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Smart Nanocarriers for Targeted Drug Delivery in treatment of oral cancer

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ABSTRACT

Oral cancer remains a significant global health challenge due to its high morbidity, recurrence rate, and resistance to conventional therapies. Traditional treatments such as surgery, chemotherapy, and radiotherapy often cause severe side effects and lack specificity, leading to damage of healthy tissues. In recent years, smart nanocarriers have emerged as a promising strategy for targeted drug delivery in the treatment of oral cancer. These nanoscale systems are engineered to enhance drug solubility, stability, and bioavailability, while ensuring site-specific delivery and controlled release of therapeutic agents. Smart nanocarriers—such as liposomes, polymeric nanoparticles, dendrimers, and stimuli-responsive systems—can be functionalized with ligands that recognize overexpressed receptors on oral cancer cells, allowing precise targeting. Furthermore, they can be designed to respond to internal (pH, redox, enzymes) or external (temperature, magnetic field, light) stimuli, triggering drug release specifically in the tumor microenvironment. This targeted approach minimizes systemic toxicity and improves therapeutic efficacy. This review explores recent advances in the design, functionality, and clinical potential of smart nanocarriers for oral cancer therapy, highlighting their role in personalized and minimally invasive treatment strategies.

Keywords: Smart Nanocarriers, Oral Cancer, Targeted Drug Delivery, Stimuli-Responsive Systems, Theranostics

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Introduction

Oral cancer is a major global health burden, with over 377,000 new cases and more than 177,000 deaths reported annually, according to the World Health Organization (1). Among various subtypes, oral squamous cell carcinoma (OSCC) is the most prevalent, accounting for more than 90% of all oral malignancies. It primarily affects tissues of the lips, tongue, floor of the mouth, and buccal mucosa (2). The disease is often diagnosed in its advanced stages, where the prognosis is significantly poorer, and treatment options are more aggressive and less effective (3, 4). Key risk factors include tobacco use, excessive alcohol consumption, human papillomavirus (HPV) infection, and poor oral hygiene (5). Conventional treatment modalities—comprising surgical excision, radiotherapy, and systemic chemotherapy—have improved survival to some extent but are still far from optimal (6). These approaches are associated with several drawbacks, including non-specific drug distribution, systemic toxicity, development of multidrug resistance, and detrimental effects on the patient's quality of life (7). Chemotherapeutic agents such as cisplatin, although widely used, exhibit significant off-target toxicity and limited tumor specificity, highlighting the need for more precise and less invasive treatment strategies (8). Nanotechnology has emerged as a powerful platform for addressing these limitations in cancer therapy (9-11). In particular, smart nanocarriers have garnered considerable attention for their ability to deliver therapeutic agents directly to tumor sites, thereby enhancing drug efficacy while minimizing collateral damage to healthy tissues (12, 13). These carriers can be engineered from a variety of materials, including lipids, polymers, dendrimers, and inorganic compounds. Moreover, they can be functionalized with targeting ligands (e.g., antibodies, peptides, or aptamers) that selectively bind to biomarkers overexpressed on oral cancer cells (14). What sets smart nanocarriers apart

from conventional drug delivery systems is their responsiveness to specific biological or external stimuli—such as changes in pH, temperature, enzymatic activity, or the application of magnetic fields or light (15, 16). This stimuli-responsiveness allows for controlled and localized drug release, enhancing therapeutic outcomes and reducing side effects (17, 18).

Additionally, many smart nanocarrier systems integrate diagnostic capabilities, enabling real-time imaging and monitoring of treatment response—a concept known as theranostics (19).

As research continues to evolve, these intelligent drug delivery systems are poised to play a transformative role in the future management of oral cancer (10, 20).

This review explores the various types of smart nanocarriers, their targeting mechanisms, therapeutic applications, and future prospects in the treatment of oral cancer (21).

Nanocarrier Systems Overview

Nanocarriers are submicron-sized delivery vehicles engineered to transport therapeutic agents—such as chemotherapeutic drugs, genetic materials, or phytochemicals—directly to the site of disease (22). In the context of oral cancer treatment, nanocarrier systems are being designed to overcome the biological barriers that limit drug efficacy, such as poor solubility, rapid degradation, multidrug resistance (23). These systems not only enhance drug accumulation in tumor tissues but also enable controlled and stimuli-responsive release of the payload (24). Several types of nanocarriers have been explored for this purpose, each with unique structural features, drug-loading capacities, and targeting capabilities (25) (Table 1).

