Latin American Journal of Pharmacy
(formerly *Acta Farmacéutica Bonaerense)*
Lat. Am. J. Pharm. **30** (8): 1525-30 (2011)

Regular Article
Received: June 3, 2011
Revised version: June 28, 2011
Accepted: June 29, 2011

Comparison of Four Models to Predict Intrinsic Solubility of Drugs

Ali SHAYANFAR [1] & Abolghasem JOUYBAN [2]*

[1] *Liver and Gastrointestinal Diseases Research Center, Tabriz University of Medical Sciences, Tabriz 51664, Iran*
[2] *Drug Applied Research Center and Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz 51664, Iran.*

SUMMARY. **The aqueous solubility of drugs/drug candidates (S_w) is one of the crucial physicochemical parameters in drug discovery studies and any computational method to predict the solubility is highly in demand in the pharmaceutical industry. This work is aimed to compare the accuracy of a recently proposed model ($logS_w$=-1.120E-0.599ClogP) composed of two computational descriptors; excess molar refraction (*E*) and calculated partition coefficient of octanol to water (*ClogP*) with the accuracies of the Hansch model, general solubility equation and linear solvation energy relationship model. These results showed that the prediction capability of the proposed model is better than those of three famous models and the *E* is a crucial descriptor for aqueous solubility prediction of drugs and drug-like molecules.**

INTRODUCTION

Aqueous solubility of drugs and drug-like molecules is one of the important and crucial parameters in drug discovery investigations. Measurement of drugs solubility is a time-consuming process and an *in silico* method for predicting the aqueous solubility of drugs and drug like molecules could be an appropriate alternative method providing a valuable tool to speed up the process of drug discovery and development [1].

The partition coefficient of octanol to water (*logP*) is an important descriptor for solubility prediction where some models are based on *logP*. For the first time, Hansch *et al.* proposed a linear relationship between aqueous solubility and *logP* [2] (Eq. [**1**]):

$$log\ S_w = A log\ P + B \quad [\mathbf{1}]$$

where S_w is the molar aqueous solubility of a drug, *A* and *B* are the model constants.

The *logP* can be measured using experimental methods such as HPLC. However, it is believed that measuring the aqueous solubility is easier than *logP*, and therefore we prefer to use the calculated *logP* values which could be calculated by some computational methods [3].

The general solubility equation (GSE) of Yalkowsky consisting of two descriptors; i.e. melting point (*mp* expressed in °C) and *logP*. GSE is the most common method in the pharmaceutical industry [4] (Eq. [**2**]):

$$log\ S_w = 0.5 - 0.01\ (mp - 25) \quad [\mathbf{2}]$$

in which the term (*mp* – 25) is set to zero, if the drug's *mp* is less than 25 °C.

The linear solvation energy relationship model (LSER) is another model developed by Abraham based on solvation properties and composed of five solute properties and its lastest version is [5] (Eq. [**3**]):

KEY WORDS: Drug and drug-like molecules, Excess molar refraction (E), Intrinsic solubility, Prediction.

* Author to whom correspondence should be addressed. Email: ajouyban@hotmail.com

$$\log S_w = 0.395 - 0.955E + 0.320\,S + 1.155A + 3.255B - 0.785AB - 3.330V \quad [3]$$

in which E is excess molar refraction of the compound which models dispersion force interaction due to the polarizability of pi- and n-electrons, S is dipolarity/polarizability representing solute-solvent interactions between bond dipoles induced dipoles, A and B are hydrogen bond acidity and basicity, respectively, which these later three descriptors (S, A and B) determined from solubility data of a compound in water and different organic solvents, V is one percent of the McGowan volume and simply can be calculated using a group contribution method [6-9]. It should be noted that these descriptors could also be calculated using Pharma-Algorithms software.

There are many mathematical methods and commercial software for aqueous solubility prediction of drugs in the literature [1,3,10-12]. The Hansch model as the first and simplest one, the GSE and LSER approaches as the golden models which were used more frequently for predicting aqueous solubility of drugs, however, the prediction error of these models are relatively high [1]. To provide a simple *in silico* prediction method, different combinations of the computed parameters were evaluated and the best developed model was (Eq. [**4**]):

$$\log S_w = -1.120E - 0.599C\,logP \quad [4]$$

which is cross-validated using various combinations of train/test data sets [13]. A prediction data set composed of aqueous solubility of 75 pharmaceutically interested compounds was also proposed for evaluating the prediction capability of the computational methods [13].

