

Utilization of biodegradable polymeric materials as delivery agents in dermatology

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Abstract: Biodegradable polymeric materials are ideal carrier systems for biomedical applications. Features like controlled and sustained delivery, improved drug pharmacokinetics, reduced side effects and safe degradation make the use of these materials very attractive in a lot of medical fields, with dermatology included. A number of studies have shown that particle-based formulations can improve the skin penetration of topically applied drugs. However, for a successful translation of these promising results into a clinical application, a more rational approach is needed to take into account the different properties of diseased skin and the fate of these polymeric materials after topical application. In fact, each pathological skin condition poses different challenges and the way diseased skin interacts with polymeric carriers might be markedly different to that of healthy skin. In most inflammatory skin conditions, the skin's barrier is impaired and the local immune system is activated. A better understanding of such mechanisms has the potential to improve the efficacy of carrier-based dermatotherapy. Such knowledge would allow the informed choice of the type of polymeric carrier depending on the skin condition to be treated, the type of drug to be loaded, and the desired release kinetics. Furthermore, a better control of polymer degradation and release properties in accordance with the skin environment would improve the safety and the selectivity of drug release. This review aims at summarizing the current knowledge on how polymeric delivery systems interact with healthy and diseased skin, giving an overview of the challenges that different pathological skin conditions pose to the development of safer and more specific dermatotherapies.

Keywords: nanocarriers, nanoparticles, biodegradable polymers, skin penetration, hair follicles

Introduction

Nanotechnology offers a vast possibility to improve delivery, bioavailability, and targeting of drugs and cosmetics to skin. Considering the good accessibility of skin, the possibility to treat skin disorders by topical therapies is very appealing. This method of administration increases patient compliance, reduces side effects, avoids the hepatic first pass metabolism, hereby enhancing the amount of drug at the site of action, and could help to reduce the dose required to obtain therapeutic effects.¹ Supramolecular drug delivery systems (DDS) applied topically to diseased skin should accumulate and release the drug at the site of action. In diseased skin, because of impaired stratum corneum (SC) and/or activated immune system, the penetration of macromolecules and particulate materials is often altered with respect to healthy skin. Thus, to avoid possible side effects, the use and development of biodegradable and biocompatible nanomaterials is necessary. In medicine, the term biodegradable describes materials

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which breakdown into molecules that are nontoxic and can be metabolized or eliminated by the body. The term biocompatible is often used to describe nondegradable materials that are eliminated by renal clearance and have been shown to be safe in *in vivo* studies. In this review, focus is given to biodegradable polymer materials that have been developed and tested as delivery agents for dermatotherapies. Some of the most investigated biocompatible polymeric materials will be also discussed. We aim to offer an overview of the different types of DDS and the key processes occurring after their topical administration. In particular, the different pathophysiological conditions occurring in skin diseases have been outlined in order to emphasize that each different pathological condition brings specific challenges that have to be taken into account when developing and investigating new carrier systems.

Types of biodegradable polymeric DDS

The first delivery systems that were investigated and marketed for dermatological and cosmetic applications were liposomes.² Thereafter, solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) were developed, which are more stable and have better skin penetration.³ In the past few years, an increasing number of polymeric carriers have been investigated for topical drug delivery.⁴ Biodegradable polymers offer certain advantages over lipid-based carriers. They can be stored over months, both hydrophobic and hydrophilic drugs can be encapsulated or adsorbed, they can be functionalized, and most importantly their physicochemical properties can be adjusted in order to achieve a controlled release of the encapsulated drug. Several different types of polymer-based DDS have been tested for drug delivery. Polymeric fibers are used in tissue engineering as scaffolds for tissue reconstruction and wound healing.^{5,6} Poly(ϵ -caprolactone) (PCL), collagen, and hyaluronic acid are some of the polymers used to prepare biological matrixes. They can be loaded with growth or angiogenic factors to favor tissue regrowth or antimicrobials to avoid wound infection.^{7,8} Hydrogels consist of hydrophilic molecules, called gelling agents, which are chemically or physically cross-linked and form a three-dimensional network with the ability to absorb high amounts of water.⁹ Hydrogels can be made of natural polymers, like alginate, chitosan, dextran, or of synthetic material like poly(ethylene glycol) (PEG), poly(lactic-co-glycolic acid) (PLGA), or a combination of natural and synthetic polymers.¹⁰ They can be loaded with a variety of drugs, mainly hydrophilic ones, and have been largely

