基于纳米技术的口腔黏膜给药系统

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摘要: 口腔黏膜给药具有药物吸收迅速、无首过效应、患者依从性好等优点。但药物溶解少、唾液携带药物进入胃肠、黏膜存在生理屏障等因素可能影响药物的黏膜渗透和生物利用度。纳米技术应用于药物口腔黏膜给药, 可克服上述不利因素, 获得高效吸收效果。本综述阐述了口腔黏膜生理结构及影响药物口腔黏膜吸收的因素, 汇总了脂质体、固体脂质纳米粒、纳米结构脂质载体、纳米乳、聚合物纳米粒、聚合物胶束、纳米混悬剂等纳米技术在口腔黏膜给药中的应用及促进药物吸收机制, 总结了目前研究存在的主要问题, 对纳米口腔黏膜给药系统应用前景进行了展望。

关键词: 口腔黏膜; 纳米技术; 脂质体; 纳米粒; 纳米乳

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Oral mucosal drug delivery system based on nano technology

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Abstract: Oral mucosal drug delivery has the advantages of rapid drug absorption, no first-pass effect and good patient compliance. However, factors such as low drug dissolution, saliva carrying the drug into the gastrointestinal tract and the existence of physiological barriers in the mucosa may affect the mucosal permeation and bioavailability of the drug. Nanotechnology applied to drug oral mucosa delivery can overcome the above disadvantages and obtain efficient absorption effect. This paper describes the physiological structure of oral mucosa and the factors affecting the absorption of drugs in oral mucosa, reviews the application of nanotechnology such as liposomes, solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsions, polymer nanoparticles, polymer micelles and nanohybrid suspensions in oral mucosal drug delivery and the mechanism of promoting drug absorption, summarizes the main problems of current research, and gives an outlook on the application of nano oral mucosal drug delivery system. The main problems of current research are summarized, and the prospects for the application of nano oral mucosal drug delivery systems are discussed.

Key words: oral mucosa; nanotechnology; liposome; nanoparticle; nanoemulsion

口腔黏膜给药是指药物经口腔黏膜直接吸收并通过颈内静脉进入体循环发挥药效, 特别适用于首过效应明显和口服生物利用度低的药物, 对酸、酶敏感的蛋白质、多肽和核酸类药物给药。药物经口腔黏膜吸收快速, 可用于急症治疗[1]。目前国内外已有多个口腔黏膜制剂上市, 包括盐酸丁丙诺啡舌下片、盐酸纳洛酮舌下片、枸橼酸芬太尼口腔贴片、复方庆大霉素膜和复方氯己定地塞米松膜等[2]。口腔黏膜给药系统被制药行业广泛关注, 但其研发存在有效吸收面积小、生理屏障、药物停留时间短及药物理化性质各异等问题[3]。近年来纳米技术飞速发展, 尤其新型纳米材料的出现

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为药物递送提供了新思路、新方法。而纳米递送系统因其具有亚微米粒径和独特的物理化学性质，可有效改善药物在口腔的溶出与释放；提高药物穿透黏液层的扩散速率；增加蛋白、多肽及核酸类药物在口腔黏膜的递送[4-6]。目前，已有多种纳米递药技术用于口腔黏膜药物递送且呈现逐年增长的趋势，如脂质体 (liposome, LPS)、固体脂质纳米粒 (solid lipid nanoparticle, SLN)、纳米结构脂质载体 (nanostructured lipid carrier, NLC)、纳米乳 (nanoemulsion, NE)、聚合物纳米粒 (polymer nanoparticle, PLNP)、聚合物胶束 (polymeric micelle, PM)、纳米混悬剂 (nanosuspension, NS) 等。本综述在简要概述口腔黏膜给药系统及影响药物黏膜吸收因素的基础上，系统汇总了基于纳米递送技术的口腔黏膜给药系统的研究进展及纳米递送技术促进药物口腔黏膜吸收的作用机制，并总结分析其存在的主要问题，以期促进纳米递送技术在口腔黏膜给药系统中的应用与发展。

1 口腔黏膜生理结构特点

口腔黏膜从外到内是由上皮层、基底膜及固有层和黏膜下层组成的结缔组织构成[7] (图 1)。其厚度因部位而异：颊部黏膜厚度在 500～800 μm，硬腭、口底、舌腹和牙龈的黏膜厚度在 100～200 μm[8]。黏膜最外层上皮细胞的角化程度也随口腔中的位置而变化，易受机械应力的牙龈和硬腭部位是角质化的，而颊部和舌下区域是非角质化的[9]。与角质化上皮细胞相比，非角质化细胞对外源性化合物的渗透性更高[10]。口腔中不同部位的黏膜渗透性由高到低依次为舌下 > 颊 > 硬腭、牙龈。

2 口腔黏膜给药系统

口腔黏膜给药系统是指制剂作用于口腔部位发挥局部治疗或通过口腔黏膜直接吸收进入体循环发挥全身治疗的一种新型给药系统，已被视为常规口服和注射给药的一种有效替代给药途径[11,12]。口腔生理环境温和，pH 值近中性且酶活性较低，药物黏膜吸收无肝脏首过代谢，具有给药方便、易于去除、患者依从性高的特点[4]。口腔黏膜的主要给药部位为舌下和颊部，其中舌下黏膜薄且非角质化，渗透性强于颊黏膜是速效药的首选给药部位，而颊黏膜的给药面积大且易于接触，给药方便且易于去除，其表面存在的黏液也具有很好的黏附性，是缓控释制剂给药的理想选择[13-15]。另外，与其他黏膜相比，口腔黏膜不易损伤、细胞更新修复快，具有一定的渗透性、坚固性和较强的抗机械刺激性，对潜在的过敏原也具有更强的耐受性，能减少给药带来的不可逆刺激或损伤[16]。

