An Evaluation of Mathematical Models for Predicting Skin Permeability

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ABSTRACT: A number of mathematical models have been proposed for predicting skin permeability, mostly empirical and very few are deterministic. Early empirical models use simple lipophilicity parameters. The recent trend is to use more complicated molecular structure descriptors. There has been much debate on which models best predict skin permeability. This article evaluates various mathematical models using a comprehensive experimental dataset of skin permeability for 124 chemical compounds compiled from various sources. Of the seven models compared, the deterministic model of Mitragotri gives the best prediction. The simple quantitative structure permeability relationships (QSPR) model of Potts and Guy gives the second best prediction. The two models have many features in common. Both assume the lipid matrix as the pathway of transdermal permeation. Both use octanol–water partition coefficient and molecular size. Even the mathematical formulae are similar. All other empirical QSPR models that use more complicated molecular structure descriptors fail to provide satisfactory prediction. The molecular structure descriptors in the more complicated QSPR models are empirically related to skin permeation. The mechanism on how these descriptors affect transdermal permeation is not clear. Mathematically it is an ill-defined approach to use many colinearly related parameters rather than fewer independent parameters in multi-linear regression. © 2007 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 97:584–598, 2008

Keywords: diffusion; partition coefficient; skin permeability; stratum corneum; transdermal permeation

INTRODUCTION

The human skin is a highly complex organ made of multi-layers of composite materials including the subcutaneous tissue, the dermis and the epidermis.[1,2] A main function of the human skin is to regulate the entry of foreign substances into the body. The barrier function of skin has attracted great scientific interest because of the relevance to a wide range of applications including transdermal delivery of drugs,[3] enhancement of sensorial and functional benefits of skin care products[4] and risk assessment of hazardous exposure to chemicals.[5]

There have been a large number of studies on skin permeability, both experimental and theoretical. *In vitro* measurement of skin permeability is relatively simple and straightforward, although the process is rather time consuming. Diffusion cell is widely used, with which excised human skin is placed between two separated compartments, one as the donor containing the permeant and the other as the receptor. Early measurement of skin

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permeability goes back to the 1960s.[6,7] Today, experimental data of skin permeability are available for over 100 chemical compounds.[8–11]

It is generally believed that transdermal permeation is primarily regulated by the stratum corneum, the outmost layer of the skin. The stratum corneum of human skin is only 10–20 μm thick, and consists of between 10 and 25 layers of dead, elongated, fully keratinised corneocytes that are embedded in a matrix of lipid bilayers.[2,12–14] A main challenge in modelling transdermal permeation is to understand the complex effect of the heterogeneous structure of the stratum corneum. Generally, there are three pathways for transdermal permeation, including the diffusion through the lipid lamellae, the transcellular diffusion through the keratinocytes and lipid lamellae, and the transport through appendages, the hair follicles and sweat ducts.[9,11,14] However, many studies regarded the lateral diffusion through the lipid lamellae as the primary pathway. Few studies have been reported on the transcellular route but much controversy still remains, in particular with regard to the permeation of hydrophilic compounds.[15–19]

Prediction of transdermal permeability has been an important topic of research in pharmaceutical, cosmetics and agrichemical industry. A number of mathematical models have been reported. Categorically, these models can be classified into empirical and mechanistic. Empirical models are experimental data-based and two approaches can be identified: quantitative structure permeability relationships (QSPR) using multiple linear regression and artificial neural network models.[10,20–24] Many QSPR models relate skin permeability to the physicochemical properties of the solutes[21,22] while others use molecular structure properties.[20] Mechanistic models are based on well-known physical laws of first principles. Attempts to predict skin permeability adopting the mechanistic approach had various degrees of success. Many mechanistic models adopted the so-called brick-and-motor model.[25] Early studies in the area were mostly on estimating the tortuous pathway length of solute diffusion through the lipid matrix.[9] Direct prediction of skin permeability from the molecular property has not been possible until recently when the scaled particle theory was adopted to predict the diffusion of small hydrophobic molecules in lipid bilayers.[26]

Most mathematical models for predicting skin permeability are empirical and few are mechanistic. There are still significant controversies among various mathematical models. Many QSPR models were derived from relatively small and closely related experimental dataset. Extension and extrapolation of various QSPR models against other datasets is rather limited. There has been much debate on which of these models provides better prediction. Wilschut et al.[11] compared five QSPR models using 123 data points of 99 chemical compounds. Since then, more experimental data have been reported.[9] Additional mathematical models have been also proposed, in particular, the mechanistic model of Mitragotri[26] and artificial neural network models.[23,27] The objective of the article is to provide a comprehensive review and evaluation of mathematical models, both empirical and mechanistic, for predicting skin permeability. A closely related area is the mathematical modelling of the process of percutaneous absorption and spatial distribution of molecules in human skin under various exposure and/or topical application conditions, either steady-state or dynamic.[14,28–31] The latter is a rather distinct subject of mathematical modelling of transdermal permeation and will not be covered in this article.

In this article, experimental measurement of skin permeability has been briefly reviewed. A large dataset of measured skin permeability for more than 200 data points has been compiled from various sources. The dataset has been used to test the validity of various mathematical models. Seven mathematical models have been compared. Discussions have been made on the drawbacks of existing models in predicting skin permeability. Highlighted are the needs in more fundamental studies on the mechanisms of transdermal permeation considering various pathways of not only lipid matrix but also corneocytes, in particular, the effect of water in terms of its mobility and interaction with stratum corneum.

EXPERIMENTAL DATA OF SKIN PERMEABILITY

In order to evaluate the predictive capability of various mathematical models, a large dataset of skin permeability has been compiled by conducting a comprehensive literature search. *In vitro* measurement of skin permeability has been a subject of research over the last 40 years and experimental data are available for many chemical compounds, mostly of pharmaceutical interest, and some for cosmetics applications or risk

assessment. *In vitro* measurement of skin permeability is relatively straightforward, although time consuming. The commonly used method is by use of a diffusion cell with which a piece of excised skin is placed between two bath solutions, mostly aqueous. The flux of the solute from the donor solution to the receptor solution across the skin is related to the concentration difference between the two bath solutions by the following equation:

$$\frac{dM}{dt} = K_p A(C_1 - C_2) \quad (1)$$

where M is the accumulative amount of substance permeating through the skin, K_p is the skin permeability, A is the surface area of the skin, C_1 and C_2 are the concentrations of the solute in the donor and receptor solutions respectively.

The underlying assumption of the above relationship is that the rate of the substance transferring across skin obeys Fick's law of diffusion. The barrier property of the skin is characterised by the permeability which can be related to the diffusion coefficient and skin-water partition coefficient of the solute as follows:

$$K_p = \frac{DK_{sc}}{\delta} \quad (2)$$

where K_{sc} is the skin-water partition coefficient, D the overall diffusivity of solute through the skin and δ the thickness of the skin.

