International Journal of Pharmaceutics 521 (2017) 259–266

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

An equation for the prediction of human skin permeability of neutral molecules, ions and ionic species

Keda Zhang[a,b], Michael H. Abraham[c], Xiangli Liu[d,*]

[a] Department of Pharmacy, Wuhan Third Hospital, Wuhan 430060, China
[b] Central Laboratory of Longhua Branch, Shenzhen People's Hospital, Second Clinical Medical College, Jinan University, Shenzhen 518109, China
[c] Department of Chemistry, University College London, London WC1H 0AJ, UK
[d] Bradford School of Pharmacy, Faculty of Life Sciences, University of Bradford, Bradford BD7 1DP, UK

ARTICLE INFO

Article history:
Received 17 January 2017
Received in revised form 19 February 2017
Accepted 20 February 2017
Available online 22 February 2017

Keywords:
Predictive model
Ionic species
Ions
Human skin
Skin permeability
Linear free-energy relationship
QSPR

ABSTRACT

Experimental values of permeability coefficients, as log K_p, of chemical compounds across human skin were collected by carefully screening the literature, and adjusted to 37 °C for the effect of temperature. The values of log K_p for partially ionized acids and bases were separated into those for their neutral and ionic species, forming a total data set of 247 compounds and species (including 35 ionic species). The obtained log K_p values have been regressed against Abraham solute descriptors to yield a correlation equation with $R^2 = 0.866$ and SD = 0.432 log units. The equation can provide valid predictions for log K_p of neutral molecules, ions and ionic species, with predictive $R^2 = 0.858$ and predictive SD = 0.445 log units calculated by the leave-one-out statistics. The predicted log K_p values for Na^+ and Et_4N^+ are in good agreement with the observed values. We calculated the values of log K_p of ketoprofen as a function of the pH of the donor solution, and found that log K_p markedly varies only when ketoprofen is largely ionized. This explains why models that neglect ionization of permeants still yield reasonable statistical results. The effect of skin thickness on log K_p was investigated by inclusion of two indicator variables, one for intermediate thickness skin and one for full thickness skin, into the above equation. The newly obtained equations were found to be statistically very close to the above equation. Therefore, the thickness of human skin used makes little difference to the experimental values of log K_p.

1. Introduction

Rapid and accurate prediction of human skin permeability of chemical compounds is very useful for developing dermal and transdermal drug delivery systems and cosmetics, as well as evaluating environmental risks due to contact with skin. Various kinds of empirical and mathematical models for the correlation and prediction of human skin permeability, as log K_p, have been reported (Baba et al., 2015; Mitragotri, 2003), and there have been a number of reviews of these models (Chen et al., 2013; Geinoz et al., 2004; Mitragotri et al., 2011; Moss et al., 2011; Neely et al., 2009). It has been known for years that the permeability of ionizable compounds depends on the pH of the donor solution, attributed to the slower rate of permeation of ionic species compared to the corresponding neutral species (Roy and Flynn, 1990; Swarbrick et al., 1984; Waters and Bhuiyan, 2016). For instance, Waters and Bhuiyan (2016) recently reported that as an in vitro skin mimic, silicone membrane encouraged permeation of the more unionized forms of pharmaceutical compounds rather than the ionized forms. However, the above reviews completely ignore the possibility of ionization and associated factors such as the dependence of permeation on pH for ionizable compounds, and our previous study represents the only attempt to include ionized species in a model for skin permeation (Zhang et al., 2012). Thus one of the most popular models for skin permeation, the Potts and Guy model (Potts and Guy, 1992), uses only the octanol-water partition coefficient (as log $P_{o/w}$) and molecular weight (MW) as compound descriptors (see Eq. (1)), with no reference to ionic species.

$$\log K_p = 0.71 \log P_{o/w} - 0.0061 MW - 6.3 \quad (1)$$

As mentioned, we have previously constructed an equation for predicting skin permeability of neutral molecules, ions and ionic species using the Abraham linear free-energy relationship (LFER) model (Zhang et al., 2012). Since then, descriptors for considerably more compounds have been obtained, including those for ionic

* Corresponding author.
E-mail address: X.Liu18@bradford.ac.uk (X. Liu).

http://dx.doi.org/10.1016/j.ijpharm.2017.02.059
0378-5173/

species (Abraham and Acree, 2016), and it is the purpose of the present work to set out an extended equation for the correlation and prediction of human skin permeability, including neutral molecules and ionic species in the same equation.

2. Methods

2.1. LFER model

Our method is based on the LFER method of Abraham, firstly applied to the properties of neutral molecules (Abraham, 1993) and subsequently extended to include ions and ionic species by Abraham and Acree (Abraham, 2011; Abraham and Acree, 2010a,b, 2016). The general equation developed by Abraham and Acree is stated as:

$$SP = c + eE + sS + aA + bB + vV + j^{+}J^{+} + j^{-}J^{-} \quad (2)$$

The dependent variable SP represents an equilibrium coefficient for a series of solutes in a given system, including partition coefficients (as log P) and rate coefficients (as log K), and in the present work permeation coefficients through human skin, as log K_p. The independent variables are the physicochemical properties or descriptors of the solutes as follows. E is the excess molar refraction in units of $(cm^3/mol)/10$, S is the combined dipolarity/polarizability, A and B are the overall solute hydrogen bond acidity and basicity, and V is McGowan's characteristic molecular volume in units of $(cm^3/mol)/100$; J^+ and J^- are the additional descriptors that are specific to ionic species. Note that $J^+ = 0$ for anions, $J^- = 0$ for cations, and both J^+ and $J^- = 0$ for neutral molecules. In the latter case, Eq. (2) reduces to an equation for neutral molecules. We use the term "ions" for permanent ions such as Na^+ and Cl^-, and the term "ionic species" for ions derived from protonation of basic compounds and deprotonation of acidic compounds. The compound descriptors for neutral molecules are obtained from a variety of experimental processes, as explained in a number of reviews (Abraham et al., 2004; Clarke and Mallon, 2012; Poole et al., 2013), and Abraham and Acree have reviewed the methods used to obtain descriptors for ions and ionic species (Abraham and Acree, 2016). The coefficients (c, e, s, a, b, v, j^+ and j^-) in Eq. (2) can be obtained by a multiple linear regression of values of SP in a given system against the known solute descriptors, and used to characterize the system of interest.

2.2. Effect of temperature and ionization

The reliability of the predictive model greatly depends upon the quality of the used database. In this study, we ensured that measurements for the selected K_p data were rigorously conducted through *in vitro* passive diffusion study across excised human skin. As regards the influence of temperature, we corrected values of log K_p at various temperatures to obtain the corresponding value at 37 °C as detailed by Abraham and Martins (2004) (see Table 1). The determination of these corrections was quite coarse and also they should theoretically vary with lipophilicity, but since they are comparatively small little error will be involved in just using the corrections in Table 1.

Table 1
Corrections to log K_p from experimental temperature to 37 °C.

Adjusted temperatures	Corrections to log K_p
from 20 °C to 37 °C	0.69
from 25 °C to 37 °C	0.48
from 30 °C to 37 °C	0.28
from 32 °C to 37 °C	0.20
from 40 °C to 37 °C	−0.11

The effect of ionization on skin permeation of compounds must be taken into consideration, K_p for neutral forms being much larger than that for ionic forms (Zhang et al., 2012). Thus the fractions of neutral and ionic forms (F_n and F_i) for each ionizable compound were carefully calculated according to the pH of the donor solution used. As for the donor solvent containing no buffer salt, the degree of ionization was derived from pK_a and concentration of solute. With compounds that are partially ionized/neutral and have known values of the fraction ionized and neutral, F_i and F_n, we separate the experimental (total) value of $K_p(t)$ into $K_p(n)$ for neutral and $K_p(i)$ for ionic species through the equation

$$K_p(t) = K_p(n) \times F_n + K_p(i) \times F_i \quad (3)$$

Then we estimate $K_p(n)$ and $K_p(i)$ using our previously established LFER equation (Zhang et al., 2012) and the neutral and ionic descriptors, and can obtain an approximation of the ratio $K_p(n)/K_p(i)$. From $K_p(n)/K_p(i)$ and the accurate values of F_i and F_n, the values of $K_p(n)$ and $K_p(i)$ of partially ionized compounds are deduced. These values are included in Table 2.

3. Results and discussion

We surveyed the literature and collected *in vitro* log K_p data of compounds recently measured, especially compounds that were ionized under the experimental conditions. As the major data sources, our previous dataset (Zhang et al., 2012) and the dataset of Baba et al. (2015). were combined in the present work. For compounds that exist in both datasets, we took the log K_p values in our previous dataset. This is because most of our log K_p values were derived from Abraham and Martins (2004), who had adjusted log K_p for ionization and temperature dependence, and had used the mean of the values where multiple values exist. Some compounds were omitted in the following cases: a) the compounds are zwitterions under original experimental conditions and b) their descriptors cannot be obtained from the experimental data listed in the current literature. We also used compounds whose log K_p had been measured by ourselves under reliable experimental conditions. Descriptors for all the neutral compounds and ionic species that we considered are listed in Table 2, together with the corresponding values of log K_p, corrected to 37 °C. The values of log K_p of the 247 compounds or species in our data set covers both 'highly permeable' and 'poorly permeable' values, varying from −10.01 to −3.00, and meets a normal distribution very well, with a mean of −6.027 and a standard deviation of 1.165, as seen in Fig. 1.

We made a distinction between skin permeation through *stratum corneum* or through full thickness skin or through intermediate thickness skin, by the use of indicator variables. For permeation through the *stratum corneum*, the indicator variable is zero because this is our 'standard system'. In column 'Inter', Table 2, all values are zero except for permeation through intermediate thickness where the indicator value = 1. In column 'Full' all values are zero except for permeation through full thickness skin where the indicator value = 1.

Regression of the values of log K_p against the descriptors in Eq. (2) and the two indicator variables 'Inter' and 'Full' leads to Eq. (4).

$$\log K_p = -5.182(0.126) + 0.185(0.085)\ E - 0.617(0.057)\ S - 0.373(0.095)\ A - 2.412\ (0.091)\ B + 1.763(0.081)\ V - 1.440(0.122)\ J^+ + 2.461(0.113)J^- - 0.121(0.099)\ \text{Inter} - 0.299(0.139)\ \text{Full}$$
$$N = 247\ \ SD = 0.430\ \ R^2 = 0.869\ \ F = 174.70\ \ PRESS = 47.550\ \ Q^2 = 0.858\ \ PSD = 0.448 \quad (4)$$

Here and elsewhere, N is the number of compounds or species studied, R^2 is the squared correlation coefficient, SD is the standard deviation, and F is the Fisher F-statistic. PRESS and Q^2 are the leave-