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Research Article

A New Model to Correlate Solubility of Therapeutic Drugs in Supercritical Carbon Dioxide

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Received: 10 February 2024; **Revised:** 10 April 2024; **Accepted:** 25 April 2024

Abstract: In this work, a new solubility model was proposed based on the enhancement factor concept. The proposed model is validated with the literature available solubility data of seventeen therapeutic drugs in supercritical carbon dioxide. The correlating ability of the proposed model was compared with the Chrastil model and Bartle et al. model. The global average absolute relative deviation (*AARD*) percentages of Chrastil, Bartle et al. and new models were 19.42%, 19.57% and 16.43%, respectively. Sublimation enthalpies of therapeutic drugs were calculated with a new model as well as with Bartle et al. model. The calculated sublimation enthalpies ranged between 8.32 to 180.23 kJ/mol and 19.5 to 280.26 kJ/mol for the Bartle et al. model and the Improved Bartle model, respectively. Finally, a statistical analysis was performed in terms of Alaike's Information Criterion (*AIC*) to differentiate models considered in this work.

Keywords: Alaike's Information Criterion (*AIC*), Bartle et al. model, Improved Bartle model, solubility, sublimation enthalpy, supercritical carbon dioxide, therapeutic drugs

Abbreviations

AIC	Akaike's information criterion
AIC_{crt}	Corrected akaike's information criterion
AARD	Average absolute relative deviation (%)
A'_1, B_1	Eq. (8) fitting parameters
A_2, B_2, C_2	Eq. (14) fitting parameters
A_3, B_3, $\Delta_{sub}C_3$	Eq. (17) fitting parameters
E	Enhancement factor
ΔH_{sub}	Sublimation enthalpy
K	Number of parameters of a model
N	Number of solubility data points
R	Universal gas constant
R^2	Square of the correlation
RMSE	Root mean squared error
SSE	Sum of squared error

DOI: https://doi.org/10.37256/fce.5220244444

T	Temperature
T_0	Reference temperature
y_2	Mole fraction
P	Pressure
P_{ref}	Reference pressure
$SCCO_2$	Supercritical carbon dioxide

Greek letters

ρ	Density (kg/m^3 or mole/m^3)
ρ_{ref}	Reference density

1. Introduction

Supercritical fluids (*SCFs*) have become a focal point in the pharmaceutical industry due to their unique properties and versatile applications.[1] The supercritical region, characterized by conditions above the critical pressure and temperature, offers distinctive behavior that distinguishes it from both liquid and gas phases. A notable illustration of this behavior is observed during the depressurization of a supercritical/subcritical fluid(s), where the fluid can transition either from a liquid phase to a gas without a distinct boundary or exhibit the presence of a boundary depending on the specific path taken.[1-7]

The pharmaceutical industry has harnessed the potential of supercritical CO_2 ($SCCO_2$) as a solvent for its operations.[2-4] $SCCO_2$ is attractive due to its unique features such as non-flammable, non-toxic, and environmentally friendliness, making it a good choice for pharmaceutical applications. Sometimes in practice, $SCCO_2$ is used along with a co-solvent to improve its performance, for such operations $SCCO_2$ is highly suitable.[3,7] In addition to these considerations, it is also interesting to note that $SCCO_2$ is the second least expensive solvent after water in industrial applications. Micronization of drugs is an emerging area of research, where $SCCO_2$ as a solvent plays a vital role in particle sizing.[4,7] The selection of a suitable process for micronization depends on the magnitude of solubility of the drug in $SCCO_2$. Notable particle making processes are rapid expansion of saturated solution (*RESS*) process and *SCF* anti-solvent processes (*SAS* Process).[8] Based on the solubility data operating conditions are tuned for *RESS* and *SAS* Process. The solubility information is usually obtained through experiments at specific condition and they are limited in number.[9] The data points are highly nonlinear which requires more parameters for data correlation, hence numerous solubility models keep on appearing in literature based on different scientific bases/arguments.[9] But, data correlating with the least parameters are preferred in practice.[9] An appropriate solubility model captures the physics involved in the dissolution process that would be meaningful.[10] Sublimation pressure is a parameter that influences the solubility of solid drugs in *SCF*. Bartle et al. utilized a two-parameter Antoine's equation to represent solubility and it is quite evidently used for the data correlation.[11-12] In the proposed work, we have extended Bartle model by considering an appropriate three-parameter vapour pressure expression. More details of the existing and proposed models are described in the following sections.

