毛囊靶向递药系统及其在痤疮和脱发治疗中的研究进展

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摘要: 皮肤附属器毛囊作为药物输送的新靶点和新途径受到诸多关注, 经皮渗透毛囊靶向递药系统的设计与开发对毛囊源性皮肤病如痤疮、脱发及毛囊炎等发挥直接高效的作用。本综述围绕毛囊的结构和生理功能、毛囊微环境、影响毛囊渗透的因素、纳米制剂促进经毛囊渗透的现状及表征毛囊靶向渗透的技术进行归纳, 并系统总结了毛囊靶向递药系统治疗痤疮和脱发的最新研究进展。最后, 探讨了毛囊靶向给药系统设计当前所面临的挑战。本综述可为毛囊源性皮肤病毛囊靶向给药系统设计提供思路与参考。

关键词: 毛囊靶向; 痤疮; 脱发; 纳米递药系统; 经皮渗透

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Advance of hair follicle targeted drug delivery systems in the treatment of acne and hair loss

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Abstract: Hair follicle (HF), one of the skin appendages, has received a lot of attention to be a new target and pathway for drug delivery. The development of hair follicle targeted drug delivery system (HFTDDS) through percutaneous permeation is particularly important for skin diseases derived from HF such as acne, hair loss, and folliculitis for their on-site action. This review describes the structure and physiological function of HF, the micro-environment of HF, and factors affecting HF permeation. Multiple nanoformulations used to improve the HF permeation and technologies to characterize the HF permeation were introduced. The latest advance of HFTDDS based on nanoformulations were systematically summarized and analyzed in the treatment of acne and hair loss. Finally, the challenges of formulating HFTDDS were discussed. The review is expected to provide some ideas and references for developing delivery systems for treating skin diseases derived from HF.

Key words: hair follicle targeted; acne; hair loss; nano-based drug delivery system; percutaneous permeation

毛囊 (hair follicle, HF) 为皮肤附属器, 是毛囊皮脂腺单位的一部分, 具有保护皮肤、分泌皮脂、生长毛发、调节体温、传递信息等生物学功能, 在创伤修复、皮肤微环境重塑过程也发挥关键作用。身体头面部毛囊占皮肤面积的10%, 而其他部位的毛囊面积仅占皮肤面积的0.1%以下[1]。毛囊是经皮给药的“输入口”之一, 也是药物在皮肤内的“蓄水池”, 对药物经皮递送具有重要作用。同时, 其在体表的位置、结构和周期性再生等功能使经毛囊给药治疗毛囊源性疾病如脱发、痤疮和毛囊炎等具独特优势[2]。毛囊靶向递药系统 (hair follicle targeted drug delivery systems, HFTDDS) 是载体经毛囊途径按疾病所需递送药物到毛囊的特定微环境发挥局部治疗作用的给药系统。HFTDDS的研究主要通过使用纳米载体递送小分子和大分子药物等进行毛囊靶向递药治疗毛囊相关疾患[3]; 随着毛囊生物学研究的发展, 经毛囊给药在基因治疗和免疫治疗中也

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显示出良好前景[4]。

本综述重点分析HFTDDS应用于痤疮和脱发的研究进展。毛囊皮脂腺单位是痤疮疾病的发源地，痤疮患病率排名全球第八，是常见的第二大皮肤病[5]；脱发疾病发生、发展影响着约2%的世界人口，其病因与毛囊的周期性活动息息相关，而毛囊干细胞的衰竭又是临床上定义脱发的另一重要致病因素[6,7]。临床上常用于治疗痤疮的药物主要有过氧化苯甲酰、阿达帕林等；治疗脱发的药物主要有非那雄胺和米诺地尔[8,9]。目前基于这些药物已上市的制剂对两大疾病治疗效果都不太理想，而且具较强的不良反应，因此，基于毛囊靶向的纳米给药系统应运而生。

目前，文献报道了多种纳米给药系统包括纳米粒、纳米胶束、纳米凝胶、纳米晶和脂质体等靶向毛囊及毛囊特定部位应用于痤疮和脱发的治疗[10]。这些纳米递药系统通过对尺寸大小的控制、功能化修饰、结合疾病微环境、辅助外界介质等不同技术对HFTDDS进行了合理的设计与优化，具有较好的临床转化价值。本综述主要总结了毛囊结构、生长周期和生理功能、影响毛囊渗透的多种因素及改善毛囊渗透的不同纳米给药系统类型，同时对表征毛囊靶向的定性、定量技术进行了概述。最后，系统总结了HFTDDS (纳米粒、脂质体、纳米胶束、纳米晶和纳米凝胶等) 应用于痤疮和脱发的研究近况 (图1)，展望了其所面临的机遇与挑战，为HFTDDS治疗痤疮和脱发的设计和开发提供参考。

1　毛囊的结构和药物作用的部位

毛囊是一个动态的微型器官，贯穿于皮肤的表皮和真皮，主要包括毛干 (hair shaft)、立毛肌 (arrector pili muscle) 和皮脂腺 (sebaceous gland) 等 (图2)。在空间结构上，毛囊自皮肤表面向下可分为5个区：漏斗部 (infundibulum，从皮肤表面到皮脂腺处)、峡部 (isthmus，从皮脂腺开口部以下至隆突处)、隆突部 (bulge，为立毛肌附着处，富含毛囊干细胞)、毛球上端或隆突底端 (suprabular) 及毛根部的毛球 (hair bulb)。毛球包裹着凹进的真皮毛乳头 (dermal dapilla)。其中漏斗部、峡部和隆突部为毛囊的恒定部分 (constant part)，一般不发生凋亡和再生；而隆突部以下为周期循环部分 (cyclic part)，受不同的信号通路、生长因子及细胞因子的调节而经历毛囊的不同生长周期而不断重塑[11,12]。皮脂腺靠近漏斗下部，通过分泌皮脂和油脂来滋养皮肤及毛发。毛囊自身具有一定的屏障特性，主要与毛囊上部组成结构 (漏斗部、皮脂腺和隆突部) 的功能相关[13]。毛囊漏斗部具有极大的表面积，协助表皮的角质层和颗粒层的生长，漏斗上部为致密角化的表皮，构成毛囊的主要渗透屏障，也是药物经皮给药在皮肤蓄积的储库。漏斗下部通常被认为是高度可渗透区域，是药物经皮渗透的主要入口。皮脂腺部位是一个潜在的亲脂类药物及脂质纳米制剂的主要治疗靶点，也是痤疮发病的主要部位和药物治疗的作用部位。位于皮脂腺下方的隆突部主要由具有高增殖、高分化能力的干细胞组成，负责毛囊的重建与再生，是基因治疗及再生医学

