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Estimation of skin permeation by liquid chromatography

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Abstract

Dermal absorption is a key process in the drug delivery studies of the pharmaceutical and cosmetic industries, as well as in the fields of dermal toxicology, risk assessment, and the exposure of environmental pollutants. This process is typically described by the skin-water permeability coefficient. However, in vivo determination is laborious and expensive. Thus, in the last few years, the development of prediction models from structure descriptors or subrogation through physico-chemical measurements has gained interest. In the present work, a previous subrogation model based on the chromatographic retention on a common C18 column has been tested for a wide set of drugs with very different chemical nature and having a wide range of permeability values. A total of 65 compounds have been used to establish the correlation between skin permeation and the HPLC retention, corrected by the McGowan volume of the drug. Afterwards it was successfully validated in terms of robustness and prediction ability. Finally, the permeability coefficient was estimated for a set of 29 new drugs, and results compared to the ones obtained by other estimation methods, as well as the available in vitro measured values, with very good agreement.

Keywords

Dermal absorption; High-Performance Liquid Chromatography; Estimation; Skin permeation

Introduction

The skin is the largest organ of the body, covering about 1.7 m^2 and comprising approximately 10% of the total body mass of an average person. The primary function of the skin is to provide a barrier between the body and the external environment (ultraviolet radiation, chemicals, allergens and microorganisms, and the loss of moisture and body nutrients). Although the skin presents a barrier to the permeation of most compounds, it provides an ideal site for the administration of therapeutic compounds for local and systemic effects [1].

Dermal absorption is a global term that refers to the transport of a chemical from the outer surface of the skin into the skin and the systemic circulation. The outermost layer of the skin, the *stratum corneum*, controls the dermal absorption process, since substances must initially permeate through it to be absorbed into the body. Hence *stratum corneum* is considered the rate-determining barrier and the absorption process can only occur by passive diffusion since skin does not have any active transport mechanism [2,3].

Dermal absorption is a key process in the drug delivery studies of the pharmaceutical and the cosmetic industries as well as in the fields of dermal toxicology, risk assessment and the exposure to environmental pollutants. It is typically described by the skin-water permeability coefficient (k_p, units in cm s^{-1}) and can be determined using experimental techniques, both *in vivo* and *in vitro* [3]. However, these methods are usually laborious, costly and ethically questionable. For this reason, there is a need for finding methods capable of predicting k_p values in a simple, economic, fast and ethical way.

To predict skin-water permeability coefficients and thus reduce the number of *in vivo* and *in vitro* assays, two types of models, empirical and theoretical, can be developed. Empirical models relate the k_p values of compounds to physicochemical descriptors, as for example descriptors of hydrophobicity, polarity, solubility, hydrogen bonding, or size [4]. In general, empirical models for skin permeation, as proposed by Patel et al. [5], usually reveal the important roles of lipophilicity and molecular size.

Theoretical models are mechanistic approaches that attempt to simulate the dynamic processes that are involved in skin permeation. They consist of mathematical transport models that relate dermal absorption to parameters like diffusion coefficients and partition coefficients, taking into account factors such as possible routes of penetration and interactions between the permeating chemicals and the skin constituents [6-8].

Linear free-energy relationships (LFERs), a particular type of Quantitative Structure-Activity Relationship (QSAR), are widely used to characterize chemical and biochemical processes. LFERs assume that the free energy change associated with the property of interest is linearly related to solute molecular descriptors. The linear solvation energy relationships (LSERs), proposed by Kamlet et al. [9], are based on the change of free energy due to the solvation process of a solute into a solvent. Among the variety of models based on these principles, the solvation parameter model developed by Abraham [10] is one of the most widely used in order to achieve a better understanding of the type and the relative strength of the chemical interactions that control any solvation process of neutral compounds [11,12]. This model has been successfully applied to characterize many biological processes, including some toxicological and environmental ones, as well as a wide range of physicochemical processes ruled by the passive transport of solutes between two phases. The solvation parameter model [10,12] has been also applied to model the human skin permeation process [12-16]. Abraham and Martins [15] proposed the following equation for characterizing the permeation of neutral solutes from aqueous solution through the human skin,

