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A quantitative structure-transportability relationship for the release of a series of substituted benzenes and pyridines from a planar polydimethylsiloxane matrix

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Abstract

The release of 52 compounds into water, loaded at their solubility limits in a filler-supported polydimethylsiloxane matrix, was studied using a quantitative structure-activity relationship (QSAR) approach. Half of the compounds studied were benzene derivatives and half were pyridine derivatives. Solubility of all the solid compounds in the matrix was related to the melting point, molecular weight, partial atomic charge of the solutes and an indicator variable for the pyridine class. Release of the compounds from the matrix into water was matrix controlled with the initial release following the square root of time relationship. The slope of the linear portion of the Q vs $\sqrt{t}$ plot was defined as the release coefficient. It was found that the release coefficient could be predicted by a QSAR model using melting point, hydrogen bonding energy group contribution, partial atomic charge and an indicator variable as predictors. Applicability of the model was examined by cross-validation. On the average, predicted results were accurate to within a factor of two for release coefficients over a 20 000-fold range.

Keywords: Controlled release; Solubility; Quantitative structure-transportability relationship; Polydimethylsiloxane matrix; Melting point; Molecular weight; Atomic charge; Hydrogen bonding group contribution

1. Introduction

Controlled release of chemicals from polymer matrices has been extensively studied in the areas of pharmaceuticals, agrochemicals, plant nutrients, veterinary drugs and flavors (Das, 1983), and especially for substances that are highly toxic and ineffective if administered by conventional means. The well-known advantages of controlled release techniques over conventional oral and parental administration include the improvement of drug efficiency, better patient compliance, and reduction of side effects and toxicity (Kydonieus, 1980). Much research has been carried out on the controlled release of pharmaceuticals during the last three decades and numerous studies have been published (Folkman and Long, 1964; Dziuk and Cook, 1966; Roseman and Higuchi, 1970; Haleblian et al., 1971; Roseman and Mansdorf, 1983; Lee and Good, 1987; Carelli et al., 1989; Otsuka and Matsuda, 1994; Veen et al., 1994).

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Table 1
Experimental and predicted log C_s, log k and selected physico-chemical properties

Compounds	MW (g/mol)	mp (°C)	Σe_+ (e)	Σe_- (e)	Σ^zHB (J/mol)	Exp. log C_s	Pred. log C_s	Residual	Exp. log k	Pred. log k	Residual
2-Amino-4-methylpyridine	108.14	100	0.308	0.564	13090	2.037	1.894	0.143	−0.535	−0.527	−0.008
3,5-Dichloropyridine	147.99	65	0.000	0.296	5490	2.581	2.527	0.054	0.577	0.741	−0.164
Picolinic acid	123.11	139	0.253	0.917	14690	1.251	1.289	−0.038	−1.335	−1.365	0.030
3-Hydroxypyridine	95.10	126	0.251	0.632	24690	1.504	1.752	−0.248	−1.500	−1.212	−0.288
2-Hydroxy-5-nitropyridine	140.10	188	0.371	0.839	26190	0.569	0.801	−0.232	−2.441	−2.257	−0.184
2-Methoxy-5-nitropyridine	154.13	108	0.122	0.827	9190	1.571	1.601	−0.030	−0.398	−0.597	0.199
2-Amino-5-nitropyridine	139.11	186	0.421	0.803	14590	0.802	0.796	0.006	−1.899	−2.001	0.102
2-Hydroxypyridine	95.10	105	0.253	0.589	24690	1.827	1.912	−0.085	−1.284	−0.920	−0.364
2-Aminopyridine	94.12	59	0.308	0.553	13090	2.175	2.237	−0.062	−0.087	−0.184	0.097
2-Amino-4,6-dimethyl pyridine	122.17	63	0.308	0.568	13090	2.134	2.097	0.037	−0.296	−0.242	−0.054
Methylnicotinate	137.14	42	0.000	0.924	11690	2.352	2.187	0.165	0.303	0.039	0.264
Nicotinic acid	123.11	236	0.252	0.936	14690	0.374	0.747	−0.373	−2.608	−2.338	−0.270
Isonicotinic acid	123.11	310	0.253	0.935	14690	−0.254	0.284	−0.538	−3.509	−3.081	−0.428
2-Amino-5-chloropyridine	128.56	135	0.308	0.552	13490	1.531	1.575	−0.044	−0.867	−1.013	0.146
5-Chloro-3-pyridinol	129.55	160	0.251	0.632	25090	1.149	1.430	−0.281	−1.572	−1.575	0.003
6-Chloronicotinic acid	157.56	198	0.252	0.923	15090	0.550	0.824	−0.274	−2.215	−2.023	−0.192
2-Hydroxynicotinic acid	139.11	260	0.508	1.230	34690	−0.178	−0.258	0.080	−3.738	−3.752	0.014
2-Amino-3,5-dichloropyridine	163.01	81	0.310	0.551	13890	1.921	1.752	0.169	−0.232	−0.479	0.247
3-Amino-2-chloropyridine	128.56	79	0.302	0.571	13490	1.749	1.905	−0.156	−0.481	−0.452	−0.029
2-Amino-4-methyl-3-nitropyridine	153.14	139	0.420	0.816	14590	1.244	1.020	0.224	−1.203	−1.514	0.311
2-Amino-3-hydroxypyridine	110.12	172	0.550	0.897	33090	0.985	0.735	0.250	−2.343	−2.494	0.151
4-Aminopyridine	94.12	160	0.308	0.587	13090	1.790	1.423	0.367	−1.266	−1.330	0.064

