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An Investigation of the Mechanism of Flux Across Polydimethylsiloxane Membranes by use of Quantitative Structure–Permeability Relationships

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Abstract

Quantitative structure-permeability relationships (QSPRs) based on readily calculated parameters have been developed to study penetration across a polydimethylsiloxane membrane.

Maximum steady-state flux values for 256 compounds through a polydimethylsiloxane membrane were taken from previous studies. Forty-three physicochemical parameters were calculated for each compound and their significance to flux determined. Removal of fourteen outliers enabled derivation of a significant three-parameter QSPR based on the number of hydrogen-bond acceptor and donor groups and sixth-order path molecular connectivity. Models based on parameters important for penetration across human skin (log P and molecular weight) were comparatively poor.

This model suggests that the mechanism of flux across a polydimethylsiloxane membrane is based mainly on hydrogen-bonding effects; as such it occurs via a mechanism of action different from that of penetration of the skin in man.

There is considerable interest in utilizing the skin as a route of administration of drugs. Transdermal drug delivery has several important advantages in comparison with other non-specific, periodic methods of drug delivery. It by-passes hepatic metabolism, reduces the potential of side effects because it enables optimization of the blood concentration-time profile, provides a predictable and extended duration of activity and reduces the frequency of dosage, which leads to better patient compliance and therapeutic efficacy (Kydonieus 1987).

The development of transdermal drug-delivery systems is hindered by a number of difficulties arising from the inherently variable nature of the skin barrier. This ensures that the provision of a therapeutically viable dose is dependent upon a number of factors, including skin condition, thickness and location on the body (Feldman & Maibach 1967; Elias et al 1981).

Excised skin and artificial membranes are employed widely in-vitro for rapid determination of product efficacy where concerns about the toxicity of novel compounds and the costs of screening large numbers of candidate formulations prohibit the use of in-vivo techniques. Although such models cannot fully replicate in-vivo conditions, they have nevertheless been widely demonstrated to provide accurate and viable indications of drug release in-vivo (Garrett & Chemburkar 1968; Lovering & Black 1974; Friend 1992).

Quantitative structure–activity relationships (QSARs) are mathematical models that relate statistically the biological activity of a compound to its physicochemical structure. Their application to pharmaceutics and drug delivery has recently been reviewed by Dearden (1994). Several recent studies have shown their importance to the prediction of skin penetration. Potts & Guy (1992) proposed a two-variable QSAR model based on hydrophobicity and molecular size to describe the penetration of organic compounds through the skin. Their model is applicable to percutaneous absorption values for a subset of their overall data set but has limited statistical accuracy for the complete data set. Several reasons for this have become apparent. Firstly, the use of human skin in-vitro is fraught with difficulty due to its biological variation. Further, the data analysed by Potts and Guy

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were obtained from several sources (Flynn 1990). Re-analysis of the data at a later date, but including other terms to describe hydrogen-bonding (Lien & Gao 1995; Pugh et al 1996) and melting point (Barratt 1995), resulted in only minor improvements in statistical fit, thus demonstrating an inability to overcome the intrinsic variability of the data set.

Recently, Chen et al (1993, 1996) have studied the penetration of a large number of heterogeneous compounds through a polydimethylsiloxane membrane. They subsequently derived quantitative structure–permeability relationship (QSPR) models of transport through the membrane for various subclasses, but did not apply this analysis to the whole data set. However, these QSPRs are based upon several properties, including the measured mole fraction solubility in isopropyl alcohol and the calculated charges on particular atoms within the molecule. Statistically the models are highly significant, although for practical purposes they require the experimental measurement of solubility in isopropyl alcohol as there is currently no readily available method for its calculation. Nevertheless, the reported data satisfy one criterion for use in QSAR analysis in that they have been determined by a consistent, accurate protocol under identical laboratory conditions (Barratt et al 1995).

The aims of this study were to re-analyse all the data presented by Chen and co-workers, to develop QSARs for membrane penetration based on readily calculated parameters, and to interpret the findings mechanistically and relate them to models of in-vivo percutaneous absorption.

Materials and Methods

Data for flux through polydimethylsiloxane

Maximum steady-state flux data (J) through the polydimethylsiloxane membrane for 256 compounds were taken from previous studies (Chen et al 1993, 1996) and are listed in Table 1. Five compounds were omitted from this analysis because of structural ambiguities in the original studies. It was noted also that thirteen compounds were common to both reports and thus these are included only once in this analysis. Briefly, flux values were determined at 30°C using isopropyl alcohol as a solvent. Neat liquids were employed as donor solutions for the measurement of liquids. Solids were used as either 50 or 90% saturated solutions in isopropyl alcohol. Receptor solutions were always maintained at or below sink conditions (Moeckly & Matheson 1991; Hu & Matheson 1993; Chen et al 1996).