$$\log k_p = -5.246 - 0.106E - 0.473S - 0.473A - 3.000B + 2.296V \tag{1}$$

n = 119 R^2 = 0.832   SD = 0.461   F= 112

This equation was obtained through the analysis of 119 compounds of different chemical type, which covered a wide range of log k_p values. *E*, *S*, *A*, *B*, and *V* are independent variables and are the solute descriptors proposed by Abraham: *E* represents the excess molar refraction, *S* is the solute dipolarity/polarizability, *A* and *B* are the solute's effective hydrogen-bond acidity and hydrogen-bond basicity, respectively, and *V* is the McGowan's solute volume. Eq. 1 shows that size is the only solute property that contributes to an increase in skin permeation (the only positive coefficient).

Over the last few years, the computational models based on calculated descriptors [17-19] have also become very useful and powerful approaches to provide estimations of k_p values. However, skin permeation models based on experimental descriptors are generally preferred when the prediction of skin-

water permeability of chemicals requires more accuracy and reliability.

In a previous study [20] the ability of different chromatographic systems, basically liquid chromatography (HPLC) and micellar electrokinetic chromatography (MEKC), were assessed to subrogate the permeation of aqueous solutions of neutral solutes through human skin. It was observed that the correlations were improved after introducing the calculated McGowan solute's volume as an additional variable. With the volume correction, the best subrogation was obtained with an HPLC system fitted with a C18 column according to the following equation,

$$\log k_p = -4.76(\pm 0.18) + 1.44(\pm 0.12) \log k - 1.16(\pm 0.10) V \tag{2}$$

$$n = 27 \qquad\qquad R^2 = 0.834 \qquad\qquad SD = 0.390 \qquad\qquad F = 126$$

This system was chosen to establish a methodology for the prediction of human skin permeability of untested compounds by chromatographic measurements. This methodology was developed only for neutral compounds at pH 7.0. This study has been expanded in the present work to compounds of pharmaceutical interest with a wide range of pK_a values, containing basic and acidic functions. Additionally, a new methodology based on fast measurements by MS (mass spectrometry) has been developed and established to predict k_p values of drugs of pharmaceutical interest.

Materials and methods

Instruments

Chromatographic measurements were performed with an Agilent Technologies 1200 Series instrument equipped with a G1312B binary pump and a G1367D autoinjector. A G1315C DAD was used at 254 nm for non-ionizable compounds and a UHD 6540 Accurate-Mass Q-TOF detector with electrospray ionization (ESI) source was used for ionizable compounds. A 100 mm, 4.6 mm i.d, 2.6 μm octadecylsilica Kinetex EVO C18 analytical column provided by Phenomenex with a core-shell Technology was used for all determinations. This material is stable within the pH range 1-12.

pH measurements were done with a MicropH 2001 pH-meter (CRISON) with a precision of ± 0.01 pH units.

Reagents

Acetonitrile LCMS grade was purchased from Fluka Analytical VWR (West Chester, PA, USA) and water was purified by a Milli-Q deionizing system from Millipore (Billerica, MA, USA) to a resistivity of 18.2 MΩ. Reagents used to prepare the buffer solutions were sodium phosphate monobasic monohydrate (Sigma-Aldrich, Puriss PA ≥99.0%), formic acid (Scharlau, eluent additive for LC-MS), acetic acid (Fluka Analytical, eluent additive for LC-MS), ethylendiamine (Fluka Analytical, Puriss PA ≥ 99.5%) and ammonia solution 25 % w/w (Sharlau, extrapur, Pharmpur, PH Eur). Most drugs were purchased from Sigma-Aldrich (Steinheim, Germany), Fluka Analytical VWR (West Chester, PA, USA), Riedel-de Haën (Seelze, Germany), Merck (Darmstadt, Germany), Carlo Erba (Milano, Italy) and Baker (Center Valley, PA, USA). Other drugs were synthesized in ESTEVE (Barcelona, Spain) only for the purpose of this study.

