

# Targeted drug delivery systems used in dentistry - A short review

Lakshmi Prabha J, Anitha Roy\*, Lakshmi T

## ABSTRACT

Targeted drug delivery is a specialized form of drug delivery which involves the controlled release of drugs in the desired location over a period of time. The main goal of target drug delivery system is to prolong, localize the target action to provide a protected drug interaction with the diseased tissues. The drug is delivered selectively to targeted areas of action or absorption and helps in preventing damage to non-targeted cells, tissues or organs. It provides a better method of drug delivery when compared to systemic dosage forms. These drugs are in the form of nanoparticles which are released in the target area, thereby avoiding interactions with healthy tissues. This can be achieved through means of active targeting or passive targeting in the region of diseased tissues. Drugs can be delivered through different vehicles such as polymeric micelles, liposomes, lipoprotein based drug carriers, nanoparticle drug carriers and dendrimers. These drug delivery systems have various applications including stem cell therapy, regenerative procedures and cancer treatments. In dentistry, the various drugs administered through this technique which is found to be beneficial in patients with gingivitis, periodontitis and other oral diseases. This study was done to assess the benefits of these target drug delivery systems to prevent discomfort or any other side effects for the patients and to analyze its scope in future dental practice. Hence, this review article aims at critically analyzing the different local drug delivery systems used in dentistry and analyze the indications, contraindications, benefits, and side effects of these systems for their effective use in patients.

**KEY WORDS:** Active targeting, Delivery vehicles, Drug delivery, Passive targeting, Target

## INTRODUCTION

The concept of target drug delivery system was first proposed by Ehrlich who postulated the term “Magic bullet” in 1906. The main challenge in target drug delivery system was based on three main factors, namely finding the particular target for the disease, finding the drug which will effectively treat the disease, and selecting appropriate target vehicles to carry the drug in stable form while preventing other interactions and damage to the healthy tissues. Targeted particle delivery has the ability to carry high-density drugs while expressing ligands on the surface of the particle simultaneously.<sup>[1]</sup> Nanomedicine is the science of development and application of nanotechnology in the field of medicine to prevent, diagnose and treat diseases at cellular, as well as molecular level.<sup>[2]</sup>

Nanoproducts delivered through target drug delivery uses the pathophysiological and anatomical changes within the diseased tissue to differentiate it from normal tissues to achieve site-specific targeted drug delivery.<sup>[3]</sup> Thus, the aim of the current review was to provide a brief outline of the targeted drug delivery system using nanoparticles and nanocarriers for various treatment purposes in dentistry.

## VARIOUS DELIVERY VEHICLES

Nanoparticles can be used as potential carriers along with targeting ligands as target drug. These have various advantages over larger systems due to their submicron size. The main characteristics of target drug delivery systems are that it should be biodegradable, biocompatible, non-toxic, and physicochemical stable. Drug release should be even, controlled, predictable, and without any effect to the drug.<sup>[4,5]</sup> The major advantages of nanoparticle drug delivery are the small size which enables them to extravasate through blood vessels and tissue especially in tumors and sustained

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Department of Pharmacology, Saveetha Dental College, Saveetha Institute of Medical and Technical Sciences, Chennai, Tamil Nadu, India

**\*Corresponding author:** Dr. Anitha Roy, Associate Professor, Department of Pharmacology, Saveetha Dental College, Saveetha Institute of Medical and Technical Sciences, Saveetha University, 162, Poonamallee High Road, Velappanchavadi, Chennai - 600 077, Tamil Nadu, India. E-mail: [anitharoy2015@gmail.com](mailto:anitharoy2015@gmail.com)

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internal drug delivery especially in cytoplasmic targets. Targeted molecules can be formulated to avoid first-pass metabolism. In addition, they may also possess properties such as optical and electrical, making it possible to track and localize the drug intracellularly. However, it has disadvantages such as toxicity and require skill and is difficult to maintain drug stability.<sup>[1,5,6]</sup>