Physicochemical properties

A total of 43 descriptors was calculated to encompass the relevant physicochemical properties of the compounds likely to affect membrane permeability. A full listing is given in Table 2 and their sources are described below.

The logarithm of the octanol–water partition coefficient (log P) was secured by use of the ClogP for Windows software (BioByte, Claremont, CA) as either a measured or a calculated value (Hansch & Leo 1979). Measured values were used in preference to calculated values.

Topological indices and molecular weight were calculated by use of MOLCONN-X (v. 2·0) software (Hall Associates, Quincy, MA). The reader is referred elsewhere for further details of such indices (Charton & Motoc 1983; Kier & Hall 1986).

Several descriptions of hydrogen-bonding were utilized, the simplest being that for the presence or absence of a hydrogen-bond donor or acceptor group on the molecule (Fujita et al (1977). A more quantitative descriptor is that proposed by Yang et al (1986) which provides a count of the number of hydrogen-bond donor or acceptor groups on each molecule. Further, the total numbers of lone pairs capable of accepting and donating hydrogen-bonds was taken according to Charton & Charton (1982). In this scheme oxygen, having two lone pairs, is assumed to be capable of accepting two hydrogen-bonds.

Statistical analysis

The complete data set was analysed by use of MINITAB (v. 10·1) statistical software for Windows (Minitab Inc., State College, PA). Stepwise regression analysis was used to determine the most significant parameters. The identification of outliers was performed by least-squares regression analysis.

Results

By use of stepwise regression analysis a three-parameter equation (equation 1) was identified as the most significant QSAR for the prediction of the maximum steady-state flux through the polydimethylsiloxane membrane (log J). Addition of further parameters did not produce a statistically significant improvement in the QSAR (the number in parentheses is the standard deviation of the coefficient of each variable).

$$\log J = -0{\cdot}563(0{\cdot}048)HA - 0{\cdot}613(0{\cdot}065)HD - 0{\cdot}746(0{\cdot}064)^{6}\chi - 0{\cdot}469 \quad (1)$$

$$n = 256;\ s = 0{\cdot}565;\ r = 0{\cdot}858;\ F = 235$$

The t-values for the variables were −11·84, −9·50 and −11·65, respectively. All the variables were significant at the 99·9% level.

Table 1. Maximum steady-state flux and relevant physico-chemical properties of the compounds considered in this study.

