REVIEW ARTICLE

Polymeric and Lipid Nanoparticles for Targeted Chemotherapy in Oral Squamous Cell Carcinoma: Advances, Challenges, and Future Prospects

Prathamesh Kolte, Priyanka Sontakke

Department of Oral Medicine and Radiology , Sharad Pawar Dental College and Hospital, Wardha, Maharashtra, India

Abstract

Oral squamous cell carcinoma (OSCC) remains a lethal malignancy with a persistently high mortality rate, largely due to late-stage diagnosis, dose-limiting systemic toxicities of conventional chemotherapy, and the development of multidrug resistance. This review comprehensively examines the transformative role of nanotechnology, specifically polymeric and lipid nanoparticles (LNPs), in overcoming these hurdles for targeted chemotherapy. We detail the advances in nanoparticle (NP) design, including the use of biodegradable polymers like poly(lactic-co-glycolic acid) and chitosan, and versatile lipid-based systems such as solid LNPs and nanostructured lipid carriers. A key focus is placed on the engineering of "smart," multifunctional NPs that respond to specific tumor microenvironment stimuli (e.g., pH, temperature, and enzymes) for spatiotemporally controlled drug release. Furthermore, we explore active targeting strategies using ligands (e.g., folic acid, hyaluronic acid) and biomimetic coatings (e.g., macrophage membranes) to enhance tumor specificity and immune evasion. Despite the promising preclinical success, significant challenges impede clinical translation, including concerns over nanotoxicity, complex scalability, tumor heterogeneity, and evolving regulatory landscapes. The future of OSCC nanomedicine lies in the convergence of artificial intelligence for rational NP design, the co-delivery of chemotherapeutics with resistance-inhibiting agents, and a steadfast push toward personalized, stimuli-responsive therapies. This review concludes that polymeric and LNPs hold immense potential to redefine the therapeutic paradigm for OSCC, offering a path to improved efficacy, reduced side effects, and better patient outcomes.

Key words: Lipid nanoparticles, oral squamous cell carcinoma, polymeric nanoparticles, targeted chemotherapy

INTRODUCTION

Oral squamous cell carcinoma (OSCC) represents a significant global health burden, accounting for approximately 90% of all oral malignancies with an estimated 377,713 new cases and 177,757 deaths annually worldwide. Despite advances in diagnostic and therapeutic modalities, the prognosis for OSCC patients remains unfavorable, with 5-year survival rates stagnating at approximately 50–60% over the past several decades. This persistent mortality rate is largely attributable to late-stage diagnosis, with approximately 50% of OSCC cases detected at advanced stages (III and IV), and the development of resistance to conventional treatment approaches.[1] The complexity of OSCC management is further compounded by its aggressive biological behavior, characterized by local invasion, lymphatic dissemination, and frequent recurrence, which collectively contribute to poor clinical outcomes and diminished quality of life for survivors. Epidemiological data project a concerning 40% rise in OSCC incidence by 2040, underscoring the urgent need for more effective therapeutic strategies to alter this trajectory.[2]

Current standard treatment modalities for OSCC, including surgical resection, radiotherapy, and chemotherapy, demonstrate considerable limitations that significantly impede

Address for correspondence:
Prathamesh Kolte, Sharad Pawar Dental College and Hospital, Datta Meghe Institute of Medical Sciences Campus, Sawangi, Wardha - 442 107, Maharashtra, India. Phone: +91-9325348838.
E-mail: prathameshkolte14@gmail.com

Received: 28-11-2025
Revised: 21-01-2026
Accepted: 02-02-2026

their therapeutic efficacy. While early-stage tumors typically respond well to surgical intervention, advanced disease requires multimodal approaches often incorporating systemic chemotherapy [Figure 1a].[3] Conventional chemotherapeutic agents, such as cisplatin, 5-fluorouracil, methotrexate, and taxanes, though widely utilized, are plagued by insufficient tumor targeting, rapid clearance, and dose-limiting systemic toxicity that often necessitate treatment modification or discontinuation [Figure 1b]. Furthermore, the development of multidrug resistance (MDR) presents a formidable obstacle to successful chemotherapy, frequently leading to treatment failure and disease progression.[4] The pathophysiological basis for this resistance involves complex mechanisms including enhanced drug efflux, activation of alternative survival pathways, epithelial–mesenchymal transition, and genetic and epigenetic alterations that collectively enable cancer cells to evade chemotherapeutic destruction. In addition, the unique physiological environment of the oral cavity, characterized by high vascularity, constant salivary flow, and epithelial turnover further compromises drug bioavailability and retention at the target site, thereby diminishing therapeutic potential.[5]

The compelling limitations of conventional chemotherapy have stimulated extensive research into nanoparticle (NP)-based drug delivery systems as a promising strategy to revolutionize OSCC treatment. NPs, typically ranging from 1 to 100 nanometers in size, offer multifunctional advantages that directly address the shortcomings of traditional chemotherapy.[3,6] Their nanoscale dimensions and tunable surface properties enable passive tumor targeting through the enhanced permeability and retention (EPR) effect, whereby NPs preferentially accumulate in tumor tissue due to its leaky vasculature and impaired lymphatic drainage. Moreover, NPs can be actively functionalized with tumor-specific ligands, such as hyaluronic acid for CD44 receptor targeting or transferrin for transferrin receptor binding, to further enhance selective cellular uptake and minimize off-target effects. The encapsulation of chemotherapeutic agents within NP matrices protects drugs from premature degradation, improves their aqueous solubility, prolongs systemic circulation, and enables controlled release kinetics that maintain therapeutic concentrations at the tumor site while reducing administration frequency. Stimuli-responsive "smart" NPs that release their payload in response to pathological cues specific to the tumor microenvironment (TME) (e.g., pH variations, enzymatic activity, redox potential, or hypoxia) represent an additional refinement that further enhances spatial and temporal control over drug delivery. These advanced nanocarriers, including polymeric NPs (PNP), lipid-based systems, inorganic NPs, and extracellular vesicles, collectively offer a versatile platform to overcome biological barriers, circumvent resistance mechanisms, and ultimately improve the therapeutic index of chemotherapeutic agents in OSCC management.[7]

OSCC - OVERVIEW AND THERAPEUTIC CHALLENGES

The selection of PNPs for OSCC therapy encompasses a range of materials, each with distinct advantages and inherent limitations that must be critically evaluated for clinical translation. Poly(lactic-co-glycolic acid) (PLGA) or PLGA NPs are among the most extensively investigated, prized for their excellent biocompatibility, biodegradability, and ability to provide sustained drug release, as demonstrated with drugs such as cisplatin and doxorubicin (DOX) [Table 1].[8] The encapsulation of chemotherapeutics within PLGA protects them from premature degradation and reduces systemic toxicity. However, a significant drawback of plain PLGA NPs is their susceptibility to rapid opsonization and clearance by the reticuloendothelial system (RES), which shortens their blood circulation time and limits tumor accumulation. To overcome this, PEGylated polymers are employed to create a stealth corona around NPs; the hydrophilic poly (ethylene glycol) chains form a steric barrier that

