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ROLE OF NOVEL DRUG DELIVERY TECHNOLOGIES IN THE TREATMENT OF PERIODONTAL DISEASES

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ABSTRACT

Periodontal diseases are termed as the infections of the structures around the teeth, which include gums, periodontal ligament and alveolar bone. In the primitive stages it affects gums called as gingivitis, in the advanced stages, it affects other tissues also. The results of conventional methods of treatment are not satisfactory because of limitations like non localization of drug, time of exposure of the infected area to drug is very limited because of wash out due to increased salivation. Novel drug delivery plays an important role in addressing the issue. Novel drug delivery systems such as gels, nano particles, fibers and patches will ensure localization of drugs for a considerable period of time and speedy recovery from infection. This article discusses different types of novel drug delivery devices used in the treatment of periodontal diseases.

INTRODUCTION

Periodontal diseases are induced by bacteria associated with dental plaque. The nature of the periodontal disease depends on the interaction among the bacterial agent, environment, and the response of the host's defense mechanisms to the bacterial assault, mainly composed of gram negative anaerobic bacteria.[i] The most common form of periodontitis is chronic periodontitis and it can be localized or generalized (more than 30% of the teeth) depending on the amount of clinical attachment loss.[ii] A new classification scheme for periodontal and peri-implant diseases and conditions and key changes from the 1999 classification were proposed in workshop conducted jointly by the American Academy of Periodontology and the European Federation of Periodontology.[iii]Periodontal diseases encompass various pathological conditions such as chronic and aggressive periodontitis, disease-associated systemic periodontitis and necrotizing periodontitis. These conditions are characterized by a destruction of the periodontal ligament, a resorption of the alveolar bone and the migration of the junctional epithelium along the tooth surface.iii It is a local inflammatory response caused by microbial infection of a subgingival pocket coupled with subgingival plaque.[iv] Although bacteria are the primary cause of

periodontal disease, the expression of microbial pathogenic factors alone may not be sufficient to cause periodontitis.Therapeutic approaches include mechanical scaling and root planing (SRP) and in some cases surgery. After development of specific plaque hypothesis suggesting that specific bacteria caused specific forms of periodontal diseases newer treatment strategies, aiming primarily at suppression or elimination of specific periodontal diseases have been established. Putative pathogens associated with periodontal diseases are susceptible to a variety of antiseptics and antibiotics.[v,vi] Antimicrobial agents may gain access into the periodontal pocket through systemic and local route of delivery. Systemic antimicrobial agents enter subgingival pockets after intestinal absorption and distribution from the blood into oral tissues, gingival crevicular fluids and saliva.[vii]Periodontium is degenerated, alveolar bone begins to resorb and gingival epithelium migrates along the tooth surface forming a 'periodontal pocket'.[viii]

Table 1: Microbial species associated with various clinical forms of periodontitis[x]

Species	Adult	Refractory	Localized Aggressive	Early Onset
Actinobacillus	++	++	+++	++
Porphyromonasgingivalis	++ +	++	0	+++
Prevotellaintermedia	++ +	+++	++	+++
Tannerella forsythia	++ +	++	0	++
Fusobacterium nucleatum	++ +	++	+	++
Eubacterium species	++	+	NE	+
Campylobacter rectus	++	+	+	++
Treponema species	++ +	++	++	+++
Candida species	NE	0	NE	NE

NE, Not Elevated in comparison to health; o, occasionally isolated; +, less than 10% of patient positive; ++, less than 50% of patients positive;+++, more than 50%of patients positive

This periodontal pocket provides ideal conditions for the proliferation of microorganisms: primarily Gram negative, facultative anaerobic species. The micro-flora originate in periodontitis is multifaceted and composed mainly of anaerobic bacteria gram negative.[ix] Moreover studies have shown that the various clinical forms of periodontitis are associated with different microbiota (Table 1).[x]