Nicotinamide	122.13	130	0.362	0.971	38690	1.332	1.202	0.130	−2.020	−1.971	−0.049
Isonicotinamide	122.13	155	0.362	0.970	38690	1.180	1.007	0.173	−2.157	−2.252	0.095
2,6-Pyridinedimethanol	139.15	114	0.426	1.055	44690	1.049	1.142	−0.093	−2.093	−2.043	−0.050
2-Hydroxy-6-methylpyridine-3-carboxylic acid	153.14	233	0.508	1.238	34690	0.038	−0.063	0.101	−3.454	−3.478	0.024
m-Nitrobenzaldehyde	151.12	57	0.256	0.588	7310	1.450	1.704	−0.254	−0.555	−0.038	−0.517
4'-Aminoacetophenone	135.17	105	0.304	0.664	11710	1.052	1.298	−0.246	−1.397	−0.882	−0.515
Methyl paraben	152.14	126	0.250	0.973	28310	0.812	0.856	−0.044	−1.549	−1.932	0.383
Ethyl paraben	166.18	116	0.250	0.970	28310	0.844	0.875	−0.031	−1.516	−1.819	0.303
Propyl paraben	180.20	95	0.250	0.970	28310	0.940	0.973	−0.033	−1.475	−1.588	0.113
Benzamide	121.14	128	0.362	0.685	35310	1.152	1.031	0.121	−1.610	−1.905	0.295
4-Hydroxybenzoic acid	138.12	215	0.502	0.987	31310	−0.040	−0.088	0.048	−3.003	−3.266	0.263
3-Hydroxybenzoic acid	138.12	201	0.500	0.982	31310	0.498	0.023	0.475	−2.873	−3.107	0.234
Benzoic acid	122.12	122	0.252	0.650	11310	1.379	1.212	0.167	−0.788	−1.109	0.321
4-Chlorobenzoic acid	156.57	239	0.252	0.650	11710	0.308	0.218	0.090	−2.299	−2.382	0.083
4-Chlorobenzyl alcohol	142.59	70	0.213	0.382	21710	1.738	1.748	−0.010	−0.403	−0.587	0.184
m-Anisic acid	152.15	106	0.252	0.970	14310	0.945	0.958	−0.013	−1.408	−1.322	−0.086
p-Anisic acid	152.15	182	0.252	0.976	14310	0.292	0.479	−0.187	−2.292	−2.090	−0.202
m-Toluic acid	136.15	108	0.252	0.650	11310	1.663	1.277	0.386	−0.647	−0.957	0.310
p-Toluic acid	136.15	180	0.252	0.654	11310	0.866	0.824	0.042	−1.494	−1.683	0.189
Phenoxyacetic acid	152.15	98	0.254	0.955	14310	1.058	1.084	−0.026	−1.450	−1.102	−0.348
2-Chlorophenoxyacetic acid	186.59	146	0.254	0.954	14710	0.566	0.582	−0.016	−2.093	−1.633	−0.460
4-Acetamidophenol	151.17	169	0.465	0.970	48510	0.157	0.296	−0.139	−3.167	−2.862	−0.305
2-Methyl-3-nitrobenzoic acid	181.15	182	0.371	0.886	12810	0.356	0.251	0.105	−2.291	−2.077	−0.214
4-Hydroxyacetophenone	136.15	109	0.250	0.713	23310	1.136	1.265	−0.129	−1.444	−1.228	0.216
4-Hydroxybenzyl alcohol	124.14	118	0.458	0.722	41310	0.657	1.089	−0.432	−2.249	−1.969	−0.280
4-Hydroxybenzamide	137.14	161	0.610	1.022	55310	−0.013	0.336	−0.349	−3.435	−3.170	−0.265
3-Hydroxy-4-methoxybenzoic acid	168.15	250	0.496	1.315	34310	−0.694	−0.671	−0.023	−3.782	−3.972	0.100
4-Fluorobenzoic acid	140.11	182	0.252	0.653	11310	1.050	0.718	0.332	−1.371	−1.772	0.401
4-Bromobenzoic acid	201.02	252	0.252	0.649	13410	0.068	−0.077	0.145	−2.428	−2.622	0.194
4-Iodobenzoic acid	248.02	272	0.252	0.649	15310	−0.412	−0.426	0.014	−2.787	−2.902	0.115

