Solubility Prediction of Drugs in Water–Polyethylene Glycol 400 Mixtures Using Jouyban–Acree Model

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A numerical method is proposed for predicting solubility of drugs in water–PEG 400 mixtures based on the Jouyban–Acree cosolvency model. The accuracy of the proposed method is evaluated by computing mean percentage deviation (MPD) and compared with that of log-linear model of Yalkowsky. The overall MPDs of the Jouyban–Acree model and the most accurate version of Yalkowsky's model are 39.8 (±46.7) % and 175.8 (±266.4) %, respectively, and the mean difference is statistically significant ($p<0.0005$). The proposed method produces acceptable residual distribution and the probability of solubility prediction with residual log of solubility <0.5 unit is 0.86. The applicability of the proposed method could be extended for predicting the solubility of drugs in water–PEG 400 mixtures at various temperatures. The impact of various log *P* values computed using different software is also studied and the results of ANOVA revealed that there are no significant differences between the accuracy of the predicted solubilities employing various log *P* values.

Key words solubility prediction; cosolvency modeling; water–PEG 400 mixture; log-linear; Jouyban–Acree

Solubilization of low soluble drug/drug candidate using various solubilization procedures is required in early stages of drug discovery studies and addition of a miscible cosolvent is the most common technique to increase solubility. In addition to experimental efforts to collect solubility data in mixed solvents, a number of models have been presented to calculate the solubility including the log-linear of Yalkowsky,[1] the extended Hildebrand solubility approach of Martin,[2] the Jouyban–Acree,[3,4] the phenomenological,[5] the modified Wilson,[6] general single[7] and Ruckenstein and Shulgin[8] models. Most of the models have been reviewed in a recent paper and a unified version of the models has been proposed.[9] Polyethylene glycol (PEG) 400 is the most common cosolvent in formulation of soft gelatin capsules, as examples, it has been used to formulate ethosuximide, bexarotene, etoposide, nifedipine, nimodipine and digoxin.[10] It has also been used in formulation of oral/injectable solutions as a solubilization agent.[10]

Computational Methods

The algebraic mixing rule[1] or log-linear model was expressed by:

$$\log X_m = f_c \log X_c + f_w \log X_w \quad (1)$$

where X_m is the solut'e solubility in water–cosolvent mixtures, f_c and f_w the volume fractions of cosolvent and water in the absence of the solute, X_c and X_w the solubilities in neat cosolvent and water, respectively. It is obvious that the X values could be exprerssed in g/l, mol/l, mole fraction *etc*. By replacing f_w with $(1-f_c)$, Eq. 1 could be re-written as:

$$\log X_m = \log X_w + (\log X_c - \log X_w) f_c \quad (2)$$

$$\log X_m = \text{intercept} + \text{slope}\, f_c \quad \text{or} \quad \log X_m = \log X_w + \sigma f_c \quad (3)$$

In which σ is the solubilization power of a cosolvent. The σ was correlated to the octanol–water partition coefficient (P) of the solute as[11]:

$$\sigma = S_0 + S_1 \log P \quad (4)$$

the regression parameters S_0 and S_1 are specific for the solvent and independent of the solutes. Eqs. 3 and 4 could be combined as:

$$\log X_m = \log X_w + (S_0 + S_1 \log P) f_c \quad (5)$$

Or:

$$\log X_m - \log X_w = S_0 f_c + S_1 f_c \log P \quad (6)$$

In which S_0 and S_1 values were computed using a no-intercept least square analysis in this work. The previously reported S_0 and S_1 values were computed by regressing slope of the log-linear model (*i.e.* σ) against log P of the solutes.