Nanocarrier Type	Targeting Mechanism	Drug (s) Loaded	Size (nm)	Targeted Biomarker	Release Trigger	In Vitro/In Vivo Model	Therapeutic Outcom
Liposomes (FA-conjugated)	Folate receptor-mediated	Doxorubicin	100	Folate receptor	pH-sensitive	SCC-15 oral cancer cells	Enhanced uptake, reduced systemic toxicity (21)
Polymeric Nanoparticles	Passive + ligand-mediated	Cisplatin	120	EGFR	Enzyme-responsive	Xenograft mouse model	Tumor reduction, low nephrotoxicity (26)
Gold Nanoparticles (AuNPs)	EPR effect + antibody-conjugated	Paclitaxel	20	HER2	Laser/light activation	CAL-27 + BALB/c nude mice	Improved drug retention, phototherml strategy (27)
Mesoporous Silica NPs	Peptide-based active targeting	Curcumin	80	Integrin αvβ3	pH and enzyme-sensitive	In vitro OSCC model	Controlled release, low toxicity (28)
Dendrimer-based carriers	Aptamer-guided targeting	5-Fluorouracil	60	Nucleolin	pH-sensitive	OSCC cell lines	Specific cytotoxicity, minimal side effects (29)
Solid Lipid Nanoparticles	Passive + mucoadhesive targeting	Docetaxel	90	CD44	pH-triggered	3D oral mucosal model	Improved bioadhesion, sustained release (30)
Quantum Dots Hybrid NPs	Ligand-functionalized targeting	Paclitaxel + imaging dye	30		Light-responsive	CD133+ oral CSC model	Theranostic use, targeting cancer stem cells (31)

Table 1. Expanded Summary of Smart Nanocarriers Evaluated for Targeted Drug Delivery in Oral Cancer Treatment

Summary of various smart nanocarrier systems evaluated for targeted drug delivery in oral cancer treatment. Each nanocarrier type—ranging from liposomes and polymeric nanoparticles to dendrimers and quantum dots—demonstrates distinct targeting mechanisms, drug payloads, and stimuli-responsive release strategies, tailored to specific biomarkers and cancer models, ultimately enhancing therapeutic efficacy and minimizing side effects.

Liposomes

Liposomes are vesicular structures composed of one or more phospholipid bilayers surrounding an aqueous core. Their biocompatibility and ability to encapsulate both hydrophilic and hydrophobic drugs make them attractive candidates for oral cancer therapy (32). Surface modification with polyethylene glycol

(PEGylation) increases circulation time, while the conjugation of ligands such as folic acid or epidermal growth factor receptor (EGFR) antibodies facilitates active targeting of tumor cells (33). Liposomal formulations like Doxil have already gained FDA approval for other cancers and serve as a model for further oral cancer-specific adaptations (34).

Polymeric Nanoparticles

These are synthesized from biodegradable and biocompatible polymers like polylactic-co-glycolic acid (PLGA), chitosan, and polyethylene glycol (PEG). Polymeric nanoparticles can offer sustained or pH-triggered drug release and are capable of penetrating deeply into tumor tissues. Their surfaces can be functionalized with specific ligands to enable receptor-mediated endocytosis into cancer cells, enhancing intracellular drug delivery (35).

Dendrimers

Dendrimers are highly branched, monodisperse polymeric structures with numerous surface functional groups. Their well-defined architecture allows precise control over drug loading and release (36). In oral cancer, dendrimers can be used to deliver small molecules, nucleic acids, or imaging agents. Their multivalency also allows the simultaneous attachment of therapeutic agents and targeting moieties (37).

Metallic Nanoparticles

Gold, silver, and iron oxide nanoparticles possess unique optical, magnetic, and electronic properties, enabling them to act as both therapeutic and diagnostic agents (theranostics) (38, 39). For example, gold nanoparticles can be used in photothermal therapy, where they absorb near-infrared light and convert it into heat, selectively killing cancer cells (40).