目前，口腔黏膜已被广泛研究用于口腔的局部治疗与强效肽、蛋白质及其他在胃肠道中受肝脏代谢和酶促降解影响的活性药物的全身递送[17]。以口腔颊部和舌下给药为例，在 PubMed 数据库中检索从 2000～2022 年发表的关于颊部和舌下给药的相关论文，其数量呈逐年增长趋势。基于口腔黏膜的局部或全身给药的应用涉及领域广泛：用于局部治疗的研究有口腔念珠菌病[18]、口腔癌[19]、伤口愈合[20]和无针麻醉[21]等；用于全身治疗的研究有糖尿病[22]、心血管类疾病[23]及其他抗真菌[24]、抗病毒[25]和疫苗[26]等。此外，适用于口腔黏膜的剂型也非常多，如黏附片、黏附膜、贴剂、凝胶剂、喷雾剂和漱口剂等。

2.1 影响药物口腔黏膜递送的因素

2.1.1 生理因素 影响药物口腔黏膜递送的生理因素主要包括黏膜渗透性、黏液和唾液等。口腔不同区域黏膜上皮角质化水平及厚度不同，黏膜渗透性不同 (表 1)。黏膜上皮约 1/3 处的颗粒层细胞间隙存在由膜被颗粒排出的脂质，是药物黏膜吸收最主要的渗透屏障[27]。唾液的分泌能促进药物释放，但唾液的冲刷会导致药物流失，不利于药物的黏膜滞留与吸收；并且唾液 pH 的变化会影响药物的解离而影响药物的黏膜渗透。黏蛋白生理条件下带负电荷，与黏液共同在上皮

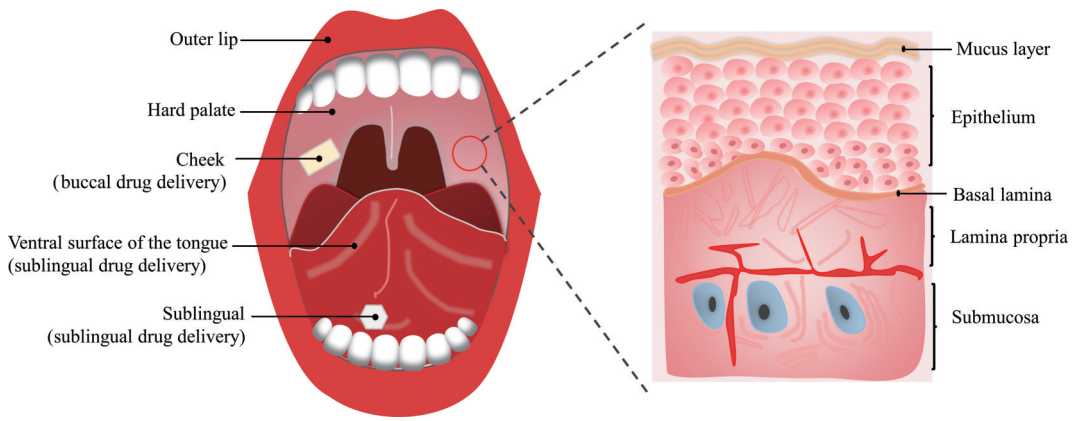

Figure 1 Schematic diagram of the physiological structure of the oral mucosa

细胞表面形成凝胶层, 发挥屏障作用, 阻碍药物吸收[28], 但其黏附作用能延长药物在黏膜的滞留时间, 有利于药物的黏膜吸收。此外, 唾液中的淀粉酶及黏液中的酯酶、氨肽酶、羧肽酶等构成口腔环境的酶屏障, 会导致药物的代谢降解, 影响药物吸收。表1总结了部分口腔黏膜给药部位在药物递送方面的生理特征[29,30]。

2.1.2 药物因素 药物自身固有的理化性质如分子质量、溶解度、油水分配系数、解离度等会影响药物的口腔黏膜的吸收。理想的适于口腔黏膜递送的药物应具备以下理化性质: 分子质量 < 800 Da, 溶解度 > 1 mg·mL^{-1}, Log*P* 值 (辛醇/水) > 2.0, 有效剂量 < 10 mg·d^{-1}, 饱和水溶液的pH值为5～9, 对黏膜无刺激性[31]。然而, 大多数药物不能同时具备所有这些性质, 如溶解度低的药物在口腔唾液中的释放少, 限制了其黏膜吸收; 而溶解度较大的药物, 脂溶性差, 不易透过脂质黏膜。此外, 药物与口腔黏膜的相互作用如静电吸附 (带正电荷的药物与带负电荷的黏蛋白) 会影响药物扩散和吸收; 药物的结晶度、稳定性、给药剂量等也会影响药物吸收。不过随着一些吸收促进剂、物理促渗技术及纳米递药技术等的应用, 上述影响已不再是绝对的限制条件。

3 纳米递送技术在口腔黏膜给药中的应用研究

纳米递药技术的发展有效解决了药物递送中存在的问题如药物水溶性差、生物利用度低、药物选择性差、毒副作用明显等。近年来, LPS、SLN、NLC、NE、PLNP、PM、NS等多种纳米递药技术在口腔黏膜给药中广泛应用[32]。这些纳米递药技术能显著改善难溶性药物的溶解与溶出, 增强药物的黏膜黏附及促进药物的黏膜渗透与吸收, 从而提高生物利用度[28,33]。图2和表2[34-49]总结了部分纳米递药技术在口腔黏膜给药中的应用研究。

