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Solubility Behaviour of Baicalin in Polar and Non-Polar Solvents: Solubility Parameters Approach

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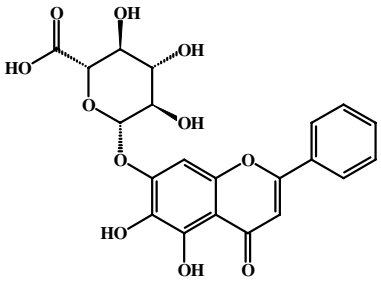
The solubility behaviour of baicalin in individual solvents ranging from non-polar to highly polar solvents was evaluated and the results were analyzed in the light of existing systems of data analysis with reference to solubility parameters. Hildbrand approach, extended Hansen's approach, four solubility parameters approach were used to analyze the solubility data and obtain partial solubility parameters of baicalin. Flory-Huggin's size connection term 'B' was found to further improve the value of regression equations. The solubility behaviour regression equations of baicalin were obtained by different approaches, such as ideal solubility model and non-ideal solubility model by Hildbrand solubiliy approach, activity coefficient and 'B' models by extended Hansen's approach and four dimensional solubility parameters approach respectively. The total solubility parameter of baicalin may be in the range of 27.79-33.29 $(J/cm^3)^{1/2}$. Different approaches were used in fitting the experimental solubility data to obtain regression equations which aim to provide a reasonable prediction of solubility of baicalin in untested solvents based on the theory of solubility parameters.

Keywords: Solubility parameters, Baicalin, Solubility behaviour.

INTRODUCTION

The solubility parameters of solvents are found to play a role in the solubilization of drug molecules, which in turn depends on the drug's chemical structure. However, the solubility parameters have not been widely employed in structure activity studies. Solubility parameter is a intrinsic physicochemical parameters of compound. That numerical value is equal to the square root of cohesive energy density and It can quantitatively reflect the molecular cohesive energy and the interaction force. The use of the solubility parameter for the selection of solvents is based on the well-known rule of chemistry: "like dissolves like", which can be used to judge the characteristic solubility regularity of drugs in solvent system and has been widely used in the design of pharmaceutical preparation[1]. The Hildbrand approach, extended Hansen's approach, the Flory-Huggins size-correction term (B) and the four-parameter approach are methods proposed to obtain partial solubility parameters of drug substances, thereby predicting their solubilities in solvents normally encountered in pharmacy, either in formulation or in pharmaceutical analysis.

Baicalin is main effective component of radix scutellariae in Chinese traditional medicine and possess a wide range of biological activity, such as antiseptic, antiinflammatory, platelet inhibition. Baicalin is almost insoluble in water and also indissoluble in liposoluble solvent. That cause the concentration in liquid preparation and the bioavailability to be low and the stability to be poor[2], thus preparation of baicalin is limited to clinical application. The precent research about dissolution of baicalin is only to measure the apparent solubility in some solvents[3-5], therefore it is lack of theoretical analysis to the regularity of the dissolution performance. The structure of baicalin is given below.



This paper aims to fit the apparent solubility in pure solvent of a model based on the solubility parameter theory. We use the mathematical model to replace numerical of apparent solubility to characterize the dissolved performance of baicalin. It can also be used to screen and predict the dissolved performance of baicalin which did not measured in solvent. This research will provide experiment and theoretical basis for the preparation design of baicalin.

EXPERIMENTAL

Baicalin was a gift from Jingsen Biological Technology Company (Shanghai, China). The set of solvents used covers a wide range on the solubility parameter scale (Table-3). Other chemicals used are of analytical grade.

Solubility measurements: The solubility of baicalin was determined in a number of solvents representative of several chemical classes ranging from nonpolar to highly polar (Table-3). Excess amounts of drug were added directly to the solvents. The flasks were shaken in a cryostat, constant temperature, reciprocating shaker (QYC-200, Shanghai Fuma Experiment Equipment Co., Ltd., China) at room temperature (25 ± 1 °C) for at least 72 h in order to achieve equilibrium, which was confirmed by comparing the concentrations in various samples equilibrated at 48, 72 and 96 h. After 72 h of equilibration, aliquots were withdrawn, filtered (0.22 μm pore size) and diluted suitably. These samples were then analyzed at 280 nm on high efficiency liquid chromatography (HPLC-1200, Agligent, America). After dilution of the samples, the solvents did not interfere with the determination results. All solubility experiments were conducted in triplicate.

