壳聚糖基材料应用于口腔黏膜给药系统的研究进展

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摘要: 口腔黏膜给药具有病患接受度高、见效快、给药方便等优点, 可避免药物在肝脏的首过效应。然而, 某些药物由于其独特的理化性质和口腔内特殊的生理环境, 使口腔黏膜给药系统的设计变得具有挑战性。壳聚糖基材料具有无毒或低毒、生物可降解等优良特性, 能有效抑制菌群的生长繁殖, 实现药物的缓释、控释和黏膜黏附。因此, 壳聚糖基材料在口腔黏膜给药系统中得到了广泛研究。本文系统阐述了口腔黏膜的生理结构特点及其给药优势, 总结了壳聚糖基材料在该系统中的相关研究, 并展望了其未来应用前景。

关键词: 壳聚糖基材料; 口腔黏膜给药系统; 壳聚糖及其衍生物; 首过效应; 纳米制剂

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Research progress of chitosan-based materials applied in oral mucosal drug delivery systems

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Abstract: Administration oral mucosal drug delivery has the advantages of high patient acceptance, rapid onset of action, convenient, etc., and it can avoid the first-pass effect of the drug in the liver. Nevertheless, the design of oral mucosal drug delivery systems is inherently challenging due to the distinctive physicochemical properties of certain drugs and the specific physiological environment of the oral cavity. Natural polysaccharide chitosan-based materials exhibit favorable characteristics, including non-toxicity or low toxicity and biodegradability. These materials can effectively inhibit bacterial growth, enable controlled drug release, and enhance mucosal adhesion. Consequently, chitosan-based materials have been the subject of extensive research in the field of oral mucosal drug delivery systems. This paper offers a comprehensive overview of oral mucosal drug delivery systems, reviews relevant studies on chitosan-based materials, and discusses future prospects for their application.

Key words: chitosan-based material; oral mucosal drug delivery system; chitosan and its derivative; first pass barrier effect; nanopreparation

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大多数药物通常通过口服途径给药, 主要的吸收部位是小肠。然而, 胃肠环境中的消化液、食物残渣及肝脏的首过效应等因素会导致药效降低。此外, 某些药物在体内的稳定性差、溶解性低、渗透性小等缺陷也会使有效药物无法通过口服途径给药[1]。近年来, 随着药物制剂的快速发展, 人们逐渐将给药途径转向非胃肠道途径[2]。

口腔黏膜给药系统是一种新型给药方式, 包括局部给药和跨黏膜给药。口腔内部存在大量黏膜和丰富的毛细血管, 药物可以直接或间接作用于口腔黏膜, 从而透过黏膜进入机体, 有效规避肝脏的首过效应, 降低全身药物的毒性, 实现局部或全身的治疗作用, 因此是传统口服剂型的有效替代品[3]。然而, 一些药物由于其水溶性差、稳定性低等缺陷导致不能通过口腔黏膜途径给药。此外, 由于口腔中微环境的影响, 如酶的降解、唾液的机械冲刷、微生物的摄入等因素也可能导致药物的生物利用度显著降低[4]。

壳聚糖是美国食品药品监督管理局批准的药用辅料之一, 又因其具有生物可降解性、无免疫原性、无毒、抗菌、抗炎、抗氧化和促进伤口愈合能力等优良特性, 被认为是最有前途的药物递送载体。利用壳聚糖基材料独特的生物相容性、黏膜黏附性、促渗作用等特点, 作为药物载体可以提高药物的溶解性、增强药物的稳定性, 延长药物在口腔黏膜的滞留时间, 促进药物的持续释放, 从而提高药物的生物利用度。因此, 壳聚糖基载体材料在口腔黏膜给药系统领域受到广泛关注[5-7]。

1 壳聚糖及其衍生物

壳聚糖 (图 1) 是一种具有巨大发展潜力的天然多聚糖。其携载的正电荷伯氨基, 可以与口腔中带负电荷的唾液酸、磺酸和黏蛋白发生静电作用, 成为一种适合通过口腔黏膜递送药物的可黏附载体材料[8]。然而, 壳聚糖的主要缺陷在于其水溶性较差, 仅能在酸性介质中溶解, 这在很大程度上限制了其在口腔黏膜给药系统中的应用[9]。

