NANOTECHNOLOGY BASED DRUG DELIVERY IN ORAL CANCER THERAPY

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**Abstract:** Oral cancer (oral cavity and oropharynx) is a common and aggressive cancer that invades local tissue, can cause metastasis, and has a high mortality rate. Conventional treatment strategies, such as surgery and chemoradiotherapy, have improved over the past few decades; however, they remain far from optimal. Currently, cancer research is focused on improving cancer diagnosis and treatment methods (oral cavity and oropharynx) nanotechnology, which involves the design, characterization, production, and application of nanoscale drug delivery systems. In medicine, nanotechnologies, such as polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, gold nanoparticles, hydrogels, cyclodextrin complexes, and liquid crystals, are promising tools for diagnostic probes and therapeutic devices. The objective of this study is to present a review of nanotechnology-based drug delivery systems for oral cancers.

**Keywords:** nanotechnology, nanoparticles, oral cancer

Cancer is any uncontrolled cell proliferation that invades and damages nearby tissue. Small, unusual, unexplained growths or sores in the lips, cheeks, sinuses, tongue, hard and soft palate, and the base of the mouth that extends to the oropharynx are signs of oral cancer.1 In the squamous cells that coat the inside of the mouth, more than 90% of different kinds of oral cancer begin. Less than 10% of oral cancers are caused by other types, including partial malignancies of the salivary glands, sarcomas, odontogenic malignancies, melanoma, and lymphoma. Lung, breast, prostate, and kidney cancers account for about 1% of metastatic tumors.2

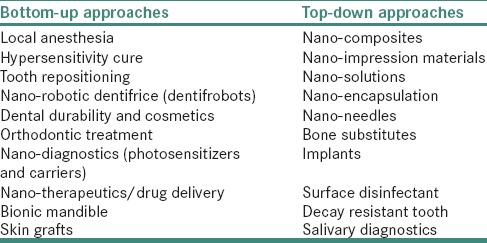
In the world, head and neck cancer (HNC) is the seventh most frequent malignancy, with more than 660,000 new cases and 325,000 fatalities per year. Given the risk factors, there seems to be an increase in the prevalence of this disease, with possible aetiological alterations being hypothesized, especially in industrialized nations. Within the past ten years, mortality rates have begun to rise as a result of increased incidence and stable survival rates.3

The majority of oral cancer cases and one-third of the global burden are found in India.1 As of yet, chemotherapy, radiation therapy, and surgery have continued to be the three main methods for managing cancer. The immune system is crippled by the cut, burn, and poison therapy, which is still the gold standard treatment for oral cancer(OC). Although conventional medicines have their own advantages, they also contain toxins. In order to preserve organs and lower long-term morbidities, developments in non-surgical care of OC have mostly focused on these two objectives.4

Nanotechnology: What Is It?

In nanotechnology, we explore for ways to execute jobs that are now being done by hand or with machinery using nanoscale devices. Nanoassemblers are tiny machines that can be programmed by a computer to carry out specific tasks. The nanoassemblers may be smaller than a cell nucleus, enabling them to enter spaces that are difficult to access with the human hand or other tools.4. oral squamous cell carcinoma(OSCC) is diagnosed and treated using nanoparticles. They are utilized in very accurate biosensors for diagnosis that transform biological signals into electrical impulses in order to detect signal molecules. The multiplex identification of salivary biomarkers of OSCC is also done using oral fluid nanosensor tests.

