Austin Chemical Engineering

Open Access

Austin Publishing Group

Mini Review

A New Solvato-Complex Model for the Calculations of Solvation Enthalpies of Drugs-Supercritical Carbon Dioxide Systems

Ramalingam Vikram[1*]; Garlapati Mahesh[2*]; Chandrasekhar Garlapati[1*]

[1]Department of Chemical Engineering, Puducherry Technological University (Erstwhile Pondicherry Engineering College), India

[2]Department of Chemical Engineering, Birla Institute of Technology and Science (BITS) Pilani, Hyderabad Campus, India

***Corresponding author: Garlapati Mahesh**

Department of Chemical Engineering, Birla Institute of Technology and Science (BITS) Pilani, Hyderabad Campus, Jawahar Nagar, Kapra Mandal, Hyderabad 500078, India

Chandrasekhar Garlapati, Department of Chemical Engineering, Puducherry Technological University (Erstwhile Pondicherry Engineering College), Puducherry-605 014, India

Email: chandrasekhar@ptuniv.edu.in; maheshg681@gmail.com

Received: August 04, 2023

Accepted: September 13, 2023

Published: September 20, 2023

Abstract

The work presents a method to calculate solvation enthalpies of drug solutes from the solubility data of drugs in supercritical carbon dioxide. Drugs considered for the study are broadly classified into anticancer drugs and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). For calculating sublimation enthalpy, Bartle et al. model was used. For calculating solvation enthalpy, a new modified Chrastil model along with Bartle et al. model was used.

Keywords: Anticancer drugs; NSAIDs; Solvation enthalpy; Sublimation enthalpy; Solubility

Introduction

Supercritical fluids' applications are spanning across several fields [1-10]. The pharmaceutical industry is making use of Supercritical Carbon Dioxide ($scCO_2$) as solvent for its product size control. Drug nano and micro particles may be prepared effectively with the help of $scCO_2$as a solvent for the particle micronization process [1]. Additionally, because to its low critical temperature, lack of toxicity and flammability, and ability to leave the system residue-free after decompression, scCO2 is the ideal medium for pharmaceutical applications. For the effective utilization of $scCO_2$, enthalpies associated with the solute dissolution (i.e., heat of solution or enthalpy of solvation) in solvent are essential. Dissolution of solid drug solute in supercritical solvents depends on its sublimation enthalpy. For efficient implementation of supercritical fluid-based processes require solubility information. The present study aims at understanding solubility phenomena of solids in supercritical carbon dioxide via the well-established solvato complex theory. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and anticancer medications are two general categories for the drugs taken into consideration for the study. The Bartle et al. model [10] was employed to determine sublimation enthalpy. In addition to the Bartle et al. model, a new modified Chrastil model was employed to calculate the solvation enthalpy. Further, this study alsogives the fundamental thermochemical information about thedrug-$scCO_2$systems [2].

Theory

Josef Chrastil [3] visualized the dissolution of solutes in solvents in terms of solvato complex formation in the year 1981 and finally proposed a model that gives the heat of solution from solubility data.

$$c = (\rho)^{\kappa} \exp\left(A_0 + \frac{A_1}{T}\right) \qquad (1)$$

Where κ and $A_0 - A_1$ are model constants.

Citation: Vikram R, Mahesh G, Garlapati C. A New Solvato-Complex Model for the Calculations of Solvation Enthalpies of Drugs-Supercritical Carbon Dioxide Systems. Austin Chem Eng. 2023; 10(3): 1103.

However,eq. (1) was corrected for its dimensional consistency in the year 2009[4,5,6].

Thus, the dimensional consistency Chrastil model is

$$y_2 = \left(\frac{RT\rho_1}{M_{scf} f^{\bullet}}\right)^{K'-1} \exp\left(B_0 + \frac{B_1}{T}\right) \quad (2)$$

Where κ' and $B_0 - B_1$ are model constants.

In this work, thedimensionally corrected Chrastil model is further improved and named as modified Chrastil model.

