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Do nanoparticles have a future in dermal drug delivery?

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ABSTRACT

More and more investigations confirm that nanoparticles are incapable of overcoming the intact skin barrier in vivo. Do nanoparticles still have a future in dermal drug delivery?
Unlike many other topically applied substances, nanoparticles have not been reported to utilize the intercellular penetration pathway and preferentially make use of the follicular penetration pathway. Deep penetration into the follicular ducts has been described for a variety of particles and appears to be strongly influenced by particle size. For targeted drug delivery, smart nanoparticles are required which are able to release their loaded drugs subsequent to internal or external trigger stimuli, and thereby enable the translocation of the active agents into the viable epidermis.
In the recent manuscript, three nanoparticles systems are summarized and compared which release their model drugs upon different trigger mechanisms. The BSA hydrogel nanoparticles release their model drug TRITC-dextran by passive diffusion due to a concentration gradient via a porous surface. The protease-triggered controlled release BSA nanoparticles release their model drug if they are applied simultaneously with protease nanoparticles, resulting in an enzymatic degradation of the particles and a release of the model drug FITC. Finally, the IR-triggered controlled release AuNP-doped BSA nanoparticles release their model drug FITC after photoactivation with wIRA.
For all three nanoparticle systems, the release of their model drugs could be observed. For the first nanoparticle system, only low follicular penetration depths were found which might by due do an agglomeration effect. For the last two nanoparticle systems, deep follicular penetration and even an uptake by the sebaceous glands were verified.
In conclusion, it could be demonstrated that nanoparticles do have a future in dermal drug delivery if smart nanoparticle systems are utilized which are able to release their drug at specific times and locations within the hair follicle.

1. Introduction

Already 20 years ago, it could be shown that nanoparticles are capable of stimulating the delivery of analgesic drugs through the blood-brain barrier [1,2], and more recently, these particulate systems have been in the focus of research regarding drug delivery through the cutaneous barrier. But do nanoparticles have a future in dermal drug delivery?

Contrary to other drug delivery systems, nanoparticles provide a variety of advantages. With the use of nanoparticles, higher concentrations of drugs can be delivered to the target structures, the solubility of strongly hydrophobic drugs can be improved and their chemical and physical stability can be increased. Moreover, a gradual, controlled release of encapsulated drugs can be triggered [3]. For topical drug delivery, primarily polymeric nanoparticles, nanoemulsions, lipid-based nanoparticles including liposomes and solid-lipid nanoparticles, metallic nanoparticles and dendrimers are utilized [3]. But is their use in dermatology reasonable?

In spite of intensive research into nanoparticle-based drug delivery and isolated reports on an improved nanoparticle-based penetration

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behavior of drugs, the relevant mechanisms of action remain largely unexplored. Now as before there is a controversial discussion whether or not nanoparticles are capable of reaching viable cells [4]. Healthy skin represents a highly efficient, multi-layered barrier. Its uppermost protective layer is the stratum corneum consisting of terminally differentiated corneocytes and one extracellular lipid matrix. Located directly below the stratum corneum, the stratum granulosum accommodates the tight junctions, which are important for barrier formation [5] by sealing of the apical intercellular spaces between the cells of the living epidermis [6]. The network of antigen presenting cells in the epidermis and the dermis has a barrier function as well. The purpose of this network is to detect and process any invading foreign particles or microbes [7]. The hair follicles, which represent invaginations of the epidermis, provide another potential penetration pathway into the skin. While the stratum corneum is still intact in the upper part of the hair follicle, i.e. in the upper infundibulum, the barrier function is weakened in the lower infundibulum as the differentiation pattern changes from epidermal to trichilemmal [8]. Latest findings revealed, however, that the hair follicle also accommodates barrier-forming tight junctions [5], which are located in the outermost layer of the external root sheath extending from the infundibulum to the suprabulbar region. They are also present in Huxley's layer of the internal root sheath in the suprabulbar region. In the hair bulb region, no barrier is detectable.

Due to the strong barrier function of the intact skin, the administration - especially the transdermal administration - of adequately dosed drugs has always been a challenging task in pharmacology. Thus, any efforts to improve dermal or transdermal penetration by means of nanoparticles may not seem plausible at first glance. Actually, in most studies addressing the penetration of various types of nanoparticles subsequent to topical application onto healthy skin, the best result found was penetration into the uppermost layers of the stratum corneum, whereas no penetration into the underlying epidermis or dermis was detected [6]. However, there are clear indications that nanoparticles are capable of penetrating into deeper dermal layers, once the integrity of the cutaneous barrier is disturbed and the immune system activated [6]. Vogt et al. [9], e.g., could show that cyanoacrylate skin surface stripping clearly enhanced particle penetration into both the hair follicle and the stratum corneum, simultaneously activating the Langerhans cells.

