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Modelling the effect of mixture components on permeation through skin

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ABSTRACT

A vehicle influences the concentration of penetrant within the membrane, affecting its diffusivity in the skin and rate of transport. Despite the huge amount of effort made for the understanding and modelling of the skin absorption of chemicals, a reliable estimation of the skin penetration potential from formulations remains a challenging objective. In this investigation, quantitative structure–activity relationship (QSAR) was employed to relate the skin permeation of compounds to the chemical properties of the mixture ingredients and the molecular structures of the penetrants. The skin permeability dataset consisted of permeability coefficients of 12 different penetrants each blended in 24 different solvent mixtures measured from finite-dose diffusion cell studies using porcine skin. Stepwise regression analysis resulted in a QSAR employing two penetrant descriptors and one solvent property. The penetrant descriptors were octanol/water partition coefficient, log *P* and the ninth order path molecular connectivity index, and the solvent property was the difference between boiling and melting points. The negative relationship between skin permeability coefficient and log *P* was attributed to the fact that most of the drugs in this particular dataset are extremely lipophilic in comparison with the compounds in the common skin permeability datasets used in QSAR. The findings show that compounds formulated in vehicles with small boiling and melting point gaps will be expected to have higher permeation through skin. The QSAR was validated internally, using a leave-many-out procedure, giving a mean absolute error of 0.396. The chemical space of the dataset was compared with that of the known skin permeability datasets and gaps were identified for future skin permeability measurements.

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1. Introduction

Skin, the largest organ of the human body, is constantly exposed to various compounds and chemical substances in everyday life. Some of these pass the skin barrier ending in blood and hence affecting metabolism and health. Understanding the mechanism of skin penetration, and therefore the level of toxicity and irritancy of the chemicals may provide the knowledge to enhance transdermal drug delivery, boost the cosmetic industry and increase the broadness and reliability of the risk assessment on dermal exposure to toxic substances (Barry, 2007).

In order for a substance to be absorbed into the body following dermal exposure, first it must be dissolved-dissipated in the stratum corneum (SC)—the outermost sub-layer of the skin, and then diffuse through the remaining sub-layers of the epidermis and into the dermis, where it will finally diffuse into the blood capillaries. The SC is the most important barrier of the skin. SC consists of layers of tightly packed, flattened, keratin-enriched, anucleate corneocytes that are embedded in an intercellular lipid matrix (Bouwstra et al., 2002). Long chain ceramides, fatty acids, cholesterol and triglycerides are lipid matrix's main constituents (Monteiro-Riviere et al., 2001). These lipids form long lamellae parallel to the corneocyte surfaces. The lipids are arranged in bilayers consisting of ordered, crystalline phases on both sides of a narrow, central band of fluid lipids (Bouwstra et al., 2002; Monteiro-Riviere, 1986). Lipophilicity of a compound dictates the partitioning behavior into corneocytes. It can be postulated that hydrophilic compounds tend to partition into the corneocyte proteins while more lipophilic compounds into the SC lipids (Raykar et al., 1988; Van der Merwe and Riviere, 2005). There is evidence in the literature (Anderson et al., 1988) which is also supported by quantitative structure–activity relationship (QSAR) studies (Ghafourian and Fooladi, 2001) which indicates the higher partitioning of more lipophilic compounds containing fewer heteroatoms into the lipid domain of SC, while partitioning to protein domain is less sensitive to the size and number of heteroatoms of penetrants.

Permeation of chemicals through skin is not only dependent on the chemical structure and properties of the penetrant itself, but also it is affected by the other chemicals present in the mixture. Solvents and other mixture ingredients can alter the permeation profile of a chemical by changing the properties of the lipid and

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protein domains of SC, solubility and therefore the thermodynamic activity of the penetrant in the mixture, and partitioning of the penetrant from the vehicle into the SC. Chemical enhancers, for example, can cause a dynamic structural disorder in the SC lipid domain that will lead to enhanced transdermal permeation (Bezema et al., 1996).