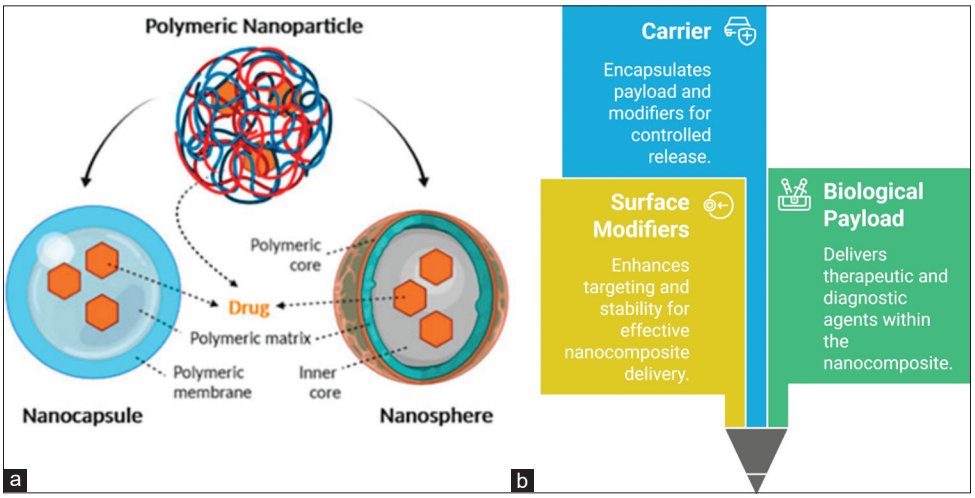

Figure 1: (a) Polymeric nanocapsules versus nanospheres; (b) smart nanoparticle components—carrier, surface modifiers, and biological payload

Table 1: Comparison of polymeric nanoparticle types used in OSCC therapy, outlining their key advantages, limitations, and representative applications

Nanoparticle type	Description	Key advantages of OSCC	Representative oral cancer applications	References
PLGA nanoparticles	Biodegradable copolymer of lactic and glycolic acids.	• Controlled, sustained drug release tuned by LA:GA ratio • Excellent biocompatibility • FDA-approved	• Cisplatin-loaded PLGA NPs for enhanced tumor uptake and reduced nephrotoxicity • Paclitaxel-PLGA formulations in 4-NQO models	[13,14]
Chitosan nanoparticles	Positively charged natural polysaccharide derived from chitin.	• Mucoadhesive, prolonging buccal residence • Opens epithelial tight junctions for improved uptake • Biodegradable	• miRNA delivery (miR-30c-5p) across oral mucosa for gene silencing • Iontophoresis-enhanced cisplatin chitosan NPs	[15,16]
PEGylated polymeric NPs	Polymers grafted with polyethylene glycol chains to form a hydrophilic "stealth" corona	• Reduced opsonization and prolonged circulation • Modular ligand conjugation for active targeting	• PLGA-PEG NPs targeting CD44-overexpressing OSCC cells via HA ligands • PEGylated dendrimeric carriers for doxorubicin	[17-19]
Hyperbranched polymer NPs	Highly branched 3D polymers with abundant internal cavities and surface functional groups.	• Very high drug-loading capacity • Multivalent surface for ligand or imaging agent attachment	• Hyperbranched polyester NPs co-loaded with chemotherapeutics and fluorescent probes for theranostic imaging	[12,20]

OSCC: Oral squamous cell carcinoma, PLGA: Poly(lactic-co-glycolic acid), NPs: Nanoparticles

reduces protein adsorption and immune clearance, thereby significantly prolonging systemic circulation and enhancing the likelihood of NP accumulation in tumors through the EPR effect. Furthermore, this PEGylated surface provides an accessible platform for conjugating targeting ligands such as the NR7 peptide or folic acid (FA), enabling active targeting to receptors overexpressed on OSCC cells and promoting receptor-mediated cellular uptake.[8] Despite these benefits, PEGylation can sometimes hinder cellular internalization, a phenomenon known as the "PEG dilemma," and can incite immune responses against polyethylene glycol (PEG) itself after repeated administrations, posing a challenge for chronic therapies.[9]

In parallel, chitosan-based NPs offer unique advantages for oral cancer, particularly their inherent mucoadhesive properties and ability to transiently open tight junctions between epithelial cells. This is especially valuable for the buccal delivery of sensitive macromolecules, such as the tumor-suppressive microRNA miR-30c-5p, enhancing mucosal penetration and protecting the payload from degradation. The cationic nature of chitosan allows for efficient complexation with negatively charged nucleic acids, but this same property can lead to instability in physiological environments and potential cytotoxicity at higher concentrations, as observed *in vitro* with reduced cell viability.[10] Finally, hyperbranched polymers represent a more recent advancement, characterized by a three-dimensional globular architecture with a multitude of surface functional groups. This structure facilitates high drug-loading capacity within intramolecular cavities and simplifies surface functionalization for targeted delivery. For instance, polydopamine-modified hyperbranched polymers have been engineered to simultaneously load chemotherapy drugs such as DOX and serve as effective photothermal agents, enabling synergistic chemo-photothermal therapy for oral cancer.[11] Nevertheless, the synthesis of hyperbranched polymers with precise and reproducible structures can be complex, and the long-term fate and clearance of certain synthetic variants from the body require more thorough investigation to ensure their safety profile.[12]

The synthesis of polymeric and lipid NPs (LNPs) for targeted chemotherapy in OSCC employs a variety of sophisticated methods designed to ensure high drug encapsulation, stability, and controlled release. A cornerstone technique for biodegradable polymers such as PLGA is the emulsion-solvent evaporation method, where the drug and polymer are dissolved in an organic solvent, emulsified in an aqueous solution, and the solvent is subsequently evaporated to form solid NPs, a process effectively used to encapsulate natural compounds such as Toosendanin for OSCC treatment [Table 2].[21] Alternative methods like nanoprecipitation (or solvent displacement) offer good control over particle size for hydrophobic drugs, while more advanced techniques such as microfluidics enable reproducible production with narrow size distributions, and spray drying provides a scalable approach suitable for industrial applications. For lipid-based systems such as liposomes, methods like thin-film hydration are used, creating lipid bilayers that can encapsulate both hydrophilic and hydrophobic molecules.[22] Furthermore, ionic gelation is a particularly valuable method for forming NPs from cationic biopolymers like chitosan, as demonstrated

Table 2: Summary of nanoparticle synthesis methods: Categories, key principles, common nanoparticle types, and representative techniques