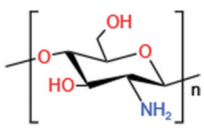


Figure 1 Structural formula of chitosan

壳聚糖通过化学修饰可以获得具备不同特性的衍生物[10], 其中包含的羟基和氨基官能团是最常见的修饰基团。改性后的壳聚糖衍生物不仅保留了原有的优良性状, 还改善了溶解性和黏膜黏附性等特点, 从而拓宽了其在口腔黏膜给药系统领域的应用。壳聚糖的常用改性方法主要包括降解、交联、接枝共聚、复合改性等[11]。研究表明, 常见的壳聚糖化学改性方法如烷基化[12]、酰化[13]、季铵化[14]、接枝共聚[15]、羧甲基化[16]等都会改变壳聚糖的固有性质。例如, 烷基化赋予壳聚糖更好的表面活性[12], 酰化提高了壳聚糖的抗菌能力, 而季铵化、羧甲基化和接枝共聚等方法则增加了壳聚糖在水中的溶解度[17]。具体常见的壳聚糖衍生物的改性方式及其特点如表 1[11,16,18-28]所示。

2 口腔黏膜给药系统

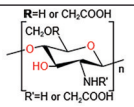
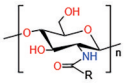
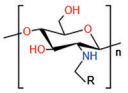
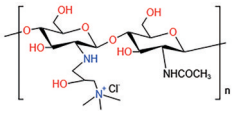
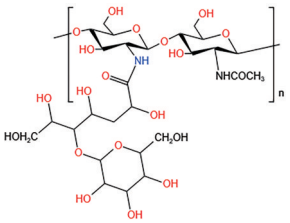
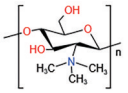
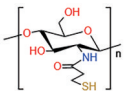
口腔黏膜给药系统是指制剂作用于口腔部位, 以实现局部治疗或通过口腔黏膜吸收后进入循环系统的新型给药系统[29]。研究口腔黏膜给药系统已经引起广泛关注, 因为该系统在传递多肽、蛋白质及其他受到肝脏代谢和酶促降解影响的活性药物方面具有潜在优势。深入探讨该系统不仅有助于改善口腔疾病的治疗效果, 还为全身给药提供了新的思路和途径[30]。因此, 口腔黏膜递送系统的研究与开发具有重要的科研探究意义和临床应用价值。

2.1 口腔黏膜生理结构特点及给药优势

口腔内不同的黏膜对药物的渗透性存在差异。牙龈 (200 μm) 和硬腭 (250 μm, 图 2A) 属于角化黏膜, 通常渗透性较差, 主要用于治疗牙龈或腭部的口腔疾病, 例如口腔感染和口炎等[31]。舌下黏膜 (100～200 μm, 图 2A) 是非角化黏膜, 渗透阻力较小, 且高度血管化, 能够快速吸收药物, 适合全身给药, 从而可达到治疗身体其他部位疾病的效果[32]。例如舌下含服硝酸甘油用于治疗心绞痛可以迅速起效[33]。然而, 舌下黏膜的表面因说话或咀嚼等动作不断被唾液冲洗, 进而对药物的吸收产生影响。颊黏膜 (500～600 μm, 图 2A) 也属于非角化黏膜, 与口腔黏膜的其他组织相比, 其表面相对固定、敏感度低, 给药更加方便。此外, 颊黏膜的血流量大, 渗透性较高, 适合长期给药, 但无法快速吸收药物以达到良好的治疗效果[34]。在组织学中, 口腔黏膜主要包括口腔上皮、固有层和黏膜下层 (图 2B)。其中, 口腔上皮是主要的一层, 通过其物理和免疫屏障功能保护身体免受环境暴露、物理化学损伤、微生物和毒素的侵害[35]。

药物从口腔黏膜进入体内主要有两种方式: 跨细胞途径 (药物进入上皮细胞后再由细胞释放到体内) 和细胞旁路途径 (药物由上皮细胞之间的间隙进入体内) (图 3), 这两种途径为口腔黏膜对药物的吸收机制提供了理论基础[35]。口腔上皮的厚度和密度因部位不同而存在差异, 因此对药物进入机体的过程尤为重要。口腔黏膜通过颈外动脉、上颌动脉 (在硬腭和面颊处)、舌动脉 (在舌部)、舌下动脉 (在舌下和牙周区)、面动脉

