RESEARCH PAPER

Hydrogel-Based Local Drug Delivery in Oral Squamous Cell Carcinoma: A Critical Narrative Review of Controlled, Stimuli-Responsive and Immunomodulatory Systems

Dr. Angeline Nivedha A[1*], Dr. Vidya B[2], Dr. C. Aishwarya[3]

[1]B.D.S., PG Student, Department of Oral and Maxillofacial Surgery, Nitte (Deemed to be University), AB Shetty Memorial Institute of Dental Sciences (ABSMIDS), Mangalore, India
ORCID ID: 0009-0008-5950-4859
Email: angelnivy2@gmail.com

[2]M.D.S., Reader, Department of Oral and Maxillofacial Surgery, Nitte (Deemed to be University), AB Shetty Memorial Institute of Dental Sciences (ABSMIDS), Mangalore, India
ORCID ID: 0000-0002-6133-7876
Email: vidyasubiraj@gmail.com

[3]B.D.S., PG Student, Department of Oral and Maxillofacial Surgery, Nitte (Deemed to be University), AB Shetty Memorial Institute of Dental Sciences (ABSMIDS), Mangalore, India
ORCID ID: 0009-0004-3762-3444
Email: 2206caishu@gmail.com

*Corresponding Author: Dr. Angeline Nivedha A, B.D.S., PG Student, Department of Oral and Maxillofacial Surgery, Nitte (Deemed to be University), AB Shetty Memorial Institute of Dental Sciences (ABSMIDS), Mangalore, India
Email: angelnivy2@gmail.com

ABSTRACT

Oral squamous cell carcinoma (OSCC) represents the predominant malignant neoplasm of the oral cavity and continues to be associated with substantial morbidity, treatment-related functional impairment, local recurrence, and mortality. Conventional management is primarily based on surgical resection with risk-adapted radiotherapy and, in selected patients, systemic chemotherapy, targeted therapy, or immunotherapy. Although systemic administration provides access to disseminated disease, it is frequently limited by inadequate drug concentrations at the primary tumour site and systemic toxicity. Local drug delivery systems have therefore attracted increasing interest as a strategy for enhancing drug exposure at the tumour while minimizing unnecessary systemic distribution. Among these platforms, hydrogels are particularly attractive because their three-dimensional hydrated networks can accommodate small molecules, nanoparticles, nucleic acids, and biologically active compounds while providing sustained release and conformal localization.

The oral cavity, however, presents distinctive challenges for local delivery, including continuous salivary clearance, enzymatic activity, pH variation, mucosal turnover, swallowing, mastication, tongue movement, and heterogeneous tumor geometry. Consequently, successful OSCC hydrogels must achieve more than drug encapsulation; they must maintain residence at the target site while providing predictable release under clinically relevant conditions. Recent developments include injectable, thermosensitive, mucoadhesive, enzyme-responsive, pH-responsive, light-responsive, and multifunctional hydrogels. These systems have been investigated for delivery of conventional chemotherapeutics such as doxorubicin and cisplatin, natural compounds such as curcumin and gambogic acid, targeted agents, and combinations involving photothermal, photodynamic, chemodynamic, ferroptotic, and immunomodulatory mechanisms.

This narrative review critically evaluates the evolution of hydrogel-based local drug delivery for OSCC, emphasizing material design, therapeutic payloads, stimuli-responsive systems, combination therapy, tumor-microenvironment targeting, and translational barriers. Particular attention is given to the gap between promising in vitro or animal-model findings and clinically meaningful local therapy. Standardization of oral-cavity-relevant retention testing, mechanical stability, drug-release assessment, toxicity evaluation, manufacturing, and clinically realistic tumor models will be essential for translating these technologies from experimental platforms into practical OSCC therapeutics.

