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Review Article

Vesicular Carriers for Follicular Drug Delivery

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Abstract

The follicular route has been explored for both topical and systemic drug delivery but its application is challenged by different limitations such as sebum flow and size-selectivity. Vesicular carriers like liposomes, niosomes, invasomes, and transferosomes, which have shown promise in overcoming these barriers, have been explored in this review study. These vesicles improve follicular penetration of drugs, with deformable carriers performing better than conventional liposomes. Also, modifying liposomes using permeation enhancers has been introduced as another choice to enhance their follicular penetration. Vesicular systems have been primarily used to deliver drugs for treating alopecia, acne, and topical infections. They have also demonstrated potential in systemic delivery of antihypertensive drugs and insulin. Local hair massage and iontophoresis techniques further improve vesicle follicular penetration.

Introduction

Transdermal drug delivery systems have gained significant attention as a means to overcome the limitations associated with oral administration, such as the harsh pH environment, enzymatic degradation, mucus and epithelial barriers, and gastrointestinal microbiota,[1] as well as patient adherence following injection administration.[2] Although transdermal drug delivery has been challenged by the presence of non-permeable corneocytes and intact stratum corneum preventing skin penetration of large hydrophilic substances,[3,4] pilosebaceous units act as feasibly permeable pathways for certain substances. The large surface area of the hair follicles provides an important absorption site for substances. In addition, they offer a portal and reservoir for dermally applied drugs.[5,6] The transfollicular drug delivery system can be utilized as an alternative to transdermal drug delivery.[7] Intrafollicular drug delivery plays an important role as a direct pathway to hair follicles. Androgenic alopecia[8] and acne vulgaris[9] are the most desired and studied disorders for intrafollicular delivery treatment.

However follicular delivery can bring notable advantages, but its application is limited by various challenges including size-selectivity of the follicles opening and sebum secretion fellow. Nanotechnology-based drug delivery systems have been demonstrated to be promising for overcoming follicular delivery-associated challenges. These systems enhance drug penetration and retention within the hair follicle.[10] Polymeric nanoparticles can be engineered to have specific properties that improve drug delivery to the hair follicle and increase drug retention.[9,11,12] Due to their small particle size, ranging from 1 to 100 nm, metallic nanoparticles can penetrate easily into the follicle root sheath.[13,14] Dendrimers can be functionalized by targeting ligands that increase their specificity for the hair follicle.[15] Solid lipid nanoparticles can encapsulate drugs and provide sustained release, improving drug retention within the hair follicle.[16,17]

Vesicular drug delivery systems (VDDSs) are well-known assemblies of a lipid bilayer that are formed as a result of amphiphilic building blocks in contact with water in the shape of a spherical vesicle in which their hydrophilic heads are pointed toward the solution, and lipophilic tales are located inside [18]. Based on different aims and components used in formation, so far, various types of vesicular carriers, including liposome,[19] niosome,[20] transfersome,[21] ethosome,[22] and phytosome[23] have been developed. These vesicles can improve the dissolution rate of lipophilic drugs,[24] enhance the stability of the therapeutic agents,[25] prolong drug release time,[26] reduce the side effects of drugs by decreasing their uptake by unwanted tissues,[27] and increase the sensitivity of the therapeutic agents to the targeted location.[28] Due to their structural properties, overpassing stratum corneum might

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be challenging for most vesicular carriers.[29] In addition to the enhanced permeation, the lipid state of VDDSs can help drugs interact with the follicular sebum and avoid their sebum flow-induced ejection, hence it can lead to increased retention.[30]

In this review article, the diverse landscape of follicular delivery using VDDSs, as promising nanomedicine carriers, has been studied. By examining the latest advancements and studies in this area, the objective is to offer a comprehensive overview of how VDDSs can enhance follicular delivery. The in-depth literature analysis aims to illuminate the potential benefits associated with utilizing VDDSs for follicular delivery as well as their optimization and improvement of their administration. By synthesizing key findings and identifying emerging trends, this review seeks to underscore the significance of VDDSs in improving the efficacy and precision of drug delivery to/through hair follicles. The review not only consolidates existing knowledge but also points towards future research directions and practical implications for optimizing therapeutic outcomes in dermatology and beyond.

Follicular drug delivery system

Follicle hair structure

Basically, hair follicles comprise two main compartments, a hair bulb and a hair shaft, which is enveloped by a root sheath (Figure 1). The cells found near the hair bulb are responsible for regulating hair development.[31] The bulge contains hair follicle stem cells and thus functions as the regulator of the hair cycle.[32] In addition, the bulge is the insertion point of the musculus arrector pili.[10] Moreover, one or more branched acinar-shaped sebaceous glands are connected to the upper region of each hair follicle through duct(s). These glands produce a lipid-enriched environment by sebum secretion. The interaction of a substance with the sebum is an essential factor in its penetration and permeation in hair follicles.[33] The region between the skin surface and the insertion point of sebaceous glands is called the infundibulum. The infundibulum outer surface is covered by an impermeable stratum corneum. Its upper part is composed of an intact keratinized epidermis while the lower part is composed of trichilemmal which is notably more permeative.[10,33]

Follicular delivery pathways

Follicle hair provides two main delivery which named Intrafollicular and transfollicular pathways. Intrafollicular is defined as passing way through the inner root sheath and targeting follicle hair. This pathway can be applied for the treatment of hair loss or follicle-related diseases.[10,34] The transfollicular, as a subset of the transdermal delivery system, is an important pathway in systemic delivery. Since the stratum corneum inhibits the permeation of a broad variety of substances, the stratum corneum gap on the hair follicle can facilitate crossing the stratum corneum. After entering the hair follicle, released drugs can penetrate through the follicle membrane and make an entrance into the dense network of blood capillaries, stem cells, and dendritic cells.[10,35] So far, the transfollicular delivery of various lipophilic drug substances, such as celecoxib[36] and vaccines,[37] has been studied.

Follicular delivery challenges

Although follicular delivery can be a desirable delivery route, some challenges can limit the transport of many substances. The main difficulties are reviewed as follows.

The hair follicle openings are size-selective. However, in comparison to the 500 Da penetrability of skin[38] follicular delivery is considered more permeable for substances, but particle size still has been reported as a key factor in the extent and depth of follicular delivery systems.[39,40] Patzelt *et al.*[41] demonstrated that the particles with 400 nm to 700 nm diameters, penetrated through hair follicles the most. Ghasemiyeh *et al.*[39] suggested 300 nm as the optimal size for hair follicle targeting. In addition, the maximal limit for penetration of particles into hair follicles was reported to be 7 µm.[42]

Whereas the inactive hair follicles which neither grow nor produce sebum are impermeable to substances,[43,44] sebum secretion led to challenging follicular penetration. The upward sebum flow can limit the movement of drugs[45] but since the flow is considerably slower than the penetration rate of nanoparticles, the secretion cannot prevent the nanoparticles from reaching the target.[46,47]

In addition, another factor that limits a drug's penetrability is its hydrophilicity.[48] The lipophilic nature of sebum makes it difficult for hydrophilic drugs to penetrate through follicles. However, nanoparticles, particularly lipid-based nanoparticles such as liposomes and transferosomes, can encapsulate these drugs and facilitate their penetration into the follicle.[10]

Vesicular Drug Delivery Systems Ability for Follicular Delivery

VDDSs are a class of drug delivery systems that have attracted notable attention in drug delivery due to their ability to carry therapeutic agents in a controlled manner (Figure 2). These systems are colloidal dispersion comprising lipid or polymer-based vesicles that can encapsulate hydrophobic or hydrophilic drugs, protecting them from degradation and improving their bioavailability.[49] VDDSs have been considered for dermal application due to their simplicity of surface modification, high compatibility, and suitability as vehicles for controlled delivery.[50,51] In addition, they have demonstrated notable permeation-enhancing abilities benefiting the dermal delivery of various medications.[52] Therefore, they are suggested to be promising platforms for follicular delivery (Table 1). So far, different types of these vesicles, including liposomes, niosomes, and transferosomes, are studied for the follicular delivery of various active pharmaceutical ingredients which are reviewed further in detail (Table 2).

