**REVIEW ARTICLE**

**Nano drug delivery in oral cancer therapy: An emerging avenue to unveil**

R. Sudhakara Reddy, Sahithi Dathar
Department of Oral Medicine and Radiology, Vishnu Dental College and Hospital, Bhimavaram, Andhra Pradesh, India

**Abstract**

Oral cancer is one of the most threatening diseases impairing the quality of life of the patient. Though many strategies are being employed for treatment of oral cancer, the eventual goal to cure cancer still remains elusive. Various drug delivery systems have been practiced to achieve better success in improving the survival rate of the patient. Until date, targeted drug delivery systems via nanoparticles are expected to be promising multi-functional platform in cancer therapeutics. The present article is a brief review of unique properties of nanoparticles and various nano drug delivery systems in oral cancer therapy.

**Keywords:** Nanoparticles, oral cancer, targeted therapy

**Correspondence:**
Sahithi Dathar, Department of Oral Medicine and Radiology, Vishnu Dental College and Hospital, Bhimavaram, West Godavari District, Andhra Pradesh, India.
Email: sahithi.dathar9@gmail.com

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**Introduction**

Oral cancer is one of the most devastating ruinous disease occurring worldwide and also in the Indian subcontinent. It refers to any cancerous growth that occurs within the oral cavity[1] and is characterized by uncontrolled and uncoordinated growth that has remarkable tendency to spread and undergo metastasis.[2,3] Oral and oropharyngeal cancer constitutes to be the sixth most common cancer in the world.[4,5] It accounts for about 5% of all the cancers globally, and 60,000 new cases of oral cancer are being encountered every year in India.[4]

Many treatment strategies had been employed for treatment of this disastrous disease such as surgery, radiotherapy and chemotherapy, either alone or in combination. Though these strategies had improved the survival rate of the patient, yet they do have certain limitations and adverse effects due to which the cure for oral cancer is still ambiguous. The foremost side effect of the chemotherapy or radiotherapy includes their non-specific site of action, due to which they lack the inherent ability to differentiate between normal and the tumor cells.[2,6] The other common side effects due to high therapeutic doses of the drugs include alopecia, malaise, and organ dysfunction leading to impaired quality of life of the patient.[2]

Owing to these facts various drug delivery systems have broadened their wings so as to improve the patient’s compliance and comfort. In the latest scenario, local drug delivery to the respective tumor sites has achieved a significant impact by means of Nanotechnology.[7,8] The word “Nano” in Greek refers to “dwarf.”[8,9] It precisely includes all the particles of size 1 billionth of a meter (<100 nm).[1,10] Thus, the main added advantage is that at this size range, nanoparticles possess a maximum surface:volume ratio, which makes them ideal for surface functionalization and incorporation of a chemotherapeutic load.[10,11] This smallest size is mainly responsible for the movement of the nanoparticles within the cells and tissues.[13]

The application and development of nanotechnology in the field of medicine were referred as Nanomedicine, which was used to diagnose, treat, and prevent diseases at the basic cellular and molecular level.[14] The current article provides a brief description of local drug delivery systems by means of various nanoparticles/nanocarriers which serves as an appropriate platform in the treatment of oral cancer.

**Challenges Brazen Out by the Nanoparticles in Local Drug Delivery**

Local oral drug delivery should be able to overcome various factors like rapid clearance of the drug from the site of absorption due to scavenging by saliva and mechanical stress, poor patient compliance because of an unpalatable taste and potential barrier region of the oral mucosa towards the absorption of the drug.[15]

The major disadvantage of the conventional chemotherapy for oral cancer lies in its high systemic toxicity and diminished ability to target specific cancer sites.
The emergence of the nanoparticles in local drug delivery had tackled many challenges like enhanced and effective drug loading, precise targeting of the tumor sites, their inherent ability to transport and control the drug release and above all, they aid in development of toxic-free environment by reducing the quantity of the drug to a particular concentration at the vicinity of the target site which makes them about 10-100 folds more efficient than the administration of the free drug.\(^{16-19}\) Besides these, biocompatibility and biodistribution are the innate characteristics of these tiny particles which had contributed to their high success rate.\(^{16,17,20}\)

Malignant tumors possess an innate ability to have rapid and uncontrolled growth and they present with fenestrated, leaky and hyperpermeable microvasculature due to rapid and defective angiogenesis and also with compromised lymphatic drainage, which contributes to enhanced permeability and retention (EPR) phenomenon.\(^{17,18,21}\) Due to this effect nanoparticles tend to accumulate preferentially and precisely at the tumor site.\(^{3,21}\) These nanocarriers thus increase the solubility, specificity, stability, multimodality, efficacy of the drugs and protect the drug from rapid clearance, thereby simultaneously reducing the adverse effects and improving the non-specificity of conventional cancer therapy.\(^{1,18}\) In addition, at the targeted site, nanoparticles had provided an added benefit that they can be endocytosed/phagocytosed, can increase the internalization of the drug within the cell, and eventually leading to delivery of the drug in proximity to the intracellular site of action.\(^{14}\)