Systemic administration has been useful in treating periodontal pockets, but repeated, long-term use of systemic antibiotics is fraught with potential danger including resistant strains and superimposed infections. Local administration, therefore provide a useful answer to these problems. The principle requirement for effectiveness of this form of therapy is that the agent reaches the base of the pocket and is maintained there by some means like reservoir for an adequate time for the antimicrobial effect to occur.[xi] Numerous local drug transport products have undergone preliminary assessments but only a few methods have been evaluated in several studies.[xii,xiii]

DRUG DELIVERY DEVICES:

Goodson et al in 1979 first proposed the concept of controlled delivery in the treatment of periodontitis. It has been observed that the local route of drug delivery can attain 100-fold higher concentrations of an antimicrobial agent at subgingival sites compared with a systemic drug regimen. This reduces the total patient dose by over 400 fold thereby reducing the potential problems with the use of systemic antibiotic drug regimens and development of drug-resistant microbial populations at non oral body sites. These can be safely used in medically compromised patients for whom surgery is not an option and contraindicated in patients with known hypersensitivity to the antimicrobial used,

asthmatics and infective conditions such as AIDS, Tuberculosis.[xiv] Local delivery devices can be of two types according to the duration of medicament release

a) Sustained Release Formulations: It follows First order kinetics i.e., the rate of elimination is directly proportional to drug concentration, providing drug delivery for less than 24 h.[xv]
b) Controlled Release Formulation: It follows Zero order (linear) kinetics i.e., the rate of elimination remains constant irrespective of drug concentration, clearance decreases with increase in concentration (or) a constant amount of the medication is eliminated per unit time.

Drug delivery systems can be classified according to the mechanism controlling drug release.

1. 'Solvent controlled' matrix systems based on macromolecular matrix permeability to small molecules after matrix swelling into hydrated medium.
2. 'Reservoir systems' controlled by drug diffusion across a polymeric membrane.
3. 'Chemically controlled systems' where the rate of drug release is controlled by the rate and extent of degradation of chemical bonds and the erosion of the polymeric matrix.

Intra pocket devices can be of two types depending on degradability.

1. Non Degradable devices (first generation)
2. Degradable devices (second generation)

Non degradable devices have the advantage that the therapist controls the removal and therefore has greater control over the time of exposure of the pocket environment to the drug. The biodegradable devices have the advantage of requiring the patient to visit once only to therapist for the placing the deivce in periodontal pocket. Professionally applied sustained subgingival drug delivery systems may be attained with drugs possessing a high intrinsic substantivity for tooth root surfaces.[xvi]

Various local drug delivery systems used in the treatment of chronic periodontitis

Fibers, Film, Injectable systems, Gels, Strips and compacts, Vesicular systems, Micro particle system and Nanoparticle systems are studied the most. The formulations are summarized in Table 2.

FIBERS: Fibers, or thread-like devices, are reservoir-type Systems, placed circumferentially into the pockets with an applicator and secured with cyanoacrylate adhesive for the sustained release of then trapped drug into the periodontal pocket. Several polymers such as poly (ε-caprolactone) (PCL), polyurethane, polypropylene, cellulose acetate propionate and ethyl vinyl acetate (EVA) have been investigated as matrices for the delivery of drug to the periodontal pocket[17].[xvii] Examples are chlorhexidinefibers and tetracycline fibers.

FILMS: Films are matrix delivery systems in which drug are distributed throughout the polymer and release occurs by drug diffusion and/or matrix dissolution.[xviii] These films were made by casting ethanol or chloroform solution into molds and allowing the solvent to evaporate. The appropriate drug and plasticizing agent were incorporated into the solution prior to casting. The dried films (200–300 μm thick) were then cut into the required shapes.[xix]

