新型载药系统在放化疗性口腔黏膜炎防治中的研究进展

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摘要: 口腔黏膜炎 (oral mucositis, OM) 是肿瘤放化疗常见的并发症, 其引发的剧烈疼痛和溃疡不仅显著降低患者生存质量, 还可导致抗肿瘤治疗中断。目前, 局部给药仍是OM防治的首选策略。然而, 传统剂型 (如漱口水、凝胶剂) 存在黏膜滞留时间短、易受唾液冲刷、药物清除快等药代动力学缺陷。近年来, 纳米、微针和水凝胶等新型载药系统凭借其良好的生物相容性和可控释放特性, 在提高药物黏膜靶向性和延长作用时间方面展现出显著优势。本文总结了上述3种载药系统在OM防治中的研究进展, 讨论了新型递送技术当前面临的挑战, 并对未来研究方向进行了展望, 旨在为开发更高效的OM治疗策略提供参考。

关键词: 口腔黏膜炎; 新型载药系统; 纳米递送; 微针; 水凝胶

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Research progress on novel drug delivery systems for chemoradiotherapy-induced oral mucositis

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Abstract: Oral mucositis (OM) is a common complication of radiotherapy and chemotherapy in cancer patients. The severe pain and ulcer caused by OM not only significantly impair patients' quality of life but may also lead to the interruption of antitumor therapy. Currently, topical drug administration remains the preferred strategy for the prevention and treatment of OM. However, conventional dosage forms (e.g., mouthwash, gel) are susceptible to salivary clearance, exhibiting pharmacokinetic limitations such as short mucosal retention time and rapid drug clearance. In recent years, novel drug delivery systems, including nanocarrier, microneedle and hydrogel, have demonstrated significant advantages in enhancing mucosal drug targeting and prolonging therapeutic duration due to their excellent biocompatibility and controlled release properties. This review summarizes the recent research progress of the above three drug delivery systems in the prevention and treatment of OM, discusses current challenges faced by advanced delivery technologies, and outlines future research directions, aiming to provide insights for the development of more effective therapeutic strategies for OM.

Key words: oral mucositis; novel drug delivery system; nanocarrier; microneedle; hydrogel

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口腔黏膜炎 (oral mucositis, OM) 作为抗癌治疗的常见并发症之一, 其临床负担日益凸显。流行病学数据显示, 放射性口腔黏膜炎 (radiation-induced oral mucositis, RIOM) 发病率超过 90%, 3 级或 4 级 RIOM 在头颈部肿瘤患者中发病率接近 85%。传统化疗中约 30%～40% 患者会出现 OM, 而放化疗联合要比单纯化疗诱发 OM 的比例更高[1]。OM 引发的剧烈口腔疼痛和吞咽困难, 不仅显著降低患者的生活质量, 还增加了医疗成本[2]。因此, 在接受抗癌治疗的同时, 有效预防和管理 OM 至关重要。

OM 病理机制可用五阶段模型来描述[3], 各阶段发生的关键生物事件 (如氧化应激、炎症反应和菌群失调等) 为其干预策略提供了多种选择。局部给药因全身吸收较少, 显著降低全身不良反应的风险。然而, 湿润的口腔环境和吞咽、咀嚼等肌肉运动, 使得药物难以在局部有效滞留, 这给局部用药带来巨大挑战[4]。因此, 研究者们开发了更适合口腔黏膜的新型载药系统, 如可增强药物渗透和改善溶解性的纳米载体、无痛穿透黏膜屏障且避开唾液冲刷的微针阵列、增强生物黏附和长效缓释的水凝胶。通过靶向递送和控释技术克服了传统剂型的局限, 增强治疗效果。本综述将重点阐述上述 3 种载药系统在 OM 防治中的研究进展及其不同设计原理和特点, 最后提出新型载药系统发展的挑战和前景展望, 为实现口腔黏膜的高效靶向治疗提供参考。

