International Journal of Nanomedicine

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Design and Application of Multiscale Systems and Scaffolds Based on Functional Polymeric Materials in Treating Chemoradiotherapy-Induced Oral Mucositis

Chuan Pi[1],*, Guoling Qin[2],*, Fuzhong Zhang[3],*, Yiwen Ren[3,4], Mengyu Luo[3,4], Daoyong Wang[3,4], Guohui Bai[3], Qixiong Zhang[5]

[1]Department of Pharmacy, Sichuan Provincial People's Hospital East Sichuan Hospital & Dazhou First People's Hospital, Dazhou, People's Republic of China; [2]Department of Nursing, Dazhou Vocational College of Chinese Medicine, Dazhou, People's Republic of China; [3]Key Laboratory of Oral Disease Research of the Education Department of Guizhou Province, Hospital of Stomatology, Zunyi Medical University, Zunyi, People's Republic of China; [4]The First Clinical Institute, Zunyi Medical University, Zunyi, People's Republic of China; [5]Department of Pharmacy, Personalized Drug Research and Therapy Key Laboratory of Sichuan Province, Sichuan Provincial People's Hospital, School of Medicine, University of Electronic Science and Technology of China, Chengdu, People's Republic of China

*These authors contributed equally to this work

Correspondence: Guohui Bai; Qixiong Zhang, Email baiguohui1228@126.com; qixiongzhang@outlook.com; zhangqixiong@uestc.edu.cn

Abstract: Chemoradiotherapy-induced oral mucositis (OM) is prevalent and complication in patients with head and neck cancers, characterized by mucosal erythema, erosion, and ulceration. OM not only causes severe pain, significantly impairs patients' quality of life, but may also disrupt the overall cancer treatment regimen. The complex and dynamic oral microenvironment presents a major challenge for effective OM management, while current clinical strategies remain limited in lack efficient drug delivery systems. In this context, functional polymeric materials have emerged as promising platforms for OM prevention and treatment due to their biocompatibility and adaptability to the oral microenvironment. This review systematically outlines the pathological changes in the oral microenvironment following radiotherapy or chemotherapy and discusses how these alterations impede conventional therapies. We then highlight recent advances in functional polymeric materials-based devices designed to target the pathological microenvironment for enhanced drug delivery and mucosal regeneration. Finally, we discuss the translational challenges and future directions of material-based strategies for OM, aiming to inform the development of more precise and effective approaches.

Keywords: chemoradiotherapy, oral mucositis, functional polymeric material, hydrogel, nanoparticle

Introduction

Cancer represents a significant public health challenge confronting the global community in the 21st century. As per the data provided by the National Institutes of Health in the United States, the annual incidence of cancer is projected to rise to 23.6 million by 2030. Radiotherapy (RT) and chemotherapy (CT) currently serve as the principal modalities for cancer treatment.[1] Nevertheless, owing to their non-specific cytotoxicity, these treatment modalities, while eradicating rapidly proliferating tumor cells, cause indiscriminately harm to actively regenerating normal tissues, consequently giving rise to a series of treatment - associated complications.[2] Among these, oral mucositis (OM) ranks as one of the most prevalent complications subsequent to radiotherapy and chemotherapy. Epidemiological data indicate that the incidence of OM is remarkably high.[3] Among patients undergoing standard chemotherapy, the incidence rate ranges from approximately 20% to 40%. Among patients receiving radiotherapy or combined chemoradiotherapy, the incidence rate can exceed 80%, and approximately one-third of these patients will develop severe (grade 3–4) OM.[2,4,5] OM induces severe pain, dysphagia, xerostomia, and secondary infections, leading to a marked reduction in patients' quality of life by impairing normal eating.

https://doi.org/10.2147/IJN.S602864
Received: 16 February 2026
Accepted: 18 April 2026
Published: 27 April 2026

Furthermore, severe OM can necessitate interruptions in radiotherapy or chemotherapy, thereby compromising overall cancer treatment outcomes.[6–8]

The onset and progression of OM are highly intricate, featuring multistage and dynamic evolution. Sonis et al classified OM into five stages according to its pathological alterations: the initiation stage, the primary injury stage, the signal amplification stage, the ulceration stage, and the healing stage. i) Initiation: radiotherapy and chemotherapy induce excessive oral reactive oxygen species (ROS) production, causing DNA damage and basal cell apoptosis. ii) Primary injury: ROS triggers innate immunity, activating P53, Wnt, NF-κB pathways and upregulating TNF-α, ILs, COX-2, CAMs. JNK activation enhances Nrf2 expression, exacerbating tissue damage. iii) Signal amplification: Pro-inflammatory cytokines establish a positive feedback loop, driving cell apoptosis and bacterial invasion via loosened epithelial junctions. PAMPs further upregulate inflammation, forming a vicious cycle. iv) Ulceration: Prolonged inflammation disrupts epithelial integrity, forming ulcers that facilitate microbial invasion into connective tissues, increasing bacteremia/sepsis risk. v) Healing: Post-treatment, stabilized oxidative stress and microbial remodeling, coupled with extracellular matrix/mesenchymal signaling, mediate epithelial regeneration.[5,9] Nevertheless, the genetic makeup of the regenerated mucosal epithelium differs from the original, potentially reducing the tissue's tolerance to radiotherapy and chemotherapy.

Currently, the management of OM primarily emphasizes preventive measures and symptomatic alleviation, including infection prevention, inflammation control, pain relief, and tissue healing promotion. Chlorhexidine mouthwash, an anti-infective agent, can reduce the incidence of OM by inhibiting the colonization of bacteria, fungi, and viruses.[10] Rebamipide, an anti-inflammatory and analgesic agent, shortens the duration of OM in cancer patients undergoing radiotherapy and chemotherapy through the suppression of ROS production in inflammatory cells and the elimination of hydroxyl radicals. Periplaneta americana Extract Liquid, a therapeutic agent facilitating tissue repair, notably mitigates the severity of OM.[11–13] Nonetheless, the dynamic oral microenvironment, which is distinguished by continuous moisture, a dense microbial community, and diverse bioactive enzymes, in conjunction with the continuous mechanical stress during mastication, causes the retention time of conventional therapeutic agents to be less than 30 minutes. As a result, these agents are insufficiently retained, leading to a bioavailability of less than 20%. This situation substantially impedes the effectiveness of the prevention, treatment, and management of OM, thus making it imperative to develop more advanced strategies for its prevention and control.[14–17]

With the progress of materials science, functional polymer materials have shown considerable potential in this field. Notably, numerous functional polymeric materials featuring outstanding biocompatibility can adhere tightly to mucosal tissues within the humid oral environment. This allows them to effectively withstand saliva flushing, enzymatic degradation, and mechanical stress from mastication, thus offering essential support for the long-term retention of drugs.[18] In light of these characteristics, functional polymeric materials, including hydrogels, patches, and microspheres, have been continuously explored and developed. These materials are capable of achieving sustained drug release at the lesion site, effectively suppressing the infiltration of inflammatory cells, and facilitating the migration of epithelial cells. Consequently, they can optimize the oral microenvironment, rendering it more favorable for the treatment of OM.[19] However, a comprehensive overview of their design and application is still absent. In this review, we systematically summarize the functional polymeric materials designed for the oral microenvironment in OM (Figure 1). Firstly, the microenvironment of OM is introduced, and the underlying reasons for its resistance to healing are explored. Subsequently, this review elaborates comprehensively expounds on the characteristics of various functional polymer materials and their action mechanisms in the treatment of OM, and simultaneously clarifies the therapeutic strategies for specific pathological stages. Ultimately, this paper deliberates on the current challenges in utilizing functional polymeric materials for OM treatment and anticipates future development trends in this field, with the aim of offering insights and inspiration for the development of next generation functional polymeric materials in this area.

The Oral Microenvironment of OM

The homeostasis of the oral microenvironment serves as the fundamental basis for maintaining mucosal health. It consists of an intact physical barrier, a suitable physiological milieu, a balanced microbial ecosystem, and effective immune surveillance.[20–22] Under normal physiological circumstances, the rich capillary blood supply, high efficiency epithelial regeneration rate, and minimal scar formation in the oral mucosal region endow mucosal lesions with rapid and efficient recuperative capacities. Consequently, oral mucosal lesions exhibit a faster healing rate compared to cutaneous

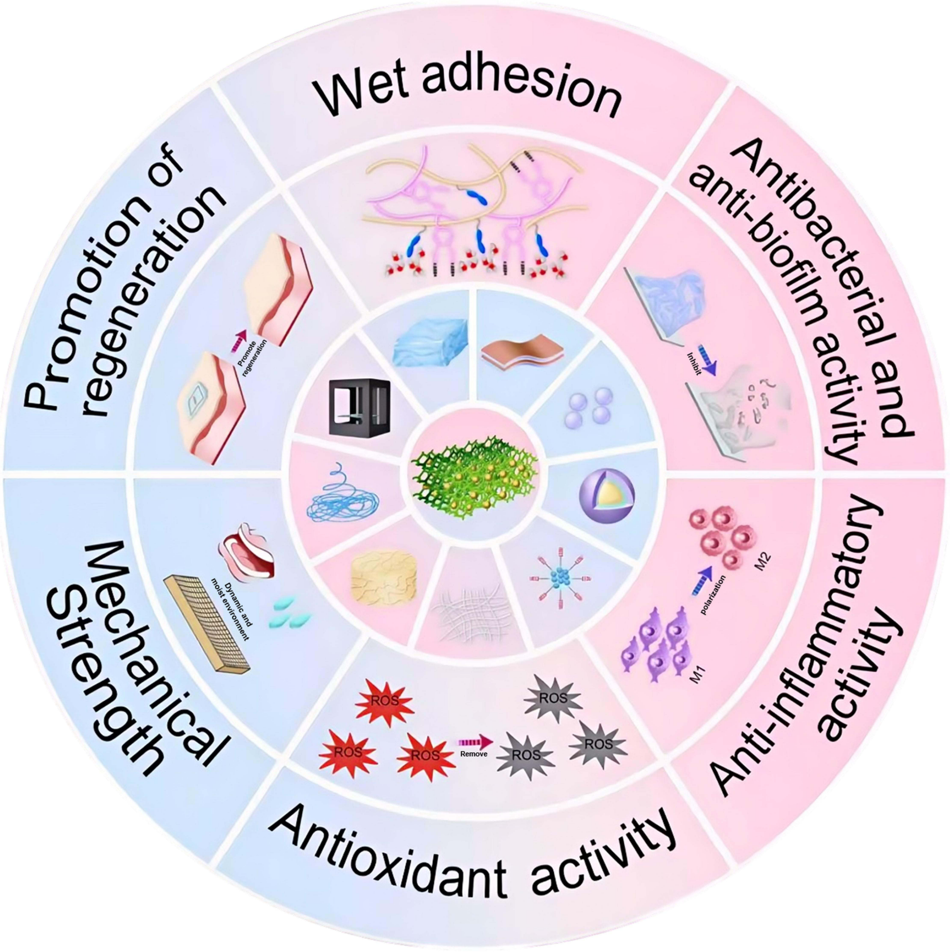

Figure 1 Schematic diagram of the classification and key properties of functional polymeric materials for OM treatment.

wounds.[23,24] Nevertheless, under the continuous influence of radiotherapy and chemotherapy, the mucosal lesions induced by OM present clinical features of delayed healing and pathological repair. The formation of this characteristic can be ascribed to the synergistic actions of multiple factors, including alterations in salivary gland function, dysregulation of microbial communities, persistent inflammatory reactions, intense oxidative stress stimuli, and impaired regeneration of vascular endothelium (Figure 2).[25,26] Therefore, comprehending the unique pathological environment and challenges of OM is not only advantageous for the treatment and prognosis of OM but also holds substantial significance for the design of polymer functional materials specifically targeting OM.

Salivary Gland Dysfunction and Alteration of Saliva Composition

Saliva functions as a weak buffer with a pH ranging from 5.5 to 7 and is predominantly composed of water, electrolytes, digestive enzymes, metabolites, mucins, and antimicrobial peptides. These components are indispensable for basic physiological functions, such as oral lubrication, the initiation of digestion, mucosal cleansing, and antibacterial defense, thus playing a crucial role in maintaining the health of the oral mucosa.[27] Research suggests that in a normal oral micro - environment, saliva contributes to the repair of mucosal lesions by promoting fibroblast proliferation and migration, accelerating keratinocyte renewal, and facilitating the release of growth factors.[19,28,29] However, cancer patients undergoing radiotherapy and chemotherapy, such as multi-drug combination therapy involving 5-fluorouracil, cyclophosphamide, methotrexate, and epirubicin, may encounter significant atrophy of the salivary glands. This condition can give rise to clinical manifestations like xerostomia and taste disorders, which may further lead to secondary complications, including mucosal atrophy, thinning, and congestion, thereby aggravating OM symptoms in cancer patients.

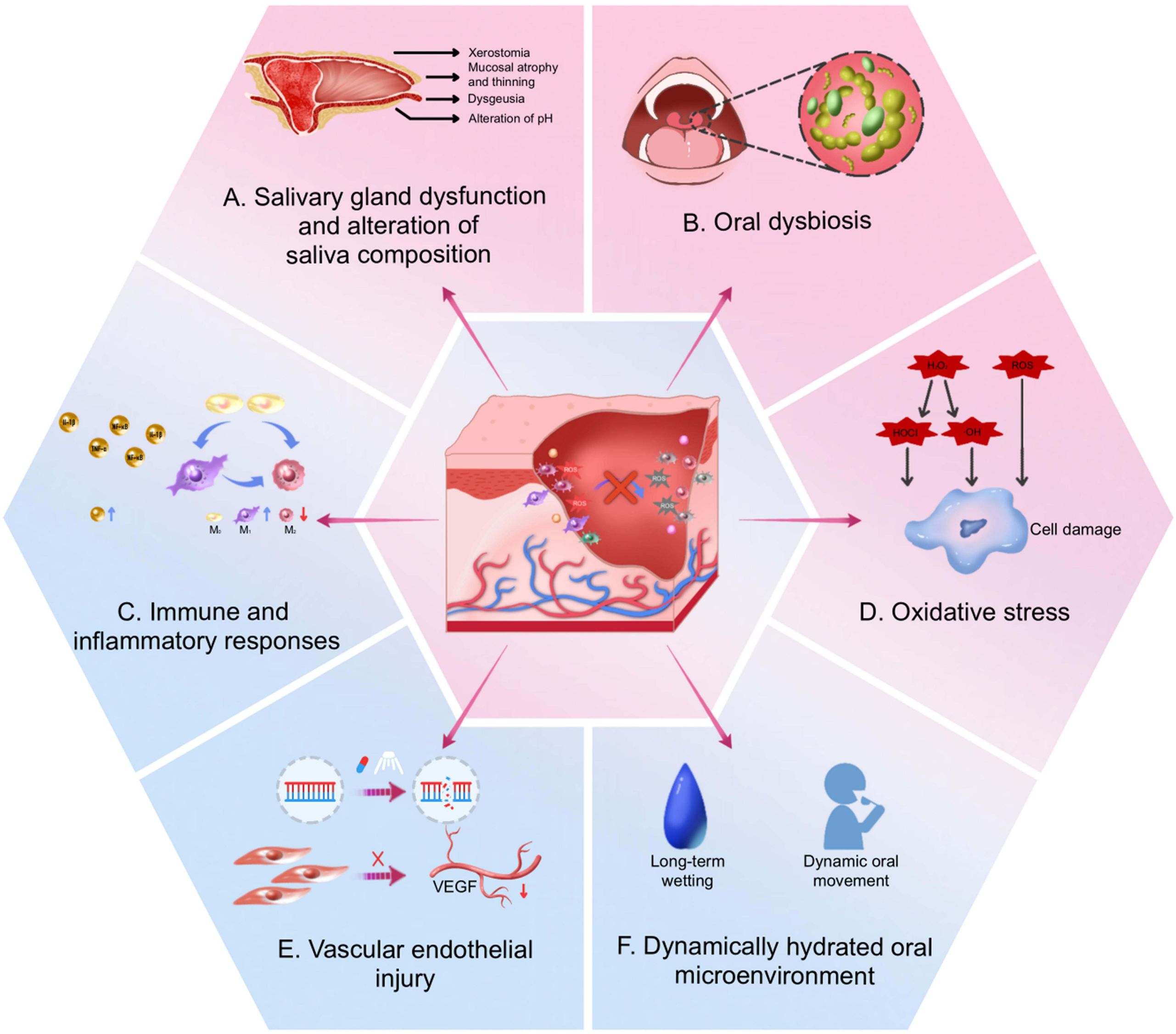

Figure 2 Schematic diagram of the pathological mechanisms of the OM microenvironment. (**A**) Radiotherapy and chemotherapy lead to atrophy of the salivary glands, causing functional disorders and compositional changes. (**B**) Radiotherapy and chemotherapy disrupt the balance of the oral microbiota, leading to the proliferation of pathogenic bacteria and the formation of biofilms (**C**) Radiotherapy and chemotherapy cause immune dysfunction, which in turn triggers inflammatory responses, intensifying local inflammatory damage. (**D**) Radiotherapy and chemotherapy induce excessive production of reactive oxygen species, triggering oxidative stress and causing structural and functional damage to mucosal. (**E**) Radiotherapy and chemotherapy cause damage to the vascular endothelium, leading to abnormalities in vascular structure and function. (**F**) The moist environment and mechanical movement within the oral cavity result in a short drug retention time, reducing bioavailability and diminishing therapeutic efficacy. Blue arrows represents up-regulation, red arrows represent down-regulation, red X represent block generation, and blue curved arrows represent polarization or transformation.

Moreover, it elevates the risk of dysphagia and pain during deglutition.[30–34] Therefore, functional polymeric materials intended for the treatment of OM should possess good wettability or enhance the secretory function of oral saliva.

Microbial Dysbiosis

The oral microbiota, serving as a critical biological determinant of the oral environment, comprises over 1,000 species of microorganisms, including bacteria, archaea, fungi, protozoa, and viruses. The substantial quantity of oral microorganisms collectively constitutes a highly diverse microbial community, which exerts a notable impact on oral health.[35] Nevertheless, radiotherapy and chemotherapy can disrupt the equilibrium of the oral microecology, thus converting the originally symbiotic microbial community into a contributing factor for OM.[36] Relevant research has indicated that chemotherapeutic agents (eg., 5-fluorouracil) can induce substantial alterations in the oral microbiota. As the degree of microbial dysbiosis escalates, the severity of OM increases accordingly.[37] Moreover, specific pathogens, such as Porphyromonas gingivalis and Candida glabrata, can directly interfere with the metabolism and proliferation of oral epithelial cells, thereby impeding the repair of oral mucosal lesions.[38] Furthermore, when bacteria and their secreted extracellular polymeric substances form biofilms, a localized anaerobic environment is established, facilitating the proliferation of Gram-negative bacteria and consequently inducing persistent infections. Additionally, biofilms also impede the effectiveness of drug treatments and enhance bacterial drug resistance.[39–41] More significantly, infections triggered by biofilm dysbiosis can further spread within local tissues, leading to deep - tissue infections such as cellulitis and abscesses, and may even induce systemic symptoms.[42] Therefore, functional polymeric materials should concentrate on regulating the oral microbial flora and effectively inhibiting biofilm formation, which will provide crucial support for the prevention and treatment of OM.