Category	Method	Key principle	Common nanoparticle types
Synthesis methods	Chemical reduction	Uses reducing agents (e.g., borohydride, citrate) to convert metal salts into zero-valent nanoparticles.	Metallic NPs (e.g., Gold, Silver)
	Coprecipitation	Achieves supersaturation in a solution to cause simultaneous nucleation and growth of nanoparticles.	Magnetic NPs (e.g., Fe_3O_4)
	Emulsion-based	Uses a surfactant-stabilized mixture of immiscible liquids (e.g., oil and water) to create nanodroplets that solidify into particles.	Polymeric NPs, lipid NPs, silica NPs
	Hydrothermal/ solvothermal	Uses a high-temperature, high-pressure reaction in a sealed vessel (autoclave) to crystallize nanoparticles.	Metal oxide, semiconductor NPs
Encapsulation methods	Solvent evaporation	Dissolves polymer and drug in an organic solvent, emulsifies in water, then evaporates the solvent to form solid matrix particles.	Polymeric NPs (e.g., PLGA)
	Spray drying	Atomizes a polymer/drug solution into a hot chamber, rapidly evaporating the solvent to form dried, spherical particles.	Polymeric NPs, lipid NPs
	Self-assembly	Relies on the spontaneous organization of amphiphilic molecules (polymers or lipids) in an aqueous solution to form structures.	Polymeric micelles, liposomes
	Coacervation/ interfacial polymerization	Forms a shell around a core droplet through polymer complexation or a polymerization reaction at the droplet interface.	Core-shell nanocapsules

OSCC: Oral squamous cell carcinoma, PLGA: Poly(lactic-co-glycolic acid), NPs: Nanoparticles

in the encapsulation of tumor-suppressive microRNAs (e.g., miR-30c-5p) for transmucosal delivery against OSCC.[10] Beyond simple encapsulation, achieving targeted delivery often requires further engineering; PEGylation the covalent attachment of PEG chains to the NP surface is a critical post-synthesis modification that creates a "stealth" corona, reducing opsonization and recognition by the immune system to dramatically prolong systemic circulation and enhance tumor accumulation via the EPR effect. This versatile toolkit of synthesis and modification methods allows for the precise fabrication of nanocarriers that can overcome the limitations of conventional chemotherapy, offering improved drug solubility, passive tumor targeting, and controlled release kinetics for treating OSCC.[3]

PNPs offer a revolutionary approach for OSCC chemotherapy, primarily due to their superior biodegradability and biocompatibility, which minimize the risk of long-term toxicity and allow for safe metabolic clearance after delivering their therapeutic payload.[5,23] A key advancement facilitated by these materials is the ability to achieve controlled drug release, enabling sustained therapeutic concentrations at the tumor site while drastically reducing the frequent, high-dose administrations required with conventional chemotherapy, which in turn mitigates systemic side effects. To further enhance specificity, PNPs leverage a dual-targeting strategy; they first passively accumulate in tumor tissue through the EPR effect, capitalizing on the leaky vasculature of OSCC tumors, and then achieve precision targeting through active mechanisms using surface-grafted ligands like FA, which selectively bind to receptors overexpressed on cancer cells, promoting receptor-mediated endocytosis. This targeted approach is highly effective for delivering common chemotherapeutic agents such as DOX and docetaxel, protecting them from premature degradation and improving their bioavailability and retention within the malignant tissue.[24] Preclinical studies, including those utilizing FA-functionalized NPs, have demonstrated enhanced efficacy through significantly increased cellular uptake and cytotoxicity in cancer cell lines, alongside reduced toxicity in animal models, as shown by greater tumor volume reduction compared to untargeted formulations or free drugs.[25] These promising preclinical outcomes have paved the way for ongoing clinical trials, marking the transition of targeted PNPs from proof-of-concept to human testing for various cancers. Despite this progress, significant challenges remain, including complex interactions with the TME such as hypoxia and high interstitial fluid pressure, that can hinder NP penetration and efficacy, as well as issues surrounding the physical and chemical stability of PNPs during storage and their scalable manufacturing, which must be addressed to ensure consistent performance and clinical viability.[5,25,26]

LNPS IN OSCC CHEMOTHERAPY

LNPs represent a paradigm shift in the therapeutic approach for OSCC, offering a sophisticated means to overcome the profound limitations of conventional chemotherapy [Figure 2a]. LNPs are composed of biodegradable and biocompatible lipids, which mimic naturally occurring biological molecules, thereby significantly minimizing the risk of systemic toxicity and adverse effects, a feature critically enhanced by novel, rapidly eliminated ionizable lipids. A cornerstone of their utility lies in their ability to encapsulate hydrophobic anticancer drugs, which typically suffer from poor aqueous solubility, low dissolution in biological fluids, and limited bioavailability; by enveloping these agents, LNPs markedly improve their solubility, stability, and ultimate therapeutic efficacy.[27,28] A key advancement in the LNP platform is the development of ionizable lipids, which are positively charged at low pH for efficient mRNA encapsulation and nearly neutral at physiological pH, enhancing biocompatibility and facilitating a potent endosomal escape mechanism via membrane disruption for cytosolic drug delivery.[29,30] Furthermore, LNPs can be engineered for controlled drug release, ensuring a sustained therapeutic effect that reduces dosing frequency and improves patient compliance. The encapsulation also shields therapeutic payloads from degradation and immune system clearance, leading to higher drug concentrations at the tumor site. Active targeting is achieved through surface functionalization with ligands like FA or hyaluronic acid, enabling specific recognition of receptors overexpressed on OSCC cells and enhancing tumoral accumulation while reducing off-target effects [Figure 2b]. A critical "stealth" characteristic is imparted by coating LNPs with PEG or other hydrophilic polymers, which reduces opsonization and recognition by the RES, thereby prolonging their circulation time in the bloodstream. This prolonged circulation, combined with passive targeting, allows LNPs to exploit the EPR effect of tumors, preferentially accumulating in malignant tissues characterized by leaky vasculature and impaired lymphatic drainage.[29] By delivering drugs specifically to the tumor site, LNPs minimize the exposure of healthy tissues to cytotoxic agents, thereby reducing systemic side effects and improving the therapeutic index. The versatility of LNPs also enables the co-delivery of multiple therapeutic agents, such as chemotherapeutics and siRNA, to surmount complex drug resistance mechanisms in cancer cells through synergistic activity. This platform further supports advanced combination therapies with immunomodulators, providing a multi-faceted strategy that increases the likelihood of treatment success. Recent innovations have also focused on overcoming the challenge of long-term storage, with studies demonstrating that lyophilized mRNA-LNPs can maintain stability and efficacy for up to 24 weeks at 4°C, and that novel piperidine-based ionizable lipids can limit reactive impurities to enhance the thermostability of liquid formulations.[31,32] Consequently, LNPs embody a versatile and potent strategy for managing OSCC, improving therapeutic outcomes, mitigating side effects, and providing a robust platform for next-generation targeted and combination therapies.