In 2013, Labouta and Schneider compared recent studies on the cutaneous penetration of inorganic particles in a review article [10]. Prima facie, cutaneous particulate penetration was observed in about half of the 40 studies under review, although in most cases the penetration was mechanically or chemically stimulated or excised mammalian skin was used for the related penetration experiments. All these measures involve a disturbance of the integrity of the skin and the cutaneous barrier, which must be taken into account when evaluating the results of the corresponding studies. In the case of in vivo skin experiments, no penetration into the viable epidermis has ever been detected.

Meanwhile it could be shown in many studies that nanoparticles are delivered efficiently and deeply into the hair follicles, with the particulate penetration generally proving to be considerably deeper than that of comparable solutions [11]. Moreover, the penetration depth seems to strongly depend on the particle size [12] rather than on the particle composition. This suggests a mechanical influence on the penetration process [13], which may be triggered by the movement of the hair inside the follicle. In this context, the optimum particle size for the deepest follicular penetration possible was determined in the range of 600 nm, which corresponds approximately to the thickness of the cuticula cells of the hair shaft [13]. Particles larger or smaller than approximately 600 nm in size showed significantly reduced follicular penetration depths. Recently, this mechanism and the size dependency could be confirmed based on theoretical models [14]. Various other parameters, such as a negative surface charge and lipophilic surface properties are also capable of heightening follicular penetration [15]. A deep follicular penetration of nanoparticles is desirable, e.g., if drugs are to be delivered directly to the target structure in the hair follicle. Some examples for application include, inter alia, the successful improvement of skin disinfection by application of polyhexanide-containing nanoparticles. Using these nanoparticles, the antiseptic was delivered into the hair follicles, where approximately 25% of the bacterial flora of the skin resides [16]. By encapsulating nanoparticles with hair-growth stimulating substances, the penetration into the hair follicle could be improved [17–19]. Specific targeting of the sebaceous glands also provides promising therapeutic options to improve the treatment of acne vulgaris, rosacea or other diseases.

However, no transfollicular penetration through the barrier of the hair follicle into the living epidermis could be demonstrated thus far. Mathes et al. [5] studied the penetration of polymer particles into the hair follicle and detected most particles in the infundibulum. A translocation into the viable cells of the external root sheath could not be demonstrated. In the infundibular region, the hair follicle is protected by two barriers, i.e., the stratum corneum and the functional tight junctions. In the lower part of the hair follicles, where the barrier consists exclusively of tight junctions, only a few particles were detectable, but no translocation at all. Consequently, this penetration pathway is also unsuitable for nanoparticle-assisted drug delivery into the living epidermis or dermis. Is there really no future for particles in dermatotherapy?

In terms of risk assessment, these findings are positive, as potential interactions between the nanoparticles and the skin or skin cells, respectively, have not been sufficiently elucidated yet. In a comprehensive study, Vogt et al. [20] investigated the interactions between skin and silica, titanium dioxide and silver particles. As a result of ex vivo experiments, the greatest amounts of topically applied particles were detected on the skin surface, whereas only trace amounts were found in a few cells after cell separation. A penetration of biologically relevant amounts was only observed if the barrier was disturbed by, e.g., inflammatory dermal diseases, structural defects to the cutaneous barrier, open wounds, or subsequent to excessive exposure to solar radiation.

Recently, a new strategy has been developed to utilize the advantages of nanoparticles for drug delivery. The underlying principle is to provide the particles with a release mechanism. If so, the only function of the carriers is to deliver the drug deeply into the hair follicle, where it is released by an internal or external mechanism. Subsequently, the released drug can penetrate into the living epidermis via the hair follicles. Care is to be taken, however, that the drug is released at the correct site and point in time. Contrary to continued drug release from carrier systems, the novel systems release their drug load in a controlled manner directly on the specific target site, thus leading to an improvement of the treatment efficiency.

For controlled release, various parameters can be taken into consideration, e.g., changes in the pH value or in temperature, radiofrequency [21], ultrasound [22] and light [23].

In the following, we present and compare results from our own studies [24,25] on the advance of stimuli-responsive controlled-release carrier systems for the transport and release of drugs within the hair follicles obtained in the frame of the Collaborative Research Center 1112.

2. Materials and methods

In order to investigate and compare different stimuli-responsive controlled release mechanisms, three different nanoparticle systems were investigated for their follicular penetration depth and release behavior within the hair follicle. The results of the bovine serum albumin (BSA) hydrogel nanoparticles are currently under review. The results of the protease-triggered controlled release BSA nanoparticles and of the infrared (IR)-triggered controlled release gold nanoparticles (AuNP)-doped BSA nanoparticles have already been published separately [24,25].

Spherical AuNPs (20 nm), calcium chloride, sodium carbonate, BSA, fluorescein isothiocyanate (FITC)-labelled BSA, dithiothreitol (DTT),