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Review

Quantitative structure-skin permeability relationships

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ABSTRACT

This paper reviews *in silico* models currently available for the prediction of skin permeability. A comprehensive discussion on the developed methods is presented, focusing on quantitative structure-permeability relationships. In addition, the mechanistic models and comparative studies that analyse different models are discussed. Limitations and strengths of the different approaches are highlighted together with the emergent issues and perspectives.

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. 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.

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 physicochemical 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

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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 and Singh, 1993; Schaefer and Redelmeier, 1996; Walters and 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.

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 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,

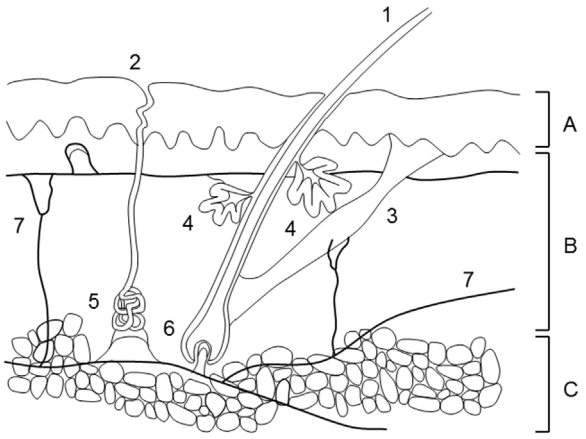

Fig. 1. Schematic representation of the skin structure: A – epidermis, B – dermis, C – hypodermis; 1 – hair shaft, 2 – pore, 3 – hair erector muscle, 4 – sebaceous gland, 5 – sweat gland, 6 – hair follicle, 7 – blood vessel.

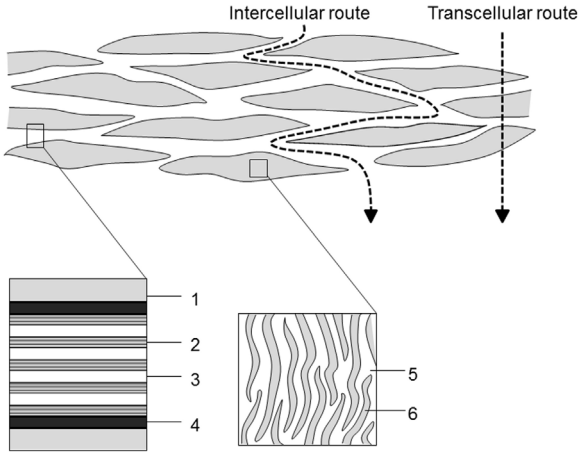

Fig. 2. Schematic diagram of stratum corneum with the main transport routes (based on Barry, 2001). 1 – cell cytoplasm, 2 – aqueous layer, 3 – lipid bilayers (ceramides, cholesterol, fatty acids), 4 – plasma membrane, 5 – lipid, 6 – keratin.

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 and 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).

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). 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 and 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 and 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).

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