Intrinsic solubility is the solubility of neutral form of ionizable compounds. Intrinsic solubility for drug and drug-like molecules were determined in high throughput solubility measurement in drug discovery and development processes [14].

An experimental data set composed of 86 intrinsic aqueous solubility of drugs was reported by Box and Comer and data fitted to the Hansch equation [15] (Eq. [**5**]):

$$\log S_w = -1.03\,\log P - 0.54 \quad [5]$$

In another article, Chu & Yalkowsky used this data set to compare the accuracy of the Hansch and GSE models after excluding five data points [16] and concluded that *logP* with *mp* (that shows the role of the crystalinity of drugs), are necessary for predicting the solubility of drugs in water.

In this study, the role of the excess molar refraction in predicting the intrinsic aqueous solubility of a wide variety of organic compounds is revisited and the accuracy of the proposed model was compared with those of Hansch, Yalkowsky and Abraham models.

EXPERIMENTAL

Experimental intrinsic aqueous solubility, *logP* and *mp* data for 81 drugs were extracted from the study of Box & Comer [15]. Abraham solvation descriptors and calculated *logP* were computed by Pharma-Algorithm software [17]. Correlations between logarithm of the aqueous solubility with *logP, mp* and *E* were investigated and also correlation between experimental and calculated *logP* was done. Solubilities were calculated by Hansch, GSE, Abraham and the proposed model. Accuracies of the models were calculated by three different criteria including the average absolute error (AAE), root mean square error (RMSE) criteria and mean percentage deviation (MPD) which are defined as Eqs. [**6**], [**7**], and [**8**], respectively:

$$AAE = \frac{\sum \left| \log S_w^{\,observed} - \log S_w^{\,calculated} \right|}{N} \quad [6]$$

$$RMSE = \sqrt{\frac{\sum \left(\log S_w^{\,observed} - \log S_w^{\,calculated} \right)^2}{N}} \quad [7]$$

$$MPD = \frac{100}{N} \sum \left| \frac{S_w^{calculated} - S_w^{observed}}{S_w^{observed}} \right| \quad [8]$$

RESULTS AND DISCUSSION

Table 1 lists the name of drugs, the experimental and predicted aqueous solubilities of drugs using four mentioned models and the corresponding descriptors for each compound. Table 2 shows the overall deviations of different models expressed as three error criteria. Similar patterns were observed for the accuracy criteria using the prediction data set of this work and another prediction data set used in a previous work [13] revealing the robustness of the models. The AAE and RMSE criteria are in logarithmic scale and therefore the resulting numbers are small. These terms were frequently used in the

