Targeted Local Drug Delivery – A Possible Approach in Dentistry

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Abstract

Drug delivery is a method of administering a pharmaceutical compound to achieve a therapeutic effect in humans and animals. Conventional therapy is a classical method of achieving drug delivery. Where, it provides drug release immediately and causes fluctuation of drug level in in blood depending on the dosage forms compared to conventional, which improves the drug potency, controlled drug release to give a sustained therapeutic effect, provide greater safety and target a drug specifically to a desired tissue. It mainly includes targeted, controlled and modulated drug delivery systems. Hence, there is an increased interest towards the application of targeted therapies in medicine and dentistry and has proven to be successful in prevention and treatment of various oro-dental disorders.

Keywords: *Biodegradable; Carrier System; Nanoparticle; Target Drug*

Introduction

Targeted drug delivery is a special form of system, where the medicament is selectively targeted or delivered only to its site of action or absorption and not to the non-target organs or tissues or cells. It improves the efficacy and reduces the side effects [1]. The drug may be delivered, to the capillary bed of the active sites, to the specific type of cell or even an intracellular region, to a specific organ or tissue by complexion with the carrier that recognises the target. The main objective of a targeted therapy, is to mainly achieve a desired pharmacological response at a selected site, thereby the drug has a specific action with minimum side effects and better therapeutic index [1]. The main reason behind the targeting of the drug is in intervention, prevention or treating a disease. Conventional dosage forms have few drawbacks like, pharmaceutical drug instability, low absorption and high membrane bounding, biological instability. The drug delivered through conventional system, has a very low specificity, shorter half life, large volume of distribution and low therapeutic index. These challenges lead to increased interest towards a targeted therapy [2]

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Requirements of drug targeting

For a drug to be targeted, it should have certain characteristics or requirements to be satisfied. Mainly it should be nontoxic, biocompatible, biodegradable and physico-chemically stable both invitro and invivo. The drug that has been delivered should be restricted to the targeted area and should have a uniform capillary distribution. It should be controllable and with predictable drug release. Amount of release is therapeutic, with minimal leakage during transit [3]. Carriers used must be bio-degradable or readily eliminated from the body without any problem. Although targeted therapy has several advantages, but still it has many limitations that hinder its application. The main disadvantage of this therapy is difficulty in predicting the exact action of drug at the specified site. Rapid clearance of targeted systems, immune reactions, insufficient localisation of targeted systems, possible toxic reactions in therapeutic dosages and tedious preparation procedures lead to decreased usage for day to day basis [4].

Carriers in targeted drug delivery:

Targeted drug delivery, can be achieved by using carrier system. Carrier is a special molecule or system essentially required for effective transportation of loaded drug to the selected site. Various pharmaceutical carriers used are polymers, microcapsules, microparticles, lipoproteins, liposomes, micelles. The important componential properties that influence drug targeting are mainly the drug delivered its concentration, particulate location and distribution, molecular weight, physicochemical properties and drug carrier interaction. In case of carrier molecule, its type, number of excipients, surface characteristics, size and density. In vivo electric field [5,6].