A problem that emerges at this stage is the difficulty of accurately predicting the diffusivity and partitioning as they are both ultimately dependent on the skin structure, changes to the skin caused by various solvents and permeants, changes of the formulation containing the permeant, and the effect of metabolizing enzymes on permeants. From the above, given also the almost unlimited possible combinations of solvent mixtures and permeants, it can be assumed that the accurate prediction of diffusion and partition from permeant and solvent chemical data is uncertain (Van der Merwe and Riviere, 2005). On the other hand large sets of empirical data provide us with valuable certainty in the process of identifying characteristics of permeant and vehicle systems that have consistent effects across a wide range of experimental conditions.

Empirical data of permeant and solvent has been used extensively with success in predicting skin permeability. This is often carried out through the use of QSAR where skin permeation profile is related to the molecular properties of compounds, given that the skin permeation is measured at consistent experimental conditions. QSAR has been efficiently used to model skin permeation of chemicals from simple systems such as saturated aqueous solutions (El Tayar et al., 1991; Abraham et al., 1995, 1999; Ghafourian and Fooladi, 2001; Moss and Cronin, 2002). Potts and Guy (1992) developed the first widely accepted QSAR model for predicting skin permeability coefficient (k_p), a linear regression model that consisted of lipophilicity measured by octanol/water partition coefficient and molecular weight. The Potts and Guy model is based on the data collated by Flynn (1990) consisting *in vitro* skin permeability coefficients of 94 compounds from aqueous solutions. On the other hand, a systematic approach to investigate the effect of mixture components is essential. This is not only due to the fact that most chemicals that the skin is exposed to are in mixtures, but also because of the impact of such mixture constituents on the skin absorption. Despite the availability of QSAR models representing the effect of chemical enhancers on the permeation of drugs (Ghafourian et al., 2004; Pugh et al., 2005), due to the lack of sufficient high quality data, such models for the effect of other mixture ingredients such as solvents are not available in the literature.

In a recent work, Riviere and Brooks (2005, 2007) investigated *in vitro* permeation of several chemicals from chemical mixtures containing various concentrations of different solvents, a surfactant (sodium lauryl sulfate, SLS) and a vasodilator (methyl nicotinic acid) (Tur et al., 1991). This comprehensive dataset provides an opportunity for understanding the effect of mixture components on the skin permeation through QSAR modelling. The aim of this investigation was to develop QSAR models to study the effect of mixture components on skin absorption of penetrants. The model will help identify the mechanisms involved in the permeation through skin and the effect of formulation factors.

2. Methods

2.1. The dataset

Skin permeation data of 12 different penetrants (Table 1) each blended in 24 different solvent mixtures (Table 2), were used in this investigation. Experimental details are fully described in Riviere and Brooks (2005). The permeability data consisted of apparent skin permeation rate constants (k_p) in cm/h measured using finite-dose *in vitro* porcine skin flow through diffusion cells. The skin was perfused using a Krebs–Ringer bicarbonate buffer spiked with dextrose and bovine serum albumin, and topically dosed nonoccluded with 20 μL of one of the 12 marker penetrant compounds (target dose of 10–20 μg/cm^2) formulated in one of the 24 specified mixtures (Table 2). Trace amounts of methanol and toluene were used to solubilize radiolabelled penetrants before dilution with nonradiolabelled compounds.

Table 1
Penetrants.

Atrazine	Pentachlorophenol
Chlorpyrifos	Phenol
Ethylparathion	p-Nitrophenol
Fenthion	Propazine
Methylparathion	Simazine
Nonylphenol	Triazine

This dataset was compared in terms of the chemical space of the penetrants with the combined datasets of Flynn (1990) and Wilschut et al. (1995). The combined dataset contains *in vitro* human skin permeability data ($\log k_p$) for 112 compounds.

2.2. Structural descriptors

The predictors (descriptors) of penetrants included connectivity indexes, quantum molecular descriptors, and group counts calculated using TSAR 3D software (Accelrys Ltd. version 3.3). The physicochemical properties of mixture components including boiling point, melting point, solubility, vapour pressure and Henry's law constant were obtained through ChemBioFinder (CambridgeSoft, 2009) online software and the SRC PhysProp database (Syracuse Research Corporation, 2009). Log *P* for solvent components and for the penetrants was calculated by the ACD/labs log D Suite (7.0.5 release). Averages of physicochemical properties for solvent mixtures were calculated using the fractions of each component e.g. boiling point of the mixture.

