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A new empirical model to correlate solubility of pharmaceutical compounds in supercritical carbon dioxide

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Abstract : *The objective of the current research is to propose a new empirical model to correlate solubility of pharmaceutical drug compounds in supercritical carbon dioxide. The predictive ability of the new model is validated with literature data. In this work twenty-seven industrially important pharmaceutical compounds are considered for the validation. The correlative accuracy of the model is evaluated in terms of absolute average relative deviation.*

Keywords: *Degree of Freedom, New Empirical Model, Pharmaceutical, Solubility, Supercritical Carbon Dioxide*

1. Introduction

Supercritical carbon dioxide ($ScCO_2$) applications are gaining industrial importance in past few decades. The accurate solubility data of processing compounds is very important for successful implementation of supercritical fluid technology [1,2]. A large amount of experimental data on the solubilities of various pharmaceutical compounds in supercritical carbon dioxide ($ScCO_2$) is available in literature. The experimental determination of solubilities of these drugs in $ScCO_2$ at various temperature and pressure conditions is very expensive. Therefore, prediction (or) correlation of solubilities is very essential. Predictive models are very difficult to develop and requires first principle based knowledge for the modeling on the other hand correlations require experimental data. Correlations have limitations in usage since they cannot be extrapolated beyond the experimental conditions.

2. Theory

The modeling of solubilities of solids (or) liquids in supercritical fluids (ScF's) become an important area of research in past few decades. Models developed are broadly classified as empirical models, semi empirical models or mathematical models. In this work empirical approach has been used to correlate the solubility of pharmaceutical drugs in supercritical carbon dioxide ($ScCO_2$). In literature various models are available for correlating the solubility of solutes in SCF's. Most frequently used solubility models are summarized in table 1. It is important to note that most of the models require density of the supercritical fluid. The required density of the supercritical fluid may be estimated using equation of state or with the help of specific ScF's equations. For the case of carbon dioxide there are several equations readily available in literature [3,4]. However, the 28-parameter model is the latest one and it is able to predict densities more accurate when compared to other models present in the literature [4].

Table 1 Summary of literature models

Model	Equation	Ref.
Chrastil	$\ln(S) = A_1 + \frac{B_1}{T} + C_1 \ln(\rho_{ScF})$	[5]
Kumar and Johnston (KJ)	$\ln(y_2) = A_2 + B_2 \rho_{ScF} + \frac{C_2}{T}$	[6]
Bartle et al.	$\ln\left(\frac{y_2 p}{p_{ref}}\right) = A_3 + B_3(\rho_{ScF} - \rho_{ref}) + \frac{C_3}{T}$	[7]
Mendez-Santiago and Teja (MST)	$T \ln(y_2 p) = A_4 + B_4 \rho_{ScF} + C_4 T$	[8]
Sung and shim (SS)	$\ln(y_2) = \left(A_5 + \frac{B_5}{T}\right)\ln(\rho_{ScF}) + \frac{C_5}{T} + D_5$	[9]
Garlapati and Madras	$\ln(y_2) = A_6 + (B_6 + C_6 \rho_{ScF})\ln(\rho_{ScF}) + \frac{D_6}{T} + E_6 \ln(\rho_{ScF} T)$	[10]
Jafari Nejad et al.	$\ln(y_2) = A_7 + B_7 p^2 + C_7 T^2 + D_7 \ln(\rho_{ScF})$	[11]
Keshmiri	$\ln(y_2) = A_8 + \frac{B_8}{T} + C_8 p^2 + \left(D_8 + \frac{E_8}{T}\right)\ln(\rho_{ScF})$	[12]
Khansary	$\ln(y_2) = \frac{A_9}{T} + B_9 p + C_9 \frac{p^2}{T} + (D_9 + E_9 p)\ln(\rho_{ScF})$	[13]
Bian	$\ln(y_2) = A_{10} + \frac{B_{10}}{T} + \frac{C_{10}\rho_{ScF}}{T} + (D + E\rho_{ScF})\ln(\rho_{ScF})$	[14]

The coefficients of these models are indicated by A_n-E_n

2.1 New empirical model It is based on degrees of freedom analysis [2]. For solubility phenomena the degree of freedom (F) is two which are absolute temperature (T) and absolute pressure (p) of the mixture. The solubility of single compound in terms of mole fraction may be represented in terms of dimensionless parameters (i.e., reduced temperature and pressure) as

$$y_2 = f(T_r, p_r) \quad (4)$$

Where

y_2 - mole fraction of solute;