Compound	*mp**	*ElogP*	*ClogP* (Biobyte Crop)	*ClogP* (Pharma-Algorithm software)	*A*	*B*	*S*	*E (0.1 cm^3mol^{-1})*	*V (0.01 cmm^3mol^{-1})*	$logS_w$ (Exp)	$logS_w$ (cal, Hansch)	$logS_w$ (*Cal, GSE*)	$logS_w$ (Cal, Abraham)	$logS_w$ (Cal, The proposed model)
1-naphthol	95	2.85	2.65	2.84	0.50	0.45	1.23	1.50	1.14	-1.98	-3.48	-2.85	-2.59	-3.38
2-naphthoic acid	186	3.28	3.06	3.29	0.57	0.50	1.40	1.47	1.30	-3.78	-3.92	-4.17	-2.83	-3.62
4-hydroxybenzoic acid	215	1.58	1.56	1.40	1.00	0.72	1.29	0.98	0.99	-1.45	-2.17	-2.96	-0.49	-1.94
4-iodophenol	94	2.91	2.89	2.92	0.67	0.40	1.16	1.42	1.03	-1.72	-3.54	-3.08	-2.17	-3.34
alprenolol	58	3.10	2.65	2.94	0.29	1.36	1.12	1.18	2.16	-2.63	-3.73	-2.48	-3.11	-3.08
amantadine	180	2.41	2.00	2.21	0.21	0.64	0.68	0.84	1.29	-1.86	-3.02	-3.05	-2.27	-2.26
amitriptyline	25	5.04	4.85	5.40	0.21	0.64	0.68	0.84	1.29	-4.39	-5.73	-4.35	-2.27	-4.18
amodiaquin	208	4.20	4.51	3.65	0.63	1.52	2.32	2.70	2.74	-5.94	-4.87	-5.84	-5.63	-5.21
astemizole	149	5.70	6.09	6.25	0.13	1.64	2.70	3.10	3.56	-5.93	-6.41	-6.83	-8.22	-7.22
atenolol	147	0.22	-0.11	1.81	0.78	1.85	1.97	1.48	2.18	-1.29	-0.77	-0.61	-1.85	-2.74
bendroflumethiazide	222	1.95	1.69	1.96	1.01	1.84	2.89	2.28	2.55	-4.33	-2.55	-3.16	-3.66	-3.73
benzocaine	92	1.89	1.92	2.04	0.23	0.76	1.43	0.94	1.31	-2.23	-2.49	-2.09	-1.82	-2.27
benzoic acid	122	1.87	1.88	2.04	0.66	0.38	0.83	0.86	0.93	-1.61	-2.47	-2.35	-1.46	-2.19
benzthiazide	232	1.73	2.13	2.35	0.81	1.84	3.00	3.04	2.74	-4.83	-2.32	-3.70	-4.93	-4.81
carprofen	198	4.29	3.98	3.83	0.88	0.74	1.88	2.29	1.93	-4.71	-4.96	-5.21	-4.72	-4.86
chloroquine	<25	4.99	5.05	5.19	0.13	1.29	1.63	1.85	2.63	-3.89	-5.68	-4.55	-5.41	-5.18
chlorpheniramine	<25	3.39	3.15	2.55	0.00	1.02	1.49	1.52	2.21	-2.66	-4.03	-2.65	-4.62	-3.23
chlorpromazine	<25	5.40	5.80	5.32	0.00	0.99	1.83	2.26	2.41	-5.08	-6.1	-5.30	-5.97	-5.72
chlorprothixene	98	5.48	5.48	5.30	0.00	0.88	1.57	2.21	2.40	-6.30	-6.18	-5.71	-6.35	-5.65
chlorzoxazone	192	2.11	1.87	2.55	0.50	0.72	1.45	1.55	1.05	-2.61	-2.71	-3.04	-1.46	-3.26
ciprofloxacin	256	-1.08	-1.17	-0.70	0.73	1.85	2.50	2.20	2.30	-3.60	0.57	-0.64	-2.78	-2.04