3.1 LPS

LPS是一种由天然或合成磷脂组成的微型囊泡状颗粒, 通常含有磷脂酰胆碱和胆固醇等生物相容性脂质, 具有良好的组织耐受性, 广泛应用于各种无创途径 (口服、透皮、鼻腔和口腔途径) 的药物递送[50,51]。LPS既能包封亲水性药物 (内水腔内), 也能包载亲脂性药物 (磷脂双分子层内)[34,52]; 其脂质双层与细胞膜结构相同, 可与细胞膜融合, 从而显著增强药物的黏膜渗透, 已用于多种药物的口腔黏膜递送, 如难溶性药物卡维地洛[53]、水溶性药物维生素B6[54]及生物大分子药物胰岛素[34]。与对照组相 (混悬液或溶液) 比, 卡维地洛LPS的口腔黏膜渗透增加了42%, 维生素B6 LPS增

Table 1 Physiological characteristics of oral mucosa in drug delivery

Tissue and structure	Turnover time/day	Surface area/cm^2	Permeability	Residence time	Blood flow
Buccal	5-7	50.2 ± 2.9	Intermediate	Intermediate	20.25
Floor of mouth-sublingual	20	26.5 ± 4.2	Very good	Poor	101.60
Gingival	–	–	Poor	Intermediate	39.08
Palatal	24	20.1 ± 1.9	Poor	Very good	13.94

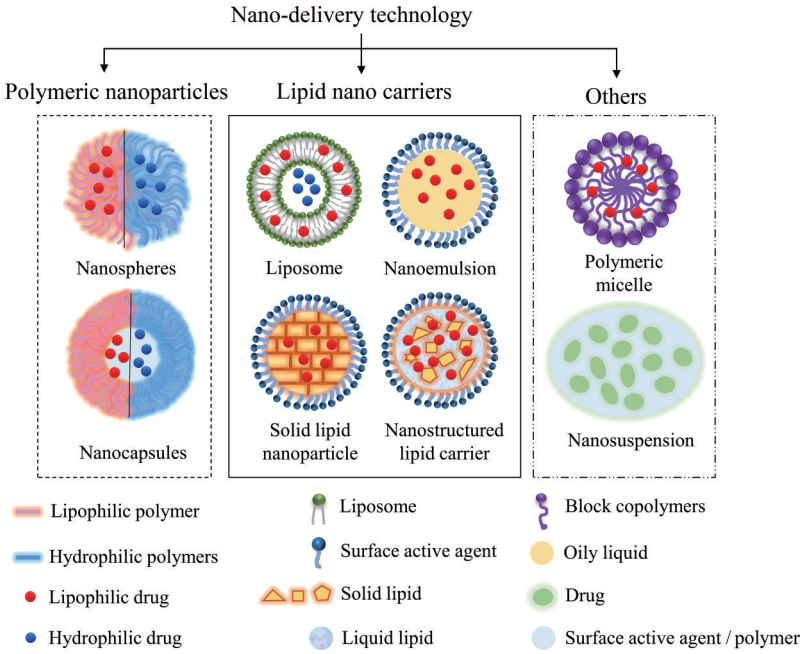

Figure 2 Schematic diagram of nano-delivery technology for oral mucosal drug delivery

Table 2 Examples of oral mucosal drug delivery applications based on nano-delivery technology. SLN: Solid lipid nanoparticle; NLC: Nanostructured lipid carrier; MPEG-PCL: Methoxy poly (ethylene glycol)-poly (*ε*-caprolactone)

Drug name	Nano-delivery technology	Nanomaterials or stabilizers	Preparation method	Dosage form	Achieved result
Insulin[34]	Liposomes	Soy lecithin	Thin-film hydration method	−	The mucosal permeability coefficient was increased by 4.33 times
Carvedilol[35]	Liposomes	Soybean phospholipids (S100)	Solvent injection method	Mucoadhesive membrane	Bioavailability was increased by 154%
Fluconazole (FZ)[36]	SLN	Tween® 80, glyceryl monostearate (GMS)	Hot homogenization	Film	Enhances mucosal adhesion and mucosal permeability of drugs
Metronidazole (MTZ)[37]	SLN	Stearic acid, cetyl alcohol, precirol, glyceryl monostearate	Solvent evaporation and hot homogenization	Gel	Extended drug release time
Acyclovir[38]	NLC	Kolliphor® HS 15, Labrafac® lipophile, WL 1349, Lipoid® S100, Tween® 80	Phase inversion method	Gel	Increased mucosal retention of drugs by more than 16 times
Triamcinolone acetonide[39]	NLC	Spermaceti, soybean oil, Tween® 80	Hot homogenization method	−	High encapsulation rate, high stability, significantly enhanced mucosal permeability
Estradiol[40]	Nanoemulsion	Transcutol P, Tween® 80	Ultrasonic homogenization method	Film	Enhance the mucosal permeability of drugs
Miconazole nitrate[41]	Self-nanoemulsifying drug delivery system (SNEDDS)	Clove oil, labrasol, propylene glycol	−	Hydrogel	Enhanced *in vitro* skin penetration and antifungal activity of the drug
Penciclovir[42]	SNEDDS	Labrasol, labrafil 1944, Lauro-FCC	−	Gel	Improved mucosal permeability and bioavailability of drugs
Digoxin[43]	Polymer nanoparticle	Zein	Nanoprecipitation method	Film	Enhanced mucosal adhesion and mucosal permeability of drugs
Curcumin[44]	Polymer nanoparticle	Zein, beta-cyclodextrin	Liquid-liquid dispersion method	Spray	Water solubility is increased by more than 100 times
Lamivudine[45]	Polymer nanoparticle	Eudragit E100	Nanoprecipitation method	Film	Extend drug release time and reduce drug toxic side effects
Antihypertensive peptide[46]	Polymer nanoparticle	Poly(lactic-*co*-glycolic acid)	Double emulsion technique	Film	Ensure the biological activity of the drug and delaying the release of the drug
Naringin[47]	Polymeric micelle	MPEG-PCL	Thin-film hydration method	Tablet	Increases the *in vitro* release rate of drugs by more than 2 times
Clotrimazole[48]	Nanosuspension	Benzyl-succinyl chitosan	Bottom-up method	Film	Improved solubility, release amount and release rate
Paclitaxel[49]	Nanosuspension	Pluronic F68, Pluronic F127	Bottom-up technique, lyophilization method	Tablet	Improved the solubility of the drug, increasing its bioavailability by 5.98 times

