International Journal of Pharmaceutics, 77 (1991) 151–162

IJP 02562

The development of a predictive method for the estimation of flux through polydimethylsiloxane membranes: I. Identification of critical variables for a series of substituted benzenes

David M. Moeckly * and Lloyd E. Matheson

Division of Pharmaceutics, College of Pharmacy, University of Iowa, Iowa City, IA 52242 (U.S.A.)

(Received 28 January 1991)
(Modified version received 29 May 1991)
(Accepted 26 June 1991)

Key words: Membrane diffusion; Linear free energy relationship; Partition coefficient; Molecular volume; Diffusion prediction; Monosubstituted benzene

Summary

The steady-state flux of 31 monosubstituted benzene derivatives was determined through polydimethylsiloxane membranes using isopropyl alcohol as the solvent. These diffusants constituted a diverse group of compounds possessing a wide range of hydrophobic, steric and electronic characteristics. Various parameters representing these physico-chemical properties were employed to develop an empirical model capable of relating the flux to these characteristics of the substituent on the benzene ring. Molecular volume and hydrophobicity greatly influenced the flux, while electronic properties of the substituent had a relatively small, but significant, effect on the flux. Higher diffusion rates were observed for compounds possessing lipophilic, exiguous, electron-donating substituents. Molar refractivity was the best descriptor of molecular volume while cyclohexane-water fragmental constants were better predictors of hydrophobicity.

Introduction

The absorption phase of drug delivery occurs in virtually all routes of administration. Absorption through some barriers, such as the skin, is the rate-limiting step in the onset of action of a drug. It is readily apparent that the ability to predict the absorption rate of a drug would be useful both in the estimation of the time course of a drug in the body and also in the selection of the best absorbed congener of a class of drugs.

Theoretical, as well as empirical relationships, emphasize the importance of the effect of partition coefficient on flux. Based on this, many studies have been performed linking flux to a hydrophobic parameter (Herzog and Swarbrick, 1971; Nasim et al., 1972; Michaels, et al., 1975; Khordagy et al., 1981; Shah et al., 1981; Bronaugh and Congdon, 1984).

Molecular size has also been shown to be an important parameter affecting flux. Hung and Autian (1972) reported that the diffusivity of a

Correspondence: L.E. Matheson, College of Pharmacy, University of Iowa, Iowa City, IA 52242, U.S.A.
* *Present address*: Sandoz Pharmaceuticals Corp., Lincoln, NE 68501, U.S.A.

series of aliphatic alcohols could be linearly related to molecular volume. It was noted that branching of an alcohol resulted in a decrease in the diffusion coefficient due to an increase in the molecular cross-sectional area.

Lacey and Cowsar (1974) concluded from a study of steroid diffusion through a polydimethylsiloxane (PDMS) membrane that diffusivity was a function of both the polarity and cross-sectional area of the molecule. Lien (1981) and Lien and co-workers (1973, 1980) performed retrospective statistical analyses on numerous sets of percutaneous absorption data using various organic phase-water partition coefficients, molecular weight, molar refractivity and solubility.

The purpose of this work was to develop a relationship between the flux of a chemical in a polymer membrane, to be used for the prediction of flux, and various physico-chemical parameters that can be easily calculated or found in the literature.

Materials and Methods

Materials

The flux of 31 monosubstituted benzene derivatives through a PDMS membrane was measured in triplicate using an in vitro technique. The diffusants are listed in Table 1 and were used as received. PDMS sheeting supported with an inert filler (Silastic Medical Grade NRV, Dow Corning Corp., Midland, MI), 0.102 cm thickness, was used as the model membrane. Two additional thicknesses, 0.0508 and 0.152 cm, were used for determination of diffusion layer contributions (Hwang et al., 1971). Isopropyl alcohol was used as the solvent for all diffusion experiments in order to increase the number of compounds that could be studied because of increased solubility in this solvent.

Equipment

A diffusion cell, designed with external stirring control (Medical Instruments, University of Iowa, Iowa City, IA), was used in the study. The diffusional opening between the cell halves is 3.2 cm in diameter and the volume of each cell half is approx. 10 ml. The outer portion of the cell including the water jacket is composed of Plexiglas, while the inner portion is Teflon. The face plates are held together by four screws. A Teflon O-ring, seated between the compartments, seals the unit upon assembly of the cell. Nylon inlet and outlet ports connect the water jacket to a water bath and a constant temperature circulator (Model IC-2, Brinkmann Instruments, Westbury, NY). Stainless-steel inlet and outlet ports allow access to the inner solution compartments. All materials which come into contact with either donor or receiver solution are made of Teflon. Circular stirrers, with a cross-hair pattern raised on their surface, are held in place and away from the membrane surface by an O-ring. A hole bored diametrically into the stirrer contains a magnetic stirring bar. The stirrers are rotated by externally mounted 48 lb magnets driven by d.c. motors (CYQM 23061-5-2, Barber-Colman, Rockford, IL) which, in turn, are controlled by a variable-voltage transformer (Tech II, Model 2800, Model Rectifier Corp., Edison, NJ). The maximum voltage setting, corresponding to a stirring speed of 575 rpm, was used for all diffusion experiments.