Table 1 Common derivatives and modifications of chitosan

Derivative name	Modification method	Structural formula	Specificity	Ref.
Carboxy chitosan	Reduction or introduction of carboxyl groups		Water solubility, biodegradability, mucous membrane adhesion, biocompatibility, antimicrobial properties, etc.	[16,18]
Acylated chitosan	Acylation		Processability, slow release effect, biocompatibility, antimicrobial properties, etc.	[11,19,20]
Alkylated chitosan	Alkylation		Antimicrobial, biocompatible, easier to dissolve, etc.	[21,22]
Quaternary chitosan	Halogenated method, quaternary ammonium salt method		Water solubility, antimicrobial, antioxidant, biocompatibility, degradability, etc.	[23,24]
Glycosylated chitosan	Branching		Simple preparation, environmental protection, low cost and high efficiency, improve drug dissolution rate, etc.	[25,26]
Methylated chitosan	Methylation		Osmotic enhancement, mucosal adhesion, antimicrobial properties, free radical scavenging ability	[27]
Thiolated chitosan	Thiolation		Osmotic enhancement, mucosal adhesion, *in situ* gelling, etc.	[28]

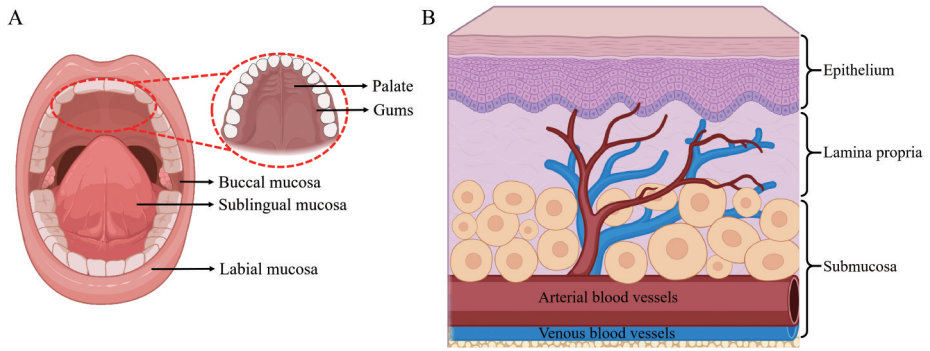


Figure 2 Sketch of the oral cavity structure (A) and oral mucosa (B)

(在软腭部和唇部) 的血液流动将药物递送。随后药物通过3条主要静脉回流, 最终流向颈内静脉, 将药物输送到全身。其复杂的血管网络和充足的血液流动为药物的吸收和利用提供了良好的平台[36,37]。

2.2 口腔黏膜给药的影响因素

2.2.1 口腔生理环境的影响 口腔中的生理环境十分特殊, 包含丰富的唾液 (pH = 6.6～7.1)。唾液中含有水、酶、蛋白质、无机盐和微生物等成分。因此, 药物在口腔中不仅会受到唾液的冲洗和稀释, 还可能受温度、

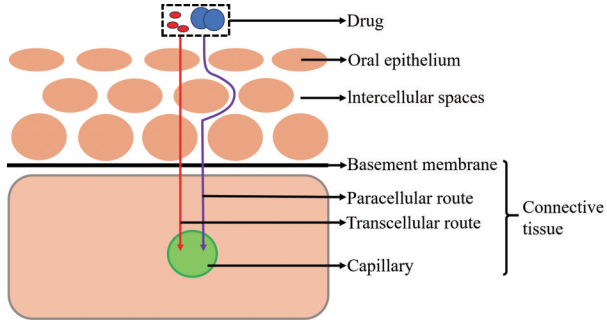


Figure 3 The main ways for drugs to enter the body through the oral mucosa

pH值和酶的影响。此外, 微生物或细胞的摄入, 机体进行咀嚼和吞咽等动作, 也会影响药物在口腔中的滞留时间, 从而影响药物的吸收和利用[38,39]。

2.2.2 药物理化性质的影响 药物自身的性质会影响其在口腔黏膜上的吸收情况, 例如溶解度、分子质量和解离度等理化性质。分子质量较低 (0～100 Da) 的药物更易通过黏膜, 大分子药物在没有合适的给药方式下生物利用度较低。低溶解度药物适用的溶剂较少, 这限制了其吸收。高溶解度药物的脂溶性相对较差, 较难通过细胞膜, 同样限制了药物的生物利用度。药物与口腔黏膜之间的相互作用也会影响药物的利用, 例如带正电荷的药物容易与带负电荷的黏蛋白发生静电作用, 从而影响药物的扩散和吸收[14]。为确保药物在口腔和全身疾病治疗中提供更安全有效的途径, 理想的口腔黏膜递送药物应具备以下理化性质: 分子质量 < 800 Da、Log*P* > 2.0、溶液 pH = 5～9、对黏膜不敏感[40]。此外, 药物的稳定性、给药剂量及是否易结晶等因素也会影响药物透过口腔黏膜[35], 不同的口腔给药剂型和给药方法可能影响药物在口腔内的停留时间、溶解和释放速度, 进而影响药物的吸收效果。

