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Data Article

An updated database of human maximum skin fluxes and epidermal permeability coefficients for drugs, xenobiotics, and other solutes applied as aqueous solutions

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Dataset link: An updated skin permeation database of compounds applied as aqueous solutions in in vitro (Original data)

ABSTRACT

The dataset represented in this article is referred to by the review article entitled "Topical drug delivery: history, percutaneous absorption, and product development" (MS Roberts *et al.*, 2021) [1]. The dataset contains maximal flux (J_{max}), and permeability coefficient (k_p) values collated from In Vitro human skin Permeation Test (IVPT) reports published to date for various drugs, xenobiotics, and other solutes applied to human epidermis from aqueous solutions. Also included are each solute's physicochemical properties and the experimental conditions, such as temperature, skin thickness, and skin integrity, under which the data was generated. This database is limited to diluted or saturated aqueous solutions of solutes applied on human epidermal membranes or isolated stratum corneum in large volumes so that there was minimal change

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toxicology

in the donor phase concentration. Included in this paper are univariate Quantitative Structure-epidermal Permeability Relationships (QSPR) in which the solute epidermal permeation parameters (k_p, and J_{max}) are related to potential individual solute physicochemical properties, such as molecular weight (*MW*), *log* octanol-water partition coefficient (*log P*), melting point (*MP*), hydrogen bonding (acceptor - H_a, donor – H_d), by scatter plots. This data was used in the associated review article to externally validate existing QSPR regression equations used to forecast the k_p and J_{max} for new therapeutic agents and chemicals. The data may also be useful in developing new QSPRs that may aid in: (1) drug choice and (2) product design for both topical and transdermal delivery, as well as (3) characterizing the potential skin exposure of hazardous substances.

Specifications Table

Subject	Pharmaceutical Sciences
Specific subject area	Determination of human skin absorption parameters based on in vitro permeation test (IVPT) data
Type of data	Table (in Mendeley repository) Figures Text file
How data were acquired	Performed literature search, extracted the data using DataThief III wherever relevant from the published reports, collected experimental result parameters for solutes along with their physicochemical properties, and tabulated in Microsoft Excel.
Data format	Raw Analyzed
Parameters for data collection	Permeability, steady-state flux, maximum flux, stratum corneum solubility, stratum corneum partition coefficient, in vitro absorption profiles through human skin
Description of data collection	Solute experimental in vitro human skin permeation data were collected from published articles, thesis, reports, and web documents. Corresponding compound physicochemical properties were considered from Drugbank, Chemspider, Pubchem, and Chemical book.
Data source location	Institution: The University of Queensland at Translational Research Institute City: Brisbane, Queensland Country: Australia
Data accessibility	The tabular database is available in therepository name: Mendeley Data Data identification number: 10.17632/8bs7hb2wj2.1 Direct URL to data:https://data.mendeley.com/datasets/8bs7hb2wj2/1
Related research article	[1] Roberts MS et al. Topical drug delivery: history, percutaneous absorption, and product development. Adv. Drug Deliv. Rev. 177 (2021): 113929.

Value of the Data

- The collected dataset can be used to explore the Quantitative drug Structure-epidermal Permeation Relationships (QSPR) that underpin drug choice and formulation design for potential topical and transdermal delivery products and potential skin exposure and toxicity for xenobiotics.
- Such relationships can also be used to assist drug discovery teams in designing and extracting chemicals, pharmaceutical scientists in designing topical or transdermal delivery products, regulators in assessing topical or transdermal delivery products efficacy and safety properties, toxicologists in evaluating xenobiotic exposure, and academic scientists interested in percutaneous absorption.
- The resulting QSPR relationships are also useful in predicting drug behavior in the skin and the body by physiologically based pharmacokinetic (PBPK) and toxicokinetic (PBTK) modelling, including in predicting dermal and systemic exposure with pharmacokinetic software such as the Simcyp® derived MechDermA model, the Gastroplus® derived Transdermal Compartmental Absorption & Transit (TCAT™) model and toxicokinetic software such as EPA's Stochastic Human Exposure and Dose Simulation (SHEDS), U.S. EPA. Swimmer Exposure Assessment Model (SWIMODEL), RISKOFDERM, EUROPOEM II, DREAM.
- This is the first major update of our Magnusson *et al.* [2] database that has been cited 295 times in Google Scholar to date (03/Apr/2022).
- This database could provide insights into validating the application range and limitations of various QSPR models such as Potts and Guy [3], Moss and Cronin [4,5], Magnusson *et al.* [2], Milewski-Stinchcombe [6], and Roberts-Sloan [7–10] for J_{max} and k_p [11,12].