A planar matrix system, or a monolithic device (Roseman and Cardarelli, 1980) is one of many different controlled release systems that have been extensively studied. Mathematical expressions for drug release from a planar system have been derived depending on the initial physical states of drug in the matrix. When drug is initially dissolved in the matrix, exact mathematical solutions (Higuchi, 1960; Paul and McSpadden, 1976; Crank, 1986) as well as a simplified short time approximation (Higuchi, 1962; Crank and Park, 1968) are available. These solutions are the fundamental theories for studying release kinetics and mechanisms. Much diffusion research has been carried out based on the these theoretical solutions (Higuchi, 1962; Desai et al., 1965; Bottari et al., 1974; Morimoto et al., 1992). The short time approximation equation for drug release into a 'sink' condition from a planar matrix system, when drug is initially dissolved in the matrix and release is matrix diffusion controlled only, is given by (Higuchi, 1962; Crank and Park, 1968):

$$Q = 2C_0\sqrt{\frac{D_e t}{\pi}} \tag{1}$$

where Q is the cumulative amount released at time t from a unit area, C_0 represents the uniform initial concentration in the matrix and D_e denotes the effective diffusion coefficient in the matrix. Eq. 1 indicates that, for short times, the cumulative amount released is linear to the square root of time, assuming that the effective diffusion coefficient is a constant. The equation is valid for drug release less than 30% (Higuchi, 1962) or 60% (Roseman and Cardarelli, 1980). Using release data and the drug concentration in the system, Eq. 1 has been used in numerous cases to determine diffusion coefficients in ointments (Higuchi, 1962; Bottari et al., 1974; Gilbert et al., 1986; Buckton and Tawburic, 1992; Vos et al., 1994), polymer matrices (Crank and Park, 1968; Shah et al., 1992; Cassidy et al., 1993; Mitchell et al., 1993) and animal skins (Liron et al., 1994).

