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Chapter 4

Nanoparticles used in oral squamous cell carcinoma

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1 Introduction

Cancer treatment presents a significant challenge because the nonselective destruction caused by therapeutic agents can damage vital organs. Nanotechnology offers potential solutions to overcome the limitations of current therapies. This field is extensively explored for the delivery of anticancer drugs and the targeted treatment of tumors. There is a critical need for new treatment strategies in managing squamous cell carcinoma of the head and neck (HNSCC). Current treatments often result in chemotherapy-related morbidity, localized damage to surrounding tissues through radiation, and disfigurement caused by surgical procedures. Chemotherapeutic agents that can specifically target and accumulate in tumor cells present a promising and appealing alternative to traditional chemotherapy, as they spare normal tissues. For over three decades, anti-tumor drugs administered in vivo have been used as pharmaceutical carriers.

Over the past few decades, traditional treatment approaches like chemoradiotherapy have shown potential for improvement, although they are still far from ideal. Nanotechnology, which involves the characterization, production, and application of nanodrug delivery systems, is now at the forefront of cancer research, with a focus on enhancing diagnostic and treatment methods. Nanomedicine typically refers to the use of nanoparticles for treatment, diagnosis, monitoring, and control of biological systems. The application of various nanomaterials, including those used for drug delivery, DNA therapies, and imaging agents, has attracted growing interest in the field (Afrasiabi et al., 2021; Chen et al., 2023; Choi et al., 2021; Cui et al., 2023).

Throughout history, humans have extensively used plant-based natural products as remedies for various illnesses. Modern pharmaceuticals are largely derived from herbs, drawing on traditional knowledge and practices. Recently, there has been a growing focus in natural product-based drug discovery on developing synthetically adaptable lead molecules that replicate the chemical properties of their natural counterparts. Nanotechnology provides several advantages in treating chronic diseases by enabling site-specific and targeted delivery of precise medications. In recent times, there have been numerous remarkable applications of nanomedicine, including the use of chemotherapeutic agents, biological agents, and immunotherapeutic agents, in the treatment of various diseases. This review offers a comprehensive update on the latest advancements in nanomedicines and nano-based drug delivery systems, highlighting the role of nanomaterials in enhancing the efficacy of both new and existing drugs (such as natural products) and enabling targeted diagnosis through disease markers.

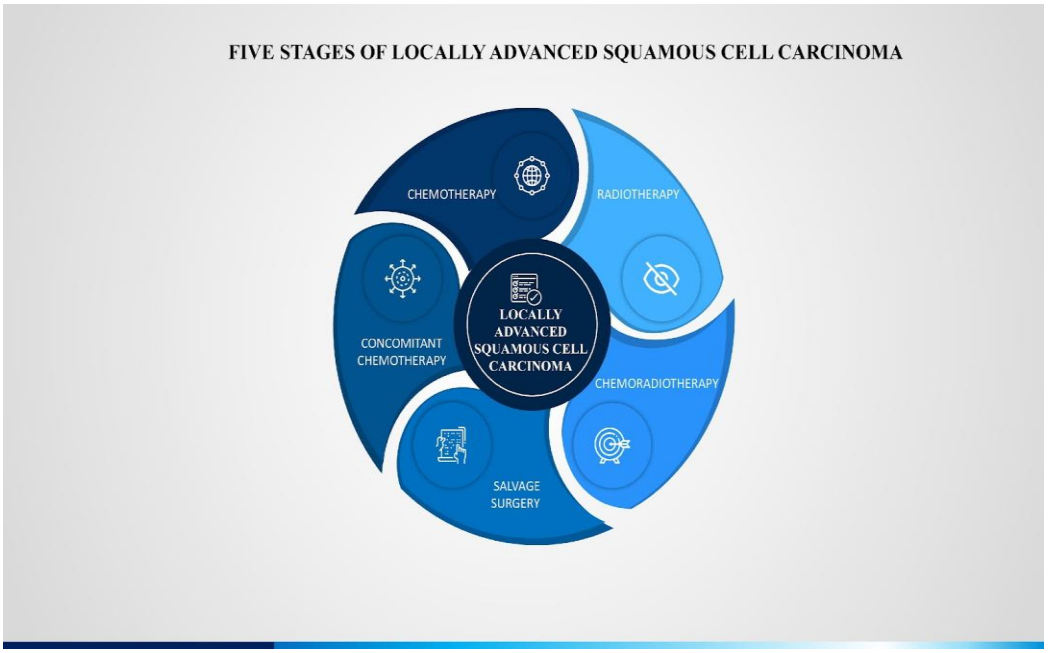
2 The Locally advanced Oral Squamous Cell Carcinoma

