The Increasing Importance of the Hair Follicle Route in Dermal and Transdermal Drug Delivery

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Contents

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5.1 Introduction

For more than 200 years, constant attempts have been made to administer drugs via the skin and to enhance percutaneous penetration by various methods including mechanical, physical, and chemical manipulations to reduce the barrier function of the skin (Helmstadter 2011). In total, three potential penetration pathways have been identified. In addition to the well-described intercellular penetration pathway being mainly responsible for the percutaneous penetration effect, also the follicular route has been spotted to be of considerable interest as especially the upper portion of the hair follicle – the infundibulum – displays an area of additional absorption. However, in different skin sites, the size and number of hair follicles can differ tremendously (Otberg et al. 2004b); thus, also the influence of the follicular penetration route can vary. The transcellular penetration pathway, on the contrary, seems to be of inferior importance.

The aim of the present chapter is to describe and define the role of the hair follicle in the penetration process and to identify mechanisms which allow follicular penetration enhancement.

Due to the architectural structure of the hair follicle, follicular penetration is a complex process and has to be divided at least into two steps as illustrated in Fig. 5.1. It has to be distinguished between the penetration into the hair follicle and, in the second step, the transfollicular penetration

N. Dragicevic, H.I. Maibach (eds.), *Percutaneous Penetration Enhancers Chemical Methods in Penetration Enhancement: Drug Manipulation Strategies and Vehicle Effects*,
DOI 10.1007/978-3-662-45013-0_5, © Springer-Verlag Berlin Heidelberg 2015

into the living tissue surrounding the hair follicle, which cannot be observed for every applied substance, yet. Previous investigations could show that mainly the physicochemical properties of a topically administered substance determine its follicular penetration depth (Patzelt et al. 2011) and whether or not the substance is able to penetrate transfollicularly. Thus, modifications of the physicochemical properties of the substances such as size can be utilized as follicular penetration enhancers or inhibitors.

In comparison to the intercellular penetration process, topical drug delivery via the hair follicles provides additional features such as fast delivery into the systemic circulation if transfollicular penetration is applicable (Otberg et al. 2008) as well as long-term intrafollicular storage (Lademann et al. 2006) if transfollicular penetration cannot be realized. These and more aspects will be discussed in this chapter.

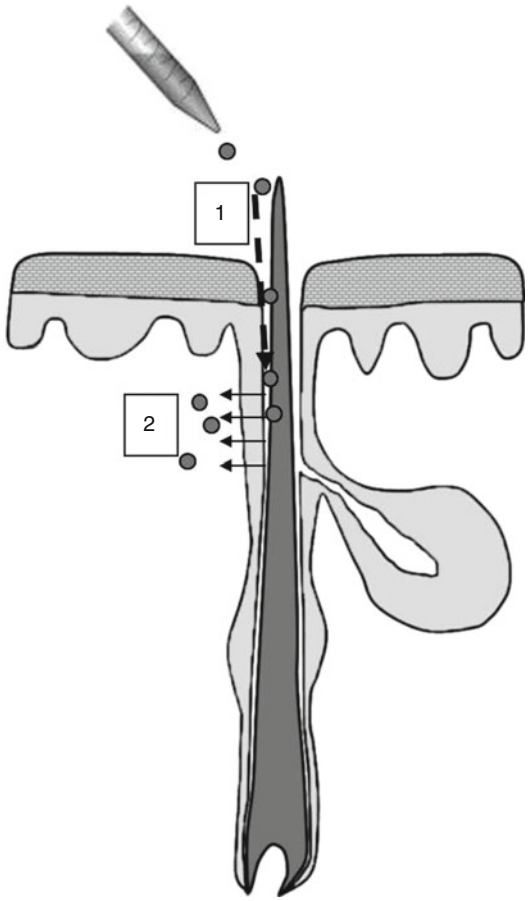

Fig. 5.1 Schematic illustration of the follicular penetration pathway which has to be divided into two steps: (*1*) intrafollicular penetration and (*2*) transfollicular penetration if allowed due to size reasons

5.2 Architectural and Physiological Features of the Hair Follicle with Regard to Follicular Penetration

Due to its complex and dynamic architectural structure, the hair follicle is predestined as a penetration and storaging organ, although the original functions of the hair follicle seem to be rather those of a sensory organ, sebum excretion and protection (Krause and Foitzik 2006). The infundibulum is the upper part of the hair follicle and consists of an upper and lower portion as depicted in Fig. 5.2. The epithelium of the upper infundibulum is continuous with the keratinized epidermis and covered by an intact stratum corneum, whereas the differentiation pattern of the lower infundibulum switches from epidermal to trichilemmal leading to an interrupted skin barrier with only few differentiated corneocytes

