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Polymeric nanoparticles-based topical delivery systems for the treatment of dermatological diseases

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Abstract

Human skin not only functions as a permeation barrier (mainly due to the stratum corneum layer), but also provides a unique delivery pathway for therapeutic and other active agents. These compounds penetrate via intercellular, intracellular and transappendageal routes, resulting in topical delivery (into skin strata) and transdermal delivery (to subcutaneous tissues and into the systemic circulation). Passive and active permeation enhancement methods have been widely applied to increase the cutaneous penetration.

The pathology, pathogenesis and topical treatment approaches of dermatological diseases, such as psoriasis, contact dermatitis, and skin cancer, are then discussed. Recent literature has demonstrated that nanoparticles-based topical delivery systems can be successful in treating these skin conditions. The studies are reviewed starting with the nanoparticles based on natural polymers specially chitosan, followed by those made of synthetic, degradable (aliphatic polyesters) and non-degradable (polyarylates) polymers; emphasis is given to nanospheres made of polymers derived from naturally occurring metabolites, the tyrosine-derived nanospheres (TyroSpheres™).

In summary, the nanoparticles-based topical delivery systems combine the advantages of both the nano-sized drug carriers and the topical approach, and are promising for the treatment of skin diseases. For the perspectives, the penetration of ultra-small nanoparticles (size smaller than 40 nm) into skin strata, the targeted delivery of the encapsulated drugs to hair follicle stem cells, and the combination of nanoparticles and microneedle array technologies for special applications such as vaccine delivery are discussed.

Keywords

polymeric nanospheres; topical delivery; psoriasis; skin; tyrosine-derived nanospheres

Introduction

The barrier function of skin can be attributed mostly to the stratum corneum layer of the epidermis, and this skin barrier also regulates the transport of compounds into the skin.

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Approaches that deliver drugs/active compounds through the skin barrier are referred to the topical route of administration (as opposed to the enteral and parenteral routes of administration). Passive and active skin penetration enhancement methods have been successfully used to improve the efficiency of either the topical delivery (the drugs/active compounds are delivered into skin strata), or transdermal delivery (drugs/active compounds are delivered into subcutaneous tissues and are taken up systemically into the body). Topically applied therapies are promising for the treatment of skin diseases such as psoriasis, contact dermatitis, and skin cancers, since the drugs are delivered directly into skin strata.

Nano-sized drug carriers have attracted much attention in the past decade as options in formulations for topical therapy. Nanoparticles (including nanospheres, solid lipid nanoparticles, micelles, and micellar-like nanoparticles), liposomes, and nanoemulsions are among the most studied systems. Inorganic and metal nanoparticles such as quantum dots and gold nanoparticles are widely used for diagnosis, and are not in the scope of this review. Rather, this paper focuses on topically applied, polymeric nanoparticle-based drug delivery systems. Nanoparticles made of natural polymers (*e.g.* chitosan) and synthetic biodegradable polymers (*e.g.* poly(lactide-co-glycolide) and poly(ε-caprolactone)) as well as non-degradable polymers (*e.g.* polyacrylates) are discussed. Special emphasis is given to the tyrosine-derived nanospheres since they consist of natural occurring metabolites and have been utilized in several products already marketed for patients. The most recent advances in the nanoparticle-based topical delivery systems elicited a few interesting questions: do the ultra-small nanoparticles penetrate into skin, can we manipulate hair follicle stem cells via drug-loaded nanoparticles that localize in the hair follicles, and will the less invasive vaccination using the combination of microneedle techniques and vaccine-loaded nanoparticles become routine clinical practice. All the above-mentioned topics are discussed in detail in this review paper.

SKIN BARRIER

Skin strata and stratum corneum as barrier

Human skin is the largest organ in the body with a surface area between 1.5 and 2.0 m^2 for adults. The skin thickness varies over the body with the thinnest part of eyelids being less than 0.1 mm thick and the thickest on the palms, soles and upper back more than 5.0 mm. Not only is the skin a protective barrier against toxic substances, pathogens, and organisms, but it is also involved in many important physiological functions such as fluid homeostasis, thermoregulation, immune surveillance, and sensory detection[1]. These functions are related to the skin's complex multiple layers with each layer associated with highly specified cells and structures. See Table 1 for details of the skin strata and Figure 1 for a schematic image of skin.

The permeation barrier properties of human skin are mostly attributed to the top layer of the epidermis, the stratum corneum. The barrier function is related to the unique structure in the stratum corneum layer that is composed of "bricks (corneocytes) and mortar (intercellular lamellar lipid bilayers)" [2].

Allied with the epidermis and dermis are skin appendages possessing different functions. The features of the common skin appendages and their functions are described in box 1.

Box 1

Skin appendages

Hair follicles are formed by the infolding of the epidermis into the dermal layer, and are composed of papilla, matrix, root sheath, hair fiber and bulge. Besides producing hair, the hair follicles contain several types of stem cells that play an important role in wound healing and re-epithelialization [3]. Associated with hair follicles are arrector pili muscles that pull hairs straight and sebaceous glands that secrete sebum to moisturize the skin and hair. Other skin appendages include eccrine sweat glands which secrete sweat and therefore regulate body temperature, apocrine glands involved with hair follicles in certain restricted regions of the body (e.g. axillae), and nails.