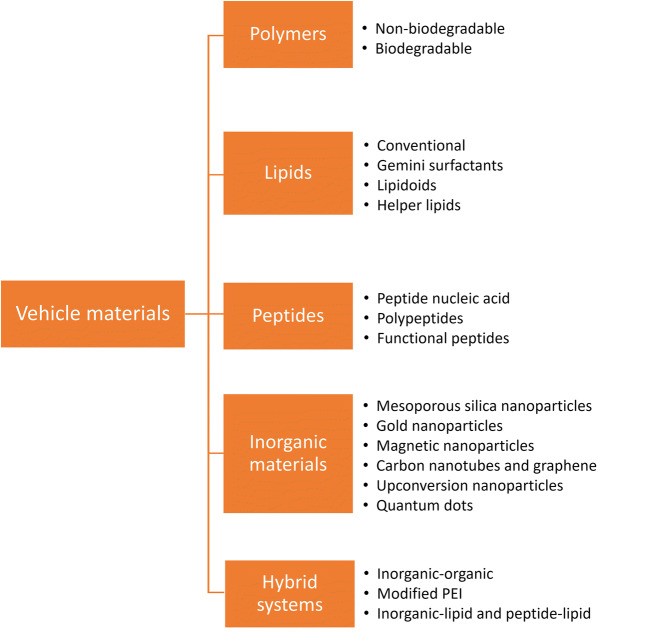
**Approaches to create nanostructures**



**NANOTECHNOLOGY IN 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

Biodegradable polymers have either hydrolytically or proteolytically labile bond in their backbone to make it chemically degradable. Biodegradable polymers break due to cleavage of covalent bonds between them and bio erodible polymers bring about erosion of the polymer due to dissolution of linking chains without bringing about any change in chemical structure of the molecule. At present two types of biodegradable polymers exists: natural polymers and syn- thetic polymers. Collagen and gelatin are two natural biodegradable polymers that are mostly used in drugs. Gelatin is cross-linked with glutaraldehyde to prepare it for drug delivery system. Synthetic biodegradable polymers are also present that include PLA, PLGA, PGA, poly(phosphazenes), poly(caprolactone), poly(anhydride), poly(phosphoesters), poly(cyanoacry- lates), poly(acrylic acid), poly(amides), poly(ortho esters), polyethylene glycol, and polyvinyl alcohol and poly (isobutylcynoacrylate), poly(ethylene oxide), and poly(paradioxane). Among these, PLGA, the copolymer of PLA and PGA are mostly used polymers in drug delivery.5,6

Non-biodegradable Polymers

Non-biodegradable polymers are commonly used in diffusion-controlled system. Due to non biodegradable polymers, there is no initial burst release in diffusion-controlled systems. The permeability and thickness of the polymer, the solubility and the release area of the drug determines the release kinetics of the drug form the diffusion controlled system. Silicone, cross-linked Polyvinyl Alcohol, and Ethyl Vinyl Acetate are mostly used in drug formulations. Silicones are used as permeable or impermeable material. The permeability or the impermeability of the silicone material is decided by the thickness and the grade used. If the polymer is non- degradable it should be ensured that it is not accumulated within the body and if it is degradable the broken components should be such that they lie below renal threshold level, non toxic and should not produce any immune response.5,6

**Conventional Lipids**

Lipid based nanoparticles are colloidal carriers composed of lipids that are solid at body temperature. The use of solid lipids prevents the drug from immediate release. The drug is included in a solid matrix that makes the diffusion of the drug to the surface difficult. Each molecule of conventional lipids has one head group, which may be temporarily or permanently charged. Ammonium, imidazolium, pyridinium, lysine or arginine are a few examples of frequent head groups. Steroids or two saturated or unsaturated hydrocarbon chains can make up the hydrophobic tails. Because of its higher gene silencing activity in comparison to its rivals, heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate (DLin-MC3-DMA) is considered the "gold standard" for siRNA delivery.7

**Gemini Surfactants**

Surface adjustment of these nanocarriers also decreases the immunogenicity of drug-carrier complexes, offers stealth by preventing opsonization and removal by phagocytes, and reduces contact with circulating blood components. Gemini surfactants are a class of lipids that have only lately become effective at delivering genes. They are two surfactant monomers joined by covalent connections at the head groups by a spacer group. In general, gemini surfactants have lower CMC than equivalent surfactant monomers, which leads to reduced surface tension, higher solubilization capacity, etc. As a result, the delivery mechanism requires less of this carrier, which in turn reduces the toxicity. An mPEG urethane gemini surfactant was synthesised and its viability as a curcumin delivery vehicle was examined. This amphiphilic gemini surfactant (GS) is biodegradable, made up of mPEG2000, urethane, quaternary amine, and a hydrocarbon linker. Recent studies have concentrated on clarifying the gemini surfactant's structure in connection to its bioactivity.8,9

**Lipidoids**

Lipidoids are lipid-like compounds created by combining amines with acrylates, acrylamides, or epoxides that are lipophilic . Due to their easy synthesis procedure without the use of catalysts or solvents, lipidoids have grown in popularity. The screening of a large library of lipidoids with a variety of architectures is made possible by this quick and straightforward production.9