2. Theory

2.1 *Chrastil model*

It is based on the concept known as solvate complex formation and it has three parameters in the model.[13-15] According to it solute concentration and solvent density are related as follows:

$$c_m = (\rho_{m1})^{\kappa} \exp\left(A_1 + B_1 / T/K\right) \tag{1}$$

where c_m and ρ_{m1} are the mass concentration of solute and solvent; κ, A_1 and B_1 are model constants. It is dimensionally inconsistent[16] and it is modified in terms of mole fraction[14] as

$$\frac{c_m}{\rho_{m1}}\frac{M_{ScF}}{M_{Solute}} = \frac{M_{ScF}}{M_{Solute}}(\rho_1)^{\kappa-1}\exp\left(A_1 + B_1/T/K\right) \tag{2}$$

Where M_{ScF}, M_{Solute} are molecular weights of supercritical solvent and solute respectively. c_m/M_{Solute} is the molar concentration of solute (c); ρ_{m1}/M_{ScF} is the molar concentration of solute; κ is known as association number.

$$mole\ ratio = Y_2 = \frac{c}{\rho_1} = \frac{M_{ScF}}{M_{Solute}}(\rho_1)^{\kappa-1}\exp\left(A_1 + B_1/T/K\right) \tag{3}$$

Mole fraction (y_2) and mole ratios (Y_2) are related as follows[16]:

$$Y_2 = \frac{c}{\rho_1} = \frac{y_2}{1-y_2} \tag{4}$$

On rearranging the relation between mole fraction and mole ratio written as[13]

$$y_2 = mole\ ratio/[1 + mole\ ratio] \tag{5}$$

$$y_2 = \frac{M_{ScF}}{M_{Solute}}(\rho_1)^{\kappa-1}\exp\left(A_1 + B_1/T/K\right) \Big/ \left[1 + \frac{M_{ScF}}{M_{Solute}}(\rho_1)^{\kappa-1}\exp\left(A_1 + B_1/T/K\right)\right] \tag{6}$$

Eq. (6) is further modified as follows[17]

$$y_2 = \exp\left(\ln(M_{ScF}/M_{Solute})\right)(\rho_1)^{\kappa-1}\exp\left(A_1 + B_1/T/K\right) \Big/ \left(1 + \exp\left(\ln(M_{ScF}/M_{Solute})\right)(\rho_1)^{\kappa-1}\exp\left(A_1 + B_1/T/K\right)\right) \tag{7}$$

$$y_2 = (\rho_1)^{\kappa-1}\exp\left(A_1' + B_1/T/K\right) \Big/ \left[1 + (\rho_1)^{\kappa-1}\exp\left(A_1' + B_1/T/K\right)\right] \tag{8}$$

Where $A_1' = A_1 + \ln(M_{ScF}/M_{Solute})$.

2.2 *Bartle et al. model*

Bartle along with her team created a well-known solubility model in 1991 and it is based on the enhancement factor concept. This model explains how a substance dissolves in a supercritical fluid solvent, and it's represented as[18-19]

$$lnE = A' + C_2\rho \tag{9}$$

$$E = \frac{Py_2}{P_v} \tag{10}$$

Where the enhancement factor is denoted by E, and it is a crucial parameter in the context of supercritical phases, where P represents pressure, and P_v signifies the vapor pressure of the pure solute. Additionally, ρ stands for the density of the supercritical phase. To estimate the sublimation pressure for the majority of solid solutes is often unavailable in the existing literature. Therefore, to address this gap, an approximation method is employed to estimate the enhancement factor.

$$E = y_2 \cdot \frac{P}{P_{ref}} \tag{11}$$

"C_2" signifies the solvation of the solute by the supercritical fluid and is presumed to remain constant regardless of temperature. On the other hand, the parameter A' is depends upon the vapor pressure of the solute, implying that it varies with changes in solute vapor pressure.

$$A' = A_2 + B_2/T \tag{12}$$

Rearranging the equations mentioned earlier provides an alternative way to express the solubility.

$$\ln\left(\frac{y_2 P}{P_{ref}}\right) = A' + C_2(\rho - \rho_{ref}) \tag{13}$$

$$\ln\left(\frac{y_2 P}{P_{ref}}\right) = A_2 + \frac{B_2}{T} + C_2(\rho - \rho_{ref}) \tag{14}$$

In Eq. (14) y_2 denotes the solubility expressed as a mole fraction, P represents the applied pressure, P_{ref} signifies the reference pressure set at 1 bar (or) 0.1 MPa, ρ stands for the density of $SCCO_2$, ρ_{ref} is the $SCCO_2$ density used as a reference (maintained at 700 kg/m^3), A_2, B_2 and C_2 are the fitting parameter of the model. The decision to set ρ_{ref} at 700 kg/m^3 is introduced to reduce the impact of experimental errors in solubility data when extrapolated to zero density.[18] The determination of $SCCO_2$ density ρ, involved the utilization of a 27-parameter equation of state[19] or NIST data (or) any other equation of state that represents CO_2 density. In this work 27-parameter equation of state is used. In Eq. (14), the parameter B_2 is intricately linked to the sublimation enthalpy. This relationship is expressed by Garlapati et al.[20]

$$\Delta H_{sub} = -B_2 R \tag{15}$$

Here, R represents the universal gas constant. The validity of Eq. (14) hinges on the assumption that the vapor pressure within the enhancement factor remains unaffected by temperature variations.[21]

2.3 *New model*

In the new model, we have followed the arguments proposed by Bartle et al. But in place of parameter an appropriate three-parameter vapor pressure expression for the solute is introduced. The vapour pressure of any solute is a function of temperature only and it is captured reasonably better with more parameters in the temperature function. From the literature, it is evident that three-parameter model is better than two-parameter model.[8,20] Thus, in this work three-parameter vapour pressure expression is used. The three-parameter vapour pressure expression is indicated in Eq. (16).[20,21]

$$A' = \frac{A_3}{R} + \frac{B_3}{RT} + \frac{\Delta_{sub} D_3}{R} \ln\left(\frac{T}{T_0}\right) \tag{16}$$

