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Deviations of drug solubility in water-cosolvent mixtures from the Jouyban-Acree model – effect of solute structure

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Deviations of the predicted solubilities using the Jouyban-Acree model from experimental data were correlated to the structural descritptors of the drugs computed by HyperChem® software. The proposed models are able to predict the solubility in water-cosolvent mixtures and reduced the mean percentage deviations (MPD) of predicted solubilities from 24%, 48%, and 53% to 16%, 33% and 38%, respectively for water-propylene glycol, water-ethanol and water-polyethylene glycol 400 mixtures, with the overall improvement in prediction capability of the model being ~13%.

1. Introduction

Solubilization of a drug candidate in water is one of the main challenges in formulation design and optimization studies and addition of a water miscible cosolvent are the most common methods to increase aqueous solubility of drugs. Our main focus is to provide a computational method to predict the solubility of drugs in water-cosolvent mixtures using a minimum number of experimental data. From our earlier work, it has been found that the Jouyban-Acree model (formerly known as the combined nearly ideal binary solvent/Redlich-Kister equation) is the most accurate one among similar models (Jouyban-Gharamaleki et al. 1999). Its general form to calculate a solute solubility in water-cosolvent mixtures at various temperatures is:

$$\ln X_{m,T} = f_c \ln X_{c,T} + f_w \ln X_{w,T} + f_c f_w \sum_{i=0}^{2} \frac{J_i (f_c - f_w)^i}{T} \quad (1)$$

where $X_{m,T}$, $X_{c,T}$ and $X_{w,T}$ are the mole fraction solubility of the solute in solvent mixture, cosolvent and water in the absence of the solute at temperature (T, K), f_c and f_w denote the volume fractions of cosolvent and water in the absence of the solute and J_i is the model constant computed using a no-intercept least square analysis (Jouyban-Gharamaleki and Hanaee 1997) for each binary solvent system. The J_i coefficients in Eq. (1) do have theoretical significance in that each coefficient is a function of two-body and three-body interaction energies that describe the attractions between the various molecules in solution which was discussed in detail previously (Acree 1992; Jouyban 2006). In the recent reports from our group, trained versions of the Jouyban-Acree model were proposed to predict the solubility of drugs in water-cosolvent mixtures. The trained models required solubility data in neat solvents (water and cosolvent) and were able to predict the solubility at various temperatures. The model for predicting solubility of drugs in water-propylene glycol mixtures (Jouyban 2007) was:

$$\ln X_{m,T} = f_c \ln X_{c,T} + f_w \ln X_{w,T} + f_c f_w \left(\frac{85.252}{T} + \frac{735.662(f_c - f_w)}{T} \right) \quad (2)$$

The corresponding models for water-ethanol (Jouyban and Acree 2006) and water-polyethylene glycol 400 mixtures (Jouyban 2006) were:

$$\ln X_{m,T} = f_c \ln X_{c,T} + f_w \ln X_{w,T} + f_c f_w \left[\frac{1667.550}{T} + \frac{1117.154(f_c - f_w)}{T} + \frac{447.643(f_c - f_w)^2}{T} \right] \quad (3)$$

and

$$\ln X_{m,T} = f_c \ln X_{c,T} + f_w \ln X_{w,T} + f_c f_w \left[\frac{909.027}{T} + \frac{818.078(f_c - f_w)}{T} + \frac{895.442(f_c - f_w)^2}{T} \right] \quad (4)$$

To continue our studies on solubility prediction methods and in order to provide improved predictions, the deviations from predicted values by the Jouyban-Acree model were analysed. To examine the possibility of a relationship between chemical structure of the drugs and the magnitude of deviation from Eqs. (2)–(4), the deviations were correlated to a number of computational descriptors of the

drugs. The applicability of the extended method has been shown using the avialable data sets the details of which have been reported in the previous papers (Jouyban 2006; 2007; Jouyban and Acree 2006).

2. Investigations, results and discussion

2.1. Computational methods

Available solubility data of drugs in water-cosolvent mixtures reported in previous papers (Jouyban 2006; 2007; Jouyban and Acree 2006) are listed in Tables 1–3. The 2D structure of each compound was drawn, converted to 3D using HyperChem 7.0 (2002), and pre-minimized by Polak-Ribiere geometry optimization using MM^+ method (HyperCube 2002). The resulting 3D structures were used as the starting point for re-minimization by Polak-Ribiere optimization using AM1 semi-empirical method. The energy optimized molecules were used to compute molecular descriptors. Gride (SAG) and approximate (SAA) surface areas, molar volume (Vol), hydration energy (HE), molar refractivity (MR), polarizability (Pol), logarithm of partition coefficient (log P), molecular weight (MW), total energy (TE), dipole moment (DM), energy of the highest occupied molecular orbital (HOMO) and energy of the lowest unoccupied molecular orbital (LUMO) were calculated using HyperChem® software. The numerical values of the descriptors and their mean values are listed in