加了35.21%, 胰岛素LPS增加了433%[34,53,54]。LPS能保护生物大分子药物免受口腔环境的影响, 提高药物的稳定性, 同时增强其在黏膜的渗透性, 可用于疫苗、蛋白质、抗原及DNA等生物大分子的口腔黏膜递送。Sahatsapan等[50]采用薄膜水合法制备了的卵磷脂酰胆碱LPS用于负载白蛋白-异硫氰酸荧光素偶联物, 并以壳聚糖-马来酰亚胺作为改性剂, 涂覆在LPS表面。以聚丙烯酰胺凝胶电泳测定释放蛋白药物的结构完整性, 结果显示, LPS负载的蛋白未出现蛋白质的结构或构象变化, 表明其具有良好稳定性。此外, 离体颊黏膜的渗透性结果表明, 改性LPS能缓慢地释放药物, 渗透量是纯药物溶液的8倍。

利用功能化基团或聚合物进行LPS的表面修饰, 制备改性LPS, 可进一步增强药物的黏膜黏附、黏液穿透及黏膜渗透能力, 进而提高药物的口腔黏膜吸收。一种由脱水山梨糖醇基非离子表面活性剂Span 60和边缘激活剂Tween® 80 (聚山梨酯80) 组成的柔性LPS具有高度的可变形性和弹性, 使其通过挤压变形轻松跨过黏膜屏障而不会发生破裂或泄漏[55]。LPS还可与物理促渗技术联用进一步克服黏膜渗透障碍。Sonaje等[19]将跨塑性LPS与物理促渗技术联用, 制备了一种带电可变形LPS-离子体, 用于负载抗癌药物顺铂和多

西紫杉醇 (图3)。结果显示, 离子体在没有外部驱动力的情况下不会进入黏膜, 而在阳极离子导入10 min后, 顺铂和多西紫杉醇在黏膜的沉积量分别为13.54和10.75 μg·cm^{-2}, 是对照组 (0.20和0.19 μg·cm^{-2}) 的67.7和56.6倍。共聚焦显微镜结果证实, 离子体通过细胞间隙穿透黏膜, 穿透的深度可通过改变离子导入的持续时间来控制 (图4)。上述研究表明LPS可通过不同功能聚合物的修饰或与多种物理化学方法联用, 满足药物在口腔不同部位的局部或全身给药的需求。

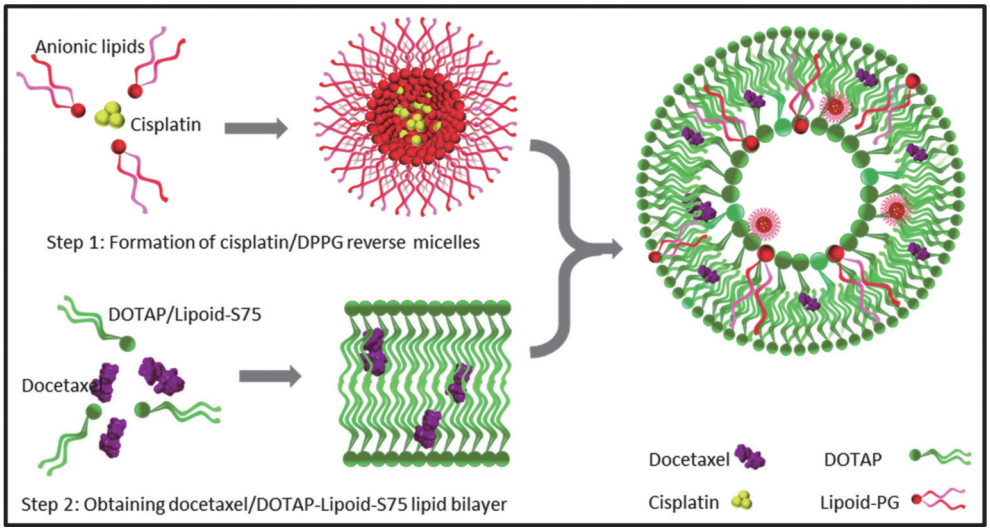

Figure 3 Formulation of electroresponsive iontosomes; cisplatin (CDDP) was formulated into the anionic reverse micelles using dipalmitoyl-*sn*-glycero-3-phospho-rac-glycerol sodium (DPPG, red) and docetaxel (DTX) was loaded in the cationic lipid bilayer of 1,2-dioleoyl-3-trimethylammonium-propane soybean phosphatidylcholine (DOTAP-Lipoid-S75, green). Then, the iontosomes were obtained by hydrating the cationic lipid bilayer with the CDDP-DPPG reverse micelles. Adapted from Ref. 19 with permission. Copyright © 2021 by MDPI

