



**INTERNATIONAL JOURNAL OF  
PHARMACEUTICAL SCIENCES**  
[ISSN: 0975-4725; CODEN(USA): IJPS00]  
Journal Homepage: <https://www.ijpsjournal.com>



## Review Article

# Unlocking Hair Follicles as Drug Reservoirs: Advances in Transfollicular Drug Delivery

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### ARTICLE INFO

Published: 30 Apr 2026

**Keywords:**

Hair follicle drug delivery,  
Transfollicular penetration,  
Nanoparticles, Reservoir  
effect, Alopecia therapy,  
Regenerative medicine.

**DOI:**

10.5281/zenodo.19920285

### ABSTRACT

Topical drug delivery is often limited because the stratum corneum act as a strong barrier, which reduces drug penetration and lowers therapeutic effectiveness. In contrast, hair follicles offer an alternative pathway for drug delivery, acting as natural reservoirs that enables deeper drug deposition, prolonged retention, localized therapeutic action. This review summarizes recent advances in transfollicular drug delivery, beginning with early studies on the reservoir effect and the influence of hair massage on drug diffusion. Recent studies suggest that nanoparticles perform better than conventional formulations in follicular drug delivery. Optimizing size to approximately 300-400nm play important role in improving the delivery of drugs to hair follicles. Alongside this, newer stimulus-responsive delivery systems, including nanostructures activated by near-infrared light, have enhanced the ability to achieves controlled and targeted drug release. These developments are particularly relevant in the management of condition such as androgenic alopecia, acne, and psoriasis, as they allow better localization of therapy within the follicles while reducing unwanted systemic exposure. Methodological challenges and innovations, including differential stripping techniques, cyanoacrylate biopsy method, and advanced imaging approaches, are critically evaluated to highlight the need for standardized assessment protocols. Recent advances in regenerative medicine, such as hair follicle organoids and biomaterial scaffolds, further extend the role of hair follicles beyond drug delivery into the field of tissue engineering. The objective of this review is to bring together physiology, formulation strategies, evaluation methods, and clinical applications to establish hair follicles as strategic drug reservoirs that bridge topical therapy and regenerative medicine.

### INTRODUCTION

Topical drug delivery is commonly used in the treatment of skin-related conditions because it is

non-invasive and helps deliver drugs directly to the affected area. It also offers benefits such as lower systemic side effects, no first-pass

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**Relevant conflicts of interest/financial disclosures:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.



metabolism, and better patient compliance. Even so, its effectiveness is often affected by the strong barrier of the stratum corneum, which makes it difficult for many drugs to reach the deeper layers of skin [8,11,14]. Because of this, many active pharmaceutical ingredients are unable to reach sufficient levels at the target site, especially in conditions affecting hair follicles such as androgenetic alopecia, acne vulgaris, and psoriasis [5,6,20]. In most cases, traditional formulations stay on the outer skin surface and therefore do not provide optimal therapeutic benefits [5,11].

In recent years, attention has shifted towards hair follicles as useful route for drug delivery. Hair follicles are specialized skin structures that begin in the epidermis and extend into the dermis, where they are linked with sebaceous glands, to form pilosebaceous unit [14,37]. These structures provide fairly open channels that allow drugs and particulate systems to overcome the stratum corneum barrier and penetrate deeper into the skin [1,13,14]. A major advantage of hair follicle-based drug delivery is its ability to act as a drug reservoir. Research has shown that drugs can be build up within the follicular ducts and remain there for longer duration, leading to sustained drug release. This process, known as the reservoir effect, plays a vital role in maintaining therapeutic drug levels over time and improving treatment results [1,3,11].

Many factors affect drug delivery to hair follicles, including drug properties such as molecular size and lipophilicity, formulation aspects like the type of vehicle and its viscosity, and skin-related conditions such as follicular density and hair growth cycle [1,13,14]. Physical factors such as massage, rubbing, and hair movement can also improve drug penetration by helping the movement of substances into the follicular openings [1,13]. The use of nanoparticles has further improved the performances of follicular drug

delivery. Nanoparticles, including polymeric nanoparticles, liposomes, and solid lipid nanoparticles, have the potential to selectively localize within the hair follicles and enable controlled drug release [2,3,12]. particle size is an important factor, with research indicating that particles size ranges of 300 to 700 nm are more appropriate for follicular targeting while smaller particles may penetrate deeper into viable epidermis and large particles may remain on the surface [2][5][12].

Recently newer techniques like microneedle and nano emulsion have been introduced to enhance drug delivery with these approaches drugs can penetrate more deeply into skin stay longer at the site and be delivered more precisely to the pilosebaceous unit [5,18]. Therefore, targeting hair follicles represents a promising strategy for overcoming the limitations of conventional topical drug delivery systems. This review aims to explore the structure and function of hair follicles, mechanisms of drug delivery, the role of nanoparticles, formulation approaches, and their applications in various dermatological conditions, with a particular emphasis on recent advances in transfollicular drug delivery [3,5,16,20].

## OBJECTIVE

This review focuses on the following objectives:

- To understand the structure and function of hair follicles and their role as a pathway for topical drugs delivery.
- The mechanism of transfollicular drug delivery is explained, including the reservoir effect and the various factors that influence drug penetration.



- The role of nanoparticles in follicular targeting is explored, with a special attention to particle size (300–700 nm) and formulation design.
- Different formulation approaches such as polymeric nanoparticles, liposomes, Nano emulsions, and microneedle systems are discussed in relation to follicular delivery.
- The use of follicular drug delivery in dermatological condition such as androgenetic alopecia, acne vulgaris, and psoriasis, and compared with conventional treatment

## STRUCTURE AND PHYSIOLOGY OF SKIN AND HAIR FOLLICLE

### Structure of Skin

The skin consists of three primary layers: the epidermis, dermis, and hypodermis (subcutaneous tissue), each playing a distinct role in barrier function and drug delivery [8,14,37]. The epidermis forms the outer layer and acts as the

main protective barrier. Its upper part, known as the stratum corneum, is made up of closely arranged dead cells and lipids, which makes drug penetration more difficult [8,11,14]. Because of this, many topical drugs fail to reach the deeper layers effectively. This becomes even more difficult in conditions involving hair follicles such as alopecia, acne, and psoriasis, where drugs need to act at a specific site [16,20].