Indexing Terms: oral squamous cell carcinoma; hydrogels; local drug delivery; mucoadhesion; controlled drug release; stimuli-responsive systems; photothermal therapy; photodynamic therapy; ferroptosis; immunotherapy

Abbreviations: OSCC, oral squamous cell carcinoma; HA, hyaluronic acid; MMP, matrix metalloproteinase; DOX, doxorubicin; PDT, photodynamic therapy; PTT, photothermal therapy; CDT, chemodynamic therapy; ROS, reactive oxygen species; GSH, glutathione; NIR, near-infrared; TME, tumor microenvironment.

Keywords: oral squamous cell carcinoma; hydrogel-based drug delivery; mucoadhesive delivery; controlled release; smart hydrogels; nanomedicine; tumor microenvironment; combination therapy; postoperative therapy
How to cite this article: *Dr Angeline Nivedha A, Dr Vidya B, Dr C. Aishwarya. Hydrogel-Based Local Drug Delivery in Oral Squamous Cell Carcinoma: A Critical Narrative Review of Controlled, Stimuli-Responsive and Immunomodulatory Systems. Int J Drug Deliv Technol. 2026;16(88s):785-791. DOI: 10.25258/ijddt.16.88s.70.*
Source of support: Nil.
Conflict of interest: None

1. Introduction

Oral squamous cell carcinoma (OSCC) is the predominant histological malignancy of the oral cavity and contributes substantially to the global burden of cancer.[1] Contemporary management is stage- and risk-adapted, with surgery central to resectable disease and radiotherapy, systemic therapy, targeted therapy, or immunotherapy incorporated according to clinical and pathological features.[2]

OSCC management is complicated by local invasion, regional lymphatic spread, field cancerization, tumor heterogeneity, and the risk of recurrence.[3] Field cancerization is particularly relevant because molecular alterations can extend beyond the clinically apparent lesion, limiting the ability of a purely local intervention to address all malignant or premalignant tissue.[4] Local therapy should therefore be considered a complementary strategy for selected accessible disease or residual tumor beds rather than a replacement for established multimodal oncological care.[3]

Local drug delivery systems aim to establish a therapeutic depot near the lesion, increasing site-specific exposure while potentially limiting systemic distribution.[5] Hydrogels, films, patches, sprays, and in situ gelling systems have all been investigated for this purpose.[6] The oral cavity nevertheless imposes unusually demanding conditions: continuous salivary flow, enzymatic activity, pH variation, microbial exposure, and mechanical abrasion from chewing and tongue movement can shorten residence time and destabilize formulations.[7]

Hydrogels are three-dimensional, water-rich polymeric networks capable of incorporating small molecules, nanoparticles, nucleic acids, and biologically active agents.[7] Their polymer composition, cross-linking density, swelling behavior, degradation kinetics, and interfacial chemistry can be tuned to generate mucoadhesive, injectable, thermoresponsive, enzyme-responsive, or otherwise stimuli-responsive systems.[8]

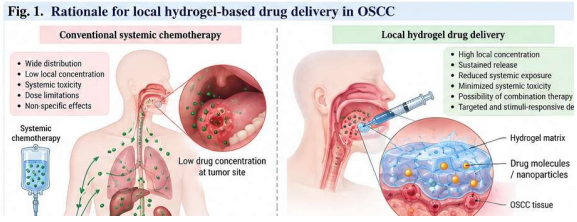


Figure 1. Rationale for local hydrogel-based drug delivery in OSCC. Systemic therapy produces broad drug distribution, whereas an appropriately designed local hydrogel can create a drug depot near an accessible lesion or postoperative tumor bed. The intended benefits are prolonged local exposure, controlled release, and reduced unnecessary systemic distribution; these remain therapeutic objectives rather than established clinical outcomes.

Literature identification and narrative synthesis

A focused narrative literature search was undertaken using PubMed/MEDLINE as the principal biomedical database, with additional citation chaining from recent reviews and primary studies. Priority was given to peer-reviewed publications from 2020 through 2026 addressing OSCC, local drug delivery, hydrogels, mucoadhesion, stimuli-responsive delivery, photothermal/photodynamic therapy, ferroptosis, immunomodulation, and postoperative local therapy. Older foundational literature was retained when necessary to explain hydrogel chemistry or oral-mucosal delivery principles. [6] Because this article is a narrative review rather than a systematic review, the search was used to identify clinically and mechanistically relevant evidence rather than to estimate pooled treatment effects.