deprenyl	<25	2.90	2.52	2.75	0.09	0.71	1.00	1.00	1.72	-2.52	-3.53	-2.02	-3.59	-2.77
desipramine	<25	4.21	4.47	4.19	0.13	0.90	1.58	1.80	2.26	-3.44	-4.88	-3.97	-5.36	-4.53
diclofenac	284	4.51	4.32	4.29	0.70	0.67	1.95	1.81	2.03	-5.45	-5.19	-6.41	-4.83	-4.60
diphenhydramine	<25	3.44	3.54	3.23	0.00	0.95	1.43	1.36	2.19	-2.93	-4.08	-3.04	-4.64	-3.46
famotidine	164	-0.81	0.26	-0.80	1.21	2.78	2.24	2.69	2.26	-2.66	0.29	-1.15	-1.18	-2.53
flufenamic	134	5.56	4.88	4.48	0.72	0.59	1.36	1.26	1.83	-5.35	-6.27	-5.47	-4.06	-4.09
flumequine	255	1.72	2.73	1.31	0.57	1.16	1.95	1.70	1.79	-3.88	-2.31	-4.53	-2.65	-2.69
fluoxetine	<25	4.61	4.57	4.65	0.13	0.78	1.19	1.01	2.24	-3.92	-5.29	-4.07	-5.04	-3.92
flurbiprofen	111	4.16	3.75	3.54	0.57	0.58	1.51	1.50	1.84	-4.11	-4.82	-4.11	-4.39	-3.80
folic acid	250	0.20	-2.17	-0.36	1.95	3.14	3.74	3.24	3.04	-5.31	-0.75	0.42	-3.95	-3.41
furosemide	295	2.56	1.87	2.27	1.25	1.50	2.37	2.07	2.10	-4.23	-3.18	-4.07	-2.97	-3.68
glipizide	209	2.58	2.53	2.63	0.85	2.19	3.71	2.52	3.30	-5.49	-3.2	-3.87	-5.15	-4.40
haloperidol	152	4.30	3.85	3.31	0.31	1.45	2.08	2.00	2.80	-5.47	-4.97	-4.62	-5.44	-4.22
hydrochlorothiazide	274	-0.07	-0.4	-0.38	1.01	1.76	2.77	2.15	1.73	-2.68	-0.47	-1.59	-1.04	-2.18
ibuprofen	76	3.97	3.68	3.44	0.57	0.51	1.01	0.78	1.78	-3.61	-4.63	-3.69	-3.85	-2.93
imipramine	<25	4.42	5.04	4.58	0.00	0.95	1.59	1.81	2.40	-4.21	-5.09	-4.54	-5.73	-4.77
lidocaine	69	2.44	1.95	1.66	0.26	1.17	1.50	1.10	2.06	-1.85	-3.05	-1.89	-3.16	-2.23
loperamide	228	4.87	4.68	3.86	0.31	1.88	2.90	2.76	3.77	-7.13	-5.56	-6.21	-7.85	-5.40
maprotiline	93	4.85	4.52	5.10	0.13	0.68	2.67	1.76	2.33	-4.69	-5.54	-4.70	-5.91	-5.03
meclofenamic acid	257	5.90	5.92	5.58	0.65	0.62	1.68	1.87	2.03	-6.86	-6.62	-7.74	-5.14	-5.44
mefenamic acid	231	5.33	4.94	4.35	0.65	0.70	1.47	1.65	1.92	-6.34	-6.03	-6.50	-4.44	-4.45
metoclopramide	147	2.74	2.21	2.27	0.50	1.63	2.31	1.50	2.34	-3.59	-3.36	-2.93	-2.85	-3.04
metoprolol	120	1.95	1.35	1.72	0.29	1.52	1.22	1.10	2.26	-1.21	-2.55	-1.80	-2.86	-2.26
nadolol	130	0.71	0.38	0.54	0.83	1.90	1.56	1.68	2.49	-1.57	-1.27	-0.93	-3.10	-2.21

