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REVIEW PAPER ON: HAIR FOLLICLE-TARGETING DRUG DELIVERY STRATEGIES FOR THE MANAGEMENT OF HAIR FOLLICLE-ASSOCIATED DISORDER

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ABSTRACT

In addition to being an essential pathway for percutaneous absorption, the hair follicle has been identified as a target for conditions like acne vulgaris and androgenetic alopecia (AGA). Drug delivery systems that target hair follicles have the potential to improve therapeutic efficacy and regulate drug release while posing few adverse effects. This makes them a viable option for treating dysfunctions linked to hair follicles. As a result, they have received a lot of interest lately in a number of study domains. Based on the unique characteristics of hair follicles, this review provides an overview of possible follicle- targeting drug delivery formulations now in use, together with a thorough evaluation of their preclinical and clinical efficacy.

A source of multipotent stem cells is found within the multicellular complex structure of the skin called the hair follicle (HF). There are drawbacks to the conventional hair restoration techniques such stem cell therapy, hair transplantation, and medication therapy. Novel strategies for HF regeneration, including as targeted HF and controlled medication release, are made possible by advancements in nanotechnology. It was believed up until recently that the formation of hair follicles could only occur through embryogenesis. But because it can happen in wound beds under specific circumstances, the phenomenon known as wound-induced hair neogenesis (WIHN) or de novo HF regeneration has drawn interest recently.

This study discusses targeting tactics specific to HF, with a focus on the applications of nanotechnology-based approaches now in use for HF regeneration as well as disorders associated to hair loss. Numerous techniques are proposed for HF regeneration, including gene therapy, tissue engineering, WIHN, hair cycle manipulation, progenitor cell stimulation, and signaling pathway activation. It has been determined that the HF is a prime candidate for hair restoration techniques based on nanotechnology. The development of HF regeneration nanotechnology-based techniques, which will be covered in the final section, could be hampered by some regulatory issues.

Keywords: Follicular Medication Administration, Androgenetic Hair Loss, Verruca Vulgaris, The Use Of Nanotechnology Little Needles.

I. INTRODUCTION

The most important channels for transdermal medication penetration into the skin are the delivery routes via hair follicles and the stratum corneum (SC). Due to the fact that non- permeable corneocytes cover a significant portion of the skin, increasing the bioavailability of transdermal medication has become a pressing pharmaceutical challenge. Large hydrophilic substances and particle structures are greatly inhibited from penetrating the skin while the SC is intact. On the other hand, the existence of hair follicles offers a means of getting above this barrier. Hair follicles deep into the dermis beneath the skin's surface provide a significant surface area for potential drug or chemical absorption. For drugs applied topically, the hair follicles serve as both gateways and reservoirs. Drug delivery that targets hair follicles has grown significantly in popularity during the last few years.

The physicochemical characteristics of the medicine and the kind of carrier used in the formulations control the drug's preferred deposition in hair follicles. Various drug delivery technologies, such as microneedles, lipid nanoparticles, and polymeric nanoparticles (NPs), have been extensively studied to improve the targeted administration of active medicinal ingredients to hair follicles. The main objective of this review is to critically introduce and assess delivery technologies that target hair follicles in order to provide a reference for safer and more sophisticated formulations intended to treat follicular diseases.

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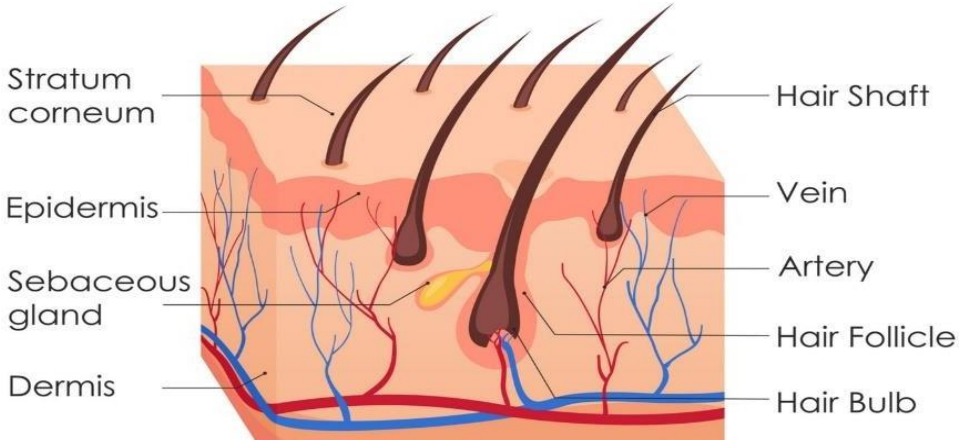
Hair:

Scalp hair is a defining element of our physical appearance with significant psychological and social impacts in our daily life. Everyone within any society has an abstract, unique and innate idea of beauty. As hair is one of the physical features which is easier to modify in terms of length, color or shape, the pursuit of the desired and idealized hairstyle to achieve beauty drives many consumers and feeds a vast global cosmetic industry.



Hair follicle:

Follicles at the interface of the hypodermis and the deep layer of the dermis are where hair originates.Another name for these follicles is hair bulbs.

The structure of the human hair follicle is fascinating, and there is still much to learn about the composition and development of hair.Three zones can be distinguished in the fair follicle.

1. The bulb and suprabulb of the lower segment
2. The isthmus, or middle segment
3. The portion above (infundibulum)

HAIR FOLLICLE ANATOMY:

The hair follicle is a complex epithelial structure and is enclosed by an outer root sheath (ORS), which helps to support hair growth, and an inner root sheath (IRS), and follows the hair fiber up to the opening of the sebaceous gland. The ORS and IRS are separated by the companion layer. The IRS can be subdivided into three distinct cell layers: Henle's layer, Huxley's layer and the cuticle of IRS. Besides these two layers, ORS and IRS, the hair follicles are composed of four other different epidermal layers: hair matrix, medulla, cortex and cuticle, as well as two dermal tissues: dermal papilla and dermal sheath. Among these layers, only the medulla is not always present, given that some hairs have no medulla and others have a medulla relatively large. Each layer itself can comprise numerous individualized cell layers characterized by specific programs of differentiation.

Within the skin, the terminal region of the hair follicle is called hair bulb, which is the structure formed by actively growing cells that produce the long, fine and cylindrically shaped hair fibers. The keratinocytes of the hair bulb have the highest proliferation rate among cells in the human body. The hair bulb comprises the hair matrix that will differentiate into the different precursors of the hair fiber, dermal papilla and surrounding dermal sheath. Additionally, the hair bulb also contains very specialized cells, the melanocytes, which produce the pigment melanin that gives color to the hair fiber. In combination with its associated structures (sebaceous and apocrine gland, arrector pili muscle), the hair follicle forms the pilosebaceous unit. The hair follicle primarily acts as a factory for pigmented, multifunctional and exceptionally durable proteinaceous fibers-hair.

Function of hair follicle:

Hair follicles and human hair are structures with multiple purposes. The formation of hair is not the only function of hair follicles. Since germ layer stem cells reside in the follicular

bulge, hair follicles are essential for skin regeneration and wound healing. The human hair is an important structure for human aesthetics and psychosocial well-being. Because they pass tactile sensations through hair follicles, hairs participate in tactile experience.

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Additionally, hair can protect against UV radiation, particularly on the scalp, face, and neck, which are places with thick hair distribution.

Operation The production and maintenance of hair growth depend on the hair follicle. Additionally, this structure influences the way the skin responds and operates.

Sensory and protective function:

Due to the presence of nerve endings, hair follicles are touch and vibration sensitive. Sensations from hair follicles aid in people's ability to recognize and react to outside stimuli. In addition, hair acts as a physical barrier to shield the skin from UV rays, mechanical trauma, and environmental stress.

Endocrine function:

Different hormones have an impact on hair follicles, which in turn affects hair growth, density, and distribution. Androgens, for example, are important in the development of male pattern baldness. Sebum, an oily material secreted by hair follicles, is produced by sebaceous glands connected to the follicles. Sebum aids in lubricating and protecting the skin and hair.

Mechanism of hair follicle:

The intricate structure of the hair follicle causes a complex process known as penetration through the follicular route, the precise mechanism of which is yet unclear .Particulate carriers tend to penetrate hair follicle orifices and deposit the drug preferentially, thus once the drug is encapsulated in them, transepidermal transport generally decreases .