The optimization analysis software 1st Opt Pro1.5 is used to fit the data with non-linear or curve models, self-organizing harmonious method is used as fitting algorithm and the convergence criteria is set to 1.00 E-10.

RESULTS AND DISCUSSION

Hildebrand solubility parameters approach: In order to quantify the expression of regular solution system, Hildebrand and Scott[6] defined the cohesive energy density (c) and solubility parameter (δ):

$$\delta = c^{1/2} = \left(\frac{\Delta U}{V}\right)^{1/2} \quad (1)$$

where ΔU is the cohesive energy of molecules that energy change of saturated liquid evaporates into the ideal gas at constant temperature and V is the molar volume.

According to the concept of solubility parameter and the first law of thermodynamics, we can estimate δ through molar enthalpy of vaporization (ΔH_V) and molar volume (V)[6]. In addition, we can directly get ΔH_V by its boiling point T_b (1 atm) and get V by molecular weight M_W and density D. The equations for the estimation of Hildebrand solubility parameters are the following:

$$\Delta U = \Delta H_V - RT \quad (2)$$

$$\Delta H_{V\,25^\circ C} = 23.7T_b + 0.020T_b^2 - 2950 \quad (3)$$

$$V = \frac{M_W}{D} \quad (4)$$

We can achieve relative parameters (ΔH_V, V, M_W, D) of baicalin on website, which is www. Chemspider.com. Using the above eqn. 2 and 4, the results would be presented on Table-2.

According to the thermodynamic principles, dissolution of drug is the process of two kinds of liquid (overcooled liquid of drug and solvent) to be mixed together. The equations are the following:

$$\Delta G_M = \Delta H_M - T\Delta S_M \quad (5)$$

$$G^E = RT\ln\gamma = H^E - TS^E \quad (6)$$

$$H^E = U^E + PV^E \quad (7)$$

ehere ΔG_M, ΔH_M and ΔS_M are the changes of free energy, enthalpy and entropy respectively in the mixing process and G^E, H^E, S^E, U^E, V^E are the excess free energy, enthalpy, entropy, internal energy and volume of real solution respectively and γ is the solute activity coefficient.

For the regular solution, thus the formula are the following:

$$\Delta G^E = U^E = V_M\varphi_1\varphi_2(C_{11} + C_{22} - 2C_{12}) \quad (8)$$

where C_{11}, C_{22}, C_{12} are the interaction between solvents and solvents, between solutes and solutes and between solvents and solutes, respectively. where φ_1 and φ_2 are the volume fraction of solvents and solutes and V_M is the bulk volume.

To further simplify eqn. 8, we introduced the London formula which consider that the molecule interaction between solute and solvent is approximately equivalent to the geometric mean of molecular interaction of the solute and solvent respectively, that is $C_{12} = (C_{11}C_{12})^{1/2}$ and then get the Scatchard-Hildebrand regular solution equation as follows:

$$\Delta H_M = V_M\varphi_1\varphi_2(\delta_1 - \delta_2)^2 \quad (9)$$

$$\ln g_2 = \frac{V_2\varphi_1^2}{RT}(\delta_1 - \delta_2)^2 \quad (10)$$

where γ_2, V_2 and δ_2 are the activity coefficient, molar volume and solubility parameter of solutes, respectively and δ_1 is the solubility parameter of solvents.

