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Advanced Drug Delivery Systems in Treating Periodontal Diseases-A Review

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Abstract: *Periodontal disease is a world-wide prevalent chronic infection which is caused by acummulation of specific microrganisms or group of microrganisms in the dental plaque,**resulting in progressive loss of the alveolar bone around the teeth with increased probing depth and recession or both.If left untreated it can lead to loosening and subsequent loss of teeth.It prevails in all groups,ethinicities ,races and both the gender.[1]**Controlled drug delivery systems represents one of the most rapidly advancing areas of science and numerous advantages include improved efficacy ,reduced toxicity and improved patients compliance and convinence.Many advanced drug delivery systems are being introduced for the intrapocket delivery of drugs at the diseased site.Non-degradable and degradable systems have been developed for the delivery of antimicrobial agents,bio-absorable dental materials,gels,ointments,films,injectables and microcapsules.*
Periodontal pocket delivery systems have emerged to a great extent with newer advances in nanotechnology which is used to regenerate the lost periodontal structures and has also shown a substantial progress .Nanorobotics is the upcoming technology creating machines or robots which assist in the repair of the tissue cells .This review approaches the main drug delivery systems for the adminstration of drugs into the periodontal pocket and also their advancements and effectiveness in periodontal therapy.
Keywords: *Drug delivery, Advanced systems, Nanotechnology.*

I. Introduction

Periodontal diseases are recognized as a major dental problem throughout the world. It is characterized by inflammation and degeneration of the gums, supportingbone, periodontal ligament and cementum. The epithelium of the gingiva migrates along the tooth surface forming periodontal pockets that provide an ideal enviroment for the growth and proliferation of the microbes.[2]More severe stages lead to the loosening and loss of the teeth.Local delivery has the advantage of achieving higher concentrations of the drug to the intended site of action using lower dosage with an associated reduction in side effects and toxic effects.For example dentrifices, mouthrinses, dentalgels, irrigation devices and syringes.

Mouth rinses and dentrifices are considered inefficent because of the short period of contact of the drug within the tissues and lack of adquate penetration into the periodontal pocket. Dental irrigation helps in the reduction of the subgingivalmicroflora and dental plaque. Gels like metronidazol, tetracycline,minocycline can allow in accurate dosage and produced small improvements in clinical and microbiological parameters.[3][4]

II. Systemic Adminstration Of Drugs

Systemic antibitoic therapy should be reserved for juvinile periodontitis ,patients with medical history requiring antibiotic coverage,patients with severe and acute periodontal infections.Metronidazole in combination with amoxicillin or ciprofloxacin have been used sucessfully for the treatment of advanced Actinomycetemcomitans.The combination of metronidazole with broad spectrum antibiotics shows colonization resistance by means of antibiotics.The treatment of periodontitis usually ivolves the systemic regimen with antibiotics which alter the pathogenic flora.Furthermore ,some tertracyclines ,by inhibiting collangenase,seem to diminsh bone destruction.Another approach is to surgically eliminatee the pocket and recontour the bone to encourage alveolar growth.Synthetic flavonoid derative is employed in the senile osteoporosis .

III. Drug Delivery Systems

DRUG DELIVERY refers to approaches,formulations,technologies and systems for transporting pharmaceutical compound in the body as needed to safely achieve therapeutic effect.It is concept heavily intergrated with dosage form and route of adminstration.Current efforts in the area of drug delivery include the development of targeted delivery in which the drug is only active in the targeted area and sustained release formulations in which drug is released over a period of time in a controlled manner from a formulation,avoid the the host defence mechanisms and circulate to its intended site of action.Types of sustained release formulations include liposomes ,drug loaded biodegradable microspheres and drug polymer conjugates.

IV. Local Drug Delivery Systems

FIBERS:Fibers or thread like devices placed circumferentially into the pockets with an applicator and secured with cyanoacrylate adhesive for the sustained release of the trapped drug into the periodontal pockets.Examples are Tetracycline fibers and Chlorhexidinefiber.Goodson's first delievry devices involved hollow fibers of cellulose acetate filled with tetracycline.By which tetracycline is simply released by diffusion through the reservoir wall as these devices are designed without rate control delivery.[5]These fibers produce rapid and sustained release of the drugs marginally into the periodontal pocket.[6]It is indicated as an adjunct to scaling and root planing for the reduction of pocket depth and bleeding on probing in patients with adult periodontitis.[7][8]

V. Injectable Drug Delivery Systems

Injectable drug delivery systems can be rapidly delivered using syringe without causing pain .It is used for the delivery of antibiotic agents directly into the peridontal pocket easily with therapeutic agents and reaches to large population of pathogens inside the pocket.The cost of the therapy is considerably reduced compared to the need of time for the placement.

