Modelling the Effect of Mixture Components on the Skin Penetration

T. Ghafourian[1], E. G. Samaras[1], J. D. Brooks[2], J. E. Riviere[2],

[1] Medway School of Pharmacy, Universities of Kent and Greenwich, Central Avenue, Chatham, Kent ME4 4TB, UK; t.ghafourian@kent.ac.uk; [2] Center for Chemical Toxicology Research and Pharmacokinetics, 4700 Hillsborough Street, North Carolina State University, Raleigh, USA.

Abstract

The permeability of a penetrant though skin is controlled by the properties of the penetrants and the mixture components, which in turn relates to the molecular structures. In this investigation the relationships between permeability coefficients and the molecular structures of the penetrants and those of the vehicle components have been analysed quantitatively. The aim of this Quantitative Structure Activity Relationship (QSAR) study was to develop statistically validated models for the prediction of permeability coefficients of other penetrants. A dataset of skin permeability of 16 penetrants each blended in 24 different solvent mixtures were assembled or QSAR analysis. Stepwise regression analysis was used for the selection of the most significant molecular descriptors and development of several regression models. The selected QSAR employed two penetrant descriptors of wiener topological index and total lipole moment, boiling point of the solvent and the difference between the melting point of the penetrant and the melting point of the solvent. The QSAR was validated internally, using a leave-many-out procedure, giving a mean absolute error of 0.454 for the log k_p value of the test set.

Introduction

Skin penetration of chemicals is the focus of research as an integral part of the human health risk assessment of chemicals to which human is exposed via the dermal route. Formulation ingredients can alter the skin penetration of a compound by affecting the barrier properties of the skin or by changing the partitioning of the compound into the SC. Most mechanistic studies on skin penetration are based on the penetration of individual chemicals (Flynn, 1990), with only few attempts towards a comprehensive investigation on the effect of chemical mixtures. Such a systematic study requires a large volume of tedious experimental measurements involving various penetrant/ mixture-component combinations (Riviere and Brooks, 2005). The relationship between chemical structures of the formulation ingredients and the skin penetration modification can be studied quantitatively using Quantitative Structure-Activity Relationship (QSAR) techniques. In this investigation skin penetration (k_p) of four chemicals, selected from Flynn and Wilschut et al datasets, were determined in 24 mixture components. The data was added to the k_p values of 12 other compounds measured using the same protocol previously. These new measurements facilitated the development of statistically validated QSAR models. Table 1 is the list of the 16 penetrants used in QSAR study.

Table 1. Penetrants

Atrazine	Pentachlorophenol
Chlorpyrifos	Phenol
Ethylparathion	ρ-Nitrophenol
Fenthion	Propazine
Methylparathion	Simazine
Nonylphenol	Triazine
Caffeine	Octanol
Codeine	Testosterone

Methods

Skin penetration data: Permeability coefficient (k_p) of caffeine, codeine, octanol and testosterone each blended in 24 different mixtures, as presented in Table 2, were obtained through flow-through diffusion cell using porcine skin. The k_p values measured in this study were merged with the previous dataset of k_p values for 12 other compounds (Riviere and Brooks, 2005). Therefore, the dataset used for the QSAR studies consisted of a total of 384 unique measurements of k_p for the penetrant/ components combinations.

Development of QSARs: Physicochemical properties of the penetrants and the solvent mixtures were assembled. The molecular descriptors of the penetrants were calculated using two software packages of ACD labs/LogD Suite (7.0.5 release) and TSAR 3D (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 SRC PhysProp database (Syracuse Research Corporation, 2009). Hildebrand solubility parameters (δ) were obtained from Hansen (1967) for the solvents and calculated according to Fedors group contribution method (1974) for the penetrants. Averages of physicochemical properties for solvent mixtures were calculated using the fractions of each component.

Several stepwise regression analyses were performed between log k_p as the dependant variable and the molecular descriptors of the penetrants and the mixture components as the predictors. In order to minimise the risk of chance correlations, the number of descriptors in the regression models were limited to four. The models were validated for penetrants using a leave-many-out cross validation procedure and Mean Absolute Error (MAE) values were determined for the test set.

Table 2. Composition of the 24 mixtures

EtOH	PG
EtOH + MNA	PG + MNA
EtOH + SLS	PG + SLS
EtOH + MNA + SLS	PG + MNA + SLS
EtOH + Water	PG + Water
EtOH + Water + MNA	PG + Water + MNA
EtOH + Water + SLS	PG + Water + SLS
EtOH + Water + MNA + SLS	PG + Water + MNA + SLS
EtOH + PG + Water	Water
EtOH + PG + Water + MNA	Water + MNA
EtOH + PG + Water + SLS	Water + SLS

EtOH-Ethanol; PG-Propylene glycol; MNA-Methyl nicotinate; SLS-Sodium lauryl sulfate.