Experimental procedures

The solubility of all solid diffusants was determined in isopropyl alcohol. An excess of material was added to 5 ml of isopropyl alcohol in a screw-capped culture tube. The tubes were rotated in a water bath maintained at 30 °C by a constant temperature circulator (Haake, Model ED, Saddle Brooke, NJ) for at least 48 h. The supernatant fluid was removed by withdrawing the solution through a pipette filter tip (2 μm, Supelco, Bellefonte, PA) fitted on a disposable Pasteur pipette preheated to 35 °C to prevent precipitation. The resulting solution was placed in a screw-capped vial and maintained at 30 °C until ready for analysis. After appropriate dilution, the concentration was determined using a UV spectrophotometer (Model 240, Gilford Laboratories, Inc., Oberlin, OH). The solubility of the solid diffusants in isopropyl alcohol is given in Table 2.

The PDMS sheeting was cut into 2 inch circles and soaked in isopropyl alcohol for at least 24 h

prior to mounting in the diffusion cell. The thickness of each membrane was measured after conditioning and before mounting in the diffusion cell, using a method described by Garrett and Chemburkar (1968).

Liquid diffusants were used as the neat liquids for the donor solutions. The donor solutions of the solid diffusants were used at 50% of their saturation solubility in isopropyl alcohol. All experiments were carried out at 30 °C.

The isopropyl alcohol, comprising the receiver solution, was placed in a jacketed beaker of either 50, 100 or 500 ml capacity, depending on the molar absorptivity and flux in order to maintain sink conditions and the absorbance of the solution in the linear region of the standard curve. Receiver solution was pumped at a rate of 9 cm^3 per min by means of Teflon tubing (1/16 inch × 1/8 inch, Cole-Parmer Instrument Co., Chicago, IL) from the diffusion cell receiver compartment to a flow-through cell mounted in the spectrophotometer to the external solution reservoir in the jacketed beaker and finally back to the diffusion cell by a dual-piston pump (Minipump, Laboratory Data Control, Chicago, IL) until a stable baseline was obtained on the spectrophotometer. Tubing length between the diffusion cell and the flow-through cell was approx. 12 inches The time for diffusion through the membrane and its time of measurement differed by less than 1 s. The path length of the flow-through cell was either 0.01 cm (Precision Cells, Farmingdale, NY) or 1 cm (Hellma, Germany). The external reservoir solution was stirred with a Teflon stirrer driven by a magnetic stirring device (Magnestir no. 214-924, Curtin Matheson Scientific Inc., Houston, TX). After establishment of the stable baseline, donor solution was pumped in a manner analogous to that of the receiver solution through the donor compartment and back to a 25 ml Erlenmeyer flask reservoir maintained at 30 °C in the water bath. Blank diffusion experiments were performed for slowly penetrating diffusants to ensure interfering materials were not leaching from the membrane material.

Absorbance values were recorded by a microcomputer (Commodore 64, Commodore Business Machines, Inc., Westchester, PA) connected to the spectrophotometer by an analog-to-digital converter (Model CBC-12/4 ADC, Chesapeake Bay Computers, Annapolis, MD). Software written for the microcomputer enabled the diffusion profile to be displayed in real time and subsequent calculation of the steady-state flux. The flux obtained experimentally for the solid diffusants was multiplied by two in order to estimate the maximal steady-state flux at saturation, since these donor solutions were at 50% of their saturation solubility. Correlation of the flux values with physico-chemical parameters was carried out using a general purpose data analysis software package (Minitab Version Release 5.1, State College, PA) installed on a mainframe computer (Model 9955, Prime Computer Corp., Natick, MA).

Results and Discussion

Benzene was selected as the penetrant for the analysis of the diffusion layer effect, since it possesses one of the highest steady-state diffusion rates among the studied compounds, making it more susceptible to boundary layer effects. A linear relationship was observed between the flux of benzene and the reciprocal of the membrane thickness, indicating membrane control (Hwang et al., 1971). More complete analysis of the data indicated that 92 and 94% of the resistance was due to membrane control for the two thicker membranes used to examine this phenomenon. The small contribution of the diffusion layer to the total resistance is not unexpected, since the PDMS membranes used were quite thick (> 500 μm) and both the donor and receiver compartments of the diffusion cell were well stirred in the plane of the membrane.

The effect of the concentration of the donor solution on flux was examined by studying the diffusion of benzoic acid at both 50 and 90% of saturation. When the experimental steady-state flux values were corrected for percent of saturation in order to estimate the maximal flux, similar values were obtained (log $J_{ss} = -2.32$ and -2.22, respectively). While the actual flux values differ by about 25%, the 50% saturation level was