T_r - reduced temperature of carbon dioxide ; T/T_C

p_r - reduced pressure of carbon dioxide ; P/P_C

For pharmaceutical-$ScCO_2$ systems, the following function form found to be suitable

$$y_2 = (a + bp_r)T_r^2 + (c + dp_r)T_r + e \quad (5)$$

3. Methodology

The absolute average relative deviation percentage (AARD) can be calculated by the following equation

$$AARD = \frac{1}{N_i}\sum_{1}^{N}\frac{\left|y_2^{cal} - y_2^{\exp}\right|}{y_2^{\exp}} \quad (6)$$

where

y_2^{cal}-solubility value calculated with models at a specified pressure and temperature;

$y_2^{\exp}$-solubility value obtained from the experiments at a specified pressure and temperature; N_i - number of experimental data points .

The model parameters for Semi-empirical models were determined by using polmath@5.1 software by non-linear regression method and the model parameters estimated for the 27 compounds are given in table 3. The density of the $ScCO_2$ required for the modelling was determined with 28 parameters equation [4].

3.1 28 parameter equation

$$\rho_{ScCO_2} = (a_1T_r^3 + a_2T_r^2 + a_3T_r + a_4)p_r^6 + (b_1T_r^3 + b_2T_r^2 + b_3T_r + b_4)p_r^5 + (c_1T_r^3 + c_2T_r^2 + c_3T_r + c_4)p_r^4 + (d_1T_r^3 + d_2T_r^2 + d_3T_r + d_4)p_r^3 + (e_1T_r^3 + e_2T_r^2 + e_3T_r + e_4)p_r^2 + (a_1T_r^3 + a_2T_r^2 + a_3T_r + a_4)p_r^6 + (f_1T_r^3 + f_2T_r^2 + f_3T_r + f_4)p_r + (g_1T_r^3 + g_2T_r^2 + g_3T_r + g_4)$$

Where a_1=0.105; a_2=-0.269; a_3=0.171; a_4=0; b_1=-2.629; b_2=7.556; b_3=-6.380; b_4=1.324; c_1=26.099; c_2=-81.318; c_3=79.364; c_4=23.260; d_1=-128.855; d_2=425.084; d_3=-451.933; d_4=152.811; e_1=322.905; e_2=-1109.777; e_3=1246.290; e_4=-455.0990; f_1=-365.706; f_2=1294.024; f_3=-1507.252; f_4=576.925; g_1=126.659; g_2=-454.597; g_3=538.577; g_4=-210.395.

4. Results

Table 2 shows range and source of binary system solubility data of pharmaceuticals in $ScCO_2$ considered for the study. Table 3, shows the correlations of the new solubility model along with AARD and overall average AARD or simply global AARD. The Global AARD of the new model is found to be 0.2074.

Tables 4 to 10, shows literature models correlation coefficients. The correlation values presented here are computed by keeping confidence intervals at a confidence level 95%. Table 10 shows the AARD values and Global AARD for the compounds studied in this work. In general, AARD may be treated a measure of good ness of the model. The model which results lower AARD may be treated as better one.

Table 2 Range and source of binary system solubility data of various pharmaceuticals in $ScCO_2$

