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Original article

An open-access data set of pig skin anatomy and physiology for modelling purposes

Laura Krumpholz[1,2], James F. Clarke[1,3], Sebastian Polak[1,3] and Barbara Wiśniowska[1,*]

[1]Pharmacoepidemiology and Pharmacoeconomics Unit, Faculty of Pharmacy, Jagiellonian University Medical College, Medyczna 9, str., Kraków 30-688, Poland
[2]Doctoral School in Medical and Health Sciences, Jagiellonian University Medical College, Łazarza Str. 16, Kraków 31-530, Poland
[3]Certara UK Ltd. (Simcyp Division), 1 Concourse Way, Sheffield S1 2BJ, UK

[*]Corresponding author: Tel: +48 12 62 05 517; Fax: +48 12 62 05 820; Email: b.wisniowska@uj.edu.pl

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Abstract

The use of animal as opposed to human skin for *in vitro* permeation testing (IVPT) is an alternative, which can reduce logistical and economic issues. However, this surrogate also has ethical considerations and may not provide an accurate estimation of dermal absorption in humans due to physiological differences. The current project aimed to provide a detailed repository for the anatomical and physiological parameters of porcine skin, with the aim of parametrizing the Multi-phase Multi-layer Mechanistic Dermal Absorption (MPML MechDermA) Model in the Simcyp Simulator. The MPML MechDermA Model is a physiologically based pharmacokinetic (PBPK) model that accounts for the physiology and geometry of skin in a mechanistic mathematical modelling framework. The database provided herein contains information on 14 parameters related to porcine skin anatomy and physiology, namely, skin surface pH, number of stratum corneum (SC) layers, SC thickness, corneocyte thickness, corneocyte dimensions (length and width), volume fraction of water in corneocyte (where SC is divided into four parts with different water contents), intercellular lipid thickness, viable epidermis thickness, dermis thickness, hair follicle and hair shaft diameter, hair follicle depth and hair follicle density. The collected parameters can be used to parameterize PBPK models, which could be further utilized to bridge the gap between animal and human studies with interspecies extrapolation or to predict dermatokinetic properties typically assessed in IVPT experiments.

Database URL: https://data.mendeley.com/datasets/mwz9xv4cpd/1

Background

When evaluating dermal absorption either *in vivo* or *ex vivo*, the gold standard would usually be to conduct a study with human patients or with excised human skin, respectively. However, this is not always possible due to logistical, economical or ethical limitations. An alternative approach is to conduct studies on animals or use excised animal skin; however, data applicability and interpretation can be challenging due to physiological differences between the animal of choice and human.

In vitro permeation testing (IVPT) is a widely used method for evaluating cutaneous permeability of topical drug products (1, 2) and dermal exposure assessment (3–5). Excised adult human skin is recommended for that purpose, and the results from such experiments have been shown to correlate well with *in vivo* data (6). The skin for these studies is commonly obtained from cosmetic surgery procedures or cadavers and stored frozen. However, the supply of human skin can often be low and expensive. In addition, each piece of skin is relatively small, usually only allowing a maximum of 6–8 diffusion cells per donor. Storage conditions might influence skin integrity, viability or enzyme activity and thus observed dermal permeation (7–10).

As an alternative, animal skin models are often used as a tool to estimate dermal absorption. The use of animal skin affords many advantages such as being easier to obtain, ability to more easily use fresh skin, and, in the case of larger animals such as pig, a large number of cells can be set up from one donor, resulting in reduced interindividual variability for investigative studies (11–14). Porcine skin is often used as it can be easily obtained from animals slaughtered for food and is most similar to human skin in morphological structure and immunohistochemical properties (15–18).

Despite their similarities, permeation of some topically applied compounds can vary significantly between porcine and human skin (19, 20); the extent of this difference depends on the nature of the compound and formulation in which it is applied. Moreover, since even *in vitro* studies of topical drugs are associated with ethical issues, credible alternative models that can help informed decision during pharmaceutical formulation development are highly beneficial.

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Physiologically based pharmacokinetic (PBPK) modelling accounts for physiology and geometry of the skin in a mechanistic modelling framework (21). One powerful feature of PBPK models is the ability to extrapolate between systems, such as from healthy individuals to a diseased population (22–24), adult to paediatric (25–27) or animal to human (28–30). To accurately extrapolate between two systems, the physiological differences between them must be well characterized. For this purpose, the current work aimed to collate a database of anatomical and physiological data describing the skin of the domestic and miniature pig. The provided data set may be utilized for the development of PBPK models. The current work aimed specifically to parameterize the *in vitro* module of the Multi-phase Multi-layer Mechanistic Dermal Absorption (MPML MechDermA) Model (IVPT module) in the Simcyp Simulator® (Certara, Princeton, NJ, USA) for porcine skin. However, since the database consists of parameters that describe skin anatomy, it can also be utilized to parametrize other PBPK dermal models such as the Transdermal Compartmental Absorption and Transit model in the GastroPlus® (Simulations Plus, Inc.) and any other models, which require such input (31).

The MPML MechDermA Model accounts for the physiology of the skin by incorporating a database of physiological data describing the geometry and structure of each layer (21). Currently, the model database incorporates nine body sites of human skin.

Data collection

The premise for the presented database was to provide a detailed repository for the anatomical and physiological parameters of the porcine skin. The literature search encompassed 20 parameters that describe skin in the MPML MechDermA Model (21). Six of these were not included in the final data set, namely, corneocyte pH, lipid and sebum viscosity, density of lipids and proteins and tortuosity, due to a lack of quantitative data in the literature. Moreover, skin temperature was not searched because under the *in vitro* conditions, this is a parameter of the experiment, not a physiological value.