Combining Eq. (16) and Eq. (13) provides an alternative way to express the solubility

$$\ln\left(\frac{y_2 P}{P_{ref}}\right) = \frac{A_3}{R} + \frac{B_3}{RT} + \frac{\Delta_{sub} D_3}{R} \ln\left(\frac{T}{T_0}\right) + C_3(\rho - \rho_{ref}) \tag{17}$$

In Eq. (17) y_2 denotes the solubility expressed as a mole fraction, P represents the applied pressure, P_{ref} signifies the

reference pressure set at 1 bar, ρ stands for the density of $SCCO_2$, ρ_{ref} is the $SCCO_2$ density used as a reference (maintained at 700 kg/m^3), A_3, B_3, C_3 and $\Delta_{sub}D_3$ are the fitting parameter of the model. Where T_0 is the reference temperature and it is fixed at 298.15 K. All other arguments hold good as that of Bartle et al. model. In Eq. (17), the parameter B_3 and $\Delta_{sub}D_3$ are intricately linked to the sublimation enthalpy and it is represented with Eq. (18). Hereafter it may be termed as Improved Bartle model.

The enthalpy at any temperature is given by the following equations is

$$\Delta H_{sub} = -B_3 + \Delta_{sub} D_3 T \tag{18}$$

3. Results and discussion

Therapeutic drugs, considered in the work include Quetiapine hemifumarate,[22] Chloroquine,[23] Codeine phosphate,[8] Flufenamic acid,[24] Lansoprazole,[25] Pindolol,[26] Carvedilol,[27] Palbociclib,[28] Amoxicillin,[29] Ketoprofen,[30] Aspirin,[30] Ketoconazole,[31] Hydroxychloroquine sulphate,[32] Clemastine fumarate,[33] Letrozole,[34] Exemestane,[35] and Metronidazole benzoate.[36] More details about therapeutic drugs such as drug group, molecular mass, and number of solubility data points, solubility range in mole fraction, temperature range in K, pressure range in bar and literature reference are indicated in Table 1. The solubility data is regressed with the following objective function (*OF*).[37]

Table 1. Solubility data range and sources for therapeutic drugs in supercritical carbon dioxide ($SCCO_2$)

Name of the drug	Drug group	*MW* (g·mol^{-1})	*N*	$y_2 \times 10^5$	*T* range (K)	*P* range (Bar)	Ref.
Quetiapine hemifumarate	Atypical antipsychotics	615.65	24	0.03-0.9	308-338	120-270	22
Chloroquine	Antimalarial	319.9	32	1.64-89.2	308-338	120-400	23
Codeine phosphate	Analgesics	406.4	24	1.29-6.5	308-338	120-270	8
Flufenamic acid	NSAID	281.234	25	0.08-21.3	313.2-333.2	80-210	24
Lansoprazole	Protonpump inhibitors	369.363	24	1.2-73.6	308.2-338.3	120-270	25
Pindlol	Beta blockers	248.321	30	2.82-22.4	298-318	80-275	26
Carvedilol	Alpha and beta blockers	406.474	28	1.12-501	308-338	160-400	27
Palbociclib	(CDK) inhibitors	447.533	24	0.08-2.02	308-338	120-270	28
Amoxicillin	Antibiotics	365.4	28	1.08-7.23	308.15-338.15	160-400	29
Ketoprofen	NSAID	254.281	25	1.07-95.1	298.2-353.2	72-350	30
Aspirin	NSAID	180.157	31	1.95-91.95	298.2-353.2	75-300	30
Ketoconazole	Imidazole antifungal	531.431	28	0.02-8.02	308-338	120-300	31
Hydroxychloroquine sulphate	Antimalarial	434	24	0.03-0.55	308-338	120-270	32
Clemastine fumarate	Antihistamine medication	343.90	24	0.016-0.941	308-338	120-270	33
Letrozole	Aromatase inhibitors	285.303	45	0.1-8.3	308-348	122- 355	34
Exemestane	Aromatase inhibitors	296.403	45	1.26-187.58	308-348	122-355	35
Metronidazole benzoate	nitroimidazole antimi crobials	275.26	40	7.00-455	308-348	122-355	36

$$OF = \sum_{i=1}^{N} \frac{\left| y_{2i}^{\exp} - y_{2i}^{cal} \right|}{y_{2i}^{\exp}} \tag{19}$$

The results are indicated in terms of *AARD*%

$$AARD\% = \frac{100}{N} \sum_{i=1}^{N} \frac{\left| y_{2i}^{\exp} - y_{2i}^{cal} \right|}{y_{2i}^{\exp}} \tag{20}$$

Where N is the number of solubility data points. Regression task was carried out in MATLAB® R2022b (student version) with inbuilt library function (*fminsearch*) which makes use of Neldar-Mead algorithm.