S.No	Compound	T (K)	p (MPa)	$y_2 \times 10^4$	N_i	Ref.
1	(s)-Boc-Piperazine	308.2-328.2	9.01-20.1	13.7-65.2	21	[10]
2	2-Methylbenzoic acid	313.2-333.2	11-24.6	9.021-57	18	[15]
3	3-Methylbenzoic acid	313.2-333.2	11-24.6	9.1-53.4	18	[15]
4	7,8-Dihydroxyflavone	308.2-318.2	9.1-25.3	0.086-3.9	6	[16]
5	Artemisnin	310.1-338.1	10.1-26	6.6-26.5	27	[17]
6	Aspirin	318-328.15	6-25	0.01-3.47	32	[18][19]
7	Azobenzene	308.2-333.2	9.12-25.3	36.4-136	14	[20][21]
8	Benzoin	308.15-328.15	12.1-24.4	0.53-4.1	19	[22]
9	Caffeine	313.5	10-30	0.63-3.7	7	[23][24][25]
10	Carbamazepine	308-348	24.3-35.5	0.1-0.95	39	[26]
11	Codeine	308-348	12.2-35.5	1-12.3	45	[26]
12	Cholestrol acetate	308.15-328.15	9.1-21	0.79-10.4	24	[27]
13	Diazepam	308-348	12.2-35.5	1.8-11.1	45	[26]
14	Erythromycin	313.15-333.15	15-30	3.8-21	8	[28]
15	Flurbiprofen	303-323	8.9-23.4	0.21-1.96	27	[29]
16	Ketoprofen	312.5-313	9-25	0.13-1.55	31	[30][31]
17	Medroxyprogesterone acetate	308-348	12.2-35.5	0.4-4.13	40	[32]
18	Methylparaben	308-348	12.2-34.4	1.1-12.1	40	[33]
19	Nimesulide	313.1-333.1	13-22	0.18-0.98	8	[34]
20	Nimodipine	313-333	10-25	0.05-0.4	21	[35]
21	Pencillin G	313.15-333.15	10-35	0.5-0.6	18	[36]
22	Pencillin V	314.85-334.85	8.08-28.02	5.7-6.2	24	[37]
23	Phenazopyridine	308-348	12.2-35.5	0.1-2	45	[19]
24	Progestrone	308.2-328.2	10.47-24.33	0.9-7.3	36	[38]
25	Taxol	308.15-318.15	20.7-48.3	0.0007-0.005	12	[39]
26	Theobromine	313-353	21.3-34.4	0.008-0.04	23	[25]
27	Theophylline	313-353	21.3-34.4	0.008-0.04	22	[40]

T: Temperature;
p: Pressure;
y_2: Solubility of compound in $ScCO_2$ in mole fraction;
N_i: Number of solubility data point;
Ref: References.

Table 3 Correlation constants for new model

SN[a]	a	b	C	d	e	AARD
1	-1.13221	0.062992	2.237892	-0.0633	-1.10387	0.3768
2	-0.06038	0.026722	0.074849	-0.02659	-0.01356	0.0817
3	-0.0392	0.026651	0.024818	-0.02656	0.01573	0.0632
4	1.181199	1.79e-04	-2.43189	-1.77e-04	1.251396	0.0784
5	-0.02594	0.00586	0.037156	-0.00531	-0.01109	0.8418
6	-0.01922	0.001749	0.036752	-0.00173	-0.0175	0.2571
7	-0.51524	0.049413	0.999988	-0.04898	-0.48159	0.1320
8	-0.00322	0.00172	0.002696	-0.00166	5.56e-04	0.0958
9	-2.43e-05	5.31e-05	-2.50e-05	5.47e-05	-2.58e-05	0.0539
10	8.27e-04	1.81e-04	-0.00227	-1.83e-04	0.001469	0.1115
11	0.012789	0.001819	-0.032	-0.00179	0.019331	0.1056
12	-5.67e-05	-1.36e-05	-3.98e-04	7.71e-05	3.89e-04	0.3061
13	-0.004	0.001512	0.004885	-0.00146	-7.85e-04	0.0657
14	0.15279	9.70e-04	-0.31299	-7.78e-04	0.160351	0.1317
15	-0.00269	-0.00269	0.003773	-9.93e-04	-0.00111	0.0555
16	-0.00781	9.97e-04	0.01423	-9.84e-04	-0.00641	0.4043
17	2.80e-04	5.19e-04	-0.00218	-4.83e-04	0.001889	0.2591
18	0.011595	0.001947	-0.02901	-0.00195	0.017625	0.1001
19	-0.31419	3.62e-04	0.666424	-3.28e-04	-0.35314	0.0687
20	7.31e-04	2.22e-04	-0.00199	-2.24e-04	0.001275	0.1533
21	-0.00111	1.83e-04	0.002015	-1.83e-04	-8.97e-04	0.2050
22	0.02923	0.00212	-0.06763	-0.00214	0.038885	0.3100
23	-4.09e-05	3.64e-04	-8.63e-04	-3.57e-04	9.18e-04	0.2178
24	-0.01962	0.001975	0.034841	-0.00171	-0.01549	0.0849
25	2.50e-05	6.28e-07	-5.38e-05	-5.46e-07	2.87e-05	0.0753
26	-2.32e-05	3.01e-06	4.60e-05	-2.65e-06	-2.33e-05	0.2970
27	5.56e-04	3.63e-05	-0.00128	-3.28e-05	7.25e-04	0.6623
					Global AARD	0.2074