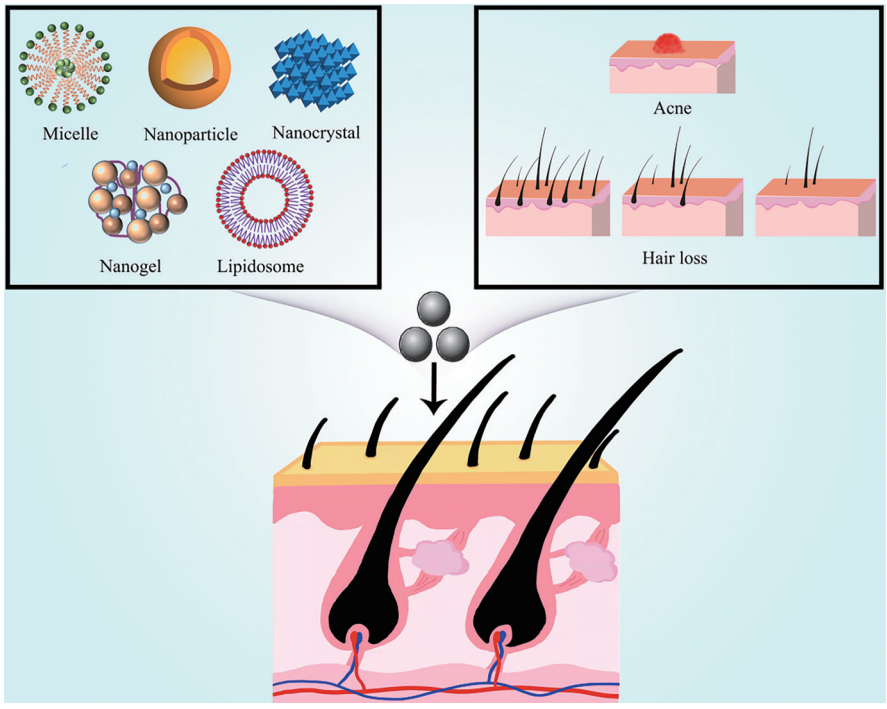

Figure 1　Schematic diagram of hair follicle targeted drug delivery systems for treating acne and hair loss

的作用靶点。整个毛囊上部周围有丰富的毛细血管和树突状细胞, 为药物经皮给药发挥全身作用或经皮免疫提供了基础; 同时, 又能通过免疫系统识别外源性物质, 并经血液系统及时清除, 以保护局部区域的生物安全[14]。毛囊下部毛球中的毛乳头是毛囊中发送和接收信号的诱导结构, 毛乳头细胞提供毛囊生长和分化必需的信号因子和营养支持并诱导毛囊再生。因此, 理想的抗脱发药物或给药系统应同时对隆突部的毛囊干细胞和毛球中的毛乳头细胞发挥作用。毛囊生长经历重复的周期性过程, 包括生长期 (anagen)、退行期 (catagen) 和休止期 (telogen)[10], 毛囊生长周期的异常变化是毛发生长疾病的主要因素[1]。抗脱发治疗的药物或给药系统主要是通过对毛囊生长周期的调控而发挥作用。

2　毛囊微环境

毛囊所处的环境及调控毛囊命运的各种信号分子构成了毛囊微环境, 毛囊的独特结构和组成决定了毛囊微环境, 且微环境的组成、变化与稳态均与毛囊周期、毛囊相关疾病病理生理及毛囊再生密切相关。首先, 毛囊微环境的组成与其自身结构相关, 如皮脂腺分泌脂质; 其次, 毛囊微环境的变化与毛囊周期相关, 毛囊周期受微环境中多种基因及信号通路如Wnt/β-连环蛋白 (β-catenin)、骨形态发生蛋白 (bone morphogenic protein, BMP)、音猬因子 (sonic hedgehog, SHH)、Notch、外异蛋白 (ectodysplasin-A, EDA)、Noggin、分泌型蛋白 (Dickkopf-1/4, DKK-1/4)、羟胺氧化酶 (hydroxylamine oxidase, Hox)、成纤维细胞生长因子 (fibroblast growth factor, FGF)、胰岛素样生长因子 1 (insulin-like growth factor-1, IGF-1)、血小板衍生生长因子 (platelet derived growth factor, PDGF)、转化生长因子 (transforming growth factor, TGF) 等[15]及结构 (毛乳头细胞、毛隆起部位等) 影响, 只有保持毛囊微环境完整、正常的动态变化, 才能保证毛囊进行正常的周期循环; 最后, 维持毛囊微环境的稳态也非常重要, 其与毛囊的再生及毛囊相关疾病的发生具有密切联系, 整个毛囊微环境的稳态都受毛囊干细胞、上皮细胞、胞外基质、信号通路等共同作用。例如, 干细胞的调控、自分化能力与毛乳头细胞的活力具有必然联系, 进而影响毛囊的再生; 同时这也是毛囊相关类疾病 (脱发) 的主要致病因素[16]。值得注意的是, 从毛囊表层到毛囊深部 (～500 μm) 的pH值改变 (6.5～7.4) 也是毛囊微环境的重要组成部分, 不同pH值对设计药物或递送系统具有指导意义[17]。

毛囊微环境中与毛发再生关系密切的因素包括毛囊中的激素水平、炎症水平、氧化应激水平、调控毛囊周期性变化的相关信号通路、毛囊的血供及毛囊干细

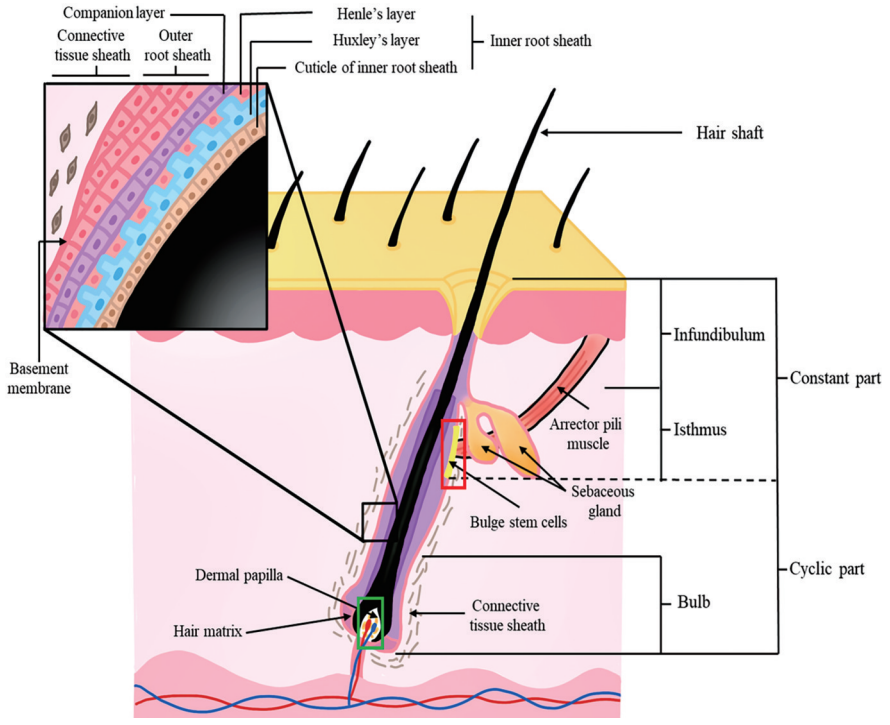

Figure 2　Schematic structure of the human hair follicle. The hair follicle contains constant part and cyclic part, separated by bulge. The constant part mainly includes infundibulum, isthmus, and bulge, and generally, apoptosis and regeneration did not occur. The cyclic part is partly regulated by different signaling pathways, growth factors, and cytokines, which constantly reshapes the growth cycles of hair follicles