Compound	log J	HA	HD	$^6\chi$
3-Nitrobenzaldehyde	−2·520	2	0	0·8935
2,5-Pyridinedicarboxylic acid	−5·205	3	2	1·1812
1-Fluoro-4-nitrobenzene	−1·600	1	0	0·9200
4-Aminoquinaldine	−3·481	1	1	1·6711
2-Ethylimidazole*	−2·975	2	0	0·2041
2-Thiophenemethanol	−2·179	1	1	0·2041
3-Hydroxypyridine	−2·685	2	1	0·2041
6-Quinolinecarboxylic acid*	−4·672	2	1	1·7091
Terephthalic acid*	−5·145	2	2	1·1812
3,5-Dimethylpyrazole	−1·791	2	0	0·0000
1,2,5-Trimethylpyrrole	−0·918	1	0	0·1925
2-Methyl-5-nitroimidazole*	−4·024	3	0	0·4646
2-Methyl-5-ethylpridine	−0·868	1	0	0·6869
Pyrrole	−0·891	1	0	0·0000
4-Nitrobenzoic acid	−3·358	2	1	1·1812
Diphenyl ether	−1·810	1	0	1·2315
Quinoline	−1·490	1	0	1·1401
2-Quinolinecarboxylic acid	−3·552	2	1	1·8571
7-Nitroindole	−2·659	2	0	1·8571
2-Methylimidazole*	−2·797	2	0	0·0000
6-Hydroxynicotinic acid	−5·100	3	2	0·9200
1-Naphthoic acid	−2·985	1	1	1·7091
4-Carboxybenzaldehyde	−3·440	2	2	1·0612
1-Methylpyrrole	−0·657	1	0	0·0000
2-Methyl-1-phenyl-2-propanol	−1·820	1	1	0·6794
2,4-Quinolinediol	−5·469	3	2	1·6711
2-Furaldehyde	−1·530	2	0	0·2041
Pyridazine	−1·865	2	0	0·0000
(2-Chloroethyl)benzene	−1·292	0	0	0·4928
Butyrophenone	−1·719	1	0	0·6869
8-Aminoquinoline	−2·278	2	1	1·4370
2,5-Dimethylfuran	−0·280	1	0	0·0000
1-Methylimidazole	−1·813	2	0	0·0000
Benzofuran	−0·948	1	0	0·9369
Pyridine	−0·695	1	0	0·0000
6-Chloronicotinic acid	−3·098	2	0	0·5656
Aniline	−1·750	2	1	0·2041
Pyrazole	−1·597	2	0	0·0000
6-Methoxyquinoline	−2·097	2	0	1·6793
Biphenyl	−2·050	0	0	1·1785
2-Thiopheneacetic acid	−2·475	2	0	0·4512
2-Thiophenemethylamine	−1·410	1	1	0·2041
Phenol	−1·570	1	1	0·2041
3,5-Dichloropyridine	−1·824	1	0	0·4512
2-Furoic acid	−2·476	2	1	0·3333
Butyl phenyl ether	−1·250	1	0	0·7815
Toluene	−0·388	0	0	0·2041
4-Chlorobenzyl alcohol	−2·504	1	1	0·6869
2,5-Dimethylpyrrole	−1·400	1	0	0·0000
4-Aminophenol	−3·910	2	2	0·3333
2,5-Dimethylthiophene	−0·468	0	0	0·0000
2-Aminobenzylalcohol	−2·630	2	2	0·4699
5-Nitro-8-hydroxyquinoline	−4·220	3	1	2·1651
2-Hydroxyquinoline	−3·813	2	1	1·4370
7-Amino-2,4-dimethyl-1,8-naphthyridine	−3·663	3	1	2·1806
Chlorobenzene	−0·540	0	0	0·2041
Furfuryl alcohol	−1·860	2	1	0·2041
2-Methyl-5-nitrobenzimidazole	−3·698	3	0	1·8106
4,7-Dichloroquinoline	−2·590	1	0	1·8028
Imidazole*	−3·019	2	0	0·0000
5-Chloro-8-hydroxyquinoline	−3·166	2	1	1·5350
6-Methoxyquinaldine	−2·247	2	0	1·9164
Benzene	−0·256	0	0	0·0000
2-Thiophenecarboxaldehyde	−1·685	1	0	0·2041
Anisole	−1·030	1	0	0·3485
Aminopyrazine	−2·587	3	1	0·2041
Picolinic acid	−3·282	2	1	0·3485
6-Aminoquinoline	−3·061	2	1	1·4370

Table 1. (*continued*).