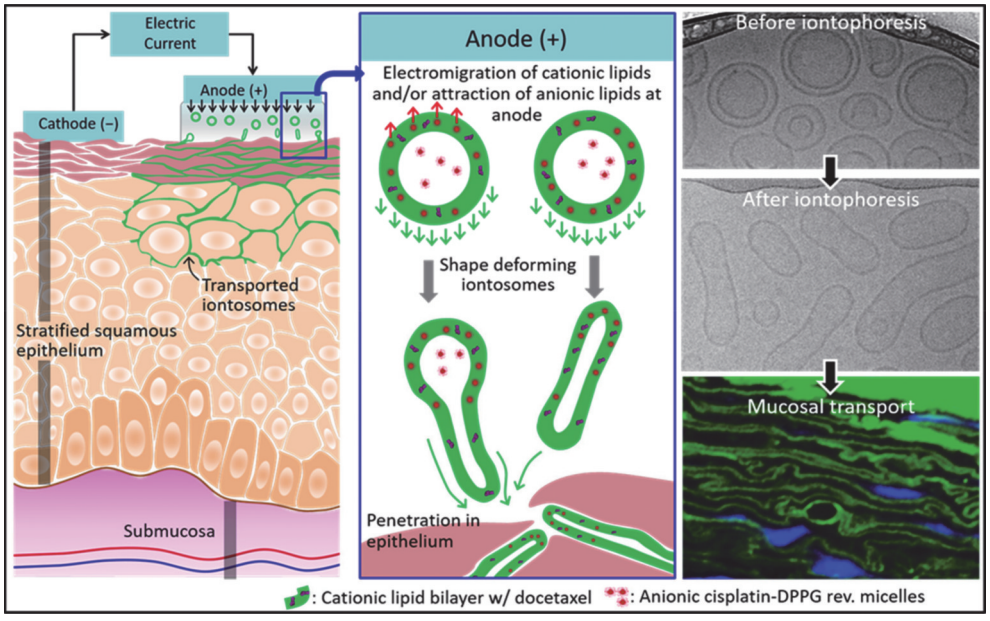

Figure 4 A schematic diagram showing the basic concept underlying anodal iontophoretic mucosal delivery of iontosomes employed and validated in this study. The cationic iontosomes (green) undergo shape deformation upon application of the current. During iontophoresis, the anionic reverse micelles (red) are attracted to the anode; at the same time, the cationic lipid bilayers electromigrate toward the mucosa. These opposing forces result in elongation of the iontosomes. Then, the deformed iontosomes enter the mucosa through the intercellular spaces in epithelium. The images on the right show the transmission electron microscopy at cryogenic temperature (cryo-TEM) and confocal micrographs of iontosomes during iontophoresis and after deposition into mucosa. The images on the right show the cryo-TEM and confocal micrographs from the current work, showing the shape deformation of iontosomes after iontophoresis and upon deposition in the mucosa. Adapted from Ref. 19 with permission. Copyright © 2021 by MDPI

3.2 SLN/NLC

SLN是以固态天然或合成的类脂为基质制成的实体骨架型纳米载体, 具有良好的生物相容性、低毒、增强负载药物控释能力等优点[56]。SLN用于口腔黏膜给药, 可通过改善难溶性药物的溶解度, 延缓水溶性药物释放, 促进药物的口腔黏膜吸收, 进而增加药物生物利用度, 适用于全身或局部给药。一种负载氯诺昔康SLN的黏附片具有良好的黏膜黏附强度 (42.5 g)、黏附时间 (7.6 h) 和可控释放行为 (12 h后释放96% ± 3.7%), 克服了氯诺昔康低水溶性和半衰期短的问题[57]; 与氯诺昔康原料药和市售氯诺昔康片相比, 负载氯诺昔康SLN的黏附片对角叉菜胶诱导的足水肿表现出早期和延长的抗炎反应, 并能有效抑制血清细胞因子水平。Ho等[37]制备的载有甲硝唑SLN的羟乙基纤维素凝胶能显著延缓甲硝唑的释放, 增加其黏膜渗透率及体外抗菌活性, 用于牙周疾病的治疗。值得注意的是, 部分表面活性剂能赋予SLN表面特殊性质 (如正电性、富含羟基等), 使SLN与黏液中的黏蛋白发生静电及氢键等相互作用, 从而增强制剂与黏膜的黏附作用, 以延长药物在口腔黏膜的滞留时间, 改善药物的黏膜吸收。Kraisit等[36]研究发现高浓度的单硬脂酸甘油酯或Tween® 80有利于氟康唑的SLN黏膜渗透, 这可能是因为Tween® 80和单硬脂酸甘油酯富含羟基, 能与黏膜表面形成较强的氢键作用, 显著增强了SLN薄膜的黏膜黏附能力。

NLC是从SLN发展而来的一种新型纳米给药系统, 是在固态脂质中混入液态脂质制备形成的脂质纳米载体。液态脂质的掺入增加了固态脂质的晶体混乱度, 提供了更多的药物负载空间, 克服了SLN载药量低及晶格重排导致的药物泄漏问题, 能达到更好的药物保护和缓控释作用[58,59], 是一种优于SLN的口腔黏膜促渗载体。Hosny等[18]采用热均质法和超声处理制备了基于山嵛酸甘油酯 (固体脂质) 和芝麻油 (液体脂质) 的NLC, 用于负载治疗口腔念珠菌病的低水溶性药物咪康唑。结果显示, 负载咪康唑的NLC粒径92 nm, 包封率也高达96%; 咪康唑NLC离体颊黏膜的渗透率 (1 472 μg·cm^{-2}) 显著优于相同浓度的咪康唑悬浮液 (470 μg·cm^{-2}) 和上市的咪康唑乳膏 (1 215 μg·cm^{-2}), 表现出较好的在体抑菌效果, 可用于口腔念珠菌病的治疗。需要注意的是, 药物的疏水性、NLC的处方组成、粒径、电荷性质及结构等均可影响NLC的黏膜促渗效果[39]。