The dermis is located below the epidermis and contains blood vessels, nerves, collagen, and structures such as hair follicles and sebaceous glands [14,37]. It acts as an important layer for follicular drug delivery, as drugs can move from the follicles into nearby tissues like the hair bulb or inflamed regions [1,13]. The hypodermis is the deepest layer and is mainly composed of fat tissue. It helps in cushioning the body and maintaining temperature [37]. Even though its role in follicular drug delivery is limited, it may still act as a reservoir for some lipophilic drugs.

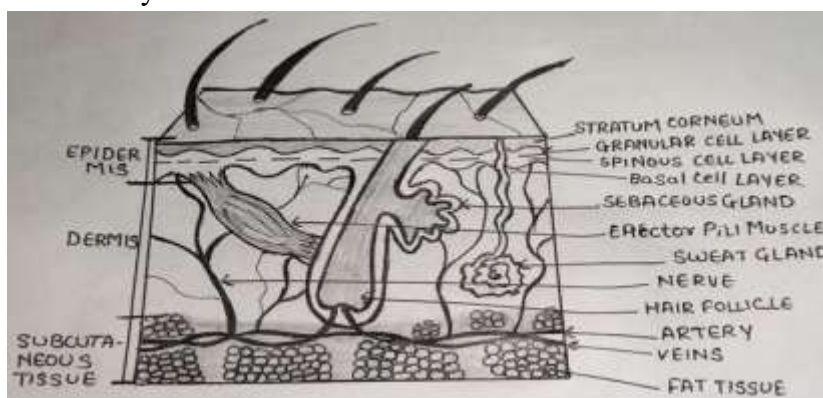


Figure 1: Structure of human skin showing epidermis, dermis, and hypodermis (Adapted from [38])

### Structure of Hair Follicle

Hair follicles are complex skin appendages that extend from the epidermal surface into the dermis, forming the pilosebaceous unit in association with the sebaceous gland and arrector pili muscle [14,37]. Each follicle can be divided into three main regions: the infundibulum, isthmus, and hair bulb, which collectively provide a relatively open

channel for topical substances to bypass the stratum corneum barrier [1,13,14].

The infundibulum is the uppermost segment of the follicle, located between the epidermal surface and the sebaceous gland orifice, and is the primary site for accumulation of topically applied drugs and particulate systems [1,13]. The isthmus refers to the short segment between the sebaceous gland and

the bulge region, and is associated with the insertion of the arrector pili muscle and adult stem cell niches [37]. Deep in the dermis, the hair bulb contains the rapidly dividing matrix cells surrounding the dermal papilla, which is a key site of action for follicle-targeted therapies in

conditions such as androgenetic alopecia and other hair-loss disorders [16,20]. The sebaceous gland, connected to the follicular infundibulum, produces sebum that can influence drug solubility and follicular penetration kinetics [14].

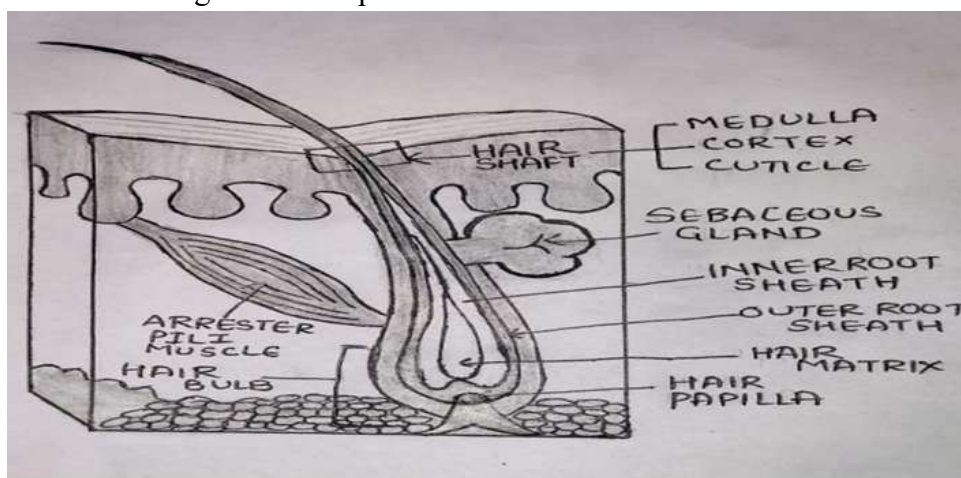


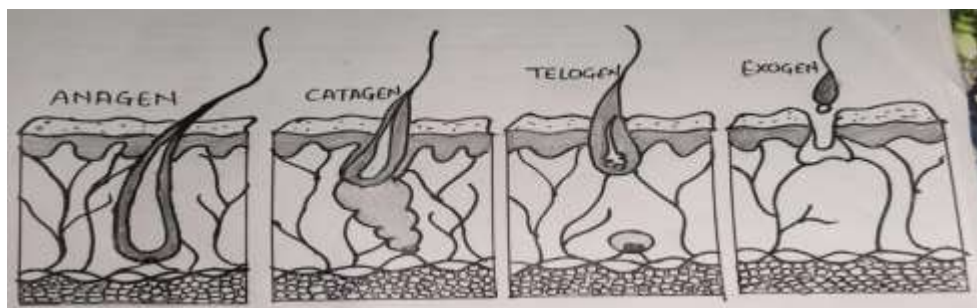
Figure 2: Structure of hair follicles (Adapted from [38])

### Hair Growth Cycle

Hair follicles undergo a continuous cyclic process known as the hair growth cycle, which is broadly divided into three phases: anagen, catagen, and telogen and the fourth phase, exogen, is often grouped with telogen and represents the shedding phase [37]. During the anagen (growth) phase, the follicle is maximally active, with elongation of the hair shaft and deep extension of the hair bulb into the dermis, creating an open, metabolically active channel that may enhance follicular penetration and reservoir formation [1,3]. In contrast, the catagen (regression) phase involves controlled apoptosis and shortening of the follicle, while the telogen (resting) phase is characterized by a

retracted follicle and reduced metabolic activity, which may limit drug entry and retention [37].