1　OM 病理机制

Sonis 于 2004 年提出 OM 五阶段模型 (起始、上调、信号放大、溃疡、愈合)[3], 各阶段呈现出不同的病理变化和临床表现 (表 1)。起始阶段, 放化疗直接诱导活性氧 (reactive oxygen species, ROS) 爆发及 DNA 损伤, 激活核因子 κB (nuclear factor κB, NF-κB) 等促炎信号通路[5-8], 从而导致基底上皮细胞凋亡[9]。此阶段, 患者通常无明显自觉症状。信号上调阶段, NF-κB 通路激活驱动肿瘤坏死因子 (tumor necrosis factor, TNF-α)、白细胞介素-1β (interleukin-1β, IL-1β)、白介素-6 (interleukin-6, IL-6)、环氧化酶-2 (cyclooxygenase-2, COX-2) 等下游促炎因子的释放, 募集单核/中性粒细胞并增强血管通透性, 形成“ROS-炎症”恶性循环[3,10]。此阶段黏膜敏感性增加, 患者可出现轻微灼热感、瘙痒感等前驱症状。信号传递和放大阶段, 初级损伤反应期间产生的各种下游分子会对易感细胞产生正反馈, 启动额外的信号传导, 从而进一步放大局部炎症反应[9,11]。临床上, 患者口腔黏膜可能出现轻微红斑, 甚至伴有自觉疼痛。尽管如此, 黏膜的完整性未受影响。溃疡阶段, 黏膜和黏膜下层的完整性遭到破坏, 溃疡中定植的口腔细菌直接刺激浸润的巨噬细胞、中性粒细胞和淋巴细胞分泌更多的促炎细胞因子, 从而扩大黏膜损伤程度[12]。中性粒细胞显著减少的癌症患者甚至可能发生菌血症或败血症[13]。由于覆盖固有层神经末梢的上皮脱落, 溃疡阶段是最痛苦的, 甚至影响患者进食及营养状况, 故此阶段的疼痛管理尤为重要[14]。随着化疗或放疗的停止, 愈合逐渐开始, 其特点是上皮细胞在细胞外基质的促进下发生增殖、迁移和分化, 局部微生物菌群重新建立, 黏膜连续性恢复[15]。此阶段, 患者溃疡逐渐愈合, 疼痛减轻。值得注意的是, 在临床实践中, 放化疗引发的损伤是一个复杂的动态演进过程, 各个阶段相互交织、存在重叠。因此, OM 的药物治疗呈现出多靶点、分阶段干预特点。早期 (起始、上调阶段) 侧重于抗氧化和抗炎, 以中断“ROS-炎症”恶性循环; 溃疡阶段则强调镇痛、抗感染和物理屏障保护; 愈合阶段则需提供适宜的微环境以促进上皮再生与菌群平衡。理想的治疗策略需兼具长效局部滞留与药物控释能力, 避免唾液冲刷, 以应对特殊的口腔环境。

2　OM 局部药物递送挑战

局部给药因其操作简便和病灶靶向富集性, 已成为 OM 防治的主要治疗形式。基于 OM 多机制病理特征, 局部治疗药物可分为抗氧化、抗菌、抗炎、镇痛、促修复和黏膜保护剂几种类型。褪黑素虽具有显著抗氧化特性, 但其口服生物利用度较低 (约 9%～33%)[16]。常用抗菌消炎药如氯己定、聚维酮碘和苄达明主要采用漱口水剂型递送, 虽可有效预防 OM 发生和降低其严重程度[17-19], 但停留在局部的作用时间短, 需频繁使用, 且容易引起味觉改变和黏膜刺激。天然抗炎药物如姜黄中提取的姜黄素虽能缓解 OM 症状, 却受限于低水溶性和生物利用度[20-22]。新上市的益普舒口腔凝胶能快速形成保护膜以效缓解口腔疼痛[23], 但该凝胶剂型易被唾液稀释, 且部分患者使用后会出现恶心等不良反应[24]。尽管现有剂型在缓解症状和促进愈合方面具有不错疗效, 但仍存在黏附性差、作用时间短、药物溶出率差等递送困境。因此, 为提高局部药物利用率和治疗效果, 研究者们开发了一系列新型载药系统克服传统剂型递送局限。

3　纳米载药系统在 OM 防治中的应用

纳米材料因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[25,26]。目前, 已有多种纳米载体用于 OM 的治疗 (图 1), 如脂质体 (liposome, LPS)、聚合物纳米粒 (polymeric nanoparticles, PNPs)、金纳米颗粒 (gold nanoparticles, AuNPs)、纳米乳凝胶、纳米纤维结