2.3. Development and validation of QSARs

Stepwise regression analysis was used to develop the models in MINITAB (version 15.1.0.0). The predictability of the models was

Table 2
Mean Composition of the 24 mixtures.

Mixture	%EtOH	%Water	%PG	%MNA	%SLS
Et	99.67	0	0	0	0
Et + MNA	99.51	0	0	0.16	0
Et + SLS	62.59	26.53	0	0	10.61
Et + MNA + SLS	62.50	26.49	0	0.13	10.60
Et + Wa	42.66	55.86	0	0	0
Et + Wa + MNA	43.79	55.78	0	0.14	0
Et + Wa + SLS	39.44	50.25	0	0	10.05
Et + Wa + MNA + SLS	39.39	50.18	0	0.13	10.04
Wa	0	99.75	0	0	0
Wa + MNA	3.03	96.59	0	0.13	0
Wa + SLS	0	90.70	0	0	9.07
Wa + MNA + SLS	2.75	87.77	0	0.12	9.13
Et + PG	42.99	0	56.73	0	0
Et + PG + MNA	42.92	0	56.65	0.14	0
Et + PG + SLS	28.39	24.15	37.54	0	9.66
Et + PG + MNA + SLS	28.36	24.13	37.50	0.12	9.65
PG	0	0	99.75	0	0
PG + MNA	2.93	0	96.70	0.12	0
PG + SLS	0	22.13	68.79	0	8.85
PG + MNA + SLS	2.69	22.29	65.76	0.11	8.92
Wa + PG	0	48.99	50.76	0	0
Wa + PG + MNA	2.98	47.46	49.18	0.13	0
Wa + PG + SLS	0	44.62	46.23	0	8.92
Wa + PG + MNA + SLS	2.71	43.20	44.76	0.11	8.98

EtOH, ethanol; PG, propylene glycol; MNA, methyl nicotinate; SLS, sodium lauryl sulfate.

examined by a leave-many-out procedure. As such, chemicals were sorted according to the ascending $\log k_p$ values; for each set of 4 solvents, the first compound was allocated to group a, the second to group b, the third to group c and the fourth to group d. This ensured that each group covered similar ranges of the skin permeation kinetics. The regression was carried for the chemicals in groups a, b and c (as the training set), and the resulting equation was used to calculate the skin permeation parameter for the remaining group d (as the test set). The procedure was carried on to leave one group out at a time (all the possible combinations of groups making the training set). The mean absolute error (MAE) of prediction was calculated as a measure of the model accuracy.

The chemical space of the present dataset was compared with that of the skin permeability dataset drawn from Flynn (1990) and Wilschut et al. (1995). The comparison was made using descriptor spaces of Potts and Guy (1992) model (i.e. molecular weight and octanol/water partition coefficient), principal component analysis (PCA) scores plot with all the descriptors being included in the analysis and PCA scores plot using the descriptors selected by stepwise regression analysis for the Flynn (1990) and Wilschut et al. (1995) dataset. PCA was carried out using MINITAB statistical software.

3. Results and discussion

The combined effect of chemical structures of the penetrants and the properties of the mixture components on the permeation rate through porcine skin was studied using QSAR. Stepwise regression analysis performed on the dataset of 288 penetrant/mixture component combinations resulted in Eq. (1), in which the descriptors were limited to two penetrant descriptors and one solvent mixture descriptor.

$$\begin{aligned}\text{Log}\,k_p &= -0.909 - 0.610\,\log P + 2.629\chi_p \\ &\quad -0.00917(\text{SolBP} - \text{SolMP}) \qquad (1)\\ S = 0.438, \quad r^2 = 0.729, \quad F = 255.2, \quad P = 0.000, \quad N = 288\end{aligned}$$

In Eq. (1), $\log k_p$ represents permeation rate constant of compounds dissolved in various solvent mixtures from porcine skin, $\log P$ is the octanol/water partition coefficient of the solute (the penetrant), $^9\chi_p$ is the 9th order path molecular connectivity index of the penetrant, and SolBP – SolMP is the difference between the boiling point and the melting point of the solvent system.