Two types of injectable drug delivery systems have been studied in periodontal diseases-biodegradable microparticles and gels.[6]

Biodegradable microparticles:**M**icroparticles based on biodegradable polymers are PLA and PGLA,poly-lactide and poly-lactide-co-glycoliderespectively.They contain tetracycline that have been designed for periodontal disease therapy.[9]Lactide /glycoide ratio determines the releae rate of tetracycline and by the pH of the medium;as the tetracycline release rate increases as the pH increases.PLGA microspheres are being used for the delivery of histatins.[10]

PLGA microspheres containing minocycline are used as an adjunct to scaling and root planing and in patients with adult periodontitis.The minocycline drug delivery system showed a significant reduction of Porphyromonasgingivalisspp 1 month after the therapy and also showed a reduction of probing depth ,whereas there was no improvement in the loss of attachment.[11]

GELS:

Semisolid or gel formulations can have some advantages of achieving local delivery into the periodontal pockets.Theyposses a higher biocompatibility and bioadhesivity allowing adhesion to the dental pocket and finally they can be rapidly eliminated through normal catabolic pathways ,decreasing the risk of anaphylactic reactions at the application site.Various gels used are tetracycline ,metronidazole ,metronidazole benzoate as well as a combination of tetracycline and metronidazole benzoate and achieved satisfactory results.[12][13]

FILMS:

Films are the matrix delivery sytems.The dimensions and shape of the flim can be easily made to correspond to the dimensions of the base of the pocket to be treated without causing any discomfort to the patient.Bigger films either could be cut or punched into appropriate sizes as to be inserted into the site of action.They are classified into degradable and non-degradable**.**Some of the filsms used are Gelatin containing chlorhexidine hydrochloride ,Polymethacrylate films for the intrapocket delivery of tetracycline,metronidazole and chlorhexidine and PLGA containing tetracycline for modulated release of drug in the periodontal pocket.[12]

VI. Strips And Compacts

Strips which comprise polymers and active ingredients for treatment of periodontal diseases have been developed. These strips are said useful for the treatment of plaques and inflammation beneath the gingival margin. The strips can be applied directly to the lesional region to be treated, and therefore, the active ingredient can be concentrated to the desired site selectively. This modified therapeutic method has been proved to be more effective than any conventional pharmacotherapy.This modified therapeutic method has been proved to be more effective than any conventional pharmacotherapy.[14][15]

Acrylic strips have been fabricated using the mixture of polymers,monomers and different concentrations of any antimicrobial agents.They were fabricated either by solvent casting or pressure melt method.strips containing metronidazole, tetracycline and chlorhexidine demonstrated a decrease in number of motile spirochete rods.In a later development ,the evaluation of amoxycillin-clavulainic acid loaded acrylic strips is reported.

Once a strip is placed in periodontal cavity, the polymer swells, expands, and reaches narrow crevices and furcations of the treated cavity, carrying active agent throughout the cavity. This provides most desirable efficacy at treatment site.[14].Highest level of antibacterial agent was released during the first 24 hrs period followed by release of therapeutic level of drugs for a subsequent 9 days period.Effect persisted even after 3 week of removal of acrylic strips.

