

Follicular targeting through nanotechnology: An overview

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18.1 Introduction

Nanotechnology refers to the practical application of any technology developed at the nanoscale, and it also refers to the reorganization of material at the atomic and molecular levels in the size range of 1 to 100 nm. Nanoscience refers to the fundamental scientific principles and concepts that underlie the field. At the nanoscale, matter exhibits unique characteristics that differ from its macroscopic counterparts. Initially, the properties of a material remain unchanged when its dimensions are lowered from their original large size. However, slight variations eventually occur. Finally, substantial modifications in properties may occur when the size decreases to less than 100 nm. Nanomaterials possess unique chemical and physical properties that can be connected for novel and advantageous uses in both industry and society. The discoveries of new phenomena, processes, and materials at the nanoscale, along with the development of new experimental and theoretical study tools, have enabled the creation of innovative nanosystems and nanomaterials in the late 20th century. This field of nanotechnology is opening up new opportunities in the realm of technology and science. Nanotechnology includes the consumption of biological, chemical, and physical systems across a range of scales, from specific atoms or molecules to submicron sizes. Additionally, it involves the incorporation of these nano forms into larger systems (Bhushan, 2016).

The pilosebaceous unit plays a vital role in processes of permeation and penetration when chemicals are applied topically. The follicle of human hair not only acts as an important reservoir but also functions as a gateway for topically applied medications and shows a

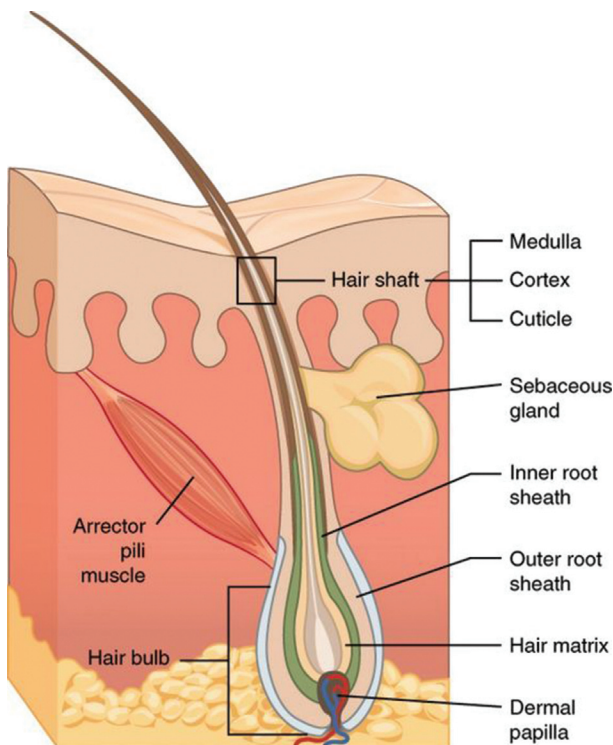
vital role in the delivery of medicine into the skin (Wosicka & Cal, 2010). In recent years, a highly appealing therapy alternative has arisen for many hair follicular illnesses: the delivery of medication specifically targeting the hair follicles (HFs). This is probably a result of the complex arrangement and life cycle of HFs. Considering that follicles on the scalp and face constitute around 10% of all HFs, it is probable that acne vulgaris and hair loss are the most common disorders directly linked to the HFs. Delivery of medications that specifically target HFs is becoming increasingly crucial in various therapeutic applications, including treatments for acne vulgaris, androgen-associated diseases, and hair loss. Follicle delivery devices play a vital role in improving the efficacy of topical treatment for these illnesses while reducing the occurrence of systemic side effects. In recent years, a highly appealing therapy alternative has arisen for many hair follicular illnesses: the delivery of medication specifically targeting the HFs. This is probably a result of the complex arrangement and life cycle of HFs. Considering that follicles on the scalp and face constitute around 10% of all HFs, it is probable that acne vulgaris and hair loss are the most common disorders directly linked to the HFs. Delivery of medications that specifically target HFs is becoming increasingly crucial in various therapeutic applications, including treatments for acne vulgaris, androgen-associated diseases, and hair loss. Follicle delivery devices play a vital role in improving the efficacy of topical treatment for these illnesses while reducing the occurrence of systemic side effects (Fang et al., 2014). In addition, formulations containing particles remained detectable in the follicles of hair for 10 days of the period, while nano-sized particles in the SC reservoir were only preserved for a single day. The findings indicate that HFs could serve as an effective means for sustained medication delivery. The physicochemical properties of the medication and carrier type employed in the preparations regulate the drug's targeted accumulation in HFs. Several systems for drug delivery, including microneedles, lipid nanoparticles (NPs), and polymeric NPs, have undergone thorough investigation to improve the precise delivery of medicinal substances or API to HFs (Patzelt et al., 2011). It may be feasible to administer precise amounts of active substances into the follicular duct using drug delivery devices and formulations designed to specifically target the human HF. Possible applications include the treatment of abnormal hair growth, disorders associated with HFs, and various skin conditions (Grymowicz et al., 2020).

18.2 Hair follicle

Hairs are an inherent trait of humans and animals that fulfill multiple purposes, such as providing thermal insulation, concealing oneself, offering physical defense, dispersing sebum and sweat, facilitating social contact, and enabling sensory awareness. The fibrous α -keratin protein used for composed of a human hair shaft and has a unique microstructure, which divides into three different zones: (1) cuticle (outer layer), (2) cortex (the main part of the fiber), and (3) medulla (inner layer) (Tung & Yasuda, 2020).

The cuticle is located within the inner root sheath and, externally, by the outer root sheath. The human hair shaft is generated by HFs, which are multicellular mini-organisms situated in the skin. It constitutes a component of the pilosebaceous unit, alongside the apocrine gland, sebaceous gland, and arrector pili muscle. HFs have many phases during their existence (see Fig. 18.1).

FIGURE 18.1 Anatomy of hair follicle: the details of hair structure and its components.



18.2.1 Anatomy and physiology of hair follicles

The hair structure (HS) undergoes growth for a finite duration, indicating the cyclical pattern of physiological HF renewal. Each phase duration and cycle varies depending on the specific human body component, as well as the length of a single hair shaft. Throughout this period of growth, there are several morphological and histological changes that take place in both HFs and hair shafts.