Compound	log J	HA	HD	$^6\chi$
2-Naphthol	−2·477	1	1	1·4370
2-Methylthiophene	−0·426	0	0	0·0000
Ethyl-2-methylbenzoate	−1·480	2	0	0·8759
Isophthalic acid	−3·987	2	1	1·0903
Methyl benzoate	−1·460	1	0	0·5690
t-Butylbenzene	−0·753	0	0	1·3544
Methyl paraben	−2·740	2	1	0·9598
3-Hydroxybenzoic acid	−3·309	2	2	0·6031
Phenylbutylamine	−1·397	1	1	0·7815
Methylbenzylamine	−1·180	1	1	0·4512
2-Chlorolepidine	−2·300	1	0	1·6711
Indole	−1·846	1	0	0·9369
8-Nitroquinoline	−3·395	2	0	1·7091
3-Quinolinecarboxylic acid	−4·410	2	1	1·8571
3-Chloroaniline	−2·015	1	1	0·4512
Benzimidazole	−2·944	2	0	0·9369
6-Nitroquinoline	−3·615	2	0	1·8571
2-Hydroxy-4-methyl quinoline	−3·876	2	1	1·6711
Benzoic acid	−2·316	1	1	0·4512
1,5-Dimethyl-2-pyrrole carbonitrile	−1·791	2	0	0·4182
Furfuryl amine*	−1·116	2	1	0·2041
5-Nitroquinoline	−2·862	2	0	1·7091
4-*t*-Butyltoluene	−0·915	0	0	1·1036
1-Methyl-2-phenoxyethylamine*	−1·630	2	1	0·7399
Phenethylamine	−1·257	1	1	0·4928
2-Amino-5-nitropyridine	−3·770	3	1	0·9200
4-Methoxy-2-quinolinic acid*	−4·617	4	2	2·8265
4-Fluoro-4-methylbenzylamine	−1·420	1	1	0·9200
1,3-Diethylbenzene	−0·774	0	0	0·7458
2,4-Dihydroxypyridine	−4·289	3	2	0·4512
1-Nitronaphthalene	−2·447	1	0	1·7091
8-Hydroxyquinaldine	−2·375	2	1	1·6260
4-Aminoacetophenone	−3·040	2	1	0·9200
Nitrobenzene	−1·556	1	0	0·4512
Benzaldehyde	−1·480	1	0	0·3485
Acetophenone	−1·640	1	0	0·4512
Ethylbenzene	−0·555	0	0	0·3485
Fluorobenzene	−0·256	0	0	0·2041
3-Chlorotoluene	−0·837	0	0	0·4512
3-Xylene	−0·580	0	0	0·4512
3-*t*-Butylphenol	−1·900	1	1	0·6625
4-Hydroxybenzoic acid	−3·530	2	2	0·9200
4-Chlorotoluene	−0·694	0	0	0·3333
Butylbenzene	−0·895	0	0	0·6371
Phenetole	−1·110	1	0	0·4928
3-Anisaldehyde	−2·090	2	0	0·7458
Methyl 3-methylbenzoate	−1·430	1	0	0·8108
4-*t*-Butylbenzoic acid	−2·759	1	1	1·2864
Ethyl paraben	−2·690	2	1	1·0866
3-Pyridinecarboxaldehyde	−1·823	2	0	0·3485
3,5-Lutidine	−0·948	1	0	0·4512
5-Chloro-3-Pyridinol	−2·621	2	1	0·4512
4-*t*-Butylpyridine	−1·227	1	0	0·5351
Nicotinic acid*	−3·760	2	1	0·4512
4-Picoline	−0·845	1	0	0·2041
3-Acetylpyridine	−1·992	2	0	0·4512
2-Aminopyridine	−2·682	2	1	0·2041
3-Aminopyridine	−1·895	2	1	0·2041
2-Chloro-6-methoxypyridine	−1·211	2	0	0·5345
2-Ethylpyridine	−0·718	1	0	0·3485
2-Chloropyridine	−1·081	1	0	0·2041
2-Butoxypyridine	−1·155	2	0	0·7815
2-Fluoropyridine	−0·878	1	0	0·2041
5-Methoxypyridine	−0·809	2	0	0·3485
2-Methoxy-5-nitropyridine	−2·653	3	0	1·0612
2-Methoxy-5-aminopyridine	−2·230	3	1	0·6869
2-Hydroxy-5-nitropyridine	−3·747	3	1	0·9200

Table 1. (*continued*).