2. Why Local Drug Delivery Is Relevant to OSCC

2.1 Limitations of conventional systemic therapy

Systemic chemotherapy exposes malignant and healthy tissues to therapeutic agents and is constrained by dose-limiting toxicity.[3] In OSCC, systemic treatment is clinically important for selected indications, but local delivery has been investigated as a means of increasing exposure at accessible lesions while limiting unnecessary distribution to healthy tissues.[5]

The principal rationale for local delivery is pharmacokinetic rather than merely technological: a sufficiently retained formulation may maintain therapeutic concentrations at the target while reducing systemic exposure.[7] Injectable and mucoadhesive hydrogels can additionally conform to irregular surfaces and accommodate controlled-release or combination strategies.[5]

Local delivery should be regarded as a complementary or targeted strategy rather than an automatic replacement for established oncological management.[3] The biological extent of OSCC, including regional and

distant dissemination in appropriate patients, means that a local hydrogel cannot independently address occult systemic disease.[4]

3. The Oral Cavity as a Challenging Environment for Hydrogel Delivery

3.1 Salivary clearance

Salivary flow promotes dilution and clearance of locally administered drugs, making residence time a critical determinant of efficacy.[7] Consequently, release kinetics measured in static buffer may overestimate the performance of a formulation that is rapidly displaced under saliva-relevant conditions.[7]

3.2 Mechanical stress

Mastication, tongue movement, speaking, and swallowing impose repeated shear and compression.[7] Adhesive hydrogel performance therefore depends not only on chemical adhesion but also on resistance to mechanical fatigue under wet conditions.[7]

3.3 Mucosal heterogeneity

The oral cavity contains keratinized and nonkeratinized mucosal regions with distinct barrier and permeability characteristics, and tumor-associated tissue disruption can further alter local transport.[7]

3.4 Enzymatic and biochemical environment

Salivary enzymes and the local biochemical environment can alter polymer degradation and payload stability.[7] The same principle can be exploited therapeutically by designing systems that respond to disease-associated enzymes, pH, redox conditions, temperature, or external light.[8]

3.5 Tumor geometry

OSCC lesions and postoperative tumor beds vary considerably in geometry and accessibility.[5] This favors formulations that can be administered in situ and conform to irregular surfaces, although the appropriate platform will depend on lesion location, size, margin status, and the intended therapeutic objective.[7]

4. Hydrogels as Local Drug Delivery Platforms

Hydrogels can be classified according to polymer source, cross-linking mechanism, physical configuration, and stimulus responsiveness.[5] These categories are not mutually exclusive because a single formulation may combine natural polymers, nanomaterials, self-healing behavior, and one or more environmental triggers.[6]

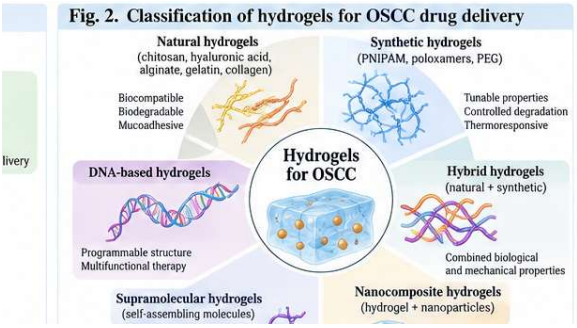


Figure 2. Classification of hydrogel systems relevant to OSCC drug delivery. Natural, synthetic, hybrid, nanocomposite, supramolecular, DNA-based, self-healing, and stimuli-responsive systems are shown as overlapping design categories. Individual formulations may combine several categories.