SN[a] , the system name and number is same as in table 2

Table 4 Correlation constants for Chrastil and KJ model

SN[a]	A_1	B_1	C_1	A_2	B_2	C_2
1	6610.8393	-14.88859-	4.5121852	11.894	0.006634	-7320.49
2	-6714.0727-	18.416531	.0128041	10.16677	0.007138	-6967.22
3	-6288.2313	-21.417754	5.2632882	8.633092	0.007493	-6566.43
4	-8172.874	3.5729983	1.7739889	13.89517	0.002595	-8346.39
5	-3480.9385	-20.793108	3.779509	0.91713	0.005354	-3721.67
6	-1.01e+04	2.7539605	19.195249	5.971093	0.006242	-6212.12
7	-3767.1813	-5.558115	1.8840931	5.29886	0.002991	-3979.07
8	-5630.8209	-25.306222	5.190845	4.588307	0.007021	-5894.48
9	-8815.6296	-24.127265	6.5161204	-35.9992	0.007728	6607.1
10	-7300.5954	-33.201381	6.663377	4.860813	0.008261	-7348.89
11	-6323.4594	-33.208653	6.6588709	4.878727	0.008714	-7338.21
12	-3816.5237	-67.951458	10.533004	-3900.07	0.012819	-7.55835
13	-4586.1175	-28.709109	5.2309213	1.219788	0.006817	-4730.53
14	-5365.5507	0.5132612	1.3999452	8.511625	0.001947	-5431.66
15	-7738.063	-16.619913	4.7722639	11.21923	0.006126	-8009.4
16	-5942.941	-33.429733	6.4110927	3.17263	0.008869	-6214.77
17	-5780.0332	-52.687342	9.1840643	-0.13541	0.011602	-5934.32
18	-5981.142	-19.64	4.4123	5.9863	0.006	-6158.03
19	-6966.742	-34.1605	6.9168	5.517	0.0098	-7379.8
20	-7654.095	-22.584	5.323	7.7841	0.00765	-7923.63
21	-7588.84	-34.551	7.072	6.0411	0.00878	-7705.04
22	-1868.353	-12.2192	1.5158	-3.85593	0.0265	-1981.45
23	-6407.27	-40.644	7.55	2.61	0.009783	-6610.82
24	-5536.5913	-39.07528	7.2781012	2.580631	0.009368	-5701.18
25	-3039.1802	-10.2185	0.6209	-1.5214	2.56e-04	-4520.41
26	3.6349	-3805.24	-26.188	0.915	0.885985	8130.9
27	6.0217	-5921.84	-33.639	0.57283	0.00814	-6083.88

SN[a] , the system name and number is same as in table 2

Table 5 Correlation constants for Bartle and MST model

SN[a]	A_3	B_3	C_3	A_4	B_4	C_4
1	18.9093	0.008921	-9231.02	2.868625	-1.16e+04	26.52561
2	18.47521	0.010729	-9285.59	3.524156	-1.21e+04	26.10496
3	17.3222	0.011172	-8930.22	3.669781	-1.19e+04	25.03482
4	20.45094	0.005317	-1.11e+04	-1.25e+04	1.672576	27.64446
5	8.896658	0.007932	-6343.75	-8419.14	2.604042	16.2049
6	14.64266	0.009818	-8848.81	-5973.37	-20.4647	4.591388
7	9.679483	0.005412	-5935.09	-7303.85	1.744956	16.67741
8	15.54971	0.010593	-9098.55	-1.19e+04	3.378301	23.32372
9	17.5228	0.017184	-10020	-11250	5.381551	15.96092
10	14.05875	0.012241	-9761.35	-13150	4.192051	21.91705
11	13.41791	0.013481	-8574.01	-12460	4.583383	21.95421
12	6.115946	0.019595	-6797.74	-12210	6.404521	15.47571
13	8.717359	0.011772	-6893.72	-10200	3.937164	16.90981
14	13.36523	0.005586	-7804.95	-9368.44	1.863626	20.69304
15	23.34812	0.009453	-11780	-14200	2.933666	31.04818
16	14.21377	0.01345	-9052.01	-12630	4.397922	22.28601
17	11.19447	0.016981	-8277.12	-13120	5.69686	20.26916
18	11.059	0.00297	-5236.52	-7892.01	2.0759	11.059
19	16.24931	0.012984	-9885.21	-1.00e+04	3.234	13.491
20	16.40717	0.011247	-10250	-8927.75	2.0098	11.9462
21	14.89218	0.014345	-9879.1	-1.02e+04	2.881	13.588
22	-1.76452	0.005638	-3298.75	-2674.2	0.8691	-1.7427
23	11.84707	0.014614	-8654.11	-9426.67	3 .03063	10.93696
24	15.06918	0.012677	-8880.79	-12230	4.065185	23.19194
25	2.86078	0.000436	-6929.03	-4851.03	0.08019	-0.4675
26	-2.49378	0.007434	-4977.67	-5065.65	1.6376	-2.066
27	8.412514	0.012437	-8031.42	-8397.24	2.8078	7.271