The nonlinear optimization procedure is employed provides *AARD*%, square of the correlation coefficient (R^2), adjusted R^2 (Adj. R^2), root mean squared error (*RMSE*), and sum of squared error (*SSE*) and they are defined in eqs. (21)-(23) and they are utilized for a comprehensive analysis to determine the best model. To improve the precision of evaluating models with varying numbers of curve fitting parameters, the average absolute relative deviation (*AARD*) is computed. This criterion offers a more accurate measure for comparing the accuracy of models by considering the average absolute differences between predicted and actual values across the data set. A higher R^2 value, nearing 1, signifies the model's proficiency in closely predicting data points compared to experimental values. Notably, R^2 can exhibit bias when comparing models with differing parameter counts. Adjusted R^2 addresses this issue by modifying R^2, enabling comparisons between models with varying adjustable parameters, even allowing for negative or equal values. Lower *RMSE* and *SSE* values, approaching zero, indicate minimal deviation and underscore the model's capability to estimate data points in close agreement with experimental values.

$$R^2 = 1 - \frac{\Sigma_{i=1}^{Ni} (y_2^{exp} - y_2^{cal})^2}{\Sigma_{i=1}^{Ni} (y_2^{\overline{exp}} - y_2^{cal})^2} \tag{21}$$

$$SSE = [\Sigma_{i=1}^{Ni} (y_2^{exp} - y_2^{cal})^2] \tag{22}$$

$$RMSE = [\frac{1}{Ni} \Sigma_{i=1}^{Ni} (y_2^{exp} - y_2^{cal})^2]^{\frac{1}{2}} \tag{23}$$

Tables 2-3 show obtained adjustable parameters for Chrastil, Bartle et al. model along with *AARD*% and square of the correlation coefficient (R^2). The definition for R^2 is given in Eq. 21. Table 4 shows obtained adjustable parameters for the new model (Improved Bartle model) along with *AARD*% and coefficient of regression (R^2). Tables 2-4 indicate that the Global *AARD*%'s of Chrastil mode, Bartle et al. model and new model are 19.42%, 19.33% and 16.44% respectively. As stated earlier the new model utilizes an appropriate expression for the solute vapour pressure, hence is observed to capture the sublimation enthalpy of the solute better than that of Bartle et al. model and these results are indicated in Table 5. The estimated enthalpies are in J/mol, however the reported values are in kJ/mol. The calculated sublimation enthalpies ranged between 8.32 to 180.23 kJ/mol and 19.5 to 280.26 kJ/mol for Bartle et al. model and Improved Bartle model respectively. For three compounds (Flufenamic acid, Ketoprofen and Aspirin) the estimated sublimation enthalpies are compared with experimental sublimation enthalpies values and it is clear that Improved Bartle model calculated values are closer to experimental values.[38-42]

Table 2. Fitting parameter and their corresponding *AARD* value for Chrastil model

Name of the drug	Model constants			*AARD*%	R^2
	κ	A'_1	B_1		
Quetiapine hemifumarate	5.2726	-20.305	-6,792.3	11.6	0.91
Chloroquine	7.0717	-34.039	-4,846.9	12.2	0.97
Codeine phosphate	2.8403	-6.2226	-6,222.6	9.48	0.93
Flufenamic acid	5.0233	-12.852	-7,410.2	11.8	0.98
Lansoprazole	6.8587	-31.641	-4,912.9	11.7	0.95
Pindlol	5.6674	-33.843	-2,030.3	15.5	0.93
Carvedilol	9.5616	-8.5159	-18,413	38.0	0.95
Palbociclib	6.4535	-39.155	-2,986.7	26.0	0.72
Amoxicilin	18.892	-69.330	-19,210	5.50	0.99
Ketoprofen	7.3556	-29.921	-6,950.4	25.3	0.93
Aspirin	4.8955	-17.528	-5,421.9	20.9	0.96
Ketoconazole	11.235	-41.814	-12,187	13.1	0.99
Hydroxychloroquine sulphate	3.8917	-6.5317	-8,391.5	24.2	0.82
Clemastine fumarate	3.0838	-10.994	-4,889.7	20.1	0.78
Letrozole	8.1666	-31.802	-8,979.2	36.8	0.97
Exemestane	7.6253	-15.823	-12,058	26.3	0.97
Metronidazole benzoate	5.8900	-24.172	-5,018.4	21.7	0.99
Global values				19.42	0.92

Table 3. Fitting parameter and their corresponding *AARD* value for Bartle model

Name of the drug	Model constants			*AARD*%	R^2
	A_2	B_2	C_2		
Quetiapine hemifumarate	19.086	-8,860.9	0.009409	11.9	0.91
Chloroquine	17.741	-7,155.5	0.012828	10.1	0.97
Codeine phosphate	17.257	-7,326.0	0.0052862	12.3	0.89
Flufenamic acid	29.281	-10,917.0	0.0096480	17.2	0.98
Lansoprazole	16.971	-6,620.9	0.012022	12.9	0.96
Pindlol	78141	-5,159.4	11.158	22.8	0.88
Carvedilol	56.066	-19,671.0	0.017510	37.7	0.93
Palbociclib	14.921	-7,303.6	0.012605	23.3	0.99
Amoxicilin	60.497	-21,678	0.0008134	38.0	0.65
Ketoprofen	18.522	-7,319.5	0.027000	21.1	0.89

Table 3. (cont.)