The phase of the hair cycle can thus influence the openness and accessibility of the follicular canal, as well as the density and orientation of follicles on the skin surface, all of which contribute to variability in follicular drug delivery outcomes [1,13]. Studies have emphasized that follicular penetration is often most pronounced shortly after application, when the follicular orifice is relatively open and sebum-related diffusion pathways are active [12]. Therefore, understanding the hair growth cycle provides additional insight into the physiological factors that modulate the efficiency of transfollicular drug delivery and follicle-targeted formulations.



**Figure 3: Hair growth Phases showing anagen, catagen, telogen and exogen (Adapted from [38])**

## LITERATURE REVIEW

Many studies have shown the significant role of hair follicles in drug delivery. Initial research by Lademann et al. reported that hair follicles act as long-term reservoirs where drugs can buildup and remain for longer duration, forming the basis of this drug delivery concept<sup>[1]</sup>. This reservoir-like behaviour is attributed to the accumulation of drugs within the follicular infundibulum and sebaceous glands, which can subsequently release the drug over time, thus enhancing local therapeutic efficacy<sup>[1,3]</sup>.

The advent of nanoparticle-based systems has significantly advanced follicular targeting. Lademann et al. reported that nanoparticles function as efficient carriers for drug delivery into hair follicles, showing preferential accumulation within the follicular orifice compared with conventional creams or solutions<sup>[2]</sup>. Subsequent work by Patzelt and Lademann emphasized that polymeric nanoparticles, in particular, can selectively lodge in hair follicles and provide sustained drug release, thereby improving the pharmacokinetic profile at the target site<sup>[3,5]</sup>. These systems also enhance drug stability, reduce systemic exposure, and minimize local irritation<sup>[3,5]</sup>.

Particle size has been identified as a critical factor influencing follicular penetration. Available findings suggest that particles in the range of 300–700 nm offers better follicular targeting, with sizes

around 300–400 nm being especially suitable for human skin<sup>[2,5,12]</sup>. Work by Lademann et al. indicated that particles of about 600–700 nm enter hair follicles more effectively in porcine models, whereas smaller particles (e.g., 20–40 nm) may move past the follicle into the living epidermis<sup>[2,13]</sup>. According to Busch et al., the penetration efficiency of a dissolved model drug into hair follicles depends on the concentration of added nanoparticles, highlighting the complex interaction between dissolved drug and particulate carrier<sup>[10]</sup>.

Apart from polymeric nanoparticles, other systems such as liposomes, nano emulsions, and microspheres have also been studied for follicular drug delivery. Lapteva et al. prepared self-assembled polymeric nanocarriers for the targeted delivery of retinoic acid to the hair follicle, showing better follicular deposition and sustained release of the active drug<sup>[4]</sup>. Tampucci et al. examined nanostructured drug delivery systems for delivering inhibitors of 5- $\alpha$ -reductase to the hair follicles, emphasizing their potential in treating androgenetic alopecia<sup>[6]</sup>. These systems improve drug solubility, enhance penetration, and allow controlled release, which helps in minimizing systemic side effects<sup>[4,6]</sup>.

Methodological advances have also contributed to a better understanding of follicular drug delivery. Pereira et al. reviewed different methods used to evaluate nanoparticle-assisted drug delivery to hair follicles, including differential stripping,

cyanoacrylate skin surface biopsies, and advanced imaging methods [7]. These methods allow for quantification of follicular deposition and penetration kinetics, although the lack of standardized protocols remains a challenge [7,14]. Recent progress in regenerative medicine has extended the role of hair follicles beyond drug delivery. Zheng and Xu described the role of hair follicle organoids and biomaterial scaffolds in hair follicle regeneration, emphasizing the value of follicles as a biological environment for tissue engineering [9].

Clinical use has especially highlighted the therapeutic benefits of follicular targeting in androgenetic alopecia, acne, and psoriasis. Tuo-Kouassi et al. presented hair follicles as an important target for supporting hair growth, showing how follicle-based delivery can increase local drug concentration while reducing systemic exposure [16]. Kumar et al. introduced a nanocrystal-based approach for targeting hair follicles in the treatment of alopecia areata, showing improved follicular persistence and therapeutic effectiveness [17]. In a similar way, Chaiwarit et al. prepared dissolving microneedles containing herbal extracts to improve transfollicular delivery, while Kuchukuntla et al. refined finasteride-loaded PLGA nanoparticles in Carbopol gel for hair growth enhancement [18,19]. Overall, these findings suggest that follicle-targeted formulations can greatly improve result in skin-related disorders [16-19].

Despite significant advancements in transfollicular drug delivery, several limitations and research gaps still exist. Most studies have

focused primarily on nanoparticle size optimization and follicular targeting; however, limited data are available regarding the long-term safety and large-scale clinical application of these systems [5,7,21].

In addition, the absence of standardized methodologies for evaluating follicular drug deposition, which makes it difficult to compare results across different studies and formulations [7,14]. Variation in skin physiology, follicular density, and experimental conditions can affect the reproducibility of results and may influence further experimental outcomes [8,14].