胞的干性等。因此, 针对脱发的毛囊靶向递药系统设计, 首先可结合毛囊微环境针对模型药物进行选择与探索, 如美国食品药品监督管理局批准上市的药物米诺地尔具有很好的促进毛周血管再生的作用; 其次, 在脱发病理条件下, 其激素水平、炎症水平、氧化应激水平都属异常, 制备出自身具备抗炎、抗氧化特性的功能性纳米制剂就凸显出极大优势, 如 Yuan 等[18]制备出一种微针介导的二氧化铈递药系统, 具有清除毛囊部位过量活性氧和促进血管生成, 进一步重塑毛囊周围微环境, 从而达到治疗雄激素性脱发的效果; 再者, 利用外界辅助刺激 (光、热、超声等) 对调节毛囊周期、毛囊的血供及毛囊干细胞的干性也有积极效果, 这些光、热、超声可结合递药系统的设计构建联合多功能的给药系统。与痤疮发病相关的因素主要有毛囊的异常角化、痤疮丙酸杆菌的失衡、脂质过度分泌及相关炎症因子分泌等。针对这四大主要发病因素可知, 在痤疮的病理条件下, 毛囊微环境存在角化过度、细菌感染、脂质富集和炎症水平失衡的特点, 值得注意的是, 毛囊自身生理结构 (皮脂腺部位) 与痤疮病因发生发展紧密相连。因此, 对于治疗痤疮的递药系统设计主要体现在实现多管齐下、精准靶向、降低对非痤疮部位皮肤的刺激性与不良反应等方面。总之, 结合疾病自身的病因病理, 设计和优化递药系统, 改善毛囊微环境, 通过干预和调控使病理环境恢复至正常水平, 对遏制毛囊相关疾病的发生发展具有重要意义。

3 影响毛囊渗透的因素

药物经毛囊渗透受多重因素影响。一方面是毛囊自身因素, 主要包括: 毛囊密度、毛囊大小、毛囊活性、毛干直径等; 另一方面是所递送物质的理化性质、不同给药系统的类型、尺寸、是否有外界辅助刺激等; 其他还包括环境温度、湿度和皮肤部位预处理不同方式等因素共同影响[19,20]。表 1[21-29]总结了影响毛囊渗透的几种重要因素, 主要包括: 粒径影响及外界辅助刺激 (如光、离子导入和纳米粒表面功能化修饰等), 对所用皮肤种属来源也进行了总结。

药物或给药系统的粒径是影响药物毛囊渗透的首要因素[21,22]。Patzelt 等[21]考察了粒径大小对毛囊渗透深度的影响, 结果显示中等粒径 (400～700 nm) 范围内纳米粒能更好地渗透入猪皮毛囊中, 同时, 通过控制粒径大小可对猪皮毛囊内的不同部位进行选择性靶向。Friedman 等[23]利用荧光标记不同形状和尺寸的金纳米粒评价影响毛囊渗透的物理因素, 结果显示形态为星状且尺寸约为 250 nm 大小的纳米粒具有更好的渗透性, 且呈现出明显毛囊皮脂腺部位靶向性。

外界辅助刺激是影响毛囊渗透的重要因素。光照射广泛应用于辅助药物经毛囊渗透。Lee 等[24]利用二氧化碳点阵激光照射增强药物、大分子及纳米粒的皮内输送, 同时可通过调节激光功率和光斑数来控制渗透深度, 进一步增强毛囊输送, 并减少了对皮肤屏障的破坏。Busch 等[25]利用低功率长波紫外线 (UVA) 发光二极管 (LED) 照射猪毛囊实现了一种具有时空靶向性的可控毛囊递药释药系统, 2 min 内释药达到 50%, 且毛囊渗透深度可达 405～613 μm, 并具有良好的生物安全性。Kigasawa 等[26]利用脂质体包裹的功能性超氧化物歧化酶联合离子导入技术经毛囊递送进入活表皮层, 显著抑制紫外线照射诱导的皮肤损伤。此外, 离子导入技术作为一种非侵入技术, 是增强局部透皮递药的经典物理方法。Jain 等[30]制备阳离子类脂质体凝胶为载体, 利用离子导入法, 明显提高硝酸异山梨酯的经皮渗透, 同时扫描电子显微镜观察显示, 随着电流密度的增加, 大多数电流向毛囊区域渗透, 毛囊的孔径也明显增大。此外, 纳米粒表面功能化修饰也可促进药物经毛囊渗透。Mahmoud 等[31]利用金纳米棒表面功能性化修饰不同配体经皮递送给药, 结果表明聚苯乙烯修饰的疏水性金纳米棒在毛囊中累积量最高, 具有明显的毛囊靶向性, 与毛囊的亲脂特性相关; 而聚乙二醇修饰的中性金纳米棒累积在皮肤真皮层, 靶向皮肤深处, 与真皮的亲水性相关。总之, 毛囊渗透受多重因

Table 1 Different factors affecting the penetration depth of drugs in hair follicles (HFs). NPs: Nanoparticles; QDs: Quantum dots; CO_2: Carbon dioxide; IRA: Infrared A; AuNPs: Gold nanoparticles; BSA: Bovine serum albumin; UVA: Ultraviolet A

Nanoformulation	Size/nm	Factor	Maximum penetration depth/μm	Skin model	Ref.
NPs	122−1 000	Particle size	~1 100	Porcine	[21]
Nanoemulsions	80, 200, 500	Particle size	588	Mice	[22]
AuNPs	250	Shape	252	Human	[23]
Nanocrystal QDs	18	Fractional CO_2 laser	75	Nude mice	[24]
Nanocapsules	~700	UVA radiation	509 ± 104	Porcine	[25]
Liposomes	100−150	Iontophoresis	400	Mice	[26]
Particles	520	Protease	866 ± 62	Porcine	[27]
AuNPs-doped BSA microparticles	545 ± 87.5	IRA radiation	717.75 ± 186.51	Porcine	[28]
NPs	79, 89	Surface functionalization	1 400	Porcine	[29]

素影响, 毛囊靶向递药系统的设计与开发需考虑这些影响因素。

4　基于纳米的给药系统促进毛囊渗透

基于纳米给药系统用于毛囊靶向递药的设计主要包括: ① 利用纳米给药系统改善所递送药物的理化性质, 从而增强局部或体内的药物递送; ② 利用纳米给药系统克服皮肤/毛囊屏障; ③ 利用纳米给药系统在毛囊的蓄积性; ④ 根据毛囊微环境设计响应性纳米给药系统, 进一步增强毛囊靶向性。目前, 用于促进毛囊渗透的纳米给药系统主要包括: 纳米粒、纳米乳、胶束、脂质体、醇质体、固体脂质纳米粒、纳米晶和纳米凝胶等。表2[32-38]总结了不同纳米给药系统的类型、制备所用的主要材料、基本表征 (粒径和电位)、所用皮肤模型、渗透部位及用于毛囊渗透的主要优势。由表2可知, 纳米给药系统的毛囊靶向性大都依赖于其纳米尺寸的优势, 一般粒径在300 nm左右; 此外, 制备所需材料也是一大主要考虑要素, 目前的纳米给药系统大都由一些生物安全性好的高分子材料, 如聚乳酸 [poly(*D*,*L*-lactide), PLA]、聚己内酯 [poly(epsilon caprolactone), PCL]、聚乙烯醇 [poly(vinyl alcohol), PVA]、聚丙烯酸 [poly(acrylic acid), PAA] 等制备而成; 再者, 一些具备毛囊自身生理结构亲和能力或结合毛囊病理微环境响应性递药系统的构建也会进一步增强纳米制剂的毛囊靶向性; 同时, 皮肤模型种属来源的选择对考察递药系统的经皮渗透也有影响, 目前通常选择猪皮、人头皮、鼠皮等作为皮肤模型, 其中猪皮因其较好的可获得性及与人类皮肤的相似性而最为常用。最后, 纳米给药系统也可根据药物作用机制及疾病发病机制设计, 精确靶向至毛囊不同部位 (如漏斗部、皮脂腺单位、毛隆起、毛球等), 从而实现药物的高效递送及疾病的靶向治疗。

