NANOTECHNOLOGY-BASED DRUG DELIVERY IN ORAL CANCER THERAPY

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Review article

**Abstract:** Oral cancer, which affects the oropharynx and oral cavity, is an often aggressive disease that can metastasize, penetrate local tissue, and have a high fatality rate. Over the past few decades, traditional therapeutic approaches like surgery and chemoradiotherapy have improved, but they are still far from ideal outcomes. Nanotechnology, which entails the design, characterization, fabrication, and use of nanoscale drug delivery systems, is the current focus of cancer research to improve cancer detection and treatment approaches (oral cavity and oropharynx). Nanotechnologies, such as liquid crystals, hydrogels, cyclodextrin complexes, solid lipid nanoparticles, gold nanoparticles, and polymeric nanoparticles, are potential instruments for diagnostic probes and therapeutic devices in medicine. This study's goal is to provide an overview of oral cancer treatment delivery methods based on nanotechnology**.**

**Keywords:** nanotechnology, nanoparticles, oral cavity and oropharynx cancer

Any unchecked cell proliferation that invades and harms adjacent tissue is referred to be cancer. Oral cancer can be detected by small, odd, inexplicable growths or sores on the tongue, lips, cheeks, palate, sinuses, and base of the mouth that extend to the oropharynx.1 More than 90% of all oral cancer types start in the squamous cells lining the inside of the mouth. Other forms, such as partial malignancies of the salivary glands, sarcomas, odontogenic malignancies, melanoma, and lymphoma, account for less than 10% of oral cancer cases. About 1% of metastatic tumors are caused by malignancies of the lung, breast, prostate, and kidney.2

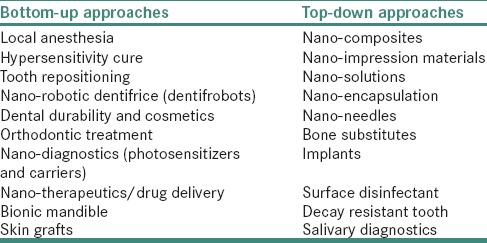
Head and neck cancer (HNC) is the seventh most common malignancy in the world, accounting for more than 660,000 new cases and 325,000 fatalities annually. Given the risk factors, this disease appears to be becoming more common, and plausible aetiological changes are being proposed, particularly in industrialized countries. Due to an increase in incidence and consistent survival rates over the previous ten years, mortality rates have started to increase.3

India accounts for one-third of the global burden and the bulk of mouth cancer cases.1 The three primary ways of treating cancer are chemotherapy, radiation therapy, and surgery. Cut, burn, and poison therapy, which is still the most effective treatment for oral cancer(OC), cripples the immune system. Although they have their benefits, traditional medicines also have toxins in them. Developments in the non-surgical treatment of OC have mostly concentrated on these two goals, which are to preserve organs and reduce long-term morbidities.4

Nanotechnology: What Is It?

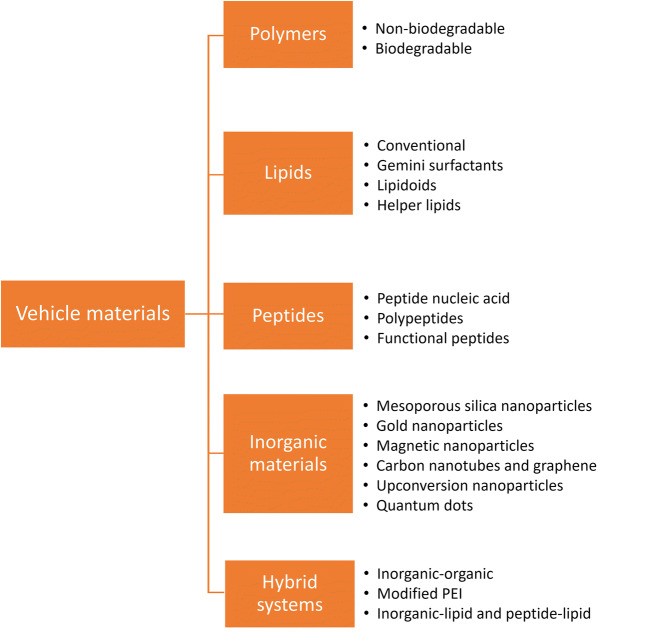
In nanotechnology, we look for ways to use tiny devices to carry out tasks that are now done by hand or with equipment. Nanoassemblers are microscopic machines that can have their actions controlled by a computer. The nanoassemblers can fit into locations that are challenging for the human hand or other equipment to reach since they may be smaller than a cell nucleus.4. Nanoparticles are used to diagnose and treat oral squamous cell cancer (OSCC). They are used in extremely precise biosensors for diagnosis, which convert biological signals into electrical impulses to find signal molecules. Using oral fluid nanosensor assays, the multiplex detection of salivary biomarkers of OSCC is also accomplished.