Compound	log J	HA	HD	$^{6}\chi$
2-Hydroxypyridine	−2·499	2	1	0·2041
2-Amino-4-methyl pyridine	−2·228	2	1	0·4512
2-Amino-5-chlorpyridine	−2·625	2	1	0·3333
Ethyl nicotinate	−1·530	2	0	0·6869
Lepidine	−1·853	1	0	1·3714
6-Methylquinoline	−1·747	1	0	1·4370
8-Hydroxyquinoline	−2·358	2	1	1·3714
2-Methyl-8-nitroquinoline	−3·827	2	0	2·1076
Quinaldine	−1·622	1	0	1·4370
6-Isopropylquinoline	−1·897	1	0	1·8571
5-Aminoquinoline	−3·113	2	1	1·3714
3-Aminoquinoline	−2·934	2	1	1·4370
4-Hydroxyquinoline	−3·688	2	1	1·3714
8-Quinoline carboxylic acid	−4·213	2	1	1·7091
4-Quinoline carboxylic acid	−4·518	2	1	1·7091
1-Isoquinoline carboxylic acid	−4·132	2	1	1·7091
2-Methyl-5-butylpyridine	−1·113	1	0	0·8910
2,6-Dimethoxypyridine*	−1·129	3	0	0·7458
6-Methoxy-8-nitroquinoline	−4·332	3	0	2·3439
2-Amino-4,6-dimethylpyridine	−2·253	2	1	0·6969
2-Methylindole	−1·983	1	0	1·1109
Naphthalene	−1·746	0	0	1·1401
1-Bromonaphthalene	−1·726	0	0	1·3714
1-Methylnaphthalene	−1·592	0	0	1·3714
2-Methoxynaphthalene	−1·918	1	0	1·6793
1,6-Dihydroxynaphthalene*	−1·883	2	2	1·8028
2-Naphthylacetic acid	−3·570	2	1	1·9059
1-Ethoxynaphthalene	−2·790	1	0	1·7984
2-Methylbenzimidazole	−2·979	2	0	1·1109
2-Hydroxybenzimidazole	−3·922	2	1	1·1109
3-Phenyl-1-propylamine	−1·457	1	1	0·6371
1-Phenyl-2-propanol	−2·015	1	1	0·5955
3-Phenyl-1-propanol	−2·324	1	1	0·6371
3-Methylthiophene	−0·407	0	0	0·0000
3-Thiopheneacetic acid	−2·411	2	1	0·4512
3-Thiophenecarboxaldehyde	−1·612	1	0	0·2041
3-Aminobenzoic acid	−3·727	2	1	0·6031
3-Toluic acid	−2·309	1	1	0·6031
3-Anisic acid	−2·579	2	1	0·8935
4-Anisic acid	−3·226	2	1	1·0612
3-Chlorobenzoic acid	−2·371	1	1	0·6031
3-Nitrobenzoic acid	−2·735	2	1	1·0903
4-Aminobenzoic acid	−3·488	2	2	0·9200
4-Chlorobenzoic acid	−3·088	1	1	0·9200
4-Acetoxybenzoic acid	−3·107	2	1	1·2449
Benzylamine	−1·387	1	1	0·3485
Benzyl alcohol	−2·222	1	1	0·3485
4-Xylene	−0·457	0	0	0·3333
1,3-Diisopropylbenzene	−1·060	0	0	1·0903
Mesitylene	−0·701	0	0	0·6969
1,3,5-Triethylbenzene	−1·083	0	0	1·1948
3-Fluoronitrobenzene	−1·620	1	0	0·6031
3-Methoxyacetophenone	−1·990	2	0	0·8935
4-Anisaldehyde	−2·070	2	0	0·9024
4-Isopropylbenzaldehyde	−1·640	1	0	0·9714
Methyl 4-*t*-butylbenzoate	−1·710	1	0	1·3544
Dibenzyl	−1·980	0	0	1·2845
3-Phenoxytoluene	−2·010	1	0	1·5262
2-Aminoacetophenone	−2·160	2	1	0·5656
2-Anisaldehyde	−2·030	1	0	0·6065
2-Chloroacetophenone	−1·830	2	0	0·5656
2-Chlorobenzaldehyde	−1·580	1	0	0·4699
2-Chloronitrobenzene	−1·540	1	0	0·5656
2-Chlorotoluene	−0·771	0	0	0·3333
Ethyl salicylate	−1·610	1	0	0·8759
2-Fluoroaniline	−1·310	1	1	0·3333
2-Fluorobenzaldehyde	−1·300	1	0	0·4699

Table 1. (*continued*).

Compound	log J	HA	HD	$^6\chi$
2-Fluoronitrobenzene	−1·840	1	0	0·5656
2-Fluoropropiophenone	−1·440	1	0	0·6727
2-Fluorotoluene	−0·349	0	0	0·3333
2-Hydroxyacetophenone	−1·780	2	1	0·5656
2-Isopropylaniline	−1·690	1	1	0·5656
2-Methoxyacetophenone	−2·020	2	0	0·7022
Methyl 2-nitrobenzoate	−2·680	2	0	1·0621
Methyl 2-methoxybenzoate	−2·190	2	0	0·9055
Methyl salicylate	−1·670	2	1	0·6727
2-Nitrotoluene	−1·720	1	0	0·5656
2-Xylene	−0·644	0	0	0·3333
2-Nitrobenzoic acid	−2·860	2	1	0·7979
Salicylic acid	−2·570	2	2	0·5656
4-Hydroxybenzamide	−3·830	2	2	0·9200
3-Hydroxy-4-methoxybenzoic acid	−4·370	3	2	1·1108
4-Chloro-3-nitroacetophenone	−3·330	2	0	1·4586
1,2,4- Trimethylbenzene	−0·740	0	0	0·5045
Phenylurea*	−3·310	1	1	0·5955
Benzohydroxamic acid	−3·270	1	2	0·5690
Benzamide	−3·070	1	1	0·4512
Ethyl cinnamate	−1·950	2	0	0·8922
Phenyl acetate	−1·650	1	0	0·5955
Benzonitrile	−1·550	1	0	0·3485
Thioanisole	−1·390	0	0	0·3485
Iodobenzene	−1·300	0	0	0·2041
Styrene	−0·711	0	0	0·3485
2-Chlorophenoxyacetic acid	−2·930	2	1	1·0178
(2-(3-Hydroxyphenoxy)ethanol	−3·540	3	2	0·8855
4-Methoxybenzyl acetate	−2·130	2	0	1·2343
Phenoxyacetic acid	−2·458	2	1	0·7399
3-Phenylbutyraldehyde	−1·959	1	0	0·6869
DL-2-Phenylpropionaldehyde	−1·686	1	0	0·5690
Propyl paraben	−2·720	2	1	1·2045
3-Chloro-4-methylaniline	−1·960	1	1	0·5045
3-Amino-1,2,4-triazole	−3·270	4	1	0·0000
2-Pyrazine carboxylic acid	−4·067	3	1	0·4512
3-Amino-5,6-dimethyl-1,2,4-triazine	−3·865	4	1	0·5045
Anthracene*	−3·839	0	0	2·5729
Acridine	−2·683	1	0	2·5729
2-Quinoxalinol	−4·164	3	1	1·4370
2,4-Dimethyl-6-hydroxypyrimidine	−3·300	3	1	0·6969
4-Methylpyrimidine	−1·022	2	0	0·2041
Isoquinoline	−1·677	1	0	1·1401
Methoxymethylphenyl sulphide	−1·684	1	0	0·6371
3-Iodoanisole	−1·805	1	0	0·5345
2-Chloroanisole	−1·761	1	0	0·4699
4-Bromoveratrole	−2·340	2	0	0·9134
4-Bromotoluene	−1·421	0	0	0·3333
2-Anisidine	−2·023	2	1	0·4699
3-Fluorobenzyl chloride	−1·120	0	0	0·5345
2-Chloro-4-fluoroacetophenone	−1·937	1	0	1·0437
4-Chloro-4-fluorobutyrophenone	−2·210	1	0	1·2045
2-Fluorobenzoic acid	−2·290	1	1	0·5656
5-Methylbenzimidazole	−3·076	2	0	1·1661

