilization can be considered as equilibrium between liquid and solid. Ideal solubility can be calculated from the knowledge of heat of fusion and melting point of drug, which is determined from differential scanning calorimetry.

4.4 Solubility Parameter (δ)

For prediction of solubility by EHSA, solubility parameter is essential. It is calculated by using Fedor"s

group contribution method. The method is based on additive properties of cohesive energy and molar volume of drug. The value of solubility parameter (δ) is calculated by formula□□□□□□□□□□□□□

Experimental determination of solubility parameter was based upon the maximum solubility of drug in cosolvent-water blend. The calculated and experimental solubility parameter values should be equal or closer to each other. For most of the cases, Dioxane and water are chosen as miscible solvent blends, which provides the experimental range of solubility parameter (δ1) 10 and 23.4 (cal/cm3)1/2 respectively

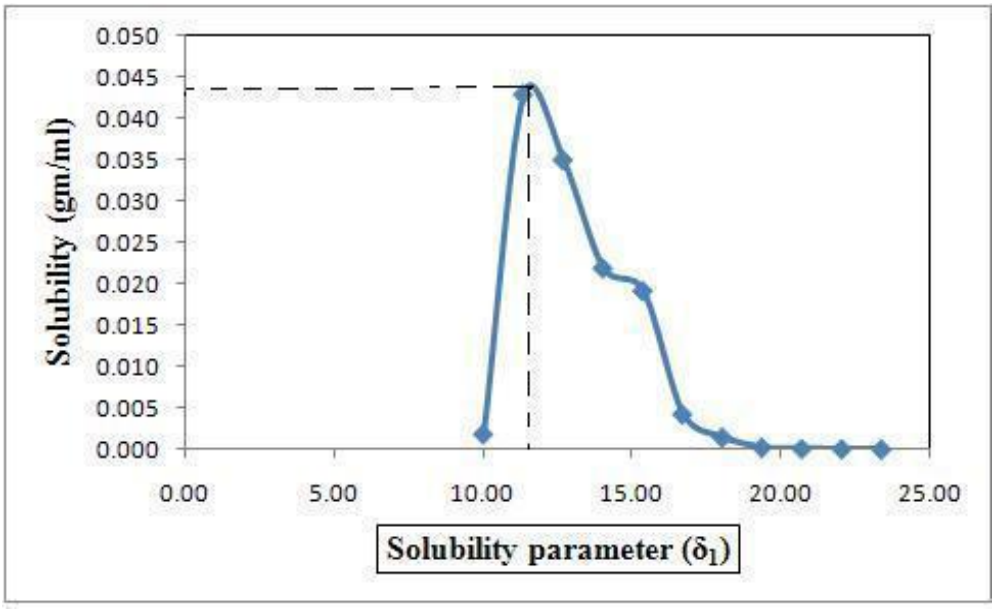

Figure 5: Plot of solubility Vs solubility parameter of 1, 4-Dioxane-water system

4.5 Extended Hildebrand Solubility Approach (EHSA)

EHSA although requires large number of input variables including molar volume of solute and solvent blend, solubility parameter of solute and solvent blend, ideal solubility of solute, etc., it is considered as better approach for solubility prediction than other approaches. Ideal mole fraction solubility (X2i) and solubility parameter of rosiglitazone maleate (δ2) was found to be 0.02126 and 10.85 (cal/cm3)1/2 respectively. These values were used further for the calculation of interaction energy (Wobs). According to EHSA, Interaction energies (Wobs) were calculated from observed mole fraction solubility (X2obs) by following equation and presented in Tables 50-62.

□ log X 2 □□□log X 2i □ A(□12 □□2 2 □ 2W)