While the release profile can be described by the diffusion coefficient and the amount of drug in the system using the theoretical equations, drug release has also been shown to be affected by the structural characteristics of the diffusant and the medium. It was found that salicylic acid releases at different rates from different lanolin ointment bases (Bottari et al., 1974). The release of benzoic acid and related compounds from a pluronic gel was found to be controlled by the physico-chemical properties of the solutes (Gilbert et al., 1986). Diffusion coefficients of progesterone derivatives in a silicone rubber were found decrease with an increasing number of hydroxy group in the diffusant structure (Chien et al., 1979). Release coefficients (the slopes of the linear Q vs $\sqrt{t}$ plots) from a polydimethylsiloxane matrix for a series of pyridine compounds were described by a quantitative structure-transportability relationship (QSTR) (Chen and Matheson, 1993). These results demonstrated that drug release could be predicted based on structural relationships without knowing the actual diffusion coefficients and concentration distributions in the matrix.

The purpose of this study was to extend the earlier structural relationship concept in order to develop a QSTR model for the prediction of the in vitro release coefficients (the slopes of the linear Q vs $\sqrt{t}$ plots) of 52 substituted benzenes and pyridines from a polydimethylsiloxane matrix.

2. Materials and methods

The 52 substituted benzenes and pyridines in this study were used as received. All the compounds together with their melting point (°C), molecular weight, selected atomic charges, hydrogen bonding energy group contribution, experimental log C_s and log k are listed in Table 1. The polydimethylsiloxane (PDMS) matrix was Silastic® sheeting, Medical Grade NRV at thicknesses of 0.102 and 0.152 cm and was obtained from Dow Corning Corp., Midland, MI.

The experimental procedures for the determination of apparent solubility (C_s, μmol/cm^3) in the PDMS matrix and release coefficient (k, μmol/cm^2 per min$^{1/2}$) were the same as described earlier (Chen and Matheson, 1993). In brief, a 3 cm polymer disc was equilibrated with a

saturated water solution containing excess solid of a given compound at 30°C for 1 week. Solubility of a drug in the matrix was determined by extracting the loaded matrix with isopropyl alcohol and measuring the concentration of the extract by a UV method. In vitro release into water at 30°C was determined using a horizontal diffusion cell with a circulating release medium. The receiver solution was measured continuously using a flow-through UV cell.

Molecular models of all compounds were generated using molecular modeling software (SYBYL 6.0, Tripos Associate, Inc., St. Louis, MO) installed on a Silicon Graphics computer (4D 120GTX, Silicon Graphics,. Inc., Mountain View, CA). Atomic charge was computed using the Gast-Hück method in the SYBYL software.

3. Results and discussion

The effect of the aqueous diffusion layer was evaluated using a permeation method (Hwang et al., 1971; Hunke and Matheson, 1981) using the same stirring rate used for the release experiments. Apparent permeability of one of the most hydrophobic compounds, 2-amino-4,6-dimethylpyridine, did not change as the thickness of the membrane was changed. Most of the compounds in the data set were more polar than 2-amino-4,6-dimethylpyridine and all the initial release profiles followed the linear square root of time relationship. Thus, it was concluded that the release from the PDMS matrix was matrix diffusion controlled under the experimental conditions.

The short time approximation given by Eq. 1 shows that the initial Q vs $\sqrt{t}$ plot is linear with the slope being described by Eq. 2:

$$\frac{dQ}{d\sqrt{t}} = 2C_0\sqrt{\frac{D_e}{\pi}} \tag{2}$$

It can be seen from Eq. 2 that the slope will change as the initial concentration is changed. However, a specific slope, k, can be defined as a constant for a given system if the initial concentration in the matrix of the releasing substance is at its solubility limit, assuming that the diffusion coefficient is a constant:

$$k = 2C_s\sqrt{\frac{D_e}{\pi}} \tag{3}$$

where k is the release coefficient and C_s represents the solubility in the matrix. The release coefficient, k, can be predicted if the solubility and the diffusion coefficient in the matrix can be estimated.