The log-linear model presents ideal mixing behaviour of the solutions and could be extended to the models possessing more constants representing the non-ideality of the observed solubility data. As it has been shown in a previous paper,[11] employing more model constants (curve-fitting parameters) provide more accurate correlation and obviously more accurate prediction. The Jouyban–Acree model is one of these models which provided the most accurate correlation among similar cosolvency models.[11] Its basic form for calculating a solute solubility in a water–cosolvent mixture is:

$$\log X_m = f_c \log X_c + f_w \log X_w + f_c f_w \sum_{i=0}^{2} A_i (f_c - f_w)^i \quad (7)$$

where A_i the solvent–solvent and solute–solvent interaction terms[3] computed using a no-intercept least square analysis. The model could be written as Eq. 8 to calculate the solubility of drugs in binary solvents at various temperatures[12]:

$$\log X_{m,T} = f_c \log X_{c,T} + f_w \log X_{w,T} + f_c f_w \sum_{i=0}^{2} \frac{J_i (f_c - f_w)^i}{T} \quad (8)$$

where $X_{m,T}$, $X_{c,T}$ and $X_{w,T}$ are the solubility of the solute in solvent mixture, cosolvent and water in the absence of the solute at temperature (T, K) and J_i is the model constant. By this extension, one is able to predict solubilities in mixed solvents at various temperatures which quite beneficial to pharmaceutical industry.

The mean percentage deviation (MPD) was used to check the accuracy of the prediction method and is calculated using Eq. 9:

$$\text{MPD} = \left(\frac{100}{N}\right)\left(\frac{\sum |\text{calculated}\ (X_m) - \text{observed}\ (X_m)|}{\text{observed}\ (X_m)}\right) \quad (9)$$

in which N is the number of solubility data points.

Results and Discussion

Available experimental solubility data of drugs in water–PEG 400 mixtures expressed in mole per liter and g/l are collected from the literature.[13,14] The data sets containing X_c and X_w values are included in this study, since the Jouyban–Acree model requires these values as input data. Details

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Table 1. Details of Solubility Data of Drugs in Water–PEG 400 (Number of Data Points in Each Set Was 5), log *P* Values, and Mean Percentage Deviations for Eqs. 10—12