SN[a] , the system name and number is same as in table 2

Table 6 Correlation constants for SS and Jafari et al. model

SN[a]	A_5	B_5	C_5	D_5	A_7	B_7	C_7	D_7
1	-58.5497	7737.879	10.96861	-2121.99	-42.1321	5.42e-04	9.40e-05	4.026268
2	-11.2007	-6722.59	3.618185	101.9999	-39.7944	7.08e-04	8.42e-05	3.734051
3	-11.2162	-5594.59	3.094479	101.9999	-39.5966	7.77e-04	7.63e-05	3.821844
4	-6.93089	-4854.7	3.344164	-495.999	-33.3619	2.76e-04	1.28e-04	1.49604
5	-16.6198	-4854.03	3.155672	205.2012	-25.735	0.001077	3.05e-05	2.355513
6	-12.633	-5790.12	3.01415	101.9968	-37.5135	7.77e-04	7.42e-05	3.15973
7	-7.54129	-3104.55	2.183468	-99.9993	-21.2846	2.57e-04	2.57e-04	1.646247
8	-35.609	-2296.31	6.723511	-495.997	-35.8265	0.001166	5.56e-05	3.204808
9	-28.6657	-7360.88	6.873878	-117	-36.959	8.74e-04	1.28e-04	2.310332
10	-23.2054	-1.07e+04	5.170757	505.9948	-27.6772	0.001335	6.29e-05	1.357898
11	-19.2966	-9446.73	4.46333	505.9957	-40.1812	6.00e-04	6.70e-05	3.66953
12	-29.2963	-5347.07	3.930477	505.9874	-29.584	5.84e-04	1.41e-04	2.6584
13	-38.1783	-1401.01	6.637053	-472.864	-26.7846	6.68e-04	4.27e-05	2.0871
14	-2.1692	-2697.82	0.999982	-137.15	-16.3887	4.27e-04	6.84e-05	0.335995
15	-37.637	-1034.82	7.87987	-990.998	-35.5574	0.00202	8.69e-05	2.531772
16	-52.321	3444.162	7.948141	-990.992	-46.8105	0.00101	7.18e-05	4.46373
17	-24.8523	-1.21e+04	4.826768	1010.999	-48.6371	6.77e-04	5.39e-05	5.00137
18	10.69193	-1.62e+04	-1.62e+04	1516	-35.9391	3.60e-04	7.13e-05	3.001338
19	-3.39087	-1.71e+04	2.323172	1516	-33.7717	0.003043	4.74e-05	2.695251
20	-91.8999	1.75e+04	15.37288	-3654.19	-49.7826	5.51e-04	1.00e-04	4.238011
21	-61.769	1388.891	11.09998	-1328.33	-58.6867	2.43e-04	1.01e-04	5.563206
22	-76.2102	1.94e+04	11.09966	-3186.2	-15.2761	8.38e-04	1.96e-05	0.738045
23	-19.5678	-1.36e+04	4.42936	1059.06	-53.9574	1.95e-04	7.39e-05	5.386747
24	-61.7655	1762.96	10.65617	-1086.62	-41.5139	0.002383	3.90e-05	4.309611
25	-12.6412	-2279.55	0.939988	-99.9999	-13.4648	0.001471	5.81e-06	-0.60247
26	-45.1072	2802.44	6.473218	-990.994	-53.4601	-4.1e-04	5.65e-05	5.108137
27	-13.9578	-1.27e+04	3.082198	1010.942	-43.6031	4.98e-04	6.23e-05	3.752013