Procedure

94 solutes of different chemical nature were injected in the HPLC system at 6 different pH values, between 2 and 11, to obtain the retention factors of the neutral species. The mobile phase composition was 40 % acetonitrile and 60 % aqueous buffer. The buffer solutions were selected according to their compatibility with the detection mode. Volatile buffers were used for mass spectrometry detection. Formic acid, acetic acid and ammonia solution were used at pH 3.0, 5.0 and 9.0, respectively. Ethylendiamine was used at pH 7.0 and 11.0. The buffer concentrations at pH 3.0, 5.0, 7.0, 9.0 and 11.0 were 10 mM and were adjusted by addition of diluted acetic acid or diluted ammonia. The detection mode was ESI+ or ESI- for ionizable compounds and UV for non-ionizable compounds. For mass spectrometry detection, the compounds were grouped for faster analysis. At pH 2.0, the detection was only performed by UV and a mixture of phosphoric acid and sodium dihydrogenphosphate was used as buffer, at a concentration of 50 mM. pH was adjusted with diluted hydrochloric acid. All experiments were done at 25 °C.

Stock solutions of the compounds at 5000 mg·L^{-1} were prepared by dissolving the appropriate weight or volume in methanol. More diluted solutions were prepared at 100 mg·L^{-1} by dissolving an aliquot of the previous stock solution in an ACN-H$_2$O mixture (40:60). Isocratic conditions were used at a flow rate of 1 mL min^{-1} and the injection volume was 10 μL. The column hold-up time was measured by injections of an aqueous solution of potassium bromide (0.1 mg mL^{-1}), whose detection was performed by UV at 200 nm. All results were the average of triplicate injections.

The HPLC retention factor (k) was calculated according to Eq. 3,

$$k = \frac{t_R - t_0}{t_0 - t_e} \tag{3}$$

where t_R corresponds to the solute retention time, t_0 is the column hold-up time determined by an aqueous potassium bromide solution, and t_e is the extra column time determined by an analysis that excludes the chromatographic column, for each different detection system.

Calculation

Microsoft Excel 2010 was used for all calculations and for multiple linear regression analysis. Solvation parameter model descriptors of the compounds (E, S, A, B, V) were obtained from Percepta [21]. MATLAB® (MathWorks) was used for Principal Components Analysis (PCA).

Model establishment and validation

Data collection

The evaluation of the consistency and quality of the experimental skin permeation data used is fundamental to the establishment of a good prediction model. For any QSAR model, experimental data should be produced from standardized experimental procedures, and obtained for a set of chemicals that cover the domain of relevant chemical properties [22].

Several studies that have focused on the determination of skin permeability coefficients [23-25] have pointed out that inter- and intra-variability within experimental k_p values is mainly due to the thickness of the skin and also to the variability inherent to different human donors. In this work, the permeation data employed was selected from the Abraham Database [15], an extensive and carefully examined data set. 65 solutes that belong to different families, with different structural complexity and with varied experimental

log k_p values were selected to develop this model. Because the permeation coefficients are from water through human skin, it might be expected that acids and bases would be partially ionized in solution depending on the pH of the solution. Values of k_p for ionized species are smaller than k_p values for the neutral species. In these cases, Abraham adjusted the literature values of the skin-water permeability coefficients for ionization in water and for a temperature of 37 °C [15].

A different set of 29 solutes was selected from other sources [5,26,27] to predict the k_p values from our model's equation and then compare them to the available literature experimental and/or estimated data.

Model establishment

A correlation between the experimental log k_p values and the parameters log k and the McGowan solute's volume (V) of the selected compounds was performed through a multiple linear regression analysis. Log k values were the ones measured at a pH in which the solutes were in the neutral form. The McGowan volume of the compounds can be easily calculated from the empirical formula and the number of single, double, and triple bounds in the molecule. Compounds with a standard residual higher than 2.5 in absolute value were considered outliers.