By measuring the steady-state flux (dM/dt) and concentrations of the two bath solutions C_1 and C_2, the permeability of the solute through the skin is derived. Early studies on *in vitro* measurements of skin permeability go back more than 30 years ago.[6,32,33] A number of studies have been reported on the subject and a large number of measured data are available, mostly scattered in the literature.[9,34–38] A dataset of 97 human skin permeability properties for 94 chemical compounds was first complied by Flynn.[8] More datasets of human skin permeability were compiled and published later.[9–11] The dataset compiled in this study is gathered from those compiled datasets. Some very recently published data are also added to the dataset.[15] Like many previous studies, some reported data have not been included if the experimental conditions were not clearly described. Only human skin data have been included. Altogether, there are 205 data points for 124 chemical compounds. Molecular weight of the chemical compounds ranges from 18 to 765 and $\log K_{ow}$ varies from −3.7 to 5.49. Full listing of the chemical compounds and their measured skin permeability is provided in Table 1.

MATHEMATICAL MODELS FOR PREDICTING SKIN PERMEABILITY

A few reviews on the mathematical models of skin permeation were reported before,[11,39,40] all on empirical QSPR models. Since then, more mathematical models for predicting skin permeability have been reported, most noticeably, the mechanistic model of Mitragotri.[26] In this study, the theoretically derived mechanistic model of Mitragotri has been compared with other most frequently quoted empirically derived QSPR models. A brief introduction of these models is given in this section.

Quantitative Structure-Permeability Relationships

Categorically, mathematical models for predicting skin permeability can be divided into empirical and mechanistic models. Most models are empirically derived, with skin permeability linearly correlated to the physicochemical properties and/or molecular structure parameters of the chemical compounds. Multi-linear regression method is often used to fit available experimental data. Such empirical models are often referred to as QSPR or quantitative structure activity relationships (QSAR). Early studies found a linear correlation of the skin permeability with the lipophilicity of the solute. A number of empirical models were proposed to relate the skin permeability to the octanol–water partition coefficient and molecular weight of molecules.[8,11,20,24,36,39] An evaluation of these models was carried out by Wilschut et al.[11] using 123 data points of 99 chemicals. The model of Potts and Guy[24] was shown to give good prediction. The mathematical model of Potts and Guy was derived by analysing the data of Flynn[8] and the best-fitted empirical equation is given in the following form

$$\log K_p = 0.71 \log K_{ow} - 0.0061\,MW - 6.3 \quad (n = 93,\ r^2 = 0.67) \quad (3)$$

where the skin permeability is in cm/s, K_{ow} is the octanol–water partition coefficient and MW is the molecular weight.

In a different approach, attempts were made to correlate skin permeability to more fundamental

Table 1. List of Chemical Compounds and Measured Skin Permeability Compared with Predicted Results by Three Mathematical Models

				Predicted logK_p (cm/s)		
Solute	logK_{ow}	MW	Measured logK_p (cm/s)	Potts and Guy[24]	Abraham et al.[42]	Mitragotri[26]
1,1,1-Trichloroethane	2.49	133	−5.90[9]	−5.35	−4.01	−5.39
2,3-Butanediol	−0.92	90.	−7.95[11]	−7.50	−6.79	−7.35
2,3-Butanediol	−0.92	90	−7.86[10]	−7.50	−6.79	−7.35
2,4,6-Trichlorophenol	3.69	197	−4.78[9]	−4.88	−4.04	−5.11
2,4-Dichlorophenol	3.06	163.	−4.78[9]	−5.12	−4.71	−5.26
2-Amino-4-nitrophenol	1.26	154	−6.74[9]	−6.35	−7.77	−6.44
2-Butanone	0.29	72	−5.90[11]	−6.53	−5.20	−6.30
2-Chlorophenol	2.15	129	−5.04[9]	−5.56	−4.95	−5.58
2-Ethoxyethanol	−0.32	90	−7.16[9]	−7.08	−6.22	−6.92
2-Naphthol	2.70	144	−5.15[10]	−5.26	−5.14	−5.34
2-Naphthol	2.70	144	−5.11[9]	−5.26	−5.14	−5.34
2-nitro *p*-phenylenediamine	0.53	153	−6.86[9]	−6.86	−8.34	−6.94
2-Phenylethanol	1.36	122	−5.44[10]	−6.08	−5.02	−6.08
3,4-Xylenol	2.30	122	−5.00[9]	−5.41	−5.18	−5.42
3-Nitrophenol	2.00	139	−5.81[9]	−5.73	−7.38	−5.79
4-Amino-2-nitrophenol	0.96	154	−6.11[9]	−6.56	−8.65	−6.65
4-Bromophenol	2.59	173	−5.00[9]	−5.52	−5.63	−5.68
4-Chloro-4-phenylenediamine	0.85	142	−6.23[9]	−6.57	−6.39	−6.62
4-Chlorocresol	3.10	142	−4.82[9]	−4.97	−5.46	−5.05
4-Chlorophenol	2.39	128	−5.00[9]	−5.39	−5.77	−5.42
4-Ethylphenol	2.58	122	−5.02[9]	−5.21	−5.22	−5.22
4-Nitrophenol	1.91	139	−5.81[9]	−5.79	−7.57	−5.85
5-Fluorouracil	−0.89	130	−8.34[8]	−7.73	−7.60	−7.73
Acetylsalicylic acid	1.19	180	−5.70[8]	−6.55	−6.45	−6.72
Aldosterone	1.08	360	−7.86[10]	−7.73	−7.49	−8.15
Aldosterone	1.08	360	−7.79[10]	−7.73	−7.49	−8.15
Amylobarbital	2.07	226	−6.20[9]	−6.21	−6.91	−6.48
Aniline	0.90	93	−5.21[9]	−6.23	−5.52	−6.10
Anisole	2.11	108	−4.69[10]	−5.46	−4.60	−5.41
Atropine	1.83	289	−7.68[8]	−6.77	−5.82	−7.13
Barbital	0.65	184	−7.51[9]	−6.96	−7.63	−7.13
Benzaldehyde	1.48	106	−4.77[10]	−5.90	−5.03	−5.83
Benzaldehyde	1.48	106	−4.41[9]	−5.90	−5.03	−5.83
Benzene	2.13	78	−4.51[9]	−5.26	−4.24	−5.08
Benzene	2.13	78	−4.35[10]	−5.26	−4.24	−5.08
Benzoic acid	1.87	122	−5.16[8]	−5.72	−5.88	−5.72
Benzyl alcohol	1.10	108	−5.78[11]	−6.18	−5.69	−6.12
Benzyl alcohol	1.10	108	−5.33[9]	−6.18	−5.69	−6.12
Benzyl nicotinate	2.40	213	−5.35[8]	−5.90	−5.01	−6.15
Boric acid	−0.22	62	−7.48[8]	−6.83	−8.89	−6.53
Boric acid	−0.22	62	−7.09[8]	−6.83	−8.89	−6.53
Boric acid	−0.22	62	−6.86[8]	−6.83	−8.89	−6.53
Butanol	0.88	74	−6.21[10]	−6.13	−5.37	−5.91
Butanol	0.88	74	−6.16[9]	−6.13	−5.37	−5.91
Butanol	0.88	74	−6.08[9]	−6.13	−5.37	−5.91
Butobarbital	1.73	212	−7.27[9]	−6.37	−7.09	−6.61
Butyl nicotinate	2.27	179	−5.34[8]	−5.78	−5.13	−5.95
Butyric acid	0.79	88	−6.56[11]	−6.28	−5.99	−6.13