Topical and transdermal delivery across skin barrier

The permeation barrier properties of human skin elicit challenging but exciting delivery avenues for drugs and other compounds into the skin strata (topical delivery) and/or to the systemic exposure (transdermal delivery). Currently, there are more than 30 transdermal products in the US market, and it is expected that the topical and transdermal drug delivery market will reach $32 billion in 2015; formulations of a number of low molecular weight drugs and macromolecules have been developed and some are currently under clinical trial [4].

Compared to the other delivery routes, topical and transdermal delivery approaches have the unique advantages: a) for skin diseases, topical delivery approaches directly deliver drugs to the site of the diseases cells/tissues; b) smaller amounts of drugs are needed to produce a therapeutic effect; c) plasma level peaking of drugs will be avoided; d) increase bioavailability due to elimination of hepatic first-pass metabolism; and e) greatly enhanced patient compliance by eliminating frequent dosing.

The cutaneous penetration pathways are a) through stratum corneum via **intercellular/ intracellular routes,** followed by the viable epidermis and dermis via partitioning/diffusion; and b) through the **appendageal pathway** [5]. These routes result in topical and transdermal delivery.

Passive and active skin penetration enhancement methods

It was not until 1960s – 1970s that the scientists reached the consensus that a) the stratum corneum is the rate-limiting barrier against percutaneous drug penetration, and b) the specific content, composition and structure of the stratum corneum lipids selectively and effectively inhibit the penetration of chemicals[2]. In addition, not all the compounds can penetrate through the stratum corneum barrier; the ones with moderate lipophilicity (octanol-water partition coefficient between 10 and 1000) and molecular weight less than 500 Daltons are able to permeate the stratum corneum and penetrate into deeper layers of skin. Box 2 illustrates the percutaneous drug penetration hypothesis.

Box 2

Percutaneous drug penetration

Generally, the permeation of drug molecules into skin is guided by passive diffusion in one dimension and can be described most simply by Fick's first law (Equation 1):

$$J = -D\frac{\partial \varphi}{\partial x} = \frac{1}{A} \times \frac{dM}{dt} \quad \text{Equation 1}$$

where J, the diffusion flux, is the amount of the substance going through a unit area during a small interval of time; D is the diffusion coefficient (or diffusivity) of the compound in the membrane; $\frac{\partial \varphi}{\partial x}$ is concentration gradient which is the driving force that leads to molecular movement into skin; A is barrier surface area; M is mass of drug [6].

Even for the compounds that favor the penetration requirements, additional means are usually implemented to enhance the transport across the skin [7]. A variety of strategies have been studied in the past three decades to overcome the barrier and optimize the cutaneous delivery of drugs, and they can be categorized into passive and active penetration enhancement methods (Figure 2).

Passive skin penetration enhancement methods—The diffusion flux, *J,* can be further described by Equation 2[6]:

$$J = \frac{D_m C_{s,m}}{L} \cdot \frac{c_v}{c_{s,v}} \quad \text{(Equation 2)}$$

Where D_m represents the diffusion coefficient of the drug in the membrane (skin), $c_{s,m}$ represents solubility of the drug in the membrane, c_v and $c_{s,v}$ are respectively the concentration and the solubility of the drug in the vehicle, and L the diffusion path length across the membrane.

In a recent proposed solute structure-skin transport model, permeation rates were linked to both partitioning of the drug between stratum corneum and the topically applied formulation and the diffusivity (the "D" in Equation 1, or the "D_m " in Equation 2) of the drug into the skin strata. The former is related to octanol-water partition coefficient and the latter to solute size and hydrogen bonding if applicable [8].

Passive penetration enhancement methods entail optimization of formulation and drug carriers to increase the flux. As can be seen from Equation 2, the strategies for passive penetration enhancement include increasing the diffusion coefficient D_m (increase the diffusivity) and solubility of the drug in the skin (increase $c_{s,m}$, and thus increase the partition coefficient) by adding chemical penetration enhancers to the formulation or using eutectic system[9]; chemical penetration enhancers (such as alcohols, sulfoxides, fatty acids, etc.) cause temporary disorder of the intercellular lipids structure in the stratum cornuem and reduce skin resistance [10]. Another strategy is to increase the ratio $c_v/c_{s,v}$ and this can be realized by a supersaturation approach and using nano-sized carriers[11].

Active skin penetration enhancement methods—For high molecular weight (>500 Da) polar and hydrophilic molecules such as plasmid DNA, peptides, and vaccines, passive skin permeation enhancement methods are not sufficient. Active skin penetration enhancement methods have been developed and categorized into electrical, mechanical and other energy-related techniques (see Figure 2, the active methods). The mechanisms involved in active penetration enhancement methods are mostly as follows: a) bypassing the stratum corneum using techniques such as microneedle array[12]; b) removing stratum corneum by abrasion[13] c) disrupting lipid packing in stratum corneum by ultrasound waves[14]; and d) generating transient aqueous pores in the lipid bilayers of stratum corneum

by electroporation[15]. Among these, significant efforts have been devoted to developing microneedle-based techniques. A brief discussion on microneedles is given below:

Microneedles are micro-scaled structures designed in an array on patches that can painlessly pierce and deliver active ingredients into skin. Various materials such as metal, silicon and degradable polymers have been fabricated into microneedles. Microneedles have been widely applied to improve skin delivery of various small molecules as well as macromolecules such as proteins[16], peptides[17], nucleic acids[18] and virus-like particles[19] to enhance its therapeutic values or vaccination efficacies. The improvement of delivery is the result of the formation of microsized channels that are opened throughout the stratum corneum allowing the drug access to the viable epidermis.

