Quantitative structure – skin permeability relationships

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Abstract

This paper reviews *in silico* models currently available for the prediction of skin permeability with the main focus on the quantitative structure-permeability relationship (QSPR) models. A comprehensive analysis of the main achievements in the field in the last decade is provided. In addition, the mechanistic models are discussed and comparative studies that analyse different models are discussed. (to be extended to 100--200 words)

Keywords

dermal absorption, mathematical modelling, QSPR, permeability, skin, stratum corneum (5 to 10 keywords)

1. Introduction

Prediction of dermal absorption is an important research topic in the pharmaceutical and cosmetics sectors and relates to the optimisation of the deposition and delivery of the active substances, as well as hazard and risk assessment. It is of particular interest in the light of the current EU regulations, such as REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) and Cosmetics Regulation that strongly recommend or require use of alternatives to animal studies. The main benefits of theoretical predictions over experimental measurements include reduction of resources and resolving ethical issues. In addition, the models may assist in the better understanding of mechanisms of absorption.

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Prediction models are of particular interest in the light of the current EU regulations, such as REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) and Cosmetics Regulation that strongly recommend or require use of alternatives to animal studies. The Cosmetics Regulation has completely banned marketing of animal tested cosmetics ingredients and products in

the EU, requiring alternative methods for the safety assessment. Within the COSMOS project - part of the SEURAT-1 cluster co-funded by the European Commission and the Cosmetics Europe, the European cosmetics industry association – computational models to support the safety assessment of cosmetics-related substances were developed. For these substances the dermal exposure route is particularly important and therefore models for the prediction of skin permeation are needed to estimate the systemic availability via the dermal route. For example skin permeation models were used in the evaluation of the extension of the Thresholds of Toxicological Concern (TTC) approach to cosmetics and included in the decision tree developed to predict the systemic dose for comparison with the TTC derived from oral data (Williams et al 2016).

There are two main types of predictive models for skin absorption: (i) quantitative structure-permeability relationship (QSPR) models that relate skin permeability to chemical structure described by physico-chemical properties and other structural descriptors; these models rely on experimental data for skin permeability and build quantitative correlations using statistical approaches; and (ii) mechanistic models that take into account the heterogeneity of the skin structure in solute transport and are derived from first principles such as mass balance, relying on additional assumptions such as Fick's laws of diffusion (Naegel et al., 2013). A number of the models reported are based on the general agreement that the rate-limiting step of permeation is often diffusion through the stratum corneum (SC), the outermost layer of the skin. Thus, an important challenge in modelling studies is to reflect the effect of the heterogeneous SC and the different possible absorption pathways, including transcellular absorption, intercellular absorption and appendageal absorption. Many studies regard passive diffusion through the lipid lamellae as the primary pathway. A smaller number of studies report the transcellular route to be important for passage of chemicals through the skin. Further challenges are how to model mixtures, transport from different vehicles, and the permeation of hydrophilic compounds.

This review provides a comprehensive analysis of the main achievements in modelling skin absorption with QSPR approaches during the last decade. In addition, the mechanistic models are discussed and comparative analyses of different models are provided.

2. Skin structure and mechanisms of skin absorption

In this section the main issues related to the structure and function of skin, as well as the mechanism of skin absorption, are briefly discussed in light of their role in the modelling of skin permeability. More detail on these topics can be found in several extensive reviews (e.g. Wiechers, 1989; Singh & Singh, 1993; Schaefer & Redelmeier, 1996; Walters & Roberts, 2002; Madison, 2003; Monteiro-Riviere, 2004, 2006).

The skin is the primary barrier to systemic absorption of topically applied chemicals and a portal to the systemic delivery of transdermal medicaments (Monteiro-Riviere, 2006). Due to its large surface area and the cutaneous circulation, which comprises 5–10% of the total cardiac output, the skin is a major route of entry into the body for some exposure scenarios. As such, the skin provides a sturdy and flexible barrier to unwanted toxic substances and pathogenic microorganisms, to water and nutrients loss and responds to mechanical forces (elasticity and cushioning). Skin defence and repair includes touch, pain, and heat sensitivity, UV protection, cutaneous metabolism, immunological activity and inflammatory response to a foreign insult.

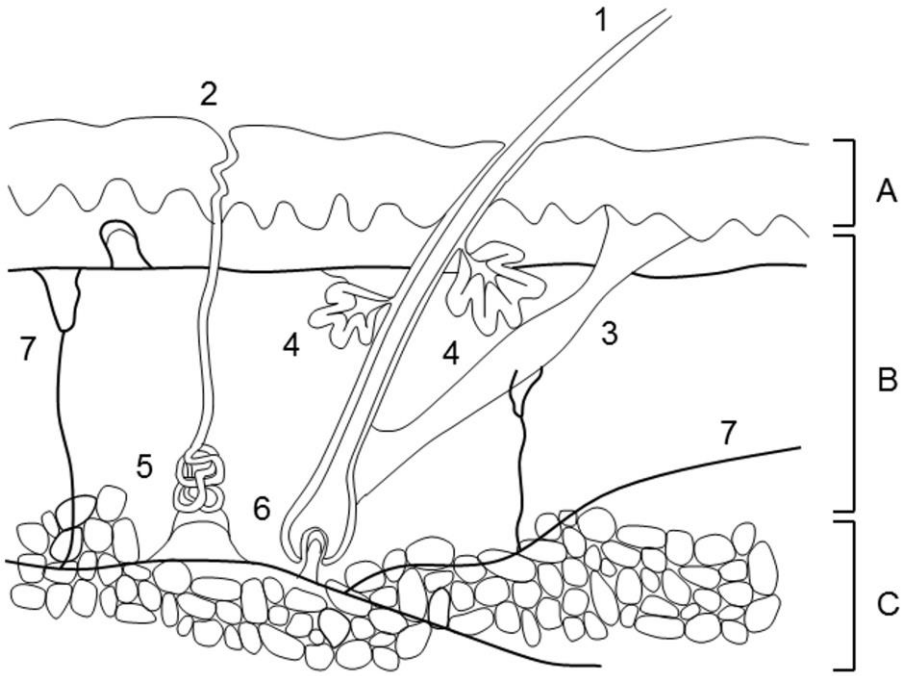

Fig. 1. Schematic representation of the skin structure: A – epidermis, B – dermis, C – hypodermis; 1 – hair shaft, 2 – pore, 3 –hair erector muscle, 4 – sebaceous gland, 5 – sweat gland, 6 – hair follicle, 7 – blood vessel.

The skin is a heterogeneous organ, containing a number of cellular layers, divided into distinct regions (Fig. 1). The epidermis is the outer region of embryonic ectodermal origin, which covers the connective tissue, while the dermis and the hypodermis are derived from the mesoderm (Kielhorn J et al. 2006). The epidermis has several layers with the following order from the external surface to inside: stratum corneum (SC, horny layer), stratum lucidum (clear layer), stratum granulosum (granular layer), stratum spinosum (spinous or prickle layer) and stratum germinativum (basal layer). The majority of cells in the epidermis are keratinocytes, formed by differentiation and

migration from the metabolically active basal layer. The cells of the adjacent layer, the stratum spinosum, are connected through desmosomes and other bridges and produce lamellar intracellular granules that, after fusion with the cell membrane, release neutral barrier lipids. The keratinocytes migrate to the outermost viable layer, the stratum granulosum, and are characterised by the presence of keratohyalin granules, polyribosomes, large Golgi bodies and rough endoplasmic reticulum.

The top-most nonviable layer, the SC, is the major barrier to permeation within the skin (Fig. 2). It is 10–50 μm thick, metabolically inactive, with low water content (5-20%). It is composed of hexagonal cornified corneocytes that do not contain nuclei or cytoplasmic organelles. The majority of their cell content is keratin, a scleroprotein with chains linked by disulfide and hydrogen bonds. The corneocytes are connected by corneodesmosomes and their protein-rich cornified cell envelope, made up of highly cross-linked proteins (loricrin, involucrin, and filagrin) and provide covalent linkage sites for the surrounding non-polar barrier lipids (Madison, 2003, Norlen, 2008, Masters, So, 2001). The intercellular substance derived from the lamellar granules is present between the SC cells and forms the intercellular lipid component of a complex SC barrier, which prevents both the penetration of substances from the environment and the loss of body fluids (Monteiro-Riviere, 2006).