Furthermore, although nanoparticle-based systems have shown encouraging results in laboratory studies, their conversion into commercially available formulations remains limited due to issues related to formulation stability, large-scale production, and regulatory approval [5,6,19].

Recent studies have also highlighted the need for more research on the interaction between nanoparticles and biological systems, including their effect on the follicular microenvironment and potential toxicity [2,10]. Additionally, emerging areas such as regenerative medicine and follicle-based tissue engineering are still underexplored and require further investigation [9,21].

Therefore, future research should focus on developing standardized evaluation techniques, improving formulation design, and conducting more clinical studies to fully utilize the potential of hair follicles as drug reservoirs [7,16,21]. The research gaps are summarized in Table 1. given below:

**Table 1: Identified Research Gaps in Follicular Drug Delivery**

Area	Existing Findings	Research Gap
Nanoparticle Size Optimization	Particles (300–700 nm) show effective follicular targeting	Long-term safety and toxicity studies are limited
Follicular Targeting Efficiency	Nanoparticles show better accumulation in hair follicles	Lack of sufficient human clinical trials
Evaluation Techniques	Methods like differential stripping and biopsy are used	No standardized or universally accepted evaluation method
Formulation Approaches	Various systems like liposomes, nano-emulsions, nanoparticles are developed	Issues related to stability, scalability, and reproducibility
Clinical Applications	Effective in diseases like alopecia, acne, and psoriasis	Limited availability of commercial formulations
Mechanistic Understanding	Reservoir effect and penetration pathways are known	Limited understanding of interaction with follicular microenvironment
Advanced Technologies	Use of microneedles and nanocarriers is increasing	Integration with regenerative medicine needed

## FACTORS AFFECTING FOLLICULAR DRUG DELIVERY

Transfollicular drug delivery is influenced by multiple factors including drug properties, formulation characteristics, physiological conditions, and external parameters. These factors collectively determine the extent of drug penetration, retention, and overall therapeutic effectiveness within the hair follicle [1,13,14].

### • Drug-related factors

Drug properties such as molecular size, molecular weight, and lipophilicity (log P) significantly influence the extent and depth of follicular penetration. Appropriately sized and lipophilic drugs exhibit greater affinity for the follicular reservoir and sebaceous microenvironment, thereby enhancing drug localization [1,13].

### • Formulation-related factors

Particle size, vehicle type, and viscosity of the formulation play a critical role in follicular targeting. Nanoparticles in the size range of 300–

700 nm tend to accumulate preferentially within hair follicles [2,5,12]. Additionally, low-viscosity vehicles and optimized nanocarrier systems enhance drug penetration and retention within the follicular region [5,15].

### • Physiological factors

Physiological parameters such as follicle density, hair cycle phase, sebum production, and skin hydration influence follicular accessibility and drug distribution [14,37]. Follicles in the anagen phase, having deeper openings, facilitate better drug entry and reservoir formation, whereas follicles in the telogen phase are comparatively less favourable [37].

### • External factors

External factors such as massage, hair movement, and skin temperature act as penetration enhancers by promoting the movement of drug particles into follicular openings and modifying follicular permeability, thereby improving transfollicular drug delivery [1,13].



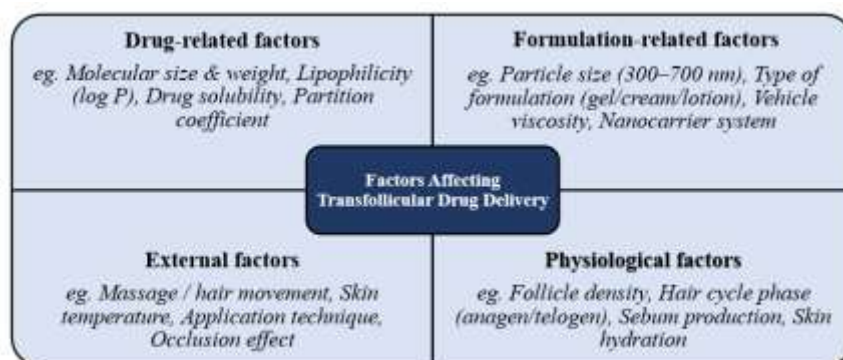


Figure 4: Schematic representation of factors affecting transfollicular drug delivery

## TYPES OF FORMULATIONS FOR FOLLICULAR DRUG DELIVERY

- **Polymeric nanoparticles**

Polymeric nanoparticles, such as systems used for delivering retinoic acid to hair follicles and finasteride-loaded DNC nanoparticles in Carbopol gel, have been reported to localize within follicles, provide sustained drug release, and support hair growth activity [4,19].

- **Liposomes and solid lipid nanoparticles (SLNs)**

Liposomes and solid lipid nanoparticles offer enhanced drug solubility, stability, and controlled release, enabling better follicular penetration and reduced systemic exposure in follicle-associated dermatological disorder [3,6].

- **Nano emulsions**

nano emulsions function as useful nanocarriers for follicular targeting, as they help in improving drug solubility and uniform distribution, which can result in better penetration and longer retention within the pilosebaceous unit [4,6].

- **Nanocrystals**

Nanocrystal-based approaches for targeting hair follicles, especially in conditions like alopecia areata, have been found to maintain drug presence in follicles for longer durations and improve local drug distribution, leading to better therapeutic results [17].

- **Microneedles**

Dissolving microneedles loaded with herbal extracts or active compounds create temporary microchannels in the skin, allowing direct delivery into follicles and improving drug penetration as well as localized action [18].