Modified Chrastil model. According to the solvato complex model, solute molecules are surrounded by solvent molecules and form a solvato complex which represents solubility. Let '*S*' is the solute, '*SF*' is supercritical fluid solvent and SSF_κ is solvato complex. Eq. (1) is used to represent the solvato complex formation. According to eq. (3) 1 molecule of S is associated with κ molecules of 'SF' in the formation of a solvato complex (SSF_κ) which is in equilibrium with SF.

$$S + kSF \Leftrightarrow SSF_k \quad (3)$$

The equilibrium constant for the solvato complex formation [4-8] may be written as eq. (4)

$$K_c = \frac{(a_c)_{SSF_k}}{(a_c)_s (a_c)^K_{SF}} \quad (4)$$

where in eq. (4) each (a_c) is expressed based on unit activity. For gases system (a_c) may be expressed in terms of fugacity as f / RT.

Thus eq. (4) is rewritten in terms of f / RT as eq. (5)

$$K_c = \frac{(f/RT)_{SSF_k}}{(f/RT)_s (f/RT)^k_{SF}} \quad (5)$$

Further eq. (5) may be written as eq. (6)

$$K_c = \frac{(f/f^\circ)_{SSF_k}}{(f/f^\circ)_s (f/f^\circ)^k_{SF}} \times \left(\frac{RT}{f^\circ}\right)^k \quad (6)$$

Where f° is a known reference state and it may be chosen as unity or critical pressure of the SF or any other known value.

let $$K_f = \frac{(f/f^\circ)_{SSF_k}}{(f/f^\circ)_s (f/f^\circ)^K_{SF}} \quad (7)$$

Then,eq. (5) may be written as eq. (8)

$$K_c = K_f \times \left(\frac{RT}{f^\circ}\right)^k \quad (8)$$

An alternative form of eq. (4) may be obtained by replacing each activity term by a product of concentration and the appropriate activity coefficient (i.e., $(a_c) = c\gamma$) thus,

$$K_c = \frac{(cy)_{SSF_K}}{(cy)_s (cy)^K_{SF}} \quad (9a)$$

(or)

$$K_c = \frac{(c)_{SSF_K}}{(c)_s (c)^K_{SF}} \times \frac{(y)_{SSF_K}}{(y)_s (y)^K_{SF}} \quad (9b)$$

Combining eq. (8) and eq.(9b) gives

$$\frac{(c)_{SSF_k}}{(c)_s (c)^k_{SF}} \times \frac{(y)_{SSF_k}}{(y)_s (y)^k_{SF}} = K_f = \left(\frac{RT}{f^\circ}\right) \quad (10)$$

$$\ln K_f = \Delta H_s / RT + q_s \quad (11)$$

For dilute systems, activity coefficient term may be treated as one. Thus,

$$\frac{(c)_{SSF_k}}{(c)_s (c)^k_{SF}} = K_f \times \left(\frac{RT}{f^\circ}\right)^k \quad (12)$$

Assuming solute is very dilute and Antoine's equation is applicable [4,5,7-9] to solute in the vapour phase then the vapour phase is expressed as eq. (13)

$$\ln\left[(c)_s / (f^\circ / RT)\right] = \Delta H_v / RT + q_v \quad (13)$$

Applying natural logarithm to eq. (12) and substituting eq. (13) results in eq. (14)

$$\ln\left\{\left[(c)_{SSF_k} / (f^\circ / RT)\right]\right\} = \Delta H_T / RT + q_T + k \ln\left\{(c)_{SF} / (f^\circ / RT)\right\} \quad (14)$$

where, $q_T = q_s + q_v \quad \Delta H_T = \Delta H_v + \Delta H_s$

Applying antilogarithm to eq. (14) gives eq. (15)

$$(c)_{SSF_k} = \exp(\alpha + \beta/T)\left(\frac{RT}{f^\circ}\right)^{k-1} (c)^k_{SF} \quad (15)$$

where, $\alpha = q_T \quad \beta = \Delta H_T / R$

Let Y be the mole ratio [10]

$$Y_{SSF_\kappa} = (c)_{SSF_\kappa} / (c)_{SF} \quad (16)$$

let the solvent molar density be $D = (c)_{SF}$

Then the cluster mole fraction is

$$y_{SSF_\kappa} = \frac{\left(\frac{RTD}{f^o}\right)^{\kappa-1} \exp(\alpha + \beta/T)}{1 + \left(\frac{RTD}{f^o}\right)^{\kappa-1} \exp(\alpha + \beta/T)} \quad (17)$$