These observed interaction energies (Wobs) were then plotted against solubility parameters of cosolvent-water blends (δ1) as shown in Figures 22-34. These plots were with best fit to the quartic polynomial regression. The polynomial coefficients were obtained from the quartic polynomial regression as shown in Table 63, which was utilized further for the calculation of regressed interaction energy (Wreg). The obtained regressed interaction energies (Wreg) were utilized further for the calculation of the regressed mole fraction solubility (X2reg) as shown in Tables 64-76. Observed interaction energy (Wobs) and Regressed interaction energy (Wreg) were then compared and it was observed that, there was not much significant difference between the observed and predicted values. This indicates that Extended Hildebrand Solubility Approach (EHSA) is better model for prediction of solubility. From observed and regressed mole fraction solubility, residuals of solubility for each cosolvent-water systems were calculated. Residual analysis confirmed that the residuals are much lesser towards lower percentage of cosolvent and also towards higher percentage of cosolvent. These residuals of solubility did not follow conceptual trend, which showed that these were the experimental errors and hence were left as such. The plots of Residuals of solubility Vs solubility parameters of all cosolvent-water blends are shown in Figure 35-47. Relationship of observed mole fraction solubility (X2(obs)) vs. regressed mole fraction solubility (X2(reg)) was then plotted for individual data set and are shown in Figure 48-60. The graphs show linear relationship of solubility behavior of rosiglitazone maleate in various cosolvents-water system namely 1, 4-Butanediol, Glycerin,

DMA, DMF, DMSO, Ethanol, NMP, PEG-200, PEG-400, PEG-600 and PG with correlation coefficient of 0.98849, 0.99676, 0.95676, 0.92056, 0.99656, 0.98624, 0.93800, 0.94715, 0.96271, 0.93465, 0.99856 respectively and indicating the better predictability of the results by this approach.

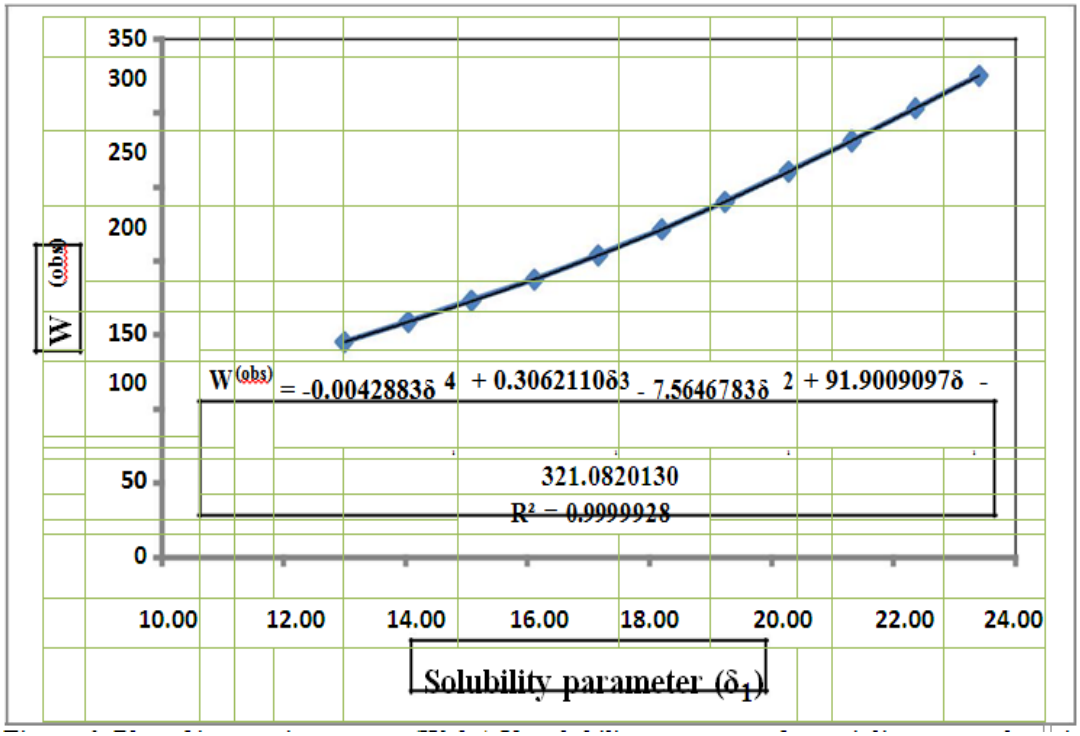

Figure 6: Plot of interaction energy (Wobs) Vs solubility parameter for rosiglitazone maleate in DMSO-water system

Table 14: Calculation of regressed interaction energy (Wcal) and regressed mole fraction solubility (Xcal) in DMSO-water blend