Table 1 Characteristics of the five stage models of oral mucositis (OM). ROS: Reactive oxygen species; NF-*κ*B: Nuclear factor *κ*B; TNF-*α*: Tumor necrosis factor; IL-1*β*: Interleukin-1*β*; IL-6: Interleukin-6; COX-2: Cyclooxygenase-2

Pathological stage	Core driving event and molecular mechanism	Cellular/histological change	Clinical characteristic	Treatment strategy
Initiation	Direct induction of ROS burst and DNA damage by radiotherapy/chemotherapy; activation of pro-inflammatory pathways such as NF-*κ*B	Apoptosis of basal epithelial cells	Patients are usually asymptomatic	Antioxidant
Upregulation	NF-*κ*B activation drives the release of pro-inflammatory factors (e.g., TNF-*α*, IL-1*β*, IL-6, COX-2), establishing a "ROS-inflammation" vicious cycle	Increased monocytes/ neutrophils; vasodilation and increased vascular permeability	Increased sensitivity of mucosa, possible prodromal symptoms such as burning sensation and itching	Anti-inflammatory
Signal amplification	Positive feedback of primary inflammatory signals on susceptible cells, further amplifying the local inflammatory response	Aggravated inflammatory cell infiltration; appearance of mild red rash on the mucosa, with integrity remaining intact	Mild erythema appears on the mucosa, and the patient may experience mild pain	Anti-inflammatory; analgesia
Ulceration	Disruption of mucosal integrity and epithelial sloughing; direct stimulation of immune cells by oral flora, leading to increased secretion of inflammatory factors and expanded tissue damage; exposure of nerve endings in the lamina propria	Massive infiltration of immune cells; formation of ulcerative lesions on the mucosa	Ulcers appear on the mucosa, and severe pain may affect the patient's eating and nutritional status	Analgesia; mucosal protection; antibacterial
Healing	Cessation of anticancer therapy; proliferation, migration, and differentiation of epithelial cells; extracellular matrix facilitates repair; reconstruction of the local microbiota	Migration of epithelial cells from the ulcer margins towards the center; gradual restoration of mucosal continuity	The ulcer gradually heals and the pain decreases	Promotion of mucosal repair

构等。这些纳米载体可以提供修饰和受控的药物释放, 增强黏膜黏附性和停留时间, 有利于降低给药频率和提高患者的依从性[27]。表2对各类纳米载药系统的核心特性进行了归纳总结。