Table 1: Numerical values of the descriptors computed using HyperChem® software

Solute	SAA	SAG	Vol	HE	log P	MR	Pol	MW	TE	DM	HOMO	LUMO
Acetaminophen (Paracetamol)	307.2	332.3	498.9	−10.71	−1.32	45.55	16.18	151.2	−46028.5	4.55	−8.462	0.283
Amoxycillin trihydrate	485.2	570.4	968.6	−18.81	−1.65	93.17	35.82	365.4	−133132.3	6.49	−9.319	−0.237
Butyl *p*-aminobenzoate	408.0	426.5	666.6	−6.02	0.50	59.15	21.68	193.3	−56813.4	3.95	−8.646	−0.019
Butyl *p*-hydroxybenzoate	415.9	414.9	652.9	−7.59	1.20	57.20	20.97	194.2	−59109.2	1.25	−9.512	−0.368
Dodecyl *p*-aminobenzoate	688.4	668.6	1100.7	−3.19	3.67	95.96	36.36	305.5	−85563.4	3.48	−8.838	−0.159
Ethyl *p*-aminobenzoate	333.1	368.3	558.3	−6.96	−0.36	50.02	18.01	165.2	−49626.0	3.96	−8.645	−0.018
Ethyl *p*-hydroxybenzoate	340.9	358.6	545.0	−8.53	0.33	48.08	17.30	166.2	−51921.8	2.99	−9.514	−0.367
Furosemide	422.2	497.6	805.2	−15.88	−3.13	82.85	27.41	330.7	−98491.0	5.82	−9.414	−0.893
Hexyl *p*-aminobenzoate	478.6	491.0	776.8	−5.31	1.30	68.35	25.35	221.3	−64000.8	3.92	−8.647	−0.021
Hydrocortisone	421.3	533.2	967.0	−9.23	2.37	97.40	38.10	362.5	−108522.1	2.52	−10.043	0.012
Ketoprofen	410.6	475.6	771.8	−8.72	2.56	79.94	28.24	254.3	−73849.2	1.96	−9.907	−0.588
Methyl *p*-aminobenzoate	300.8	333.0	501.3	−7.60	−0.70	45.27	16.18	151.2	−46033.5	4.06	−8.665	−0.044
Methyl *p*-hydroxybenzoate	308.7	325.8	488.3	−9.16	−0.01	43.33	15.46	152.2	−48329.2	1.39	−9.535	−0.397
Octyl *p*-aminobenzoate	548.6	550.5	885.5	−4.58	2.09	77.55	29.02	249.4	−71188.2	3.91	−8.648	−0.021
Propyl *p*-aminobenzoate	370.1	399.3	612.8	−6.49	0.11	54.55	19.85	179.2	−53219.7	3.95	−8.646	−0.018
Propyl *p*-hydroxybenzoate	378.0	391.4	600.7	−8.06	0.80	52.60	19.13	180.2	−55515.5	2.99	−9.513	−0.367
Salicylic acid	240.2	283.6	424.0	−12.19	−0.04	38.56	13.63	138.1	−44749.0	1.24	−9.474	−0.555
Theophylline anhydrate	299.9	342.4	519.9	−5.40	−1.31	45.11	17.04	180.2	−57035.3	3.24	−9.082	−0.378
Theophylline hydrate	300.0	338.3	520.8	−5.42	−1.31	45.11	17.04	180.2	−65082.6	1.55	−9.108	−0.416
Mean:	392.5	426.4	677.1	−8.41	0.27	62.09	22.78	216.9	−66747.9	3.33	−9.138	−0.240

Table 2: Numerical values of the descriptors computed using HyperChem® software for water-ethanol set

Solute	SAA	SAG	Vol	HE	log P	MR	Pol	MW	TE	DM	HOMO	LUMO
Acetanilide	288.7	316.9	471.7	−4.24	−0.29	43.95	15.54	135.2	−38633.8	2.97	−8.911	0.095
Alanine (Beta)	240.3	244.7	335.3	−12.14	−0.89	20.70	8.35	89.1	−30653.8	3.70	−10.152	0.998
Alanine (DL)	226.8	241.0	330.8	−10.90	−0.53	20.50	8.35	89.1	−30653.6	4.51	−10.702	1.107
Aminocaproic acid	340.4	336.5	496.1	−8.89	0.15	34.66	13.86	131.2	−41440.3	2.27	−9.819	1.001
Asparagine (L)	247.6	289.7	418.6	−17.02	−2.02	28.35	11.63	132.1	−46096.9	3.17	−10.587	0.945
Aspartic acid (L)	261.5	288.0	410.3	−16.84	−1.15	26.53	10.91	133.1	−48398.4	3.66	−10.781	0.444
Benoz [a] pyrene	290.4	430.9	737.6	−2.81	1.36	93.43	31.68	252.3	−62832.3	0.04	−7.922	−1.111
Caffeine	337.4	366.1	569.5	−2.33	−1.06	50.01	18.87	194.2	−60617.4	3.66	−8.945	−0.322
Chrysene	301.2	415.6	698.2	−2.93	1.82	85.55	28.98	228.3	−56929.5	0.00	−8.372	−0.675
Furosemide	422.2	497.6	805.2	−15.88	−3.13	82.85	27.41	330.7	−98491.0	5.82	−9.414	−0.893
Glycine	201.1	216.7	281.3	−11.57	−1.07	16.00	6.52	75.1	−27065.7	2.71	−10.294	0.916
Glycylglycine	284.6	305.5	435.2	−13.55	−2.15	28.81	11.63	132.1	−46093.5	3.07	−10.208	0.682
Hexachlorobenzene	388.0	360.4	564.8	−0.24	0.26	59.25	22.00	284.8	−69423.7	0.00	−9.911	−1.040
Leucine (L)	310.8	319.5	479.1	−7.73	0.66	34.17	13.86	131.2	−41435.9	1.08	−10.222	0.929
Nalidixic acid	366.0	425.0	683.1	−5.36	1.39	63.59	23.76	232.2	−70945.3	5.68	−9.170	−0.706
Niflumic acid	377.1	448.1	718.5	−9.88	0.96	71.20	24.86	282.2	−99136.5	3.72	−8.791	−0.958
Norleucine (DL)	325.3	333.6	492.6	−7.53	0.73	34.22	13.86	131.2	−41440.2	1.14	−10.313	0.908
Oxolinic acid	365.2	432.0	701.8	−10.58	−1.59	68.83	24.97	261.2	−83568.1	8.10	−8.864	−0.693
Paracetamol	307.2	332.3	498.9	−10.71	−1.32	45.55	16.18	151.2	−46028.5	4.55	−8.462	0.283
Pentachlorobenzene	359.8	343.3	530.4	−0.46	0.48	54.54	20.07	250.3	−61123.5	0.79	−9.786	−0.891
Perylene	282.3	425.8	730.7	−2.74	1.36	93.43	31.68	252.3	−62830.5	0.00	−7.858	−1.155
Salicylic acid	240.2	283.6	424.0	−12.19	−0.04	38.56	13.63	138.1	−44749.0	1.24	−9.474	−0.555
Sulphamethiazine	404.5	472.2	777.4	−11.62	−0.50	79.31	26.19	278.3	−78205.2	7.54	−9.145	−0.446
Sulphanilamide	273.7	326.7	490.6	−13.26	−1.98	47.76	14.27	172.2	−49060.7	6.26	−9.157	−0.325
Valine (DL)	274.6	286.7	422.8	−8.99	0.34	29.49	12.02	117.2	−37843.0	2.53	−10.197	1.018
Mean:	308.7	349.5	540.2	−8.82	−0.33	50.05	18.04	184.2	−54947.8	3.13	−9.498	−0.018

Table 3: Numerical values of the descriptors computed using HyperChem® software for water-polyethylene glycol 400 set