*Compound omitted from equation 2.

In equation 1 HA and HD are, respectively, the number of hydrogen-bond acceptor and donor groups on the molecule, $^6\chi$ is the sixth-order path molecular connectivity, n is the number of observations, s is the standard error of the estimate, r is the correlation coefficient and F is Fisher's statistic.

Table 3 shows the correlations between each of the variables used in equation 1. There were no significant correlations between the variables.

Analysis of the values predicted by equation 1 identified 14 compounds with significant residuals. These outliers are highlighted in Table 1 and their significance is discussed below.

When these outliers had been removed, repetition of the stepwise regression analysis revealed that the

Table 2. The physicochemical properties used in this study.

Logarithm of the octanol–water partition coefficient
Indicator variables for the presence of groups capable of accepting or donating hydrogen-bonds
Number of groups capable of accepting and donating hydrogen-bonds
Number of lone pairs on groups capable of accepting and donating hydrogen-bonds
Molecular weight
Zero- to tenth-order simple and valence-corrected path molecular connectivities
Third-order simple and valence-corrected cluster molecular connectivities
Fourth-order simple and valence-corrected path-cluster molecular connectivities
Sixth-order simple and valence-corrected chain molecular connectivities
Zero- to third-order Kappa and first- to third-order Kappa alpha indices

Table 3. Correlation matrix of the variables used in equation 1.

	$^6\chi$	HA
HA	0·288	
HD	0·124	0·327

same three parameters modelled steady-state flux with an improved correlation coefficient (equation 2).

$$\log J = -0{\cdot}561(0{\cdot}042)HA - 0{\cdot}671(0{\cdot}056)HD - 0{\cdot}801(0{\cdot}057)^6\chi - 0{\cdot}383 \quad (2)$$

$$n = 242;\ s = 0{\cdot}464;\ r = 0.900;\ F = 338$$

The t-values for the variables were −13·48, −11·92 and −14·05, respectively. All variables are significant at the 99·9% level.

Discussion

The accurate prediction of transdermal drug penetration is a problematic task for which many alternatives have been sought; not all of these have been successfully validated by a thoroughly mechanistic approach. Percutaneous drug penetration is often quantified by measurement of steady-state flux across a membrane (J). Flux can be derived directly from Fick's first law of diffusion such that:

$$J = D_m K_p(\Delta C_m/t) \quad (3)$$

where: D_m is the diffusion constant of the penetrant, K_p is the permeability coefficient of the penetrant, ΔC_m is the concentration gradient across the membrane and t is the thickness of the membrane.

Thus if one assumes that the diffusion constant, concentration gradient and membrane thickness are constant, flux is directly proportional to permeability coefficient. According to Blank (1969) this model can be applied only to relatively low concentrations of penetrant as deviations from Fick's first law become apparent when the concentration increases greatly.