Log P was the most significant descriptor of the equation (the first to be selected by the stepwise regression analysis). It can be seen in Eq. (1) that $\log P$ of penetrants has a negative effect on the skin permeation rate. This is opposite to the common knowledge that lipophilic compounds have higher skin permeation profiles, as evidenced also in Potts and Guy's model (1992). The negative relationship between $\log k_p$ and $\log P$ could be due to the fact that most of the drugs in this particular dataset are more lipophilic than the compounds in the datasets normally used in QSAR studies of skin permeability. Fig. 1 shows a graph between $\log k_p$ and $\log P$ for the penetrants of this study and the penetrants of Wilschut et al. (1995) and Flynn (1990). The opposite trends of the relationships between $\log k_p$ and $\log P$ for the two datasets are evident despite the poor correlations. The figure also shows that compounds of the present dataset have relatively higher $\log P$ values than compounds in the combined datasets of Wilschut et al. (1995) and Flynn (1990). This follows the well established nonlinear relationship of biological activity with lipophilicity described by parabolic (Hansch and Clayton, 1973) or bilinear (Kubinyi, 1977) models. Compounds with extreme lipophilicity can be expected to partition into the skin and remain there, with little permeation to the aqueous receptor phase. This has been shown for example for tetrahydrocannabinol (Challapalli and Stinchcomb, 2002), with extremely high $\log P$ value of 6.84 as calculated by ACD log D/Suite. López et al. (1998) showed a bilinear relationship between lipophilicity of phenyl alcohols and the permeability coefficient through rat skin, where the k_p was reduced for compounds with $\log P$ values higher than around 5.

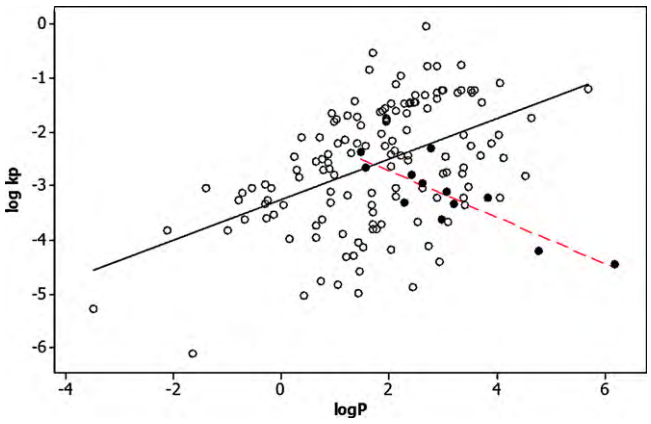


Fig. 1. Comparison of the lipophilicity of the drugs in the two datasets of Riviere's (solid circles) and Flynn (1990) and Wilschut et al. (1995) dataset (empty circles).

There are a number of other factors that may have contributed to the observed negative relationship between $\log k_p$ and lipophilicity. One is the finite-dose nature of the experiments with skin dosed with a limited amount of drug. The limited availability of the compound could result in a large fraction of the lipophilic compounds being concentrated in the skin according to their skin/water partition coefficients. A second factor is the differing nature of the receptor phase which contained albumin.

$^9\chi_p$ is the second most significant descriptor of Eq. (2). This molecular connectivity descriptor indicates the presence of nine-atom chains in the molecules. The positive coefficient of this descriptor indicates a better permeation of compounds containing long chain fragments. The penetrants with the highest $^9\chi_p$ values were chlorpyrifos, fenthion and nonylphenol. These penetrants have the maximum molecular weight of 350 Da which is still smaller than the size expected to limit the absorption. According to Barry (2007) a molecule's ideal molecular mass, in order to penetrate the SC is less than 600 Da. In addition, according to Lipinski's rule of five, chemicals with molecular weight of above 500 Da may have biological membrane penetration problems (Lipinski et al., 1997).

The third descriptor of the equation, SolBP–SolMP, represents the difference between melting and boiling points of the solvent mixtures, where the higher the difference, the lower the skin absorption of compounds from the vehicle. It is therefore expected that compounds formulated in vehicles with small boiling and melting point gaps will have better permeation through skin. The difference between these two properties has been attributed to the molecular symmetry, with highly symmetrical molecules having much larger melting points and decreased boiling points (Slovokhotov et al., 2007). In the solvents used in this study, the biggest difference in the melting and boiling points is for propylene glycol. Therefore the vehicles containing higher concentrations of this solvent will lead to lower permeation of the penetrants studied in this investigation.