4.1 Natural polymer hydrogels

Natural polymers used in oral hydrogel research include chitosan, hyaluronic acid, alginate, gelatin, collagen, and cellulose derivatives.[8] Their appeal derives from biocompatibility, biodegradability, tunable functional groups, and, for some polymers, intrinsic mucoadhesive behavior.[7]

4.2 Synthetic and hybrid hydrogels

Synthetic polymers provide greater control over molecular weight, degradation, mechanical properties, and functional groups, while hybrid systems can combine biological compatibility with improved mechanical or stimulus-responsive performance.[6] Poloxamers and PNIPAM-containing networks are particularly relevant to thermoresponsive delivery.[8]

5. Hydrogel-Based Delivery of Conventional Chemotherapeutic Agents

5.1 Doxorubicin

Doxorubicin is among the best-characterized chemotherapeutic payloads for experimental OSCC hydrogels.[9] An injectable hyaluronic-acid hydrogel containing doxorubicin-loaded biodegradable micelles was cross-linked through an MMP-2-responsive peptide; the system demonstrated enzyme-responsive release, cytotoxicity against SCC-15 cells, and tumor-growth inhibition in vivo.[9]

5.2 Cisplatin

Cisplatin remains an important systemic agent in selected head and neck cancer settings.[2] A recent DNA-hydrogel platform incorporated cisplatin with zinc oxide nanoparticles and demonstrated enhanced cisplatin delivery and antitumor activity in preclinical models, while also exploring diagnostic functionality.[10]

5.3 Erlotinib

Targeted agents can also be combined with local depots.[11] Erlotinib-loaded liposomes were incorporated into a gel formulation for localized

OSCC delivery, illustrating a two-level strategy in which the hydrogel controls residence while the nanocarrier controls drug encapsulation and release.[11]

6. Natural Bioactive Compounds and Hydrogels

6.1 Curcumin

Curcumin is attractive for local delivery but is limited by physicochemical properties that restrict conventional bioavailability.[12] A mucoadhesive curcumin emulgel demonstrated controlled release, mucosal permeation, and tumor-cell-selective activity.[12] A later thermosensitive chitosan-coated nanocapsule hydrogel improved retention on porcine buccal mucosa.[13]

6.2 Gambogic acid

Gambogic acid has been investigated using an injectable thermosensitive hydrogel containing gambogic-acid-loaded micelles.[14] In OSCC-bearing mice, the formulation provided sustained local release and was associated with modulation of the tumor immune microenvironment, including increased cytotoxic T-cell activity.[14]

7. Targeted and Tumor-Responsive Hydrogels

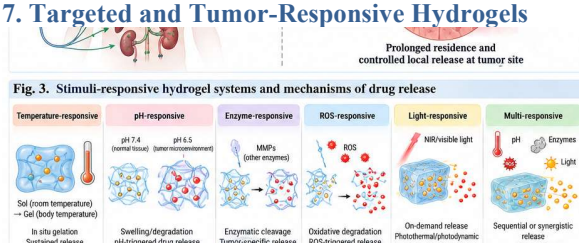


Figure 3. Stimuli-responsive mechanisms for drug release from OSCC hydrogels. Temperature, pH, tumor-associated enzymes, reactive oxygen species, external light, and combinations of stimuli can modulate hydrogel swelling, degradation, drug release, or therapeutic activation.

7.1 Enzyme-responsive hydrogels

Enzyme-responsive hydrogels use disease-associated proteolytic activity to regulate matrix degradation or payload release.[9] MMP-2-responsive cross-linking has already been demonstrated in an OSCC hydrogel system, providing a direct example of tumor-microenvironment-responsive delivery.[9] Other tumor-directed hydrogel strategies have used supramolecular designs to target OSCC-associated molecular pathways, broadening the concept of local responsive therapy beyond protease-triggered release.[15]

7.2 pH-responsive hydrogels

pH-responsive systems exploit differences in local acidity to alter swelling, degradation, or drug release.[6] Such systems can be combined with other responsive mechanisms to increase control over local exposure.[8]

7.3 Thermoresponsive hydrogels

Thermosensitive hydrogels can be administered as relatively low-viscosity liquids and undergo sol-gel transition near physiological temperature.[13] In OSCC research, curcumin nanocapsule hydrogels and gambogic-acid systems have demonstrated this approach while also improving local retention.[14]

