Modelling the Effect of Mixture Components on the Skin Penetration

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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 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 Relationships (QSAR) were employed to relate the effects of different concentrations of solvents blended with various penetrants, upon skin absorption. The permeability data consisted from studies that took place using In-vitro porcine-skin flow through diffusion cells. Average of physicochemical properties for every solvent mixture were calculated. QSAR software was used fir the calculation of the structural descriptors. Stepwise regression analysis and regression analysis were used for modelling. The penetrant descriptors log P, the ninth order path connectivity index and the solvent predictor,namely the difference between boiling and melting points, gave the best correlation and the most reliable QSAR

Introduction

The success of a transdermal drug formulation depends on the ability of drug to penetrate the skin in sufficient quantities in order to achieve the desired therapeutic effect. From a drug delivery perspective, penetration of the drug depends not only on the nature of the drug but also on the nature of the other ingredients present in the mixture (formulation). As a result, desirable penetration rates could be achieved by altering the formulation of a drug. However, the data used in most prediction models are based on experimental data for individual chemicals because very limited experimental data are available for chemical mixtures. While it is frequently difficult to assess the absorption of individual chemicals, it is challenging to quantitatively assess the absorption from chemical mixtures.

Aims

The aim of this investigation was to develop QSAR models for the effect of mixture components on skin absorption of penetrants. The model will help identify the mechanisms involved in the penetration through skin and the effect of formulation factors.

Methods

1. The dataset:

The permeability data was obtained from diffusion cell studies using porcine skin. Penetration data was available for 12 different penetrants (Table 1) each blended in 24 different solvent mixtures (Table 2).

Table1; Penetrants	
Atrazine	p-Chlorophenol
Chlorpyrifos	Phenol
Ethylparathion	p-Nitrophenol
Fenthion	Propazine
Methylparathion	Simazine
Nonylphenol	Triazine

Table2; Solvent Mixtures
Ethanol
Methylnicotinic acid
Propylene glycerol
Sodium lauryl sulfate
Water

2. Molecular descriptors:

- The predictors (descriptors) of penetrants included connectivity indexes, quantum molecular descriptors, group counts (e.g. Vamp) were calculated in the TSAR 3D (Accelrys) software.
- The physico-chemical properties of mixture components (boiling point, melting point, solubility, vapor pressure and Henry's law constant) were obtained through Chemfinder online software and the Syracuse Research Corporation (SRC) website.
- Log P for solvent components and for the penetrants was calculated by the ACD/labs logD Suite.
- Average of physicochemical properties for every solvent mixture were calculated, e.g. boiling point of the mixture.

3. Development and Validation of QSARs:

Stepwise regression analysis was used to develop models.
The present dataset was compared with the skin permeability dataset drawn from Flynn (1990) and Wilschut et al (1995) in order to identify compounds that are needed to be tested for their skin permeability from similar solvent mixtures, in order for the model to be validated. The comparison was made visually using descriptor spaces of Potts and Guy (1992) model, 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.

Results

Logkp = - 0.909 – 0.610 logP + 2.62 $^{9}\chi_p$ – 0.00917 (SolBP-SolMP) Eq 1

N = 288 S = 0.438 r^2 = 0.729 F = 255.2

log P: Partition coefficient
$^{9}\chi_p$:9th order path molecular connectivity index
SolBP-SolMP: the difference between the boiling and the melting points of the solvent
N :the number of data points
S: standard deviation
R^2: the squared correlation coefficient

- ***The negative correlation between skin penetration and lipophilicity:***

Penetrants too lipophilic

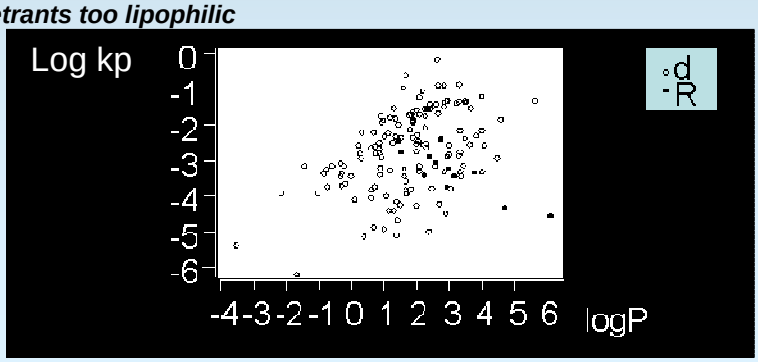
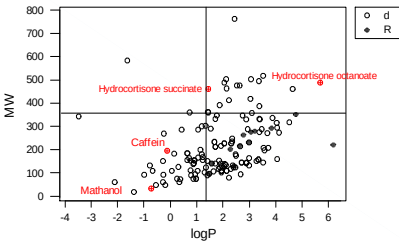


Fig 1. Relationship between log kp and liopophilicity of the skin absorption dataset of Wilschut et al (1995) (group d) and the chemicals used in this study (group R)

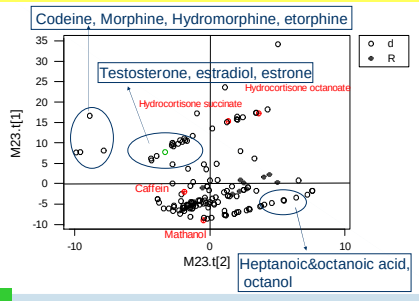
- ***The need for rigorous validation:***

Measurements needed for external validation set:

Potts and Guy (1992) model



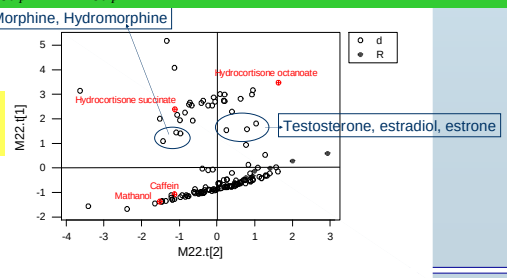
PCA scores plot using all the descriptors



QSAR for Wilschut et al and Flynn dataset:

$$\log kp = -2.91 + 0.62 \log P + 5.21\ {}^{10}\chi_p^v - 1.64\ {}^{6}\chi_p^v \quad n = 139 \quad s = 0.548 \quad R^2 = 0.757 \quad F = 140$$

PCA scores plot using the selected descriptors



Conclusion

In conclusion skin penetration of drugs from different vehicle systems can be modelled using QSAR. However, rigorous validation of such models for estimation purposes will require a large volume of data. The negative relationship between log kp 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 common permeability datasets used in QSAR studies of skin permeability. For validation of this model, skin penetartion of the drugs identified in the graphs (or one compound out of each group identified) is necessary to be determined in similar solvent mixtures.

References

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