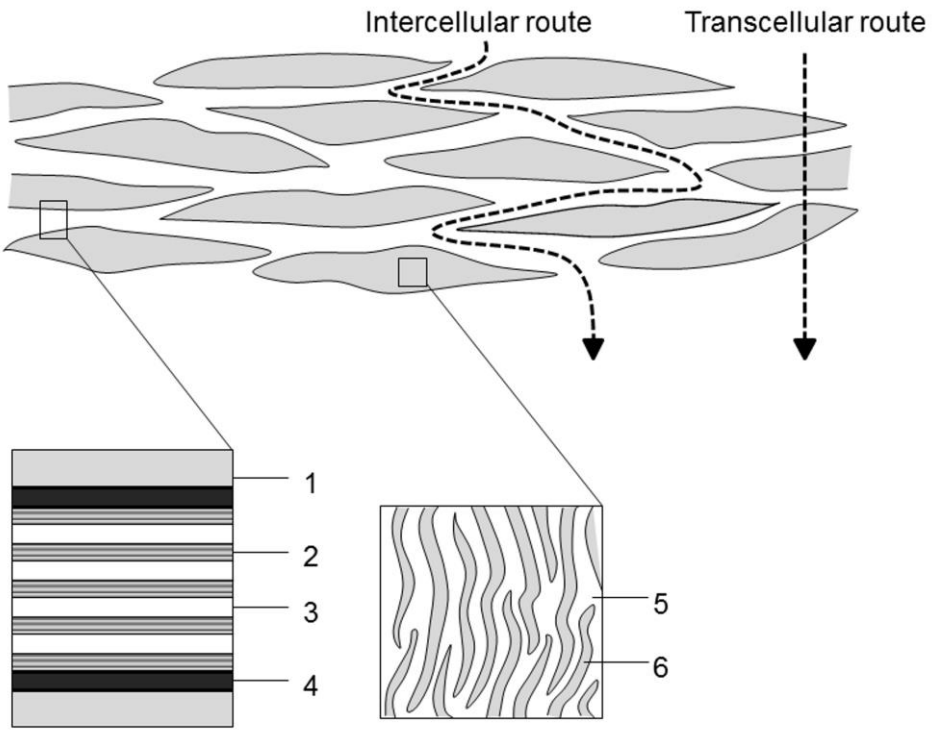

Fig. 2. Schematic diagram of stratum corneum with the main transport routes (based on Barry, 2001). 1 – cell cytoplasm, 2 – aqueous layer, 3 – lipid bilayers (ceramides, cholesterol, fatty acids), 4 – plasma membrane, 5 – lipid, 6 – keratin

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The hydrophobic lipid composition of the intracellular spaces includes: 45–50% ceramides, 25% cholesterol, 15% long-chain free fatty acids, and 5% other lipids, the most important being cholesterol sulfate, cholesterol esters and glucosylceramides (Wertz et al., 1987; Law et al., 1995; Madison, 2003, de Jager et al., 2003; Ponec et al., 2003). The ceramides consist of a sphingosine or a phytosphingosine base to which a non-hydroxy, an α-hydroxy, fatty acid is chemically linked. The length of the fatty acid chains is mostly between 24-26 methylene groups. Despite its low

content, cholesterol sulfate has been shown to be involved in the regulation of the desquamation process. How the skin lipids are organised architecturally is still not fully understood – both a single gel phase (Norlen, 2001) and the coexistence of a liquid crystalline and a crystalline phase (Bouwstra, Ponec, 2006; Forslind, 1994; Kitson et al., 1994) were initially assumed. Later, a model based on bilayers of fully extended ceramides with asymmetrically distributed cholesterol molecules associated with the ceramide sphingoid moiety was proposed (Iwai et al., 2012). The authors speculated that a SC lipid matrix, in which cholesterol and free fatty acid segregated into different bands, allows for crystalline-like hydrocarbon chain packing on the fatty acid sides of the stacked extended ceramide bilayer system. In addition to keratinocytes, the epidermis contains two dendritic cell types, melanin producing cells, adjacent to the basal layer (melanocytes) and cells participating in the immune recognition in metabolically active epidermal layers (Langerhans cells) (Ahmed, 1979; Romani et al., 2003).

A thin basement membrane separates the epidermis from the dermis (Fig. 1), where blood vessels, sensory nerves (pressure, temperature, and pain) and lymphatics are located. Its main functions are to provide nutritional support for the avascular epidermis, being a barrier to infection and a water storage organ. Beneath the dermis is a layer of loose connective tissue commonly known as the hypodermis (subcutis); it consists of superficial fascia with elastic fibres and aids in binding the skin to the underlying fascia and skeletal muscle (Monteiro-Riviere, 2006). The skin appendages originate in this layer: eccrine sweat glands, apocrine sweat glands, sebaceous glands and hair follicles with their associated erector muscles (Fig. 1).

The transport of chemicals through the skin is a complex process, mediated by the following mechanisms: transcellular absorption (through the keratin-packed corneocytes by partitioning into and out of the cell membrane); intercellular absorption (around the corneocytes in the lipid-rich extracellular regions) and appendageal absorption (through the shunts provided by the hair follicles,

sweat glands, and sebaceous glands). The routes mediated by intercellular and transcellular absorption are considered as the most important for skin permeation of chemicals (Fig. 2). The tortuous intercellular pathway around the corneocytes has been identified as the major route of penetration across SC due to the relative impermeability of the cornified envelope, implying that SC lipids play a key role in the skin barrier function (Michaels et al., 1975; Elias, 1981; Grubauer et al., 1987; Mao-Qiang et al., 1993; Bouwstra et al., 2001, 2003a; Ponec et al., 2003). The route associated with appendageal absorption may be important at early time points following application of the penetrant and in areas with significant density and size of appendages which may act as a drug reservoir for some materials (Kielhorn et al. 2006).

3. Skin absorption parameters estimated in QSPR studies

Typically QSPR models for skin absorption are based on experimental data derived from *in vitro* assays where steady-state conditions are ensured. The solute (penetrant) transport through the skin under steady-state conditions can be described by Fick's first law. It relates the amount of a solute Q, crossing the skin membrane of area A, over a time period T, with the constant concentration gradient across the two interior surfaces of the skin ΔC_s, the diffusion coefficient in the skin membrane D, and the path length h, as follows:

$$Q = D \cdot A \cdot T \cdot \Delta C_s / h \quad (1)$$

Here the assumption is that the SC behaves like a pseudo-homogenous membrane. Thus the steady-state skin flux J_{ss} (mol/cm^2/hour) can be defined as:

$$J_{ss} = Q / (A \cdot T) = (D \cdot \Delta C_s) / h \quad (2)$$

Commonly, the concentration at path length h is zero or very small (sink conditions). Also, the

concentration of the chemical at path length 0 is in a local equilibrium with the vehicle, and can be given by:

$$C = K_m \cdot C_v \quad (3)$$

where K_m is the pseudo-homogeneous partition coefficient between the SC and the vehicle and C_v is the vehicle concentration.

Under these conditions, eq. 2 becomes:

$$J_{ss} = D \cdot K_m \cdot C_v / h = K_p \cdot C_v \quad (4)$$

where K_p (permeability coefficient, cm/h) is the steady-state flux of the substance normalised by the concentration (remaining constant over a range of concentration values) C_v, i.e.:

$$K_p = J_{ss} / C_v \quad (5)$$

It can be defined from eq. 4 as follows (Crank, 1975):

$$K_p = D \cdot K_m / h \quad (6)$$

The permeability coefficient K_p is the preferred dependent variable in the QSPR models. Usually it is calculated for an aqueous vehicle. Over time, a substantial database of experimentally determined K_p values from aqueous vehicles has been compiled, which is useful for deriving models (Mitragorti et al., 2011).

Typically, the steady-state flux J_{ss} is assessed from an *in vitro* experiments in which the donor concentration of the penetrant is maintained constant (i.e. infinite dose conditions), while the receiver phase provides "sink" conditions. Over time, the flux approaches a steady-state value and the cumulative amount penetrating the skin increases linearly with time. J_{ss} is determined from the slope of the linear portion of the graph of the cumulative amount penetrated over the time. K_p is the

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ratio of J_{ss} and the vehicle concentration C_v (see eq. 5).

The maximum flux, J_{max}, will be observed when maximum solubility S_s of a solute in the SC is achieved, so that eq. 2 can be written as:

$$\boldsymbol{J_{max} = D \,.\, S_s / h} \qquad \textbf{(7)}$$

Based on K_p and the maximal solubility of the chemical in the vehicle (S_v), the maximum flux can be represented as follows:

$$\boldsymbol{J_{max} = K_p \,.\, S_v} \qquad \textbf{(8)}$$

Despite the fact that only few studies predict J_{max}, it is a very useful parameter as it does not depend on the formulation, providing the formulation is saturated. J_{max} should be constant as long as the chemical is at its maximum thermodynamic activity in the vehicle (Kroes et al., 2007)**.** It must be noted that when calculating J_{max} (eq. 8) K_p and S_v must be determined in the same vehicle.

4. Main data sources for modelling purposes

A large number of skin absorption data have been generated, some of them published in non-proprietary sources. However, due to the lack of an established standard experimental procedure, there is high variability in experimental skin permeability values. This is as a result of the influence of a number of factors such as subject variability (i.e. species, sex and age), application site, dosing regime, occlusion, as well as inter-laboratory variations. Conversely, the key points for the development of predictive QSPR models are consistency and reliability of the experimental permeability data. Variations in the factors that influence these data increase the error and decrease the statistical reliability of the developed models (Moss et al., 2002a).

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All data discussed in the following/Table 1 are public

The section below shortly discusses the main datasets that have been published in the scientific literature and used for QSPR modelling (summarised in Table 1).

Flynn dataset (Flynn, 1990). This was the first significant dataset of experimental permeability properties compiled. Due to this fact it is considered as a milestone in the development of QSPRs for skin permeability. It includes 97 permeability coefficients for 94 compounds, tested *in vitro* through human skin and *in vivo* in humans for toluene, ethyl benzene, and styrene (Flynn, 1990). The compounds cover a broad range of molecular weights (18 to 765) and logarithm of the octanol-water partition coefficient (log P) values (−3 to 6); however the lipophilicity distribution is uneven – there are only small numbers of either highly lipophilic or highly hydrophilic compounds (Russell and Guy, 2009). Being a compilation of 15 different literature sources, this dataset has a high degree of uncertainty due to inter-laboratory and intra-laboratory variability including use of skin obtained from different sources and body locations (Moss et al., 2002a). Some groups have reanalysed the data included in the dataset. Johnson et al., 1995 re-examined the results for steroids previously measured by Scheuplein et al., 1969 and included them in the Flynn dataset. Degim et al., 1998 reanalysed other compounds (naproxen, atropine, and nicotine), for which experimental values differed by one or two log units from those published by Flynn.