**Helper Lipids**

Extensive research has shown that Lipid nanoparticles generally consists of additional lipid nanomaterials besides cationic or ionizable lipids to stabilize the RNA delivery system, such as phospholipids, cholesterol, and polyethylene glycol lipids. "Helper lipids" are frequently used in lipid-based gene delivery methods to increase transfection effectiveness, stabilize particles, or facilitate intracellular trafficking. Helper lipids, as opposed to cationic and ionizable lipids, are neutral substances. One of the most popular helper lipids is 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), whose cone-like molecular structure encourages membrane fusion and/or bilayer breakdown. Additionally, cholesterol is utilized as a helper lipid in liposome formulations because it can improve cell membrane fluidity and stabilize bilayer lipids, leading to increased efficacy and stability.10,11

**Peptides/Proteins for Oral Cancer Therapy**

Additional synthetic peptides are available for oral targeted delivery. Because it can target goblet cells, CSKSSDYQC (CSK) peptide is frequently used to enhance the hypoglycemic impact. According to Du et al., functional peptide-conjugated transferrin receptor-specific nanocarriers boosted intracellular absorption, changed intracellular trafficking, and improved transcytosis in polarized cells for targeted oral drug delivery. Polypeptides can also be formed into dendrimers, which can have any combination of the three units—the core, the branches, and the dendrimer surface—and use amino acids as its building components. Peptide dendrimers might offer the required positively charged groups for the genetic material to complex with, the potential to cross biological membranes, and the buffering power required to avoid endosomes.12

**Mesoporous silica nanoparticles (MSN):**

Highly cytocompatible MSNs make it possible to load drugs in the following fields: 1) Combination with other medications to enhance their subpar efficacy and provide responsive drug delivery at the same time. 2) Offer a shared nanoplatform of medications that can be used in combination to treat infectious illnesses and biofilms while preventing drug resistance. 3) Offer various drugs using a common nanoplatform to treat ailments like tumors and dental hypersensitivity. 4) MSNs have shown to be desirable bioactive materials for bone regeneration due to their good surface characteristics and porosity. The biological applications of MSNs in stomatology, including antibiofilm, anticancer, lowering dentin sensitivity, and promoting osteogenesis for bone regeneration, have been the subject of recent research breakthroughs. 13,14

**Gold nanoparticles**

First off, it is possible to create nanoparticles with a variety of morphologies and structures, including nanospheres, nanorods, nanowires, nanoarrows, etc. Each of which has special characteristics, traits, and uses. Second, to create new hybrid materials that can be further covered, functionalized, or combined with medications or other molecules for cell targeting and drug delivery, AuNPs can be made of pure gold, composites (grafted with polyethylene glycol, cysteine, etc.), or doped with other metals. Multidrug-resistant oral cancer cells in vitro are killed by the combination of AuNPs with folic acid ligands and the potential anti-cancer drug bilirubin by targeting the overexpressed folate receptors in cancer cells. Moreover, Xia C et al. reported the size of AuNPs have influence for the anti-tumor effect and their research prove that the ultrafine AuNPs (3 ​nm in diameter) could effectively inhibit the growth of OSCC tumors in vivo15

**Magnetic nano particles**:

The drug delivery systems have the most potential because magnetic nanoparticles can be made functional by binding to a variety of molecules, such as chemotherapeutic drugs, radionuclides, nucleic acids, and antibodies. A magnetic field can then be used to direct and gather them. Another treatment method is the induction of hyperthermia with an alternating magnetic field. The usage of magnetic nanoparticles could help fight cancer medication resistance. They also aid in the realization of a "theranostics" sector that combines diagnostic research and therapeutic intervention. 16

**Carbon Nanotubes (CNTs):**

Graphene sheets are rolled into cylindrical shapes to create NTs, which are hollow tubes. Six different forms of CNTs exist: single-walled (SWCNT), multi-walled (MWCNT), nano flower, nanobud, fullerites, and torus. They have been widely used in the field of nanotechnology due to their distinctive structures and properties, such as high aspect ratios, tremendous strength, ultra-lightweight, large surface area, rich surface chemical functionalization, significant electronic and thermal properties, and size stability. The therapeutic uses of CNTs were reevaluated by Mangla Bharti et al. in 2020 as one of the most inventive and adaptable nanovectors, theranostics, and cutting-edge drug delivery techniques for very effective transport of genes, medicines, and biomolecules, as well as bioimaging and biosensor applications.17

