NANOTECHNOLOGY-BASED DRUG DELIVERY IN ORAL CANCER THERAPY

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

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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.

Bottom-up approaches	Top-down approaches
Local anesthesia	Nano-composites
Hypersensitivity cure	Nano-impression materials
Tooth repositioning	Nano-solutions
Nano-robotic dentifrice (dentifrobots)	Nano-encapsulation
Dental durability and cosmetics	Nano-needles
Orthodontic treatment	Bone substitutes
Nano-diagnostics (photosensitizers and carriers)	Implants
Nano-therapeutics/drug delivery	Surface disinfectant
Bionic mandible	Decay resistant tooth
Skin grafts	Salivary diagnostics

Figure 1: Approaches to Create Nanostructures

I. 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.
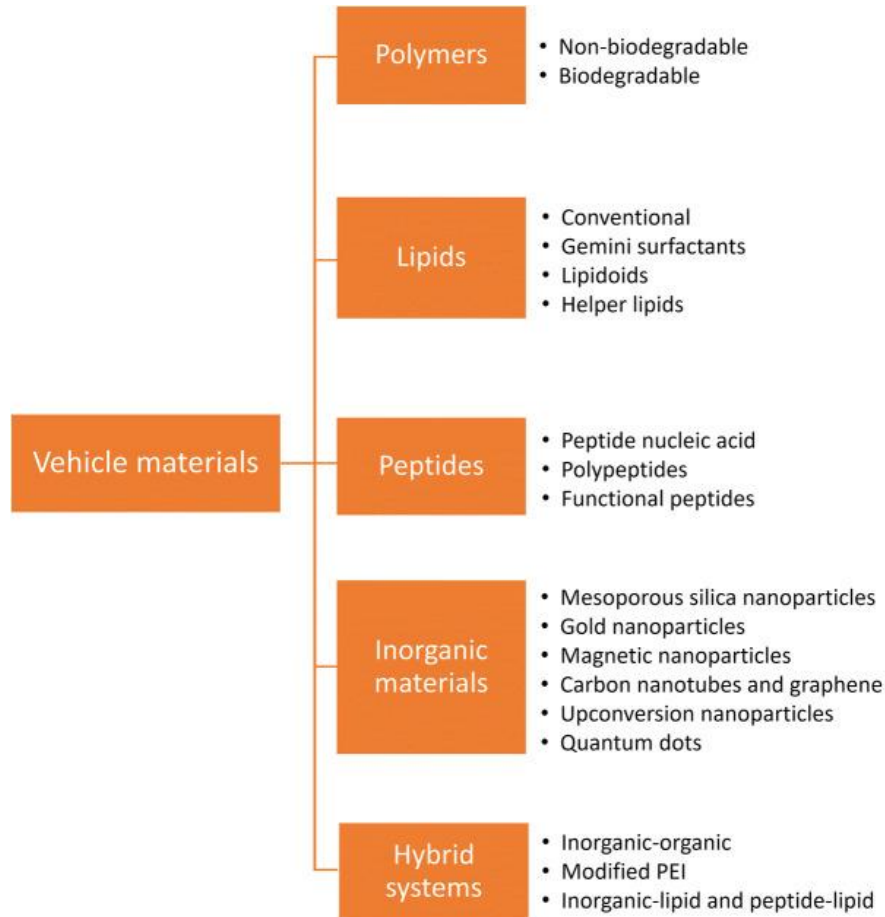
Figure 2

1. **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(phosphoesters), 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]

2. **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.]