Model validation

The model required an internal validation to evaluate its robustness, and an external validation to evaluate its predictive ability. To this aim, the total data set of 65 compounds was divided into two sets, the training set for the internal validation and test set for the external validation [28]. To construct the two subsets a representation of scores after principal components analysis (PCA) was performed based on the Abraham's molecular descriptors of the compounds. The scores plot distributes the solutes according to their physicochemical properties, so it is easier to do a representative division of the global set of compounds into the two subsets.

The training set, which is aimed at evaluating the robustness of the model, usually has around 50-70% of the selected compounds. The remaining compounds are used in the test set, which evaluates the predictive ability of the model. The correlation is repeated only with the training set compounds. The results of this second correlation must be compared to the global correlation. If the model is robust, the coefficients of both correlations should be similar. Traditional statistical parameters such as the determination coefficient (R^2), the standard deviation (SD), and the F statistic were also considered to evaluate the robustness of the model. Additionally, the leave-multiple-out cross-validation coefficient, Q^2_{LMO} [29,30], was calculated. This coefficient is a parameter that assesses how the results of a statistical analysis will generalize to an independent data set.

The test set was used to perform the external validation of the model, i.e. ensure its predictive ability. The external validation consists in predicting the biological property value of the test set compounds with the training set equation. Then, predicted log k_p values are plotted against the experimental values. To ensure that the model has a good predictive ability, the slope must be close to 1 and the origin ordinate close to 0.

Results and Discussion

Establishment of a model to predict k_p values

Table 1 shows the 65 compounds selected to establish the model, their experimental log k_p values, chromatographic retention factors, log k values, and McGowan volumes, *V*. A multiple linear regression

analysis was done between the experimental log k_p values and the two parameters log k and V. The set of compounds comprises a wide variety of chemical classes and structural complexity. This is important in order to make the model general enough to predict k_p values of compounds of very different chemical nature. Results are shown in Equation 4 and Figure 1.

Table 1. Experimental log k_p values, log k values of the neutral species and McGowan solute's volume of the compounds selected to establish the model

Compounds	log k_p	log k	McGowans's Volume (V)
2,4-Dichlorophenol	-4.30	0.556	1.0199
2-Amino-4-nitrophenol	-6.54	-0.089	1.0491
2-Chlorophenol	-4.56	0.237	0.8975
2-Hydroxybenzoic acid (Salycilic acid)	-5.33	0.080	0.9904
2-Isopropyl-5-Methylphenol (Thymol)	-4.35	0.849	1.3387
2-Naphtol (beta-naphthol)	-4.65	0.419	1.1441
2-Nitrophenol	-4.08	0.343	0.9493
2-Nitro-p-phenylenediamine	-6.66	-0.187	1.0902
2-Phenylethanol	-5.20	0.003	1.0569
3-Methylphenol (m-Cresol)	-4.89	0.172	0.9160
3-Nitrophenol	-5.33	0.145	0.9493
4-Amino-2-nitrophenol	-5.91	-0.010	1.0491
4-Bromophenol	-4.52	0.361	0.9501
4-Chloro-3-methylphenol (4-Chloro-m-cresol)	-4.34	0.474	1.0384
4-chlorophenol	-4.52	0.299	0.8975
4-Ethylphenol	-4.53	0.380	1.0569
4-Hydroxybenzyl alcohol	-6.26	-0.560	0.9747
4-Hydroxy-methylphenylacetate	-5.26	-0.177	1.2722
4-Hydroxyphenylacetamide	-6.89	-0.606	1.1724
4-Hydroxy-phenylacetic acid	-6.06	-0.539	1.1313
4-Methylphenol (p-cresol)	-4.83	0.169	0.9160
4-Nitrophenol	-5.33	0.091	0.9493
5,5-Diethylbarbituric acid (Barbital)	-7.29	-0.377	1.3739
5-Ethyl-5-phenylbarbituric acid (Phenobarbital)	-6.68	-0.059	1.6999
5-Fluorouracil	-6.82	-0.977	0.7693
8-Methoxypsoralen	-5.12	0.376	1.4504
Aniline	-4.73	0.018	0.8162
Aspirin (Acetylsalicylic acid)	-5.69	-0.165	1.2879
Atropine	-7.15	0.551	2.2820
Benzaldehyde	-3.93	0.221	0.8730
Benzene	-4.27	0.587	0.7164
Benzoic acid	-5.15	-0.073	0.9317
Benzyl alcohol	-5.30	-0.113	0.9160
Benzyl nicotinate	-4.87	0.569	1.6393
Caffeine	-7.08	-0.487	1.3632
Chlorpheniramine	-6.14	1.009	2.2098