Excised human skin has been widely used for estimation of drug flux. However, because such techniques are limited by the availability, quality and consistency of tissue samples, excised skin from various animals, particularly the neonatal pig and Rhesus monkey, has been used, and has been shown to provide an accurate indication of drug flux across human skin (Bartek et al 1972; Wester & Maibach 1976). Such models are frequently used where excised human skin is not available. Further, several synthetic membranes have been widely used for rapid, convenient and inexpensive estimation of drug flux, particularly where a large number of candidate formulations must be rapidly screened. Polydimethylsiloxane (for example, Silastic Medical Grade NRV, Dow Corning, Midland, MI) and dialysis membranes have been commonly used for this purpose (Foley et al 1992). Finally, several mathematical models, loosely defined under the umbrella of QSAR, have been proposed for prediction of the penetration of compounds through an artificial membrane in order to interpret the resultant flux mechanistically and relate it to other test systems.

In this study a three-parameter model has been developed that describes the maximum steady-state flux through the polydimethylsiloxane membrane. As well as being statistically valid a QSAR must be capable of withstanding 'lateral' validation. More conventionally, this implies that the model must be mechanistically coherent and be comparable with other models for similar systems. Mechanistic interpretation of equation 2 suggests that flux through a polydimethylsiloxane membrane is controlled largely by hydrogen-bonding and to a lesser extent by molecular topology.

The description of hydrogen-bonding phenomena is a complex and time-consuming process often requiring experimental measurements (Dearden 1990). In this study a more simplistic approach to the assessment of hydrogen-bonding has been utilized, namely indicator variables for the determination of the presence or absence of groups capable of accepting or donating a hydrogen-bond or counts relating to the number, or type, of such groups. Equation 2 shows that a simple count of the number of groups on a molecule that are able to accept or donate hydrogen-bonds is inversely related to flux

through the membrane. Descriptors of molecular topology are more difficult to interpret. In this study the negative sign of the coefficient $^6\chi$ represents a decrease in flux as molecular topology is increased. $^6\chi$ is based on a count of the number of paths of six atoms, irrespective of the presence of heteroatoms and is therefore a measure of molecular bulk (Dearden et al 1988). It might also encode more subtle information concerning the presence of five-membered rings as opposed to six- (and greater) membered rings. Mechanistically, a more bulky molecule is less likely to pass through the membrane.

Equation 2 is not the same, nor does it quite reach the same level of statistical significance, as those obtained by Chen et al (1993, 1996) which include considerably more parameters and were developed only on subsets of the data set analysed herein. Despite this, there are some noticeable similarities. The original analysis found a negative correlation with a number of parameters based on molecular charges. This was rationalized as describing hydrogen-bonding effects which might promote self-association and thus a reduced tendency to interact with the membrane (Chen et al 1993). Again, the original researchers found molecular weight, a crude but effective measure of molecular bulk, to be inversely related to flux.

Topological indices were not calculated in the original study. The other terms in the QSAR included a cross-product term for the charges and indicator variables of imidazole and amine molecules. However, Chen et al (1993) found that the most significant parameter in terms of the fraction contribution to the QSAR was the molar solubility in isopropyl alcohol, which itself could be related to hydrogen-bonding. Such a large contribution term raises the possibility that flux through this membrane is more dependent upon solubility in isopropyl alcohol than on the nature of the membrane. Selection of vehicle and partitioning of the drug between the membrane and the solvent will significantly affect drug flux. For instance, alcohols have been widely employed to enhance the flux of molecules across the skin (Obata et al 1993).

Consideration of the outliers removed from a QSAR is essential. An outlier to a QSAR is identified normally by having a large standard residual (Lipnick 1991). There are several reasons for their occurrence in QSAR studies, e.g. chemicals might be acting by a mechanism different from that of the majority of the data set. It is also likely that outliers might be a result of random experimental error that might be significant when analysing large data sets. Although it is acceptable to remove a small number of outliers from a QSAR (Martin 1978; Wold & Sjöström 1978; Brüggemann et al 1990; Devillers & Lipnick 1990) it is noted that it is not acceptable to remove outliers repeatedly from a QSAR analysis simply to improve a correlation. In the current work a total of fourteen outliers was omitted. There are common structural themes present in these compounds such as the presence of one or more readily ionizable groups, a five-membered ring structure, or nitrogen heterocyclic molecules. However, none of these structural features is unique to the data set. Further analysis of the data set excluding compounds with functional groups similar to those found to be outliers, including carboxylic acids, five-membered rings, and nitrogen heterocyclic molecules, failed to improve the correlation significantly. Currently no consistent physicochemical explanation can be made to account for these outliers. It can therefore be assumed they are the result of natural variance within the data and are a result of experimental error.