Table 1. Basic characterizations of different prepared vesicles.

	Drug name	PS (nm)	EE (%)	ZP (mV)	PDI	Ref
Liposome	Insulin	243.4 ± 17.6	-	63.1 ± 13.1	0.120 ± 0.030	53
	Carboxyfluorescein	319.4	-	-13.6	0.25	54
	Adapalene	86.66 ± 3.5	97.01 ± 1.84	-	0.24 ± 0.04	53
	Finasteride	2160 ± 130	89.0 ± 7.6	-	1.56 ± 0.30	55
	Cardamonin	137.03 ± 1.56	96.56 ± 2.00	-32.80 ± 1.68	0.12 ± 0.03	56
	Voriconazole	114.1 ± 1.0	86.2 ± 0.6	-11.6 ± 9.42	0.017 ± 0.005	57
	Caffeine	137.1 ± 1.3	48	2.3 ± 0.7	0.06 ± 0.03	58
	Caffeine	115 ± 1.4	-	0.07 ± 0.009	-	59
	Chloramphenicol	97.5 ± 12.0	-	-36.6 ± 4.0	0.22 ± 0.04	60
	Minoxidil	317 ± 4	69.08 ± 3.07	-13.97 ± 0.451	0.203 ± 0.016	61
	Minoxidil and tretinoin	149.33 ± 1.4	83.53 ± 0.0424 (MDX) 71.402 ± 0.26 (TRET)	7.74±0.22	0.39 ± 0.0135	62
Niosome	Superoxide Dismutase	152 ± 11	59.1±6.3	-30		63
	Finasteride	2380 ± 80	93.0 ± 1.0	-	0.85 ± 0.17	55
	Tretinoin and Bicalutamide	319.20 ± 8.50	>99 and 94.63 ± 0.50	-29.70 ± 0.36	1.07	64
	Oryza sativa	107.97 ± 1.89	-	69.80 ± 3.61	-	65
	Finasteride	259.72 ± 0.32	94.00 ± 0.86	-26.21 ± 0.56	0.236 ± 0.006	66
	Aconitine	97.88 ± 63.25	82.68 ± 2.14	-47.63 ± 0.31	0.25 ± 0.10	67
	Caffeine	135.2 ± 2.3	46	-42.6 ± 2.4	0.15 ± 0.02	58
	Finasteride	325 ± 4.70	-	-32.38 ± 1.33	0.46 ± 0.03	68
Invasome	Caffeine	139 ± 1.5	-	-	0.1 ± 0.005	59
	Isotretinoin	148 ± 3.8	85.78 ± 1.76	-69.2	0.169	69
Transferosome	Phyllanthus emblica (Gallic acid, chlorogenic acid, and ellagic acid)	228	46.4 ± 0.4 (GAL) 79.1 ± 1.1 (CHL) 97.8 ± 0.2 (ELL)	-	0.25	70
	Caffeine	158.3 ± 4.0	47	-18.3 ± 0.2	0.14 ± 0.04	58
Ethosome	Nebivolol	73.50±0.08	86.46±0.15	33.75±1.20	0.31±0.07	71
Transethosome	Olmesartan Medoxomil	222.60 ± 2.59	58.54 ± 1.30	-20.81 ± 0.34	0.11 ± 0.06	72
Cubosome	Minoxidil	131.10 ± 1.41	80.4 ± 4.04	-23.5 ± 0.42	0.185 ± 0.0	73

Liposomes

Liposomes are prepared with the emulsification of natural or synthetic lipids in an aqueous medium. They are mainly composed of a bilayer of phospholipids, cholesterol, and an aqueous medium.[74] Liposomes are biologically inert and biodegradable, ensuring safety in their use. Their composition primarily consists of phospholipids, natural constituents of cell membranes, which minimizes the risk of toxicity, antigenicity, or pyrogenicity. Their adaptability to various sizes, compositions, and surface modifications allows for customization to meet specific formulation requirements. Liposomes are capable of encapsulating a wide array of hydrophilic and lipophilic drug substances, effectively protecting these substances from degradation by enzymes.[75,76] Liposomes are utilized for different delivery routes such as dermal delivery.[77] Therefore, their application for follicular delivery was investigated in numerous studies. However, liposomes, due to their rigidity, are not as specified as deformable vesicles for follicular delivery.[78]

Adapalene has been widely applied topically for the treatment of a pilosebaceous unit disorder, known as acne vulgaris.[79] Since the action site of adapalene is the hair follicle, Kumar and Banga prepared adapalene-loaded liposomes for intrafollicular delivery. An *in vitro* permeation study showed that 15 hours after topical administration on porcine ear skin, hair follicle concentration of adapalene, when loaded into liposomes, was 4 times higher than conventional adapalene. However, there was no significant difference in the amount of adapalene recovered in the stratum corneum between liposomal and conventional solution formulations. Moreover, using confocal laser scanning microscopy (CLSM) revealed that in contrast to the adapalene solution in PEG 400 that could not penetrate through the hair shaft, the liposomes could traverse alongside it.[53]

Kajimoto and co-workers[80] labeled dioleoyl phosphatidylethanolamine and insulin with two different fluorescent substances, 4-nitrobenzo-2-oxa-1,3-diazolyl, and rhodamine, respectively. Then, they prepared

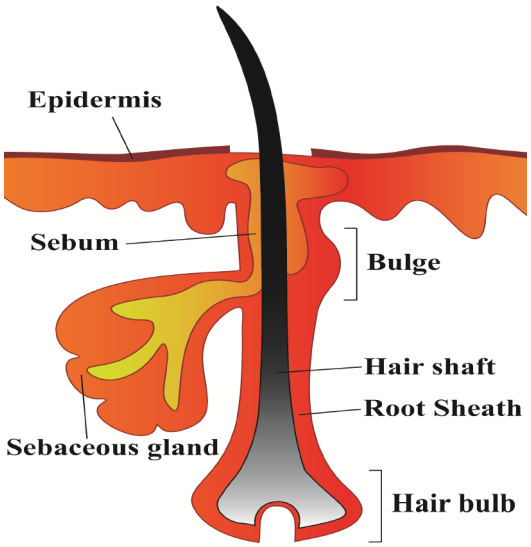

Figure 1. Structure of hair Follicle.

liposomal insulin formulation using the labeled drug and phospholipid. They evaluated follicular delivery of the liposomal and conventional delivery of the labeled insulin, using both *in vivo* investigation on rat skin, immediately and 18 hours after topical application. In contrast to the plain solution of insulin which was not efficient in follicular penetration, considerable follicular delivery and site retention (18 hours after iontophoresis) of liposomes were observed. While topical minoxidil is an FDA-approved treatment for androgenic alopecia,[81] applying tretinoin can enhance its efficiency by upregulation of follicular sulfotransferase enzymes.[82] Therefore, Kochar *et al.*[62] loaded a combination of minoxidil and tretinoin into liposomes for intrafollicular delivery. The *ex vivo* permeation study on rat skin demonstrated that tretinoin could not penetrate through the skin, but minoxidil liposomes, after 6 hours, penetrated less than 20% through the skin, whereas in combination with tretinoin in the liposomes, it could penetrate about 30%. They performed a CLSM investigation, using Rhodamine 6G (as minoxidil) and Coumarin 6 (as tretinoin), and displayed that the liposomes permeated skin through hair follicles.

In 2024, Liu *et al.*[56] claimed that Cardamonin can be effective in hair growth when used topically and prepared Cardamonin-loaded liposomes to increase its intrafollicular penetration. They performed an *in vitro* permeation study on mice skin. The liposome retentions from the hair follicles and dermis were 68.79 and 23.76 folds compared to the plain cardamonin. The test was repeated in porcine ear skin and the liposomal formulation penetrated significantly more than the free drug.