3.1 LPS LPS是以两亲性磷脂分子为基本单元形成的双层膜囊泡结构, 因其低毒、可降解及良好的组织相容性成为局部药物递送的理想纳米载体[28]。基于独特的双亲性分子排列, 该体系可实现亲水性药物内核包载

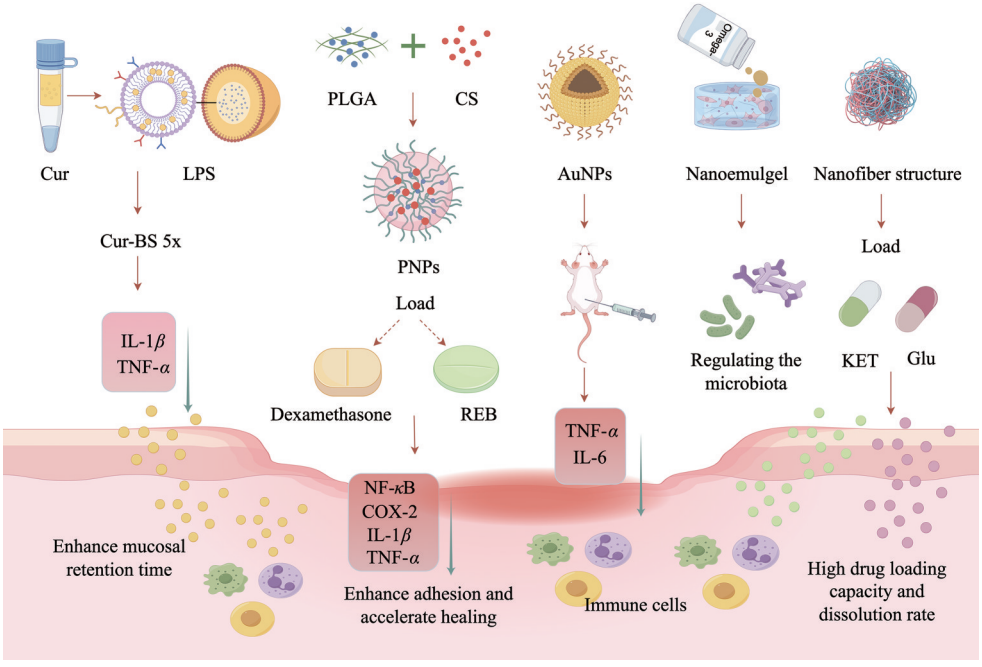


Figure 1 Nano drug delivery carriers and their mechanism of action for treating OM. Cur: Curcumin; cur-BS: Curcumin-loaded bicosome systems; LPS: Liposome; PLGA: Poly (lactic-*co*-glycolic acid); CS: Chitosan; PNPs: Polymeric nanoparticles; REB: Rebamipide; AuNPs: Gold nanoparticles; KET: Ketoprofen; Glu: Glutamine

Table 2　Comparison of the characteristics of nano-drug delivery systems for the prevention and treatment of OM. RIOM: Radiation-induced oral mucositis

Nanocarrier type	Main material	Advantage	Limitation
Liposome	Phospholipids, cholesterol	Co-delivery of hydrophilic and hydrophobic drugs; good biocompatibility and biodegradability	Potential drug leakage; poor long-term storage stability
Polymeric nanoparticles	PLGA, chitosan, alginate, gelatin	Stable structure, easy storage; controllable release; easy surface modification	Synthetic polymers may have poor biocompatibility; degradation products might induce local immune reactions
Gold nanoparticles	Gold, surface-modified molecules	Targeted delivery; inherent antibacterial and anti-inflammatory properties	High preparation cost; potential toxicity upon long-term exposure or high-dose use
Nanoemulsion gel	Oil phase, aqueous phase, surfactant, gel matrix	Combine high permeability with long-term retention; high drug loading capacity, thermodynamically stable	Complex formulation composition; the precise release of drugs is difficult
Nanofiber structure	Synthetic/natural polymers	High surface area-to-volume ratio, high drug loading capacity	Insufficient mechanical strength; high preparation cost

与疏水性药物膜间嵌入的协同负载模式, 从而在保障药物稳定性的同时实现可控释放; 其次, 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。LPS已成为姜黄素等易降解生物活性化合物的理想递送系统[29]。Vergara等[30]评估了负载姜黄素的双组分脂质体 (curcumin-loaded bicosome systems, cur-BS) 对化疗诱导的小鼠OM的疗效。通过体外渗透、释放谱分析和抗炎功效等实验发现, 高浓度cur-BS不仅下调了IL-1β和TNF-α的表达, 还通过扩散和基质松弛的机制提供了缓释, 增强了姜黄素在黏膜深层的保留。LPS的独特结构增强了姜黄素在口腔黏膜的渗透和生物利用度, 增强了抗炎、抗氧化能力, 从而有效地靶向OM的起始与炎症反应阶段。虽然LPS作为药物递送系统具有明显优势, 但也存在药物容易渗漏、长期储存稳定性不足等缺陷。

3.2　PNPs　PNPs是一类粒径为1～100 nm的微粒系统, 由聚合物分子通过物理或化学方法组装而成。它们兼具聚合物的可加工性、生物相容性及化学多样性, 同时因纳米尺寸效应 (如高比表面积、量子限域效应) 而表现出独特的理化性质。PNPs通常包含聚乳酸羟基乙酸 [poly (lactic-*co*-glycolic acid), PLGA]、藻酸盐、明胶、壳聚糖等生物材料, 能抵抗蛋白酶降解, 并通过药物包埋实现可控释放, 从而减少给药频率[31]。Takeuchi等[32]开发了一种壳聚糖包被瑞巴派特的PNPs, 显著增强了口腔黏膜黏附性, 延长了药物在口腔的滞留时间, 并加速了OM的愈合。Ribeiro等[33]通过溶剂乳化–蒸发法制备负载地塞米松的PNPs, 通过下调NF-κB、COX-2及TNF-α等促炎因子, 有效预防了5-氟尿嘧啶诱导的OM。该策略精准靶向了OM病理进程中的主要炎性信号通路 (NF-κB), 从源头上抑制了炎症瀑布式放大。然而, 过强的黏附可能导致PNPs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。因此, 黏附性并非越强越好, 需在“滞留”与“穿透”之间寻求平衡。

