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Finite and infinite dosing: Difficulties in measurements, evaluations and predictions ☆

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ABSTRACT

Due to the increased demand for reliable data regarding penetration into and permeation across human skin, assessment of the absorption of xenobiotics has been gaining in importance steadily. In vitro experiments allow for determining these data faster and more easily than in vivo experiments. However, the experiments described in literature and the subsequent evaluation procedures differ considerably. Here we will give an overview on typical finite and infinite dose experiments performed in fundamental research and on the evaluation of the data. We will point out possible difficulties that may arise and give a short overview on attempts at predicting skin absorption in vitro and in vivo.

Contents

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1. Introduction

In the past decades, the importance of absorption of xenobiotics into and through the skin has been growing steadily. First, there is a requirement to optimize the delivery of dermatological drugs into various skin strata for maximum therapeutic effect. Second, the transdermal and topical routes have become popular alternatives to more traditional methods of drug delivery. A third stimulus has been the realization that the skin offers an often neglected route for uptake of potentially harmful or toxic substances in everyday use in the agrochemical, chemical, cosmetic, household, and pharmaceutical sectors [1–6]. The REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) regulation of the EU explicitly requests this information [7]. In summary, there is an increasing demand for data describing the rate, degree, and route of penetration of compounds into and permeation of these substances across human skin.

While in vivo experiments are inherently difficult to perform and evaluate due to the large number of processes involved, in vitro experiments facilitate studying skin absorption by reducing the overall complexity. Obviously, it is of fundamental importance that relations between the data obtained in vitro and in vivo exist. As was shown repeatedly such relations exist and hence in vitro experiments may be suitable for predicting in vivo absorption [8–10].

In literature an overwhelmingly large variety of experimental setups and evaluation procedures for such in vitro experiments can be found. Here we will give an overview on typical finite and infinite dose experiments performed in fundamental research. Both types of experiments feature commonalities in experimental setup and evaluation, but some crucial differences exist, too, especially when it comes to evaluation and prediction of dermal uptake. We will not only address possible difficulties that may arise in experimental setup and evaluation, but also review attempts at predicting skin absorption in vivo. Specific topics like pharmacokinetic modeling, transdermal therapeutic systems, and quantitative structure-permeability relationships are beyond the scope of this article although some of the concepts presented here apply as well.

1.1. Skin structure and permeation pathways

A number of the aforementioned difficulties are rooted in the special structure of human skin. To allow for a fundamental understanding of the causes of these difficulties, we will give a short outline of the composition and the properties of this barrier.

The human skin is made up of three distinctive layers, the avascular epidermis, the dermis and the subcutaneous fatty tissue, with each layer having different properties and adding to the overall functionality of the organ. Substances that are taken up through the skin may enter the blood stream in the top layers of the dermis. Thus, the main barrier to overcome in transdermal uptake is the outermost layer of the skin, the epidermis. This skin layer can be divided into two layers, the superficial stratum corneum or horny layer (10–20 μm thick) and the viable epidermis (50–100 μm thick).

The stratum corneum is composed of dead and partially desiccated epidermal cells (corneocytes). The thin cells are embedded in a continuous lipid matrix and overlap with each other [11,12]. Often this special arrangement is referred to as the so-called brick and mortar model [13]. Protein is present in both the extra- and intracellular phases. Due to its usually low water content in vivo, the stratum corneum can be considered as a lipophilic phase. The cells making up the stratum corneum are generated in the viable epidermis, which features a much higher water content than the stratum corneum. Therefore, the viable epidermis can be considered as a primarily hydrophilic phase.

The brick and mortar model outlined above does not include hair follicles and sweat glands, which pierce the epidermis and hence also the stratum corneum at various places. The roots of the hair, sebaceous glands, and sweat glands are located “deep down” in the dermis.

The potential pathways into and through the skin and their contribution to the absorption of substances have been the subject of many investigations. Because the stratum corneum acts as the main barrier, emphasis has usually been placed on understanding the transport through this layer. Basically, two different routes can be distinguished: 1) transport through the stratum corneum matrix and 2) transport through appendages.

The transport through the stratum corneum matrix follows the less than 0.1 μm-wide intercellular regions winding around the flat, cornified cells (intercellular pathway). In spite of its length this tortuous pathway is probably the major transport route for most chemicals – especially when a large amount of substance has been applied. A transport along a shorter route through the cells is hindered by the densely cross-linked protein structure (transcellular pathway).

Uptake may also happen via other direct and possibly faster routes such as through the sweat ducts or along the follicular route. Since the appendages have a very small fractional surface area, their contribution to the so-called steady-state flux is probably small. Shortly after the application of a substance to the skin, however, the intra-appendageal transport may be greater than that through the stratum corneum matrix [14]. Recently, the follicular route has been gaining in importance [15].

For some lipophilic substances, a local deep tissue penetration has been observed. These results seem to contradict the idea that substances permeating through the skin are taken up in the upper layers of the dermis and that the permeant concentration is effectively zero in the dermis. However, these findings have recently been attributed to the binding of the permeants to plasma proteins and being transported to the lower regions with the blood [16].

1.2. Molecular properties determining transdermal uptake

Small and lipophilic molecules can enter cells by simple passive diffusion through the lipid bilayers of the cell membrane. But what are the molecular properties that influence the speed with which the molecules overcome the barrier? Early studies showed a correlation between the speed with which a molecule diffuses through membranes and its lipoid solubility and size [17]. It was observed