Immunity and Inflammatory Response

Local immune dysfunction in the oral cavity and persistent inflammatory responses constitute the core pathological mechanisms underlying the onset of OM. Firstly, the radiotherapy and chemotherapy processes induce a decline in patients' systemic immunoglobulin levels, resulting in immune dysfunction. This inhibits the body's pathogen-elimination ability, heightens the oral mucosa's susceptibility to bacterial infections, and subsequently triggers severe oral mucosal lesions, such as lichenoid lesions and polymorphous erythema.[43–46] Secondly, radiotherapy and chemotherapy can disrupt the balance of the immune microenvironment by interfering with the polarisation of macrophages. Specifically, they promote the long-term dominance of pro-inflammatory M1 macrophages, which stimulate inflammation and delay tissue repair by releasing TNF-α, IL-1β and other substances. Meanwhile, chemoradiotherapy inhibits the polarisation of anti-inflammatory M2 macrophages. Under normal physiological conditions, M2 macrophages can suppress the inflammatory cascade by secreting anti-inflammatory factors such as IL-10 and TGF-β. They also promote the activation of fibroblasts, angiogenesis and the migration and proliferation of epithelial cells, thereby accelerating wound healing. When the polarization of M2 macrophages is inhibited, the aforementioned tissue repair process is interrupted and anti-inflammatory and pro-regenerative signals are weakened. This delays the tissue repair process and ultimately hinders the healing of oral mucosal injuries.[47,48] In brief, radiotherapy and chemotherapy establish a unique "high-inflammation, low-defense" immune microenvironment in the oral cavity of cancer patients. Therefore, the core characteristics of functional materials for treating OM should include excellent anti-inflammatory and immune-regulatory capabilities.

Oxidative Stress and Vascular Endothelial Injury

Upon stimulation by radiotherapy or chemotherapy, mucosal tissue not only releases a substantial quantity of inflammatory factors but also initiates severe oxidative stress responses. This results in the rapid destruction of epithelial tissue, gives rise to vascular lesions, and hinders the formation of new blood vessels. Vascular endothelial cells (VECs), which constitute the structural foundation of the oral mucosal microvascular system, play a pivotal role in maintaining tissue nutrient delivery, immune regulation, and microenvironmental homeostasis.[49] During the pathological progression of OM, VECs emerge as an early and critical target of injury. Radiation and cytotoxic drugs directly inflict damage on the DNA of vascular endothelial cells and induce their apoptosis. Concurrently, radiotherapy and chemotherapy activate pro-inflammatory pathways, leading to the overexpression of cytokines such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). This causes the disruption of the vascular barrier, the initiation of micro-thrombosis, and ultimately leads to impairment of the mucosal microcirculation.[50,51] More gravely, pathogenic microorganisms can invade the peripheral circulation via the damaged vasculature, resulting in bacteremia and endotoxemia.[52] At this juncture, the mucosal tissue, afflicted by ischemia, hypoxia, and the accumulation of metabolic waste products, creates a harsh microenvironment that is challenging to self-repair.[53,54] Therefore, the design of functional polymeric materials capable of targeted protection of VECs, modulation of pro-angiogenic factors, and amelioration of the oxidative stress microenvironment has become a crucial direction in OM treatment.

Dynamically Hydrated Oral Microenvironment

In comparison to other tissues like the skin, the oral cavity sustains a consistently humid microenvironment and endures mechanical stress during mastication. These features substantially restrict the bioavailability of oral medications, thus imposing rigorous demands on the functional polymeric materials utilized in the treatment of oral diseases.[55] The continuous secretion of endogenous saliva, along with the exogenous moisture introduced by food and beverages, is the primary contributor to the humidity of the oral microenvironment. The combined influence of these factors can disrupt the cross-linked network of materials, impeding their adhesion to the tissue surface.[56] Moreover, the movements related to mastication, speech, and swallowing, driven by the oral cavity and the adjacent maxillofacial regions, frequently lead to deformation and detachment of these materials due to their inadequate mechanical strength. As a result, it is difficult for them to adhere to the mucosal surface for a sufficient period.[16,57,58]

An ideal oral functional polymeric material should display strong wet adhesion and outstanding mechanical strength, enabling it to resist the effects of saliva flow and oral mucosal movement. However, it is crucial to note that an excessively high level of adhesion and mechanical strength in functional polymeric materials does not necessarily confer benefits. Materials with high viscosity and strength often face challenges in degradation within the oral cavity, and a pronounced foreign body sensation may disrupt daily physiological activities such as eating, ultimately reducing patient compliance with these materials.[19] Additionally, high strength materials can cause mucosal abrasion due to mechanical incompatibility with the surrounding tissues, potentially resulting in secondary damage.[59] Therefore, functional polymeric materials used in oral medical treatment must possess adhesion and mechanical strength that are suitable for the oral microenvironment.

Micro-Nano Hydrogels for OM Treatment

Due to their distinctive physicochemical properties, hydrogel materials exhibit considerable potential in the treatment of OM.[60] Firstly, as three-dimensional hydrophilic networks with a water content generally surpassing 90%, hydrogels can simulate the moist microenvironment of the native extracellular matrix (ECM). This offers continuous hydration and a physical barrier to the wound area, while facilitating cell proliferation, migration, and tissue facilitating cell proliferation, migration, and tissue regenerationregeneration.[61,62] Secondly, hydrogels possess outstanding biocompatibility and controllable drug release characteristics, allowing for the accurate delivery of bioactive molecules, including antimicrobial agents, anti-inflammatory drugs, or growth factors, to the inflammatory site. This significantly elevates local drug concentrations and diminishes systemic adverse effects.[63] This precise and sustained local therapeutic approach presents notable advantages in ameliorating the OM microenvironment and enhancing the efficacy of tumor treatment. Noteworthy, hydrogel materials demonstrate extensive applicability throughout the five pathological stages of OM as posited by Sonis et al Capable of establishing a physical barrier in vivo and facilitating controlled drug release, they are especially significant for the signal amplification stage (for modulating inflammation) and the ulceration stage (for protecting wound surfaces and promoting healing).

In recent years, hydrogel design has increasingly gravitated towards functionalization and intelligence, resulting in the development of diverse functional polymeric hydrogel systems specifically tailored for OM treatment.[64,65] Among these functional hydrogels, in situ hydrogels have attracted substantial attention because of their unique injectability and environmentally responsive gelation properties. Once applied to the lesion site, its liquid precursor can swiftly transform into an adhesive three-dimensional network structure in response to environmental stimuli such as temperature, pH, light, or ultrasound. This “sol-to-gel” transition feature enables it to precisely adapt to irregular mucosal surfaces, achieving prolonged retention and thus providing an excellent platform for the controlled and sustained release of drugs.[18,66–68] The subsequent section will concentrate on discussing the most representative functional polymeric hydrogels therein.

To meet the therapeutic requirements of the intricate pathological processes of OM, functional hydrogels present multi-level intervention strategies. Firstly, in the context of fundamental antimicrobial and physical barrier functions, the chitosan-gelatin in situ hydrogel developed by the V. Tamara Perchyonok et al can establish a long-lasting protective layer on the mucosal surface owing to its outstanding bioadhesiveness. Moreover, it offers sustained antimicrobial activity through the controlled release of nystatin.[69] Secondly, with respect to pain management, a crucial aspect of OM treatment, the poloxame-based spray gel developed by Li et al promptly form a film on the mucosal surface, achieving long term analgesia

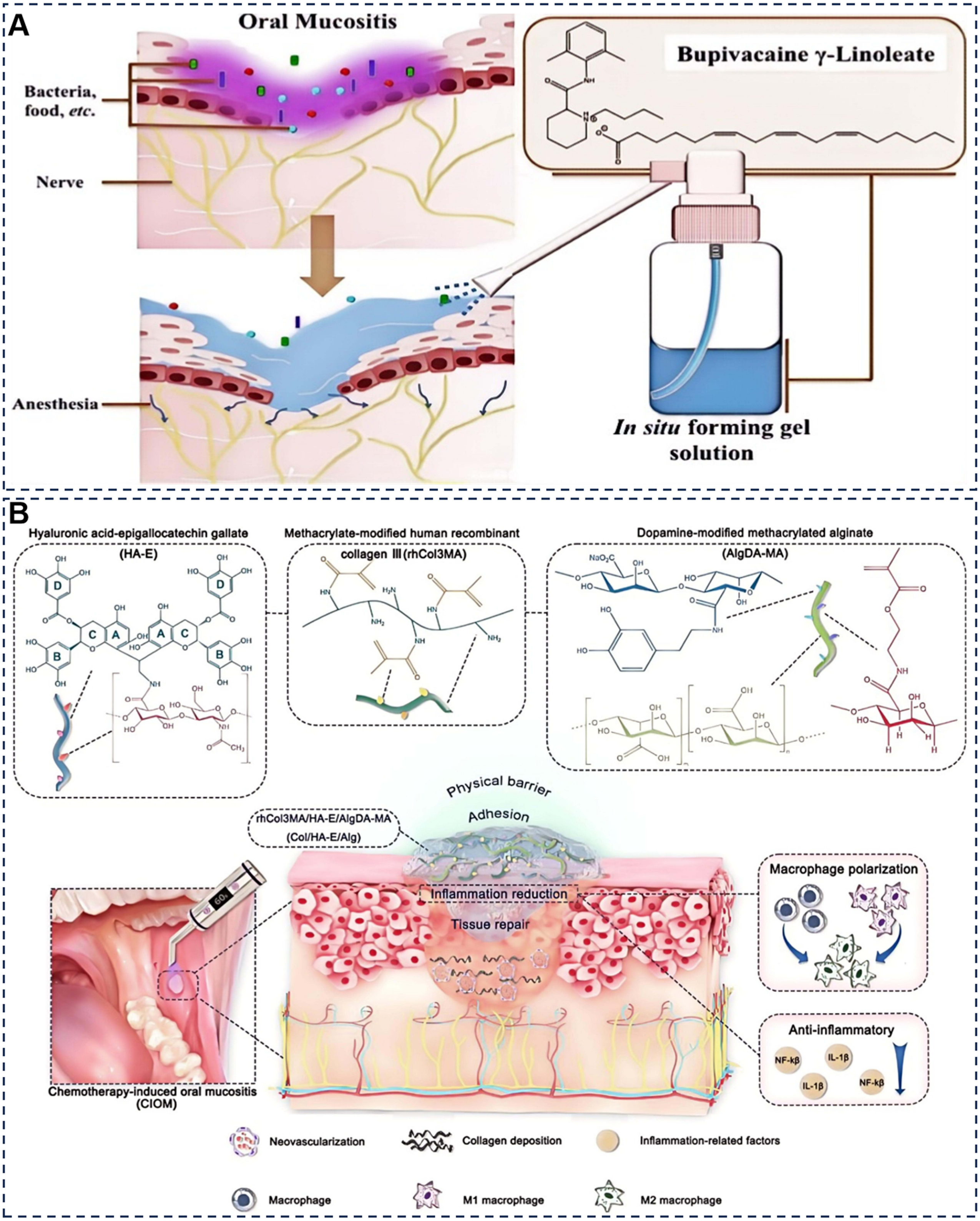

Figure 3 (**A**) Mucoadhesive in situ forming gel containing a novel drug molecule, Bupivacaine γ-Linoleate, for oral mucositis pain control. Reproduced with permission from Ref.[70] Copyright 2020, Elsevier. (**B**) Schematic of Col/HA-E/Alg Hydrogel Structure and Treatment Mechanism for Chemotherapy-Induced Oral Mucositis (CIOM). Reproduced with permission from Ref.[73] Copyright 2025, American Chemical Society. Blue curved arrow represents macrophages polarized toward M2 and The blue straight arrow represents down-regulation.

(Figure 3A).[70] In subsequent investigations, the incorporation of sodium lauryl sulfate as a solubilizer notably enhanced the drug loading capacity for poorly soluble analgesic agents, prolonging therapeutic effects while mitigating side effects.[71] Furthermore, Zhang Y et al incorporated the active components of the oral care solution into a hydrogel. By leveraging its sustained release characteristics, this formulation continuously inhibits the NF-κB signaling pathway, thereby intervening in the inflammatory progression of OM, facilitating mucosal repair, and alleviating pain.[72]

Furthermore, the design of in situ hydrogels is progressing towards multifunctional integration and self-driven therapy. For instance, a multicomponent hydrogel founded on human recombinant collagen III not only demonstrates outstanding wet tissue adhesion but also simultaneously exerts antioxidant, anti-inflammatory, and immunomodulatory functions. Through the promotion of angiogenesis and collagen deposition, it comprehensively enhances the wound healing microenvironment of OM (Figure 3B).[73] Additionally, Pan et al fabricated a semi-interpenetrating network hydrogel that co-loads oridonin and DNase I, which notably expedites the repair of OM lesions while synergistically offering antimicrobial and anti-inflammatory effects.[74]

It is worthy of note that advanced hydrogel systems also present advantages in synergistic therapy and precise regulation of drug release. The guanosine-polyvinyl alcohol (G-PVA) hydrogel developed by Ding et al shows remarkable performance in this aspect. This system is constructed through a one pot synthesis method to form a supramolecular structure, which provides a strong wet adhesion of 74.16 kPa for stable retention in the oral cavity, thus laying a foundation for precise local delivery. Furthermore, this hydrogel can significantly alleviate radiation-induced oxidative stress and DNA damage, reducing the lesion area by 52.23% in an animal model. This underscores its synergistic therapeutic effects in mucosal protection and oxidative regulation, presenting a promising new clinical strategy for preventing OM (Figure 4A).[65]

In the terms of inflammation regulation, Shao et al engineered an in situ mucoadhesive hydrogel encapsulating the tripeptide KPV. Through the inhibition of pro-inflammatory cytokines IL-1β and TNF-α, the up-regulation of the anti-inflammatory cytokine IL-10, and the facilitation of epithelial proliferation and differentiation (manifested as the up-

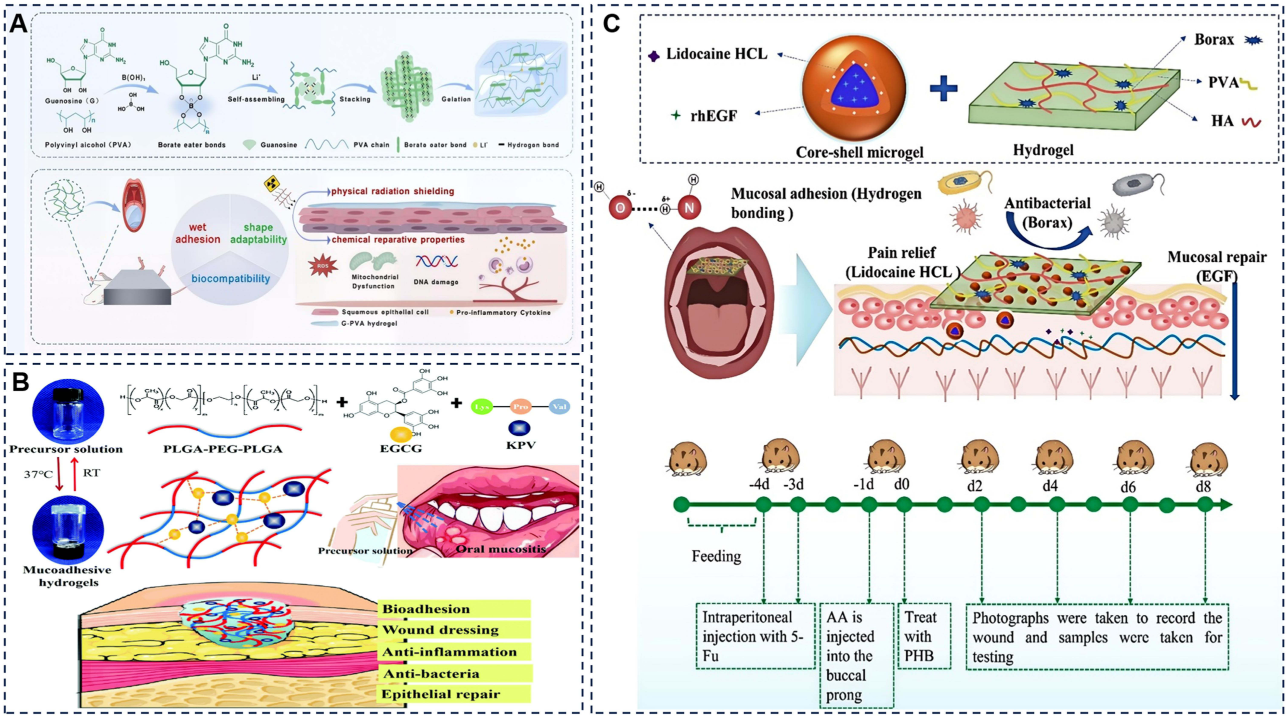

Figure 4 (**A**) Schematic Illustration of G-PVA hydrogel for efficient treatment of radiation-induced oral mucositis. Reproduced with permission from Ref.[65] Copyright 2025, Royal Society of Chemistry. (**B**) Schematic Illustration of Action of KPV@PPP In Situ Mucoadhesive Hydrogel in Treating Chemotherapy-Induced Oral Mucositis. Reproduced with permission from Ref.[18] Copyright 2022, Royal Society of Chemistry. (**C**) Schematic Illustration PHB hydrogel for efficient treatment of CIOM. Reproduced with permission from Ref.[75] Copyright 2025, Elsevier.

regulation of CK10 and PCNA expression), this hydrogel concurrently attains anti-inflammatory, antibacterial, and tissue repair efficacy (Figure 4B).[18]

Additionally, Wu et al constructed a hyaluronic acid-based composite hydrogel (PHB). By embedding core-shell microgels to encapsulate the growth factor (core) and lidocaine (shell), this hydrogel facilitates temporally regulated drug release. This hydrogel demonstrates outstanding mucosal adhesion (with a displacement of merely 5.5 mm within 24 hours), remarkable antibacterial characteristics, and sustained drug release over a 24 hour period, synergistically promoting analgesia, tissue regeneration, and expediting the healing of otitis media (Figure 4C).[75]