Nanoassemblies ensure even distribution of the drug, and pelleted nanoparticles remain adhered to the mucosa, leading to good absorption via oral mucosa and sustained release of the drug.\(^{13,22}\) Localized drug delivery by means of nanoparticles through intratumoral administration had further prevented the systemic circulation of many toxic drugs. The various advantages of nano drug delivery systems are briefly depicted in Figure 1.

**Targeted Therapy by Nanoparticles**

Local drug delivery via oral mucosa occurs either by active or passive targeting. Passive targeting occurs by accumulation of drug or drug-carrier system at a specific site due to physico-chemical or pharmacological factors\(^{23}\) and occurs either by transcellular route (crossing the cell membrane and passing through the cell) or by paracellular route (passing between the cells).\(^{15}\) Active targeting refers to definite interactions between drug/drug carrier and the target cells, usually through specific ligand-receptor interactions.\(^{24}\)

Nanosystems with different compositions and biological properties are being extensively investigated for targeted therapy.\(^{19}\) The targeting of the tumor site by means of nanoparticles or nanocarriers is mainly focused on improving the therapeutic efficacy of the anticancer drugs. The nanoparticle embedded with the anticancer drug is shown in Figure 2.

**Active targeting**

Active targeting (ligand based therapy) utilizes a specific modification of drug carrier nanosystems with active targeting agents which possess a selective affinity to recognize and interact with a particular cell. It is an attractive approach which uses "ligands" that harbor homing of therapeutic moieties at specific epitopes.\(^{5}\) Various targeting agents include vitamins, carbohydrates, lipids, peptides, and proteins. However, active agents, like ligands for the receptors and antibodies to the surface proteins have been used widely to target particular tumor cells The process of active targeting by the nanoparticles is shown in Figure 4.

![Figure 1: Advantages of nano drug delivery systems](image1)

![Figure 2: Nanoparticle incorporated with the anticancer drug](image2)
Nanoparticles against Multi Drug Resistance (MDR)

MDR or chemoresistance is a phenomenon where the cancer cells exhibit a diminished response over the course of chemotherapy as they tend to acquire defense mechanisms against the drugs by over expressing drug efflux pumps, by enhancing the metabolism of the drug, and by increasing self-repairing ability or expressing altered drug targets.\(^7\) To overcome this and to improve the therapeutic efficacy, combination therapy has been adopted in many clinical setups as a primary treatment regimen for cancer. Though it has shown an improvement in the efficacy of the regimen, yet the usage of multiple drugs require multiple targets which can further delay the cancer adaptation process to the provided therapy. Due to the different pharmacokinetics of the multiple drugs, drug dosage and scheduling the optimization of the drugs is also difficult.\(^7\) Nanoparticles also have the capacity to accumulate in cells without getting recognized by P-glycoprotein, which is one of the main mediators of MDR, resulting in the increased concentration of drugs within the cell.\(^28\)

Chemo-resistance also occurs due to poorly vascularized tumor areas which can reduce drug access to the tumor site and thus protect cancerous cells from cytotoxicity.\(^3\) The acidic environment in tumors shows resistance against basic drugs. Therefore, an elegant approach of incorporating nanoparticles with the combination therapy has come into light so as to overcome this phenomenon. Nano drug assemblies have shown to conquer the mechanism of chemoresistance by neutralizing or exploiting the drug efflux pumps by silencing the drug resistance genes and inhibiting the drug resistance proteins.\(^{19}\) On the other hand, nanocarriers have shown to suppress MDR independent of drug efflux pumps by silencing both B-cell lymphoma 2 and hypoxia-inducible factor alpha genes where the former one regulate the process of apoptosis and later one code for transcription factor in cellular response toward hypoxia.\(^{29}\)

Nanotechnology Avenues for Oral Cancer Therapy

In the latest era, various avenues by means of nanosystems have been evolved and driven into research so as to achieve the success in improving the survival rate of the patient. The common nanoparticles exemplified for the treatment of drug resistant cancer cells mainly include polymeric nanoparticles, liposomes, dendrimers, carbon nanotubes, nanoshells, magnetic nanoparticles (MNPs), and gold nanoparticles.\(^{8,11,29,30}\)