TABLE 1

Hydrophobic, volume and electronic substituent parameters

Label	Compound	Substituent	Hydrophobic		Substituent parameters							
			f_{oct}	f_{chex} [b]	Volume							Electronic
					MW (g/M)	V_x (A^3) [c]	MR (ml/M) [d]	Molecular connectivity [a]				σ_p [d]
								$^0\chi^v$	$^1\chi^v$	$^0\chi$	$^1\chi$	
A	Benzene sulfonamide [e,f]	$-SO_2NH_2$	−1.53	−3.62	80.1	105.0	12.30	2.00	1.16	3.50	1.79	0.75
B	Phenyl urea [e,g]	$-NH(C=O)NH_2$	−0.94	−3.66	59.0	105.0	13.70	1.99	0.99	3.28	1.97	−0.24
C	Benzohydroxamic acid [e,g]	$-(C=O)NHOH$	−1.91	−4.20	60.0	92.3	11.20	1.86	0.93	3.28	2.03	0.00
D	Benzamide [e,g]	$-(C=O)NH_2$	−1.11	−3.83	44.0	76.2	9.81	1.49	0.74	2.58	1.49	0.36
E	Benzoic acid [e,h]	$-COOH$	−0.09	−3.12	45.0	65.7	6.93	1.36	0.68	2.58	1.49	0.45
F	Biphenyl [g]	$-C_6H_5$	2.20	2.04	77.1	145.0	25.40	3.39	2.16	4.11	3.15	−0.01
G	Bibenzyl [g]	$-CH_2CH_2C_6H_5$	2.95	2.79	105.0	242.0	34.70	4.80	3.12	5.53	4.13	−0.12
H	Ethyl cinnamate [g]	$-CH=CHCO_2CH_2CH_3$	1.27	1.11	99.1	221.0	27.20	4.18	2.32	5.41	3.51	0.03
I	Diphenylmethane [g]	$-CH_2C_6H_5$	2.42	2.26	91.1	153.0	30.00	4.09	2.62	4.82	3.63	−0.09
J	Phenyl ether [g]	$-OC_6H_5$	2.34	2.07	93.1	181.0	27.70	3.80	2.32	4.82	3.63	−0.03
K	Aniline [h]	$-NH_2$	−0.85	−2.19	16.0	32.7	5.42	0.58	0.29	1.00	0.58	−0.66
L	Nitrobenzene [i]	$-NO_2$	−0.08	−0.69	46.0	59.0	7.36	1.26	0.59	0.58	0.33	0.78
M	Phenylacetate [g]	$-O(C=O)CH_3$	−0.59	−0.75	59.0	88.3	12.50	2.32	1.11	3.28	1.97	0.31
N	Acetophenone [g]	$-(C=O)CH_3$	−0.14	−0.61	43.0	83.5	11.20	1.91	0.95	2.58	1.48	0.50
O	Phenol [e,h]	$-OH$	−0.34	−3.10	17.0	24.3	2.85	0.45	0.22	1.00	0.58	−0.37

P	Benzonitrile [g]	-CN	−0.21	−0.60	26.0	43.3	6.33	0.95	0.47	1.71	1.12	0.66
Q	Benzaldehyde [g]	-(C=O)H	−0.38	−0.85	29.0	50.3	6.88	0.99	0.52	1.71	1.12	0.42
R	Methylbenzoate [i]	$-(C=O)OCH_3$	0.27	0.11	59.0	109.0	12.90	2.32	1.07	3.28	2.03	0.45
S	Thioanisole [g]	$-SCH_3$	0.81	0.65	47.1	79.9	13.80	2.23	1.84	1.71	1.12	0.00
T	Iodobenzene [g]	-I	1.45	1.29	127.0	78.2	13.90	2.50	1.25	1.00	0.58	0.18
U	Butylphenyl Ether [g]	$-O(CH_2)_3CH_3$	1.86	1.70	73.1	152.0	21.70	3.53	2.20	3.83	2.62	−0.32
V	Phenetole [g]	$-OCH_2CH_3$	0.80	0.53	45.1	84.1	12.50	2.12	1.20	2.41	1.62	−0.24
W	Anisole [g]	$-OCH_3$	0.27	0.00	31.0	61.7	7.87	1.41	0.61	1.71	1.12	−0.27
X	Butylbenzene [g]	$-(CH_2)CH_3$	2.29	2.13	57.1	133.0	19.60	3.12	2.06	3.12	2.12	−0.16
Y	Styrene [g]	$-CH=CH_2$	1.25	1.09	27.0	72.4	11.00	1.28	0.70	1.71	1.12	−0.04
Z	Ethylbenzene [g]	$-CH_2CH_3$	1.23	1.07	29.1	68.5	13.30	1.71	1.06	1.71	1.12	−0.15
a	Chlorobenzene [g]	-Cl	0.92	0.76	35.4	45.6	6.03	1.13	0.57	1.00	0.58	0.23
b	Benzotrifluoride [g]	$-CF_3$	1.33	1.17	69.0	73.7	5.02	1.63	0.82	3.50	1.79	0.54
c	Toluene [i]	$-CH_3$	0.70	0.54	15.0	40.4	5.65	1.00	0.50	1.00	0.58	−0.17
d	Benzene [k]	-H	0.18	0.02	1.0	8.2	1.03	0.00	0.00	0.00	0.00	0.00
e	Fluorobenzene [g]	-F	0.40	0.00	19.0	19.3	0.92	0.38	0.19	1.00	0.58	0.06

[a] Calculated using methods reported by Kier and Hall (1976a,b, 1983).
[b] Calculated using Eqn 11 and values in Seiler (1974).
[c] Calculated using equations and values in Verloop et al. (1976).
[d] Obtained from Hansch and Leo (1983).
[e] Contains a hydrogen-donating substituent.
[f] Pfaltz and Bauer Chemical Co., Stamford, CT.
[g] Aldrich Chemical Co., St. Louis, MO.
[h] Fisher Scientific, Fairlawn, NJ.
[i] Sigma Chemical Co., St. Louis, MO.
[j] Sargent-Welch Scientific Co., Skokie, IL.
[k] J.T. Baker Chemical Co. Phillipsburg, NJ.

TABLE 2

Solubility of solid diffusants in isopropyl alcohol

Compound	Solubility	
	mg/ml	M
Benzenesulfonamide	49.9	0.318
Biphenyl	77.4	0.503
Phenyl urea	82.4	0.606
Benzamide	77.5	0.641
Benzohydroxamic acid	103.0	0.752
Bibenzyl	152.0	0.835
Benzoic acid	311.0	2.55
Phenol	1020.0	10.8

deemed to be adequate for this work. Saturated solutions and pure liquid solutes are defined as having an activity of unity (Ferguson, 1939; Klotz, 1964). The effect of donor concentration on the flux of ethylbenzene, as a representative of the liquid diffusants, was also examined and found to be linear as can be seen from the data in Table 3.

