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In vitro models for evaluating safety and efficacy of novel technologies for skin drug delivery

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ABSTRACT

For preclinical testing of novel therapeutics, predictive in vitro models of the human skin are required to assess efficacy, absorption and safety. Simple as well as more sophisticated three-dimensional organotypic models of the human skin emerged as versatile and powerful tools simulating healthy as well as diseased skin states. Besides addressing the demands of research and industry, such models serve as valid alternative to animal testing. Recently, the acceptance of several models by regulatory authorities corroborates their role as important building block for preclinical development. However, valid assessment of readout parameters derived from these models requires suitable analytical techniques. Standard analytical methods are mostly destructive and limited regarding in-depth investigation on molecular level. The combination of adequate in vitro models with modern non-invasive analytical modalities bears a great potential to address important skin drug delivery related questions. Topics of interest are for instance the assessment of repeated dosing effects and xenobiotic biotransformation, which cannot be analyzed by destructive techniques. This review provides a comprehensive overview of current in vitro skin models differing in functional complexity and mimicking healthy as well as diseased skin states. Further, benefits and limitations regarding analytical evaluation of efficacy, absorption and safety of novel drug carrier systems applied to such models are discussed along with a prospective view of anticipated future directions. In addition, emerging non-invasive imaging modalities are introduced and their significance and potential to advance current knowledge in the field of skin drug delivery is explored.

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1. Introduction

1.1. Anatomy and physiology of the human skin

The skin is one of the largest organs in the human body referring to its surface area and weight. Its main function is to form an effective barrier to protect the organism from environmental influences including physical, chemical and thermal damaging. Specifically, the complex multi-layered organization of human skin provides a protective shield against external threats such as harmful chemicals, hazardous UV-radiation and microbial invasion. Skin tissue is a dynamically changing biological structure that undergoes continuous self-renewal. The outermost dead cell layer is sloughed off in regular recurring cycles and replaced by new cells arising from the basal layer and moving upward to the skin surface by a series of cellular differentiation events. From a histological point of view, the skin is composed of three main layers: the epidermis (outermost layer), the dermis (connective tissue layer below the epidermis) and the subcutis (lowermost layer) [1].

Depending on the body site, considerable variations in epidermal thickness are observable ranging from 0.1 mm at the eyelids up to 1.5 mm at the palms and soles of the feet. Keratinocytes are the most abundant cell type within the avascular epidermal layer. Terminally differentiated keratinocytes (also designated as corneocytes) form the outermost horny skin layer (stratum corneum (SC)), which is mainly contributing to the barrier properties of the human skin. The general structural organization of the SC can be described as “brick and mortar”-concept. Within this structure, the corneocytes - as flattened, dead cell bodies of keratinocytes - represent the bricks, which are surrounded by an intercellular lipid matrix constituting the “mortar” as depicted in Fig. 1 with exemplary fluorescence-based visualization of the SC as skin barrier (Fig. 1). As an effective biological barrier, the SC controls the penetration of drugs into the skin and simultaneously protects the body from water loss. The lower three sublayers - stratum granulosum, stratum spinosum and stratum basale - constitute the viable part of the epidermis harboring a number of other cell populations such as melanocytes, Langerhans cells and Merkel cells [2,3].

The basement membrane separates the epidermal compartment from the underlying connective tissue and particularly reinforces

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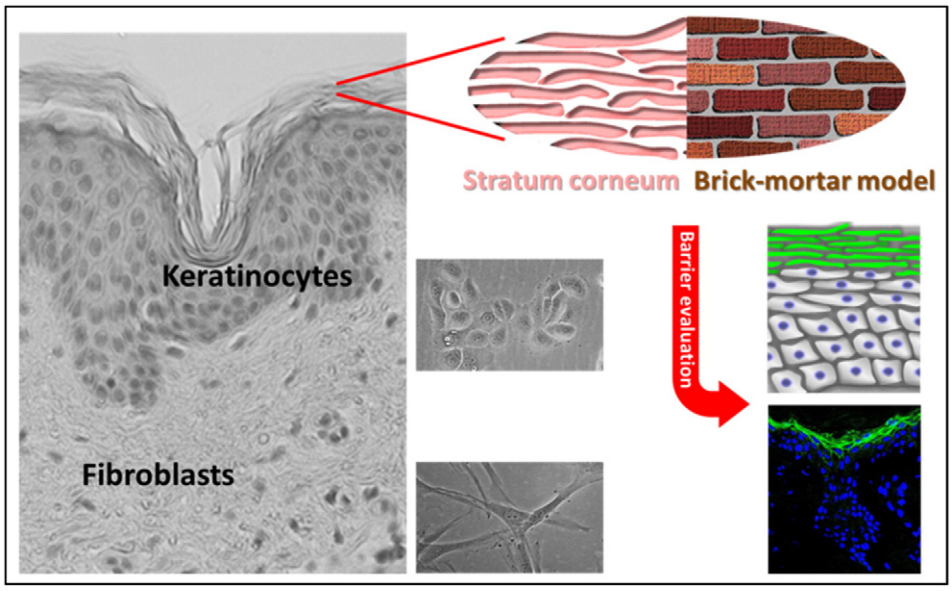