根据具体的临床目的可合理设计不同的纳米给药系统用于药物经毛囊渗透。按照上述毛囊的形态及作用靶点可知, 毛囊的漏斗部是最常适用于药物经毛囊渗透的靶部位, Pelikh等[39]将姜黄素制备成纳米晶制剂, 实现了毛囊漏斗部的靶向给药。毛囊的皮脂腺结构适用于聚合物纳米粒及脂质纳米载体的靶向给药。此外, 还包括与毛囊干细胞相关的毛囊隆起区、毛囊漏斗部周围与免疫研究相关的抗原提呈细胞区域, 通过靶向到具体部位实现精准递药。纳米给药系统的生物安全性及其与皮肤的生物相容性均需在设计给药系统的时候充分考虑, 才能在增强毛囊渗透的同时, 真正安全地将药物递送到毛囊疾患部位达到靶向治疗的目的。

5　表征毛囊靶向的定性、定量技术

近年来, HFTDDS设计与应用已成为一个重要的研究领域, 表征毛囊靶向的定性和定量的技术和手段

Table 2　Different nanoformulations promote drug penetration to HFs. PLA: Poly (*D*,*L*-lactide); PLO: Pluronic lecithin organogel; ROX: Roxithromycin; PCL: Poly(epsilon caprolactone); PVA: Poly(vinyl alcohol); CLZ: Clotrimazole; ECZ: Econazole nitrate; FLZ: Fluconazole; MPEG-hexPLA: Methoxy-poly(ethylene glycol)-hexyl substituted polylactide; mEGF: Mouse epidermal growth factor; DPPC: 1,2-Dipalmitoyl-*sn*-glycero-3-phosphatidylcholine; TPGS: *D*-*α*-Tocopherol polyethylene glycol 1000 succinate; PAA: Poly(acrylic acid); PNIPAm: Poly(*N*-isopropylacrylamide); IDCC: Indodicarbocyanine; NCs: Nanocrystals; SLMs: Solid lipid microparticles

Nanoformulation	Main constituent	Basic characterization	Skin model	Penetration site	Main advantage	Ref.
NPs	PLO, ROX, PCL, PVA	300 nm, −8 mV	Human scalp	Pilosebaceous unit	Using polymeric NPs formulated either into the aqueous suspension or semisolid topical formulation, can achieve preferential targeting to the pilosebaceous unit	[32]
NPs	PLA	150 nm, −20 mV	Porcine	Hair bulb	PLA NPs can effectively transport and release lipophilic and hydrophilic compounds into the HFs	[33]
Micelle	CLZ, ECZ, FLZ, MPEG-hexPLA	70−165 nm	Porcine, human	Hair follicle	Using MPEG-dihexPLA micelle formulations resulted in significantly higher drug deposition in both porcine and human skin	[34]
Ethosomes	mEGF, ethanol, DPPC	40 ± 10 nm	Mice	Pilosebaceous unit	The ethosomal system possesses enhanced topical drug delivery efficiency, could reach each site of the pilosebaceous unit	[35]
SLMs	Phosphatidylcholine, lecithin	/	Porcine ear	Infundibulum	SLMs dispersion is suitable for HFs targeting and the targeted release of active ingredient(s) at the site of action	[36]
NCs	Curcumin, TPGS, PAA	300 nm, −16 mV	Porcine ear	Infundibulum	The NCs are incorporated can have a tremendous influence on the dermal penetration efficacy and the ability to target the HFs	[37]
Nanogels	PNIPAm, hydroxyethyl cellulose, IDCC	600−700 nm	Porcine ear	Hair follicle	The depth of nanogel penetration was proportional to their sizes, and release the drug under the thermoresponsive stimuli	[38]

也得到发展, 用于确定、量化药物在毛囊的渗透, 主要分物理技术和药剂学手段。其中物理技术主要包括放射自显影术、激光多普勒血流仪[40]、共聚焦激光扫描显微镜[41]和共聚焦拉曼光谱[42], 物理技术表征的优点是可视化药物递药后靶向毛囊的具体部位和蓄积程度。药剂学手段主要包括: ① 利用离体和在体经皮渗透实验, 显微分离有毛囊皮肤和无毛囊皮肤, 比较药物在有毛囊皮肤和无毛囊皮肤的渗透情况[43]; ② 用聚合物材料或蜡人工选择性闭合毛囊, 然后进行经皮渗透实验[1], 比较药物经毛囊闭合与未闭合的皮肤渗透的差异; ③ 用胶带黏贴结合氰基丙烯酸酯剥离毛囊, 然后提取毛囊中的药物进行检测[44]。

物理技术主要用于定性, 主要借助显微镜进行直观观察纳米制剂毛囊靶向性。如 Sahle 等[38]使用吲哚二碳菁染料标记纳米凝胶, 香豆素 6 标记模型药物, 利用离体猪耳皮进行离体渗透实验后借助共聚焦激光扫描显微镜观察各成分在毛囊部位的蓄积情况, 以获得基于树枝状聚甘油和 *N*-异丙基丙烯酰胺设计的热响应纳米凝胶毛囊靶向递送药物的特性。这种方法的局限性主要在于对于无自发荧光特性的药物或制剂本身, 需小分子荧光材料进行替代或标记才能进行毛囊靶向的考察, 这可能会受限于药物自身的渗透特性, 且无法对蓄积在毛囊部位的成分进行精准定量。而药剂学手段主要应用于定量, 本课题组在利用猪皮进行离体经皮渗透实验后, 在显微镜下分离有毛囊区域和无毛囊区域, 从而比较药物在毛囊区域和非毛囊区域的渗透情况考察制剂的毛囊靶向性[43], 这种定量技术的优点是可准确定量药物在毛囊部位的蓄积量, 其主要局限性是对操作人员技术水平有较高的要求, 且需更高的时间成本。

通过上述技术或手段对毛囊靶向递药进行定性或定量研究, 有利于探究纳米递药系统在毛囊部位的命运, 更准确了解在体局部的药物分布。但值得注意的是, 目前用于研究毛囊渗透的动物在体模型建立仍有一定挑战, 不同动物的毛囊与人毛囊都存在一定的差异性, 猪皮的可获得性及其与人皮在分子组成及厚度比较接近, 因此常用猪皮研究 HFTDDS 的毛囊递药。进一步探究与论证稳定的、低差异性的动物毛囊模型对研究毛囊渗透具有重要意义。

6 毛囊靶向递药系统治疗痤疮

痤疮是一种毛囊皮脂腺单位的慢性炎症性疾病, 其发病因素包括雄激素引起的皮脂生成增加、毛囊过度角质化、炎症及痤疮丙酸杆菌定植等[45]。青少年痤疮发病率高达 20%[45]。目前常用过氧化苯甲酰、维甲酸和抗生素联用改善轻、中度痤疮; 口服异维 A 酸治疗重度痤疮, 但其治疗效果都不理想且具有较大不良反应。基于纳米的 HFTDDS 应用于痤疮治疗的优势主要有: ① 相对较小的载体尺寸能促进药物渗透到痤疮发病中心 (毛囊皮脂腺); ② 多功能型纳米系统的设计 (如联合光热和光动力疗法), 有利于抗痤疮药物的精准控制释放, 从而减少对非靶点部位的不良反应; ③ 纳米递药系统可通过“包装”抗痤疮药物, 达到缓释, 同时降低药物对皮肤的刺激性。通过对纳米递药系统的组成成分、尺寸大小及释放特性等方面进行优化促进新型抗痤疮递药系统的发展。