Lieb and Stein (1971) have proposed two different mechanisms for diffusion through biological and polymeric membranes. The mechanisms are designated as s-type for simple liquids and p-type diffusion for polymeric media. A highly solvated polymeric membrane would operate as an s-type barrier, since diffusion would occur mainly through the solvent rather than the polymer. In all probability, diffusion through a swollen membrane operates by a combination of s-type and p-type diffusion (Zentner et al., 1978). PDMS expands somewhat in the presence of isopropyl alcohol ($\sim 12\%$) and to an even greater extent when exposed to aromatic solvents such as toluene and benzene (Dow Corning, 1982). The greatest

TABLE 3

Effect of donor concentration on steady-state flux for ethylbenzene through 50 μm thickness silastic membrane

Concentration (% w/w)	Steady-state flux (μM cm^{-2} s^{-1})
10	0.052
20	0.110
40	0.252
60	0.341
100	0.603

effect of membrane expansion on the diffusion process occurs when the membrane is solvated to the point where the p-type mechanism is converted to the s-type. The observed linear relationship between the steady-state flux and the donor concentration of ethylbenzene suggests that diffusion through PDMS membrane occurs via the p-type mechanism. The slope of this relationship would be expected to increase with donor concentration if swelling of the membrane caused conversion from p- to s-type diffusion.

Undoubtedly, some additional swelling is caused by a number of the more nonpolar diffusants, such as the alkyl- and halogen-substituted benzenes, since they were used as the neat liquid on the donor side; however, the fact that the diffusion runs for these penetrants were over in 40–60 min and the equal or greater uncertainty in performing these experiments at low diffusant concentration and multiplying by a large factor to obtain maximal steady-state flux caused us to choose the neat liquid diffusant approach as the more satisfactory experimental method. The linearity of the entire data set extending to the more polar solid diffusants at 50% saturation levels in isopropyl alcohol supports the presence of only a relatively small effect caused by any additional swelling by the nonpolar penetrants. Moreover, other problems arise when using low donor concentrations, such as inordinately long diffusion times, less accurate low absorbance measurements and difficulty in maintaining a constant concentration gradient.

Steady-state flux was calculated from diffusion profiles generated from the concentration of drug appearing on the receiving side of the diffusion cell at various time intervals. Experimental flux is described by the following equation which assumes the absence of diffusion layers:

$$J_{ss} = \frac{D_m K C}{h_m} \qquad (1)$$

where D_m represents the diffusion coefficient within the membrane, C is the donor concentration, K denotes the distribution coefficient between the bulk solution and membrane and h_m is the membrane thickness. The experimental

steady-state flux values are given in Table 4. The largest coefficient of variation for any of the 31 compounds studied was 6.33% and the average coefficient of variation was 2.95 ± 1.60%.

The relationship between steady-state flux and partition coefficient as shown in Eqn 1 is well known. The partition coefficient between the bathing solution and the membrane is the best hydrophobic parameter to utilize, but possesses the disadvantage of requiring experimental determination. Consequently, the use of hydrophobic parameters, which can be calculated using an additive, fragmental approach, as predictors of flux has become common (Schuhmann and Taubert, 1970; Yalkowsky and Flynn, 1973; Hansch and Leo, 1983). Rekker's (1977) fragmental constant, representing partitioning behavior in an octanol-water system, f_{oct}, was chosen for use in this work. Experimental steady-state flux values listed in Table 4 were regressed against the

TABLE 4

Experimental and calculated steady-state flux values for monosubstituted benzenes carried out in triplicate

Compound	Experimental log J_{ss}	Calculated log J_{ss}					
		Eqn 4		Eqn 12		Eqn 13	
		Calc. log J_{ss}	Residual	Calc. log J_{ss}	Residual	Calc. log J_{ss}	Residual
Benzenesulfonamide	−3.39	−3.17	−0.22	−3.11	−0.28	−3.34	−0.05
Phenyl urea	−3.31	−2.85	−0.46	−3.25	−0.06	−3.09	−0.22
Benzohydroxamic acid	−3.27	−3.36	0.09	−3.28	0.01	−3.21	−0.06
Benzamide	−3.07	−2.57	−0.50	−2.99	−0.08	−3.06	−0.01
Benzoic acid	−2.22	−1.45	−0.77	−2.41	0.19	−2.51	0.29
Biphenyl	−2.05	−1.56	−0.49	−1.63	−0.42	−1.64	−0.41
Bibenzyl	−1.98	−1.95	−0.03	−2.10	0.12	−2.09	0.11
Ethyl cinnamate	−1.95	−2.50	0.55	−2.22	0.27	−2.24	0.29
Diphenylmethane	−1.94	−1.88	−0.06	−1.93	−0.01	−1.92	−0.02
Phenyl ether	−1.81	−1.70	−0.11	−1.82	0.01	−1.82	0.01
Aniline	−1.75	−1.90	0.15	−1.84	0.09	−1.52	−0.23
Nitrobenzene	−1.72	−1.49	−0.23	−1.32	−0.40	−1.57	−0.15
Phenylacetate	−1.65	−2.44	0.79	−1.79	0.14	−1.87	0.22
Acetophenone	−1.64	−1.94	0.30	−1.62	−0.02	−1.77	0.13
Phenol	−1.57	−1.22	−0.35	−2.04	0.47	−1.81	0.24
Benzonitrile	−1.55	−1.48	−0.07	−1.18	−0.37	−1.39	−0.16
Benzaldehyde	−1.48	−1.68	0.20	−1.35	−0.13	−1.46	−0.02
Methylbenzoate	−1.46	−1.79	0.33	−1.43	−0.03	−1.57	0.11
Thioanisole	−1.39	−1.45	0.06	−1.26	−0.13	−1.23	−0.16
Iodobenzene	−1.30	−0.95	−0.35	−0.97	−0.33	−1.02	−0.28
Butyl phenyl ether	−1.25	−1.45	0.20	−1.46	0.21	−1.34	0.09
Phenetole	−1.11	−1.32	0.21	−1.20	0.09	−1.08	−0.03
Anisole	−1.03	−1.26	0.23	−1.04	0.01	−0.89	−0.14
Butylbenzene	−0.85	−0.88	0.03	−1.08	0.23	−1.02	0.17
Styrene	−0.711	−0.80	0.09	−0.81	0.10	−0.76	0.05
Ethylbenzene	−0.555	−0.74	0.19	−0.76	0.20	−0.67	0.11
Chlorobenzene	−0.540	−0.54	0.00	−0.53	−0.01	−0.57	0.03
Benzotrifluoride	−0.510	−0.10	−0.41	−0.25	−0.26	−0.42	−0.09
Toluene	−0.388	−0.68	0.29	−0.60	0.21	−0.48	0.10
Benzene	−0.256	−0.61	0.35	−0.43	0.18	−0.37	0.12
Fluorobenzene	−0.256	−0.42	0.16	−0.32	0.06	−0.29	0.03

