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Nanocarriers for drug delivery into and through the skin — Do existing technologies match clinical challenges?

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ABSTRACT

The topical application of drug-loaded particles has been explored extensively aiming at a dermal, follicular or transdermal drug delivery. This review summarizes the present state of the field of polymeric nanocarriers for skin application, also covering methodologies to clinically characterize their interaction and penetration in skin in vivo. Furthermore, with a focus on a clinical perspective, a number of questions are addressed: How well are existing nanoparticle systems penetrating the skin? Which functions of new carrier concepts may meet the clinical requirements? To which extend will instrumental imaging techniques provide information on the biological functions of nanocarriers? Which issues have to be addressed for translating experimental concepts into a future clinical application?

1. Introduction

The opportunity of delivering bioactive molecules by penetration into or permeation through the skin has tremendous implications for a local therapy of skin diseases as well as vaccination or systemic delivery of drugs with poor peroral bioavailability. According to their natural function, however, the skin is a very efficient barrier, at least in a healthy state. This outlines the clinical challenges, which are associated with topical administration: How to realize a transport of pharmaceutics to their respective target site, ideally allowing for a long lasting pharmacological effect?

More specifically, one challenge is to find the right balance between enhancing the penetration of active compounds through the skin barrier and at the same time ensuring sufficient retention to maintain therapeutic drug concentrations within the skin. Increasing the selectivity by delivering bioactives specifically to lesional skin is another important task to address. Last but not least, encapsulation may allow to effectively deliver molecule classes, which are sensitive to degradation and not yet available for topical therapies such as peptides, proteins or nucleic acids.

A variety of concepts has been proposed to overcome skin barrier functions and improve drug delivery compared to conventional creams or ointments particularly for substances, which are hardly penetrating the skin because of their size or relative hydrophilicity. For enhanced drug penetration, substances, which chemically disturb the skin structure [1], have been more critically discussed compared to occlusion-mediated skin hydration and diffusion enhancement. Low-frequency ultrasound can be used to temporarily disturb the skin barrier by means of shock waves and acoustically-induced microjets resulting from cavitation [2]. Electroporation by high voltage pulses temporarily creates aqueous pores in cell membranes for substance diffusion [3]. Ablation by laser techniques allows destroying skin layers in a controlled fashion, thereby enhancing drug penetration depth through artificial vertical channels [4]. Microneedle arrays mechanically damage the skin, forming diffusion paths for subsequently applied formulations. If coated with drug, used as hollow needles for microinjection, or being made from an immediately dissolving material, microneedles can directly deposit drug substances into the skin [5–7].

Nano-sized carrier systems represent alternative approaches, but could also be powerful additions to the above mentioned skin delivery technologies to facilitate drug delivery by topical application. Ideally, they should allow the transport of incorporated or coupled substances into the skin without the need to previously damage the natural barrier function. Nanocarriers may facilitate drug delivery to structural features of the skin like hair follicles, interact with skin lipids to mediate transportation and/or allow creating depots of drug in the skin for a sustained or stimuli-induced release [8–10].

Considering possible routes of nanoparticle transport into healthy and damaged skin, this review reports on the functions of various polymer-based nanocarriers for skin application, present techniques to study nanoparticle skin penetration and cellular interaction, and finally

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discusses clinical achievements and perspectives of nanocarriers for dermal applications.

2. Skin anatomy and skin diseases

Healthy skin is very efficient in fulfilling its task as a biobarrier. It is organized as a multilayer structure, which can roughly be categorized into hypodermis, dermis and the non-vascularized epidermis, the latter being covered by the stratum corneum (Fig. 1) [11]. This uppermost anatomic compartment of the skin consists of terminally differentiated corneocytes embedded in a complex lipid matrix and is a major physicochemical and anatomic barrier. Corneocytes and matrix are not only stacked in a "brick-and-mortal" pattern [12], but are interconnected by corneodesmosomes and specialized anchoring structures, which contribute to the mechanical stability. Advances in high-resolution microscopy techniques including electron microscopy [13] and Raman spectromicroscopy revealed a highly organized matrix system containing hydrophilic and hydrophobic compartments as a result of a sophisticated lipid organization [14]. Although hardly detectable under normal conditions or on tissue sections, the presence of aqueous regions has been postulated based on sonophoresis experiments [15] and studies on the penetration of deformable carrier systems across intact skin [16].

The stratum corneum essentially contributes to the fact, that penetration of most molecules across intact skin barrier is limited. Despite a more refined view on its ultrastructure with more differentiated insights on penetration pathways of large molecules [17], the original "500 Dalton rule" of dermatopharmacy as maximum molecular weight (MW) for skin penetration is still relevant [18].