### Nanoparticles

The word “nano” in Greek means “Dwarf.” The nanoparticles have smaller size and possess maximum surface volume which helps in the incorporation of the drugs.<sup>[7]</sup> They are a novel modality that couple a ligand to a drug vehicle of nanosize to achieve increased drug efficacy at the target site. They include a variety of submicron colloidal nanosystems of size <1 µm. They may be inorganic, liposome, or polymer-based colloidal systems which act as attractive drug carriers for several decades. The major advantage of these nanoparticles is their small size which makes penetration of biological barriers easier and their ability to encapsulate high-density drugs along with an attachment of shielding ligands. These ligands prolong the circulation of nanoparticles in the blood and to help interactions with specific cells or tissues. Their biological activity depends on cellular internalization of drug-containing particles. The molecular mechanisms mediating the internalization process depends on the size of the particles, and effective internalization is seen when nanoparticles are targeted against internalizing receptors showing increased therapeutic activity in some tumor models. Another advantage of nanoparticles is its usefulness in overcoming certain kinds of drug resistance where some tumor cells are able to expel intracellular drugs into extracellular medium acquiring drug resistance. They have the inherent ability to transport and control drug release to the target which increases its efficacy in the desired site and provides a toxic-free environment by reducing the drug concentration required. They also prevent the circulation of the toxic drugs in the systemic circulation through intratumoral drug administration.<sup>[2]</sup> Nanoparticles are used in the treatment of diseases such as tumors, brain diseases, Ebola and some infectious diseases.<sup>[8]</sup> To deliver drugs for these therapies, the drugs are encapsulated, entrapped, absorbed, attached, or dissolved into the matrix of the nanoparticle which releases it at the required site of action.<sup>[9]</sup> The two main nanoparticle drug delivery systems include liposomes and solid biodegradable nanoparticles.<sup>[1]</sup>

### Liposomes

Liposomes are a composition of amphiphilic phospholipids and cholesterol in bilayers that encapsulate an aqueous interior. Liposomes as a

modality for target drug delivery were first proposed by Gregoriadis.<sup>[2]</sup> Liposomes have given promising results in improving therapeutic benefits, reducing side effects and increasing patient compliance as they mimic the bio-membrane. They can also be formulated as bioadhesives which are retained by the enamel thereby increasing the contact time and residence in the oral cavity.<sup>[10,11]</sup> They are formulated into smaller structures that can encapsulate hydrophilic drugs in the aqueous interior or hydrophobic drugs in the bilayer. Encapsulation is done by two methods of loading, namely pH gradient method or ammonium sulfate method. Incorporation of polyethylene glycol (PEG) to the lipid surface enhances its surface properties by acting as a barrier to prevent interactions with plasma proteins thereby retarding recognition by the reticuloendothelial system (RES). This leads to increased circulation time of the liposomes.<sup>[1]</sup> Phosphatidylcholine based liposomes are aimed at targeting bacterial biofilms whereas succinylated con a bearing liposomes are used for delivery of triclosan to the biofilm of *Staphylococcus epidermidis* and *Proteus vulgaris*. However, the use of liposomes in target drug delivery has the following drawbacks, namely poor control over drug release, low encapsulation efficacy, and poor stability during storage.<sup>[8]</sup>

### Solid Biodegradable Nanoparticles

Solid biodegradable nanoparticles are those which are widely used over liposomes for the advantage of having varying polymer compositions, morphology which can effectively control release characteristics over a long period of time. These include aliphatic polyesters specifically hydrophobic polylactic acid, hydrophilic polyglycolic acid and their copolymers such as poly lactide-co-glycolide. These materials have a history of use in various clinical applications over 30 years and are established as safe to use in humans.<sup>[1]</sup>

### Micelles

Micelles are also a group of lipid-based polymers with spherical nanostructures, but they lack a lipid bilayer or an inner cavity. They have a typical size of 10–80 nm and can carry different drugs with better longevity, decreased circulation time, and stability. They have better penetration and flexibility to move into target sites due to their small size which helps in enhancing the drug effect on the target site.<sup>[2,12]</sup> These drug delivery agents target cancer cells and are believed to possess magnetic resource imaging (MRI) contrast characteristics.<sup>[13]</sup>

### Dendrimers

Dendrimers are three dimensional, multibranching structures which are well defined, unimolecular, monodisperse particles ranging from 1 to 10 nm in

size. It is the best route of target drug delivery for both water-soluble and insoluble drugs due to the branching structures which offers a larger surface area for the drug to bind.<sup>[2,14]</sup> Multifunctional dendrimers are synthetically prepared in conjugation with fluorescein isothiocyanate used for imaging, folic acid for targeting cancer cells which overexpress folate receptors and paclitaxel as a chemotherapeutic drug.<sup>[15]</sup>

### Polymers

Polymeric nanoparticles have the capacity to deliver low molecular weight drugs along with macromolecular proteins and genes. In comparison to liposomes, these nanoparticles have less toxicity, high stability, better loading capacity for water-soluble drugs with sustained release of drugs, and versatile physicochemical properties.<sup>[2,16]</sup> There is rapid evolution in the use of biodegradable polymers due to their property of prevention of rapid clearance by RES and decreased the dosage of drugs due to enhanced plasma half-life. Polyketals are biocompatible, hydrophobic polymers which are readily synthesized recently using biodegradable ketal linkages which aid in forming nanoparticles to encapsulate hydrophobic drugs or proteins.<sup>[17]</sup> PEG is a hydrophilic polymer helps in forming a stealth layer to reduce the non-specific uptake of the drug which leads to better stability of the nanoparticles and targeting of the site.<sup>[16,18]</sup>