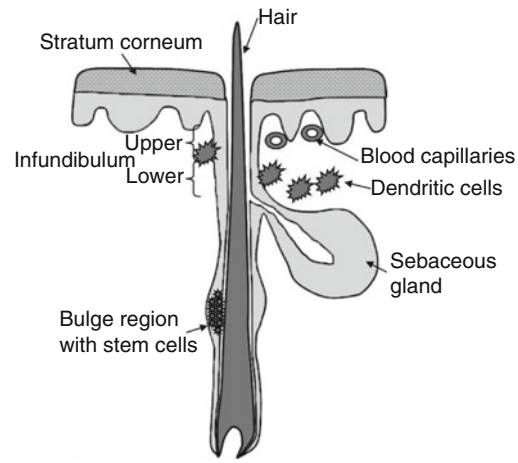

Fig. 5.2 Schematic overview of the follicular architecture especially depicting the structures relevant to the follicular penetration process such as the infundibulum surrounded by the blood capillaries and dendritic cells, the sebaceous gland, and the bulge region with stem cells

remaining (Blume-Peytavi and Vogt 2011) that are more prone to transfollicular penetration in this region. Moreover, the whole follicular infundibulum is supplied by a dense capillary network and surrounded by a high number of immune cells, on the one hand allowing the rapid systemic uptake of substances once penetrated transfollicularly and, on the other hand, rendering the hair follicle to be a promising target for immune therapy or topical vaccination (Patzelt et al. 2011; Vogt et al. 2008).

Additionally, as depicted in Fig. 5.2, also the sebaceous gland and the bulge region of the hair follicle which is hosting the stem cells are interesting structures within the hair follicle, at the same time being attractive targets for therapeutic interventions (Patzelt et al. 2011). The sebaceous gland is the organ of sebum excretion and additionally associated with a diversity of pathologies such as acne (Thiboutot 2004). It was suggested that by increasing the distribution of corresponding drugs in the sebaceous gland, the therapeutic effectivity could be significantly improved (Rolland et al. 1993). Respective efforts have already been made (Morgan et al. 1993; Ridolfi et al. 2012; Rolland et al. 1993), and some promising antiacne products are already on the market. The multipotent, highly proliferative, and easily accessible stem cells located in the bulge region (Ohyama 2007) are also to be integrated in the therapeutic concepts for cutaneous regenerative medicine or gene correction of congenital hair disorders or genetic skin diseases.

In total, more than 20 different cell types are involved in the structure of the hair follicle which underlies cyclical activity (Rogers 2004). Three different hair follicle types, namely, lanugo, vellus, and terminal hair follicles, have to be distinguished. Whereas the same hair follicle produces lanugo hairs in the fetal period and vellus hairs in the childhood, it produces terminal hairs in the adulthood (Blume-Peytavi and Vogt 2011). In total, each human individual displays an estimated number of five million hair follicles (Krause and Foitzik 2006) underlining its potential in the penetration process. The morphometry of vellus and terminal hair follicles has been well documented already (Vogt et al. 2007). A schematic overview of the follicular architecture is depicted in Fig. 5.2.

5.3 Mechanisms of Follicular Penetration and Transfollicular Penetration

5.3.1 Mechanisms of Follicular Penetration

The follicular penetration of topically applied substances represents a complex process which has not been clarified in detail until now. Whereas the retention of the particles in the follicular duct has been well documented, researchers are controversially discussing which substances are able to penetrate transfollicularly into the deeper skin layers, whereby the size next to other physicochemical properties seems to be the predominant parameter (Labouta and Schneider 2013). In the last years, predominantly particulates such as liposomes and micro- and nanoparticles have attracted attention as a result of their capability to improve penetration into the hair follicle. Here, a clear size dependency could be observed demonstrating that 320 nm sized polymer particles covalently labeled with a fluorescent dye penetrated significantly deeper into the hair follicles than the same fluorescent dye in nonparticulate form (Lademann et al. 2007). The optimum size for particles to penetrate deeply into the hair follicle was determined to be in the range of 400–700 nm, whereas larger and smaller particles reached significantly lower penetration depths (Patzelt et al. 2011) or remained even on the skin surface in the case of very large particles (Schaefer and Lademann 2001; Toll et al. 2004). As this effect was demonstrated for different solid particle preparations such as PLGA particles and silicium oxide particles, it was assumed that follicular particle penetration is a predominantly mechanical effect independently from the particle preparation (Patzelt et al. 2011). In Fig. 5.3, the dependency of the penetration depth on the particles' size is schematically represented. Lademann et al. (2009) hypothesized