VII. Advanced Drug Delivery Systems

Periodontal Chip:

A pharmaceutical composition which is applied to the peridontal pocket for the purpose of treating periodontal diseases.The pharmaceutical composition which is provided in the form of the gel,sheet,film or bar-like formulation ,releases a controlled and effective amount of an active ingredient at the periodontal pocket.There are many advantages of using periodontal chip like it may employ those antimicrobial agents which are not suitable for systemic adminstration,such as various broad spectrum antibitotics.[30]

It is available commerically as Periocol-CG which is small,orange brown in a rectangular chip form ,rounded at one end for easy insertion into the periodontal pockets.Controlled-release of biodegradable Chlorhexidine (CHX) (2.5 mg) chip when used as an adjunct to scaling and root planing reduces probing depth (PD) and improves the clinical attachment level (CAL) in adult periodontitis, following 1 hour of scaling and root planing (SRP) in patients free of supragingival calculus, the chip was placed in target sites with PD 5 to 8 mm which bleed on probing. Chip placement was repeated at 3 and/or 6 months if PD remained ≥ 5 mm.[16]

VIII. Nano Drug Delivery Systems

Mordern drug delivery systems are designed to provide a targeted contolled slow drug release system.Nanotechnology advances are the cornerstone of a paradigm shift in targeting and safely delivering agents thereby improving controlled release,improving patient safety delivering agents and compliance,and reducing side effects.Through the use of the collodial chemistry example liposomes and micelle encapsulation,dendrimers and nano crystals.

Nano materials are currently being investigated for novel drug delivery and tissue engineering. Local targeted delivery has been enhanced by use of nanosensors, nanoswitches, and other nano delivery systems. Triclosannano particles were able to reduce gingival inflammation. [17]Arestin is one such example where tetracycline incorporated into microspheres and has shown promising results when locally delivered into periodontal pockets

The main aim of nano drug delivery system is the entry of the drug into the cell by endocytosis only using nanoparticles as carriers and a targeted delivery of the drug to the desired tissue or cell so as to minimize the side effects.Examples of nanoscale delivery vechicles are now under investigation include polymeric particles,dendrimers,nanoshells,liposomes,magneticnanoparticles,gold nanoparticles etc.

IX. Nanoparticles

A nanoparticle is a subnicroscopic solid material with the size ranging from 1-100nm.Materials used in the prepartion of nanoparticles are sterlizible ,non toxic and biodegradable like albumin ,ethylcellulose,gelatin polyesters etc.They may be biodegradable or may not be.[18][19]Nowadays,themsot common resin composites i.emicrohybrids and nanofilledcomposites,comprise filler particles ranging from 2-600 nm.Other dental nanotechnologies on the delivery of molecules that facilitates the remineralization by means of non-invasive dental techniques.In a differnet direction ,casein phosphopeptideamphorphous calcium phospate are nanoparticles that bind to bifilms,plaque,bacteria,hydroxyapetite and the surrounding soft tissues,localizingbioavalaible calcium and phosphate and serving as mineral precursors for remineralization.

Various Nanoparticles are:Nanopores,Nanotubes,Fullerenes ,Quatum dots,Nanoshells,Dendrimers,Liposomes,Nanospheres,Nanorods,Nanowires,Nanocapsules ,Nanowires.

Nanopores:

Nanopores are usually of diameters less than 20nm.Nanodevices under development with enhanced gating efficiency could play vital roles in biosensing and drug delivery. Smartnanodevicewith both "sense" and "release" functionalities for drug delivery based on a nanoporous material, mesoporous silica nanoparticles.There are recent progresses in designing intelligently gated nanoporous devices in material science and nanotechnology.[20]

Drug Delivery Using NanoporesAnd Ultrasound:

Ultrasound is a mechanical wave with frequencies greater than 20khz.Biological effects of ultrasound can often attributed either to temperature rise or cavitation activity.[21]Ultrasound is used for release of the drugs at the site of interest to perform minimally invasive,localizedtherapy.Zeolites containing network of nanopores less than 20 nm.Substitution of the nanozeolitesinitates the trapping of the arbitary drug into the nano-pores of the zeolite,which can be recovered after a time interval.Then the trapped drug can be released using ultrasonic waves to vibrate the structure of the nano-pore zeolite.This enables to augument the drug release in the damaged pocket and side effects . But still this hypothesis needs clinical data to confirm it.

Quantum Dots:

Non -toxic indium phosphide quantum dots were synthesized by the solvothermal method and then embedded into the dental resin to tune the emission color of the resin.In periodontal therapy it improves the healing of the periodontal inflammation provided by the cadmium-free and lead-free quantum dots.

Liposomal Drug Delivery:

Liposomes are attractive drug delivery or targeting vechiles by virtue of therir compatibility with the biological components and the range and extent of pay loads that they can carry.