In order to validate the reported QSAR, a leave-many-out procedure as explained in Section 2 was used and mean absolute error calculated. Fig. 2 is the graph between observed and predicted $\log k_p$. The r^2 between observed and predicted $\log k_p$ and the MAE were 0.654 and 0.396, respectively.

The level of uncertainty in predictions made by any QSAR is characterized by the validity tests, but it also depends on the diversity of the training set which defines the domain of applicability. Any QSAR model is expected to perform best for the chemicals that are similar

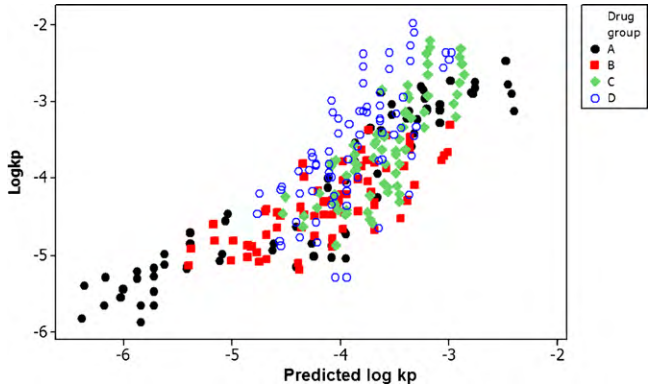


Fig. 2. Plot of observed $\log k_p$ against predicted $\log k_p$.

to those in the training set (Weaver and Gleeson, 2008). Applicability of Eq. (1) will be limited to the prediction of $\log k_p$ for new molecules that are similar to those of our dataset. Therefore, the chemical space of the penetrants included in this dataset was compared to that of the combined datasets of Flynn (1990) and Wilschut et al. (1995). Comparison of the physicochemical properties of the penetrants in the two datasets above were made first by looking at the molecular descriptors of the widely accepted Potts and Guy model (1992) consisting of $\log P$ and molecular weight (MW) as in Fig. 3a. The figure shows that our dataset does not include any hydrophilic chemicals and $\log P$ values are all above 1.5. The other limitation of the dataset is the relatively low molecular weights of the chemicals in comparison with datasets of Flynn and Wilschut et al. Therefore, a few high molecular weight and low lipophilicity chemicals can be identified for future measurements. Examples are hydrocortisone octanoate, caffeine and methanol, as it can be seen in the figure.

As a second strategy, the two datasets were compared using all the calculated molecular descriptors, a total of 128. This was made possible through the use of principal component analysis (PCA). PCA is a data reduction method which takes the information from original molecular descriptors and generates the same number of new descriptors (PCs), with the first PC containing the maximum information of the original dataset, and the second PC being the second most informative. Therefore, the plot between PC1 and PC2 (the scores plot) provides a good overview of the information content of the dataset. The first two principal component score vectors, PC1 and PC2, are plotted in Fig. 2b. The figure shows that the chemicals of the current dataset are located in the bottom left quarter of the plot, with relatively low PC1 and PC2 values. By visual inspection of the graph, several groups of chemicals belonging to datasets of Flynn and Wilschut et al. were identified in the plot to cover various ranges of PC1/PC2. These are chemicals with high PC1 and PC2 values such as codeine and morphine, compounds with high PC1 and varying values of PC2 including steroids such as testosterone and hydrocortisone octanoate, and compounds with very low PC1 and PC2 values such as octanol.

