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QSAR treatment of drugs transfer into human breast milk

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Abstract—A satisfactory model is developed using CODESSA PRO for the correlation and prediction of milk to plasma concentration ratios (*M*/*P* ratio) for diverse pharmaceuticals. A set of experimentally derived *M*/*P* ratio values were collected from the literature for 115 widely used pharmaceuticals. The experimental logarithmic *M*/*P* ratios were tested with more than 850 theoretical molecular descriptors including constitutional, topological, geometrical, quantum chemical, thermodynamic, and electrostatic types. Based on the data set, for 100 commonly used drugs, a seven-parameter QSAR model was derived that shows a satisfactory ($R^2 = 0.791$) correlation between predicted and observed values of log(*M*/*P*) ratio.

1. Introduction

Breast feeding is highly beneficial to the health of both mothers and infants: breast milk is the ideal food source for infants providing, among other important benefits, enhanced protection to the infants against many common infectious diseases.[1] Human milk reduces exposure to contaminated food sources, enhances nutritional status and prevents infections.[2] Breast feeding has psychological and physiological benefits for the mother; thus the incidence of pre-menopausal breast cancer is decreased for women with a longer duration of breast feeding. Breast feeding has been shown to enhance mother–infant bonding and may enhance both maternal self-esteem and self-efficacy by allowing a mother to provide very personal and optimal nourishment to her infant.[3] Because of the significant role of breast milk, the investigation of contamination from mother's medication in her breast milk is important.

Many women need to take medication while breast feeding. The accumulation of a specific medication in milk is associated with a risk to the infant that can exceed the benefits of breast feeding.[4] Several factors such as molecular weight, lipid–water solubility, ionization of the drug, protein bonding and pH of the milk or drug are concerned in the accumulation of a drug in breast milk and its absorption by the baby.[5]

The milk to plasma concentration ratio (*M*/*P* ratio) of a drug is generally used to estimate the infant's exposure to drugs through breast milk. The *M*/*P* ratio is an attempt to quantify the equilibrium concentration between breast milk and blood. It is equivalent to the drug concentration in the breast milk (BM) divided by its concentration in the maternal plasma (MP).[6]

Theoretically, the *M*/*P* ratio can be expressed by Eq. 1

$$M/P = \frac{c^{\mathrm{d}}_{\mathrm{BM}}}{c^{\mathrm{d}}_{\mathrm{MP}}} \tag{1}$$

where

M/*P*: the milk to plasma concentration ratio,
$c^{\mathrm{d}}_{\mathrm{BM}}$: the drug concentration in human breast milk,
$c^{\mathrm{d}}_{\mathrm{MP}}$: the drug concentration in human maternal plasma.

Due to the complex nature of milk, there are several factors that can affect the evaluation of the concentration ratio between milk and plasma. Rasmussen[7–9] observed the influence of pH differential between milk and plasma and assumed that only the unbound, unionized form of a molecule may traverse the membranes in the

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mammary alveoli. However, unbound drugs may also (i) bind to proteins in milk and plasma, and (ii) partition into fat globules in milk.[10] It is generally assumed that passive diffusion is the process that controls the transfer of drugs between milk and plasma, and this holds for many drugs.[11] However, several unexplained but significant differences between the values expected and obtained for *M*/*P* ratios, suggest that active transport processes are also present in the mammary gland. Indeed, McNamara and co-workers[12,13] confirmed that cimetidine and nitrofurantoin were transferred into human milk by active transport. The involvement of two organic cation transporters in the active transfer of cimetidine and nitrofurantoin into human milk was also suggested.[14]

Although the *M*/*P* ratio is useful for the estimation of drug concentrations in breast milk, there are difficulties in obtaining reliable and reproducible measurements.[15] The quality of the experimental milk to plasma concentration values is of critical importance for building a reliable predictive model. It is difficult to enroll nursing women in a trial solely to assess the pharmacokinetics of a compound in milk and plasma. The accurate determination of the milk to plasma ratio requires careful attention to experimental detail in the collection of serial milk and plasma samples as well as judicious selection of human subjects.[10]

The tendency for a drug to accumulate in human milk is almost never known when a drug appears on the market, and it is seldom measured subsequently, which poses difficulties for clinicians who need to advise women on the safety of breast feeding.[4] Lack of knowledge of the concentration of a drug in breast milk increases the difficulty in assessing the risk to the infant of exposure to these agents through nursing. Unfortunately, for many common drugs the *M*/*P* ratio value is not known. Therefore, even an approximate prediction of the experimental concentration of a drug in breast milk for given dosage to the mother would be very useful in a clinical setting.