Table 1. Continued…

Compounds	log k_p	log k	McGowans's Volume (V)
Codeine	-7.20	0.116	2.2057
Corticosterone	-6.84	0.230	2.7389
Dexamethasone	-7.27	0.172	2.9132
Diclofenac	-5.30	0.995	2.0250
Diethylcarbamazine	-6.15	-0.049	1.7241
Digitoxin	-8.15	0.642	5.6938
Ephedrine	-5.49	0.314	1.4385
Estradiol	-5.61	0.534	2.1988
Ethylbenzene	-3.00	1.065	0.9982
Fentanyl	-4.89	1.144	2.8399
Fluocinonide	-6.33	0.904	3.4603
Hydrocortisone	-7.22	-0.055	2.7976
Ibuprofen	-5.30	1.007	1.7771
Indomethacin	-5.39	1.001	2.5299
Isoquinoline	-5.11	0.220	1.0443
Lidocaine	-5.42	0.764	2.0589
Methyl 4-hydroxybenzoate	-5.12	0.002	1.1313
Methyl phenyl ether (Anisole)	-4.68	0.543	0.9160
Naproxen	-4.97	0.557	1.7821
Nicotine	-6.03	0.061	1.3710
o-Phenylenediamine	-6.70	-0.313	0.9160
Phenol	-5.27	-0.006	0.7751
p-Phenylenediamine	-6.98	-0.415	0.9160
Progesterone	-4.90	1.130	2.6215
Resorcinol	-6.70	-0.412	0.8338
Scopolamine	-7.90	-0.036	2.2321
Sufentanil	-4.84	1.379	3.1051
Testosterone	-5.54	0.557	2.3827
Toluene	-3.64	0.826	0.8573

$$\log k_p = -4.47(\pm0.12) + 1.98(\pm0.13) \log k - 1.02(\pm0.07) \, V \qquad (4)$$

n = 63 R^2 = 0.826   SD = 0.461   F = 143

From the 65 substances, only atropine and chlorpheniramine were excluded from the regression analysis because their standard residuals were greater than 2.5 in absolute value. Both coefficients in equation 4 have statistical meaning at a 95 % level of confidence, and log k has the highest contribution to skin permeation. Note that the log k coefficient is almost twice in absolute value the V coefficient. Log k contributes in a positive way, which suggests that a high retention factor implies a better dermal absorption. The V coefficient applies a negative correction to the log k_p value, more important for those compounds with higher volume.