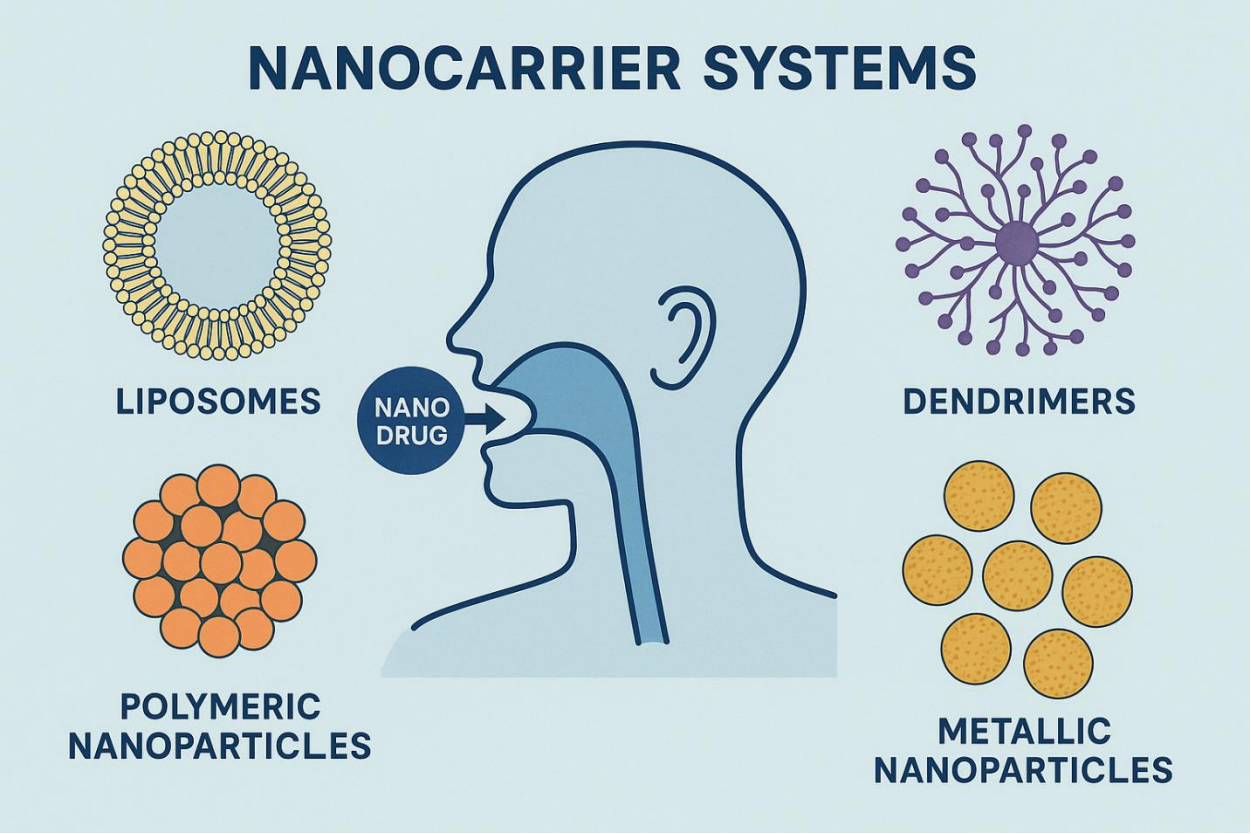

Figure 1. Types of Nanocarrier Systems in Smart Drug Delivery

Nanocarriers are submicron-sized delivery vehicles engineered to transport therapeutic agents—such as chemotherapeutic drugs.

Targeting Mechanisms

Effective targeting is a fundamental advantage of smart nanocarriers, allowing them to deliver therapeutic agents specifically to tumor tissues while sparing healthy

cells. Two major targeting strategies are employed: passive and active targeting, often enhanced by stimuli-responsive mechanisms (41).

Passive Targeting

Passive targeting exploits the Enhanced Permeability and Retention (EPR) effect, a phenomenon in which nanoparticles preferentially accumulate in tumor tissues due to the leaky vasculature and poor lymphatic drainage commonly found in solid tumors (42). Nanocarriers sized between 10–200 nm can penetrate and remain within the tumor microenvironment longer than free drugs, enhancing local drug concentration and therapeutic efficacy (43). While effective, EPR alone may not provide sufficient specificity, especially in heterogeneous tumor environments like those seen in oral cancers (44).

\Active Targeting

Active targeting involves modifying the surface of nanocarriers with ligands such as antibodies, peptides, or aptamers that recognize and bind to specific receptors overexpressed on oral cancer cells. Common targets include EGFR, folate receptors, CD44, and integrins. This ligand–receptor interaction facilitates receptor-mediated endocytosis, increasing intracellular drug delivery and reducing off-target effects (45).