Predictions of *M*/*P* ratio of some drugs in breast milk have been investigated in several publications. Atkison and Begg[16] classified nearly 50 drugs into acidic, basic, and neutral groups. They performed calculations on *M*/*P* ratio values of drug molecules using a phase distribution model, and then compared these calculated *M*/*P* ratio values with experimental *M*/*P* ratio values collected from literature using multiple linear regression analyses. The logarithmic scale was used in their model. After refining the data of the initial set, the multiple linear regressions analysis gave $R^2 = 0.9306$ for 15 acidic drugs and $R^2 = 0.829$ for 27 basic drugs, respectively. However, the experimental *M*/*P* ratios for several drugs (penicillin, cimetidine etc.) are reported as questionable. Atkison and co-workers[17] attempted to predict *M*/*P* ratio values for 10 basic drugs by a model utilizing p*K*a, plasma–protein binding and octanol/water partition coefficients. The predicted *M*/*P* ratio values were compared with experimental *M*/*P* ratio values using multiple regression analysis ($R^2 = 0.970$).

Agatonovic-Kustrin et al.[18] used a set of 60 drug compounds to correlate *M*/*P* ratios using an artificial neural network. A total of 61 calculated structural descriptors, including constitutional, topological, geometrical, and quantum chemical, were generated for each of the 60 compounds. They obtained a fit of 0.96 for the best neural network model (26-5-5-1) by the correlation of predicted versus experimentally derived *M*/*P* ratio. The same author subsequently[6] used experimentally derived *M*/*P* values of 123 drugs and 71 molecular descriptors to test and validate a nine-descriptor nonlinear computational neural network model. The model included the percent of oxygen, parachor, density, highest occupied molecular orbital (HOMO), topological indices, and shape indices. The developed model indicates that molecular size (parachor, density), shape (topological indices, molecular connectivity indices), and electronic properties are all important for drug transfer into breast milk.

Larsen et al.[4] treated 69 compounds using Atkinson's phase model, but no significant correlation was obtained. It was concluded that three physicochemical characteristics are not sufficient to describe the complex movement of xenobiotics across the mammary epithelium. A comprehensive review of QSAR/QSPR studies for the prediction of *M*/*P* ratio has been published by Fleishaker.[10]

Major pharmaceutical companies all devote considerable effort toward the elucidation of structural effects on biological properties, particularly of medicinally useful compounds. Quantitative structure–property relationship/activity relationship (QSPR/QSAR) methodology is an essential tool in medicinal chemistry.[19] In recent years, methodology for a general QSAR/QSPR approach has been developed and coded as the CODESSA PRO software package. CODESSA PRO enables the calculation of numerous quantitative descriptors solely on the basis of molecular structural information.[20,21] Research using CODESSA PRO has successfully correlated and predicted many diverse physical properties[22] including gas chromatographic properties, quantitative structure–toxicity relationships, melting and boiling point, solvent scales, and refractive indexes.[23] Recently, the QSPR treatments of (i) the binding energies for 1:1 complexation systems between various organic guest molecules and β-cyclodextrin,[24] (ii) the in vitro minimum inhibitory concentration (MIC) of 3-aryloxazolidin-2-one antibacterials required to inhibit growth of *Staphylococcus aureus*[25] and have been reported.

The present investigation attempts to develop a correlation for the prediction of *M*/*P* ratios of drugs in human breast milk using theoretical molecular descriptors calculated by the CODESSA PRO software.