### Carbon Nanotubes

Nanotubes are well organized, hollow, single, or multiple graphene sheets rolled into a cylinder which can enter living cells without causing any cell death or damage to their size or shape. They have high potency in nanodrug delivery, however, safety of these nanotubes remains obscure due to their needle-like fiber shape and toxicity due to lack of clinical trials using carbon nanotubes.<sup>[2,19]</sup>

### Gold Nanoparticles

Gold nanoparticles are available in various sizes with good biocompatibility, easy functionalization, high dispersity, non-cytotoxicity, and ability to conjugate with other molecules without alteration of its biological properties. Their inert nature, small size, and high surface area-volume ratio render it extensively useful in various fields of biomedical sciences and nanodrug delivery systems.<sup>[20]</sup> Monodisperse spheres of gold nanoparticles are produced by synthetically reducing gold salts like hydrogen tetrachloroaurate with the help of reducing agents like citrate.<sup>[21]</sup>

### Nanodiamonds

Nanodiamonds are allotropes of carbon which are approximately 2–8 nm in diameter. They possess functional groups to which a wide spectrum of

compounds are attached, namely chemotherapy agents and other drugs.<sup>[22]</sup> They possess various unique physical characteristics which are used in the biomedical field. They are smaller in size, less corrosive, high mechanical properties, biocompatible, excellent biomarkers, and biosensors.<sup>[23]</sup> In the recent years, nanodiamonds are used widely to immobilize proteins and to deliver drugs to the target areas. These, when bound to doxorubicin and encapsulated into polymeric microfilms, were used for sustained release of drugs.<sup>[2,22]</sup> The hardness of these nanodiamonds is suitable for its application in implants and cutting tool for surgeries.<sup>[23]</sup> They can be formulated into the dental material and used as a filling, veneer, and for reconstruction procedures. It provides esthetic appearance which is similar to natural enamel when dry. Nanodiamonds, when used as toothpaste, are said to cure gum diseases.<sup>[24]</sup>

### Nanogel

Nanogel is a novel core-shell polymeric formulation and is biocompatible polymers. This is a colloidal system of sub-micrometer range with aggregates prepared from hydrophilic polymers having gel-like characteristics. They possess characteristics of both nanoparticles and hydrogels with high potential in gene and protein delivery.<sup>[25]</sup>

## TYPES OF TARGET DRUG DELIVERY

Target drug delivery in the oral mucosa is by two methods, namely active targeting and passive targeting. This is done to improve the therapeutic efficacy of the drug in the tumor site with the help of different drug compositions and enhanced biological properties.<sup>[2]</sup>

### Active Targeting

Active targeting is the definite interaction between the drug/drug carrier and the target cells through specific ligand-receptor interactions. This method uses nanosystems of specific modifications to selectively recognize and interact with a particular cell. Various targeting agents used for active targeting are vitamins, carbohydrates, lipids, peptides, and surface proteins.<sup>[2,26]</sup>

### Passive Targeting

Passive targeting involves the accumulation of the drug or the drug carrier system at a specific site which leads to the targeted release of the drug over a period of time. This occurs due to physicochemical or pharmacological factors through transcellular or paracellular routes. Nanosystems exhibit this type of targeting due to the electron paramagnetic resonance effect of the tumor. During the transport, the drug must

remain encapsulated until the particle binds to the target.<sup>[27]</sup> However, these nanoparticles are obstructed by mucosal barriers, non-specific uptake by the particles and non-specific delivery of the drug. Thus appropriate size and functionalization of the antibodies are required to decrease non-specific toxicity.<sup>[2]</sup>

## APPLICATIONS

### In Dental Caries

Dental caries is an irreversible disease most commonly caused by multiple bacterial species and nutrients that facilitate bacterial acidogenesis.<sup>[28]</sup> Although treatment of dental caries has not been specifically found other than the effect of fluoride, an innovative method for treatment of dental caries is primarily targeting the etiologic bacteria and diseased tissues.<sup>[29]</sup> This treatment is based on the identification of multiple protein targets in *S. mutans* which is the main etiologic factor to develop multitarget treatments for dental caries and other species which contribute to caries.<sup>[30]</sup>