**Approaches to create nanostructures :**



**NANOTECHNOLOGY IN THE TREATMENT OF ORAL CANCER** :

It demonstrates a huge potential for improving cancer treatments by operating on at least two levels: giving a pharmaceutical agent new qualities (changed pharmacokinetics, greater stability, decreased toxicity, etc.), and directing the agent directly to the tumor.



Biodegradable Polymers

To be chemically degradable, biodegradable polymers have either hydrolytically or proteolytically labile bonds in their backbone. While bio erodible polymers cause erosion of the polymer due to the dissolution of connecting chains without changing the chemical structure of the molecule, biodegradable polymers break due to the cleavage of covalent connections between them. There are currently two different forms of biodegradable polymers: synthetic and natural polymers. Two naturally occurring biodegradable polymers, collagen, and gelatin, are mostly utilized in pharmaceuticals. To make gelatin suitable for a drug delivery system, glutaraldehyde is used to cross-link it. In addition, synthetic biodegradable polymers like polyethylene glycol, polyvinyl alcohol, poly(isobutyl cyanoacrylate), poly(phosphazenes), poly(caprolactone), poly(anhydride), poly(phosphodiester), poly(cyanoacrylates), and poly(acrylic acid) are present. Among these, PLGA, the copolymer of PLA and PGA are the most used polymers in drug delivery.5,6

Non-biodegradable Polymers :

Diffusion-controlled systems frequently use non-biodegradable polymers. In diffusion-controlled systems, there is no first burst release because of nonbiodegradable polymers. The drug's release kinetics from the diffusion-controlled system are determined by the polymer's permeability, thickness, solubility, and release area. The main ingredients in medication formulations include silicone, cross-linked polyvinyl alcohol, and ethyl vinyl acetate. Silicones can be employed as materials that are permeable or impermeable. The grade and thickness of the silicone substance are what determine its permeability or impermeability. If the polymer is not biodegradable, it must be prevented from building up inside the body, and if it is, the broken components must be below the renal threshold level, nontoxic, and should not produce any immune response.5,6.

**Conventional Lipids :**

Colloidal carriers called lipid-based nanoparticles are made of lipids that are solid at body temperature. Drug release is delayed as a result of the usage of solid lipids. Drug diffusion to the surface is challenging due to the drug's inclusion in a solid matrix. Conventional lipids have one head group per molecule, which may or may not be irreversibly charged. Common head groups include ammonium, imidazolium, pyridinium, lysine, or arginine. The hydrophobic tails can be made composed of steroids or two saturated or unsaturated hydrocarbon chains. Heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate (DLin-MC3-DMA) is regarded as the "gold standard" for siRNA delivery due to its superior gene silencing activity in comparison to its rivals.7

**Gemini Surfactants  :**

The surface modification of these nanocarriers also reduces the immunogenicity of drug-carrier complexes, provides stealth by delaying opsonization and phagocyte clearance, and minimizes interaction with blood components in circulation. Gemini surfactants are a subclass of lipids that have recently shown promise as gene carriers. They are two surfactant monomers connected at the head groups by covalent bonds created by a spacer group. Gemini surfactants often have lower CMC than similar surfactant monomers, which lowers surface tension and increases solubilization capacity, among other benefits. Because of this, the delivery method uses less of this carrier, which lowers the toxicity. The viability of a mPEG urethane gemini surfactant as a means of delivering curcumin was investigated. 8,9

**Lipidoids :**

By mixing amines with lipophilic acrylates, acrylamides, or epoxides, lipidoids are lipid-like molecules produced. Lipidoids have become more and more popular due to their simple production process without the usage of catalysts or solvents. This simple and rapid synthesis allows the screening of a vast library of lipidoids with different topologies.9