**Quantum Dots (QDs):**

These nano-crystals consist of a semiconductor core that is encased in a semiconductor-based shell. QDs are promising carriers for biomedical applications due to their unique optical characteristics. Drug loading onto QD nanocarriers can be accomplished through coupling, adsorption, dispersion, dissolution, and dissolution. QDs nanocarriers boost drug efficacy and therapeutic index, promote drug molecule absorption, and lessen negative effects to enhance the physicochemical features of medications. One distinctive quality of QDs is that they bind to the proteins of cancer cells and glow extremely brightly under UV light, making it simple to pinpoint the tumor spots. QDs are more effective at detecting and cellular absorption of drug particles.18

**Upconversion nanoparticles**:

Clinical data demonstrated that near-infrared (NIR) laser light could enable effective delivery of anti-EGFR/Au conjugates into the malignant cells with the deep penetration because Au NPs on the surface could be easily modified to absorb the NIR, thereby achieving the maximum therapeutic effects. In vitro experiments demonstrated that OSCC cells did not require high energy to produce photothermal destruction for anti-EGFR/Au conjugates. Lucky et al. prepared a kind of biocompatible up-conversion nanoparticles with encapsulation of PEGylated titanium dioxide (TiO2), which enhanced tissue penetration using NIR and effectively targeted the EGFRs on the surface of OSCC cells to inhibit the tumor proliferation.17

**Inorganic nanoparticles**

NPs in this category are not composed of neither carbon nor organic compounds. The most prevalent scenarios of this kind of material are semiconductor, metal, and ceramics. Metal NPs are formed exclusively from metal predecessors and can be mono-, bi-, or poly-metallics. Alloys or multiple layers (core-shell) can be used to create bimetallic NPs. Semiconductor NPs are made from materials with properties that are halfway between those of metals and nonmetals. When compared to bulk semiconductor materials, these NPs display considerable property changes with bandgap tuning and have discrete wide bandgaps. The inorganic solids known as ceramic NPs are composed of carbonates, carbides, phosphates, and metal and metalloid oxides such as calcium and titanium.19

**Combinational (Polymeric-Inorganic) Nanoparticles**

The targeted drug delivery method that enables the reduction of toxicity and improvement of therapeutic efficacy is acknowledged as one of the advanced therapeutic benefits of combination medication therapy. Vincristine (VCR), a phytochemical anticancer, and plasmonic gold nanorods (GNRs), photothermal reagents, were used to create a combinational chemo-photothermal therapy by Darwish et al. for OSCC treatment. The produced combinational therapeutic nanoprobes were shown as promising candidates for prospective clinical translation when the amide connections were broken, causing the sustained VCR release under acidic intracellular conditions.20

**Liposomes for Oral Cancer Therapy**

A collection of single- or multi-layered microscopic particles called liposomes have phospholipids, cholesterol, and a lipid that resembles a membrane as their principal ingredients. The most popular drug delivery method to boost drug accumulation at target sites is liposomes, which are non-toxic to normal tissues or cells. This method has drawn substantial attention for the administration of drug release and use of drug delivery with very effective therapy. For more than 50 days, these LVs could maintain stability in solutions. Due to the unique interactions between aluminum and phosphate, LVs formed bonds with AlClPc molecules that could distribute in cellular organelles and go through a process of disaggregation after being absorbed by the OSCC. This information could serve as a starting point for a more in-depth investigation of the intracellular mechanism of PDT for oral cancer in the future.20

**Cyclodextrins**

Cyclodextrins (CD), a kind of cyclic oligosaccharides that are produced when starch is broken down by enzymes, have the ability to interact with hydrophobic guests, such as the anticancer medicines docetaxel, cisplatin, methotrexate, and paclitaxel, to form complexes. Through the use of phospholipid compound technology and a hydroxypropyl-beta-cyclodextrin (HP--CD) inclusion approach, Wang et al. developed a type of soluble supramolecular complexes that significantly increased the solubility and oral bioavailability of two curcuminoids.21