These changes can be categorized into four distinct phases (Lai-Cheong & McGrath, 2017): (1) Anagen, which is the phase of proliferation and growth, (2) Catagen, the phase of apoptosis and regression, (3) Telogen (resting phase) and (4) exogen, (shedding phase).

18.2.2 Hair cycle

Hair is formed through the coordinated actions of multiple layers of keratinocytes within the follicles of hair. Hair growth is a complex and recurring process that is regulated by various hormones and cytokines. The growth cycle duration is influenced by some factors such as the location of hair growth, stage of development and age nutritional habits, and environmental changes. The key players in this process are mostly cytokines, which are the hormones that can direct the follicle to endure specific variations. This allows each hair to be in a distinct stage of the growth cycle in comparison to the neighboring hairs. HFs undergo cyclical growth,

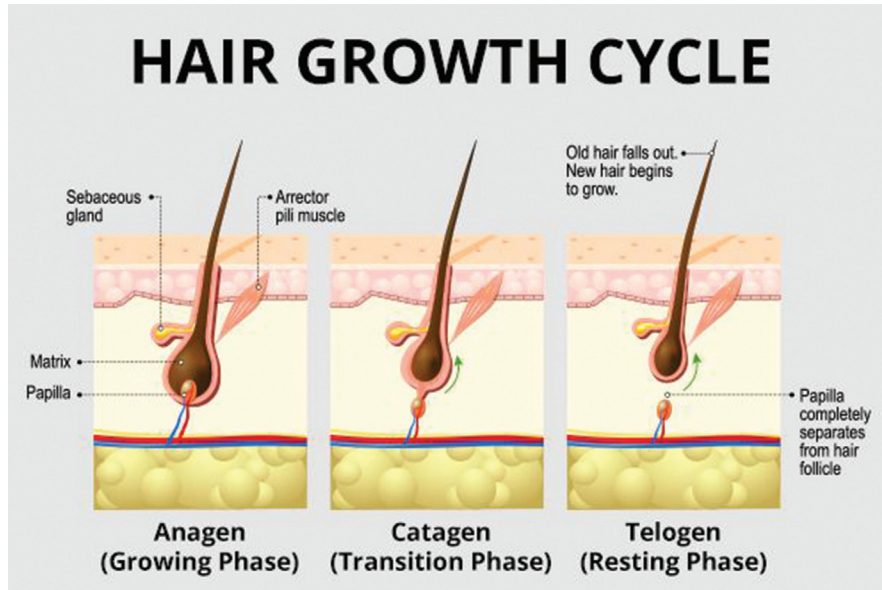


FIGURE 18.2 Hair growth cycle: different phases of the hair growth cycle.

characterized by alternating phases of fast growth and hair shaft creation, and phases of HF regression driven by apoptosis, followed by periods of relative HF quiescence. Specifically, it can be categorized into three main phases (Oh et al., 2016; Timar, 2020):

1. *Phase I:* Anagen (growth phase)
2. *Phase II:* Catagen (involution)
3. *Phase III:* Telogen (resting phase before hair shedding) (see Fig. 18.2).

18.2.2.1 Anagen phase

The anagen stage is a period of intense growth, in which the hair spreads and assumes its distinctive onion characteristics, as well as producing hair fibers. The process can be divided into six stages and labeled I to VI. During early hair growth (anagen I–V or proanagen), hair cells proliferate, surround the growing skin roots, spread down to the skin, and begin to turn into HFs and roots on the inside of the box. The final stage of hair growth (anagen VI or metanagen) involves the complete remodeling of hair fibers. It is characterized by an epithelial hairball covering the dermal papilla deep in the epidermis and then a new hair from the epidermis. In HFs, this phase can extend for years (see Fig. 18.2) (Yang & Cotsarelis, 2010).

18.2.2.2 Catagen phase

The catagen phase commences with the realization of the anagen growth phase. During the initial degree of the catagen phase, there is an exceptional decline within the diversity and proliferation of hair matrix keratinocytes. Additionally, the melanocytes cease their building of pigment activity, and the manufacturing of the hair shaft is finalized. The follicles of hair

experience apoptosis-caused regression, leading to a decrease in diameter by approximately 1/6th of their ordinary size. In the catagen segment, a distinct shape called the club hair has evolved. It is secured within the telogen follicle by the keratinized, brush-like structure at its base, which is encased by epithelial cells of the outer root sheath. The dermal papilla transforms into a cluster of dormant cells located near the regressing HF epithelium. It transitions from the subcutis to the interface between the subcutis and dermis to maintain touch with the inferior portion of the HF epithelium, which includes the bulge and secondary hair germ. This stage has a period of numerous weeks (see Fig. 18.2) (Tung & Yasuda, 2020).

18.2.2.3 Telogen phase

It follows the catagen phase, in which the hair enters a state of relaxation. This time can vary from a few weeks for eyelashes to up to 8 months for hair on the scalp. While the hair does not undergo growth at this stage, in this phase the dermal papilla remains in a nation of rest. Telogen follicles of hair are prominent using the absence of melanocytes, which are liable for developing pigment, as well as the absence of the internal root sheath (IRS). Their dermal papilla is firmly linked to a minute cap of secondary hair germ keratinocytes that reside in HF stem cells. Around 10% to 15% of all HFs are within the telogen phase at any given time. Three following the final touch of this stage, the hair undergoes a method known as the exogen phase, in the course of which it comes out. After a few weeks, the follicle of hair initiates the segment of increase by using activating stem cells located within the bulge area. The presence of follicular stem cells and a unique touch among epithelial, mesenchymal, and melanocyte, cells are very important for the maintenance and regulation of the hair cycle. The bulge location of HFs having stem cells that may function a with ease to be had deliver of homogenous multipotent stem cells which might be important for the functioning and development of the follicle of hair, which includes the pigmentation of HFs (see Fig. 18.2) (Oh et al., 2016).