The introduction of checkpoint inhibitors has brought significant advancements in treating patients with recurrent or metastatic squamous cell carcinoma of the head and neck (Dong et al., 2022; Elsaady et al., 2023; Li et al., 2023; Lin et al., 2021). For locoregionally advanced disease, which is considered potentially curable, the combination of chemotherapy and radiotherapy (chemoradiotherapy) continues to be the standard organ-preserving approach. However, treatment outcomes for locoregionally advanced squamous cell carcinoma of the head and neck, often linked to alcohol and tobacco use, remain unsatisfactory. Locally advanced disease is characterized by higher T stages (T3 and T4) and extensive neck involvement (N2 or higher). While nonsurgical organ-preservation strategies have gained prominence, primary and salvage surgeries remain crucial options in managing primary head and neck cancers.

3 Nano based drug delivery systems containing anti-cancer agents

Chemotherapy and radiotherapy are widely utilized in treating and managing Oral Squamous Cell Carcinoma (OSCC) (Nour et al., 2022; Park et al., 2021; Sa et al., 2024; Wang et al., 2021). However, it is crucial to balance their efficacy with potential safety risks. Nanotechnology presents exciting possibilities for overcoming the drawbacks of these traditional treatments. This emerging field is rigorously researched for its capability to enhance the administration of anticancer drugs and improve precision in targeting

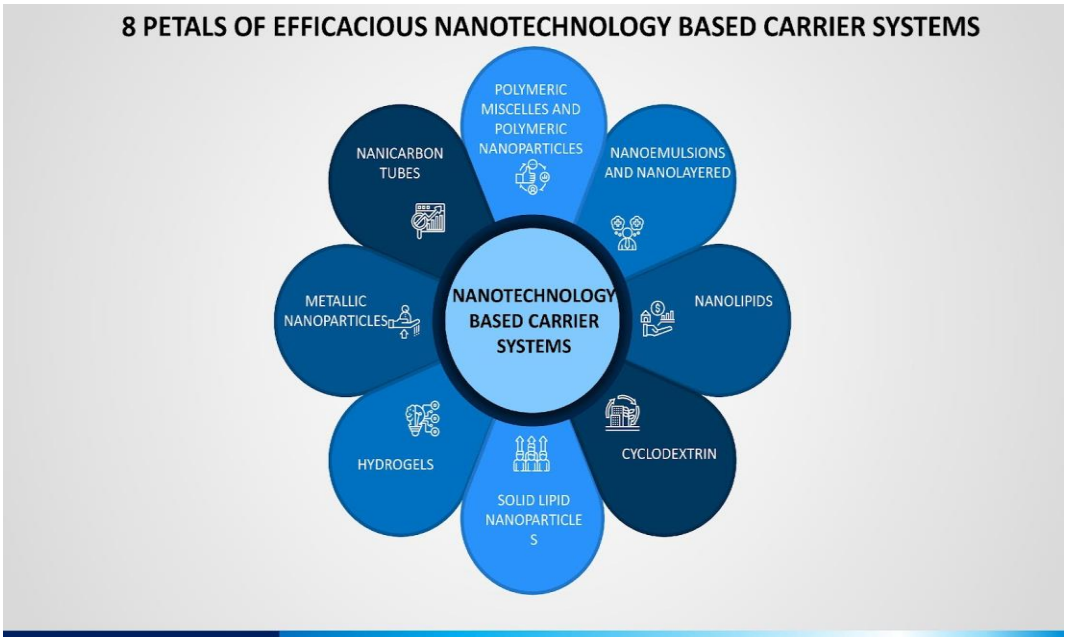
tumors. A variety of nanotechnology-based delivery systems are currently being explored for their precise cancer cell targeting capabilities. These systems include polymeric nanoparticles, polymeric micelles, nanoemulsions, layered nanoemulsions, nanoliposomes, solid lipid nanoparticles, nanolipid carriers, cyclodextrin complexes, hydrogels, metallic nanoparticles, carbon nanotubes, and receptor-mediated drug delivery systems, among others.