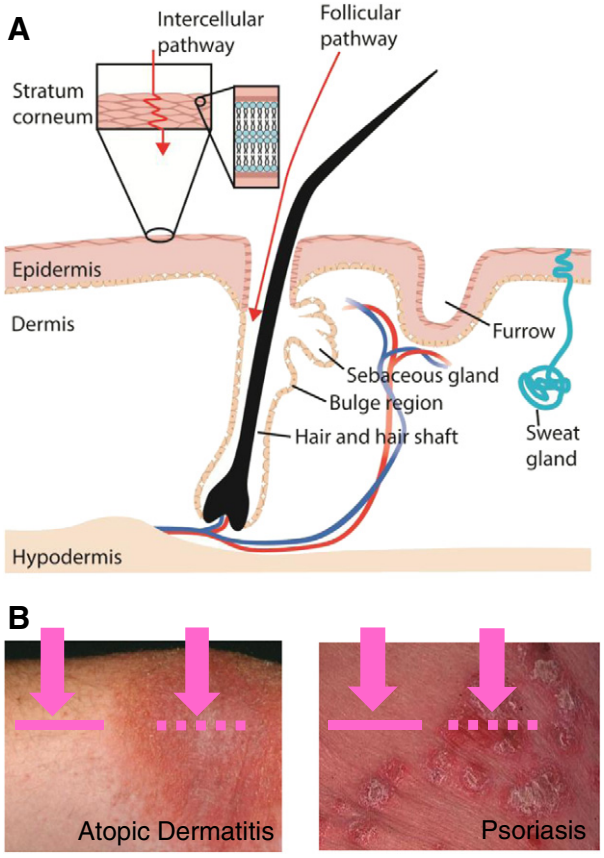

Fig. 1. Schematic representation of skin anatomy and main entrance routes for nanoparticles (A) as well as clinical images of intact and diseased skin (B). As illustrated, inflammatory processes differentially affect the skin barrier. Acute atopic dermatitis is characterized by confluent papulovesicles, psoriasis patients exhibit hyperproliferative plaques with characteristic scales.

In contrast, the hair follicles represent important reservoir structures and shunt penetration pathways. In fact, the pilosebaceous units are key anatomic compartments for particle-based drug delivery systems. Hair follicle types and dimensions vary significantly among the different body regions [19]. While scalp terminal hair follicles and dilated acne pores can conveniently be reached with particles in the submicron size range [20], penetration in body vellus hair follicles is limited to smaller particles sizes [21].

Furthermore, sebum and sweat flow contribute to the complex microenvironment on the skin surface. As a result, topical formulations have to be adjusted to the intended body region for treatment, e.g., scalp hair treatment versus acne therapy or barrier restoration of dry skin of lower legs. All in all, the impact of the skin surface microenvironment and, similarly, of the skin microbiome on penetration processes and carrier-skin barrier-interactions is only poorly understood.

Once a carrier passes the stratum corneum, tight junctions between stratum granulosum cells act as paracellular diffusion barrier as demonstrated for soluble proteins, including immunoglobulins and bacterial toxins [22]. Only limited information is available on the interactions of nanocarriers with this important skin barrier element. Yet, the observation that activation of epidermal Langerhans cells can result in increased scanning activities and active modulation of tight junctions to take up large molecules [23], illustrates the dynamics in the interplay between barrier, microbiome, topical actives and biological processes in the skin. Those insights also provide the rationale for the exploration of transcutaneous immune cell targeting strategies [24].

In case of diseased skin, the skin barrier structure and function can change in many different ways. In chronic lesional skin affected by inflammatory disorders like atopic dermatitis or psoriasis, the differentiation process of the keratinocytes, the biosynthesis of the stratum corneum [25], its lipid composition and organization are altered [26]. Inflammatory infiltrates, the release of mediators as well as altered microbial colonization all contribute to significant changes in the microenvironment of lesional skin, which are associated with shifts in conditions like pH or transepidermal water loss. Also, the function of tight junctions is affected by the disease process [27]. Although both skin diseases can be easily distinguished clinically and exhibit distinct histological changes, impaired barrier function and increased percutaneous absorption rates have been demonstrated for both diseases [28,29]. However, an increased penetration into skin did not apply to all molecules studied [30]. In fact, the penetration rates in diseased skin obtained in clinical studies on humans show rather moderate increases [31].

With a better understanding of penetration pathways across diseased skin, polymer-based nanocarrier systems specifically designed to take advantage of the skin barrier alterations in lesional skin could help addressing some of the clinical challenges in dermatotherapy. E.g., atopic dermatitis and psoriasis respond well to treatment with topical corticosteroids, but disadvantages result from the chronic course of the diseases with recurrent episodes and long-term corticosteroid treatments, which are associated with the risk of dermal atrophy and vasculopathy [32]. With respect to such low molecular weight drug molecules, patients would greatly benefit from delivery systems, which improve the selectivity of the therapy, i.e., by targeted delivery of the corticosteroids to the infiltrates or by a prolonged release from reservoirs, which maintain high concentrations at the site of action, hereby allowing for reduced applications frequencies. In contrast, as a result of its high molecular weight, the calcineurin-inhibitor cyclosporin A ($MW = 1203\ g \cdot mol^{-1}$) does not reach sufficient penetration rates for topical applications [33]. Topically applied tacrolimus ($MW = 804\ g \cdot mol^{-1}$) is effective for the treatment of acute dermatitis, but only to very limited extent for psoriasis [33], although both diseases are associated with compromised skin barrier function compared to healthy skin and respond to systemic treatment with calcineurin-inhibitors. For such molecules, effective transportation across the skin barrier is the challenge.