1. Data Description

The collected constrained dataset as shown in **Table 1** [13] contains 476 records of 145 drugs, chemicals, and xenobiotics applied to *in vitro* human epidermal membranes from aqueous solutions either diluted or saturated in infinite dose amounts (constant concentration). This is the recent dataset updated from the 1960s to 2021 which is an extension of Magnusson *et al.* [2] aqueous training set (87 records of 64 solutes from 21 published reports). This new extended dataset contains 389 new records of 116 solutes from 47 published reports. There are few compounds in common between the original Magnusson *et al.* [2] dataset and this extended dataset making the count as 145 solutes. This database contains both epidermal permeability coefficients (k_p) used in many studies as the key measure for solute permeation through the skin [3–5] and the lesser-used maximal flux (J_{max}) [1,6–10,14] reported or derived from steady-state epidermal flux (J_{ss}) from aqueous solutions after adjustment for solute concentration effects. A key focus in the associated review [1] is J_{max} because, from a clinical or toxicological perspective, it is a more meaningful parameter than k_p [6–9] in that it characterizes the maximum steady-state exposure expected for drugs, chemicals, and xenobiotics. This exposure, defined by the maximum dose deliverable over a time period after application [2,6], equals the saturated compound flux (J_{sat}) from a saturated thermodynamically stable system, with solubility S_v that does not affect epidermal integrity:

$$J_{max} = \frac{D_{sc}S_{sc}}{h_{sc}} = \frac{D_{sc}S_{sc}}{h_{sc}S_v}S_v = \frac{K_{sc}D_{sc}}{h_{sc}}S_v = k_pS_v = J_{sat} \quad (1)$$

where S_{sc} and S_v are the solute's solubility in the SC and vehicle, respectively, D_{sc} is a solute's diffusion coefficient over an SC pathlength h_{sc}, K_{sc} is the solute's stratum corneum to vehicle partition coefficient, where $K_{sc}= S_{sc}/ S_v$, and k_p is the epidermal permeability coefficient, where $k_p=K_{sc}D_{sc}/h_{sc.}$ The significance of J_{max} is evident in the work of Higuchi [15]. In principle, higher fluxes may be achieved from supersaturated solutions as a result of their transient higher solubility in those solutions [16] and can be facilitated through the evaporation of topical products applied to the skin as a thin film.