18.2.3 Types of hair follicles

The terminal follicles, such as eyebrows and lashes, are hair that is not influenced by androgens. On the other hand, vellus follicles, found on the chest, beard, pubic region, and scalp axillae, are hair that is dependent on hormones. The hair shafts are composed of terminal hairs that are 0.2 cm long and have a thickness of 0.60 mm. These hairs are pigmented and have medullae. The majority of scalp hairs lack a medulla, and the medullae are only seen in conspicuous terminal hair strands. It typically penetrates the hypodermis by more than 3 mm. The residual adult body is adorned with vellus hair, which is short (less than 2 cm) and thin (with a diameter of less than 30 mm). Typically, these hairs lack pigmentation and best reach a depth of 1 mm inside the epidermis. Certain follicles of hair can undergo a transitional phase between vellus and terminal hair. The HFs within the scalp area are usually organized in a follicular unit, consisting of one to four terminal hairs and one to two vellus hairs, surrounded by branches of the arrector pili muscle (Galbraith, 2010; Yang & Cotsarelis, 2010).

18.3 Nanotechnology in drug delivery

A follicular delivery system based on NPs can effectively target follicles of hair. The follicles are enclosed by a network of blood arteries, stem cells, and dendritic cells. These objects are

ideal candidates for medication delivery. In recent years, the subject of nanotechnology has become increasingly significant. Numerous items, such as cosmetics and medications, already include NPs in their composition (Diksha et al., 2021). Nanotechnology's swift progress has resulted in the proliferation of its uses in medicine, giving rise to a distinct branch called nanomedicine (Lei et al., 2024).

Nanotechnology has yielded significant advancements in various biology-related domains, including diagnostics, drug administration, and molecular imaging. Nanotechnologies have been employed in regenerative medicine to replace lost tissues or cells, including HFs. The term "nano-pharmaceuticals" encompasses functional nanostructures used for biomarker detection, as well as nanomaterials employed in regenerative medicine and drug delivery (Kumar et al., 2022). Furthermore, formulations based on nanotechnology demonstrate enhanced stability, safety, and biocompatibility (Correia et al., 2023). Nanotechnology-based techniques offer a compelling strategy for targeting and regenerating at the HF level.

18.3.1 Follicular delivery and targeting

Deliver the materials at the target site of HFs, NPs have the capacity to function as a method for actively targeting follicles of hair. These are enclosed by using complicated linkages of blood arteries, stem cells, and dendritic cells. All of them are highly suitable candidates for pharmaceutical shipping. The follicular pathway allows for systemic absorption via the blood capillaries positioned around the bulge location. Studies have shown that minoxidil and caffeine may be immediately recognized within the plasma following topical application via the follicular course. Potential goals for medications and nanocarriers include other sorts of cells or structures, together with matrix cells, Langerhans cells, and melanocytes. There are four places of the follicles that may be categorized for medicine and delivery of NPs: the bulge area, the sebaceous duct, the hair matrix, and the follicular infundibulum (Matos et al., 2023). The epithelium of the highest sections is indistinguishable from the interfollicular epidermis. However, the epithelium of the infundibulum and vellus is less thick compared to the interfollicular epidermis. Reduced size and not fully specialized corneocytes are present in this area. This section of the structure of the follicle, which has a decreased ability to block drugs, offers a quick and easy method for applying substances topically. Furthermore, follicles provide the advantage of being a highly effective storage site for long-term purposes when compared to the SC, therefore offering the potential for continuous drug administration (Pereira et al., 2023).

The investigation conducted by many researchers indicated that the NPs exhibited a tenfold extended retention time in the HF reservoir within the stratum corneum (SC). Another advantage of follicular delivery is its ability to penetrate more profoundly into the epidermal layers, attributed to the presence of the follicular infundibulum inside the dermal layer. Follicles generally demonstrate activity in sebum secretion and hair development.

Approximately 30% of follicles remain dormant and closed as a result of dry sebum. The permeant typically undergoes diffusion into active follicles while being unable to penetrate inactive follicles due to the obstruction caused by cell debris and dry sebum. Certain NPs can facilitate the opening of closed follicles, hence enhancing the efficiency of follicular transport. Research has shown that NPs preferentially penetrate the follicles over the SC, leading to substantial accumulation inside the follicular reservoir. Upon deposition in the follicles, the

drug can be released from the NPs and affect the targeted cells or structures. Massage can improve the follicular absorption of NPs. Massage induces movement in the hair shaft, acting as a mechanical pump that drives particles into the follicles. A contrasting mechanism to follicular delivery is the sebum flow and hair growth, which can impede the movement of NPs due to the upward flow in contrast to the downward delivery through follicular penetration (Lademann et al., 2006; Pereira et al., 2021).

18.3.2 Dermatological diseases treated via follicular delivery

The application of medications or NPs directly to HFs, to specifically target them, is a subject of study in the treatment of skin illnesses, particularly those connected to the appendages. Potential applications encompass the treatment of hair growth problems and inflammation. Follicular targeting of medications and nanomedicines is an effective treatment for hair loss. Alopecia refers to the loss of hair on the scalp, which can occur either as a result of an inflammatory process (known as alopecia areata) or an androgenic process (known as androgenetic alopecia) (Pereira et al., 2018). The prevalence of androgenetic alopecia in Caucasian males is 96%, whereas alopecia areata affects 2.1% of the population. A considerable segment of the human population is affected by hair loss. Although the illness is not lethal, it has significant social implications for the individual owing to the considerable change in the patient's appearance. Androgenetic alopecia results from a shortened anagen phase, leading to increased hair loss and the transformation of robust terminal follicles into fine vellus follicles. Conversely, hirsutism and hypertrichosis can result in a prolonged anagen phase, during which vellus follicles are converted into terminal follicles. The utilization of the follicular absorption approach may also prove advantageous in the treatment of marine abnormalities. Follicular targeting facilitates the direct administration of topically applied agents to the sebaceous glands, providing an effective approach for addressing sebaceous gland disorders like as acne, seborrheic rosacea, and eczema. Among these, acne is the most often utilized disease model for developing nanoparticulate formulations that incorporate active ingredients such as retinoic acid and its derivatives. Acne vulgaris, the predominant dermatological condition, impacts more than 80% of people at some stage in their lives. Acne is a complex condition with multiple factors contributing to its development. It presents with numerous symptoms, including nodules, comedones, cysts, papules, and inflammation of the HFs and sebaceous glands (Higgins & Christiano, 2014). Recent studies have demonstrated that several NP kinds can efficiently target HFs for acne therapy. These include polymeric NPs, liposomes, and solid lipid NPs. Follicles serve as a habitat for the colonization of *Staphylococcus aureus*. Furuncles, impetigo, folliculitis, subcutaneous abscesses, and sycosis are diseases that can result from a skin infection caused by *S. aureus*. These diseases are caused by the release of exfoliative toxins. The treatment of *S. aureus* infections through the administration of NPs directly to the follicles of hair is a potential possibility, although there is currently a paucity of research in this area (Gu et al., 2022; Güngör & Kahraman, 2021).