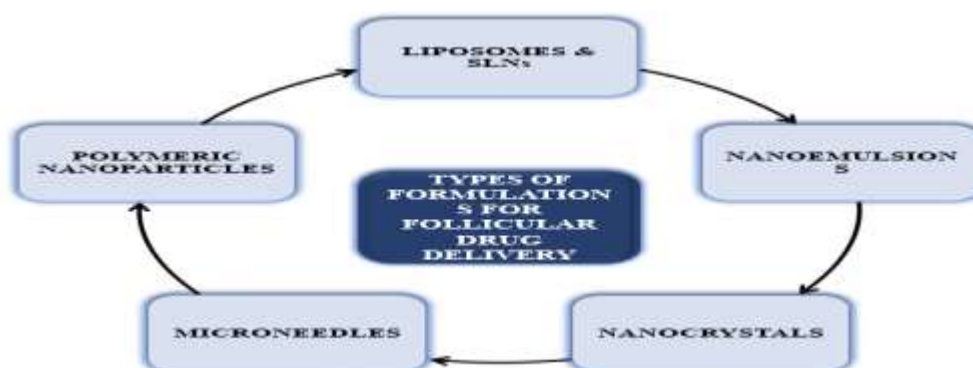


Figure 5: Schematic representation of types of formulations approaches used in follicular drug delivery

## METHODOLOGY

This review article was prepared based on an analysis of previously published research and review articles related to transfollicular drug delivery. Data were collected from scientific databases such as PubMed and Google Scholar using relevant keywords, including hair follicle drug delivery, transfollicular delivery, and nanoparticles in dermatology [3,5,11].

Only recent and relevant studies published since 2006 were selected to ensure inclusion of recent research findings. Both experimental and review articles focusing on follicular targeting, nanoparticle-based drug delivery systems, and dermatological applications were included [1,2,5,16,21].

The selected literature was carefully reviewed and compared to identify key findings and recent development in follicular drug delivery systems. Particular emphasis was placed on nanoparticle-based targeting, formulation strategies, and clinical applications [3,5,7]. The collected data were then organized and summarized to provide a clear understanding of mechanisms, formulation approaches, and therapeutic outcomes of transfollicular drug delivery [11,14].

## EVALUATION METHODS FOR FOLLICULAR DRUG DELIVERY

Several methodological approaches have been used to evaluate follicular drug delivery and nanoparticle localization within the pilosebaceous unit. The most commonly applied techniques include:

- **Differential stripping**

This technique involves sequential removal of corneocyte layers from the skin surface using adhesive tapes, followed by quantification of drug

content in each tape. The method allows assessment of how much drug remains in the upper stratum corneum versus the follicular orifices and upper follicular ducts [7,31].

- **Cyanoacrylate skin surface biopsy (CSSB)**

A thin cyanoacrylate layer is applied to the skin, allowed to cure, and then peeled off to collect superficial skin and follicular content. The follicle-bound material is then analysed to quantify drug or nanoparticle deposition specifically within hair follicles, providing information on follicular reservoir formation [7,35].

- **Advanced imaging techniques**

Confocal laser scanning microscopy (CLSM), two-photon microscopy, and other imaging modalities enable visualization of fluorescently labelled drugs or nanoparticles within follicles in situ. These techniques provide spatial information on follicular penetration depth, distribution patterns, and kinetics of reservoir formation without the need for destructive sampling [25,33].

Despite their advantages, these evaluation methods lack universally standardized protocols, making direct comparison across different studies and formulations challenging [7,14].

## RESULT

### Mechanism of Transfollicular Drug Delivery

The mechanism of transfollicular drug delivery begins with the application of a topical formulation on the skin surface. The drug penetrates through the hair follicle openings, thereby bypassing the barrier of the stratum corneum. Once inside, the drug accumulates within the follicular duct and sebaceous gland, forming a localized depot known as the reservoir

effect, which allows prolonged drug retention within the follicle [1,3].

The accumulated drug is then released in a controlled and sustained manner over time, maintaining a therapeutic level at the target site. The released drug gradually diffuses into the deeper layers of the skin, including the dermis, where it reaches specific target sites such as the hair bulb, sebaceous glands, and inflamed tissues [5,16].

Factors such as hair movement, massage, and formulation properties can further enhance penetration into the follicles. Nanoparticle-based systems further enhance this process by increasing follicular targeting and retention due to their optimal size and surface characteristics [2,5,12]. Overall, this pathway improves drug delivery efficiency, reduces systemic exposure, and enhances therapeutic outcomes.

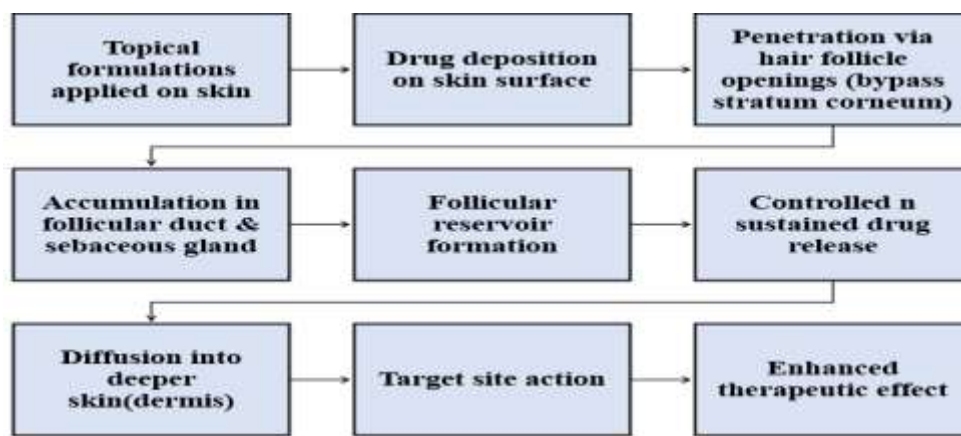


Figure 6: Schematic representation of the mechanism of follicular drug delivery

### Comparison of Conventional and Follicular Drug Delivery Systems

A comparison between conventional topical drug delivery and follicular (nanoparticle-based) delivery highlights the advantages of follicular

targeting. Conventional systems generally show limited penetration and rapid drug loss from the skin surface, whereas follicular delivery provides deeper penetration and targeted action at specific sites within the skin, resulting in improved drug retention and enhances therapeutic effectiveness.