investigated for drug delivery in medicine. Organogels are gelling agent networks able to incorporate oil or organic solvents. Polymers like poly(ethylene) and PEG, as well as copolymers of methacrylic acid¹¹ and methyl methacrylate (MMA) are commonly used. These polymers are nonbiodegradable but are considered biocompatible;¹² because of their lipophilic nature they can incorporate hydrophobic drugs and have a better skin penetration.¹³ Hydrogels have also been used to disperse nanocarriers enhancing their distribution on the skin surface and were applied as a delivery system for wound healing.^{14,15} Nanogels are nanoscaled organogels and hydrogels. Using appropriate linkers it is possible to make nanogels stimulus-responsive (eg, temperature, pH, light).^{16,17} Thus, the release of encapsulated drugs can be controlled by exploiting the unique parameters of diseased skin or even using an external trigger. The small size and the deformability of nanogels favor their accumulation in the SC and in the hair follicle canal. Polymeric spheres are made of several polymer chains which in water spontaneously “roll-up” to form spherical particles. Both natural and synthetic polymers have been used. Natural polymers are derived from animals as well as plants and include polysaccharides, such as cellulose, chitin, starch, alginate, galactan, hyaluronic acid, dextran, and gellan,¹⁸ or protein-based carriers like albumin, gelatine, collagen, milk and silk proteins, soy proteins, and lectins.^{19,20} Polydepsiptides are synthetic peptide polymers which are degraded into biocompatible amino acids.²¹ Their composition can be adjusted to achieve an optimal complexation of the loaded drug and to control their physicochemical properties such as hydrophobicity/hydrophilicity. The most studied synthetic biodegradable polymers used to prepare micro and submicron spheres for drug delivery are poly(lactic acid) (PLA),²² PLGA and PCL.^{23,24} PLA particles are prepared from renewable sources. They allow for an easy-scalable and low cost production and are degraded to lactic acid, a resorbable and non-toxic monomer.²⁵ Polymeric micelles are auto-assembled micelles made of amphiphilic macromolecules such as di- or tri-block copolymers. Examples of biodegradable micelles are those based on PEG, PLA, PCL, or chitosan, whereas poly(amidoamine) (PAMAM) micelles are considered biocompatible. The advantages of such particles are their small size, the solubilization of hydrophobic drugs, and the possibility to functionalize their surface with targeting units.²⁶ Dendrimers and dendritic polymers consist as macromolecules with a branched structure in which different types of drugs can be intercalated or covalently bound. Dendritic core-multishell nanocarriers have amphiphilic architecture

consisting of a hydrophobic inner shell and a hydrophilic outer shell allowing the encapsulation of lipophilic drugs and the control of surface polarity. Polyester dendrimers made of glycerol, succinic acid, phenylalanine, and lactic acid are promising biodegradable carriers.²⁷

Polymeric carriers are available in different sizes ranging from nanometer to submicron and micrometer dimension. In general, the organic nature of the polymer and the three-dimensional conformation confer them flexibility and deformability, which are important requisites for penetration across tissue barriers.

Key processes after topical application

Interaction with the stratum corneum

The SC is made of protein-rich cells embedded in a lipid extracellular matrix. This arrangement has been referred to as the bricks and mortar model.²⁸ In addition, corneocytes are anchored together by means of intercellular proteic structures called corneodesmosomes.²⁹ Depending on their composition, size, and shape, macromolecules and supramolecular carriers interact differently with this very complex barrier. It has been postulated that lipid-based particles have the tendency to merge with the skin lipid layers, whereas polymeric particles, being more hydrophilic, might have different interactions with the extracellular lipids of the SC.³⁰ However, even if the components of polymeric carriers do not fuse with the lipids of the SC, the interaction with the SC may change their three-dimensional conformation leading to adsorption, destabilization, or agglomeration. Furthermore, the SC is covered with sebum, rich in lipids and proteins, which can interact with the applied polymeric materials destabilizing them or changing the way they interact with other skin components. A number of different commensal bacteria strains reside on the skin surface, in skin furrows and appendages and might interact with applied materials. The pH on the surface of the SC is 4.2–5.6.³¹ Such an acidic pH can influence the colloidal stability of particles. The acidic pH increases the rate of hydrolysis and the activity of pH-sensitive enzymes, which in turn might accelerate the degradation of polymeric particles.³² Finally, the SC is a dynamically evolving structure and, near to a more compact region (stratum compactum), a looser part can be distinguished due to desquamation processes (stratum disjunctum; Figure 1). Thus, substances accumulated in the stratum disjunctum are rapidly eliminated by the shedding of the outermost layers, whereas the SC can function as a reservoir for those particulate materials penetrating deeper. Once released, the drugs can diffuse across the SC to the viable skin layers. Three