MULTIFUNCTIONAL AND STIMULI-RESPONSIVE NPS

The TME presents unique physiological characteristics, including acidic pH, elevated temperature, and overexpressed enzymes, providing distinctive opportunities for developing smart NP systems that can precisely target cancer cells

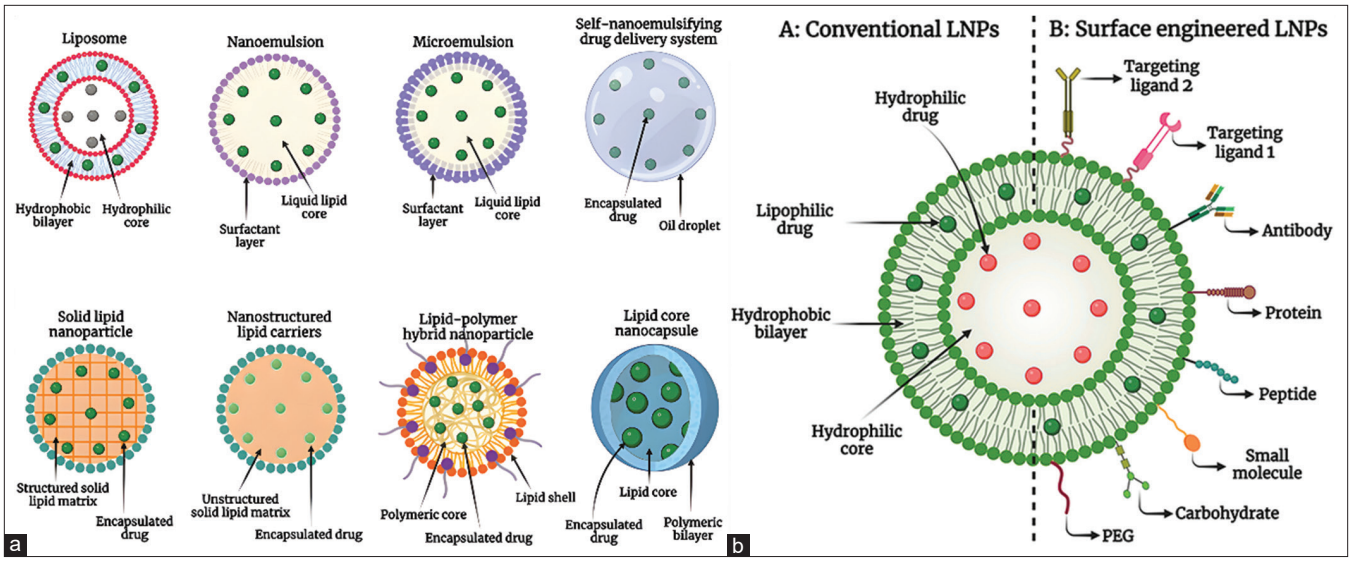

Figure 2: Lipid nanoparticle platforms and surface engineering: (a) Structural variants—including liposomes, nano-/microemulsions, SNEDDS, solid lipid nanoparticles, nanostructured lipid carriers, lipid–polymer hybrids, and lipid core nanocapsules—depicted by their core, bilayer, and surfactant architectures. (b) Comparison of conventional versus surface-engineered lipid nanoparticles showing functionalization with polyethylene glycol, targeting ligands, antibodies, proteins, peptides, carbohydrates, and small molecules

while minimizing systemic toxicity. Recent advances in stimuli-responsive NPs have leveraged these TME-specific conditions to achieve controlled drug delivery and enhanced therapeutic efficacy [Figure 3].

pH-responsive NP systems

Recent preclinical research has demonstrated significant advancements in the design and efficacy of pH-responsive NP systems for targeted chemotherapy in OSCC, with innovative platforms showing promise in enhancing drug delivery, minimizing systemic toxicity, and improving anti-tumor outcomes. A pivotal 2023 study constructed an FAP-targeted nano-drug delivery system, NPF@DOX, using PEGylated nano-graphene oxide to deliver DOX. This system was engineered to leverage the acidic TME, exhibiting a pH-stimulated drug release profile; furthermore, it possessed a high photothermal conversion efficiency (52.48%), and the localized heat generated under near-infrared (NIR) irradiation synergistically promoted DOX release and apoptosis, resulting in superior tumor suppression both *in vitro* and *in vivo* compared to individual therapies.[33] In a 2024 study, researchers developed a biomimetic approach with macrophage membrane-camouflaged pH-sensitive NPs (MM@DOX NPs) for OSCC therapy. The core of these NPs was formed by grafting phenylboronic acid (PBA) onto a polymer and loading DOX via pH-sensitive boronate ester bonds; these bonds remain stable at physiological pH (7.4) but cleave in the acidic TME (pH 5.5), triggering selective drug release. The encapsulation with a RAW264.7 macrophage membrane conferred immune evasion and natural tumor-targeting capabilities, leading to enhanced cellular uptake in HN6 and SCC15 OSCC cell lines, a prolonged circulation half-life (9.26 h vs. 1.94 h for free DOX), increased tumor accumulation, and potent tumor suppression with good biocompatibility *in vivo*.[34] Another cutting-edge strategy reported in a 2025 article involved the synthesis of glutathione/pH-responsive copper-based cascade nanocomplexes designed to induce immunogenic cell death in OSCC through a novel combination of cuproptosis, ferroptosis, and necroptosis, highlighting a move beyond traditional chemotherapy toward activating multiple programmed cell death pathways. Collectively, these studies underscore a strong research focus on combining stimuli-responsive drug release, primarily to acidity, with active targeting mechanisms, such as specific ligands or biomimetic coatings, to achieve precise and effective treatment for OSCC, marking a sophisticated evolution in nanomedicine approaches for this aggressive malignancy.[35]

OSCC remains one of the most prevalent malignancies of the head-and-neck region, accounting for approximately 90% of oral cancers worldwide. Despite advances in surgical and chemoradiation therapies, OSCC continues to exhibit high morbidity and mortality, primarily due to drug resistance, systemic toxicity, and limited tumor specificity of conventional chemotherapeutics such as DOX. Recent developments in nanotechnology have offered novel strategies for targeted drug delivery, improving therapeutic efficacy, and minimizing adverse effects. NPs enable passive tumor targeting through the EPR effect, yet their clinical translation is hindered by rapid clearance and immunogenicity. Consequently, active targeting strategies using biomimetic nanocarriers have gained attention for improving tumor localization and immune evasion. Among these, cell membrane-coated NPs have emerged as an innovative platform capable of mimicking the biological properties of source cells. In particular, macrophage membranes exhibit intrinsic tumor-homing ability through the CCR2–CCL2 axis and α4β1/VCAM-1 interactions, allowing efficient tumor infiltration and prolonged systemic circulation. The study by Yang *et al*. (2024) developed MM@DOX NPs using poly(methyl vinyl ether-alt-maleic anhydride)-PBA (PMVEMA-PBA) as a pH-responsive carrier. The boronate ester bond between PBA and DOX hydrolyzes under acidic TMEs, enabling selective drug release at the tumor site. The design concept and synthesis pathway of MM@DOX NPs were clearly depicted in Figure 4a, which illustrates the formation of PMVEMA-PBA, subsequent DOX loading, and macrophage membrane coating. The schematic also demonstrates the mechanism of pH-triggered DOX release and the NP's tumor-targeting process in the acidic microenvironment. This figure effectively summarizes the multifunctional design strategy of the nanocarrier system, integrating responsive drug release with immune evasion and tumor specificity. Transmission electron microscopy images in Figure 4b further validated the successful construction of the NPs, showing a distinct core–shell morphology in which the macrophage membrane surrounds the DOX-loaded NP core. The core–shell configuration confirmed the structural integrity and successful membrane coating, which imparted stability and biomimetic properties to the