Stimuli-Responsive Release

Smart nanocarriers can also be engineered to respond to internal (e.g., pH, enzymes, redox conditions) or external (e.g., light, heat, magnetic fields) stimuli, triggering controlled and site-specific drug release for maximum therapeutic impact (46).

Key Therapeutic Agents Delivered via Smart Nanocarriers

Smart nanocarriers offer a versatile platform for the delivery of a wide range of therapeutic agents in the treatment of oral cancer, including chemotherapeutic drugs, natural compounds (47). The encapsulation of these agents into nanocarriers enhances their solubility, stability, and bioavailability, while minimizing systemic toxicity (48).

Chemotherapeutic Agents

Commonly used drugs such as cisplatin, 5-fluorouracil (5-FU), paclitaxel, and docetaxel have been successfully incorporated into various nanocarriers to overcome their limitations, such as nephrotoxicity, poor water solubility, and non-specific distribution. For instance, cisplatin-loaded liposomes or PLGA nanoparticles demonstrate improved tumor accumulation and reduced renal toxicity. Similarly, paclitaxel-loaded polymeric micelles or lipid nanoparticles enhance cellular uptake and provide sustained drug release (49).

Natural Phytochemicals

Compounds like curcumin, resveratrol, and berberine possess significant anticancer, antioxidant, and anti-inflammatory properties. However, their clinical utility is restricted by poor solubility and rapid metabolism (50). Nanocarrier systems such as solid lipid nanoparticles, nanoemulsions, and dendrimers improve their pharmacokinetics and target delivery to oral tumors, showing promising preclinical outcomes (51).

Genetic Therapeutics

Smart nanocarriers have been engineered to deliver small interfering RNA (siRNA), microRNA (miRNA), and plasmid DNA for gene silencing or gene therapy in oral cancer (52). These strategies target oncogenes or restore tumor suppressor gene expression. For example, siRNA-loaded chitosan nanoparticles can silence genes responsible for chemoresistance or cell proliferation, offering a personalized approach to treatment (53).

Combination Therapies

Nanocarriers can co-deliver multiple agents (e.g., a chemotherapeutic and a gene therapy agent) within a single system, allowing for synergistic effects and multi-modal treatment. This is particularly useful in overcoming drug resistance and targeting the complex biology of oral tumors (54). Overall, these therapeutic payloads, when combined with targeted and responsive nanocarrier systems, represent a highly promising strategy for improving oral cancer treatment outcomes (55) (Figure 2).

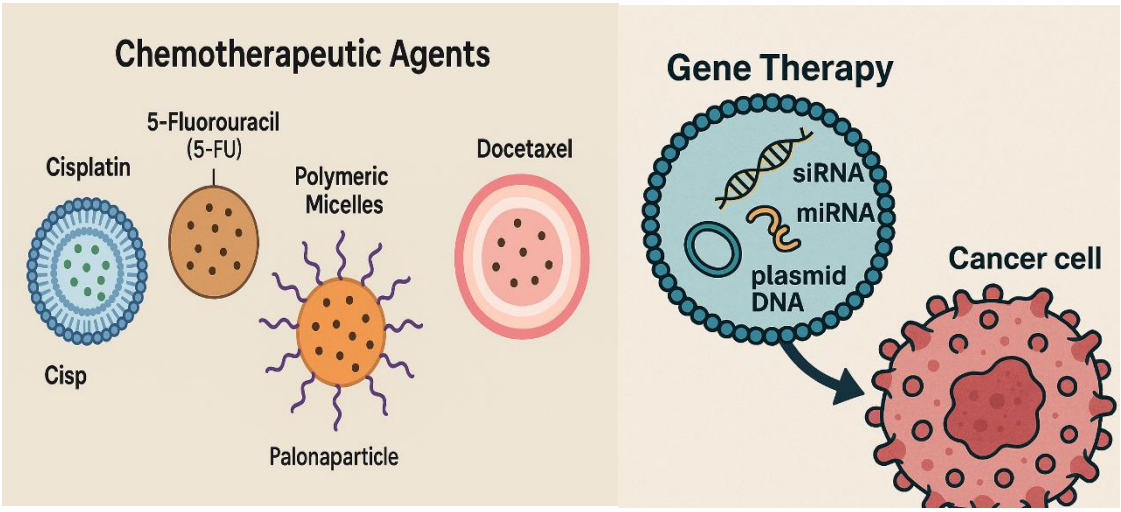

Figure 2. Combination Therapies

Nanocarriers can co-deliver multiple agents (e.g., a chemotherapeutic and a gene therapy agent) within a single system, allowing for synergistic effects and multi-modal treatment.