In 2018, Santos *et al.*,[57] compared follicular pathway effects on the cutaneous delivery of liposomes and nanostructured lipid carriers. They used voriconazole as the model drug,

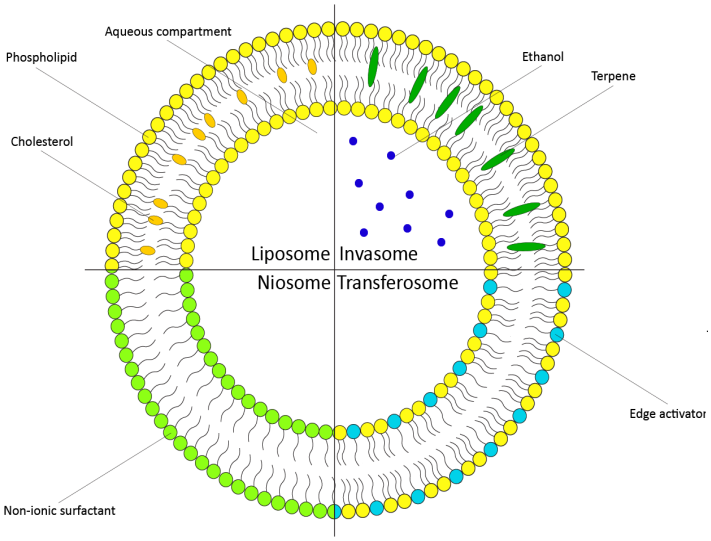

Figure 2. Structure of the main vesicles for follicular delivery.

which is an anti-fungal medicine with broad systemic side effects.[83] They evaluated the permeation of voriconazole-loaded carriers through full-thickness excised porcine skin and re-evaluated them by applying follicle-blocked skin. It was demonstrated that after blockage of follicles, when liposomes were used as carriers, retention of liposomal drug from stratum corneum was increased by 10 times, and from the rest of the skin was decreased by 70%. They suggested the transfollicular delivery was the reason for improved penetration of liposomes through the porcine skin in comparison to nanostructured lipid carriers.[57]

Jung *et al.*[54] measured the porcine hair follicle penetration depth of liposomal and conventional formulations, applying curcumin and carboxyfluorescein as model drugs due to their fluorescein properties. They performed an *ex vivo* study on porcine ear skin and evaluated the formulation's skin deposition by laser scanning microscopy. Both amphoteric and cationic liposomes had penetrated 69% of the follicle depth, 5 days after topical application. On the other hand, conventional liposomes could penetrate only about 30% of the follicle depth.

Since deformability is essential for penetration across follicles, using permeation enhancers has been studied to evaluate the efficiency of the liposomes' deformability on their penetrability. In 2016, Abd *et al.*,[58] in order to produce deformable liposomes, added oleic acid to liposome formulation. Since caffeine efficiency in hair growth is demonstrated,[84] they prepared caffeine-loaded deformable liposomes and compared their intrafollicular delivery through abdominal full-thickness human skin in Franz diffusion cells with conventional liposomes and pure drugs. Caffeine retention from hair follicles for oleic acid-contained liposomes was 3.5 ± 0.7 μg/cm^2, which was significantly higher than conventional liposomes (1.7 ± 0.4 μg/cm^2).[58] Chloramphenicol can be applied as a treatment for topical infections.[85] Hsu *et al.*,[60] used deoxycholic acid as a permeation enhancer to prepare a flexible liposomal formulation for chloramphenicol. They performed an *in vitro* study on mouse dorsal skin to compare follicular penetration of the chloramphenicol loaded-deformable and rigid liposomes. A 3-fold improvement in follicular uptake of chloramphenicol was reported for the flexible liposomes compared with the rigid liposomes. Kumar *et al.*[61] loaded minoxidil into oleic acid-modified liposomes and investigated their *ex vivo* follicular permeation. Hair follicle retention of the oleic acid liposomal minoxidil gel after an *ex vivo* application on full-thickness pig ear skin was 4.48 ± 1.39%, while minoxidil conventional solution retention was 0.45 ± 0.13%. In addition, a CLSM study, 24 hours after topical administration, demonstrated that rhodamine B hair follicle penetrability was considerably higher in the liposomal gel formulation compared to the conventional solution (Figure 3).

To conclude, it can be claimed that deformability has an essential role in the penetrability of liposomes. Therefore, although liposomes have been demonstrated to be effective in the improvement of follicular permeation, flexible liposomal carriers, such as niosomes, invasomes, transferosomes, transethosomes, ethosomes, and cubosomes might be notably better choices compared to conventional liposomes. These liposomal vehicles are applied for the follicular delivery of various drugs which are reviewed as follows.

Niosomes

Niosomes are composed of a bilayer of non-ionic

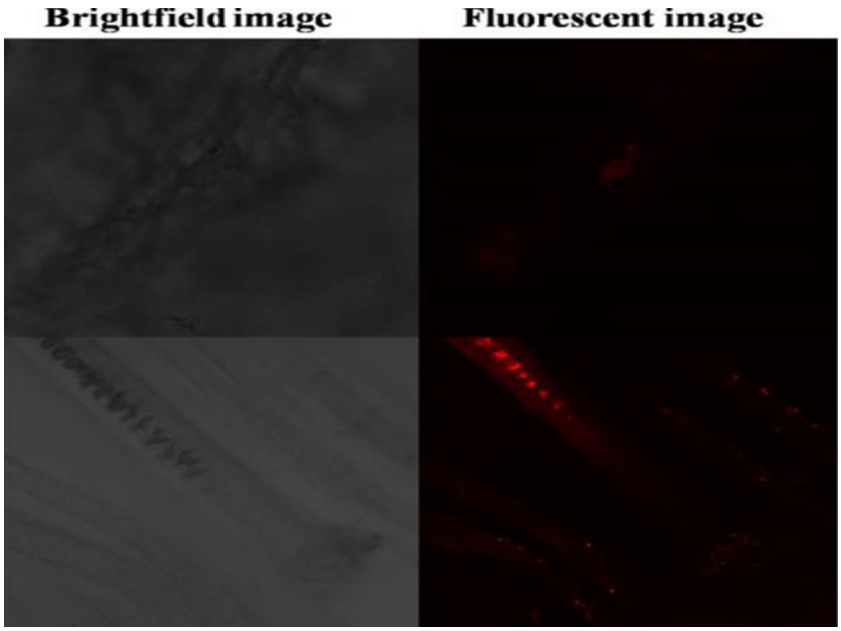

Figure 3. Confocal laser scanning microscopy images of rhodamine B in conventional solution (upper) as control and oleic acid-modified liposomal gel formulation (lower) on porcine skin after 24 hours, showing brightfield (left) and fluorescence (right) images. Adapted from Ref. 61.

surfactants, including Brij,[86] Span,[87] and Tween,[88] and lipids such as cholesterol. The membrane enhances their skin deposition by reducing surface tension, enhancing vesicle flexibility, and increasing fusion with biological membranes.[89-92] Increased flexibility and fusion with biological membranes can lead to improved follicular delivery. Niosomes demonstrate improved stability over liposomes, which can be attributed to their high concentration of surfactants. This higher concentration not only enhances skin penetration but also leads to increased bioavailability.[93] Compared to the other vesicular carriers, niosomes exhibit enhanced patient adherence due to their non-lipidic composition. In addition, using non-ionic surfactants instead of lipids makes niosomes cheaper in cost and chemically more stable.[94] In addition, these surfactants have shown lower irritation than ionic surfactants.[95]