2. Results

2.1. Data set

A set of 115 drug compounds (Table 1) and their experimentally derived milk to plasma concentration ratio

Table 1. Experimental and predicted values of log(*M*/*P*) ratio for 115 various drugs

No.	Drug	*M*/*P*	Average	log(*M*/*P*) obs.	log(*M*/*P*) pred.	log(*M*/*P*) err.	Ref.
1	Acetaminophen	0.81		−0.092	−0.207	0.116	26
2	Acyclovir	2.35		0.371	0.108	0.263	27
3	Alprazolam	0.36		−0.444	−0.348	−0.095	28
4	Amitriptyline	0.83		−0.081	−0.228	0.147	29
5	Amphetamine	5.15		0.712	0.685	0.027	30
6	Ampicillin	0.295		−0.530	−0.077	−0.453	31
7	Atenolol	4.5	2.692	0.315	0.254	0.176	32
		1.1–3.1					33
		2.07[c]					34
8	Aztreonam[a]	0.005	0.007	−2.155	−2.067	−0.088	35
		0.009					35
9	Baclofen	0.82		−0.086	0.010	−0.096	35
10	Bupivacaine	0.37		−0.432	0.019	−0.451	36
11	Bupropion	5.545		0.744	0.401	0.344	37
12	Caffeine	0.51		−0.292	−0.182	−0.110	38
13	Captopril[b]	0.031					39
14	Carbenicillin	0.02		−1.699	−1.542	−0.157	40
15	Cefotaxime[b]	0.065					41
16	Cefprozil	0.628		−0.202	−0.626	0.424	42
17	Ceftriaxone	0.04		−1.398	−1.562	0.164	43
18	Cephalothin[b]	0.14					44
19	Cephapirin[b]	0.13					44
20	Chloramphenicol[a]	0.58	0.655	−0.184	−0.395	0.211	40
		0.73					45
21	Chloroprothixene	1.16		0.065	−0.116	0.181	46
22	Chloroquine	1.96[c]–4.26		0.293	0.104	0.188	47
23	Cimetidine	1.7		0.230	0.525	−0.295	48
24	Ciprofloxacin	2.81		0.533	0.151	0.382	49
25	Citalopram	1.8		0.255	0.162	0.093	50
26	Codeine	2.16		0.335	0.342	−0.007	26
27	Colchicine[b]	0.44					51
		1.82					51
		0.59					51
28	Cotinine	0.78		−0.108	−0.049	−0.059	52
29	Dapsone[a]	0.22–0.45		−0.475	−0.543	0.068	47
30	Decarboetoxyloratadine[b]	0.8					53
31	Demethylcitalopram	1.75		0.255	0.222	0.033	50
32	Desipramine	1.45		0.161	0.356	−0.195	54
33	Diazepam	0.16		−0.796	−0.536	−0.260	55
34	Digoxin	0.55		−0.260	−0.187	−0.073	56
35	Diltiazem	0.98		−0.092	−0.207	0.116	57
36	Disopyramide	1.03		0.013	−0.850	0.863	29
37	Dothiepin-*S*-oxide[b]	1.18					58
38	Doxepin	1.37		0.137	−0.248	0.385	59
39	Doxorubicin	1.19		0.076	−0.100	0.176	60
40	Erythromycin	0.41		−0.387	−0.225	−0.162	40
41	Ethanol	0.89		−0.051	0.151	−0.201	61
42	Ethosuximide[a]	0.78	0.82	−0.086	−0.377	0.291	62
		0.86					63
43	Fentanyl	2.45		0.389	0.015	0.374	64
44	Flecainide[b]	2.54					65
45	Fluconazole	0.74		−0.131	−0.400	0.269	66
46	Fluoxetine	0.68		−0.168	−0.225	0.057	67
47	Flurbiprofen	0.019		−1.721	−0.938	−0.784	68
48	Fluvoxamine	1.32		0.121	−0.103	0.223	69
49	Hydrochlorothiazide	0.95[c]	0.5	−0.301	−0.393	0.092	70
		0.05					71
50	Indomethacin[b]	0.75					72
51	Labetalol[a]	0.8–2.6		0.230	0.117	0.114	73
52	Lamotrigine	0.6		−0.222	−0.179	−0.042	74
53	Levodopa[a]	0.32–0.28		−0.523	−0.529	0.006	75
54	Loratadine[b]	1.2					53
55	Medroxyprogesterone	0.72		−0.143	−0.424	0.281	76
56	Mepindolol	0.38		−0.415	0.252	−0.667	77
57	Methadone	0.83		−0.081	−0.250	0.169	78
58	Methotrexate	0.04		−1.398	−1.538	0.140	79
59	Metoclopramide	0.915		−0.039	−0.028	−0.011	80

(*continued on next page*)

Table 1 (*continued*)