3.3　AuNPs　AuNPs因其表面易于修饰的特性能够高效负载药物并实现精准的靶向释放[34]。其突出的抗菌性能在药物递送领域展现出显著的协同治疗优势[35]。在5-氟尿嘧啶诱导的仓鼠OM模型中, 腹腔注射高剂量AuNPs (250 μg·kg^{-1}) 显著降低了TNF-α、IL-6水平, 这可能与AuNp的抗炎、抗氧化特性密切相关[36]。尽管该研究是通过腹腔注射给药证实了AuNPs的抗炎效果, 但其优异的抗菌、抗炎特性及表面易于功能化的特点, 为未来开发AuNPs的局部漱口水、凝胶或黏膜黏附膜剂等提供了实证参考, 有望成为干预OM信号上调与放大阶段的潜力策略。然而, AuNPs的临床应用仍面临两大挑战: 合成成本较高, 以及长期局部使用的生物安全性尚需系统评估。

3.4　纳米乳凝胶　纳米乳凝胶是一种结合纳米乳剂与凝胶优势的新型递药系统, 兼具高渗透性和长效滞留特性。其乳剂组分可保护药物免遭酶解, 并增强黏膜渗透性, 而凝胶基质则通过提高黏附性延长局部滞留时间, 同时优化热力学稳定性。相较于传统纳米载体, 纳米乳凝胶具有载药量高、渗透性强及低刺激性等优势[37,38]。Morsy等[39]制备的Omega-3纳米乳凝胶不仅可预防RIOM的发生, 还可调控口腔微生物稳态。纳米乳凝胶通过结合乳剂与凝胶的优势, 有效提升了药物的渗透与滞留。但由于药物的释放需要经历从凝胶基质中扩散和从乳滴中释放两个过程, 其释放动力学受多种因素影响, 精准调控以实现按需释放的难度较大。除了这种“液–固”结合的递送策略, 静电纺丝技术构建的固态纳米纤维支架, 以其高比表面积和仿生细胞外基质结构, 为OM治疗提供了另一条独特的递送路径。

3.5　纳米纤维结构　纳米纤维结构主要通过静电纺

丝技术编织而成, 由于其高面积体积比和材料多样性, 在药物递送方面具有显著潜力。静电纺丝技术通过电荷驱动机制优化了治疗剂的渗透和递送效率[40]。Tort等[41]采用静电纺丝技术成功开发了负载谷氨酰胺的黏膜黏附纳米纤维结构, 因其载药量大、黏附性强并且高药物溶出率等优异性能, 可作为治疗OM的有效递送措施。因酮洛芬口服容易出现胃肠道出血和肾功能不全等不良反应, Reda等[42]通过静电纺丝技术制备了负载酮洛芬的纳米纤维结构, 不仅载药量大, 且稳定释放, 经局部颊侧输送减轻了家兔OM的严重程度。虽然纳米纤维在OM治疗中具有载药量大的优势, 但大规模静电纺丝技术仍面临挑战。

4 微针载药系统在OM防治中的应用

微针是微米大小的尖锐突出物, 当应用于皮肤时, 具有微创性和无痛性[43], 通过破坏上皮或纤维生物屏障, 促进药剂渗透到皮肤或黏膜中, 直接递送药物至深层组织或毛细血管, 提高了大分子药物的生物利用度[44,45]。根据结构特性, 微针主要被分为实体、涂层、空心、可溶性及水凝胶几种类型 (图2)。可溶性微针具有一定的机械强度, 可插入口腔黏膜, 形成多个微小通道, 随后溶解到液体中, 迅速释放药物, 在口腔黏膜疾病中应用最为广泛[46-48]。Qu等[49]开发的白及多糖可溶性微针, 负载曲安奈德介孔多巴胺纳米颗粒用于治疗OM (图2)。该体系结合了纳米颗粒的优异性能, 不仅具备快速溶解 (< 3 min) 和高效穿透性, 还能协同曲安奈德、白及多糖和透明质酸的抗炎作用, 降低TNF-α水平, 显著缩小了大鼠的溃疡面积。在OM防治中, 微针载药系统因其操作简便且能有效规避唾液冲刷, 尤其适用于需长期或频繁给药的患者, 提升治疗依从性。