Brammann 等[46]通过将过氧化苯甲酰纳米晶体掺入阿达帕林固体脂质微粒, 显著提高了过氧化苯甲酰在毛囊部位的累积, 联合亲脂性阿达帕林本身具有的毛囊皮脂腺亲和性, 该给药系统实现了两药联用协同治疗痤疮的效果。此外, Gokce 等[8]利用氨基修饰带正电荷的树枝状大分子递送阿达帕林, 通过与细胞膜上呈负电荷的分子间相互作用, 实现了阿达帕林毛囊部位的靶向递送, 显著提高痤疮的治疗效果, 且呈现出良好的皮肤耐受性。Paithankar 等[47]利用金包裹二氧化硅微粒组成的混悬液注入耳前腺和猪皮脂腺, 通过外界辅助脉冲光照射, 明显促进了在毛囊皮脂腺部位的渗透与累积, 进一步有效治疗面部寻常痤疮。

在上述文献调研基础上, 表 3[8,46-51]总结了具有毛囊靶向的治疗痤疮的不同纳米给药系统类型、构成给药系统的主要成分、递送的药物及可能的毛囊靶向机制。

7 毛囊靶向递药系统治疗脱发

脱发是指由多种原因引起的身体正常生长部位的毛发脱落, 包括雄激素性脱发、斑秃及自身免疫性疾病、化疗及精神疾患等引起的脱发[52], 其中雄激素性脱发为主要脱发类型。雄激素性脱发的临床上治疗药物都存在一定的局限性, 如米诺地尔局部给药易引起心脏不适、接触性皮炎及面部多毛等; 口服非那雄胺会带来一定程度的男性性功能障碍等不良反应。基于纳米的毛囊靶向递药系统在增效减毒方面具有优势。

脂质载体为毛囊靶向递药系统的常见载体, Shamma 等[53]利用液体脂质纳米粒靶向递送螺内酯治疗脱发, 共聚焦激光扫描显微镜结果显示该制剂在毛囊部位显著聚集。此外, 外界辅助刺激 (如超声、磁、热等) 也能有效促进纳米递药系统的毛囊靶向能力。Liao 等[54]利用层层自组装白蛋白微泡递送米诺地尔, 在辅助超声能量刺激下, 明显促进毛发的生长, 缩短了治疗周期, 且在不造成皮肤损伤的情况下增加角质化毛干的直径和毛囊的大小。Fang 等[55]利用微针递送

Table 3　Hair follicle targeted drug delivery system in the treatment of acne. MPEG-dihexPLA: Methoxy-poly(ethylene glycol)-poly(hexyl-substituted lactic acid) copolymer; PSU: Pilosebaceous unit; PAMAM: Poly(amidoamine)

Nanoformulation	Main constituent	Drug	Targeting mechanism	Ref.
PAMAM dendrimer-based nanocarriers	PAMAM	Adapalene	Amine-terminated PAMAMs dendrimers interact with negatively charged molecules	[8]
Nanocrystals and SLMs	Phosphatidylcholine, poloxamer 407, poloxamer 188, lecithin, cholesterol, and stearic acid	Benzoyl peroxide and adapalene	Nano scales and lipophilicity of SLMs	[46]
Microparticles	Gold, silica	Gold coated silica	Assisted light stimulation	[47]
NPs	Ethyl cellulose, methyl cellulose	*α*-Mangostin	Appropriate particle size (400 nm)	[48]
Polymeric micelles	MPEG-dihexPLA	Retinoic acid	Interaction between micelles and PSU	[49]
Polymeric NPs	Delonix (DLX)	Isotretinoin	Appropriate particle size (230 nm)	[50]
NPs	Chitosan, hyaluronic acid	Clindamycin	Appropriate particle size (362 ± 19 nm/ 417 ± 9 nm)	[51]

介孔氧化铁封装米诺地尔, 在辅助磁−热刺激下, 与未进行任何处理的小鼠相比, 10 天后, 小鼠的毛发密度提高了 8 倍, 同时具有良好的生物安全性。Yang 等[56]利用毛发来源的角蛋白制备的微针共递送间充质干细胞衍生的外泌体和小分子药物 UK5099 实现了低剂量、高效果, 小鼠模型上 6 天内呈现明显的色素沉积及毛发再生。本课题组结合毛囊微环境中的脂质组成, 利用可溶性微针递送仿生脂质纳米载体负载非那雄胺, 显著增强了非那雄胺在毛囊部位的渗透与累积, 具有明显的促毛发再生效果, 为非那雄胺毛囊靶向递药系统设计提供了范例[43]。

在上述文献调研基础上, 本综述对具有毛囊靶向的治疗脱发 (雄激素性脱发和斑秃两种类型脱发) 的不同纳米给药系统的类型、纳米给药系统的主要组成、递送的药物及可能的毛囊靶向机制进行了总结 (表 4[9,18,43,53-72])。

8　总结与展望

毛囊作为皮肤附属器, 其发育、生长与周期循环都受毛囊微环境中的成分相互调控作用的影响。毛囊源性疾病与毛囊独特的结构和组成相关, 但可利用其独特的结构和组成设计 HFTDDS, 了解毛囊结构各部分的主要生理功能和微环境的组成有利于合理设计 HFTDDS。

纳米递药系统在近年来应用于各种疾病的靶向治疗 (如肿瘤、脑部疾病等) 显现出明显优势, 这也为 HFTDDS 带来了新机遇, 结合毛囊结构特异性及毛囊源性疾病的病理生理, 设计与优化合适的纳米递药系统以达到理想的毛囊靶向递送[73-75]。基于纳米的 HFTDDS 的合理设计需考虑以下几个方面: ① 紧密结合毛囊解剖结构和毛囊周期活动; ② 纳米制剂的类型、处方组成、形状和尺寸大小与经毛囊渗透深度的关系; ③ 药物从纳米制剂中的释放机制、靶向毛囊的微观部位、在毛囊中的滞留时间等; ④ 纳米递药系统与光、热、微针等多种技术的联用。深入探究这些问题可为 HFTDDS 设计提供理论指导。

此外, 对经毛囊渗透进行定性、定量研究可精准了解药物或纳米递药系统在毛囊微环境的作用部位。目前, 已有多种技术广泛应用于实验室或临床研究中检测经毛囊的渗透, 但仍存在一个明显的限制性因素, 即所用模型皮肤 (人、鼠背、猪耳) 之间存在一定的差异性, 如何建立完整的、系统的皮肤模型评价体系尤为重要[76,77]。再者, 还需进一步深入探讨毛囊靶向递药系统设计中, 各组织成分 (皮肤角质层、角蛋白等)、各种细胞 (毛囊漏斗部周围的免疫细胞等) 之间的相互作用机制, 以及在毛囊各部位的分布情况等[78]。

痤疮和脱发是与毛囊最相关的两大毛囊源性疾病, 其发病率也越来越高, 特别是脱发, 对不同年龄段的人都有影响。通过文献总结, 目前的 HFTDDS 治疗痤疮和脱发的给药系统主要集中在脂质纳米载体, 其处方优化主要针对的是粒径的控制 (与毛囊渗透部位相关)、表面修饰 (亲脂或亲水)、阴阳离子的结合和联合外界辅助刺激 (光、热、超声及微针) 等方面以提高药物经毛囊递送治疗痤疮和脱发。有趣的是, 毛囊自身及毛囊靶向药物递送系统的研究开发与再生医学也密切相关。作为一种微型器官, 毛囊自身具有促进组织修复的能力, 其含有的角蛋白成分也可作为组织再生的材料供体。同时, 以毛囊干细胞为靶点也是治疗毛囊源性疾病或皮肤再生医学的一个重要研究领域。总之, 了解毛囊的结构、生理功能和相关生物学信息, 合理、优化设计 HFTDDS, 对毛囊源性疾病的治疗或再生医学具有重要意义。