**Helper Lipids :**

To stabilize the RNA delivery system, extensive study has demonstrated that lipid nanoparticles typically contain other lipid nanomaterials in addition to cationic or ionizable lipids, such as phospholipids, cholesterol, and polyethylene glycol lipids. In lipid-based gene delivery techniques, "helper lipids" are routinely utilized to improve transfection efficiency, stabilize particles, or promote intracellular trafficking. Helper lipids are neutral compounds as opposed to cationic and ionizable lipids. 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), whose cone-like molecular shape promotes membrane fusion and/or bilayer disintegration, is one of the most well-known helper lipids. Additionally, because it can increase cell membrane fluidity and stabilize bilayer lipids, cholesterol is used as a helper lipid in liposome formulations. This results in increased efficacy and stability.10,11

**Peptides/Proteins :**

There are more artificial peptides that can be delivered orally. CSKSSDYQC (CSK) peptide is widely utilized to increase the hypoglycemic effect since it can target goblet cells. Functional peptide-conjugated transferrin receptor-specific nanocarriers improved transcytosis, altered intracellular trafficking, and increased intracellular absorption in polarized cells for targeted oral drug delivery, according to Du et al. Dendrimers, which can contain any combination of the three units—the core, the branches, and the dendrimer surface—and use amino acids as their building blocks, can also be created from polypeptides. Peptide dendrimers may provide the positively charged groups that genetic material needs to complex with them, the ability to penetrate biological membranes, and the endosome-avoiding buffering capacity.12

**Mesoporous silica nanoparticles (MSN):**

Drug loading in the following areas is feasible with highly cytocompatible MSNs: 1) In combination with other drugs to improve their inadequate efficacy and simultaneously offer responsive drug delivery. 2) Provide a centralized nano platform of drugs that can be combined to treat infectious diseases and biofilms while avoiding drug resistance. 3) Provide diverse medications to address conditions like tumors and dental hypersensitivity utilizing a common nano platform. 4) Due to their favorable surface properties and porosity, MSNs have been demonstrated to be promising bioactive materials for bone regeneration. Recent scientific advances have focused on the biological applications of MSNs in stomatology, including antibiofilm, anticancer, decreasing dentin sensitivity, and encouraging osteogenesis for bone regeneration. 13,14

**Gold nanoparticles :**

First off, a range of morphologies and structures, such as nanospheres, nanorods, nanowires, and nanowarrows, among others, can be used to make nanoparticles. Each of these has unique qualities, attributes, and applications. Second, AuNPs can be constructed of pure gold, composites (grafted with polyethylene glycol, cysteine, etc.), or doped with other metals to form new hybrid materials that can be further coated, functionalized, or coupled with pharmaceuticals or other compounds for cell targeting and drug administration. Targeting the overexpressed folate receptors in cancer cells, the combination of AuNPs with folic acid ligands and the prospective anti-cancer medication bilirubin kills multidrug-resistant oral cancer cells in vitro. Furthermore, Xia C et al. discovered that the size of AuNPs influences their anti-tumor effects, and their findings demonstrate that ultrafine AuNPs (3 nm in diameter) can successfully stop OSCC tumor growth in vivo.15

**Magnetic nanoparticles**:

Because magnetic nanoparticles can be rendered functional by binding to a range of molecules, including chemotherapeutic medicines, radionuclides, nucleic acids, and antibodies, the drug delivery systems offer the greatest promise. Then they can be gathered and directed using a magnetic field. The induction of hyperthermia using an alternating magnetic field is another therapy strategy. Magnetic nanoparticles may be used to combat cancer drug resistance. Additionally, they support the development of the "theranostics" industry, which combines diagnostic study with therapeutic intervention.16

**Carbon Nanotubes (CNTs):**

To make NTs, which are hollow tubes, graphene sheets are rolled into cylindrical shapes. There are six different types of CNTs: torus, nano flower, nano bud, fullerites, and multi-walled (MWCNT). Due to their distinctive structures and characteristics, such as high aspect ratios, incredible strength, ultralightweight, large surface areas, rich surface chemical functionalization, significant electronic and thermal properties, and size stability, they have been widely used in the field of nanotechnology. As one of the most innovative and adaptable nano vectors, theranostics, and cutting-edge drug delivery techniques for highly effective transport of genes, medications, and biomolecules, as well as for bioimaging and biosensor applications, the therapeutic uses of CNTs were reevaluated by Mangla Bharti et al. in 2020.17