Name	log *P*[a)]	Eq. 10	Eq. 11	Eq. 12
Acetazolamide	−0.30	13.7	37.6	39.2
Adenine	−0.10	6.9	90.8	49.4
Adenosine	−1.30	13.6	80.6	45.0
p-Aminobenzoic acid	0.00	16.5	25.3	24.6
Aminopyrine	0.80	38.9	797.7	707.0
Ampicillin	1.40	37.9	106543.9	118929.7
Aspirin	1.20	13.4	75.4	78.3
Atropine	1.50	19.1	681.2	791.5
Azathioprine	0.90	35.4	13.3	13.3
Benzamide	0.70	24.9	494.5	417.3
Benzoic acid	1.90	12.5	92.0	130.0
Bumetanide	2.80	50.1	50.4	45.2
Butamben	3.60	17.9	30.6	44.2
Butylparaben	3.50	15.2	36.0	58.5
Carbamazepine	2.70	27.0	103.1	175.7
Chloramphenicol	1.00	27.0	42.6	40.2
Chlorthalidone	−0.70	32.1	75.4	76.6
Chlorzoxazone	2.20	23.5	36.8	60.0
Cimetidine	0.40	20.2	629.6	475.9
Clofazimine	7.50	69.0	470.9	4900.9
Cortisone	1.20	41.0	102.1	106.5
Dapsone	0.90	50.1	67.7	68.5
Deoxycorticosterone	3.40	56.6	170.1	420.6
Dexamethasone	2.10	10.8	41.3	53.5
Diflunisal	4.30	22.4	247.9	952.3
Diosgenin	5.70	1091.6	5848.6	21375.9
Disopyramide	2.90	200.6	1861.1	3345.2
Equilin	3.50	11.5	46.7	25.4
Estradiol-17-alpha	4.10	23.8	50.2	59.2
Estriol	2.90	21.8	57.0	91.4
Estrone	3.70	6.7	32.1	63.7
Ethylparaben	2.40	17.6	49.7	67.4
Fenbufen	3.00	87.0	35.7	70.8
Flufenamic acid	5.60	19.2	461.5	2628.3
Flurbiprofen	4.10	34.7	36.0	47.6
Glafenine	3.90	15.8	59.8	210.2
Griseofulvin	2.40	47.5	78.1	77.5
Guaifenesin	0.60	17.2	293.7	237.2
Guanine	−0.9	47.0	362.6	160.1
Hydrochlorothiazide	−0.10	39.7	63.0	68.0
Hydrocortisone	1.40	10.4	239.0	271.4
Hydroflumethiazide	0.50	29.9	50.3	46.4
Ibuprofen	3.70	51.8	38.1	59.6
Indapamide	2.10	19.3	53.4	47.1
Indoprofen	1.70	25.0	51.2	47.9
Iopanoic acid	5.20	23.7	52.6	32.8
Ketoprofen	2.80	20.2	45.8	35.3
Mefenamic acid	5.30	59.0	57.1	340.1
Methylparaben	1.90	43.7	422.1	575.2
Metronidazole	0.00	50.6	850.6	562.5
Minoxidil	−1.50	32.7	74.6	35.2
Nadolol	1.30	56.2	4950.0	5293.7
Nalidixic acid	0.20	220.1	141.1	102.1
Naphthalene	3.40	37.0	38.9	13.9
2-Naphthol	2.70	37.0	154.3	288.8
Naproxen	3.00	9.6	52.4	36.0
Norethisterone	3.40	51.7	42.6	135.8
Norfloxacin	1.50	269.3	1118.6	1263.9
Paracetamol	0.30	17.0	78.8	63.3
Phenacetin	1.60	20.6	63.6	85.8
Phenolphthalein	3.30	51.5	72.1	63.3
Phenylbutazone	3.50	174.8	61.0	161.2
Prednisolone	1.70	15.6	46.5	62.7
Primidone	−1.00	40.6	30.6	35.9
Progesterone	4.00	133.7	390.9	1032.9
Propylparaben	2.90	18.3	48.0	73.1
Quinidine	3.40	77.3	1656.5	3767.8
Quinine	3.40	77.4	651.7	1467.8
Salicylamide	1.40	5.3	32.0	33.2
Salicylic acid	2.10	9.0	47.9	65.7
Sulfadiazine	−0.10	7.3	66.0	68.6
Sulfamethazine	0.80	16.2	42.8	40.4
Sulfamethoxazole	0.90	23.6	68.3	68.8
Sulfanilamide	−0.70	31.7	54.4	32.1
Sulfathiazole	0.30	12.6	47.5	52.5
Tenoxicam	−0.30	31.1	58.5	63.3
Thiamphenicol	−0.30	34.4	17.8	31.8
Triamcinolone	1.10	6.0	42.8	42.6
1,2,3-Trichlorobenzene	3.80	23.9	75.3	72.1
Trimethoprim	0.80	19.0	137.9	120.7
Xanthine	−0.60	3.5	220.7	95.5
Overall MPD:		52.8	1639.7	2148.4
Overall MPD after one excluded data set:		39.8	328.4	688.6

a) log *P* values taken from Rytting *et al.*[16] which are calculated using ACD software.

Table 2. The Model Constants of Log-Linear of Yalkowsky Using 79 Data Sets (Excluded Set Are Ampicillin and Diosgenin) and Various log *P* Values

log *P* values	Ref.	S_0 (±S.E.)	S_1 (±S.E.)
ACD[a)]	16	1.383 (±0.073)	0.577 (±0.028)
KowWin®	17	1.608 (±0.082)	0.480 (±0.032)
ACD[b)]	17	1.281 (±0.079)	0.608 (±0.031)
ClogP	17	1.341 (±0.072)	0.629 (±0.029)
Experimental	17	1.320 (±0.079)	0.616 (±0.033)
—	16	1.45 (±0.15)	0.57 (±0.06)
—	15	1.26 (±0.22)	0.74 (±0.07)

a) log *P* values taken from Rytting *et al.*[16] *b*) log *P* values taken from Machatha and Yalkowsky.[17]

of data, MPD values and the overall MPD (±S.D.) are listed in Table 1. The data is fitted to Eq. 8, and the trained model is:

$$\log X_{m,T} = f_c \log X_{c,T} + f_w \log X_{w,T} + f_c f_w \left[\frac{394.82}{T} - \frac{355.28(f_c - f_w)}{T} + \frac{388.89(f_c - f_w)^2}{T} \right] \quad (10)$$