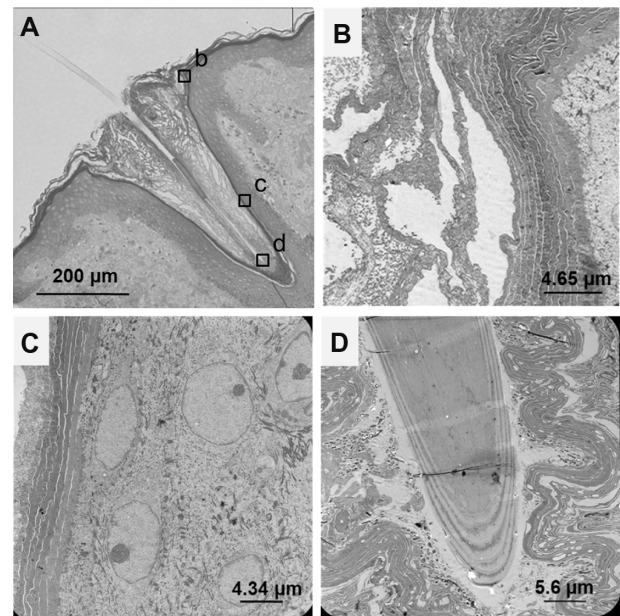


Figure 1 Human terminal hair follicle. (A) Light microscopy image of a longitudinal section showing the hair follicle infundibulum and the hair shaft. The infundibulum is filled with cell debris and sebum. Insets (b–d) are regions of the hair follicle that were observed by means of transmission electron microscopy (B, C and D respectively), using an ultrafine section prepared from the same sample block. (B) The SC in the apical part of the hair follicle orifice consists of several corneocytes layers. Bacteria colonies are visible as well. (C) The SC in the hair follicle infundibulum is thinner than the SC in the upper part of the hair follicle orifice and in the inter-follicular epidermis. (D) Image of the hair shaft and the inner root sheath.

Abbreviation: SC, stratum corneum.

penetration pathways have been described for topically applied substances: the intercellular, the transcellular, and the transfollicular route.^{33–35} In general, the penetration pathway and rate of diffusion of released drugs depend on their lipophilicity/hydrophilicity, their molecular weight, and the carrier type.

Hair follicle pathway

The hair follicle canal of the pilosebaceous unit represents a reservoir where micro-, submicron-, and nano-sized material can penetrate and accumulate (Figure 1).

It took a while before the hair follicle was taken into consideration as a possible portal to skin penetration. In fact, hair follicle orifices represent only 0.1% of the skin surface³⁶ and it was assumed that the sebum impedes the penetration of material in the hair follicle canal. Only in the last decade a number of studies demonstrated the importance of the transfollicular pathway, especially for the preferential penetration of particulate materials. Particles that accumulate in the hair follicle are protected from SC turnover and persist for days before they are cleared.³⁷ The size of the hair follicle orifices ranges between $172 \pm 70 \mu\text{m}$ in terminal hair follicles and $86 \pm 37 \mu\text{m}$ in vellus hair follicles,³⁸ and the interaction surface of hair follicle infundibulum was calculated to be

approximately 0.68 and 0.068 cm² for empty or full follicles, respectively.³⁹ Consequently, the hair follicle infundibulum represents not only a reservoir but also a considerable surface area where interaction between accumulated material and skin structures can occur. The hair follicle is a shunt for a more rapid penetration of substances. When the hair follicle orifices were selectively closed, the applied substances reached the same blood values in volunteers with open hair follicles.^{40,41} This might be due to the fact that the SC barrier in the deep infundibulum is thinner (Figure 1C) and molecules can diffuse more rapidly here than on the skin surface where the SC consists of several more layers (Figure 1B). In addition, those carriers accumulated in the hair follicle canal release the loaded drug, thereby generating a high local concentration of the drug which is a driving force for its diffusion to the viable skin. The removal of the hair follicle content (sebum, cells debris, and eventually bacteria) favors the penetration of topically applied particulate materials.⁴²

Translocation across the stratum corneum

Even if the debate on the translocation of particulate material across the SC is not yet closed, in general, it is believed that only lipophilic molecules with a molecular weight below 500 Dalton can pass the skin barrier, whereas the penetration of hydrophilic molecules, macromolecules, and nanoparticles is significantly impaired.^{43–45} Liposomes, solid lipid nanoparticles, and polymeric DDS were shown to enhance the skin penetration of loaded substances but there is no evidence for the translocation of entire particles across the intact SC of healthy skin. On the contrary, it seems that components of the lipid-based particles dissolve into the lipids of the SC enhancing its permeability.^{46,47} In the case of polymer-based carriers, data on the penetration across the SC are poor due to the fact that most of the studies cited in this article detected the released fluorochrome (or drug), but only a few studies attempted to find out the fate of the carrier after topical application. Interestingly, there is one report claiming that 200–250 nm poly(*N*-isopropylacrylamide) (NIPAM) and poly(*N*-isopropylacrylamide-co-acrylic acid) (NIPAM-co-AAc) nanogels penetrated across epidermal sheets of pig ears. Indeed, these biocompatible carriers were detectable by means of transmission electron microscopy (TEM) in the acceptor medium of the Franz diffusion cell.⁴⁸ However, these results apply to epidermal sheets isolated by heating at 60°C (which might damage the lipid matrix and corneodesmosomes) and not to full thickness skin. This underlines how challenging it is to visualize and elucidate

the interaction between carriers and the skin barrier at the subcellular level.