作者贡献: 熊莎是本文的主要完成人; 刘紫艺和肖婷协助图片和表格的整理; 徐月红负责本文的思路整理和文章修改工作。

利益冲突: 所有作者声明无任何利益冲突。

Table 4 Hair follicle targeted drug delivery system in the treatment of hair loss. NLCs: Nanostructured lipid carriers; SLN: Solid lipid nanoparticles; MBs: Microbubbles; PLGA: Poly(lactic-*co*-glycolic acid); PLLGA: Poly(*L*-lactide-*co*-glycolide); UK5099: 2-Cyano-3-(1-phenyl-1*H*-indol-3-yl)-2-propenoicacid; MSC: Mesenchymal stem cell; CRISPR-Cas9: Clustered, regularly interspaced, short palindromic repeats-CRISPR associated protein 9; sgRNA: Single-guide RNA; DPPE: 1,2-Dipalmitoyl-*sn*-glycero-3-phosphoethanolamine; DSPE-PEG-PDP: 1, 2-Distearoyl-*sn*-glycero-3-phosphoethanolamine-*N*-[PDP(polyethylene glycol)-2000]; DSPE-mPEG$_{2000}$: 1, 2-Distearoyl-*sn*-glycero-3-phosphoethanolamine-*N*-[methoxy (polyethylene glycol)-2000]; PVP: Polyvinylpyrrolidone; ROS: Reactive oxygen species; PGA: Poly(γ-glutamic acid); PDGF: Platelet-derived growth factor

Nanoformulation	Main constituent	Drug	Targeting mechanism	Ref.
NPs	PLLGA	Minoxidil	Appropriate particle size (100−150 nm) and lipophilicity of NPs	[9]
Microneedle patch	Hyaluronic acid, DSPE-mPEG$_{2000}$, PVP-K90	Ceria nanozyme	Assisted ROS-responsive stimulation	[18]
Microneedles and lipid nanocarriers	Glyceryl monostearate, squalene, and Poloxamer 188	Finasteride	Appropriate particle size (179.70 ± 2.84 nm) and lipophilicity	[43]
NLCs	Transcutol®, Compritol®, Tween 80, absolute ethanol, olive oil, and acetone	Spironolactone	Appropriate particle size (215.6 ± 20.4 nm) and lipophilicity of NLCs	[53]
Albumin-shelled MBs	Albumin, chitosan oligosaccharide lactate	Minoxidil	Assisted ultrasound stimulation	[54]
Microneedle patch	Mesoporous iron oxide nanoraspberry, PVA	Minoxidil	Assisted magnetic-thermal stimulation	[55]
Microneedle patch	Keratin and MSC-derived exosomes	UK5099	Autologous	[56]
SLN	Suppoire® NAI50, Montane® 80PHA, Montanox® 20PHA, and Phosal® 50PG	Minoxidil	Appropriate particle size (190 nm) and lipophilicity of SLN	[57]
NLCs	Squalene, cetyl palmitate, Forestall®, Phospholipon 80H®, and Pluronic F68	Diphencyprone	Appropriate particle size (208−265 nm) and lipophilicity of NLCs	[58]
Microemulsions	Oleic acid, poly-ethylene glycol 600, and span 20	Minoxidil	Pre-treating with alkali (ethanolamine) made the hair shaft to swell and open	[59]
NPs	PLGA	Finasteride	Appropriate particle size (300 nm)	[60]
Solid effervescent formulations	Anhydrous citric acid, tartaric acid, sodium bicarbonate, and saccharose	Minoxidil	Effervescent reaction	[61]
Ethosomes	Soya phosphatidylcholine, isopropylmyristate, oleic acid and thymol	Finasteride	Appropriate particle size (100−300 nm)	[62]
NPs	Methyl *p*-hydroxybenzoate, propyl *p*-hydroxybenzoate, and mannitol	Minoxidil	Appropriate particle size (90−300 nm)	[63]
Phospholipid vesicles	Lipoid® S75 and soybean lecithin	Co-loading finasteride and baicalin	Appropriate particle size (100 nm)	[64]
Nanoemulsions	Clove oil and Kolliphor® P188	Minoxidil	Appropriate particle size of nano-sized droplets (< 200 nm)	[65]
Nanocapsules	Poly-ε-caprolactone and formic acid	Latanoprost	Appropriate particle size (197.8 ± 1.2 nm) and assisted manual massage	[66]
Albumin-shelled MBs	Albumin and perfluoropropane	Minoxidil	Assisted ultrasound stimulation	[67]
Microbubble-nanoliposomal particle	Lecithin, cholesterol, DPPE, DPPC, DSPE-PEG-PDP	Cas9/sgRNA	Assisted ultrasound activated	[68]
Hydrogel NPs	PGA, chitosan	Herbal extract	Appropriate particle size (400 nm)	[69]
NPs	Squalene, hexadecyl palmitate, and anti-PDGF receptor β antibody	Minoxidil	Appropriate particle size (195 nm) and lipophilicity	[70]
Lipid nanocarrier	Squalene	Co-loading diphencyprone and minoxidil	Appropriate particle size (177 nm) and lipophilicity	[71]
Microbubbes	Lysozyme	Minoxidil	Assisted ultrasound stimulation	[72]

References

[1] Patzelt A, Lademann J. Drug delivery to hair follicles [J]. Expert Opin Drug Deliv, 2013, 10: 787-797.

[2] Blume, Peytavi U, Vogt A. Human hair follicle: reservoir function and selective targeting [J]. Br J Dermatol, 2011, 165: 13-17.

[3] Weiner N. Targeted follicular delivery of macromolecules *via* liposomes [J]. Int J Pharm, 1998, 162: 29-38.

[4] Vogt A, Mandt N, Lademann J, et al. Follicular targeting - a promising tool in selective dermatotherapy [J]. J Invest Dermatol Symp Proc, 2005, 10: 252-255.

[5] Ramkar S, Sah AK, Bhuwane N, et al. Nano-lipidic carriers as a tool for drug targeting to the pilosebaceous units [J]. Curr Pharm Des, 2020, 26: 3251-3268.

[6] Patel R, Prabhu P. Nanocarriers as versatile delivery systems for effective management of acne [J]. Int J Pharm, 2020, 579:

119140.

[7] Mehak, Singh K, Nanda R, et al. Recent advances in topical nanotechnological strategies for treatment of alopecia [J]. J Pharm Res Int, 2021, 33: 326-351.

[8] Gokce BB, Boran T, Calik FE, et al. Dermal delivery and follicular targeting of adapalene using PAMAM dendrimers [J]. Drug Delivery Transl Res, 2021, 11: 626-646.

[9] Takeuchi I, Hida Y, Makino K. Minoxidil-encapsulated poly (*L*-lactide-*co*-glycolide) nanoparticles with hair follicle delivery properties prepared using W/O/W solvent evaporation and sonication [J]. Biomed Mater Eng, 2018, 29: 217-228.

[10] Wosicka H, Cal K. Targeting to the hair follicles: current status and potential [J]. J Dermatol Sci, 2010, 57: 83-89.

[11] Mistriotis P, Andreadis ST. Hair follicle: a novel source of multipotent stem cells for tissue engineering and regenerative medicine [J]. Tissue Eng Part B, 2013, 19: 265-278.