Polymers

Polymeric nanoparticles have shown to possess more efficacy as a versatile carrier system for targeted delivery of anticancer drugs like paclitaxel.\(^8\) These have the capacity to deliver not only the low molecular weight drugs but also macromolecules such as proteins and genes. Hydrophilic polymers like polyethylene glycol (PEG) aids in stabilization of the nanoparticles and in better targeting of the site because they help in forming a stealth layer that tend to reduce the nonspecific uptake of the drug by the cells.\(^7,8,27\)

Compared to liposomes, polymeric nanoparticles are usually less toxic, highly stable, with more versatile physicochemical properties, sustained release of the drug, and better loading capacity for water insoluble drugs.\(^{21}\) In the recent years, biocompatible and hydrophobic polymers like polyketal are readily synthesized, with biodegradable ketal linkages forming their backbone which can further aid to form nanoparticles that can encapsulate hydrophobic drugs or proteins.\(^{30}\)

These polymers are one of the most widely investigated nanoparticles in vitro, yet many challenges and drawbacks are needed to be resolved before their application in the clinical setup.\(^6\) Liu et al., had reported that paclitaxel nanocrystal formulation using D-α-tocopheryl PEG have significant therapeutic benefits than the free drug in taxol-resistant cancer cells.\(^31\)

Lipid based nanoparticles

They are in the form of liposomes and micelles. Liposomes are spherical encapsulated spheres and consist of lipid bilayer which loads an aqueous phase to store the drugs. Due to these lipid bilayers formed through hydrophobic interaction, liposomes...
are considered to be excellent platforms for the delivery of hydrophobic as well as hydrophilic drugs. Food and Drug Administration (FDA) had approved commercial liposomes like doxorubicin encapsulated liposomes (Doxil), which have shown to have strong antitumor activity against a wide range of cancers.\textsuperscript{[8,30,32]}

Micelles are also spherical lipid nanostructures, but they do not have a lipid bilayer or inner cavity and have a typical size of 10-80 nm and due to this smaller size they show shorter circulation time within the body.\textsuperscript{[30]} Lipid-polymer conjugate micelles are also made which can probably carry different drugs like paclitaxel and have shown to exhibit better longevity and stability. Amphiphilic diblock copolymer forming micelles are being tried to deliver paclitaxel to treat breast cancer, advanced pancreatic cancer and non-small cell lung cancer.\textsuperscript{[32]} The advantage of such agents due to the smaller size is enhanced penetration into the target and flexible movement to the site.\textsuperscript{[30]}

Dendrimers

These are unimolecular, monodisperse, multi-branched and three dimensional structures with well-defined molecular weights with a size of 1-10 nm. Their typical branching quality aids in the provision of larger surface area for drug molecules and is one of the most elegant paths for targeted delivery of both water soluble and insoluble drugs.\textsuperscript{[7,8]} Owing to their branching nature, Tekade et al., had co-encapsulated methotrexate (a hydrophobic anticancer drug) and all-trans retinoic acid (a hydrophilic agent with mild anticancer activity) in $5\text{poly}(propyleneimine)$ dendrimer and reported that this conjugation was effective than free drug delivery when performed on HeLa cell lines.\textsuperscript{[7,33]}

Carbon nanotubes

Carbon nanotubes can enter living cells without causing any cell death or any obvious damage due to their typical size and shape.\textsuperscript{[30]} But for biological applications they require covalent or non-covalent functionalization for the better aggregation and higher solubility. Conceptually they are well organized, hollow nanotubes and are formed when single or multiple graphene sheets are rolled into a shape of a cylinder and are highly advertised for their potency in novel nano based drug delivery agents.\textsuperscript{[32]} Safety of these nanotubes has to be considered because of its needle-like fiber shape\textsuperscript{[8]} and issues with respect to their toxicity still remains obscure and inconclusive, due to which probably no clinical trials have been tried by using carbon nanotubes.\textsuperscript{[32,34]}

Nanoshells

They are nanoparticles assembled layer by layer. These polymeric nanoshells (2060 nm) of diblock copolymers can be made by self-assembly of oppositely charged polymers to form a shell like structure. A system of folic acid conjugated nanoparticles was developed for targeted delivery of docetaxel by means of a biodegradable polymer core and mixed lipid monolayer shell.\textsuperscript{[8]}

Gold nanoparticles

Gold nanoparticles are attached to a molecule called tumor necrosis factor (TNF) alpha which accumulate in particular cancer sites but does not appear to reside in other regions of the body, which thus limits the toxic effects of TNF on healthy cells.\textsuperscript{[33]}

The benefits of gold nanoparticles owe to their ease of preparation in various ranges of sizes, good biocompatibility, easy functionalization and their inherent ability to conjugate with other biomolecules without altering their biological properties.\textsuperscript{[30]} They have also shown to have non cytotoxicity and high dispersity. Hence, they have been extensively used in various biomedical applications and drug delivery systems due to their toxicity, small size and high surface area-to-volume ratio.\textsuperscript{[11]}