DERMATOLOGICAL DISEASES: PATHOLOGY, PATHOGENESIS AND TOPICAL TREATMENT APPROACHES

Major challenges for the treatment of skin diseases

In this section, the pathology and pathogenesis of several skin diseases i.e. psoriasis, contact dermatitis and skin cancer are discussed. The major challenges in treatment of these skin diseases include poor efficiency of drug delivery into the disease site and risks of increased toxicity associated with approaches used to improve the drug delivery efficiency. Despite the achievements in the passive and active skin penetration enhancement methods, many skin disease patients are still waiting for treatment based on safer and more efficient cutaneous delivery of therapeutics across the stratum corneum barrier.

Psoriasis

Pathology and pathogenesis—Psoriasis is a chronic, autoimmune disease affecting as many as 7.5 million Americans and 2% to 3% of the world population (data from National Psoriasis Foundation website). The most prevalent form of psoriasis, plaque psoriasis, is recognized by psoriatic plaques of red lesions covered by silvery white flakes on top of the skin. The pathogenesis of psoriasis is associated with both genetics and the immune system[20]. As the current understanding of psoriasis, a stimulation of dermal dendritic cells activates the immune system including macrophages and T-cells and promotes the interaction between epidermal keratinocytes and the immune system. These events result in the up-regulated production of cytokines, which in turn causes the over-proliferation of keratinocytes starting from the basal layer of the epidermis and the overall skin inflammation associated with psoriasis lesion formation [21, 22].

Topical Treatment for psoriasis—The standard of care for psoriasis can be categorized into systemic treatment, phototherapy and topical treatment. Figure 3 illustrates these approaches and the associated side effects; the general concept applies for the treatment of other dermatological conditions as well.

The application of systemic treatment and phototherapy is limited to treating severe psoriasis patients only, and this is due to the toxicity and carcinogenicity of these approaches. Topical treatment approaches are safer, and the drugs are targeted to the basal layer of epidermis where psoriasis originates. A number of topically applied formulations are available for psoriasis patients upon prescription: anti-inflammatory agents such as corticosteroids are the most frequently applied; examples of other agents are anthralin, synthetic Vitamin D_3 and Vitamin A. Over the counter (OTC) formulations containing salicylic acid and coal tar are also available [23]. The most common side effects of topical treatments are skin irritation, thinning of the skin, and dilated blood vessels [24]. Controlled drug encapsulation and release systems that not only decrease the side effects of the applied

agents, but also enhance drug permeation into deeper epidermis layers would be ideal for psoriasis treatment.

Contact dermatitis

Pathology and pathogenesis—Contact dermatitis is a common dermatological disorder caused by repeated direct contact of skin with external factors (allergens and irritants). This skin disease is characterized by a wide range of clinical features, such as inflammation, redness, erythema, burning, pruritus, and the formation of vesicles (a circumscribed, fluid-containing, epidermal elevation) and pustules [25]. There are two types of contact dermatitis: irritant (ICD) and allergic (ACD) contact dermatitis. ICD represents about 70% of the contact dermatitis, and it is a non-specific, local and immediate inflammatory reaction of the innate immune system to low molecular weight chemicals. ACD is a delayed-type hypersensitivity response with a skin inflammation mediated by hapten-specific T-cells (adaptive immune response)[26].

Topical treatment for dermatitis—Topical products marketed for contact dermatitis may contain a combination of ingredients in various forms including creams, ointments, gels, lotions, and sprays. The most commonly used drugs are topical formulations of hydrocortisone, oral antihistamines, and other antipruritic agents such as calamine. Topical astringent products such as aluminum acetate and zinc oxide also serve as a protective covering for inflamed skin and promote drying of moist, wet, and oozing lesions[27].

Skin Cancer

Pathology and pathogenesis—Skin cancer is malignant growth of cells that forms in the tissue of the skin. Most common skin cancers are keratinocyte cancers (basal cell carcinoma that starts in the basal layer of epidermis and squamous cell carcinoma that starts in the upper part of epidermis) and melanoma characterized as the malignant tumor of melanocytes. Ultraviolet radiation, particularly UVB is the major risk factor in the development of squamous and basal cell carcinoma[28]; the formation of cancer cells is triggered by DNA damage[29], loss of activity of tumor suppressor genes such as P53[30] and activation of oncogenes[31]. Other risk factors such as HPV (human papillomavirus) infection and immunosuppression disease were also reported to be associated with skin cancer[32].

Topical treatment for skin cancer—Creams and solution formulations of fluorouracil (5-FU)[33] and imiquimod[34] are the most widely applied topical treatments for squamous and basal carcinoma. 5-FU, a uracil analog, is an anti-metabolite competing with normal metabolites. It acts as a thymidylate synthase inhibitor and ultimately leads to the thymine-less death of the rapidly dividing cancerous cells[35]. Imiquimod is an immune-enhancing drug that specifically binds to TLRs (toll-like receptors) such as TLR-7 and TLR-8 on macrophage, Langerhans and dendritic cells. The binding of imiquimod with TLRs results in the up-regulation and secretion of proinflammatory cytokines such as TNF-α, IL-12 and interferons, and ultimately the activation of TH1 dominant immune response. Examples of FDA approved topical drugs for squamous and basal carcinoma treatments are Efudex (5%, 2% 5-FU) and Aldara (5% imiquimod).