Solute	SAA	SAG	Vol	HE	log P	MR	Pol	MW	TE	DM	HOMO	LUMO
Acetazolamide	344.7	368.1	548.5	−16.71	0.44	47.78	16.13	222.2	−63915.4	7.23	−9.861	−1.362
Adenine	179.1	286.2	414.1	−14.17	−1.22	36.81	13.71	135.1	−40176.7	2.18	−8.769	−0.112
Adenosine	294.1	436.1	713.2	−23.42	−2.10	63.40	24.66	267.2	−87055.2	3.79	−8.965	−0.370
p-Aminobenzoic acid	253.9	298.1	443.5	−12.17	−0.74	40.50	14.34	137.1	−42453.5	4.51	−8.728	−0.122
Aminopyrine	405.7	445.0	742.5	−0.96	0.12	72.67	26.64	233.3	−66066.8	2.23	−8.626	0.397
Ampicillin	434.3	535.8	927.9	−11.01	−0.63	91.57	35.18	349.4	−101610.3	4.01	−9.331	−0.139
Aspirin	301.4	350.7	534.5	−8.30	−0.26	48.00	17.38	180.2	−58671.4	1.85	−9.875	−0.605
Atropine	402.2	497.4	861.9	−7.21	0.95	84.95	31.78	289.4	−84447.8	5.53	−9.653	−0.034
Azathioprine	326.0	433.2	686.3	−15.25	0.59	69.71	25.86	277.3	−81277.8	9.93	−8.741	−1.357
Benzamide	238.8	284.3	418.4	−6.39	0.12	38.78	13.71	121.1	−35049.2	3.59	−9.941	−0.215
Benzoic acid	248.4	279.5	408.3	−6.81	0.98	36.96	12.99	122.1	−37355.0	2.42	−10.084	−0.468
Bumetanide	521.4	590.0	991.8	−11.91	−1.48	103.37	34.47	364.4	−107514.0	5.85	−8.979	−0.981
Butamben	408.0	426.5	666.6	−6.02	0.50	59.15	21.68	193.3	−56813.4	3.95	−8.646	−0.019
Butylparaben	415.9	414.9	652.9	−7.59	1.20	57.20	20.97	194.2	−59109.2	1.25	−9.512	−0.368
Carbamazepine	288.2	426.1	700.0	−6.53	−0.28	79.99	27.42	236.3	−64993.6	3.51	−8.605	−0.452
Chloramphenicol	442.2	484.8	805.4	−15.31	−0.25	76.21	28.02	323.1	−99962.0	7.05	−10.338	−1.197
Chlorthalidone	392.3	494.0	817.4	−12.35	−0.81	89.33	29.48	338.8	−96997.0	6.05	−10.103	−1.074
Chlorzoxazone	251.9	311.0	461.1	−12.78	0.04	44.16	15.63	169.6	−50067.1	0.76	−9.394	−0.511
Cimetidine	483.0	506.9	804.0	−14.86	−0.59	72.48	27.10	252.3	−67679.5	3.93	−8.401	0.222
Clofazimine	580.5	732.6	1273.9	−4.64	1.16	153.32	52.76	473.4	−122942.4	2.17	−8.016	−1.244
Cortisone	428.1	533.6	959.6	−8.94	2.74	96.47	37.55	360.5	−107868.0	6.66	−10.018	−0.008
Dapsone	350.7	433.7	695.4	−16.09	−2.94	76.31	23.93	248.3	−68028.2	6.24	−8.897	−0.247
Deoxycorticosterone	427.0	522.0	939.6	−5.59	4.07	94.41	36.83	330.5	−93738.4	1.67	−10.105	−0.096
Dexamethasone	450.2	545.2	992.8	−8.54	3.18	101.67	39.11	390.5	−121667.1	6.07	−10.187	−0.484
Diflunisal	343.2	401.5	645.8	−12.66	−0.64	67.33	23.11	250.2	−85461.4	1.09	−8.926	−0.892
Diosgenin	490.3	640.3	1179.5	−2.25	5.32	120.26	47.39	414.6	−115293.0	2.86	−9.276	1.230
Disopyramide	503.5	584.7	1036.5	−3.52	1.53	110.93	40.52	339.5	−92903.9	4.94	−8.762	−0.118
Equilin	357.0	472.8	794.4	−7.02	2.28	82.94	30.66	268.4	−74291.0	1.90	−8.894	0.288
Estradiol-17-alpha	352.8	474.7	809.5	−8.77	2.19	82.91	31.41	272.4	−75588.2	2.87	−8.751	0.479
Estriol	367.2	481.4	833.0	−13.70	1.42	84.27	32.04	288.4	−82982.2	0.60	−8.842	0.385
Estrone	355.8	468.6	798.2	−6.70	2.72	82.09	30.85	270.4	−74938.6	1.65	−8.921	0.323
Ethylparaben	340.9	358.6	545.0	−8.53	0.33	48.08	17.30	166.2	−51921.8	2.99	−9.514	−0.367
Fenbufen	433.7	476.8	774.8	−9.62	1.93	79.91	28.24	254.3	−73853.8	2.38	−9.112	−0.885
Flufenamic acid	374.0	455.3	727.8	−9.28	0.87	75.38	25.56	281.2	−97632.4	2.04	−9.564	−0.528
Flurbiprofen	381.3	449.9	726.0	−6.34	1.48	74.72	26.23	244.3	−74384.0	1.74	−9.118	−0.483
Glafenine	504.4	613.4	1014.6	−16.32	−2.01	107.80	38.18	372.8	−109211.2	3.83	−8.906	−0.787
Griseofulvin	490.6	552.2	928.8	−4.81	−1.61	91.27	33.53	352.8	−108494.8	6.80	−9.207	−0.654
Guaifenesin	344.1	386.5	614.9	−13.33	−1.20	55.96	20.32	198.2	−63528.8	2.19	−8.904	0.321
Guanine	209.4	300.3	436.8	−15.80	−1.46	37.50	14.22	151.1	−47563.3	6.18	−8.519	−0.121
Hydrochlorothiazide	368.1	407.4	654.7	−13.72	−3.24	67.06	19.75	297.7	−84647.5	9.26	−9.780	−1.048
Hydrocortisone	421.3	533.2	967.0	−9.23	2.37	97.40	38.10	362.5	−108522.1	2.52	−10.043	0.012
Hydroflumethiazide	376.1	421.3	685.5	−12.65	−2.45	67.55	19.39	331.3	−112557.4	8.44	−9.910	−1.350
Ibuprofen	428.1	437.8	706.8	−5.19	2.75	64.11	24.00	206.3	−58911.7	1.73	−9.403	0.195
Indapamide	374.3	498.5	885.6	−7.64	−1.27	101.40	33.86	365.8	−101857.2	5.22	−8.941	−1.020
Indoprofen	417.2	497.4	823.9	−7.01	0.40	86.08	30.65	281.3	−81882.2	4.69	−8.736	−0.571
Iopanoic acid	477.5	494.0	836.1	−8.38	2.10	95.79	36.77	570.9	−79895.9	3.78	−8.961	−0.453
Ketoprofen	410.6	475.6	771.8	−8.72	2.56	79.94	28.24	254.3	−73849.2	1.96	−9.907	−0.588
Mefenamic acid	375.0	454.6	744.1	−7.23	0.61	78.73	27.67	241.3	−68599.9	3.14	−8.561	−0.253
Methylparaben	308.7	325.8	488.3	−9.16	−0.01	43.33	15.46	152.2	−48329.2	1.39	−9.535	−0.397
Metronidazole	296.4	330.7	507.0	−8.71	−0.09	40.93	15.58	171.2	−56963.7	6.38	−9.736	−0.733
Nadolol	523.8	571.3	961.7	−13.92	−0.55	88.82	33.74	309.4	−93140.4	3.84	−9.219	0.065
Nalidixic acid	366.0	425.0	683.1	−5.36	1.39	63.59	23.76	232.2	−70945.3	5.68	−9.170	−0.706
Naphthalene	235.4	301.7	458.9	−2.31	1.67	49.15	16.62	128.2	−32049.2	0.00	−8.711	−0.265
2-Naphthol	250.8	312.6	479.4	−9.01	0.65	50.76	17.25	144.2	−39442.2	1.46	−8.570	−0.345
Naproxen	395.0	437.2	709.8	−9.55	0.56	70.65	25.32	230.3	−67953.3	1.17	−8.679	−0.425
Norethisterone	422.0	506.5	884.4	−1.54	3.41	87.42	33.80	298.4	−82080.2	3.96	−9.978	−0.002
Norfloxacin	429.4	510.6	860.6	−7.41	−1.90	87.74	31.81	319.3	−100621.6	7.33	−8.821	−0.700
Paracetamol	307.2	332.3	498.9	−10.71	−1.32	45.55	16.18	151.2	−46028.5	4.55	−8.462	0.283
Phenacetin	385.8	398.9	612.0	−4.51	−0.95	55.07	19.85	179.2	−53201.5	4.37	−8.357	0.361
Phenolphthalein	393.9	515.3	871.4	−18.15	0.21	99.79	34.65	318.3	−93010.4	6.62	−9.070	−0.647
Phenylbutazone	460.0	552.9	936.7	−2.91	1.84	98.38	35.04	308.4	−86717.4	0.89	−8.931	0.094
Prednisolone	417.2	533.1	956.0	−9.53	2.45	98.49	37.91	360.5	−107861.5	5.79	−9.982	−0.273
Primidone	317.9	403.1	647.4	−6.25	0.72	63.18	23.54	218.3	−64193.2	3.35	−9.652	0.165
Progesterone	423.2	514.8	919.5	1.32	4.63	92.71	36.19	314.5	−86349.5	4.40	−10.019	0.006
Propylparaben	378.0	391.4	600.7	−8.06	0.80	52.60	19.13	180.2	−55515.5	2.99	−9.513	−0.367
Quinidine	388.1	542.3	942.7	−5.01	−0.28	100.72	36.98	324.4	−90964.5	3.36	−8.443	−0.303
Quinine	411.4	553.2	953.4	−5.94	1.13	99.72	36.98	324.4	−90966.7	3.26	−8.527	−0.300
Salicylamide	235.6	289.1	433.3	−12.42	−0.91	40.38	14.34	137.1	−42434.7	2.41	−9.449	−0.315
Salicylic acid	240.2	283.6	424.0	−12.19	−0.04	38.56	13.63	138.1	−44749.0	1.24	−9.474	−0.555
Sulfadiazine	332.7	418.1	677.3	−14.37	−1.49	69.04	22.52	250.3	−71018.6	7.34	−9.177	−0.503