8. Light-Responsive Hydrogel Systems

8.1 Photothermal therapy

Photothermal therapy (PTT) converts externally applied light, commonly near-infrared light, into localized heat.[16] An injectable IR820/methylcellulose hydrogel containing doxorubicin-loaded mesoporous silica nanoparticles demonstrated combined chemo-photothermal activity in OSCC models, with light-responsive drug release providing an additional level of control.[17]

8.2 Photodynamic therapy

Photodynamic therapy (PDT) relies on photosensitizer activation and generation of reactive oxygen species.[18] Hydrogel systems can retain photosensitizers or photothermal agents near the lesion, creating a localized platform for externally triggered therapy.[16]

8.3 Combination therapy

Recent OSCC studies increasingly combine chemotherapy with PTT or PDT rather than relying on a single mechanism.[16] These multifunctional systems are exemplified by NIR-responsive doxorubicin hydrogels and newer multi-responsive formulations.[16]

9. Hydrogel-Mediated Ferroptosis and Chemodynamic Therapy

Redox-directed hydrogel therapy is an emerging strategy in OSCC.[19] A 2025 injectable self-healing hydrogel combined chemodynamic and photothermal effects to increase oxidative stress, deplete glutathione, and promote ferroptosis in preclinical OSCC models.[19]

10. Immunomodulatory Hydrogels

Hydrogel design is increasingly being linked to the tumor immune microenvironment.[14] Gambogic-acid hydrogel delivery has been associated with local immune modulation.[14] An implantable postoperative hydrogel vaccine has been developed to treat residual OSCC after resection through combined photoimmunotherapy and immune stimulation.[20]

11. Multifunctional and Smart Hydrogels

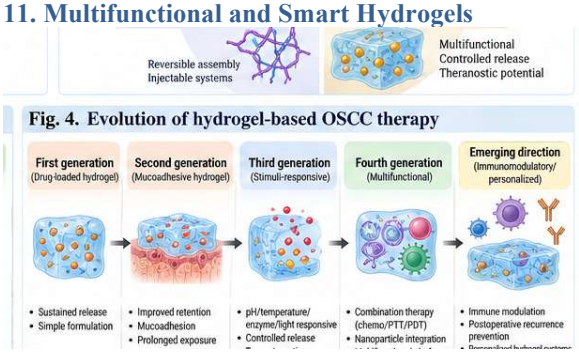


Figure 4. Evolution of hydrogel-based OSCC therapy. The conceptual progression extends from passive sustained-release systems to mucoadhesive, stimuli-responsive, multifunctional,

immunomodulatory, and postoperative platforms. The sequence represents a research trajectory rather than a validated clinical staging system.

The field is moving from passive drug-loaded hydrogels toward multifunctional systems that integrate tumor-responsive release, photothermal or photodynamic therapy, chemodynamic/ferroptotic mechanisms, and immune modulation.[21] A recent postoperative hydrogel vaccine further illustrates the potential for local treatment of residual disease rather than treatment of the primary lesion alone.[20]

12. Preclinical Evidence

Most OSCC hydrogel evidence remains preclinical, with substantial heterogeneity in polymer chemistry, payload, release conditions, tumor models, irradiation protocols, and outcome measures.[9] The evidence therefore supports proof of concept rather than clinical effectiveness.[22] Direct comparisons between formulations should be avoided unless experimental conditions are genuinely comparable.[22]

Table 1. Representative hydrogel-based approaches investigated in OSCC

Study/approach	Hydrogel/platform	Payload	Main concept	Evidence
Ferreira et al., 2020	Mucoadhesive emulgel	Curcumin	Local delivery and mucosal permeation	In vitro/ex vivo [12]
MMP-responsive system	HA hydrogel + micelles	Doxorubicin	Tumor-enzyme-responsive release	In vitro/in vivo [9]
Gambogic acid system	Thermosensitive hydrogel	Gambogic acid	Local chemotherapy + immune modulation	Mouse OS [14]
Zhao et al., 2025	DNA hydrogel	Cisplatin + ZnO nanoparticles	Drug delivery + diagnostic potential	In vitro/in vivo [10]
Recent ferroptosis system	Injectable self-healing hydrogel	Cu-based components + PDA	PTT/CDT/ferroptosis	In vitro/in vivo [19]
Recent postoperative system	Implantable hydrogel	Photo/immune agents	Residual tumor control	In vivo [20]