(*Continued*)

Table 1. (*Continued*)

Solute	logK_{ow}	MW	Measured logK_p (cm/s)	Predicted logK_p (cm/s) Potts and Guy[24]	Abraham et al.[42]	Mitragotri[26]
Caffeine	−0.07	194	−7.14[8]	−7.53	−7.13	−7.72
Caffeine	−0.07	194	−6.35[8]	−7.53	−7.13	−7.72
Chloroxylenol	3.27	156	−4.83[9]	−4.93	−5.15	−5.06
Chlorpheniramine	3.38	275	−6.22[9]	−5.58	−4.41	−5.93
Codeine	1.19	299	−7.87[9]	−7.28	−6.62	−7.65
Corticosterone	1.94	346	−7.56[10]	−7.04	−6.64	−7.45
Corticosterone	1.94	346	−7.08[10]	−7.04	−6.64	−7.45
Corticosterone	1.94	346	−6.81[10]	−7.04	−6.64	−7.45
Coumarin	1.39	146	−5.60[8]	−6.20	−4.87	−6.28
Coumarin	1.39	146	−5.46[8]	−6.20	−4.87	−6.28
Decanol	4.57	158	−4.65[9]	−4.02	−3.82	−4.16
Decanol	4.57	158	−4.30[10]	−4.02	−3.82	−4.16
Dexamethasone	1.83	392	−7.75[10]	−7.39	−7.97	−7.84
Diclofenac	4.51	296	−6.56[8]	−4.90	−4.70	−5.30
Diclofenac	4.51	318	−5.30[10]	−5.04	−4.70	−5.45
Diethylcarbamazine	0.37	199	−7.45[9]	−7.25	−6.62	−7.45
Digitoxin	1.85	765	−8.44[9]	−9.65	−10.33	−9.99
Dihydromorphine	0.93	287	−8.38[9]	−7.39	−6.45	−7.74
Dimethylethylamine	0.70	73	−6.26[8]	−6.25	−5.56	−6.02
Dimethylethylamine	0.70	73	−5.95[8]	−6.25	−5.56	−6.02
Ephedrine	1.13	165	−5.78[9]	−6.51	−6.78	−6.63
Estradiol	4.01	272	−6.08[10]	−5.11	−5.64	−5.47
Estradiol	4.01	272	−6.05[10]	−5.11	−5.64	−5.47
Estradiol	4.01	272	−6.02[10]	−5.11	−5.64	−5.47
Estradiol	4.01	272	−6.01[10]	−5.11	−5.64	−5.47
Estradiol	4.01	272	−5.97[10]	−5.11	−5.64	−5.47
Estradiol	4.01	272	−5.95[10]	−5.11	−5.64	−5.47
Estradiol	4.01	272	−5.94[10]	−5.11	−5.64	−5.47
Estradiol	4.01	272	−5.94[10]	−5.11	−5.64	−5.47
Estradiol	4.01	272	−5.84[9]	−5.11	−5.64	−5.47
Estradiol	4.01	272	−5.82[10]	−5.11	−5.64	−5.47
Estradiol	4.01	272	−5.77[10]	−5.11	−5.64	−5.47
Ethanol	−0.31	46	−7.06[8]	−6.80	−5.91	−6.40
Ethanol	−0.31	46	−6.65[9]	−6.80	−5.91	−6.40
Ethanol	−0.31	46.	−6.56[9]	−6.80	−5.91	−6.40
Ethyl benzene	3.15	106	−3.48[11]	−4.71	−3.66	−4.66
Ethyl nicotinate	1.32	151	−5.77[8]	−6.28	−5.64	−6.37
Ethyl nicotinate	1.32	151	−5.74[8]	−6.28	−5.64	−6.37
Ethylether	0.89	74	−5.36[9]	−6.12	−4.72	−5.90
Etorphine	2.79	411	−6.00[9]	−6.83	−5.46	−7.29
Fentanyl	4.05	336	−5.81[9]	−5.48	−4.45	−5.90
Fentanyl	4.05	336	−5.56[9]	−5.48	−4.45	−5.90
Fluocinonide	3.19	494	−6.33[9]	−7.05	−7.32	−7.53
Griseofulvin	2.18	353	−6.44[8]	−6.90	−6.24	−7.33
Griseofulvin	2.18	353	−6.27[8]	−6.90	−6.24	−7.33
Heptanoic acid	2.42	130	−5.26[11]	−5.38	−5.22	−5.41
Heptanol	2.31	116	−5.05[9]	−5.37	−4.68	−5.35
Heptanol	2.31	116	−4.98[9]	−5.37	−4.68	−5.35
Hexanoic acid	1.92	116	−5.41[11]	−5.65	−5.49	−5.62

Table 1. (*Continued*)