No.	Drug	*M*/*P*	Average	log(*M*/*P*) obs.	log(*M*/*P*) pred.	log(*M*/*P*) err.	Ref.
60	Metoprolol	2.81		0.506	0.357	0.149	81
61	Metronidazole[a]	1.08	1.03	0.013	0.148	−0.135	82
		0.98					83
62	Mexiletine	1.48		0.170	0.351	−0.181	84
63	Midazolam	0.09		−1.046	−0.760	−0.286	85
64	Minoxidil	0.76		−0.137	0.052	−0.189	86
65	Moclobemide	0.8		−0.167	0.177	−0.344	87
66	Morphine	2.46		0.391	0.409	−0.018	26
67	Nadolol	4.6		0.663	0.593	0.070	88
68	Naproxen[b]	0.16					89
69	*N*-Demethylsertraline	1.64		0.215	−0.029	0.244	90
70	*N*-Desmethyldoxepin	1.275		0.106	−0.228	0.334	59
71	Nefazodone	0.27		−0.569	−0.032	−0.537	91
72	Nefopam	1.2		0.079	0.170	−0.091	92
73	Nicotine	2.92		0.465	0.388	0.077	52
74	Nitrendipine	0.3		−0.523	−0.831	0.309	93
75	Nitrofurantoin[b]	6.21					13
76	Nordothiepin	0.85		0.043	−0.078	0.121	58
77	Nordothiepin sulfoxide[b]	1.86					58
78	Norethisterone	0.175		−0.757	−0.384	−0.373	94
79	Norfluoxetine	0.56		−0.252	−0.412	0.161	67
80	Nortriptyline	0.65		−0.187	−0.176	−0.011	29
81	Noscapine	0.29		−0.538	−0.984	0.447	95
82	Ofloxacin[b]	1.19					49
83	*O*-desmethylvenlafaxine	3.06		0.486	0.604	−0.118	96
84	Oxazepam	0.1		−1.000	−0.610	−0.390	97
85	Oxprenolol	0.37		−0.432	−0.123	−0.309	98
86	Paracetamol[a]	0.76	0.785	−0.105	−0.137	0.031	99
		0.81					26
87	Paroxetine[a]	0.39	0.6	−0.222	−0.086	−0.136	100
		0.69					101
		0.72					101
88	Pefloxacin	0.96		−0.018	−0.171	0.154	38
89	Penicillin	0.37		−0.432	−0.730	0.298	40
90	Perfenazine	0.9		−0.046	−0.473	0.427	102
91	Pethidine	1.25		0.097	−0.023	0.119	91
92	Phenacetine	0.67		−0.174	−0.124	−0.049	26
93	Phenytoin[a]	0.13	0.155	−0.810	−0.895	0.086	62
		0.18					63
94	Prednisolone	0.13		−0.886	−0.417	−0.469	103
95	Procainamide	3.18		0.502	0.235	0.268	104
96	Propranolol[a]	0.32	0.48	−0.319	0.310	−0.629	105
		0.36					106
		0.76					105
97	Pseudoephedrine	2.5		0.398	0.464	−0.066	107
98	Pyrimethamine	0.46–0.66		−0.252	−0.386	0.134	47
99	Quazepam[b]	4.18					108
100	Quinapril	0.12		−0.921	−0.791	−0.129	109
101	Rosaramicin	0.12		−0.921	−0.898	−0.023	110
102	Salicylate	0.05		−1.301	−1.685	0.384	26
103	Sertraline	1.93		0.286	−0.173	0.458	90
104	Suprofen	0.014		−1.854	−1.691	−0.163	111
105	Temazepam	0.14		−0.854	−0.613	−0.241	97
106	Theobromine	0.82		−0.086	0.143	−0.230	112
107	Theophylline[a]	0.67	0.715	−0.146	−0.017	−0.129	113
		0.76					114
108	Tolmetin	0.0055		−2.26	−1.325	−0.935	115
109	Trazodone	0.53		−0.276	−0.625	0.349	116
110	Valproic acid	0.05		−1.301	−0.859	−0.442	117
111	Venlafaxine	4.14		0.617	0.305	0.312	96
112	Verapamil	0.6		−0.222	−0.229	0.007	118
113	Zidovudine[a]	1.11–1.78		0.160	0.044	0.116	119
114	Zolpidem	0.13		−0.886	−0.917	0.031	120
115	Zonisamide	0.92		−0.036	0.121	−0.157	121