5 水凝胶载药系统在OM防治中的应用

水凝胶是一种高吸水性三维聚合物网络结构, 凭借其优异的生物相容性和可设计的理化特性 (如可注射原位成胶、温度/pH响应性、组织黏附性) 已成为大部分药物递送的理想载体[50]。根据原料来源不同, 水凝胶可分为天然型 (如胶原蛋白、透明质酸、藻酸盐) 和合成型 (如聚丙烯酰胺、聚乙烯醇等), 二者均具有良好的生物相容性与可调控的药物释放能力, 不仅能增强药物渗透性, 还可延长药物在黏膜局部的滞留时间[51,52]。值得注意的是, 由透明质酸、壳聚糖、白及多糖等天然聚合物构成的水凝胶, 不仅能为溃疡创面提供物理屏障和湿润的愈合环境, 还兼具固有的抗炎与抗氧化活性, 通过负载不同类型的药物和化合物, 从而实现对OM多个病理环节的协同干预 (图3)。

Zhao等[53]开发的可喷涂原位水凝胶, 通过负载富勒烯醇可清除ROS从而保护黏膜上皮细胞的增殖和迁移, 不仅能有效缓解RIOM, 同时还可调节口腔微生态平衡。Ding等[54]设计的双功能鸟苷−聚乙烯醇超分子水凝胶, 通过动态硼酸酯键交联, 融合物理屏蔽与化学修复特性, 具有显著的湿黏附性、生物相容性和口腔环境适应性, 不仅减轻了氧化应激, 还能保护细胞免受直接损伤。体内动物研究表明, 这种超分子水凝胶显著降低了RIOM的发生。Shao等[55]以温度敏感的PLGA-PEG-PLGA (PPP) 为基质、具有固有抗菌活性的表没食子儿茶素没食子酸酯 (EGCG) 为黏附增强剂, 成功制备了装载三肽KPV的原位黏膜黏附水凝胶 (KPV@PPP_E)。这种水凝胶能在溃疡创面持续保留

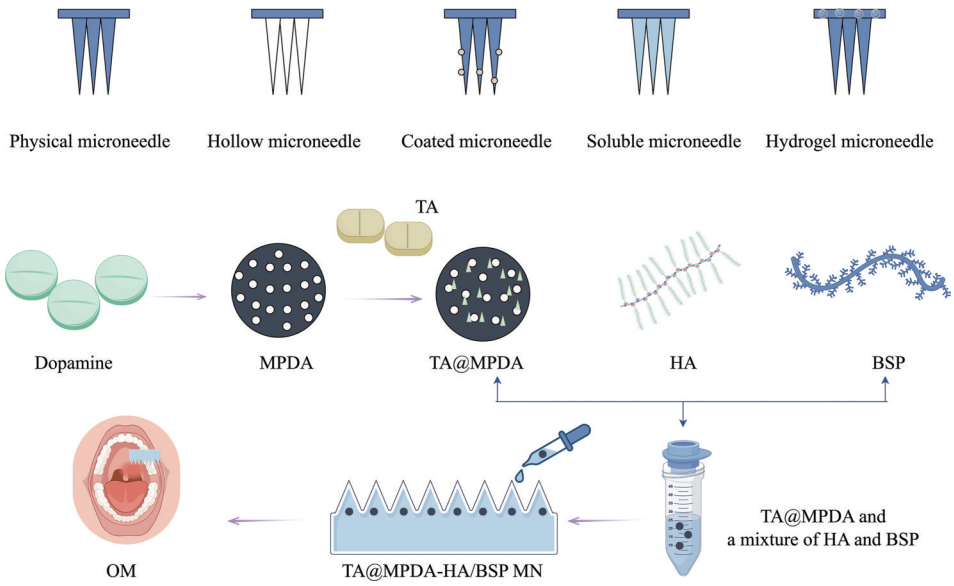


Figure 2 Classification of microneedles and TA@MPDA-HA/BSP MN's preparation and application. TA: Triamcinolone acetonide; MPDA: Mesoporous polydopamine nanoparticles; HA: Hyaluronic acid; BSP: *Bletilla striata* polysaccharide; MN: Microneedle