13. What Is Missing From Current Preclinical Models?

Translation requires testing under conditions that reproduce the oral environment, including saliva-relevant chemistry, mechanical loading, mucosal adhesion, and clinically relevant residence times.[23] Orthotopic OSCC models and standardized retention and pharmacokinetic endpoints should complement conventional cell-line and subcutaneous models.[21]

14. Advantages of Hydrogel-Based Local Drug Delivery in OSCC

Potential advantages include prolonged local residence, controlled release, conformability to irregular lesions, and the ability to combine multiple therapeutic modalities within one platform.[5]

15. Limitations and Translational Challenges

Major translational barriers include limited clinical evidence, unpredictable retention under oral mechanical and salivary stresses, formulation-to-formulation variability, toxicity of complex nanomaterials, tumor heterogeneity, manufacturing scale-up, and regulatory complexity.[23] The need to consider tissue regeneration and reconstruction after

OSCC therapy further broadens the translational challenge.[24]

16. Proposed Translational Framework

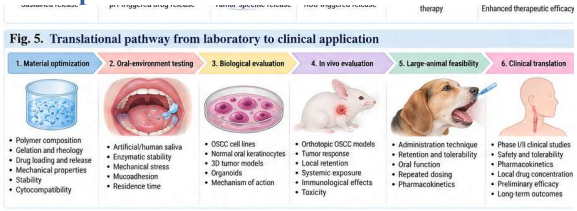


Figure 5. Proposed translational pathway for OSCC hydrogel development. A staged framework is proposed from material optimization through oral-environment testing, biological evaluation, orthotopic in vivo studies, feasibility testing, and early clinical translation.

Future development should follow a staged pathway: material optimization and physicochemical characterization; saliva- and mechanics-relevant testing; biological evaluation; orthotopic in vivo assessment; feasibility and tolerability studies; and early clinical studies focused initially on safety, retention, pharmacokinetics, and local exposure.[25]

17. Future Perspectives

Future systems may incorporate personalized payload selection, sequential or multi-stage release, postoperative therapy, immune modulation, and patient-specific manufacturing.[20] Photosensitive hydrogel systems targeting tumor-associated pathways may also support more precisely localized photodynamic and photothermal treatment.[26]

18. Critical Appraisal of the Current Evidence

Current evidence establishes biological plausibility but remains dominated by in vitro and murine studies.[9] The key translational question is whether a formulation can remain at an anatomically relevant site, deliver a reproducible therapeutic dose under salivary and mechanical stress, and maintain acceptable safety.[23]

19. Conclusion

Hydrogels provide a versatile platform for localized OSCC therapy because their network architecture can support sustained release, mucoadhesion, nanoparticle incorporation, and stimulus-responsive behavior.[5] The research landscape has progressed toward multifunctional chemotherapy, PTT/PDT, chemodynamic and ferroptotic approaches, and postoperative immunomodulation, but clinical evidence remains absent or very limited for these advanced systems.[19]

Graphical Abstract

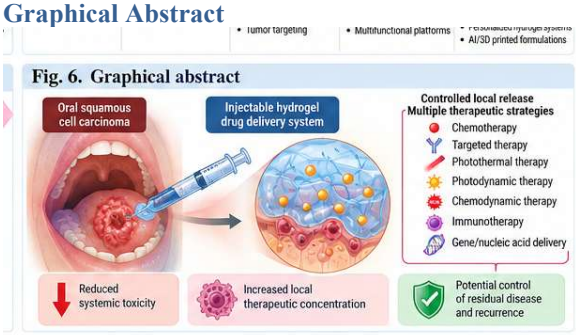


Figure 6. Graphical abstract. Hydrogel-based local delivery is being investigated as a localized therapeutic depot for OSCC, supporting sustained release and combination approaches. The potential benefits shown are investigational and require clinical validation.[26]