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Wilschut et al. dataset (Wilschut et al., 1995). The dataset consists of 123 permeability coefficients for 99 different compounds applied *in vitro* to human skin in an aqueous solution and is compiled from the literature. These chemicals represent various chemical classes, including monoaromatic hydrocarbons, volatile halogenated hydrocarbons, phenols and steroids.

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Kirchner et al. dataset (Kirchner et al., 1997). A larger database of 114 skin permeability values was prepared from the Flynn dataset (51 chemicals, Flynn, 1990), together with additional data from regulatory reports (Health Canada, years range). However, the database contained

permeability coefficients for 63 compounds, which were not experimental values, but had been calculated using the "Potts and Guy" linear equation (Frasch and Landsittel, 2002, see below).

Patel et al. dataset (Patel et al., 2002). Patel and co-authors compiled a comprehensive dataset containing 186 permeability coefficients for 158 structurally diverse compounds from human *in vitro* skin data of Flynn (1990) and Wilschut et al. (1995). They removed some compounds (atropine, diclofenac, naproxen, nicotine) that were considered as outliers.

Vecchia et al. dataset (Vecchia et al., 2003). Vecchia and Bunge (2003a) collected a diverse data set of 170 permeability coefficients for 127 compounds covering molecular weights from 18 to 584 and log P values from -3.1 to 4.6.

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Magnusson et al. dataset (Magnusson et al., 2004b). The complete dataset contains 278 J_{max} values that are acquired or estimated from experimental data of various sources. The basic set includes J_{max} values of 64 different solutes (87 records) from aqueous solution across a human skin. Additional records are available for: an aqueous vehicle with full- and split-thickness skin (56 records); some pure solutes (34 records); an aqueous vehicle with ionisable solutes (54 records) and solutes from a propylene glycol vehicle (36 records). The data cover a wide range of physicochemical properties with log P values ranging from -5.7 to 8.7, molecular weight (MW) from 18 to 765 g/mol, melting point (M_{pt}) from 147 to 582 K and aqueous solubility (S_{aq}) from $6.9x10^{-7}$ mol/l to $8x10^{-6}$ mol/l.

EDETOX database, 2004. It has been developed in the frame of multipartner EU project and is freely available from the University of Newcastle web page (http://research.ncl.ac.uk/edetox/). EDETOX contains over 4800 studies for 320 chemicals (Kielhorn et al. 2006). The database contains data from *in vitro* and *in vivo* percutaneous penetration studies using different species. EDETOX provides information about chemical name, vehicle used, origin of the skin sample,

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membrane thickness, exposure time, length of study, percentage of dose absorbed, percentage recovery, flux, K_p, lag time, where available, and the source publications (Soyei and Williams, 2004, Williams, 2006).

Lian et al. dataset, 2008. The dataset is compiled from a number of publications (Wilschut et al., 1995; Johnson, 1997; Patel et al., 2002; Mitragotri, 2003). Only human skin data are included. Altogether, there are 205 data points for 124 chemical compounds. MW values of the chemical compounds ranges from 18 to 765 and log P varies from -3.7 to 5.49.

Oklahoma State University (OSU-KP) database, **(Neely et al., 2009).** It is based on published data in drug permeation enhancer studies and is developed to support modelling efforts. The criteria for inclusion are the following: (a) presence of well documented experimental conditions; (b) permeation coefficients measured under comparable circumstances; (c) structure of the included molecules generated and optimiSed using computational chemistry software; (d) M_{pt} and log P values of the molecules accurately calculated; (e) human or porcine skin is used. After applying these criteria, the OSU-KP database consisting of approximately 260 data points for 169 molecules was constructed for modelling studies.

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Lehman et al. dataset, 2011 (Lehman et al., 2011). The data are collected for compounds with absorption through human skin measured *in vitro* and *in vivo*. A total of 92 measured data were collected for 30 organic compounds; for some of these were from both *in vitro* and *in vivo* experiments conducted in the same laboratory.

Samaras et al. dataset, 2012. The dataset is based on the EDETOX database extract and extended by data collected through an exhaustive literature search for human skin flux data. It contains 536 flux reports for 272 unique chemicals. The chemicals are either applied as neat (around 10% of the data) or formulated in simple mixtures with the majority of the vehicles

containing water as a constituent. In many cases, finite or infinite dosing conditions were specified explicitly in the source. In other cases, if the application volume is above 100 µl it is taken as 'infinite', if donor volume is between 50 and 100 µl then, provided that the percentage of absorption is less than 20%, it is considered as an 'infinite', otherwise a 'finite' application.

Chen et al. dataset, 2013. It consists of human skin permeability of hydrophilic solutes with low hydrophobicity (log P < 0.5) compiled from various published sources. In total there are 71 data points for 23 hydrophilic and 12 low hydrophobic solutes.

Alves et al. datasets, 2015. Two *in vitro* skin permeability datasets with skin permeability coefficients were compiled from the literature − human and rodent data − consisting of 186 and 96 compounds, respectively. The activity range of the compounds in the datasets is from −5.52 to −0.69 and from −4.85 to −0.94, respectively.

Brown et al. dataset, 2016. A new *in vitro* skin permeability database is compiled from the literature. It contains 392 data points for 245 organic chemicals derived from human skin only and using only water as a vehicle. The range of the data in the dataset is the following: log P values from − 6.8 to 7.6; MW from 18 to 765 and log K_p from 5.8 to 0.1.

Table 1. Summary of the main datasets used in skin absorption modelling studies.

Data set	Skin permeability parameter	Number of compounds	Total number of data records
Flynn, 1990	K_p	94	97

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For example:

In vitro or in vivo; human/pig/rodent etc

How many literature sources used to compile the dataset? (or how many different laboratories?)

- featured characteristics of the dataset, e.g. broad structural diversity or specific chemical classes included: variability: only human data; only data with same vehicle considered…

-MW / log P range, but probably not known for all datasets

Wilschut et al, 1995	K_p	99	123
Kirchner et al., 1997	K_p	114	114
Patel et al., 2002	K_p	158	186
Vecchia et al., 2003	K_p	127	170
Magnusson et al., 2004b	J_{max}	64	278
EDETOX database, 2004	flux, K_p	320	>4800
Lian et al., 2008	K_p	124	205
OSU-KP database	K_p	169	260
Lehman et al., 2011	% absorbed	30	92
Samaras et al., 2012	flux	272	536
Chen et al., 2013	K_p	35	71
Alves et al., 2015	K_p	186/96	211
Brown et al., 2016	Kp	245	392

5. Review of existing quantitative structure-skin permeability predictive models

Since the beginning of the 1990s the modelling of the skin absorption has been exploited

intensively. A number of review articles have periodically discussed and analysed the models published in the scientific literature (Moss et al., 2002a; Vecchia & Bunge, 2003a,b; Walker et al., 2003; Fitzpatrick et al., 2004; Geinoz et al., 2004; Degim, 2006; Kielhorn et al., 2006; Mitragorti et al., 2011; Moss et al., 2012; Anissimov, 2014, Dumont et al., 2015). The latter one reviews in addition *in silico* tools for the prediction of skin metabolism that are behind the scope of this paper, but does take into account that the skin is a metabolically competent organ and some chemicals are absorbed across the skin and metabolised into active compounds.

There is a special issue "Modelling the human skin barrier—towards a better understanding of dermal absorption" of the *Advanced Drug Delivery Reviews* (volume 65, 2013) that gives an overview of the state of the art in the computational tools development. QSPR models are also discussed among the others. In addition, a number of comparative studies have evaluated the models developed (Bouwman et al., 2008; Lian et al., 2008; Farahmand et al., 2009; Brown et al., 2012).

In this paper we focus on the published QSPRs for skin absorption. A broader scientific area is considered by additionally involving models that predict skin enhancers' (compounds penetrating into skin to reversibly decrease the barrier resistance) effectiveness, models accounting for the experimental conditions, and mechanistic models. A list of the published QSPR models is summarised in Table 2.

5.1. QSPR models based on molecular size and/or lipophilicity parameters

Most of the published QSPR models for passive, diffusion-controlled skin absorption are linear regression equations involving two structural descriptors. They indicate that molecular size (molecular volume (MV) or MW) and hydrophobicity (expressed as log P) are the main determinants of the transdermal penetration. The models are described by the following general

equation:

$$\log K_p = a + b \log P - c\, MW \quad (9)$$

In fact, eq (9) encapsulates the main parameters that play a role in the membrane permeation.

Compound diffusivity is, in general, size dependent (large molecules diffuse more slowly than small ones). Various studies have investigated whether MW or MV is a more effective parameter to describe molecular size in the models (Barratt, 1995; Potts & Guy, 1995; Patel et al., 2002). However, it must be pointed out that for datasets with relatively similar values for the MV/MW ratio, MW could be used as it is easier to derive. Otherwise, the MV is considered to provide better estimates (Kielhorn et al., 2006).

Lipophilicity is experimentally determined as a partition coefficient (log P) or as a distribution coefficient (log D, referring to a pH-dependent mixture of neutral and ionic forms of the compounds). As a ratio of two concentrations at equilibrium, the partition coefficient is the net result of all intermolecular forces between a solute and the two phases between which it partitions (Geinoz et al., 2004).

Potts and Guy (1992) described a simple QSPR based on permeant size (expressed as MW) and hydrophobicity (log P) to model the permeability coefficients collected by Flynn, 1990. The following equation is reported after removal of one outlier:

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$$\log K_p = 0.71 \log P - 0.0061\, MW - 6.3 \quad (10)$$

$n = 93$, $r^2 = 0.67$

The above model has been discussed in a number of later studies (Moss et al., 2002b; Geinoz et al., 2004). The weakest point of the model is the incomplete statistics. On the other hand, the model has a clear mechanistic interpretation: as the permeants become more lipophilic, their permeability

increases due to better partitioning into the skin but, as they become larger, their diffusion into the skin is reduced.