The temperature-responsive hydrogels, which experience reversible sol-gel phase transitions, present significant potential for localized drug delivery within the oral cavity. Thermosensitive materials, including Poloxamer and Poly (N-isopropylacrylamide) (PNIPAAm), display a phenomenon wherein the polymer molecular chains are highly hydrated via hydrogen bonding when the temperature is below the lower critical solution temperature (LCST). At this stage, the system exists in a flowing sol state. As the temperature surpasses the LCST, thermal energy disrupts the interaction between the polymer and water, and the hydrophobic segments prevail in intermolecular cross-linking, consequently forming a three-dimensional gel network (Figure 5A).[76–78] The primary advantage of this type of thermosensitive gel resides in its superior clinical applicability and retention capacity at the lesion site. The precursor solution can comprehensively cover irregular wounds. Triggered by body temperature, it rapidly gels and adheres to the mucosal surface, effectively resisting saliva erosion and mechanical perturbations. This offers an ideal platform for long-term drug sustained release and notably enhances drug delivery efficiency and patient compliance.[79] This is clearly manifested in the gelation and adhesion process of the PolyLA - SQBA hydrogel (Figure 5B).[80] For example, Bakhshi et al developed a thermosensitive adhesive hydrogel based on trimethyl chitosan derivatives, which was capable of achieving sustained drug release and mucosal retention in animal models, effectively promoting the healing and epithelial regeneration of OM (Figure 5C).[81,82]

The pH-responsive hydrogel, endowed with the capabilities of environmental sensing and intelligent feedback, exhibits distinctive advantages in the local targeted therapy of OM. Its mechanism of action originates from the alterations in the ionization states of ionizable groups (eg., carboxyl groups, amino groups, etc.) within the polymer network under diverse pH environments, which subsequently result in phase behavior transitions, such as swelling, contraction, or degradation, of the gel network structure (Figure 6A).[76,83] Under the pathological conditions of oral mucositis, inflammatory tissues generate a substantial amount of lactic acid through metabolic activities, establishing a weakly acidic microenvironment (pH 5.5–6.5), which is notably lower than the neutral pH condition of healthy oral mucosa. This disparity provides a crucial basis for pH-responsive hydrogels to achieve targeted drug delivery to inflammatory sites. Consequently, pH-sensitive polymers, such as chitosan, sodium alginate, and their derivatives (eg., methacrylated sodium alginate), as well as polyacrylic acids (eg., carbomer), are extensively utilized to construct therapeutic carriers for the treatment of OM.[84]

Galbis et al demonstrated that by modulating the composition of the dispersion system of chitosan-based hydrogels, the swelling behavior, rheological strength, and drug release kinetics of the hydrogels can be precisely regulated, thereby attaining adaptive responses to the microenvironment of the lesion site and long-term drug control.[86] The pH-responsive delivery system developed by Li et al can initiate the release of antibacterial agents and immunomodulators in the weakly alkaline environment of periodontal pockets. By targeting multiple points to intervene in the "infection-inflammation-bone destruction" vicious cycle, it offers a novel approach for the combined treatment of periodontal-related diseases.[87] The SCSC hydrogel constructed with sodium alginate and carboxymethyl chitosan, through the "sensing-response-treatment" mode, not only enhances the retention and efficacy of the drug in the lesion area but also significantly improves the accuracy and safety of the treatment (Figure 6B).[85]

In comparison with endogenous stimulus-responsive hydrogels, light-responsive and sonoresponsive hydrogels, characterized by their non-invasive nature, remote controllability, and superior spatiotemporal resolution, have demonstrated significant potential in the treatment of oral cavity diseases. The oral cavity is a cavity that allows for direct observation and facile operation. The core mechanism involves the conversion of external physical stimuli (light or sound) into chemical or physical signals, which subsequently precisely regulate the drug release behavior or structural alterations of the gel system, facilitating remote "on-demand" control of the treatment process.[88,89] Photo-responsive hydrogels are typically functionalized by incorporating photosensitive groups (eg., azobenzene, spiropyran, etc.) into the polymer network. Under specific wavelengths of light, these groups can undergo reversible isomerization, dimerization, or cleavage reactions, leading to changes in the conformation, hydrophobicity, or crosslinking degree of the polymer network, thereby enabling the on demand controlled release of drugs.[89,90] The

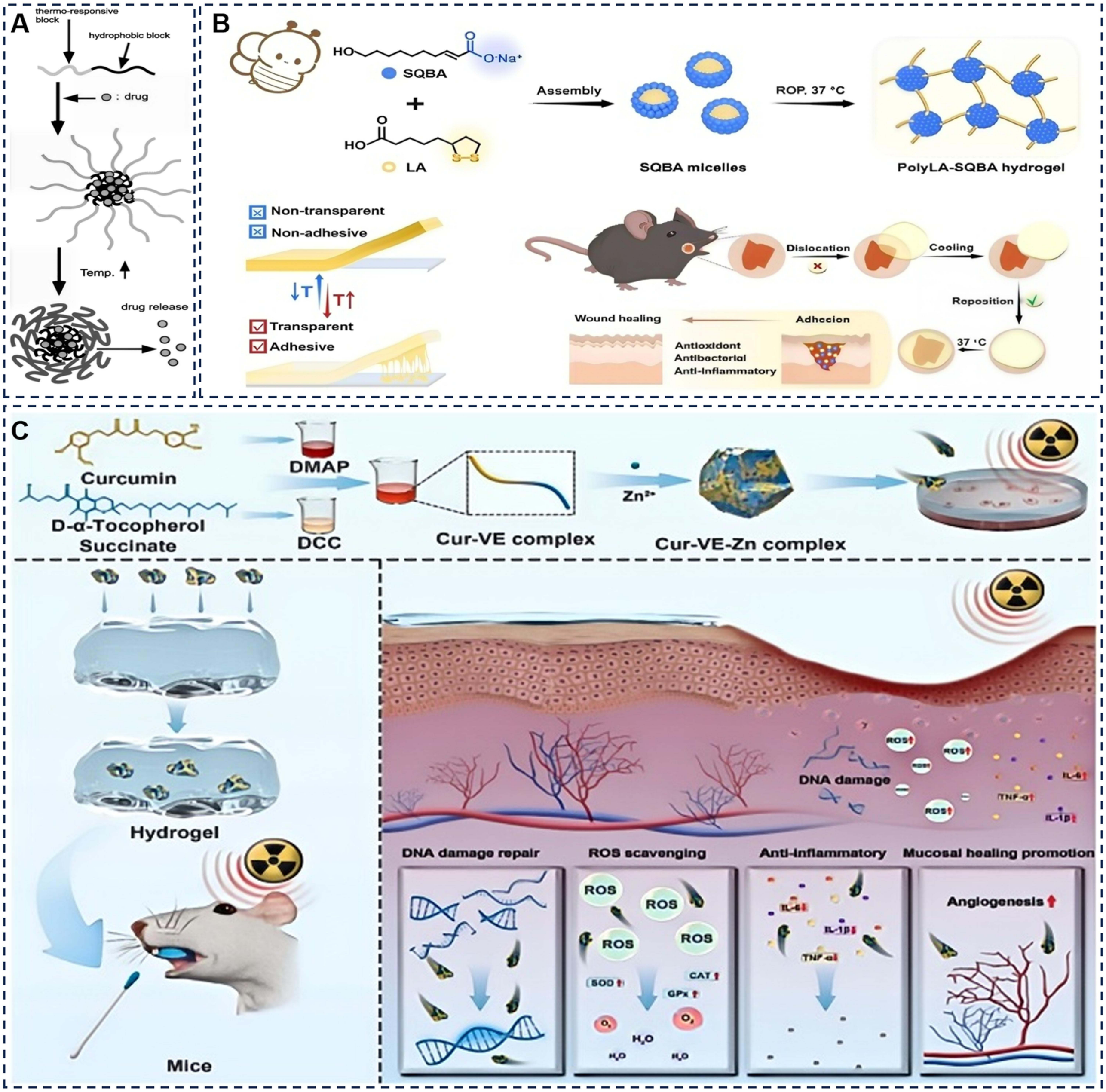

Figure 5 (**A**) Drug release from thermoresponsive polymeric micelles upon temperature increase. Reproduced with permission from Ref.[78] Copyright 2015, Elsevier. (**B**) Schematic illustration of the preparation, characteristics, and applications of PolyLA-SQBA thermoresponsive hydrogel. Reproduced with permission from Ref.[80] Copyright 2025, Elsevier. (**C**) Schematic diagram of a thermoresponsive multifunctional hydrogel based on Cur-VE-Zn complex for the treatment of oral mucositis. Reproduced with permission from Ref.[82] Copyright 2025, Elsevier. Blue down arrow represents down-regulation and red up arrow represents up-regulation.

molecular structure and light response mechanism of the photosensitive groups upon which the photosensitive hydrogel relies are presented in Figure 7A.

Professor Zhao et al developed a light-responsive antibacterial chitosan hydrogel named DCS-RuB2A2. In the dark, it can provide a physical barrier for oral mucosal wounds and support the growth of mesenchymal stem cells. When exposed to visible light, it can activate the antibacterial function and achieve the repair of oral mucosal defects (Figure 7B).[91] Shen et al[92] designed a near-infrared light-responsive nanocomposite hydrogel loaded with gold nanoparticles and chemotherapy drugs. This hydrogel can utilize the photothermal effect of the gold nanoparticles to induce local heating under near-infrared laser irradiation. This not only triggers the explosive release of the drugs but also synergizes with the photothermal therapeutic effect, enhancing the killing effect on deep tumors (Figure 7C).[92] Acoustic responsive hydrogels (commonly referred to as

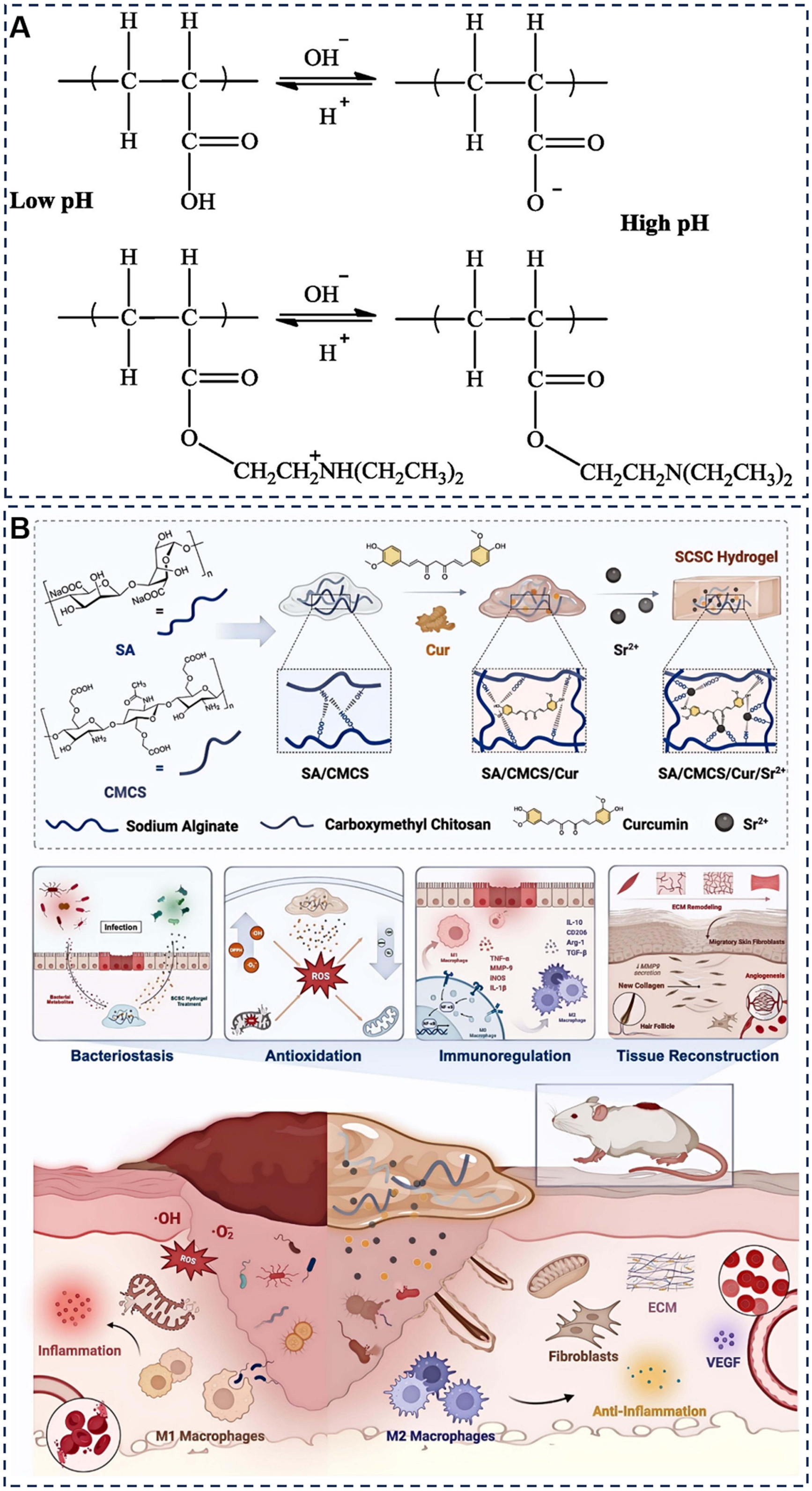

Figure 6 (**A**) Chemical structural changes of pH-responsive functional groups. Reproduced with permission from Ref.[83] Copyright 2015, Elsevier. (**B**) Schematic illustration of a pH-responsive composite hydrogel based on SA/CMCS for multi-mechanistic therapy of wound infection and skin regeneration. Reproduced with permission from Ref.[85] Copyright 2025, Elsevier.

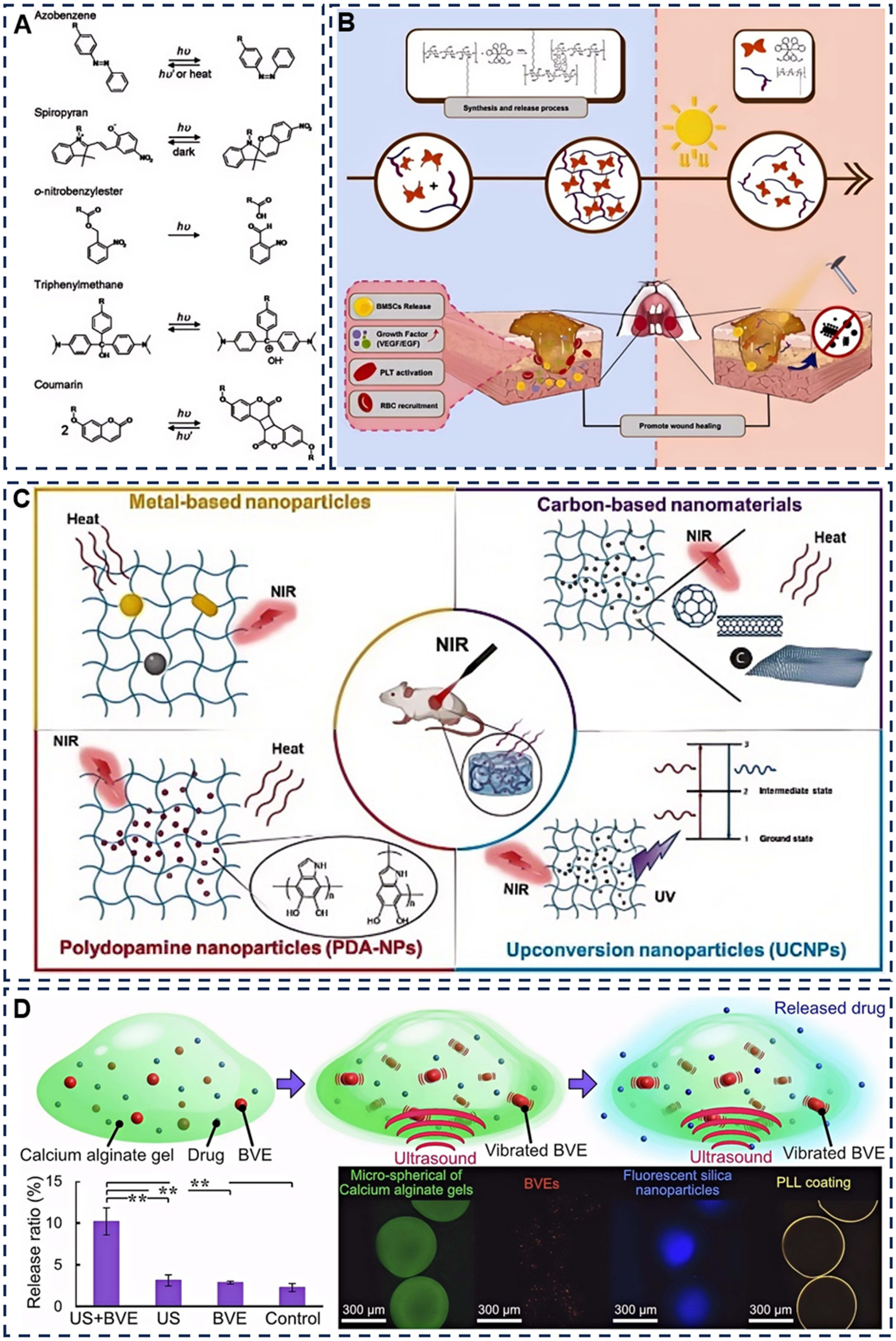

Figure 7 (**A**) Molecular structures of typical photosensitive groups used for constructing light-responsive hydrogel systems. Reproduced with permission from Ref.[88] Copyright 2011, Elsevier. (**B**) Schematic diagram of DCS-RuB2A2 light-responsive antibacterial hydrogel promoting oral mucosal repair. Reproduced with permission from Ref.[91] Copyright 2022, KeAi Communications Co. Ltd. (**C**) Schematic illustration of the near-infrared (NIR) photothermal-responsive mechanism of a NIR-responsive nanocomposite hydrogel based on metal nanoparticles. Reproduced with permission from Ref.[92] Copyright 2021, American Chemical Society. (**D**) Working mechanism and in vitro drug release results of an ultrasound-responsive drug-loaded hydrogel. Reproduced with permission from Ref.[93] Copyright 2024, Elsevier. ** represent $p < 0.01$.

ultrasonic responsive) primarily trigger their responses through the mechanical effects, cavitation effects, or thermal effects generated by ultrasonic irradiation.[89] For example, the reversible host-guest cross-linked hydrogel designed by Fabiilli et al exhibits reversible dissociation and reformation of its cross-linked network upon low-intensity pulsed ultrasound irradiation. This not only enables on-demand drug release but also makes multiple, pulsed drug administration feasible due to its self-healing property (Figure 7D).[93–95]

Nevertheless, despite the substantial potential demonstrated by light-responsive and sono-responsive systems, these systems continue to encounter a series of translational obstacles. Firstly, the posterior buccal, pharyngeal, and retrolingual regions within the oral cavity are deeply situated and spatially restricted, characterized by intricate anatomical structures. These features impose constraints on direct visualization and manipulation. This phenomenon is especially pronounced in patients with radiation-induced trismus, where the severely limited jaw opening significantly hampers the placement of instruments and the precise targeting of light/ultrasound beams. Secondly, the dynamically hydrated microenvironment and pathological tissue characteristics of oral mucositis (including edema, ulceration, and vascular hyperpermeability) further compromise the efficacy of stimulus signals. Ultimately, current clinical light/NIR and ultrasound devices for localized stimulation are mainly designed for readily accessible sites such as the skin or anterior oral mucosa, and are deficient in miniaturized, flexible, and sterile operable probes appropriate for the deep oral cavity. Consequently, for patients presenting with concurrent severe trismus and mucosal hypersensitivity, the direct utilization of ultrasound/laser probes for detecting deep-seated lesions in posterior buccal and pharyngeal regions is not currently clinically viable for routine application.[96,97]

To address the continuous mechanical stress and the "high-inflammation, low-defense" immune dysregulation in the oral environment of OM, multifunctional hydrogels with self-healing properties have emerged as a cutting-edge research direction. Such hydrogels can resist structural damage caused by shear forces while effectively regulating immune responses. For instance, Yu et al developed a multifunctional self-healing hydrogel based on chitosan, whose dynamic imine bond and hydrogen bond networks endow the material with excellent self-healing capabilities. This enables it to rapidly repair structural damage induced by mechanical stress, maintaining long-term mucosal adhesion and stable drug release. More importantly, the hydrogel can effectively modulate the polarization of macrophages from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype, thereby creating an immune microenvironment conducive to repair at the wound site.[98]

Micro-Nano Patch for OM Treatment

Oral mucosal patches function as a localized drug delivery system, which facilitates targeted drug delivery and sustained release through their bilayer structure, exhibiting substantial advantages in the treatment of OM.[39,99] The outer layer acts as a barrier against external stimuli, while the inner layer directly administers drugs to the lesion site.[100,101] This bilayer configuration not only enhances the adhesive stability of the patch in moist environments but also ensures extended retention within the dynamic oral cavity, thus maintaining stable drug concentrations and promoting the healing of OM.[102,103] When integrated with microneedle array technology, innovative patch designs enable deep drug delivery, effectively alleviating mucosal inflammation and promoting tissue repair.[104,105] Functional polymeric patches, tailored to specific clinical requirements across diverse treatment scenarios, present a wide array of application prospects, demonstrating a trend towards precision, personalization, and minimally invasive approaches in clinical research. In addition, the robust adhesiveness and sustained drug release characteristics of patches render them highly suitable for the treatment of the ulceration stage, which is the core phase necessitating long-term analgesic and anti-inflammatory effects. Moreover, they can intervene in the signal amplification stage (for early-stage intervention) and the healing stage (to offer a protective microenvironment).