SN[a] , the system name and number is same as in table 2

Table 7 Correlation constants for Garlapati- Madras model

SN[a]	A_6	B_6	C_6	D_6	E_6
1	-60.0573	11.09999	-0.00143	-4808.5	0.250091
2	-7.72304	0.99999	5.63e-04	-6553.37	1.012754
3	-2.68082	0.999999	7.08e-04	-6350.32	0.494814
4	-17.4257	1.579172	-3.02e-04	-7455.6	1.740556
5	-75.2431	0.999985	-5.19e-04	-1483.22	5.587322
6	23.57215	28.2466	-0.00516	-195.684	2.829176
7	4.715104	9.666533	-0.00209	-72.0036	1.544098
8	-15.1088	0.999985	5.36e-04	-5428.6	1.149205
9	-12.6639	-1	0.001064	-766.196	0.594093
10	-5.08889	-1	0.001024	-6907.76	1.316049
11	-1.68081	-1	0.001132	-6185.98	1.054745
12	-8.18077	-0.99998	0.001722	-3710.28	0.622993
13	-3.14514	-1	9.12e-04	-4449.24	0.862583
14	41.91554	-0.99991	8.30e-04	-6288.57	-2.1637
15	-14.8943	0.999998	3.04e-04	-6906.3	1.546091
16	-18.7533	0.999994	7.37e-04	-5697.08	1.347591
17	-9.46455	-0.99997	0.001463	-5521.57	1.2991
18	-5.65506	-0.99999	7.22e-04	-5682.23	1.432376
19	-14.3862	4.70065	5.13e-04	-7319.23	-0.53054
20	-12.7308	1.46051	5.34e-04	-7483.39	1.0101
21	-1.34082	24.32382	-0.00499	-1.75e+02	3.150844
22	13.47284	0.999958	5.51e-04	-2638.97	-1.82978
23	-99.1007	-1.03898	-4.79e-04	-808.986	8.142699
24	-140.649	21.4887	-0.00268	-4394.51	1.395999
25	-17.005	4.264557	-1.04e-04	-1.04e-04	-1.40399
26	-89.7105	11.59345	-0.00157	-3361.91	1.395994
27	-165.72	-0.01816	-0.00112	21.62673	-2.24966

SN[a] , the system name and number is same as in table 2

Table 8 Correlation constants for Keshmiri model

SN[a]	A_8	B_8	C_8	D_8	E_8
1	-7.05987	-8267.13	5.05e-04	3.111656	312.699
2	-7.05974	-7788.91	6.99e-04	2.81284	306.3807
3	-7.05976	-8027.45	7.68e-04	2.557774	422.4052
4	7.598696	-8872.14	2.82e-04	0.999984	153.2265
5	-7.09966	-4987.28	0.001087	0.999995	437.2635
6	-0.96907	-8643.48	8.64e-04	0.999999	597.2067
7	-0.42791	-4988.01	2.46e-04	0.999999	214.5215
8	-58.7667	-58.7667	-58.7667	-58.7667	-58.7667
9	-4.06481	-6361.78	8.74e-04	1.15664	361.3035
10	-11.0998	-2372.84	0.001398	1.927767	-314.074
11	81.42578	-3.91e+04	5.67e-04	-11.0444	5056.64
12	-99.9978	2.42e+04	0.001185	13.51619	-3629.57
13	-65.7094	1.50e+04	6.96e-04	9.911329	-2679.86
14	6.94	-6937.73	2.28e-04	0.145906	324.367
15	-61.5992	1.09e+04	0.00197	10.237	-2420.88
16	-102	2.06e+04	0.00102	16.03632	-3783.04
17	-8.07743	-1.15e+04	6.77e-04	1.591944	1137.42
18	9.475029	-1.26e+04	3.60e-04	-0.24103	1100.224
19	70.97314	-3.31e+04	0.00303	-10.6962	4447.887
20	-41.6165	901.4052	5.47e-04	7.750788	-1156.96
21	-61.5997	4807.715	2.61e-04	10.71966	-1731.98
22	-109.9	3.21e+04	9.31e-04	15.82528	-5001.95
23	61.59998	-3.59e+04	6.09e-04	-9.11425	4844.177
24	77.50449	-3.69e+04	0.002412	-11.6732	5125.568
25	-6.69491	-1923.07	0.001485	-1.24561	198.0172
26	-4.66957	-1.45e+04	-4.43e-04	0.735058	1511.36
27	20.18979	-1.97e+04	4.70e-04	-2.58397	2229.082