Table 2: Comparison between conventional topical drug delivery and follicular (nanoparticle-based) drug delivery

Parameter	Conventional topical delivery [8]	Follicular (nanoparticle-based) delivery [2,5,12]
Penetration depth	Limited to upper stratum corneum and very superficial epidermis	Reaches deeper follicular and dermal regions
Targeting specificity	Non-specific, diffuse distribution	Preferential accumulation in hair follicles
Drug retention time	Short; rapid clearance from surface	Prolonged retention due to reservoir effect
Systemic exposure	Moderate to high, depending on dose and area	Reduced due to localized follicular depot
Role of formulation	Creams/ointments with limited control	Nanoparticles, liposomes, microneedles enable controlled release
Efficacy in follicular diseases	Often suboptimal	Enhanced in conditions like alopecia, acne, psoriasis [5][16][17]

## DISCUSSION

Follicular drug delivery, particularly when combined with nanoparticle-based systems, represents a promising strategy for overcoming the limitations of conventional topical therapies. The findings summarized in this review indicate that targeting the pilosebaceous unit enhances localized action, prolongs drug retention, and reduces systemic exposure, thereby improving therapeutic outcomes in follicle-associated disorders such as androgenetic alopecia and acne vulgaris.

- **Role of nanoparticles in follicular targeting**

Nanoparticles, especially in the size range of 300–700 nm, show significant accumulation within hair follicles and act as an efficient carrier that bypasses the stratum corneum barrier while forming a depot within the follicular canal. This selective localization amplifies follicular targeting, optimizes drug release kinetics, and reduces the risk of off-target effects on the surrounding epidermis<sup>[5,12]</sup>.

- **Significance of the reservoir effect**

The accumulation of drugs in the follicular duct and sebaceous gland enables prolonged release, maintaining therapeutic levels at the target site and reducing the frequency of dosing. The reservoir effect is particularly valuable in chronic follicular diseases, where sustained drug levels are required for long-term disease control, yet systemic exposure must be minimized<sup>[1,3,11]</sup>.

- **Role of microneedles in enhancing penetration**

Dissolving microneedles, and other physical enhancement approaches involves non-follicular delivery by forming microchannels in the skin and

enabling direct entry to follicular openings, which supports deeper penetration of nanoparticles and other active ingredients. This strategy supports follicular targeting by improving the uniform distribution of drug deposition within the pilosebaceous unit without significantly increasing systemic absorption<sup>[5,18]</sup>.

- **Clinical relevance in alopecia and acne**

Follicular targeting systems such as finasteride-loaded PLGA nanoparticles and nanocrystal-based approaches have shown better effectiveness in hair growth disorders and inflammatory follicular diseases like androgenetic alopecia and acne. In these conditions, localised delivery through the follicular reservoir increases drug concentration at the disease site and supports the need for minimally invasive, targeted therapies, which in turn improve patient compliance and reduce side effects<sup>[16,17,19]</sup>.

## ADVANTAGES AND LIMITATIONS

### Advantages of Follicular Drug Delivery

Hair follicle-based drug delivery systems offer several advantages over conventional topical delivery systems. One of the major benefits is targeted drug delivery, where the drug is preferentially localized within the pilosebaceous unit, improving therapeutic efficacy in follicle-associated disorders such as alopecia, acne, and psoriasis<sup>[5,16,21]</sup>.

Another key advantage is prolonged drug retention, as hair follicles act as natural reservoirs that allow drugs to accumulate and release slowly over time, thereby maintaining therapeutic levels for an extended period<sup>[1,3]</sup>. This reduces the frequency of application and improves patient compliance.



Follicular delivery also results in reduced systemic exposure and side effects, as the drug remains localized within the follicles rather than being absorbed into systemic circulation [5,11]. In addition, nanoparticle-based systems improve drug stability, enhance penetration, and enable controlled and sustained release of drugs [2,5,12].

Furthermore, this approach can bypass the stratum corneum barrier, which is the main limitation of conventional topical drug delivery, thereby improving overall drug bioavailability at the target site [8,14].

### **Limitations of Follicular Drug Delivery**

Despite its advantages, follicular drug delivery also has some limitations. One of the major challenges is the lack of standardized evaluation techniques, which makes it difficult to compare results across different studies and formulations [7,14].

Another limitation is the variations in skin physiology, including differences in hair follicle density, hair growth cycle, and sebum production, which can affect drug penetration and reproducibility of results [8,14].

Even though nanoparticle-based systems have shown good results in laboratory studies, their clinical use is still limited due to challenges related to formulation stability, large-scale manufacturing, and regulatory approval [5,6,19].

Also, there are concerns about the long-term safety and toxicity of nanoparticles, particularly their interaction with the follicular microenvironment and potential accumulation within the skin [2,10].

Finally, the high cost and complexity of advanced formulations, such as nanocarriers and microneedles, may limit their widespread commercial use [5,18].

### **FUTURE PERSPECTIVES**

Hair follicle-targeted drug delivery is a fast-growing area with strong future potential. One of the key focuses is the design of advanced nanoparticles with optimized size, surface properties, along with stimulus-responsive behaviour to achieve more precise and controlled drug delivery within the follicular environment [5,13].

Future research will likely focus on improving and standardizing evaluation methods, including better imaging and quantitative techniques, to make it easier to compare results across studies and support regulatory approval [7,14]. Another important direction is combining follicular drug delivery with regenerative medicine, where hair follicles can act as biological sites for tissue regeneration, stem cell therapy, and hair follicle Growth [9,21].