The dissolution process carried out spontaneously was based on the premise that ΔG_M must be negative, Because mix is always the increase of entropy, $\Delta S_M >> 0$.

$$\Delta G_M \le 0 \begin{cases} \Delta H_M = 0, \delta_1 = \delta_1 \\ \Delta H_M \to 0, \delta_1 \to \delta_2 \\ |T\Delta S_M| > |\Delta H_M| \end{cases} \quad (11)$$

That is the approximate basis of using Hildebrand solubility parameter to characterize drug solubility[6,7]. The physical meaning of δ is the work that solute or solvent molecular must overcome itself intermolecular forces in the process of dissolution and δ is a parameter to characterize the intermolecular interaction force, also called one dimension solubility parameter. Whether the solubility parameters of two substances are equal or similar to determine whether they can dissolve together.

For this type of solution that a solid drug is dissolved in liquid, according to Hildebrand solubility parameter and the equilibrium thermodynamic theory, we apply the following model to analyze the calculated problem of drug solubility.

(1) Ideal solution $$\ln X_2^i = \frac{\Delta H_f}{R}\left(\frac{1}{T_0} - \frac{1}{T}\right) \quad (12)$$

(2) Regular solution

$$\ln X_2 = \frac{\Delta H_f}{R}\left(\frac{1}{T_0} - \frac{1}{T}\right) - \frac{V_2\varphi_1^2}{RT}(\delta_1 - \delta_2)^2 \quad (13)$$

(3) Non regular solution

$$\ln X_2 = \frac{\Delta H_f}{R}\left(\frac{1}{T_0}-\frac{1}{T}\right)-\frac{V_2\varphi_1^2}{RT}(\delta_1^2-\delta_2^2-2\omega)$$

$$\omega = \frac{1}{2}\left((\delta_1^2+\delta_2^2-\frac{\log\gamma_2}{A}\right) \quad A = \frac{V_2\varphi_1^2}{2.303RT} \qquad (14)$$

where X_2^i, ΔH_f, and T are the mole fraction of ideal solution, the molar enthalpy(solution enthalpy), melting point and melting temperature of solute, respectively. X_2 is the mole fraction of the solute and ω is the parameter of the polar solution. ΔH_f is 27950.55 J/mol, X_2^i is 0.01096, as determined by aqueous solubility of different temperature of baicalin from the reference[5] and calculated using the eqn. 12. The apparent solubility of baicalin were fitted by eqn. 13 and 14, and the statistical values for the prediction of Hildebrand solubility parameters are presented in Tables 2, 4 and 5.

Hansen solubility parameters approach: Hansen extended the original Hildebrand parameter to three-dimensional solubility parameters (Hansen solubility parameters) for polar and hydrogen bonding systems[7,8]. According to this concept, the total solubility parameter is separated into three different types of partial solubility parameters, δ_d representing the dispersion forces, δp representing the dipolar interactions and δ_h representing generalized electron transfer bonding including hydrogen bonding and acid-base interaction[9]. These quantities are related by the expression:

$$\delta_T^2 = \delta_d^2+\delta_p^2+\delta_h^2 \qquad (15)$$

Hansen's total solubility parameter corresponds to the Hildebrand parameter. Nevertheless, these two quantities are probably different when they are obtained by different methods.

According to the chemical structure of compound, using the additivity principle with group contribution method can estimate the Hansen solubility parameters (HSP) of baicalin, the representative methods are Fedors, Small, Van Krevelen, Hoy, Stefais-Panayiotou, *etc*[7,9,10]. This article we use Stefais-Panayiotou method in HSPiP 3rd to estimate the HSP of baicalin. According to the group division principle of Stefais-Panayiotou method, the baicalin group division is shown in Table-1 and the estimation results in Table-2.

TABLE-1
ORDER GROUPS OF BAICALIN STRUCTURE

	First-order groups	Second-order groups
Baicalin	5 × -CH <, 1 × -CH = C <, 6 × Ac H, 4 × Ac, 1 × -COOH, 3 × -OH, 2 × AcOH, 3 × > O, 1 × > C = 0	C(cyclic) = O, C-O-C=C, AC-O-C

Y-MB method is also a tool for estimating HSP, which obtained by Hiroshi Yamamoto through artificial neural networks for a number of compounds known HSP modeling and training optimization and can be estimated directly from the SMILES code or 3D structure of compounds[11]. This article we also use Y-MB module in HSPiP 3rd to estimate the HSP of Baicalin and the estimation results in Table-2.

