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Prediction of flux through polydimethylsiloxane membranes using atomic charge calculations: application to an extended data set

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Abstract

The maximum steady state flux of 171 compounds through PDMS membranes was predicted using a refinement of a previously developed empirical quantitative structure-transportability relationship (QSTR) produced using the reported flux data for 103 compounds. The model utilized partial atomic charge, solubility, and molecular weight as predictors. The predicted data set includes a variety of substituted benzenes, naphthalenes, thiophenes, benzimidazoles, pyridines, quinolines, isoquinolines, pyrimidines, triazoles and lesser numbers of other heterocyclic classes of compounds over a wide range of polarity. Maximum steady state flux was measured using isopropyl alcohol as solvent. Molecular models of all the compounds were simulated using SYBYL 6.0 molecular modeling software. The atomic charge of each individual compound was computed with the Gast-Hück method using the same software. Results show that the simple QSTR equation is capable of accurately predicting the steady state flux of a variety of compounds. Contribution of atomic charge to mass transport phenomena was further verified by the prediction of the apparent permeability calculated from the steady state flux data. Permeability decreases significantly as the atomic charge of diffusant is increased. Predicted results show that atomic charges can be used to represent the polarity and be correlated to the polarity-related properties of an electrically neutral compound.

Keywords: Steady state flux; Permeability; Prediction; Polydimethylsiloxane membrane; Quantitative structure-transportability relationship; Molecular modeling; Atomic charge

1. Introduction

It is well known that steady state flux through a membrane can be described by Eq. 1 when diffusion is membrane controlled and the concentration of diffusant in the receiver solution is kept at a negligible level (Daynes, 1920; Crank and Park, 1968):

$$J_{ss} = \frac{KDC_d}{h} \quad (1)$$

where J_{ss} is the steady state flux, K represents the partition coefficient of the diffusant between

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the membrane and the solvent, D denotes the diffusion coefficient in the membrane, C_d is the concentration of the diffusing substance in the donor solution, and h represents the thickness of membrane.

A special case for Eq. 1 arises when the donor concentration is set to the solubility limit. Flux reaches a maximum value and can be described by Eq. 2:

$$J_{mss} = \frac{PC_s}{h} \quad (2)$$

where J_{mss} is the maximum steady state flux, P represents the membrane permeability, with $P = KD$, and C_s is the solubility of a diffusant in the solvent.

Eq. 2 shows that the maximum steady state flux is a constant for a given system since all the other terms in the equation are constants. Flux at solubility limit is, in some case, similar to drug adsorption through biological barriers when a suspension or other solid dosage form of a low solubility drug is administered. The use of solubility may also be advantageous in that the relative activity of different diffusants in the donor solutions may be considered the same if the relative activity of a pure substance is defined as being one. However, permeability is not easy to determine. As a result, prediction of flux using Eq. 2 is difficult when the values of the required parameters are not available.

As indicated for Eq. 2, permeability is the product of partition coefficient and diffusion coefficient, both of which are related to the solute-solvent-membrane interaction energy. Theoretical expressions for the interaction energy and hence permeability can be derived but the utility of such expressions may be compromised by both the various simplifying assumptions used in the equation development and the exceedingly tedious computation process. Alternatively, permeability and hence flux can be effectively estimated using simple quantitative structure-transportability relationships since the solute-solvent-membrane interaction energy is determined by the structural characteristics of the interacting species.

In recent years, extensive studies have correlated the maximum steady state flux of different classes of compounds through a polydimethylsiloxane (PDMS) membrane to some easily accessible physico-chemical properties. Several specific models using predictors such as hydrophobic fragmental constants, molar refractivity, Hammett's s constants, mole fraction solubility and melting point have been developed for the prediction of flux of substituted benzenes (Moeckly and Matheson, 1991; Matheson et al., 1991), pyridines (Hu and Matheson, 1993) and quinolines (Matheson and Hu, 1993). Structural fragmental constants' methods have also been developed for different types of compounds (Laoratthaphong, 1989; Yang, 1992). In recent studies, a universal model using partial atomic charges as predictors (Chen et al., 1993) and a CoMFA model (Liu and Matheson, 1994) were developed for the prediction of flux of different classes of aromatic and heterocyclic compounds.

Microscopic partial charge may be considered as the intrinsic cause of macroscopic polarity of a compound. Partial charge has been successfully used to estimate pKa, NMR shift, Hammett's constants (Gasteiger and Marsili, 1980; Marsili and Gasteiger, 1980), partition coefficient (Klopman et al., 1985; Bodor et al., 1989), and hydrophobic index (Kantola et al., 1991). Other applications of atomic charges have been recently reviewed (Cramer et al., 1993).

The purpose of this paper is to validate the capability of a previously developed QSTR model for predicting the diffusional properties of an extended data set. Maximum steady state flux through a PDMS membrane of 171 new compounds with a wide range of polarity was predicted using a refinement of the reported model. The contribution of partial atomic charge to mass transport phenomena was further verified by the correlation of atomic charge to apparent permeability through PDMS membranes.

2. Materials and methods

2.1. Determination of steady state flux, solubility and permeability

Measurement of both the maximum steady

state flux through PDMS membrane (Silastic® sheeting, Medical Grade NRV, Dow Corning Corp., Midland, MI) using isopropyl alcohol (IPA) as solvent and the solubility in IPA was carried out using the previously reported methods (Moeckly and Matheson, 1991; Hu and Matheson, 1993). In brief, both steady state flux and solubility were determined at 30°C. Neat liquids were used as the donor solutions for the determination of maximum flux of liquid diffusants, and, either 50% or 90% saturated solutions in IPA were used as the donor solutions for solid diffusants. Receiver solution was kept at a 'sink' condition. Steady state flux was measured at a time region greater then 2.7 times lag time. Steady state flux was normalized to a membrane thickness of 0.1016 cm for all the compounds. Flux of solid diffusant was also normalized to the solubility in IPA to obtain the maximum steady state flux value.