The prediction capability of Eq. 10 is compared with those of the log-linear model of Yalkowsky using reported model constants:

$$\log X_m = \log X_w + (1.26 + 0.74 S_1 \log P) f_c \quad (11)$$

by Millard *el al.*[15] and

$$\log X_m = \log X_w + (1.45 + 0.57 \log P) f_c \quad (12)$$

by Rytting *et al.*[16]

The maximum MPD value for Eq. 10 is 1091.6% (for diosgenin). The data set of diosgenin in water–PEG 400 was questionable, since the authors reported −2.618 in Table 1 of the reference[13] for log of aqueous solubility of diosgenin against −5.075 in Table 2 of the same reference.[13] In addition to the numerical value of aqueous solubility of diosgenin, the solubility behavior of the solute in water–PEG 400 mixture (75 : 25) was also unusual, *i.e.* the solubility decreased with 25% cosolvent addition and then increased with

Table 3. Various log *P* Values and the Mean Percentage Deviations (MPDs) of the Log-Linear Model Using log *P*s

Solute	log *P* values					MPD values using different log *P*s				
	ACD[a]	ACD[b]	KowWin®[b]	ClogP[b]	logP_{exp}[b]	ACD[a]	ACD[b]	KowWin®[b]	ClogP[b]	logP_{exp}[b]
Acetazolamide	−0.30	−0.26	−0.73	−1.25	−0.26	35.5	33.6	36.9	58.9	34.2
Adenine	−0.10	−0.03	−0.73	−0.29	−0.11	72.9	59.2	58.4	47.4	57.4
Adenosine	−1.30	−1.02	−1.38	−2.27	−1.12	70.7	74.0	145.8	46.9	70.3
p-Aminobenzoic acid	0.00	0.83	0.96	0.98	0.73	22.7	51.8	127.9	90.1	49.0
Aminopyrine	0.80	0.76	0.60	0.57	0.90	695.9	552.5	780.1	500.3	742.4
Aspirin	1.20	1.20	1.13	1.02	1.25	64.2	53.5	78.8	49.3	66.7
Atropine	1.50	1.50	1.91	1.32	1.82	597.6	524.5	1129.4	498.0	930.5
Azathioprine	0.90	0.90	−0.09	0.01	0.10	13.4	19.0	37.2	47.3	46.0
Benzamide	0.70	0.70	0.74	0.65	0.65	426.7	353.3	647.0	390.3	364.4
Benzoic acid	1.90	1.90	1.87	1.88	1.87	83.0	76.6	87.2	90.2	81.7
Bumetanide	2.80	2.78	2.57	3.36	−0.30	50.9	51.2	52.0	41.3	70.2
Butamben	3.60	3.60	2.78	2.98	3.02	33.5	32.8	56.3	46.8	48.2
Butylparaben	3.50	3.50	3.47	3.57	3.57	34.9	35.0	41.7	40.9	38.3
Carbamazepine	2.70	2.70	2.25	1.98	2.32	94.8	91.9	64.3	56.7	69.9
Chloramphenicol	1.00	1.00	0.92	1.28	1.14	37.4	32.9	46.5	64.9	42.9
Chlorthalidone	−0.70	−0.74	1.59	0.45	—[c]	75.7	76.3	51.2	70.9	—[c]
Chlorzoxazone	2.20	2.29	1.99	1.87	—[c]	33.3	34.7	28.3	26.1	—[c]
Cimetidine	0.40	0.40	0.57	0.35	0.47	544.2	441.8	995.6	481.6	537.7
Clofazimine	7.50	7.50	7.55	6.69	7.48	456.0	604.2	165.8	322.8	723.3
Cortisone	1.20	1.20	1.81	1.30	1.47	85.1	68.1	253.8	109.9	132.9
Dapsone	0.90	0.90	0.77	0.89	0.97	69.0	70.4	67.3	69.0	68.7
Deoxycorticosterone	3.40	3.40	3.12	3.25	2.88	152.2	153.7	76.3	168.5	73.3
Dexamethasone	2.10	2.10	1.72	1.75	1.89	38.6	36.9	32.7	32.9	34.2
Diflunisal	4.30	4.30	4.41	4.39	3.56	226.1	244.7	164.8	414.8	107.1
Disopyramide	2.90	2.90	2.96	2.58	2.65	1702.9	1664.9	1615.1	1427.8	1397.2