Equation (4) is very similar to the previous equation (2). Direct comparison of the parameters in both cases reveals almost the same values for the V coefficient and the intercept, and only a slight difference in the log k coefficient. This difference is mainly attributed to the number and variety of compounds studied. Since the present work covers a larger number of compounds and they are more representative of a wide chemical space, it is considered that equation 4 might be more robust than Eq. 2.
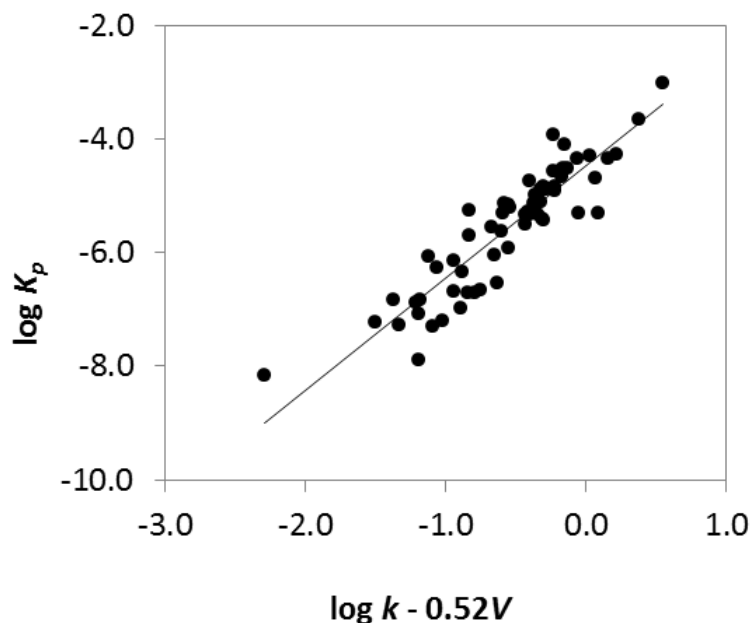
Figure 1. Correlation between log k_p experimental values and log k and V of the set of 65 compounds selected to establish the model

As described previously, to validate the model, the global set of 63 compounds was divided into two sets: the training set (42 compounds) and the test set (21 compounds). A multiple linear regression between experimental log k_p values and log k and V was performed with the 42 compounds of the training set. Equation 5 and Figure 2a show the results of the regression.

$$\log k_p = -4.57(\pm 0.13) + 2.06(\pm 0.17)\log k - 0.98(\pm 0.08) V \qquad (5)$$

$n = 42 \qquad R^2 = 0.832 \qquad SD = 0.450 \qquad F = 97 \qquad Q^2_{LMO} = 0.832$
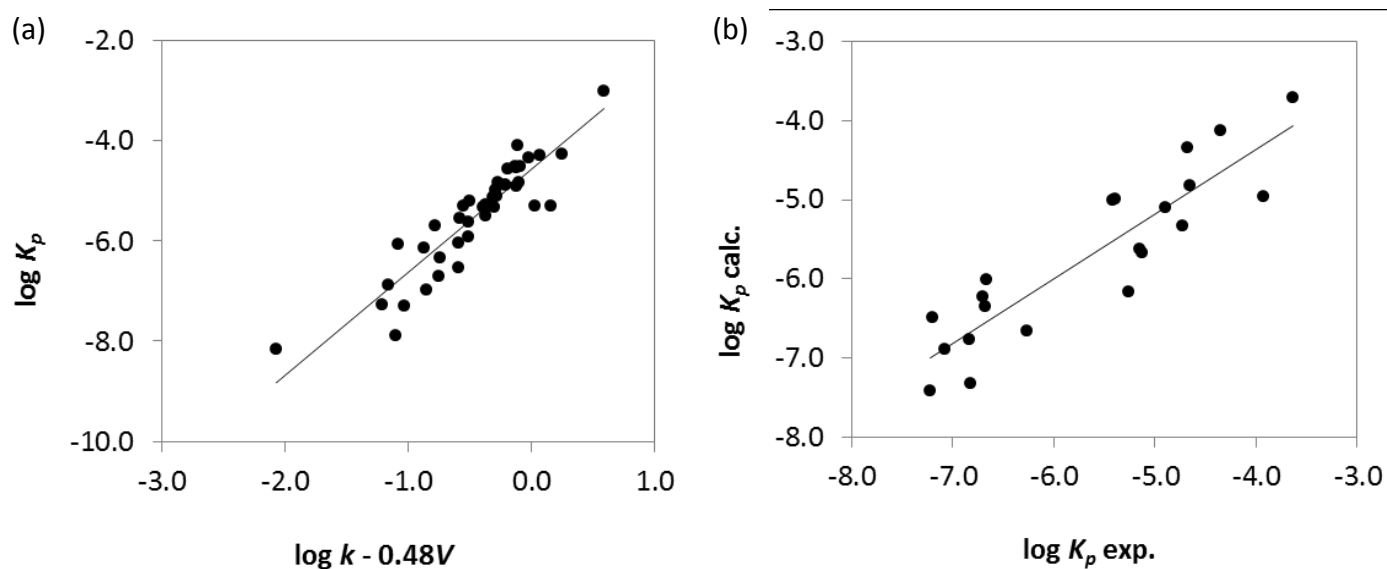