Finasteride, as an anti-androgenic agent, can effectively treat androgenic alopecia, but its systemic absorption is associated with serious systemic side effects.[96] In order to avoid the side effects, Tabbakhian *et al.*[55] evaluated intrafollicular administration of finasteride after preparing finasteride-loaded negatively charged multilamellar liposomes and niosomes with >2 μm particle sizes. They compared their pilosebaceous unit targeting ratio to finasteride hydroalcoholic solution by applying the formulations to the ventral mid-section of the hamster ear in an *ex vivo* study. The pilosebaceous unit targeting ratios of multilamellar niosomes, multilamellar liposomes, and the hydroalcoholic solution were reported to be 0.38 ± 0.04, 0.27 ± 0.04, and 0.06 ± 0.01, respectively.The results were in agreement with the studies suggesting that an increase in deformability could improve vesicles' follicular delivery. Furthermore, the study demonstrated that vesicles larger than 2 μm still had more affinity to pilosebaceous units in comparison to conventional substances. Furthermore, in 2023, Liu *et al.*,[66] applicated suspension, hydroethanolic solution, and niosomal formulation of finasteride on rat skin to evaluate their transdermal delivery. They reported that 12 hours after application, the drug accumulation of the solution and niosomal formulation in hair follicles was 1.08 ± 0.06 μg/cm^2 and 21.04 ± 0.04 μg/cm^2. Furthermore, the suspension was not detected in the follicles. The results indicated the hair follicle targeting ability of niosomes was 20 times more than the solution. Moreover, the finasteride retention results from the full skin layer and stratum corneum for the solution were 26.9 ± 0.02 μg/cm^2 and 21.47 ± 0.08 μg/cm^2, and for the niosomes were 52.61 ± 0.01 μg/cm^2 and 11.31 ± 0.05 μg/cm^2. Therefore, though retention of niosomes from the stratum corneum was lower than the solution, drug retention below the stratum corneum was about 7 times more when applied in niosomal formulation compared to the conventional solution. According to the contrast in niosomes accumulation in the stratum corneum and below the stratum corneum, it can be concluded that the niosomes were delivered to the below stratum corneum through transfollicular delivery. Moreover, Rungseevijitprapa *et al.*[68] prepared finasteride-loaded proniosomes to investigate their ability to hair growth stimulation in mice. They performed an *in vitro* study on the permeation of the proniosomes through porcine skin with or without blockage of the hair follicles. Twenty-four hours after topical application, proniosomes permeated through the conventional skin significantly more than the follicle-blocked porcine skin indicating the follicular penetration effect on the niosomes permeation. In addition, improved penetration of finasteride in niosomal formulation, compared to conventional solution form, through both follicle-blocked and non-blocked porcine skins, was displayed.

Topical retinoids and anti-androgens can treat acne vulgaris; therefore, topical administration of tretinoin, as a retinoid, and bicalutamide, as an anti-androgen, combination can result in a promising acne treatment.[97,98] Ghasemiyeh *et al.*,[64] prepared a niosomal formulation of the bicalutamide and tretinoin combination to improve

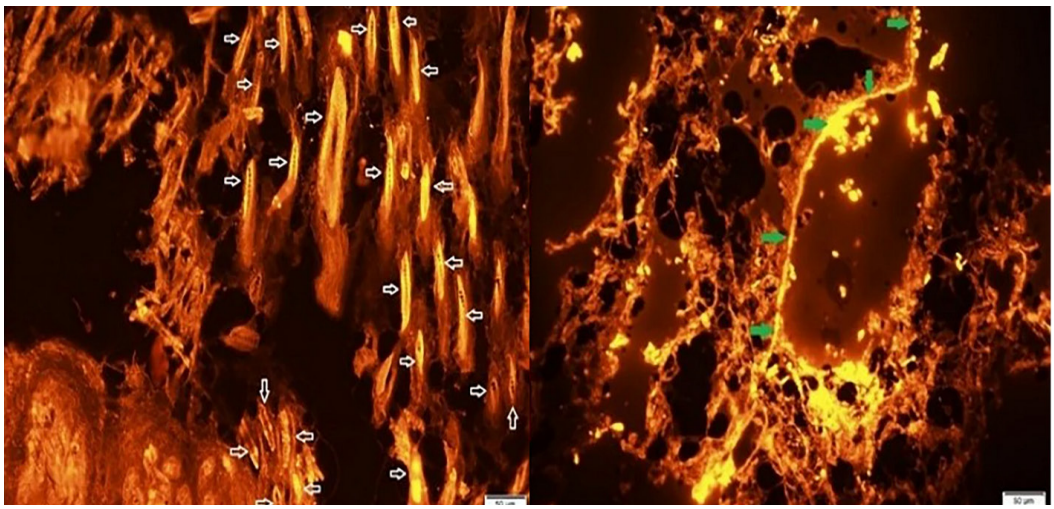

Figure 4. Fluorescence images of hamster skin 2 hours after topical application, comparing rhodamine B solution (left) and rhodamine B-loaded niosomes (right). Hair follicles are indicated by arrows. Adapted from Ref. 64.

their intrafollicular delivery and pilosebaceous unit targeting. Using the fluorescence microscopy technique, they signified the predominant route of permeation and penetration of niosomes through skin and skin organelles and indicated that in contrast to the conventional gel formulation, niosomal gel significantly targeted the hair follicles (Figure 4). Furthermore, Manosroi *et al.*[65] suggested that the drug concentration reduction in blocked-hair follicles skin compared to opened-hair follicles skin was due to follicular delivery inhibition. Therefore, they concluded that *in vitro* follicular delivery of *Oryza sativa* (which has indicated notable ability in hair loss treatment after topical administration[99]), after its topical application on porcine skin in conventional and niosomal solutions, was 0.312 ng and 1.849 ng, respectively, per follicle hair. Wu *et al.*,[67] compared transdermal delivery of aconitine through rat skin, in solution, tincture, and multilamellar niosomal formulations. Performing an *in vitro* deposition study on rat skin, they demonstrated that the concentration of the niosomes in hair follicles was significantly higher than in the solution and tincture.

Since alopecia areata is associated with an increase in free radicals, different anti-oxidants, including superoxide dismutase, can be considered alopecia areata treatments.[100] Karami *et al.*[63] produced niosomal superoxide dismutase for intrafollicular delivery. The *in vitro* permeation studies showed that the permeation of the niosomes through hairy and non-hairy guinea pig skin was 52.8 % and 20.8 %, 48 hours after topical administration. Hence, they suggested follicular delivery as its main delivery route which was in accordance with its high molecular weight and hydrophilic characteristics. On the other hand, conventional superoxide dismutase solution demonstrated 34.6 % and 12.4 % permeation through the mentioned skins, respectively, indicating that the niosomal formulation can permeate more feasibly in comparison with the conventional solution. Furthermore, they repeated the permeation test of both formulations after the extraction of lipids from both skins. The only notably different result was the 40.6 % reduction of niosomes permeation through hairy skin after the lipid extraction. They concluded that the interaction between sebum and niosomes plays an important role in hair follicle accumulation of superoxide dismutase.

Invasomes

Invasomes are flexible vesicles consisting of a phospholipid bilayer, hydro-ethanolic core, and one or a mixture of terpenes.[101] Ethanol can enhance the deformability of the membrane phospholipids creating a flexible structure resulting in permeation improvement.[102] Terpenes can improve the penetrability by disrupting the stratum corneum lipids' tight structure.[103] However the potency of terpenes was demonstrated to be higher compared with other permeation enhancers, which resulted in more penetrability of invasomes than the other vesicles, but it is crucial to account for their toxicity.[104] It is shown that utilizing natural terpenes, instead of synthetic ones, can considerably reduce their toxicity.[105]

In order to compare follicular penetration of conventional liposomes with invasomes to determine the effect of flexibility on penetrability, Trauer *et al.*[59] conjugated rhodamine to 1,2-Dipalmitoyl-sn-glycero-3-phosphorylethanolamines of the vesicles and loaded them with carboxyfluorescein to differentiate between the vesicles and release drug penetrability. With the aid of massaging, liposomes and invasomes reached penetration depths of 500 μm and 700 μm. However, carboxyfluorescein penetrated to an approximate depth of 1200 μm, regardless of the applied liposome type.