Hansen proposed a method using Hansen ball to handle the dissolution issue of polymer compounds. There can get a three-dimensional sphere with $2\delta_d$-δ_p -δ_h drawing for each polymer material and HSP value is defined as the center of the sphere and radius R_0 represents the range of dissolved area. Researchers generally consider the corresponding point of good solvent in the ball and poor solvent outside the ball and can use the difference R_a between the solvent and solute, relatively cohesive energy RED (R_a/R_0) to determine[9].

$$R_a = [4(\delta_{ds}-\delta_{dp})^2+(\delta_{ps}-\delta_{pp})^2+(\delta_{hs}-\delta_{hp})^2]^{1/2} \qquad (16)$$

However, it is very inappropriate in practical applications because the need for three-dimensional structure of polymer and solvent and Hansen ball method is mainly used for the solution of polymer material, less used for dissolution properties of small molecule drugs. Martin extended the Hansen method, used HSP to characterize the dissolution behaviour of crystal drug molecules[12], namely:

$$\frac{\log\gamma_2}{A} = C_0+C_1(\delta_{1d}-\delta_{2d})^2+C_2(\delta_{1p}-\delta_{2p})^2+C_3(\delta_{1h}-\delta_{2h})^2 \qquad (17)$$

where C_0 and C_i(i = 0, 1, 2, 3) are the constants and fitting parameters and δ_{id}, δ_{ip}, δ_{ih} (i = 1, 2) are the HSP parameters of drug and solvent respectively.

In fact, the real drug solution often deviates from the regular solution,due to the interactions between solute and solvent and differences in molecular size. Barton introduced the Flory-Huggin interaction correction factor B which is used

TABLE-2
SOLUBILITY PARAMETER VALUES $(J/cm^3)^{1/2}$ FOR BAICALIN BY DIFFERENT METHODS

Method/system	Solubility parameter					
	δ_T	δ_d	δ_p	δ_h	δ_a	δ_b
Estimated from ΔH_m^v, V_m	28.56					
Estimated from T_b, M_W, D	27.79					
Hildbrand parameter[a]	31.91					
Hildbrand parameter[b]	30.63					
Stefais-panayiotou	27.60	23.3	13.5	2.1		
Y-MB	35.39	20.8	16.5	23.4		
Hansen parameter[c]	33.29	23.98	12.9	19.16		
Hansen parameter[d]	32.09	25.77	13.14	13.9		
Y-MB[f]	32.64	20.8	16.5	18.99	8.2	22
Four parameter[e]	29.5	23.6	14.52	10.10	3.87	13.18
Four parameter[f]	27.79	24.30	10.34	8.66	4.39	8.54

[a]Using regular solution model fitting, eqn. 13; [b]using informal solution model fitting, eqn. 14; [c]Using activity coefficient $\log\gamma_2/A$ fitting, eqn. 17; [d]using Flory-Huggin's size connection term 'B' fitting, eqn. 19; [e]Using activity coefficient $\log\gamma_2/A$ fitting, eqn. 21; [f]using Flory-Huggin's size connection term 'B' fitting, eqn. 22

to improve accuracy of the model in Hansen extension method[13].

$$B = RT[\ln \gamma_2 - \ln(V_2/V_1) - 1 + (V_2/V_1)/V_2\varphi_1^2] \quad (18)$$

$$B = D_0 + D_1 (\delta_{id}-\delta_{2d})^2 + D_2(\delta_{ip}-\delta_{2p})^2 + D_3(\delta_{ih}-\delta_{2h})^2 \quad (19)$$

where D_0 and D_1 (i = 0, 1, 2, 3) are the constants and fitting parameters, respectively. The apparent solubility of baicalin were fitted by eqn. 17 and 19 and the statistical values for the prediction of Hansen solubility parameters are presented in Tables 2, 4 and 5.