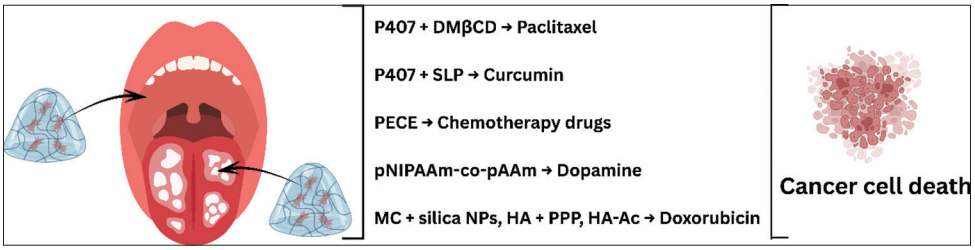

Figure 3: Nanocomposite hydrogel delivery systems for oral cavity cancer treatment inducing tumor cell death

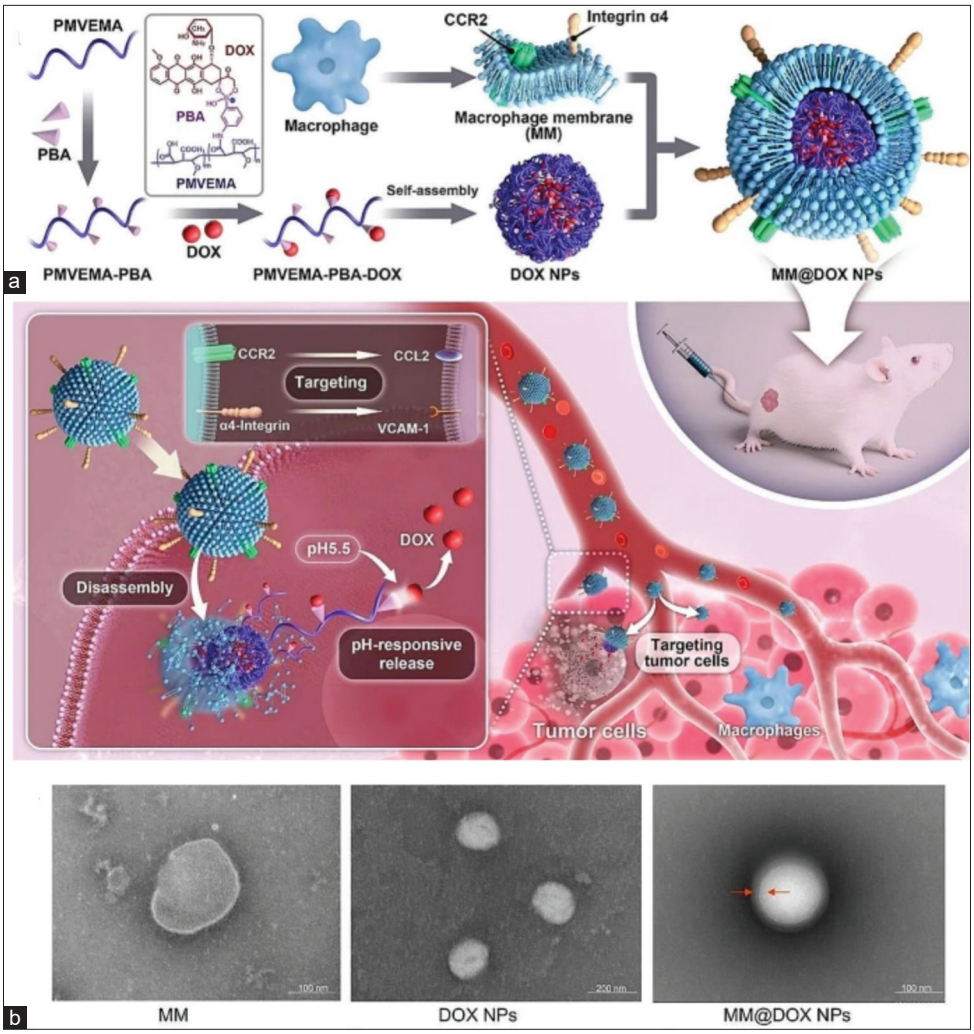

Figure 4: Schematic illustration and characterization of macrophage membrane-coated pH-sensitive nanoparticles (MM@DOX NPs) for targeted oral squamous cell carcinoma (OSCC) therapy. (a) The synthetic route and functional mechanism of MM@DOX NPs. Phenylboronic acid (PBA) is grafted onto poly (methyl vinyl ether-alt-maleic anhydride) (PMVEMA) to form PMVEMA-PBA, which conjugates with doxorubicin (DOX) to produce PMVEMA-PBA-DOX nanoparticles. These are subsequently coated with macrophage membranes (MM) containing CCR2 and integrin α4 receptors, enabling tumor targeting via CCR2–CCL2 and α4β1–VCAM-1 interactions. The MM@DOX NPs exhibit pH-responsive DOX release (at pH 5.5) in the tumor microenvironment, promoting localized drug delivery and enhanced therapeutic efficacy in OSCC-bearing mice. (b) Transmission electron microscopy images showing the morphology of isolated MM, uncoated DOX NPs, and MM@DOX NPs. The distinct core–shell structure in MM@DOX NPs (indicated by red arrows) confirms successful MM encapsulation around the DOX-loaded nanoparticle core. Scale bars: 100 nm (left and right) and 200 nm (middle). Adapted from Yang, *et al.* under the terms and conditions of the Creative Commons Attribution (CC-BY) license (CC-BY 4.0). (f) Available at Yang *et al.*[34]

nanocarrier. The combined evidence from Figures 1 and 2b demonstrates how the macrophage membrane encapsulation and pH-responsive polymer design work synergistically to enhance OSCC-targeted therapy. *In vitro* and *in vivo* studies revealed that MM@DOX NPs achieved superior cellular uptake in OSCC cell lines (HN6 and SCC15), minimized macrophage phagocytosis, and exhibited a controlled, pH-dependent DOX release profile. *In vivo* fluorescence imaging demonstrated enhanced tumor accumulation and an extended half-life (9.26 h vs. 1.94 h for free DOX), while antitumor efficacy tests in HN6-bearing mice showed significant tumor growth suppression without systemic toxicity. These findings confirm that MM@DOX NPs provide an efficient, biomimetic, pH-responsive nanoplatform that combines immune evasion, controlled drug release, and targeted tumor accumulation for the improved treatment of OSCC.[34]

Temperature-responsive NPs

Based on current research, temperature-responsive NPs represent a promising frontier in targeted chemotherapy for OSCC. These "smart" drug delivery systems are designed to release their therapeutic payload in response to temperature increases, thereby improving drug specificity for tumors and reducing systemic side effects. The following literature

review summarizes key developments in this field, focusing on thermo-sensitive polymers, gold-polymer hybrid NPs, and thermosensitive nanogels.