W(obs)	W(cal)	X2(obs)	X2(cal)	Residual
325.04862	325.00969	1.44268E-06	1.37751E-06	4.5173E-02
303.04034	302.99934	1.20733E-05	1.14999E-05	4.7497E-02
280.93561	281.22089	2.49174E-05	3.49595E-05	-4.0301E-01
260.40951	260.13607	9.32708E-05	6.74509E-05	2.7683E-01
240.16340	240.08624	1.34105E-04	1.22390E-04	8.7355E-02
221.32347	221.29233	2.85114E-04	2.74813E-04	3.6128E-02
203.67494	203.85489	6.95532E-04	8.59449E-04	-2.3567E-01
187.63976	187.75406	3.29485E-03	3.75271E-03	-1.3896E-01
173.06241	172.84958	2.14330E-02	1.75820E-02	1.7968E-01
158.86170	158.88078	4.38127E-02	4.44539E-02	-1.4635E-02
145.44109	145.46661	6.17217E-02	6.27874E-02	-1.7266E-02

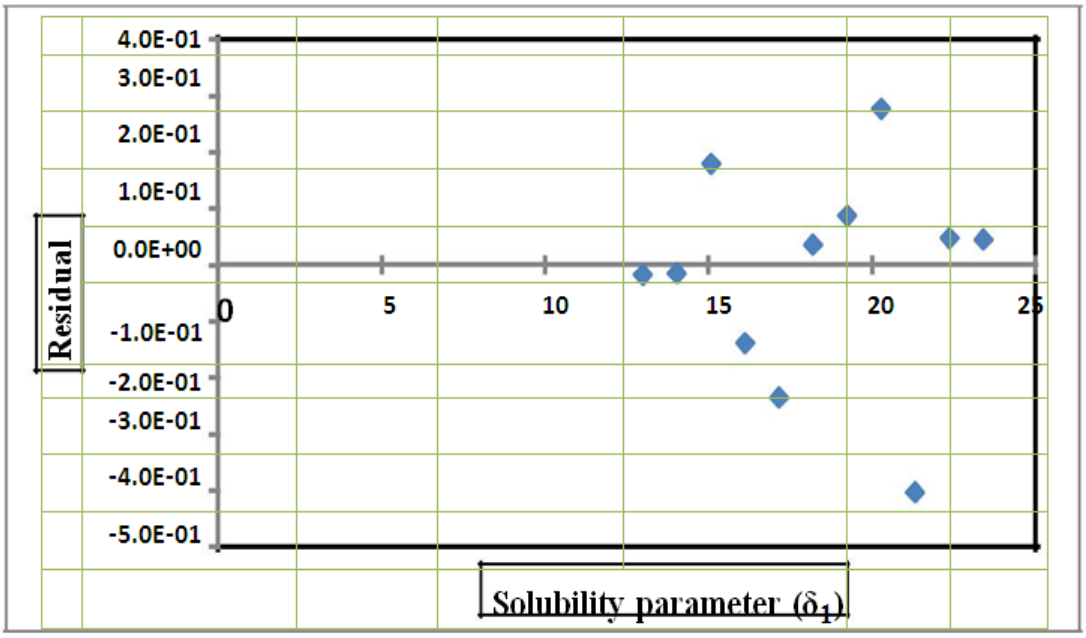

Figure 7: Plot of residuals of solubility vs. solubility parameter for rosiglitazone maleate in DMSO-water system

