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Modeling the solubility of ketoprofen in mono-solvents at various temperatures

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Summary

Aim: To report a correlative model to calculate the solubility of ketoprofen in mono-solvents at various temperatures. **Methodology:** Previously reported solubility data of ketoprofen in a number of mono-solvents at various temperatures are re-analyzed using a recently developed model employing Abraham, Hansen and Catalan parameters as input values. The accuracy of the model is evaluated by computing the standard deviation of residuals (SDRs) and compared with those of previous models. **Results:** The new model provided very accurate correlation for the solubility of ketoprofen in the investigated mono-solvents at various temperatures. The obtained SDR is 2.20 where the SDRs of previously reported models are 1.54 to 2.56. The new model correlates whole solubility data using a single model, whereas other models correlate the solubility data in each mono-solvent using a separate set of model constants. **Conclusion:** The trained model provided reasonably accurate results for ketoprofen by using Abraham, Hansen and Catalan parameters of the mono-solvents as input values.

Keywords: Solubility, van't Hoff model, mono-solvents, correlation, temperature.

Resumen

Modelación de la solubilidad del ketoprofeno en mono-solventes a varias temperaturas

Objetivo: reportar un modelo correlativo para calcular la solubilidad del ketoprofeno en mono-disolventes a varias temperaturas. **Metodología:** los datos de solubilidad de ketoprofeno reportados anteriormente en varios mono-solventes a varias temperaturas se analizan nuevamente utilizando un modelo desarrollado recientemente que emplea los parámetros de Abraham, Hansen y Catalan como valores de entrada. La precisión del modelo se evaluó calculando la desviación estándar de los residuos (DER) y se compara con los modelos anteriores. **Resultados:** el nuevo modelo proporcionó una correlación muy precisa de la solubilidad del ketoprofeno en los mono-solventes investigados a varias temperaturas. El DER obtenido es 2,20 mientras que los DER de los modelos reportados anteriormente variaron de 1,54 a 2,56. El nuevo modelo correlaciona todos los datos de solubilidad utilizando un solo modelo, mientras que otros modelos correlacionan los datos de solubilidad en cada mono-solvente utilizando un conjunto separado de constantes. **Conclusión:** el modelo entrenado proporcionó resultados razonablemente precisos para la solubilidad del ketoprofeno utilizando los parámetros de Abraham, Hansen y Catalan de los mono-solventes como valores de entrada.

Palabras clave: Solubilidad, modelo de van't Hoff, mono-solventes, correlación, temperatura.

Resumo

Modelando a solubilidade do cetoprofeno em monossolventes em várias temperaturas

Objetivo: relatar um modelo correlativo para calcular a solubilidade do cetoprofeno em monossolventes em várias temperaturas. **Metodologia:** os dados de solubilidade relatados anteriormente para o cetoprofeno em vários monossolventes em várias temperaturas são reanalisados usando um modelo desenvolvido recentemente usando os parâmetros de Abraham, Hansen e Catalan como valores de entrada. A precisão do modelo foi avaliada pelo cálculo do desvio padrão dos resíduos (DP) e comparada com modelos anteriores. **Resultados:** o novo modelo forneceu uma correlação altamente precisa da solubilidade do cetoprofeno nos monossolventes

investigados em várias temperaturas. O DER obtido é de 2,20 enquanto o DER dos modelos relatados anteriormente variou de 1,54 a 2,56. O novo modelo correlaciona todos os dados de solubilidade usando um único modelo, enquanto outros modelos correlacionam os dados de solubilidade em cada monossolvente usando um conjunto separado de constantes. **Conclusão:** o modelo treinado forneceu resultados razoavelmente precisos para a solubilidade do cetoprofeno usando os parâmetros Abraham, Hansen e Catalan dos monossolventes como valores de entrada.

Palavras-chave: Solubilidade, modelo de van't Hoff, monossolventes, correlação, temperatura.

Introduction

Ketoprofen (2-(3-benzoylphenyl)-propionic acid) is a potent analgesic and anti-pyretic drug prescribed as a painkiller. It is a low soluble in water and possesses a chiral center, but it is used as a racemic mixture. The solubility of pure S-ketoprofen is more than that of the racemate [1]. Ketoprofen is a class II drug, low solubility and high permeability, in the biopharmaceutical classification system with a partition coefficient (log *P*) of approximately 3.12 [2]. Its aqueous solubility at 37 °C is 0.45 mg/mL was increased to 34.88 mg/mL after converting as a sodium salt [3]. The solubility of ketoprofen was also increased by addition of ethanol [4] and propylene glycol [5] as the pharmaceutical cosolvents. Solubility of ketoprofen in organic solvents are available from the literature [6] but shows variability up to 300%. As an example, the molar solubility of ketoprofen in ethanol at 298.2 K were reported as 1.038 (or 0.0701 in mole fraction) [7], 0.957 (or 0.0640 in mole fraction) [8], 0.672 (or 0.0441 in mole fraction) [9] and 1.746 [10]. Possible reasons for such discrepancies in the experimental solubilities arise from; drug purity, solvent purity, lack of equilibration, temperature, analysis method, laboratory technique, typographical error, polymorphism or enantiomeric forms of the drug [11]. Soto *et al.* [12] reported the solubility data of ketoprofen in eight monosolvents at various temperatures.