Equilin	3.50	3.53	−2.81	2.90	—[c]	48.5	47.4	77.9	56.6	—[c]
Estradiol-17-alpha	4.10	4.10	3.94	3.78	3.86	52.0	50.8	60.8	53.3	54.2
Estriol	2.90	2.90	2.81	3.20	2.45	53.8	53.1	48.2	83.2	42.9
Estrone	3.70	3.70	3.43	3.38	2.95	31.0	31.3	37.4	29.8	43.9
Ethylparaben	2.40	2.40	2.49	2.51	2.47	46.9	45.6	48.8	56.6	51.1
Fenbufen	3.00	3.00	3.18	3.14	3.20	34.2	34.2	34.0	50.5	47.9
Flufenamic acid	5.60	5.60	5.15	4.88	4.32	431.5	512.8	102.8	260.6	83.2
Flurbiprofen	4.10	4.10	3.81	3.75	4.16	37.3	36.5	48.3	38.7	32.4
Glafenine	3.90	3.49	0.42	3.04	—[c]	56.5	43.4	74.2	38.8	—[c]
Griseofulvin	2.40	2.40	1.92	1.75	2.18	78.3	78.3	78.7	78.8	78.5
Guaifenesin	0.60	0.57	−1.05	0.10	—[c]	252.1	197.4	62.0	114.5	—[c]
Guanine	−0.90	−0.98	−1.05	−1.28	−0.94	307.2	200.9	526.5	137.7	229.9
Hydrochlorothiazide	−0.10	−0.07	−0.07	−0.40	−0.07	64.9	66.9	56.6	69.7	66.1
Hydrocortisone	1.40	1.40	1.62	1.70	1.65	204.7	173.4	341.5	363.2	300.9
Hydroflumethiazide	0.50	0.50	0.22	−0.25	0.36	47.8	47.0	49.4	63.3	49.4
Ibuprofen	3.70	3.70	3.79	3.68	3.50	38.8	38.6	44.0	36.0	41.3
Indapamide	2.10	2.09	5.78	2.94	—[c]	55.0	56.3	421.2	35.6	—[c]
Indoprofen	1.70	2.77	2.32	2.74	2.77	52.9	26.9	39.3	23.5	23.7
Iopanoic acid	5.20	4.19	3.00	4.89	—[c]	53.6	65.3	72.4	52.6	—[c]
Ketoprofen	2.80	2.80	3.00	2.76	3.12	48.0	48.6	45.8	44.4	34.9
Mefenamic acid	5.30	5.30	5.28	4.94	4.29	51.7	63.3	28.0	52.8	32.5
Methylparaben	1.90	1.86	2.00	1.99	1.96	372.7	322.6	457.7	484.5	415.9
Metronidazole	0.00	−0.01	0.00	−0.46	−0.02	736.4	580.9	1195.7	353.7	623.8
Minoxidil	−1.50	0.69	1.35	0.48	1.33	61.9	976.0	3400.7	856.5	2617.3
Nadolol	1.30	1.29	1.17	0.38	0.71	4369.9	3772.7	4725.1	1333.5	1945.7
Nalidixic acid	0.20	1.00	1.64	1.32	1.50	123.7	260.8	644.1	432.4	491.7
Naphthalene	3.40	3.35	3.17	3.32	3.30	41.2	42.6	50.6	36.6	40.8
2-Naphthol	2.70	2.70	2.69	2.65	2.78	140.7	136.1	130.3	161.0	170.5
Naproxen	3.00	3.00	3.10	2.82	3.26	54.1	54.4	54.8	54.1	45.0
Norethisterone	3.40	3.38	2.99	2.78	2.97	36.0	34.7	21.0	18.9	20.3
Norfloxacin	1.50	1.48	−0.31	−0.99	−1.26	1006.4	885.7	215.4	43.1	28.2
Paracetamol	0.30	0.34	0.27	0.49	0.48	70.9	63.8	103.0	82.8	78.1
Phenacetin	1.60	1.60	1.67	1.77	1.57	50.4	40.4	76.0	88.8	46.5
Phenolphthalein	3.30	2.63	3.06	2.63	2.41	72.8	76.6	75.2	75.9	77.1
Phenylbutazone	3.50	3.16	3.52	3.38	3.23	54.5	44.8	46.9	64.7	47.7
Prednisolone	1.70	1.49	1.40	1.38	1.59	40.2	31.3	35.1	32.1	36.0
Primidone	−1.00	0.40	0.73	0.88	0.91	27.8	160.9	451.7	390.9	378.3
Progesterone	4.00	4.00	3.67	3.77	3.87	361.2	378.1	184.4	376.4	370.2
Propylparaben	2.90	2.90	2.98	3.04	3.04	45.7	45.1	44.8	57.8	53.3
Quinidine	3.40	3.40	3.29	2.79	2.36	1512.8	1524.8	1087.2	898.2	458.4
Quinine	3.40	3.44	3.29	2.79	2.36	595.1	631.3	426.1	350.1	169.8
Salicylamide	1.40	1.40	1.03	1.28	1.28	30.8	29.8	29.6	30.0	29.5