3 Nano based drug delivery systems containing anti-cancer agents

Chemotherapy and radiotherapy are prevalent methods for treating and managing Oral Squamous Cell Carcinoma (OSCC). However, it is crucial to balance their efficacy against potential safety risks (Yan et al., 2022; Zhou et al., 2021; Zhou et al., 2022). Nanotechnology presents innovative approaches that could overcome the drawbacks of traditional treatments. This burgeoning area is actively researched for its capabilities to enhance the administration of anticancer drugs and improve the precision of tumor targeting. A variety of nanotechnology-derived delivery systems are currently being explored for their precise cancer cell targeting capabilities. These systems range from polymeric nanoparticles and micelles to nanoemulsions, layered nanoemulsions,

nanoliposomes, solid lipid nanoparticles, nanolipid carriers, cyclodextrin complexes, hydrogels, metallic nanoparticles, carbon nanotubes, to receptor-mediated drug delivery systems.



4 Carriers for Oral Squamous Cell Drug Delivery Systems

A. Polymeric Nanoparticles

Polymeric nanoparticles are minuscule structures, generally measuring between 10 and 100 nm, crafted from polymers that are either biodegradable or biocompatible. These nanoparticles are essential for the targeted delivery of medications used in cancer therapies. A variety of biodegradable polymers such as polyethylene glycol (PEG), polylactic acid (PLA), poly(D,L-lactide), poly(D,L-glycolide), poly(lactide-co-glycolide) (PLGA), polycyanoacrylate, chitosan, gelatin, and sodium alginate are frequently utilized in their production. Numerous methods like in situ polymerization, ionic gelation, double emulsification, spray drying, emulsion/solvent evaporation, emulsion cross-linking, thermal cross-linking, reverse micellar techniques, and supercritical fluid technology are used in their fabrication. Within these particles, anticancer medications are either dissolved, dispersed, encapsulated, or bound to the polymer matrix, creating a depot for sustained release.

B. Nanoemulsion

Nanoemulsions are thermodynamically stable, homogenous mixtures of two immiscible liquids—typically oil and water—forming a single phase with droplet sizes from roughly 0.5 to 100 µm. The oil component in nanoemulsions acts as a solubilizer for hydrophobic drugs, enhancing their solubility and allowing for reduced dosages compared to aqueous systems. Authors engineered a multi-layer nanoemulsion for buccal administration intended for the treatment of oral cancers. This formulation was later converted into a mucoadhesive buccal tablet that provided prolonged and localized release of antimitotic nanomedicines. The nanoemulsions were formulated using a blend of polyethoxylated emulsifiers, tocopherol-enriched oil phase, and were loaded with genistein. Table 1 shows various types of nanoparticles used in the treatment of Oral Squamous Cell Carcinoma (OSCC).