SN[a] , the system name and number is same as in table 2

Table 9 Correlation constants for Khansary model

SN[a]	A_9	B_9	C_9	D_9	E_9
1	-1.54e+04	-1.87832	12.49138	8.273662	0.070478
2	-5659.13	-0.79376	-0.77837	1.532915	0.137608
3	-5367.55	-0.99062	-0.73455	1.405234	0.166214
4	-7351.91	0.451223	-0.14903	1.843425	-0.06206
5	-1041.46	-0.84683	-2.07785	-1.01025	0.173641
6	-4899.41	-0.93603	-0.78973	0.795455	0.159028
7	-4318.93	-0.44342	0.373005	1.373043	0.059522
8	-3545.2	-1.17534	-1.04707	0.116511	0.201447
9	-9902.07	1.57286	-0.32198	3.162167	-0.21591
10	-4025.64	-0.07771	-0.30433	-0.21607	0.031763
11	-2258.64	-0.02016	-1.16126	-0.83083	0.042796
12	-666.203	-1.15966	-0.3596	-1.39577	0.190506
13	-3460.46	-0.67025	-0.22139	0.234632	0.109891
14	-2763.63	0.760171	-0.54394	-0.02888	-0.09443
15	-4103.86	-0.40941	-1.56409	0.065775	0.102205
16	-3007.85	-1.2065	-2.74365	-0.6397	0.240223
17	-2193.29	-0.78073	-1.06813	-0.92133	0.152376
18	-4894.83	-0.47637	-0.4277	0.821211	0.085127
19	-1218.67	-0.80638	-3.81745	-1.90781	0.20839
20	-6646.86	-1.09091	-1.27096	1.165052	0.190653
21	-3968.33	-0.1687	-1.24116	-0.35571	0.064056
22	-1437.21	-0.82073	-0.54745	-0.69454	0.136758
23	-3947.13	-0.83853	-1.08252	-0.16642	-0.16642
24	-1271.92	-0.6593	-1.52418	-1.15791	0.143245
25	-351.208	-0.18611	-0.66435	-2.79479	0.058939
26	-3524.66	-1.00142	-1.0404	-0.73157	0.174286
27	-2638.67	-0.34976	-1.04039	-1.06956	0.086594

SN[a] , the system name and number is same as in table 2

Table 10 Correlation constants for Bian et al. model

SN[a]	A_{10}	B_{10}	C_{10}	D_{10}	E_{10}
1	-64.4467	1.51e+04	-27.7911	2.817913	0.011739
2	-5.1551	-5211.55	-2.12544	1.981808	0.001424
3	-14.1387	-1453.68	-6.39013	1.713318	0.003239
4	-18.8888	-3245.64	-6.09544	3.293766	0.002271
5	-47.3986	-8910.69	7.35331	10.95421	-0.00425
6	-103.422	1.57e+04	-26.8358	8.686323	0.010272
7	-38.5398	4235.27	-10.4097	3.848375	0.003907
8	-58.7667	-58.7667	-58.7667	-58.7667	-58.7667
9	-4.77495	9426.076	-46.3871	-4.12573	0.020937
10	39.59694	-1.83e+04	12.94402	-0.99998	-0.00368
11	2.235254	-1.11e+04	5.547277	2.669106	-0.00145
12	-13.2562	1980.982	-6.98773	-1.47059	0.00466
13	19.77885	1769.553	-8.19284	-6.08179	0.005181
14	93.86576	-2.02e+04	17.32352	7.990706	0.003699
15	-59.4132	1980.974	-14.0198	7.349304	0.005666
16	-62.7955	1981	-12.4734	7.734644	0.00503
17	41.08628	-4430.86	-2.03144	-7.58155	0.003569
18	21.11628	-6883.47	0.695949	-2.21892	9.45e-04
19	-2.73247	-2.37e+04	21.15701	9.222976	-0.00891
20	-12.6567	-5638.91	-2.7243	2.640069	0.190653
21	-8.52161	5060.325	-15.1341	-3.22445	0.007691
22	-74.296	1.89e+04	-26.783	2.36907	0.010908
23	-7.75757	-5670.47	-1.08972	1.543121	0.001438
24	-43.8535	-2121.99	-4.11296	6.509654	0.001783
25	-8.28712	-1.37e+04	12.68101	4.25184	-0.00471
26	-34.5503	-2079.96	-2.16499	4.343082	6.84e-04
27	-21.378	-2079.97	-4.90551	2.159179	0.002584