Fig. 1. Structural organization of human skin with special focus on the "brick and mortar" concept of the SC with exemplary fluorescence-based visualization of the SC as skin barrier using involucrin known as specific marker for terminal differentiation of keratinocytes (green), while cell nuclei are visualized in blue.

cellular crosstalk within these different layers. This highly specialized structure mainly acts as supportive interface for cell attachment, thus allowing for hierarchical cell organization.

Directly beneath this zone, the dermis exhibits a highly vascularized and collagen-rich compartment. The dermal part consists of a network-like organization mainly composed of large collagen and thin elastin fibers, which are responsible for the favorable mechanical characteristics of human skin as indicated by its excellent mechanical strength and flexibility to withstand applied external forces until a critical level is reached. It further contains smaller blood vessels for nourishment and waste transport as well as sensory nerves. Other structural components embrace hair follicles, sebaceous glands and sweat glands with ducts to the skin surface deeply embedded in the dermal compartment. The lowermost layer is represented by the subcutis with fibroblasts, macrophages and adipocytes as resident cells in this region. The subcutis plays an important role by anchoring the dermis to the further down located deep fascia and bones via fibrous bands. Larger blood vessels, nerves and fatty tissue are further structure-forming elements within this subcutaneous layer with the main function of energy supply and thermal insulation [4].

Based on this complex structure and physiology, the development of skin models which accurately mimic the in vivo situation in human skin is quite challenging. Thus, important key features for evaluation of novel drugs/delivery systems have to be identified, and an ideal model has to be complex enough to be predictable, but at the same time as simple as possible to allow for reproducible and wide-spread use in research and industry.

1.2. Drug absorption through the human skin

Currently, human skin attracts profound interest as route of administration for drug delivery to evoke either local or systemic therapeutic effects. However, the stratum corneum as outermost layer of the human skin represents an excellent barrier and hampers the transdermal delivery of therapeutic agents. In general, there are two main routes of penetration, which can be targeted for drug delivery: trans-appendageal or trans-epidermal. The trans-appendageal route constitutes transport via the pores and shafts embracing sweat glands and hair follicles with their associated sebaceous glands. Due to their relatively small fractional area constituting only 0.1 % of the total skin area, these routes of penetration are usually considered to be of minor importance. However, they serve as important mode of entry for ions and large polar molecules, which can hardly pass through the stratum corneum. As second mode of molecule transport, the trans-epidermal route describes diffusion through the intact stratum corneum, wherein two micro-routes exist: the transcellular and the intercellular pathway. The principal pathway taken by a drug is mainly driven by its partition coefficient (log P). Hydrophilic drugs favorably diffuse via the transcellular compartment, even though the low water content of the stratum corneum demonstrates a challenging aspect. In contrast, lipophilic drug preferentially traverse the stratum corneum via the intercellular domain.

The passage through the intact stratum corneum (either transcellular or intercellular) is considered as predominant route by which most of the substances penetrate the skin. Nevertheless, it became apparent that the intercellular route is widely considered to represent the principal mode of entry for permeation of both, hydrophilic and lipophilic drugs due to the densely packing of proteins within the corneocytes, which make them almost impermeable [5–7].

1.3. Drug delivery to the human skin: advanced carrier systems

Most active compounds demonstrate a poor penetration capacity into the human skin [8]. Therefore, enormous efforts have been invested to develop intelligent drug delivery systems overcoming the skin barrier with particular emphasis on increasing therapeutic activity and minimizing undesirable side-effects [9]. A broad spectrum of carrier systems can be found for topical application (Fig. 2). Conventional carrier systems for topical application include liquids (e.g. sprays) as well as semi-solid (e.g. ointments, creams) and solid systems (e.g. patches) [10]. Further enhancement techniques for transdermal drug delivery have been introduced ranging from drug encapsulation into specific vehicles (liposomes, nanoparticles, patches), the use of chemicals or barrier disruption by microneedles. Vesicular carriers such as liposomes consist of a lipid bilayer with an aqueous phase inside, thus allowing for entrapment of either lipophilic or hydrophilic molecules combined with the possibility of changing size, charge and surface properties depending on the therapeutic demands [11]. Nanoparticles are ideal vehicles for the trans-follicular route as they accumulate in the hair follicle being capable of deeper penetrating into the hair follicle compared to molecules in solution, thus acting not only as major entry point but also as reservoir of topically applied substances [12–15]. Polymeric patches are

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