Table 1 Various types of nanoparticles used in the treatment of Oral Squamous Cell Carcinoma (OSCC)

Sr No.	**Nanoparticle Type**	**Material Composition**	**Targeting Mechanism**	**Drug/Agent Delivered**	**Clinical Phase**	**Key Benefits**
1	Liposomes	Lipid bilayer	Passive targeting (Enhanced Permeability and Retention effect)	Chemotherapeutics (Doxorubicin)	Phase II	Reduced systemic toxicity, enhanced drug accumulation in tumor cells
2	Solid Lipid Nanoparticles	Lipids	Passive targeting	Paclitaxel	Preclinical	Improved solubility and bioavailability of hydrophobic drugs
3	Polymeric Nanoparticles	Polylactic-co-glycolic acid (PLGA)	Active targeting (ligands for cancer markers)	Cisplatin	Preclinical	Controlled drug release, targeted drug delivery
4	Gold Nanoparticles	Gold	Active targeting	siRNA, gene therapy	Preclinical	High precision targeting,

			(Antibodies or peptides)			photothermal therapy potential
5	Dendrimers	Polyamidoamine (PAMAM)	Active targeting (surface modifications)	Methotrexate	Preclinical	High drug load capacity, multiple functional groups for conjugation
6	Magnetic Nanoparticles	Iron oxide	Magnetic targeting	Hyperthermia therapy	Phase I	Remote control targeting, localized hyperthermia
7	Quantum Dots	Semiconductor crystals	Fluorescence imaging	Imaging for surgery guidance	Preclinical	Real-time tumor imaging, high luminescence
8	Ceramic Nanoparticles	Silica, alumina	Passive targeting	Radio-sensitizers	Preclinical	Enhanced radiation therapy effectiveness, low reactivity
9	Mesoporous Silica Nanoparticles	Silica	Drug reservoirs	Chemotherapeutics (5-Fluorouracil)	Phase I	High drug loading capacity, controlled release
10	Albumin Nanoparticles	Human serum albumin	Active targeting (gp60 receptor)	Taxanes	Phase II	Natural biocompatibility, enhanced permeability

C. Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLNs) are colloidal delivery systems with particle sizes between 50 and 1000 nm. These carriers consist of a solid lipid core that solubilizes lipophilic drugs. The core is made from various lipids such as monoglycerides (e.g., glycerol monostearate), diglycerides (e.g., glycerol behenate), triglycerides (e.g., tristearin), fatty

acids (e.g., stearic acid), steroids (e.g., cholesterol), and waxes (e.g., cetyl palmitate), which maintain a solid state at ambient temperatures. To stabilize the core, SLNs may include lipophilic surfactants like Span series or hydrophilic surfactants such as poloxamers and tween series.

D. Nanolipid Carriers

Nanolipid carriers (NLCs) emerged as an advanced alternative to solid lipid nanoparticles (SLNs) to overcome limitations such as limited drug capacity, potential degradation during processing, drug leakage, and uneven release dynamics. NLCs feature a matrix of solid lipids with integrated liquid lipid compartments, which helps in preventing lipid crystallization and enhancing drug encapsulation and release dynamics. The inclusion of minor amounts of liquid lipids enhances the efficiency of drug loading, addressing issues like drug resistance and dose-dependent toxicity through surface modification of the NLCs.

5 Nanocarrier based drug delivery systems

Treating cancer presents a significant challenge due to the nonselective action of therapeutic agents, which can damage vital organs. While conventional treatments like chemotherapy and radiotherapy are widely accepted for managing and treating OSCC, their benefits must be carefully weighed against potential risks to ensure safety.

Nanotechnology offers promising solutions to overcome the limitations of these traditional therapies. This rapidly advancing field is extensively researched for its ability to deliver anticancer agents and specifically target tumors. A variety of effective nanotechnology-based carrier systems are under investigation, including polymeric nanoparticles, polymeric micelles, nanoemulsions and layered nanoemulsions, nanoliposomes, solid lipid nanoparticles, nanolipid carriers, cyclodextrin complexes, hydrogels, metallic nanoparticles, carbon nanotubes, and receptor-mediated drug delivery systems.