Some of the flux and solubility data in this study was collected in previous studies (Liu, 1990; Moeckly and Matheson, 1991; Matheson et al., 1991; Yang, 1992; Hu and Matheson, 1993; Matheson and Hu, 1993).

Apparent permeability was calculated from the steady state flux data by Eq. 3, which is a rearrangement of Eq. 2.

$$P = \frac{J_{mss}h}{C_s} \quad (3)$$

where P is the apparent permeability (cm/s), J_{mss} represents the maximum steady-state flux (μmol/s per cm^2), h denotes the thickness of membrane (cm), and C_s is either the solubility in IPA for solid diffusant or the concentration of pure substance for liquid diffusant (μmol/ml).

The 103 compounds used as training data were taken from Table 1 of the earlier report (Chen et al., 1993). The 171 new compounds used for the prediction of both steady state flux and apparent permeability in the present study include the mono-, di- and tri- substituted compounds of the following classes of, as well as the unsubstituted structures of, benzene, naphthalene, pyridine, pyrrole, quinoline, isoquinoline, furan, thiophene, triazole, benzimidazole, indole, pyrimidine, and some other miscellaneous heterocyclic compounds. Substituents consist of a wide variety of functional groups.

2.2. Molecular modeling and atomic charge calculation

Molecular models of all the compounds were created using a molecular modeling software package (SYBYL 6.0, Tripos Associates, Inc., St. Louis, MO) on a workstation (SiliconGraphics 4D 120GTX, Silicon Graphics, Inc., Mountain View, CA). Atomic charges were calculated using the Gast-Hück method in the same software package.

All the 171 new compounds along with their molecular weight (MW, g/mol), solubility (C_s, μmol/ml) and the selected atomic charges are listed in Table 1. The C_s values for liquid diffusants were calculated from the density of the pure substances, since neat liquids were used in the diffusion experiments.

3. Results and discussion

The Gast-Hück method used in this study is one of several approximate schemes for estimating atomic charges. Other methods (Levine, 1988; Tripos, 1992) may result in different charges, and hence, different regression coefficients. But, the final results may be similar (Klopman and Iroff, 1981; Kantola et al., 1991; Cramer et al., 1993).

Partial atomic charges were chosen previously (Chen et al., 1993) as predictors for flux according to the following empirical selection rules:

(1) the charge on a hydrogen atom is higher than 0.1 and the hydrogen atom is not involved in intramolecular hydrogen bonding;

(2) the charge is on heteroatoms which contain unshared electron pairs, all of which are unconjugated.

The identification of intramolecular hydrogen bonding that is needed to satisfy the first selection rule can be accomplished by either using literature results or molecular modeling results. The software used in this study can display the intramolecular hydrogen bond. In the predicted

Table 1
Selected parameters, experimental and predicted flux and apparent permeability

Compounds	MW	log C_s	Σe_+	Σe_-	Exp. log J_{mss}	Pred. log J_{mss}	Residual	Exp. log P	Pred. log P	Residual
Nitrobenzene	123.11	3.987	0.121	0.226	−1.556	−1.470	−0.086	−6.536	−6.451	−0.086