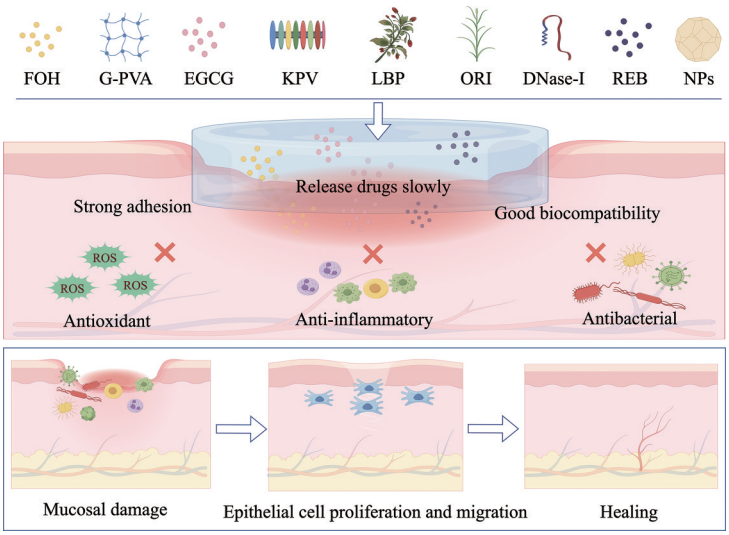


Figure 3　Schematic illustration of hydrogel-based drug delivery systems for the prevention and treatment of oral mucositis. FOH: Fullerenols; G-PVA: Guanosine-polyvinyl alcohol; EGCG: Epigallocate-chin-3-gallate; LBP: *Lycium barbarum* polysaccharide-glycoprotein; ORI: Oridonin; DNase-I: Deoxyribonuclease-I; NPs: Nanocrystals

至少 7 h, 可有效抵抗唾液冲刷, 延长局部作用时间, 实现无创、精准的局部给药。同时, KPV@PPP_E 水凝胶保留了 KPV 的抗炎和促修复能力, 对金黄色葡萄球菌有很强抗菌功效。在化疗诱导的 OM 大鼠模型中, KPV@PPP_E 水凝胶显著改善了动物的摄食量与体重, 促进了牙龈组织形态修复, 并有效抑制了炎症因子表达。Jiang 等[56]构建的枸杞多糖糖蛋白热敏水凝胶通过激活 Nrf2 通路抑制氧化应激与铁死亡, 使大鼠的放射性溃疡面积减少 57%。Pan 等[57]开发的基于 ε-聚赖氨酸和羟乙基淀粉的半互穿网络水凝胶系统, 通过协同可控释放冬凌草甲素和脱氧核糖核酸酶- I, 有效清除中性粒细胞胞外诱捕网并加速 OM 溃疡愈合。为了增强瑞巴派特对 OM 的治疗效果, Nagai 等[58]开发了一种包含瑞巴派特纳米晶体 水凝胶, 通过珠磨法减小瑞巴派特的粒径, 使其以纳米晶体形式释放, 经网格蛋白介导的内吞作用被仓鼠颊囊组织摄取, 减轻了仓鼠 OM 的发生, 促进口腔伤口愈合。这些创新设计通过整合黏附、抗菌、抗氧化及控释等功能, 为 OM 的治疗提供了高效、安全的解决方案, 展现出广阔的临床应用前景。

纳米载药系统、微针与水凝胶作为应对 OM 局部治疗挑战的前沿策略, 在机制与应用上呈现显著的互补性, 同时各自也面临技术瓶颈。表 3 总结比较了 3 类载药系统在 OM 防治中的特点。