Carriers penetration across disrupted skin barriers

When developing DDS for skin disorders, the different features of diseased skin have to be considered. Whereas in healthy skin particulate carriers penetrate in the SC and in the hair follicle canals releasing there the loaded drugs (Figure 2A), in unhealthy skin, where the integrity of the SC is altered, carrier systems might cross the SC barrier and enter the epidermis and dermis (Figure 2B). Several methods have been developed to bypass the SC, for example by disrupting it with adhesive tapes and abrasion,⁴⁹ altering it with permeabilizing agents,^{50,51} or using microneedles.⁵² Most of these procedures were tested for transdermal drug delivery or transcutaneous vaccination strategies. Only a small number of studies investigated the penetration of particles across diseased animal or human skin.^{53,54} In fact, most animal studies report the diffusion of the released drugs and their efficacy but not on the fate of the used carrier systems.^{54–56} Most authors found significantly higher drug permeability in inflamed skin than in healthy skin.^{55,56} These results are explained with the swelling of the tissue and the increased intercellular fluid in the epidermis which might alter the structure of tight junctions. However no direct evidence for nanoparticle translocation was provided.

In general, those studies using ultraviolet⁵⁷ irradiation or mechanical methods to disrupt the SC and activate the immune system showed that topically applied nano-materials can be detected in the viable skin layers.^{58–60} Once particles cross the SC, they might also reach the subcutaneous lymph nodes after being taken up by skin antigen presenting cells or by passive transport following the lymph drainage.⁶¹ All these findings underline the need for further knowledge on the interactions and fate of the carrier system after topical application on diseased skin.

Most skin diseases are associated with different degrees of SC disruption.²⁹ Disease-specific differences, however, can have a tremendous impact on how carrier systems interact with skin. In atopic dermatitis and contact eczema, defects in expression of tight junction components and flaggrin are responsible for the dysfunction of the SC resulting in a higher susceptibility to external allergens and opportunistic infections.⁶² Thus, it is reasonable to think that particulate materials have easy access. Nanoparticles which can penetrate the epidermis and dermis can interact with immune system cells and be taken up by phagocytic cells.