Aqueous solubility of drugs could be calculated using a number of published models including the general solubility equation (GSE) of Yalkowsky [13], the linear solvation energy relationship (LSER) approach of Abraham [14], a combined two parameters model [15] and some other models/software which were reviewed in a previous publication [16]. The solubility of drugs in organic solvents could also be computed using some published models including an adopted version of GSE for calculating the solubility of drugs in octanol [17], a model proposed by Dearden *et al.* to calculate

the solubility of solutes in cyclohexane [18], the Abraham solvation model [19] and the KAT-LSER model [20]. All these models were briefly reviewed in a recent work [21] and calculate the solubility of drugs in a given solvent or the solubility of a drug in various solvents at an isothermal condition. Efficient crystallization process of drugs is required in the pharmaceutical industry, since the small amount of impurities may cause severe health problems. Selection of an appropriate solvent and finding a suitable temperature range are crucial to provide an efficient crystallization method and the trial and error approach is commonly used in practice, since there is no a good model to simulate these conditions so far. The aim of this short communication is to report a new model for correlating the solubility of ketoprofen in the mono-solvent systems at various temperatures. The model provides useful information for calculating the solubility of ketoprofen in different solvents at various temperatures, which are in demand in many industrial applications.

Methods and materials

The reported experimental solubility data of ketoprofen in eight mono-solvents, *i.e.* methanol, ethanol, 2-propanol, 1-butanol, acetonitrile, ethyl acetate, 1,4-dioxane and toluene at seven temperatures ranging from 273.15 to 303.15 K [12] is re-analyzed in this work. Soto et al. correlated the solubility data using some mathematical models and reported the accuracy of the calculations using the standard deviation of residuals (*SDR*). The *SDR* values were computed by:

$$SDR = \left[\frac{\sum \left(x_2^{cal} - x_2 \right)^2}{N-1} \right]^{1/2} \tag{1}$$

where N is the number of experimental data points, x_2^{cal} is the calculated solubility and x_2 is the experimental solubility of ketoprofen in the mono-solvent systems.

The van't Hoff equation is widely used for correlating the solute solubility of a given drug in a certain mono-solvent at temperatures varying in a narrow range. The model is presented as:

$$\ln x_2 = \alpha + \frac{\beta}{T} \tag{2}$$

in which, α and β are the model constants. The α and β terms represent the entropic and enthalpic changes in the solution. In the proposed model it has been assumed that these changes could be correlated using a combination of Abraham solvation parameters (AP_i), Hansen solubility parameters (HP_i) and Catalan parameters (CP_i) [21]. The numerical values of AP_i, HP_i and CP_i for the investigated mono-solvents are listed in table 1. The general form of the proposed model is:

$$\ln x_2 = \left(\alpha_0 + \sum_{i=1}^{5} \alpha_{i,Ap} Ap_i + \sum_{i=1}^{3} \alpha_{i,HP} HP_i + \sum_{i=1}^{4} \alpha_{i,CP} CP_i \right) + \left(\frac{\beta_0 + \sum_{i=1}^{5} \beta_{i,Ap} Ap_i + \sum_{i=1}^{3} \beta_{i,HP} HP_i + \sum_{i=1}^{4} \beta_{i,CP} CP_i}{T} \right) \quad (3)$$

where α and β terms are the model constants.

Table 1. The Abraham, Hansen and Catalan parameters of the investigated solvents.

Solvent						
Abraham →	*c*	*e*	*s*	*a*	*b*	*v*
Acetonitrile	0.41	0.08	0.33	-1.57	4.39	3.36
n-Butanol	0.17	0.40	-1.01	0.06	-3.96	4.04
1,4-Dioxane	0.10	0.35	-0.08	-0.56	-4.83	4.17
Ethyl acetate	0.33	0.37	-0.45	-0.70	-4.90	4.15
Ethanol	0.22	0.47	-1.04	0.33	-3.60	3.86
Isopropanol	0.10	0.34	-1.05	0.41	-3.83	4.03
Methanol	0.28	0.33	-0.71	0.24	-3.32	3.55
Toluene	0.14	0.53	-0.72	-3.01	-4.82	4.55
Hansen →	δ_D	δ_P	δ_H			
Acetonitrile	11.59	12.95	16.34			
n-Butanol	16.00	5.70	15.80			
1,4-Dioxane	19.00	1.80	7.40			
Ethyl acetate	15.80	5.30	7.20			
Ethanol	15.80	8.80	19.40			
Isopropanol	12.97	10.35	15.68			
Methanol	15.10	12.30	22.30			
Toluene	18.00	1.40	2.00			

(Continued)

Solvent⁻						
Abraham →	*c*	*e*	*s*	*a*	*b*	*v*
Catalan →	*SP*	*SdP*	*SA*	*SB*		
Acetonitrile	0.65	0.97	0.04	0.29		
n-Butanol	0.67	0.66	0.34	0.81		
1,4-Dioxane	0.74	0.31	0.00	0.44		
Ethyl acetate	0.66	0.60	0.00	0.54		
Ethanol	0.63	0.78	0.40	0.66		
Isopropanol	0.63	0.81	0.28	0.83		
Methanol	0.61	0.90	0.61	0.55		
Toluene	0.78	0.28	0.00	0.13		

Source: Jouyban *et al.* [21].