Various strategies in drug targeting [5] are, passive, active, ligand mediated, physical, dual, double inverse and combination targeting. Passive targeting utilises, the natural course of bio-distribution of the carrier. The colloids which are taken up by the reticulo-endothelial system can be ideal vectors for passive targeting. Active targeting involves the modification or functionalization of the drug carriers so that the contents are delivered exclusively to the site corresponding to which carrier is architectured. It can be affected at different levels like first order or organ compartmentalization, second order or cellular targeting, third order or intercellular organelles targeting. In first order targeting, there is a restricted distribution of drug carrier system to the capillary bed of a pre-determined target site, organ or tissue. In second order targeting, the drug is selectively delivered to a specific cell type such as tumor cells and to the normal cells. In third order targeting, drug is delivered to the intracellular organelles of the target cells. Inverse targeting is a reverse of passive system which avoids the passive uptake of colloidal carriers by the reticuloendothelial system. It can be achieved, by suppressing the function of reticulo-endothelial system by pre-junction of a large amount of blank colloidal carriers or macromolecules [5]. Ligands are carrier surface groups, which can be selectively direct the carrier to the pre-specified site, housing the appropriate receptor units to serve as homing device to the carrier or drug. The ligands confer recognition and specificity upon drug carrier and endow them with an ability to approach the respective target selectivity and deliver the drug. Physical targeting involves environmental changes like pH, temperature, light intensity, electric field and ionic strength. Dual targeting is an approach where, the carrier molecule itself, have their own therapeutic activity and thus increase the therapeutic effect of the drug. Double targeting is of two types, it can be achieved by spatial and temporal control. In spatial control, drugs are targeted to specific organs, tissues, cells or even subcellular component. In temporal control, the rate of the drug delivery is controlled to the target site. Combination targeting systems are equipped with carriers, polymers and homing devices of molecular specificity that could provide a direct approach to the target site [5,6, 7].

Delivery systems

Drug delivery, is a method or process of administrating a pharmaceutical compound to achieve a therapeutic effect. It is achieved through delivery systems, which help in delivering or carrying the drug to the specified site. The various delivery systems used are nanotubes, nanowires, nano shells, quantum dots, gold nano, dendrimers niosomes virosomes, liposomes, nanocrystals, magnetic nanoparticles, nanorobots [8]. Nano tubes are the hollow cylinder tubes made of carbon atoms, which can be filled and sealed for potential drug delivery they measure about 10 to 100 micrometers [9,10]. Nanowires are the thin wires which are usually microns in size, they localize the pinpoint damaged site. It has its wide applicating in patients with neurological disorders [8]. Nanoshells are the hollow silica spheres, covered with gold. Antibodies can be attached to their surfaces, enabling shells to target a particular cell in the body [8]. Quantum dots are miniscule silica particles, which are mainly the semiconductor particles, which are useful in various diagnostic and therapeutic purposes. Gold nano can be nanoparticles that are coated or made of gold particles. They are helpful in detection of DNA and protein markers. It has its wide applications in cancer treatment and genetic engineering [11]. Dendrimers are precisely defined [10,12]. Synthetic nanoparticles that are approximately 510nm in diameter. They are made up of layers of polymer surrounding a central core. They contain different sites to which the drugs are attaches and delivered. They have wide applications in gene transfection and medical imaging [8,9]. Liposomes are small microscopic vesicles in which an aqueous volume is entirely composed by membrane of lipid molecule. The drug molecules can either be encapsulated in aqueous space or intercalated into the bilayers [13,14,15]. Niosomes are non- ionic surfactant vesicles which can entrap both hydrophilic or lipophilic drugs either in aqueous phase or vesicular membrane made of lipid materials. It seems to have better stability than liposomes. Virosomes are immuno-modulating liposomes consist of glycoprotein

of viruses. They helpful in genome grafting and cellular microinjection [16,17,18,19]. Nanocrystals are nanoparticles with lesser than 100nm in diameter. Nanorobots include the technology of creating robots at nanoscale diameters, it is a hypothetical designing principle, which is still in research. It is claimed that they specifically delivered to certain areas and get targeted [8,9].

Applications of targeted drug delivery:

The applications of targeted drug delivery mainly include in treating oral mucosal lesions, in treating endodontic infections, cancer therapy and treating patients with periodontitis [20]. In treating oral mucosal lesions, various drugs are targeted using different strategies like usage of quantum dots, liposomes [13,14,15] which are bio-compatible, biodegradable and nonimmunogenic. Which ultimately reduce the toxicity and side effects of drugs. They have a wider role, with increased therapeutic effect as an antimicrobial, antiviral, antitumoral and also used in gene therapeutics. Folate targeting and sono poration have proven to be useful in treating patients with oral cancer. The major importance of nano particles, compared to the other conventional medicinal drugs is that the targeting of the nanoparticles to the specific tumor tissue. Compared to the microparticulate systems, nanoparticles can easily traverse in the blood vessels and the tumor tissue. In targeting the cancer tissue mainly by active and passive targeting modalities. In passive targeting, the injectable drug carriers have been surface modified to evade the reticule endothelial system. They are lived for longer time they have a greater advantage of reaching the blood vessels surrounding the solid tumors. The nanoparticulate molecules have enhanced permeability and retention. Active targeting is by conjugating a ligand to the surface of the particle, such ligand only target the specific cancerous tissue. Most of the studies till date, have focused on the tissue specific antigen mainly the tissue specific antigen. Liposomal carriers and the polymeric nanoparticles are the major important pathways of the targeted drug delivery [13]. Although other nanomicelle systems and studies are still being undertaken.

Periodontic and endodontic diseases are the conditions which mainly occur due to the inflammatory responses from the teeth and the supporting tissues. Endodontic and periodontal pathologies are both biofilm mediated diseases. Thus suppression of the microorganisms and the bio films is challenging. The recurrence of the infection is more common due to the adaptive nature of the microorganisms, protective extracellular polysaccharide matrix formation and development of resistance to microbial agents. To circumvent these challenges, nanomaterials in the form of nanofibers and nanoparticles have been considered in dental therapies. The micro and nano particles are used for localised delivery of the anti-infective agents for the periodontal and endodontic diseases. The micro particles seem to have a greater potential in improving the strategies in management of the endodontic and periodontal diseases. They are very effective when directed against the periodontal pockets and root canals as they have prolonged antibacterial effect and extremely effective. Among all the natural and synthetic polymers available, copolymers of lactic and glycolide family are the most studied and versatile with reference to its availability, release profile, biodegradation time and biocompatibility [21,22,23,24].

In controlling periodontal pathogens, various antibiotics such as doxycycline, tetracycline and minocycline are used. When these antibiotics, encapsulated with the polylactic glycolic acid blend spheres, it is observed the minimal inhibitory concentration was more than required in the gingival crevicular fluid, with continuous drug release up to a week. There was significant improvement in the plaque and gingival index scorings with relative attachment levels. Calcium hydroxide nanospheres are seen to be more effective in endodontic therapy compared to the conventional calcium hydroxide. The nanoparticles can also be used in dental materials, as nanoparticles, for improving the physicomechanical properties of the dental materials. Polymeric nanoparticles such as chitosan nanoparticles, serve as a prophylactic approaches for prevention of bacterial biofilm formation and possibility of penetration into the already formed biofilms. In addition to chitosan, polylactic glycolic acid and cellulose acetate phthalate nanoparticles have been used optimally as antibacterial agents for endodontic and periodontal disease management [25]. Charged and surface charged nanoparticles have direct interaction with the microorganisms and they are helpful in the selective eradication. It is a process where selectively the bacteria are eradicated by binding to the opposite charged bacteria or pathogens. The concept utilised in both endodontics and periodontics is by usage of the photosensitisers encapsulate with the nanoparticles, in the active photodynamic therapy to eradicate the microorganisms [25]. The principle is that

the photosensitiser is preferentially taken by the bacteria and the activation of the light generates free radicals and singlet oxygen which kills the microorganisms. Specific targeting nanoparticles is a strategy where a particular and specific pathogen can be identified and targeted. It is possible via conjugation of the antibodies with the respective nanoparticles. Immunoliposomes have been used to for the precise delivery of these Antimicrobial agents for specific plaque control. Although there are currently only a limited number of endodontic and periodontal nanodrug delivery systems, there is a future hope of developing and applying these nanoparticles in the endodontic and periodontal perspective [25,26].

Conclusion

Targeted drug delivery is an effective and alternative pathway for the modern dentistry. Although it is beneficial in several ways, the delivery systems still have to be I proved for they effective delivery into the targeted tissues. And there is a hope in near future that nano targeted dentistry will improve the treatment outcomes.

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