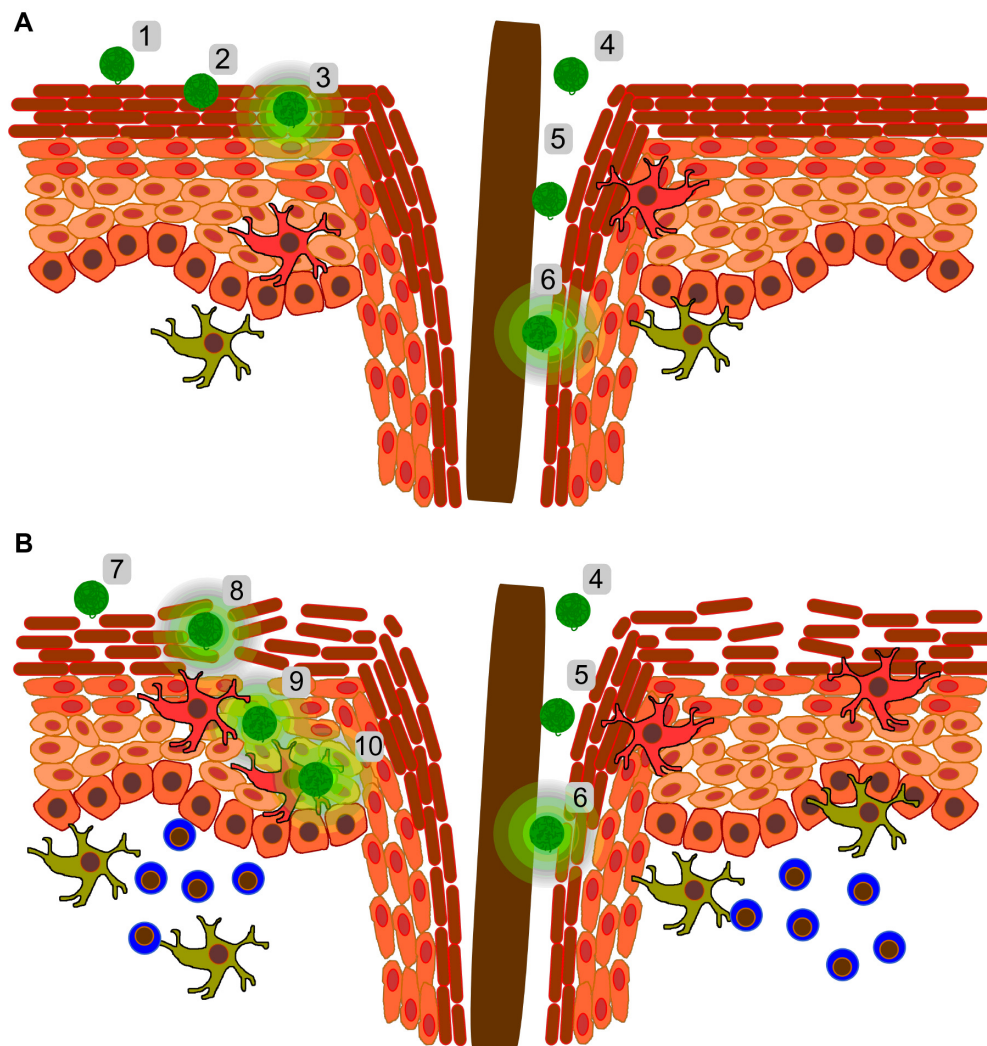


Figure 2 Skin penetration of polymeric carriers and drug release in (A) healthy skin and (B) hypothesis of polymer particle behavior in diseased skin. **Notes:** (A) When the skin barrier is intact, topically applied carriers interact with the skin surface (1, 4) and accumulate in the SC (2) and in the hair follicle canal (5). There, they degrade and/or release the loaded substances (3, 6). (B) In most skin conditions, the skin barrier is disrupted and the skin immune system is activated. Topically applied substances interact with the altered skin surface (7), penetrate across the SC (8), enter the skin viable layers (9), and can be taken up by activated dendritic cells or macrophages (10). Polymeric particles can degrade and/or deliver their loads in the SC (8), in the intercellular space (9), or upon internalization in the cells (10). **Abbreviation:** SC, stratum corneum.

Because atopic and contact dermatitis are associated with altered immune responses, certain nanoparticles might exacerbate the symptoms of the pathology, as was found for polystyrene nanoparticles.⁶³ In psoriasis, keratinocyte hyperproliferation and abnormal SC stacking leads to epidermal thickening and the formation of scales. The cytokine milieu induces vasodilatation and cell infiltration. Even if the SC is thicker, tight junction proteins are altered leading to increased skin permeability to topically applied drugs.⁶⁴ Nevertheless, this does not apply to all types of molecules and nanoparticles. In fact, Prow et al found that penetration of ZnO₂ nanoparticles was not increased in psoriatic skin compared to a non-lesional skin region of the same patient.⁶⁵ However, no data are available with regard to the penetration of more flexible particles

like polymer-based nanocarriers. Skin barrier properties are also altered during skin infection. For example, dermatophytes secrete proteolytic enzymes which degrade the SC allowing them to invade and disseminate through it⁶⁶ and at the same time altering skin permeability. In general, during bacterial and fungal infections, the SC is more permeable and the skin immune system is activated with the presence of cell infiltrates and vasodilatation similar to the situation found in eczema. Nevertheless, depending on the type of pathogen and the stage of disease, different degrees of inflammation, skin dryness, and desquamation are present. The skin barrier is compromised in aged skin as well.⁶⁷ It has been shown that elderly skin is dry and scaly. The reason for these defects is related to lower lipid levels in lamellar

bodies⁶⁸ and a decrease in epidermal filaggrin.⁶⁹ In addition, aged skin manifests epidermal and dermal atrophy, flattening of the epidermal rete ridges, as well as reduced numbers of fibroblasts and mast cells.⁶⁷

On the other hand, there are other skin conditions that are characterized by a less permeable skin barrier. In hypertrophic scars, for example, even if the amount of hydrophobic ceramide is decreased, the SC is irregular and thicker. Another example is acne vulgaris, which is characterized by a hyperproliferation of keratinocytes in the hair follicle at the level of the sebaceous gland duct and an increased production of sebum which result in a strong barrier to the penetration of hydrophilic molecules and nanoparticles.

Cellular uptake

Once a carrier system or a drug has successfully crossed the skin barrier and has reached the viable epidermis layers, it can diffuse across the extracellular space and/or be taken up by epidermis and dermis cells (Figure 2B). Whereas small amphiphilic drugs can diffuse across the cell membrane, macromolecules like proteins, nucleic acids, as well as nano- and submicron-material can be internalized by cells only via the energy-dependent mechanism of endocytosis.^{70,71} In general, only certain types of cells can internalize particulate material with size above 200 nm.⁷⁰ For example, when dendritic cells were co-cultured with T-cells and incubated with fluorescently labeled bacteria and polystyrene particles (200 nm), we found that only dendritic cells internalized both particles (unpublished data, Figure 3).