The solvato complex mole fraction (y_{SSF_κ}) and solute's solubility in mole fraction (y_2) are related as follows [8-11]

$$y_2 = y_{SSF_\kappa} / \left(1 + \kappa y_{SSF_\kappa}\right) \quad (18)$$

Thus, the expression for the solubility in terms of mole fraction (y_2) is

$$y_2 = \frac{\left(\frac{\left(\frac{RTD}{f^o}\right)^{\kappa-1} \exp(\alpha + \beta/T)}{1 + \left(\frac{RTD}{f^o}\right)^{\kappa-1} \exp(\alpha + \beta/T)}\right)}{1 + \kappa\left(\frac{\left(\frac{RTD}{f^o}\right)^{\kappa-1} \exp(\alpha + \beta/T)}{1 + \left(\frac{RTD}{f^o}\right)^{\kappa-1} \exp(\alpha + \beta/T)}\right)} \quad (19)$$

Eq.(19) can be used to fit the solubility data. The model parameter β multiplied by universal gas constant result in enthalpy of reaction.

Bartle et al. model. [10] It is a well-known model developed based on the concept of enhancement factor. According to it solubility of a substance in supercritical solvent is expressed as

$$\ln\left(\frac{y_2 P}{P_{ref}}\right) = A_1 + \frac{B_1}{T} + C_1(\rho_1 - \rho_{ref}) \quad (20)$$

Eq. (20) can be used to fit the solubility data. The model parameter B_1 multiplied by universal gas constant results in the enthalpy of sublimation.

Results and Discussion

The new modified Chrastil model and Bartle et al. models are evaluated with the help of literature available solubility data of some anticancer drugs and NSAIDs.The anti-cancer drugs used in the work are Loxoprofen [12], Crizotinib [13], Azathioprine [14], 5-Fluorouracil [15], Busulfan [16] and Temozolomide [17]. Similarly, NSAIDs used in the work are Apirin [18], Celecoxib [19], Diclofenac acid [20], Flubiprofen[21], Ketoprofen[22], Nabumetone [23], Naproxen [24], Niflumic acid [19], Phenylbutazone [23], Salicylamide [23]. Model fitting is done with the objective function (OF), eq. (19) [10]

$$OF = \sum_{i=1}^{N} \frac{\left|y_{2i}^{\exp} - y_{2i}^{calc}\right|}{y_{2i}^{\exp}} \quad (21)$$

Table1 and Table 2 show the model constants. Parameter β from Eq. (19) and Parameter B_1 from Eq. (20) can be used to get the values enthalpy of reaction and enthalpy of sublimation by multiplying with universal gas constant. Solvation enthalpiesare estimated from the difference between heat of reaction and heat of sublimation and negative sign is assigned due to its exothermic nature.Table. 3 shows the calculated sublimation and

Table 1: Modified Chrastil model parameters.

Compound in scC_o2	MW(g/mol)	κ	α	β	AARD%
Loxoprofen	246.36	3.145	-17.752	-1751.345	5.464
Crizotinib	440.34	3.562	-20.035	-2410.529	8.760
Azathioprine	277.26	3.748	-17.638	-3471.322	6.1200
5-Fluorouracil	130	1.935	-9.979	-2608.703	3.580
Busulfan	246.304	5.532	-26.009	-3384.372	11.640
Temozolomide	194.15	4.418	-15.504	-3926.280	9.491
Apirin	180.15	5.131	-19.251	-4708.040	5.556
Celecoxib	381.4	6.122	-29.413	-4654.547	2.650
Diclofenac acid	296.1	8.099	-28.147	-7740.365	8.001
Flubiprofen	244.2	7.226	-28.998	-5851.683	8.822
Ketoprofen	254.28	7.109	-30.864	-5136.980	10.900
Nabumetone	228.29	6.104	-24.401	-4264.952	2.909
Naproxen	230.26	5.422	-25.433	-3947.850	7.000
Niflumic acid	282.22	4.738	-27.363	-2342.740	3.040
Phenylbutazone	308.4	6.846	-31.772	-3358.685	4.815
Salicylamide	137.14	4.829	-19.168	-4246.843	3.957

Table 2: Bartle et al. model parameters.