Clinical and Preclinical Studies

A growing body of preclinical evidence supports the efficacy of smart nanocarriers in the treatment of oral cancer (56).

For example, PLGA nanoparticles loaded with cisplatin have demonstrated improved bioavailability and selective cytotoxicity against oral squamous cell carcinoma cells in vivo. Similarly, curcumin-loaded solid lipid nanoparticles exhibited enhanced anti-tumor effects through apoptosis induction and inhibition of angiogenesis in preclinical trials (57).

Several clinical trials are underway or in early phases to evaluate the safety, tolerability, and effectiveness of nanoparticle-based drug delivery systems in head and neck cancers, which include oral cancers. Some FDA-approved nanomedicine formulations—such as Doxil (liposomal doxorubicin) and Abraxane (albumin-bound paclitaxel)—though primarily approved for other cancers, are being explored for potential repurposing in oral cancer treatment (58).

Moreover, theranostic nanocarriers, which combine diagnostic imaging with therapy, are being investigated for real-time tumor tracking and personalized treatment (59).

Challenges and Future Perspective

Despite the promising advancements in smart nanocarriers for oral cancer treatment, several challenges must be addressed to facilitate their successful clinical translation (60, 61). One of the primary concerns is biocompatibility and long-term toxicity, particularly for inorganic nanomaterials like gold and silver nanoparticles (62). While many systems show safety in preclinical models, their accumulation in organs and potential immune responses raise concerns for long-term use in humans (63).Scalability and reproducibility of nanocarrier synthesis also present significant hurdles. Producing nanoparticles with consistent size, charge, drug loading efficiency, and release profiles at a large scale remains technically demanding and costly (64). Additionally, regulatory pathways for approval are complex, as nanomedicines often do not fit neatly within existing drug classification frameworks. This slows down their entry into clinical practice (65).Another major barrier is the heterogeneity of oral tumors, which limits the effectiveness of a “one-size-fits-all” approach (66). Future developments must focus on personalized nanomedicine, where treatments are tailored to an individual’s tumor profile, possibly through integration with AI-driven diagnostics and real-time biosensors (67-68). Despite these challenges, the future remains optimistic. Ongoing research and interdisciplinary collaboration between materials scientists, oncologists, and regulatory bodies are critical to overcoming these barriers and unlocking the full potential of smart nanocarriers in oral cancer therapy (69- 71).

Conclusion

The treatment of oral cancer remains a clinical challenge due to the limitations of conventional therapies, including systemic toxicity, poor tumor selectivity, and therapeutic resistance. Smart nanocarriers represent a transformative advancement in targeted drug delivery, offering enhanced specificity, controlled release, and the potential for personalized treatment. These systems utilize both passive and active targeting mechanisms and can be engineered to respond to specific biological or external stimuli, thereby improving drug localization and minimizing off-target effects.

Various types of nanocarriers—such as liposomes, polymeric nanoparticles, dendrimers, and lipid-based systems—have demonstrated encouraging results in preclinical studies. They have successfully delivered a range of therapeutic agents including chemotherapeutics, natural compounds, and genetic materials, often with improved efficacy and reduced toxicity. Some are even entering early-phase clinical trials.

Despite their promise, challenges such as toxicity concerns, manufacturing complexity, and regulatory uncertainty must be addressed. Future research should focus on optimizing these systems for clinical safety, cost-effectiveness, and patient-specific adaptability. The integration of smart nanotechnology with real-time diagnostics and AI-driven analytics holds significant potential to advance the field of oral oncology.

With sustained innovation and cross-disciplinary efforts, smart nanocarriers are poised to become a cornerstone in the next generation of oral cancer therapy.

Declaration of Interest

The authors of this article declared no conflict of interest.

Ethical Considerations

Not applicable.

Authors' Contributions

All authors equally contributed to this study.

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Transparency of Data

In accordance with the principles of transparency and open research, we declare that all data and materials used in this study are available upon request.

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Declaration

In order to correct and improve the academic writing of our paper, we have used the language model ChatGPT.

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