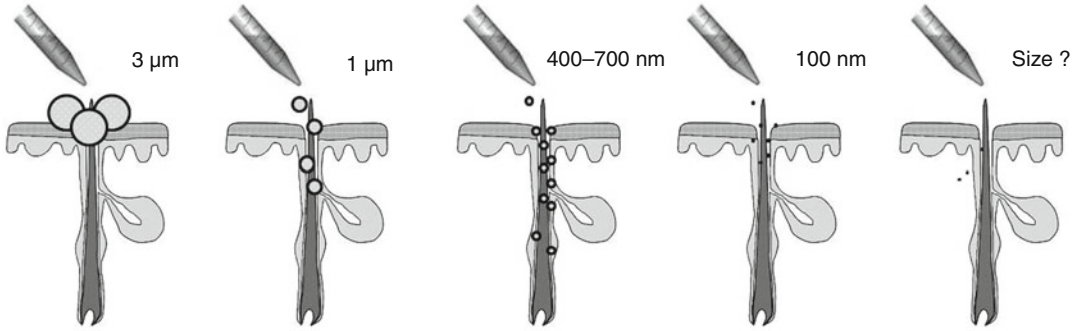

Fig. 5.3 Dependency of the penetration depth of the particles on the particles' size. Large particles (>3 µm) are only located on the skin surface and in the follicular orifice. Particles between 400 and 700 nm penetrate significantly deeper into the hair follicles than larger or smaller particles. A size threshold below which transfollicular penetration occurs has not been determined, yet

that the surface structure of the hair and the hair follicle, which is determined by the thickness of the keratin cells in the cuticula, being 530 nm in human hairs and 320 nm in porcine hairs, might act as a pumping system delivering the particles deeply into the hair follicle as demonstrated in Fig. 5.4. Whereas the movement of the hair occurs physiologically in vivo, it could be shown that this effect can be simulated in vitro by massage appliance (Lademann et al. 2007; Patzelt et al. 2011).

Once penetrated into the hair follicles, substances are stored over several days (Lademann et al. 2006) within this protected area if transfollicular penetration is not feasible. Whereas the reservoir of the stratum corneum is relatively unprotected and thus easily depleted by daily processes such as textile or water contact in combination with the physiological desquamation process removing one layer of corneocytes per day, the hair follicle represents a protected reservoir which can only be depleted by such slow outward-directed processes as sebum flow and hair growth. Previous investigations could show that a particle-containing formulation was still detectable within the hair follicle after 10 days, whereas the stratum corneum reservoir had already been almost completely depleted after 1 day (Lademann et al. 2006) as presented in Fig. 5.5. This long-term storage effect could be effectively utilized for therapeutic purposes as the application of drug-loaded particles with

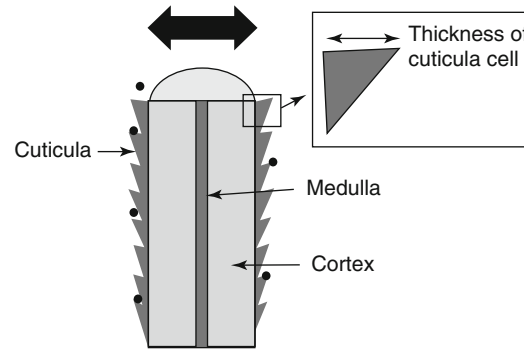

Fig. 5.4 Schematic cross section of a hair illustrating the specific structure of the cuticula cells. It has been hypothesized that this surface structure which is determined by the thickness of the cuticula cells might act as a pumping system delivering the particles deeply into the hair follicles when cuticula thickness and particle size are similar

retarded release could diminish the application frequency and thus increase the compliance of patients and the therapeutic outcome.