3 壳聚糖基材料在口腔黏膜给药系统中的应用

壳聚糖基材料具有无毒性、抑菌性、黏膜黏附性、促渗作用和优异的生物相容性等优势[41], 可以制造成不同的形状和尺寸, 例如纳米纤维、纳米颗粒 (nanoparticles, NPs)、微球、膜、凝胶等[42]。因此, 壳聚糖基材料在口腔黏膜药物递送载体方面得到广泛研究。其最新相关研究见表2[43-51]。

3.1 壳聚糖应用于口腔黏膜给药系统的制剂类型

壳聚糖可以采用多种药物剂型用于口腔黏膜给药系统, 主要包括固体剂型 (如片剂、膜剂等)、半固体剂型 (如凝胶)、液体剂型 (如混悬液) 及其他剂型[52](图4), 其中片剂、膜剂、凝胶剂和液体制剂是常用的剂型。

3.1.1 片剂 黏附片具有较大的药物容量和比表面积, 因此药物释放效率更高, 能显著提高药物的生物利用度[53]。例如, Paris 等[54]基于壳聚糖和透明质酸

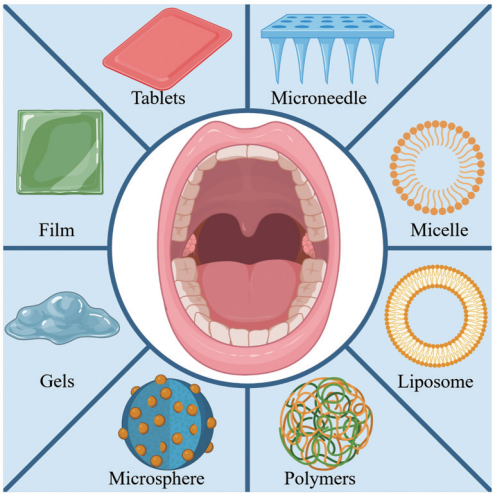


Figure 4 Dosage forms of drugs for oral mucosal administration

Table 2 Recent studies related to chitosan-based materials in oral mucosal drug delivery systems

Chitosan-based material	Loaded drug	Dispenser type	Method of preparation	Special feature	Goal	Ref.
Boronated chitosan	Linezolid	Microneedles		Non-toxic, mucosal adhesion, biocompatibility	Treatment of oral biofilms	[43]
Chitosan	Dexamethasone	Hydrogel patch		Excellent mucosal adhesion, slow drug release profile, along with sealing properties, interfacial toughness, cytocompatibility	Treatment of mouth ulcers	[44]
Chitosan	Curcumin	Films	Solvent evaporation technique	Mucosal adhesion, promote drug penetration	Oral cancer	[45]
Chitosan	Miconazole nitrate	Polymeric matrix	Thin film evaporation method	Mucosal adhesion, slow release of drugs, antimicrobial activity	Treatment of oral candidiasis	[46]
Chitosan	Enalapril maleate	Mucoadhesive buccal tablet	Direct compression method	Mucoadhesive strength of 24.32 ± 0.30 g, the swelling index was 90.74% ± 0.25% and drug release was sustained up to 10 h	Treatment of hypertension	[47]
Chitosan	Tizanidine hydrochloride	Mucoadhesive buccal tablet		Better swelling, favourable mucosal adhesion properties, stability, bioavailability that is three times higher than that of commercial products	Buccal drug delivery	[48]
Chitosan	Desmopressin	Nanofiber-on-foam-on-film system		Three times higher adhesion than unchitosan, maintains drug stability, pro-osmotic effect, biocompatible	Buccal drug delivery	[49]
Chitosan	Gentamicin sulfate	Oral patches	One-pot electrophoretic deposition	Mucosal adhesion, biocompatibility, antimicrobial activity	Localised oral bacterial infections	[50]
Thiolated chitosan	Crocin	Hydrogel		Mucosal adhesion, slow drug release promotes wound healing	Aphthous stomatitis	[51]