Name of the drug	Model constants			*AARD*%	R^2
	A_2	B_2	C_2		
Aspirin	18.404	-5,933.0	0.0088078	15.02	0.96
Ketoconazole	37.600	-14,564.0	0.017450	9.30	0.99
Hydroxychloroquine sulphate	24.518	-10,703.0	0.0090956	26.5	0.86
Clemastine fumarate	14.719	-7,179.9	0.0066739	20.1	0.76
Letrozole	28.942	-11,426.0	0.010993	15.14	0.98
Exemestane	38.695	-14,018.0	0.012557	19.8	0.97
Metronidazole benzoate	19.006	-1,001.0	0.010348	15.5	0.92
Global values				19.57	0.91

Table 4. Fitting parameter and their corresponding *AARD* value for improved Bartle model

Name of the drug	Model constant				*AARD*%	R^2
	A_3	B_3	C_3	$\Delta_{sub}D_3$		
Quetiapine hemifumarate	180.48	-74,944.1	0.123338	0.173513	10.8	0.92
Chloroquine	147.49	-59,490.8	0.106652	338.4546	9.97	0.97
Codeine phosphate	523.13	-174,320	0.044513	355.5233	10.8	0.91
Flufenamic acid	343.75	-57,167.1	0.081563	194.9633	16.8	0.98
Lansoprazole	-51.61	-3,098.71	0.098571	159.2962	11.9	0.96
Pindlol	77,985.32	-101,747	111.1083	-186.3583	19.7	0.96
Carvedilol	1,566.94	-490,534	0.120486	-1,034.095	34.7	0.96
Palbociclib	152.77	-112,032	0.087796	79.65061	22.6	0.94
Amoxicilin	11.199	-33,244.36	0.224369	455.4159	18.8	0.99
Ketoprofen	-38.22	-58,079.9	0.09231	8.30568	18.4	0.98
Aspirin	130.92	-53,645.3	0.073646	38.05401	14.6	0.97
Ketoconazole	986.28	-322,101	0.14207	-633.003	8.73	0.99
Hydroxychloroquine sulphate	1,560.78	-494,650	0.068593	-1,252.005	23.6	0.86
Clemastine fumarate	2,346.04	-724,773	0.064885	-2,046.57	16.2	0.84
Letrozole	351.19	-130,164	0.091512	-107.5582	14.9	0.98
Exemestane	1,973.99	-610,630	0.106245	-1,514.146	12.9	0.99
Metronidazole benzoate	-7.094	-19,659.3	0.03959	-0.60970	14.0	0.95
Global values					16.43	0.95

Table 5. Experimental and estimated sublimation enthalpies value for therapeutic drugs

Compound	Temperature (K)	ΔH_{sub} (Eq.7) (Bartle model) kJ·mol^{-1}	ΔH_{sub} (Eq.10) (Improved Bartle model) kJ·mol^{-1}	ΔH_{sub} Experimental kJ·mol^{-1}	Ref.
Quetiapine hemifumarate	300	73.66	74.99	-	
Chloriquine	298.15	59.49	160.35	-	
Codine phosphate	298.15	60.90	280.26	-	
Flufenamic acid	298.15	90.76	115.35	121.3	40-41
Lansoprazole	298.15	55.04	50.59	-	
Pindlol	298.15	42.89	46.184	-	
Carvedilol	298.15	163.54	182.21	-	
Palbociclib	298.15	60.72	135.77	-	
Amoxicilin	298.15	180.23	169.02	-	
Ketoprofen	298	60.8	60.55	110	41, 20
Aspirin	308	49.3	65.4	109.70	42, 20
Ketoconazole	298.15	121.08	133.37	-	
Hydroxychloroquine sulphate	298.15	88.98	121.36	-	
Clemastine fumerate	298.15	59.69	114.58	-	
Letrozole	308	94.99	97	-	
Exemestane	298.15	116.54	159.18	-	
Metronidazole benzoate	298.15	8.32	19.5	-	

The analysis conducted in this study involved examining the relationship between experimental data (comprising 501 data points) and predicted data generated by the models (described by Eqs. (14) and (17)). The Parity Plots visually represent a comparison of various models, where the proximity of points to the diagonal line ($y = x$) indicates the agreement between estimated and experimental solubility data. It is clear that improved model is superior to the existing Chrastil model and Bartle et al. model. This improvement is evident in the clustering of data points. Figures 1, 2, 3, 4 and 5 illustrate how the Improved Bartle model provides a better fit with the experimental data compared to the Chrastil model and Bartle et al. model.