Topical isotretinoin is a promising medicine for acne vulgaris.[106] In order to increase isotretinoin penetration through hair follicles and improve its pilosebaceous unit targeting, Dwivedi *et al.*[69] prepared isotretinoin invasomal gel. Using an *ex vivo* study, they demonstrated that after 8 hours of topical application of isotretinoin-loaded gels, the maximum drug permeated from the conventional gel was

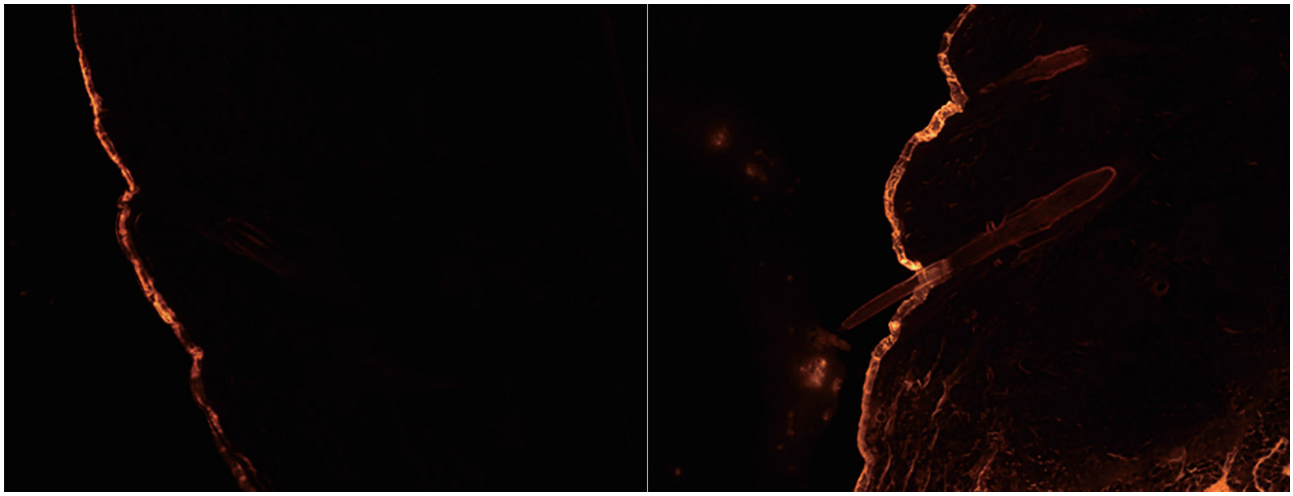

Figure 5. Fluorescence images of pig ears 30 minutes after topical application of rhodamine B-labeled Phyllanthus emblica extract-loaded transferosomes (right) and the conventional solution (left). Adapted from Ref. 70.

31.97% ± 1.31, and from the invasomal gel was 85.21 % ± 1.88. In addition, applying CLSM, indicated that invasomes, in a gel formulation, could reach the pilosebaceous follicular unit traversing alongside the hair shaft. They showed that after 6 hours of topical application of rhodamine B, loaded into the conventional and invasomal gel, it could penetrate the depths of 20.24 µm and 31.49 µm.

Transferosomes

Transferosomes are composed of phospholipids, ethanol/aqueous core, and edge activators, such as surfactants or bile salts, which help to destabilize the lipid bilayers and increase the deformability of the vesicles.[107] This unique property allows transferosomes to squeeze themselves up to 5 to 10 times which is the most among vesicular carriers, through the narrow intercellular spaces of the stratum corneum, the outermost layer of the skin, and deliver drugs into the deeper layers.[108] Transferosomes are biocompatible and biodegradable as they are composed of natural phospholipids, transferosomes exhibit excellent biocompatibility and biodegradability. In addition, acting as a drug depot, transferosomes facilitate the slow and sustained release of their contents, which is beneficial for systemic and topical drug delivery.[109] They have shown great potential in enhancing the permeation of both hydrophilic and lipophilic drugs, and their ability to encapsulate a wide range of drug molecules makes them a promising carrier system for transdermal drug delivery.[110] Hence, their penetrability into hair follicles is suggested to be considerable, and many researchers have evaluated their ability.

In 2022, Wongrakpanich *et al.*[70] revealed fluorescence images of rhodamine B-labeled Phyllanthus emblica extract-loaded transferosomes and solution after topical administration on pig ear skin. The successful intrafollicular delivery of the transferosomes, in comparison to the conventional solution, was indicated (Figure 5).In 2016, Abd *et al.*[58] performed a permeation study on full-thickness human skin in Franz diffusion cells. It was demonstrated that 24 hours after application, hair follicle permeation of caffeine loaded-transferosomes (5.3 ± 3.3 µg/cm^2) was considerably more than conventional solution (0.8 ± 0.2 µg/cm^2), conventional liposomes (1.7 ± 0.4 µg/cm^2), and niosomes (2.2 ± 0.5 µg/cm^2).

Fresta *et al.*,[111] compared pilosebaceous follicle targeting ability of transferosomes with hydroalcoholic solution, solid lipid nanoparticles, and liquid crystal nanocarriers. An hour after topical administration of different formulations of minoxidil on rat skin, transferosomes, solid lipid nanoparticles, liquid crystal nanocarriers, and hydroalcoholic solution demonstrated 47% ± 8, 42% ± 9, 91% ± 7, and 13% ± 8 presence in pilosebaceous follicle hair level respectively. After 48 hours, the presence in the mentioned level was reported to be 13% ± 7, 18% ± 7, 74% ± 8, and 1% ± 0, respectively. It was concluded that although transferosomes showed immensely higher targeting and retention ability in comparison to the hydroalcoholic solution, their abilities were notably poorer than liquid crystal nanoparticles.It should be noted that in this study optimization has not been performed for the formulation of the transferosome sample; therefore, the results cannot be generalized and interpreted as the inferiority of transferosomes in follicular delivery.

Miscellaneous

Various vesicular systems have been investigated, so far. Flexible vesicles have the potential for follicular delivery due to their high permeability and penetrability. Thus far, follicular delivery of glycerosomes,[112] cubosomes,[73] hyalurosomes,[112] ethosomes,[71] and transethosomes[72] have been studied. Glycerosomes, a harmless and nontoxic topical drug delivery system, can be formed at room temperature unlike conventional liposomes.[113,114] They exhibit improved entrapment, fluidity, and stability, while also increasing water content in the stratum corneum, effectively minimizing obstacles in transdermal drug delivery.[115-117] Cubosomes demonstrate bioadhesive properties, allowing for sustained release of incorporated drugs.[118] Hyalurosomes containing hyaluronic acid, which has an affinity for CD44 receptors, are targeted for cells and tissues overexpressing this receptor. In addition, hyaluronic acid is commonly used as a moisturizing agent

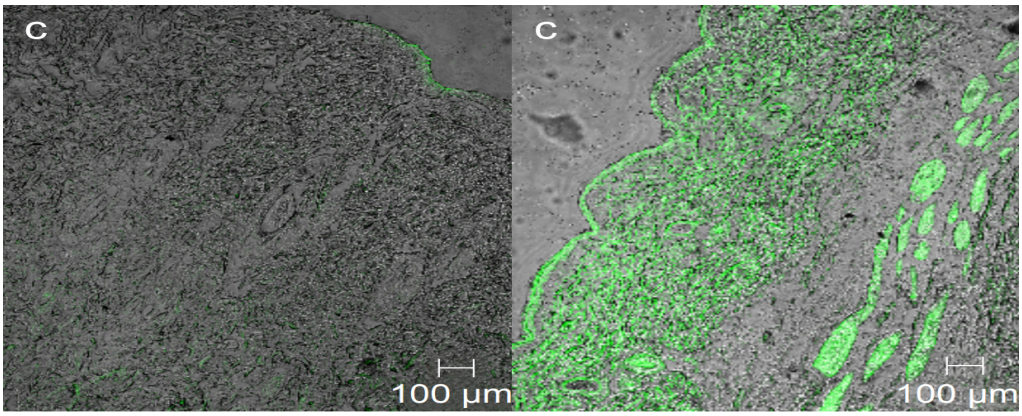

Figure 6. Confocal laser scanning microscope photomicrographs (merge between fluorescence and transmitted lights) of 1% fluorescein diacetate solution (left) and fluoro-labeled transethosomes. Adapted from Ref. 72.