Table 2: Periodontal formulations

System	Polymer Matrix	Drug Incorporation
Fibers	Cellulose acetate	Tetracycline HCl
		Chlorhexidine
	Ethylene vinyl acetate	Tetracycline HCl
	Poly (ε-caprolactone) (PCL)	Tetracycline HCl
Films	Ethylcellulose	Metronidazole, Minocycline, Tetracycline HCl
	Cross-linked atelocollagen	Tetracycline
	Gelatin (BycoW protein)	Chlorhexidine diacetate
	Cross-linked gelatin + glycerine	Chlorhexidinedigluconate
	Chitosan	Taurine
	Chitosan + PLGA	Iproflavone
	Sodium alginate	Ofloxacin and metronidazole[xx]
	Calcium alginate	Ofloxacin[xxi]
	Sodium alginate	Cephalexin[xxii]
	Chitosan	Moxifloxacin[xxiii]
	Chitosan + PCL	Metronidazole
	PLGA	Tetracycline
	Poly(ortho ester)	Metronidazole
	Eudragit LW and Eudragit SW	Clindamycin
	PCL	Minocycline
Gels	Chitosan	Metronidazole
	HEC + polyvinylpyrrolidone	Tetracycline
	HEC + polycarbophil	Metronidazole
	Poloxamer 407 + Carbopol 934P	Propolis
	Poloxamer 407 + Carbopol 934P	Metronidazole
	PLGA	Tetracycline
Vesicles	Phosphatidylinositol	Triclosan
	Immunoliposomes	Anti-oralis
Micro particles	Pluronic F 127	Tetracycline
	PLGA	Tetracycline
	PLGA + PCL	Doxycycline
Nano particles	PLGA	Harunganamadagascariensis leaf extract
	Chitosan	Antisense oligonucleotide
	Cellulose acetate phthalate	Triclosan
	PLGA	Triclosan
Other systems	Poly(ethylene-co-vinyl acetate)	Acyclovir
		Chlorhexidine

A Sustained release biodegradable device composed of hydrolyzedgelatin matrix, cross linked with gluteraldehyde, glycerin and water into which 2.5 mg chlorhexidinegluconate has been incorporated named PerioChip® have been developed in 1998. It is a small, orange-brown, tombstone-shaped chip (4.0×0.5×0.35 mm) and has been approved by FDA[20].[xxiv] The adjunctive use of the chlorhexidine chip results in a significant reduction of pocket depth when compared with both scaling root planing alone and the adjunctive use of a placebo chip.[xxv,xxvi,xxvii] Perio Chip releases chlorhexidine in a biphasic manner, initially releasing approximately 40% of the chlorhexidine within the first 24 h, and then releasing the remaining chlorhexidine in an almost linear fashion for 7–10 days.[xxviii]

PERIOCHIP®is a biodegradable chip, which contains 2.5 mg of ChlorhexidineGluconate that has been shown to be an effective and well tolerated adjunctive treatment for reduction of pocket depth (PD) in patients with adult periodontitis with a PD greater than or equal to 5mm, when used with scaling and root planning.

GELS: Mucoadhesive metronidazole (MTZ) containing gel systems based on hydroxyethyl cellulose, carbapol 974, and polycarbophil have been used in the studies. Gel is applied subgingivally with the help of blunt cannula or syringe. The gel is only marginally effective in decreasing the anaerobic bacterial count. This may be due to the lownumber of bacteria susceptible to MTZ or due to presence of bacterial biofilm. Locally applied controlled release DOX gel may partly counteract the negative effect of smoking on periodontal healing following no surgical therapy.[xxix] The first tetracycline gel was tetracycline base loaded into the microtubularexcepienthalloysite, which was coated with chitosan to further slow down drug release. The safety profile, long–term retention, antimicrobial activity suggests that tetracycline containing copolymer gels represent a safe and effective biodegradable therapy for periodontitis.