Maheen et al developed a bilayer mucoadhesive patch based on poly (methyl methacrylate- co-methyl methacrylate) and gelatin. The gelatin layer provides long term mucosal adhesion, and the methacrylic acid layer enables programmed controlled drug release. This design allows for the co-loading of ropivacaine and itopride, synergistically managing both the local pain associated with OM and systemic nausea and vomiting symptoms.[103] Li et al incorporated zinc tannate nanoparticles into tannic acid modified polyvinyl alcohol to fabricate a patch with strong wet adhesion. This patch sustainably releases zinc ions and enhances mucosal repair by activating the KLF5/FoxO signaling pathway, offering an innovative solution for wound healing in OM (Figure 8A).[104] Similarly, Elhabal et al developed a dual function

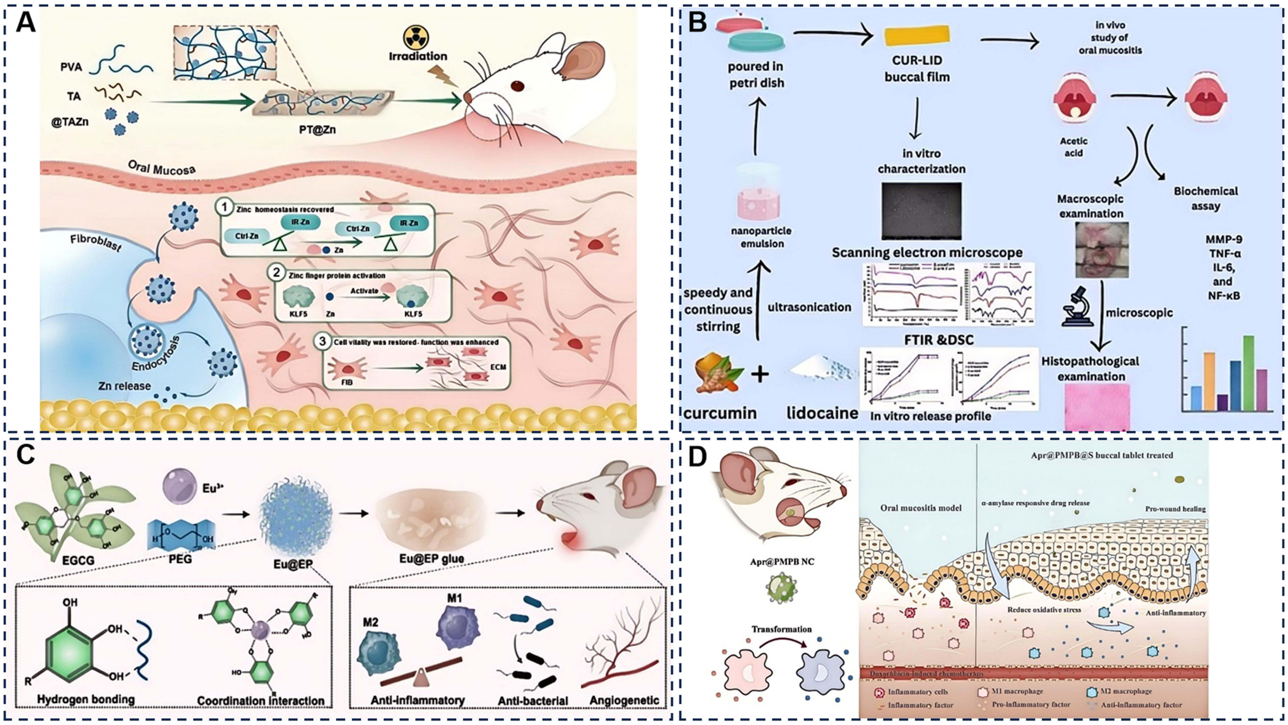

Figure 8 (**A**) Fabrication of PT@Zn hydrogel and its therapeutic mechanism for radiation-induced oral mucositis via zinc homeostasis regulation and KLF5 activation. Reproduced with permission from Ref.[104] Copyright 2025, Elsevier. (A1) Following cellular phagocytosis, the zinc tannate nanoparticle release zinc ions, consequently restoring zinc homeostasis; (A2) Zinc supplementation activates the KLF5/FoxO signaling pathway in mucosal epithelial fibroblasts to enhance cellular activity; (A3) Upon activation, mucosal epithelial fibroblasts facilitate collagen secretion and extracellular matrix formation. (**B**) Fabrication, characterization, and in vivo assessment of curcumin-lidocaine dual-action nanoemulsified mucoadhesive buccal films for non-invasive oral mucositis therapy targeting MMP-9 and NF-κB pathways. Reproduced with permission from Ref.[106] Copyright 2025, Taylor & Francis Group. (**C**) Schematic illustration of the functional hydrogel system based on EGCG-Eu^{3+} coordination for anti-inflammatory, antibacterial, and angiogenic therapy. Reproduced with permission from Ref.[107] Copyright 2025, Elsevier. (**D**) Schematic diagram of Apr@PMPB@S buccal tablet for anti-inflammatory and wound-healing on chemotherapy-induced oral mucositis. Reprinted from Ref.[108] Wiley.

nanoemulsified mucoadhesive buccal film loaded with curcumin and lidocaine. This film enables efficient localized drug release and provides combined anti-inflammatory, analgesic, and mucosal healing effects. By inhibiting the MMP-9 and NF-κB pathways, it accelerates wound healing, presenting an effective approach for treating OM (Figure 8B).[106]

Within the field of biomimetics, biologically inspired patch designs have substantially improved wet adhesion and stability. For instance, Ryu et al devised a mussel inspired polysaccharide oral patch termed “Chitoral”. Upon coming into contact with saliva, it promptly forms an insoluble adhesive layer, which subsequently transforms into a persistently adherent hydrogel, offering a long standing local milieu for drug retention.[109] Wang et al established a polyphenol coacervate derived bioadhesive glue founded on the dynamic covalent bonding between EGCG and PEG, emulating mussel inspired wet adhesion. This system attains sustained and controlled release of anti-inflammatory polyphenols, demonstrating synergistic biological effects in suppressing inflammation, preventing infection, and facilitating tissue repair (Figure 8C).[107]

Additionally, responsive patches facilitate cascade, sustained, and comprehensive drug release, effectively suppressing OM. For example, Zhang et al, conducted a salivary amylase-responsive buccal tablet was developed. It initiates the enzyme mediated release of the anti-inflammatory drug apremilast and integrates it with the ROS scavenging ability of porous manganese-substituted Prussian blue nanocubes, thus alleviating inflammation and promoting tissue repair. This system notably improves drug retention and efficacy at the oral lesion site, presenting a novel therapeutic approach for OM (Figure 8D).[108]

Microneedle patches, as a novel transdermal drug delivery system, offer a minimally invasive and highly efficient approach for the treatment of oral mucosal diseases.[110] Microneedles are capable of penetrating the mucosal physical barrier in a minimally invasive fashion. Among these, dissolvable microneedles (DMNs) dissolve rapidly in tissue fluid, facilitating targeted drug delivery and precise drug release.[111] Xiao et al developed a novel detachable and dissolvable microneedle patch (DC@MNs). This patch employs ceria nanozymes loaded at the needle tips to scavenge ROS while modulating the ferroptosis pathway. It effectively penetrates the mucosal barrier, enabling targeted therapy to synergistically mitigate oxidative damage and iron overload, thereby presenting an innovative localized treatment strategy for the prevention and treatment of OM.[112]

Subsequently, Tang et al designed a core–shell structured dual functional microneedle patch. The outer shell enables the rapid release of lidocaine to achieve immediate analgesia, whereas the inner core facilitates the sustained release of dexamethasone to exert long term anti-inflammatory and pro-healing effects. Through a spatiotemporal controlled-release strategy, synergistic therapy is accomplished (Figure 9A).[113] Similarly, Chen et al constructed a multifunctional microneedle patch based on methacrylated carboxymethyl chitosan. This patch offers rapid analgesia via the release of local anesthetics and provides antibacterial protection. The co-loaded exosomes and folic acid-modified magnetic nanoparticles synergistically modulate immunity, promote angiogenesis and epithelial repair, thus effectively accelerating the healing of oral mucositis wounds (Figure 9B).[114] Moreover, Qu et al employed mesoporous polydopamine nanoparticles (MPDA) for drug loading and dissolvable microneedle technology to prepare a composite microneedle patch (TA@MPDA-HA/BSP MNs). This patch rapidly dissolves and efficiently delivers drugs, significantly promoting oral wound healing in a rat model at a dosage merely 10% of that of conventional formulations, presenting an efficient, low dose strategy for the local treatment of oral mucositis (Figure 9C).[115]

In response to the requirement for deep mucosal drug delivery, Xian et al devised a silk fibroin/tannic acid-based bilayer microneedle patch. This patch integrates robust wet adhesion with a drug sustained-release capacity that endures for up to 7 days, thereby attaining painless deep targeted delivery across the mucosa.[110] Li et al developed a transmucosal delivery system comprising a transparent collagen-polyvinylpyrrolidone (PVP) composite microneedle array integrated with a pH-responsive, double-layer functionalized backing. Leveraging the intrinsic mucosal adhesiveness of hyaluronic acid (HA), the system achieves robust mucoadhesion. PVP imparts optimal mechanical strength to enhance microneedle penetration efficacy; and the dual-layer backing enables precise, pH-triggered drug release. These features collectively improve both the efficiency of transmucosal delivery and the temporal consistency of release kinetics. This hierarchical structural design represents a novel strategy for advancing deep mucosal drug delivery platforms.[116]

Notably, the clinical application of microneedle patches should be distinguished according to the severity of OM. For Grade 1–2 OM or prophylactic purposes, microneedles can be directly applied to relatively intact mucosa to accomplish non-invasive or minimally invasive drug delivery. Conversely, in the case of Grade 3–4 OM, there are exposed ulcers lacking epithelial protection and with exposed nerve endings. Direct application of microneedles may exacerbate pain and tissue damage.

Targeting secondary infections often associated with OM, patches also demonstrate precise preventive and therapeutic effects. For example, Funahara et al developed a miconazole oral patch. Through the localized, sustained, and controlled release of antifungal drugs, it effectively inhibits Candida albicans biofilm formation, providing a critical clinical approach for preventing and treating secondary fungal infections in OM.[117]

In a word, patches assume a crucial role in analgesia, anti-inflammation, and tissue repair for OM owing to their stable protective barrier, controllable drug release characteristics, and favorable patient tolerance and compliance. As an efficient and non-invasive localized delivery platform, patches have emerged as an indispensable instrument in the clinical management of OM.[103,118,119]

Micro-Nano Drug Delivery Systems for OM Treatment

Micron-based DDSs, with particle sizes ranging from 1 to 1000 μm, predominantly exist in the forms of microspheres, which are characterized by a hollow structure, and microcapsules, which feature a core-shell structure. These micron-based systems are deliberately designed with a specific particle size to accurately meet the requirements for mucosal surface retention.[120] Although micron-based DDSs encounter difficulties in penetrating biological barriers, they exhibit strong mucosal adhesiveness, allowing them to withstand saliva erosion and achieve long-term, sustained drug release. This characteristic renders them ideal carriers for chronic oral lesions and clinical situations that demand long-term maintenance treatment. For instance, Ana Sofia Ferreira and Filipa Teixeira significantly enhanced the stability of active ingredients and realized controlled release by encapsulating extracts of actinidia arguta leaves and chestnut shells within microparticles.[121,122] Additionally, Jiang et al fabricated microcarriers using chitosan. The mucosal adhesion properties and drug release regulatory capabilities of these microcarriers effectively prolonged the drug retention time and notably improved the therapeutic efficacy.[123]

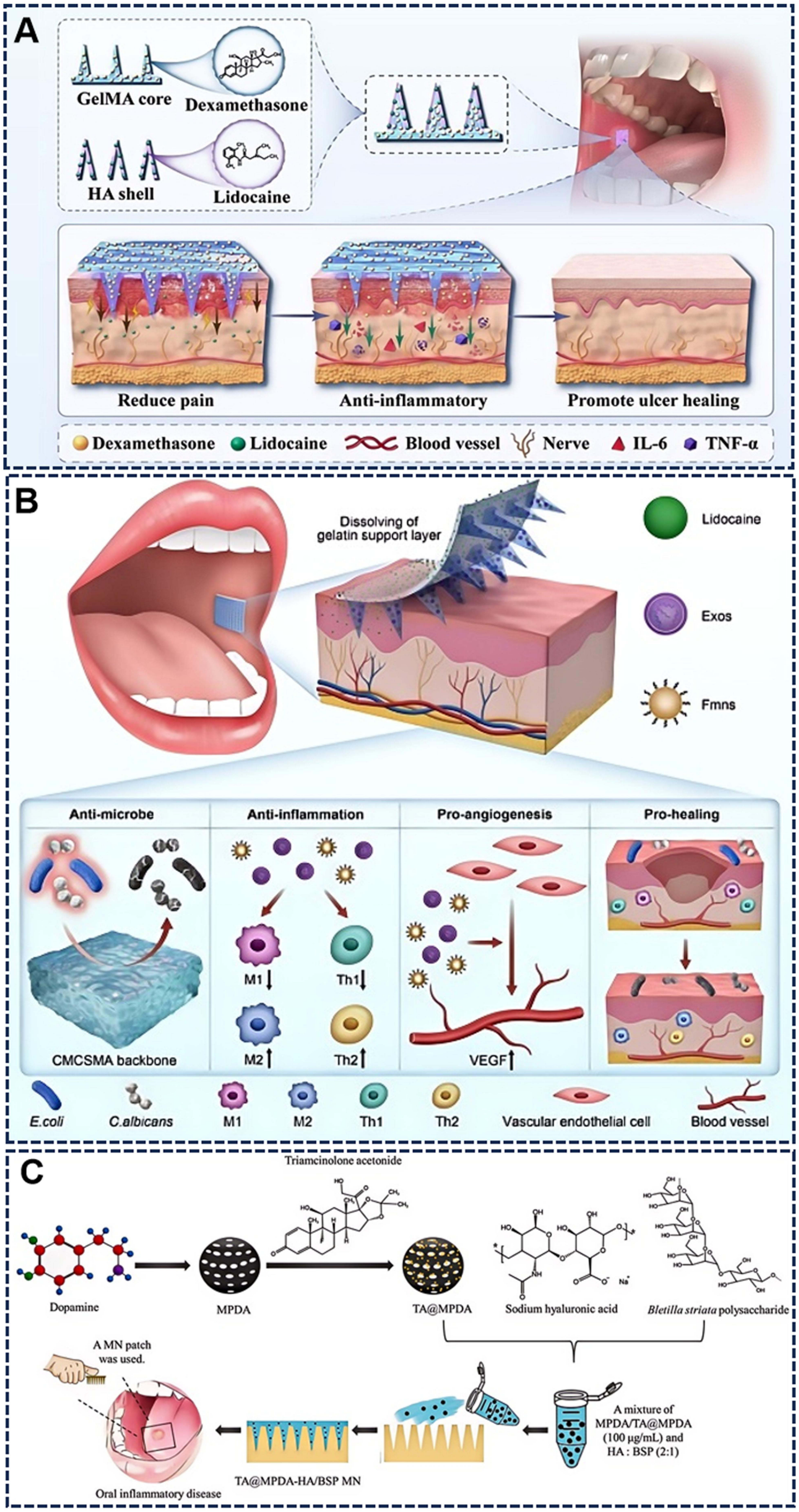

Figure 9 (**A**) Schematic Illustration of the Mechanism of Core–Shell Structured Hydrogel Microspheres (GelMA/HA) Loaded with Dexamethasone and Lidocaine in Treating Oral Ulcers. Reproduced with permission from Ref.[113] Copyright 2024, Elsevier. (**B**) A multifunctional microneedle patch to ensure mucosal penetration for sustained delivery of therapeutic exosomes and magnetic nanoparticles that synergistically promotes oral mucosal regeneration. Reproduced with permission from Ref.[114] Copyright 2024, Elsevier. Black down arrows represent down-regulation and black up arrows represent up-regulation, and red bending, red down, and red to the right arrows all represent inducing effects. (**C**) Schematic illustrations of the preparation of TA@MPDA-HA/BSP MN patch and its application in oral inflammatory disease. Reprinted from Ref.[115] Copyright 2023, Frontiers.

Nano-based DDSs are characterized as nanostructures with at least one dimension ranging from 1 to 100 nm. In contrast to micron-based DDSs, which demonstrate mucosal surface retention properties, nanoscale DDSs, owing to their scale-dependent functional attributes and high specific surface area, promote the penetration of biological barriers and strengthen interactions with target cells.[124] Moreover, through the precise modulation of both scale and physicochemical properties, nano-based DDSs can realize targeted drug delivery, regulate the release rate, and mitigate systemic adverse reactions.[125–127] Presently, this class of materials constitutes a crucial research emphasis in the field of OM.[128] Common nanomedicine delivery systems mainly include subtypes such as nanoparticles (NPs), nanomicelles, and nanofibers. Each subtype exhibits distinct structural and functional features, collectively constituting the core framework of nanomedicine delivery.