Solute	logK_{ow}	MW	Measured logK_p (cm/s)	Predicted logK_p (cm/s) Potts and Guy[24]	Abraham et al.[42]	Mitragotri[26]
Hexanol	2.03	102	−5.44[9]	−5.48	−4.86	−5.41
Hexanol	2.03	102	−5.26[10]	−5.48	−4.86	−5.41
Hexanol	2.03	102	−5.11[9]	−5.48	−4.86	−5.41
Hydrocortisone	1.61	362	−8.35[10]	−7.37	−7.85	−7.79
Hydrocortisone	1.61	362	−7.48[9]	−7.37	−7.85	−7.79
Hydrocortisone	1.61	362	−7.19[10]	−7.37	−7.85	−7.79
Hydrocortisone hemipimelate	3.26	504	−6.30[9]	−7.06	−7.95	−7.53
Hydrocortisonehemisuccinate	1.89	462	−6.76[9]	−7.78	−9.03	−8.24
Hydrocortisone hexanoate	4.48	461	−5.30[9]	−5.93	−6.23	−6.42
Hydrocortisone hydroxyhexanoate	2.79	477	−6.60[9]	−7.23	−7.60	−7.70
Hydrocortisone methylpimelate	3.70	519	−5.82[9]	−6.84	−6.88	−7.32
Hydrocortisone methylsuccinate	2.60	476	−7.23[9]	−7.36	−7.66	−7.83
Hydrocortisone N,N-dimethylsuccinamate	2.03	489	−7.72[9]	−7.85	−8.39	−8.31
Hydrocortisone octanoate	5.49	489	−4.76[9]	−5.38	−5.72	−5.88
Hydrocortisone pimelamate	2.30	504	−6.61[9]	−7.74	−8.61	−8.21
Hydrocortisone propinate	2.80	418	−6.02[9]	−6.86	−7.00	−7.33
Hydrocortisone succinamate	1.43	462	−8.14[9]	−8.10	−9.39	−8.56
Hydromorphone	1.60	285	−8.38[8]	−6.90	−6.04	−7.26
Ibuprofen	3.97	206	−5.00[8]	−4.74	−4.43	−4.99
Indomethacin	4.27	358	−5.39[10]	−5.45	−5.48	−5.90
Isoquinoline	2.08	129	−5.33[9]	−5.61	−4.67	−5.64
Lidocaine	2.44	234	−5.96[10]	−6.00	−5.80	−6.28
Mannitol	−3.01	182	−8.51[8]	−9.55	−11.54	−9.68
Mannitol	−3.01	182	−8.18[8]	−9.55	−11.54	−9.68
Mannitol	−3.01	182	−8.16[8]	−9.55	−11.54	−9.68
Mannitol	−3.01	182	−7.92[8]	−9.55	−11.54	−9.68
Mannitol	−3.01	182	−7.77[8]	−9.55	−11.54	−9.68
m-Cresol	1.96	108	−5.38[9]	−5.57	−5.49	−5.52
Meperidine	2.72	247	−5.99[9]	−5.88	−4.67	−6.19
Methanol	−0.77	32	−6.86[9]	−7.04	−6.15	−6.52
Methanol	−0.77	32	−6.56[9]	−7.04	−6.15	−6.52
Methanol	−0.77	32	−6.35[8]	−7.04	−6.15	−6.52
Methyl nicotinate	0.83	137	−6.07[8]	−6.55	−5.90	−6.59
Methyl nicotinate	0.83	137	−6.02[8]	−6.55	−5.90	−6.59
Methyl nicotinate	0.83	137	−5.97[8]	−6.55	−5.90	−6.59
Methylhydroxybenzoate	1.96	152	−5.60[9]	−5.84	−6.61	−5.93
Morphine	0.89	285	−8.59[9]	−7.41	−7.94	−7.75
Naproxen	3.18	230	−6.95[9]	−5.45	−5.15	−5.73
Naproxen	3.18	230	−6.10[8]	−5.45	−5.15	−5.73
Naproxen	3.18	230	−4.97[10]	−5.45	−5.15	−5.73
N-Hexyl nicotinate	3.51	207	−5.30[8]	−5.07	−4.63	−5.32
Nicorandil	0.43	211	−7.13[8]	−7.28	−9.39	−7.51
Nicotine	1.17	162	−6.04[8]	−6.46	−5.66	−6.58
Nicotine	1.17	162	−5.54[8]	−6.46	−5.66	−6.58
Nicotine	1.17	162	−5.28[9]	−6.46	−5.66	−6.58
Nicotinic acid	0.36	123	−8.18[8]	−6.80	−7.00	−6.78
Nitroglycerine	1.62	227	−5.51[9]	−6.54	−11.93	−6.80
n-Nitrosodiethanolamine	−1.28	134	−8.78[11]	−8.03	−8.52	−8.04
Nonanol	3.77	144	−4.78[9]	−4.50	−4.09	−4.60

(*Continued*)

Table 1. (*Continued*)

Solute	logK_{ow}	MW	Measured logK_p (cm/s)	Predicted logK_p (cm/s) Potts and Guy[24]	Abraham et al.[42]	Mitragotri[26]
o-Cresol	1.95	108	−5.36[9]	−5.57	−5.49	−5.52
Octanoic acid	3.05	144	−5.16[11]	−5.01	−4.98	−5.10
Octanol	3.00	130	−4.84[9]	−4.96	−4.32	−5.00
Octanol	3.00	130	−4.77[8]	−4.96	−4.32	−5.00
Octanol	3.00	130	−4.51[10]	−4.96	−4.32	−5.00
o-Phenylenediamine	0.15	108	−6.90[9]	−6.85	−6.66	−6.78
Ouabain	−2.00	585	−9.66[9]	−11.29	−13.90	−11.69
p-Cresol	1.94	108	−5.31[9]	−5.58	−5.44	−5.53
Pentanoic acid	1.39	102	−6.26[11]	−5.94	−5.76	−5.85
Pentanol	1.51	88	−5.78[9]	−5.77	−5.14	−5.62
Phenobarbital	1.47	232	−6.89[9]	−6.67	−7.24	−6.95
Phenol	1.46	94	−5.64[9]	−5.84	−5.81	−5.72
Phenol	1.46	94	−5.44[10]	−5.84	−5.81	−5.72
Phenol	1.46	94	−5.27[9]	−5.84	−5.81	−5.72
Piroxicam	3.06	331	−7.37[9]	−6.15	−9.53	-6.56
p-Phenylenediamine	−0.30	108	−7.18[9]	−7.17	−6.78	−7.10
Progesterone	3.87	314	−6.44[10]	−5.47	−4.16	−5.88
Progesterone	3.87	314	−6.08[10]	−5.47	−4.16	−5.88
Propanol	0.25	60	−6.48[9]	−6.49	−5.64	−6.18
Propanol	0.25	60	−6.41[9]	−6.49	−5.64	−6.18
Propanol	0.25	60	−6.33[9]	−6.49	−5.64	−6.18
Propranolol	3.48	257	−6.48[8]	−5.40	−6.00	−5.73
Propranolol	3.48	257	−6.33[8]	−5.40	−6.00	−5.73
Resorcinol	0.80	110	−7.18[9]	−6.40	−7.19	−6.35
Salicyclic acid	2.26	138	−5.76[9]	−5.54	−5.76	−5.60
Salicyclic acid	2.26	138	−5.48[8]	−5.54	−5.76	−5.60
Salicyclic acid	2.26	138	−5.44[8]	−5.54	−5.76	−5.60
Salicyclic acid	2.26	138	−5.42[8]	−5.54	−5.76	−5.60
Salicyclic acid	2.26	138	−5.07[10]	−5.54	−5.76	−5.60
Scopolamine	0.98	303	−7.86[9]	−7.45	−6.73	−7.82
Styrene	2.95	104	−3.74[11]	−4.84	−3.90	−4.78
Sucrose	−3.70	342	−8.84[9]	−11.02	−15.85	−11.37
Sufentanil	3.95	387	−5.48[9]	−5.85	−4.56	−6.31
Testosterone	3.32	288	−6.21[10]	−5.70	−4.87	−6.08
Testosterone	3.32	288	−5.83[10]	−5.70	−4.87	−6.08
Testosterone	3.32	288	−5.48[8]	−5.70	−4.87	−6.08
Testosterone	3.32	288	−4.95[8]	−5.70	−4.87	−6.08
Thymol	3.30	150	−4.84[9]	−4.87	−4.73	−4.98
Toluene	2.73	92	−3.56[11]	−4.92	−3.93	−4.81
Trichloromethane	1.97	119	−5.35[8]	−5.63	−4.20	−5.62
Urea	−2.11	61	−7.39[9]	−8.17	−7.96	−7.84
Water	−1.38	18	−7.26[9]	−7.39	−6.36	−6.71
Water	−1.38	18	−7.08[10]	−7.39	−6.36	−6.71
Water	−1.38	18	−6.86[9]	−7.39	−6.36	−6.71
Water	−1.38	18	−6.80[8]	−7.39	−6.36	−6.71
Water	−1.38	18	−6.72[8]	−7.39	−6.36	−6.71
Water	−1.38	18	−6.71[8]	−7.39	−6.36	−6.71
Water	−1.38	18	−6.68[8]	−7.39	−6.36	−6.71
Water	−1.38	18	−6.60[8]	−7.39	−6.36	−6.71