**Hydrogels**

In addition to offering a biocompatible milieu for cell adhesion and proliferation, hydrogels have numerous special benefits on the targeted drug delivery systems due to their three-dimensional (3D) porosity and interconnected structures. The targeted drug delivery systems' unique benefit is localized application, which allows for the direct implantation of various hydrogel formulations into the site of an injury or lesion rather than intravenously injecting tiny nanoparticles into the bloodstream. In this instance, hydrogel carriers can regulate the hydrogel topologies, network pores, and gelation methods (physical and chemical gelation) to adjust the drug release times for a long time (several months).22

**Biomimetic Nanoparticles**

Although natural or synthetic materials have been used as targeted drug carriers for treatments, these materials' modest drug payloads, oral bioavailability, and transport efficiency are still major issues that need to be addressed. In order to improve the bioavailability and targeting ability of therapeutic medications, biomimetic techniques are here researched to highlight the structure-property of biomimetic carriers.23

**Vitamin-Coated Nanoparticles**

Due to the receptor-mediated endocytosis absorption pathway, vitamin B12 (VB12) can combine with an intrinsic factor to form a complex in the stomach, which is easily converted into nanoparticles to increase the effectiveness of oral administration. For instance, Chalasani et al. discovered that utilizing streptozotocin-induced diabetic rats, covalent coupling of VB12 to insulin-loaded dextran led a greater pharmacological availability compared to the pure nanoparticles. Similar to this, the oral absorption of insulin was enhanced by VB12-modified nanoparticles made of trimethylchitosan or calcium phosphate.23

**Exosomes**

Exosomes are secreted by a variety of cells, including dendritic cells, macrophages, mesenchymal stem cells, endothelial cells, and epithelial cells. Because of their various nanosized dimensions and natural formation, exosomes have recently attracted a lot of attention from researchers for use in biology. Exosomes play an important part in the administration of different biomolecules or chemotherapeutic agents for intercellular exchange. This is due of their strong adhesion capabilities to cell membranes, which raises the possibility that they could serve as a novel vehicle for targeted drug delivery applications.23

**Virus-Like Particles (VLPs)**

VLPs are often created when viral capsids or envelope proteins produced from viruses self-assemble. VLPs are easily controlled by changing VLP proteins through genetic and chemical engineering to give their multifunction due to the surface biophysical and chemical properties. Although VLPs have been thoroughly examined for their efficacy as oral antigen carriers in vaccination, it is still unknown whether they have superior delivery qualities in other treatments for oral cancer.24

**Nanovectors for gene therapy:**

The three main components of gene therapy are gene delivery, transfection, and gene expression regulation. Due to its adaptable chemical structure and potential for high loading capacity, cationic polymers have long been regarded as a crucial form of non-viral gene therapy vector. They can create a complex (polyplex) by neutralizing the negatively charged genetic material and delivering the payload to the desired cells. The peptide RALA/p53 encoding pDNA vectors have been examined by Neves et al. at various nitrogen to phosphate group (N/P) ratios.24

**Future trends :**

**Cancer nanovaccines:**

The earliest type, prophylactic vaccines, triggers humoral and cellular immunity and is administered into healthy individuals in order to avoid them from getting cancer. The human papillomavirus vaccine is an example of a prophylactic vaccine. For those who already have cancer, there is a second type of vaccine called cancer Nanovaccine. They could be designed, manufactured and introduced into the human body to improve health, including cellular repairs at the molecular level. The Nanovaccine is so small that it can easily enter the cell; therefore, This has lead to the advancement of contrast agents, diagnostic devices, analytical tools, application of physical therapy and drug delivery vehicles. The consumption of drug and related side-effects can be considerably lowered by depositing the active agent at the preferred location.

**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 :**

Oral cancer is the sixth most common malignant cancer, affecting the health of people with an unacceptably high mortality rate. Despite numerous clinical methods in the diagnosis and therapy of oral cancer (e.g., magnetic resonance imaging, computed tomography, surgery, and chemoradiotherapy), they still remain far from optimal. Therefore, an urgent need exists for effective and practical techniques of early diagnosis and effective therapy of oral cancer. Currently, various types of nanoparticles have aroused wide public concern, representing a promising tool for diagnostic probes and therapeutic devices. Their inherent physicochemical features, including ultrasmall size, high reactivity, and tunable surface modification, enable them to overcome some of the limitations and achieve the expected diagnostic and therapeutic effect. 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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