naproxen	153	3.24	2.82	3.01	0.57	0.75	1.49	1.54	1.78	-4.14	-3.88	-3.60	-3.77	-3.53
niflumic acid	203	3.88	3.79	3.92	0.72	0.77	1.42	1.33	1.79	-4.47	-4.54	-5.07	-3.49	-3.84
nitrofurantoin	263	-0.54	-0.47	0.31	0.24	1.34	2.03	1.65	1.45	-3.33	0.02	-1.41	-0.98	-2.03
norfloxacin	228	-1.03	-0.99	0.88	0.73	1.84	2.43	1.98	2.27	-2.75	0.52	-0.54	-2.51	-2.74
nortriptyline	58	4.39	4.31	5.02	0.13	0.72	1.30	1.69	2.26	-3.99	-5.06	-4.14	-5.90	-4.90
orphenadrine	<25	3.84	3.99	3.64	0.00	0.95	1.38	1.39	2.33	-3.17	-4.5	-3.49	-5.15	-3.74
papaverine	148	2.95	3.77	3.70	0.00	1.47	2.76	2.19	2.59	-4.30	-3.58	-4.50	-4.66	-4.67
paracetamol	170	0.46	0.49	0.23	0.91	0.93	1.66	1.12	1.17	-1.00	-1.01	-1.44	-0.63	-1.39
phenobarbital	174	1.47	1.37	1.40	0.52	1.29	1.81	1.56	1.70	-2.28	-2.05	-2.36	-1.90	-2.59
phenylbutazone	105	3.25	3.38	3.21	0.00	1.63	2.45	2.15	2.43	-4.39	-3.89	-3.68	-3.67	-4.33
phthalic acid	230	0.85	0.73	1.32	1.14	0.77	1.46	0.94	1.15	-1.49	-1.42	-2.28	-0.72	-1.84
pindolol	169	1.83	1.49	2.15	0.60	1.51	1.53	1.70	2.01	-3.79	-2.42	-2.43	-2.53	-3.19
piroxicam	199	1.98	1.89	2.39	0.72	2.12	3.12	2.56	2.25	-4.75	-2.58	-3.13	-2.01	-4.30
pramoxine	<25	3.56	4.17	4.39	0.00	1.24	1.38	1.09	2.43	-3.02	-4.21	-3.67	-4.27	-3.85
probenecid	195	3.70	3.37	3.40	0.57	1.29	1.92	1.25	2.16	-4.86	-4.35	-4.57	-3.09	-3.44
procaine	61	2.14	2.54	2.19	0.23	1.27	1.62	1.11	1.98	-1.72	-2.74	-2.40	-2.56	-2.56
prochlorperazine	<25	4.88	4.90	4.93	0.00	1.47	2.11	2.63	2.82	-4.87	-5.57	-4.40	-6.05	-5.90
promethazine	60	4.56	4.90	4.23	0.00	1.09	1.72	2.14	2.28	-4.19	-5.24	-4.75	-5.15	-4.93
propranolol	96	3.48	2.75	3.04	0.29	1.36	1.44	1.76	2.15	-3.50	-4.12	-2.96	-3.53	-3.79
pyrimethamine	234	2.69	2.91	2.51	0.45	0.99	2.01	2.26	1.85	-4.10	-3.31	-4.50	-3.87	-4.03
quinacrine	87	5.44	6.71	6.40	0.13	1.56	2.05	2.63	3.20	-4.35	-6.15	-6.83	-7.06	-6.78
quinine	57	3.50	2.79	2.29	0.23	1.81	1.71	2.40	2.55	-2.81	-4.15	-2.61	-4.01	-4.06
sertraline	<25	4.30	5.35	4.90	0.13	0.67	1.44	1.83	2.26	-4.84	-4.97	-4.85	-6.17	-4.98
sulfamerazine	236	0.15	0.57	0.33	0.59	1.41	2.52	2.10	1.86	-3.10	-0.69	-2.18	-2.39	-2.55
sulfasalazine	220	3.61	3.83	3.74	1.07	1.57	2.76	2.92	2.70	-6.28	-4.26	-5.28	-5.48	-5.51
sulfathiazole	189	0.07	0.72	0.87	0.59	1.21	2.60	2.06	1.69	-2.70	-0.61	-1.86	-2.30	-2.83
sulindac	183	3.42	3.16	3.67	0.57	1.39	2.72	2.26	2.57	-4.52	-4.06	-4.24	-4.89	-4.73
terfenadine	147	5.42	6.09	5.90	0.63	1.80	2.04	2.55	4.01	-7.74	-6.12	-6.81	-9.05	-6.39
tetracycline	173	-1.40	-0.91	-0.34	1.73	3.27	3.59	3.36	3.10	-3.09	0.90	-0.07	-3.78	-3.56
thymol	52	3.30	3.20	3.15	0.50	0.42	0.78	0.84	1.34	-2.19	-3.94	-2.97	-2.84	-2.83
thyroxine	236	3.21	3.49	2.39	1.03	1.31	2.83	4.14	3.07	-4.26	-3.85	-5.10	-8.49	-6.07
tolmetin	156	2.79	2.21	2.92	0.57	0.97	1.93	1.54	1.98	-4.13	-3.41	-3.02	-3.67	-3.47
tramadol	80	2.65	3.10	2.24	0.31	1.30	1.15	1.23	2.23	-2.24	-3.27	-3.15	-3.58	-2.72
trichlormethiazide	270	0.97	0.85	0.53	1.09	1.78	2.95	2.38	2.12	-3.41	-1.54	-2.80	-2.46	-2.98
verapamil	<25	3.98	4.47	4.86	0.00	1.89	3.00	1.76	3.79	-3.97	-4.64	-3.97	-6.78	-4.88
warfarin	161	3.54	0.31	2.33	0.31	1.23	2.28	1.98	2.31	-4.77	-3.75	-4.39	-3.61	-3.61