This therapeutic effectivity could even be enhanced when the correct skin site is chosen for the application. Otberg et al. (2004b) measured the follicular density, the volume of the follicular infundibula per square centimeter of skin, and the surface of the follicular infundibula per square centimeter of skin. The latter corresponds to the additional absorption area provided by the hair follicles. They could show that the forehead and the calf regions had the highest follicular volume per square centimeter of skin surface which was

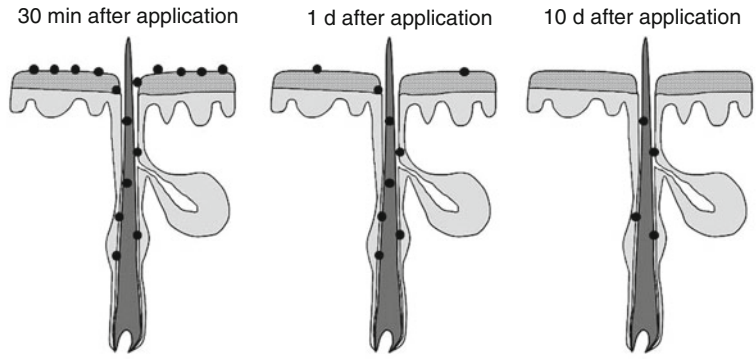

Fig. 5.5 The hair follicle is a long-term reservoir for topically applied substances. Directly after application, the applied particles are distributed on the skin surface and within the hair follicle. After 1 day, the stratum corneum reservoir is significantly depleted, whereas the particles are still available within the hair follicle. After 10 days, part of the particles are still detectable within the hair follicle

explained by the high follicle density on the forehead and the large hair follicles on the calf. It was estimated that the reservoir volumes of the hair follicles and of the stratum corneum were comparable in these body regions as demonstrated in Fig. 5.6, whereas the reservoir of the hair follicles in the region of the forearm was significantly lower by a factor of 20 in comparison to the stratum corneum reservoir.

The investigation of follicular penetration still represents a challenge as it requires spatial resolution. Nowadays, several methods are available to investigate follicular penetration reasonably. These methods have been recently summarized by Meidan et al. (2010) and include, inter alia, the selective artificial closing technique, where the hair follicles are selectively blocked with a varnish-wax mixture and thus excluded from the penetration process (Teichmann et al. 2006), the usage of a sandwich model (Barry 2002), where the top skin layer blocks the shunts in the bottom layer or the differential stripping method (Teichmann et al. 2005). Further novel optical devices are, e.g., autoradiography (Fabin and Touitou 1991), confocal laser scanning microscopy (Lademann et al. 2010) or combined confocal laser scanning microscopy with confocal Raman spectroscopy (Caspers et al. 2003).

Next to methodological challenges, also the selection of adequate model systems plays a superior role as could be demonstrated recently. Patzelt et al. (2008) could demonstrate that for

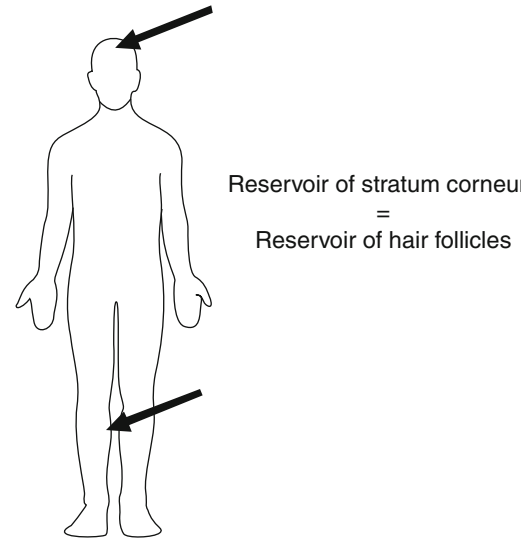

Fig. 5.6 The largest follicular reservoir can be found on the calf and the forehead. Here, the follicular reservoir is comparable to the stratum corneum reservoir

experiments performed on the same volunteers and each on the contralateral skin site, the in vitro follicular reservoir was only 10 % of the in vivo follicular reservoir. It was assumed that the elastic fibers surrounding the hair follicle contract during the excision. Whereas the removed skin sample can be re-stretched to its original size by expanding the interfollicular elastic fibers, those surrounding the hair follicle remain contracted and reduce the follicular reservoir significantly. Based on these observa-

tions, it can be stated that excised skin is not an appropriate model to investigate follicular penetration. However, in vivo investigations are not always feasible as substances or methods are mostly too injurious. As a result, the porcine ear model has been determined to be a suitable ex vivo model as the full skin can remain fixed on the underlying cartilage during the experiments, and the good and well-documented similarities of porcine and human skin architecture and structure allow a reasonable evaluation of the obtained data (Lademann et al. 2010).