For melanoma, no topical treatment has been approved by FDA since it is often hindered by the high metastatic properties of the cancer; surgery in combination with systemic treatment of monoclonal antibody such as Yervoy™ (Ipilimumab) or oral uptake of Zelboraf® (Vemurafenib) tablets were more preferred.

POLYMERIC NANOPARTICLES-BASED TOPICAL DELIVERY SYSTEMS

Nano-sized carriers have been extensively studied in the past decades for various biomedical applications including disease diagnostics, drug delivery, gene delivery and vaccination. The using of nano-sized carriers benefits in (a) sustained and controlled release of drugs; (b) stabilization of compounds by providing chemical and physical protection; (c) higher concentration in tumors due to the ***Enhanced Permeation and Retention*** (EPR) effect [36]; (d) cell and tissue specific targeting by conjugating antibodies and peptides to carrier surfaces; and (e) gene delivery via preparing drug-vehicle complexes that can be internalized. Great efforts have been devoted to the commercialization of nanomedicine technologies. Several nanoparticle-based treatments have already been approved by FDA, such as Estrasorb (micellar nanoparticles) for topical menopause therapy and Abraxane (albumin-bounded paclitaxel nanoparticles) for breast cancer treatment.

Nano-sized carriers such as polymeric nanoparticles, solid lipid nanoparticles, liposomes, and nano-emulsions have been widely applied as topical formulations to enhance cutaneous delivery[37, 38]. Among these nano-sized carriers, polymeric nanoparticles with readily-tunable chemical and physical features can effectively protect unstable drugs from degradation/denaturation, decrease the side effects of toxic drugs by producing controlled release, and enhance the cutaneous penetration of the drugs across the skin barrier by increasing the concentration gradient. Here, we focus on polymeric nanoparticles-based topical delivery systems.

Natural polymeric nanoparticles

Natural polymeric nanoparticles are composed of polymers occurring in nature such as chitosan, alginate, gelatin and albumin. These natural polymers are usually obtained from extraction followed by various purification procedures. The tendency of these natural polymers to form hydrogels makes them ideal carriers for oligonucleotides, peptides, proteins and water-soluble drugs. For example, Pilocarpine hydrochloride-loaded gelatin nanoparticles were reported for topical ophthalmic use [39]; oxybenzone-loaded gelatin microspheres, although not in the nano-sized range, were used for sunscreen applications[40]. Table 2 shows a summary of topical delivery systems based on natural polymeric nanoparticles.

Among various natural polymeric nanoparticles, chitosan-based nanoparticles have been most frequently applied for topical skin delivery. Chitosan, the N-deacetylated derivative of chitin, is a natural biodegradable, cationic polymer composed of mainly glucosamine units. Its anti-oxidant, anti-inflammatory and anti-microbial properties make chitosan a suitable vehicle for delivering therapeutics to treat dermatological disorders. Moreover, at physiological pH, the primary amine groups of chitosan are protonated, and therefore chitosan is positive-charged. The positive charge can be used to form nanoparticles in solution via cross-linking with polyanions, to efficiently encapsulate negative-charged drugs via electrostatic interaction, and to promote cellular internalization of drug-containing chitosan nanoparticles. A few examples of topically applied, chitosan-based nanoparticle systems are given below.

Kim et al.[41] encapsulated retinol, a vitamin A derivative in chitosan nanoparticles. The encapsulation of retinol in chitosan nanoparticles minimized the irritation and toxicity of retinol, and the retinol-loaded chitosan nanoparticles can be potentially used for acne and anti-wrinkle treatment. Nanoparticle fabrication based on the cross-linking between chitosan and polyanions such as tripolyphosphate (TPP) was developed. Hasanovic et al.[43] demonstrated that the encapsulation of aciclovir (an anti-viral drug) into chitosan-TPP

nanoparticles resulted in significantly increased drug stability, decreased photo degradation, and enhanced drug penetration through porcine skin.

Moreover, chitosan nanoparticles and chitosan-TPP nanoparticles were shown to deliver macromolecules such as antisense oligonucleotides and plasmid DNA for topical gene therapy. Ozbas-Turan et al.[42] reported that topically applied antisense oligonucleotide-loaded chitosan nanoparticles at a dose range of 15–90 μg showed the highest inhibition of beta-gal expression at 6 days post-transfection in rats. The same group also reported that chitosan-TPP nanoparticles exhibited high loading efficiency for plasmid DNA pSV-β-Gal and that the DNA-containing nanoparticles showed transfection in baby rat skin[44].

The electrostatic interaction between chitosan and lecithin was also used to prepare nanoparticles for the purpose of skin delivery. Şenyiğit et al.[45] reported that chitosan-lecithin nanoparticles in a chitosan gel formulation delivered a corticosteroid clobetasol-17-propionate to epidermis and dermis as effectively as a commercial cream. In another study, Tan et al.[46] demonstrated that under in vitro and in vivo conditions, quercetin as loaded in chitosan-lecithin nanoparticles had higher skin permeation and increased accumulation in epidermis as compared to quercetin applied in propylene glycol solution.