Numerous factors pertaining to the physicochemical properties of drug molecules, such as the oil-water partition coefficient, molecular weight, and size, as well as those of carriers, such as particle size, lipophilicity, surface charge, and so forth, influence the delivery process to hair follicles.

Hair growth cycle:

Once it leaves the hair follicle, hair normally grows in a set cycle. There are three distinct stages in a hair development cycle, which are as follows: During the anagen (growth) phase, hair begins to sprout from the root. This stage often lasts three to seven years.

Phase of catagen (transition): follicle atrophy and a delay in hair growth are noticed during this period. Catagen normally lasts between two and four months. The same hair follicle begins to produce new hairs during the telogen (resting) phase, which replaces the lost ones. This typically lasts for four or three months.

Hair follicles are not just "resting" during the Telogen phase, as evidenced by current research. In order to support tissue repair and promote increased hair growth, a variety of cellular processes take place during this period. Stated differently, the development of healthy hair is facilitated by the Telogen phase. Additionally, within the same growth cycle, every hair follicle will experience a different stage. There's a chance that some cysts are growing, while others might be at rest. Or perhaps some hairs are falling out and some are in the

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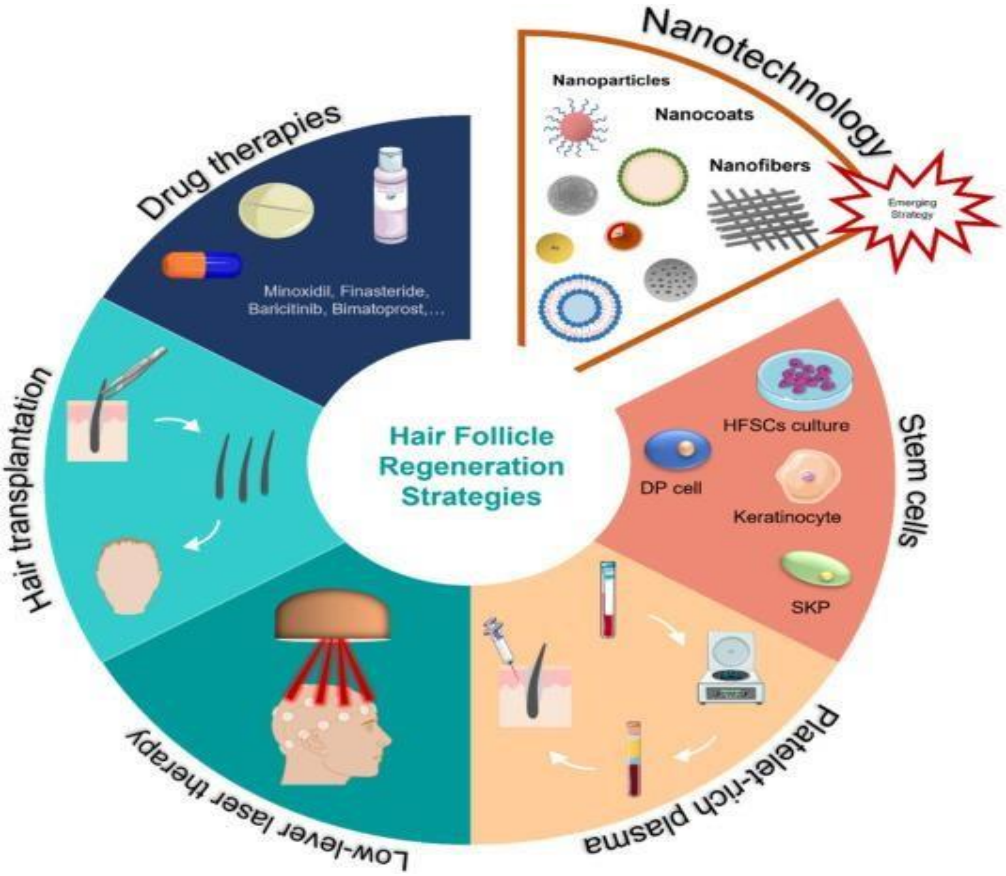
growth stage. An individual will typically lose 100 hairs a day, according to studies. However, approximately 90% of your hair follicles are most likely in the anagen phase at this time.