[12] Kiani MT, Higgins CA, Almquist BD. The hair follicle: an underutilized source of cells and materials for regenerative medicine [J]. ACS Biomater Sci Eng, 2018, 4: 1193-1207.

[13] Patzelt A, Lademann J. Recent advances in follicular drug delivery of nanoparticles [J]. Expert Opin Drug Deliv, 2020, 17: 49-60.

[14] Costa C, Cavaco-Paulo A, Matama T. Mapping hair follicle-targeted delivery by particle systems: what has science accomplished so far? [J]. Int J Pharm, 2021, 610: 121273.

[15] Cui X, Zeng WH, Xia Y. Advances in molecular mechanisms regulating the development and cycling of hair follicles [J]. Chin J Derm Venereol (中国皮肤性病学杂志), 2019, 33: 1081.

[16] Luengo J, Schneider M, Schneider AM, et al. Human skin permeation enhancement using PLGA nanoparticles is mediated by local pH changes [J]. Pharmaceutics, 2021, 13: 1608-1622.

[17] Dimde M, Sahle FF, Wycisk V, et al. Synthesis and validation of functional nanogels as pH-sensors in the hair follicle [J]. Macromol Biosci, 2017, 17: 1600505.

[18] Yuan A, Xia F, Bian Q, et al. Ceria nanozyme-integrated microneedles reshape the perifollicular microenvironment for androgenetic alopecia treatment [J]. ACS Nano, 2021, 15: 13759-13769

[19] Mak WC, Richter H, Patzelt A, et al. Drug delivery into the skin by degradable particles [J]. Eur J Pharm Biopharm, 2011, 79: 23-27.

[20] Gorzelanny C, Mess C, Schneider SW, et al. Skin barriers in dermal drug delivery: which barriers have to be overcome and how can we measure them? [J]. Pharmaceutics, 2020, 12: 684-715.

[21] Patzelt A, Richter H, Knorr F, et al. Selective follicular targeting by modification of the particle sizes [J]. J Control Release, 2011, 150: 45-48.

[22] Su R, Fan W, Yu Q, et al. Size-dependent penetration of nanoemulsions into epidermis and hair follicles: implications for transdermal delivery and immunization [J]. Oncotarget, 2017, 8: 38214-38226.

[23] Friedman N, Dagan A, Elia J, et al. Physical properties of gold nanoparticles affect skin penetration *via* hair follicles [J]. Nanomed Nanotechnol Biol Med, 2021, 36: 102414.

[24] Lee WR, Shen SC, Al-Suwayeh SA, et al. Skin permeation of small-molecule drugs, macromolecules, and nanoparticles mediated by a fractional carbon dioxide laser: the role of hair follicles [J]. Pharm Res, 2013, 30: 792-802.

[25] Busch L, Avlasevich Y, Zwicker P, et al. Release of the model drug SR101 from polyurethane nanocapsules in porcine hair follicles triggered by LED-derived low dose UVA light [J]. Int J Pharm, 2021, 597: 120339.

[26] Kigasawa K, Miyashita M, Kajimoto K, et al. Efficient intradermal delivery of superoxide dismutase using a combination of liposomes and iontophoresis for protection against UV-induced skin damage [J]. Biol Pharm Bull, 2012, 35: 781-785.

[27] Mak WC, Patzelt A, Richter H, et al. Triggering of drug release of particles in hair follicles [J]. J Control Release, 2012, 160: 509-514.

[28] Lademann J, Richter H, Knorr F, et al. Triggered release of model drug from AuNP-doped BSA nanocarriers in hair follicles using IRA radiation [J]. Acta Biomater, 2016, 30: 388-396.

[29] Al Mahrooqi JH, Khutoryanskiy VV, Williams AC. Thiolated and PEGylated silica nanoparticle delivery to hair follicles [J]. Int J Pharm, 2021, 593: 120130.

[30] Jain S, Chaudhari BH, Swarnakar NK. Preparation and characterization of niosomal gel for iontophoresis mediated transdermal delivery of isosorbide dinitrate [J]. Drug Deliv Transl Res, 2011, 1: 309-321.

[31] Mahmoud NN, Alkilany AM, Dietrich D, et al. Preferential accumulation of gold nanorods into human skin hair follicles: effect of nanoparticle surface chemistry [J]. J Colloid Interface Sci, 2017, 503: 95-102.

[32] Glowka E, Wosicka-Frackowiak H, Hyla K, et al. Polymeric nanoparticles-embedded organogel for roxithromycin delivery to hair follicles [J]. Eur J Pharm Biopharm, 2014, 88: 75-84.

[33] Fernandes B, Silva R, Ribeiro A, et al. Improved poly (*D*, *L*-lactide) nanoparticles-based formulation for hair follicle targeting [J]. Int J Cosmet Sci, 2015, 37: 282-290.

[34] Bachhav YG, Mondon K, Kalia YN, et al. Novel micelle formulations to increase cutaneous bioavailability of azole antifungals [J]. J Control Release, 2011, 153: 126-132.

[35] Xing XJ, Yang L, You Y, et al. Study of the biological function and penetration pathways of the mouse epidermal growth factor ethosomal delivery system [J]. Exp Dermatol, 2011, 20: 945-947.

[36] Brammann C, Bornemann C, Kannewurf R, et al. Solid lipid microparticles for hair follicle targeting of adapalene and benzoyl peroxide - release through targeted erosion [J]. J Drug Deliv Sci Technol, 2020, 60: 101990.

[37] Pelikh O, Eckert RW, Pinnapireddy SR, et al. Hair follicle targeting with curcumin nanocrystals: influence of the formulation properties on the penetration efficacy [J]. J Control Release, 2021, 329: 598-613.

[38] Sahle FF, Giulbudagian M, Bergueiro J, et al. Dendritic polyglycerol and *N*-isopropylacrylamide based thermoresponsive nanogels as smart carriers for controlled delivery of drugs through the hair follicle [J]. Nanoscale, 2017, 9: 172-182.

[39] Pelikh O, Keck CM. Hair follicle targeting and dermal drug delivery with curcumin drug nanocrystals-essential influence of excipients [J]. Nanomaterials, 2020, 10: 2323-2348.

[40] Vandersee S, Erdmenger U, Patzelt A, et al. Significance of the follicular pathway for dermal substance penetration quantified by laser Doppler flowmetry [J]. J Biophotonics, 2016, 9: 276-281.

[41] Subongkot T, Wonglertnirant N, Songprakhon P, et al. Visualization of ultradeformable liposomes penetration pathways and their skin interaction by confocal laser scanning microscopy [J]. Int J Pharm, 2013, 441: 151-161.

[42] Saar BG, Contreras-Rojas LR, Xie XS, et al. Imaging drug delivery to skin with stimulated Raman scattering microscopy [J]. Mol Pharm, 2011, 8: 969-975.

[43] Cao S, Wang Y, Wang M, et al. Microneedles mediated bioinspired lipid nanocarriers for targeted treatment of alopecia [J]. J Control Release, 2021, 329: 1-15.

[44] Cunha-Filho M, Rocha JL, Duarte NCB, et al. Development of a reversed-phase high-performance liquid chromatographic method for the determination of propranolol in different skin layers [J]. Biomed Chromatogr, 2021, 35: e4987.

[45] Williams HC, Dellavalle RP, Garner S. Acne vulgaris [J]. Lancet, 2012, 379: 361-372.