Table 3. (Continued)

Solute	log *P* values					MPD values using different log *P*s				
	ACD[a]	ACD[b]	KowWin®[b]	ClogP[b]	log P_{exp}[b]	ACD[a]	ACD[b]	KowWin®[b]	ClogP[b]	log P_{exp}[b]
Salicylic acid	2.10	2.06	2.24	2.19	2.24	44.3	40.8	50.7	53.8	52.1
Sulfadiazine	−0.10	−0.12	−0.34	−0.09	−0.07	66.9	68.4	65.2	67.4	67.6
Sulfamethazine	0.80	0.80	0.76	1.07	0.28	40.1	37.3	47.4	53.0	38.6
Sulfamethoxazole	0.90	0.90	0.48	0.55	0.89	69.1	70.1	69.9	71.5	69.6
Sulfanilamide	−0.70	−0.72	−0.55	−0.57	−0.70	45.4	33.7	111.4	45.8	35.8
Sulfathiazole	0.30	0.30	0.72	0.72	0.05	49.9	53.1	29.4	39.4	56.3
Tenoxicam	−0.30	1.52	2.40	1.61	0.81	60.1	16.0	94.7	17.0	38.9
Thiamphenicol	−0.30	−0.27	−0.33	−0.10	−0.27	22.0	26.8	21.5	17.9	25.0
Triamcinolone	1.10	0.83	0.96	0.67	1.16	39.9	32.6	42.3	32.1	40.6
1,2,3-Trichlorobenzene	3.80	4.27	3.81	4.04	4.09	75.5	73.7	76.0	73.7	74.0
Trimethoprim	0.80	0.80	0.73	0.88	0.91	118.7	97.7	156.8	134.0	129.4
Xanthine	−0.60	−0.81	−1.15	−0.70	−0.73	181.9	87.3	191.4	123.8	112.9
Overall MPD:						232.7	228.9	298.1	175.8	220.6

a) log *P* values taken from Rytting *et al.*[16] *b*) log *P* values taken from Machatha and Yalkowsky.[17] *c*) Experimental log *P* values have not been reported in the reference.[17]

further increase in PEG 400 concentration in the mixture. We assumed that this was due to a typographical error and therefore, this data set was excluded from the computations. The overall MPD (±S.D.) for 80 data sets is 39.8 (±46.7). The maximum MPDs for Eqs. 11 and 12 are 106543.6 and 118929.7% (both for ampicillin). The numerical value of log *P* of ampicillin using ACD software reported by Rytting *et al.*[16] is 1.4 whereas the corresponding values using KowWin®, ClogP® and the experimentally obtained values were −0.88, −1.20 and −0.81, respectively.[17] To compare the results of the models using similar conditions, MPD of ampicillin was excluded from the comparison. The overall MPDs (±S.D.s) of Eqs. 11 and 12 were 328.4 (±884.9) and 688.6 (±2546.0) %, respectively which are significantly ($p<0.02$) higher than overall MPD (39.8) of Eq. 10.