Table 1. (*Continued*)

Solute	$\log K_{ow}$	MW	Measured $\log K_p$ (cm/s)	Predicted $\log K_p$ (cm/s) Potts and Guy[24]	Abraham et al.[42]	Mitragotri[26]
Water	−1.38	18	−6.56[9]	−7.39	−6.36	−6.71
Water	−1.38	18	−6.48[8]	−7.39	−6.36	−6.71
Water	−1.38	18	−6.43[10]	−7.39	−6.36	−6.71
Water	−1.38	18	−6.42[8]	−7.39	−6.36	−6.71
Water	−1.38	18	−6.41[9]	−7.39	−6.36	−6.71
Water	−1.38	18	−6.37[10]	−7.39	−6.36	−6.71
Water	−1.38	18	−6.36[9]	−7.39	−6.36	−6.71
Water	−1.38	18	−6.36[10]	−7.39	−6.36	−6.71
Water	−1.38	18	−6.32[8]	−7.39	−6.36	−6.71

molecular structure parameters of the free energy of solute transfer in lipid, rather than the lipophility.[20,41–44] Abraham et al.[42] argued that $\log K_{ow}$ is an empirical colligation variable that linearly relates to the size, polarity and hydrogen bonding ability of the permeant. They tried to relate the skin permeability to the linear free energy descriptors, referred to as Abraham descriptors by some researchers. By analysing the skin permeability of 47 compounds, Abraham et al. derived the following empirical equation:

$$\log K_p = -5.241 + 0.437R_2 - 0.41\pi_2^H - 1.631\sum\alpha_2^H - 3.286\sum\beta_2^H + 2.012V_x \quad (n = 47, r^2 = 0.9567) \tag{4}$$

where the skin permeability is in cm/s, R_2 is an excess molar refraction, π_2^H the dipolarity–polarisability, $\sum\alpha_2^H$ the overall hydrogen bond acidity, $\sum\beta_2^H$ the overall hydrogen bond basicity and V_x is the McGowan characteristic molecular volume.

This more complicated multi-linear regression approach has been taken by others and slightly different empirical equations were reported.[41,42] Table 2 lists the most frequently quoted QSPR models for predicting skin permeability. These QSPR models were evaluated in this study. No attempts have been made to include all the QSPR models reported in the literature.

Mechanistic Models

Despite of numerous studies on the mechanisms of transdermal permeation, very few mechanistic models are available and capable to predict skin permeability directly. Most studies have been concerned with the tortuous pathways of transdermal permeation, including the interaction with the heterogeneous structures of stratum corneum. The 'brick and mortar' model proposed by Michaels et al.[25] has been adopted by many researchers to estimate the diffusion length of solute in the tortuous lipid matrix.[9,44] Assuming transdermal

Table 2. List of Mathematical Models for Predicting Skin Permeability

Mathematical Equations[a]	References
$K_p(\text{cm/s}) = 5.6 \times 10^{-6} K_{ow}^{0.7} \exp(-0.46r^2)$	Mitragotri[26]
$\log K_p(\text{cm/s}) = 0.71\log K_{ow} - 0.0061\,\text{MW} - 6.3$	Potts and Guy[24]
$\log K_p(\text{cm/s}) = 0.84\log K_{ow} - 0.07(\log K_{ow})^2 - 0.27H_b - 1.84\log\text{MW} + 0.8337$	Lien and Gao[48]
$\log K_p(\text{cm/s}) = 0.82\log K_{ow} - 0.0093\,\text{MV} - 0.039\,\text{MPt} - 5.9163$	Barratt[21]
$\log K_p(\text{cm/s}) = 0.0256\,\text{MV} - 1.72\sum\alpha_2^H - 3.93\sum\beta_2^H - 4.85$	Potts and Guy[41]
$\log K_p(\text{cm/s}) = -0.59\pi_2^H - 0.63\sum\alpha_2^H - 3.48\sum\beta_2^H + 1.79V_x - 5.05$	Abraham et al.[43]
$\log K_p(\text{cm/s}) = 0.44R_2 - 0.49\pi_2^H - 1.48\sum\alpha_2^H - 3.44\sum\beta_2^H + 1.94V_x - 5.13$	Abraham et al.[42]

[a] K_{ow}, octanol–water partition coefficient; MW, molecular weight; H_b, number of hydrogen bonds; MV, molecular volume; MPt, melting point; $\sum\alpha_2^H$, solute hydrogen bond acidity; $\sum\beta_2^H$, solute hydrogen bond basicity; π_2^H, solute dipolarity/polarisability; V_x, McGowan characteristic molecular volume; R_2, excess molar refraction.

permeation solely occurs through the lipid matrix, Johnson et al.[9] proposed the following expression for the skin permeability

$$\frac{1}{K_p} = \frac{\delta\tau^*}{K_m D_{lat}} + \frac{2}{k_l} + \frac{n}{K_M k'} \quad (5)$$

where δ is the thickness of SC, τ^* the effective tortuosity, K_m the lipid bilayer/water partition coefficient, D_{lat} lateral diffusion coefficient of solute along the plane of lipid bilayers, k_l the mass transfer coefficient across lipid bilayers and k' the transmembrane mass transfer coefficient.