Acetophenone	120.15	3.933	0.000	0.379	−1.640	−1.307	−0.333	−6.566	−6.233	−0.333
Benzaldehyde	106.12	3.993	0.134	0.362	−1.480	−1.535	0.055	−6.466	−6.521	0.055
Ethylbenzene	106.17	3.912	0.000	0.000	−0.555	−0.649	0.094	−5.460	−5.554	0.094
Fluorobenzene	96.10	4.028	0.000	0.000	−0.256	−0.509	0.253	−5.277	−5.529	0.253
3-Chlorotoluene	126.59	3.928	0.000	0.000	−0.837	−0.772	−0.065	−5.758	−5.693	−0.065
m-Xylene	106.17	3.913	0.000	0.000	−0.580	−0.649	0.069	−5.486	−5.554	0.069
3-*tert*-Butylphenol	150.22	3.760	0.249	0.000	−1.900	−2.115	0.215	−6.653	−6.868	0.215
4-Hydroxybenzoic acid	138.12	3.229	0.502	0.363	−3.530	−3.294	−0.236	−7.752	−7.516	−0.236
4-Chlorotoluene	126.59	3.927	0.000	0.000	−0.694	−0.772	0.078	−5.614	−5.692	0.078
Butylbenzene	134.22	3.807	0.000	0.000	−0.895	−0.900	0.005	−5.695	−5.700	0.005
Phenetole	122.17	3.898	0.000	0.318	−1.110	−1.249	0.139	−6.001	−6.140	0.139
Propiophenone	134.18	3.876	0.000	0.378	−1.630	−1.434	−0.196	−6.499	−6.303	−0.196
m-Anisaldehyde	136.15	3.918	0.134	0.682	−2.090	−2.095	0.005	−7.001	−7.006	0.005
Methyl 3-methylberizoate	150.18	3.850	0.000	0.357	−1.430	−1.523	0.093	−6.273	−6.366	0.093
4-*tert*-Butylbenzoic acid	178.23	3.087	0.253	0.344	−2.759	−2.924	0.165	−6.839	−7.005	0.165
Ethyl paraben	166.18	3.356	0.250	0.362	−2.690	−2.672	−0.018	−7.039	−7.021	−0.018
3-Pyridinecarboxaldehyde	107.11	4.025	0.136	0.649	−1.823	−1.807	−0.016	−6.841	−6.825	−0.016
3,5-Lutidine	107.16	3.943	0.000	0.312	−0.948	−1.114	0.166	−5.884	−6.049	0.166
5-Chloro-3-pyridinol	129.55	3.044	0.251	0.307	−2.621	−2.611	−0.010	−6.658	−6.648	−0.010
4-*tert*-Butylpyridine	135.21	3.830	0.000	0.264	−1.227	−1.295	0.068	−6.050	−6.119	0.068
Nicotinic acid	123.11	1.725	0.252	0.644	−3.760	−3.598	−0.162	−6.478	−6.317	−0.162
4-Picoline	93.13	4.012	0.000	0.307	−0.845	−0.970	0.125	−5.850	−5.974	0.125
3-Acetylpyridine	121.14	3.959	0.000	0.665	−1.992	−1.734	−0.258	−6.944	−6.686	−0.258
3-Aminopyridine	94.12	3.814	0.304	0.309	−2.682	−2.045	−0.637	−7.489	−6.852	−0.637
2-Aminopyridine	94.12	3.808	0.304	0.287	−1.895	−2.042	0.147	−6.696	−6.843	0.147
2-Chloro-6-methoxypyridine	143.57	3.925	0.000	0.259	−1.211	−1.281	0.070	−6.129	−6.199	0.070
2-Ethylpyridine	107.16	3.942	0.000	0.298	−0.718	−1.093	0.375	−5.653	−6.027	0.375
2-Chloropyridine	113.55	4.024	0.000	0.282	−1.081	−1.056	−0.025	−6.098	−6.073	−0.025
2-Butoxypyridine	151.21	3.809	0.000	0.274	−1.155	−1.429	0.274	−5.957	−6.231	0.274
2-Flouropyridine	97.07	4.065	0.000	0.265	−0.878	−0.896	0.018	−5.936	−5.955	0.018
2-Methoxypyridine	109.13	3.978	0.000	0.274	−0.809	−1.045	0.236	−5.780	−6.016	0.236
2-Methoxy-5-nitropyridine	154.13	1.991	0.122	0.516	−2.653	−3.272	0.619	−5.637	−6.256	0.619
2-Methoxy-5-aminopyridine	124.14	3.876	0.298	0.287	−2.230	−2.174	−0.056	−7.099	−7.043	−0.056
2-Hydroxy-5-nitropyridine	140.10	1.838	0.371	0.473	−3.747	−3.837	0.090	−6.578	−6.668	0.090
2-Hydroxypyridine	95.10	3.310	0.253	0.274	−2.499	−2.204	−0.295	−6.802	−6.506	−0.295
2-Amino-4-methylpyridine	108.14	3.387	0.308	0.296	−2.228	−2.422	0.194	−6.608	−6.802	0.194
2-Amino-5-chlorpyridine	128.56	2.723	0.308	0.286	−2.625	−2.983	0.358	−6.341	−6.699	0.358
Ethyl nicotinate	151.17	3.865	0.000	0.644	−1.530	−1.959	0.429	−6.388	−6.817	0.429