3. **Conventional Lipids:** Colloidal carriers called lipid nanoparticles are made of lipids that are stable at body temperature. Due to the use of lipids, the release of the drug is slow. Since the drug is contained in the solid matrix, diffusion of the drug to the surface is difficult. Normal lipids have one head per molecule, which may or may not carry an irreversible charge. The head group contains ammonium, imidazolium, pyridinium, lysine, or arginine. The hydrophobic tail may contain one steroid or two saturated or unsaturated hydrocarbon chains. Heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butyrate (DLin-MC3-DMA) is considered the "gold standard" for siRNA delivery due to its high genetic efficiency.[7]

4. **Gemini Surfactants:** Modification of the surface of these nanocarriers also reduces the immunogenicity of the drug, delays opsonization and removal by phagocytes, providing stealth and reducing interaction with the bloodstream. Gemini surfactants are a subclass of lipids that have recently shown promise as carriers. These are two surfactant monomers attached to the head group by a covalent bond formed by a spacer group. Gemini surfactants generally have the advantage of lower CMC than similar surfactant monomers, thus reducing surface tension and increasing solubility power. Therefore, this method of delivery uses fewer carriers and therefore reduces toxicity. The feasibility of MPEG carbamate Gemini surfactant-based curcumin delivery was investigated. [8,9]

5. **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]

6. **Helper Lipids:** To improve RNA delivery, extensive studies have shown that in addition to cationic or ionizable lipids, lipid nanoparticles often contain other lipid nanomaterials such as phospholipids, cholesterol, and polyethylene glycol lipids. In lipid-based gene transfer technology, "helper lipids" are often used to enhance transcriptional activity, stabilize products, or facilitate transport within the body. These lipids are neutral compounds, unlike cationic and ionizable lipids. 1,2-Dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE) is one of the best-known lipids whose conical molecular shape promotes membrane fusion and/or bilayer disassembly. Additionally, cholesterol is used as a lipid component in liposome formulations because it can increase cell membrane fluidity and stabilize bilayer lipids. This increases efficiency and stability. [10, 11]

7. **Peptides/Proteins:** Many different types of peptides can be taken by mouth. CSKSSDYQC (CSK) peptide is widely used to improve hypoglycemic effects because it targets goblet cells. According to Du et al., functional peptide-conjugated transferrin receptor-specific nanocarriers improve transcytosis, alter intracellular trafficking, and increase intracellular uptake in polarized cells for oral drug delivery. Dendrimers can also be made from polypeptides, which can have combinations of three units (core, branch, and dendrimer surface) and use amino acids as building blocks. Peptide dendrimers can provide useful groups required for complex genetic material, the ability to enter biological cells, and the buffering ability to avoid endosomes. [12]

8. **Mesoporous Silica Nanoparticles (MSN):** Through cytocompatible MSNs, drugs can be loaded into the following areas: 1) Used with other drugs to increase their effectiveness during drug delivery. 2) Provide a drug-centered nano platform that can be combined to treat bacterial infections and biofilms while avoiding the use of antibiotics. 3) Use spherical nanoplatforms to deliver a variety of drugs for the treatment of diseases such as cancer and tooth sensitivity. 4) Due to their good properties and porosity, MSNs have been proven to be bioactive materials for bone. Recent studies have focused on the biological uses of MSNs in oral medicine, including antibacterial, anti-inflammatory, dentin desensitization, and osteogenic effects that promote bone regeneration. [13,14]

9. **Gold Nanoparticles:** First, various morphologies and structures can be used to produce nanoparticles, such as nanospheres, nanorods, nanowires, and nanarrows. Each has its unique properties, characteristics, and uses. Second, AuNPs can be made from pure gold, composites (grafted with polyethylene glycol, cysteine, etc.), or doped with other metals to create new hybrid materials that can be continuously coated, functionalized, or combined with drugs or other cellular compounds. Targeting and drug delivery. The combination of AuNPs with folate ligands and the possible anticancer drug bilirubin targeting folate receptors overexpressed in cancer cells kills multidrug-resistant oral cancer cells in vitro. Additionally, Xia C et al. He found that the size of AuNPs affected their anti-inflammatory properties, and his results showed that ultrathin AuNPs (3 nm in diameter) could inhibit the growth of OSCC tumors in vivo. [15]

10. **Magnetic Nanoparticles:** Drug delivery systems hold the greatest promise because magnetic nanoparticles can function by binding to a variety of molecules, including chemotherapeutic drugs, radionuclides, nucleic acids, and antibodies. They can then be picked up using magnetic material. Using alternating magnetic fields to induce hyperthermia is another treatment option. Magnetic nanoparticles can be used to prevent cancer. They also support the development of the "therapeutics" sector, which combines clinical research with clinical programs. [16]