Four dimensional solubility parameters approach: Hydrogen bond component δ_h of HSP cannot reflect Lewis acid-base interactions between groups well in dealing with the complex structure of the drug molecule. Beerbower established a system of four-dimensional solubility parameter on the basis of Karger acid -base solubility parameter[14,15], through the extension of δ_h for electron donating component δ_a and electron accepting component δ_b ($\delta_h^2 = 2\delta_a\delta_b$), namely:

$$\delta_T^2 = \delta_d^2 + \delta_p^2 + 2\delta_a\delta_b \quad (20)$$

where δ_d, δ_p, δ_a and δ_b are the dispersion force, polar force (orientation and induction force), the electron accepting and electron donating effect, respectively.

In this article we also use Y-MB module in HSPiP 3rd to estimate the four dimensional solubility parameters of baicalin[11] (Table-2). Four dimensional solubility parameters are commonly used in fitting drug solubility model[16], namely:

$$\frac{\log \gamma_2}{A} = C_0 + C_1 (\delta_{1d}-\delta_{2d})^2 + C_2(\delta_{1p}-\delta_{2p})^2 + C_3(\delta_{1a}-\delta_{2a})(\delta_{1b}-\delta_{2b}) \quad (21)$$

$$B = D_0 + D_1(\delta_{1d}-\delta_{2d})^2 + D_2(\delta_{1p}-\delta_{2p})^2 + D_3(\delta_{1a}-\delta_{2a})(\delta_{1b}-\delta_{2b}) \quad (22)$$

The apparent solubility of baicalin were fitted by eqn. 21 and 22 and the statistical values for the prediction of four dimensional solubility parameters are presented in Tables 2, 4 and 5. Solubility parameters of solvents[12,13,14], solu-bility and activity coefficient of baicalin are presented in Table-3.

Conclusion

Solubility parameter theory has been used widely in chemical industry, polymers, cosmetics processing, pharmaceutic adjuvant and controlled release preparation research, but the application in traditional Chinese medicine (TCM) is few. The solubility behaviour of baicalin was evaluated and the results where analyzed in the light of existing systems of data analysis with reference to solubility parameters. This test use different methods (Hildbrand, Hansen, Four dimensional

TABLE-3
SOLUBILITY PARAMETER OF SOLVENT AND SOLUBILITY AND ACTIVITY COEFFICIENT OF BAICALIN

Solvent	V_1 (cm^3/mol)	Solubility parameter ($(J/cm^3)^{1/2}$)						S(exp) (μg/mL)	x_2(exp)	γ_2(exp)
		δ_T	δ_d	δ_p	δ_h	δ_a	δ_b			
PEG400	163.000	19.82	19.18	3.49	3.58	na	na	17760.63	6.5100×10^{-3}	1.68
Ethylether	100.925	15.40	14.50	2.90	5.10	0.00	3.00	2.17	4.9035×10^{-7}	22351.75
Ethyl acetate	98.000	18.21	15.14	5.32	9.21	10.84	3.89	35.76	7.8504×10^{-6}	1396.15
Acetone	75.176	20.05	15.55	10.43	6.96	4.91	4.91	498.38	8.3954×10^{-5}	130.55
Acetic acid	56.175	21.36	14.53	7.98	13.50	14.32	6.34	603.77	7.6005×10^{-5}	144.20
Butyl alcohol	92.069	23.12	15.96	5.73	15.75	13.09	9.41	386.57	7.9748×10^{-5}	137.44
Ethanol	59.055	26.60	15.75	8.80	19.44	16.98	11.25	1616.90	2.1407×10^{-4}	51.20
Methanol	42.548	29.67	15.14	12.28	22.30	17.19	14.53	2494.25	2.3804×10^{-4}	46.04
Propylene glycol	73.444	30.28	16.78	9.41	23.32	28.85	9.41	1302.93	2.1450×10^{-4}	51.10
Ethylene glycol	56.561	32.70	16.98	11.05	25.77	36.61	9.00	7080.34	9.0005×10^{-4}	12.18
Water	18.045	47.88	15.55	15.96	42.35	13.71	65.47	48.94	1.9787×10^{-6}	5539.16

na : Solvent contributions to this solubility parameter were not available

TABLE-4
USING DIFFERENT METHODS TO ANALYZE THE DISSOLUTION BEHAVIOR (SOLUBILITY PARAMETER) OF BAICALIN IN INDIVIDUAL SOLVENTS n = 10