In addition to topical application onto skin, chitosan-based nanoparticles were capable of delivering drugs to nasal[47] and ocular mucosa[48], and intestinal epithelia[49].

Synthetic polymeric nanoparticles

The most widely used polymeric nanoparticles are prepared from synthetic polymers. Since natural polymers vary in purity and often lack the batch-to-batch consistency, it is hard to obtain reproducible particles and controlled release pattern for the encapsulated drug(s). On the contrary, synthetic polymers can be supplied with good purity and batch-to-batch reproducibility; and the drug release from synthetic polymeric nanoparticles can be also be modeled[50]. Compared to nanoparticles based on natural polymers, nanoparticles from synthetic polymers have been applied predominantly for hydrophobic/lipophilic drugs. Hydrophilic, biologically active molecules can be loaded into synthetic polymer-based nanoparticles by using the double emulsion method; however, since the volatile organic solvents are often applied, it is a challenge to maintain the biological activity of the molecules.

Commonly used synthetic polymers for drug delivery applications include biodegradable aliphatic polyesters such as polylactides (PLA), poly(lactide-co-glycolide) copolymers (PLGA), and poly(ε-caprolactone) as well as non-degradable polymers such as poly(methyl methacrylate) and polyacrylates. Table 3 lists the topically applied synthetic nanoparticle systems.

Nanoparticles made of biodegradable polymers—PLGA copolymers are biocompatible and biodegradable; in the body, the final degradation compounds i.e. lactic acid and glycolic acid are eventually removed by citric acid cycle[50]. These copolymers are the most commonly applied synthetic polymers for nanoparticle preparation, and PLGA nanoparticles have been widely employed for topical delivery.

Tomado et al.[52] prepared spherical PLGA nanoparticles that encapsulated with indomethacin by an emulsion solvent evaporation method and applied these indomethacin-loaded nanoparticles for transdermal delivery. An *In vitro* permeation study using rat skin showed that transdermal delivery of indomethacin was enhanced when it was loaded in PLGA nanoparticles. Since the surface of these nanoparticles was negatively charged, iontophoresis could be used to enhance drug penetration through the skin.

Shah et al.[53] utilized PLGA and chitosan to prepare surface modified bilayered nanoparticles with oleic acid. Two anti-inflammatory compounds, spantide II and ketoprofen were incorporated into PLGA inner core and chitosan outer layer, respectively. Nano gel formulation of these particles was created using hydroxypropyl methylcellulose (HPMC) and Carbopol to further enhance drug delivery to the deeper skin layers by improving the skin contact time and avoiding the water loss from the skin. *In vitro* human skin permeation study of this nano gel system exhibited significant increase in penetration of spantide II and ketoprofen in epidermis and dermis layers as compared to the control groups. *In vivo* studies were performed using an allergic contact dermatitis model and a psoriatic plaque like model; in both cases, drug-loaded nano gel formulation obtained better treatment effect as compared to the control groups.

Poly(ε-caprolactone) is another synthetic polymer that is widely employed for the preparation of nanoparticle formulations due to its biocompatibility, biodegradability and mechanical properties. In addition, due to its semi-crystalline structure, its degradation is delayed compared with amorphous polyesters. Alvarez-Roman et al. [54] reported the preparation of octyl methoxycinnamate-loaded poly(ε-caprolactone) nanoparticles for epidermal delivery of the loaded sunscreen agent; the results suggested better sun protection and partial protection against erythema.

Nanoparticles made of non-degradable polymers—Nanoparticles formulated with non-degradable polymers have also been studied for cutaneous delivery of active compounds. For example, Turos el al.[57] developed a water-based emulsion system using non-degradable polyacrylate polymers. This new nano-formulation contains antibiotic-conjugated polyacrylate nanoparticles in which the drug monomer (an *N*-thiolated β-lactam antibiotic) is incorporated into the polymeric matrix by emulsion polymerization. *In vitro* screens illustrated antimicrobial activity of this nanomedicine against methicillin-resistant *Staphylococcus aureus* and also proved that this dosage form was nontoxic to human dermal broblasts. This group also performed an *in vivo* study of their penicillin-conjugated nanoparticle emulsion on a dermal abrasion model and observed an accelerated wound healing process by an average of 3 to 5 days[58].

Tyrosine-derived nanospheres

A unique type of nanospheres, made of tyrosine-derived polymers from naturally occurring metabolites, has been developed at the New Jersey Center for Biomaterials, Rutgers University. The chemical structure of a typical ABA block copolymer used to prepare such nanospheres is shown in Figure 4: the A blocks, poly(ethylene glycol) is hydrophilic, and the B block made from tyrosine-derived diol and suberic acid is hydrophobic. In aqueous medium, the block copolymers self-assemble to nanospheres with size approximately 70 nm[59]. The nanospheres are trademarked as Tyrospheres™.