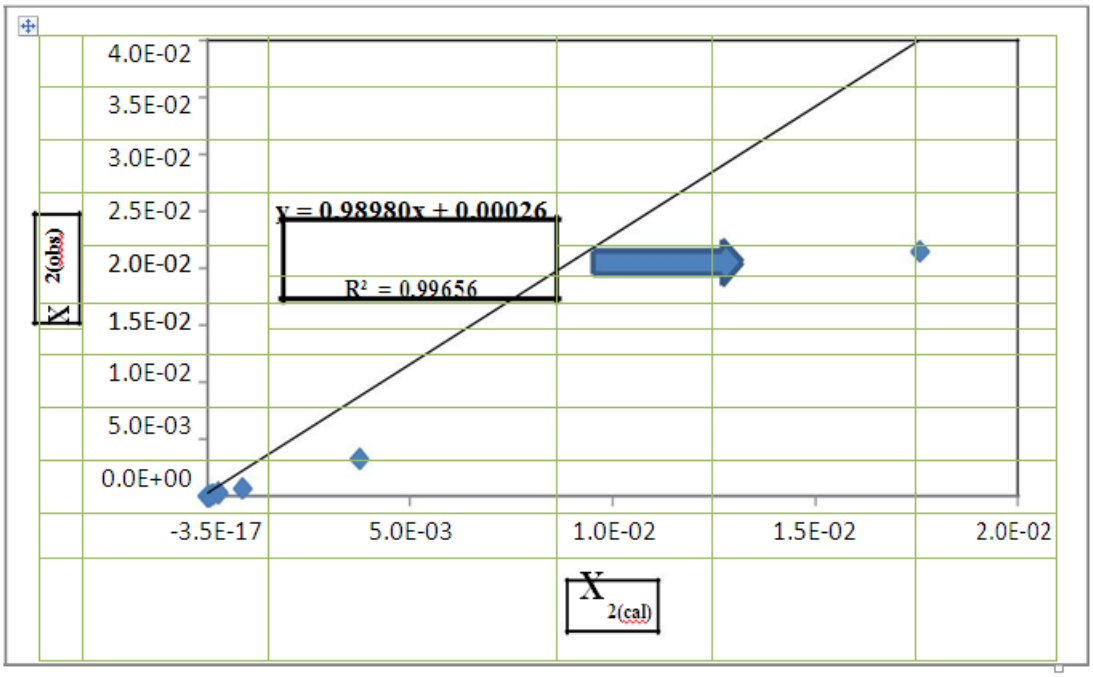

Figure 8: Predictability of Extended Hildebrand Solubility Approach for rosiglitazone maleate in DMSO-water system

5. CONCLUSIONS

1.Purity check of all cosolvents was carried out with respect to density, boiling point and refractive index in duplicate, which is in good agreement with reported standard values.

2.Wavelength of maximum absorbance for rosiglitazone maleate was found to be 248.5 nm in various cosolvents-water blends and it does not differ from the spectrum of drug in methanol, which shows λmax at 248.5 nm.

3.The calibration curve of rosiglitazone maleate was prepared according to method of preparation given in the literature. The solutions were prepared in the concentration range of 10 to 60 µg/ml in methanol and analyzed at λmax of drug, it obeys Lambert-Beer law with regression 0.9979.

4. Heat of fusion and melting point of drug was found to be 87.47 (J/Gm) and 235-240° C, which is in good agreement with standard value.

5.FT-IR Spectroscopy of rosiglitazone maleate helps to identify the presence of functional groups.

6.Log p value i.e. partition coefficient of rosiglitazone maleate was found to be - 0.0367.

7.As drug is poorly water soluble, its aqueous solubility was found to be 0.0646 mg/ml.

8.There is not much significant difference in solubility of rosiglitazone maleate in buffer systems as compared to aqueous system.
9. The solubility of rosiglitazone maleate, a poorly water soluble drug, was studied in various water miscible cosolvents-water blends. The cosolvents investigated were 1, 4-Butanediol, Glycerin, DMA, DMF, DMSO, 1, 4-Dioxane, Ethanol, Methanol, NMP, PEG-200, PEG-400, PEG-600 and Propylene glycol.
10.The solubility of rosiglitazone maleate was found to be more in various cosolvent-water blends especially in DMA, DMF, DMSO, 1, 4-Dioxane and NMP. The rise in solubility was in good proportionate to the concentration of cosolvent in the blend
11.The solubility of rosiglitazone maleate in cosolvent-water blends roughly followed the log linear model, which is widely accepted to explain the solubilization behavior of poorly soluble compounds.
12.With Yalkowsky approach, solubilization power was found to be high for rosiglitazone maleate in 1, 4-Dioxane>DMF>NMP>PG>methanol>DMSO and were in close proximity to each other, which indicate their usefulness in enhancing the solubility of drug.
13.With yalkowsky approach, since the available data set is for single solute (rosiglitazone maleate) with different cosolvents-water blends and hence there is a need of large number of solubility data sets for different solutes (within same category/structural formula) in particular cosolvent water blends to predict significance of A‟ and B‟ values by this approach, here these values are inclusive. Further studies can be expected in this direction.
14.Extended hildebrand solubility approach was found to provide a linear relationship for rosiglitazone maleate in cosolvents-water system namely, 1, 4-Butanediol, Glycerin, DMA, DMF, DMSO, Ethanol, NMP, PEG-200, PEG-400, PEG-600 and PG, indicating the better predictability of the results by this approach. For 1, 4-Dioxane-water and methanol-water system, linearity graph was still observed but much more number of data points are deviating from linearity. This indicates that Extended Hildebrand Solubility Approach (EHSA) may not be suitable approach for predicting solubility behavior of rosiglitazone maleate in these two cosolvents-water system, thus the log linear approach was adopted for these cosolvent systems.
15.The interaction existing in solutions were better studied by Extended Hildebrand Solubility Approach for various cosolvent-water systems as compared to yalkowsky approach.
16.Experimentally determined solubility parameter of rosiglitazone maleate was in good agreement with that of theoretically calculated solubility parameter by Fedor‟s Group Contribution Method.