Apparent solubility of structurally similar compounds in a polymer matrix has been shown to be related to the melting point of the solute (Michaels et al., 1975; Chien, 1976; Lee et al., 1985; Chen and Matheson, 1993). The melting point relationship also exists for the more diversified chemical structures of the present data set. Correlation results are given by Eq. 4.

$$\log C_s = 2.515 - 0.0103\text{mp} \tag{4}$$

$$s = 0.389\ r^2 = 0.735 \quad F = 138.67\ n = 52$$

where C_s is the apparent solubility in the PDMS matrix (μmol/cm^3), mp represents the melting point of the solute (in °C), s denotes the standard error of estimation, r^2 is the coefficient of determination, F represents the variance ratio and n is the number of compounds. The coefficient of the melting point in Eq. 4 is similar to the value of -0.01 proposed by Yalkowsky and co-workers for aqueous solubility of rigid molecules (Yalkowsky and Valvani, 1980; Yalkowsky and Banerjee, 1992). The similarity indicates that melting of a solute can also be designated as part of the dissolution process of a solid compound in a polymer matrix.

A scatter plot (not shown) showed that the log C_s data of the pyridine compounds lie on a separate line than those for the benzene compounds. This indicated that solubility was affected by the ring structures of the two types of compounds. Other research in this laboratory has found that a pyridine derivative is capable of specific binding to the polymer matrix, especially by adsorption on the silica filler in the polymer matrix, resulting in an apparently higher solubility in the matrix than in the pure polymer. To account for the specific structural effect for the adsorption of

pyridines by the filler, an indicator variable, I_p, was included for pyridine compounds as given by Eq. 5.

$$\log C_s = 2.219 - 0.010\text{mp} + 0.499 I_p \quad (5)$$

$$s = 0.298 \; r^2 = 0.848 \; F = 136.27 \; n = 52$$

Correlation was significantly improved by including the indicator variable for the pyridine compounds. However, the standard error of estimation for Eq. 5 was still fairly large. This is not surprising since Eq. 5 did not take the solute-medium interaction into account for each individual compound.

The solute-solvent interaction has been shown to be important in the estimation of solubility in solution (Hildebrand et al., 1970; Yalkowsky et al., 1975). Intermolecular interactions can be classified into polar and nonpolar interactions (Barton, 1983). The nonpolar interaction is due mainly to the dispersion force, which is proportional to the sizes of the interacting molecules (Levine, 1988). For convenience, molecular weight was used as a rough estimator for molecular size. Molecular weight has been frequently used as one of the predictors in structural relationship studies for partition coefficients (Bodor et al., 1989; Bodor and Huang, 1991), flux (Chen et al., 1993), skin permeability coefficients (Pugh and Hadgraft, 1994) and pharmacokinetic parameters (Herman and Veng-Pedersen, 1994). The polar interaction may include all kinds of dipolar interactions and hydrogen bonding. Since polar interactions are electrostatic in nature, atomic charge may be used for correlation. In fact, partial atomic charges have been used in numerous cases to represent the electrostatic interactions for QSAR studies (Gasteiger and Marsili, 1980; Marsili and Gasteiger, 1980; Klopman and Iroff, 1981; Gerhards and Mehler, 1985; Bodor and Huang, 1991, 1992; Kantola et al., 1991; Chen et al., 1993; Cramer et al., 1993).