Liposomes are small spherical systems that are synthesized from cholesterol and non-toxic phospholipids.Theypossess different characteristics depending upon the lipid of choice in the production process. Because they are natural materials, liposomes are considered attractive, harmless drug delivery carriers that can circulate in the blood stream for a long time.Liposomes release their contents by four ways:adsorption,endocytosis,lipidexchange,orfusion.When liposome entrapped drugs our adminstered they preferentialy act on the the site of infection and inflammation. Recently liposomal encapsulation of drugs offers advantages over other drug delivery systems.

AmBisome is an FDA approved liposomal formulation of amphotericin B ,which used widely for the treatment against Candida spp,Aspergillusspp,Fusariumspp, and other fungi infections,visceralleishmaniasis and methylmalonicacidaemia patients[22][23]AMB released by AmBisome while acting on the outer cell of candida spp,has a greater pharmakokineticsthan free AMB drug,including prolonged half-life of systemic circulation,reduced plasma clearance rate ,decreased renal toxicity and enhanced therapeutic efficacy.[24][25]Another sucessful example is Polyyxin B-loaded loposome which has been reconginzed for treating P.aeruginosa related infections but it has faced some of harmful side effects like muscular disordes,neuromuscularblockade,ototoxicity and nephrotoxicity.Butliopsomal encapsulation with Polymyxin B loaded liposomes reduced the occurence of side effects.[26]Ampicillin-loaded liposomes have shown elevated drug stability and higher antimicrobial activity against Salmonella Typhimurium and liposomal vancomycin have significantly enhanced intercellular killing of methicillin-resistant Staphylococcus auerus.

Gene delivery using bubble liposomes for periodontal therapy:

The combination of Bubble liposomes and ultrasound provides an efficient technique for delivering plasmid DNA into the gingiva. This technique can be applied for the delivery of a variety of therapeutic molecules into target tissue, and may serve as a useful treatment strategy for periodontitis.

X. Polymeric Micelles

Polymeric micelles ,aresupramolecular assembly of amphiphilic block copolymers or polymer -lipid conjugates or other surface active molecules that self assemble in aqueous media to form structures with the hydrophobic core.[27]polymer micelles can be used for drug delivery as the hydrophobic interior has the capacity to hold drugs which are poorly soluble in aqueous solution."liposome" is used to indicate a micelle structure containing poorly soluble drug with a diameter <1 μm. Some may also refer to this as a "nanoparticle" or "micelle".

Micelle formation:When the amphipathic molecules are dispersed in water ,micellles formed above critical concentration are know as Critical Micelle Concentration.Ahigh CMC causes rapid exchange of the constitution components,fastdisintergration upon dilution and less stability.The molecules will rearrange to form micelles.

Micelles made up of block co-polymers are composed of hydrophobic PEG block and a hydrophobic block based on poly (aspartic acid) or poly (benzyl aspartate)with doxorubicin conjugation.The diameter of the micelles can be manipulated so as to allow the EPR effect to be observed.This will allow the accumulation of the drug at the targeted site,such as an inflamed tissue.

XI. Liquid Crystals

Liquid crystals have both properties of liquids and crystals.Molecules in the crystals are highly ordered ,whereas molecules in the liquid are free to diffuse in a random way.Ingeneralliquidcrstals can be classified as thermotropic phase formed by a change of temperature and lyotropicmesophases when mixed with a solvent.

Lyotropic crystals are reversed bicontinuous cubic and hexagonal mesophases, attracting more and more attention because of their unique microstructures and physicochemical properties. Various bioactive molecules such as chemical drugs, peptides and proteins can be solubilized in either aqueous or oil phase and be protected from hydrolysis or oxidation. Furthermore, several studies have demonstrated sustained release of bioactive molecules from lyotropic crystals.

Liquid crystals have wide range of applicarions.Liquid crystals loaded with an active drug component can be adminsteredorally,to increase the bioavailibility of poorly water-soluble drug.The formulations needs to resist the digestive process to exhibit a sustained release of oral drugs.Recentlyphytantriol is used to to form liquid crystals which exhibit non -digestible liquid crystal partickes as a novel sustained drug delivery

system.Liquid crystals used as topical drug produced suitabke lamellar liquid crystal formulations.It consists of liquid paraffin as the oil phase and a mixture of two non-ionic surfactants and azelic acid as a active drug substance.They provide a sustained release and provide long term hydration of the skin and serves as a goodcandidate for mucosal drug delivery.