In this context, it has to be emphasized that full skin samples including the subcutaneous tissue are very important for follicular penetration investigations. For diffusion cell experiments, however, mostly split skin or epidermal skin is utilized where at least the subcutaneous tissue is discarded meaning that the lower part of the hair follicle which reaches deeply into the subcutaneous tissue is cut off. This means that the inferior part of the hair follicle is open and the topically applied substances can diffuse directly into the receptor medium as demonstrated in Fig. 5.7. Similar concerns have already been raised by Senzui et al. (2010).

In addition to physicochemical properties of the applied substance and the pumping effect transporting the substances into the hair follicle by hair movement, also the activity status of the hair follicles seems to play an important role and decides whether or not follicular penetration occurs at all. As mentioned earlier, each hair follicle undergoes continuous cycling, which includes the complete remodeling of its nonpermanent portion and which influences the hair growth and sebum excretion activity of each hair follicle. A previous study could demonstrate that it can be distinguished between active hair follicles, which provide hair growth and/or sebum excretion and are open for penetration, and inactive hair follicles which provide neither hair growth nor sebum flow and are thus inaccessible for topically applied substances (Otberg et al. 2004a). For these inactive follicles a cover consisting of dried sebum and desquamated corneocytes was detected in the follicular orifices that prevents any penetration process. In the forearm region, one fourth of the hair follicles were shown to be unreceptive for penetration.

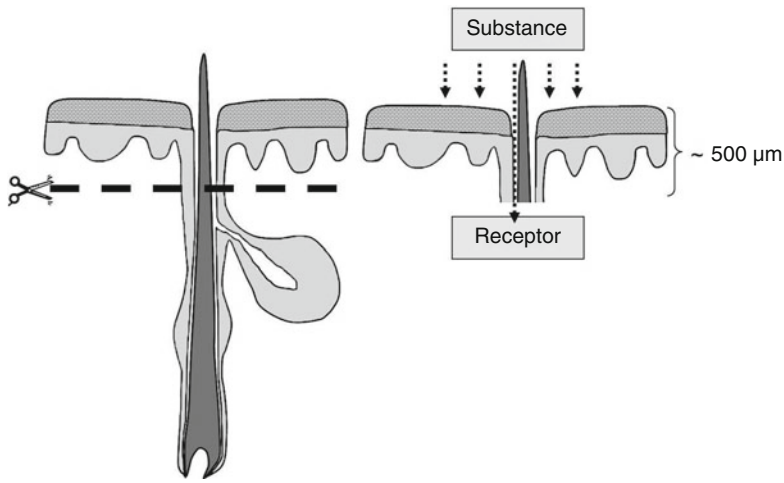

Fig. 5.7 Removing the subcutaneous tissue leads to a violation of the distal hair follicle. If, as usual, only the upper part of the skin is utilized for diffusion cell experiments, the topically applied substance can just diffuse into the receptor medium via the open inferior part of the hair follicle. Thus, the utilization of diffusion cell experiments is not an appropriate method to investigate follicular penetration