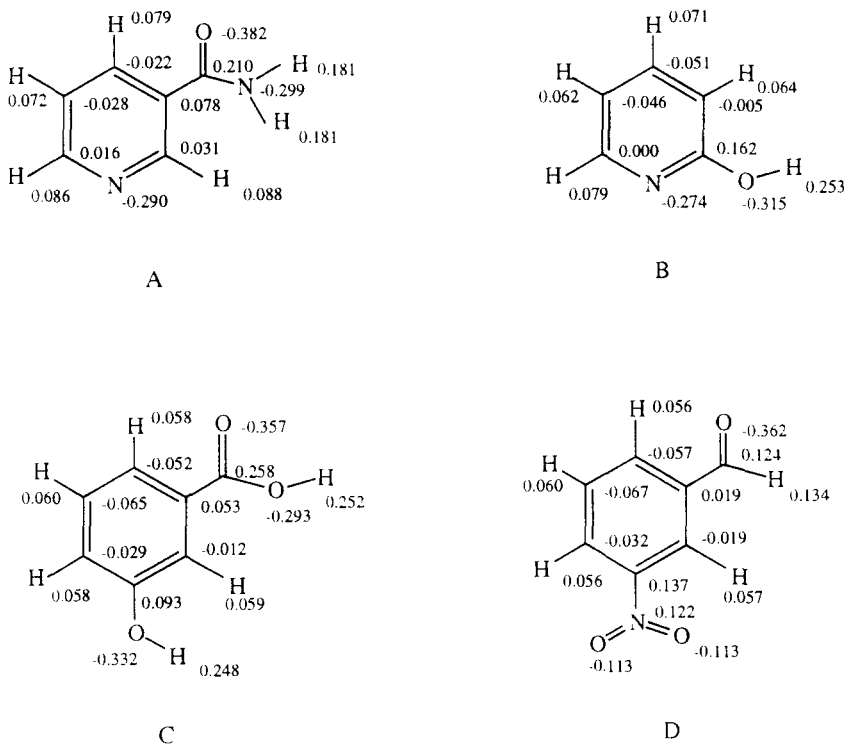

Fig. 1. Calculated atomic charges of nicotinamide (A), 2-hydroxypyridine (B), 3-hydroxybenzoic acid (C), and 3-nitrobenzaldehyde (D).

There are many different methods for the computation of atomic charge distribution. The various methods will result in different charge values. However, it has been shown that the overall correlation results for partition coefficients were similar using charges calculated from different methods (Klopman and Iroff, 1981; Kantola et al., 1991). It has also been pointed out that different methods could be used equally well as long as calculations were done consistently (Cramer et al., 1993). The method used in this study is an empirical combination of the Gasteiger-Marsili method and Hückel method (Tripos, 1992). Atomic charges computed using this method have been shown to correlate with flux through PDMS membrane (Chen et al., 1993; Liu and Matheson, 1994). Examples of calculated atomic charges are shown in Fig. 1.

Various criteria have been used in the selection of atomic charges for QSAR studies (Bodor and Huang, 1991, 1992; Cramer et al., 1993). In this study, the following charges were used:

1. The positive charge on a hydrogen atom if it was higher than 0.1.
2. The positive charge of the nitrogen atom in a nitro group.
3. The negative charge of all other nitrogen and oxygen atoms.

The final equation for the correlation of apparent solubility in the PDMS matrix was generated by least-square regression and is given by Eq. 6:

$$\log C_s = 3.457 - 0.00399\mathrm{MW} - 0.992\Sigma e_+ - 0.867\Sigma e_- - 0.00738\mathrm{mp} + 0.380 I_p \quad (6)$$

$$s = 0.175\ r^2 = 0.951\ F = 177.25\ n = 52$$

where MW is molecular weight of solute, Σe_+ represents the summation of the charge on hydrogen atoms with a charge greater than 0.1 and the positive charge of a nitrogen atom in the nitro group, Σe_- denotes the summation of the absolute charge values of negatively charged nitrogens and oxygens and other terms are the same as those defined in Eq. 4 and 5. Inclusion of molecular weight and charge terms significantly improved the quality of fit. The critical value for the regression at a 99% confidence level is $F_{0.01}(5,46) = 3.50$. The high F value indicated that the relationship given by Eq. 6 was very significant.

