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Review Article

LOCAL DRUG DELIVERY SYSTEMS IN THE TREATMENT OF PERIODONTITIS: A REVIEW

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ABSTRACT

Periodontitis, a disease involving supportive structures of the teeth prevails in all groups, ethnicities, races and both genders. It is a localised inflammatory response caused by bacterial infection of a periodontal pocket associated with subgingival plaque. Periodontal diseases include conditions such as chronic periodontitis, aggressive periodontitis and necrotizing periodontitis. Aggressive forms of periodontitis can be localized or generalized. Antibacterial agents have been used effectively in the management of periodontal infection. The effectiveness of mechanical debridement of plaque and repeated topical and systemic administration of antibacterial agents are limited due to the lack of accessibility to periodontopathic organisms in the periodontal pocket. Systemic administration of drugs leads to therapeutic concentrations at the site of infection, but for short periods of time, forcing repeated dosing for longer periods. Local delivery of antimicrobials has been investigated for the possibility of overcoming the limitations of conventional therapy. The use of sustained release formulations to deliver antibacterials to the site of infection (periodontal pocket) is gaining interest. These products provide a long-term, effective treatment at the site of infection at much smaller doses. This review approaches the main delivery systems for the administration of drugs to the periodontal pocket, their usefulness, as well as the advancement of these systems effectiveness in the periodontal therapy.

Keywords: Periodontal disease, Periodontal pocket.

INTRODUCTION

Periodontal disease is a general term which encompasses several pathological conditions affecting the tooth supporting structures. Periodontal diseases include conditions such as chronic periodontitis, aggressive periodontitis, systemic disease-associated 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.[1] It is a localised inflammatory response caused by bacterial infection of a periodontal pocket associated with subgingival plaque.[2] Although bacteria are the primary cause of periodontal disease, the expression of microbial pathogenic factors alone may not be sufficient to cause periodontitis. Periodontal pathogens produce harmful by-products and enzymes that break extracellular matrices as well as host cell membranes to produce nutrients for their growth. In doing so, they initiate damage directly or indirectly by triggering host-mediated responses that lead to self-injury.[3] In the early phase of the disease (gingivitis), inflammation is confined to the gingiva but extends to deeper tissues in periodontitis, leading to gingival swelling, bleeding and bad breath. In the late phase of the disease, the supporting collagen of the

periodontium is degenerated, alveolar bone begins to resorb and gingival epithelium migrates along the tooth surface forming a 'periodontal pocket'.[2] This periodontal pocket provides ideal conditions for the proliferation of microorganisms: primarily Gram negative, facultative anaerobic species. The microflora found in periodontitis is complex and composed mainly of Gram negative anaerobic bacteria.[3] Moreover; studies have shown that the various clinical forms of periodontitis are associated with different microbiota[4] (Table 1). The periodontal pocket, however, remains and if it continues to harbour the bacteria associated with the disease, a potential for a further destructive phase exists. The disease may then require extensive treatment, failing which the teeth may be lost. Therefore, clearance of the subgingival infection and elimination of the periodontal pocket are considered a priority in the treatment of periodontitis. Figure 1 summarises the possible pathogenic mechanism of periodontal diseases.

Advances in the understanding of the aetiology, epidemiology and microbiology of the periodontal pocket flora have revolutionised the therapeutic strategies for the management of periodontal disease progression.[2] The value of administering antimicrobial agents as an inexpensive and rapid means of augmenting mechanical periodontal debridement is worth consideration. The therapeutic success or failure depends not only on the antimicrobial activity of the chemotherapeutic agent but also on the location of infection, carrier system and route of administration.[5] This review highlights the current approaches to periodontal therapy and aims to identify areas where further research may lead to an effective treatment for periodontal infectious disease. This review also addresses practical problems regarding the use of currently available systems and summarises some key factors for the development of improved intra-pocket delivery systems approaching to ideal characteristics with a high degree of acceptance by the professionals as well as the patients.

Drug Delivery Devices

There are two possible approaches to improve the drug action: (i) Sustained and controlled drug release to reduce or eliminate side effects by improving the therapeutic index; (ii) Site specific drug delivery to minimize systemic effects. These two strategies have been explored by the association of drugs with different vehicles, either naturals or synthetics. However, most of these systems failed to realize their potential in clinical phase studies. In this respect, it is critical not to under-estimate problems such as weak therapeutic activity resulting from a limited accessibility to the tissue to be treated or toxicity and/or immunogenicity of the delivery system.[6] Synthetic polymers have proved to be extremely interesting because they can be tailor-made to meet pharmacological or biological requirements. Drug delivery systems can be classified according to the mechanism controlling drug release. We distinguish three categories: (i) Solvent controlled' matrix systems based on macromolecular matrix permeability to small molecules after matrix swelling into hydrated medium; (ii) Reservoir systems' controlled by drug diffusion across a polymeric membrane; (iii) 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. For all these systems, the basic polymer can be of natural origin such as proteins[7]or collagen[8], semi-synthetic such as cellulose derivatives[9,10] or synthetic, all of which must preferably degrade during use. Natural polymers have been considered as biodegradable carriers.[11] However; most of them have disadvantages inherent to their structure, including limited half-life, complexity of composition and immunogenicity due to the polymer itself or to its degradation by-products. Many polymer based systems for antibiotic delivery in the treatment of periodontal diseases have been studied and evaluated in vitro and/or in vivo. Unfortunately, the majority of the studies provide little indication of the effect of the preparation on the progression of periodontitis. In addition, few clinical data were reported and therefore no association between changes in the flora and changes in disease patterns could be established. Some of these systems are not resorbable, while most are biodegradable. Non biodegradable systems have to

be removed after complete drug release, which may cause irritation and inflammation of the treated site. Conversely, a biodegradable sustained release drug delivery system which can be placed into the periodontal pocket and maintain therapeutic concentrations for prolonged periods of time would be advantageous.