Figure 2. (a) Correlation between log k_p experimental values and log k and V of the set of compounds selected in the training set. **(b)** Estimated *vs.* experimental log k_p values for the compounds of the test set

Comparison of the intercept and the coefficients of Eq. 5 to those of Eq. 4 demonstrate that nearly the same equation is obtained with less compounds, which means that the model is robust, *i.e.* with fewer points the physical meaning of the coefficients does not change. Adequate determination coefficient,

standard deviation and F values were obtained. Q^2_{LMO} was higher than 0.6 and it can be ensured that none of the compounds present in the training set has had a big influence in the final model equation.

To perform the external validation, the log k_p values of the 21 compounds of the test set were predicted through the training set equation (Eq. 5). Agreement between experimental and predicted k_p values is shown in Figure 2b and through Equation 6:

$$\log k_{p,pred} = -1.08(\pm0.53) + 0.82(\pm0.09) \log k_{p,exp} \tag{6}$$

n = 21 R^2 = 0.807   SD = 0.469   F = 80 Q^2_{LMO}=0.983

According to statistics, the model shows good prediction ability: the slope and intercept of the trend line are not significantly different from unity and zero, respectively, at 95% confidence level according to Student's *t* test. The determination coefficient is above 0.6, the correlation cross-validation coefficient is above 0.5 and Fisher's F parameter is significant.

Prediction of log k_p values

As a first step, skin permeability coefficients of the neutral species of a set of 20 solutes were determined through the model equation (Eq. 4), after measuring their retention factors in the HPLC system. Table 2 shows the experimental log k_p values [26, 27] for these compounds, the values predicted through Eq. 4, and also the values predicted by the solvation parameter model (Eq. 1). For the latter prediction the knowledge of solvation parameter model descriptors of the compounds is necessary. There is quite good agreement between the experimental log k_p values and the values obtained by Eq. 4. In most cases the error is around 10%, and is similar to the error presented by the Abraham model (Eq. 1). Figure 3 represents the experimental values against the log k_p obtained by both models. The solid line represents the theoretical line of slope equal to one and zero intercept. The plot clearly indicates that the accuracy of both models is very similar, with points equally distributed at both sides of the theoretical line, and with similar dispersion. Only famotidine presents an anomalous low log k_p value when predicted by the Abraham model.

In a second step, log k_p values were predicted again through Eq. 4 and then through Eq. 1 for another set of 9 compounds, for which experimental log k_p values were not known. Only for five of them were the values calculated by Patel et al. (5) available.

As indicated in Table 3, comparison of the data demonstrates that values obtained through chromatographic measurements (Eq. 4) and through the Abraham model (Eq. 1) are in general consistent. However, Patel's predictions are systematically lower compared to the other two models.

Finally log k_p values for four compounds of pharmaceutical interest (capsaicin, oxycodone, tramadol, and warfarin) are proposed for the first time.