Table 2. The reviewed studies on applying vesicles for follicular drug delivery.

Active ingredients	Vesicle type	Purpose of use	Investigation methods	Key findings	Ref.
Minoxidil	Liposome	Hair-loss	• In vivo hair regrowth evaluation in mice • In vivo skin deposition evaluation on hamster ear skin	• The liposomes improved the efficiency of plain minoxidil.	124
Adriamycin	Liposome	Cancer	• In vivo delivery study through rat skin • Image analysis	• Cationic liposomes with iontophoresis showed improved adriamycin delivery through follicular routes compared to the conventional liposomes. • Positive charges of cationic liposomes facilitated rapid drug through iontophoretic movement.	125
Finasteride	Liposome Niosome	Androgenic Alopecia	• Optical microscopy • In vitro permeation study through hamster flank skin • In vivo deposition study through hamster ear skin	• Both liposomes and niosomes enhanced finasteride delivery to the pilosebaceous unit. • Surfactant type (for niosomes) and phospholipid type (for liposomes) were notably effective on drug permeation and deposition in hamster skin.	55
Curcumin	Liposome	-	• In vivo follicular penetration evaluation on porcine ear skin by confocal laser scanning microscopy	• Amphoteric liposomes, as well as cationic liposomes, were penetrated considerably more than anionic liposomes.	54
Insulin	Liposome	Diabetes	• In vivo investigation of formulation efficacy on rat skin	• Iontophoresis improved follicular delivery of the liposomes. • Liposomes' ability in systemic delivery of macromolecules by transfollicular was proved.	80
Oryza sativa	Niosome	Androgenic Alopecia	• In vitro penetration through porcine skin by Franz diffusion cells	• The niosomes demonstrated considerably higher follicular penetration, compared with plain drug.	65
Caffeine	Liposome Invasome	Hair loss	• In vivo follicular penetration evaluation on human full-thickness skin by confocal laser scanning microscopy	• Invasomes penetrated to deeper levels of follicle compared to liposomes. • Massaging of the site led to improved penetration through hair follicles.	59
Adapalene	Liposome	Acne	• Transmission electron microscopy • Differential scanning calorimetry • Stability storage at 25°C, 4°C, -20°C • In vitro penetration through porcine skin by Franz diffusion cells • In vivo follicular penetration evaluation on pig ear skin by confocal laser scanning microscopy	• Liposomal formulation showed more hair follicle delivery of adapalene compared with Differin® gel and adapalene solution in PEG 400 • Liposomes remained stable after three months when stored in refrigerated condition.	53

Table 2. Continued.

Caffeine	Liposome Transferosome Niosome Modified liposome	Hair loss	• In vitro permeation through abdominal full-thickness human skin	• Modification of liposomes with oleic acid, in contrast to eucalyptol, was effective on hair follicle targeting. • Eucalyptol-modified liposomes had more encapsulation efficiency compared to other vesicles • Niosomes demonstrated the most improved permeation profiles compared.	58
Isotretinoin	Invasome	Eosinophilic pustular folliculitis	• Deformability • Ex vivo permeation through rat skin • Transmission electron microscopy • Cell cycle analysis • In vivo follicular penetration evaluation by confocal laser scanning microscopy	• Direct proportion of lecithin and permeation enhancer on vesicle permeability. • Increased topical flux, permeation coefficient, and cumulative permeated drug.	69
Chloramphenicol	Liposome Modified liposome	Methicillin-resistant S. aureus (MRSA)	• Differential scanning calorimetry • In vitro permeation through mouse skin • Antibacterial evaluation by broth microdilution technique • Disk diffusion assay • Flow cytometry • Intracellular MRSA killing • Neutrophil and keratinocyte toxicity • In vivo cutaneous irritation	• Addition of deoxycholic acid or dimyristoyl-phosphatidylcholine to liposome led to increased follicular uptake • The addition of dimyristoyl-phosphatidylcholine to liposomes decreased the MRSA death rate. • Deoxycholic acid enhanced the antimicrobial effect of the liposomes • Negligible toxicity and irritation were reported after using deoxycholic acid-modified liposomes.	60
Minoxidil	Modified liposome	Alopecia areata	• Differential scanning calorimetry • Thermogravimetric analysis • X-ray diffraction study • Transmission electron microscopy • In vitro drug release study through dialysis membrane • Ex vivo permeation through pig ear skin • Ex vivo drug deposition study in hair follicles • In vivo follicular penetration evaluation on rat skin by confocal laser scanning microscopy	• Oleic acid-modified liposomes were capable of improving minoxidil delivery into hair follicles.	61
Voriconazole	Liposome	Fungal infection	• Transmission electron microscopy • In vitro permeation through porcine skin • Antifungal evaluation by broth microdilution technique	• Compared with nanostructured lipid carriers, skin permeation of the prepared liposomes was slower. • Follicle blockage resulted in a 10-fold enhancement of drug retention in the stratum corneum.	57

Table 2. Continued.

Superoxide dismutase	Niosome	Alopecia areata	• Stability storage at 2-8°C with the aid of atomic force microscopy • In vitro drug release study through dialysis membrane • In vitro skin permeation study	• Replacing Labrafil® with sodium lauryl sulfate, as the surfactant, increasing the solid lipid/ liquid lipid ratio, and enhancing the lipid/ surfactant ratio resulted in enlarged vesicle size. • Permeation of the drug in both free and niosomal forms was notably more through hair skin than non-hairy skin, proving the role of hair follicles in the permeation process. • Lipid extraction led to decreased drug skin permeation, indicating the importance of sebum in follicular delivery. • Niosomes size was unchanged after 6 months of storage at 2-8°C.	63
Olmesartan medoxomil	Transethosome Transferosome	Hypertension	• Transmission electron microscopy • Differential scanning calorimetry • Stability storage at 4°C and 25°C • Vesicle elasticity evaluation • Ex vivo permeation study through rat skin and shed snake skin • In vivo skin penetration evaluation on rat skin by confocal laser scanning microscopy • In vivo investigation of formulation efficacy on rats • Histopathological study • Pharmacodynamic study • Dermatokinetic study	• Drug permeation of transferosome-loaded drugs through both rat skin and shed snake skin was considerably more than conventional suspension, but notably lower than transethosomal formulation. • Transethosomes were stable after45 days of storing at 4°C but were changed after 45 days of storing at 25°C. • Confocal scanning laser microscopy proved the transfollicular pathway of the formulations. • Topical application of Olmesartan Transethosomal formulation into rats demonstrated more sustained release than Angiosartan® 10 mg.	72
Finasteride and baicalin	Liposome Hyalurosome Glycerosome Glycerol-hyalurosome	Alopecia	• In vitro evaluation of cell proliferation and cytotoxicity • In vivo hair regrowth evaluation in mice • Histological observation	• All the vesicles were more successful than conventional suspension in the intrafollicular delivery. • While the results after administration of glycerol-hyalurosomes were the best amongst the vesicles, the other vesicles did not show significant results compared to each other.	112
Minoxidil	Transferosome	Alopecia	• In vitro drug release using Franz diffusion cells • In vitro percutaneous permeation analysis • In vivo follicular penetration evaluation on pig ear skin by confocal laser scanning microscopy • In vivo investigation of formulation efficacy on rats	• Using transferosome improved Efficacy, follicle penetration, and side effects compared with free drug. • The improvements achieved by transferosomes were not significantly different with solid lipid nanoparticles and were less than liquid crystal nanocarriers.	111

Table 2. Continued.