5.3.2 Mechanisms of Transfollicular Penetration

Transfollicular penetration of topically applied substances and mechanisms of transfollicular penetration have not been fully clarified, so far. It can be assumed, yet, that transfollicular penetration occurs mainly in the region of the infundibulum and specifically in the lower portion of the infundibulum where the barrier is interrupted due to the switch of a differentiation pattern as mentioned above and depicted in Figs. 5.1 and 5.3. For smaller non-particulates, i.e., substances such as caffeine or minoxidil, a rapid transfollicular penetration and systemic uptake has already been reported (Blume-Peytavi et al. 2010; Otberg et al. 2008). Interestingly, the systemic uptake was significantly faster (already after 5 min) when the hair follicles were accessible in comparison to skin areas where the hair follicles were selectively blocked previously. Here, the substances needed approximately 20 min to be detectable in the circulation. For particles the situation seems to be different, yet. There are clear indications that the transfollicular penetration process is predominantly determined by the size of the applied particles, although a clear size threshold for transfollicular penetration could not be defined so far. Recently, Labouta and Schneider (2013) reviewed the current literature focusing on skin penetration of inorganic particles. It could be shown that about half of the studies reported particle penetration or permeation. However, most studies' protocols involved either mechanical or chemical penetration enhancers (Dixit et al. 2007; Krishnan et al. 2010; Labouta et al. 2011; Mortensen et al. 2008; Paliwal et al. 2006; Upadhyay 2006; Zhang and Monteiro-Riviere 2008) or utilized excised either animal or human skin in in vitro diffusion cell experiments. With regard to risk assessment or mechanistic investigations concerning transfollicular penetration, the utilization of penetration enhancers or of in vitro diffusion cell experiments seems to be not reasonable as described above as overestimation of particle penetration can occur if penetration is either artificially enhanced or investigations are performed with dermatomed or split skin which always includes a violation of the distal hair follicle so that topically applied substances can just diffuse into the receptor medium. Whereas the contraction effect of the elastic fibers surrounding the hair follicle assumed by Patzelt et al. (2008) might be able to inhibit the diffusion of larger particles, it might explain that the detected diffusion of very small particles into the receptor medium is erroneously interpreted as penetration. This theory is supported by the fact that for all human in vivo studies reported by Labouta and Schneider (2013), no particle penetration or permeation could be detected. Only some studies were performed in vivo on animal skin, and within this group, only few studies reported a penetration into deeper skin layers of very small particles. The authors assumed that the gold nanoparticles utilized in their study might interact hydrophobically with the skin lipids leading to a disruption of the skin lipid layer structure, subsequent increased skin permeability and penetration into deeper skin layers (Huang et al. 2010). This assumption still needs further verification.

Summarizing the recent findings on transfollicular penetration, it can be stated that particles are well suitable to deliver active substances into the hair follicle, whereas transfollicular penetration is rather unlikely. For particles larger than 100 nm, intercellular or transfollicular permeation has not been observed in intact skin, yet; for smaller particles further research is necessary to define a clear threshold below which transfollicular and intercellular penetration can occur, which is also an important aspect with regard to risk assessment.

5.4 Enhancement of Follicular Penetration

As summarized above, particulate nanocarriers are excellent delivery systems for active substances into the hair follicle, which moreover, represents an interesting target site and permits fast access into the deeper viable skin layers by bypassing the complex intercellular penetration

pathways. The disadvantage – or advantage in terms of risk assessment – however is that particles have not been reliably demonstrated to penetrate intercellularly or transfollicularly.

Therefore, new approaches have to be developed to utilize the advantages of particulate delivery – such as deep follicular penetration, long-term follicular storaging, sustained release, and shielding from degradation – also for transfollicular transport of active substances.

One option is to utilize particles exclusively for delivery of substances into the hair follicle and its specific target sites. Recently, it was demonstrated that an antiseptic associated with approximately 300 nm sized carrier particles originating from a fat emulsion on the basis of medium- and long-chain triglycerides (Lipofundin® MCT/LCT, Braun, Germany) was able to achieve longer lasting antiseptic effects than the same substance in a non-particulate form (Ulmer et al. 2012). The study was based on the assumption that about 25 % of the resident bacteria colonizing the skin reside within the hair follicles (Lange-Asschenfeldt et al. 2011). Conventional non-particulate antiseptics, however, are not able to eradicate all bacteria from this follicular reservoir which leads to a fast recolonization of the skin. In contrast, it was shown that the particle-based antiseptic was able to penetrate deeply into the hair follicle. The recolonization was consequently retarded. Other examples for improved follicular penetration and optimized therapeutic effects include the application of encapsulated hair-growing substances or acne or rosacea therapeutics (Rolland et al. 1993; Shim et al. 2004; Tsujimoto et al. 2007). Some of the products are already commercially available (Papakostas et al. 2011).

If intrafollicular penetration of a therapeutic is not sufficient, strategies have to be developed to enhance the transfollicular permeation of the particles or of the active substance alone after particulate delivery into the hair follicle.

An easy, but invasive approach to translocate substances to the viable skin is to disturb the skin barrier prior to the application of the substance or particles, respectively. Here, several techniques are available such as cyanoacrylate skin surface biopsies, chemical enhancers, microneedles, electroporation, or ultrasound (Lawson et al. 2007; Vogt et al. 2008).