Steady-state flux is expressed in units of $\mu M\ cm^{-2}\ s^{-1}$.

f_{oct} values listed in Table 1 for each substituent. The results of this regression are given by the following equation:

$$\log J_{ss} = 0.320 f_{oct} - 1.72$$

$$r^2 = 0.205;\ \text{S.D.} = 0.789;\ n = 31;\ F_{1,29} = 6.371 \qquad (2)$$

It is obvious that flux is not highly correlated with only lipophilicity and that other parameters will be needed.

Some interesting trends are apparent when the flux data in Table 4 are compared to the corresponding f_{oct} values in Table 1. When these values are compared for substituents such as iodo vs chloro and butyl vs methyl, an inverse relationship is observed between flux and substituent molecular volume. Another example can be seen by examining the f_{oct} values for ethyl cinnamate and benzotrifluoride (1.27 and 1.33, respectively). Even though these values are almost the same, these compounds exhibit a large difference in flux ($\log J_{ss} = -1.95$ and -0.510, respectively). This disparity can again be explained in terms of molecular volume differences of the substituents.

The addition of a volume term can also be justified on the basis of an equation developed by Lieb and Stein (1969) which states that diffusivity is inversely related to molecular volume expressed as a function of molecular weight. To test this hypothesis, regression analysis was performed by adding a substituent molecular weight term listed in Table 1 to the previous regression analysis to obtain the following equation:

$$\log J_{ss} = 0.560 f_{oct} - 0.0218\text{MW} - 0.705$$

$$r^2 = 0.661;\ \text{S.D.} = 0.525;\ n = 31;\ F_{2,28} = 23.257 \qquad (3)$$

Inclusion of the MW term improves the model considerably when compared to Eqn 2. Molecular weight, however, is only a crude indicator of molecular volume since it is a bulk or partial volume term that describes the volume of a large group rather than individual atoms. Consequently, bulk volume terms include a fraction of free space associated with each molecule which can result in considerable error in the estimation of molecular volume (Hall and Kier, 1981).

Molar refractivity (MR), on the other hand, is a molecular property. The relationship among molar refractivity, molecular weight and polarizability as expressed by the Lorentz-Lorenz equation is well known. Molar refractivity can readily be calculated for any substituent (Martin, 1978) and since this parameter is an additive, constitutive property, the molar refractivity of a substituent can be expressed as a sum of the molar refractivities of its fragments. MR values are listed in Table 1 for each substituent. When MR is substituted for MW, a greater degree of correlation is found as shown by Eqn 4:

$$\log J_{ss} = 0.804 f_{oct} - 0.106\text{MR} - 0.641$$

$$r^2 = 0.849;\ \text{S.D.} = 0.350;\ n = 31;\ F_{2,28} = 38.376 \qquad (4)$$

Another method for the estimation of molecular volume is through the use of the Verloop volume, V_v, which can be calculated from length and width parameters (Verloop et al., 1976). V_v values are tabulated in Table 1. Regression analysis employing V_v as the volume parameter yielded the following equation:

$$\log J_{ss} = 0.683 f_{oct} - 0.0141 V_v - 0.64$$

$$r^2 = 0.762;\ \text{S.D.} = 0.439;\ n = 31;\ F_{2,28} = 28.817 \qquad (5)$$

Verloop volume does provide a significant improvement in fit over MW as an indicator of molecular volume, but is not as good as molar refractivity. The fact that MR provides the better fit suggests that flux is also a function of the polarizability portion of MR.