Machatha and Yalkowsky[17] compared the accuracy of the log *P* values computed by three software, *i.e.* ClogP®, ACDlogP and KowWin® with the corresponding experimental log *P* values in octanol/water system and found that the ClogP® provided the most accurate log *P* values among the other software. In this work, the impact of the various log *P* values on the prediction capability of the log-linear model was studied using data of drugs in water–PEG 400 mixtures. To keep a similar comparison conditions, all available log *P* data was used to train Eq. 6 and the back-calculated solubilities were used to compute MPDs. Data sets of diosgenin and ampicillin was excluded from this study. Table 2 showed the constants of the log-linear model and Table 3 listed the numerical values of various log *P* values and the MPDs for 79 studied solubility data sets. The log *P* values computed using ACD software reported by Rytting *et al.*[16] and Machatha and Yalkowsky[17] are used to train separate models. There were a number of discrepancies between reported log *P*s, as examples see log *P*s of *p*-aminobenzoic acid, indoprofen, minoxidil and nalidixic acid in Table 3. These variations are reflected in different MPD values for the drugs. However, the mean difference of MPDs for two sets of log *P*s is not statistically significant (paired *t*-test, $p>0.80$). In addition, the overall MPD differences of various log *P*s were examined using one-way ANOVA and the results revealed that there is no significant differences ($p>0.68$) which means that one could use log *P*s computed using various software and/or experimental log *P* values to predict solubility by the log-linear model.

Rytting *et al.*[16] proposed a quantitative structure property relationship (QSPR) to compute drug solubility in each solvent composition of water–PEG 400 mixtures. The general form of the QSPR model was:

$$\log X_m = c_0 + c_1 MW + c_2 V_m + c_3 RB + c_4 HBA + c_5 HBD + c_6 RD + c_7 D_m \quad (13)$$

Where MW is the molecular weight (g/mol), V_m the molecular volume (Å^3), RB the number of rotatable bonds, HBA the number of hydrogen-bond acceptors, HBD the number of hydrogen bond donors, RG the radius of gyration (Å), D_m the molecular density (ratio of molecular weight to volume) and c_0—c_7 are the model constants.[16] The authors trained the model using two subsets for each solvent composition and reported the accuracy of the predictions using residuals in log units sorted in 5 subgroups. To compare the accuracy of the proposed model and the log-linear model using ACD and ClogP data, the residuals in log units were computed and the results listed in Table 4. Relatively similar residual distributions are observed for ACD data (both results taken from a previous paper[16] and computed in this work) and ClogP data by using log-linear model. The order of the favored residual distributions could be presented as Jouyban–Acree>log-linear>QSPR model. The overall relative frequency of residuals for predicted solubilities in water-PEG 400 mixtures is shown in Fig. 1 confirming the same order. The probability of solubility prediction with log residual of <0.5 for Jouyban–Acree, best version of the log-linear and QSPR models are 0.86, 0.68 and 0.54, respectively. The corresponding probabilities for log residual of <1.0 are 0.97, 0.80 and 0.78.

To show the applicability of the proposed method for predicting solubility of drugs in water–PEG 400 mixtures at various temperatures, the solubility data of paracetamol taken from a reference[14] were predicted using Eq. 10. Figure 2 shows the predicted and experimental solubilities of paracetamol in water–PEG 400 mixtures at 30 °C. As it has been shown, good agreement has been found between predicted and experimental solubilities and the MPD was 12.8%.

In using the proposed prediction method, one should consider that:

Table 4. Residual log X_m for Various Models Studied in Five Subgroups Reported by Rytting *et al.*[16]