Minoxidil and Tretinoin	Liposome	Androgenic alopecia	• Ex vivo permeation study through rat skin by Franz diffusion cell • Ex vivo skin deposition study on skin with the aid of confocal laser scanning microscopy • In vivo skin diffusion study	• Permeability and follicular targeting of the liposomal formulation was significantly more than the conventional solution. • Any irritation was not reported after using the liposomal formulation.	62
Finasteride	Proniosome	Androgenic alopecia	• Attenuated total reflection-Fourier transform infrared spectra evaluation • Differential Scanning Calorimetry • In vitro permeation study through porcine skin • In vitro release study through a dialysis membrane • Storage stability study • In vivo hair regrowth study in mice • Skin irritation test in rabbits	• Proniosomes permeated through the skin notably more than the plain drug. • Extensive decrease in proniosomes permeability through blocked follicles skin compared with unblocked follicles skin, indicated the importance of follicular delivery in the permeation process. • Stability of the proniosomes at 4°C, 25°C, and 40°C were stable for 4 months. • Increased hair regrowth ability of finasteride, when loaded into proniosomes, was improved. • The proniosomes did not cause any irritation.	68
Phyllanthus emblica	Transferosome	Alopecia	• In vivo permeation study through porcine ear skin with the aid of fluorescence image analysis	• Applying transferosomes resulted in increased hair follicle penetration.	70
Aconitine	Multilamellar Niosome		• Small angle X-ray scattering analysis • Wetting angle measurement • In vitro drug release study through dialysis membrane • In vitro transdermal test on rat skin • In vivo follicular penetration evaluation on rat skin by confocal laser scanning microscopy • Preliminary skin irritation test	• Loading aconitine into multilamellar niosomes improved its hair follicle targeting, whereas Poly (lactide-co-glycolide) nanoparticles mostly accumulated in superficial hair follicles. • Irritation was not observed after 7 days of continuous administration on mice skin.	67
Tretinoin and bicalutamide	Niosome	Acne vulgaris	• Transmission electron microscopy • Differential scanning calorimetry • In vivo follicular penetration evaluation on hamster skin by confocal laser scanning microscopy	• Niosomes could successfully target hair follicles.	64

Table 2. Continued.

Finasteride	Niosome	Androgenic alopecia	• Physical stability study at 4°C. • Transmission electron microscopy • In vitro drug release through dialysis membrane • In vitro permeation through rat skin by Franz diffusion cells • In vivo follicular penetration evaluation on rat skin by confocal laser scanning microscopy	• The particle size of the niosomes remained unchanged for 6 months at 4°C. • Hair follicle targeting of the niosomes was considerably higher than the hydroethanolic solution and suspension of the drug. • The effect of the niosomal finasteride on hair regeneration in androgenic alopecia-induced rats, exceeded both the finasteride suspension and positive control (minoxidil solution).	66
Minoxidil	Cubosome	Androgenic alopecia	• X-ray diffraction study • Stability storage at room temperature • In vitro drug release through dialysis membrane • In vivo hair regrowth evaluation in rats • Draize test • Histopathological study • In vivo follicular penetration evaluation on rat skin by confocal laser scanning microscopy	• Cubosomes could deliver minoxidil into the hair follicles. • According to confocal laser scanning microscopy, 24 hours after administration, cubosomes were maintained in the hair follicles while the conventional solution did not residue. • Any significant changes in cubosomes properties was assessed, after 45 days of storing cubosomes at room temperature. • Skin tolerability and safety of the cubosomes were indicated.	73
Nebivolol	Ethosome	Hypertension	• Transmission electron microscopy • Permeation study • *F*ollicular penetration evaluation by confocal laser scanning microscopy • *In vivo* investigation of drug efficacy	• Drug transfollicular delivery in ethosomal formulation was demonstrated. • Efficiency of topically applied ethosomal was considerably higher compared to oral tablet.	71

Vesicular Systems Efficiency through FDD

According to the *in vivo* studies, as a consequence of intrafollicular and transfollicular delivery, drug-loaded vesicles have demonstrated notable effects on the treatment of diseases in mice or rats. Their influences are reviewed and classified in intrafollicular and transfollicular as follows.

Intrafollicular

Hair follicle targeting as a result of intrafollicular delivery, can be a promising technique for treatment of hair loss. Therefore, various studies have evaluated the efficiency of different drugs after loading into vesicular carriers and applied for intrafollicular delivery.

Ciotti *et al.*[124] prepared minoxidil loaded-sodium sulfate modified-liposomes. They evaluated the minoxidil intrafollicular delivery in solution and rigid and flexible liposomes, after daily topical administration on mice skin. They showed that the mean time for the appearance of "black skin" on mice was 16.4 ± 5.2, 10.4 ± 3.3, and 8.8 ± 1.5 days for solution, rigid liposomes, and flexible liposomes, respectively. In addition, it took 16.8 ± 4.1 days for rigid and 14.0 ± 3.7 days for flexible liposomes, for mice to get coated in full hair.

Co-loaded glycerosomes, hyalurosomes, liposomes, and glycerol-hyalurosomes by finasteride and baicalin were formulated and applied them topically, once daily, over the dorsal skin of mice and measured the mice hair length. On the 12th day of the study, the hair length of mice treated with finasteride and baicalin loaded into liposomes, glycerosomes, hyalurosomes, and glycerol-hyalurosomes, was 3.4 ± 0.4 mm, 3.7 ± 0.8 mm, 4.3 ± 0.4 mm, and 3.6 ± 0.5 mm, respectively. In addition, on the 21st day, treatment with the same formulations, caused 10.1 ± 0.9

mm, 9.8 ± 1.8 mm, 9.9 ± 1.4 mm, and 12.1 ± 1.6 mm hair growth, respectively. On the other hand, finasteride-only dispersion and liposome formulation managed to grow hair length up to 6.5 ± 0.9 mm and 8.1 ± 1.1 mm, 21 days after the beginning of the study.[112]

Rungseevijitprapa *et al.*[68] compared the hair growth stimulation ability of finasteride (1% w/v) proniosomes with finasteride (1% w/v) conventional solution and blank proniosomes (as the control group) after daily application on the dorsal skin of mice for four weeks. In contrast to finasteride conventional solution, the hair growth in the finasteride proniosomes-treated group was significantly improved compared with the control group.

The ability of minoxidil solution and cubosomal minoxidil was investigated to boost hair growth in Wistar rats. One mg/cm^2 of minoxidil 5 times/week was used and evaluated the hair growth using a 0-5 scoring system. After 3 weeks, the hair growth score of cubosomal minoxidil-treated rats was 4.2 ± 0.4, while the score of minoxidil solution-treated rats was 2.2 ± 0.8 and the control group received a 1.2 ± 0.4 score.[73]

Liu and coworkers administrated testosterone solution (5 mg/1 mL) topically in mice dorsal skin with the aim of inducing androgenic alopecia. Afterward, they shaved them and treated them with finasteride solution, minoxidil commercial solution (50 mg/1 mL), or niosomal finasteride twice daily. The regenerated hair weight in the mouse dorsal skin with the same area on the 28th day of the treatment presented the treatment performance quantitatively. The control group (non-alopecia-induced mice) demonstrated 56.4 mg regenerated hairs. The niosomal finasteride showed the most regeneration (49.4 mg) among treatments, which was more than the minoxidil group (44.1 mg) and the finasteride solution group (4.0 mg).[66]

Transfollicular

Transfollicular delivery can be a promising route for systemic absorption of drugs with low oral bioavailability. So far, the efficiency of olmesartan meoxomil and insulin in the treatment of hypertension and diabetes-induced rats has been studied.

In 2019, Albash *et al.*[72] induced hypertension in rats using methylprednisolone acetate (171.00 ± 4.00 mmHg) and compared the efficacy of transethosomal olmesartan medoxomil through the transfollicular delivery pathway to Angiosartan® 10 mg tablet. Transethosomes could maintain normal blood pressure values (127.50 ± 4.33 mmHg) up to 24 hours after administration. On the other hand, 8 hours after administration, angiotensin tablets failed (140.10 ± 6.40 mmHg) to keep the blood pressure at normal values (Figure 7).