Kier and Hall (1981) have proposed that molecular connectivity (χ values) may be used to estimate molecular volume. Molecular connectiv-

ity is a method that encodes and quantifies information about size, branching, cyclization, unsaturation and heteroatom content. As the name implies, molecular connectivity describes the connection of one atom to another. The zero-order ($^0\chi$) term is dependent on the number of atoms and the first-order molecular connectivity term ($^1\chi$) takes branching into account as well. Both reflect the general characteristics of molecular volume (Kier and Hall, 1976a,b, 1980, 1983; Kier, 1980). Since these simple connectivity values fail to distinguish between carbon atoms and heteroatoms, valence delta values were developed to enable calculation of zero-order ($^0\chi^v$) and first-order ($^1\chi^v$) valence molecular connectivity values (Kier and Hall, 1976a). These values are useful in detecting dependence on molecular type.

Like MR and V_v, molecular connectivity is a molecular property. Four different χ values are listed in Table 1: zero-order valence, $^0\chi^v$; first-order valence, $^1\chi^v$; zero order, $^0\chi$; and first order, $^1\chi$. All four parameters are regressed separately with f_{oct} against log J_{ss} as shown in the following equations:

$$\log J_{ss} = 0.772 f_{oct} - 0.718\,{}^0\chi^v - 0.535$$

$$r^2 = 0.781;\ \text{S.D.} = 0.422;\ n = 31;\ F_{2,28} = 27.887 \qquad (6)$$

$$\log J_{ss} = 0.844 f_{oct} - 1.16\,{}^1\chi^v - 0.679$$

$$r^2 = 0.794;\ \text{S.D.} = 0.409;\ n = 31;\ F_{2,28} = 25.316 \qquad (7)$$

$$\log J_{ss} = 0.534 f_{oct} - 0.454\,{}^0\chi - 0.684$$

$$r^2 = 0.699;\ \text{S.D.} = 0.494;\ n = 31;\ F_{2,28} = 25.903 \qquad (8)$$

$$\log J_{ss} = 0.627 f_{oct} - 0.693\,{}^1\chi - 0.748$$

$$r^2 = 0.744;\ \text{S.D.} = 0.456;\ n = 31;\ F_{2,28} = 30.591 \qquad (9)$$

Steady-state flux appears to be dependent on the specific atom types present in a substituent, since a better fit resulted from those expressions (Eqns 6 and 7) involving the valence molecular connectivity values. Again, MR provided a better fit of the data.

While the f_{oct} and MR variables relate reasonably well to J_{ss}, there appeared to be systematic deviations upon examination of the calculated flux values. It appeared that all but one of the diffusants containing a hydrogen-donating substituent (as indicated in Table 1) penetrated the membrane more slowly than predicted by Eqn 4. An indicator variable, HB, was set to a value of unity if the substituent possessed hydrogen-donating ability and to zero otherwise in an attempt to isolate this property. Substituents were deemed to be hydrogen donors if they fell into the 'A' category established by Leo and Hansch (1971). Aniline was described as a marginal donor by these authors. A better fit was obtained by not considering it to be a hydrogen donor. The inclusion of the HB term results in a significant improvement in the regression equation:

$$\log J_{ss} = 0.564 f_{oct} - 0.0909\text{MR} - 0.854\text{HB} - 0.534$$

$$r^2 = 0.932;\ \text{S.D.} = 0.239;\ n = 31;\ F_{3,27} = 55.760 \qquad (10)$$

Work has been performed that suggests the HB term in Eqn 10 is actually a correction term to account for the hydrogen bonding difference between octanol and membrane/skin barriers. Jetzer et al. (1986) demonstrated that oil-water partition coefficients based on hexane, methylene chloride and chloroform better described diffusion through both human and mouse skin as well as silicone rubber membranes. Hansch et al. (1975) suggested that the increased correlation resulting from inclusion of a hydrogen-donating variable into a regression equation may indicate the need for conversion from an octanol-water to an alkane-water partitioning system.

Seiler (1974) attempted a conversion from octanol (PC_{oct}) to cyclohexane-water (PC_{chex}) parti-

tion coefficients by means of a regression analysis of the difference between the octanol-water and cyclohexane-water log PC values of over 200 compounds. The difference was totally explained by the substituents present on the molecules. On this basis, a new additive, constitutive substituent constant was defined as:

$$I_h = \log PC_{oct} - \log PC_{chex} - 0.16 \qquad (11)$$

where I_h is the incremental increase in partition coefficient due to hydrogen bonding.

To test this hypothesis, f_{oct} was transformed into the corresponding f_{chex} value using Seiler's I_h variable and Eqn 11. These values are listed in Table 1. The f_{chex} parameter was regressed along with MR against log J_{ss}:

$$\log J_{ss} = 0.464 f_{chex} - 0.0876MR - 0.351$$

$$r^2 = 0.939;\ \text{S.D.} = 0.223;\ n = 31;\ F_{2,28} = 187.958 \qquad (12)$$

It is clearly evident that f_{chex} more accurately describes the partitioning system represented by the isopropyl alcohol-PDMS system by comparing the correlation of Eqn 12 with that of Eqn 4 ($r^2 = 0.849$). Intuitively, the cyclohexane-water solvent system should be favored over the octanol-water system, since PDMS, which possesses little hydrogen bonding ability, more closely resembles cyclohexane in this regard.

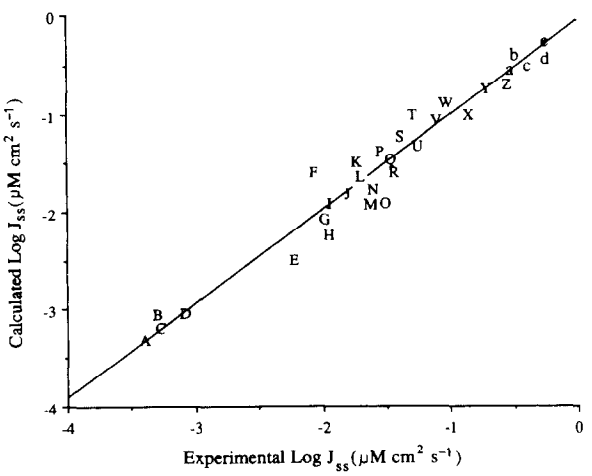

Fig. 1. Correlation between experimental and calculated log J_{ss} using Eqn 13.