Lepidine	143.19	3.879	0.000	0.308	−1.853	−1.383	−0.470	−6.725	−6.255	−0.470
6-Methylquinoline	143.19	3.871	0.000	0.298	−1.747	−1.373	−0.374	−6.611	−6.237	−0.374
8-Hydroxyquinoline	145.16	2.588	0.000	0.294	−2.358	−2.213	−0.145	−5.939	−5.793	−0.145
2-Methyl-8-nitroquinoline	188.19	1.423	0.127	0.522	−3.827	−3.880	0.053	−6.243	−6.295	0.053
Quinaldine	143.19	3.869	0.000	0.301	−1.622	−1.379	−0.243	−6.484	−6.241	−0.243
6-Isopropylquinoline	171.00	3.686	0.000	0.298	−1.897	−1.674	−0.223	−6.576	−6.353	−0.223
5-Aminoquinoline	144.18	3.021	0.308	0.302	−3.113	−2.895	−0.218	−7.127	−6.910	−0.218
3-Aminoquinoline	144.18	3.393	0.302	0.299	−2.934	−2.635	−0.299	−7.320	−7.021	−0.299
4-Hydroxyquinoline	145.16	2.590	0.258	0.316	−3.688	−3.033	−0.655	−7.271	−6.616	−0.655
8-Quinolinecarboxylic acid	173.17	1.169	0.000	0.651	−4.213	−3.862	−0.351	−6.375	−6.024	−0.351
4-Quinolinecarboxylic acid	173.17	1.282	0.252	0.640	−4.518	4.210	−0.308	−6.793	−6.485	−0.308
1-Isoquinolinecarboxylic acid	173.17	1.421	0.252	0.625	−4.132	−4.112	−0.020	−6.546	−6.526	−0.020
2-Methyl-5-butylpyridine	149.24	3.781	0.000	0.306	−1.113	−1.483	0.370	−5.887	−6.257	0.370
2,6-Dimethoxypyridine	139.15	3.879	0.000	0.554	−1.129	−1.734	0.605	−6.001	−6.606	0.605
6-Methoxy-8-nitroquinoline	204.19	0.940	0.128	0.843	−4.332	−4.624	0.292	−6.265	−6.557	0.292
2-Amino-4,6-dimethylpyridine	122.17	3.660	0.308	0.298	−2.253	−2.336	0.083	−6.906	−6.990	0.083
2-Methylindole	131.18	3.610	0.226	0.000	−1.983	−1.989	0.006	−6.586	−6.592	0.006
Naphthalene	128.17	2.784	0.000	0.000	−1.746	−1.524	−0.222	−5.523	−5.302	−0.222
1-Bromonaphthalene	207.08	3.857	0.000	0.000	−1.726	−1.342	−0.384	−6.576	−6.192	−0.384
1-Methylnaphthalene	142.20	3.848	0.000	0.000	−1.592	−0.926	−0.666	−6.433	−5.766	−0.666
2-Methoxynaphthalene	158.20	2.528	0.000	0.321	−1.918	−2.378	0.460	−5.439	−5.899	0.460
1-Ethoxynaphthalene	172.23	3.789	0.000	0.313	−1.883	−1.638	−0.245	−6.665	−6.420	−0.245
1,6-Dihydroxynaphthalene	160.17	3.497	0.501	0.000	−3.570	−3.444	−0.126	−8.060	−7.934	−0.126
2-Naphthyaetic acid	186.21	3.177	0.252	0.357	−2.790	−2.922	0.132	−6.960	−7.092	0.132
2-Methylbenzimidazole	132.17	3.136	0.232	0.318	−2.979	−2.516	−0.463	−7.108	−6.645	−0.463
2-Methyl-5-nitrobenzimidazole	177.16	2.249	0.342	0.555	−3.698	−3.753	0.055	−6.940	−6.995	0.055
2-Hydroxybenzimidazole	134.14	1.681	0.498	0.300	−3.922	−4.292	0.370	−6.596	−6.966	0.370
3-Phenyl-1-propylamine	135.21	3.847	0.236	0.330	−1.457	−1.404	−0.053	−6.297	−6.244	−0.053
1-Phenyl-2-propanol	136.19	3.838	0.210	0.392	−2.015	−2.070	0.055	−6.846	−6.900	0.055
3-Phenyl-1-propanol	136.19	3.869	0.209	0.395	−2.324	−2.048	−0.276	−7.186	−6.911	−0.276
3-Methylthiophene	98.17	4.015	0.000	0.000	−0.407	−0.530	0.123	−5.415	−5.538	0.123
3-Thiopheneacetic acid	142.18	3.569	0.252	0.364	−2.411	−2.384	−0.027	−6.973	−6.946	−0.027
3-Thiophenecarboxaldehyde	112.15	4.022	0.130	0.282	−1.612	−1.464	−0.148	−6.627	−6.479	−0.148
3-Aminobenzoic acid	137.14	2.007	0.552	0.357	−3.727	−4.228	0.501	−6.727	−7.228	0.501
m-Toluic acid	136.15	3.330	0.252	0.357	−2.309	−2.497	0.188	−6.632	−6.819	0.188
m-Anisic acid	152.15	3.193	0.252	0.677	−2.579	−2.852	0.273	−6.765	−7.038	0.273
3-Chlorobenzoic acid	156.57	3.071	0.252	0.357	−2.371	−2.797	0.426	−6.435	−6.862	0.426
3-Nitrobenzoic acid	167.12	3.341	0.374	0.583	−2.735	−3.046	0.311	−7.069	−7.380	0.311
4-Aminobenzoic acid	137.14	2.637	0.556	0.363	−3.488	−3.826	0.338	−7.118	−7.456	0.338
p-Anisic acid	152.15	2.223	0.252	0.681	−3.226	−3.483	0.257	−6.442	−6.699	0.257
4-Chlorobenzoic acid	156.57	2.291	0.252	0.357	−3.088	−3.304	0.216	−6.372	−6.588	0.216
4-Acetoxybenzoic acid	180.16	2.511	0.252	0.725	−3.107	−3.501	0.394	−6.611	−7.005	0.394