In the later work of Moss and Cronin, 2002b an improved version of Potts and Guy model, using MW and log P as descriptors, was provided. It is based on 116 compounds and yields good correlation between K_p and selected descriptors with $r^2 = 0.82$ (a complete statistical analysis was reported).

Shen et al. [2014] adopted the Potts and Guy model to fragrance ingredients. Motivated by the limitation that assumes 100% skin absorption for chemicals which lack experimental data, the authors developed a practical and mechanistically reasonable skin absorption model (SAM) specific for fragrance chemicals. The model relies on the methodology of Kroes et al. [2007] that proposed three different default skin absorption ranges depending on the J_{max} values: <10% ($J_{max} \leqslant 0.1$ μg/cm^2/h) for poorly-absorbed chemicals; < 40% (0.1 μg/cm^2/h < $J_{max} \leqslant 10$ μg/cm^2/h) for moderately-absorbed chemicals; and ⩽ 80% (J_{max} >10 μg/cm^2/h) for highly-absorbed chemicals. For 105 compounds with experimentally determined *Kp* values, the Potts and Guy's QSPR model was updated for *Kp* calculation and subsequently corrected according to Cleek and Bunge [1993] for J_{max} calculation. In the final model log P and S were averaged from several software packages. Based on the SAM, the authors proposed a practical workflow for to predict skin absorption for fragrances. Applying it they demonstrated that none of the 131 chemicals used in the study had skin absorption >80%.

In the frame of the European Union COSMOS project (http://www.cosmostox.eu/), which developed computational models for predicting the chronic toxicity of cosmetic-related ingredients, the estimation of bioavailability after dermal administration was among the important tasks. To this end, Steinmetz et al. rebuilt Potts and Guy's QSPR by incorporating a larger dataset to increase the

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applicability domain (to cite the poster? Alov et al, SEURAT meeting, 2015?). A statistical tool to assess data quality (cf. confidence score, CS) was used to improve the model robustness. It is based on the number and variability of conflicting data (Steinmetz et al., 2014). The compilation of skin permeability coefficient values from the literature resulted in 343 different K_p values being compiled for 226 compounds. Fifty-five of these compounds have more than a single K_p value, hence the arithmetic means and the confidence scores were calculated. Physico-chemical properties, i.e. MV and lipophilicity (XLogP) were calculated with the Chemistry Development Kit (CDK) within KNIME or EPI Suite. The model was validated with 10-fold cross-validation, which led to CS-adjusted RMSE (Root Mean Square Error) of 0.79 ± 0.2. The model is freely available through the COSMOS KNIME WebPortal (http://knimewebportal.cosmostox.eu/).

The non-linear dependence of skin transport on chemical properties, particularly when diverse structures with broad range of log P values are considered, is of great interest for researchers. Parabolic dependencies on log P have been incorporated in some models to account for the non-linear characteristics of the structure-property relationships (e.g. Lien and Gao, 1995). A non-linear regression QSPR model (SKINPERM QSPR model) was also developed by ten Berge (2009) using the measured K_p through human skin *in vitro* as a dependent variable and log P and MW as independent variables. The training set consisted of substances with a wide range of lipophilicity (log P between - 4.49 and 6.13). In total 182 measured permeability coefficients were used. The model is based on the assumption for two pathways of permeation in the SC – the transcellular route through the corneocytes and the intercellular route through the extracellular lipids (Fig. 2). A test set of 27 structures was used for external validation. It is reported that the predicted values are mostly within one order of magnitude of the experimentally observed values (no quantitative estimation of the external prediction is given). The model slightly overpredicts hydrophilic substances as reported in the later study of monopropylene glycol and dipropylene glycol (Fasano et

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al., 2011). The reason, according to the authors, is underrepresentation of hydrophilic substances in the training group of the model. It is suggested that highly hydrophilic compounds do not cross the SC through the intercellular lipid matrix and, essentially, the only pathway available to these molecules is through the corneocytes. In this case, J_{ss} and K_p are related only to MW and log P has no influence. Otherwise, log P is a determinant of the relative importance for the lipid intercellular pathway and the aqueous transcellular pathway across the SC (Fasano et al., 2011).

The maximum flux is a valuable parameter of a solute's dermal permeation. The advantage of J_{max} compared to K_p is that it does not depend on the formulation applied (Kroes et. al., 2007; Zhang et al., 2009). However relatively few studies have predicted J_{max} as a dependent variable in QSPR models. Kasting et al. (1987) developed a predictive model of log J_{max} for 35 diverse drugs based on octanol solubility (log S_{oc}) and MV. Magnusson et al. (2004b) developed a regression model to predict J_{max} values from aqueous solution across human skin with MW only as a significant parameter:

Commented [CM27]: Note, this statement is repeated from above, but it is important!

$$\log J_{max} = -0.019MW - 3.90 \quad (11)$$

$n = 87$, $r^2 = 0.847$, $p<0.001$

The model was validated on different sets of compounds and a final model included all 278 entries (multiple entries per compound). The model has $r^2 = 0.688$. The addition of other physicochemical parameters such as M_{pt} and hydrogen bond (HB) acceptor capability only slightly improved the regression. The later work of Zhang et al. (2009) outlined that J_{max} for similar sized phenolic solutes showed a bilinear relationship with lipophilicity. The key conclusion was that for more lipophilic solutes, the dependence of J_{max} on lipophilicity resulted from variations in SC solubility, and not from diffusional or partitioning barrier effects at the SC–viable epidermis interface.

5.2. Multiparameter models

Commented [CM28]: I am not really sure of the exact definition of multiparameter here…. Potts and Guy QSAR is effectively multi (two) parameter so what is the difference…

Lipid-water partition coefficients, solubility, melting point, molecular size and hydrogen bonding have been recognised as the main structural determinants of structure – skin penetration relationships. A number of multiparameter models have been proposed in the literature extending the approaches broadly referred to as QSPRs above. Such multiparameter models incorporate more descriptors and thus may result in improved fit. In addition, inclusion of more structural parameters in the QSPR equations could help for in a better mechanistic understanding (Mitragotri et al., 2011), but may be restrained by statistical criteria if techniques such as regression analysis are used.

The transformed Potts & Guy and Roberts & Sloan equations correlate the maximum flux of solutes with their MW, as well as aqueous (S_{aq}) and lipid (isopropyl myristate, S_{ipm})solubilities. . The basis for the dependence of the maximum flux on S_{aq} as well as S_{ipm} has been attributed to the existence of a high-capacity lipid-aqueous series pathway in addition to a parallel lower-capacity lipid-only pathway through the SC (Roberts and Sloan, 1999, 2000).

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Commented [AW30]: Is this the transcellular route?

Linear free-energy relationship (LFER) models are based on a number of physicochemical parameters relevant to solute solvation processes (Abraham et al., 1997; Abraham and Martins, 2004; Zhang et al., 2012). The model uses the following descriptors of the penetrants: HB donor acidity, HB acceptor basicity, dipolarity/polarisability, excess molar refractivity (MR), and McGowan's characteristic volume (the MV calculated by a 2-D fragment contribution method). As such, it attempts to reflect the importance of molecular size, i.e. in the MV term, and log P is represented indirectly in the form of MV, polarisability, MR and HB activity.

The importance of hydrophobicity, molecular size and HB ability to model skin absorption was also mentioned by Patel at al. (2002). They developed a multiple linear regression (MLR) QSPR models for a training set of 158 compounds. The most significant parameters were logP, MW,

sssCH (the sum of E-state indices for all methyl groups) and ABSQon (the sum of absolute charges on oxygen and nitrogen atoms).

The aim of the work of Magnusson et al. (2004a) was to develop simple rules for rapid screening of compounds with potentially high dermal absorption by predicting J_{max}. The model was based on MW, M_{pt}, log P, log S and the number of atoms available for HB - subdivided into HB donor (HB-d) and acceptor (HB-a) atoms. According to the authors, these properties reflect the fundamental determinants of flux - size, polarity, and HB capacity. Linear discriminant analysis was used for model derivation with the following boundary values reported:

(i) Bad penetrants: MW > 213g/mol; $M_{pt} \geq 223$K; HB-d ≥ 0; HB-a ≥ 3; log P > 1.2; log S < -1.6

(ii) Good penetrants: MW $\leq$ 152g/mol; $M_{pt} \leq 432$K; HB-d ≤ 2; HB-a ≤ 3; log P < 2.6; log S $\geq$ -2.3

The success of the predictor combinations was quantified with the most significant prediction from the combination of three descriptors MW/ HB/ log P or MW/ log S/ M_{pt}, with a correct prediction rate of approximately 70%.

Xu et al. (2013) further elaborated the discriminant rules and reduced them in number to two. Thus solutes with MW $\geq$ 400 or log P $\leq$ 1 or log P $\geq$ 4 were considered poor penetrants. Further these authors proposed an U-optimal distance-based design procedure for the selection of training and test sets that meet the conditions of having a wide coverage of the structural space, maximal diversity within training and test sets and maximal similarity between them. For that purpose they use a large candidate set of 4534 solutes.

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The study of Baert et al. (2007) on a set of 116 compounds from the literature using 1630 parameters is interesting from a statistical point of view. The authors classified the compounds into

a distinct number of permeability classes using the CART (classification and regression trees) methodology and developed statistical models using a boosted CART, BRT approach and MLR analysis. The best models were based on lipophilicity/ hydrophobicity and molecular stereochemical complexity.