(hyaluronic acid, HA) 制备了舌下贴片, 并负载了卵清蛋白 (ovalbumin, OVA) 作为模型蛋白。通过荧光分子断层扫描发现, OVA 液体制剂给药后在 10 min 内快速分散, 而与舌下片一同给药后 30 min 内仍可检查到信号。说明壳聚糖所带正电荷通过静电相互作用赋予了舌下片黏膜黏附性能, 使蛋白质与黏膜之间的接触时间延长。在给药 2 min 后使用共聚焦显微镜观察到贴片给药与溶液给药相比黏膜表面的 OVA 含量更高, 且贴剂给药 10 min 后 OVA 便渗透到舌下上皮细胞。表明壳聚糖可促进蛋白质的被动渗透, 从而提高了通过黏膜输送的蛋白质量。然而, 黏附片的主要缺陷在于灵活性欠佳, 容易破碎, 在运输过程中不够便利[55]。

3.1.2 膜剂 膜剂是一种柔软薄片状的药物剂型, 常放置于颊内或舌下区域。它具有起效快、利于药物穿透吸收和不损伤正常组织的优点[56]。常见的膜剂是由聚合物基质组成的单层或多层复合载药薄膜。与片剂和凝胶剂相比, 膜剂具有更高的延展性、灵活性和柔韧性。此外, 膜剂的弹性高、抗撕裂、耐拉伸折叠、状态更加稳定[57]。Medeiros 等[58]基于壳聚糖和质子离子液体制备了薄膜, 在体外黏膜黏附研究中发现, 制备的薄膜拉伸应力在 46.3～123.8 $mN·mm^{-1}$ 之间, 所有薄膜均表现出良好的黏膜黏附强度, 表明壳聚糖通过静电相互作用赋予了薄膜出色的黏膜黏附性能。

3.1.3 凝胶剂 凝胶剂是一种药物与辅料制成的均一、混悬或乳状的稠厚液体或半固体制剂。与固体制剂相比, 凝胶剂在使用时没有明显的异物感, 它常被用于口腔内的局部给药, 能够减少给药的频率并提高药物的安全性[59]。Ayensu 等[60]制备了壳聚糖基凝胶, 在体外试验中研究发现, 壳聚糖和硫醇化壳聚糖凝胶的峰值黏附力分别为 4.5 ± 0.7 和 5.8 ± 0.2 N, 总黏附功分别为 6.5 ± 1.0 和 19 ± 0.8 mJ, 表明巯醇化壳聚糖因分子内二硫键的形成赋予了凝胶更好的黏膜黏附性能。体外药物溶出度研究显示, 壳聚糖和硫醇化壳聚糖凝胶的牛血清白蛋白在 1 h 内的释放率分别约为 57% 和 45%, 随后进入恒定的受控释放阶段, 最终释放量分别为 (91.5 ± 3.7)% 和 (94.4 ± 7.3)%, 表现出良好的缓释性和较高的释放率。

3.1.4 液体制剂 液体制剂是指将药物以一定形式 (如微囊、微球、脂质体等载体) 分散于液体介质中制成的分散体系。微囊是由载体材料将药物包裹在其中空区域形成的; 微球则可以将药物结合在载体中或吸附在颗粒表面, 并通过修饰颗粒表面赋予其他性质, 如黏附性和靶向性[61]; 脂质体能够提高水溶性较差药物的给药效率和治疗指数, 延长药物的半衰期, 降低某些药物因直接接触引起的毒性反应, 并改善药物的生物相容性[62]。Chen 等[63]通过使用羧甲基壳聚糖 (carboxymethyl chitosan, CMCS) 制备了 200 nm 球形自组装脂质体, 该脂质体尺寸分布均匀, 能够有效包载卡维地洛 (carvedilol, Car) 并可用于颊黏膜, 以避免首过效应的影响。X 射线衍射图表明, 该脂质体将 Car 转变为非结晶状态, 从而提高其溶解性。离体黏膜渗透试验发现, 不含磷脂的壳聚糖脂质体最大渗透量为 14.1 $μg·cm^{-2}$, 而 Car 本身的最大渗透量为 8.8 $μg·cm^{-2}$, 说明壳聚糖脂质体增强了 Car 的黏膜渗透作用。Garcia 等[64]利用喷雾干燥法制备了含有精油的壳聚糖微粒, 结果显示, 这种壳聚糖微粒降低了精油对口腔黏膜上皮细胞的毒性。天竺葵精油和柠檬草精油对变形梭菌和白色念珠菌混合生物膜半数最低生物膜抑制质量浓度范围分别在 512～4 096 和 2 048～4 096 $μg·mL^{-1}$ 之间, 而壳聚糖负载的柠檬草精油和天竺葵精油的范围分别为 512～2 048 和 1 024～2 048 $μg·mL^{-1}$ 之间。表明精油经壳聚糖负载后增强抗生物膜活性。