[a]Average *M*/*P* values.
[b] Drugs that were excluded from the statistical analysis.
[c] Single *M*/*P* values used instead of average values.

values used in this study were collected from different literature sources. In the present study, the logarithmic function was used for the M/P ratio. The M/P ratio values together with the respective literature references are given in Table 1. Within the sources, the experimental M/P ratio values were obtained from plasma and milk samples by different analytical methods such as high liquid performance chromatography, HPLC, gas chromatography, GC, gas-liquid chromatography, GLC, and radioimmunoassay, RIA.

2.2. Methodology

Two-dimensional molecular structures of the 115 drug molecules were drawn using ISIS/Draw 2.4.[122] Pre-optimization and three-dimensional conversions were performed using the molecular mechanics force field method (MM+) included in Hyperchem 7.0.[123] The final optimization of the molecules was carried out using the semi-empirical AM1 parameterization[124] within the quantum-chemical program CMOPAC (embedded in CODESSA PRO). A gradient norm of 0.01 kcal/Å was used as the optimization completion criterion. AM1 force calculations were also carried out to produce the thermodynamic parameters for individual molecules. The optimized molecular structures were used in the CODESSA PRO[125] program to calculate constitutional, topological, geometrical, thermodynamic, quantum chemical, and electrostatic descriptors.

The best multilinear regression (BMLR) procedure was used to find the best correlation models from selected non-collinear descriptors. The BMLR selects the best two-parameter regression equation, the best three-parameter regression equation etc., based on the highest R^2 value in the stepwise regression procedure. During the BMLR procedure the descriptor scales are normalized, centered automatically and the final result is given in natural scales. This result gives the best representation of the property in the given descriptors pool.

A major decision in developing successive QSAR is when to stop adding descriptors to the model during the stepwise regression procedure. A simple technique to control the model expansion is the so-called 'break point' in the improvement of the statistical quality of the model, by analyzing the plot of the number of descriptors involved in the obtained models versus squared correlation coefficient (and cross-validated squared correlation coefficient) values corresponding to those models. Frequently, the statistical improvement of the regression model is less significant (ΔR^2, $\Delta R^2_{cv} < 0.02/0.05$) after a certain number of dependent variables in the model ('break point'). Consequently, the model corresponding to the break point is considered the best/optimum model.

2.3. Preselection of consistent experimental M/P values

Before starting the statistical analysis of the M/P ratios, a preselection of the data was performed in order to refine the most reliable experimental values. As already mentioned, drug transfer into human breast milk is a complex process involving multicomponent media. Therefore, special attention is needed regarding the uniformity of data.

A closure inspection confirms that most of the M/P ratio data used in Atkinson's M/P analysis[16] were assessed by an 'area under curve technique' considered as one of the most appropriate measures of drug distribution between plasma and milk. Therefore, we have taken the 40 compounds used[16] to represent a preselected consistent group and used this set of 40 compounds as a test set for the validation of the remaining data. Thus, a QSAR treatment was applied to this data set and multilinear regression equations up to nine parameters were developed. The application of the 'break point' algorithm, as previously described, led to the conclusion that the 'best' model has four parameters (see Fig. 1).

The 4-parameter QSAR model (Table 2) built on Atkinson's data was then used to predict $\log(M/P)$ ratio values for the remaining 75 compounds (see Fig. 2).

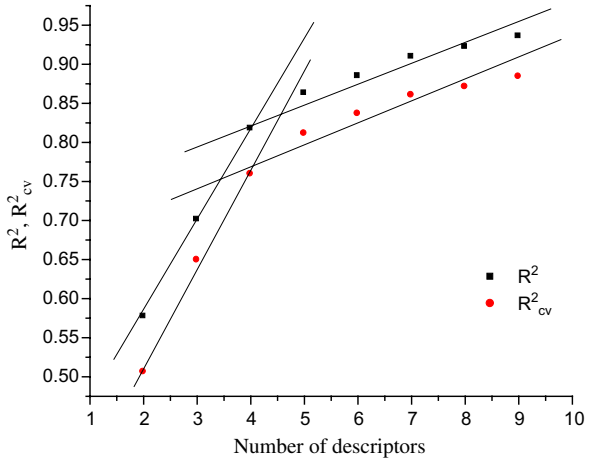

Figure 1. Correlation coefficients R^2 and R^2_{cv} versus number of descriptors for the multilinear QSAR equations developed using 40 data points ('Atkinson's data set').