[46] Brammann C, Mueller-Goymann CC. Incorporation of benzoyl peroxide nanocrystals into adapalene-loaded solid lipid microparticles: part I - nanocrystalline benzoyl peroxide [J]. Int J Pharm, 2019, 564: 171-179.

[47] Paithankar DY, Sakamoto FH, Farinelli WA, et al. Acne treatment based on selective photothermolysis of sebaceous follicles with topically delivered light-absorbing gold microparticles [J]. J Invest Dermatol, 2015, 135: 1727-1734.

[48] Pan-In P, Wongsomboon A, Kokpol C, et al. Depositing alpha-mangostin nanoparticles to sebaceous gland area for acne treatment [J]. J Pharmacol Sci, 2015, 129: 226-232.

[49] Lapteva M, Moeller M, Gurny R, et al. Self-assembled polymeric nanocarriers for the targeted delivery of retinoic acid to the hair follicle [J]. Nanoscale, 2015, 7: 18651-18662.

[50] Ogunjimi AT, Chahud F, Lopez R. Isotretinoin-Delonix polymeric nanoparticles: potentials for skin follicular targeting in acne treatment [J]. Int J Pharm, 2021, 610: 121217.

[51] Tolentino S, Pereira MN, Cunha-Filho M, et al. Targeted clindamycin delivery to pilosebaceous units by chitosan or hyaluronic acid nanoparticles for improved topical treatment of acne vulgaris [J]. Carbohydr Polym, 2021, 253: 117295.

[52] Willems A, Sinclair R. Alopecias in humans: biology, pathomechanisms and emerging therapies [J]. Vet Dermatol, 2021, 32: 596-e159.

[53] Shamma RN, Aburahma MH. Follicular delivery of spironolactone *via* nanostructured lipid carriers for management of alopecia [J]. Int J Nanomed, 2014, 9: 5449-5460.

[54] Liao AH, Lu YJ, Lin YC, et al. Effectiveness of a layer-by-layer microbubbles-based delivery system for applying minoxidil to enhance hair growth [J]. Theranostics, 2016, 6: 817-827.

[55] Fang JH, Liu CH, Hsu RS, et al. Transdermal composite microneedle composed of mesoporous iron oxide nanoraspberry and PVA for androgenetic alopecia treatment [J]. Polymers (Basel), 2020, 12: 1392.

[56] Yang G, Chen Q, Wen D, et al. A Therapeutic microneedle patch made from hair-derived keratin for promoting hair regrowth [J]. ACS Nano, 2019, 13: 4354-4360.

[57] Padois K, Cantieni C, Bertholle V, et al. Solid lipid nanoparticles suspension *versus* commercial solutions for dermal delivery of minoxidil [J]. Int J Pharm, 2011, 416: 300-304.

[58] Lin YK, Al-Suwayeh SA, Leu YL, et al. Squalene-containing nanostructured lipid carriers promote percutaneous absorption and hair follicle targeting of diphencyprone for treating alopecia areata [J]. Pharm Res, 2013, 30: 435-446.

[59] Maitra M, Goyal AK, Rath G. A novel approach for follicular delivery of minoxidil for treatment of alopecia [J]. J Drug Deliv Sci Technol, 2017, 41: 113-123.

[60] Roque LV, Dias IS, Cruz N, et al. Design of finasteride-loaded nanoparticles for potential treatment of alopecia [J]. Skin Pharmacol Physiol, 2017, 30: 197-204.

[61] Pereira MN, Schulte HL, Duarte N, et al. Solid effervescent formulations as new approach for topical minoxidil delivery [J]. Eur J Pharm Sci, 2017, 96: 411-419.

[62] Wilson V, Siram K, Rajendran S, et al. Development and evaluation of finasteride loaded ethosomes for targeting to the pilosebaceous unit [J]. Artif Cells Nanomed Biotechnol, 2018, 46: 1892-1901.

[63] Nagai N, Iwai Y, Sakamoto A, et al. Drug delivery system based on minoxidil nanoparticles promotes hair growth in C57BL/6 mice [J]. Int J Nanomed, 2019, 14: 7921-7931.

[64] Mir-Palomo S, Nacher A, Ofelia Vila-Buso MA, et al. Co-loading of finasteride and baicalin in phospholipid vesicles tailored for the treatment of hair disorders [J]. Nanoscale, 2020, 12: 16143-16152.

[65] Cardoso SA, Barradas TN. Developing formulations for drug follicular targeting: nanoemulsions loaded with minoxidil and clove oil [J]. J Drug Deliv Sci Technol, 2020, 59: 101908.

[66] Oliveira ACS, Oliveira PM, Cunha-Filho M, et al. Latanoprost loaded in polymeric nanocapsules for effective topical treatment

of alopecia [J]. AAPS PharmSciTech, 2020, 21: 305-312.

[67] Liao AH, Lin KH, Chuang HC, et al. Low-frequency dual-frequency ultrasound-mediated microbubble cavitation for transdermal minoxidil delivery and hair growth enhancement [J]. Sci Rep, 2020, 10: 4338.

[68] Ryu JY, Won EJ, Lee HAR, et al. Ultrasound-activated particles as CRISPR/Cas9 delivery system for androgenic alopecia therapy [J]. Biomaterials, 2020, 232: 119736.

[69] Kim HS, Kwon HK, Lee DH, et al. Poly(γ -glutamic acid)/chitosan hydrogel nanoparticles for effective preservation and delivery of fermented herbal extract for enlarging hair bulb and enhancing hair growth [J]. Int J Nanomed, 2019, 14: 8409-8419.

[70] Aljuffali IA, Pan TL, Sung CT, et al. Anti-PDGF receptor beta antibody-conjugated squarticles loaded with minoxidil for alopecia treatment by targeting hair follicles and dermal papilla cells [J]. Nanomed Nanotechnol Biol Med, 2015, 11: 1321-1330.

[71] Aljuffali IA, Sung CT, Shen FM, et al. Squarticles as a lipid nanocarrier for delivering diphencyprone and minoxidil to hair follicles and human dermal papilla cells [J]. AAPS J, 2014, 16: 140-150.

[72] Liao AH, Huang YJ, Chuang HC, et al. Minoxidil-coated lysozyme-shelled microbubbes combined with ultrasound for the enhancement of hair follicle growth: efficacy *in vitro* and *in vivo* [J]. Front Pharmacol, 2021, 12: 668754.

[73] Yan WL, Lang TQ, Yin Q, et al. Progress on active tumor-targeting nano drug delivery systems for improving tumor immunotherapy [J]. Acta Pharm Sin (药学学报), 2022, 57: 46-63.

[74] Huang MY, Yang X, Xing JF, et al. Strategies for enhancing nanoscale brain targeting drug delivery [J]. Acta Pharm Sin (药学学报), 2019, 54: 629-637.

[75] Chen LQ, Shen XR, Huang Y. Research progress of endoplasmic reticulum targeting drug delivery system for anti-tumor immunotherapy [J]. Acta Pharm Sin (药学学报), 2022, 57: 76-84.

[76] Knorr F, Patzelt A, Darvin ME, et al. Penetration of topically applied nanocarriers into the hair follicles of dog and rat dorsal skin and porcine ear skin [J]. Vet Dermatol, 2016, 27: 256-e60.

[77] Raber AS, Mittal A, Schaefer J, et al. Quantification of nanoparticle uptake into hair follicles in pig ear and human forearm [J]. J Control Release, 2014, 179: 25-32.

[78] Vogt A, Rancan F, Ahlberg S, et al. Interaction of dermatologically relevant nanoparticles with skin cells and skin [J]. Beilstein J Nanotechnol, 2014, 5: 2363-2373.