The Akaike Information Criterion (*AIC*) serves as a statistic based mathematical tool to assess the goodness of the models for the correlation purpose. In the realm of statistics, an *AIC* value is used for comparing various models and also helps in identifying the most suitable model that best matches the given dataset.[43] In the case of data points more than 40, *AIC* is used, and it is defined as follows:

$$AIC = N \ \ln\left(\frac{SSE}{N}\right) + 2K \tag{24}$$

where K represents number of parameter and N represents number of data points. In the case of data points less than 40, AIC_{crt} is used, and it is defined as follows:

$$AIC_{crt} = AIC + \frac{2K(K+1)}{N-K-1} \tag{24}$$

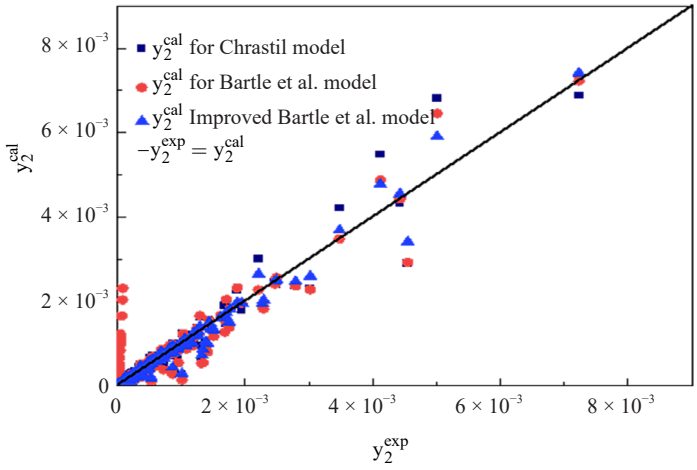

Figure 1. Parity plot of the solubility data estimated by the proposed model (Eq. (8)), (Eq. (14)) and (Eq. (17)) with corresponding experimental data

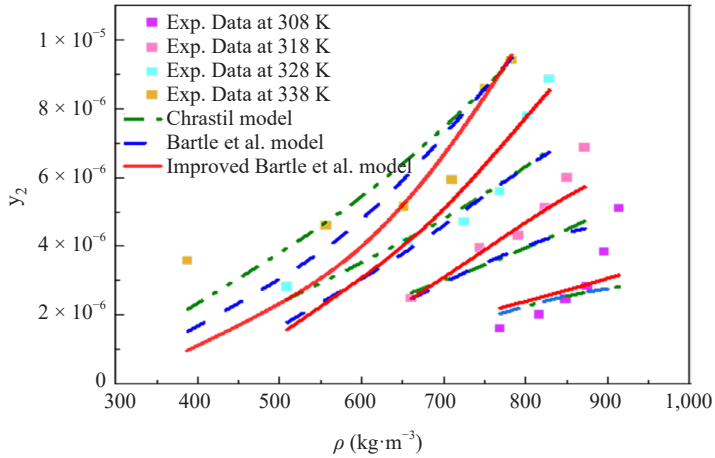

Figure 2. y_2 vs. ρ, data fit for the Chrastil model, Bartle et al. model and Improved Bartle model for Clemastine fumarate

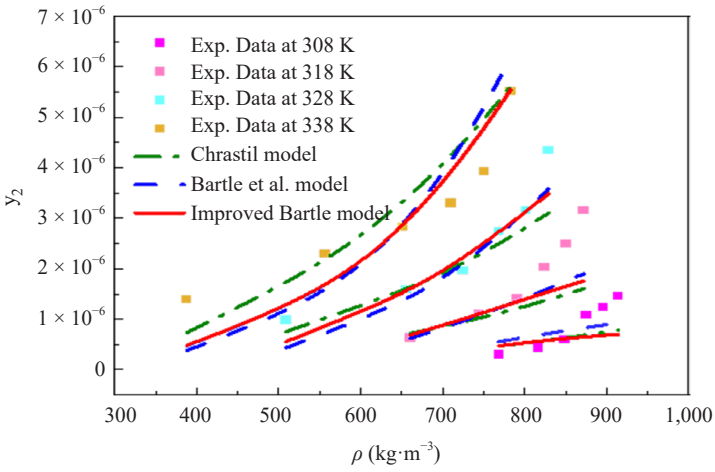

Figure 3. y_2 vs. ρ, data fit for the Chrastil model, Bartle et al. model and Improved Bartle model for Hydroxychloroquine sulfate

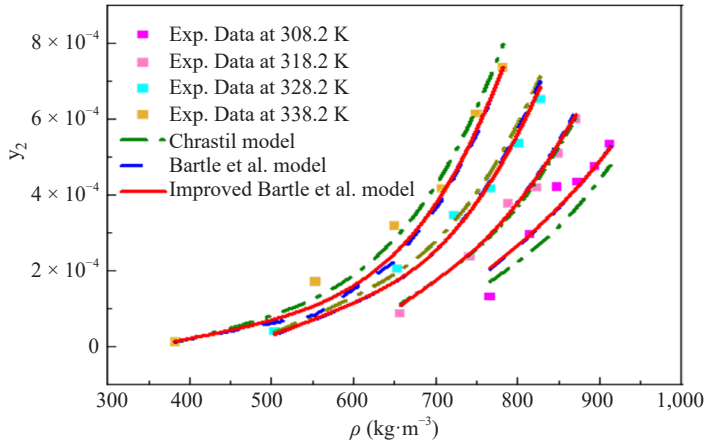

Figure 4. y_2 vs. ρ, data fit for the Chrastil model, Bartle et al. model and Improved Bartle model for Lansoprazole drug