Table 2. The best four-parameter correlation for Atkinson's data set ($F = 37.44$)[a]

#	X	$\pm\Delta X$	t-test	R^2	R^2_{cv}	S^2	Descriptor
0	2.658	0.400	6.651				Intercept
1	−0.405	0.037	−10.949	0.329	0.265	0.373	Number of double bonds, D_1
2	0.213	0.027	7.939	0.577	0.506	0.347	Final heat of formation/# atoms, D_2
3	−6.550	0.966	−6.782	0.701	0.649	0.218	Relative number of C atoms, D_3
4	0.085	0.015	5.792	0.811	0.759	0.108	HACA-1 (Zefirov PC), D_4

[a] Formulae of the descriptors are given in the supplemental material.

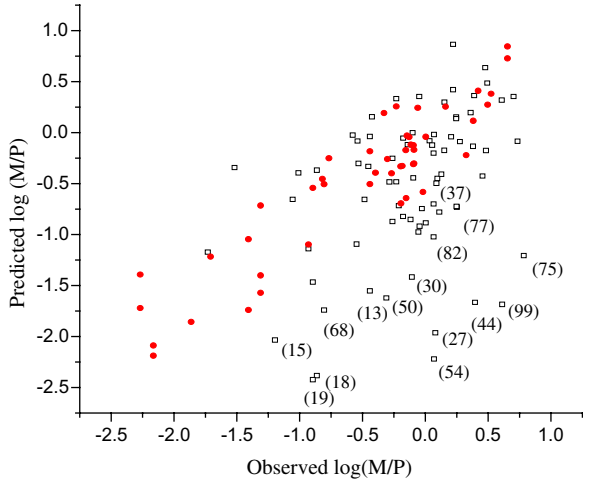

Figure 2. Predicted versus observed log(*M*/*P*) based on the four-parameter correlation equation (Table 2) for the initial data set (115 data points): empty squares—remaining 75 data points, solid circles—Atkinson's data points.

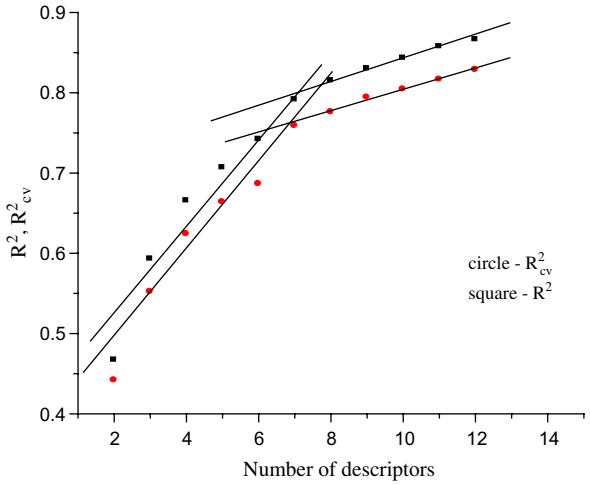

Figure 3. Correlation coefficients R^2 and R^2_{cv} versus number of descriptors for the multilinear QSPR equations developed using 100 data points.

Figure 2 reveals that of the remaining 75 data points, 15 deviate significantly from the Atkinson-data derived model. Most of these experimental values were reported in just 10 references (Kafetzis et al.,[41,44] Giamarellou et al.[49,51] Hilbert et al.,[53,89] Lebedevs et al.,[58,65] Gerk et al.,[13] Gural and co-workers.[108]). As they differ significantly from the model obtained from Atkinson's data, these 15 data points were excluded from further statistical analysis, reducing our working initial data set to 100 *M*/*P* ratios. In Table 1 such excluded compounds are labeled by superscript 'b'. Atkinson's data set includes only one drug (Ceftriaxone) for which the *M*/*P* ratio is from Kafetzis et al.[43]

For 31 drugs, more than one experimental value has been reported and for 16 of them the average value has been taken. In three cases, we chose the value that was closer to the fit of the QSAR model (Table 2). These compounds are denoted in Table 1 by 'a' and 'c' superscripts, respectively.