Among diverse types of nanomaterials, NPs present substantial advantages in augmenting drug delivery efficiency, enhancing drug delivery efficacy, and elevating binding affinity with epithelial cells, attributed to their high specific surface area and distinctive structural features.[129] Encapsulating drugs within NPs effectively enhances drug stability and solubility while modulating release characteristics to attain targeted delivery. Vilar et al utilized polyvinylpyrrolidone (PVP) to cap and modify gold NPs (10 nm), leading to the preparation of PVP-capped AuNPs, and explored their effects on experimental OM induced by 5-fluorouracil (Figure 10A).[130] Research has demonstrated that PVP-capped AuNPs achieved a significant reduction of CT-induced OM severity in hamsters through inhibition of innate immune inflammatory factors including NF-κB, TNF-α, IL-1β, COX-2, TGF-β, and SMAD 2/3 (Figure 10B).[130,131] Furthermore, PVP-AuNPs can diminish the expression of Kelch-like ECH-associated protein 1 (KEAP1), promote the upregulation of nuclear factor erythroid-2-related factor-2 (Nrf2), and consequently result in an increase in antioxidant enzymes (GSH, HO-1, and NADPH), thereby demonstrating their potential to scavenge ROS and provide protective effects against OM (Figure 10C).[130,131] Additionally, Khan et al discovered that AuNPs (6 nm) synthesized from the leaf extract of Clerodendrum inerme demonstrated remarkable antibacterial and biofilm inhibitory

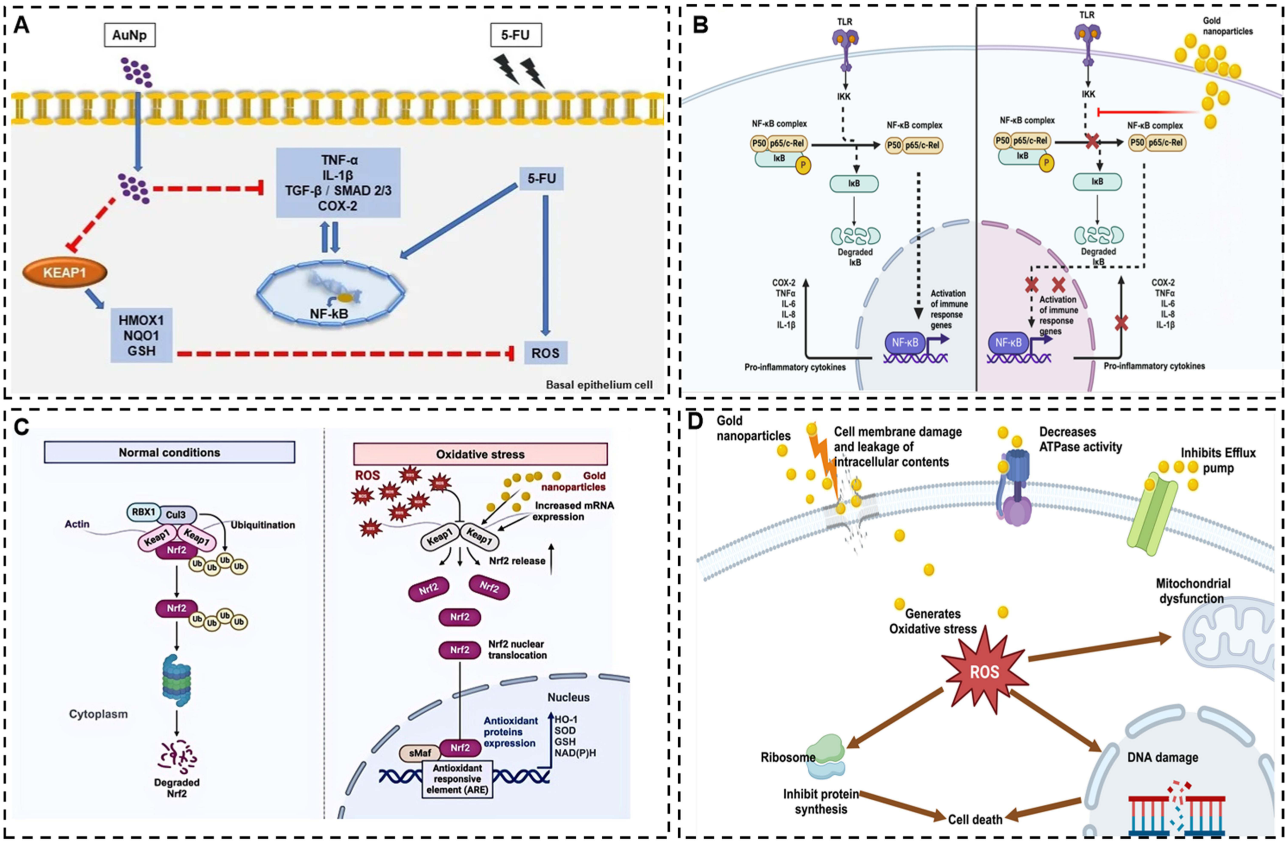

Figure 10 (**A**) Mode of action of gold nanoparticles (AuNps) in alleviating 5-fluorouracil (5-FU)-induced oral mucositis in hamsters. Reproduced with permission from Ref.[130] Copyright 2020, MDPI. (**B**) AuNPs block/inhibit nuclear translocation of NF-κB by reacting with IKK kinase inhibiting the downstream inflammatory response. (**C**) Cytoprotective response of AuNPs against ROS through the KEAP1-NRF2 pathway. (**D**) Proposed antimicrobial mechanisms of AuNPs. Reproduced with permission from Ref.[131] Copyright 2024, Springer Nature.

https://doi.org/10.2147/IJN.S602864

characteristics (Figure 10D).[131,132] Takeuchi et al administered rebamipide via chitosan-coated polylactic-co-glycolic acid (PLGA) NPs. This approach significantly enhanced mucosal adhesion and sustained-release properties, resulting in a marked reduction in the area of oral lesions in mice and facilitating the healing process.[133] Ribeiro et al treated a hamster model of OM with dexamethasone-loaded PLGA NPs. This strategy effectively suppressed the expression of inflammatory factors such as IL-1β and TNF-α, maintained the integrity of the mucosal structure, and concurrently reduced the dosage and systemic toxicity. It demonstrated the dual benefits of precise treatment and reduced toxicity while enhancing therapeutic efficacy.[134]

Nanomicelles are nano-based DDSs formed via the self-assembly of amphiphilic polymers in aqueous solutions. Their hydrophobic cores enable the efficient encapsulation of lipophilic drugs, whereas their hydrophilic shells endow them with remarkable water solubility, biocompatibility, and mucosal retention capabilities. This structural configuration effectively surmounts the clinical challenges related to liposoluble drug delivery by augmenting drug stability and enhancing targeted delivery efficiency. For instance, Liu et al encapsulated the anti-inflammatory drug cannabidiol within fucoidan nanomicelles, leading to the accumulation and sustained release of the drug at the inflammatory site. This, in turn, reduced the area of oral lesions in mice and inhibited the infiltration of inflammatory cells (Figure 11A).[135] Analogously, Delavarianto et al utilized curcumin micelles for the treatment of OM. This treatment strategy effectively postponed the onset of symptoms and alleviated the severity of lesions by improving the bioavailability and anti-inflammatory activity of curcumin.[136]

Nanofibers, as one-dimensional fibrous materials with nanoscale diameters, can adhere closely to diseased mucous membranes, thus enabling continuous and precise drug delivery. For example, Choi et al developed poly(methyl methacrylate-co-methyl methacrylate)/chitosan composite nanofibers loaded with human growth hormone (hGH). These nanofibers facilitated the sustained release regulation of the drug and significantly promoted the complete regeneration of oral lesion tissues in dogs (Figure 11B and C).[137] Similarly, the glutamine supported sodium alginate/polyethylene oxide (PEO) nanofibers designed by Tort et al possess excellent mucosal adhesion properties and controllable release behavior. Consequently, they provide an efficient local drug delivery platform for oral mucosal applications and demonstrate the potential of nanofibers in the treatment of OM.[138]

In brief, the micron-based DDSs, characterized by their excellent mucosal retention capabilities, maintain the effective concentration at the lesion surface via continuous drug release, which is conducive to long-acting treatment. In contrast, nano-based DDSs, capitalizing on their capacity to penetrate biological barriers and their precise targeting features, can efficiently deliver drugs to the deeper layers of mucous membranes, thus expediting the wound healing process. Besides, micro-nano drug delivery systems exert their effects throughout the process from the primary injury stage to the healing stage. Their core therapeutic effects are most pronounced in the signal amplification and ulceration stages. Targeted modulation of inflammatory cascades and microbial invasion during these stages is of crucial significance.

Other Functional Polymeric Materials-Based Micro-Nano Devices for OM Treatment

First, medical sponges fabricated from high molecular functional materials such as gelatin, chitosan, or alginate, characterized by their highly open and interconnected porous network structures, exert a positive influence on optimizing the local microenvironment. This structure can not only rapidly absorb and retain excessive exudate from the wound surface via physical mechanisms like capillary action, thereby maintaining a moist microenvironment that is conducive to cell migration and proliferation, but also effectively prevent secondary damage resulting from exudate accumulation.[139] Simultaneously, owing to its excellent plasticity, the medical sponge can serve as an ideal flexible drug storage depot, capable of loading and achieving the controlled release of various therapeutic drugs.For example, Alagha et al demonstrated that by loading dexamethasone into collagen-chitosan sponges, they verified that this carrier could achieve sustained drug release and effectively inhibit the persistent inflammation induced by OM.[140] Additionally, sponges functionalized with chitosan oligosaccharides and hyaluronic acid also exhibited the capacity to actively establish an anti-inflammatory microenvironment through methods such as regulating macrophage polarization. Research has indicated that the application of sponges loaded with recombinant epidermal growth factor in canine oral soft tissue wound models can significantly enhance the healing kinetics and accelerate the re-epithelialization process.[141] Notably, through the

https://doi.org/10.2147/IJN.S602864

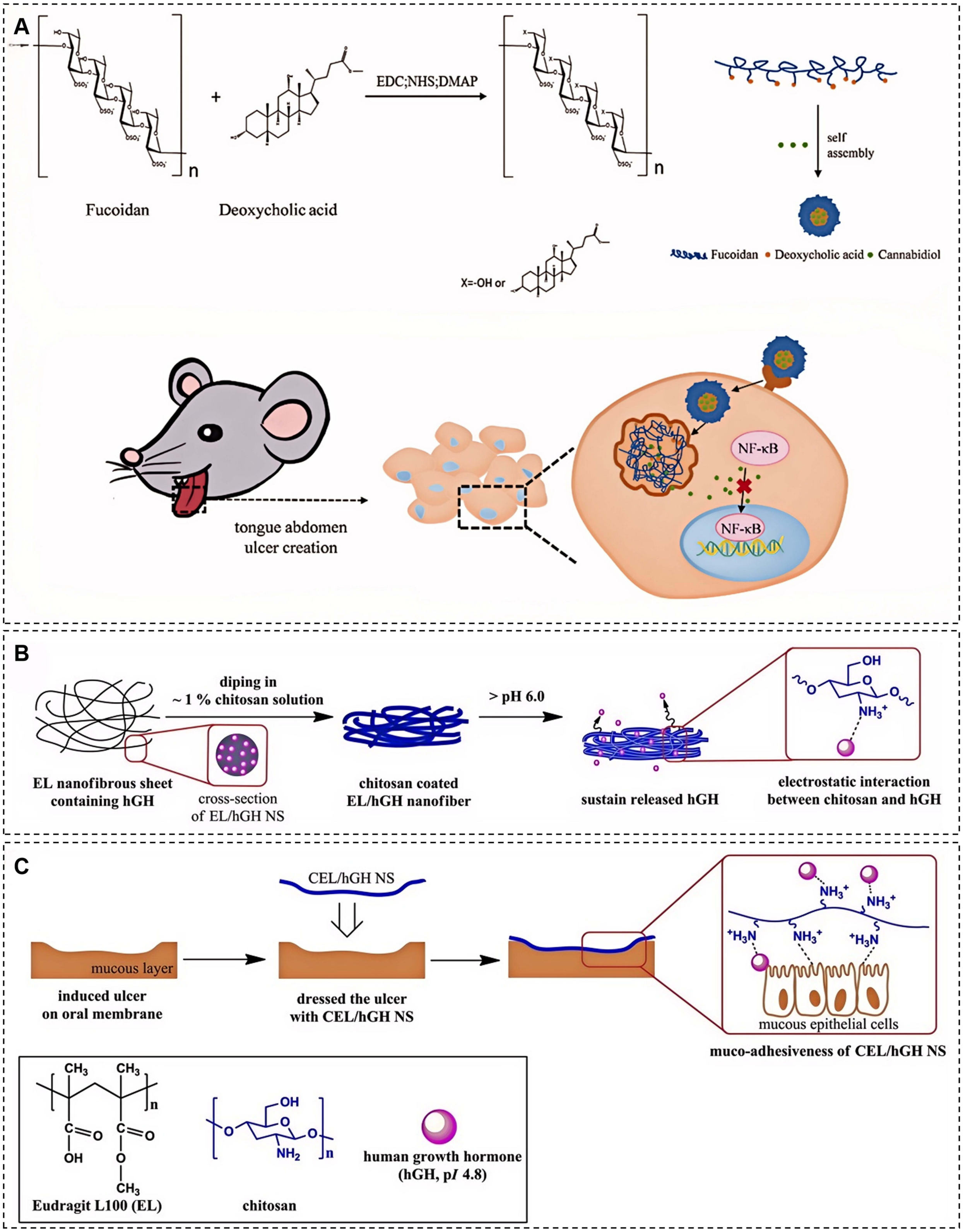

Figure 11 (**A**) Preparation of cannabidiol/fucoidan–deoxycholic acid nanomicelles and their delivery to inflamed tongue tissue. Reproduced with permission from Ref.[135] Copyright 2022, Taylor & Francis Group. (**B**) Preparing the chitosan-coated Eudragit L100/human growth hormone nanofibrous sheet (CEL/hGH NS) for controlling the release of hGH. (**C**) Treatment of an ulcer with the CEL/hGH NS after inducing the ulcer on the oral mucous membrane by 50% acetic acid.Reproduced with permission from Ref.[137] Copyright 2015, Wiley.

introduction of advanced functional materials such as MXene, medical sponges are transitioning from passive dressings to intelligent responsive platforms that integrate rapid hemostasis, efficient antibacterial properties, controlled drug release, and active wound healing promotion (Figure 12A).[142]

It is noteworthy that traditional medical sponges are prone to swell excessively, causing strong foreign body sensation, which further aggravates dysphagia and even poses a risk of suffocation. In contrast, the clot-like pore-gradient nanofibrous sponge with dual functions of "external filtration/internal adsorption" developed by Zhou et al is

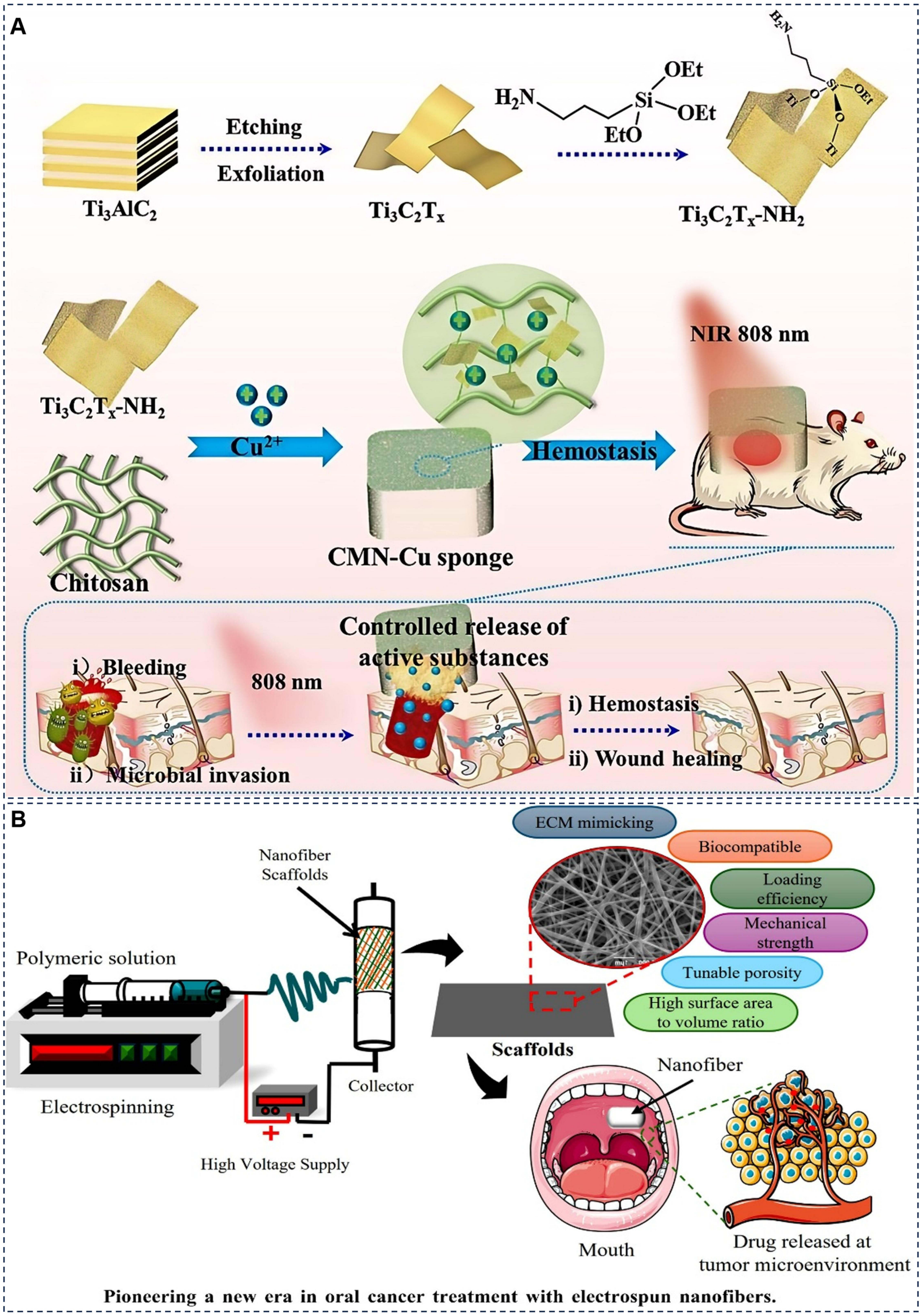

Figure 12 (**A**) Schematic diagram of the preparation and application of an MXene-based smart sponge with photothermal-responsive functionality. Reproduced with permission from Ref.[142] Copyright 2024, Elsevier. (**B**) Schematic illustration of nanofibers fabricated via electrospinning technology for the treatment of oral diseases. Reproduced with permission from Ref.[143] Copyright 2025, with permission from Bentham Science Publishers.