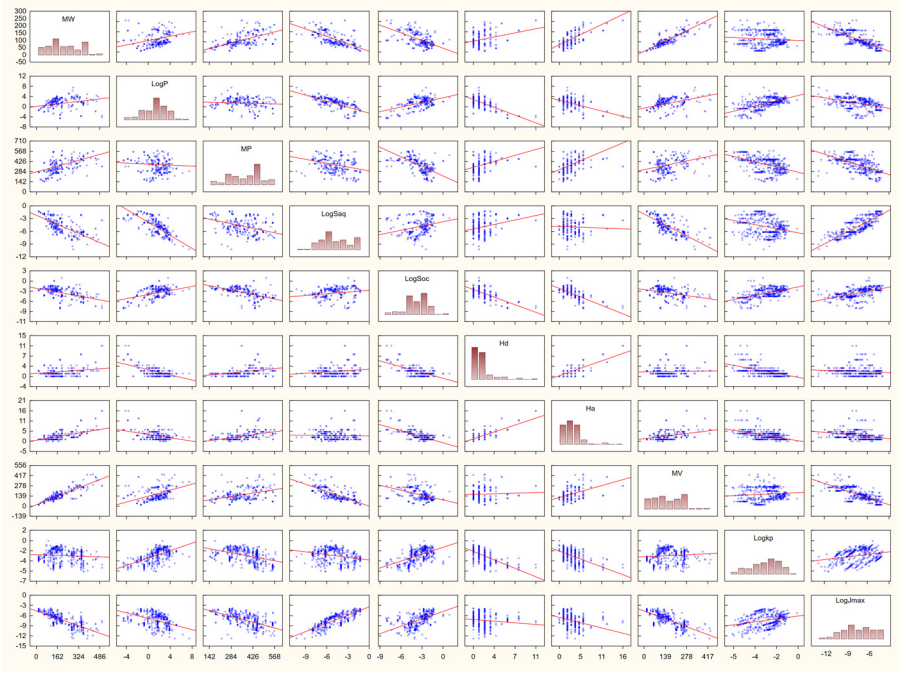

Fig. 1. Frequency distribution of various solute physicochemical (*MW*, *log P*, *MP*, log S_{aq}, *log* S_{oc}, H_d, H_a, *MV*) and skin permeation properties (*log* k_p and *log* J_{max}), along with their inter-relationships

The overall database possesses wide distribution of compound physicochemical properties and permeation parameters i.e., molecular weight (*MW*) ranging from 18 to 504, lipophilicity, defined as the logarithm of the octanol-water partition coefficient (*log P* or *log* $K_{o/w}$) ranging from -4.6 to 7.7, melting point (*MP*) in Kelvin ranging from 147 to 573, log aqueous solubility (*log* S_{aq}) ranging from -10 to 1.24 mol/mL, log octanol solubility (*log* S_{oc}) ranging from -8 to 0.88, hydrogen bond donor (H_d) ranging from 0 to 11, hydrogen bond acceptor (H_a) ranging from 0 to 16, molecular volume (*MV*) ranging from 17 to 434 cm^3 per mole, experimental temperature (^oK) ranging from 295 to 312, epidermal thickness (mm) from 0.01 to 0.128, epidermal permeability coefficients (*log* k_p, cm/h) ranging from -5.52 to -0.08 and epidermal maximum flux (*log* J_{max}, mol/cm^2/h) ranging from -12.99 to -3.88. Here Octanol solubility was calculated as $S_{oc} = S_{aq} * K_{o/w}$ and molecular volume (*MV*) was estimated using Fedors' (1974) group contribution method [17] or obtained from the ChemSpider [18] database.

The frequency distribution of these solute physicochemical and skin permeation properties, along with their inter-relationships were shown comprehensively using scatter-matrix plots as shown in Fig. 1. The same data in Fig. 1 was represented by considering a third physicochemical property as a covariate to analyze the relationship between skin permeation parameter and compound property as shown in Fig. 2 and Fig. 3 for *log* J_{max} and *log* k_p respectively.