Although these nanoscale structures are much smaller than a single cell, they are large enough to carry multiple functional groups that can attach to the cell surface. This capability allows for modifications to the cell's surface properties and alters the distribution patterns, making them highly effective for targeted cancer therapy.

6 Nanomaterial based photodynamic therapy for oral squamous cell carcinoma

Photodynamic therapy represents an innovative method currently under investigation for treating oral squamous cell carcinoma (OSCC). Initial small-scale clinical trials have indicated its effectiveness against epithelial premalignant conditions and superficial cancers. Treatments typically involve the application of hematoporphyrin derivatives, their conjugates, or 5-ALA104 either topically or via the intravenous route. These substances function as photosensitizers that selectively target malignant cells. The activation of these photosensitizers is triggered by exposing the affected tissue to a certain light wavelength. Upon activation, the photosensitizer conveys its energy to oxygen molecules, resulting in the production of reactive oxygen species that damage the tissue. Despite its potential, the major drawback of this therapy is cutaneous photosensitivity; however, newer agents like 5-ALA have shown to minimize this side effect.

Although promising, the application of photodynamic therapy is restricted by factors such as the depth, size, and location of the tumor. To address these limitations, our research explores the combination of photodynamic therapy with lipid platinum chloride nanoparticles (NPs) administered after the initial treatment. Lipid platinum chloride NPs, a formulation of cisplatin using liposomes as carriers, have demonstrated significant tumor suppression in various types of cancer. These nanoparticles are characterized by their ability to release platinum transiently for 3-4 hours and sustainably thereafter, benefiting from the neighboring effect. Administering photodynamic therapy prior to lipid platinum chloride NPs aims to create a potent cytotoxic environment that boosts the effectiveness of subsequent chemotherapy.

This enhancement is supported by the SUPR effect observed after photodynamic therapy. Our prior studies also indicated that pre-treatment with photodynamic therapy before gene silencing could improve therapeutic outcomes. In this context, our findings are pioneering, showing that the combination of photodynamic therapy with lipid platinum chloride nanoparticles substantially increases treatment efficacy while reducing the adverse effects associated with chemotherapy.

7 Metal Nanoparticles in Oral squamous cell carcinoma

A diverse array of metal nanoparticles, including gold nanoparticles, nanocages, silver nanoparticles, and superparamagnetic nanoparticles, have been extensively explored for their therapeutic potential in anti-inflammatory treatments and wound healing. Among

these, SPIONs (superparamagnetic iron oxide nanoparticles) have gained recognition as promising candidates for various biomedical applications. Their nanoscale size and distinctive paramagnetic properties enable these particles to accumulate effectively at tumor sites.

However, the use of platinum-based nanoparticle compounds, such as those containing cisplatin, is often limited due to associated organ toxicity. To address this limitation, platinum nanoparticles coated with Ptbeads nanocomposites have shown encouraging results in the treatment of oral squamous cell carcinoma.

Gold nanoparticles, characterized by their vivid red color, exist in multiple forms, including gold nanocages, nanoshells, solid nanoparticles, and colloidal nanoparticles, and have attracted significant interest in cancer research. Additionally, gold and silver nanoparticles have been successfully used to create arrays for detecting the serum biomarker p53, a key indicator in head and neck squamous cell carcinoma.

Conclusion

This chapter highlights the diverse types of nanoparticles utilized in the treatment of oral squamous cell carcinoma. Among the various nanoparticle-based systems explored, drug delivery systems have proven to be particularly critical in supporting radiotherapy and chemotherapy. Within these systems, polymeric micelles play a key role as receptors. Additionally, several carriers have emerged as essential for drug delivery in squamous cell carcinoma, including polymeric nanoparticles, nanolipid carriers, solid lipid nanoparticles, and nanoemulsions. These carriers are central to advancing targeted and effective therapeutic approaches.

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