Strategies for management of hair follicle for associated disorder:



Hair follicles can efficiently overcome intricate intercellular permeation pathways and permeate deeper skin layers, which makes the hair follicles become an intriguing target site. Owing to the intricacy of follicular penetration, three distinct approaches that capitalize on the targeting of hair follicles have been implemented and are schematically depicted in . Particles based on nanotechnology are used to introduce therapeutic agents into the hair follicle's pre-selected target locations. Furthermore, by penetrating the skin's barrier and delivering the therapeutic materials straight to the areas surrounding the hair follicle, microneedles can accomplish precise and quick mapping. Alternatively, to deeply carry medication into the hair follicle, where external stimulations speed up the active release of medications, nanoparticles with a particular release mechanism are used.

The stratum corneum, the outer layer of the epidermis, and HFs (follicular penetration pathway) are the most often used transdermal routes for skin penetration. The trans-epidermal penetration route, also known as penetration through the stratum corneum, has certain restrictions and can happen directly across or around the corneocytes. The stratum corneum acts as a significant barrier to big hydrophilic materials and particle structures when applied topically because of its natural makeup. Corneocytes, which are keratin- filled anucleate cells encased in a lipid sheath, make up this barrier, which stops nearly all substances and medications with molecular weights more than 500 Da from penetrating . The primary route for smaller medications to pass the stratum corneum is through the intercellular channel, which encircles the corneocytes and involves a lipid pathway.

Nanotechnology-based formulations for follicular drug delivery:

Using nanostructured drug delivery methods, such as polymeric nanoparticles, nanoemulsions, lipid nanoparticles, and metallic nanoparticles, is the main focus of current follicular drug delivery tactics. provides a summary of NPs associated with hair follicle delivery. Diverse categories of nanoparticles exhibit distinct behavioral patterns and varying physicochemical attributes with respect to skin and follicular penetration.

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Particle size affects targeting delivery and retention in hair follicles, even if the precise process by which nanoformulations target hair follicles is unknown. Additionally, the occlusive effect plays a significant role in the mechanism by which nanoparticles enter hair follicles. Particles that are nanosized can ensure that they are in close touch with the superficial SC connections. The hydrated SC will expand the gap between the water molecules once it evaporates.

The fundamental benefits of local ”rug delivery systems utilizing nanoparticles can be summed up as follows: improved solubility, sustained drug release, higher drug accumulation, and improved physical and chemical stability . The penetration of follicular medications acquired through nanotechnology-based formulations improves by generating particles of small size to enlarge the surfaces with the SC, even if hair follicles make up less than 0.1% of the entire skin area . Drug-loaded nanoparticles, in particular, preferentially enter and collect in hair follicle orifices, which serve as drug reservoirs for regulated drug diffusion, allowing physicians to lower dosages and frequency of medication to mitigate negative effects.

Nanomaterials for Drug Delivery in Androgenetic Alopecia:

1. Lipid nanoparticles:

Medication can enter the body through the skin via the transappendageal route (cutaneous appendages) or the transepidermal route (unbroken epidermis) . Among these appendages is the hair follicle, which facilitates the entry of pharmaceuticals applied topically and helps them pass through the skin. With low drug concentrations, targeted therapy achieves the desired effect by increasing the bioavailability of medicine. Solid lipid nanoparticles or a solid matrix containing a blend of liquid, amorphous, or unsaturated lipids (nanostructured lipid carriers) are among the most studied lipid nanosystems. It has been demonstrated that size ranges smaller than 100 nm are necessary for the onset of cutaneous medication release.

Moreover, diameter ranges of about 200 nm have been found to favor drug release at the isthmus section of the hair follicles. Solid lipid nanoparticles having a diameter of 190 nm that contained minoxidil accumulated better in the layers of pig skin than commercially available items. Despite the superior penetration of solid lipid nanoparticles, stability remains a problem due to the possibility of solid lipids forming crystalline networks. This can lead to drug ejection during storage, especially when the solid lipid matrix is composed of a highly pure lipid.