A primary strategy involves the use of thermo-sensitive polymers, with poly(N-isopropylacrylamide) and its copolymers being the most extensively researched. These polymers exhibit a lower critical solution temperature, typically between 32°C and 37°C, below which they are hydrophilic and swollen, and above which they undergo a reversible phase transition to a hydrophobic and collapsed state.[36,37] This coil-to-globule transition is a crucial mechanism for controlled drug release. For instance, one study designed a dual pH- and thermo-sensitive copolymer hydrogel using N-isopropyl acrylamide and acrylamide. This system demonstrated a sharp phase transition above 40°C and released nearly 100% of its loaded curcumin cargo over 4 h at 40°C and acidic pH, conditions that can mimic a heated TME.[36] Molecular dynamics simulations further support the application of poly(N-isopropyl methacrylamide) (PNIPAM)-based systems, showing that increased temperature weakens the intermolecular attractions between the polymer carrier and the chemotherapeutic drug DOX, thereby facilitating drug release.[38]

Building on this concept, gold-polymer hybrid NPs have been developed to synergistically combine photothermal therapy with triggered chemotherapy. Gold NPs (GNPs) possess strong photothermal conversion abilities, meaning they can efficiently absorb NIR light and convert it into heat. This property can be harnessed for two purposes: First, the generated heat can directly ablate cancer cells (photothermal therapy), and second, it can trigger drug release from a thermo-responsive polymer component in the hybrid structure. This approach allows for external, spatiotemporal control over treatment. As reviewed by researchers, such GNP hybrid nanostructures enable multimodal therapy, where the heat generated by the gold component on NIR irradiation simultaneously promotes local drug release and induces hyperthermia, leading to superadditive or synergistic effects in killing tumor cells.[39] This method significantly improves therapeutic efficacy against cancer cells while minimizing damage to healthy tissues that are not exposed to the laser.

Furthermore, thermosensitive nanogels, cross-linked hydrogel NPs that swell or shrink with temperature changes, have emerged as a versatile platform. These nanogels can encapsulate a large amount of water and therapeutic agents, releasing their cargo upon collapsing when the temperature exceeds their volume phase transition temperature (VPTT).[37,40] A key advancement in this area is the development of nanogels designed for integration with clinical hyperthermia systems. In one feasibility study, researchers synthesized thermoresponsive nanogels from a copolymer of PNIPAM and PNIPAM, tuning its VPTT to 38°C. They then used a magnetic resonance system capable of focused radio frequency heating to successfully trigger the release of a model protein from these nanogels, demonstrating a novel theranostic platform that combines diagnostic imaging, thermal intervention, and controlled drug release.[40] This illustrates a crucial step toward clinically translating this technology for localized drug delivery in anticancer treatments.

Enzyme-responsive NPs

While enzyme-responsive NPs represent a promising frontier in targeted chemotherapy for OSCC by leveraging the tumor's unique biochemical signature, a critical analysis reveals significant challenges that must be overcome for their successful clinical translation.[5] The fundamental promise of these systems lies in their design to remain inert in the circulation and healthy tissues, only releasing their chemotherapeutic payload upon encountering specific enzymes that are overexpressed within the TME of OSCC, such as matrix metalloproteinases, hyaluronidase, and cathepsins.[41,42] This specificity can, in theory, maximize drug efficacy at the tumor site while minimizing the systemic toxicity that plagues conventional chemotherapy.[5] For instance, the strategic incorporation of enzyme-cleavable linkers, peptides, or polymer matrices allows the NP to disassemble or change morphology in response to enzymatic activity, facilitating targeted drug release.[41] This approach can be further refined by combining enzyme-responsiveness with other targeting strategies; for example, NPs can be functionalized with ligands that bind to receptors overexpressed on OSCC cells (e.g., estimated glomerular filtration rate or CD44) to achieve dual targeting—first to the tumor cell itself, and then to its enzymatic environment.[43] The use of biocompatible, natural polymers such as hyaluronic acid and chitosan, is particularly advantageous, as they are not only biodegradable but can also be inherently susceptible to degradation by enzymes like hyaluronidase, which is abundant in the OSCC TME.[44]

However, a critical examination exposes several formidable hurdles. A primary concern is the heterogeneous expression of enzymes within and between OSCC tumors.[45] This variability can lead to inconsistent and unreliable drug release profiles, as the triggering stimulus may not be uniformly present, ultimately resulting in sub-therapeutic drug concentrations in some areas of the tumor and compromising overall treatment efficacy.[41] Furthermore, the complexity of the OSCC TME presents physical and biological barriers; the dense extracellular matrix and high interstitial fluid pressure can impede the deep penetration of NPs, preventing them from reaching the core of the tumor where enzymatic triggers might be most needed. From a manufacturing and clinical standpoint, the journey from bench to bedside is fraught with obstacles.[42] The synthesis of enzyme-responsive nanocarriers is often complex and difficult to scale up with batch-to-batch consistency, especially when using natural polymers. Issues of potential immunogenicity and the long-term fate

of the nanocarrier components within the body also require comprehensive safety evaluations that are currently lacking. Finally, while enzyme-responsive systems are "smart," they often exhibit lower drug encapsulation efficiency compared to more conventional nanocarriers such as liposomes, which can limit the therapeutic payload delivered per dose.[41]