Table 3: (Continued)

Solute	SAA	SAG	Vol	HE	log P	MR	Pol	MW	TE	DM	HOMO	LUMO
Sulfamethazine	405.2	473.4	778.2	−11.62	−0.50	79.31	26.19	278.3	−78205.2	7.63	−9.133	−0.441
Sulfamethoxazole	369.3	432.0	688.9	−16.50	−1.54	68.63	22.22	253.3	−73914.6	6.84	−9.259	−0.634
Sulfanilamide	273.7	326.7	490.6	−13.26	−1.98	47.76	14.27	172.2	−49060.7	6.26	−9.157	−0.325
Sulfathiazole	333.0	411.7	664.5	−14.39	−1.50	68.63	22.75	255.3	−67460.4	6.24	−9.189	−0.660
Tenoxicam	378.7	477.5	804.4	−12.53	−3.90	88.72	29.84	337.4	−94657.8	3.55	−9.028	−1.348
Thiamphenicol	509.4	526.4	871.1	−13.63	−1.04	83.66	29.15	356.2	−103629.3	2.77	−10.646	−1.217
Triamcinolone	419.3	539.3	975.6	−13.83	1.48	99.38	38.46	394.4	−126119.4	2.86	−10.173	−0.476
1,2,3-Trichlorobenzene	297.9	302.9	452.1	−1.03	0.93	45.10	16.22	181.5	−44519.6	2.06	−9.785	−0.365
Trimethoprim	413.9	520.9	861.4	−15.71	−2.22	82.79	30.63	290.3	−88279.4	1.97	−8.790	0.075
Xanthine	225.8	290.9	421.0	−11.74	−1.80	35.32	13.37	152.1	−49870.3	6.64	−9.270	−0.222
Mean:	373.9	446.5	736.4	−9.65	0.27	73.88	26.61	263.8	−76431.0	3.95	−9.239	−0.365

Tables 1–3. The diversity of the drugs studied is reflected in the magnitude of the descriptors range, e.g. in Table 1, log P ranging from −3.13 to 3.67 and dipole moment ranging from 1.24 to 6.49. To provide a normalized range for the numerical values of the descriptors, they were multiplied in $f_c f_w$ and then divided by the mean values of the descriptors reported in the last rows of Tables 1–3. As an example, the normalization of the HOMO (HOMO′) of a drug dissolved in water-propylene glycol was calculated by:

$$\mathrm{HOMO}' = \frac{f_c \cdot f_w \cdot \mathrm{HOMO}}{\text{Mean of HOMO}(= -9.138)} \qquad (5)$$