3.1.5 微针 微针是近年来新兴的第三代透皮 (黏膜) 给药形式, 具有微米级的针状结构, 几乎不与神经末梢产生相互作用, 因此给药不会引起疼痛。药物可以通过微针尖端进入皮肤或黏膜并释放, 以达到治疗目的[65]。Zeng 等[66]基于羟丙基三甲基氯化铵壳聚糖 (hydroxypropyltrimethylammonium chloride chitosan, HACC) 和 HA 制备了多功能多糖复合微针贴片, 背面使用 HACC 以增强抗菌性能。活死染色及板涂层结果显示, 添加 HACC 后死菌/活菌比值显著高于对照组且平板菌落数量明显减少, 表明添加 HACC 的微针贴剂具有广泛的抗菌活性。动物实验结果进一步证明, 微针的 HACC 背部具有良好的抗菌效果, 可为口腔溃疡的愈合提供适宜的微环境。

3.2 壳聚糖在口腔黏膜给药系统中应用的优势

在口腔黏膜给药系统中的应用优势主要体现在以下几个方面: 首先, 黏膜黏附作用延长了药物的停留时间[67]; 其次, 控释缓释作用实现了按需给药[68]; 最后, 促渗作用增加了药物进入体内的总量[69], 并改善了部分药物的理化性质[70]。这些优势的协同作用显著提高了药物的生物利用度。

3.2.1 黏膜黏附作用 口腔环境特殊, 舌搅拌、唾液冲刷、吞咽动作等皆会导致药物损失, 从而影响药物在口腔中的滞留和吸收。而壳聚糖与黏膜上黏蛋白产生各种相互作用力 (静电相互作用、氢键和疏水效应、共价相互作用等), 使药物在口腔黏膜上更好地滞留。

壳聚糖具有正电荷, 能够通过静电作用与黏蛋白的负电荷结合, 使其在口腔黏膜上表现出黏附特性, 这是壳聚糖作为口腔给药载体材料的重要影响因素[38]。

研究发现, 法匹拉韦 (favipiravir tablets, FVR)−壳聚糖−海藻酸盐 (alginic acid sodium salt, ALG) NPs (FVR-MCS-ALG-NPs) 比未使用壳聚糖包被的法匹拉韦−海藻酸盐NPs (FVR-ALG-NPs) 具有更高的黏蛋白黏附效果, 两种NPs分别与黏蛋白作用1 h后, FVR-MCS-ALG-NPs的zeta电位显著变化, 粒径明显增大, 这是由于壳聚糖的*D*-氨基葡萄糖分子中带正电荷的胺基与黏蛋白的唾液酸残基之间的静电相互作用所致。此外, FVR-MCS-ALG-NPs与黏蛋白的结合效率为 (46.8 ± 9.1)%, 显著高于FVR-ALG-NPs (13.0 ± 3.1)%, 说明静电相互作用为FVR-MCS-ALG-NPs提供了更好的黏膜黏附性能, 并增加了药物在黏膜上的停留时间[71]。

氢键和疏水效应也会对壳聚糖的口腔黏膜黏附性能产生影响。Sogias等[72]使用比浊滴定法进行测定, 在不同壳聚糖/黏蛋白 (*w*/*w*) 溶液 (pH = 2) 中添加0.2 mol·L^{-1} NaCl发现, 滴定曲线中的黏蛋白颗粒聚集浊度的最大值从0.05上升至接近0.1, 这表明壳聚糖与黏蛋白之间的黏附作用不仅由静电相互作用形成。为了进一步探究其他相互作用对壳聚糖黏附性能的影响, 研究者在上述不同质量比的溶液中使用了10%乙醇进行比浊滴定。结果显示, 溶液中的乙醇降低了黏蛋白的初始浊度, 使最大浊度值的位置急剧变化到接近0.15。这证实了壳聚糖与黏蛋白之间不仅存在静电相互作用, 同时还存在氢键和疏水效应, 这些作用共同影响了黏附性能。