Also, personalized treatment approaches can be developed based on individual differences in skin type, follicle density, and disease condition, allowing for more effective and patient-specific therapies. Emerging technologies such as microneedles, nanocrystals, and hybrid delivery systems can also be expected to improve drug penetration and retention, leading to better outcomes in dermatological conditions [17,18,19].

However, to fully realize the potential, future studies should focus on long-term safety evaluation, large-scale clinical trials, and cost-effective formulation strategies. This will help move these systems from laboratory research to real clinical and commercial use [5,7,21].

### **CONCLUSION**

Hair follicle-based drug delivery is an effective and promising approach for targeted therapy, as it



helps overcome the limitations of conventional topical delivery systems by providing improved penetration, sustained release, and reduced systemic side effects [1,3,5]. The use of advanced technologies such as nanoparticles, microneedles, and nanostructured formulations also improves the efficiency of follicular targeting and enables targeted drug delivery to the pilosebaceous unit [5,18,19].

Clinically, this approach has shown strong potential in the treatment of androgenetic alopecia, acne vulgaris, and psoriasis, where localized drug action and the reservoir effect play an important role in therapeutic success [5,16,17]. However, challenges such as a lack of standardized evaluation methods, limited clinical use, and concerns about long-term safety must be addressed.

Future research should focus on formulation optimization, large-scale clinical studies, and combining with advanced technologies, which will be essential to fully utilize the potential of hair follicles. This will help establish hair follicles as a strategic drug reservoir, bridging topical therapy and regenerative medicine [7,9,14].

## REFERENCES

1. Lademann J, Richter H, Schaefer UF, Blume Peytavi U, Teichmann A, Otberg N, Sterry W. Hair follicles – A long term reservoir for drug delivery. *Skin Pharmacol Physiol*. 2006;19(2):81-87. doi:10.1159/000091979.
2. Lademann J, Richter H, Teichmann A, Otberg N, Blume Peytavi U, Luengo J, Weiß B, Schaefer UF, Lehr CM, Wepf R, Sterry W. Nanoparticles – An efficient carrier for drug delivery into the hair follicles. *Eur J Pharm Biopharm*. 2007;66(2):159-164. doi:10.1016/j.ejpb.2006.10.019.
3. Patzelt A, Lademann J. Drug delivery to hair follicles. *Expert Opin Drug Deliv*. 2013;10(6):787-797. doi:10.1517/17425247.2013.789859.
4. Lapteva M, Möller M, Gurny R, Kalia YN. Self assembled polymeric nanocarriers for the targeted delivery of retinoic acid to the hair follicle. *Nanoscale*. 2015;7(44):18651-18662. doi:10.1039/c5nr04770f.
5. Patzelt A, Lademann J. Advances in follicular drug delivery of nanoparticles. *Expert Opin Drug Deliv*. 2020;17(6):595-605. doi:10.1080/17425247.2020.1761902.
6. Tampucci S, Paganini V, Burgalassi S, Chetoni P, Monti D. Nanostructured drug delivery systems for targeting 5  $\alpha$  reductase inhibitors to the hair follicle. *Pharmaceutics*. 2020;12(9):868. doi:10.3390/pharmaceutics12090868.
7. Pereira MN, Nogueira LL, Cunha Filho M, Gratieri T, Gelfuso GM. Methodologies to evaluate the hair follicle targeted drug delivery provided by nanoparticles. *Pharmaceutics*. 2021;13(6):851. doi:10.3390/pharmaceutics13060851.
8. McKnight G, Shah J, Hargest R. Physiology of the skin. *Med Princ Pract Surg*. 2021;6:100005. doi:10.1016/j.mpsur.2021.11.005.
9. Zheng W, Xu CH. Innovative approaches and advances for hair follicle regeneration. *ACS Biomater Sci Eng*. 2023;9(5):2251-2276. doi:10.1021/acsbiomaterials.2c00876.
10. Busch L, Asadzadeh D, Klein AL, Suriyaamporn P, Vollrath MK, Keck CM, Meinke MC. The penetration efficiency of a dissolved model drug into hair follicles depends on the concentration of added nanoparticles. *Drug Deliv Transl Res*. 2025;15:1444-1452. doi:10.1007/s13346-024-01718-3.