The numerical values of the deviations from the Jouyban-Acree model were computed using:

$$Y = \ln X_{m,T} - \left[f_c \ln X_{c,T} + f_w \ln X_{w,T} + f_c f_w \left(\frac{85.252}{T} + \frac{735.662(f_c - f_w)}{T} \right) \right] \qquad (6)$$

The solvent system (e.g. water-propylene glycol) is the same and the effect of solutes' structure on the solubility could be refelected in $f_c \ln X_{c,T} + f_w \ln X_{w,T}$ term if we accept the ideal mixing behaviour. This is obviously not the case as significant model constants of the Jouyban-Acree, i.e. 85.252 and 735.662 were calculated. The constants of the Jouyban-Acree model should represent possible two- and three-body interactions between the dissolved solute, water and cosolvent as described in details by Acree (1992). Using Eqs. (2)–(4) to predict the solubility of different solutes assumes that the solute-water, solute-cosolvent and water-cosolvent-solute interactions are not dependent on the solute's structure. However, this is an oversimplification of the phenomenon which could produce deviations from experimental solubilities. Due to varying degrees of deviations observed for different solutes, it is reasonable to assume that the deviations will depend on the chemical structure of the solutes. Rubino and Obeng (1991) reported that the chemical structure of the salt affects the extent of diviations from nonideal behaviour. Therefore, such deviations should be a function of the chemical structure of drugs, and could be expressed mathematically in terms of the normalized descriptors as:

$$Y = f(\mathrm{SAA}', \mathrm{HE}', \log \mathrm{P}', \ldots) \qquad (7)$$

Equation (7) could be arranged as a quanitative structure property relationship (QSPR). To calculate the numerical values of the QSPR model constants, least squares method was used. The validity of the QSPR was evaluated using F test, the significance of the descriptor's contribution in the model was checked using t-test and the descriptors were included in the QSPR with the significance level of < 0.05.

The mean percentage deviation (MPD) was used to measure the accuracy of the prediction method and is calculated using:

$$\mathrm{MPD} = \frac{100}{N} \sum \frac{| X_m^{\text{Calculated}} - X_m^{\text{Observed}} |}{X_m^{\text{Observed}}} \qquad (8)$$

in which N is the number of solubility data points in each set. The OMPD (OMPD) was also computed using Eq. (9).

$$\mathrm{OMPD} = \frac{\sum_{1}^{\mathrm{NDS}} \mathrm{MPD}}{\mathrm{NDS}} \qquad (9)$$

The accuracy of the predictions was also compared with the accuracy of similar trained models proposed by Yalkowsky and co-workers (Millard et al. 2002). The Yalkoswky's trained models for aqueous mixtures of propylene glycol, ethanol and polyethylene glycol 400 were:

$$\ln X_m = \ln X_w + (1.34 + 1.77 \log \mathrm{P})\, f_c \qquad (10)$$

$$\ln X_m = \ln X_w + (0.92 + 2.14 \log \mathrm{P})\, f_c \qquad (11)$$

$$\ln X_m = \ln X_w + (2.90 + 1.70 \log \mathrm{P})\, f_c \qquad (12)$$

Where X_w is the aqueous solubility of the drug.

3.1. Solubility prediction in water-propylene glycol mixtures

The numerical values of the computed descriptors for the 19 solutes dissolved in water-propylene glycol mixtures were listed in Table 1. The normalized descriptors were regressed against numerical values of Y and the variables were included in the model when they were statistically significant at the level of less than 0.05. The most accurate QSPR model was:

$$\begin{aligned} Y_{\text{pred}} = &- 10.537(\pm 1.204)\, \mathrm{SAA}' - 1.384(\pm 0.509)\, \mathrm{HE}' \\ &- 0.391(\pm 0.075)\, \log \mathrm{P}' + 37.906(\pm 4.257)\, \mathrm{MR}' \\ &- 37.270(\pm 4.936)\, \mathrm{MW}' + 12.371(\pm 2.356)\, \mathrm{TE}' \\ &- 3.816(\pm 0.738)\, \mathrm{DM}' + 3.143(\pm 0.776)\, \mathrm{HOMO}' \\ &- 0.366(\pm 0.126)\, \mathrm{LUMO}' \qquad (13) \end{aligned}$$

$$N = 257, \qquad r = 0.673, \qquad s = 0.275$$

The calculated F value was 23, which was statistically significant ($p < 0.0005$). We suggest that the solubilities of the drugs in water-cosolvent mixtures are calculated using

Table 4: Number of solubility data points in water-propylene glycol mixtures for each set (N) at temperature (t, °C) and mean percentage deviation (MPD) for the proposed and the previous methods

No.	Solute[a]	N	t	Eq. (14)	Eq. (2)	Eq. (10)
1	Acetaminophen	12	20	2.6	6.8	74.5
2	Acetaminophen	11	25	4.4	9.5	74.7
3	Acetaminophen	11	30	5.4	8.4	75.2
4	Acetaminophen	11	35	4.9	8.1	74.4
5	Acetaminophen	11	40	4.7	6.2	73.6
6	Amoxycillin trihydrate	5	25	7.4	8.0	62.8
7	Butyl *p*-aminobenzoate	11	27	21.0	37.0	74.8
8	Butyl *p*-aminobenzoate	6	37	4.7	12.8	74.6
9	Butyl *p*-hydroxybenzoate	11	27	38.2	43.5	68.3
10	Dodecyl *p*-aminobenzoate	6	37	17.2	45.2	74.4
11	Ethyl *p*-aminobenzoate	11	27	18.2	14.9	75.3
12	Ethyl *p*-aminobenzoate	6	37	30.2	27.1	72.2
13	Ethyl *p*-hydroxybenzoate	11	27	9.4	15.1	70.4
14	Furosemide	13	25	12.1	50.0	80.2
15	Hexyl *p*-aminobenzoate	6	37	26.8	61.8	72.4
16	Hydrocortisone	5	25	12.7	8.9	13.3
17	Ketoprofen	11	25	35.3	36.2	78.4
18	Ketoprofen	11	37	28.1	38.6	77.7
19	Methyl *p*-aminobenzoate	11	27	16.5	14.0	74.5
20	Methyl *p*-hydroxybenzoate	11	27	14.4	9.3	70.7
21	Octyl *p*-aminobenzoate	6	37	12.8	41.5	76.6
22	Paracetamol (Acetaminophen)	11	25	27.0	30.7	79.2
23	Propyl *p*-aminobenzoate	11	27	22.6	30.4	74.4
24	Propyl *p*-hydroxybenzoate	11	27	14.1	27.1	68.1
25	Salicylic acid	11	25	8.8	6.8	75.2
26	Theophylline anhydrate	8	30	34.8	26.6	62.9
27	Theophylline hydrate	8	30	3.0	25.9	62.7
			Overall MPDs	16.2	24.1	70.8
			±SD	±10.9	±15.9	±12.4