18.3.3 Strategies for hair follicle targeting

The HFs can skip intricate networks between cells and penetrate deeper layers of the skin, making them an intriguing target location. Due to the intricate nature of follicular penetration,

three distinct approaches that exploit follicles of hair targeting have been utilized. NPs are employed to transport medicinal compounds to specific locations within the HF (Kumar et al., 2017). In addition, microneedles can penetrate the epidermal barrier and administer medicinal ingredients directly to the areas around the follicle of hairs, resulting in precise and rapid distribution. NPs with a specialized release mechanism are used to transport medicinal compounds deep into the follicles of hair. Exogenous stimulations speed up the release of the medications in this area (Gu et al., 2022; Wosicka-Fraćkowiak et al., 2015).

18.4 Nano particulate delivery into hair follicles

18.4.1 Polymeric nanoparticles

A variety of NP forms demonstrate a possible use in follicular absorption (Kumar et al., 2019). For follicular delivery, polymeric NPs have drawn the most interest among them. To prepare polymeric NPs for administration into the follicle, polymer materials such as polyvinyl alcohol, polystyrene, polylactic acid, polyethyleneimine, cellulose, and polyglycolic acid are used (Kumar et al., 2022), or polymer materials such as polyvinyl alcohol, polystyrene, polylactic acid, polyethyleneimine, and polyglycolic acid are used (Begines et al., 2020; Pourmadadi et al., 2024). The initial NPs created for follicular targeting are polystyrene nanosystems (Parmar et al., 2023).

To examine skin penetration and distribution, carboxylate-modified polystyrene NPs with average diameters of 20 nm and 200 nm were utilized. In this work, the dispersion of polymeric NPs coated with fluorescein isothiocyanate in pig ear skin was monitored using confocal laser scanning microscopy (CLSM). Horizontal slices of skin samples can be visualized at numerous depths parallel to the sample surface using the noninvasive CLSM approach (Alvarez-Román et al., 2004).

Morgen et al. (2011) evaluated the ability of polymeric NPs, wearing the lipophilic medicinal drug UK-157,147, to specifically target the HFs. This chemical is a pharmaceutical agent that acts as a potassium channel opener. It was specially created by Pfizer for the purpose of treating alopecia. Ethyl cellulose was the principal constituent of the polymeric nanosystems. The NPs had an average length of 96 nm and a polydispersity index of 0.18. The fluorescence microscopy images found that the NPs were the best gift on the floor of the rabbit ear pores and skin and inside the HFs after a 2-h treatment. A test was carried out to evaluate the impact of UK-157,147-loaded NPs on the hair improvement of C₃H mice. At day 25, hair showed significant changes observed at the dorsal area of 50% of the mice handled with polymeric nanocarriers containing 1% drug. On day 35, the boom of hair was determined in 70% of the mice that obtained nanostructures as treatment. No discernible skin soreness changed into visible at some point of the testing (Morgen et al., 2011).

18.4.2 Metallic nanoparticles

Metallic NPs are often rigid particles made up of various metallic compounds, including metals such as silver, iron, and gold, as well as metal oxides like titanium oxide, zinc oxide, and iron oxide. Pharmaceutical compounds can be encapsulated within the core of particles or

adsorbed onto the particulate surface, facilitating the targeted delivery of active substances. Metallic nanodispersions, inclusive of quantum dots (QD) and gold NPs, are very suitable for diagnostic applications. A novel category of semiconductor-based totally QDs has been newly advanced as an imaging agent that could surpass the limitations of traditional organic fluorophores QD possess slim band emissions and show off sizable ultraviolet absorption spectra, bearing in mind the simultaneous imaging of many goals with single light source. Certain steel NPs are selected for comparing their capability to penetrate HFs by using topical administration (Devi et al., 2024; Venkatesh, 2018).

Baroli et al. (2007) investigated the ability of iron sulfate (Fe_2SO_4) NPs, measuring under 10 nm, to penetrate the skin. *In vitro*, skin permeation experiments utilized human skin as the barrier for penetration. After the experiment, the skin underwent preparation for transmission electron microscopy and light microscopy. Following cleansing, the metallic NPs remained in the grooves of the skin's surface. used in several topical skin-care formulations, especially in sunscreen (Baroli et al., 2007). Moreover, the iron NPs were identified within the HFs and in their immediate vicinity. The iron deposits were located at a depth of 170 μm from the skin's surface, reaching the viable epidermis. However, the particles were incapable of permeating through the entire thickness of the skin (Yan et al., 2013). Zinc oxide (ZnO) and Titanium dioxide (TiO_2) NPs are widely utilized in various skin-care products that are applied topically, particularly in sunscreens (Lu et al., 2015).

Lekki et al. (2007) documented the detection of TiO_2 NPs, measuring around 20 nm, in the follicles of hair of both pig and human skin using autoradiography and ion microscopy techniques. The particles were observed at depths of several 100 μm within the follicles, and in certain instances, even at a depth of 400 μm . The region above the hair had a maximum concentration with a Ti value of 2.5 mg/g. No particles were detected in the sebaceous glands or essential tissues Lekki et al. documented the detection of TiO_2 NPs, measuring around 20 nm, in the follicles of hair of both pig and human skin using autoradiography and ion microscopy techniques. The particles were observed at depths of several 100 μm within the follicles, and in certain instances, even at a depth of 400 μm . The region above the hair had a maximum concentration with a Ti value of 2.5 mg/g. No particles were detected in the sebaceous glands or essential tissues (Lekki et al., 2007).

Zvyagin et al. (2008) employed scanning electron microscopy, multiphoton microscopy, and energy-dispersive X-ray methods to evaluate the penetration depth of zinc oxide NPs into human skin *in vivo*. The metallic NPs possess a diameter of 18 nm. A dosage of roughly 0.3 g of nano-dispersions was administered to the skin of human subjects for a duration of 5 min. Analysis revealed that zinc oxide NPs were found to persist in the SC and collect within the skin furrows and HFs (Zvyagin et al., 2008).