TyroSpheres™ have demonstrated their ability to (a) self-assemble together with a number of lipophilic drugs exemplified by paclitaxel[59, 60]; (b) retain the activity of the encapsulated drug[59,61]; (c) efficiently deliver a wide range of hydrophobic compounds into the skin [62, 63, 60]; (d) cause no detrimental effects to skin[62]; (e) process into more viscous formulation using HPMC, a pharmaceutically acceptable thickening agent [60, 62]; (f) control the over-proliferation of keratinocytes by sustained release of encapsulated paclitaxel[60]; and (g) preferentially deposit paclitaxel into the epidermis, thus eliminating the adverse side effects associated with systemic exposure [60]. These results demonstrate the applicability of Tyrospheres™ in the treatment of skin diseases such as psoriasis.

SUMMARY AND PERSPECTIVES

Topically applied, polymeric nanoparticles-based drug delivery systems for the treatment of skin diseases have a number of advantages including the fact they:

- **a.** effectively enhance the skin permeation of therapeutics, especially the poorly water-soluble lipophilic drugs, via increasing the drug concentration gradient across the skin;
- **b.** improve the drug stability;
- **c.** decrease the side effects such as skin irritation of applied drugs;
- **d.** deliver drugs directly to the disease site and minimize the systemic exposure.

However, compared to the formulations developed in the industrial setting, the nanoparticles-based drug delivery systems have, in general, shown only limited degree of enhancement in skin permeation. Any “game changing” techniques enabling rapid, more effective, and targeted delivery of therapeutics would be the “holy grail” for the pharmaceutical and skin care society. Below, we offer our perspectives on potential breakthroughs in the nanoparticles-based skin delivery systems are:

Skin penetration of nanoparticles

Several recent studies using various nanoparticles demonstrated the penetrating feasibility of nanoparticles penetrating across the mucus membranes [64, 65] and the skin barrier [66]. In one study, the biodistribution and elimination of a series of near-infrared (NIR) fluorescent nanoparticles, either inorganic/organic hybrid (INP) or the organic ones (ONP), with varying chemical composition, shape, size, and surface charge, were quantified in rat models after lung instillation [65]. It was demonstrated that nanoparticles with hydrodynamic diameter in the rage of approximately 6 to 34 nm and a non-cationic surface charge translocated rapidly from the lung to mediastinal lymph nodes. Nanoparticles with hydrodynamic diameter < 6 nm could traffic rapidly from the lungs to lymph nodes and the bloodstream, and then be subsequently cleared by the kidneys [65]. A most recent paper reported that spherical nucleic acid-nanoparticle conjugates (SNA-NCs), featuring of 13 nm gold cores surrounded by a dense shell of highly oriented, covalently immobilized siRNA, freely penetrated keratinocyte layer in vitro, mouse skin, and human epidermis within hours after application [66].

These recent discoveries may suggest that nanoparticles smaller than a certain size can penetrate efficiently through the epithelial barriers. The mechanisms of the penetration are yet to be elucidated. Whether or not the skin appendages such as hair follicles play a significant role in such rapid penetration is open to discussion. Safety concerns should also be addressed before any clinical trials begin.

Targeted delivery of active reagents to hair follicle stem cells

The localization of topically applied nanoparticles in hair follicles was reported by several investigators[7, 55, 56], and a straight forward application would be the delivery of hair growth ingredients for the treatment of hair loss [51]. Moreover, the localization of nanoparticles in the hair follicles may promote the delivery of active reagents that manipulate the proliferation and differentiation of hair follicle stem cells. The potential applications could be addressed to the treatment of dermatological conditions and wound healing.

Combining microneedles and nanoparticles

A number of studies have indicated the accumulation of topically applied nanoparticles on the surface of stratum corneum or in hair follicles, and the approach of combining nanoparticles and microneedle arrays could potentially facilitate the nanoparticle deposition or permeation into the deeper skin layers. Zhang et al.[67] reported increased deposition of a fluorescent probe in both epidermis and dermis from 160 nm PLGA nanoparticles after microneedle treatment on skin. Coulman et al.[68] confirmed the diffusion of 138 nm polystyrene nanoparticles to the interior surface of microchannels after the skin was treated with microneedles. These studies have shown the feasibility of using microneedles to enhance delivery of drug-loaded nanoparticles to deeper layers of skin where most dermatological diseases originate.

Moreover, combination of the microneedle and the targeted nanoparticles techniques can provide an alternative route to deliver drugs into specific cells/tissues. Specific targeting of mast cells and lymphocytes that lie in the dermis can improve the treatment of allergic and inflammatory associated skin diseases.

Besides treating dermatological diseases, another attractive application of combining microneedles and nanoparticles technologies lies in the area of vaccine delivery. Microneedles were shown to deliver antigen to epidermal and intradermal layers having large number of antigen presenting cells, such as Langerhans and dendritic cells [69].

Although many studies have shown the improvement of topical delivery via microneedles and nanoparticles, the mechanisms of colloid movement through micron-sized channels are still poorly understood and require future investigation. Safety issues such as transcutaneous penetration of nanoparticles and systemic uptake of drugs also need to be studied.