[a] For more details of solubility data sets including their references, see a previous paper (Jouyban, 2007)

a combination of the Jouyban-Acree (Eq. (2)) and the proposed QSPR model (Eq. (13)); i.e.:

$$\ln X_{m,T} = \left[f_c \ln X_{c,T} + f_w \ln X_{w,T} + f_c f_w \left(\frac{85.252}{T} + \frac{735.662(f_c - f_w)}{T} \right) \right] + Y_{Pred} \quad (14)$$

and MPD and IPD values were computed as accuracy criteria. From MPD point of view, as listed in Table 4, the acetaminophen data set at 20 °C produced the minimum MPD (2.6%), the butyl *p*-hydroxybenzoate data set at 27 °C produced the maximum MPD (38.2%), and the OMPD was 16.2 (±10.9). In comparison, the OMPD of the previous model (Jouyban 2007), i.e. 24.1 ± 15.9, was larger. There is a significant improvement in the prediction capability of the Jouyban-Acree model by using QSPR model (paired t-test, $p < 0.003$). Equation (10) has been proposed for solubility prediction of drugs dissolved in water-propylene glycol mixtures and produced relatively higher MPD in comparison with the proposed QSPR method where its OMPD (± SD) was 70.8 ± 12.4%. The log P values of Table 1 were used in the computations.

The solubility of four alkyl *p*-aminobenzoates in water-cosolvent at 27 °C was used to illustrate the goodness of fit of the predicted solubilities with the experimental data. As shown in Fig. 1, the trend of solubility changes in the binary mixture could be successfully reproduced using Eq. (14).

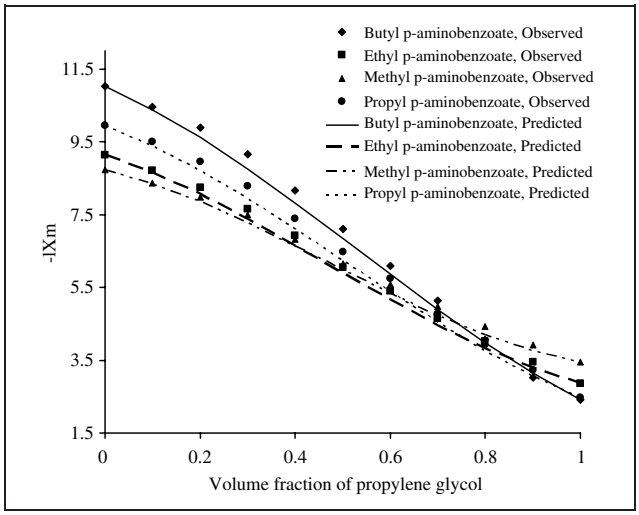

Fig. 1: The observed and predicted −ln Xm of alkyl aminobenzoates in water-cosolvent mixtures using Eq. (14)

2.3. Solubility prediction in water-ethanol mixtures

Similar calculations were performed to build up a QSPR model for representing deviations of computed solubilities in water-ethanol mixtures from the Jouyban-Acree model and the resulted equation was:

$$\ln X_{m,T} = f_c \ln X_{c,T} + f_w \ln X_{w,T} + f_c f_w \left[\frac{1667.550}{T} + \frac{1117.154(f_c - f_w)}{T} + \frac{447.643(f_c - f_w)^2}{T} \right] - 22.809(\pm 3.409)\,SAA' + 48.689(\pm 6.551)\,Vol' + 0.209(\pm 0.070)\log P' - 39.334(\pm 4.510)\,MR' + 19.154(\pm 3.696)\,MW' - 25.308(\pm 2.873)\,TE' + 1.432(\pm 0.345)\,DM' + 18.041(\pm 3.861)\,Pol' \quad (15)$$

Table 5: Number of solubility data points in water-ethanol mixtures for each set (N) at temperature (t, °C) and mean percentage deviation (MPD) for the proposed and the previous methods

No.	Solute[a]	N	t	Eq. (15)	Eq. (3)	Eq. (11)
1	Acetanilide	13	25	41.7	41.9	82.7
2	Alanine (Beta)	7	25	42	50.5	7939.7
3	Alanine (DL)	7	25	22.8	24.9	9712
4	Aminocaproic acid	7	25	49.7	55.4	48032.3
5	Asparagine (L)	5	25	31.6	20.4	1671.4
6	Aspartic acid (L)	7	25	25.3	25.6	3431.4
7	Benoz [a] pyrene	6	23	41.9	43.3	79.6
8	Caffeine	11	25	21.1	27.2	73.8
9	Chrysene	6	23	19.9	21.7	80.7
10	Furosemide	13	25	41.8	115.5	81.4
11	Glycine	7	25	16.7	30.9	10184.6
12	Glycylglycine	7	25	24.7	41.6	9219.7
13	Hexachlorobenzene	6	23	29.6	108.9	78.7
14	Leucine (L)	7	25	47	22.9	7762
15	Nalidixic acid	13	25	50.3	19.7	57.3
16	Niflumic acid	9	25	11.5	335.4	59.5
17	Norleucine (DL)	7	25	58.4	25.7	5716.4
18	Oxolinic acid	11	20	20.8	19.3	66.7
19	Oxolinic acid	11	25	23.7	21.3	66.3
20	Oxolinic acid	11	30	26.2	23.4	64.5
21	Oxolinic acid	11	35	29.4	26.2	64
22	Oxolinic acid	11	40	33.1	29.4	62
23	Paracetamol	13	25	26.8	25.1	85
24	Paracetamol	7	20	54.8	53.7	124.7
25	Paracetamol	7	25	45.8	45.5	112.8
26	Paracetamol	7	30	46.3	46	107.5
27	Paracetamol	7	35	30.3	30.9	94.5
28	Paracetamol	7	40	35.7	35.5	87.8
29	Pentachlorobenzene	6	23	60.6	138.3	74.4
30	Perylene	6	23	19.4	19	82.1
31	Salicylic acid	11	25	16.3	44.9	78.6
32	Sulphamethiazine	11	25	32.6	37.9	90.6
33	Sulphanilamide	12	25	18.2	16.7	85.8
34	Valine (DL)	7	25	38.3	12.7	13035.3
			Overall MPDs	33.4	48.1	3489
			± SD	± 13.1	± 58.1	± 8733.0

[a] For more details of solubility data sets including their references, see a previous paper (Jouyban and Acree, 2006)

Table 5 lists the MPD values for predicted solubilities of the studied data sets using three numerical methods. The minimum and maximum MPDs for the proposed method were 11.5 and 60.6%, respectively, for niflumic acid and pentachlorobenzene data sets. In comparison with Eq. (3), MPD of niflumic acid decreased from 335.3 to 11.5%, while MPD of valine increased from 12.7 to 38.3%. The OMPD (± SD) of the proposed method was 33.4 ± 13.1, while that of the previous method (Jouyban and Acree 2006) was calculated from the reported data to be 48.1 ± 58.1%.