References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229-263. doi:10.3322/caac.21834.
2. Jagadeesan D, Sathasivam KV, Fuloria NK, Balakrishnan V, Khor GH, Ravichandran M, et al. Comprehensive insights into oral squamous cell carcinoma: diagnosis, pathogenesis, and therapeutic advances. Pathol Res Pract. 2024;261:155489. doi:10.1016/j.prp.2024.155489.
3. Asarkar AA, Chang BA, de Bree R, Kowalski LP, Guntinas-Lichius O, Bradley PJ, et al. Primary management of operable locally advanced oral cavity squamous cell carcinoma: current concepts and strategies. Adv Ther. 2024;41(6):2133-2150. doi:10.1007/s12325-024-02861-6.
4. Sundaram E, Pal US, Sowmya MV, Kumar V, Yadav S. Field cancerisation in oral squamous cell carcinoma patients: a systematic review. J Maxillofac Oral Surg. 2025;24(2):416-431. doi:10.1007/s12663-024-02287-1.
5. Liu L, Wu D, Tu H, Cao M, Li M, Peng L, et al. Applications of hydrogels in drug delivery for oral and maxillofacial diseases. Gels. 2023;9(2):146. doi:10.3390/gels9020146.
6. Huang M, Huang Y, Liu H, Tang Z, Chen Y, Huang Z, et al. Hydrogels for the treatment of oral and maxillofacial diseases: current research, challenges, and future directions. Biomater Sci. 2022;10(22):6413-6446. doi:10.1039/D2BM01036D.
7. Yeruva T, Yang S, Doski S, Duncan GA. Hydrogels for mucosal drug delivery. ACS Appl Bio Mater. 2023;6(5):1684-1700. doi:10.1021/acsabm.3c00050.