3. Discussions

3.1. General QSAR model for the prediction of *M*/*P* partition coefficient

A QSAR treatment was applied to the reduced data set of 100 drugs. To find the optimal number of descriptors, multiple parameter correlations were developed for up to 12 descriptors. The 'best' model according to the 'break point' rule described in the previous section has seven descriptors, as is shown in Figure 3.

The corresponding QSAR equation is described in Table 3, together with its statistical characteristics and a plot of predicted versus experimental values of log(*M*/*P*) for 100 drugs is given in Figure 4.

The seven descriptors involved in the model (Table 3) can be classified as follows: (i) two constitutional (relative number of nitrogen atoms, D_5, number of double bonds, D_6), (ii) one topological (average structural information content first order, D_{11}), (iii) two electrostatic (HACA-2 Zefirov PC, D_7, HA dependent HDCA—2/SQRT (TMSA) MOPAC PC, D_{10}), (iv) one quantum-chemical (Total molecular electrostatic interaction, D_9), and (v) one thermodynamical (Total heat capacity at 300 K/#atoms, D_8). According to the *t*-test values ($|t|$), the importance of the descriptors involved in the model decreases in the following order: $D_5 > D_6 > D_7 > D_8 > D_9 > D_{10} > D_{11}$.

Previous work[16,10] indicated that factors influencing the passage of a drug from plasma into human milk included (i) size of the molecule and molecular weight, (ii) whether its protein bound, (iii) the pH of drug, (iv) its solubility in lipids and water, and (v) diffusion rates.

Table 3. The general QSAR model for prediction of log(*M*/*P*)—the seven-parameter multilinear regression equation ($F = 49.632$)[a]

#	*X*	±Δ*X*	*t*-test	R^2	R^2_{cv}	S^2	Descriptor
0	4.215	0.521	8.095				Intercept
1	15.353	1.360	11.291	0.001	0.389	0.463	Relative number of N atoms, D_5
2	−0.266	0.026	−10.377	0.466	0.432	0.249	Number of double bonds, D_6
3	0.585	0.071	8.195	0.497	0.456	0.237	HACA-2 (Zefirov PC), D_7
4	−2.280	0.306	−7.442	0.626	0.571	0.178	Total heat capacity (300K)/#atoms, D_8
5	−0.438	0.063	−6.894	0.685	0.627	0.152	Total molecular electrostatic interaction, D_9
6	−8.775	1.502	−5.840	0.731	0.678	0.131	HA dependent HDCA-2/SQRT(TMSA) (MOPAC),D_{10}
7	3.212	0.626	5.134	0.791	0.758	0.103	Average Structural Information content (order 1), D_{11}

[a] Formulae of the descriptors are given in the supplemental material.

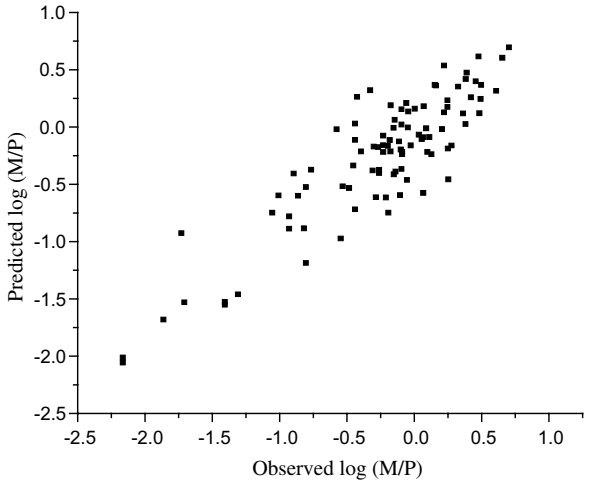

Figure 4. Predicted versus observed log(*M*/*P*) ratio according to the general QSAR model (Table 3).

The descriptors involved in our model (Table 3) reflect possible connections between these factors and the processes behind the *M*/*P* concentration ratios.