The third method for comparison of the datasets involved the use of a selection of molecular properties that are specifically involved in the skin permeation of compounds. To this end, stepwise regression analysis was used for the selection of molecular descriptors affecting compounds' absorption through skin. In this analysis, the dataset of Flynn and Wilschut et al. containing the skin permeation rate constant through human skin using the saturated aqueous solutions as the donor phase was used. In stepwise regression analysis, the skin permeation rate constant ($\log k_p$) was the dependent variable and all the molecular descriptors were the independent variables. Stepwise regression analysis selected three

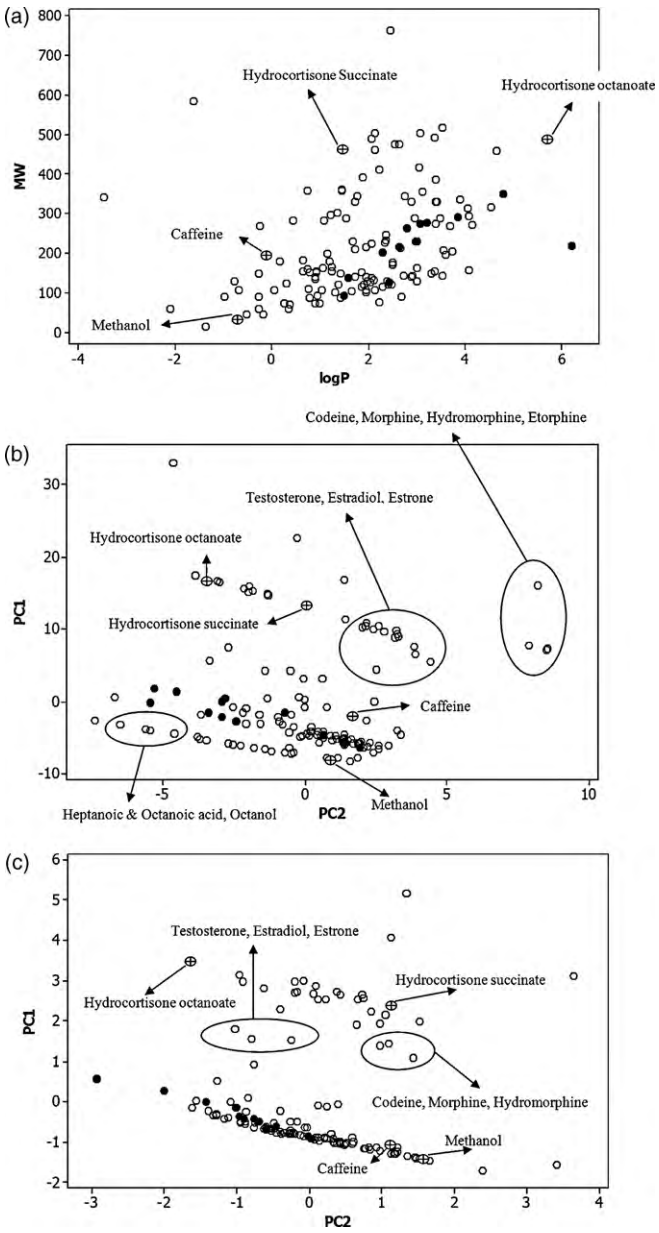
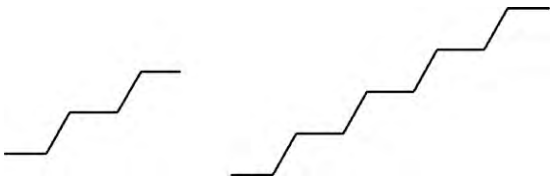


Fig. 3. Plots comparing chemical diversity of the penetrants of the present dataset (solid circles) with that of the combined dataset of Flynn (1990) and Wilschut et al. (1995) (empty circles). (a) Plot between $\log P$ and molecular weight; (b) scores plot between the first and the second principal components of PCA using all the descriptors; (c) scores plot between the first and the second principal components of PCA using descriptors of Eq. (2).

descriptors and resulted in Eq. (2) below.

$$\log k_p = -2.91 + 0.62 \log P + 5.21^{10}\chi_p^v - 1.64^{6}\chi_p^v$$
$$S = 0.548, \quad r^2 = 0.757, \quad F = 140, \quad P = 0.000, \quad N = 139 \qquad (2)$$

In Eq. (2), $\log P$ is the octanol/water partition coefficient, $^{10}\chi_p^v$ and $^{6}\chi_p^v$ are 10th and 6th order valence corrected path molecular connectivity indexes of the penetrants, respectively. Molecular connectivity indexes are topological descriptors of molecular structures indicating the frequencies of occurrence of certain fragments in the molecules. Path molecular connectivity indexes indicate the frequency of non-branched chains of certain lengths, in this case six-atom and ten-atom chains as shown in Scheme 1 below (Todeschini and Consonni, 2000).