Fitting method	Fitting formula	R	s	F
Hildbrand[a]	$\ln X_2 = -76267\text{-}0.0219 \times (\delta_1\text{-}31.9134)^2$	0.9592	4.3565	85.3666
Hildbrand[b]	$\ln X_2 = -4.5135\text{-}0.1034. \times [(\delta_1^2\text{+}30.6283^2\text{-}2 \times (30.3283 \times \delta_1 + 5.0715)]$	0.9305	783.4314	51.6356
Hansen[c]	$\frac{\log \gamma^2}{A} = 7.3157 + 0.3445 \times (\delta_{1d}\text{-}23.9781)^2 + 0.4079 \times (\delta_{1p}\text{-}12.905)^2 + 0.0888 \times (\delta_{1h}\text{-}19.1589)^2$	0.9887	105.6553	349.4314
Hansen[d]	$B = -38.5015 + 0.8287 \times (\delta_{id}\text{-}25.7665)^2 + 0.2329 \times (\delta_{ip}\text{-}13.1398)^2 + 0.1666 \times (\delta_{1h}\text{-}13.9011)^2$	0.9971	89.1371	1392.9064
Four[e]	$\frac{\log \gamma_2}{A} = 14.9233 + 0.3303 \times (\delta_{1d}\text{-}23.6061)^2 + 0.3491 \times (\delta_{1p}\text{-}14.5193)^2 + 0.0418 \times (\delta_{1a}\text{-}3.8672) \times (\delta_{1b}\text{-}13.1781)$	0.9631	345.6114	102.3872
Four[f]	$B = -5.2019 + 0.6413 \times (\delta_{id}\text{-}24.2982)^2 + 0.5817 \times (\delta_{1p}\text{-}10.3355)^2 + 0.1041 \times (\delta_{1a}\text{-}4.3879) \times (\delta_{1b}\text{-}8.5415)$	0.9903	300.6145	407.3670

[a]Using Hildbrand solubility parameter fitting regular solution model, eqn. 13; [b]Using Hildbrand solubility parameter fitting informal solution model, eqn. 14; [c]Using Hansen solubility parameter fitting activity coefficient $\log\gamma_2/A$, eqn. 17; [d]Using Hansen solubility parameter fitting Flory-Huggin's size connection term 'B', eqn. 19; [e]Using four solubility parameter fitting activity coefficient $\log\gamma_2/A$, eqn. 21; [f]Using four solubility parameter fitting Flory-Huggin's size connection term 'B', eqn. 22; R: correlation coefficient; s:sum of squares of residues; F: statistic