Basac et al. (2007) developed multiparameter QSPR models using 101 compounds from the Patel et al. (2002) dataset. The models were based on topostructural, topochemical, shape or three-dimensional (3D) descriptors and quantum chemical indices. The statistical methods applied were ridge regression (RR), principal components regression (PCR) and partial least squares regression (PLS). Full statistical analysis of the models has been reported. The cross-validated correlation coefficients for the full set and subsets were 0.67 – 0.87. The RR results were found to be superior to PLS and PCR regressions. The models indicated that HB descriptors, molecular size, branching and cyclicity can be highly significant in predicting dermal absorption and can be considered as general descriptors necessary for its modelling.

An attempt to elucidate how skin permeability relates to the skin sensitisation potential of chemicals (skin permeability has been identified as a necessary step in the OECD AOP for skin sensitisation) was performed by Alves et al. (2015) who derived QSAR models to predict human skin permeability by applying the random forest method (RFM). The curated dataset included 186 unique compounds with log K_p values in the range from -5.52 to -0.69, retrieved from the literature (Chauhan and Shakya, 2010; Flynn, 1990). A number of 2D structural descriptors were calculated by the DRAGON (Talete, SRL, Milan, Italy) and HitQSAR software (Kuz'min et al, 2008). The best RFM QSAR models were compared to those obtained by the DERMWIN module in the EPISuite package (US EPA, 2006); the latter estimated log K_p by the two parameter (log P and MW) MLR model. The best RFM model showed better external predictivity than the DERMWIN model (predictive q^2 of 72% vs. 43%, respectively) considering the applicability domain restriction

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(the coverage of the chemical space 77% vs. 100%, respectively). When compared to the same set of compounds (143 compounds, 100% coverage), the predictive accuracy of both models more similar (71% vs. 66%, respectively).

In the more recent multiparameter studies there is a tendency toward considering the non-linear nature of the skin penetration in the models. Thus, some studies investigated the possible non-linearity of the data and use further non-linear methods for modelling. Moss et al. (2009) revealed inherent non-linearity of the used skin permeability dataset by applying principal component analysis (PCA) and further explored the utility of Gaussian processes to develop a predictive model. The authors compared their model with previously published QSPR models and a single linear network model and concluded that the non-linear approach was more appropriate for the analysis of the dataset employed. Fatemi and Malekzadeh (2012) developed linear and nonlinear models based on MLR and artificial neural network (ANN) methods. The dependent variable was the experimental flux (in log scale). The CODESSA software was used to generate the molecular descriptors. No priority was given to any of the models in the study, however consideration of the statistical parameters indicated ANN were slightly better. The better performance of non-linear models was described by Neely at al. (2009) using ANN.

In summary, the recent trend in the QSPR modelling using multiparameter models is to explore wider and more diverse datasets with structures described by a large number of descriptors and to combine various statistical methods to derive predictive models. Some of these studies have focused on the methodological aspects aiming at testing and comparing different statistical procedures, others attempted to obtain a more detailed insight into the mechanisms of absorption. Generally, careful attention should be paid to the physicochemical and biological meaning of a model, otherwise the interpretation of models can be quite complicated and not justified mechanistically.

5.3. QSPR models for transdermal enhancers

Commented [AR36]: Not only QSPRs, also molecular modelling – adapt heading to "Modelling…" ?

Penetration enhancers are designed to facilitate the transport of compounds with limited percutaneous absorption and thus are of interest for delivery systems in the pharmaceutical and cosmetic industries. Their effectiveness is measured as an Enhancement Ratio (ER), which is the ratio of the flux in the presence of a fixed concentration of an enhancer to the delivery rate when the enhancer is missing in the formulation. Mechanisms of enhancement include interaction with intercellular lipids of the SC, interaction with intracellular proteins of the corneocytes or increasing partitioning of the solute into the SC due to the presence of the enhancer (Iyer et al., 2007). Modelling the effectiveness skin penetration enhancers is a relatively new field and classical QSPR models may help predict the ER ratio of enhancers. In more recent studies experimental and molecular modelling approaches have been applied to help in elucidating the mechanisms of action of the enhancers.

Karande et al. (2005) investigated more than 100 enhancers representing several chemical functionalities. Using Fourier transform infrared spectroscopy they showed that, regardless of their chemical nature, the enhancers perturb the skin barrier via extraction or fluidisation of the lipid bilayers. They proposed two kinds of models, respectively, for extractors and fluidisers. The models correlated the ratio ER/IP (IP, irritation potential) with dominant molecular features that govern changes in the microscopic organisation of the SC (log P, HB capacity, polarity, and dispersion). These models point to the main constraints in optimising the balance between the potency and membrane safety of the enhancers. Based on the models, the authors designed more than 300 potential enhancers that were screened *in silico* and subsequently tested *in vitro* for molecular delivery. Of them, 110 showed ER/IP > 3.8 thus confirming the usefulness of the models.

A dataset of dermal enhancers was collated by Pugh et al. (2005) and classified using

discriminant analysis. The dataset has been further exploited using several machine learning methods, including the K-nearest-neighbour regression, single layer networks, radial basis function networks and the SVM classifier (Moss at al., 2012). The best classification results were obtained with the SVM method without dealing with imbalanced data.

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Iyer at al. (2007) reported QSPR models for four skin penetration enhancer datasets differing in the structures of the enhancers and penetrants. The models use classical and 4D-fingerprint descriptors. Based on the different descriptors in the best QSPR models for the different datasets, the authors conclude that there are different mechanisms of penetration that depend on the chemistry of the enhancer as well as that of the penetrant molecule.

Zheng et al. (2008) used classical QSPR models and a model, denoted as MI-QSAR (Membrane-Interaction QSAR), to investigate penetration enhancers. The data involved 103 transdermal penetration surfactant-like and nonpolar enhancers, of different chemical nature, collected from experimental studies. In total, 24 classical QSAR intramolecular (HOMO, LUMO, dipole moment, MV, MW, MR, polar surface area (PSA), number of HB acceptors and donors, Kier and Hall topological descriptors, partial atomic charges etc.) and intermolecular (aqueous and 1-octanol solvation free energies, log P, hypothetical phase transition temperatures, etc.) descriptors were used. QSPR models were built and optimised by MLR and the genetic function approximation (GFA). The MI-QSAR models featured descriptors determined from the trajectories of molecular dynamics (MD) simulation of a transport of an organic compound through a phospholipid monolayer or bilayer (dimyristoylphosphatidylcholine molecules, DMPC, used in MD). The most informative MD parameter was the integrated spatial difference which captured the time-average change in the structure of the monolayer molecular assembly due to the presence of an embedded molecule, in this case, a penetration enhancer. This descriptor dominated the MI-QSAR models and greatly reduced their size and complexity as compared to the QSAR models developed using classic

intramolecular descriptors derived solely from the structure of penetration enhancers of comparable statistical characteristics. The integrated spatial difference parameter is relatively straightforward to interpret: the bigger the "holes" created in the monolayer by the penetration enhancer, the greater the value of the ER. The next informative, but less significant descriptors, were the classical aqueous solvation free energy and dipole moment (in one model) and PSA and Kappa topological index (in another model). Overall, the MI-QSAR models indicated that good nonpolar penetration enhancers make larger "holes" in the monolayer and preferentially enter the monolayer. The study was a step forward to a better understanding of the mechanisms of enhanced transport through the skin and supports the evidence about interactions of the enhancers with intercellular lipids of the SC, which leads to a disorganisation of these highly ordered structures and, thus, enhances the intercellular diffusivity through the SC. Additionally, it can increase the partition of the compound into the SC.

To explore the structure–activity relationship for terpenes as transdermal penetration enhancers, unsaturated menthol analogues were synthesised and evaluated *in vitro* by Chen et al. (2013). Molecular modelling was applied to investigate the enhancer induced alteration in different skin lipid domains. The results suggested that polar head groups of the SC lipids are the main binding site for enhancer's action. Thus, the authors concluded that the compounds studied enhanced drug transport by interacting with the polar domain of the skin lipids, instead of affecting the arrangement of the hydrophobic chains. According to the docking results the compound with the best enhancement activity had the greatest affinity to the polar groups of the ceramides. Therefore, its preferential interaction with the polar group of the lipids was offered as a reasonable explanation for its best enhancement activity.

The opportunities of using MD methodology to predict the mechanism of action of skin enhancers were well reviewed by Notman and Anwar (2013). The limitations related to the long

time- and length-scale processes and the main challenges related to the lack of definitive experimental data about the organisation of the skin lipids were discussed. The MD case studies were reviewed including DMSO coarse grained and atomistic simulations, ethanol atomistic simulations and oleic acid coarse-grained simulations.

5.4. Models accounting for the formulation and experimental conditions

The models of Potts and Guy, and Abraham and Martins, together with their variations are based on measurements from an infinite dose in aqueous solution, which is not sufficient to predict absorption from a more complex multicomponent vehicle and under finite dose conditions, which is a more realistic exposure scenario. As a determinant of percutaneous absorption, it is well known that the delivery vehicle is as important as the penetrant itself. An increase in the complexity of the delivery vehicle (formulation) also increases the potential for interactions to occur between the chemical, vehicle and skin consequently affecting the absorption process. *In vitro* studies have shown that the interactions arising within the chemical–vehicle–skin system synergistically alter the chemical's ability to partition into and diffuse through the skin barrier (Karadzovska and Riviere, 2013). Therefore, in order to be useful for realistic risk assessment estimates, vehicle and mixture component effects should also be considered in the QSPR models. These facts motivated the development of the chemical mixture models (Riviere and Brooks, 2005, 2007, 2011). In addition to the descriptors involved in the models of Potts and Guy and Abraham and Martins, these models incorporate properties of the solvent or the mixture through the so-called "mixture factor" (MF) which account for mixture interactions by using physicochemical properties of the mixture components. The MF is calculated based on percentage composition of the vehicle/mixture components and physicochemical properties selected using PCA (Riviere and Brooks, 2005, 2007, 2011).