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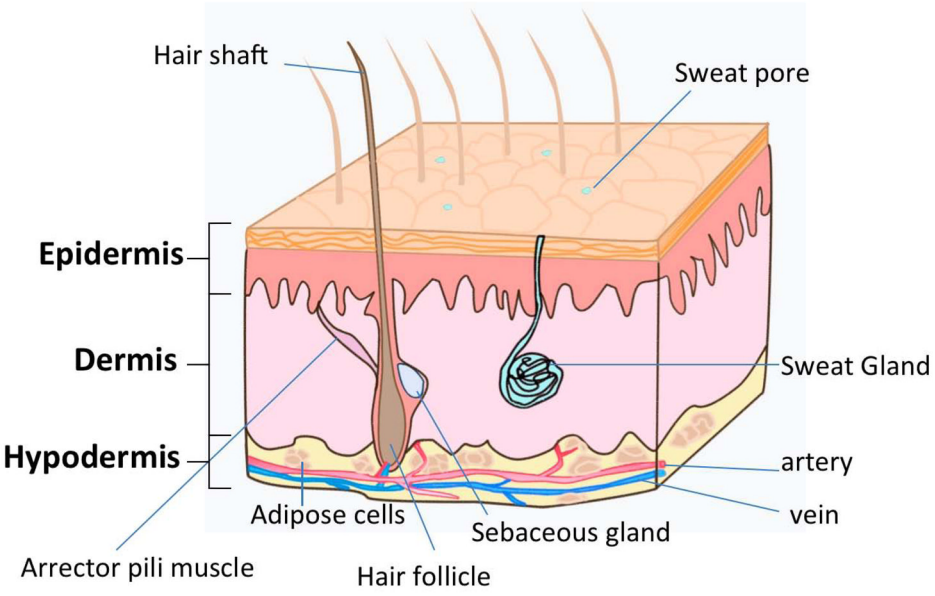

Figure 1.
A schematic image of epidermis, dermis and hypodermis structure. The appendages such as hair shaft and hair follicle, sweat gland, sebaceous gland, and arrector pili muscle are illustrated.

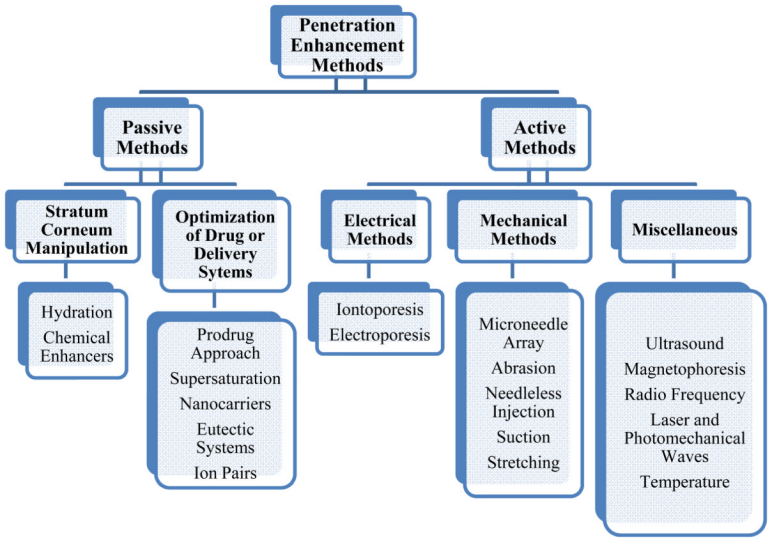

Figure 2.
An overview of passive and active skin penetration enhancement methods.

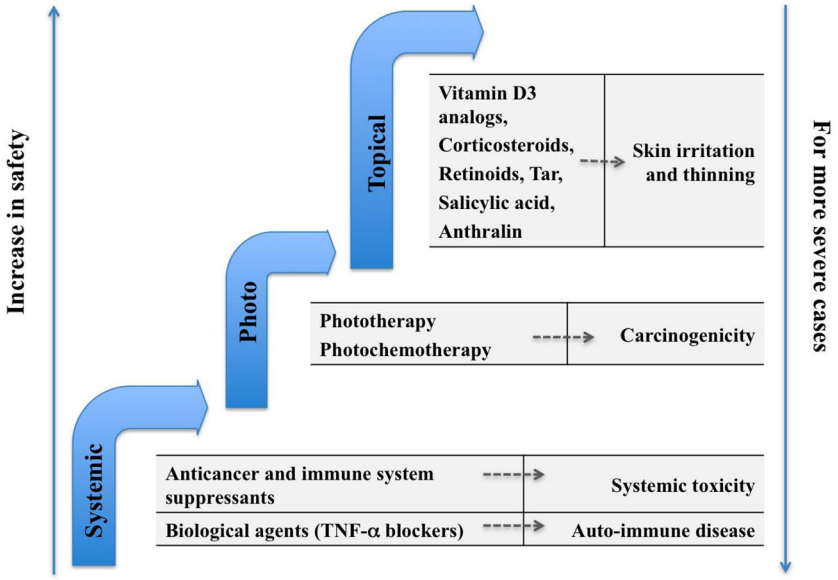

Figure 3.

Standard of care for psoriasis categorized as systemic approach, phototherapy and topical approach. Under each category, the current treatment options (on the left columns) and the side effects (on the right columns) are given.