Table 1 (Continued)

Compounds	MW	log C_s	Σe_+	Σe_-	Exp. log J_{mss}	Pred. log J_{mss}	Residual	Exp. log P	Pred. log P	Residual
Benzyl amine	107.16	3.962	0.242	0.319	−1.387	−1.159	−0.228	−6.342	−6.114	−0.228
Benzyl alcohol	108.14	3.985	0.213	0.382	−2.222	−1.793	−0.429	−7.200	−6.771	−0.429
p-Xylene	106.17	3.912	0.000	0.000	−0.457	−0.650	0.193	−5.362	−5.554	0.193
1,3-Diisopropylbenzene	162.28	3.722	0.000	0.000	−1.060	−1.138	0.078	−5.775	−5.853	0.078
Mesitylene	120.20	3.857	0.000	0.000	−0.701	−0.777	0.076	−5.551	−5.626	0.076
1,3,5-Triethylbenzene	162.28	3.725	0.000	0.000	−1.083	−1.136	0.053	−5.801	−5.854	0.053
1-Fluoro-3-nitrobenzene	141.10	3.973	0.120	0.226	−1.620	−1.594	−0.026	−6.586	−6.559	−0.026
3-Methoxyacetophenone	150.18	3.862	0.000	0.699	−1.990	−2.038	0.048	−6.845	−6.894	0.048
p-Anisaldehyde	136.15	3.915	0.132	0.685	−2.070	−2.097	0.027	−6.978	−7.004	0.027
4-Isopropylbenzaldehyde	148.21	3.819	0.133	0.366	−1.640	−1.923	0.283	−6.452	−6.735	0.283
Methyl 4-*tert*-butylbenzoate	192.26	3.714	0.000	0.344	−1.710	−1.865	0.155	−6.417	−6.572	0.155
Bibenzyl	182.27	2.921	0.000	0.000	−1.980	−1.788	−0.192	−5.894	−5.702	−0.192
3-Phenoxytoluene	184.24	3.756	0.000	0.260	−2.010	−1.657	−0.353	−6.759	−6.406	−0.353
2′-Aminoacetophenone	135.17	3.913	0.304	0.386	−2.160	−2.271	0.111	−7.066	−7.176	0.111
o-Anisaldehyde	136.15	3.918	0.131	0.684	−2.030	−2.092	0.062	−6.941	−7.003	0.062
2′-Chloroacetophenone	154.60	3.933	0.000	0.377	−1.830	−1.528	−0.302	−6.756	−6.454	−0.302
2′-Chlombenzaldehyde	140.57	3.948	0.134	0.362	−1.580	−1.788	0.208	−6.521	−6.729	0.208
1-Chloro-2-nitrobenzene	157.56	3.932	0.122	0.226	−1.540	−1.734	0.194	−6.465	−6.659	0.194
2-Chlorotoluene	126.59	3.932	0.000	0.000	−0.771	−0.769	−0.002	−5.696	−5.694	−0.002
Ethyl salicylate	166.18	3.833	0.000	0.364	−1.610	−1.649	0.039	−6.436	−6.474	0.039
2-Fluoroaniline	111.12	4.015	0.149	0.000	−1.310	−1.261	−0.049	−6.318	−6.269	−0.049
2-Fluorobenzaldehyde	124.11	3.977	0.000	0.365	−1.300	−1.282	−0.018	−6.270	−6.253	−0.018
1-Fluoro-2-nitrobenzene	141.10	3.977	0.122	0.226	−1.840	−1.598	−0.242	−6.810	−6.568	−0.242
2-Fluoropropiophenone	152.17	3.860	0.000	0.381	−1.440	−1.566	0.126	−6.293	−6.419	0.126
2-Fluorotoluene	110.13	3.954	0.000	0.000	−0.349	−0.648	0.299	−5.296	−5.595	0.299
2′-Hydroxyacetophenone	136.15	3.919	0.000	0.385	−1.780	−1.429	−0.351	−6.692	−6.341	−0.351
2′-Isopropylaniline	135.21	3.849	0.300	0.000	−1.690	−2.181	0.491	−6.532	−7.023	0.491
2′-Methoxyacetophenone	150.18	3.861	0.000	0.700	−2.020	−2.041	0.021	−6.874	−6.895	0.021
Methyl 2-nitrobenzoate	181.15	3.849	0.127	0.587	−2.680	−2.325	−0.355	−7.522	−7.167	−0.355
Methyl 2-methoxybenzoate	166.18	3.843	0.000	0.679	−2.190	−2.124	−0.066	−7.026	−6.960	−0.066
Methyl salicylate	152.15	3.887	0.000	0.364	−1.670	−1.522	−0.148	−6.550	−6.402	−0.148
2-Nitrotoluene	137.14	3.928	0.118	0.230	−1.720	−1.594	−0.126	−6.641	−6.515	−0.126
o-Xylene	106.17	3.914	0.000	0.000	−0.644	−0.648	0.004	−5.551	−5.555	0.004
2-Nitrobenzoic acid	167.12	3.361	0.127	0.587	−2.860	−2.550	−0.310	−7.214	−6.904	−0.310
Salicylic acid	138.12	3.345	0.252	0.364	−2.570	−2.503	−0.067	−6.908	−6.841	−0.067
4-Hydroxybenzamide	137.14	2.841	0.610	0.390	−3.830	−3.822	−0.008	−7.664	−7.657	−0.008
3-Hydroxy-4-methoxybenzoic acid	168.15	1.654	0.496	0.684	−4.370	−4.338	−0.032	−7.017	−6.985	−0.032
4-Chloro-3-nitroacetophenone	199.50	1.839	0.127	0.609	−3.330	−3.771	0.441	−6.162	−6.603	0.441
1,2,4-Trimethylbenzene	120.20	3.861	0.000	0.000	−0.740	−0.774	0.034	−5.594	−5.628	0.034
Phenylurea	136.15	2.782	0.590	0.391	−3.310	−3.799	0.489	−7.085	−7.574	0.489
Benzohydroxamic acid	137.14	2.873	0.470	0.657	−3.270	−3.315	0.045	−7.136	−7.181	0.045
Benzamide	121.14	2.807	0.362	0.385	−3.070	−3.058	−0.012	−6.870	−6.857	−0.012