Applicability of Eq. 6 was examined by a cross-validation method (Myers, 1990). Ten compounds were removed from the data set. Half of the removed data was from the benzene class and the other half was from the pyridine class. The remaining data were used to generate an equation for the prediction of the solubility of the removed data. The procedures were repeated five times until all the compounds were predicted. Equation coefficients of the five cross-validation runs are listed in Table 2. Data in the table shows that all the coefficients in the cross-validation runs are within the 95% confidence ranges for the coefficients in Eq. 6, indicating that the equation coefficients are stable upon the reduction of sample size and the change in the data values. The relationship between the experimental and the predicted values from the cross-validations are given by Eq. 7:

$$\mathrm{Exp.}\log C_s = -0.015 + 0.990\,\mathrm{Pred.}\log C_s \quad (7)$$

$$s = 0.210\ r^2 = 0.921\ F = 596.33\ n = 52$$

Table 2
Bonferoni joint confidence ranges for coefficients in Eq. 4 and coefficients in cross-validation runs

Predictor	Bonferroni joint confidence range	Validation 1	Validation 2	Validation 3	Validation 4	Validation 5
Constant	3.457 ± 0.517	3.527	3.380	3.493	3.507	3.458
MW	−0.00399 ± 0.00303	−0.00419	−0.00346	−0.00496	−0.00417	−0.00409
Σe_+	−0.992 ± 0.704	−0.994	−0.987	−1.404	−1.181	−0.661
Σe_-	−0.867 ± 0.391	−0.866	−0.898	−0.787	−0.791	−0.875
mp	−0.00738 ± 0.00133	−0.00748	−0.00748	−0.00625	−0.00748	−0.00785
I_p	0.380 ± 0.155	0.363	0.425	0.430	0.330	0.353

The standard error of prediction is greater than that of fitting, which is expected since prediction of unknown data is almost always more difficult than data fitting. The prediction residual includes both experimental error as well as the equation weakness. Experimental error was found to be less than 10%, which was negligible in the logarithmic scale. It was obvious that the prediction error reflected the weakness of the QSAR relationship. Some other physico-chemical properties may be helpful for the explanation of solubility. However, on average, predicted results using the current relationship are still accurate to within 1.62-times the experimental solubility. Eq. 7 shows that 92% of the variation in log C_s can be predicted. Predicted log C_s results from cross-validation are listed in Table 1.

The apparent diffusion coefficient in the PDMS matrix, D_e, was calculated using the release coefficient by Eq. 8, which was a rearrangement of Eq. 3:

$$D_e = \frac{\pi k^2}{240 C_s^2} \tag{8}$$

where k is the release coefficient (μmol/cm^2 per min$^{1/2}$), C_s represents the apparent solubility in the matrix (μmol/cm^3) and $240 = 4 \times 60$ (s/min).

The diffusion coefficient has been found to be related to the activation energy of the diffusion process (Barrer, 1939). It is determined by the properties of and the degree of interaction between the diffusant and the diffusion medium (Flynn et al., 1974). PDMS has been shown to be capable of hydrogen bonding (West et al., 1961). Thus, hydrogen bonding energy should be part of the interaction energy. In this study, the hydrogen bonding energy group contributions were taken from the literature (Barton, 1983) and are listed in Table 1. Regression analysis showed that the apparent diffusion coefficient in the PDMS was related to the hydrogen bonding energy group contribution, molecular weight and melting point as given by Eq. 9:

$$\log D_e = -5.781 + 0.0116\text{MW} - 0.00782\text{mp} - 0.0137\sqrt{\Sigma^2\text{HB}} \tag{9}$$

$$s = 0.348\ r^2 = 0.852\ F = 92.23\ n = 52$$

Regression statistics showed that $|t| \geq 6.09$ for all the predictors in Eq. 9, indicating that all the terms were significantly related to apparent diffusion coefficient. The sign for the MW in Eq. 9, however, was not as expected. Diffusion coefficients in solutions usually decrease as molecular weight is increased (Jacobs, 1967). However, the relationship has been shown not to exist among compounds of different classes or functional groups, and the polymer-drug interaction is more important in determining diffusion coefficient than size (Morimoto et al., 1992). The positive relationship may also be due to the existence of other predictors. In the presence of melting point and the hydrogen bonding energy group contribution, the primary effect of molecular weight on diffusion coefficient may have been changed from a logical representation of size to merely accommodating the combination of parameters.