From the idealised 'brick-and-mortar' model, the effective tortuosity was derived as follows:

$$\tau^* = 1 + \frac{2g}{\delta}\ln\left(\frac{d}{2s}\right) + \frac{Ndt}{sh} + \left(\frac{d}{1+\omega}\right)^2\left(\frac{\omega}{\delta g}\right)(N-1) \quad (6)$$

where d is the diameter of keratinocyte, t the height of keratinocyte, g and s are the vertical and lateral thicknesses of lipid pathways (gap between keratinocyte), ω the offset ratio and N the number of keratinocyte layers.

No closed-form formulation for predicting skin permeability was given by Johnson et al.[9] Challenges remain in developing structure-transport relationship for lipid matrix. More studies were made on the partition properties of solutes between lipid bilayer and various solvents including octanol, olive oil, hexadecane and decadiene,[34,45–47] some involving molecular dynamics simulations. Significant progress was only made very recently with the mechanistic approach when Mitragotri[26] presented a scaled particle theory on solute partition and diffusion across lipid bilayers. The partition of a solute to SC lipid bilayers was still described by the following widely quoted empirical relationship.

$$K_m = K_{ow}^n \quad (7)$$

with n varying between 0.7 and 0.86.

The equation for the diffusion coefficient of a solute in the lipid matrix was nevertheless derived mathematically based on the scaled particle theory. Assuming a solute diffuses through about 100 lipid bilayers across the SC, for the diffusion coefficient of a solute in lipid matrix was derived as

$$D_{lip} \approx D_o \exp(-0.4r^2) \quad (8)$$

where r is the molecular radius.

Note that the above equation is in the same format of the Wilke–Chang equation for solute diffusion in an isotropic model hydrocarbon solution for molecules of size 50–500 Da, which reads as

$$D_o = 2.0 \times 10^{-5}\exp(-0.06r^2) \quad (9)$$

Substituting Eq. (9) into Eq. (8), Mitragotri[26] derived the following equation for the diffusion coefficient of a solute in the lipid matrix

$$D_{lip} = 2.0 \times 10^{-5}\exp(-0.46r^2) \quad (10)$$

Combining Eqs. (7) and (10), the following equation for predicting skin permeability was obtained

$$K_p = \frac{D_{lip}K_m}{\tau\delta} = 5.6 \times 10^{-6}K_{ow}^{0.7}\exp(-0.46r^2) \quad (11)$$

where the skin permeability is in cm/s and $\tau\delta$ is given as 3.6 cm.

The above mechanistic model for predicting skin permeability has been evaluated along with the other frequently quoted empirical QSPR models listed in Table 2.

RESULTS AND DISCUSSIONS

To test and compare the seven mathematical models, predictions have been made for the skin permeability of the chemical compounds listed in Table 1, using the equations listed in Table 2. For the prediction of each mathematical model, the linear correlation coefficient R-square and the mean absolute errors (MAEs) between the predicted skin permeability and measured data have been computed. MAE between predicted permeability and experimental data is calculated by the following equation:

$$\text{MAE} = \left|\frac{(\log K_p^{obs} - \log K_p^{pre})}{\log K_p^{obs}}\right| \quad (12)$$

where $\log K_p^{obs}$ is the experimental value, $\log K_p^{pre}$ is the model prediction.

A summary of the linear correlation coefficient and MAE for the seven mathematical model predictions are listed in Table 3. A separate analysis of the hydrophobic solutes only suggests that both the correlation coefficient and MAE hardly changed for all the models. This is due to the fact that there are few hydrophilic compounds in the datasets. For the whole dataset, the deterministic model of Mitragotri[26] gives the best

Table 3. Comparison of Skin Permeability Models: Correlation Coefficient and Mean Absolute Error between Predicted Results and Measured Data

	Entire Dataset		Hydrophobic Solutes	
Mathematical Equations	Correlation Coefficient, R^2	Mean Absolute Error, MAE	Correlation Coefficient, R^2	Mean Absolute Error, MAE
Mitragotri[26]	0.698	0.088	0.658	0.091
Potts and Guy[24]	0.676	0.091	0.610	0.089
Lien and Gao[48]	0.564	0.402	0.526	0.408
Barratt[21]	0.463	0.632	0.514	0.658
Potts and Guy[41]	0.364	0.274	0.159	0.304
Abraham et al.[43]	0.535	0.140	0.504	0.138
Abraham et al.[42]	0.535	0.120	0.455	0.114

prediction, with a correlation coefficient of $R^2 = 0.698$ and MAE of 0.088. The simple empirical QSPR model of Potts and Guy[24] gives the second best prediction, with the correlation coefficient of R^2 and MAE of 0.676 and 0.091, respectively.

Table 3 suggests that apart from the simple QSPR model of Potts and Guy[24], all other QSPR models did not give satisfactory prediction of the skin permeability for the compounds listed in Table 1. Of the many QSPR models, the one of Potts and Guy is the earliest in its kind and the simplest in its form. The other QSPR models in Table 2 were developed later on. These later developed QSPR models are more complicated by using a number of molecular structure descriptors rather than the simple lipophilicity parameter K_{ow}. The linear free energy descriptors or the so-called Abraham descriptors were used by several studies.[41–43] Others used the more complicated hydrogen bond descriptors.[10,40] However, this evaluation study suggests that all these later developed models fail to give improved prediction. In fact, all these more complicated QSPR models performed worse than the simple QSPR model of Potts and Guy.[24] As an example, Figure 1 shows the prediction using the latest QSPR equation of Abraham et al.[42] The model produced a correlation coefficient of $R^2 = 0.535$ and the MAE of 0.120. Clearly, the model did not perform well and there are many out-lying data points that cannot be predicted.