3.3 NE/自纳米乳

NE是由水相、油相、表面活性剂和助表面活性剂等自发形成, 粒径为1～100 nm的热力学稳定、各向同性、透明或半透明的均相分散体系[60]。NE纳米级粒径能克服传统乳剂的乳化、沉降和聚结等缺点, 比传统乳剂具有更强的动力学稳定性[60]。NE应用于口腔黏膜给药, 能增加难溶性药物溶解度、延长作用时间, 其较低的表面张力也有利于透过黏膜水化层, 促进黏膜吸收, 提高药物生物利用度。Abdella等[40]开发了一种用于激素替代疗法的雌二醇口腔黏附膜, 评估比较了基于共溶剂和NE两种策略制备的雌二醇口腔黏附膜的制剂学性质。结果显示, 基于NE的雌二醇口腔黏附膜6 min内药物释放达80%, 而共溶剂法需10.5 min才能达到相似的释药效果; 负载雌二醇NE的口腔黏附膜离体黏膜渗透效果良好, 10 h渗透量约15%, 而共溶剂法24 h渗透量只有5.8%; 应用R编程语言卷积模型基于体外药物释放数据评估血药浓度, C_{max}为740.74 ng·mL^{-1}, T_{max}为7 min, 基于NE的口腔黏附膜是递送雌二醇治疗更年期症状的有效策略。

自纳米乳给药系统 (self-nanoemulsifying drug delivery systems, SNEDDS) 是由油相、表面活性剂和助表面活性剂组成的一种热力学稳定的混合体系[61]。可在含水环境经温和搅拌自发形成粒径小于100 nm的O/W型NE, 具有良好的物理化学稳定性, 广泛用于改善难溶性药物的生物利用度。SNEDDS可进一步制成凝胶、黏附片等剂型用于口腔黏膜给药, 促进药物的黏膜吸收。Hosny等[42]以薰衣草挥发油作为油相制备了负载喷昔洛韦的SEDDS, 并将优化的喷昔洛韦−薰衣草挥发油SNEDDS包埋壳聚糖基质中制成水凝胶用于口腔黏膜递送治疗口唇疱疹, 其离体黏膜渗透量是市售1%喷昔洛韦乳膏的两倍, 相对生物利用度达到了180%, 显著增强了喷昔洛韦的生物利用度, 且以薰衣草挥发油作为油相有助于协同改善疱疹症状, 并缓解与疱疹相关的疼痛。

3.4 PLNP

PLNP是指由可生物降解的天然或合成聚合物制备的粒径为10～1 000 nm的固态胶体粒子, 包括纳米囊、纳米球等[62]。PLNP具有生物相容性、生物可降解性、良好的药物包封能力和缓控释特性, 结构多样且可调控设计, 广泛用于药物增溶、促吸收及靶向递送等[63]。PLNP在口腔黏膜给药中的应用除改善药物溶解性、促进黏膜渗透外, 还可显著增强黏膜黏附能力, 以延长黏膜滞留时间, 增加药物黏膜吸收。PLNP与口腔黏膜黏附主要是通过静电或氢键相互作用, 由于黏蛋白的亲水性和负电性 (唾液酸), 阳离子聚合物和具有与黏蛋白形成氢键的能力的聚合物制备的PLNP更适合用于口腔黏膜递送。目前文献[4,63]报道的聚合物有聚乳酸−羟基乙酸共聚物、聚甲基丙烯酸酯、壳聚

糖、透明质酸等。研究表明, PLGA纳米粒能显著促进阿昔洛韦的口腔黏膜吸收, 最大血药浓度 (C_{max}) 和药时曲线下面积 ($AUC_{0-\alpha}$) 分别是口服阿昔洛韦对照组的3和8倍[64]。负载抗凝血药低分子肝素的两种聚甲基丙烯酸酯Eudragit® RS和Eudragit® RL纳米粒的离体猪黏膜120 min渗透量分别为0.1%和0.08%, 而溶液对照组未检测到肝素的黏膜渗透[65]。

特定官能团如儿茶酚改性聚合物能与黏蛋白中的巯基官能团形成共价键, 产生强效黏附作用, 从而增强纳米粒的黏膜黏附, 促进药物的黏膜吸收。黏附性研究结果显示, 经人工唾液冲洗后, 负载多柔比星的儿茶酚改性琥珀酰壳聚糖/透明质酸纳米粒仍有60%以上的黏膜组织保留率, 而未经儿茶酚修饰的纳米粒只有10%黏膜组织保留率[66]。负载胰岛素的硫醇化三乙基壳聚糖纳米粒480 min的离体黏膜渗透量为11.1 μg, 三乙基壳聚糖纳米粒为9.8 μg, 而壳聚糖纳米粒只有1.8 μg; 这是因为壳聚糖硫醇化后可与黏蛋白形成共价二硫键增强黏附作用, 且硫醇化的壳聚糖具有更强的促渗作用[67]。由于聚合物实际是和黏液层黏附, 过强的黏液黏附可能导致PLNP无法穿透黏液层, 而随着黏液层的流动丢失, 降低药物的黏膜吸收。此外, PLNP的粒径和电荷性质会影响其黏膜渗透, 小粒径及正电荷的PLNP更有利于口腔黏膜渗透[5]。