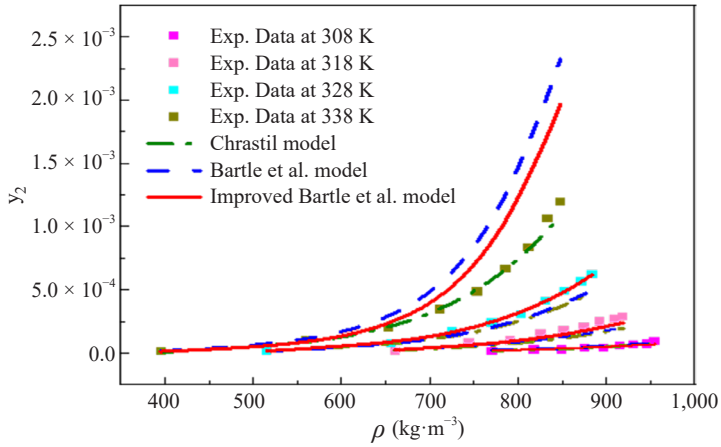

Figure 5. y_2 vs. ρ, data fit for the Chrastil model, Bartle et al. model and Improved Bartle model for Exemestane drug

Tables 6-8 display the statistical parameters (*AIC*, AIC_{crt}, *RMSE* and *SSE*) for Chrastil, Bartle et al. and the Improved Bartle model (New model). For data points less than 40, the global values of *AIC* are 894.3 and 933.75 for the Bartle et al. model and the Improved Bartle model respectively. For data points greater than 40, the global values of AIC_{crt} are 609.29 and 626.67 for Bartle et al. model and the Improved Bartle model respectively. A model with the lowest *AIC* is better because it captures more information from experimental data making it the preferred model.

Table 6. Statistical parameters for Chrastil model

Compound data points $N < 40$	*AIC*	AIC_{crt}	*RMSE*	*SSE*
Quetiapine hemifumarate	-681.94	-680.74	5.9654×10^{-7}	8.5406×10^{-12}
Chloroquine	-638.72	-637.87	4.2168×10^{-5}	5.6899×10^{-8}
Codeine phosphate	-589.81	-588.61	4.066×10^{-6}	3.9678×10^{-10}
Flufenamic acid	-589.49	-588.35	6.7126×10^{-6}	1.1265×10^{-9}
Lansoprazole	-473.91	-472.71	4.5479×10^{-5}	4.964×10^{-8}
Pindlol	-645.78	-644.85	1.6588×10^{-5}	1.1006×10^{-8}

Table 6. (cont.)

Compound data points $N < 40$	AIC	AIC_{crt}	$RMSE$	SSE
Carvedilol	-414.36	-413.36	5.4952×10^{-4}	8.4551×10^{-6}
Palbociclib	-601.44	-600.24	3.1915×10^{-6}	2.4446×10^{-10}
Amoxicillin	-526.16	-525.16	7.4628×10^{-5}	1.55940×10^{-7}
Ketoprofen	-468.65	-467.51	7.53858×10^{-5}	1.42113×10^{-7}
Aspirin	-632.13	-631.24	3.3895×10^{-5}	3.5616×10^{-8}
Ketoconazole	-730.66	-729.66	1.9364×10^{-6}	1.0499×10^{-10}
Hydroxychloroquine sulphate	-679.93	-678.73	6.2196×10^{-7}	9.284×10^{-12}
Clemastine fumarate	-654.76	-653.56	1.0508×10^{-6}	2.6499×10^{-11}
Global values	-	-593.75		
Compound data points $N > 40$				
Letrozole	-1,068.36	-	7.3136×10^{-6}	1.9256×10^{-9}
Exemestane	-817.43	-	1.1884×10^{-4}	5.0843×10^{-7}
Metronidazole benzoate	-635.18	-	3.6953×10^{-4}	4.3697×10^{-6}
Global values	-840.32			

Table 7. Statistical parameters for Bartle model

Compound data points $N < 40$	AIC	AIC_{crt}	$RMSE$	SSE
Quetiapine hemifumarate	-573.35	-572.15	4.7345×10^{-7}	4.9314×10^{-12}
Chloroquine	-665.24	-664.38	4.7345×10^{-7}	$2.4844e \times 10^{-8}$
Codeine phosphate	-578.25	-577.05	5.4034×10^{-6}	6.4233×10^{-10}
Flufenamic acid	-587.66	-586.51	7.2712×10^{-6}	1.2160×10^{-9}
Lansoprazole	-479.72	-478.52	4.2086×10^{-5}	3.8967×10^{-8}
Pindlol	-646.71	-645.52	1.9520×10^{-5}	1.0669×10^{-8}
Carvedilol	-434.32	-433.32	3.9928×10^{-4}	4.1450×10^{-6}
Palbociclib	-650.74	-649.54	1.1934×10^{-6}	3.1331×10^{-11}
Amoxicillin	-717.37	-716.32	1.5810×10^{-6}	6.2490×10^{-11}
Ketoprofen	-500.84	-499.69	4.1277×10^{-5}	3.9187×10^{-8}
Aspirin	-636.70	-635.81	3.2548×10^{-5}	3.0721×10^{-8}
Ketoconazole	-732.98	-731.98	1.9280×10^{-6}	9.6648×10^{-11}
Hydroxychloroquine sulphate	-684.50	-683.3	5.9072×10^{-7}	7.6769×10^{-12}
Clemastine fumarate	-657.01	-655.81	1.0473×10^{-6}	2.4131×10^{-11}
Global values	-	-609.29		
Compound data points $N > 40$				
Letrozole	-1161.70	-	2.3721×10^{-6}	2.4196×10^{-10}
Exemestane	-836.38	-	8.8089×10^{-5}	3.3367×10^{-7}
Metronidazole benzoate	-684.82	-	1.8233×10^{-4}	1.2633×10^{-6}
Global values	-894.3	-		