more appropriate for the treatment of OM, especially for grade 3–4 lesions accompanied by massive inflammatory exudate. The outer layer of this sponge is characterized by a relatively dense pore structure which can impede saliva erosion and prevent unregulated swelling. Meanwhile, the inner layer possesses interconnected macropores with high adsorption capacity, which can safely handle large volume of inflammatory exudate while maintaining structural stability. This dual-functional design not only addresses the issues of traditional sponges in the confined oral environment, but also provides a novel framework for the development of safe and effective oral sponges that can precisely adapt to the dynamic oral microenvironment and enhance patient compliance.[144]

Secondly, electrospinning technology is capable of fabricating three-dimensional fiber networks characterized by a high specific surface area, high porosity, and a biomimetic extracellular matrix topological structure.[145] This carrier system not only has the capacity to efficiently load and stably safeguard bioactive molecules but also can realize intelligent responsive drug release via rational material design, thereby forming a composite interface with both long term physical barrier and precise drug delivery. The entire process of electrospinning technology and its application scenarios in oral treatment are presented in Figure 12B.[143,146] For instance, through the construction of core-shell structure fibers, the active ingredients can be encapsulated within the core and protected by the shell layer, achieving zero-order kinetic sustained release over several days.[147] The introduction of pH-sensitive materials enables the targeted pulsed release of the drug in the inflammatory microenvironment (with a weakly acidic pH).[148] Among these, coaxial electrospinning technology serves as the core approach for fabricating core-shell structured fibers, offering an ideal platform for the delivery of bioactive factors. Jiang et al designed a coaxial electrospinning method, in which the core-shell structure can effectively encapsulate and protect biologically unstable molecules, achieve precise programming of release kinetics through material regulation, realize sustained drug release, and actively regulate the tissue repair process.[149] Additionally, Zhou et al developed a coaxial electrospinning technique with mucosal adhesion properties, which can significantly extend the local retention time of the drug. This approach overcomes the limitations of traditional dosage forms, such as rapid clearance and frequent administration caused by saliva flushing. Simultaneously, it actively promotes tissue regeneration as an active factor carrier.[150]

Finally, three dimensional (3D) printing technology, founded on the layer-by-layer accumulation principle of additive manufacturing, offers an individualized solution at the level of precise medical care for the treatment of OM (Figure 13A).[151] This technology can accurately fabricate personalized scaffolds that precisely match the shape of the affected area using biocompatible materials, relying on the highly accurate digital 3D model of the patient's oral cavity. Yu et al demonstrated that the embedded 3D printing technology realizes precise control of the drug loading amount and the gradient distribution of functional substances by parameterizing the filling patterns and nozzle sizes.[152] It has achieved precise control of the drug loading capacity and the gradient distribution of functional substances, providing engineering and technical support for the on demand customization of personalized oral mucosal adhesion membranes. Based on this, the multi material 3D printing technology can construct smart scaffolds with functional zones.[153] For instance, the outer layer is constructed with hydrophobic and slow release antibacterial materials to form an anti-infection barrier, while the inner layer integrates hydrophilic hydrogels loaded with growth factors to promote mucosal regeneration (Figure 13B).[154] For instance, Tagami et al successfully developed a drug loaded ionic liquid/methacrylic acid polymer mucosal adhesion membrane via pressure assisted micro-injection 3D printing technology, achieving a breakthrough optimization in drug solubility and drug release in response to the inflammatory microenvironment (Figure 13C).[155]

To enhance readability, we have summarised the pathological characteristics of OM mentioned in this paper, along with the design requirements for functional polymeric materials and typical case studies (Table 1).

Limitations and Future Perspectives

Functional polymer materials offer a variety of solutions for preventing and treating OM. Each type of material has its own unique advantages and limitations. Firstly, hydrogels possess excellent biocompatibility, enabling controlled drug release in response to multiple stimuli and integrating multiple therapeutic functions. However, some responsive systems have operational limitations in clinical settings, and the encapsulation efficiency of poorly soluble drugs is relatively low. Secondly, patch exhibits excellent wet adhesion and mucosal retention properties, enabling minimally invasive drug delivery to deep mucosal layers. However, conventional patches struggle to achieve effective drug release in deep tissues.

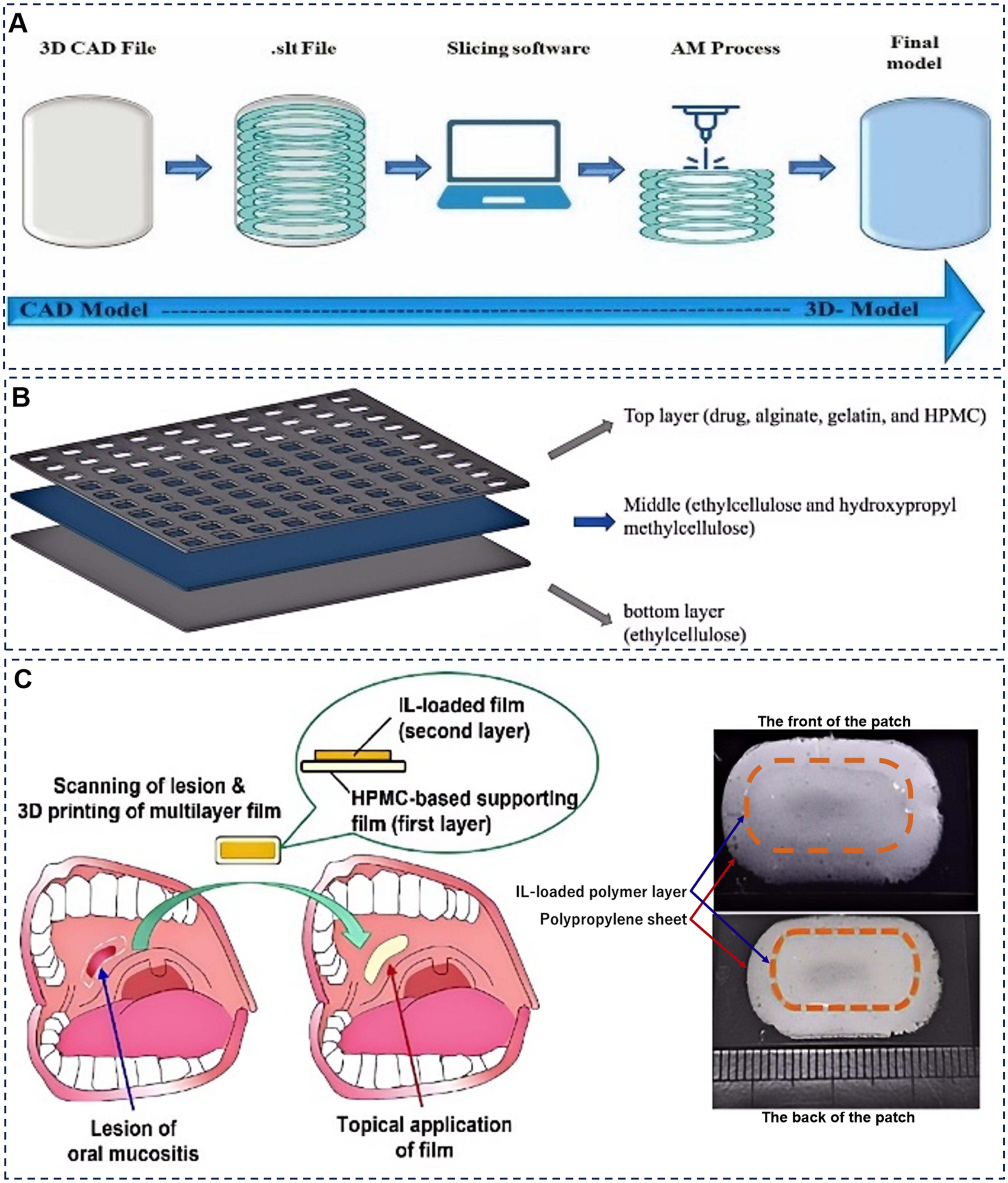

Figure 13 (**A**) Overall process of 3D printing technology for personalized oral therapy. Reproduced from Ref.[151] Copyright 2022, Springer Nature. (**B**) Schematic diagram of a functionally zoned multilayer adhesive oral film structure. Reproduced from Ref.[154] Copyright 2022, Springer Nature. (**C**) Schematic illustration of applying a 3D-printed film to an oral mucositis site, and structure of a multilayer film consisting of an IL-loaded layer and an HPMC-based supporting layer. Reproduced from Ref.[155] Copyright 2022, MDPI.

Table 1 Relationship Between OM Pathological Mechanisms and Functional Polymer Materials

Pathological Characteristics of OM	**Design Requirements for Materials**	**Typical Functional Polymer Materials**	**References**
Salivary Gland Dysfunction and Alteration of Saliva Composition	Possesses good wettability or may improve salivary secretion function	Poloxamer-based spray gel, Chitosan-gelatin in situ hydrogel	[69,70]
Microbial Dysbiosis	Regulates the oral microbiome and inhibits biofilm formation	Chitosan-gelatin in situ hydrogel, Miconazole oral patches, Gold nanoparticle, MXene-based smart sponge, pH-responsive electrospun fibers	[69,114,129,139,145]
Immunity and Inflammatory Response	Possesses excellent anti-inflammatory and immunomodulatory properties	KPV@PPP in situ hydrogel, Curcumin- Lidocaine Buccal Film, Dexamethasone-loaded PLGA nanoparticles, Cannabidiol-loaded fucoidan nanomicelles, Curcumin micelles, Collagen-chitosan sponge, 3D Printing Scaffold	[18,103,131–133,137,149]
Oxidative Stress and Vascular Endothelial Injury	Reduces oxidative stress, protects vascular endothelial cells, and regulates angiogenic factors	G-PVA hydrogel, TA@MPDA-HA/BSP Microneedle Patch, Gold nanoparticle	[65,112,127]
Dynamically Hydrated Oral Microenvironment	Adhesion and Mechanical Strength Compatible with Oral Microenvironment	G-PVA hydrogel, Chitosan oral patches, EGCG-PEG bioadhesive gel, Actinidia arguta leaves extract microparticles, chitosan microsphere, Buccal adhesive nanofibers, Sodium alginate/PEO electrospun nanofibers, Ectrospun nanofibers, 3D Printer Mucoadhesive Films	[65, 104, 105, 118, 120, 134, 135, 143, 151]

Moreover, it is difficult to precisely control the mechanical strength of the microneedle tips of microneedle patches, which substantially influences drug release efficiency due to variations in the dynamic oral microenvironment. Subsequently, micro-nano DDSs exhibit significant performance complementarity and application limitations in mucosal drug delivery. The micron-based DDSs, with its excellent mucosal adhesion properties, can achieve sustained drug release. However, their particle size limits their ability to penetrate the mucosal epithelial barrier and lacks flexibility in drug loading strategy design and drug release kinetics regulation. The nano DDSs, leveraging the advantages of the nano scale, can efficiently penetrate the mucosal barrier, significantly enhancing the targeted delivery efficiency and bioavailability, and effectively overcoming the dissolution and delivery obstacles of hydrophobic drugs. However, their mucosal retention time is relatively short, and the long-term biological safety, immunogenicity, and in vivo metabolic fate of some nano carrier materials still need to be verified through systematic preclinical and clinical studies. In addition, medical sponges can efficiently absorb exudate from wound surfaces and have a high drug loading capacity. However, their interfacial adhesion strength and inherent mechanical strength are insufficient., making them prone to displacement or structural failure in the dynamic oral environment, which affects the continuity of treatment. Electrospun membrane with biomimetic structures, not only support microenvironment-responsive drug release and cell behavior regulation, but also promote tissue integration. However, their mechanical integrity and mucosal interface bonding strength are limited. Furthermore, functional modification is highly sensitive to the spinning process parameters, restricting reproducibility and large-scale application. 3D printing can fit the lesion site precisely and achieve personalized design of drug loading and functions. However, its preparation process is complex, time-consuming, and costly. The synergy between the material degradation kinetics and the oral mucosa regeneration process still needs to be improved through systematic optimization of the material-biological interface.

Given the various challenges faced by functional polymer materials,as mentioned above, the treatment of OM requires strategies to be formulated from multiple aspects, such as material design, carrier construction and clinical translation. In terms of material design, intelligent dynamic adaptive polymer systems with multiple microenvironmental response capabilities such as pH, enzymes, and redox should be developed. Furthermore, the biomimetic wet adhesion mechanism of mussels and the principle of tissue self-repair should be integrated to collaboratively optimize the interface adhesion strength, mechanical strength, and degradability of the materials, in order to adapt to the oral physiological environment and the drug release requirements of OM at different pathological stages. In terms of carrier construction, it can be designed based on core-shell, layered or gradient micro-nano structures to construct a multi-drug co-delivery platform comprising spatially separated drug-loading chambers and programmable controlled-release channels. This effectively avoids compatibility conflicts between drugs and enables temporally controllable synergistic release kinetics. In terms of clinical translation, it is essential to enhance the deep cross-disciplinary collaboration among materials science, oral medicine, oncology and pharmaceutical engineering, integrate advanced manufacturing technologies such as microfluidic chips, electrospinning and 3D bioprinting, in order to optimize the scalable production process and establish a complete chain of quality control standards; Simultaneously, by simplifying the administration operation procedures, reducing the foreign matter sensation of materials and improving patient comfort, the clinical applicability, safety and patient compliance of the treatment regimens can be significantly enhanced, thereby accelerating the efficient translation of basic research findings into clinical practice.

It is noteworthy that with the evolution of artificial intelligence (AI) technology, the profound integration of AI and the design of functional polymer materials is propelling a substantial transformation in the research paradigm of this field, offering a completely novel approach for realizing precise, efficient, and intelligent material research and development.[156]

First, the AI conducts dynamic analysis of clinical images, pathological omics data, and biomarker data via deep learning algorithms. It constructs a multi-parameter coupled model to precisely identify the pathological stage of OM and enables the materials to realize dynamically responsive drug delivery.[157] For instance, through the analysis of wound characteristics including size, depth, and severity of infection, personalized material design is facilitated to achieve intelligent drug delivery.[158] Second, AI can be integrated with intelligent sensing technology to implement realtime monitoring of the wound-healing process of OM.[159] By continuously monitoring the key physiological indicators of the OM area, such as temperature, humidity, pH value, and the dynamic changes in inflammatory factor concentrations, the polymer carrier can achieve locally responsive drug release and mitigate systemic risks.[159] Finally, by analyzing the data generated by these sensors, the AI can assess the effectiveness of the treatment based on functional polymeric materials and provide data support for strategy adjustments.[159–161]

In a word, with the accumulation of more experimental data, AI-driven functional polymeric materials are anticipated to emerge as a crucial approach for the personalized treatment of OM patients.

Conclusion

In conclusion, this review elucidates the pivotal role of functional polymeric materials in advancing the prevention and treatment of OM. By counteracting the disruption of oral microenvironment homeostasis induced by radiotherapy or chemotherapy, which includes xerostomia, dysbiosis, inflammatory cycles, and oxidative stress, and surmounting the rapid drug clearance in the dynamic oral cavity, these materials present customized therapeutic strategies. Among various materials, hydrogels show considerable promise due to their biocompatibility, mucosal adhesion, and ability to provide controlled drug release in response to local conditions. Additionally, micron- and nano-patches or DDSs enable localized, sustained, or targeted therapy, enhancing drug retention and bioavailability. Integration with AI-driven sensing and data analytics further facilitates real-time monitoring and personalized treatment design. Future efforts should prioritize clinical translation and interdisciplinary collaboration to realize precision, patient-centered OM management with enhanced efficacy and safety.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

We sincerely acknowledge the financial support from Zunyi Medical University Academic New Talent Cultivation and Innovation Exploration Special Project Plan [1350-077], Zunyi Municipal Science and Technology Program [2025HZ290, 2025SYS1], Natural Science Foundation of Sichuan [2025ZNSFSC1733], Sichuan Province Traditional

Chinese Medicine Research Project [25MSZX428], Dazhou Science and Technology Project [25YYJC0026], Dazhou Traditional Chinese Medicine Research Project [2025LHZRPY08, 2025LHZRZD02].

Disclosure

The authors report no conflicts of interest in this work.