The most statistically significant descriptor is the relative number of *N* atoms (D1). This descriptor together with D_7 and D_{10} reflect possible hydrogen bonding donor and acceptor interactions between the molecules. In our data set only six compounds do not possess nitrogen atoms. Hydrogen bonding of the drug molecule either as the donor or acceptor to protein is certainly important. Thus, these descriptors can relate to drug molecules–protein bonding in the human breast milk to the water–lipid partition coefficient.

The diffusion of molecules in and between different media is another essential factor that influences drug excretion to human breast milk. In general, it depends both on the shape and the symmetry of the drug molecules. The topological descriptor, D_{11}, describes the connectivity and branching in a molecule and relates to molecular shape and symmetry.

Molecular volume and shape are also related to the second significant descriptor—*number of double bonds*, D_6. As is known, the double bonds possess smaller bond length. Larger values of this descriptor decrease the penetration of the drug molecule into human milk as shown by the minus sign for this descriptor.

The descriptor, D_8, is connected with the molecular volume (mass). The quantum-chemical descriptor, D_9, characterizes the energy of the electrostatic interactions between the chemically bonded atoms. It can be of importance in determining conformational change within the molecule, which in turn may affect protein bonding and diffusion of the drug in human breast milk. Consequently, this descriptor may also be related to log(*M*/*P*) values.

3.2. Predictive power of the general QSAR model

In order to validate the models, the parent 100 data points were divided into three subsets (A–C): the first, fourth, seventh, etc. data points comprise the first subset (A), the second, fifth, eighth, etc. comprise the second subset (B), and the third, sixth, ninth, etc. comprise the third subset (C). The three training sets were prepared as the combinations of any two subsets (A and B), (A and C), and (B and C), respectively. For each training set the correlation equation was derived with the same descriptors in Table 3. Then, the equation obtained was used to predict log(*M*/*P*) values for the compounds from the corresponding test set. The efficiency of QSAR models to predict log(*M*/*P*) ratio value was also estimated using the internal cross-validation. The correlation coefficients and standard deviations of linear correlations between experimental and predicted for test sets of log(*M*/*P*) values were also calculated and the results are shown in Table 4. The averages values of R^2 (Fit) and R^2 (Pred) are very close (0.792 and 0.763, respectively), which suggests relatively stable predictivity of the model. In addition, as can be seen from Table 4 average sample variances are close to each other.

4. Conclusions

Rationalization of the distribution of drugs between breast milk and human maternal plasma is not simple. Due to the high complexity of both media, it is not possible to derive predictive equations for the respective distribution coefficients from first principles. A substantial obstacle that hinders building highly predictive models is the difficulty in obtaining consistent experimental *M*/*P* ratios. There are many criteria for collecting 'homogeneous' *M*/*P* ratios based on the experimental methodology for measuring the *M*/*P* values, the number of volunteers involved in the treatment, pre- and post-feeding ratios and the experimental group producing the final ratios. We used an approach for selection that relies on 'area under curve' calculated data of the Atkinson data set. In this way we were able to refine the data and obtain a relatively good QSAR model. Our present attempt to correlate the log(*M*/*P*) with theoretically calculated molecular descriptors has led to a relatively successful QSAR model that relates this complex molecular

Table 4. Internal validation of the QSAR model

Training set	*N*	R^2 (Fit)	R^2_{cv} (Fit)	S^2 (Fit)	Test set	*N*	R^2 (Pred)	R^2_{cv} (Pred)	S^2 (Pred)
A + B	67	0.798	0.744	0.108	C	33	0.761	0.672	0.107
A + C	67	0.825	0.784	0.104	B	33	0.694	0.653	0.108
B + C	66	0.752	0.692	0.103	A	34	0.833	0.795	0.115
Average		0.792	0.740	0.105			0.763	0.706	0.110

property to structural characteristics of the drug molecules. Notably, all descriptors appearing in the best seven-parameter regression equation have been derived from theoretical molecular calculations. The current computational power available for chemical research allows such calculations for large data sets in realistic time. Thus, in principle, the QSAR model developed in our present work can be used for the prediction of the distribution coefficient between human breast milk and plasma for a wide range of common drugs. The descriptors appearing in this model may also have physical meaning, being primarily related to the electrostatic and hydrogen bonding interactions between the drug molecule and the surrounding media.

In conclusion, the results of the present work confirm the utility of the theoretical molecular descriptors and the QSPR models derived on their basis for the effective prediction of complex biomedical molecular properties.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2004.12.015.

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