Ethylcinamate	176.22	3.775	0.000	0.363	−1.950	−1.750	−0.200	−6.718	−6.518	−0.200
Phenylacetate	136.15	3.897	0.000	0.364	−1.650	−1.412	−0.238	−6.540	−6.301	−0.238
Benzonitrile	103.12	3.991	0.000	0.328	−1.550	−1.080	−0.470	−6.534	−6.064	−0.470
Thioanisole	124.21	3.930	0.000	0.105	−1.390	−0.916	−0.474	−6.313	−5.839	−0.474
Iodobenzene	204.01	3.951	0.000	0.000	−1.300	−1.261	−0.039	−6.244	−6.205	−0.039
Butylphenylether	150.22	3.794	0.000	0.318	−1.250	−1.499	0.249	−6.037	−6.287	0.249
Styrene	104.15	3.941	0.000	0.000	−0.711	−0.617	−0.094	−5.645	−5.551	−0.094
2′-Chlorophenoxyacetic acid	186.59	2.911	0.254	0.663	−2.830	−3.255	0.425	−6.734	−7.159	0.425
3-*tert*-Butylphenol	150.22	3.760	0.263	0.000	−1.900	−2.176	0.276	−6.653	−6.929	0.276
Methyl 4-*tert*-butylbenzoate	192.26	3.714	0.000	0.344	−1.710	−1.865	0.155	−6.417	−6.572	0.155
4-*tert*-Butylbenzoic acid	178.23	3.087	0.253	0.344	−2.759	−2.924	0.165	−6.839	−7.005	0.165
4-*tert*-Butyltoluene	148.25	3.760	0.000	0.000	−0.920	−1.022	0.102	−5.673	−5.775	0.102
2-(*m*-Hydroxyphenoxy)ethanol	154.17	3.470	0.458	0.711	−3.540	−3.001	−0.539	−8.003	−7.464	−0.539
4-Methoxybenzyl acetate	180.00	3.784	0.000	0.693	−2.130	−2.274	0.144	−6.907	−7.051	0.144
Phenoxyacetic acid	152.15	3.506	0.254	0.664	−2.458	−2.645	0.187	−6.957	−7.144	0.187
3-Phenylbutyraldehyde	148.21	3.828	0.135	0.375	−1.959	−1.932	−0.027	−6.780	−6.753	−0.027
dl-2-Phenylpropionaldehyde	134.18	3.877	0.137	0.372	−1.686	−1.811	0.125	−6.556	−6.681	0.125
3-Methoxyacetophenone	150.18	3.862	0.000	0.699	−1.990	−2.038	0.048	−6.845	−6.894	0.048
m-Nitrobenzaldehyde dimethylacetal	197.00	3.781	0.230	0.912	−2.250	−2.867	0.617	−7.024	−7.641	0.617
Ethyl 2-(4-chlorophenoxy) -2-methylpropionate	242.71	3.672	0.000	0.614	−2.010	−2.634	0.624	−6.675	−7.299	0.624
Propyl paraben	180.20	3.407	0.250	0.362	−2.720	−2.730	0.010	−7.120	−7.130	0.010
2-Isopropylaniline	135.21	3.849	0.296	0.000	−1.690	−2.164	0.474	−6.532	−7.006	0.474
3-Chloro-4-methylaniline	141.60	3.916	0.296	0.000	−1.960	−2.162	0.202	−6.869	−7.071	0.202
3-Amino-1,2,4-triazole	84.08	2.771	0.689	0.470	−3.270	−3.638	0.368	−7.034	−7.403	0.368
2-Pyrazinecarboxylic acid	124.10	1.397	0.253	0.862	4.067	−3.929	−0.138	−6.457	−6.319	−0.138
3-Amino-5,6-dimethyl-1,2,4-triazine	124.15	1.451	0.326	0.739	−3.865	−3.930	0.065	−6.309	−6.374	0.065
Anthracene	178.23	0.802	0.000	0.000	−3.839	−3.137	−0.702	−5.634	−4.932	−0.702
Acridine	179.22	2.780	0.000	0.303	−2.638	−2.323	−0.315	−6.411	−6.096	−0.315
2-Quinoxalinol	146.15	1.242	0.258	0.526	−4.164	−4.015	−0.149	−6.399	−6.251	−0.149
2,4-Dimethyl-6-hydroxypyrimidine	124.14	2.446	0.257	0.535	−3.300	−3.093	−0.207	−6.739	−6.532	−0.207
4-Methylpyrimidine	94.12	4.040	0.000	0.535	−1.022	−1.307	0.285	−6.055	−6.340	0.285
Isoquinoline	129.16	3.930	0.000	0.297	−1.677	−1.242	−0.435	−6.600	−6.165	−0.435
Methoxymethylphenyl sulfide	154.23	3.832	0.000	0.443	−1.684	−1.692	0.008	−6.509	−6.517	0.008
3-Iodoanisole	234.04	3.924	0.000	0.321	−1.805	−1.965	0.160	−6.722	−6.882	0.160
4-Chlorobenzalcohol	142.59	3.549	0.213	0.382	−2.504	−2.300	−0.204	−7.046	−6.842	−0.204
3-Chloroaniline	127.57	3.976	0.300	0.000	−2.015	−2.049	0.034	−6.984	−7.018	0.034
2-Chloroanisole	142.59	3.930	0.000	0.320	−1.761	−1.365	−0.396	−6.684	−6.288	−0.396
4-Bromoverratrole	217.07	3.842	0.000	0.647	−2.340	−2.407	0.067	−7.175	−7.242	0.067
4-Bromotoluene	171.04	3.910	0.000	0.000	−1.421	−1.073	−0.348	−6.324	−5.976	−0.348
o-Anisidine	123.16	3.948	0.294	0.327	−2.023	−2.122	0.099	−6.964	−7.063	0.099
3′-Fluorobenzylchloride	144.58	3.917	0.000	0.110	−1.120	−1.065	−0.055	−6.030	−5.974	−0.055
2-Chloro-4′-fluoroacetophenone	172.59	3.373	0.000	0.482	−1.937	−2.170	0.233	−6.303	−6.535	0.233
4-Chloro-4′-fluorobutyrophenone	200.64	3.784	0.000	0.505	−2.210	−2.121	−0.089	−6.987	−6.897	−0.089
4-Fluoronitrobenzene	141.10	3.974	0.119	0.228	−1.600	−1.591	−0.009	−6.567	−6.559	−0.009
4-Methoxybenzylacetate	180.20	3.783	0.000	0.697	−2.130	−2.282	0.152	−6.906	−7.058	0.152
Ethyl 2-methylbenzoate	164.21	3.798	0.000	0.361	−1.480	−1.654	0.174	−6.271	−6.445	0.174
2-Fluorobenzoic acid	140.11	3.453	0.252	0.359	−2.290	−2.443	0.153	−6.736	−6.890	0.153
5-Methylbenzimidazole	132.17	3.525	0.369	0.306	−3.076	-2.680	−0.396	−7.594	−7.198	−0.396

data set, compounds which were shown to be capable of intramolecular hydrogen bonding include salicylic acid, methyl salicylate, ethyl salicylate, 8-hydroxyquinoline, 8-quinolinecarboxylic acid, 2-fluoroaniline, 2-fluorobenzaldehyde, 2′-hydroxyacetophenone and 2-nitrobenzoic acid.

An unconjugated electron pair(s) was defined as the unshared electron pair(s) in the outer shell of the atom which must not form a hyperconjugated system with a neighboring π-electron system.