Consequently, a novel class of lipid particles known as nanostructured lipid carriers was developed. It is possible to encapsulate finasteride and minoxidil in nanostructured lipid carriers, which have excellent chemical and physical stability while kept in storage. Compared to solid lipid nanoparticles, minoxidil-containing nanostructured lipid carriers demonstrated superior stability over a three-month period and demonstrated an excellent entrapment effectiveness of 92.5 0.3%). Furthermore, minoxidil encapsulated in nanostructured lipid carriers had 10.7 times greater skin permeability than minoxidil-containing solid lipid nanoparticles. Oleic acid, which is present in the formulation, has the potential to improve permeability. Notably, there is a strong correlation between lipid content and trapping effectiveness. Clobetasol propionate was more successfully entrapped within nanostructured lipid carriers when there was greater oleic acid present, with an entrapment efficiency of over 70%.

It has been demonstrated that adding more liquid lipid, oleic acid, to the mixture promotes an amorphous form in the solid lipid matrix, decreasing the crystallinity of the particles and improving encapsulation efficiency. This was explained by the existence of the unentrapped medication in the nanostructured lipid carriers' dispersion or by the location of lipids containing dissolved clobetasol propionate in the outer shell. The nanostructured lipid carriers of oleic acid (liquid lipid) and glyceryl behenate (solid lipid; Comprtol 888 ATO) contained clobetasol propionate. When minoxidil was present in nanostructured lipid carriers, a comparable release profile was observed. The lipid particles' size was lowered by oleic acid, which increased their surface area and might have contributed to an early rise in release rate. The follicular deposition of an alternative particle system, known as squarticles, that encapsulates diphenylcyclopropenone or minoxidil, formed from tallow-derived lipids (squalene and fatty esters), was two to seven times larger than that of controls containing free medications. These findings were confirmed by Confocal imaging . The polymeric coating is another aspect affecting nanosystems' efficiency in targeting drugs through hair.

Coating may have an effect on the drug's release profile and bioavailability at the action site. The availability of

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the drug at the site of action was impacted by the faster drug release (72% over 36 hours) provided by uncoated nanostructured lipid carriers carrying dutasteride as opposed to those coated with 5% stearic acid–chitosan. The uncoated particles exhibited a superior permeability for dutasteride (6.1 ± 1.1 g/cm2 with a diameter of 187.6 ± 7.0 nm) in comparison to the coated particles (2.8 ± 0.4 g/cm2 with a diameter of 220.1 ± 11.9 nm) .

2. Liposomes:

Drugs that are hydrophilic or lipophilic can be trapped inside the phospholipid bilayer structures known as liposomes, which have aqueous cores. Liposomes are lipophilic, which helps this system enter lipid-filled hair follicles. They are therefore suitable for cosmetic and medicinal uses due to their ease of manufacture and capacity to increase the skin's absorption of active substances. Because of their phospholipid makeup, liposomes can interact with the lipids in the stratum corneum to enable MXD to permeate the epidermis or to pass through the hair follicles to form MXD depots. It has been studied to apply MXD topically using liposomes.

Liposomes can linger in the bloodstream for extended periods of time since they are biocompatible and biodegradable. However, stability issues such aggregation, drug leakage, hydrolysis, and changed particle size limit their effectiveness .The presence of positively charged polymers may cause the skin's tight connections to break, which could enhance MXD skin penetration. When finasteride-containing liposomes were incorporated into a 2% w/w methylcellulose gel, the skin of the abdominal animals showed much more penetration than that of a conventional gel containing finasteride and a finasteride hydroalcoholic solution .Liposomal phospholipids have the ability to combine and alter the intercellular lipid distribution, which facilitates medication accumulation and enhances skin delivery.

3. Polymeric nanoparticles:

Biodegradable and biocompatible polymers or monomers, such as chitosan, cellulose, polystyrene, PLA, PLGA, polyvinyl alcohol, and polyethyleneimine, are used to create polymeric nanoparticles in the nanometer range . NPs with a diameter of between 1 and 1000 nm have a higher chance of entering their target organs or tissues through various physiological barriers . NPs cannot completely breach the epidermal barrier, but they can become firmly embedded in the hair follicle. Additionally, the particle-target cell interaction is improved by the large surface-area-to-volume ratio. While systems of time-dependent NPs enter the follicle with preference, optimal-size NPs exhibit higher follicular accumulation. Consequently, polymer-based synthetic nanotechnology-based formulations have garnered growing interest as a follicular medication delivery treatment over the past ten years.