While the correlation described by Eqn 12 is good, systematic deviations can still be observed upon comparison of the predicted and experimental flux values shown in Table 4. Upon inspection, it is apparent that the steady-state flux of those compounds with electron-donating substituents are underestimated, while those with electron-withdrawing groups are overestimated. This implied that the inclusion of an electronic parameter would improve the correlation seen in Eqn 12. Hammett's σ_p values, as listed in Table 1, were added to the parameters in Eqn 12 to yield the following regression equation:

$$\log J_{ss} = 0.456 f_{chex} - 0.0898MR - 0.389\sigma_p - 0.289$$

$$r^2 = 0.963;\ \text{S.D.} = 0.177;\ n = 31;\ F_{3,27} = 196.457 \qquad (13)$$

The σ_p values were selected over σ_m, but either could be used since they are highly correlated (Hansch et al., 1973). The flux values predicted using Eqn 13 are shown in Table 4. A plot of experimental vs calculated log J_{ss} is shown in Fig. 1, verifying that Eqn 13 is an excellent estimator of log J_{ss}, especially in light of the diversity of the compounds in the data set. The cyclohexane-water partition coefficients span a range of 4 orders of magnitude while the molar refractivities of the substituents vary over a 30-fold range.

The statistics for the regression model represented by Eqn 13 are listed in Table 5. The correlation matrix indicates no collinearity problems between f_{chex} and MR because of the number of observations included in the data set in which hydrophobicity and molar volume are not correlated.

Residual analysis can be useful in locating outliers in the data set. The standardized residual for the estimation of flux for all compounds was less than 2 with the exception of biphenyl. All other compounds with multiple benzene rings

TABLE 5

Regression statistics for Eqn 13

Predictor	Coefficient	SD	t ratio
Constant	−0.289	0.06726	−4.29
f_{chex}	0.456	0.01896	24.04
MR	−0.0898	0.00440	−20.43
σ	−0.389	0.09413	−4.14

Analysis of variance

Source	Degrees of freedom	Sum of squares	Mean square error
Regression	3	21.8748	7.2916
Error	27	0.8500	0.0315
Total	30	22.7249	

Correlation matrix

	f_{chex}	MR
MR	0.520	
σ	−0.193	−0.204

(diphenylmethane, bibenzyl and phenyl ether) have small standardized residuals (−0.12, 0.69 and 0.03, respectively). One obvious difference between these compounds and biphenyl is the point of attachment of the phenyl ring. Hansch et al. (1975) have noted a lack of additivity of π values for phenyl groups attached to another aromatic ring. Based on this, it may be more accurate to describe biphenyl as belonging to a biphenyl series rather than as a substituted benzene derivative. The fit of Eqn 13 can be improved somewhat by deleting biphenyl from the regression analysis to yield the following equation:

$$\log J_{ss} = 0.459 f_{chex} - 0.0876\text{MR} - 0.387\sigma_p - 0.301$$

$$r^2 = 0.971;\ \text{S.D.} = 0.159;\ n = 30;\ F_{3,26} = 237.543 \qquad (14)$$

The steady-state flux of some benzene derivatives has been described as an additive, constitutive process. Not unexpectedly, the flux increased with increasing hydrophobicity, with a hydrophobic parameter estimating the cyclohexane-water partition coefficient best simulating the PDMS-isopropyl alcohol system, while an increase in substituent volume caused a decrease in the flux. Molar refractivity produced the best correlation among all the tested volume parameters. Electron-donating substituents enhanced the flux, while electron-withdrawing groups reduced it.

References

Bronaugh, R.L. and Congdon, E.R., Percutaneous absorption of hair dyes: Correlation with partition coefficient. *J. Invest. Dermatol.*, 83 (1984) 124–127.

Dow Corning Technical Bulletin 51–247, Dow Corning Corp., Midland, MI, 1982.

Ferguson, J., Use of chemical potentials as indexes of toxicity. *Proc. Roy. Soc., Ser. B*, 127 (1939) 387.

Garrett, E.R. and Chemburkar, P.B., Evaluation, control and prediction of drug diffusion through polymeric membranes. *J. Pharm. Sci.*, 57 (1968) 944–948.

Hall, L.H. and Kier, L.B., The relation of molecular connectivity to molecular volume and biological activity. *Eur. J. Med. Chem.*, 16 (1981) 399–407.

Hansch, C., Leo, A., Unger, S.H., Kim, K.H., Nikaitani, K. and Lien, E.J., Aromatic Substituent Constants for Structure-Activity Correlations. *J. Med. Chem.*, 16 (1973) 1207–1216.

Hansch, C., Vittoria, A., Silipo, C. and Jow, P.Y.C., Partition coefficients and the structure-activity relation of the anesthetic gases. *J. Med. Chem.*, 18 (1975) 546–548.

Hansch, C. and Leo, A., Pomona College Medicinal Chemistry Project, Issue 23, 1983.

Herzog, K.A. and Swarbrick, J., Drug permeation through thin-model membranes. III: Correlations between in vitro transfer, in vivo absorption, and physiochemical parameters of substituted benzoic acids. *J. Pharm. Sci.*, 60 (1971) 1666–1668.