Gold Nanoparticles:

Colloidal gold ,a sol comprised of nanoparticles of AU termed as gold nanoparticles, have been proven to be powerful tools in various nanomedicinal and nanomedicalapplications.Recently it has been used in diagnostic imaging,biosensing and binary cancer therapeutic techniques.It provides non-toxic carriers for drug and gene delivery applications. With these systems, the gold core imparts stability to the assembly, while the monolayer allows tuning of surface properties such as charge and hydrophobicity. An additional attractive feature of AuNPs is their interaction with thiols, providing an effective and selective means of controlled intracellular release.But however its not used much in periodontal therapy.

Nanotubes:

Carbon nanotubes are tubular structures like a sheet of graphite rolled into a cylindrical capped at one or both the ends by a buckyball.These tubes are about 10,000 times thinner than a human hair .Nanotubes can be found in several forms; single-wall (having one single shell), double-wall and multi-wall. Depending on the growth process, single-wall, double-wall or multi-wall nanotubes can be selectively produced.

Carbon nanotubes come in a variety of diameters and lengths. Depending on the growth process and treatment, nanotubes can be selectively produced with properties ranging from 1 to15 micrometers in length and diameters from 2 to 100 nanometers. These nanotube powder comes in agglomerate and aligned bundles and can be put into dispersion using ultrasound process.

Industrial Lab On Chip Delivery:

Salivary secretions contain a variety of molecules that reflect important pathophysiology activities.Quantitativechanges of specific salivary biomarkers could have significance in the diagnosis and management of oral and systemic diseases.In recent years,advancements in the fields of microfluidic and lab-on-chip technologies have provided oppurtunities for the implementation of nanoparticle production process owing to the miniaturisation of the fluidic nature.Some advantages are controlibility and uniformity of the nano material characteristics.

Nanogenerators:

Nanogenerator is a technology that coverts mechanical or thermal energy as produced by small-scale physical change into electricity.Piezoelectricnanogenerators can convert mechanical energy into electric current by bending and then releasing zinc oxide nanowires,which are both piezoelectric and semiconducting.Thenanogenerator based on Zno nanowire can be applied for implantable devices since Zno is not only biocompatible but also can be synthesized upon the organic substrate,rendering the nanogenerator to be biocompatible.[28]

Nanorobots:

Nanoroboticsor molecular robotics is an emerging research area.The field of nanorobotics deals with two areas,the first are involve the design,simulation,control and coordination of robots with nanoscale.They are made of assemblies of nanoscalecoponents with the demions between 1 to100 mm.The second area deals with manipulation of nanoscale components with nanomanipulators.Nano manipulation and nano assembly play a critical role in the development artificial nanorobots[29].

Advantages:The process is fast in a very small scale of operation,as the results are very accurate.Advanced technique which less painful .Moreover the changes of recurrence is completely eliminated.Itcan be used for preventive and restorative and curative procedures

Disadvantages:It might take several years for the implementation.its is very costly.And any introduction of artificial intelligence or artificial reconstruction will result in robots going out of control of humans.

Maintance of oral hygiene:A mouthwash full of smart nanomachines could identify and destroy the pathogenic bacteria and allowing the other harmless flora to flourish in the ecosystem.Further the devices would identify particles of food ,plaque or tartar and lift them off the teeth and rinse it away.It would be able to reach beyond surfaces which couldn be reached by bristles,fibers or floss.Subocclusally dwelling nanorobots metabolizes the trapped organic matter supra and sub-gingivally and continues to perform calculus debrimenting.It also prevents to tooth decay and halitosis.Thenanorobots do not increase the risk of septic shock because the pathogens are completely digested by the harmless sugars,amino acids.

XII. Conclusion

From the Advancements in the periodontal drug delivery systems ,it can be said that the antibiotic free ,mucoadhesive ,biodegradable nanoparticles technology has an immense oppurtunity for designing a novel,low dose and effective treatment.

Nanodentistry will make possible the maintance of comprehensive oral health by employing nanomaterials,biotechnology,including tissue engineering and dental nanorobotics.Although this technology is at an early stage,it has already made a significant clinical and commercial impact.

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