Data gathering was performed between January and May 2022. PubMed, Google Scholar bibliographic databases and other potential sources, via the Google search engine, were searched. There was no time limit for the search query. The following keywords and their combinations were used: 'pig', 'porcine', 'swine', 'skin', 'morphology', 'histology', 'physiology', 'anatomy', 'properties', 'pH', 'stratum corneum', 'corneocyte', 'viable', 'dermis', 'epidermis', 'hair', 'follicle', 'shaft', 'orifice', 'thickness', 'length', 'width', 'water', 'fraction of water', 'water content', 'lipid', 'protein', 'sebum', 'viscosity', 'density' and 'tortuosity'. Searches resulted in 24 861 records. The papers containing any related numerical parameters were considered eligible. Forty-nine publications were included in the analysis, and the relevant data were extracted manually into a standardized Excel spreadsheet. If the experimental parameter values were not obtained originally by the authors of the publication, cross-references were retrieved if feasible. Additional, potentially relevant data sources were also identified by checking reference list in the eligible papers.

All data were extracted manually from the relevant papers. Whenever numerical values were not specified in the text, but the microscopic picture together with the scale bar was given or data were presented on the chart, they were obtained using the ImageJ 1.53k and GetData Graph Digitizer 2.26 software, respectively. Units were unified. In one paper, the given units were assumed to be incorrect due to an editorial error, so they were changed from millimetres (mm) to the micrometres (μm), and the information about this was added to the 'comments' column (32). Whenever the standard error (SE) was given instead of standard deviation (SD), but there was sample size (n) reported, the SD value was calculated. Furthermore, coefficient variation was calculated when the SD value was available. Parameters were split by the body site (such as ear, abdomen and back), and if there was any detailed information on the specific part of the body site (such as the inner or outer part of the ear), it was also included in the body site column. In the MPML Model for the fraction of water in corneocytes, the stratum corneum (SC) layers were divided into four equal-sized bins. Therefore, in the current work, the water content for the whole SC was expressed as mean values for 0–25%, 25–50%, 50–75% and 75–100% of the depth, for the top, middle 1, middle 2 and bottom layers, respectively. The SC thickness for each calculation was taken from the specific paper. In some papers, the viable epidermis (VE) thickness was not given, but it was possible to calculate by subtracting the SC thickness from whole epidermis thickness. A similar approach was taken to extract the corneocyte thickness, where it was calculated as the thickness of SC divided by the number of layers of SC, with the respect of intercellular lipid thickness sourced from the study by Charalambopoulou *et al.* (33).

Database structure

The database is provided in the form of a Microsoft Excel spreadsheet. It contains information on 14 parameters related to the porcine skin anatomy and physiology, i.e. skin surface pH, number of SC layers, SC thickness, corneocyte thickness, corneocyte dimensions (length and width), volume fraction of water in corneocyte (where SC is divided into four parts with different water contents), intercellular lipid thickness, VE thickness, dermis thickness, hair follicle and hair shaft diameter, hair follicle depth and hair follicle density. Each parameter was described using characteristics shown in Table 1. Missing data were left blank in the data set; additional important information can be found in the 'comments' column.

Database utilization

The database consists of porcine skin parameters, which may influence drug penetration, permeation and absorption,

Table 1. Characteristics used to describe porcine skin parameters

Group of characteristics	Names of characteristics
Value	Mean, range, SD, SE, CV%
Sample	Body site, species, sample size, age, type of animal (pig or minipig)
Experiment	Methods, skin condition (*ex vivo*/*in vivo*/fresh/frozen)
Others	Source (author and year, DOI/PMID) and additional comments

specifically those required to parameterize the *in vitro* module of the MPML MechDermA Model. Therefore, the data can be used to generate an *ex vivo* porcine skin model, which enables ether predictions of dermatokinetic properties, or perform interspecies extrapolation. However, the model will need to be verified for this purpose. Furthermore, the database contains information about the type of skin (*ex vivo*/*in vivo*/fresh/frozen) and which specific porcine skin location was used, as well as the type of pig (pig or minipig), species and age, so it may be utilized to analyse the influence of those physiological subsets on the outcome of dermal absorption experiments.

Database limitations

Relevant parameters were extracted manually; however, due to the lack of consistency in nomenclature and methods, there is some uncertainty. Anatomically, epidermis is a part of the skin that is divided into the SC and VE. However, often, in the literature, a sample of VE is referred as the epidermis. Whenever the word 'epidermis' was used, and no procedure that would suggest that by this word, authors meant 'viable epidermis' only was mentioned in the Methods section, the 'viable epidermis' thickness was calculated as the difference between the total thickness of 'epidermis' and the 'stratum corneum' thickness if both were provided. Moreover, there was some inconsistency in the definition of 'rete pegs' in the VE. The dermoepidermal junction is undulating, and it is possible to distinguish the 'thinner part' (without rete pegs) and 'thick part' (with rete pegs). However, the authors did not always state which part had been included in their measurements of 'viable epidermis thickness'. Whenever such information was available, this is written in the 'comments' column.

Database access

The data set of pig skin anatomy and physiology is freely available under the open-access license at https://data.mendeley.com/datasets/mwz9xv4cpd/1 and as a Supplementary file.

Supplementary data

Supplementary data are available at *Database* Online.

Conflict of interest.

The authors declare no conflicts of interest.

Author contributions

B.W. and S.P. participated in conceptualization; L.K and B.W. participated in investigation; LK and JC participated in data curation; L.K., B.W. and J.C. participated in writing—original draft; B.W. participated in project administration; L.K. participated in writing—editing; B.W. and J.C. participated in writing—review; B.W participated in supervision. All authors have read and agreed to the published version of the manuscript.

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