INJECTABLE GELS: Along with the solid devices, semisolid formulations have also received reasonableattention for the localized delivery of drugs. For retention in the pocket, the formulationneeds to undergo a change into a sticky semisolid or solid phase so that it will preventthe drug from being washed out of the pocket by the gingival crevicular fluid (GCF) flow. Inspite of the relatively faster release of the incorporated drug, these gels can be moreeasily prepared and administered. They possess higher biocompatibility andbioadhesivity, allowing adhesion to the dental pocket and they can be rapidlyeliminated through normal catabolic pathways, reducing the risk of irritation or allergichost reactions at the application site. Various oleogels and hydrogels for the delivery oftetracycline (2.5%), metronidazole (25%) metronidazole benzoate (40%), as well as acombination of both tetracycline (2.5%) and metronidazole benzoate (40%), has beentested and satisfactory results have been achieved. The gels composed of cellulosederivatives such as hydroxypropylmethyl cellulose and hydroxyethyl cellulose do notappear to have sustained release properties. Despite the rapid drug release and poorretention of these gels, positive clinical results were obtained in moderate to deep periodontitis. Bioadhesion or mucoadhesion is a preliminary requirement for prolonged release of the drug at the site. Chitosan, a novel biodegradable natural polymer, in a gel form (1%, w/w) with or without 15% metronidazole, had demonstrated effectiveness in the treatment of chronic periodontitis. Bioadhesive semisolid, polymeric system can be utilized as an important intra-pocket delivery vehicle because it can easily pass through a cannula into a periodontal pocket where it solidifies *in situ* to deliver the therapeutic agent for a prolonged period. These systems exhibit a pseudo plastic flow and thermo responsive behavior, existing as a liquid at room temperature and gel at 34–37°C. Another system composed of Poloxamer 407 and Carbopol 934P and containing propolis extract (red or brown resinous substance collected by honeybees from tree buds) was designed for the treatment of periodontal disease. Moxifloxacin loaded periodontal films were prepared with chitosan crosslinked with sodium citrate using solvent casting technique. The films showed initial burst release followed by sustained release of moxifloxacinupto 15 days.[xxiii] Sodium alginate was employed for the first time as periodontal film by Katakam et al.[xxii]

Sodium alginate films were prepared by solvent casting method followed by ionic gelation using calcium chloride as crosslinking agent to form calcium alginate films. Various drugs such as combination of ofloxacin-metronidazole, ofloxacin and cephalexin were used as antimicrobial agents in the periodontal films of sodium alginate.[xx,xxi,xxii] The Atrigel loaded with 10% doxycycline hyclate showed high levels of doxycycline (250 mg/mL) in the Gingival Cervicular Fluid (GCF) for a period of seven days. The levels of 10–20 mg/mL were still present for three to five days after the polymer had been removed. In another study Atrigel containing 5% sanguinarine was found to be superior to the control in the treatment of adult periodontitis and the findings have been recently confirmed in a human clinical trial. Biodegradable gels are other useful prospects for the delivery of therapeutic agents into periodontal pockets. Bioerodible lactic glycolic acid gels were found to be safe and tetracycline levels observed at days 3 and 8 probably represent significant antimicrobial efficacy. Use of a clindamycin hydrochloride gel inserted into the periodontal pockets once a week for two weeks enhanced the effect of scaling and root planing on the sub gingival micro flora of adult periodontitis.[xxx]

Tetracycline or a mixture of tetracycline and citric acid gels has been used in moderate pockets, using a 5 min burnishing technique to burnish the gel into the roots subgingivally, with or without root planing. Tetracycline plus citric acid had been used to attain attachment gain. An adverse effect caused by the low pH of citric acid is that it delays wound healing. Beneficial effects of the acidic gel is that it can cause elimination or diminution of surface smear layer resulting from incomplete removal or translocation of dentin, plaque, calculus and cementum following root planing. Surface demineralization may occur and this could enhance new attachment by detoxifying the root. Non-root planed surfaces showed altered morphology, indicating potential chemical dissolution of the surface and demineralization.[xxx] Studies have supported the positive role of antiinflammatory agents in the treatmentof periodontal disease. Williams and co-workers have investigated the effect of topicalapplication of a non steroidalantiinflammatory drug flurbiprofen on periodontal disease progression in beagle dogs. Dogs treated with 0.3 mg flurbiprofen applied to thegingival margin daily shows considerably less tooth loss than untreated control dogsover the seven-month study.[xxx]