Langerhans cells in the epidermis are cells specialized in taking up particulate materials penetrating across a disrupted skin barrier. Also, keratinocytes, which are the most represented cells in the epidermis (90%), can internalize

penetrated materials. Nevertheless, in vitro experiments with freshly isolated epidermis cells have shown that, depending on the particle size, keratinocytes are less prone than Langerhans cells to take up particles.⁵⁹ In the dermis, penetrated material comes in contact with cells like fibroblasts, mast cells, and T-cells. However, macrophages and dendritic cells are most likely to internalize them. Once internalized, the carrier systems can undergo degradation in the acid and hydrolytic environment of lysosomes and release the loaded drug.⁷² Hydrolysis and enzymatic degradation may be exploited as a mechanism for drug release, though the same reactions may be deleterious for certain loaded molecules such as proteins or nucleic acids.²³ To avoid degradation, endosomal escape has to be achieved.⁷³ On the other hand, for vaccination purposes, the uptake of antigen-loaded carriers by antigen presenting cells and their intracellular degradation is advantageous, being the steps necessary for major histocompatibility complex (MHC)-I and MHC-II presentation.²²

Polymer degradation and drug release

Once applied on the skin surface, polymeric biomaterials may be degraded by chemical and/or enzymatic reactions depending on the nature of the polymer. Hydrolytic enzymes, including proteases, esterases, glycosidases, and phosphatases, can catalyze the water mediated cleavage of different chemical bonds. The degradation of polymer particles is often a complex process and the release of the loaded drug exhibits often non-linear kinetics. The degradation of the polymer may interfere with the release of the drug, inhibiting or accelerating it, or might degrade the loaded drugs.⁷⁴ Ideally, a biodegradable polymer should decompose into non-toxic products and should degrade in a controlled manner. In this way, not only the safety but also the selectivity and efficacy of the drug are enhanced. For example, hydrolysis of the drug-carrier bond can be controlled by introducing linkers cleavable by enzymes that are localized predominantly in the diseased tissue or target cell.⁷⁵ These processes are influenced by skin parameters like temperature, pH, and protein concentration.^{76,77} Also, it is possible to include degrading enzymes in the polymer matrix.⁷⁴ The type of polymer, the nature of interactions between drug and polymer, and the affinity of the drug to skin components determine the time and the place where the carrier is degraded and the drug released. Polymers can be readily hydrolyzed after penetration in the SC, upon penetration in the epidermis and dermis, or only after cellular uptake (Figure 2B).

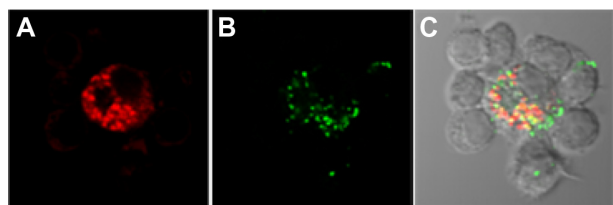


Figure 3 Confocal fluorescence images showing the uptake of *Escherichia coli* particles and polystyrene particles (200 nm) by dendritic cells (unpublished data). Dendritic cells derived from peripheral blood mononuclear cells were co-cultured with T-cells and incubated with inactivated *E. coli* particles labeled with a pH sensitive dye that becomes fluorescent in an acidic environment (**A**; red) and FITC-loaded 200 nm polystyrene particles (**B**, green). The overlay image (**C**) shows that the bigger cells (ie, dendritic cells), but not T-cells, had internalized particles. Both *E. coli* and polystyrene particles were co-localized in intracellular acidic compartments.

Abbreviation: FITC, fluorescein isothiocyanate.

The release of a loaded drug may also take place by other processes like conformational changes of the particles (destabilization, swelling, or shrinkage). Upon topical application, drugs adsorbed on the carrier surface may be released by affinity-driven diffusion or by exchange with skin components like proteins. The physicochemical properties of the carriers seem to play an important role in drug release and diffusion.^{78,79}

Challenges for carrier-based dermatotherapies

Whereas transdermal delivery implies the transport of actives across the whole healthy skin to reach the systemic compartment or regions beneath the skin (eg, skeletal or muscular tissues), the treatment of skin pathological conditions implies the local delivery of actives to skin regions with altered parameters. The knowledge on the pathophysiology and mechanisms underlying a number of skin conditions has enormously increased in the past years, showing that diseased skin is morphologically, physiologically, and biologically different from healthy skin.⁸⁰ Thus, different strategies can be developed taking into consideration the special conditions which characterize affected skin and exploiting them to achieve a more selective delivery of the drug.