The purpose of an in-vitro model is to replace in-vivo testing, especially where concerns of potential toxicity and expense might mitigate against in-vivo testing. Polydimethylsiloxane membranes are considered as adequate replacements for excised human or animal skin in in-vitro experiments. To consider this issue further lateral validation of QSARs enables comparison between test systems, particularly with regard to mechanisms of action (Barratt et al 1995). On the basis of in-vitro measurements Potts & Guy (1992) proposed a basic model for percutaneous absorption through human skin:

$$\log K_p = 0{\cdot}71 \log P - 0{\cdot}0061\ MW - 6{\cdot}3 \quad (4)$$

where log K_P is the logarithm of the permeability coefficient across excised human skin in-vitro.

No data are available to enable investigation of the relationship between the passage of organic compounds through the polydimethylsiloxane membrane and that through human skin. To do this a QSAR was generated to correlate the Chen data with the parameters proposed by Potts & Guy (1992). The data set with outliers removed gave a slightly better correlation:

$$\log J = 0.674\ (0.049) \log P - 0.0272\ (0.0018) MW + 0.301 \quad (5)$$

$$n = 242;\ s = 0 \cdot 719;\ r = 0 \cdot 736;\ F = 141$$

Equation 5 is valid in that the t-values for the variables, 13·81 and −15·22, respectively, are significant at the 99·9% level. However, it is limited as a predictive model as the statistical fit it produces is worse than that obtained by Potts and Guy

($r = 0{\cdot}818$). It seems that the compounds are not crossing the polydimethylsiloxane membrane by the same mechanism as that assumed for human skin. Thus the use of polydimethylsiloxane for extrapolation to human skin in the development of topical formulations should be regarded with caution.

Human skin is a highly complex organ. It is essentially a stratified epithelium consisting of five distinct layers. The outermost layer of the skin, the stratum corneum, is responsible for limiting the passage of exogenous chemicals across the skin and into the systemic circulation (Scheuplein & Blank 1971). It consists of two alternating amorphous lipophilic and hydrophilic layers. The majority of cells are lipophilic, containing keratin and skin fat. Less common are the hydrophilic cells, consisting mainly of corneocytes. The water content of the stratum corneum is highly variable, depending both on the moisture content of the external environment of the body and on the location on the body from where the skin is obtained. It varies with the position of the tissue, with the water content generally decreasing as the external interface is approached. The stratum corneum has been shown to contain 40% water by weight in an environment where the relative humidity is between 33 and 50%. It has also been estimated that, by weight, the stratum corneum is further composed of 40% protein, mostly keratin, and 15–20% lipid, predominantly triglycerides, cholesterol, fatty acids and phospholipids (Anderson & Cassidy 1973). In contrast, polydimethylsiloxane membranes such as silastic are homogenous, fully lipophilic barriers and as such are incapable of simulating fully the complex properties of the stratum corneum.

A model barrier membrane consisting of alternating or integrated hydrophilic and hydrophobic layers would provide a more accurate representation of stratum corneum barrier function. Several attempts have been made to replicate such properties in novel membrane systems (Sun et al 1997; Yamaguchi et al 1997). However, although these systems have both lipophilic and hydrophilic regions, thus providing a more valid representation of the structure of the stratum corneum, they have so far failed to attract widespread use. Nevertheless, a polydimethylsiloxane membrane can provide useful and important information concerning drug release from a particular system, although it has been reported that flux across polydimethylsiloxane membranes grossly overestimates flux across either human or porcine skin (Santi et al 1991; Woolfson et al 1992; Yamaguchi et al 1997). It can thus be employed in preliminary studies and might be predictive of trends, if not absolute values.

In conclusion, the skin is a viable and important alternative route for the administration of an increasing range of diverse therapeutic agents. Efforts to develop successful formulations are hampered by the availability and quality of human skin such that alternatives, including various animal skins, artificial membranes and mathematical models, are commonly utilized. This study has investigated the flux of compounds through an artificial membrane using QSAR as a tool to investigate the mechanisms of penetration. An easily comprehensible mechanism is proposed largely on the basis of the hydrogen-bonding capacity and the molecular topology of a penetrant. Further modelling of the data with parameters of known importance in the prediction of penetration across human skin suggests that there is little commonality in the two membranes. Therefore any model derived using flux data through polydimethylsiloxane membranes must be treated in the same light, as providing limited information concerning the flux of drugs across human skin in-vivo.

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