The empirical model previously developed correlating flux through the PDMS membrane to partial atomic charges, mole fraction solubility and molecular weight is given in Eq. 4 (Chen et al., 1993):

$$\log J_{mss} = 0.256 - 4.176 \sum e_H - 1.388 \sum e_p + 3.807 (\sum e_H \times \sum e_p) + 0.634 \log MF - 0.008\ MW - 0.753\ \text{imidazole} + 0.626\ \text{amine} \quad (4)$$

$$s = 0.217;\ r^2 = 0.972;\ F = 468.3;\ n = 103$$

where J_{mss} is the maximum steady-state flux (μmol/s/cm^2), e_H denotes the charge value on a hydrogen with charge higher than 0.1; e_P is the absolute charge value of a heteroatom which contain unshared electron pairs in the outer shell and all of which are unconjugated; MF represents mole fraction solubility of diffusant in isopropyl alcohol; MW denotes molecular weight (g/mol); imidazole and amine are indicator variables for the imidazole class and for aliphatic amines.

Comparison of Eqs. 2 and 4 shows that the mole fraction solubility term in Eq. 4 corresponds to the solubility term in Eq. 2, and all the other terms on the right hand side of Eq. 4 described the membrane permeability, a product of partition coefficient and diffusion coefficient. Both the partition coefficient and the diffusion coefficient depend on the solute-solvent-membrane interaction energy. Molecular interaction modes can be classified into three types: dispersion, polar, and hydrogen bonding interactions (Hansen, 1967). Dispersion energy is related to polarizability, which in turn is related to the size of the interacting species. In addition, the energy for the creation of a cavity in the membrane during the diffusion process is also related to the size of the diffusing molecule. Molecular weight is an approximation of molecule size and thus the MW term explained part of the interaction energy of the system. Both polar and hydrogen bonding interactions are electrostatic in nature. Consequently, the charge terms in Eq. 4 roughly characterized the polar and hydrogen bonding interaction in the system.

It is interesting to observe that atomic charge correctly represents the electronic interaction between the diffusion medium and most of the compounds under study. One of the advantages of using partial atomic charge is that partial charges provide digitized parameters for many different structural characteristics. The difference between benzene and pyridine can be represented by the partial charge of the nitrogen on the pyridine ring and serves as an example of such an advantage. The polarity difference among different substituents can also be compared in terms of atomic charge. However, partial charge, calculated by the present method and chosen by the stated rules, does not explain the specific electronic effect of the imidazole ring system and compounds of aliphatic amine.

The atomic charge of the nitrogen in a nitro group was not used in the previous model by the stated selection rules since this nitrogen does not contain an unshared electron pair in the outer shell according to hybridization theory. The nitrogen in the nitro group possesses a positive charge value, while the nitrogen in all other groups possesses a negative charge value. Subsequent examination found that if the positive charge of the nitrogen in nitro group is included, better predicted results can be obtained for nitro compounds. Thus, the positive charge on the nitrogen in a nitro group was included in addition to the charges selected by the previously stated rules.

In addition, molar solubility of a diffusant is easier to determine then mole fraction solubility and thus is a more convenient parameter to be used in QSTR study. For the above reasons, the QSTR model was reanalyzed using the original data set (Chen et al., 1993). The resultant relationship is given by Eq. 5:

$$\log J_{mss} = -2.497 - 4.339 \sum e_+ - 1.531 \sum e_- + 4.065 (\sum e_+ \times \sum e_-) + 0.649 \log C_s - 0.00651 \text{ MW} - 0.640 \text{ imidazole} + 0.689 \text{ amine} \quad (5)$$

$s = 0.238$; $r^2 = 0.966$; $F = 386.5$; $n = 103$

where Σe_+ is summation of the charge values of hydrogen atoms with charge higher then 0.1 and the positive charge of a nitrogen atom in a nitro group, and Σe_- represents the sum of the absolute charge values of all other heteroatoms with unshared electron pairs in the same molecule.

Both the regression coefficients and the quality of the calculation using Eq. 5 are similar to those of Eq. 4. The change of the constant term in Eq. 5 resulted from the use of solubility in units of μmol/ml, which was about 1000 times larger in value than mole fraction solubility. Better prediction results were obtained by using Eq. 5 rather than Eq. 4.

Eq. 5 was applied to predict the flux of 171 new compounds which were not included in the equation development. In the present data set, the imidazole class is not included. Thus, the indicator variable for this type of compound can be removed and the model for prediction is further simplified to Eq. 6.

$$\log J_{mss} = -2.497 - 4.339 \sum e_+ - 1.531 \sum e_- + 4.065 (\sum e_+ \times \sum e_-) + 0.649 \log C_s - 0.00651 \text{ MW} + 0.689 \text{ amine} \quad (6)$$

Predicted results using Eq. 6 are listed in Table 1. The excellent relationship between the predicted and the experimental maximum steady-state flux is expressed by Eq. 7:

$$\text{Exp. } \log J_{mss} = -0.088 + 0.954 \text{ Pred. } \log J_{mss} \quad (7)$$

$s_p = 0.268$; $r_p^2 = 0.922$; $F_p = 2002$; $n = 171$

where the subscript p represents prediction.

Ideally, the slope of the plot of experimental versus predicted flux should be unity and the intercept should be zero. The t-ratio of the intercept in Eq. 7 is -1.77, which shows that the intercept is not significantly different from zero. The coefficient of 0.954 in Eq. 7 is also close to the ideal value of unity. The small standard error of prediction indicates that accurate prediction is attained. The prediction capability of Eq. 6 is also demonstrated by the number of new compounds that the equation predicted. Usually, the number of new data points that a conventional quantitative structure-activity relationship (QSAR) model can predict well is much smaller than the number of compounds used to develop the model. Results in this study show that atomic charge approach is not subject to such a limitation. The number of new compounds predicted by Eq. 6 is almost twice the number used to develop the model. In addition, new classes of compounds, such as triazoles, pyrimidines, isoquinolines, acridine and anthracene, plus new functionalities such as urea, amide, acetal and organic sulfide are also included in the predicted data set. The excellent predicted results for such an extended data set indicate that the atomic charge model is robust.