**Quantum Dots (QDs):**

These nano-crystals are made up of a semiconductor shell surrounding a semiconductor core. As a result of their distinctive optical properties, QDs are attractive carriers for biomedical applications. Through coupling, adsorption, dispersion, dissolution, and dissolution, drugs can be loaded onto QD nanocarriers. To improve the physicochemical properties of medicines, QDs nanocarriers increase medicinal efficacy and therapeutic index, encourage drug molecule absorption, and reduce side effects. The ability of QDs to connect to the proteins of cancer cells and glow incredibly brightly under UV light makes it easy to identify the locations of tumors. Drug particle detection and cellular absorption are both improved by QDs.18

**Upconversion nanoparticles**:

Because Au NPs on the surface could be easily changed to absorb the NIR, clinical evidence showed that near-infrared (NIR) laser light might enable effective delivery of anti-EGFR/Au conjugates into the malignant cells with deep penetration. In vitro tests showed that OSCC cells could create photothermal destruction for anti-EGFR/Au conjugates without needing a lot of energy. utilizing PEGylated Titanium Dioxide (TiO2) as an encapsulant, Lucky et al. created a type of biocompatible up-conversion nanoparticle that improved tissue penetration utilizing NIR and efficiently targeted the EGFRs on the surface of OSCC cells to prevent tumor growth.17

**Inorganic nanoparticles :**

This type of NP is devoid of both carbon and organic components. Ceramics, metals, and semiconductors are the most typical applications for this type of material. Metal NPs, which can be mono-, bi-, or poly-metallic, are only created from metal antecedents. To make bimetallic NPs, alloys or several layers (core-shell) can be employed. Materials with characteristics that fall somewhere between those of metals and nonmetals are used to create semiconductor NPs. These NPs exhibit significant property changes with bandgap tuning and have distinct broad bandgaps when compared to bulk semiconductor materials. The inorganic solids referred to as ceramic NPs are made up of metal and metalloid oxides including calcium and titanium, as well as carbonates, carbides, and phosphates.19

**Combinational (Polymeric-Inorganic) Nanoparticles :**

One of the more sophisticated therapeutic advantages of combination medicine therapy is the targeted drug delivery approach that permits the decrease of toxicity and improvement of therapeutic efficacy. By combining chemo-photothermal therapy with vincristine (VCR), a phytochemical anticancer, and plasmonic gold nanorods (GNRs), photothermal reagents, Darwish et al. successfully treated OSCC. When the amide linkages were broken, resulting in the prolonged VCR release under acidic intracellular circumstances, the generated combinational therapeutic nanoprobes were demonstrated as promising candidates for prospective clinical translation.20

**Liposomes :**

The main components of liposomes are phospholipids, cholesterol, and a lipid that resembles a membrane. Liposomes are a collection of single- or multi-layered tiny particles. Liposomes, which are non-toxic to healthy tissues or cells, are the most widely used drug delivery technique to increase drug accumulation at target areas. This technique has received a lot of attention since it combines highly effective therapy with the administration of medication release. These LVs could sustain stability in solutions for more than 50 days. The LVs made bonds with AlClPc molecules because of the special interactions between aluminum and phosphate, which allowed them to disseminate in cellular organelles and undergo a process of disaggregation after being absorbed by the OSCC. This knowledge could provide the basis for a more thorough investigation.20

**Cyclodextrins :**

When starch is broken down by enzymes, cyclic oligosaccharides called cyclodextrins (CD) are created. CD can interact with hydrophobic substances like the anticancer drugs docetaxel, cisplatin, methotrexate, and paclitaxel to form complexes. To greatly improve the solubility and oral bioavailability of two curcuminoids, Wang et al. created soluble supramolecular complexes using phospholipid compound technology and a hydroxypropyl-beta-cyclodextrin (HP--CD) inclusion technique.21

**Hydrogels :**

Due to their three-dimensional (3D) porosity and linked structures, hydrogels have many unique advantages on the targeted drug delivery systems in addition to providing a biocompatible environment for cell adhesion and proliferation. Localized application, a feature of targeted drug delivery systems, enables direct implantation of different hydrogel formulations into the region of an injury or lesion as opposed to intravenously injecting small nanoparticles into the bloodstream. In this situation, hydrogel carriers can modify the hydrogel topologies, network pores, and gelation processes (physical and chemical gelation) to modify the drug release times for a lengthy period (a few months).22