Scheme 1. Six-atom and ten-atom fragments for the calculation of path molecular connectivity indexes, ${}^{6}\chi_{p}^{v}$ and ${}^{10}\chi_{p}^{v}$, respectively.

The three descriptors selected by stepwise regression analysis were used in PCA and the scores plot between the first and the second PCs (Fig. 3c) was used to compare the datasets. Fig. 3c is similar to Fig. 3b in identifying certain compounds from the dataset of Flynn and Wilschut et al. such as steroids, narcotic analgesics and small polar molecules such as caffeine and methanol which are not present in the current dataset.

Therefore, an overview of Fig. 3a and b can identify several areas of the chemical space that are missing from the present dataset. From these groups of chemicals, caffeine, 1-octanol, testosterone and codeine were selected for further studies and the *in vitro* measurements are currently being undertaken.

4. Conclusion

In conclusion skin permeation of drugs from different vehicle systems can be modelled using QSAR given the availability of an appropriate dataset containing diverse permeants and vehicles. Vehicle effects were well predicted in this work. However, rigorous validation of such models for estimation purposes will require a large volume of data. In this study, the negative relationship was obtained between $\log k_p$ and $\log P$. This was attributed to the fact that most of the drugs in this particular dataset are more lipophilic than the compounds in the common permeability datasets used in QSAR studies of skin permeability. Therefore, it can be envisaged that these highly lipophilic agents concentrate in the SC with little ability to partition into the aqueous receptor phase. This scenario is relevant for many pesticides and lipophilic contaminants encountered in environmental exposure scenarios. For further validation of this model, skin permeation of the compounds identified through the comparison of the datasets is necessary to be determined in similar solvent mixtures.

References

Abraham, M.H., Chadha, H.S., Martins, F., Mitchell, R.C., Bradbury, M.W., Gratton, J.A., 1999. Hydrogen bonding part 46. A review of the correlation and prediction of transport properties by an LFER method: physicochemical properties, brain penetration and skin permeability. Pestic. Sci. 55, 78–88.

Abraham, M.H., Chadha, H.S., Mitchell, R.C., 1995. The factors that influence skin penetration of solutes. J. Pharm. Pharmacol. 47, 8–16.

Anderson, B.D., Higuchi, W.I., Raykar, P.V., 1988. Heterogeneity effects on permeability–partition coefficient relationships in human stratum corneum. Pharm. Res. 5, 566–573.

Barry, B.W., 2007. Transdermal drug delivery. In: Aulton, M.E. (Ed.), Aulton's Pharmaceutics, the Design and Manufacture of Medicines, 3rd ed. Churchill Livingstone, Elsevier, pp. 580–585.

Bezema, F.R., Marttin, E., Roemele, P.E.H., Brussee, J., Bodde, H.E., deGroot, H.J.M., 1996. H-2 NMR evidence for dynamic disorder in human skin induced by the penetration enhancer Azone. Spectrochim. Acta. Mol. Biomol. Spectrosc. 52, 785–791.

Bouwstra, J.A., Honeywell-Nguyen, P.L., Gooris, G.S., Ponec, M., 2002. Structure of the skin barrier and its modulation by vesicular formulations. Prog. Lipid Res. 42, 1–36.

CambridgeSoft, 2009. ChemBioFinder, http://www.cambridgesoft.com/databases, retrieved September 19–22, 2009.

Challapalli, P.V.N., Stinchcomb, A.L., 2002. In vitro experiment optimization for measuring tetrahydrocannabicol skin permeation. Int. J. Pharm. 241, 329–339.

El Tayar, N., Tsai, R.S., Testa, B., Carrupt, P.A., Hansch, C., Leo, A., 1991. Percutaneous penetration of drugs: a quantitative structure–permeability relationship study. J. Pharm. Sci. 80, 744–749.