3.5 PM

PM是指两亲性聚合物在水中达到一定浓度后自组装形成的以疏水性基团为内核、亲水基团为外壳的分子有序聚集体[68]。PM具有载药范围广、结构稳定、体内滞留时间长、毒副作用小等特点, 广泛用于药物的增溶、缓释及靶向递送等[69]。PM用作口腔黏膜促渗载体, 其疏水内核可溶解疏水性药物, 从而增加难溶性药物的溶解度, 而PM的亲水性外壳和较小的粒径有利于黏液穿透, 从而促进药物的口腔黏膜吸收。Suksiriworapong等[70]研究发现硫代*d*-*α*-生育酚聚 (乙二醇) 1000琥珀酸 (TPGS-Cys) 胶束能显著增加伊曲康唑的口腔黏膜渗透和抗白色念珠菌活性, 可进一步开发成口腔黏膜制剂, 用于伊曲康唑的黏膜递送, 以治疗白色念珠菌。Zhou等[71]研制了负载两性霉素B的甲氧基聚乙二醇−聚己内酯−接枝−聚乙烯亚胺 (MPEG-PCL-*g*-PEI) 胶束, 用于局部治疗口腔白色念珠菌。体外释放显示, 负载两性霉素B的MPEG-PCL-*g*-PEI胶束在正常口腔条件 (pH 6.8) 和白色念珠菌感染条件 (pH 5.8) 下均能持续释放药物, 其冻干粉经直压制成的含片可维持8 h的药物释放, 满足抗真菌要求。虽然胶束未能明显改善两性霉素B对浮游白色念珠菌的抗菌作用, 但显著增强了对白色念珠菌体生物膜状态的抗真菌活性。需要注意的是, 一些单共聚物胶束由于分子结构类型和长度限制, 存在药物负载量低、体内稳定性差或无法有序地调节药物的吸收和释放等性能缺陷, 通常使用两种或两种以上的嵌段共聚物制成混合PM, 以提高稳定性和载药能力。

3.6 NS

NS是通过粉碎或凝聚法制备而成的“纯”药物纳米分散体, 通常由少量表面活性剂或聚合物稳定[72,73]; 根据药物存在状态可分为纳米结晶和无定型纳米粒。NS通过减小粒径, 显著改善难溶性药物溶出速率和生物利用度, 具有处方简单、载药量高、低毒、适用范围广等优点[74]。NS最早用于改善难溶性药物的口服生物利用度, 之后逐步扩展到注射、透皮、肺部、口腔黏膜等多种给药途径[73]。NS通过改善难溶性药物的溶解和溶出, 增加口腔黏膜附近的药物浓度梯度, 进而促进药物的扩散和黏膜吸收, 提高药物生物利用度。Soroushnia等[75]采用超声分散法制备抗癫痫药物咪达唑仑NS, 粒径为197 nm, 与普通混悬剂相比, 咪达唑仑NS的体外溶出度增加了1.3倍; 兔颊黏膜给药, C_{max}和AUC_{0-t}分别增加了111.90%和275.08%, 生物利用度显著增加。

与前述纳米载体技术相比, NS辅料用量少, 最大的优势在于其高载药量和速释特点, 尤其适用于制备成口腔膜剂 (黏附膜、速溶膜等), 无需水送服且黏膜吸收快速, 适合儿童、老人及其他吞咽困难人群用药。药代动力学研究显示, 与普通混悬剂相比, Soroushnia等[76]制备的咪达唑仑NS速溶膜AUC和C_{max}显著增加, T_{max}显著缩短; 与市售片剂相比, Elshafeey等[77]制备的帕罗西汀NS速溶膜生物利用度增加了78.43%, T_{max}由3.08 h (片剂) 缩短至0.94 h (速溶膜)。此外, NS的物理稳定性问题是其开发和应用的主要挑战, 口腔膜剂既可实现NS的固体化, 改善NS稳定性; 还能维持药物NS的速释特性。Karagianni等[78]制备的伊曲康唑NS速溶膜维持了与伊曲康唑NS一致的速释行为, 口腔膜剂是实现NS固体化, 改善NS稳定性的良好选择。

4 纳米递药技术促进口腔黏膜吸收的作用机制

口腔黏膜给药后, 药物制剂需在黏膜滞留一定时间, 经释放、黏液层扩散及黏膜渗透, 吸收进入体内, 发挥治疗作用。纳米递药技术促进药物的口腔黏膜吸收主要是作用于这几个环节, 其促进黏膜吸收的作用机制主要有[5,44,79]: ① 改善药物溶解与溶出。BCSII (Biopharmaceutics Classification System II) 类药物具有低水溶性、高渗透性, 不存在黏膜渗透障碍, 药物的溶解释放是黏膜吸收的主要限速步骤。纳米递药技术可