18.4.3 Lipid nanoparticles

A copious quantity of sebum is gifted in the ducts of follicles. The sebum ingredients can interact with lipids because of their analogous systems and lipophilic nature. According to this concept, lipid NPs could be beneficial for interacting with sebum, after which collecting within the follicles of hair. Nanoemulsions, liposomes solid lipid NPs, and nanostructured lipid providers may be classified as lipid NPs that own a pliable nature (Wosicka-Fraćkowiak et al., 2015).

Liposomes, while used for delivery of drugs as carriers, can increase the quantity of time that tablets stay within the bloodstream and speed up the process using which tumors absorb the medicine. This ultimately complements the effectiveness of remedies for resistant tumors. These are extraordinarily small vesicles made up of phospholipid bilayers that resemble membranes, and they're discovered in a watery solution. Liposomes containing phospholipids facilitate the interplay among vesicles and sebum, permitting them to input into follicles of hair. Nanoemulsions are a type of emulsion that is widely identified for their potential to beautify pores and skin permeability, increase the duration of movement at the pores and skin, and protect the drug from instability. SLN and NLC are novel lipid NPs derived from strong lipids. SLNs are composed entirely of strong lipids, while NLCs are composed of a stable matrix that carries liquid lipid nano-compartments.

Li et al. (2013) have engineered flexible liposomes to evaluate the efficacy of transcutaneous immunization using ovalbumin in Balb/c mice. The liposomes were produced with a size range of 200 to 400 nm. Fluorescence microscopy revealed fluorescently labeled vesicles in sweat glands and follicular ducts after topical application. This indicates that the appendageal route is significant in the transport of flexible liposomes. The effectiveness of transcutaneous immunization was evaluated by quantifying serum IgG levels. The liposomes applied topically generated an immunological response that was similar to the immune response generated by the positive control (ovalbumin solution supplied through subcutaneous injection) (Li et al., 2013).

A research was done by Desai et al. (2013) to investigate the percutaneous absorption of ibuprofen from two NP types: nanostructured lipid carriers (NLC) measuring 140 nm, and oleic acid-modified polymeric NPs measuring 195 nm. The objective was to ascertain whether NP transport predominantly happened via nonfollicular or follicular channels. Confocal microscopy was utilized to examine the spatial arrangement of lipid NPs in pig ear skin. Subsequently, the HFs were obstructed, and the absorption of skin in a laboratory setting was compared between the obstructed follicles and the nonobstructed ones.

The lipid NPs demonstrated much more fluorescence in the skin relative to the control solution. The HFs exercised control. The concentration of the medicine in the skin was comparable regardless of the HFs being occluded or patent. The results underscore the importance of both nonfollicular and follicular (intercellular and transcellular) pathways for the transport of lipid NPs. The ear thickness in the mouse model of allergic contact dermatitis was determined at 165 μm . Following a 72-h treatment, the thickness was decreased to 87, 50, and 39 μm by ibuprofen solution, NLC, and oleic acid-containing NPs, respectively.

18.5 Nanotechnology-based formulations for follicular drug delivery

The current approaches for delivering drugs to HFs primarily revolve around utilizing nanostructured systems for the delivery of drugs, including nanoemulsions, lipid NPs, polymeric NPs, and metallic NPs. Different types of NPs exhibit distinct behaviors and varying physicochemical properties when it comes to penetrating the skin and follicles of hair. While the precise method by which nano-formulations specifically target HFs remains uncertain, the size of the particles plays a vital role in directing the transport and retention of these formulations in the HFs. In addition, the occlusive effect plays a significant role in the penetration of

NPs into follicles of hair (Kolenyak dos Santos et al., 2013). NPs can provide direct contact with the surface connections of the SC. Following the process of evaporation of water, the hydrated SC will expand the gap of keratinocytes, thus improving the transportation of drugs to the follicles of hairs. The overall advantages of NP local drug delivery systems can be succinctly described as follows: improved chemical and physical stability, heightened accumulation of drugs, greater solubility, and prolonged release of pharmaceuticals. While HFs make up less than 0.1% of the entire skin area, the use of nanotechnology-based formulations allows for better penetration of medications into the follicles by producing microscopic particles that increase the surface area with the SC. Specifically, NPs containing drugs tend to enter and gather in the openings of HFs. These follicles act as storage areas for the drugs, allowing for regulated release and diffusion. This can help lower the required doses and frequencies of medication administration, hence minimizing the negative effects of the treatment (Correia et al., 2023; Shaikh et al., 2023).

18.6 Mechanism of follicular targeting

The mechanism of action of nano-formulations in follicular drug delivery system, first, the prepared nano-based formulation is applied on the surface of the skin topically due to the NPs size, the drug penetrates in penetrates to the pores of skin through the openings of HFs. These HFs help the drug-based nano-formulation in entering and penetrating various nano-formulations, then this formulation is retained in the follicular reservoirs by the diffusion mechanism the drug is released gradually from the follicles. The drug diffuses around the dermal and epidermis tissues and is attached to the target site of HFs to get an effective therapeutic response, and then the drug is metabolized, excreted, and cleared from the HFs by natural processes (Patzelt et al., 2011), Additionally, these tiny NPs are more prone to reaching the deeper layer of the epidermis. Smaller substances tend to enter the epidermis by the transfollicular pathway and reach the tissues around the follicles of hair. However, particles of the ideal size tend to collect mostly within the follicles of hair. Customized designs must be executed by precisely managing the particle size to meet the specific needs for pharmaceutical positioning. Furthermore, the ability to dissolve microneedles to penetrate the skin and deliver their loaded therapies straight into the dermal layers, thereby enriching follicles of hair, makes them a promising option for targeting follicles of hair (see Fig. 18.3) (Fang et al., 2014).

Moreover, the impact of the surface charge of NPs on their ability to target HFs has been well investigated; however, it still lacks clarity. Curiously, there are contradictory results among several investigations. A new study demonstrated that HFs can efficiently accumulate NPs that have a negative surface charge and lipophilic surface characteristics. PLGA NPs with a negative charge and PLGA NPs coated with phospholipids were found to enhance the absorption of follicles on a pig ear skin model. However, a separate study showed that NLCs containing cationic surfactants had a greater tendency to accumulate in HFs (see Fig. 18.4) (Gökçe & Güngör, 2020).