As a noninvasive alternative, the triggered release of substances from particle preparations has recently been introduced. In this approach, the particles exclusively serve as delivery systems to the desired penetration depth within the hair follicle which can be controlled by the particle size. Having reached the desired depth, the particles release their active agent by a specific triggering signal which can then translocate independently to the viable skin. The principle is illustrated in Fig. 5.8. By utilizing these stimuli-responsive controlled release systems, site-selective, controlled release patterns can be achieved leading to increased therapeutic efficacy and decreased side effects (Zhu et al. 2005).

At the moment, research especially focuses on the identification of appropriate

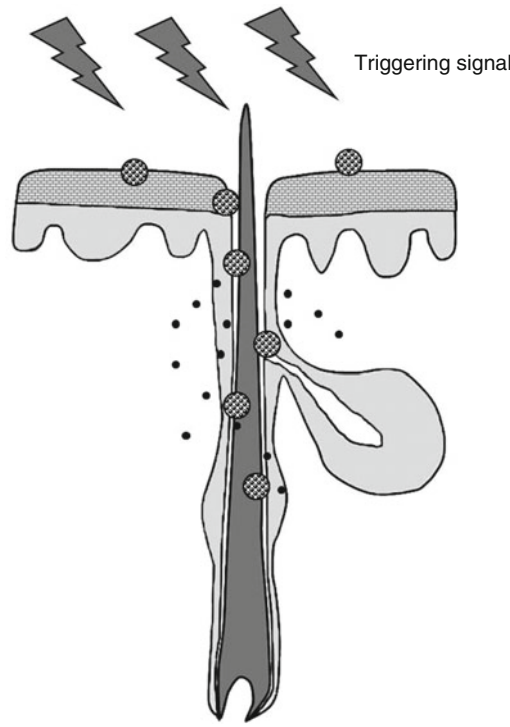

Fig. 5.8 Principle of stimuli-responsive release systems. The particles deliver the drug molecules to the desired depth within the hair follicle. After external or internal stimulus, the active drug is released from the particle and translocates independently to the deeper viable skin layers

stimuli-responsive release systems. Mak et al. (2011, 2012) recently introduced a release system based on the interaction of the particles with a protease. When the protease was likewise applied in particulate form, similar penetration depths were reached for the particles and the protease leading to a release of the active substance from the delivering particles also at significant depths of the hair follicle. Even an uptake of the model drug by the sebaceous gland could be detected.

Additional general approaches of controlled drug release include the application of high-frequency magnetic fields (Hu et al. 2008), ultrasound (Huang 2008), radiofrequency (Brazel 2009), light (Pissuwan et al. 2011), and pH drifts (Zhu et al. 2005). Controlled drug release could also be observed after utilizing CdS nanoparticles as caps for mesoporous channels and disulfide bond-reducing molecules physically blocking the drugs of certain sizes from leaching out (Lai et al. 2003). A new promising concept is also the application of gold nanoparticles in combination with near-infrared light. Gold nanorods have an absorption band in the near-infrared region and convert absorbed light energy into heat and can therefore act as a controller of a drug release system when combined with near-infrared light (Yamashita et al. 2011).

Most of these approaches have still to be verified in combination with particles in the follicular situation, which will certainly be a topic of future investigations.

Conclusion

The optimization of drug delivery to and via the hair follicle is getting more and more important as the hair follicle offers target sites of therapeutic interest and represents a rapid access to the deeper skin layers and the circulation if transfollicular penetration is feasible. Current aspects of optimized follicular drug delivery involve the adaptation of particulate carrier systems which have been demonstrated to deliver substances preferably deep into the hair follicle without allowing transfollicular penetration, yet. New approaches specifically aim at the development of controlled drug release systems where the particles only serve as transporters deep into the hair follicle. Here, the active drug is released by a specific triggering signal and can translocate independently to the deeper viable skin layers surrounding the hair follicles, subsequently. The controlled drug release represents a promising concept to utilize the advantageous delivering attributes of particles also for transfollicular penetration.

Acknowledgments We would like to thank the Foundation "Skin Physiology" of the Donor Association for German Science and Humanities for financial support. Parts of this work were realized within the BMBF project "Topische Vakzinierung mit funktionalen Nanopartikeln." The authors acknowledge that this work was supported by a grant funded by the German Ministry of Education and Research (BMBF, grant no, 13N9197). Furthermore, we thank Ulrich Schäfer and Claus-Michael Lehr (University of Saarbrücken) for providing particle preparations and Reinhardt Renneberg (Hong Kong University of Science and Technology) for providing the particles for the triggered release experiments.

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