CHALLENGES AND FUTURE PROSPECTS

Despite the transformative potential of NP-based systems in revolutionizing oncology through enhanced drug targeting and reduced systemic toxicity, their clinical translation is critically hampered by significant challenges pertaining to safety, manufacturing, and biological complexity. A primary barrier is the concern over nanotoxicity, where certain materials, even biocompatible natural polymers like chitosan, can induce adverse effects such as pro-inflammatory cytokine release and dose-dependent cardiotoxicity *in vivo* due to non-specific organ accumulation, underscoring that toxicity is not merely a function of the administered dose but is intrinsically governed by variable physicochemical properties such as size, shape, and surface chemistry.[46] Compounding this safety challenge is the formidable hurdle of scaling up production while ensuring batch-to-batch consistency, as conventional laboratory synthesis methods for complex formulations such as PNPs are prone to variability, making the transition to industrial-scale, reproducible manufacturing a non-trivial obstacle that impacts both economic viability and regulatory compliance.[46,47] Furthermore, the biological efficacy of these systems is contested by tumor heterogeneity and the evolution of MDR mechanisms, such as the overexpression of ATP-binding cassette transporters like P-glycoprotein, which actively efflux chemotherapeutic agents from cancer cells, drastically reducing intracellular drug concentration and therapeutic efficacy. In response, the field is advancing sophisticated strategic solutions, including the engineering of NPs for the co-delivery of chemotherapeutic drugs alongside efflux pump inhibitors or gene-editing tools such as siRNA and CRISPR/Cas9 to directly silence or knock out resistance genes, thereby resensitizing tumors to treatment.[48] The future outlook is being radically shaped by the integration of artificial intelligence, as demonstrated by platforms like TuNa-AI, which can optimize NP recipes and ingredient ratios to improve successful formation, enhance drug encapsulation, and reduce the use of harmful excipients, thereby accelerating the rational design of safer and more effective nanocarriers.[49] Concurrently, the push towards personalized nanomedicine is evident in the development of stimuli-responsive NPs that leverage the TME (e.g., acidic pH, overexpressed enzymes) for precise, spatiotemporal control over drug release.[50] However, the ultimate clinical translation of these innovative platforms is inextricably linked to navigating the evolving and complex regulatory landscapes for Nanotechnology-Enabled Health Products in key regions such as the EU and the US, which necessitates early and continuous engagement with regulatory bodies to define clear pathways for approval, ensuring that the immense promise of nanomedicine can be safely and effectively translated into tangible patient benefits.[51]

CONCLUSION

Polymeric and LNPs represent a transformative approach for treating OSCC, directly addressing the critical limitations of conventional chemotherapy. By enabling targeted drug delivery through passive and active mechanisms, these nanocarriers enhance efficacy at the tumor site while significantly reducing systemic toxicity. The development of "smart," stimuli-responsive systems that release drugs in response to the TME (e.g., pH or enzyme triggers) further refines this precision. Despite promising preclinical results, challenges in scalability, long-term safety, and navigating regulatory pathways remain key hurdles for clinical translation. The future of this field lies in leveraging artificial intelligence for NP design and advancing combination strategies to overcome drug resistance, ultimately paving the way for more effective and personalized nanomedicine for OSCC patients.

REFERENCES

1. González-Moles MÁ, Aguilar-Ruiz M, Ramos-García P. Challenges in the early diagnosis of oral cancer, evidence gaps and strategies for improvement: A scoping review of systematic reviews. Cancers (Basel) 2022;14:4967.
2. Tan Y, Wang Z, Xu M, Li B, Huang Z, Qin S, *et al*. Oral squamous cell carcinomas: State of the field and emerging directions. Int J Oral Sci 2023;15:44.
3. Cui S, Liu H, Cui G. Nanoparticles as drug delivery systems in the treatment of oral squamous cell carcinoma: Current status and recent progression. Front Pharmacol 2023;14:1176422.
4. Sha J, Bai Y, Ngo HX, Okui T, Kanno T. Overview of evidence-based chemotherapy for oral cancer: Focus on drug resistance related to the epithelial-mesenchymal transition. Biomolecules 2021;11:893.
5. Herrada Céspedes A, Reyes M, Morales JO. 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.
6. Yusuf A, Almotairy AR, Henidi H, Alshehri OY, Aldughaim MS. Nanoparticles as drug delivery systems: A review of the implication of nanoparticles' physicochemical properties on responses in biological systems. Polymers (Basel) 2023;15:1596.
7. Mitchell MJ, Billingsley MM, Haley RM, Wechsler ME, Peppas NA, Langer R. Engineering precision nanoparticles for drug delivery. Nat Rev Drug Discov 2021;20:101-24.
8. Wang ZQ, Liu K, Huo ZJ, Li XC, Wang M, Liu P,