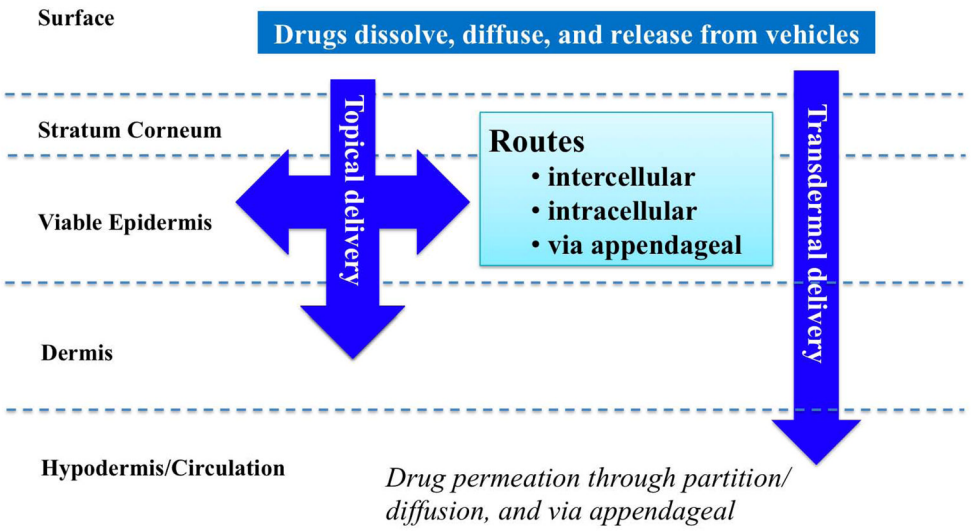

Figure 4.

Tyrosine-derived, ABA-type poly(ethylene glycol)-*b*-oligo(desaminotyrosyl-tyrosine octyl ester suberate)-*b*-poly(ethylene glycol) triblock copolymer used in the preparation of Tyrospheres™.

Table 1

Nature of skin strata: cellular and molecular components and associated functions

	Anatomical feature	Cellular components		Molecular components	Function
Epidermis					
Stratum Corneum	A cornified layer possessing a "bricks and mortar" structure	Corneocytes, the dead cells lacking nuclei and organelles		Intercellular lamellar lipid bilayers	Contributes significantly to the permeation barrier properties of skin
Stratum Lucidum	A thin and clear/translucent layer found only in certain areas of thick skin	The major cells of the viable epidermis are keratinocytes (90–95%). As the keratinocytes in the basal layer of epidermis proliferate, the daughter cells migrate superficially and differentiate, forming the shallower layers	Flattered and dead keratinocytes filled with eleiden, an intermediate form of keratin	Oily lamellar bodies containing lipids and proteins	Water proof barrier preventing fluid loss
Stratum Granulosum	A highly differentiated granular layer		Keratinocytes becoming granular cells that contain keratohyalin granules		
Stratum Spinosum	A spinous layer where keratinization begins		Adjacent keratinocytes are joined together by desmosomes; Langerhans cells (the dendritic cells)	Cytokeratins, the intermediate filaments of keratin, and desmosomes	Cytokeratin-desmosome networks provide structural support, helping the skin resist abrasion. Langerhans cells contribute to the immunological response of the skin
Stratum Basale	The deepest layer of epidermis		Melanocytes produce melanin that contributes to skin pigmentation and protects the skin from harmful ultraviolet radiation; Merkel-Ranvier cells (the oval receptor cells) contribute to sensory reception).		This is where the epidermal (keratinocytes) differentiation initiates
Dermis					
Papillary Dermis	A layer intertwined with the overlaying epidermis, forming rete pegs and rete ridges along the dermal-epidermal junction	Fibroblasts, macrophages, and adipocytes		Collagen, elastin, glycos-aminoglycans and glycoproteins	Provides tight contact between epidermis and dermis
Reticular Dermis	A layer of dense collagen and elastic fiber matrix				Main source of the strength, flexibility and elasticity of the skin.

Table 2

Topical delivery systems based on natural polymeric nanoparticles.

Natural Polymeric Nanoparticles	Encapsulated Drug	Target treatment or effect	Particle size	Ref
Gelatin	Pilocarpine HCL	Ophthalmic use	300~500 nm	39
Chitosan	Retinol	Wrinkled skin, acne	50–200 nm	41
Chitosan-TPP	Antisense oligonucleotides	Overexpressed genes	221 nm	42
	Aciclovir	Anti-viral in herpes infections	350–700 nm	43
	Plasmid DNA	Genetic immunization	200–287 nm	44
Lecithin-chitosan	Clobetasol-17-propionate	Antineoplastic, anti-inflammatory	250 nm	45
	Quercetin	Antioxidant, delay UV mediated oxidant	95–168 nm	46

Table 3

Topical delivery systems based on synthetic polymeric nanoparticles.

Synthetic polymers	Encapsulated drug/model compounds	Target treatment or effect	Particle size	Ref.
Biodegradable				
PLGA	Hinokitol, 6-benzyaminopurin	Hair growth	182–210 nm	51
PLGA	indomethacin	Analgesic for transdermal delivery	100 nm	52
PLGA-chitosan	spantide II and ketoprofen	Anti-inflammatory	169 nm	53
Poly(ε-caprolactone)	Octyl methoxycinnamate	Sunscreen effect	255–427 nm	54
Poly(ε-caprolactone)-block-PEG	minoxidil	Anti-hairloss	40 &130 nm	55
Non-biodegradable				
Polystyrene	Nile red	Hydrophobic dye (to study release mechanism)	28–31 nm	7
Poly(methyl methacrylate)	Nile red	Hydrophobic dye (to study release mechanism)	68–100 nm	56
Polyacrylate	*N*-thiolated β-lactam	Antibiotic for wound healing	40 nm	57