Compound in $scCO_2$	A_1	B_1	C_1	AARD%
Loxoprofen	9.8241	-4861.2	0.0065735	9.059
Crizotinib	11.249	-5918.3	0.0074427	9.181
Azathioprine	13.842	-6657.7	0.0070575	7.965
5-Fluorouracil	6.7262	-4566.4	0.0031683	8.081
Busulfan	13.598	-5642.1	0.0080076	8.309
Temozolomide	16.717	-5990.5	0.0067908	8.167
Apirin	23.387	-8806.3	0.0094876	4.417
Celecoxib	18.477	-8510.7	0.010633	1.979
Diclofenac acid	33.180	-12034	0.012394	6.656
Flubiprofen	29.603	-11036	0.013167	10.955
Ketoprofen	23.803	-9266.4	0.012444	8.858
Nabumetone	24.730	-8557.1	0.010614	6.093
Naproxen	17.940	-7712.0	0.0087871	6.284
Niflumic acid	10.528	-5665.6	0.0086509	2.761
Phenylbutazone	22.922	-8008.4	0.011965	7.076
Salicylamide	20.712	-8032.3	0.0085627	6.058

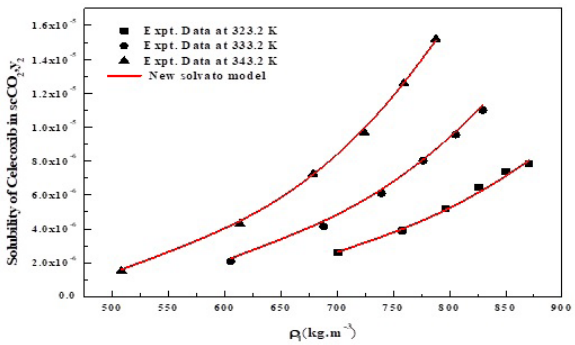

Figure 1: Correlating ability of the new model for the Celecoxib-$scCO_2$ system.

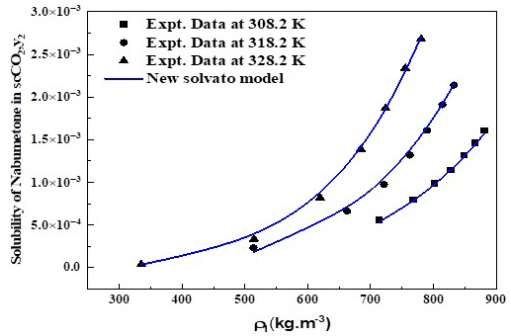

Figure 2: Correlating ability of the new model for the Nabumetone-$scCO_2$ system.

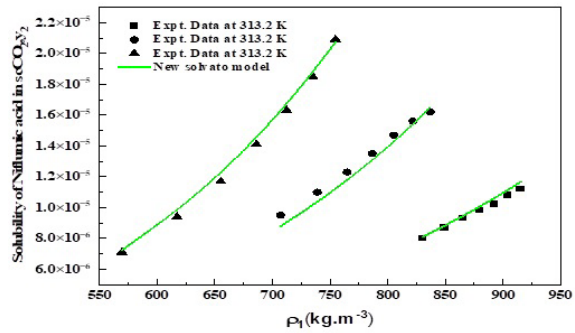

Figure 3: Correlating ability of the new model for the Niflumic acid-$scCO_2$ system.

Table 3: Calculated heat of reaction, sublimation enthalpies, literature reported solvation enthalpy using Chrastil model, eq. (1) [3,12-24].