**Biomimetic Nanoparticles :**

The low drug payloads, oral bioavailability, and transport efficiency of natural or synthetic materials utilized as targeted drug carriers for therapies are still significant concerns that need to be solved. Here, biomimetic approaches are investigated to emphasize the structure of biomimetic carriers to enhance the bioavailability and targeting capacity of therapeutic drugs.23

**Vitamin-Coated Nanoparticles :**

Vitamin B12 (VB12) can interact with an intrinsic factor to form a complex in the stomach because of the receptor-mediated endocytosis absorption pathway. This complex is easily transformed into nanoparticles to improve oral administration. For instance, Chalasani et al. found that covalent attachment of VB12 to insulin-loaded dextran led to a higher pharmacological availability compared to the pure nanoparticles in streptozotocin-induced diabetic rats. Similar to this, VB12-modified nanoparticles composed of trimethyl chitosan or calcium phosphate improved the oral absorption of insulin.23

**Exosomes :**

Many different types of cells, such as dendritic cells, macrophages, mesenchymal stem cells, endothelial cells, and epithelial cells, produce exosomes. Exosomes have recently received a lot of attention from researchers for application in biology because of their diverse nanosized dimensions and natural creation. Exosomes are crucial when delivering various biomolecules or chemotherapeutic drugs for intercellular exchange. This is because they have excellent adhesion properties to cell membranes, which suggests that they might make a unique delivery system for specific drugs.23

**Virus-Like Particles (VLPs) :**

When viral capsids or envelope proteins made by viruses self-assemble, VLPs are frequently formed. Due to the surface biophysical and chemical properties, VLPs are easily manipulated by modifying VLP proteins through genetic and chemical engineering. Although the effectiveness of VLPs as oral antigen carriers in immunization has been widely studied, it is still unclear whether they have superior delivery capabilities in other treatments for oral cancer.24

**Nanovectors for gene therapy:**

Gene delivery, transfection, and gene expression regulation are the three primary facets of gene therapy. Cationic polymers have long been regarded as an essential type of non-viral gene therapy vector due to their adjustable chemical structure and potential for high loading capacity. By neutralizing the negatively charged genetic material and transferring the payload to the desired cells, they can produce a complex (polyplex). Neves et al. have investigated the peptide RALA/p53 encoding pDNA vectors at various nitrogen-to-phosphate group (N/P) ratios.24

**Future trends :**

**Cancer nano vaccines:**

Prophylactic vaccines are the oldest type and are given to healthy people to prevent cancer. They stimulate humoral and cellular immunity. A preventive vaccine is the human papillomavirus vaccine. A second kind of vaccine called the cancer Nanovaccine is available for people who already have the disease. They might be created, produced, and injected into the body of a person to enhance health, including molecular cellular repairs. Due to the Nanovaccine's small size and ease of cell entry, contrast agents, diagnostic instruments, analytical tools, the use of physical therapy, and drug delivery systems have all advanced as a result. Placing the active ingredient at the desired location can significantly reduce drug consumption and its associated negative effects.

**Smart polymers** :

Smart synthetic polymers used in cancer immunotherapies were discussed in three aspects: enzyme-, pH-, and redox-responsive.  Studies indicate that smart polymeric nanoparticles could improve tumor immunotherapy, relieve immunosuppression, and prevent cancer cells from escaping the immune system. Smart stimulus-responsive synthetic biopolymers may help with tumor immunotherapy.7

**Conclusion :**

With an unacceptable high fatality rate, oral cancer is the sixth most prevalent cancer and negatively impacts people's health. Despite using a variety of clinical techniques (such as surgery, chemoradiotherapy, computed tomography, and magnetic resonance imaging), the diagnosis and treatment of oral cancer are still far from ideal. Therefore, there is a pressing need for efficient and doable methods for the early detection and treatment of oral cancer. Different kinds of nanoparticles, which are promising tools for medicinal devices and diagnostic probes, are currently causing widespread public concern. Because of their innate physicochemical characteristics, such as their ultrasmall size, high reactivity, and customizable surface modification, they can get around some restrictions and produce the desired diagnostic and therapeutic results. In this review, we introduce different types of nanoparticles that emerged for the diagnosis and therapy of oral cancers. Then, the challenges and future perspectives for nanoparticles applied in oral cancer diagnosis and therapy are presented.

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