STRIPS AND COMPACTS

Strips are thin and elongated matrix bands in which drugs are distributed throughout the polymer. Generally, strips are made up of flexible polymers having a position securing mechanism, and accommodate a wide range of interproximal spacing.[xxxi]Acrylic strips have been fabricated using a mixture of polymers, monomers and different concentrations of antimicrobial agents. Strips were fabricated either bysolvent casting or pressure melt method. Strips containing tetracycline, metronidazole or chlorhexidine demonstrated a decrease in number of motile rods, notably spirochetes. In a later development, the evaluation of amoxicillin–clavulanic acid loaded acrylic strips is reported. Highest level of antibacterial agent was released during the first 24 h period followed by release of therapeutic level of drugs for a subsequent nine day period. The effect persisted even after three week of removal of acrylic strips. Tissue adhesive implants were made using n-butyl-2-cyanoacrylate as a drug trapping material and slowly release the drug when used in the structure of a biodegradable local drug delivery device. Ornidazole dental implants containing ethyl cellulose, hydroxy propyl

cellulose, hydroxy propyl methyl cellulose, eudragit-RL-100 and di butyl phthalate by solvent casting technique result showed that drug release was initially high on day one to achieve an immediate therapeutic level of drug in pocket, followed by a marked fall in release by day two.[xxxii]Chlorhexidine slow release devise has been made and it is antibacterial effect has been evaluated by agar diffusion test.

VESICULAR SYSTEMS

Liposomal system was designed to mimic the bio-membranes in terms of structure and behaviour and hence investigated intensively for targeting periodontal biofilms. The targeting of vesicles to adsorbed films of bacteria was thought to be due to the interaction of the surface polymers of the bacterial 'glyco-calyx' with vesicles incorporating lipids with polyhydroxy head groups. The adsorption of cationic vesicles over biofilms of skin associated bacteria Staphylococcus epidermidis, having negative charge succcinylated Con A-bearing liposomes (proteoliposomes) have been foundto be effective for the delivery of triclosan.[xxxiii]Triclosan is a very effective bactericide, which is only sparingly soluble in water, but it is capable of being trapped in the liposomal bilayers. Even after very short exposures the succinylated Con A-bearing vesicles are retained by the bacteria eventually delivering triclosan in the cellular interiors to cause selective targeting of the invading pathogens.[xxxiv]

MICROPARTICLE SYSTEM

These are dissolution-controlled polymeric reservoir devices, which may deliver their content with a prolonged release profile in the salivary or crevicular fluid. Microcapsules prepared from lactic acid/glycolic acid copolymers have been proposed for delivery of tetracycline and minocycline. PLGA microspheres containing minocycline have been formulated and have been used for the elimination of Porphyromonasgingivalis from the periodontal pocket and lesd to reduction in periodontal pocket depth in chronic periodontiits.[xxxv,xxxvi,xxxvii]Microparticles of poly (dl-lactic-coglycolic acid) (PLGA) containing chlorhexidine free base, chlorhexidine di gluconate and their association or inclusion complex with methylated-beta-cyclodextrin (HPBCD) were prepared with single emulsion, solvent evaporation technique.[xxxviii]

A local drug delivery system containing ofloxacin base on swelling controlled system was developed by Nakahara et al., (2003). This comprised hydroxypropyl cellulose (HPC) and methacrylic acid copolymers (MACS) as its base material and ofloxacin, a superior pyridone quinolone derivative as a drug to be delivered. This product acts in a bi-phasic manner, first rapid release of ofloxacin from HPC and followed by slow release from MACS.[xxxix] Recently to regenerate periodontal tissues, a sandwich membrane composed of a collagen sponge scaffold and gelatin microspheres containing basic fibroblast growth factor (bFGF) in a controlled-release system was developed.[xl]