Ethosome is stimulated via the content of phospholipid and ethanol. It turned out that vesicle length grows while phospholipid concentration increases, ethosome length decreases while ethanol attention increases. Percutaneous channels via the SC and open HFs allowed

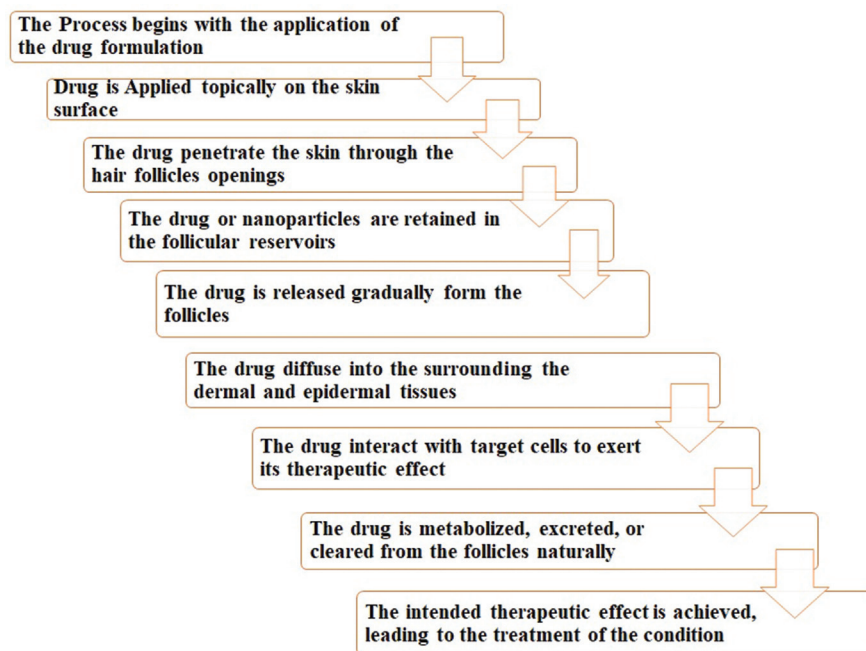


FIGURE 18.3 Mechanism of action of follicular drug targeting. This figure describes how the follicular drug delivery system works.

the ethosomes to enter the skin. Top layer pores and skin vesicles have been breaking up throughout percutaneous penetration that allows the therapeutically active tablets to regularly permeate at the same time as the upper dermis is maintained through phospholipids. The cautioned mechanism relies upon the interplay between phospholipids and ethanol, which will increase the charge at which capsules can permeate the ethosomes. Alcohol works well to grow penetration. At physiological temperature, the subcutaneous lipid layer of skin is tightly prepared and packed. The T_m of SC lipids is decreased by using ethanol, and their fluidity is multiplied. This results in a disruption of the skin's lipid bilayer enterprise and a decrease in skin lipid density. Additionally, ethanol can also play a function in malleableization and softening of the vesicle bilayer. The disorganized bilayer (SC lipid layer) is extra without difficulty penetrated by way of these bendy, squishy ethosome vesicles.

18.7 Application of follicular targeting in dermatology

Follicular targeting in dermatology is an emerging strategy that leverages the unique structure of HFs to deliver therapeutic agents directly into the skin. HFs serve as natural reservoirs, making them ideal targets for localized drug delivery, which can enhance the efficacy and reduce systemic side effects of dermatological treatments. Here are some applications of follicular targeting in dermatology:

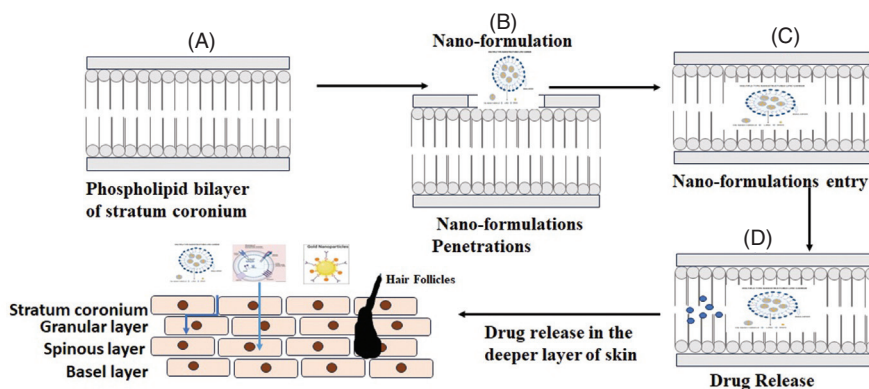


FIGURE 18.4 Mode of action of nano-formulations in follicular targeting, how ethosome works for delivery of drug at the follicular site by diffusion mechanism.

18.7.1 Acne treatment

HF are directly involved in the pathogenesis of acne, making them a prime target for treatment. Follicular targeting allows for the delivery of anti-inflammatory (Chandra et al., 2015), antimicrobial, and keratolytic agents (like benzoyl peroxide, retinoids, or antibiotics) directly into the sebaceous glands located within HFs. This approach can enhance drug concentration at the site of action, improving treatment outcomes while minimizing irritation to the surrounding skin (Ji et al., 2024).

18.7.2 Hair loss and alopecia

Follicular targeting can enhance the delivery of hair growth-promoting agents, such as minoxidil or finasteride, directly to the hair roots, where they are most needed. This can improve drug bioavailability and effectiveness, potentially leading to better clinical outcomes in treating conditions like androgenetic alopecia or other forms of hair loss (Jain et al., 2016; Ji et al., 2024).

18.7.3 Psoriasis and eczema

Inflammatory skin diseases like psoriasis and eczema often involve the HFs. Follicular targeting allows for localized delivery of corticosteroids, immunomodulators, or other anti-inflammatory agents, which can reduce inflammation (Chadha et al., 2020). It can also provide targeted relief while minimizing systemic absorption and side effects. (Lauterbach & Müller-Goymann, 2015; Su & Fang, 2008).

18.7.4 Pigmentation disorders

For conditions like hyperpigmentation or melasma, follicular targeting can be used to deliver skin-lightening agents, such as kojic acid, directly to the melanocytes located in the

HFs. This targeted delivery can enhance the efficacy of the treatment while reducing the risk of irritation or side effects (Chandra et al., 2015; Jain et al., 2016).