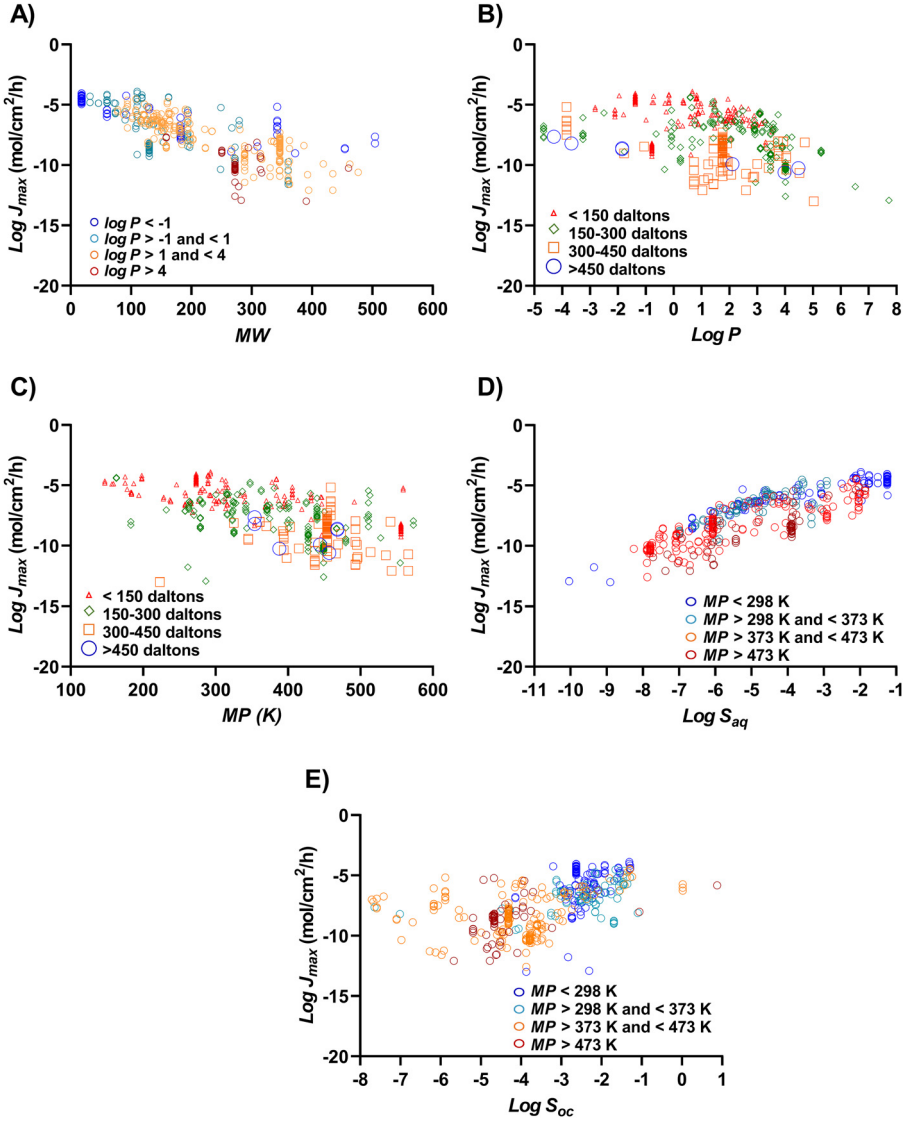

Fig. 2. Interrelationship of J_{max} for human epidermal permeation of solutes from aqueous solutions with solute physicochemical properties: Plot of A) *log* J_{max} vs. *MW* showing polarity as a covariate, B) *log* J_{max} vs. *log P* showing *MW* as a covariate, C) *log* J_{max} vs. *MP* showing *MW* as a covariate, D) *log* J_{max} vs. *log* S_{aq} showing *MP* as a covariate, and E) log J_{max} vs. *log* S_{oc} showing *MP* as a covariate.