Modelling the effect of mixture components on the permeation, Ghafourian et al. (2010a, b) found that compounds formulated in vehicles with small boiling and melting point gaps would be expected to have higher permeation through skin. The models developed by Samaras et al. (2012) incorporate the effects of the *in vitro* experimental conditions by using parameters such as skin thickness, exposure type, and states of pre-hydration or occlusion of the skin. In the linear models the most prominent factors influencing permeability were the donor concentration, lipophilicity, size and polarity of the penetrants and the difference between the melting and boiling points of the vehicles; in the non-linear models skin occlusion played the most significant role.

Commented [AW38]: Did they offer an explanation for this?

Gutha et al. (2014) proposed an *in silico* prediction model that considered mixture-related effects. The authors adopted the MF approach of Riviere and Brooks (2005, 2007, 2011) to predict dermal absorption of new substances from specific formulations. The data set contained 56 test substances applied in more than 150 mixtures in *in vitro* experiments utilising human and rat skin. The compounds' structures were described by the Abraham descriptors; the physicochemical parameters for the mixture ingredients were log P, the topological polar surface area (TPSA), HBA and HBD. In total, 87 MFs were calculated as descriptors for each mixture of a test substance. The MLR equation for the penetrant-predictive mixture model involved the five Abraham descriptors and MF; in addition, the species indicator and the receptor fluid indicator variables were set. The final valid model included R2, TPSA and the species indicator, however, statistical analysis was relatively poor (r^2 (goodness of fit) = 0.38, Q^2_{LOO} (internal validation by leave-one-out procedure) = 0.35, Q^2_{EXT} (external predictivity) = 0.41). In addition, a 'formulation-predictive mixture' model was developed, in which the substance-specific descriptors were replaced by a class variable (a parameter that bundles the experimental outcome for one specific substance applied in several formulations). This model yielded a better fit (r^2 = 0.75) and predictivity (Q^2_{EXT} = 0.73) and could be applied during formulation development to assess the absorption effects.

As already discussed, most QSPRs are developed for infinite dose conditions. In practice, dermal exposure mostly occurs under finite dose conditions. A simple model to predict finite dose dermal absorption from infinite dose data (K_p and lag time) and the SC/water partition coefficient ($K_{SC/W}$) was developed by Buist et al. (2010). For the predictions QSPRs were used to estimate the $K_{SC/W}$. The predicted values were either similar to the measured *in vitro* values or overestimated them.

Kasting and co-workers developed a model that takes into account the transient conditions or the time dependency of skin penetration (reviewed in Dancig et al., 2013). These are actually real-life exposure situations, such as a finite dose, short exposure times, multiple exposures and/or removals. In addition, the model takes into account the skin heterogeneity. The simulations require only the chemical structure. The partition and diffusion coefficients were estimated from physical properties which can be obtained exclusively from the molecular structures. The model is implemented in a web-based program (http://www.cdc.gov/niosh/topics/skin/finiteSkinPermCalc.html).

5.5. Mechanistic models

Commented [AW39]: This implies that QSPR models are not mechanistic, which is not entirely the case. Should we reword this to "Mass-balance models"

The majority of the QSPR models are developed with the assumption that the intercellular lipid pathway is the route of transdermal permeation and the corneocytes are impermeable. However, as mentioned above, it appeared that the lipid-pathway models are not suitable for to predict the skin permeability of hydrophilic solutes. Generally, statistical QSPR models underpredict the skin permeability of hydrophilic solutes by 2–6 orders of magnitude (for log P < -2) and thus they are limited to hydrophobic compounds (Chen et al., 2013).

Mass-balance, or mechanistic, models attempt to predict skin permeability by taking into account the heterogeneous structure of the skin barrier rather than assuming it as a pseudo-homogenous membrane. Usually the skin is presented by the "brick-and-mortar" model – bricks represent the

corneocytes and mortar represents the lipid phase (Talreja et al., 2001). The transport of solutes through different routes of diffusion (pathways of transdermal permeation) is considered.

The model of Mitragotri (Mitragotri, 2003) considered four routes of diffusion: (i) free-volume diffusion through lipid bilayers; (ii) lateral diffusion along lipid bilayers; (iii) diffusion through pores; and (iv) diffusion through shunts. The model relates the aqueous pores in the SC lipids and shunts to the aqueous pathway, while the corneocytes are considered impermeable. The contribution of the shunts to the skin permeability is estimated to be independent of molecular size and property. The model appears to predict the skin permeability of hydrophilic solutes well.

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The biphasic microtransport model (Wang et al., 2006, 2007) considers both the intercellular and transcellular pathways, but suggests that SC permeation for most compounds is dominated by the transcellular pathway regardless of their lipophilicity. It fails to give a satisfactory prediction of the skin permeability of hydrophilic solutes due to the fact that the solute transfer across the lipid phase is represented by a transfer coefficient, obtained by fitting to skin permeability data which include mostly hydrophobic solutes.

The model of Chen et al. (Chen et al., 2010, 2013) described three types of mass transfer of solutes as follows: (i) in the lipid matrix; (ii) in the corneocyte phase, and (iii) across the lipid–corneocyte interface. The solute transfer in the lipids contributes to both the intercellular pathway and the transcellular pathway due to its continuous nature, whereas the solute transfer in corneocytes and across the lipid–corneocyte interface is related only to the transcellular pathway. Hydrophilic solutes are still considered to be able to partition into the SC lipid according to log P, without separately lending to aqueous pores. The results indicate that the transcellular pathway is very important for the transdermal permeation of hydrophilic solutes and can contribute to more than 95% of the overall skin permeability.

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6. Conclusions

Commented [AW43]: Should we mention the use of QSPRs in the dermal TTC approach, as a possible application in safety assessment?

In recent years many efforts have been invested in developing predictive and reliable QSPR models for skin permeability. Some simple models have been derived that are quite useful for screening purposes. A good example is the Potts and Guy model, which provides adequate predictions based on a simple two-parameter regression equation and has been widely used for many years. However, the complex biological mechanisms regulating dermal absorption and the numerous factors involved in this process represent a challenge and set higher requirements to the theoretical predictive approaches, whose use is increasingly encouraged in both pharmaceutical and safety assessment area.

In the present review, a comprehensive discussion on the currently available methods for the prediction of skin absorption is presented, focusing on quantitative structure-permeability relationships. Limitations and strengths of different approaches are highlighted together with the emergent issues and perspectives. One of the key limitations in the prediction of skin absorption stems from the data used to develop the QSPR models. Many of these models are developed from datasets with limited chemical heterogeneity, while others are compiled from various investigators and laboratories employing different experimental protocols resulting in a high variability of data. The experimental skin permeability datasets have mostly been collected for aqueous vehicles, using infinite conditions. This leads to an additional limitation of the models, since in the real-life situations finite doses are applied for short exposure times.

Based on the analysis of the existing models and following the good practice for developing robust and predictive QSPR models several recommendations can be specified for the purposes of the skin permeability QSPRs:

(i) High-quality data are required. It is recommended that the data be adjusted for similar skin origin and experimental conditions. Additionally, an assessment of the chemical space of the current data is recommended. Different forms of the dependent variable (permeability parameter) can be experimentally derived, e.g. the maximum flux could be a more suitable parameter than the permeability coefficient to account for dermal absorption potential;

(ii) Special attention is to be given to the outliers in the data including applicability domain outliers. The process of the outlier detection should also consider mechanistic reasoning;

(iii) Special attention is also to be paid to variable scaling and descriptor significance, as models based on non-significant descriptors do not afford mechanistic insights and may lead to overfitting of the data. Selection of the most informative descriptors is to be performed on a rational base that is directly related to the mechanism of the skin permeability;

(iv) A combination of linear and non-linear methods is to be considered in the modelling process. Such a combination could allow for a more adequate description of the behaviour of solutes of different physicochemical nature;

(v) Experimental conditions are to be taken into consideration when the training and test sets are generated as they could have a significant impact on the prediction results. Especially, the effects of the non-aqueous solvents and formulations (including vehicles and skin enhancers) should be considered and some modelling efforts are to be put on simulation of finite dose conditions and on considering the heterogeneous skin structure.

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Commented [AW45]: On the other, wouldn't infinite dose conditions lead to a more conservative (larger) assessment of absorption potential?

Table 2. Summary table of the QSPR models for skin permeability in chronological order (for the

abbreviations see the list below the table)

Commented [AR46]: Can no. of compounds in test and training sets be given?