通过减小药物粒径或将药物溶于载体基质内改善药物的溶解和溶出, 进而促进药物的口腔黏膜吸收; ② 促进药物的黏液层扩散。口腔黏膜细胞表面覆盖着由黏蛋白、水、无机盐等构成的黏液层, 是口腔内药物吸收的首道屏障。纳米递药技术使用的一些表面活性剂或聚合物能降低黏液层的黏度, 促进药物的黏液层扩散; 荷电中性的纳米粒具有黏液惰性, 可载带药物扩散透过黏液层[80]。此外, 纳米材料中引入二硫键断裂剂或蛋白水解酶, 可降解黏蛋白纤维网络破坏黏液屏障, 促进纳米粒的黏液层扩散[81]; ③ 增加药物的口腔黏膜渗透。口腔黏膜上皮是口腔黏膜的保护屏障, 同时也是口腔黏膜给药的主要渗透屏障。LPS、SLN、NLC等脂质纳米载体具有与生物膜相似的脂溶性, 可通过与生物膜融合, 增加药物的口腔黏膜渗透[82]。小粒径的纳米粒能通过细胞间隙吸收, 从而增加药物的口腔黏膜渗透; ④ 增强药物的黏膜黏附, 延长药物口腔滞留时间。唾液冲刷、不自主吞咽动作等会导致药物流失, 影响药物的黏膜滞留与吸收。一些功能化纳米粒能与黏液中的黏蛋白相互作用, 增强纳米粒的黏膜黏附, 延长药物的黏膜滞留时间, 促进药物的口腔黏膜吸收[28]。将纳米粒与黏膜黏附制剂如黏附膜、黏附片结合, 不仅可增强黏膜黏附, 还可促进药物黏膜渗透, 是改善药物口腔黏膜吸收的理想策略。

5 基于纳米递药技术的口腔黏膜给药系统研究的问题与思考

5.1 口腔黏膜给药系统的载药量限制

由于口腔黏膜吸收面积有限且给药体积过大, 易引起口腔不适, 口腔黏膜给药通常只适用于活性强、给药剂量小的药物。各种纳米递药技术均需一定量的赋形剂如表面活性剂、聚合物、脂质材料等, 将其引入到口腔黏膜给药制剂尤其是口腔膜剂, 会进一步降低制剂的载药量, 影响药物的口腔黏膜递送。多次给药虽然可克服载药量低的问题, 但会降低药物的递送效率及患者的用药依从性。因此, 如何提高载药量是纳米载体类递药技术应用于口腔黏膜给药研究的重要问题之一。开展高载药纳米递药技术研究可克服载药量低的问题, 提高基于纳米递药技术的口腔黏膜给药系统的载药量[83]。

5.2 纳米递药技术的黏膜促渗机制与安全性

纳米递药技术应用口腔黏膜给药研究多数只注重改善药物的黏膜渗透性, 但纳米递药技术促进药物黏膜渗透的机制如纳米粒能否整体透过口腔黏膜, 药物的促渗途径是什么等尚不完全清楚。此外, 纳米递药技术不仅能促进药物的黏膜吸收, 还可能改变药物的药动学性质, 可能引起毒副反应; 纳米粒本身的黏膜滞留与蓄积也可能导致黏膜刺激, 产生安全性问题。开展纳米递药技术的口腔黏膜促渗机制研究, 系统评价纳米递药技术口腔黏膜给药的安全性, 有利于更好地进行基于纳米递药技术的口腔黏膜给药剂型的设计, 促进纳米递药技术在口腔黏膜给药系统中的应用研究。

5.3 基于纳米递药技术的口腔黏膜给药系统的综合质量评价

目前, 基于纳米递药技术的口腔黏膜给药系统研究尚处于基础研究阶段, 尚缺乏系统的综合质量评价, 一定程度上限制了基于纳米递药技术的口腔黏膜给药制剂的开发和临床转化。纳米递药技术应用于口腔黏膜给药需与适宜的剂型如黏附片、黏附膜等结合, 然而制剂成型材料的加入如黏附聚合物、成膜聚合物及增塑剂等可能会导致纳米粒的聚集; 脂质纳米粒可能在机械压力如压片时变形[84], 也可能因加热如热熔挤出或薄膜浇铸时发生脂质相变, 进而影响药物的口腔黏膜递送。因此, 制剂的质量评价除常规的评价外, 还需关注纳米粒的理化性质表征, 尤其是制剂成型后能否维持纳米粒的再分散特征。建立健全的基于纳米递药技术的口腔黏膜给药制剂综合质量评价体系有助于推动相关药物的制剂开发和临床转化。

6 总结与展望

口腔黏膜给药具有避免胃肠道降解和肝脏首过效应, 提高药物生物利用度, 改善患者用药依从性等优点。LPS、SLN、NLC、NE、PLNP、PM、NS等纳米递药技术能克服口腔黏膜的屏障作用, 通过改善难溶性药物的溶解性, 促进药物的黏液穿透; 增加药物的黏膜渗透及增强药物的黏膜黏附等促进药物的口腔黏膜吸收。然而, 由于口腔黏膜给药系统的载药量限制、纳米递药技术的黏膜促渗机制不清楚及安全性、质量评价等问题, 阻碍了纳米递药技术在口腔黏膜给药中的应用研究与开发。开展高载药纳米递药技术研究, 研究纳米递药技术的口腔黏膜促渗机制, 系统评价纳米递药技术口腔黏膜给药的安全性, 建立健全的基于纳米递药技术的口腔黏膜给药制剂综合质量评价体系, 有助于促进纳米递药技术在口腔黏膜给药系统中的应用研究, 推动相关药物的制剂开发和临床转化。本综述系统总结了各种纳米递药技术在口腔黏膜给药中的应用研究进展及其促进药物口腔黏膜吸收的作用机制, 并总结分析了研究中存在的主要问题。随着纳米递药技术及理论的发展和完善, 其在口腔黏膜给药中的应用将越来越广泛, 基于纳米递药技术的口腔黏膜给药系统的问题将被逐一克服, 加速推动相关药物制剂的研发与应用。

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