5.1 Future Scope

The solubility behavior of rosiglitazone maleate in dimethylsulfoxide-water binary mixtures within the accuracy. Ex-vivo solubilization may be carried out to evaluate the solubility of drug. These methods are potential usefulness in preformulation and formulation studies during which solubility prediction is important for drug design and needed to prove the enhanced solubility of Rosiglitazone maleate.

REFERENCES

1. Patric J. Sinko, "*Martin's Physical Pharmacy and Pharmaceutical Sciences"* ,5th edition, Lippincott
2. Williams and Wilkins: Philadelphia, 2006; pp 120-127, 233-246.
3. Sweetana S; Akers M.J; "*Solubility principles and practices for parenteral drug dosage form development*", 1996; J. Pharm. Sci. Technol. pp 330-342.
4. Gennaro A. R; "*Remington: The Science and Practice of Pharmacy"*, 20th ed.; Lippincott Williams and Wilkins: Philadelphia, 2000; pp 209, 224-225.
5. Aulton M. E; "*The Science of Dosage Form Design",* 2nd ed.; Churchill Livingstone: Philadelphia, 2002; pp 23, 311-312.
6. Van de Waterbeemed H; "*Oral drug absorption, Prediction and assessment*. In: Dressman JB, Lenneras H, editors. Drugs and Pharmaceutical Sciences". New York: Marcel Dekker publishing; 2000. pp 38.
7. Avis K. E; Lieberman H. A; Lachman L; "*Pharmaceutical dosage forms: parenteral medications",* 2nd ed.; Marcel Dekker Inc.: New York, 1992; pp 173-192.
8. Gharamaleki, A. J; M. Jalali, B; Acree, W.E. "*Solubility correlation of structurally related drugs in binary solvent mixtures. Int. J. P'ceutics".* 1998; *166*, pp *205-209.*
9. Barton, A. F. M. *CRC "Handbook of Solubility Parameters and other Cohesion Parameters"*, 2nd ed.; CRC Press: New York, 1983; pp 7-59, 157-185.
10. Burke, J. "*Solubility Parameters: Theory and Application. The American Institute for Conservation"*, 1984; *3*, pp 7-27.
11. Shinde, A. J., "*Solubilization of Poorly Soluble Drugs: A Review"*. 2008. www.pharmainfo.net.
12. Gibson, M. "*Pharmaceutical Preformulation and Formulation, Interpharm/CRC"*: New York, 2004; pp 21, 198, 331.
13. Marcus, E. B; Thorsteinn, L. "*Cyclodextrins as pharmaceutical solubilizers. Advanced Drug Delivery Reviews".* 2007; pp 1-85.
14. Szejtli, J. *"Molecular Encapsulation by Cyclodextrins. Cyclolab Cyclodextrin R&D Laboratory"*, Ltd., Budapest, pp 1-33.
15. Ni, N; Sanghvi, T; Yalkowsky, S. H. "*Solubilization and preformulation of carbendazim. Int. J. P'ceutics"*. 2002; *244*, pp 99-104.
16. Brahmankar D., Jaiswal S. "*Biopharmaceutics and Pharmacokinetics a treatise"*. Vallabh Prakashan, 2002; pp 164-165, 297-298.

17. Swarbrick, J; Boylan, J. C. "*Cosolvents and Cosolvency- Encyclopedia of Pharmaceutical Technology"*, Marcel Dekker: New York, 1990; 3, pp 375-398.
18. Yan, H; Ping, Li; Yalkowsky, S. H. "*Solubilization of Fluasterone in cosolvent/cyclodextrin combinations. Int. J. P'ceutics"*. 2003; *264*, pp 25-34.
19. Chaudhari, P; Sharma, P; Barhate, N. Kulkarni, P; Mistry, C. "*Solubility enhancement of hydrophobic drugs using synergistically interacting cyclodextrins and cosolven"t. Curr. Sci.* 2007; *92*, pp 1586-1591.