et al. A cell-targeted chemotherapeutic nanomedicine strategy for oral squamous cell carcinoma therapy. J Nanobiotechnology 2015;13:63.
9. Kesharwani P, Kumar V, Goh KW, Gupta G, Alsayari A, Wahab S, *et al*. PEGylated PLGA nanoparticles: Unlocking advanced strategies for cancer therapy. Mol Cancer 2025;24:205.
10. Fang YP, Lin YC, Lin CY, Wang PJ, Chang TY, Hsieh YJ. Transmucosal delivery of miR-30c-5p by chitosan nanoparticles for oral squamous cell carcinoma. Int J Nanomedicine 2025;20:9179-94.
11. Yin X, Li Z, Zhang Y, Zeng X, Wang Q, Liang Z. Polydopamine surface-modified hyperbranched polymeric nanoparticles for synergistic chemo/photothermal therapy of oral cancer. Front Bioeng Biotechnol 2023;11:1174014.
12. Chen J, Zhang Y. Hyperbranched polymers: Recent advances in photodynamic therapy against cancer. Pharmaceutics 2023;15:2222.
13. Alsaab HO, Alharbi FD, Alhibs AS, Alanazi NB, Alshehri BY, Saleh MA, *et al*. PLGA-based nanomedicine: History of advancement and development in clinical applications of multiple diseases. Pharmaceutics 2022;14:2728.
14. Rahman Z, Zidan AS, Habib MJ, Khan MA. Understanding the quality of protein loaded PLGA nanoparticles variability by Plackett-Burman design. Int J Pharm 2010;389:186-94.
15. Mohammed MA, Syeda JT, Wasan KM, Wasan EK. An overview of chitosan nanoparticles and its application in non-parenteral drug delivery. Pharmaceutics 2017;9:53.
16. Saberi Riseh R, Vatankhah M, Hassanisaadi M, Varma RS. A review of chitosan nanoparticles: Nature's gift for transforming agriculture through smart and effective delivery mechanisms. Int J Biol Macromol 2024;260:129522.
17. Suk JS, Xu Q, Kim N, Hanes J, Ensign LM. PEGylation as a strategy for improving nanoparticle-based drug and gene delivery. Adv Drug Deliv Rev 2016;99:28-51.
18. Shi L, Zhang J, Zhao M, Tang S, Cheng X, Zhang W, *et al*. Effects of polyethylene glycol on the surface of nanoparticles for targeted drug delivery. Nanoscale 2021;13:10748-64.
19. Rabanel JM, Hildgen P, Banquy X. Assessment of PEG on polymeric particles surface, a key step in drug carrier translation. J Control Release 2014;185:71-87.
20. Bal-Öztürk A, Tietilu SD, Yücel O, Erol T, Akgüner ZP, Emik S, *et al*. Hyperbranched polymer-based nanoparticle drug delivery platform for the nucleus-targeting in cancer therapy. J Drug Deliv Sci Technol 2023;81:104195.
21. Chen L, Feng C, Shi Z, Wang J, Wang T, Wang Y, *et al*. PLGA-based herb Toosendanin delivery system for efficient therapy of oral squamous cell carcinoma. BMC Complement Med Ther 2025;25:217.
22. Yanar F, Carugo D, Zhang X. Hybrid nanoplatforms comprising organic nanocompartments encapsulating inorganic nanoparticles for enhanced drug delivery and bioimaging applications. Molecules 2023;28:5694.
23. Kamaly N, Yameen B, Wu J, Farokhzad OC. Degradable controlled-release polymers and polymeric nanoparticles: Mechanisms of controlling drug release. Chem Rev 2016;116:2602-63.
24. Eltaib L. Polymeric nanoparticles in targeted drug delivery: Unveiling the impact of polymer characterization and fabrication. Polymers (Basel) 2025;17:833.
25. Fallatah MM, Alradwan I, Alfayez N, Aodah AH, Alkhrayef M, Majrashi M, *et al*. Nanoparticles for cancer immunotherapy: Innovations and challenges. Pharmaceuticals (Basel) 2025;18:1086.
26. Ketabat F, Pundir M, Mohabatpour F, Lobanova L, Koutsopoulos S, Hadjiiski L, *et al*. Controlled drug delivery systems for oral cancer treatment-current status and future perspectives. Pharmaceutics 2019;11:302.
27. Chaudhary AA, Fareed M, Khan SU, Alneghery LM, Aslam M, Alex A, *et al*. Exploring the therapeutic potential of lipid-based nanoparticles in the management of oral squamous cell carcinoma. Explor Target Antitumor Ther 2024;5:1223-46.
28. Maier MA, Jayaraman M, Matsuda S, Liu J, Barros S, Querbes W, *et al*. Biodegradable lipids enabling rapidly eliminated lipid nanoparticles for systemic delivery of RNAi therapeutics. Mol Ther 2013;21:1570-8.
29. Jung HN, Lee SY, Lee S, Youn H, Im HJ. Lipid nanoparticles for delivery of RNA therapeutics: Current status and the role of *in vivo* imaging. Theranostics 2022;12:7509-31.
30. Zhao F, Luppi B, Chao PH, Yang J, Zhang Y, Feng R, *et al*. Biodegradable polymers with tertiary amines enhance mRNA delivery of lipid nanoparticles via improved endosomal escape. Biomaterials 2026;324:123541.
31. Hashiba K, Taguchi M, Sakamoto S, Otsu A, Maeda Y, Ebe H, *et al*. Overcoming thermostability challenges in mRNA-lipid nanoparticle systems with piperidine-based ionizable lipids. Commun Biol 2024;7:556.
32. Young RE, Hofbauer SI, Riley RS. Overcoming the challenge of long-term storage of mRNA-lipid nanoparticle vaccines. Mol Ther 2022;30:1792-3.
33. Li R, Liu C, Wan C, Liu T, Zhang R, Du J, *et al*. A targeted and pH-responsive nano-graphene oxide nanoparticle loaded with doxorubicin for synergetic chemo-photothermal therapy of oral squamous cell carcinoma. Int J Nanomedicine 2023;18:3309-24.
34. Yang L, Li H, Luo A, Zhang Y, Chen H, Zhu L, *et al*. Macrophage membrane-camouflaged pH-sensitive nanoparticles for targeted therapy of oral squamous cell carcinoma. J Nanobiotechnology 2024;22:168.
35. Sun Y, Li E, Zhong W, Deng Z, Zhou Z, Wong KH, *et al*. GSH/pH-responsive copper-based cascade nanocomplexes inducing immunogenic cell death through cuproptosis/ferroptosis/necroptosis in oral squamous cell carcinoma. Mater Today Bio 2025;30:101434.
36. Santhamoorthy M, Vy Phan TT, Ramkumar V,

Raorane CJ, Thirupathi K, Kim SC. Thermo-sensitive poly (n-isopropylacrylamide-co-polyacrylamide) hydrogel for pH-responsive therapeutic delivery. Polymers (Basel) 2022;14:4128.
37. Abuwatfa WH, Awad NS, Pitt WG, Husseini GA. Thermosensitive polymers and thermo-responsive liposomal drug delivery systems. Polymers (Basel) 2022;14:925.
38. Pasban S, Raissi H. PNIPAM/Hexakis as a thermosensitive drug delivery system for biomedical and pharmaceutical applications. Sci Rep 2022;12:14363.
39. Ali AA, Abuwatfa WH, Al-Sayah MH, Husseini GA. Gold-nanoparticle hybrid nanostructures for multimodal cancer therapy. Nanomaterials (Basel) 2022;12:3706.
40. Ji Y, Winter L, Navarro L, Ku MC, Periquito JS, Pham M, *et al*. Controlled release of therapeutics from thermoresponsive nanogels: A thermal magnetic resonance feasibility study. Cancers (Basel) 2020;12:1380.
41. Li M, Zhao G, Su WK, Shuai Q. Enzyme-responsive nanoparticles for anti-tumor drug delivery. Front Chem 2020;8:647.
42. Sun H, Li Y, Xue M, Feng D. Tumor microenvironment-responsive nanoparticles: Promising cancer PTT carriers. Int J Nanomedicine 2025;20:7987-8001.
43. Tian H, Zhang T, Qin S, Huang Z, Zhou L, Shi J, *et al*. Enhancing the therapeutic efficacy of nanoparticles for cancer treatment using versatile targeted strategies. J Hematol Oncol 2022;15:132.
44. Hou J, Xue Z, Chen Y, Li J, Yue X, Zhang Y, *et al*. Development of stimuli-responsive polymeric nanomedicines in hypoxic tumors and their therapeutic promise in oral cancer. Polymers (Basel) 2025;17:1010.
45. Sahu K, Firdous A, Raza MA, Saoji SD, Patravale VB, Ajazuddin A. Enzyme-responsive natural nanocarriers for RNA delivery in the tumor microenvironment: A comprehensive review. J Drug Deliv Sci Technol 2025;114:107455.
46. Li M, Zhou S, Zhang Y, Li J, Zhang K. Advancements in tumor-targeted nanoparticles: Design strategies and multifunctional therapeutic approaches. Nanomaterials (Basel) 2025;15:1262.
47. Herdiana Y, Wathoni N, Shamsuddin S, Muchtaridi M. Scale-up polymeric-based nanoparticles drug delivery systems: Development and challenges. OpenNano 2022;7:100048.
48. Park S, Lu GL, Zheng YC, Davison EK, Li Y. Nanoparticle-based delivery strategies for combating drug resistance in cancer therapeutics. Cancers (Basel) 2025;17:2628.
49. Martinez M. AI Engineers Nanoparticles for Improved Drug Delivery. United States: Duke Pratt School of Engineering; 2025.
50. Waititu A, Waithira T, Mwaura A. Nanoparticle-mediated drug delivery: Enhancing therapeutic efficacy and minimizing toxicity. Eng Proc 2025;109:19.
51. Rodríguez-Gómez FD, Monferrer D, Penon O, Rivera-Gil P. Regulatory pathways and guidelines for nanotechnology-enabled health products: A comparative review of EU and US frameworks. Front Med (Lausanne) 2025;12:1544393.

Source of Support: Nil. **Conflicts of Interest:** None declared.