Table 1. Experimental and predicted solubility of drugs with four different models and the corresponding descriptors for each compound. * *mp* data were taken from references [15,16].

Model	AAE	RMSE	MPD (%)
Results of this work			
Hansch	1.200	1.533	83358.2
GSE	0.785	1.147	666081.9
Abraham	1.121	1.305	1702.6
The proposed model	0.743	0.906	605.0
Results of a previous work [13]			
GSE	0.822	-	6234.9
Abraham	1.179	-	6813.2
The proposed model	0.670	-	758.4

Table 2. Deviations of four investigated models in this study.

literature, however, by concerning them as accuracy criteria it is hard to judge on the practical applicability of a predictive model. The MPD is an adapted term from relative standard deviation (RSD) which is commonly used to report the reproducibility and repeatability of of an experimental procedure. We prefer this criterion since it could be directly compared with the RSD values of a repeated experiment by various research groups and/or by a given research group in different days. As an example, the overall mean of the RSD values for a solubility experiment within a given laboratory is around 4 % and it could be increased between different

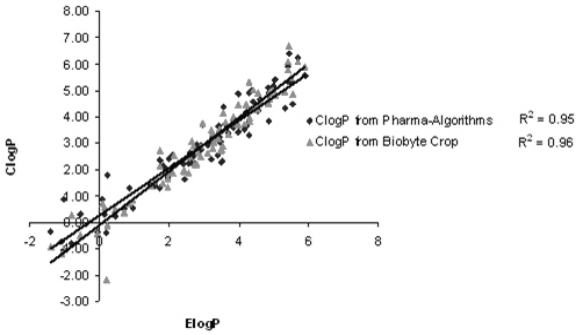

Figure 1. Correlation between *ElogP* and *ClogP* calculated by two different software.

laboratories (ranging from 17 % to 988 % (for details see Table 7 of reference [20]). A number of reasons could be considered for these variations including: solute purity, insufficient equilibration time, temperature variations, analytical methods used for quantification of the dissolved drug, laboratory techniques, typographical errors, polymorphism and enantiomeric forms of the drug [21]. If any computational method could predict the solubility with the MPD of less than 4 %, it means that the method is able to predict the data perfectly and no further experiments are required. It should be added that there is no such a model to predict an important property of drugs, i.e. aqueous solubility, within an acceptable error levels and the efforts should be continued to develop more accurate models. The results show that AAE, RMSE and MPD of the proposed model are lower than Hansch, GSE and Abraham models. There are good correlations between MPD and AAE or RMSE values of the solubility models as have been shown in a previous work [22] (see Fig. 5 of reference [22]).

The numerical values of the descriptors could affect the prediction capability of a model and there are possibilities of using experimental or calculated *logP* values for the drugs. The results of numerical analysis showed that there are good correlations between experimental and computational *logP* values. Figure 1 shows the correlation between experimental *logP* (*ElogP*) with calculated *logP* (*ClogP*) computed by Biobyte Corp [16] and Pharma-Algorithms [17] software that were used in GSE and the proposed model, respectively, in which *ClogP* calculated by Biobyte Corp and Pharma-Algorithms show good correlation with *ElogP* (R > 0.95). There is no significant difference between calculated $logS_w$ of the proposed model using *ElogP* and *ClogP* calculated by Biobyte Corp and Pharma-Algorithms (AAE of 0.762, 0.760 and 0.743, respectively). Computation of *ClogP* is straightforward and no experimental efforts are required, therefore we recommend to use *ClogP* instead of *ElogP* in the predictions.

Figure 2 represents correlation between $logS_w$ with *ClogP* (calculated by Pharma-Algorithm software), *E* and *mp*. Correlation coefficient (R) between $logS_w$ with *ElogP, mp* and *E* are 0.57, 0.21, and 0.54, respectively. So these results prove that *logP* is very critical descriptor in predicting the aqueous solubility of drugs. Another useful descriptor is *E* that is correlated with *logP* better than *mp*. Furthermore, experimental determination of *mp* with high or low values is questionable [18] and there is no available computational method to predict *mp* with reasonable prediction error. The *E* is composed of two descriptors: the *V* and molar refraction (*MRx)* that are indicators of aqueous solubility of a compound because these descriptors can be calculated by atomic fragmental and the number of bonds in the molecule [13].

Eric *et al*. showed that uniform experimental data improve the accuracy of models and updating existing data sets leads to change accuracy of the solubility prediction model in the literature [19]. But the AAE of calculated solubility using trained model by intrinsic solubility data in this study is 0.727 and calculated solubility using trained model by apparent solubility in previous work is 0.743 [13]. Careful review of the results revealed that the proposed model could be employed to predict the apparent and/or intrinsic solubility of drugs.

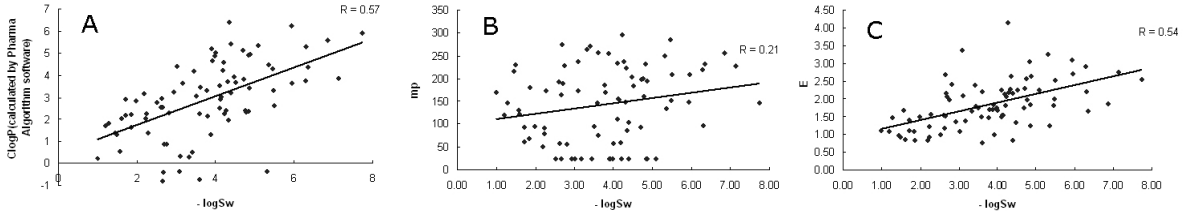

Figure 2. Correlation between aqueous intrinsic solubility ($logS_w$) with (**A**) experimental *logP(Elog P)* (**B**) melting point (*mp,* °C) and (**C**) excess molar refraction (*E*).