6　总结与展望

OM 作为抗癌治疗的常见并发症, 严重影响患者的生活质量, 并增加医疗负担。局部药物治疗通过直接作用黏膜病灶并减少全身不良反应, 被视为 OM 管理的理想策略。然而, 口腔是具有唾液冲刷和黏膜运动的湿润环境, 传统剂型难以使药物在其中持续维持有效浓度, 治疗效果受到限制。近年来, 新型载药系统的发展为增强 OM 局部治疗效率提供了新的可能。通过将药物封装于脂质体、聚合物纳米粒等纳米载体中, 显著提高了难溶性药物 (如姜黄素) 的溶解性与稳定性, 增强了黏膜渗透能力, 并且实现药物的靶向递送与可控释放, 在抗炎、抗氧化及促进黏膜修复方面展现出

Table 3　Comparison of the characteristics of three novel drug delivery systems for the prevention and treatment of OM

Drug delivery system	Core advantage	Major limitation	Applicable drug type	Current research stage
Nanocarrier	Improve the solubility of drugs; enhance mucosal permeability	Susceptible to rapid clearance by saliva	Small molecule drugs; natural products (e.g., curcumin)	Preclinical research (animal models)
Microneedle	Painless penetration of the mucosal barrier, enabling direct delivery to the lesion site; avoids salivary washout	Limited drug loading capacity; insufficient mechanical strength	Macromolecular drugs (e.g., proteins, antibodies) and highly potent small molecules	Preclinical research (animal models)
Hydrogel	Excellent bioadhesion, enabling prolonged local retention; provides a physical barrier and a moist environment	Lower biocompatibility of synthetic materials; insufficient mechanical strength	Broadly applicable, particularly suitable for drugs requiring sustained release (e.g., small molecules, proteins, cytokines)	Preclinical research (animal models)

独特优势。微针通过无痛穿透黏膜屏障, 避开唾液冲刷, 实现大分子药物的高效递送, 可快速释放药物, 从而加速溃疡创面愈合。水凝胶凭借优异的生物黏附性显著延长药物在口腔黏膜的滞留时间, 有效抵抗唾液冲刷, 为溃疡创面提供了理想的物理屏障和愈合环境。同时, 还能通过响应外界刺激实现靶向可控释放。

尽管这几种新型载药系统在基础研究中显示出令人鼓舞的结果, 但其临床转化仍面临多重挑战。首先, 安全性评价方面: 纳米材料在体内长期暴露、微针在口腔组织中的相容性, 以及水凝胶降解产物的潜在毒性, 均需进行系统、长期的生物安全性评估; 其次, 规模化生产方面: 纳米系统的批次间质量控制、微针阵列的精密加工与成本控制, 以及水凝胶性能的稳定性, 均是实现大规模工业化生产的现实难题; 此外, 监管审批方面: 新型复杂制剂面临着比传统剂型更为严格的监管审批路径, 其质量源于设计理念、明确的理化特性与体内外相关性证据, 是获得监管批准的前提。

为推进新型载药系统在OM防治中的实际应用, 未来研究应采取更具针对性与可操作性的措施。针对纳米载药系统, 应优先开发天然来源、温和安全的药用辅料, 并推动微流控等先进工艺以实现规模化、可控化生产。针对微针, 重点在于优化其在湿润口腔环境下的力学性能, 平衡机械强度与溶解行为, 并发展适应口腔曲面的柔性贴片设计。例如, 可通过引入海藻酸钠等亲水聚合物与明胶共混, 以调控其在唾液中的溶胀行为与机械强度。针对水凝胶, 需深入开展长期植入的生物相容性研究, 优先选用胶原蛋白、明胶、壳聚糖、海藻酸盐等天然高分子材料, 并积极推进对pH、ROS或酶等微环境敏感的智能型水凝胶开发, 实现药物的精准按需释放。

综上, 通过智能集成不同系统的优势, 构建协同递药平台 (如纳米粒−微针复合系统、纳米粒−水凝胶复合载体等), 形成功能互补的联合策略, 将是未来OM局部靶向治疗的重要发展方向。同时, 应积极推进制造工艺标准化、加强天然制剂的安全性评价, 开展多中心大样本临床研究, 系统积累真实世界疗效与安全性数据, 为最终临床转化提供坚实基础。

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