There are two major drawbacks of the many late developed QSPR models for predicting skin permeability. Firstly, the relationship between the skin permeability with the molecule structure descriptors introduced in these more complicated models is mostly empirical. With the early simple model of Potts and Guy, the relationship of solute diffusion through the skin with the solute partition property and molecular size is very clear and well established. In some aspects, the simple model of Potts and Guy can be regarded as semi-deterministic. The deterministic nature of the Potts and Guy model will be further discussed later. On the other hand, with all the other late developed QSPR models, the relationship of the hydrogen bond descriptors with the solute diffusion in lipid matrix and hence the transdermal permeability is complex and not clearly established. The second drawback of all the other late developed QSPR models is that their mathematical approach is ill-defined. The common practice of multi-linear regression is to use as less as possible the number of parameters in the equation, preferably those that are perpendicular and independent. In practice, principal component analysis is often used to reduce the number of parameters. It was argued by many of the late

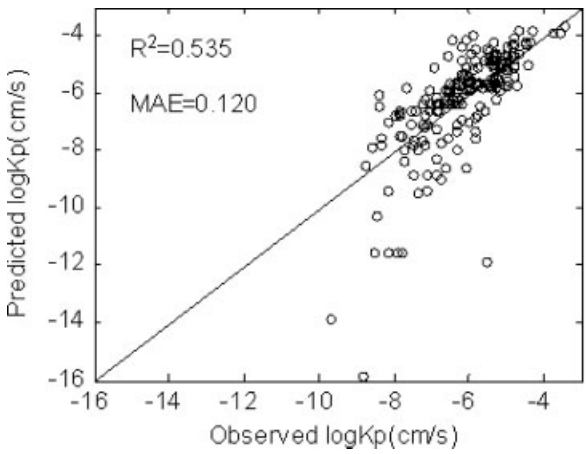

Figure 1. Skin permeability: a comparison of experimental data with the prediction of the more complicated QSPR model of Abraham et al.[42]

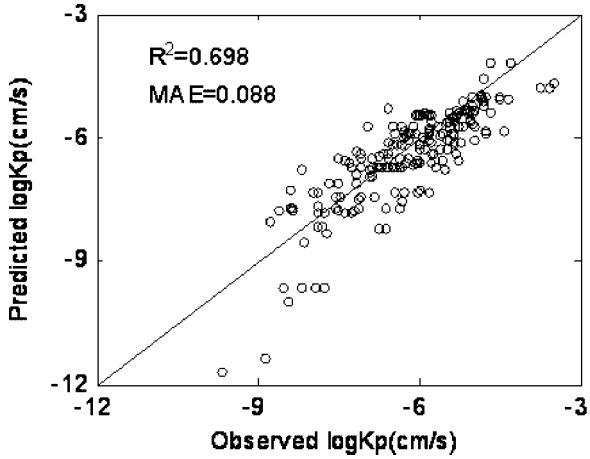

Figure 2. Skin permeability: a comparison of experimental data with the prediction of the mechanistic model of Mitragotri.[26]

developed more complex QSPR models that the hydrogen bond descriptors are collinearly related to the lipophilicity. If this is the case, it should be sufficient to use the single lipophilicity parameter. Replacing the simple lipophilicity parameter K_{ow} with more complicated inter-related molecular structure descriptors is bound to introduce errors and cause problems.

Plotted in Figures 2 and 3 are the skin permeability predicted by the two best models of Mitragotri[26] and Potts and Guy[24] compared against the experimental data. That the two models of Mitragotri[26] and Potts and Guy[24] gave the best prediction is not a coincidence. Although

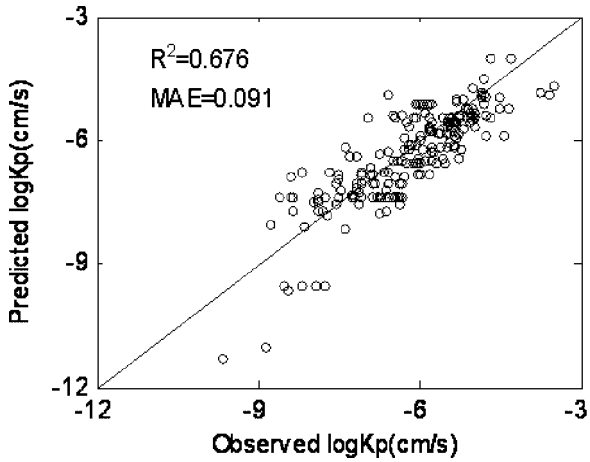

Figure 3. Skin permeability: a comparison of experimental data with the prediction of the simple QSPR model of Potts and Guy.[24]

derived in quite different manners, with the Mitragotri model derived theoretically using the scaled particle theory of solute diffusion in lipid and that the Potts and Guy statistically by multi-linear regression, the two models share many common features. Both models have the same underlying assumption, that is the tortuous lipid matrix is the pathway for transdermal permeation. Both models predict skin permeability from the two physicochemical properties of the octanol–water partition coefficient and the molecular size or weight of the solute. With the Mitragotri equation, the solute radius of diffusion for a molecule in lipid bilayers is related to the molecular weight by $4\pi r^3/3 = 0.91$ MW. Thus, the Mitragotri equation can be also read as

$$K_p = 5.6 \times 10^{-6} K_{ow}^{0.7} \exp(-0.1662\,\mathrm{MW}^{2/3}) \quad (13)$$

or

$$\log K_p = 0.7\log(K_{ow}) - 0.0722\,\mathrm{MW}^{2/3} - 5.2518 \quad (14)$$

This formulation is remarkably similar to the statistically derived empirical QSPR equation of Potts and Guy. The main difference is that for the Mitragotri model the power index of the molecular weigh is 2/3, slightly lower than 1. The coefficients of the last two terms of the two models are also slightly different. Clearly, the mechanistic model of Mitragotri outperformed all the statistically derived QSPR models and provided the most satisfactory prediction of skin permeability. The salient point is that the mechanistic approach based on the fundamental theory of solute diffusion in lipid matrix is better than the empirically derived multi-linear regression models.

There are also limitations with the mechanistic model of Mitragotri. Figure 4 suggests that there are still significant under and over predictions of skin permeability for may chemical compounds by the Mitragotri model. While some of the discrepancies may be due to errors in the original experimental data, as commented elsewhere, the Mitragotri model is found to under-predict the skin permeability of the hydrophilic compounds by few orders of magnitudes. Generally, this is also the case for other models. Under-prediction of skin permeability for hydrophilic compounds by mathematical models has been also pointed out by some earlier studies.[11,15] Figure 4 and in particular Table 4 suggests that the under-prediction of skin permeability by various models increases with the hydrophilicity of the solutes. For