8. Samiraninezhad N, Asadi K, Rezazadeh H, Gholami A. Using chitosan, hyaluronic acid, alginate, and gelatin-based smart biological hydrogels for drug delivery in oral mucosal lesions: a review. Int J Biol Macromol. 2023;252:126573. doi:10.1016/j.ijbiomac.2023.126573.
9. Li W, Tao C, Wang J, Le Y, Zhang J. MMP-responsive in situ forming hydrogel loaded with doxorubicin-encapsulated biodegradable micelles for local chemotherapy of oral squamous cell carcinoma. RSC Adv. 2019;9(54):31264-31273. doi:10.1039/C9RA04343H.
10. Zhao D, Liu L, Wang GP, Cheng X. Programmable DNA hydrogels with zinc oxide nanoparticles and cisplatin for diagnosis and treatment of oral squamous cell carcinoma. Adv Healthc Mater. 2025;14(4):e2402895. doi:10.1002/adhm.202402895.
11. Hariharan K, Mehta T, Shah J, Dave H, Sami A, Omri A. Localized delivery of erlotinib using liposomal gel formulations for the treatment of oral squamous cell carcinoma. Int J Pharm. 2023;642:123144. doi:10.1016/j.ijpharm.2023.123144.
12. Ferreira SBS, Slowik KM, Hoshino LVC, Baesso ML, Murdoch C, Colley HE, et al. Mucoadhesive emulgel systems containing curcumin for oral squamous cell carcinoma treatment: from pre-formulation to cytotoxicity in tissue-engineering oral mucosa. Eur J Pharm Sci. 2020;151:105372. doi:10.1016/j.ejps.2020.105372.
13. Ortega A, da Silva AB, da Costa LM, Zatta KC, Onzi GR, da Fonseca FN, et al. Thermosensitive and mucoadhesive hydrogel containing curcumin-loaded lipid-core nanocapsules coated with chitosan for the treatment of oral squamous cell carcinoma. Drug Deliv Transl Res. 2023;13(2):642-657. doi:10.1007/s13346-022-01227-1.
14. Chen X, Chen DR, Liu H, Yang L, Zhang Y, Bu LL, et al. Local delivery of gambogic acid to improve anti-tumor immunity against oral squamous cell carcinoma. J Control Release. 2022;351:381-393. doi:10.1016/j.jconrel.2022.09.010.
15. Li Z, Cao L, Yang C, Liu T, Zhao H, Luo X, Chen Q. Protocatechuic acid-based supramolecular hydrogel targets SerpinB9 to achieve local chemotherapy for OSCC. ACS Appl Mater Interfaces. 2022;14(32):36379-36394. doi:10.1021/acsami.2c07534.
16. Wu Y, Chen F, Huang N, Li J, Wu C, Tan B, et al. Near-infrared light-responsive hybrid hydrogels for the synergistic chemo-photothermal therapy of oral cancer. Nanoscale. 2021;13(40):17168-17182. doi:10.1039/D1NR04625J. PMID:34636386.
17. Bai L, Yang M, Wu J, You R, Chen Q, Cheng Y, et al. An injectable adhesive hydrogel for photothermal ablation and antitumor immune activation against bacteria-associated oral squamous cell carcinoma. Acta Biomater. 2024;186:229-245. doi:10.1016/j.actbio.2024.07.027.
18. Song S, Sun X, Wang Y, Wang M, Shi Z, Sun D, et al. Sodium alginate hydrogel loaded with upconversion nanoparticles and magnesium ions enhances bone regeneration and photodynamic tumor therapy. Front Pharmacol. 2025;16:1543678. doi:10.3389/fphar.2025.1543678.
19. Zhang X, Li M, Pang X, Wang WL, Wang XC, Shen ZL, et al. An injectable hydrogel with photothermal and chemodynamic therapies for targeted promotion of ferroptosis in oral squamous cell carcinoma. Nanoscale. 2025;17(16):10277-10291. doi:10.1039/D4NR05147E.
20. Chen L, Yin Q, Zhang H, Zhang J, Yang G, Weng L, et al. Protecting against postsurgery oral cancer recurrence with an implantable hydrogel vaccine for in situ photoimmunotherapy. Adv Sci (Weinh). 2024;11(46):e2309053. doi:10.1002/advs.202309053.
21. Shi C, Liu B, Feng L, Wei B, Yu S, Chen P. Design and evaluation of multi-responsive PNIPAM-g-Dextran-sodium alginate blended smart hydrogel for enhanced chemo-photodynamic therapy against oral squamous cell carcinoma. Colloids Surf B Biointerfaces. 2026;259:115293. doi:10.1016/j.colsurfb.2025.115293.
22. Herrada Céspedes J, Reyes J, Morales M. Advanced drug delivery systems for oral squamous cell carcinoma: a comprehensive review of nanotechnology-based and other innovative approaches. Front Drug Deliv. 2025;5:1596964. doi:10.3389/fddev.2025.1596964.
23. Ruslin M, Cao J, Ullah M, Palungan J, Azizah W, Wa Ode RC, et al. Local drug delivery for oral squamous cell carcinoma under oral cavity. Eur J Pharm Biopharm. 2026;225:115114. doi:10.1016/j.ejpb.2026.115114.
24. Ormenisan A, Bors A, Beresescu L, Bereczki-Temistocle DL, Beresescu GF. Bioactive hydrogels and scaffolds for oral mucosal regeneration after oral squamous cell carcinoma therapy: a comprehensive review. Medicina (Kaunas). 2026;62(3):558. doi:10.3390/medicina62030558.

25. Peng Y, Jiang Z, Xu S, He L, Jiang T, Yang Y, et al. Designing adhesive hydrogels for oral diseases treatment. Mater Today Bio. 2026;37:102911. doi:10.1016/j.mtbio.2026.102911.
26. Feng Y, Zhao J, Zhang M. Photosensitive ropivacaine- and chlorin e6-loaded hydrogel targeting the substance P-tachykinin receptor 1-toll-like receptor 7 axis enhances photodynamic and photothermal therapy against oral cancer. Acta Biomater. 2026 Sep 3. doi:10.1016/j.actbio.2026.09.003. PMID:42692233.