Hung, G.W.C. and Autian, J., Use of thermal gravimetric analysis in sorption studies. II: Evaluation of diffusivity and solubility of a series of aliphatic alcohols in polyurethane. *J. Pharm. Sci.*, 61 (1972) 1094–1098.

Hwang, S.T., Tang, T.E.S. and Kammermeyer, K., Transport of dissolved oxygen through silicone rubber membrane. *J. Macromol. Sci.-Phys.*, B5 (1971) 1–5.

Jetzer, W.E., Huq, A.S., Ho, N.F.H., Flynn, G.F., Duraiswamy, N. and Condie, L., Permeation of mouse skin and silicone rubber membranes by phenols: Relationship to in vitro partitioning. *J. Pharm. Sci.*, 75 (1986) 1098–1103.

Khordagy, L., Khalafallah, N. and Khalif, S., In vitro transport of substituted benzoic acids across liquid and solid barriers and its correlation to in vivo data. *Pharm. Acta Helv.*, 56 (1981) 222–224.

Kier, L.B. and Hall, L.H., *Molecular Connectivity in Chemistry and Drug Research*, Medicinal Chemistry Series, Academic Press, London, Vol. 14, 1976a.

Kier, L.B. and Hall, L.H., Molecular connectivity. VII: Specific treatment of heteroatoms. *J. Pharm. Sci.*, 65 (1976b) 1806–1809.

Kier, L.B. and Hall, L.H., Derivation and significance of valence molecular connectivity. *J. Pharm. Sci.*, 70 (1981) 583–589.

Kier, L.B. and Hall, L.H., General definition of valence delta-values for molecular connectivity. *J. Pharm. Sci.*, 72 (1983) 1170–1173.

Kier, L.B., Molecular connectivity as a descriptor of structure for SAR analyses. In Yalkowsky, S.H., Sinkula, A.A. and Valvani, S.C. (Eds), *Physical Chemical Properties of Drugs*, Dekker, New York, 1980, pp. 277–319.

Klotz, I.M., *Chemical Thermodynamics*, W.A. Benjamin, New York, 1964, pp. 348–358.

Lacey, R.E. and Cowsar, D.R., Factors affecting the release of steroids from silicones. *Adv. Exp. Med. Biol.*, 47 (1974) 117–144.

Leo, A. and Hansch, C., Linear free energy relations between partitioning solvent systems. *J. Org. Chem.*, 36 (1971) 1539–1544.

Lieb, W.R. and Stein, W.D., Biological membranes behave as nonporous polymeric sheets with respect to diffusion of nonelectrolytes. *Nature*, 224 (1969) 240–243.

Lieb, W.R. and Stein, W.D., Implications of two different types of diffusion for biological membranes. *Nat. New Biol.*, 234 (1971) 220–222.

Lien, E.J. and Tong, G.L., Physico-chemical properties and percutaneous absorption of drugs. *J. Soc. Cosm. Chem.*, 24 (1973) 371–384.

Lien, E.J. and Wang, P.H., Lipophilicity, molecular weight, and drug action: Reexamination of parabolic and bilinear models. *J. Pharm. Sci.*, 69 (1980) 648–650.

Lien, E.J., Structure activity relationships and drug disposition. *Annu. Rev. Pharmacol. Toxicol.*, 21 (1981) 31–61.

Martin, Y.C., *Quantitative Drug Design*, Medicinal Research Series, Dekker, New York, Vol. 8, 1978.

Michaels, A.S., Chandrasekaran, S.K. and Shaw, J.E., Drug permeation through human skin: Theory and in vitro experimental measurement. AIChE, 21 (1975) 986–996.

Nasim, K., Meyer, M.C. and Autian, J., Permeation of aromatic organic compounds from aqueous solutions through polyethylene. *J. Pharm. Sci.*, 61 (1972) 1775–1780.

Rekker, R.F., *The Hydrophobic Fragmental Constant; Its Derivation and Application. A Means of Characterizing Membrane Systems*, Pharmaco Chemistry Library, Elsevier, New York, Vol. 1, 1977.

Schuhmann, R. and Taubert, H.D., Long-term application of steroids enclosed in dimethylpolysiloxane (Silastic). *Acta Biol. Med. Germ.*, 24 (1970) 897–910.

Seiler, P., Interconversion of lipophilicities from hydrocarbon/water systems into the octanol/water system. *Eur. J. Med. Chem.*, 9 (1974) 473–479.

Shah, P.V., Monroe, R.J. and Guthrie, F.E., Comparative rates of dermal penetration of insecticides in mice. *Toxicol. Appl. Pharmacol.*, 59 (1981) 414–423.

Technical Bulletin 51–247, Dow Corning Corp., Midland, MI, 1982.

Verloop, A., Hoogenstraaten, W. and Tipker, J., Development and application of new steric parameters in drug design. In Ariens, E.J. (Ed.), *Drug Design*, Academic Press, New York, Vol. 7, 1976, pp. 165–319.

Yalkowsky, S.H. and Flynn, G.L., Transport of alkyl homologs across synthetic and biological membranes: A new model for chain length-activity relationships. *J. Pharm. Sci.*, 62 (1973) 210–217.

Zentner, G.M., Cardinal, J.R. and Kim, S.W., Progestin permeation through polymer membranes II: Diffusion studies on hydrogel membranes. *J. Pharm. Sci.*, 67 (1978) 1352–1355.