TABLE-5
ANALYSIS THE DISSOLUTION BEHAVIOR (SOLUBILITY PARAMETER) OF BAICALIN IN INDIVIDUAL SOLVENTS

Solvent	$\ln x_2$ (exp)	$\ln x_2$ (cal)				$\log\gamma_2$ (exp)	$\log\gamma_2$ (cal)				B (exp)	B (cal)			
		Regular solution	Error	Informal solution	Error		HSP	Error (%)	Four	Error (%)		HSP	Error (%)	Four	Error (%)
PEG400	-5.0344	na	na	na	na	0.2262	na	na	na	na	6.3241	na	na	na	na
Ethylether	-14.5281	-13.6056	-0.0635	-27.4886	0.8921	4.3493	4.3477	-0.0004	4.0867	-0.0409	102.5624	104.0071	0.0141	103.9958	0.0140
Ethyl acetate	-11.7549	-11.7438	-0.0009	-19.4398	0.6538	3.1449	2.9908	-0.0490	2.8217	-0.1028	76.2456	72.98043	-0.0428	67.3639	-0.1165
Acetone	-9.3852	-10.7123	0.1414	-15.0503	0.6036	2.1158	2.1358	0.0094	1.8653	-0.1189	58.5221	57.73782	-0.0134	53.8963	-0.0790
Acetic acid	-9.4847	-10.0684	0.0615	-12.3573	0.3029	2.1590	2.2848	0.0583	2.2980	0.0643	67.8366	72.41795	0.0675	65.1163	-0.0401
Butyl alcohol	-9.4366	-9.3218	-0.0122	-9.3020	-0.0143	2.1381	2.3159	0.0831	2.6213	0.2263	54.9158	54.57266	-0.0062	63.7245	0.1604
Ethanol	-8.4492	-8.2454	-0.0241	-5.1423	-0.3914	1.7093	1.6839	-0.0148	2.0057	0.1718	56.2291	54.06555	-0.0385	60.5034	0.0760
Methanol	-8.3431	-7.7367	-0.0727	-3.5592	-0.5734	1.6632	1.5817	-0.0490	1.8793	0.1288	68.4165	66.99545	-0.0208	77.1268	0.1273
Propylene glycol	-8.4472	-7.6849	-0.0902	-3.4769	-0.5884	1.7084	1.4238	-0.1666	1.4162	-0.1699	50.0617	46.48975	-0.0714	46.4060	-0.0730
Ethylene glycol	-7.0131	-7.6400	0.0894	-3.9054	-0.4431	1.0856	1.3150	0.2114	0.9970	-0.0877	44.0545	49.95596	0.1340	42.9210	-0.0257
Water	-13.1331	-13.2162	0.0063	-34.2957	1.6114	3.7434	3.7505	0.0019	3.5734	-0.0377	185.2969	184.6802	-0.0033	183.1771	-0.0114

na : Parameters of PEG400 were not bring into fitting

solubility parameters approach) to analyze the dissolution behaviour of Baicalin in individual solvents and fit many kinds of solubility parameter based on the solubility parameter theory. In fitting process, we found that when eliminated the biggest apparent solubility in PEG400, the goodness-of-fittest of different fitting methods were improve, so infer that Baicalin dissolved in PEG400 may have other effect contribution and this paper were not taking PEG400 data into the fitting of model.

Based on the Hildbrand solubility parameter, when using regular solution and informal solution model to fit, we found that regular solution model is better in fitting, it was related with the calculation accuracy of polar solution parameter ω (the informal model), but it doesn't mean that the solution of baicalin is more conform to the regular solution model. The Hildbrand solubility parameters values of fitting were found to be 31.91, 30.63 $(J/cm^3)^{1/2}$, slightly larger than the values of direct estimation method (28.56, 27.79 $(J/cm^3)^{1/2}$).

Based on the Hansen solubility parameter, using activity coefficient and Flory-Huggin interaction correction factor B to fit, we found that goodness-of-fittest improved after inducted correction factor B, the value of correlation coefficient raised from 0.9887 to 0.9971, the fitting error range of log γ_2 value narrowed down from -0.1666-0.2114 to -0.0714-0.1340. Hansen solubility parameters values of fitting were found to be 33.29 (23.98,12.9,19.16) $(J/cm^3)^{1/2}$ and 32.09 (25.77, 13.14, 13.9) $(J/cm^3)^{1/2}$, between the estimation results of Stefais-Panayiotou method and Y-MB method.

Based on the four dimensional solubility parameter, using activity coefficient and Flory-Huggin interaction correction factor B to fit, we also found goodness-of-fittest improved after inducted correction factor B, the value of correlation coefficient raised from 0.9631 to 0.9903, the fitting error range of log γ_2 value narrowed down from -0.1699-0.2263 to -0.1165-0.1604. Four dimensional solubility parameter values of fitting were found to be 29.50 (23.60, 14.52, 3.87, 13.18) $(J/cm^3)^{1/2}$ and 27.79(24.30, 10.34, 4.39, 13.9, 8.54) $(J/cm^3)^{1/2}$, less than the values of Y-MB method estimation. The estimation results showed that baicalin exist donor and ceptor electronic solubility parameters and δ_a, δ_b, it coincide with that the structure of baicalin contained donor and ceptor electronic groups (H bond donors: 6, H bond acceptors: 11).

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