The contribution of atomic charges to flux was further correlated to the apparent permeability (P). The previously reported data of 103 compounds (Chen et al., 1993) was again used as a training data set to develop an equation for prediction. Results are given by Eq. 8.

$$\log P = -3.490 - 4.339 \sum e_+ - 1.531 \sum e_- + 4.065 (\sum e_+ \times \sum e_-) - 0.351 \log C_s - 0.00651 \text{ MW} - 0.640 \text{ imidazole} + 0.689 \text{ amine} \quad (8)$$

$s = 0.238$; $r^2 = 0.814$; $F = 59.3$; $n = 103$.

Except for the constant and the solubility terms, all the other coefficients and the standard error of estimation in Eq. 8 are the same as those in Eq. 5. The difference in the constants resulted

from the multiplication of flux by a membrane thickness of 0.1016 cm. The change of coefficient for log C_s also resulted from the division of flux by solubility in Eq. 3, and the coefficient of log C_s in Eq. 8 was exactly as expected. The negative sign for log C_s in Eq. 8 indicates that solutes with higher solubility in the IPA solvent will be less likely to partition into the membrane. As a result, partition coefficient and hence permeability may be smaller for a more soluble substance. The excellent agreement of Eqs. 5 and 8 shows that the attribution of charge effects to apparent permeability is valid. The decrease in R-square and the F-value for Eq. 8 resulted from a smaller range of log P than J_{mss} in the same data set.

Eq. 8 was used to predict the apparent permeability of 171 new compounds. Predicted results are listed in Table 1. It is interesting to note that the prediction residual is the same for both log P and log J_{mss} for each compound, and, as a result, the standard error of prediction for log P remains the same as that for log J_{mss}. A standard error of 0.264 shows that prediction is statistically accurate to within a factor of two. These results indicate that the explanatory capability of the predictors remains the same for both targeted properties.

The advantage of using the present approach for flux and permeability is that all the parameters needed are easily accessible. The only parameter that required experimental measurement is solubility. Solubility in IPA can also be estimated using a fragmental approach that has been developed in this laboratory and will be reported separately. Thus, permeability and flux of small molecules through the PDMS membrane can now be predicted without knowing the actual partition coefficient and the diffusion coefficients in the membrane.

References

Bodor, N., Gabanyi, Z and Wong, C.K., A new method for the estimation of partition coefficient. *J. Am. Chem. Soc.*, 111 (1989) 3783–3786.

Chen, Y., Yang, W.L. and Matheson, L.E., Prediction of flux through polydimethylsiloxane membranes using atomic charge calculations. *Int. J. Pharm.*, 94 (1993) 81–88.

Cramer, C.J., Famini, G.R. and Lowrey, A.H., Use of calculated quantum chemical properties as surrogates for solvatochromic parameters in structure-activity relationship. *Acc. Chem. Res.*, 26 (1993) 599–605.

Crank, J. and Park, G.S., *Diffusion in Polymer*, Academic Press, NY, 1968 pp. 1–39.

Gasteiger, J. and Marsili, M., Iterative partial equilization of orbital electronegativity — A rapid access to atomic charges. *Tetrahedron*, 36 (1980) 3219–3228.

Daynes, H.A., The process of diffusion through a rubber membrane. *Proc. Roy. Soc. London*, A97 (1920) 286–307.

Hansen, C., The three dimensional solubility parameter-key to paint component affinities. I. Solvents, plasticizers, polymers and resins. *J. Paint Technol.*, 39(1967) 104–117.

Hu, M.W. and Matheson, L.E., The development of a predictive method for the estimation of flux through polydimetbylsiloxane membranes: III. Application to a series of substituted pyridines. *Pharm. Res.*, 10 (1993) 732–736.

Kantola, A., Villar, H.O. and Loew, G.H., Atom based parametrization for a conformationally dependent hydrophobic index. *J. Compt. Chem.*, 12 (1991) 681–689.

Klopman, G., Namboodiri, K and Schochet, M., Simple method of computing the partition coefficient. *J. Compt. Chem.*, 1 (1985) 28–38.

Klopman, G. and Iroff, D., Calculation of partition coefficients by the charge density method. *J. Compt. Chem.*, 2 (1981) 157–160.

Laoratthaphong, P., *Ph.D. Thesis*, The University of Iowa, Iowa City, Iowa, 1989.

Levine, I.N., *Physical Chemistry*, 3rd Edn., McGraw-Hill, New York, 1988, pp. 685–693.

Liu, R., *Ph.D. Thesis*, The University of Iowa, Iowa City, Iowa, 1990.

Liu, R. and Matheson, L.E., Comparative molecular Field analysis combined with physicochemical parameters for prediction of polydimethylsiloxane membrane flux in isopropanol. *Pharm. Res.*, 11 (1994) 257–266.

Marsili, M. and Gasteiger, J., π-Charge distribution from molecular topology and π orbital electronegativity, *Croatica Chemica Acta*, 53 (1980) 601–614.

Matheson, L.E. and Hu, M.W., The development of a predictive method for the estimation of flux through polydimetbylsiloxane membranes: IV. Application to a series of substituted quinolines. *Pharm. Res.*, 10 (1993) 839–842.

Matheson, L.E., Vayumhasuwan, P. and Moeckly, D.M., The development of a predictive method for the estimation of flux through polydimetbylsiloxane membranes: II. Derivation of a diffusion parameter and its application to multisubstituted benezenes. *Int. J. Pharm.*, 77 (1991) 163–168.

Moeckly, D.M. and Matheson, L.E., The development of a predictive method for the estimation of flux through polydimetbylsiloxane membranes: I. Identification of critical variables for a series of substituted benzenes. *Int. J. Pharm.*, 77 (1991) 151–162.

Tripos, *SYBYL® Manual*, Tripos Assoc. Inc., St. Louis, MO, 1992.

Yang, W.L., *Ph.D. Thesis*, University of Iowa, Iowa City, Iowa, 1992.