18.7.5 Local anesthesia

Follicular targeting can improve the delivery of local anesthetics, such as lidocaine, for dermatological procedures (e.g., biopsies and minor surgeries). This targeted approach ensures that the anesthetic is concentrated in the dermal and subdermal layers, providing effective and rapid pain relief (Shipton, 2012).

18.7.6 Immunotherapy for skin cancer

HFs are rich in immune cells, making them an attractive target for immunotherapies aimed at treating skin cancers like melanoma. By targeting the follicles, immunostimulatory agents can be delivered directly to the immune cells, potentially enhancing the antitumor response (Gupta et al., 2017).

18.7.7 Antiaging treatments

Targeting HFs for antiaging treatments can enhance the delivery of antioxidants, peptides, and other rejuvenating agents to the deeper layers of the skin, where they can promote collagen production and reduce the appearance of fine lines and wrinkles (Pozos-Nonato et al., 2023).

18.7.8 Antiviral and antifungal treatments

Follicular targeting can be beneficial in treating viral and fungal infections localized in the skin, such as herpes simplex or tinea capitis. By delivering antiviral or antifungal agents directly into the infected follicles, the treatment becomes more effective in eliminating the pathogen and reducing symptoms (Gupta et al., 2017).

18.8 Nanotechnology from a dermatologist's perspective

The expectations around nanotechnology are predominantly optimistic and have permeated various academic disciplines within the field of medicine, industries, and the scientific community at large. In September 2011, Friedman et al. (2011) conducted research in the United States to assess the fundamental comprehension and observation of nanotechnology in dermatology education programs. The evaluation of investigators, interns, and professors in this field was conducted through an online questionnaire that was randomly sent to personnel of a dermatological community. Out of a hundred participants, 23% was the response rate. Participants responded to questions using a 5-point scale that ranged from strongly disagree to strongly agree. The survey received responses from interns and residents in about equal proportions, with 52% of interns and 47.75% of residents participating. The majority of respondents (69.57%) did not participate in any educational activities on nanotechnology.

Additionally, a significant proportion (60.87%) agreed with the idea of incorporating nanotechnology education into the dermatology residency curriculum, while a smaller percentage (13.04%) disagreed. Additionally, they reached a consensus that a significant amount of nano-research has the potential to enhance our comprehension of cutaneous disorders (78.26%), facilitate progress in diagnosing skin diseases (73.91%), and improve therapies (78.26%). Overwhelmingly, the majority of participants (82.60%) acknowledged the significance of enhancing scientific research and allocating funds toward nanotechnology (78.26%). Unsurprisingly, participants exhibited concerns regarding the safety of nanotechnology in both the cosmetic (69.57%) and pharmaceutical (60.87%) industries. Moreover, a significant majority (86.96%) expressed a positive response about the necessity for further research to assess the safety of nanomaterials (de Souza et al., 2012).

18.9 Future perspective

The transportation of the HF of NPs has garnered significant interest during the last decade. The objectives of the investigations on follicle-mediated NP delivery can be categorized into two elements. The primary purpose is to load active substances that can be used to prevent or treat dermatological problems. The second test is to assess the potential danger of nanoparticulate penetration into the skin, which could raise concerns about toxicity. The primary worry with nanosystems is the potential for detrimental impacts on cells and organisms, which can be attributed to their reduced size and increased specific surface area in comparison to bulk materials. The shortcomings of nanomedicines in biological applications are frequently not a result of inadequate therapeutic/diagnostic effectiveness, but rather due to toxicological concerns. It is crucial to comprehend the detrimental impact of NPs on the hair and skin follicles. The issue at hand is the assessment of the potential hazards associated with the absorption of metallic NPs, specifically ZnO and TiO₂, found in sunscreens. This topic can provoke novel thoughts on the estimation of the potential infiltration of hazardous particles into the air and skin follicles for future research. The environment contains harmful particles known as particle pollution or particulate matter (Chaudhury et al., 2014).

There is a significant amount of research investigating the efficiency of NPs in facilitating the penetration of follicles in animals, both *in vitro* and *in vivo*. Nevertheless, there is a shortage of research examining the clinical application of follicle-mediated NP delivery in human subjects. Additional research involving a substantial number of human volunteers or patients is necessary to validate and elucidate the results obtained from animal studies. There have been limited studies conducted to understand the mechanisms by which NPs are delivered into HFs. Conducting fundamental research is essential to fully understand the intricate mechanics involved in delivering NPs to the HFs. It is crucial to develop appropriate animal models for follicle-mediated delivery. Additionally, there is a dearth of research investigating the impact of particle size on the delivery and absorption into follicles. Furthermore, there is a scarcity of studies evaluating the efficacy of different types of NPs in targeting follicles. This leads to the promotion of such endeavors aimed at enhancing the understanding of follicular delivery using nanomedicine. The majority of studies examining the absorption of NPs by follicles have employed microscopic techniques to observe the distribution of

particles. Nevertheless, these profiles offer a solely subjective assessment with limited objective analysis. Additional quantitative examination is required to provide the necessary evidence of follicular delivery. Currently, a technique called differential stripping/cyanoacrylate skin-surface biopsy is used to measure the amount of medication or NP accumulation in the HFs (Barua & Mitragotri, 2014). There is a pressing need for new and innovative techniques to objectively quantify the penetration of follicles soon. Once the NPs have penetrated the HFs, they must interact with or be absorbed by the cells to have a pharmacological effect. Alternatively, the drug should be liberated from the NPs to initiate the subsequent treatment. Our understanding of the molecular mechanisms involved in follicular delivery is relatively limited. It is advised that additional research be conducted to clarify the cellular and molecular pathways. In summary, the potential of using NPs to penetrate HFs shows great promise for both preventive and therapeutic purposes, particularly in treating conditions connected to HFs, including alopecia and acne (Tapfumaneyi et al., 2022).

18.10 Challenges and future directions

18.10.1 Challenges

These are some challenges that come with the follicular drug delivery system:

18.10.1.1 Safety and toxicity concerns

The incorporation of NPs into the body, namely via the dermal route, elicits apprehensions over potential toxicity. Comprehensive safety studies are necessary due to the incomplete understanding of the long-term effects of NPs on skin cells, tissue, and systemic circulation. The interaction between NPs and the skin or immune cells may lead to potential immunological responses or allergic reactions.