The accuracy of the proposed model was compared with those of previously applied models by Soto *et al.* [12] employing the *SDR* values. Soto *et al.* used an empirical three-parameter model represented as:

$$\ln x_2 = \frac{c_1}{T^2} + \frac{c_2}{T} + c_3 \tag{4}$$

the Buchowski-Ksizczak equation:

$$\ln\left[1 + \frac{\lambda\left(1 - x_2\right)}{x_2}\right] = \lambda h\left[\frac{1}{T} - \frac{1}{T_m}\right] \tag{5}$$

and an activity coefficient (y_2) based model of Svard-Rasmuson [22]:

$$\ln\gamma_2 = \frac{c_4}{T}\left(1 - e^{-\left(\frac{c_5}{T} - \frac{c_5}{T_m}\right)^{c_6}}\right); \quad \{c_6 \geq 2\} \tag{6}$$

In Eqs. (4)-(6), *c* terms, λ and *h*, are the model constants, T_m is the melting point of ketoprofen.

Results and discussion

The significant (p<0.05) parameters obtained from the regression analysis of ketoprofen solubility data in the investigated mono-solvents at various temperatures is:

$$\ln x_2 = \left(35.789 - 14.658c + 17.622e - 1.959a - 0.064b - 2.048\delta_D - 8.735SA\right) + \left(\frac{4552.248 + 4429.264c - 5751.595e + 1859.422a - 431.710\delta_P - 5582.527SB}{T}\right) \quad (7)$$

in which, c, e, a and b are the AP_i parameters, δ_D and δ_p are HP_i, SA and SB are CP_i parameters. The significant contribution of an independent variable on the correlation/prediction capability of a model is evaluated by using t-test in which the equality of the model constant with zero is tested for the independent variable under investigation. The model constant is considered significant when the p values is less than 0.05. Equation (7) correlated the solubility data of ketoprofen in the investigated mono-solvents with the R>0.999 and F value of 1870 (N=56). The F test examines the significance of a correlation of the dependent variable with the included independent variables in the built model and is a function of the number of cases (i.e. N or the number of investigated solubility data points in this work) and the number of independent variables. The F value is considered significant when p is less than 0.05. The *SDRs* for the calculated solubility data for each mono-solvent along with the *SDRs* for the above mentioned models were listed in table 2. The overall *SDR* values for equations (2), (4), (5) and (6) are 2.04, 2.15, 2.56 and 1.54, respectively, whereas the corresponding value for equation (7) is 2.20. It is obvious that all these overall *SDR* values could be considered as acceptable error ranges. It should be added that the proposed model was trained for all investigated solvents whereas other models should be trained for each mono-solvent using separate model constants.

Table 2. The standard deviation of residuals (*SDR x 1000*) of various equations for correlating ketoprofen in the investigated mono-solvents at various temperatures.

Solvent	Eq. (2)	Eq. (4)[a]	Eq. (5)[a]	Eq. (6)[a]	Eq. (7)
Acetonitrile	0.88	0.242	0.758	0.177	0.88
n-Butanol	2.61	2.975	3.136	0.744	3.63
1,4-Dioxane	2.48	3.406	4.123	1.489	2.48
Ethyl acetate	2.37	1.408	2.366	0.293	2.08
Ethanol	2.02	2.649	2.726	1.385	2.09
Isopropanol	1.87	2.398	2.439	2.418	2.22
Methanol	3.61	3.817	4.509	5.749	3.70
Toluene	0.50	0.299	0.445	0.093	0.52
Overall	2.04	2.15	2.56	1.54	2.20

[a] Taken from Ref. [12].

Conclusion

Concerning the above mentioned results, it is evident that the proposed model is a promising one for the mathematical representation of the solubility data of ketoprofen dissolved in mono-solvent systems at various temperatures. The model has the advantage of accurate solubility correlation capability in the mono-solvents at various temperatures. The data is required in the process design and scale up calculations in the chemical/pharmaceutical industries. Some drugs possess polymorphic forms, however, there is no independent variable to represent the characteristics of the polymorphs of a drug, so the proposed model could not be used to calculate the solubility of polymorphic forms and this could be considered as a disadvantage for the model.

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Disclosure statement

The author declares that he has no conflict of interest.

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