11. Verma A, Jain A, Hurkat P, Jain SK. Transfollicular drug delivery: current perspectives. *Res Rep Transdermal Drug Deliv.* 2016;5:1 17. doi:10.2147/rrtd.s75809.
12. Liu X, Grice JE, Lademann J, Otberg N, Trauer S, Patzelt A, Roberts MS. Hair follicles contribute significantly to penetration through human skin only at times soon after application as a solvent deposited solid in man. *Br J Clin Pharmacol.* 2011;72(5):768 774. doi:10.1111/j.1365 2125.2011.04022.x.
13. Lademann J, Knorr F, Richter H, Jung S, Meinke MC, Rühl E, Alexiev U, Calderon M, Patzelt A. Hair follicles as a target structure for nanoparticles. *Skin Pharmacol Physiol.* 2014;27(5):250 257. doi:10.1159/000362680.
14. Oláh A, Szöllösi AG, Bíró T. The channel physiology of the skin. *Adv Exp Med Biol.* 2016;990:1 93. doi:10.1007/978 3 319 32089 2\_1.
15. Patzelt A, Richter H, Dähne L, Walden P, Wiesmüller KH, Wank U, Sterry W, Lademann J. Influence of the vehicle on the penetration of particles into hair follicles. *Pharmaceutics.* 2011;3(3):581 592. doi:10.3390/pharmaceutics3030581.
16. Tuo Kouassi AN, N'Guessan Gnaman KC, Aka Any Grah S, Anin AL, Lia AJ, N'Guessan A, Dally I, Yao MA, Koffi AA. Hair follicles: strategic targets for promoting hair growth. *J Drug Deliv Ther.* 2025;15(9):124 135. doi:10.22270/jddt.v15i9.7341.
17. Kumar P, Kumar V, Sahoo S, Singh SK. Enhancing alopecia areata management: nanocrystal driven strategy for targeting hair follicles. *Int J Pharm.* 2025;125557. doi:10.1016/j.ijpharm.2025.125557.
18. Chaiwarit T, Chanabodeechalermrung B, Jantrawut P, Ruksiriwanich W, Sainakham M. Fabrication and characterization of dissolving microneedles containing *Oryza sativa* extract complex for enhancement of transfollicular delivery. *Polymers (Basel).* 2024;16(16):2377. doi:10.3390/polym16162377.
19. Kuchukuntla M, Palanivel V, Ananthula M. Optimization and transfollicular delivery of finasteride loaded PLGA nanoparticles laden carbopol gel for treatment of hair growth stimulation. *Curr Bioact Compd.* 2024;20(7):1 19. doi:10.2174/01157340722699982401010436 01.
20. Guo Y, Li Z, Guo L, Li J, He J, Zeng W, et al. Hair follicle targeting drug delivery strategies for the management of hair loss related and follicular disorders. *Chin Med J (Engl).* 2022;135(9):1037 1049. doi:10.1097/CM9.0000000000001957.
21. Marks JG Jr, Miller JJ. *Lookingbill and Marks' Principles of Dermatology.* 6th ed. Philadelphia: Elsevier; 2020.
22. James WD, Elston DM, Berger TG. *Andrews' Diseases of the Skin: Clinical Dermatology.* 13th ed. Philadelphia: Elsevier; 2016.
23. Davis A. Getting the dose right in dermatological therapy. In: *Dermatological Therapy.* Boca Raton: CRC Press; 2007. p. 197–213. doi:10.3109/9780849375903 13.
24. Contri RV, Fiel LA, Pohlmann AR, Guterres SS, Beck RC. Transport of substances and nanoparticles across the skin and in vitro models to evaluate skin permeation and/or penetration. In: *Skin Permeation and Drug Delivery.* Berlin: Springer; 2011. p. 3–35. doi:10.1007/978 3 642 19792 5 1.
25. Cristina F, Vieira L, Bentley MVLB. Confocal laser scanning microscopy as a tool for the investigation of skin drug delivery systems and diagnosis of skin disorders. In: *Recent Advances in Microscopy for Dermatological Research.* Rijeka: InTech; 2013. p. 1–15. doi:10.5772/55995.



26. Lauer AC, Lieb LM, Ramachandran C, Flynn GL, Weiner ND. Transfollicular drug delivery. *Pharm Res.* 1995;12(2):179-186. doi:10.1023/a:1016250422596.
27. Friedman N, Merims S, Elia J, Benny O. Ex vivo skin permeability tests of nanoparticles for microscopy imaging. *Bio Protocol.* 2022;12(7):e4375. doi:10.21769/bioprotoc.4375.
28. Antunes AF, Pereira P, Reis C, Rijo P. Nanosystems for skin delivery: from drugs to cosmetics. *Curr Drug Metab.* 2017;18(5):412-425. doi:10.2174/1389200218666170306103101.
29. Lademann J, Richter H, Meinke MC, Sterry W, Patzelt A. Which skin model is the most appropriate for the investigation of topically applied substances into the hair follicles? *Skin Pharmacol Physiol.* 2010;23(1):47-52. doi:10.1159/000257263.
30. Grams Y, Bouwstra J. Penetration and distribution in human skin focusing on the hair follicle. In: *Dermatotoxicology and Dermatopharmacology.* Boca Raton: CRC Press; 2005. p. 213-228. doi:10.1201/9780849359033\_15.
31. Lademann J, Schanzer S, Richter H, Meinke MC, Weigmann HJ, Patzelt A. Stripping procedures for penetration measurements of topically applied substances. In: *In Vitro Skin Permeation and Penetration.* Berlin: Springer; 2017. p. 205-214. doi:10.1007/978-3-662-53270-6\_11.
32. Lauer AC. Percutaneous drug delivery to the hair follicle. *J Toxicol Cutan Ocul Toxicol.* 2001;20(4):475-495. doi:10.1081/cus.120001871.
33. Zhang LW, Monteiro Riviere NA. Use of confocal microscopy for nanoparticle drug delivery through skin. *J Biomed Opt.* 2012;18(6):061214. doi:10.1117/1.jbo.18.6.061214.
34. Rhein L, Zatz JL, Motwani M. Targeted delivery of actives from topical treatment products to the pilosebaceous unit. In: *Dermatotoxicology and Dermatopharmacology.* Boca Raton: CRC Press; 2007. p. 237-266. doi:10.3109/9781420018417\_20.
35. Rangsimawong W, Ngawhirunpat T. Techniques for follicular penetration studies. *Int J Pharm Sci.* 2015;11(2):31-44. doi:10.14456/ijps.2015.8.
36. Meidan VM. Methods for quantifying intrafollicular drug delivery: a critical appraisal. *Expert Opin Drug Deliv.* 2010;7(9):1095-1108. doi:10.1517/17425247.2010.503954.
37. Waugh A, Grant A. *Ross & Wilson: Anatomy and Physiology in Health and Illness.* 12th ed. Edinburgh: Elsevier Saunders; 2014.
38. Pathak K, Vaidya A. *Cosmetic Science: Concepts and Principles.* Pune: Nirali Prakashan; 2018.

**HOW TO CITE:** Sheetal Singh, Shani Vishwakarma, Vanita Lokhande, Sayali Shelke, Unlocking Hair Follicles as Drug Reservoirs: Advances in Transfollicular Drug Delivery, *Int. J. of Pharm. Sci.*, 2026, Vol 4, Issue 4, 5013-5027. <https://doi.org/10.5281/zenodo.19920285>