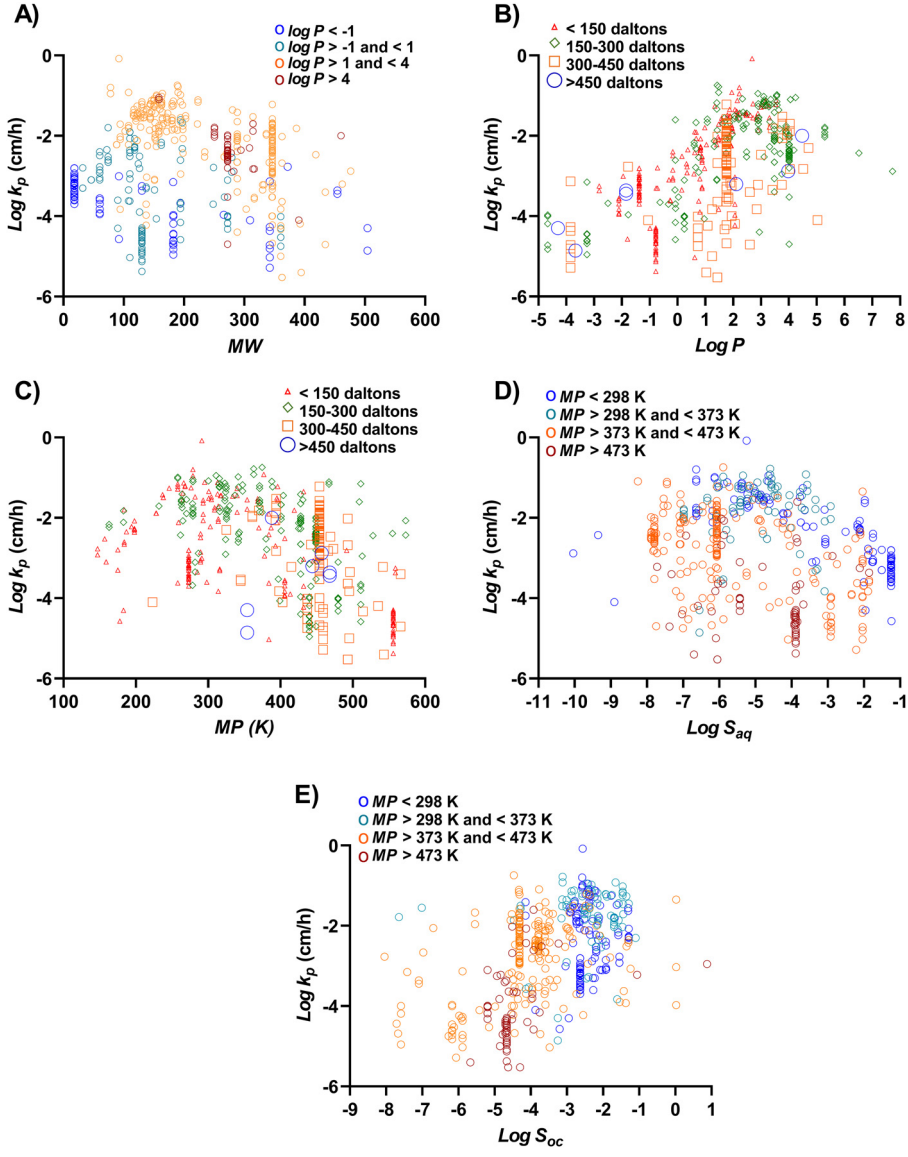

Fig. 3. Interrelationship of k_p for human epidermal permeation of solutes from aqueous solutions with solute physicochemical properties: Plot of A) *log* k_p vs. *MW* showing polarity as a covariate, B) *log* k_p vs. *log P* showing *MW* as a covariate, C) *log* k_p vs. *MP* showing *MW* as a covariate, D) *log* k_p vs. *log* S_{aq} showing *MP* as a covariate, and E) log k_p vs. *log* S_{oc} showing *MP* as a covariate.

2. Experimental Design, Materials and Methods

To generate the database shown in Table 1 [13], a comprehensive search was performed on Google, PubMed, Google Scholar, and other scientific publishing sites using the keywords: "*in vitro*", "human skin", "permeation", "penetration", "permeability", "aqueous solutions", "saturated systems" and "flux". Using some inclusion criteria, various skin permeation-related data parameters mainly k_p, $J_{ss,}$ and J_{max} were collected from these published reports. Those criteria were:

- All these reports were research publications, scientific reports, university-related theses, and personal communications that are publicly available and easily accessible.
- Most of these data were primarily from publications and were referenced accordingly in the reference column in **Table 1** as author and year.
- k_p, J_{max} were extracted directly if present or else calculated from k_p, and saturated solubility or J_{ss} and experimental concentration using Eq.1 and making sure the units for k_p and J_{max} were *cm/h* and *mol/cm²/h* respectively.
- Only the reports with undamaged skin were considered and included their skin integrity tests performed (electrical conductivity, transepidermal water loss (TEWL), tritiated water permeability, physical examination, sucrose transport, etc.,) along with their skin selection criteria (resistance measurements, flux comparisons before and after the experiments and other methods) in this database.
- Only human epidermal and isolated stratum corneum membranes were considered to account for the barrier resistance and data uniformity assuming very minimal resistance offered by the viable epidermis.
- Only data from aqueous solutions and buffers used as a vehicle were included and the alcoholic or non-aqueous co-solvents data were ignored.
- Only unionized solutes with fraction unionized (f_{ui}) > 0.9 were selected in this database based on Eq. 2 as shown below:

$$f_{ui} = 1 - \frac{10^{(pH-pKa)}}{1+10^{(pH-pKa)}} \tag{2}$$

Moreover, J_{max} was calculated using Eq. 1, considering the same aqueous solubility as in the buffer applied in *in vitro* experiments, and assuming no ionization occurred at skin or experimental pH conditions of 5.5 to 7.4 based on the solute pKa.