It is interesting to note that apparent diffusion coefficient was also related to melting point. Apparent diffusion coefficient was calculated based on the apparent solubility in the matrix. It has been shown that fillers in the PDMS membrane could adsorb diffusant (Flynn and Roseman, 1971). A separate experiment in our study has verified this adsorption effect. As a result, apparent solubility in the PDMS matrix included both the results of partitioning and adsorption by the filler, which was determined by the equilibrium concentration, or the true solubility under the conditions in this study. Solubility is related to melting point. Consequently, apparent diffusion coefficient was related to melting point by the inclusion of the effect of adsorption.

Release coefficient is determined by both the solubility and the apparent diffusion coefficient as given by Eq. 3. Thus, parameters related to solubility and apparent diffusion coefficient should also be related to release coefficient. The parameters in Eq. 6 and 9 were combined and related to log k. Results are given by Eq. 10:

$$\log k = 1.955 - 1.212\Sigma e_+ - 0.970\Sigma e_- - 0.0108\text{mp} - 0.0072\sqrt{\Sigma^2\text{HB}} + 0.237 I_p \tag{10}$$

$$s = 0.216\ r^2 = 0.963\ F = 232.79\ n = 52$$

Table 3
Bonferoni joint confidence ranges for coefficients in Eq. 8 and coefficients in cross-validation runs

Predictor	Bonferroni joint confidence range	Validation 1	Validation 2	Validation 3	Validation 4	Validation 5
Constant	1.955 ± 0.390	2.178	1.908	1.817	1.955	1.903
Σe_+	-1.212 ± 1.042	−0.774	−1.413	−1.276	−1.419	−1.160
Σe_-	-0.970 ± 0.516	−1.114	−0.989	−0.898	−0.866	−0.925
mp	-0.0108 ± 0.0016	−0.0110	−0.0108	−0.0100	−0.0109	−0.0113
$\sqrt{\Sigma HB}$	-0.00720 ± 0.00339	−0.00860	−0.00663	−0.00737	−0.00673	−0.00683
Pyridine	0.237 ± 0.166	0.245	0.284	0.271	0.156	0.252

As expected, molecular weight is no longer important for log k since molecular weight has opposite effects on solubility and apparent diffusion coefficient. Regression statistics showed that $|t| \geq 3.21$ for all the predictors in Eq. 10, indicating that all the terms are significantly related to log k. Variance inflation factors (VIF) were less than 2.4 for all terms. Thus, collinearity among predictors was not a problem. The critical value for the overall significance of the regression is $F_{0.01}(5,46) = 3.50$. The F value of 232.79 is much greater than the critical value. Thus, the relationship given by Eq. 10 is very significant.

Cross-validations with 10 or 11 compounds excluded in each run showed that Eq. 10 was robust and reliable. Bonferroni joint confidence range (Myers, 1990) for regression coefficients in Eq. 10 and the respective coefficient values for each cross-validation run are listed in Table 3. The results in Table 3 show that equation coefficients in cross-validation runs are within the 95% confidence ranges. Predicted log k values resulted from cross-validations are listed in Table 1. Over a 20000-fold range, average release coefficients were predicted within 1.79-times the experimental value on average.

It has been shown that the apparent solubility of structurally different compounds in a PDMS matrix is related to the structural properties of solutes and can be predicted using a quantitative structure-solubility relationship approach. Apparent diffusion coefficient in the matrix was also related to the structural characteristics of diffusant. Short time release coefficients of solutes into water, when loaded at their solubility limits in the PDMS matrix, can be predicted without knowing their actual diffusion coefficients in the matrix. The QSAR concept may be applicable for drug release from other polymer matrices though the exact QSAR relationship may vary from one polymer system to another, depending on the specific interactions involved. Thus, QSAR may be worth consideration in the development of controlled release formulations.

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