共价相互作用能带来更好的口腔黏膜黏附性能。壳聚糖基材料可以引入巯基、儿茶酚 (catechol, Cat) 等基团与口腔黏膜形成共价键。Pornpitchanarong等[73]成功制备了儿茶酚官能化的琥珀酰壳聚糖 (SCScat) 和含儿茶酚的HA (HAcat), 并使用离子凝胶法将SCScat与HAcat制备成NPs。经体外黏附性研究结果表明, 未经Cat修饰的颗粒在唾液冲刷作用下仅有约50%的黏膜组织保留率, 而经过Cat修饰后的颗粒保留率超过60%。主要原因在于Cat通过Michael反应和Schiff反应与黏蛋白的硫醇和胺基团形成作用力更强的共价键, 从而延长了NPs在口腔黏膜的保留时间, 提高了其应用潜力。

壳聚糖和黏蛋白之间的黏膜黏附相互作用主要来源于静电引力、氢键和疏水效应。静电引力可能是壳聚糖黏附的主要机制, 但也受氢键和疏水效应的影响。经过改性的壳聚糖如硫代壳聚糖、琥珀酰壳聚糖等, 因其含有巯基、邻苯二酚基团等, 可以与黏膜形成共价键, 从而相比静电引力具备更强的黏附性能。

3.2.2 控释缓释 壳聚糖基材料应用于口腔黏膜给药系统具有良好的控释和缓释特性, 可以有效地将药物输送到病变组织, 极大提高治疗效果, 并减少给药对健康组织的毒性。

壳聚糖基材料通常采用微环境刺激响应释放药物, 如pH、温度[74]、ROS[75]、酶[76]、谷胱甘肽[77]等, 其中pH是常见的药物释放响应方式。Cai等[78]设计了一种基于羧甲基壳聚糖和氧化葡聚糖 (oxidized-dextran, ODex) 的可注射羧甲基壳聚糖水凝胶 (CMCS-OD), 并对其携载的药物embelin (Emb) 进行了释放曲线测定, 结果显示, 在pH = 5.0的环境中前8 h释放率为15%, 而在pH = 7.4时, 仅释放了10%。交联的CMCS-OD网络由许多酰胺键组成, 酰胺键可以与氢离子反应产生阳离子-NH_3, 在酸性条件下, 会产生大量-NH_3, 从而提高凝胶系统的缓冲能力, 使网络结构松动, 有利于Emb的释放。研究还发现, 在37 ℃时Emb释放量高于25 ℃, 这主要是因为Emb在较高温度下的溶解度和扩散系数增加, 说明CMCS-OD输送系统对pH值和温度具有积极的响应性。进一步研究发现, CMCS-OD输送系统在12 h后释放速率逐渐降低, 24 h时趋于稳定, 48 h后释放速率保持不变, 到第15天, 累积释放率达到90%, 累积释放质量几乎达到1 800 μg。在不同的pH值和温度条件下, Emb的释放模式相似, 说明CMCS-OD输送系统具有良好的缓释效果。

3.2.3 渗透增强 壳聚糖基材料通过与黏膜相互作用, 打开细胞间的紧密连接, 从而刺激药物通过黏膜细胞, 增强药物的渗透性[27]。高度脱乙酰化和高分子质量的壳聚糖具有更高的渗透增强作用。而改性壳聚糖如季铵化壳聚糖、硫醇化壳聚糖等比壳聚糖本身具有更好的渗透效果[79]。

Wang等[80]由壳聚糖、海藻酸钠和乙基纤维素 (ethyl cellulose ether, EC) 制备的单向释放含憎水层EC薄膜, 通过蛋白质印迹和免疫荧光表明, 给药后2～6 h显著抑制了TR146细胞中闭锁连接蛋白-1 (zonula occludens protein 1, ZO-1) 的表达, 2、4和6 h时, EC组ZO-1表达较正常组分别下降29.08%、28.48%和24.71%, 表明壳聚糖对药物渗透性的增强作用可能与ZO-1蛋白的调控有关。Rahbarian等[81]制备了负载胰岛素的硫代三乙基壳聚糖NPs, 通过离体渗透研究发现, 硫代三乙基壳聚糖NPs在离体黏膜中的渗透量为11.1 μg, 三乙基壳聚糖NPs为9.8 μg, 而未被修饰的壳聚糖NPs为1.8 μg, 说明改性壳聚糖比壳聚糖具有更好的渗透增强效果, 是口腔黏膜给药的潜在渗透增强剂。