Magnetic nanoparticles

In the past few years, magnetic nanoparticles have become one of the most investigated and studied systems in the field of nanotechnology. The iron oxide nanoparticles when coated with oleic acid and embedded with anticancer agents such as doxorubicin and paclitaxel, have shown loading efficiency up to 95%.\textsuperscript{[30]}

Nanodiamonds

In the latest decades, nanodiamonds are being used to immobilize proteins and deliver drug molecules. These structures bound to doxorubicin and were encapsulated into a polymer microfilm in order to achieve the slow and sustained release of the drug for a period of 1 month.\textsuperscript{[30]}

With the advent of nanotechnology in oral cancer, many researches are being expanded more in terms of early detection of the disease. In the latest decade, US Food and FDA had approved of a nanoparticle-based system for a clinical trial in humans for treatment of solid tumors. As per the documented literature, there are more in vitro and animal studies with very few clinical studies elucidating the therapeutic effects of nanoparticles in oral cancer.\textsuperscript{[38]}

The usage of nanostructures like quantum dots (QDs) (nanoparticles with quantum confinement properties, like size-tunable light emission) along with magnetic resonance imaging, can be widely applied in diagnosis and imaging of the tumor. Later, QDs-photosensitizers complexes as Photodynamic therapeutic agents was put forward by Samia et al. which can mediate the targeted cellular destruction.\textsuperscript{[50]}

Huang et al., had reported that conjugated gold nanorods to anti-epidermal growth factor receptor antibodies were able to differentiate human oral cancer cells from human nonmalignant epithelial keratinocyte cells and thus proposed that they can be used as diagnostic signatures for cancer cells.\textsuperscript{[37]} Hirsch et al., had demonstrated that silica-gold nanoshells labeled with antibodies specific to oncoprotein were shown to the target and destroy the oral squamous cancer cells in a minimal invasive way.\textsuperscript{[58]}

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Lin et al., had reported that curcumin showed both anticancer and antioxidant properties especially in low doses and performed an in vitro suppression of oral squamous cell carcinoma (OSCC) cell lines by ultrasound mediated delivery of curcumin microemulsions (with a mean size of 40-50 nm). The results showed the cytotoxic effects of curcumin microemulsions on OSCC-25 cells by causing damage and rupture of the cells followed by the treatment.

Damasceii et al., had evaluated the efficacy of intra-arterial infusion of paclitaxel integrated into human albumin nanoparticles for use as induction chemotherapy in advanced squamous cell carcinoma of the tongue in a preliminary study conducted among 23 patients and two catheter related complications had occurred.

Endo et al., designed an in vitro study and evaluated the efficacy and safety of NC-6004 (polymeric micelles carrying cisplatin) for OSCC.

Morazadeh Khivai et al., had reported a study demonstrating the better therapeutic efficacy of doxorubicin and methotrexate loaded nanoparticles on squamous cell carcinoma of the tongue when compared to the commercial doxorubicin and methotrexate among 70 male rats which were induced by 4-nitroquinoline 1-Oxide.

Yu et al., had revealed the anti-tumor effects of herpes simplex virus thymidine kinase loaded PEG-poly(γ-benzyl-L-glutamate) nanoparticles on OSCC and their anticancer effects were determined both in vitro and in vivo.

Holpuch et al., had determined the feasibility of SLNs as viable local drug carriers of poorly water soluble and unstable chemo preventive compounds to human oral carcinoma cell lines.

Kakkar et al., had reported an in vitro release of curcumin-loaded SLNs by diffusion phenomenon and suggested that its enhanced oral bioavailability will be effective in cancer therapy.

Sulfikkarali et al., had showed better potentiality of naringenin (NAR, which is an antioxidant)-loaded nanoparticles in Syrian hamsters and suggested as useful drug delivery system for targeted delivery of naringenin for oral cancer chemoprevention.

Candido et al., had demonstrated the action of polyphosphate-coated magnetic nanoparticles (MNP’s) on oral cancer cells and suggested that Syrian hamsters, when treated by magneto-hyperthermia using MNPs, had showed significant and time dependent cancer regression.

Conclusion

Nanotechnology perhaps holds its promise as an innovative avenue for oral cancer therapy. Many in vitro and animal studies have been driven into research which has shown their instinctive abilities to alleviate many challenges in cancer therapy. Indeed, this emerging branch of science is extensively anticipated to explore its domain into clinical setup over the next couple of years. Since these tiny particles unveiled many miracles in the field of medicine, future research has to be done, so that the seeds of this new technology can certainly meet the needs of the mankind.

References