SN[a] , the system name and number is same as in table 2

Table 11 AARD values obtained for literature models

SN[a]	MST	Bartle	Madras	SS	KJ	Chrastil	Bian	Keshmiri	Khansary	Jafari
1	0.5041	0.4766	0.2786	0.3841	0.5075	0.3905	0.5075	0.4279	0.3011	0.4342
2	0.1601	0.1565	0.1069	0.1584	0.1218	0.0847	0.1136	0.8170	0.1100	0.0864
3	0.1879	0.1807	0.1283	0.2896	0.1377	0.1027	0.1231	0.0930	0.1252	0.0922
4	0.1843	0.2000	0.0459	0.0484	0.0496	0.0485	0.0452	0.0583	0.0334	0.0382
5	0.3430	0.3336	0.1962	0.1883	0.2641	0.1879	0.2311	0.2042	0.2042	0.1993
6	0.2543	0.2013	0.1580	0.1887	0.2080	0.1446	0.1534	0.1504	0.2628	0.1283
7	0.2360	0.2177	0.1388	0.1421	0.1786	0.1400	0.0817	0.1525	0.1430	0.1500
8	0.1852	0.1920	0.1150	0.1160	0.1242	0.1125	0.1268	0.0851	0.0880	0.0856
9	0.4063	0.4062	0.2583	0.0308	0.2669	0.3070	0.1088	0.0753	0.0263	0.0741
10	0.5481	0.5568	0.3864	0.3963	0.3844	0.3979	0.3867	0.2431	0.2086	0.2327
11	0.6288	0.6526	0.5248	0.5748	0.5298	0.5751	0.5355	0.4952	0.4749	0.4767
12	0.3916	0.3910	0.5241	0.3395	0.2777	0.3049	0.2596	0.1220	0.1947	0.1222
13	0.2265	0.2250	0.1287	0.1532	0.1327	0.1537	0.0755	0.0693	0.0873	0.0773
14	0.2831	0.2869	0.1669	0.2278	0.1743	0.1780	0.1746	0.1688	0.1068	0.1505
15	0.4103	0.4112	0.3263	0.2975	0.1832	0.3002	0.2995	0.1117	0.0872	0.1108
16	0.3837	0.3672	0.3547	0.3255	0.3764	0.3081	0.4884	0.4194	0.4941	0.3908
17	0.3102	0.3147	0.2200	0.2532	0.2199	0.2167	0.1638	0.1541	0.1370	0.1514
18	0.2111	0.2016	0.1073	0.3123	0.1081	0.1359	0.0987	0.0983	0.1013	0.0827
19	0.2344	0.2346	0.2019	0.1939	0.2171	0.1916	0.1785	0.1703	0.1747	0.1793
20	0.8473	0.1906	0.1429	0.1842	0.1832	0.1103	0.1381	0.1160	0.1890	0.1209
21	0.3792	0.3859	0.3210	0.3333	0.3088	0.3319	0.2297	0.3174	0.1645	0.3210
22	0.2474	0.2430	0.2835	0.3176	0.2677	0.2614	0.3636	0.3569	0.3130	0.2936
23	0.2464	0.2446	0.4276	0.1768	0.1398	0.1769	0.1428	0.2760	0.1654	0.1329
24	0.5793	0.5610	0.5311	0.4320	0.5193	0.4248	0.4536	0.3062	0.6540	0.2757
25	0.4193	0.5349	0.3557	0.3880	0.4195	0.3890	0.1924	0.0708	0.0280	0.0747
26	0.3438	0.3426	0.3326	0.2940	0.3020	0.2944	0.2994	0.3155	0.2828	0.3188
27	0.9129	0.9531	0.9057	0.9047	0.8860	0.9101	0.9146	0.8882	0.7707	0.9149
Global AARD	0.3728	0.3504	0.2840	0.2834	0.2773	0.2659	0.2550	0.2505	0.2196	0.2117

SN[a] , the system name and number is same as in table 2

5. Conclusions

The solubilities of 27 industrially important pharmaceuticals compounds in supercritical carbon dioxide ($ScCO_2$) are correlated using a new empirical model, which is developed based on degree of freedom analysis. The correlating ability of new model is compared against the existing solubility models such as Chrastil, Kumar and Johnston (KJ)(1988), Bartle et al., Mendez-Santiago and Teja (MST)(1999), Sung and Shim (SS)(1999), Garlapati and Madras (2010), Jafari Nejad et al., Keshmiri(2014), Khansary(2015), Bian et al., (2016). The correlating abilities of various models are compared in terms of global AARD (overall arithematic average relative deviation). The proposed model is found to correlate better than the existing models in terms of overall AARD.

The correlating ability of the models in terms of AARD are found to be in order as:

New model < Jafari < Khansary < Keshmiri < Bian < Chrastil < Kumar and Johnston (KJ) < Sung and Shin (SS) < Garlapati and Madras < Bartle < Mendez-Santiago and Teja (MST).

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