References

1. Kaushik I, Ramachandran S, Prasad S, Srivastava SK. Drug rechanneling: a novel paradigm for cancer treatment. *Semin Cancer Biol*. 2021;68:279–290. doi:10.1016/j.semcancer.2020.03.011
2. Epstein JB, Thariat J, Bensadoun RJ, et al. Oral complications of cancer and cancer therapy: from cancer treatment to survivorship. *CA Cancer J Clin*. *Nov–Dec*. 2012;62(6):400–422. doi:10.3322/caac.21157
3. Elad S, Yarom N, Zadik Y, Kuten-Shorrer M, Sonis ST. The broadening scope of oral mucositis and oral ulcerative mucosal toxicities of anticancer therapies. *CA Cancer J Clin*. 2022;72(1):57–77. doi:10.3322/caac.21704
4. Maria OM, Eliopoulos N, Muanza T. Radiation-induced oral mucositis. *Front Oncol*. 2017;7:89. doi:10.3389/fonc.2017.00089
5. Cinausero M, Aprile G, Ermacora P, et al. New frontiers in the pathobiology and treatment of cancer regimen-related mucosal injury. *Front Pharmacol*. 2017;8:354. doi:10.3389/fphar.2017.00354
6. Gobbo M, Ottaviani G, Perinetti G, et al. Evaluation of nutritional status in head and neck radio-treated patients affected by oral mucositis: efficacy of class IV laser therapy. *Support Care Cancer*. 2014;22(7):1851–1856. doi:10.1007/s00520-014-2155-x
7. Xia J, Tao X, Hu Q, et al. Expert consensus on the prevention and treatment of radiochemotherapy-induced oral mucositis. *Int J Oral Sci*. 17 (1):54. doi:10.1038/s41368-025-00382-8
8. Anderson C, Saunders D. Oral mucositis in head and neck cancer patients. *Semin Radiat Oncol*. *Apr*. 2025;35(2):271–277. doi:10.1016/j.semradonc.2025.02.011
9. Sonis ST. The pathobiology of mucositis. *Nat Rev Cancer*. 2004;4(4):277–284. doi:10.1038/nrc1318
10. Bescos R, Ashworth A, Clarke C, et al. Effects of Chlorhexidine mouthwash on the oral microbiome. *Sci Rep*. 2020;10(1):5254. doi:10.1038/s41598-020-61912-4
11. Chaitanya B, Pai KM, Yathiraj PH, Fernandes D, Chhaparwal Y. Rebamipide gargle in preventive management of chemo-radiotherapy induced oral mucositis. *Oral Oncol*. 2017;72:179–182. doi:10.1016/j.oraloncology.2017.07.024
12. Nakamura M, Shinohara A, Onikubo T, et al. Efficacy of rebamipide-gargle for chemotherapy-induced oral mucositis. *J Clin Oncol*. 2013;31 (15_suppl):9637. doi:10.1200/jco.2013.31.15_suppl.9637
13. Sun W, Jian Y, Feng X, Zhao M, Liu Y. Efficacy of Kangfuxin liquid for preventing and treating chemotherapy-induced oral mucositis: a systematic review and meta-analysis of randomized controlled trials. *Front Pharmacol*. 2025;16:1565345. doi:10.3389/fphar.2025.1565345
14. Yan Y, Liu T, Tian X, Liu J, Chen Q, Zhao H. A double-layer thin oral film for wet oral mucosa adhesion and efficient treatment of oral ulcers. *J Mater Chem B*. 2024;12(12):3015–3021. doi:10.1039/d3tb02976j
15. Fonseca-Santos B, Chorilli M. An overview of polymeric dosage forms in buccal drug delivery: state of art, design of formulations and their in vivo performance evaluation. *Mater Sci Eng C Mater Biol Appl*. 2018;86:129–143. doi:10.1016/j.msec.2017.12.022
16. Paderni C, Compilato D, Giannola LI, Campisi G. Oral local drug delivery and new perspectives in oral drug formulation. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2012;114(3):e25–e34. doi:10.1016/j.oooo.2012.02.016
17. Ferreira AS, Macedo C, Silva AM, Delerue-Matos C, Costa P, Rodrigues F. Natural products for the prevention and treatment of oral mucositis—a review. *Int J Mol Sci*. 2022;23(8):4385. doi:10.3390/ijms23084385
18. Shao W, Chen R, Lin G, et al. *In situ* mucoadhesive hydrogel capturing tripeptide KPV: the anti-inflammatory, antibacterial and repairing effect on chemotherapy-induced oral mucositis. *Biomater Sci*. 2022;10(1):227–242. doi:10.1039/d1bm01466h
19. Zhang W, Zhao J, Zou X, Yu J, Liao J, Huang F. Multifunctional hydrogels for the healing of oral ulcers. *J Biomed Mater Res A*. 2025;113(1):e37776. doi:10.1002/jbm.a.37776
20. Squier CA, Kremer MJ. Biology of oral mucosa and esophagus. *J Natl Cancer Inst Monogr*. 2001;29):7–15. doi:10.1093/oxfordjournals.jncimonographs.a003443.
21. Dewhirst Floyd E, Chen T, Izard J, et al. The Human Oral Microbiome. *Journal of Bacteriology*. 2010;192(19):5002–5017. doi:10.1128/jb.00542-10
22. Dawes C, Pedersen AM, Villa A, et al. The functions of human saliva: a review sponsored by the world workshop on oral medicine VI. *Arch Oral Biol*. 2015;60(6):863–874. doi:10.1016/j.archoralbio.2015.03.004
23. Iglesias-Bartolome R, Uchiyama A, Molinolo AA, et al. Transcriptional signature primes human oral mucosa for rapid wound healing. *Sci Transl Med*. 2018;10(451). doi:10.1126/scitranslmed.aap8798
24. Ballestas SA, Turner TC, Kamalakar A, et al. Improving hard palate wound healing using immune modulatory autotherapies. *Acta Biomater*. 2019;91:209–219. doi:10.1016/j.actbio.2019.04.052
25. Lalla RV, Sonis ST, Peterson DE. Management of oral mucositis in patients who have cancer. *Dent Clin North Am*. 2008;52(1):61–77. doi:10.1016/j.cden.2007.10.002.
26. Sonis ST. Mucositis: the impact, biology and therapeutic opportunities of oral mucositis. *Oral Oncol*. 2009;45(12):1015–1020. doi:10.1016/j.oraloncology.2009.08.006
27. Marcotte H, Lavoie MC. Oral microbial ecology and the role of salivary immunoglobulin A. *Microbiol Mol Biol Rev*. 1998;62(1):71–109. doi:10.1128/MMBR.62.1.71-109.1998
28. Boink MA, van den Broek LJ, Roffel S, et al. Different wound healing properties of dermis, adipose, and gingiva mesenchymal stromal cells. *Wound Repair Regen*. 2016;24(1):100–109. doi:10.1111/wrr.12380
29. Torres P, Castro M, Reyes M, Torres VA. Histatins, wound healing, and cell migration. *Oral Dis*. 2018;24(7):1150–1160. doi:10.1111/odi.12816

30. Yang J, Liu Y, Yao H, et al. Effect of Dendrobium officinale on radioactive oral mucositis of nasopharyngeal carcinoma and changes of oral microecology. *Integr Cancer Ther*. 2025;24:15347354251313524. doi:10.1177/15347354251313524
31. Jensen SB, Pedersen AM, Vissink A, et al. A systematic review of salivary gland hypofunction and xerostomia induced by cancer therapies: prevalence, severity and impact on quality of life. *Support Care Cancer*. 2010;18(8):1039–1060. doi:10.1007/s00520-010-0827-8
32. Cheng KK, Leung SF, Liang RH, Tai JW, Yeung RM, Thompson DR. Severe oral mucositis associated with cancer therapy: impact on oral functional status and quality of life. *Support Care Cancer*. 2010;18(11):1477–1485. doi:10.1007/s00520-009-0771-7
33. Salvatori O, Puri S, Tati S, Edgerton M. Innate immunity and saliva in Candida albicans-mediated oral diseases. *J Dent Res*. 2016;95 (4):365–371. doi:10.1177/0022034515625222
34. Lalla RV, Peterson DE. Oral mucositis. *Dent Clin North Am*. 2005;49(1):167–184. doi:10.1016/j.cden.2004.07.009
35. Zhang Y, Wang X, Li H, Ni C, Du Z, Yan F. Human oral microbiota and its modulation for oral health. *Biomed Pharmacother*. 2018;99:883–893. doi:10.1016/j.biopha.2018.01.146
36. Bertolini M, Costa RC, Barão VAR, et al. Oral microorganisms and biofilms: new insights to defeat the main etiologic factor of oral diseases. *Microorganisms*. 2022;10(12). doi:10.3390/microorganisms10122413
37. Hong BY, Sobue T, Choquette L, et al. Chemotherapy-induced oral mucositis is associated with detrimental bacterial dysbiosis. *Microbiome*.;7 (1):66. doi:10.1186/s40168-019-0679-5.
38. Haverman TM, Laheij A, Nie M, et al. Exploring the role of oral microorganisms in the pathogenesis of mucositis by assessing their impact on metabolic activity and reproductive capacity of epithelial cells in vitro. *Support Care Cancer*. 2020;28(10):4729–4735. doi:10.1007/s00520-020-05318-y
39. Jia B, Zhang B, Li J, et al. Emerging polymeric materials for treatment of oral diseases: design strategy towards a unique oral environment. *Chem Soc Rev*.;53(7):3273–3301. doi:10.1039/d3cs01039b.
40. Min Z, Yang L, Hu Y, Huang R. Oral microbiota dysbiosis accelerates the development and onset of mucositis and oral ulcers. *Front Microbiol*. 2023;14:1061032. doi:10.3389/fmicb.2023.1061032
41. Gugnacki P, Sierko E. Is there an interplay between oral microbiome, head and neck carcinoma and radiation-induced oral mucositis? *Cancers*. 2021;13(23). doi:10.3390/cancers13235902
42. Tu Y, Ren H, He Y, Ying J, Chen Y. Interaction between microorganisms and dental material surfaces: general concepts and research progress. *J Oral Microbiol*. 2023;15(1):2196897. doi:10.1080/20002297.2023.2196897
43. Huang W, Fan Y, Cheng X, et al. A preliminary study on the effect of head and neck chemoradiotherapy on systematic immunity. *Dose Response. Oct–Dec*. 2019;17(4):1559325819884186. doi:10.1177/1559325819884186
44. Umazume M, Ueta E, Osaki T. Reduced inhibition of Candida albicans adhesion by saliva from patients receiving oral cancer therapy. *J Clin Microbiol*. 1995;33(2):432–439. doi:10.1128/jcm.33.2.432-439.1995
45. Duong TA, Valeyrie-Allanore L, Wolkenstein P, Chosidow O. Severe cutaneous adverse reactions to drugs. *Lancet*. 2017;390 (10106):1996–2011. doi:10.1016/s0140-6736(16)30378-6
46. Aytekin N, Tüklübay M, Kayhan KB. Oral lichen planus versus oral lichenoid lesions: retrospective study. *Int Dental J*. 2024;74:S258. doi:10.1016/j.identj.2024.07.165
47. Xia W, Liu Y, Jiang X, et al. Lean adipose tissue macrophage derived exosome confers immunoregulation to improve wound healing in diabetes. *J Nanobiotechnology*.;21(1):128. doi:10.1186/s12951-023-01869-4.
48. Bowen J, Cross C. The role of the innate immune response in oral mucositis pathogenesis. *Int J Mol Sci*. 2023;24(22). doi:10.3390/ijms242216314
49. Jing F, Mu J, Liu J, Hu C, Wu F, Gao Q. Senescent vascular endothelial cells promote oral squamous cell carcinoma progression through complement C3 activation. *Arch Oral Biol*. 2025;174:106242. doi:10.1016/j.archoralbio.2025.106242
50. Gruber S, Dörr W. Tissue reactions to ionizing radiation-Oral mucosa. *Mutat Res Rev Mutat Res*. 2016;770(Pt B):292–298. doi:10.1016/j.mrrev.2016.07.007
51. Ali H. SCUBE2, vascular endothelium, and vascular complications: a systematic review. *Biomed Pharmacother*. 2020;127:110129. doi:10.1016/j.biopha.2020.110129
52. Gualtero DF, Lafaurie GI, Buitrago DM, Castillo Y, Vargas-Sanchez PK, Castillo DM. Oral microbiome mediated inflammation, a potential inductor of vascular diseases: a comprehensive review. *Front Cardiovasc Med*. 2023;10:1250263. doi:10.3389/fcvm.2023.1250263
53. Ansari MJ, Bokov D, Markov A, et al. Cancer combination therapies by angiogenesis inhibitors; a comprehensive review. *Cell Commun Signal*.;20(1):49. doi:10.1186/s12964-022-00838-y.
54. Ingrosso G, Saldi S, Marani S, et al. Breakdown of symbiosis in radiation-induced oral mucositis. *J Fungi*. 7(4). doi:10.3390/jof7040290
55. Nam S, Mooney D. Polymeric tissue adhesives. *Chem Rev*. 2021;121(18):11336–11384. doi:10.1021/acs.chemrev.0c00798
56. Cui C, Liu W. Recent advances in wet adhesives: adhesion mechanism, design principle and applications. *Prog Polym Sci*. 2021;116:101388. doi:10.1016/j.progpolymsci.2021.101388
57. Madhav NV, Shakya AK, Shakya P, Singh K. Orotransmucosal drug delivery systems: a review. *J Control Release*. 2009;140(1):2–11. doi:10.1016/j.jconrel.2009.07.016
58. Mao Y, Xu Z, He Z, Wang J, Zhu Z. Wet-adhesive materials of oral and maxillofacial region: from design to application. *Chin Chem Lett*. 2023;34(1):107461. doi:10.1016/j.cclet.2022.04.059
59. Yang Y, Yuan J, Ni Y, et al. Spatiotemporal self-strengthening hydrogels for oral tissue regeneration. *Compos Part B Eng*. 2022;243:110119. doi:10.1016/j.compositesb.2022.110119
60. Asadi N, Pazoki-Toroudi H, Del Bakhshayesh AR, Akbarzadeh A, Davaran S, Annabi N. Multifunctional hydrogels for wound healing: special focus on biomacromolecular based hydrogels. *Int J Biol Macromol*. 2021;170:728–750. doi:10.1016/j.ijbiomac.2020.12.202
61. Solanki D, Vinchhi P, Patel MM. Design considerations, formulation approaches, and strategic advances of hydrogel dressings for chronic wound management. *ACS Omega*. 2023;8(9):8172–8189. doi:10.1021/acsomega.2c06806
62. Yang Q, Peng J, Xiao H, Xu X, Qian Z. Polysaccharide hydrogels: functionalization, construction and served as scaffold for tissue engineering. *Carbohydr Polym*. 2022;278:118952. doi:10.1016/j.carbpol.2021.118952
63. Chen A, Deng S, Lai J, et al. Hydrogels for Oral Tissue Engineering: challenges and Opportunities. *Molecules*. 28(9). doi:10.3390/molecules28093946

64. Zhao S, Wang R, Ma Q, et al. Hydrogel-based therapeutics for diabetic oral wounds: from mechanisms to applications. *Adv Healthc Mater*. 2025;14(32):e02205. doi:10.1002/adhm.202502205
65. Ding Z, Hu X, Liang W, Zheng S, Luo X, Zhao H. Dual-functional guanosine-based hydrogel: high-efficiency protection in radiation-induced oral mucositis. *J Mater Chem B*. 2025;13(9):3039–3048.PMID: 39895385. doi:10.1039/d4tb02380c
66. Ying H, Zhou J, Wang M, et al. *In situ* formed collagen-hyaluronic acid hydrogel as biomimetic dressing for promoting spontaneous wound healing. *Mater Sci Eng C Mater Biol Appl*. 2019;101:487–498. doi:10.1016/j.msec.2019.03.093
67. Quan Y, Shao H, Wang N, Gao Z, Jin M. Microenvironment-sensitive hydrogels as promising drug delivery systems for co-encapsulating microbial homeostasis probiotics and anti-inflammatory drugs to treat periodontitis. *Mater Today Bio. Jun*. 2025;32:101711. doi:10.1016/j.mtbio.2025.101711
68. Oliva N, Conde J, Wang K, Artzi N. Designing hydrogels for on-demand therapy. *Acc Chem Res*. 2017;50(4):669–679. doi:10.1021/acs.accounts.6b00536
69. Perchyonok VT, Zhang S, Oberholzer T. Chitosan and gelatin based prototype delivery systems for the treatment of oral mucositis: from material to performance in vitro. *Curr Drug Deliv. Feb*. 2013;10(1):144–150. doi:10.2174/1567201811310010020
70. Li T, Bao Q, Shen J, Lalla RV, Burgess DJ. Mucoadhesive *in situ* forming gel for oral mucositis pain control. *Int J Pharm*. 580:119238. doi:10.1016/j.ijpharm.2020.119238
71. Li T, Lalla RV, Burgess DJ. Enhanced drug loading of *in situ* forming gels for oral mucositis pain control. *Int J Pharm*. 595:120225. doi:10.1016/j.ijpharm.2021.120225
72. Zhang Y, Mao R, Liu Z, et al. Efficacy and safety of NAHAO® hydrogel in amelioration of chemoradiotherapy-induced oral mucositis: an preliminary clinical study (ChiCTR2200064766). *J Stomatol Oral Maxillofac Surg*. 2023;124(6s):101568. doi:10.1016/j.jormas.2023.101568
73. Kang Y, Xiong Y, Lu B, et al. Application of *in situ* mucoadhesive hydrogel with anti-inflammatory and pro-repairing dual properties for the treatment of chemotherapy-induced oral mucositis. *ACS Appl Mater Interfaces*. 16(28):35949–35963. doi:10.1021/acsami.4c03217
74. Pan Y, Wang M, Wang P, et al. Effects of a semi-interpenetrating network hydrogel loaded with oridonin and DNase-I on the healing of chemoradiotherapy-induced oral mucositis. *Biomater Sci*. 2024;12(17):4452–4470. doi:10.1039/d4bm00114a
75. Wu Y, Jiang L, Li K, et al. Hyaluronic acid-based composite hydrogels embedded with core-shell microgels with properties of mucosal adhesion and combined drug administration for chemoradiotherapy induced oral mucositis. *Int J Biol Macromol*. 2025;322(Pt 2):146575. doi:10.1016/j.ijbiomac.2025.146575
76. Qiu Y, Park K. Environment-sensitive hydrogels for drug delivery. *Adv Drug Deliv Rev.* 53(3):321–339. doi:10.1016/s0169-409x(01)00203-4
77. Klouda L, Mikos AG. Thermoresponsive hydrogels in biomedical applications. *European Journal of Pharmaceutics and Biopharmaceutics*. 2008;68(1):34–45. doi:10.1016/j.ejpb.2007.02.025
78. Klouda L. Thermoresponsive hydrogels in biomedical applications: a seven-year update. *Eur J Pharm Biopharm*. 2015;97(Pt B):338–349. doi:10.1016/j.ejpb.2015.05.017
79. Yu MK, Park J, Jon S. Targeting strategies for multifunctional nanoparticles in cancer imaging and therapy. *Theranostics*. 2012;2(1):3–44. doi:10.7150/thno.3463
80. Qi Y, Shao J, Luo Z, et al. In vivo adhesion fault-tolerant coenzyme/queen bee acid nanomicelles self-crosslinked thermoresponsive adhesive hydrogel for efficient oral ulcer treatment. *Bioact Mater.* 2025;52:460–473. doi:10.1016/j.bioactmat.2025.06.023
81. Rezazadeh M, Jafari N, Akbari V, et al. A mucoadhesive thermosensitive hydrogel containing erythropoietin as a potential treatment in oral mucositis: in vitro and in vivo studies. *Drug Deliv Transl Res*. 2018;8(5):1226–1237. doi:10.1007/s13346-018-0566-9
82. Duan J, Chen M, Wang M, He R, Li K, Shi L. Hierarchically assembled curcumin-vitamin E-zinc thermo-gel for multi-synergistic prevention and treatment of radiation-induced oral mucositis. *Mater Today Bio*. 2025;35:102525. doi:10.1016/j.mtbio.2025.102525
83. Ullah F, Othman MB, Javed F, Ahmad Z, Md Akil H. Classification, processing and application of hydrogels: a review. *Mater Sci Eng C Mater Biol Appl*. 57:414–433. doi:10.1016/j.msec.2015.07.053
84. Gupta P, Vermani K, Garg S. Hydrogels: from controlled release to pH-responsive drug delivery. *Drug Discov Today.* 2002;7(10):569–579. doi:10.1016/s1359-6446(02)02255-9
85. Zhang X, Liu Y, Wang Z, et al. pH-responsive and self-adaptive injectable sodium alginate/carboxymethyl chitosan hydrogel accelerates infected wound healing by bacteriostasis and immunomodulation. *Carbohydr Polym*. 354:123322. doi:10.1016/j.carbpol.2025.123322
86. Iglesias N, Galbis E, Valencia C, De-Paz MV, Galbis JA. Reversible pH-sensitive chitosan-based hydrogels. influence of dispersion composition on rheological properties and sustained drug delivery. *Polymers*. 2018;10(4). doi:10.3390/polym10040392
87. Sha Z, Wu Y, Zheng Y, et al. Advances in pH-responsive drug delivery systems for periodontitis treatment. *Drug Deliv.* 2025;32(1):2522109. doi:10.1080/10717544.2025.2522109
88. Tomatsu I, Peng K, Kros A. Photoresponsive hydrogels for biomedical applications. *Adv Drug Deliv Rev.* 2011;63(14–15):1257–1266. doi:10.1016/j.addr.2011.06.009
89. Hernot S, Klibanov AL. Microbubbles in ultrasound-triggered drug and gene delivery. *Adv Drug Deliv Rev.* 60(10):1153–1166. doi:10.1016/j.addr.2008.03.005
90. Huebsch N, Kearney CJ, Zhao X, et al. Ultrasound-triggered disruption and self-healing of reversibly cross-linked hydrogels for drug delivery and enhanced chemotherapy. *Proc Natl Acad Sci U S A*. 111(27):9762–9767. doi:10.1073/pnas.1405469111
91. Qi W, Dong N, Wu L, et al. Promoting oral mucosal wound healing using a DCS-RuB(2)A(2) hydrogel based on a photoreactive antibacterial and sustained release of BMSCs. *Bioact Mater.* 2023;23:53–68. doi:10.1016/j.bioactmat.2022.10.027
92. Shen KH, Lu CH, Kuo CY, Li BY, Yeh YC. Smart near infrared-responsive nanocomposite hydrogels for therapeutics and diagnostics. *J Mater Chem B*. 9(35):7100–7116. doi:10.1039/d1tb00980j
93. Yamakawa R, Onoe H, Kurashina Y. Hydrogel carrier with bubble vibration enhancer for ultrasound-triggered drug release. *Ultrason Sonochem*. 2025;112:107173. doi:10.1016/j.ultsonch.2024.107173
94. Aliabouzar M, Quesada C, Chan ZQ, et al. Acoustic droplet vaporization for on-demand modulation of microporosity in smart hydrogels. *Acta Biomater.* 164:195–208. doi:10.1016/j.actbio.2023.04.037
95. Campos JC, Cunha D, Ferreira DC, Reis S, Costa PJ. Oromucosal precursors of in loco hydrogels for wound-dressing and drug delivery in oral mucositis: retain, resist, and release. *Mater Sci Eng C Mater Biol Appl*. 2021;118:111413. doi:10.1016/j.msec.2020.111413