Poly(lactide-co-glycolide) copolymer nanoparticles containing finasteride have been synthesized and characterized. The polymer's non-toxicity was demonstrated in tests conducted on a Saccharomyces cerevisiae model, indicating the systems' excellent potential for treating alopecia and their biocompatibility . Additionally, pharmaceuticals can be contained in shells by polymeric nanoparticles to prevent deterioration, increasing shelf life and controlling drug release. At room temperature, clobetasol propionate-containing lecithin/chitosan nanoparticles stay stable for three months . Polymeric finasteride microspheres showed sustained drug release after an initial burst release for as long as 5-7 weeks in another study . Because polymers encourage homogenous, stable systems that release drugs in a controlled way, they are an effective non-invasive drug loading and administration method in hair follicles.

4. Metallic nanoparticles:

Drug molecules can be adsorbed on the particle surface of metallic nanoparticles, such as TiO2, ZnO , and iron oxide , or they can be enclosed inside the particle core of metallic nanoparticles, such as iron, gold, or silver. According to the earlier research , metallic nanoparticles with a diameter of less than 10 nm might passively enter the skin's hair follicle pores and travel to the deepest section of the follicle.

Gold nanoparticles (GNPs) are an appealing metallic nanoparticle for hair follicle- targeting delivery because of their many special properties, including strong visible light absorption and excellent control over size and form. Acne vulgaris has been treated using gold microparticles (GMPs) that have silica cores inside . Targeting the sebaceous glands, GMPs given to the skin surface collected copiously within the PSU via the follicular channel and in combination with diode laser pulses, allowing a direct intercept to the pathophysiology.

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Additionally, research revealed that the metallic nanoparticles' size, shape, and surface ligands may have an impact on how well the particles penetrate hair follicles. For example, Friedman et al. investigated the impact of form and size on GNPs in relation to their potential for permeating hair follicles. It was discovered that 40 nm diameter particles could reach a depth of 210 nm, 250 nm particles could reach up to 252 nm, and 530 nm particles could not reach any depth at all Research on the morphology of GNP has demonstrated that, in comparison to nanorods, spherical particles have less penetration.

Additionally, it is possible for nanostars to concentrate in large quantities within the PSU, suggesting that anisotropic forms of nanoparticles are important for particle accumulation. Functionalized surface ligands on gold nanorods (GNRs), such as cationic, hydrophobic, neutral, and anionic ligands, have been shown to affect drug deposition into hair follicles in human skin sheets in addition to size and shape.

Mahmoud et al. suggested that because of the lipophilic nature of the follicular compartments, hydrophobic polystyrene (PS)-GNRs may be more beneficial for hair follicle-targeting than PEGylated GNRs. As such, a bran-new composite formulation might allow metallic nanoparticles to penetrate follicles more deeply.

5. Microneedle:

As a novel delivery system, microneedles (MNs) can directly transport medications into hair follicles by breaking through the SC barrier and releasing the medicine that is loaded into the epidermal and dermal layers. Microchannels can be created by MNs with sufficient mechanical strength puncturing into the skin. These microchannels have the advantages of being relatively cheap, self-administering, and causing very little pain . It's amazing that using MNs by themselves might activate hair growth signaling in pathways and HFSCs while also recruiting growth factors through micro-wounds. MNs have recently been used to treat conditions involving hair follicles in an effort to improve follicular drug delivery by reducing dosage frequency and increasing the effectiveness of percutaneous absorption. Yuan et al. recently developed a patch of ceria nanozyme (CeNZ)-encapsulated microneedles (Ce-MNs) that allows for faster and higher-quality hair regrowth.

Through MNs, the CeNZs were effectively injected 200–300 nm deep into the epidermis, where they were able to reduce oxidative stress and promote angiogenesis to change the microenvironment of the hair follicle [105]. In addition, Fang et al. created a microneedle patch that is dissolvable in polyvinyl alcohol (PVA) and loaded with minoxidil and mesoporous iron oxide (MIO) (MX-MIO@MNs) to promote hair growth. The external magnetic field may activate MX-MIO@MNs, resulting in regulated drug release and localized heating.