Compound in $scCO_2$	ΔH_{RXN} = - β×R kJ/mol	ΔH_{SUB}= -B_1×R kJ/mol	$\Delta H_{SOLVATION}$ = -(ΔH_{SUB} - ΔH_{RXN}) kJ/mol	Literature Reported Solvation Enthalpies using eq. (1), kJ/mol
Loxoprofen	14.561	40.416	-25.855	-16
Crizotinib	20.041	49.205	-29.164	-18.628
Azathioprine	28.861	55.352	-26.491	-18.83
5-Fluorouracil	21.689	37.965	-16.276	-
Busulfan	28.138	46.908	-18.77	-19.49
Temozolomide	32.643	49.805	-17.162	-20.7
Apirin	39.143	73.216	-34.073	-
Celecoxib	38.698	70.758	-32.06	-
Diclofenac acid	64.353	100.051	-35.698	-
Flubiprofen	48.651	91.753	-43.102	-
Ketoprofen	42.709	77.041	-34.332	-
Nabumetone	35.459	71.144	-35.685	-
Naproxen	32.822	64.118	-31.296	-
Niflumic acid	19.478	47.104	-27.626	-
Phenylbutazone	27.924	66.582	-38.658	-
Salicylamide	35.308	66.781	-31.473	-

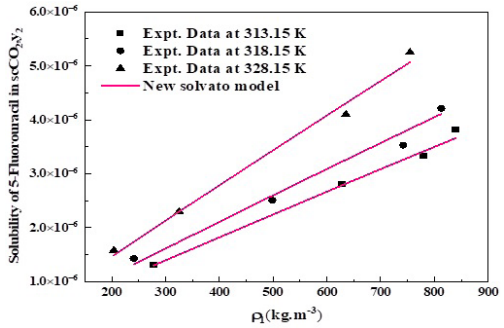

Figure 4: Correlating ability of the new model for the 5-Fluorouracil-scCO$_2$ system.

solvation enthalpies. It is important to note that the calculated sublimation and solvation enthalpies values are in J/mol, however, the results were tabulated in terms of kJ/mol in Table 3. The correlating ability of the new model is shown in Figs .1-4 for celecoxib-scCO$_2$, nabumetone-scCO$_2$, niflumic acid-scCO$_2$ and 5-fluorouracil-scCO$_2$ systems.Newmodel correlates the solubility data quite well. Literature reported solvation enthalpies of some drugs using Chrastil model, eq.(1) are also indicated in Table 3.

Conclusion

In this work, a new solvato complex model has been proposed and solubilities of some anti-cancer drugs and NSAIDs were successfully evaluated and correlating ability of the new model is observed to be good in terms of AARD%. Sublimation enthalpy of drugs was estimated with Bartle et al. model. Finally, with the help of both the model parameters solvation enthalpies of drugs were computed.