96. Sankar V, Hearnden V, Hull K, et al. Local drug delivery for oral mucosal diseases: challenges and opportunities. *Oral Diseases*. 2011;17:73–84. doi:10.1111/j.1601-0825.2011.01793.x
97. Cheng QS, Xu PY, Luo SC, Chen AZ. Advances in adhesive materials for oral and maxillofacial soft tissue diseases. *Macromolecular Bioscience*. 2025;25(3):e2400494. doi:10.1002/mabi.202400494
98. Yu Q, Yan Y, Huang J, et al. A multifunctional chitosan-based hydrogel with self-healing, antibacterial, and immunomodulatory effects as wound dressing. *International Journal of Biological Macromolecules*. 2023;231:123149. doi:10.1016/j.ijbiomac.2023.123149
99. Zhang Q, Chen J, Zhang T, et al. A bilayer polyurethane patch with sustained growth factor release and antibacteria for re-epithelization of large-scale oral mucosal defects. *ACS Appl Mater Interfaces*. 2024;16(34):44561–44574. doi:10.1021/acsami.4c09841
100. Colley HE, Said Z, Santocildes-Romero ME, et al. Pre-clinical evaluation of novel mucoadhesive bilayer patches for local delivery of clobetasol-17-propionate to the oral mucosa. *Biomaterials*. 2018;178:134–146. doi:10.1016/j.biomaterials.2018.06.009
101. Varoni EM, Altomare L, Bonetti L, et al. Bilayer chitosan-based patches for steroidal drug delivery on the oral mucosa. *Journal of Drug Delivery Science and Technology*. 2024;99:105919. doi:10.1016/j.jddst.2024.105919
102. Hu S, Pei X, Duan L, et al. A mussel-inspired film for adhesion to wet buccal tissue and efficient buccal drug delivery. *Nat Commun*. 2021;12(1):1689. doi:10.1038/s41467-021-21989-5
103. Maheen S, Awan MS, Abbas G, et al. Design, statistical optimization, in vitro and biological characterization of Eudragit L100-gelatin based buccoadhesive bilayer patch for managing oral mucositis. *Int J Biol Macromol*. 2025;308(Pt 2):142070. doi:10.1016/j.ijbiomac.2025.142070
104. Li X, Wang K-Y, Qin W, et al. Zinc-releasing adhesive oral patch for prevention of radiation-induced oral ulcerative mucositis. *Chemical Engineering Journal*. 2025;517:164307. doi:10.1016/j.cej.2025.164307
105. Kraisit P, Yonemochi E, Furuishi T, Mahadlek J, Limmatvapirat S. Chitosan film containing antifungal agent-loaded SLNs for the treatment of candidiasis using a Box-Behnken design. *Carbohydr Polym*. 2022;283:119178. doi:10.1016/j.carbpol.2022.119178
106. Fathy Elhabal S, Saeed Farahat M, Teaima MH, AE N, Fouad SA, El-Nabarawi M. A Dual-Action Nanoemulsified Mucoadhesive Polymeric Buccal Film of Curcumin-Lidocaine: non-Invasive targeting Oral Mucositis Treatment via MMP-9 and NF-κβ Pathways. *J Drug Target*. 2026;1–59. doi:10.1080/1061186x.2026.2613056
107. Wang N, Liu M, Liu H, Cui J, Ge S, Li J. Polyphenol coacervate-derived bioadhesive glue with mussel-mimicking secretion behavior for treating chemotherapy-induced oral mucositis. *Chemical Engineering Journal*. 2025;526:171308. doi:10.1016/j.cej.2025.171308
108. Zhang Y, Wang T, Dong X, et al. Salivary amylase-responsive buccal tablets wipe out chemotherapy-rooted refractory oral mucositis. *Adv Sci*. 2024;11(11):e2308439. doi:10.1002/advs.202308439
109. Ryu JH, Choi JS, Park E, et al. Chitosan oral patches inspired by mussel adhesion. *J Control Release*. 2020;317:57–66. doi:10.1016/j.jconrel.2019.11.006
110. Cheng X, Yang Y, Liao Z, et al. Drug-loaded mucoadhesive microneedle patch for the treatment of oral submucous fibrosis. *Front Bioeng Biotechnol*. 2023;11:1251583. doi:10.3389/fbioe.2023.1251583
111. Zhu T, Yu X, Yi X, et al. Lidocaine-loaded hyaluronic acid adhesive microneedle patch for oral mucosal topical anesthesia. *Pharmaceutics*. 14(4). doi:10.3390/pharmaceutics14040686
112. Xiao Y, Song C, Ye H, et al. A ferroptosis-targeting detachable dissolvable microneedle as a combined therapeutic strategy for radiation-induced oral mucositis. *Chemical Engineering Journal*. 2025;505:158959. doi:10.1016/j.cej.2024.158959
113. Tang Q, Song C, Wu X, et al. Dual-functional core–shell microneedle patches for oral ulcers treatment. *Chemical Engineering Journal*. 2024;500:157041. doi:10.1016/j.cej.2024.157041
114. Chen F, Zhao Z, Liu X, et al. A multifunctional microneedle patch loading exosomes and magnetic nanoparticles synergistically for treating oral mucosal lesions. *Applied Materials Today*. 2024;40:102382. doi:10.1016/j.apmt.2024.102382
115. Qu X, Guo X, Zhu T, Zhang Z, Wang W, Hao Y. Microneedle patches containing mesoporous polydopamine nanoparticles loaded with triamcinolone acetonide for the treatment of oral mucositis. *Front Bioeng Biotechnol*. 2023;11:1203709. doi:10.3389/fbioe.2023.1203709
116. Li XJ, Li Y, Meng Y, et al. Composite dissolvable microneedle patch for therapy of oral mucosal diseases. *Biomater Adv*. 2022;139:213001. doi:10.1016/j.bioadv.2022.213001
117. Funahara R, Soutome S, Funahara M, et al. Effects of a miconazole oral patch on preventing development of oral candidiasis in patients with head and neck cancer undergoing radiotherapy: results of a preliminary study quantifying the prevalence of Candida albicans in saliva. *Support Care Cancer*. 2022;30(1):907–914. doi:10.1007/s00520-021-06480-7
118. Wang P, Wang T, Zhang H, et al. A double layer oral film loaded with doxepin hydrochloride for the treatment of chemotherapy-induced oral mucositis. *Front Pharmacol*. 2025;16:1673190. doi:10.3389/fphar.2025.1673190
119. Freires IA, Rosalen PL. How natural product research has contributed to oral care product development? a critical view. *Pharm Res*. 2016;33(6):1311–1317. doi:10.1007/s11095-016-1905-5
120. Lengyel M, Kállai-Szabó N, Antal V, Laki AJ, Antal I. Microparticles, microspheres, and microcapsules for advanced drug delivery.Sci. *Pharm*. 2019;87(3):20. doi:10.3390/scipharm87030020
121. Ferreira AS, Silva AM, Laveriano-Santos EP, et al. Development and characterization of spray-drying microparticles loaded with chestnut shells extract: new insights for oral mucositis therapy. *Powder Technology*. 2024;446:120182. doi:10.1016/j.powtec.2024.120182
122. Teixeira F, Silva AM, Sut S, et al. Development and characterization of microparticles with Actinidia arguta leaves extract by spray-drying: a new mind-set regarding healthy compounds for oral mucositis. *Antioxidants*. 2023;12(8):1496. doi:10.3390/antiox12081496
123. Jiang WZ, Cai Y, Li HY. Chitosan-based spray-dried mucoadhesive microspheres for sustained oromucosal drug delivery. *Powder Technol*. 2017;312:124–132. doi:10.1016/j.powtec.2017.02.021
124. Hasirci N. Micro and nano systems in biomedicine and drug delivery. In: *Nanomaterials and Nanosystems for Biomedical Applications*. Springer; 2007:1–26. doi:10.1007/978-1-4020-6289-6_1
125. Wilczewska AZ, Niemirowicz K, Markiewicz KH, Car H. Nanoparticles as drug delivery systems. *Pharmacol Rep*. 2012;64(5):1020–1037. doi:10.1016/s1734-1140(12)70901-5
126. Wang S, Tan M, Zhong Z, Chen M, Wang Y. Nanotechnologies for Curcumin: an ancient puzzler meets modern solutions. *J Nanomater*. 2011;2011:1–8. doi:10.1155/2011/723178
127. Aminu N, Chan SY, Toh SM. Development and validation of a stability-indicating HPLC-UV method for the simultaneous determination of flurbiprofen and triclosan in dental nanogel formulations. *J Phys Sci*. 2018;29(Suppl. 1):1–7. doi:10.21315/jps2018.29.s1.1

128. Manish G, Vimukta S. Targeted drug delivery system: a review. *Res J Chem Sci*. 2011;1(2):135–138.
129. De jong WH, Borm PJ. Drug delivery and nanoparticles:applications and hazards. *Int J Nanomedicine*. 2008;3(2):133–149. doi:10.2147/ijn.s596
130. Vilar CJF, Ribeiro SB, de Araújo AA, et al. Effect of gold nanoparticle on 5-fluorouracil-induced experimental oral mucositis in hamsters. *Pharmaceutics*. 2020;12(4):304. doi:10.3390/pharmaceutics12040304
131. Choudhury M, Brunton P, Dias G, et al. Gold nanoparticles as innovative therapeutics for oral mucositis: a review of current evidence. *Drug Deliv Transl Res*. 2025;15(7):2323–2353. doi:10.1007/s13346-024-01748-x
132. Khan SA, Shahid S, Lee CS. Green synthesis of gold and silver nanoparticles using leaf extract of Clerodendrum inerme; characterization, antimicrobial, and antioxidant activities. *Biomolecules*. 2020;10(6):835. doi:10.3390/biom10060835
133. Takeuchi I, Kamiki Y, Makino K. Therapeutic efficacy of rebamipide-loaded PLGA nanoparticles coated with chitosan in a mouse model for oral mucositis induced by cancer chemotherapy. *Colloids Surf B Biointerfaces*. 2018;167:468–473. doi:10.1016/j.colsurfb.2018.04.047
134. Ribeiro SB, de Araújo AA, Oliveira MMB, et al. Effect of dexamethasone-loaded PLGA nanoparticles on oral mucositis induced by 5-fluorouracil. *Pharmaceutics*. 2021;13(1):53. doi:10.3390/pharmaceutics13010053
135. Liu Y, Qi X, Wang Y, Li M, Yuan Q, Zhao Z. Inflammation-targeted cannabidiol-loaded nanomicelles for enhanced oral mucositis treatment. *Drug Deliv*. 2022;29(1):1272–1281. doi:10.1080/10717544.2022.2027572
136. Delavarian Z, Pakfetrat A, Ghazi A, et al. Oral administration of nanomicelle curcumin in the prevention of radiotherapy-induced mucositis in head and neck cancers. *Spec Care Dentist*. 2019;39(2):166–172. doi:10.1111/scd.12358
137. Choi JS, Han SH, Hyun C, Yoo HS. Buccal adhesive nanofibers containing human growth hormone for oral mucositis. *J Biomed Mater Res B Appl Biomater*. 2016;104(7):1396–1406. doi:10.1002/jbm.b.33487
138. Tort S, Acartürk F. Preparation and characterization of electrospun nanofibers containing glutamine. *Carbohydr Polym*. 2016;152:802–814. doi:10.1016/j.carbpol.2016.07.028
139. Flores C, Lopez M, Tabary N, et al. Preparation and characterization of novel chitosan and β-cyclodextrin polymer sponges for wound dressing applications. *Carbohydr Polym*. 173. 535–546. doi:10.1016/j.carbpol.2017.06.026
140. Alagha A, Nourallah A, Hariri S. Characterization of dexamethasone loaded collagen-chitosan sponge and in vitro release study. *Journal of Drug Delivery Science and Technology*. 2020;55:101449. doi:10.1016/j.jddst.2019.101449
141. Ben Amara H, Thoma DS, Schwarz F, Song HY, Capetillo J, Koo KT. Healing kinetics of oral soft tissue wounds treated with recombinant epidermal growth factor: translation from a canine model. *J Clin Periodontol*. 2019;46(1):105–117. doi:10.1111/jcpe.13035
142. Huang Y, Wang X, Luo B, et al. MXene-NH(2)/chitosan hemostatic sponges for rapid wound healing. *Int J Biol Macromol*. 2024;260(Pt 1):129489. doi:10.1016/j.ijbiomac.2024.129489
143. Tripathi D, Gupta T, Rai AK, Pandey P. Pioneering a new era in oral cancer treatment with electrospun nanofibers: a comprehensive insight. *Anticancer Agents Med Chem*. 2025;25(7):468–489. doi:10.2174/0118715206348821241119100134
144. Zhou F, Yang Y, Li Y, et al. Blood clot inspired pore-gradient nanofiber sponge with “outer filtration” and “inner adsorption” bifunction for rapid stop of uncontrolled hemorrhage. *BMEMat*. 2025;3(3):e70002. doi:10.1002/bmm2.70002
145. Yu S, Huang Q, Cheng J, Huang Y, Xiao C. Pore structure optimization of electrospun PTFE nanofiber membrane and its application in membrane emulsification. *Separation and Purification Technology*. 2020;251:117297. doi:10.1016/j.seppur.2020.117297
146. Yang Y, Han M, Kong J, et al. Application of electrostatic spinning technology for oral mucosal drug delivery. *AIP Advances*. 2025;15 (7):070702. doi:10.1063/5.0268833
147. Li X, Su Y, Liu S, Tan L, Mo X, Ramakrishna S. Encapsulation of proteins in poly(L-lactide-co-caprolactone) fibers by emulsion electrospinning. *Colloids Surf B Biointerfaces*. 75(2):418–424. doi:10.1016/j.colsurfb.2009.09.014
148. Yang C, Yu DG, Pan D, et al. Electrospun pH-sensitive core-shell polymer nanocomposites fabricated using a tri-axial process. *Acta Biomater*. 35:77–86. doi:10.1016/j.actbio.2016.02.029
149. Jiang H, Wang L, Zhu K. Coaxial electrospinning for encapsulation and controlled release of fragile water-soluble bioactive agents. *J Control Release*. 2014;193:296–303. doi:10.1016/j.jconrel.2014.04.025
150. Zhou Y, Wang M, Yan C, Liu H, Yu DG. Advances in the application of electrospun drug-loaded nanofibers in the treatment of oral ulcers. *Biomolecules*. 12(9). doi:10.3390/biom12091254
151. Pavan kalyan BG, Kumar L. 3D printing: applications in tissue engineering, medical devices, and drug delivery. *AAPS PharmSciTech*. 2022;23 (4):92. doi:10.1208/s12249-022-02242-8
152. Yu JY, Kim HW, Park HJ. Customized oral mucosal adhesive film-based functional-substance delivery system using embedded 3D printing method. *Food Hydrocolloids*. 2022;131:107762. doi:10.1016/j.foodhyd.2022.107762
153. Zhu C, Gemeda HB, Duoss EB, Spadaccini CM. Toward multiscale, multimaterial 3d printing. *Adv Mater*. 2024;36(34):e2314204. doi:10.1002/adma.202314204
154. Koopaie M, Nassar D, Shokrolahi M. Three-dimensional bioprinting of mucoadhesive scaffolds for the treatment of oral mucosal lesions; an in vitro study. *3D Printing in Medicine*. 2022;8(1):30. doi:10.1186/s41205-022-00157-5
155. Tagami T, Okamura M, Ogawa K, Ozeki T. Fabrication of mucoadhesive films containing pharmaceutical ionic liquid and eudragit polymer using pressure-assisted microsyringe-type 3d printer for treating oral mucositis. *Pharmaceutics*. 14(9). doi:10.3390/pharmaceutics14091930
156. Kauark-Fontes E, Araújo ALD, Andrade DO, et al. Machine learning prediction model for oral mucositis risk in head and neck radiotherapy: a preliminary study. *Support Care Cancer*. 2025;33(2):96. doi:10.1007/s00520-025-09158-6
157. Satheeshkumar PS, El-Dallal M, Mohan MP. Feature selection and predicting chemotherapy-induced ulcerative mucositis using machine learning methods. *Int J Med Inform*. 2021;154:104563. doi:10.1016/j.ijmedinf.2021.104563
158. Subramanian RR, Sudharsan RR, Vairamuthu B, Dewi DA. Neural network models for diagnosing recurrent aphthous ulcerations from clinical oral images. *Sci Rep*. 2025;15(1):29519. doi:10.1038/s41598-025-06951-5
159. Deng D, Liang L, Su K, et al. Smart hydrogel dressing for machine learning-enabled visual monitoring and promote diabetic wound healing. *Nano Today*. 2025;60:102559. doi:10.1016/j.nantod.2024.102559
160. Szymczak P, Szczurek E. Artificial intelligence-driven antimicrobial peptide discovery. *Curr Opin Struct Biol*. 2023;83:102733. doi:10.1016/j.sbi.2023.102733
161. Johnson KB, Wei WQ, Weeraratne D, et al. Precision medicine, ai, and the future of personalized health care. *Clin Transl Sci*. 2021;14 (1):86–93. doi:10.1111/cts.12884