The hydrophobic medicines that the releasing MIOs also managed to catch are essential for the human body's ability to restore hair. With the right mechanical properties, MX-MIO@MNs may effectively transfer minoxidil-loaded MIOs to the skin, increasing hair growth by more than eight times while causing no discomfort. Others, like Cao et al. created squalene-containing microneedles that interacted with FIN NLCs in order to improve the permeability to hair follicles and lessen the negative effects that oral administration had on the system. The uptake of coumarin 6 (C6)-NLCs in human dermal papilla cells was significantly enhanced by the lipidic composition of NLCs, which mimicked the natural components of hair follicles.

Pathophysiology:

Understanding the structure of hair follicles and the hair cycle is essential to treating hair diseases. The hair cycle comprises three unique phases: telogen, catagen, and anagen. The growth phase, or anagen phase, lasts between two and seven years, depending on the person. Hair length is determined by the duration of this time. The dermal papilla, which supplies the growing hair with essential blood flow and nourishment, is where the anagen phase starts. A centimeter of hair grows every month.

The catagen phase denotes the change from growth to rest phases. During the catagen phase, which typically lasts for two weeks, the hair separates from its blood supply. A period of relative quiescence that can last up to four months is reflected in the telogen phase, which is the final or resting phase. Shedding of hair occurs during the telogen period.

There are numerous forms of alopecia that fall into two categories: scarring and non-scarring. Telogen effluvium is typically a self-limiting hair loss disorder brought on by times of elevated stress during which an excessive number of hairs (approximately 25% to 50%) prematurely and simultaneously enter the telogen phase. The ensuing hair loss happens two or four months following the trigger. Similar illness known as anagen

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effluvium is most frequently brought on by chemotherapy drugs.

Hair follicles are destroyed by the autoimmune system in cases of alopecia areata. In androgenic alopecia, the activities of androgens, particularly dihydrotestosterone (DHT), result in hair follicle shrinking, a reduction in the length of the anagen phase, and hair loss. Observation and the hair pull test help doctors differentiate between trichotillomania, telogen effluvium, and alopecia during a history and physical examination. A recurrent, impulsive hair-pulling disorder called trichotillomania causes noticeable breaks in hair strands in several parts of the body. Additionally, some patients could consume the hair they pull, which could result in digestive issues.

Another behavioral variation brought on by tightly pulled hairstyles, as observed in gymnasts, is traction alopecia. Systemic lupus can result in non-scarring alopecia or discoid lupus, which is a type of lupus that leaves scars. It takes a complete physical examination and medical history to identify less prevalent causes of alopecia, like syphilis. “Moth-eaten” alopecia is typically the result of secondary syphilis. Since a fungal invasion of the hair shaft causes patches of hair loss, tinea capitis is a condition to be closely watched in pediatric populations.

In both keratosis pilaris and acne vulgaris, abnormal keratinization leading to greater cohesion of keratinocytes inside the pilosebaceous unit is suspected. In particular, follicular hyperkeratinization causes keratosis pilaris and acne vulgaris by obstructing hair follicles and the pilosebaceous unit. Please be aware that the pathophysiology of acne vulgaris involves several significant pathways. The inflammation of hair follicles caused by a fungal or bacterial infection is known as folliculitis. Another inflammatory disease that involves blockage of the hair follicle in apocrine-rich parts of the body (groin, axilla) is calledhidradenitis suppurativa.

Issues of hair follicles:

Problems with hair follicles are the root cause of several hair disorders. It is important to see a dermatologist if you believe you have a hair condition or if you are experiencing symptoms that are not explained, such as hair loss.

Androgenetic alopecia:

Male pattern baldness, sometimes referred to as androgenetic alopecia, is a disorder that affects the hair follicles on the scalp and their growth cycle. The hair cycle weakens and slows down until it finally stops. As a result, no new hair is produced by the follicles. The U.S. National Library of Medicine estimates that 30 million women and 50 million men suffer from androgenetic alopecia.