3.2.4 提高药物生物利用度 一些药物因自身理化特性导致其生物利用度较低, 从而限制了它们的应用。而壳聚糖基材料可以通过增强药物的溶解性和稳定性等方式, 提高此类药物的生物利用度[82]。

盐酸替扎尼定 (tizanidine hydrochloride, TZN) 容易氧化, 并且在光热条件下不稳定, Arpa等[83]使用谷氨酸壳聚糖和壳聚糖共轭壬二酸酯负载TZN制得了口腔贴片。体内研究表明, 与商业产品相比生物利用度约提高了3倍, 表明壳聚糖基材料可以有效增加TZN的全身生物利用度, 并降低给药剂量和频率。

姜黄素水溶性差且具有光敏性和化学不稳定性, 这限制了其生物利用。但Ortega等[84]将姜黄素负载于涂有壳聚糖的脂质核心纳米胶囊中, 发现姜黄素的水溶性为0.78 μg·mL^{-1}, 而使用壳聚糖NPs包载后姜黄素的质量浓度提升至90 μg·mL^{-1}, 使姜黄素的水解性提高了约100倍, 从而提高其生物利用度。

4 展望与挑战

口腔黏膜给药作为新型给药途径, 已得到广泛研究, 但是某些药物由于其自身的理化性质或受到口腔内特殊环境的制约, 导致口腔黏膜给药系统的设计受到挑战。壳聚糖基材料具备强黏附性、缓释、控释、促渗作用、改善药物的理化性质, 能够保护药物免受口腔环境的侵害, 延长药物在口腔黏膜上的滞留时间, 延缓药物的释放, 减少药物损耗, 可以打开上皮细胞的紧密连接, 促进药物吸收, 增加药物的生物利用度, 并且壳聚糖具有大量正电荷和丰富的化学修饰位点, 易于改性并制备适用于口腔黏膜给药的各种剂型。除此之外, 壳聚糖基材料能够包载药物、蛋白和核酸等, 可以克服物理和生物障碍, 减少不良反应, 而且应用成本低, 制备工艺简便, 可批量生产, 因此壳聚糖基材料在口腔黏膜给药系统的实际应用中具有可行性, 并表现出巨大发展潜力。本文介绍了壳聚糖基材料及口腔黏膜给药系统, 并全面综述了壳聚糖基材料在口腔黏膜给药系统中的研究与应用, 旨在为进一步研究口腔黏膜给药系统提供借鉴和启示。

壳聚糖基材料可与3D打印技术、纳米技术、生物技术等其他先进技术相结合, 进一步革新口腔黏膜给药系统。如结合刺激响应或智能系统实现特定时间或部位的药物释放, 利用纳米级载体实现药物和成像剂的联合给药, 或与靶向治疗方法相结合。这些进步有可能彻底改变给药方式, 并提高口腔黏膜给药系统的治疗效果。然而, 壳聚糖基材料在临床研究和市场转化之间存在差距, 改性壳聚糖的安全性和质量评价等存在问题, 壳聚糖基材料作为载体在口腔黏膜给药系统中载药能力, 稳定包裹药物能力, 准确控制药物释放时间, 释放效果的持续性, 对口腔微生态的影响, 降解产物的去向等方面仍存在许多疑问, 这些阻碍使壳聚糖基材料在口腔黏膜给药系统中的开发与应用受到了挑战, 仍需要进一步的实验来证明它们在人类中的优异疗效和生物安全性。因此, 未来的研究应侧重于开展高载药量的口腔黏膜递药技术, 系统评价壳聚糖基材料的稳定性和安全性, 明确递药机制, 尽快实现壳聚糖基材料的适当标准化, 以提高其在口腔黏膜给药系统临床应用的可能性。 此外, 壳聚糖基材料的研究方向应多元化发展, 如改进壳聚糖的物理或化学修饰方法, 合成更具有优越性能的产物, 壳聚糖基材料与其他生物材料聚合合成多组分和多功能平台, 用于口腔黏膜给药系统的壳聚糖基材料不断优化并与其他尖端技术进行整合发展。综上所述, 基于壳聚糖基材料的口腔黏膜给药系统具有良好的应用前景。

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