Flynn, G.L., 1990. Physicochemical determinants of skin absorption. In: Gerrity, T.R., Henry, C.J. (Eds.), Principles of Route-to-route Extrapolitation for Risk Assessment. Elsevier, New York, NY, pp. 93–127.

Ghafourian, T., Fooladi, S., 2001. The effect of structural QSAR parameters on skin penetration. Int. J. Pharm. 217, 1–11.

Ghafourian, T., Zandasrar, P., Hamishekar, H., Nokhodchi, A., 2004. The effect of penetration enhancers on drug delivery through skin: a QSAR study. J. Control. Release 99, 113–125.

Hansch, C., Clayton, J.M., 1973. Lipophilic character and biological-activity of drugs. 2. Parabolic case. J. Pharm. Sci. 62, 1–21.

Kubinyi, H., 1977. Quantitative structure–activity-relationships. 7. Bilinear model, a new model for nonlinear dependence of biological-activity on hydrophobic character. J. Med. Chem. 20, 625–629.

Lipinski, C.A., Lombardo, F., Dominy, B.W., Feeney, P.J., 1997. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv. Drug Del. Rev. 23, 3–25.

López, A., Faus, V., Díez-Sales, O., Herráez, M., 1998. Skin permeation model of phenyl alcohols: comparison of experimental conditions. Int. J. Pharm. 173, 183–191.

Monteiro-Riviere, N.A., Inman, A.O., Mak, V., Wertz, P., Riviere, J.E., 2001. Effect of selective lipid extraction from different body regions on epidermal barrier function. Pharm. Res. 18, 992–998.

Monteiro-Riviere, N.A., 1986. Ultrastructural evaluation of the porcine integument. In: Tumbleson, M.E. (Ed.), Swine in Biomedical Research, vol. 1. Plenum, New York, pp. 641–655.

Moss, G.P., Cronin, M.T., 2002. Quantitative structure–permeability relationships for percutaneous absorption: re-analysis of steroid data. Int. J. Pharm. 238, 105–109.

Potts, R.O., Guy, R.H., 1992. Predicting skin permeability. Pharm. Res. 9, 663–669.

Pugh, W.J., Wong, F.F., Michniak, B.B., Moss, G.P., 2005. Discriminant analysis as a tool to identify compounds with potential as transdermal enhancers. J. Pharm. Pharmacol. 57, 1389–1396.

Raykar, P.V., Fung, M.C., Anderson, B.D., 1988. The role of protein and lipid domains in the uptake of solutes by human stratum corneum. Pharm. Res. 5, 140–150.

Riviere, J.E., Brooks, J.D., 2007. Prediction of dermal absorption from complex chemical mixtures: incorporation of vehicle effects and interactions into a QSPR framework. SAR QSAR Environ. Res. 18, 31–44.

Riviere, J.E., Brooks, J.D., 2005. Predicting skin permeability from complex chemical mixtures. Toxicol. Appl. Pharmacol. 208, 99–100.

Slovokhotov, Y.L., Batsanov, A.S., Howard, J.A.K., 2007. Molecular van der Waals symmetry affecting bulk properties of condensed phases: melting and boiling points. Struct. Chem. 18, 477–491.

Syracuse Research Corporation, 2009. SRC PhysProp database, http://www.syrres.com/what-we-do/databaseforms.aspx?id=386, retrieved September 20, 2009.

Todeschini, R., Consonni, V., 2000. Handbook of Molecular Descriptors. Wiley-VCH.

Tur, E., Maibach, H., Guy, R.H., 1991. Percutaneous penetration of methyl nicotinate at 3 anatomic sites—evidence for an appendageal contribution to transport. Skin Pharmacol. 4, 230–234.

Van der Merwe, D., Riviere, J.E., 2005. Comparative studies on the effects of water, ethanol and water/ethanol mixtures on chemical partitioning into porcine stratum corneum and silastic membrane. Toxicol. In Vitro 19, 69–77.

Weaver, S., Gleeson, M.P., 2008. The importance of the domain of applicability in QSAR modeling. J. Mol. Graph. Model. 26, 1315–1326.

Wilschut, A., Berge, W.F., Robinson, P.J., McKone, T.E., 1995. Estimating skin permeation. The validation of five mathematical skin permeation models. Chemosphere 30, 1275–1296.