CONCLUSION

E is a crucial descriptor for aqueous solubility prediction, *logP* is a well-established descriptor employed in most of aqueous solubility prediction methods and their combination as a multiple linear regression model works perfectly. The accuracy of the proposed QSPR model is better than three mentioned famous models. The proposed model could be applied for aqueous intrinsic solubility estimation of drugs and drug-like molecules and provides a useful computational tool for drug discovery and development investigations. Its prediction capability is the most accurate among other models, but it is not a perfect method and further investigations are required to provide better prediction tools.

REFERENCES

1. Jouyban, A., M.A.A. Fakhree & A. Shayanfar (2008) *Res. Pat. Chem. Eng.* **1**: 220-31.
2. Hansch, C., J.E. Quinlan & G.L. Lawrence (1968) *J .Org. Chem.* **33**: 347-50.
3. Katritzky, A.R., M. Kuanar, S. Slavov, C.D. Hall, M. Karelson, I. Kahn *et al.* (2010) *Chem. Rev.* **110**: 5714–89.
4. Ran, Y., N. Jain & S.H. Yalkowsky (2001) *J. Chem. Inf. Comput. Sci.* **41**: 1208-17.
5. Stovall, D.M., C. Givens, S. Keown, K.R. Hoover, R. Barnes, C. Harris *et al.* (2005) *Phys. Chem. Liq.* **43**: 351-60.
6. Abraham, M.H. & J. Le (1999) *J. Pharm. Sci.* **88**: 868-80.
7. Abraham, M.H., A. Ibrahim & A.M. Zissimos (2004) *J. Chromatogr. A* **1037**: 29-47.
8. Abraham, M.H., A. Ibrahim, A.M. Zissimos, Y.H. Zhao, J. Comer & D.P. Reynolds (2002) *Drug Discov. Today* **7**: 1056-63
9. Abraham, M.H., R.E. Smith, R. Luchtefeld, A.J. Boorem, R. Lou & W.E. Acree Jr. (2010) *J. Pharm. Sci.* **99**: 1500-15.
10. Faller, B. & P. Ertl (2007) *Adv. Drug Deliv. Rev.* **59**: 533-45.
11. Dearden, J.C. (2006) *Expert Opin. Drug Discov.* **1**: 31-52.
12. Taskinen, J., U. Norinder, B.T. John & J.T. David (2007) *In silico predictions of solubility,* in: Taylor J.B., Triggle D.J. – Comprehensive Medicinal Chemistry II – Elsevier, Oxford, , pp. 627-48.
13. Shayanfar, A., M.A.A. Fakhree & A. Jouyban (2010) *J. Drug Del. Sci. Tech.* **20**: 467-76.
14. Alsenz, J. & M. Kansy (2007) *Adv. Drug Deliv. Rev.* **59**: 546-67.
15. Box, K.J. & J.E.A. Comer (2008) *Current Drug Metab.* **9**: 869-78.
16. Chu, A.K. & S.H. Yalkowsky (2009) *Current Drug Metab.* **10**: 1184-91.
17. Pharma-Algorithms (2008) ADME Boxes, Version 4.0, PharmaAlgorithms Inc., Toronto, Canada.
18. Delaney, J.S. (2005) *Drug Discov. Today* **10**: 289-95.
19. Eric S., M. Kalinici, A. Popovici, H. Makic, E. Civic & M. Bektasevic (2010) *J. Serb. Chem. Soc.* **75**: 483-95.
20. Jouyban A. (2008) *J. Pharm. Pharmaceut. Sci.* **11**: 32-58.
21. Jouyban A. (2009) *Handbook of Solubility Data for Pharmaceuticals,* CRC Press, Boca Raton.
22. Jouyban A., Sh. Soltanpour, S. Soltani & W.E. Acree Jr. (2007) *J. Pharm. Pharmaceut. Sci.* **10**: 263-77.