Alopecia areata:

Alopecia areata is an autoimmune disease. The immune system mistakes the hair follicles for foreign cells and attacks them. It often causes hair to fall out in clumps. It can lead to alopecia universalis, which is a total loss of hair all over the body.

Alopecia areata currently has no known cure, however there are a number of treatment options based on:

The amount of hair lost how old the person is (children may need a different sort of treatment) and how long the hair loss has been happening where it is Options for treatment could involve any or all of the following:

Corticosteroid topical Injectable minoxidil, corticosteroids, anthralin, contact immunotherapy, JAK inhibitors, or other medications that affect your immune system all over your body

Clinical Application:

While hair follicle-targeting medication delivery approaches are still constrained by clinical trial regulatory approval, innovative treatments are presently being tested on small patient populations. Roque et al. used a modified emulsification/solvent diffusion process to create FIN-loaded PLGA nanoparticles . All of the formulation excipients did not result in erythema or any other undesirable effects during clinical safety testing. Melatonin was encapsulated in vitamin C-based nanovesicles by Hatem et al. in order to improve skin retention and therapeutic efficacy .Subsequent research revealed that, in comparison to melatonin solution, melatonin nanovesicles clinically enhanced hair density and diameter and decreased hair loss.

Furthermore, topical use of gold-coated silica microparticles has been studied in two separate prospective randomized controlled clinical trials for the treatment of mild to severe acne vulgaris. In every study, microparticles with a 120-nm-diameter silica core and a 15-nm-thick gold shell that allowed for extensive penetration into the sebaceous glands looked to be a statistically beneficial treatment. After 28 weeks in Trial 1,

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there was a considerable reduction in inflammatory acne vulgaris lesions, reaching −61% of the baseline.

According to the current research, drug delivery that targets hair follicles may result in fewer side effects and more potent therapies. Numerous studies have been conducted to far on the topic of enhanced follicular penetration when tactics such as nanocarrier systems are employed. However, there are still very few hair follicle- targeting-based products on the market. Research on follicular permeability in vitro or in vivo has dominated most investigations, and there is currently little information available regarding their clinical usefulness.

The relative translation continues"to be very difficult. On the one hand, it is very challenging to generate the same clinical outcomes from laboratory penetration trials. In the lab, we frequently utilize the skin of pigs, rats, mice, or hamsters in place of human skin, and the consequences of their penetration are always very different. However, there are still questions regarding the potential toxicity of nanoparticles, necessitating more research into the risks and long-term storage of nanomaterials in hair follicles.

II. CONCLUSION

It has been discovered that hair follicle-targeting drug delivery formulations yield overall performance increases that, when compared to traditional formulations, improve therapeutic efficacy by improving skin and follicle drug delivery and reducing adverse effects. The medications that are trapped in hair follicles allow for a sustained and regulated release, which improves patient compliance and therapeutic efficacy based on the unique characteristics of the hair follicles. The ability of the hair follicle to function as a penetration pathway for the treatment of illnesses related to hair follicles, such as acne vulgaris and hair loss, has been discovered in recent years.

Overall, hair follicle-targeting medication delivery is a good idea thus far, but there are still obstacles to overcome. Hair follicles are more than a complex structure. For instance, the majority of human hair follicles stay in the anagen phase for two to six years. When the hair follicle cycle transforms, they experience significant modifications. When creating formulations, different cycle statuses must be taken into account since they undoubtedly alter follicular penetration.

Moreover, the sebaceous content inhibits the build-up of nanoparticles within the hair follicle. Because the dry sebum and cell debris would clog the hair follicles, topically applied substances cannot enter "closed" hair follicles. Future research should concentrate on expanding the dosages of medications that can reach the hair follicle when the SC is present. Not to mention, each disease has unique features, making it challenging to develop a delivery system that works for a novel bioactive chemical intended for a specific skin condition and goal. According to reports, hair mobility is important for the nanoparticles' ability to target hair follicles. Subsequent research should take into account the influence of hair as well as the interactions between particles and hair follicles in illness states such as hair loss. Therefore, choosing appropriate nanocarrier types and more trustworthy skin models that can replicate the sick condition is crucial for follicle- targeting drug delivery penetration tests going forward.

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