References

1. Sodeifian G, Usefi MMB. Solubility,extraction, and nanoparticles production in supercritical carbon dioxide: A mini-review. Chembioeng REV. 2022; 10: 133-66.
2. Garlapati C, Madras G. New empirical expressions to correlate solubilities of solids in supercritical carbon dioxide. Thermochimicaacta. 2009; 496: 54-8.
3. Chrastil J. Solubility of solids and liquids in supercritical gases. J Phys Chem. 1982; 86: 3016-21.
4. Garlapati C, Madras G. Solubilities of solids in supercritical fluids using dimensionally consistent modified solvate complex models. Fluid Phase Equilib. 2009; 283: 97-101.
5. Garlapati C, Madras G. Solubilities of palmitic and stearic fatty acids in supercritical carbon dioxide. J Chem Thermodyn. 2010; 42: 193-7.
6. Mahesh G, Garlapati C. Correlating solubilities of some parabens in SupercriticalCarbon dioxide using modified Wilson's model, Austin Chem. Eng. 2023; 10: 1096.
7. Cheng KW, Tang M, Chen YP. Calculations of solid solubility in supercritical fluids using a simplified cluster solvation model. Fluid Phase Equilib. 2003; 214: 169-86.
8. Li Q, Zhong C, Zhang Z, Liu Y, Zhou Q. An Equilibrium Model for the Correlation of the Solubility of Solids in Supercritical Fluids with Cosolvent. Sep Sci Technol. 2003; 38: 1705-19.
9. Lamb DM, Barbara TM, Jonas J. NMR study of solid naphthalene solubilities in supercritical carbon dioxide near the upper critical end point. J Phys Chem. 1986; 90: 4210-5.
10. Sridar R, Bhowal A, Garlapati C. A new model for the solubility of dye compounds in supercritical carbon dioxide. Thermochim Acta. 2013; 561: 91-7.
11. Bartle KD, Clifford AA, Jafar SA, Shilstone GF. Solubilities of solids and liquids of low volatility in supercritical carbon dioxide. J Phys Chem. 1991; 20: 713-56.
12. Zabihi S, Esmaeili-Faraj SHE, Borousan F, Hezave AZ, Shirazian S. Loxoprofen solubility in supercritical carbon dioxide: experimental and modeling approaches. J Chem Eng Data. 2020; 65: 4613-20.
13. Sodeifian G, Garlapati C, Roshanghias A. Experimental solubility and modeling of crizotinib (anti-cancer medication) in supercritical carbon dioxide. Sci Rep. 2022; 12: 17494.
14. Sodeifian G, Razmimanesh F, Saadati Ardestani NS, Sajadian SA. Experimental data and thermodynamic modeling of solubility of azathioprine, as an immunosuppressive and anti-cancer drug, in supercritical carbon dioxide. J Mol Liq. 2020; 299: 112179.
15. Zhan S, Zhao Q, Chen S, Wang J, Liu Z, Chen C. Solubility and partition Coefficients of 5-fluorouracil in ScCO$_2$ and ScCO$_2$/poly(L-lactic acid). J Chem Eng Data. 2014; 59: 1158-64.
16. Pishnamazi M, Zabihi S, Jamshidian S, Hezaveh HZ, Hezave AZ, Shirazian S. Measuring solubility of a chemotherapy-anti cancer drug (busulfan) in supercritical carbon dioxide. J Mol Liq. 2020; 317: 113954.
17. Zabihi S, Khoshmaram A, Pishnamazi M, Borousan F, Hezave AZ, Marjani A, et al. Thermodynamic study on solubility of brain tumor drug in supercritical solvent: temozolomide case study. J Mol Liq. 2021; 321: 114926.
18. Huang Z, Lu WD, Kawi S, Chiew YC. Solubility of aspirin in supercritical carbon dioxide with and without acetone. J Chem Eng Data. 2004; 49: 1323-7.
19. Tsai CC, Lin HM, Lee MJ. Solubility of niflumic acid and celecoxib in supercritical carbon dioxide. J Supercrit Fluids. 2014; 95: 17-23.
20. Zeinolabedini Hezave AZ, Esmaeilzadeh F. Solubility measurement of diclofenac acid in the supercritical CO2. J Chem Eng Data. 2012; 57: 1659-64.
21. Duarte ARC, Coimbra P, de Sousa HC, Duarte CMM. Solubility of flurbiprofen in supercritical carbon dioxide. J Chem Eng Data. 2004; 49: 449-52.
22. Stassi A, Bettini R, Gazzaniga A, Giordano F, Schiraldi A. Assessment of solubility of ketoprofen and vanillic acid in supercritical CO2 under dynamic conditions. J Chem Eng Data. 2000; 45: 161-5.
23. Su CS, Chen YP. Measurement and correlation for the solid solubility of nonsteroidal anti-inflammatory drugs (NSAIDs) in supercritical carbon dioxide. J Supercrit Fluids. 2008; 43: 438-46.
24. Macnaughton SJ, Kikic I, Foster NR, Alessi P, Cortesi A, Colombo I. solubility of anti-inflammatory drugs in supercritical carbon dioxide. J Chem Eng Data. 1996; 41: 1083-6.