The efficiency of transfollicular delivery of liposomal insulin with the aid of 1 hour of 0.45 mA/cm^2 iontophoresis, was evaluated on blood glucose levels in streptozocin-induced diabetic Sprague Dawley rats. Blood glucose levels of non-treated and diabetic rats were 123 ± 6 mg/dL and 403 ± 56 mg/dL. Intraperitoneal injection of 5 UI/kg dose of insulin in diabetic rats led to an immediate decrease in blood glucose level. Four hours after the injection, the blood glucose level started increasing, and 18 hours after the injection, it returned to the basal level. On the other hand, topical administration of liposomal insulin with iontophoresis slowly reduced blood glucose level and decreased to about 20% of basal level 18 hours after iontophoresis, and the effect remained till 24 hours after iontophoresis.[53]

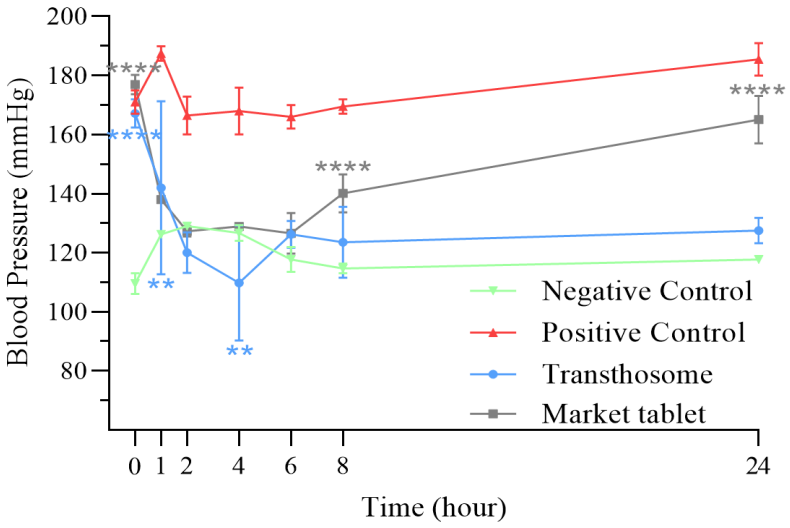

Figure 7. Influence of oral administration of Angiosartan® tablet and transfollicular administration of transethosomal Olmesartan on Blood pressure level of methylprednisolone acetate -induced hypertensive rats. Values are mean ± SD of blood pressure level (mmHg) (n = 6). *p < 0.05, **p < 0.01, ***p < 0.001, and ****p < 0.0001 as compared to the negative control group (Tukey's multiple comparisons test). Data adapted from Ref.72.

Vesicular Systems Follicular Delivery-improvement Methods

In order to improve follicular delivery of different formulations, massaging and iontophoresis techniques have been studied. Their efficiency for vesicular carrier-based formulations has been demonstrated as follows.

Iontophoresis

Iontophoresis improves the permeation of drugs through barriers employing enhanced diffusion, direct electrophoresis, or electroosmosis.[126-129] The use of iontophoresis can result in skin irritation or erythema at the application site when certain currents are applied. Studies have demonstrated that a current intensity below 0.5 mA/cm² is physiologically acceptable.[130-132]

Han *et al.*[125] investigated the iontophoresis effect on follicular delivery. They applied cationic liposomal and conventional formulations of Adriamycin topically on rat skin, with and without iontophoresis, and examined the drug transportation by fluorescence microscopy. It was indicated that 20 minutes of subsequent iontophoresis at 0.2 mA/cm² increased the fluorescence intensity of cationic liposomes from 85.7 to 214 and conventional solution from 33.0 to 52.5. The effect of iontophoresis on cationic liposomes was more intensive due to their increased positive charges and the doubled diffusive permeability. In 2011, Kajimoto et al. used iontophoresis to improve the penetration of insulin-loaded liposomes into Sprague Dawley rat follicles. They applied iontophoresis in 0.3 or 0.45 mA/cm² current densities for either 1 or 2 hours. It was revealed that 1 hour of 0.45 mA/cm² could improve penetration depth into follicles, significantly more than 1 or 2 hours of 0.3 mA/cm². On the other hand, continuing the 0.45 mA/cm² current for another hour significantly decreased the follicular delivery depth. The reduction might be caused by excluding the previously delivered liposomes from the follicles due to impairments such as long-time iontophoresis-induced inflammation.[53] Alvi *et al.*,[133] in 2021, demonstrated that iontophoresis with 0.2 mA/cm² current enhanced the accumulation of gold-coated curcumin-loaded liposomes within the skin pores. In addition, they indicated that extending iontophoresis time from 5 to 20 minutes improved its efficiency in drug accumulation.

It should be noted that although sonophoresis has offered promising applications in transdermal delivery, it is not applied to follicular delivery. A study by Sarheed *et al.*[134] indicated that utilizing sonophoresis for 45 seconds during transdermal delivery. It was reported that increasing sonophoresis time led to a decrease in follicular contribution in transdermal delivery. It was explained that ultrasound disrupts the topmost corneocytes in the stratum corneum, decreasing barrier function and partially blocking the follicular orifice, which reduces follicular penetration.

Massage

Massaging has been proven to increase the follicular penetration depth of different substances.[135,136] The safety and ease of the massaging process, compared to iontophoresis, make it more applicable and improve patient adherence. An *in-silico* simulation suggested that radial hair movement causes a flashing ratchet effect-like effect.[137] So far, massaging has been applied with the aim of enhancing the penetration of different liposomal vesicles, including transferosomes,[70] niosomes, liposomes, and invasomes.[59] Trauer *et al.*[59] demonstrated that 3 minutes of massaging could improve the penetrability of invasomes from 137.3 ± 26.5 µm to 698.8 ± 90.7 µm. In addition, the 3 minutes-massaging increased the penetration depth of liposomes from 93.2 ± 11.7 µm to 477.2 ± 61 µm. It means that although without massaging, both the liposomes and invasomes were not able to reach the bulge region or sebaceous gland, massaging enabled them to reach the target site.

Conclusion

In conclusion, vesicular carriers present a promising approach for enhancing follicular drug delivery. While conventional liposomes have shown limited efficacy due to their rigidity, deformable vesicles such as modified liposomes, transferosomes, niosomes, and invasomes exhibit greater potential for penetration through hair follicles. Techniques like topical hair massage and iontophoresis can further improve the penetrability of these vesicles.

Follicular delivery, as a non-invasive and patient-compliant topical route, holds significant potential for treating follicle-related disorders. The efficacy of vesicular carriers is further optimized through their adjustable particle size, enabling enhanced follicular delivery. Notably, current findings suggest that the transfollicular pathway plays a crucial role in transdermal delivery, making follicular delivery an attractive method for both topical treatments and systemic drug delivery.

The safety, non-toxic nature, and improved bioavailability of vesicular carriers, along with their superior elimination half-life compared to oral administration and intraperitoneal injection of plain drugs, make them an optimistic drug delivery option. Further research should explore the potential of vesicular drug delivery systems in the systemic delivery of various therapeutic agents and their application in different diseases. Moreover, investigating the follicular penetrability of other deformable vesicular carriers like menthosomes and flavosomes could yield valuable insights for future advancements in drug delivery.

Author Contributions

Mostafa Amirinejad: Conceptualization, Methodology, Formal Analysis, Data Curation, Writing - Original Draft. Atoosa Haghighizadeh: Formal Analysis Data Curation, Writing - Original Draft. Leila Etemad: Formal Analysis, Visualization, Writing - Review & Editing. Omid Rajabi:

Conceptualization, Project Administration, Supervision, Writing - Review & Editing.

Conflict of Interest

The authors claim that there is no conflict of interest.

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