Table 8. Statistical parameter for Improved Bartle

Compound data points $N < 40$	AIC	AIC_{crt}	$RMSE$	SSE
Quetiapine hemifumarate	-695.85	-693.74	1.2556×10^{-7}	4.4013×10^{-12}
Chloroquine	-665.11	-663.62	2.7949×10^{-5}	2.3434×10^{-8}
Codeine phosphate	-583.71	-581.60	4.6257×10^{-6}	4.7074×10^{-10}
Flufenamic acid	-587.72	-585.61	6.9778×10^{-6}	1.1199×10^{-9}
Lansoprazole	-483.16	-481.05	3.7575×10^{-5}	3.1061×10^{-8}
Pindlol	-665.87	-664.27	1.3719×10^{-5}	5.2695×10^{-9}
Carvedilol	-451.86	-450.12	2.8165×10^{-4}	2.0625×10^{-6}
Palbociclib	-654.94	-652.83	1.0488×10^{-6}	2.4202×10^{-11}
Amoxicillin	-761.95	-760.13	6.6731×10^{-7}	1.1133×10^{-11}
Ketoprofen	-513.13	-511.13	3.1019×10^{-5}	2.2129×10^{-8}
Aspirin	-636.22	-634.68	3.1757×10^{-5}	2.9247×10^{-8}
Ketoconazole	-755.36	-753.62	1.2474×10^{-6}	4.0456×10^{-11}
Hydroxychloroquine sulphate	-687.11	-687.11	5.3659×10^{-7}	6.3344×10^{-12}
Clemastine fumarate	-658.14	-658.14	9.8113×10^{-7}	2.1178×10^{-11}
Global values	-	-626.67		
Compound data points $N > 40$				
Letrozole	-1,163.40	-	2.2765×10^{-6}	2.2285×10^{-10}
Exemestane	-941.40	-	2.6823×10^{-5}	3.0938×10^{-8}
Metronidazole benzoate	-696.46	-	1.5374×10^{-4}	8.9821×10^{-7}
Global values	-933.75	-		

The relative goodness of the models considered in the work can be evaluated by taking magnitude difference between the AIC values as mentioned below.[44]

$$\Delta AIC_i = AIC_i - AIC_{\min} \text{ (for data points } (N > 40)) \quad (26)$$

$$\Delta AIC_{crti} = AIC_{crti} - AIC_{crt\min} \text{ (for data points } (N < 40)) \quad (27)$$

Where $AIC_{\min}$ is minimum value of AIC between the models, $AIC_{crt\ min}$ is minimum value of AIC_{crt} between the models. Based on the values ΔAIC or ΔAIC_{crt} we can say that, how the models are significantly different. If the difference is more than 10, then the models considered for the comparison are significantly different; otherwise, if the difference is less than 10, the models considered for the comparison are insignificant.[44] From Tables 6-8 the calculated global ΔAIC or ΔAIC_{crt} using Eq (26) and Eq (27) are 93.43, 39.45 and 17.38, respectively, which indicates that Chrastil, Bartle et al. and Improved Bartle Model are insignificantly different for all the data points considered in the work.

4. Conclusion

In this work, a new equation for the solubility correlation is proposed based on the concept of enhancement and it

is termed as Improved Bartle model. The proposed solubility model is compared with the existing Chrastil model and Bartle et al. model by considering seventeen drug compounds solubility data in $SCCO_2$. The newly proposed model demonstrates a strong correlation ability compared to existing Chrastil model and Bartle et al. model, as evidenced by its favorable Global *AARD*% (16.43%), Global R^2 (0.95) and Global *AIC* (-933.75) and Global AIC_{crt} (-626.67) Additionally, the new model and existing Bartle et al. models are used to calculate sublimation enthalpies of therapeutic drugs in $SCCO_2$. For the new model calculated sublimation enthalpies are observed to range between 19.5 to 280.26 kJ/mol.

Acknowledgment

The corresponding authors are thankful to the PTU Campus for the necessary facilities.

Data sharing policy

The data that supports the findings of this study are available from the authors of this article.

Compliance with ethical standards

This article does not contain any studies with human or animal subjects.

Conflict of interest

The authors declare no competing financial interest.

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