The computed log P values reported in Table 2 were used to predict solubility of drugs in water-ethanol mixtures employing Eq. (11). The resulted MPDs were listed in Table 5 and for amino acid data sets very high MPDs were observed. Replacing the computed log P with the reported log P of Millard et al. (2002) in Eq. (11), produced a significant reduction in MPDs of amino acids. As an example, MPD of aminocaproic acid reduced from 48032.3 to 105.2%. The resulted reductions for other solutes were not significant, whereas, increased MPDs were observed using the reported log P of acetaminophen (i.e. 0.51) by Millard et al. (2002). Equation (11) is simpler than our proposed method from a practical point of view, however, its only variable representing the solute parameter is log P and therefore, its accuracy is very sensitive to the numerical variations of log P.

2.4. Solubility prediction in water-polyethylene glycol 400 mixtures

The resulted equation for solubility of drugs in water-polyethylene glycol 400 mixtures was:

$$\begin{aligned}\ln X_{m,T} = {} & f_c \ln X_{c,T} + f_w \ln X_{w,T} \\ & + f_c f_w \left[\frac{909.027}{T} + \frac{818.078(f_c - f_w)}{T} \right. \\ & \left. + \frac{895.442(f_c - f_w)^2}{T}\right] + 13.653(\pm 2.287)\ SAA' \\ & - 60.819(\pm 6.861)\ Vol' + 2.902(\pm 0.409)\ HE' \\ & + 38.176(\pm 4.171)\ MR' - 5.101(\pm 1.559)\ MW' \\ & + 9.491(\pm 2.173)\ TE' + 2.467(\pm 1.015)\ HOMO' \\ & - 0.763(\pm 0.217)\ LUMO' \end{aligned} \quad (16)$$

Details of MPD values for predicted solubilities in water-propylene glycol 400 are listed in Table 6. Equation (16) produced the minimum MPD of 4.6% for progesterone and the maximum MPD of 256.8% for diosgenin. The OMPD (± SD) was 335.0 ± 31.0% and was less than the corresponding MPD of the basic form of the Jouyban-Acree model, i.e. 53.0 ± 126.5%. The minimum and maximum MPDs of the predictive model of Yalkowsky, i.e. Eq. (12), were 23.7% (for quinine) and 13172.0% (for

Table 6: Number of solubility data points in water-polyethylene glycol 400 mixtures for each set (N) at temperature (t, °C) and mean percentage deviation (MPD) for the proposed and the previous methods

No.	Solute[a]	N	t	Eq. (16)	Eq. (4)	Eq. (12)
1	Acetazolamide	5	23	39.3	13.7	55.1
2	Adenine	5	23	34.3	6.9	50.8
3	Adenosine	5	23	51.2	13.6	55.9
4	Aminopyrine	5	23	22.7	38.9	221.0
5	Ampicillin	5	23	52.7	37.9	3812.3
6	Aspirin	5	23	22.6	13.4	53.6
7	Atropine	5	23	41.2	19.1	301.8
8	Azathioprine	5	23	23.0	35.4	29.1
9	Benzamide	5	23	24.4	24.9	153.3
10	Benzoic acid	5	23	25.2	12.5	40.7
11	Bumetanide	5	23	27.6	50.1	74.7
12	Butamben	5	23	34.1	17.9	73.0
13	Butylparaben	5	23	38.3	15.2	69.7
14	Carbamazepine	5	23	33.8	27.0	73.7
15	Chloramphenicol	5	23	25.9	27.0	47.1
16	Chlorthalidone	5	23	37.5	32.1	76.8
17	Chlorzoxazone	5	23	13.0	23.5	63.1
18	Cimetidine	5	23	31.5	20.2	63.1
19	Clofazimine	5	23	77.5	69.0	79.4
20	Cortisone	5	23	22.2	41.0	1550.4
21	Dapsone	5	23	49.4	50.1	79.5
22	Deoxycorticosterone	5	23	24.2	56.6	1223.4
23	Dexamethasone	5	23	33.0	10.8	450.8
24	Diflunisal	5	23	20.2	22.5	75.5
25	Diosgenin	5	23	256.8	1091.6	13172.0
26	Disopyramide	5	23	83.2	200.6	498.0
27	Equilin	5	23	19.5	11.5	61.8
28	Estradiol-17-alpha	5	23	43.2	23.8	71.3
29	Estriol	5	23	43.1	21.9	60.0
30	Estrone	5	23	28.7	6.7	36.2
31	Ethylparaben	5	23	35.6	17.6	69.2
32	Fenbufen	5	23	36.6	87.0	39.1
33	Flufenamic acid	5	23	21.0	19.2	68.2
34	Flurbiprofen	5	23	23.6	34.7	67.9
35	Glafenine	5	23	31.2	15.8	79.1
36	Griseofulvin	5	23	54.4	47.5	79.8
37	Guaifenesin	5	23	32.7	17.2	54.7
38	Guanine	5	23	15.9	47.0	43.2
39	Hydrochlorothiazide	5	23	42.7	39.7	78.9
40	Hydrocortisone	5	23	41.8	10.4	1511.4
41	Hydroflumethiazide	5	23	33.1	29.9	77.7
42	Ibuprofen	5	23	31.5	51.8	50.3
43	Indapamide	5	23	20.6	19.3	76.3
44	Indoprofen	5	23	16.1	25.0	67.1
45	Iopanoic acid	5	23	17.8	23.7	73.6
46	Ketoprofen	5	23	25.4	20.2	40.3
47	Mefenamic acid	5	23	36.0	59.0	75.8
48	Methylparaben	5	23	48.8	43.7	53.3
49	Metronidazole	5	23	20.9	50.6	485.7
50	Nadolol	5	23	27.6	56.1	272.7
51	Nalidixic acid	5	23	37.3	220.1	532.9
52	Naphthalene	5	23	24.9	37.0	65.6
53	Naphthol	5	23	39.2	37.0	64.5
54	Naproxen	5	23	28.6	9.6	74.2
55	Norethisterone	5	23	28.5	51.7	138.4
56	Norfloxacin	5	23	124.8	269.3	44.7
57	*p*-Aminobenzoic acid	5	23	9.9	16.5	52.7
58	Paracetamol	5	23	23.6	17.1	66.5
59	Phenacetin	5	23	5.5	20.6	67.2
60	Phenolphthalein	5	23	50.7	51.5	79.5
61	Phenylbutazone	5	23	83.2	174.8	41.2
62	Prednisolone	5	23	32.9	15.6	297.3
63	Primidone	5	23	16.4	40.6	309.7
64	Progesterone	5	23	4.6	133.7	2622.4
65	Propylparaben	5	23	39.3	18.3	69.2
66	Quinidine	5	23	19.7	77.3	47.3
67	Quinine	5	23	16.3	77.4	23.7
68	Salicylamide	5	23	16.5	5.3	72.1
69	Salicylic acid	5	23	22.1	9.0	65.7
70	Sulfadiazine	5	23	21.8	7.3	75.2