Skin inflammatory conditions

The treatment of atopic dermatitis, contact eczema, and psoriasis is achieved using anti-inflammatory drugs (steroidal and non-steroidal) or immunomodulatory and immunosuppressive drugs (eg, tacrolimus). These actives are administered topically or, in severe cases, orally or intravenously. One of the main problems of topical treatment with glucocorticoids is to reach effective concentrations of the anti-inflammatory drug in the epidermis avoiding drug localization in the dermis or its rapid diffusion to the systemic compartment. Glucocorticoid localization in the dermis leads to induction of metalloproteases and degradation of connective tissue, resulting in thinning of skin and skin atrophy. On the other hand, the rapid clearance of the drug from skin to the systemic compartment is responsible for reduction of drug efficacy. Nanocarriers offer the possibility to improve the efficacy and safety of corticosteroids by creating depots in the SC, hair follicle canal, and epidermis as well as local release of the drug in a sustained manner.^{81,82} In the case of macrolide drugs, like tacrolimus, there is a need for a better penetration across the SC especially in the case of psoriasis where keratinocytes over-proliferation results in plaque formation.

In fact, the high molecular weight and the hydrophilic nature of the molecule impede its diffusion into the skin. The use of carrier systems that can increase its penetration across the SC and thereby protect it from degradation would increase the efficacy of this topical treatment. Furthermore, a better and more selective delivery of the drug to the dendritic and T-cell infiltrates in inflamed skin would reduce the side effects and increase the therapeutic activity of the drug. It is now recognized that skin dendritic cell subsets are involved in chronic inflammatory skin conditions and in the initiation of skin allergic reaction. Therefore, particle-based targeting of dendritic cells and their modulation seems to be a promising strategy against such skin conditions where an overreaction of skin immune cells is involved.⁸³

The skin penetration profile of small hydrophobic molecules, like non-steroidal anti-inflammatory drugs, can also be improved by encapsulation in particles. The delivery of flufenamic acid by PLGA particles resulted in a more prolonged and localized drug release in the epidermis, whereas surface modified PLGA and chitosan nanoparticles formulated in a gelling agent were successfully used to deliver spantide II and ketoprofen to allergic contact dermatitis and psoriatic plaque-like skin models.^{24,54} Polymer particles, because of their ability to protect encapsulated drugs, also have the potential to optimize the topical delivery of nucleic acid molecules, such as small interfering ribonucleic acid (siRNA) for the regulation of cytokines' expression and control of inflammatory skin diseases.⁸⁴

Skin infections

The therapy of skin infections can also profit from a more selective and effective delivery of the antimicrobial drug. Especially in the case of pathogens colonizing the lower infundibulum, the use of nanocarriers that accumulate in the hair follicle canal and thus the achievement of high concentrations of antimicrobials can decisively improve the outcome of a topical therapy. Another challenge is the reduction of unwanted toxicity of antimicrobials toward skin cells. In the case of antibiotic-resistant strains, besides the development of new generations of antibiotics, new therapeutic approaches include the application of DDS for the slow but sustained release of toxic substances such as metal ions or nitric oxide, thus limiting their side effects. For example, hydrogel (polyethylene glycol, chitosan)-glass composites have been tested for the sustained release of nitric oxide, whereas silver nanoparticles are used as a source of silver ions.^{85,86} Biodegradable gelatin fibers loaded with antimicrobial silver nanoparticles

were also tested as dressing materials in the treatment of wounds and chronic wounds.⁸⁷

Hair follicle associated disorders

The targeting of drugs to the pilosebaceous unit by means of nano- and submicron carriers can be exploited to treat hair follicle-associated inflammation, hair growth, and sebaceous gland disorders like alopecia and acne, respectively. For example, to treat alopecia androgenetica the drug should be targeted to the hair bulb where the hair shaft is generated. For this purpose, minoxidil was formulated on 40 nm poly(ϵ -caprolactone)-block-poly(ethyleneglycol) carriers with positive results.⁸⁸ For the treatment of acne vulgaris, the drug should be targeted to the infundibulum at the level of the sebaceous gland. Thus, microspheres accumulating preferentially in the hair follicle infundibulum would be the carrier of choice.⁸⁹ The release of the loaded drug can take place due to diffusion gradients or can be triggered by the special environment within the hair follicle canal.⁹⁰ We have shown that 228 nm PLA particles accumulated in the hair follicle infundibulum realizing a sustained release of the loaded lipophilic dye Nile red for up to 24 hours.⁹¹ Later, we found that the type of loaded dye also played an important role with regard to release kinetics and stability of the PLA particles in the hydrophobic environment of the hair follicle infundibulum.⁹⁰ Carrier systems can also improve the tolerability of retinoids for the treatment of acne. Despite their promising anti-aging and anti-comedogenic properties, these drugs can cause irritation and pain and their encapsulation in carrier systems can help to reduce this side effect. Most studies used lipid-based carriers but polymers have also been used in combination with emulsions or lipid carrier systems. For example, Cho et al used PEG-PCL-PEO triblock copolymers to stabilize retinol emulsions, whereas Ridolfi et al used chitosan-solid lipid nanoparticles to deliver tretinoin.^{92,93}