### In Oral Cancer

Oral cancer is the most disastrous disease with a very little survival rate in most cases. This disease is characterized by uncontrolled and uncoordinated growth in any part of the oral cavity with remarkable spread and metastatic nature. Being the sixth most common type of cancer, it accounts for up to 5% of global and 60,000 cases in India.<sup>[31]</sup> Various treatment modalities have been proved inefficient whereas nanoparticles targeted drug delivery system shows promising results. Nanoparticles help to overcome the basic disadvantage of conventional chemotherapy by targeting the specific cancer sites. The common nanoparticles used for the treatment of drug-resistant cancer cells are polymeric nanoparticles, liposomes, dendrimers, carbon nanotubes, nanoshells, magnetic nanoparticles (MNP's) and gold nanoparticles.<sup>[2]</sup> Significant therapeutic results were obtained with paclitaxel nanocrystal formulation using D-tocopheryl PEG in comparison to free drug in Taxol-resistant cancer cells.<sup>[32]</sup> Paclitaxel is also delivered through amphiphilic diblock copolymer forming micelles to treat certain cancers.<sup>[33]</sup> Strong anticancer activity against a wide spectrum of cancers was shown by liposomes like Doxil (doxorubicin encapsulated liposomes).<sup>[4]</sup> Dendrimers such as coencapsulated methotrexate and all-trans retinoic acid in 5 polypropyleneimine dendrimer on conjugation were seen to be effective on HeLa cell lines when compared to free drugs.<sup>[6,34]</sup> Tumor necrosis factor-alpha, when attached to gold nanoparticles, accumulates in particular cancer sites limiting the toxic effect to other regions of the body.<sup>[35]</sup> Conjugation of gold nanorods to anti-epidermal growth factor receptor antibodies was used as diagnostic tools to distinguish oral cancer

cells from normal epithelial keratinocytes.<sup>[36]</sup> Silica gold nanoshells were labeled with antibodies specific to oncoproteins to target and destroy oral squamous cell carcinoma in a minimally invasive technique.<sup>[37]</sup> Nanostructures like quantum dots (QDs) along with MRI are applied in diagnosis and imaging of tumors. These are then targeted by QDs-photosensitizers complexes used as photodynamic therapeutic agents to mediate targeted cellular destructions.<sup>[38]</sup> MNP's like iron when coated with oleic acid and embedded with anticancer agents such as doxorubicin and paclitaxel have shown increased loading efficacy. Thus, MNP's have become a topic of recent investigations in the field of nanotechnology.<sup>[39]</sup> However, in the recent era, there is a success in improving the survival rate of cancer treatment due to various nanoparticles research.<sup>[40]</sup>

### In Periodontitis

The local drug delivery in periodontitis was first proposed by Goodson *et al.* in 1979 and has been proven to promote periodontal healing with the help of antimicrobial therapy. Periodontal disease involves severe pathological conditions ranging from simple gum inflammation to severe disease which results in damage to soft tissue and bones. Effectiveness of the antimicrobial therapy depends on whether the target drug reaches the base of the pocket and the time duration for which it stays to allow sufficient time for the antimicrobial effect to occur.<sup>[41]</sup> This system delivers the drug to the target site, namely the periodontal pockets while reducing the exposure to the other body sites. It helps in sustained drug release and to reach sites that are difficult to access with the help of instruments.<sup>[42,43]</sup> The various antimicrobials used in target delivery systems for the treatment of periodontitis include tetracycline (actisite), doxycycline (Atridox), minocycline (microsphere and ointment), metranidazole, chlorhexidine, periochip, periocol-CG, hyaluronic acid (gengigel), coenzyme Q<sub>10</sub> (perio Q), and simvastatin.<sup>[44]</sup> Other herbs that are used for local drug delivery for the treatment of periodontitis include eucalyptus extract, neem leaf, green tea, bloodroot and chamomile.<sup>[42,45]</sup> Local application of mouth rinses, gels, and toothpastes also can be used to control periodontal diseases involving pockets. This is achieved by either subgingival irrigation or by incorporating the drug into devices to insert into periodontal pockets. Chitosan/oligonucleotide tripolyphosphate (TPP) nanoparticles were prepared by adding TPP to chitosan/oligonucleotide complex and helps in the sustained release of oligonucleotides. Antisense oligonucleotide loaded chitosan-TPP nanoparticle was used for local administration in periodontal diseases.<sup>[46]</sup> Biocompatible nanoparticles, namely 2-hydroxyethyl methacrylate and polyethyleneglycol dimethacrylate were also used.<sup>[47,48]</sup>

## CONCLUSION

Target drug delivery is a novel method in dentistry used to treat various conditions such as periodontitis, oral cancer, and dental caries. This helps in delivering a high concentration of drug to the disease site, reducing the side effects of the drug and avoiding damage to the healthy tissues. The use of nanomedicines for the treatment of oral diseases can be beneficial as it reduces the sites exposed to the drug and has a long time action.

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