11. **Carbon Nanotubes (CNTs):** To make NTs (hollow tubes), graphene sheets are rolled into cylindrical shapes. There are six different types of carbon nanotubes: toroidal carbon nanotubes, nanoflower carbon nanotubes, nanobud carbon nanotubes, fullerite carbon nanotubes, and multi-walled carbon nanotubes (MWCNT). They are widely used due to their special structure and properties such as high ratio, excellent strength, ultra-lightness, wide specific area, rich chemical activity, excellent electrical and thermal energy, and sustainability of nanotechnology. Mangla Bharti evaluated CNTs as one of the most innovative and flexible nanocarriers, theranostics, and cutting-edge drug delivery

technologies for the delivery of genes, drugs, and biomolecules, as well as bioimaging and biosensor applications. 2020.[17]

12. **Quantum Dots (QDs):** These nanocrystals have a semiconductor shell around a semiconductor core. Due to their unique optical properties, quantum dots are attractive carriers for biomedical applications. Drugs can be transported via binding to QD nanocarriers, adsorption, dispersion, dissolution, and dissolution. To improve the physical and chemical properties of drugs, quantum dot nanocarriers can increase the effectiveness and therapeutic index of the drug, promote the absorption of drug molecules, and reduce side effects. Quantum dots can bind to the proteins of cancer cells and emit brilliant light under ultraviolet light, making it easier to locate the tumor. Quantum dots can improve the immune system and cellular support. [18]

13. **Upconversion Nanoparticles:** Because gold nanoparticles on the surface are modified to absorb near-infrared light, clinical evidence shows that near-infrared (NIR) lasers can deliver anti-EGFR/gold conjugates to deep malignant tumors. In vitro experiments showed that OSCC cells could be damaged by anti-EGFR/Au conjugates without the need for high energy. Lucky and colleagues used polyethylene glycol titanium dioxide (TiO2) as the encapsulant. Create a biocompatible upconverting nanoparticle that uses near-infrared rays to increase tissue permeability and effectively target EGFR on the surface of OSCC cells to prevent tumor growth. [17]

14. **Inorganic Nanoparticles:** Such nanoparticles do not contain carbon and organic matter. Ceramics, metals, and semiconductors are the most common uses of these materials. Metal nanoparticles can be monometallic, bimetallic, or multimetallic and consist of metallic materials. Alloys or multilayers (core-shell) can be used to create bimetallic nanoparticles. Materials with metal and non-metal properties are used in the construction of semiconductor nanoparticles. These nanoparticles exhibit significant modulation by band gap modification and have a wider band gap compared to bulk semiconductor materials. Inorganic solids called ceramic nanoparticles consist of iron and metalloid oxides, including carbonates, carbides, and phosphates, as well as calcium and titanium. [19]

II. COMBINATIONAL (POLYMERIC-INORGANIC) NANOPARTICLES

One of the most difficult aspects of drug addiction treatment is the use of medications that can reduce toxicity and increase effectiveness. Darwish and colleagues combined chemo photothermal therapy with vincristine (VCR), a phytochemical anticancer drug, and plasmonic gold nanorods (GNRs), a photothermal agent. Effective treatment of OSCC. When the amide bond is broken, it results in prolonged release of the VCR into the acidic intracellular environment, and the resulting combinatorial therapeutic nanoprobes prove to be candidates for future therapeutic translation. [20]

1. **Liposomes:** The main components of liposomes are phospholipids, cholesterol, and membrane-like lipids. Liposomes consist of one or more small layers. Liposomes are non-toxic to soft tissues or cells and are the most commonly used pharmaceutical tools to enhance drug accumulation at the target. This technology has attracted widespread attention because it provides effective treatment with controlled drug delivery. These LVs

remained stable in solution for more than 50 days. Due to the specific interaction of aluminum and phosphate, LVs form bonds with AlClPc molecules, allowing them to enter the organelle and undergo the depolymerization process after uptake by OSCC. This information may provide the basis for further research. [20]