Thus, considering these criteria, the resulted data were tabulated in **Table 1** [13] by collecting various solute physicochemical properties from Chemspider [18], PubChem [19], ChemicalBook [20], and DrugBank [21] along with k_p, and J_{max} values:

- Compound name
- Chemical Abstract Service (CAS) number
- Molecular weight (*MW*) in Daltons
- Octanol-water partition coefficient (*Log P* or *Log* $k_{o/w}$)
- Melting Point (*MP*) in Kelvin
- Aqueous solubility represented as *Log* S_{aq} in the units of *mol/mL*
- Octanol solubility represented as *Log* S_{oc} in the units of *mol/mL*
- Hydrogen Donor (H_d)
- Hydrogen Acceptor (H_a)
- Molecular Volume (*MV*) in the units of cm^3 per mol
- Experimental temperature (T_{exp}) in the units of Kelvin
- Skin thickness in mm: 0.01 and 0.075 mm indicates isolated stratum corneum thickness, 0.1 and 0.128 mm indicate heat separated epidermis membrane.
- Skin integrity test column was captured wherever reported
- Skin selection criteria were captured wherever reported
- Skin permeability in cm/h represented as *Log* k_p
- Maximum flux in mol/cm^2/h represented as *Log* J_{max}
- Reference column was labeled in the form of author and year from the published report

If the parameters were unknown, the respective cells are empty in **Table 1** [13]. Here based on the applied donor solution whether it is non-saturated and saturated or neat liquid, the data was classified as t and t* respectively in the column name called 'set'. All this dataset was tabulated using Microsoft excel software 2016. While making the relationships as shown in Fig. 2 and Fig. 3, the data was sorted using a filter application and arranged accordingly. The main application of this new dataset (n=389) is validating the well-known J_{max} models of Magnusson *et al.* [2], Milewski-Stinchcombe [6], Abbott *et al.* [14], and Roberts-Sloan [7,9] using the Magnusson *et al.* [2] aqueous dataset (n=87) as a testing set. This was shown in Fig. 5 in the co-submitted paper of MS Roberts *et al.* [1], which also provided updated regression equations for each best-fit model along with the model diagnostic parameters such as adjusted correlation coefficient (R_{adj}^2), root means square error (RMSE), and Akaike information criteria (AIC). These statistical graphs are shown in Fig. 1 as scatter matrix plots generated using Statistica® version 13 (TIBCO® Data Science). Fig. 2 and Fig. 3 were plotted using GraphPad Prism® version 9.

Table 1 *In vitro* human epidermal Permeation Test (IVPT) dataset of various drugs, xenobiotics, and other solutes detailing their physicochemical properties, experimental conditions, and their human epidermal permeation parameters from aqueous solutions (k_p and J_{max}) [13]. The contents of this very large table are located in the Mendeley Data Repository, Data identification number: 10.17632/8bs7hb2wj2.1 and the data can be accessed by Direct URL: https://data.mendeley.com/datasets/8bs7hb2wj2/1. Values highlighted in green (or the data records from row 1 to 87) are the Magnusson aqueous training dataset containing 87 data records of 64 compounds whereas those in orange (or the records from row 88 to 476) are the 389 data records of 116 solutes all other solutes defined in this new database and used for external validation in [1]. Together, the combined dataset contains a total of 476 data records of 145 solutes and has a listing of:

[a]MW-molecular weight (Dalton), [b]log K_{ow} or log P – logarithm of octanol-water partition coefficient, [c]MP- melting point in Kelvin, [d]Log S_{aq}- logarithm of aqueous solubility (mol/mL), [e]Log S_{oc}- logarithm of octanol solubility (mol/mL), [f]H_d- hydrogen donor, [g]H_a- hydrogen acceptor, [h]MV- molecular volume (cm^3 per mol), [i]T_{exp}- experimental temperature, [j]skin thickness in mm: 0.01 and 0.075 mm indicates isolated stratum corneum thickness, 0.1 and 0.128 mm indicates heat separated epidermis membrane, [l]k_p-skin permeability in cm/h and [m]log J_{max}-logarithm of maximum flux (mol/cm^2/h).

Ethics Statement

No animal or human ethics are involved.

CRediT Author Statement

Hanumanth Srikanth Cheruvu: Data collection, Analysis, Methodology, Software, Manuscript writing; **Xin Liu:** Data verification, Manuscript proofreading; **Jeffrey E Grice:** Data verification, manuscript editing; **Michael S. Roberts:** Conceptualization, Supervision, Reviewing, and editing.

Declaration of Competing Interest

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Data Availability

An updated skin permeation database of compounds applied as aqueous solutions in in vitro (Original data) (Mendeley Data).