Model	Parameter * ---------- data source	No. of com-pounds	Statistical method	Significant descriptors	Note
Flynn (1990)	K_p ---------- literature sources (Flynn data set)	94	-	MW, log P	qualitative model
El Tayar et al. (1991)	K_p ---------- literature sources	18 ÷ 22	LR	**Δ**logP(o-h), logP	
2-parameters model of Potts & Guy (1992)	K_p ---------- Flynn dataset (Flynn, 1990)	93	LR	MW, log P	no outlier analysis
3-parameters model of Potts & Guy (1995)	K_p ---------- Flynn dataset	37	LR	MV, Hd, Ha	
Wilschut et al. (1995)	K_p ---------- various literature sources	99			
Barratt (1995)	K_p ---------- Flynn dataset	60 ÷ 91	LR	MV, log P, mpt	hydro-cortisones excluded from the data set
Lien & Gao (1995)	K_p ---------- Flynn dataset	16 ÷ 23	LR, parabolic	MW, log P, $(\log P)^2$, Hb	*in vivo* data used for the lipophilic vehicle

Model	Parameter * ---------- data source	No. of com-pounds	Statistical method	Significant descriptors	Note
	========== R *in vivo* ---------- (Lee et al.1994)		regression		(ethanol and panasate 800)
Abraham LFER models (Abraham et al, 1995, 1997)	K_p ---------- various literature sources	46 (1995) 53 (1997)	LR	Abraham solute descriptors: $\Sigma\alpha^{H}_2$, $\Sigma\beta^{H}_2$, π^{H}_2, R_2, Vx	
Kirchner et al. (1997)	K_p ---------- Flynn dataset + regulatory data (Health Canada)	114 (51 from Flynn data set)	LR	MV, log P	K_p for 63 compounds calculated with the Potts & Guy model
Cronin et al. (1999)	K_p ---------- Flynn dataset; (Kirchner et al, 1997)	107 ÷ 114	LR	MR, log P, H_{LP}, $^4\chi^v$	
Pugh et al. (2000)	log (D/h) ---------- (Wilschut et al. 1995; Degim et al, 1998)	41	PCA and LR	Charge, MW	57 log K_p and log (D/h) values used
Lim et al. (2002)	K_p ---------- Flynn dataset	92	LR, ANN	QC descriptors: dipole, polarizability, sum(N,O), sum(H)	

Model	Parameter * ---------- data source	No. of com-pounds	Statistical method	Significant descriptors	Note
Moss et al. (2002)	K_p ---------- Flynn dataset; (Kirchner et al, 1997; Johnson et al, 1995; Degim et al, 1998)	116	LR	Log P, MW,	steroid data replaced; data re-analysed
Patel et al. (2002)	K_p ---------- Flynn dataset & (Wilschut et al, 1995)	143 ÷158	LR	Log P, MW, SsssCH, ABSQon	
Estrada et al. (2003)	flux ---------- (Ursin et al., 1995)	12 commercial solvents	LR	Methyl groups bonded to heteroatoms or to CH_2 groups	*in vivo* living skin, topological sub-structural approach in the modelling
Moody & MacPherson (2003)	K_p ---------- Flynn dataset; (Kirchner et al, 1997)	39 ÷ 71	LR	MW, log P, surface tension in water	
Pannier et al, (2003)	K_p ---------- Flynn dataset; data from Abraham et al. (1997)	37-94	Cluster analysis (ANFIS)	MW, log P; Abraham solute descriptors: $\Sigma\alpha^H_2$, $\Sigma\beta^H_2$, π^H_2, R_2, Vx	

Model	Parameter * ---------- data source	No. of com-pounds	Statistical method	Significant descriptors	Note
Abraham LFER model (extended) (Abraham & Martins, 2004)	K_p ---------- various literature sources	119	LR	Abraham solute descriptors: $\Sigma\alpha^H_2$, $\Sigma\beta^H_2$, π^H_2, R_2, Vx	K_p values adjusted for ionisation and temperature
Magnusson et al. (2004)	J_{max}	278	LR		Jmax values estimated from the product of the reported Kp and Saq)
Geinoz et al. (2004)	K_p ---------- Flynn dataset; (Kirchner et al, 1997); various literature sources	20 ÷ 107	Stepwise LR	MW, MR, log P, Vw Abraham solute descriptors: π^H_2, $\Sigma\alpha^H_2$, $\Sigma\beta^H_2$	
Karande et al. (2005)	ER / IR (enhancement ratio / irritation potential) ---------- own data	102 enhancers (extractors and fluidisers)	Non-linear relations	Log P, Hb, polarity, dispersion	Different equations for extractors and fluidisers
Chemical mixture model (Riviere & Brooks, 2005)	K_p ---------- own data	16 compounds 288 treatment combinations	LR	Compounds: Abraham solute descriptors: $\Sigma\alpha^H_2$, $\Sigma\beta^H_2$, π^H_2, R_2, Vx Vehicles: MF	Vehicle: water, ethanol, propylene glycol

Model	Parameter * ---------- data source	No. of com-pounds	Statistical method	Significant descriptors	Note
Pugh et al., 2005	ER ---------- literature sources	73 skin enhancers	Discriminant analysis	carbon chain length, HB numbers, MW	
Katritzky et al. (2006)	K_p various literature sources	143	LR; ANN	log Pexp, Kier & Hall index; rotational entropy; Zefirov Partial Charge, H-acceptor FCPSA; molecular fragments	CODESSA PRO and ISIDA software used
Ding et al. (2006)	$C_{E=10}$ (Chantasart et al. 2004)	16 skin enhancers	Stepwise LR	Log P, position of the hydroxyl group	branched-chain alkanols used
Majumdar et al. (2006)	J_{max} Flynn dataset	62-76	LR	MW, solubilities in octanol (Soct) and water (Saq)	Roberts & Sloan (transformed Potts & Guy) model
Neumann et al. (2006)	Kp (Wilschut et al. data set; other sources	110	RR and *k*-nearest-neighbour	SOLV, log P, MW	
Basak et al. (2007)	K_p (Patel et al. 2002)	22 ÷ 101	RR, PCR, PLS	hydrogen bonding descriptors, molecular size, branching and cyclicity	Kirchner at al., 1997 dataset dropped from the data
Iyer et al., (2007)	ER various literature sources	Four datasets: 61, 44, 42, and	MLR	classic QSAR descriptors and	4D-fingerprint descriptors developed

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Model	Parameter * ---------- data source	No. of com-pounds	Statistical method	Significant descriptors	Note
		17 compounds		4D-fingerprints	by the 4D-QSAR paradigm.
Stoick et al. (2007)	K_p various literature sources	CHEP +10 structural analogues	LR	MW, log P	DERMWIN™ model (US EPA, 2006)
Baert et al. (2007)	K_p literature sources (Magnusson et al, 2004 ; Patel et al., 2002 ; Buchwald et al, 2001)	116	PCA, CART, stepwise LR	10 most significant: lipophilic, 2D topological, 3D MoRSE, shape-related, etc.	1630 descriptors generated
Iontophoretic model (Mudry et al, 2007)	flux through pork skin characterized by to C+ own data	16 cations	LR & nonlinear regression	MW, cation hydrodynamic radius, cationic mobility	
Luo et al. (2007)	K_p literature and regulatory sources	340		Log P, χ^0, SsssCH	MDL's QsarIS software for the other descriptors; 306 compounds out of 340 used in the training set
Chemical	K_p (*in vitro* PSFT	10 ÷ 12	Stepwise LR	Compounds: Abraham solute descriptors:	24 mixtures

Model	Parameter * ---------- data source	No. of com-pounds	Statistical method	Significant descriptors	Note
mixture model (extended) (Riviere & Brooks, 2007)	diffusion cells) AUC (IPPSF *ex vivo* model) own data	compounds 50 ÷ 288 treatment combinations		$\Sigma\alpha^{H}_2$, $\Sigma\beta^{H}_2$, π^{H}_2, R_2, Vx Vehicles: MF	(*in vitro* PSFT diffusion cells) 5 mixtures (IPPSF *ex vivo* model)
Yamaguchi et al. (2008)	D_{SC} and D_{VED} *in vitro* own data on rat skin	10	LR, parabolic regression	Log P, HBD	
MI-QSAR model (Zheng et al. 2008)	ER(*J*) skin penetration enhancement various literature sources	103 enhancers penetrants: hydrocortisone & hydrocortisone acetate	LR	integrated spatial difference (MD parameter), aqueous solvation free energy; dipole moment; PSA, Kappa topological index	24 classical QSAR descriptors derived; MD parameter derived from MD trajectories of simulations in DPMC layers
Liou et al. (2009)	K_p own data	13 non-steroidal anti-inflammatory drugs	LR	MW, solubility parameter □, biological parameters of the skin (elasticity and hydration of the	Model is workable for drugs with Log P < 2

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Model	Parameter * ---------- data source	No. of com-pounds	Statistical method	Significant descriptors	Note
				skin)	
Neely et al. (2009)	K_p Oklahoma state university database (OSU-KP)	160	GA, ANN, LR	most significant: L3s, log P, nArCOOR, number of single bonds, polarity	over 1500 descriptors generated with CODESSA and Dragon software
ten Berge (2009)	K_p (Vecchia & Bunge, 2003)° +12 additional compounds	182	Nonlinear regression	MW, log P	
Zhang et al. (2009)	J_{max} own data	10	nonlinear regression	Log P	Similar size of the structures
Buist et al. (2010)	finite dose absorption, (%) own data		Equations based on Kp and lag time (infinite dose experiments		Used QSARs to estimate the $K_{SC,W}$
Chauhan & Shakya (2010)	K_p various literature sources	150-153/58 training set/test set	GA, iPLS	log P, Snar and hydrogen bond acceptors	e-DRAGON and ADME Pharma Algorithms-Abrahams descriptors

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Model	Parameter * ---------- data source	No. of com-pounds	Statistical method	Significant descriptors	Note
Ghafourian et al. (2010a)	K_p own data	12 compounds; 24 solvent mixtures	Stepwise LR	log P, $^9\chi_p$, SolBP–SolMP	TSAR 3D software
Ghafourian et al. (2010b)	Kp own data	96 new Kp values + 288 Kp values from (Riviere et al., 2005)	Stepwise LR	log P, $^9\chi_p$, SolBP–SolMP	TSAR 3D software
Lee at al. (2010)	P_e own data	61	MLR	PISA, donorHB, accptHB, glob; EA	44 non-proprietary structures provided in the table; PEG 400 used as the organic co-solvent
Chemical mixture model (extended) (Riviere & Brooks, 2011)	K_p (*in vitro* PSFT diffusion cells) AUC (IPPSF *ex vivo* model)	16 ÷ 20 compounds 119 ÷ 384 treatment combi-nations	Stepwise LR	Compounds: Abraham solute descriptors: $\Sigma\alpha^H_2$, $\Sigma\beta^H_2$, π^H_2, R_2, Vx Vehicles: MF (the best MF descriptors HBA, 1/Mp)	Vehicle: water, ethyl alcohol, propylene glycol, sodium lauryl sulfate, methyl-nicotinic acid