	<0.5		0.5—1.0		1.0—1.5		1.5—2.0		>2.0	
	%	N	%	N	%	N	%	N	%	N
QSPR (Rytting model[16])										
25% PEG 400	47.7	18	31.6	12	7.9	3	5.3	2	7.9	3
50% PEG 400	63.2	24	15.8	6	13.2	5	5.3	2	2.6	1
75% PEG 400	52.6	20	23.7	9	10.5	4	13.2	5	0.0	0
Log-linear (reported results[16])										
25% PEG 400	76.3	29	15.8	6	5.3	2	2.6	1	0.0	0
50% PEG 400	57.9	22	34.2	13	5.3	2	2.6	1	0.0	0
75% PEG 400	36.8	14	31.6	12	21.1	8	5.3	2	5.3	2
Log-linear (ACD Rytting data)										
25% PEG 400	53.1	43	24.7	20	13.6	11	4.9	4	3.7	3
50% PEG 400	65.4	53	19.8	16	8.6	7	6.2	5	0.0	0
75% PEG 400	80.2	65	14.8	12	3.7	3	1.2	1	0.0	0
Log-linear (ClogP data)										
25% PEG 400	53.8	43	32.5	26	11.3	9	1.3	1	1.3	1
50% PEG 400	72.5	58	15.0	12	10.0	8	1.3	1	1.3	1
75% PEG 400	78.8	63	17.5	14	2.5	2	1.3	1	0.0	0
Jouyban–Acree model										
25% PEG 400	88.9	72	8.6	7	2.5	2	0.0	0	0.0	0
50% PEG 400	80.2	65	17.3	14	2.5	2	0.0	0	0.0	0
75% PEG 400	88.9	72	8.6	7	1.2	1	1.2	1	0.0	0

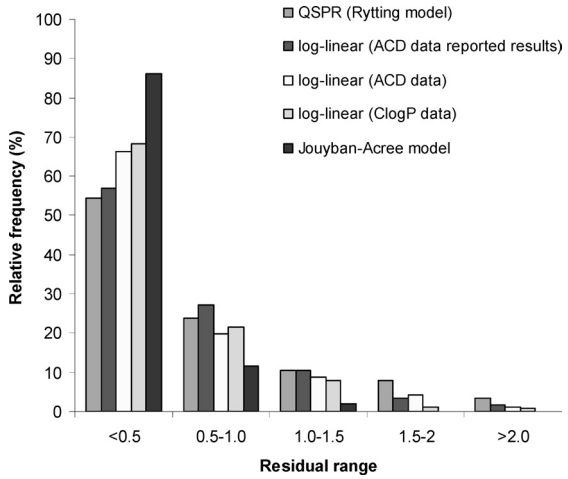

Fig. 1. Relative Frequency of Residuals (in log Units) for Predicted Solubilities in Water–PEG 400 Mixtures Using Various Numerical Methods

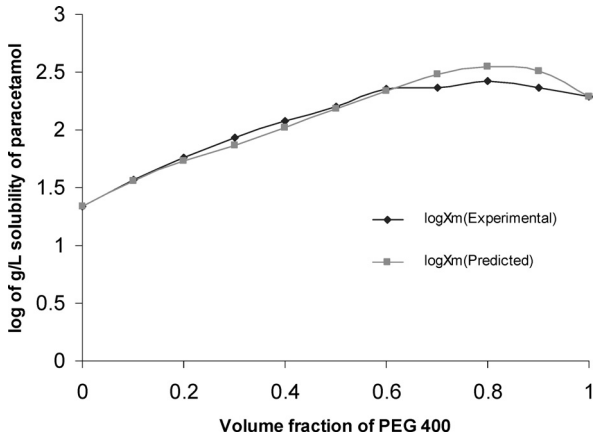

Fig. 2. Logarithm of Experimental Solubilities of Paracetamol in Water–PEG 400 Mixtures at 30 °C Taken from a Reference[14] and the Predicted Values Using Eq. 10 *versus* Volume Fraction of PEG 400

1. Solubility of the solute of interest in water and PEG 400 should be determined and used as input variables of the model.
2. The solvent composition of the mixed solvent system should be expressed as volume fraction (f_c for volume fraction of PEG 400 and f_w for volume fraction of water).
3. Temperature should be expressed as absolute temperature (K).

Conclusion

In conclusion, the proposed method provides more accurate predictions in comparison with previously established log-linear model of Yalkowsky and QSPR model of Rytting *et al.* The proposed method in this work employs one more datum in comparison with log-linear model, however, it does not require any more physico-chemical property like log *P*. The prediction method is successfully extended to the various temperatures which are obviously required in drug formulation and also crystallization studies.

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