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References

[1] M.S. Roberts, H.S. Cheruvu, S.E. Mangion, A. Alinaghi, H.A. Benson, Y. Mohammed, A. Holmes, J. van der Hoek, M. Pastore, J.E. Grice, Topical drug delivery: History, percutaneous absorption, and product development, Adv. Drug. Deliv. Rev. 177 (2021) 113929.
[2] B.M. Magnusson, Y.G. Anissimov, S.E. Cross, M.S. Roberts, Molecular size as the main determinant of solute maximum flux across the skin, J. Invest. Dermatol. 122 (2004) 993–999.
[3] R.O. Potts, R.H. Guy, Predicting skin permeability, Pharm. Res. 9 (1992) 663–669.
[4] G.P. Moss, M.T. Cronin, Quantitative structure–permeability relationships for percutaneous absorption: re-analysis of steroid data, Int. J. Pharm. 238 (2002) 105–109.
[5] M. Cronin, J. Dearden, G. Moss, G. Murray-Dickson, Investigation of the mechanism of flux across human skin in vitro by quantitative structure–permeability relationships, Eur. J. Pharm. Sci. 7 (1999) 325–330.
[6] M. Milewski, A.L. Stinchcomb, Estimation of maximum transdermal flux of nonionized xenobiotics from basic physicochemical determinants, Mol. Pharmaceutics 9 (2012) 2111–2120.
[7] J. Juntunen, S. Majumdar, K.B. Sloan, The effect of water solubility of solutes on their flux through human skin in vitro: A prodrug database integrated into the extended Flynn database, Int. J. Pharm. 351 (2008) 92–103.
[8] J. Thomas, S. Majumdar, S. Wasdo, A. Majumdar, K.B. Sloan, The effect of water solubility of solutes on their flux through human skin in vitro: an extended Flynn database fitted to the Roberts–Sloan equation, Int. J. Pharm. 339 (2007) 157–167.
[9] S. Majumdar, J. Thomas, S. Wasdo, K.B. Sloan, The effect of water solubility of solutes on their flux through human skin in vitro, Int. J. Pharm. 329 (2007) 25–36.
[10] W.J. Roberts, K.B. Sloan, Correlation of aqueous and lipid solubilities with flux for prodrugs of 5-fluorouracil, theophylline, and 6-mercaptopurine: A Potts–Guy approach, J. Pharm. Sci. 88 (1999) 515–522.
[11] H.S. Cheruvu, Modeling approaches to predict human skin absorption of drugs and other chemicals, The University of Queensland, Ph.D. thesis (2021) 248.
[12] H.S. Cheruvu, X. Liu, J.E. Grice, M.S. Roberts, Modeling percutaneous absorption for successful drug discovery and development, Expert Opin. Drug Discovery 15 (2020) 1181–1198.
[13] H.S. Cheruvu, An updated skin permeation database of compounds applied as aqueous solutions in in vitro, Mendeley Data V1 (2022), doi:10.17632/8bs7hb2wj2.1.
[14] S. Abbott, C.M. Hansen, H. Yamamoto, R.S. Valpey, Hansen Solubility Parameters in Practice, in: S. Abbott (Ed.), Hansen-Solubility.com, 2013.
[15] T. Higuchi, Physical chemical analysis of percutaneous absorption process from creams and ointments, J. Soc. Cosmet. Chem. 11 (1960) 85–97.
[16] R.J. Scheuplein, Mechanism of percutaneous adsorption: I. Routes of penetration and the influence of solubility, J. Invest. Dermatol. 45 (1965) 334–346.
[17] R.F. Fedors, A method for estimating both the solubility parameters and molar volumes of liquids, Polymer Engineering & Science 14 (1974) 147–154.
[18] H.E. Pence, A. Williams, ChemSpider: an online chemical information resource, in, ACS Publications, 2010.
[19] S. Kim, J. Chen, T. Cheng, A. Gindulyte, J. He, S. He, Q. Li, B.A. Shoemaker, P.A. Thiessen, B. Yu, PubChem 2019 update: improved access to chemical data, Nucleic Acids Res. 47 (2019) D1102–D1109.
[20] ChemicalBook, https://www.chemicalbook.com/, (2006).
[21] D.S. Wishart, C. Knox, A.C. Guo, S. Shrivastava, M. Hassanali, P. Stothard, Z. Chang, J. Woolsey, DrugBank: a comprehensive resource for in silico drug discovery and exploration, Nucleic Acids Res. 34 (2006) D668–D672.