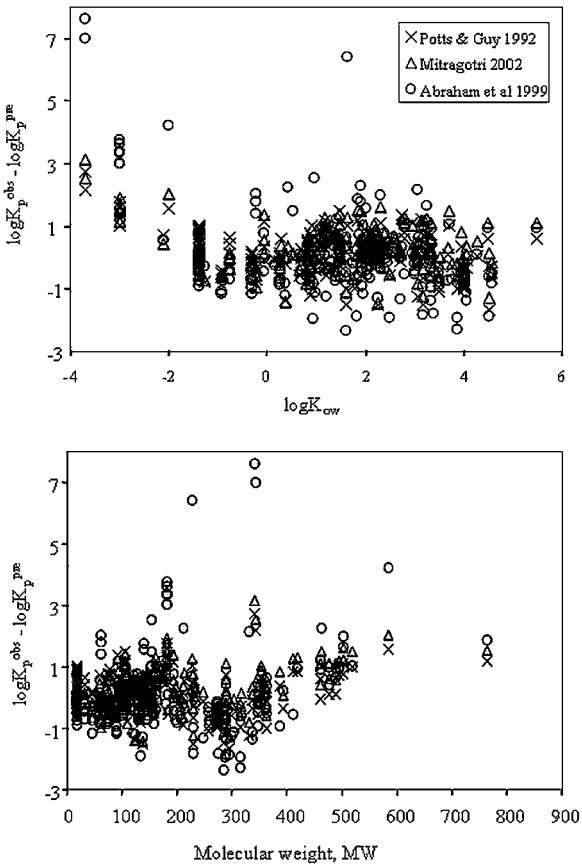

Figure 4. Comparison of predicted errors of skin permeability by different models of Potts and Guy[24] (×), Abraham et al.[42] (○), and Mitragotri[26] (△).

highly hydrophilic solutes ($K_{ow} < 0.01$), the underprediction of the skin permeability reached 2–4 orders of magnitude by the best models of Mitragotri[26] and Potts and Guy.[24] The underprediction of skin permeability by the more complicated QSPR model of Abraham et al.[42] is even higher. Apart from the effect of the solute hydrophilicity, Figure 4 suggests that molecular weight does not have clear influence on the model prediction. It should be pointed out that there are also some inconsistencies in the quoted K_{ow} values for some solutes in the literature. For instance, in the article of Mitragotri,[15] the quoted logK_{ow} values for atropine and chloropheniramine are −2.22 and −0.33, respectively. However, according to Hansch et al.,[49] the logK_{ow} values of these two solutes are 1.83 and 3.38, hence they are hydrophobic, not hydrophilic. In our article the K_{ow} values from Hansch et el. are used. When the K_{ow} values quoted by Mitragotri[15] are used, the predicted values of skin permeability are orders of magnitude lower than the experimental data for the two compounds. The inconsistency in the K_{ow} values will undoubtedly affect the prediction of skin permeability by various models.

Water consists of more than 50% mass fraction of saturated skin. There have been several studies on the mobility of water in the skin and its effect on transdermal permeation.[15,17,50] However, despite of many studies, little progress has been made in predicting the effect of hydrophilic pathways on transdermal permeation. Mitragotri[15] presented a model that considers four possible skin permeation pathways for both hydrophilic and hydrophobic solutes. The four pathways are free-volume diffusion through lipid bilayers, lateral diffusion along lipid bilayers, diffusion through aqueous pores in lipid bilayers and diffusion through shunts. The last two pathways are relevant for the permeation of hydrophilic compounds. Mitragotri[15] considered the diffusion through shunts for large molecules and estimated the contribution to be *ca.* 2e–9 cm/s. According to Mitragotri's four pathway model, the contribution from the diffusion through the aqueous pores in lipid bilayers is also relatively small because the porosity of these

Table 4. Skin Permeability of Hydrophilic Compounds: Comparison of Experimental Data with Predictions of Potts and Guy[24] and Mitragotri[26] Models

			LogK_p (cm/s)		
Compounds	LogK_{ow}	MW	Measured Data	Potts and Guy[24]	Mitragotri[26]
Sucrose	−3.70	342	−8.84	−11.02	−11.37
Mannitol	−3.01	182	−8.51	−9.55	−9.68
Mannitol	−3.01	182	−8.18	−9.55	−9.68
Mannitol	−3.01	182	−8.16	−9.55	−9.68
Mannitol	−3.01	182	−7.92	−9.55	−9.68
Mannitol	−3.01	182	−7.77	−9.55	−9.68
Urea	−2.11	60	−7.39	−8.17	−7.84
Ouabain	−2.00	584	−9.66	−11.29	−11.69

aqueous pores is estimated to be *ca.* 10^{-5} to 10^{-6}. This amount of water content in the lipid bilayer is apparently negligibly small compared to the overall water content in SC. Indeed, the results of Mitragotri[15] showed that the dependence of skin permeability on solute hydrodynamic radius was still significantly under predicted for most hydrophilic compounds.

Clearly, in order to develop more accurate mechanistic models capable of prediction transdermal permeation of both hydrophilic and lipophilic compounds, further studies are needed to include the hydrophilic pathway into earlier mechanistic model of Mitragotri.[26]

CONCLUSIONS

Seven mathematical models for predicting skin permeability have been compared. A large dataset of experimentally measured skin permeability for 124 chemical compounds have been compiled and used to test the seven models. The results indicates that the mechanistic model of Mitragotri gives the best prediction, with a correlation coefficient of $R^2 = 0.698$ and MAE of 0.088. The model of Mitragotri is derived theoretically based on the scaled particle theory of solute diffusion in lipid bilayers. It assumes the lipid matrix as the pathway of transdermal permeation. The equation predicts skin permeability from two parameters, the octanol–water partition coefficient and molecular size. These two parameters are highly relevant to solute diffusion in lipid.

The simple QSPR model of Potts and Guy provided the second best prediction, with the correlation coefficient of R^2 and MAE of 0.676 and 0.091, respectively. The simple empirical model, although derived empirically by multi-linear regression of experimental data, has many features in common with the mechanistic model of Mitragotri. In particular, the model also assumes the lipid matrix as the pathway of transdermal permeation and uses the same parameters of the octanol–water partition coefficient and molecular size. The equation is very similar in form to the theoretical equation of Mitragotri.

A number of more complicated empirical models have been proposed for predicting skin permeability. These models introduced more complicated molecular structure parameters such as hydrogen bond descriptors. It is shown that all the more complicated QSPR models fail to provide satisfactory prediction. A major limitation of these more complicated models is that the molecular structure descriptors are empirically related to skin permeation. The mechanism on how these molecular descriptors affect transdermal permeation is not clear. Many of molecular structure descriptors introduced in the more complicated QSPR models are also colinearly related to lipophilicity. Mathematically, it is an ill-defined approach to use many colinearly related parameters rather than fewer principal independent parameters.

There are still limitations with the mechanistic model of Mitragotri and the simple QSPR model of Potts and Guy. Both models significantly underpredict the skin permeability of many hydrophilic compounds. The mechanistic model of Mitragotri considers solute diffusion through the lipid matrix as the only pathway of transdermal permeation and the hydrophilic pathway is ignored. Water consists of more than 50% mass fraction of saturated skin. Further studied are needed to unravel the mechanisms of transdermal permeation through both hydrophilic and lipophilic pathways.

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