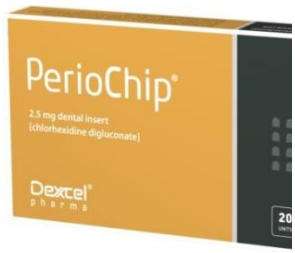
NANOPARTICLE SYSTEMS

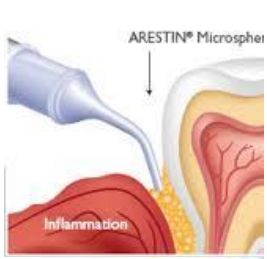
Modern drug delivery systems are designed for targeted controlled slow drug release. Up to now polymer or microparticle-based hydrogels have been applied in dentistry, which can affect the rate of release because of their structure. Recently, intensive research has been performed all over the world to improve the effectiveness of delivery systems. The nanoparticulate system provides several advantages as compared with microspheres, microparticles and emulsion-based delivery systems,

including high dispersibility in an aqueous medium, controlled release rate and increased stability. Nanoparticles owing to their small size penetrate regions that may be inaccessible to other delivery systems, such as the periodontal pocket area below the gum line. These systems reduce the frequency of administration and further provide a uniform distribution of the active agent over an extended period of time. Biocompatible nanoparticles composed of 2-hydroxyethyl methacrylate (HEMA) and polyethyleneglycoldimethacrylate (PEGDMA) could be used as a drug delivery system for dental applications. List of commercial periodontal products presented in various dosage forms is given in Table 3 and Fig. 1.

Table 3: List of commercial periodontal products presented in various dosage forms[xl]

Product	Antimicrobial agents	Dosage form	Manufacturer
Actinide®	Tetracycline	Non resorbale fiber	Alzacorp
Arestin®	Minocycline	Biodegradable powder in syringe	Oropharma corp Warminster
Atridox®	Doxycycline	Biodegradable mix in syringe	Atrix Labs, Ft, Collins, Co
Dentamycin®	Minocycline	Biodegradable mix in syringe	Sunstar Corp. , Tokyo, Japan
Elyzol®	Metronidazole	Biodegradable mix in syringe	Dumex Crop. Co Denmark
Periochip®	Chlorhexidene	Biodegradable device	DexcelPharmaInc Jerusalem
Periochop®	Chlorhexidene / Tertracycline	Film	Perioproducts Ltd
Periochip®	Gluconate	Inserts	Perioproducts Ltd
Gluconate®	Metronidazole	Inserts	Perioproducts Ltd
Elyzol®	Minocycline	Gel	Dumexpharma
Atrigel®	Doxycycline	Gel	Atridox (atridox lab)





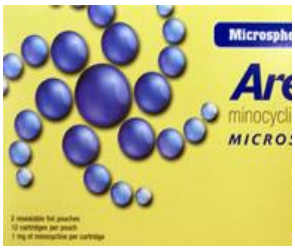


Fig 1: Commercial periodontal products available in market [xli,xlii,xliii,xliv,xlv,xlvi]

Future perspectives: Targeted gene therapy *in vivo*

Major advances have been made over the past decade in the reconstruction of complex periodontal and alveolar bone wounds that have resulted from disease or injury. Developments in scaffolding matrices for cell, protein and gene delivery have demonstrated significant potential to provide "smart" biomaterials that can interact with the matrix, cells and bioactive factors. The targeting of signaling molecules or growth factors (via proteins or genes) to periodontal tissue components has lead to significant new knowledge generation using factors that promote cell replication, differentiation, matrix biosynthesis and angiogenesis. A major challenge that has been less studied is the modulation of the exuberant host response to microbial contamination that plagues the periodontal wound microenvironment. For improvements in the outcomes in periodontal regenerative medicine, scientists will need to examine dual delivery of host modifiers or anti-infective agents to optimize the results of therapy. Further advancements in the field will continue to rely heavily on multidisciplinary approaches combining engineering, dentistry, medicine, and infectious disease specialists in repairing the complex periodontal wound environment.

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