2. **Cyclodextrins:** When starch is broken down by enzymes, cyclic oligosaccharides called cyclodextrins (CDs) are produced. CD can form complexes with hydrophobic drugs such as the antibiotics docetaxel, cisplatin, methotrexate, and paclitaxel. To improve the solubility and oral bioavailability of two curcuminoids, Wang et al. Soluble supramolecular complexes were formed using phospholipid complexation technology and hydroxypropyl-β-cyclodextrin (HP--CD) addition technology.[21]

3. **Hydrogels:** Due to their three-dimensional (3D) porosity and structural connectivity, hydrogels have many advantages in drug delivery systems, in addition to providing a biocompatible environment for cell adhesion and proliferation. Topical application is a unique form of targeted drug delivery that allows the implantation of different hydrogel structures directly at the site of injury or disease, rather than injecting small nanoparticles into vessels. In this case, the hydrogel carrier can change the hydrogel topology, network pores, and gelation process (physical and chemical gelation) to alter drug release over a longer period (months).[22]

III. 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]

IV. VITAMIN-COATED NANOPARTICLES

Vitamin B12 (VB12) can interfere with important substances in the body by forming a complex in the stomach due to its receptor-mediated endocytosis absorption pathway. This complex is easily converted into nanoparticles to improve oral health. For example, Chalasani et al. found that covalent binding of VB12 to insulin-loaded dextran resulted in improved screening of streptozotocin-induced diabetic rats compared to pure nanoparticles. Similarly, VB12-modified nanoparticles composed of trimethyl chitosan or calcium phosphate increase the oral absorption of insulin.[23]

1. **Exosomes:** Many different cell types produce exosomes, such as dendritic cells, macrophages, mesenchymal stem cells, endothelial cells, and epithelial cells. Exosomes have recently attracted great attention from researchers for their applications in biology because they are very nanosized and natural. Exosomes are important in delivering various biomolecules or chemotherapeutic drugs for cell-to-cell exchange. This is because they have good adhesion properties to cell membranes, suggesting that they will create specialized delivery for certain drugs.[23]

2. **Virus-Like Particles (VLPs) :** VLPs generally form by self-assembly of viral capsids or bacterial envelope proteins. Due to their biophysical and chemical properties, VLPs can be easily manipulated by genetic and chemical engineering to alter VLP proteins. Although the effectiveness of VLPs as oral vaccines in vaccines has been extensively studied, it is not yet clear whether they can be applied more effectively to other oral cancer treatments.[24]

3. **Nanovectors for Gene Therapy:** Gene delivery, gene transfer, and gene regulation are the three main areas of gene therapy. Cationic polymers have long been recognized as an important type of non-bacterial purification due to their chemical structure and high loading capacity. They neutralize negatively charged genetic material, forming complexes (polymers) and transferring the load to the desired cells. Neeb et al. The peptide RALA/p53 encoding pDNA vectors with different nitrogen-phosphorus groups (N/P) was examined. [24]

V. FUTURE TRENDS

1. **Cancer Nano Vaccines:** Vaccines are the oldest type and are used to prevent cancer in healthy people. They support humoral and cellular immunity. The vaccine is against human papillomavirus. The second vaccine, called a cancer nano vaccine, is available for people who already have cancer. They can be designed, manufactured, and injected into the human body to improve health, including cellular molecular repair. The small size and easy entry into cells of nano vaccines have led to advances in different agents, diagnostic tools, organ systems, and drug delivery. Putting active ingredients where they should be can reduce dosage and adverse effects. [25, 26]

2. **Smart Polymers:** Smart synthetic polymers for cancer therapy are discussed from three perspectives: enzyme response, pH response, and redox response. Research shows that smart polymer nanoparticles can improve tumor immunity, reduce the immune system, and prevent cancer from escaping from the body. Synthetic biopolymers responsive to smart stimuli may help treat cancer. [25, 26]

VI. 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 used in the diagnosis and treatment of oral cancer. Then, challenges and prospects for the use of nanoparticles in oral cancer diagnosis are presented.

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