Results and Discussion

Stepwise regression analysis of different combinations of solvent properties and molecular descriptors of the penetrants resulted in a number of QSAR models from which 4 were selected based on the goodness of fit (R^2 values). In order to reduce the risk of chance correlations, only four descriptors were allowed in the equations. The selected equations are listed in Table 3. In equations 1-4, (P) indicates the descriptors for the penetrants and (V) indicates the vehicle descriptors. It can be seen that each equation consists of 2-3 penetrant descriptors and 1-2 vehicle descriptors, with equations 1-3 containing 1 combined vehicle-penetrant descriptor. In equations 1-4, Δmp is the difference between the melting point of the penetrant and that of the solvent, W is the Wiener topological, δ is the Hildebrand solubility parameter, E_{HOMO} is the energy of the highest occupied molecular orbital, BP is the boiling point, N_{atoms} is the total number of atoms in the molecules, BP-MP is the difference between the boiling and melting points of a compound, and Lipole is the total lipole moment of the penetrants.

The Table shows that QSAR model 1 is robust in terms of prediction of log kp for those new penetrants that fall within the applicability domain of the model. Figure 1 is the plot of observed versus predicted log k_p values using Equation 1. The equation shows that low melting point chemicals of small molecular size have higher penetration rates from skin. Moreover, skin penetration of chemicals is more efficient when they are dissolved in high boiling (and melting) point solvents. The outliers in the graph with underestimated log k_p values are testosterone dissolved in different vehicles, most notably in ethanol-water, ethanol-water-methyl nicotinate, water and water-methyl nicotinate.

Table 3. QSAR models obtained from stepwise regression; N is the number of datapoints (penetrant/ vehicle combinations); S, the standard deviation; R^2, the squared correlation coefficient and MAE is mean absolute error of prediction

No	Equation	N	S	R^2	MAE
1	$Logk_p$ = - 0.956 - 0.00322 Δmp - 0.000320 *W(P)* - 0.0121 BP(V) - 0.114 *Lipole(P)*	384	0.478	0.70	0.45
2	$Logk_p$ = - 310 - 0.000315 *W* (P) – 0.00771 δ(V).E_{HOMO}(P) – 0.0102 BP(V) – 0.0750 *Lipole(P)*	384	0.494	0.68	0.49
3	$Logk_p$ = - 2.48 – 0.0474 N_{atoms}(P) – 0.00798 δ(V).E_{HOMO}(P) – 0.0102 BP(V) – 0.0723 *Lipole(P)*	384	0.516	0.65	0.50
4	$Logk_p$ = -4.29 – 0.0474 N_{atoms}(P) – 0.00904 *BP-MP(V)* – 0.345 E_{HOMO}(P) – 0.0790 *Lipole(P)*	384	0.522	0.64	0.49

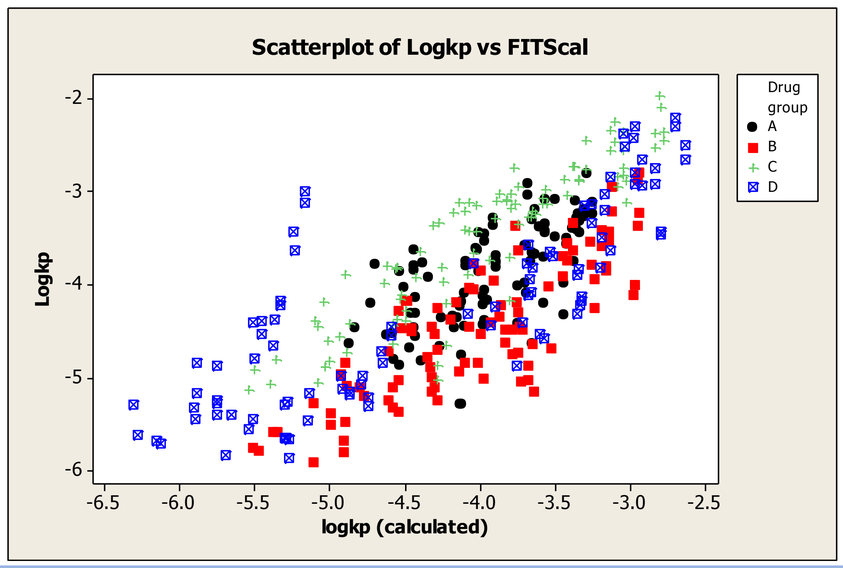

Figure 1. Scatterplot of observed log k_p vs. log k_p calculated by equation 1

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