Table 2. Comparison of experimental (*in vitro*) and predicted log k_p values

| Compounds	*In vitro* log k_p values		Predicted log k_p values	
	[26]	[27]	This method	[15]
Aminopyrine	-6.55	-	-6.45	-6.97
Antipyrine	-7.74	-	-6.56	-7.31
Atrazine	-5.56	-	-5.26	-5.45
Catechol	-	-6.07	-5.88	-5.96
Cortexolone	-7.68	-	-6.72	-5.94
Cortisone	-	-7.38	-7.29	-6.74
Estriol	-7.95	-	-7.09	-6.67
Estrone	-6.00	-	-5.29	-5.11
Famotidine	-	-8.35	-7.63	-10.49
Flurbiprofen	-3.40	-	-4.60	-4.09
Griseofulvin	-6.44	-	-5.93	-5.92
Hydroquinone	-	-6.51	-6.32	-6.44
Hydroxyprogesterone	-6.78	-	-5.80	-5.08
Ketoprofen	-4.71	-	-5.43	-5.06
Ketorolac	-	-5.80	-5.79	-5.72
Piroxicam	-6.02	-	-6.19	-7.18
Prednisolone	-7.91	-	-7.46	-6.90
Pregnenolone	-6.38	-	-4.93	-4.70
Propanolol	-	-6.05	-4.96	-5.71
Ranitidine	-	-7.61	-7.17	-7.97
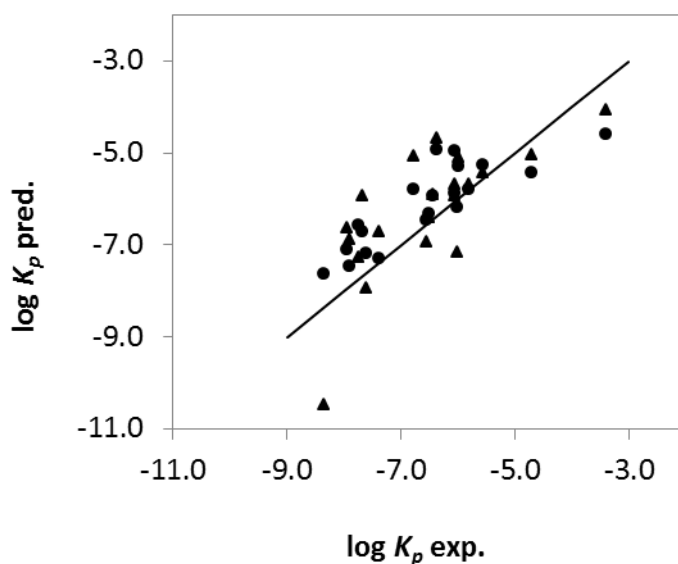
Figure 3. Experimental *vs.* predicted log k_p values. For each compound, log k_p is predicted through the chromatographic model (●) and through the solvation parameter model (▲)

Table 3. Prediction of log k_p values through different estimation models

Compounds	This method	[15]	[5]
2-Toluidine	-5.09	-5.22	-5.83
3-Xylene	-3.37	-3.93	-4.41
Cumene	-3.11	-3.59	-6.14
N.N-Dimethylaniline	-4.20	-4.62	-5.29
Pyridine	-5.56	-5.90	-6.10
Capsaicin	-5.41	-4.19	-
Oxycodone	-5.89	-7.05	-
Tramadol	-5.16	-5.02	-
Warfarin	-5.37	-5.25	-

Conclusions

A methodology has been developed for the prediction of skin permeability of neutral species. The method is based on measurements on an HPLC system fitted with a C18 column, coupled to UV-vis and MS detection. The model has been established with a set of 63 compounds with different chemical natures and structural complexity, which ensures the applicability of the model to a wide range of compounds. The chromatographic retention factor is the parameter that makes the highest contribution to the calculation of the permeation through skin, the k_p value being greater as the retention increases. On the contrary, the McGowan volume decreases the permeation value. The model has been validated, showing both good robustness and good prediction ability. The prediction ability has been further tested by comparison of the results to other prediction models (Abraham and Patel). Results from this work are similar (both in accuracy and precision) to the results obtained through Abraham's model. However, the permeation coefficients obtained through Patel's model seem to be slightly lower. The main advantage of the present methodology is that k_p can be directly obtained from simple chromatographic retention measurements and the McGowan's molecular volume of the compounds, without the need of additional molecular descriptors calculation and/or determination.

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