18.10.1.2 Regulatory and ethical issues

The regulatory frameworks for nanotechnology in dermatology are now in a state of ongoing development. Ensuring adherence to safety standards and acquiring regulatory approval for novel nano-formulations can be intricate and time-intensive. Important ethical factors include obtaining patient consent and ensuring transparency in disclosing information about the utilization of nanotechnology in products.

18.10.1.3 Manufacturing and scalability

Acquiring NPs with consistent size, shape, and surface qualities might pose challenges, potentially impacting the reliability and efficacy of the final product. Scaling up manufacturing operations from a small-scale laboratory to a larger commercial scale, while maintaining adherence to quality and safety standards, is a significant challenge.

18.10.1.4 Penetration and targeting efficiency

Although HFs offer a route for NPs to penetrate deeply, it is still difficult to achieve consistent and regulated distribution of NPs to the follicles. The efficacy of targeting HFs can

be influenced by the barrier qualities of the SC, the density of HFs, and individual variances in skin and hair types.

18.10.1.5 Stability and formulation issues

Preserving the stability of NPs in formulations is essential for preserving their efficacy over time. Stability can be influenced by factors such as aggregation, degradation, and interactions with other substances. Another problem is to produce formulations that possess both visual appeal and user-friendliness, while also preserving the functional qualities of NPs.

18.10.2 Future directions

18.10.2.1 Advancements in nanocarrier design

Current research endeavors to create novel nanocarriers, including stimulus-responsive or intelligent NPs, that can release active substances upon encountering specified stimuli, such as pH, temperature, or light. Another interesting topic involves improving the selectivity and effectiveness of targeting HFs by creating NPs that can selectively bind to HF cells or structures.

18.10.2.2 Personalized and precision dermatology

By combining nanotechnology with personalized medical approaches, it is possible to develop customized treatments that take into account an individual's skin type, genetic composition, and unique dermatological diseases. Creating diagnostic instruments that utilize NPs to administer contrast agents or biosensors for the identification of certain biomarkers in the skin has the potential to significantly improve personalized dermatology.

18.10.2.3 Clinical trials and real-world applications

Additional clinical trials are needed to assess the safety, effectiveness, and long-term impacts of follicular targeting nano-formulations in various patient populations. The process of turning encouraging laboratory discoveries into practical dermatological products necessitates cooperation among researchers, doctors, and industry collaborators.

18.10.2.4 Exploring new therapeutic areas

In addition to their conventional usage in treating acne and hair loss, follicular targeting nano-formulations show promise for treating a range of other illnesses, including skin cancer, inflammatory skin diseases, and microbial infections. Investigating the application of NPs for the administration of cutting-edge treatments, such as gene therapy, stem cell therapy, and vaccinations, is an additional promising pathway.

18.10.2.5 Regulatory harmonization and public awareness

It is crucial to establish uniform norms and standards for nanotechnology in dermatology worldwide to ensure widespread acceptance and market entry. Enhancing public knowledge and instruction regarding the advantages and potential drawbacks of nanotechnology in dermatology can contribute to the development of consumer trust and approval. The field of using nanotechnology to target HFs is expected to experience substantial growth and

TABLE 18.1 List of marketed nano-formulations for follicular targeting.

Product name	Active ingredients	Nanotechnology	Indication	Manufacturer
Nanominox	Minoxidil	Nanoparticles	Hair loss (alopecia)	Kose Corp
Nanosome Hair Stimulating Complete (Revita)	Minoxidil, biotin, caffeine	Liposome (nanosome)	Hair loss	DS Laboratories
Nanoxidil (Spectral DNC-N)	Nanoxidil	Nanosomes	Hair growth and hair loss prevention	DS Laboratories
Lipoxins	Minoxidil	Liposomes	Androgenic alopecia	Max Biocare
Follicapil	Botanical extracts	Nanoemulsions	Hair loss	Biogenesis
Nanogen Serum VEGF	Growth factors (VEGF)	Nanofibers	Hair thinning and growth	Nanogen
Tricovel Chrono Biogenina™	Biotin, methionine, cysteine	Nanotechnology complex	Hair strength and growth	Giuliani Pharma
Lipogaine Big3	Minoxidil, biotin	Nanoliposomes	Hair loss	Lipogaine

advancements. To fully maximize the benefits of this method in enhancing dermatological treatments and patient results, it is crucial to tackle the obstacles and make use of the latest technical breakthroughs.

18.11 Marketed nano-formulations for follicular drug delivery

These are some marketed formulations enlisted in used in follicular drug targeting (see [Table 18.1](#)) ([Costa et al., 2021](#); [Hoover et al., 2024](#)).

18.12 Conclusion

To summarize, the use of nanotechnology for follicular targeting is an advanced method in dermatology that improves the delivery and effectiveness of medicinal products. This novel approach leverages the distinctive composition and characteristics of HFs to enhance the depth and precision of active chemical absorption. This technique has the potential to be used for several dermatological diseases, such as hair loss, acne, psoriasis, and skin aging, among others. Nanotechnology offers several benefits for follicular targeting, including increased stability and bioavailability of active substances, decreased systemic adverse effects, and greater patient compliance. Through the exact targeting of HFs, these nano-formulations can deliver medications directly to the intended site of action. This enhances therapeutic results and reduces the likelihood of negative side effects. Although the potential for this technology

is excellent, it is essential to acknowledge and tackle the obstacles and constraints it presents. These factors encompass the requirement for comprehensive safety assessments, potential concerns regarding the toxicity of nanomaterials, and the intricacy of expanding manufacturing for clinical and commercial purposes. Moreover, additional investigation is required to comprehensively comprehend the mechanisms of follicular penetration and the enduring impacts of nano-formulations on skin well-being. Continued advancements in research and development in this field have the potential to transform dermatological medicines by utilizing nanotechnology to target HFs, providing patients with new and more effective treatment alternatives. Successful incorporation of this technology into clinical practice necessitates a cooperative endeavor involving researchers, physicians, and regulatory entities to guarantee secure and efficient execution. In the end, this method has the potential to facilitate tailored and precise medical care in the field of dermatology, enhancing the effectiveness of treatments for different skin disorders.

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