Model	Parameter * ---------- data source	No. of com-pounds	Statistical method	Significant descriptors	Note
	own data				
Fatemi & Malekzadeh (2012)	flux ---------- (Fiserova-Bergerova et al, 1990)	132	LR; ANN	7 electronic, quantum-chemical, topological parameters	Flux measured in $mg/cm^2.h$; CODESSA software used for descriptors
LFER model of Abraham (united) (Zhang et al, 2012)	K_p ---------- (Abraham and Martins, 2004; Singh et al, 1994); ---------- measurements of 18 ionized solutes	118	LR	Abraham solute descriptors: $\Sigma\alpha^H_2$, $\Sigma\beta^H_2$, π^H_2, R_2, Vx Extra terms for ionic solutes: J^+, J^-	Neutral and ionic solutes simultaneously included in the model
Moss et al., 2012	ER ---------- From Pugh et al., 2005	71 skin enhancers	Various machine learning methods	log P, log S, MW, carbon chain length, HB numbers	
Sun et al. (2012)	K_p ---------- literature sources	19-140	PCA, GP	MW, solubility parameter, log P, counts of the number of hydrogen bonding acceptor (HA) and donor groups (HD)	Human, pig, rodent, and synthetic membrane permeability data used

Model	Parameter * ---------- data source	No. of com-pounds	Statistical method	Significant descriptors	Note
Samaras et al. (2012)	flux ---------- various literature sources and EDETOX database	272 compounds (neat or in mixtures)	Stepwise LR, RT	Compounds: (donor), MW, vsurf G, SlogPVSA4, fiAB, VAdjMa Vehicles: BP−Mp(mix)	Models incorporate: membrane thickness and finite/infinite dosing; Vehicle: water, polyethy-lene-glycols, petro-latum, mineral oil
Chemical mixture model (artificial membranes) (Karadzovska & Riviere, 2013)	absorption through 3 artificial membranes ---------- own data	6 compounds 32 treatment combinations	Stepwise LR	Compounds: Abraham descriptors: $\Sigma\alpha^{H}_{2}$, $\Sigma\beta^{H}_{2}$, π^{H}_{2}, R_2, Vx Vehicles: MF Indicator variables for: - vehicles - saturation	Vehicle: propylene glycol, water, ethanol
Chen et al., 2013	ER ---------- own data	Four penetration enhancers	docking		Docking calculations performed using AutoDock software
Gutha et al., 2014	K_p ----------	56 compounds	MLR Stepwise	Compounds: Abraham descriptors: $\Sigma\alpha^{H}_{2}$, $\Sigma\beta^{H}_{2}$, π^{H}_{2}, R_2, Vx	Two models proposed:

Model	Parameter * ---------- data source	No. of com-pounds	Statistical method	Significant descriptors	Note
	own data	more than 150 mixtures	MLR PCR	Mixtures: MF (log P, TPSA, HBA, HBD) Indicator variables for species and receptor fluid Class variable	"penetrant-predictive mixture" model (moderate statistics) "formulation-predictive mixture" model
Shen et al., 2014	K_p ---------- Flyn data set EDETOX database	105 compounds	MLR	MW, log P	Model used for calculation of *Jmax* and percent absorption values of fragrance chemicals
Steinmetz et al., 2015	K_p ---------- literature sources	226 compounds	MLR	Log P, MW	Confidence Scoring used to improve robustness of the model
Alves et al., 2015	K_p ---------- Chauhan and Shakyia Flynn data set	186 compounds	RFM	2D DRAGON and SiRMS descriptors;	DRAGON and HitQSAR software used for calculation of the descriptors

* Log-form used as a dependent variable in the models with K_p, R, flux, D, AUC, Pe, $C_{E=10}$ and absorption.

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List of abbreviations used in Table:

3D MoRSE: 3D-MoRSE (3D-Molecule Representation of Structures based on Electron diffraction)

descriptors

ABSQon: Sum of absolute charges on oxygen and nitrogen atoms

accptHB: Number of hydrogen bonds that would be accepted by the solute in solution

ANN: Artificial Neural Network

ANFIS: Adaptive Neural Fuzzy Inference System

AUC: Area under the curve

BP: Boiling point

BP−Mp(mix): Difference between the boiling and melting points of the mixture (donor phase)

$C_{E=10}$: Aqueous solution concentration of an enhancer that could yield 10-fold permeant transport enhancement to the control (no enhancer present)

CART: Classification and regression trees

CHP: Hydroxyethylpiperazine, a commercial mixture of 1,4-piperazinediethanol, piperazine, hydroxyethylpiperazine, and water

D: Diffusion coefficient in the skin membrane

$D_{SC,}$ D_{VED}: Diffusion coefficients in stratum corneum (SC) and viable epidermis and dermis (VED)

DMPC: Dimyristoylphosphatidylcholine

(donor): Donor concentration (g/ml)

donorHB: Number of HB that would be donated in solution

EA (eV): Quantum mechanically calculated electron affinity

ER(J): Skin penetration enhancement: the ratio of hydrocortisone (HC) or hydrocortisone acetate (HCA) penetration with, and without, a common fixed concentration of the test enhance

fiAB: Fraction of molecules ionized as anion and cation at pH 7.4

FCPSA: Fractional charged partial surface area

GA: Genetic algorithm

glob: Globularity descriptor (molecular shape descriptor)

GP: Gaussian processes

H: Path length in the skin (see Eq. 1)

Ha: Hydrogen bond acceptor activity

Hb: Hydrogen bond forming ability (donor hydrogens + acceptor electron lone pairs)

Hd: Hydrogen bond donor activity

H_{LP}: Total number of lone pairs that can accept hydrogen bonds on the molecule

HBA: Hydrogen bond acceptor number

HBD: Hydrogen bond donor number

iPLS: Interval partial least-squares algorithm

IPPSF: Isolated perfused porcine skin flap model, an *ex vivo* biologically intact perfused tissue preparation shown to correlate to *in vivo* human dermal absorption

J^+, J^-: Extra terms for ionic solutes (J+ = 0 for anions, J− = 0 for cations; $J^+ = J^- = 0$ for neutral compounds)

Jmax: Maximum skin flux, mg/cm^2.h

Kp Permeability coefficient

$K_{SC,W:}$ Stratum corneum/water partition coefficient

L3s: 3rd component size directional *WHIM* index / weighted by atomic electrotopological states (WHIM: weighted-holistic-invariant molecular) (Todeschini et al., 1997), http://www.vcclab.org/lab/indexhlp/whimdes.html

Log P:	logarithm of the octanol/water partition coefficient
ΔlogP(o-h):	log P(octanol) – log P(heptane)
LR:	Linear regression
MD:	Molecular dynamics
MF:	Mixture factor (accounts for physicochemical properties of the vehicle/mixture components)
MLR	Multiple linear regression
Mpt:	Melting point
MR:	Molecular refractivity
MV:	Molecular volume
MW:	Molecular weight
nArCOOR:	Number of esters
PCR:	Principal components regression
Pe:	Normalised permeability
PISA:	pi (carbon and attached hydrogen) component of solvent-accessible surface area
PLS:	Partial least squares regression
PSA:	Polar surface area
PSFT:	*in vitro* porcine skin flow-through diffusion cells
R:	Rat skin permeability= log(%permeation/(100-%permeation)
R_2:	Excess molar refractivity, $cm^3\ mol^{-1}$)/10 (Abraham solute descriptor)
RFM	Random forest method
RR:	Ridge regression

RT: Regression tree

Saq: Aqueous solubility

SiRMS 2D simplex representation of molecular structure

SlogPVSA4: Sum of van der Waals surface area of atoms with log P contributions in the range of (0.1–0.15) (MOE, 2011)

Snar: Narumi simple topological index (related to molecular branching)

SolBP–SolMP: Difference between melting and boiling points of the solvent mixtures

SOLV: Solvation free energy in water computed with MOPAC2002 using the COSMO continuum solvation model

SsssCH: Sum of E-state indices for all methyl groups

sum (H): sum of charges of hydrogen atoms bonding to nitrogen or oxygen atoms

sum(N,O): sum of charges of nitrogen and oxygen atoms

toC+: Cation transport number in the skin

TPSA: Topological polar surface area

VAdjMa: Vertex adjacency information which depends on the number of heavy-heavy bonds (MOE, 2011)

Vx: McGowan characteristic volume of the solute in (cm3 mol−1)/100 (Abraham solute descriptor)

Vw: van der Waals volume

vsurfG: Molecular globularity–how spherical a molecule is, where values above 1 is non-perfect spheres (Cruciani, 2000)

π^{H}_{2}: Dipolarity/polarisability (Abraham solute descriptor)

$\Sigma\alpha^{H}_{2}$: Hydrogen bond donor acidity (Abraham solute descriptor)

$\Sigma\beta^{H}_{2}$: Hydrogen bond acceptor basicity (Abraham solute descriptor)

$^{4}\chi^{v}$: Fourth order valence-corrected molecular connectivity

χ^{0}: Zero order molecular connectivity chi index (quantification of both the molecular size and the degree of skeletal branching)

$^{9}\chi_{p}$: 9^{th} order path molecular connectivity index

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Declaration of interest

The authors declare no conflict of interest.

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