The targeting of drugs to perifollicular immune system cells by means of polymer particles might be useful for the treatment of alopecia areata. This autoimmune disease is characterized by infiltrating cluster of differentiation (CD) 4 and CD8 T-cells directed against auto-antigens and results in the destruction of the hair shaft. The targeted inhibition of overreacting cells by means of particulate carriers might be a possible therapy. For example, 75 μ m cationized gelatine particles were used to deliver siRNA as a new therapeutic approach, targeting the T-box21 gene (Tbx21) to repress the expression of interferon- γ gene.⁹⁴ Another possible treatment is the topical application of diphenylcyclopropenone (DCP), which is an irritant and diverts T-cells from the hair shaft. However, the treatment is painful

(irritation) and can be done only by trained personnel. The use of particles might allow a slow but sustained release of the substance minimizing the irritating effect.

Skin cancer

Polymeric carrier systems like dendrimers, microspheres, and nanogels, besides lipid-based carriers, are ideal systems for the topical delivery of chemotherapeutic agents and siRNAs to treat skin malignancies.⁹⁵ In fact, the topical delivery of anti-proliferative agents and photosensitizing agents has the advantage of reducing side effects and improving the compliance of the patients. Such carrier systems, eg, PLA or PAMAM based particles, have been tested for the topical delivery of drugs to different types of skin tumors.^{96–99}

Targeting the skin immune system

Skin possesses a large number of immune active cells, from keratinocytes to different sub-types of skin resident T-cells, macrophages, dendritic cells, and mast cells. The fact that mainly dendritic cells are prone to take up particulate material suggested using submicron carriers to target this cell population.¹⁰⁰ Dendritic cells are potent antigen presenting cells and represent the bridge between innate and adaptive immune response. It has been shown that targeting antigens to the skin by means of virus particles (MVA), but also using PLA particles, induces potent cellular responses as well as skin and mucosal humoral immunity.^{101,102} Thus, different types of nanoparticles are actually under investigation as vaccine delivery systems against cancer and infectious diseases.¹⁰³ In order to deliver a sufficient amount of antigen to skin dendritic cells, it is important that particles are delivered across the skin barrier and that they are taken up by the target cells. For this reason, different physical methods (eg, stripping, microneedles, electroporation, or iontophoresis) have been developed to overcome the skin barrier.¹⁰⁴ Thus, for vaccination purposes it is mandatory to use biodegradable and compatible material to avoid intolerance responses or accumulation of particles in secondary lymphatic organs.

Gene therapy

Another special challenge for drug delivery is the targeting of therapeutic genes to skin cells. Very promising is also the delivery of siRNA molecules in order to control the post-transcriptional pathways of gene expression. To achieve this goal several obstacles have to be overcome. The deoxyribonucleic acid (DNA) or RNA moieties have to be transported across the skin barrier, be protected from degrading nucleases, be taken up by cells, and reach its target

in the cytoplasm or in the cell nucleus. Polymer materials are intensively investigated as delivery agents because of the possibility to protect the nucleic acid and to achieve a sustained release and expression of the therapeutic gene. Despite all obstacles, there are encouraging reports describing the successful in vivo expression of genes after topical delivery of DNA loaded on cationic or PEGylated liposome as well as chitosan nanoparticles.^{105–107} Tissue growth, vaccination, anticancer treatment, and anti-inflammatory therapy can be achieved by gene transfer or regulation of gene expression.^{108,109} Principally, all skin diseases with a genetic basis could be treated by delivery of the missing or dysfunctional gene.

Conclusion

Several studies showed the efficacy and advantages of biodegradable polymeric materials as carriers or delivery systems in dermatology. These materials are safe and offer tools to develop carrier systems tailored for each specific dermatological disease. For this purpose, future work should focus on a more detailed knowledge of the interactions occurring between polymeric carrier systems and skin environment. Drug permeation and efficacy measurements should be complemented by detailed investigation on carrier skin penetration, uptake by skin cells, mechanism of degradation and drug-release, as well as toxicological properties. Also, it is important that such investigations are conducted using skin models of the specific pathological conditions to be treated. Investigating the interaction of delivery systems with disrupted skin barrier or activated immune system will allow tailoring polymeric materials in order to enhance the selectivity and specificity of drug delivery. The fact that new polymer-based carrier systems are being developed and that the number of their dermatological applications is constantly increasing demonstrates the huge potential of these biodegradable and versatile materials.

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Disclosure

The authors report no conflicts of interest in this work.

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