Table 6: (Continued)

No.	Solute[a]	N	t	Eq. (16)	Eq. (4)	Eq. (12)
71	Sulfamethazine	5	23	26.2	16.2	62.9
72	Sulfamethoxazole	5	23	38.2	23.6	77.7
73	Sulfanilamide	5	23	30.2	31.7	67.6
74	Sulfathiazole	5	23	21.0	12.6	72.0
75	Tenoxicam	5	23	5.6	31.1	77.8
76	Thiamphenicol	5	23	17.6	34.4	54.1
77	Triamcinolone	5	23	36.7	6.0	66.2
78	Trichlorobenzene	5	23	18.3	23.9	78.8
79	Trimethoprim	5	23	40.6	19.0	73.3
80	Xanthine	5	23	29.7	3.5	42.7
			Overall MPDs	35.0	53.0	394.0
			± SD	± 31.0	± 126.5	± 1552.3

[a] For more details of solubility data see Rytting et al. (2005)

diosgenin) and the OMPD (±SD) was 394.0 ± 1552.3%. In using Eq. (12), one should consider that the log P is the only variable representing the effects of solute structure of the solutes. As noted in Section 2.3, for solubility of amino acids in water-ethanol mixtures, the same modifications in MPD values were observed for solubility of drugs in water-polyethylene glycol 400 mixtures. For example, MPD of 2622.4% for progesterone data using log P = 4.63 (Table 3) was reduced to 854.0% using log P = 3.87 (taken from Millard et al. 2002). The MPD of 47.3% for quinidine data using log P = −0.28 (Table 3) was increased to 1149.8% using log P = 2.64 (Millard et al. 2002). Since the MPD alterations using different log P values were observed in both directions, we considered log P computed by HyperChem® software in the calculations.

Figure 2 shows the plot of the predicted lnXm *versus* observed values for three water-cosolvent systems studied in this work. There are good agreements between the predicted and observed values for a wide solubility range from lnXm ∼−25 to ∼7. The high correlation coefficient (R = 0.9905) within a wide solubility range revealed that the proposed QSPR model is capable of improving the accuracy of the predicted solubilities. This finding is also confirmed when correlation coefficients of the basic form of the Jouyban-Acree model (R = 0.9896) and that of the Yalkowsky's model (R = 0.7916) are considered.

The proposed QSPR models improved the capability of the Jouyban-Acree model for predicting the solubility of drugs in water-cosolvent mixtures at various temperatures by 8, 15 and 15% from previous investigations for aqueous mixtures of propylene glycol, ethanol and polyethylene glycol 400 and the overall MPD reduction is ∼13%. For practical applications, the expected prediction error using the proposed method is $\sim 28\% \left(= \frac{16 + 33 + 35}{3} \right)$ for the proposed method. The improvement in the accuracy of the proposed QSPR model was because of the effects of solute structures on the solubility in water-cosolvent mixtures. These effects is represented by various normalized descriptors. The physico-chemical interpretation of the variables and their coefficients are not too simple, especially when the relatively large number of the coefficients and their algebraic signs is kept in mind. We consider the proposed model as a gray box, since one could find some justifications on the effects of descriptors such as vol' or MR'. When one ignores the QSPR model, the basic form of the Jouyban-Acree model is resulting. It is a simple model with three/two curve-fitting parameters for each cosolvent, however, produced a relatively high prediction error, i.e. $\sim 42\% \left(\frac{24 + 48 + 53}{3} \right)$. The basic model contains a contribution from ideal mixing behavior of the drugs in water-colsolvent mixtures and 2 or 3 additional terms representing non-ideal mixing behavior of the solution. The Jouyban-Acree model produces more accurate predictions in comparison with the log-linear model of Yalkowsky which is the simplest cosolvency model available. The log-linear model requires only aqueous solubility data of the drug of interest, whereas our proposed and previous models require solubility data in water and neat cosolvent. Today, the simplicity could not be considered as an advantage, since all research units in academia and industry are well equipped with high technology and the computer facilities including user-friendly software. Therefore, the application of the proposed QSPR model is recommended in industry, however, further improvement in the prediction methods is needed.

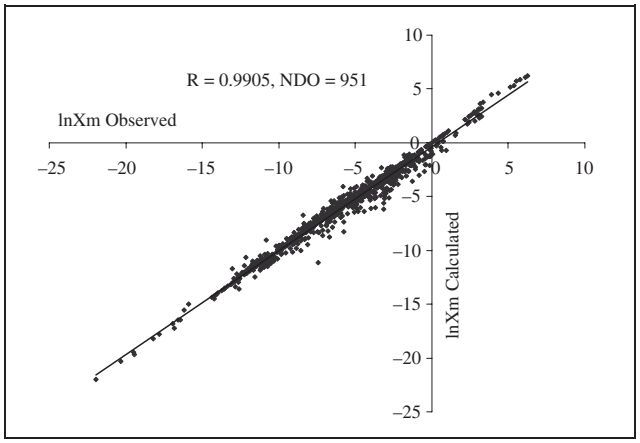

Fig. 2: The observed and predicted lnXm of drugs in three water-cosolvent mixtures studied the proposed model

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