Indeed, in addition to improving compliance over systemic antibiotics, biodegradable devices are cost effective as they will not require a second visit to the periodontist for removal. To be useful for periodontal therapy, it is desirable to have a bioerodible drug delivery system that can maintain an effective drug release rate in the periodontal pocket while simultaneously eroding throughout the duration of treatment up to several days.

Periodontal Local Drug Delivery

Goodson et al in 1979 first proposed the concept of controlled delivery in the treatment of periodontitis. The effectiveness of this form of therapy is that, it reaches the base of periodontal pocket and is maintained for an adequate time for the antimicrobial effect to occur. Periodontal pocket provides a natural reservoir bathed by gingival crevicular fluid that is easily accessible for the insertion of a delivery device. These delivery systems are also called sustained release, controlled-release, prolonged release, timed release, slow release, sustained action, prolonged action or extended action. There are distinct phases in a periodontal treatment plan where a dental practitioner can use this sustained release device

- As an adjunct to Scaling and Root planing.
- Periodontal maintenance therapy: Recurrent periodontitis usually involves only a few teeth. These sites are ideal for the treatment with this device.
- For whom surgery is not an option or those who refuse surgical treatment.
- Sustained release device is a less invasive treatment option and it requires less time compared to surgical treatment.

So patients with moderate periodontitis should receive non-surgical therapy to halt periodontal disease and limit the extent of surgical intervention needed in the future. Intra pocket devices can be divided in two broad categories depending on degradability. Nondegradable devices (first generation) and degradable devices (second generation) Non degradable devices have the advantage that the therapist controls the removal of the device and therefore has greater control over the time of exposure of the pocket environment to the drug. The degradable device has the advantage of requiring the patient pay only a single visit to therapist for the insertion of the device. This minimizes the patient visits and ensures compliance. Patient revisit for the removal of the device can be avoided.

Local Drug Delivery Systems for Treating Periodontitis

Various local drug delivery system for treating periodontitis-Fibers, Film, Injectable systems, Gels, Strips and compacts, Vesicular systems, Microparticle system, Nanoparticle system etc.

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(ecaprolactone) (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.[14] Examples are Chlorhexidine fibers and tetracycline fibers.

Films

A far more widely used form of intra-pocket delivery device has been in the shape of film, prepared either by solvent casting or direct milling. Bigger films either could be applied within the cavity onto the cheek mucosa or gingival surface or could be cut or punched into appropriate sizes so as to be inserted into the site of action. Films are matrix delivery systems in which drugs are distributed throughout the polymer and release occurs by drug diffusion and/or matrix dissolution or erosion. This dosage form has several advantageous physical properties for intra-pocket use. [15] The dimensions and shape

of the films can be easily controlled according to the dimensions of the pocket to be treated. It can be rapidly inserted into the base of the pocket with minimal discomfort to the patient. If the thickness of the film does not exceed 400 mm, and it has sufficient adhesiveness, it will remain submerged without any noticeable interference with the patient's oral hygiene habits. Films that release drugs by diffusion alone are prepared using water-insoluble non-degradable polymers, whereas those that release by diffusion and matrix erosion or dissolution use soluble or biodegradable polymers.[16] Films of various polymers have been made for the controlled release of therapeutic agents. Sustained release devices composed of cross-linked fish gelatin (bycoprotein) containing chlorhexidine diacetate or chlorhexidine hydrochloride have been developed by Steinberg. Films based on synthetic biodegradable polymers such as poly (Lactide-co-glycolide) (PLGA) containing tetracycline have been developed for modulated-release of drug in the periodontal pocket as slab like device.[17]

Injectable Systems

Injectable systems are particularly attractive for the delivery of antibiotic agents into the periodontal pocket. The application can be easily and rapidly carried out, without pain, by using a syringe. Thus, the cost of the therapy is considerably reduced compared to devices that need time to be placed and secured. Moreover, an injectable delivery system should be able to fill the pocket, thus reaching a large proportion of pathogens.

Microparticles

Microparticles based system of biodegradable poly alpha hydroxy acids such as poly lactide (PLA) or poly (lactide-co-glycolide) PLGA containing tetracycline has been designed for periodontal disease therapy. PLGA microspheres containing minocycline have been formulated and have been used for the elimination of Porphyromonas gingivalis from the periodontal pocket. 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.[18] Non-biodegradable as well as biodegradable materials have been investigated for the preparation of microspheres. These materials include the polymers of natural origin, modified natural substances and synthetic polymers. They could preferably be formulated as a chip or could be part of a dental paste formulation, or otherwise be directly injected into the periodontal cavity. Tetracycline-containing microcapsules in Pluronic F127 were reported to form gel at body temperature and hold the microcapsules in the periodontal pocket for the duration of treatment. PLGA microcapsules and microspheres have been proposed for the delivery of tetracycline and histatins. These microparticulate systems provide stability to the encapsulated drug. The in vitro drug release from such systems depends upon the polymer (Lactide:Glycolide) ratio, molecular weight, crystallinity and pH of the medium. Some questions, however, related to the retention of such formulations in the periodontal pocket need clarification.[19]

Gels

Mucoadhesive, metronidazole containing gel systems based on hydroxyethyl cellulose, corbopol 974, and polycarbophil have been made. Gel is applied sublingually with the help of blunt cannula and syringe. The gel is only marginally affective in decreasing the anaerobic bacterial count. This may be due to low number of bacteria susceptible to MTZ or due to presence of bacterial biofilms. Locally applied controlled release DOX gel may partly counteract the negative effect of smoking on periodontal healing following no surgical therapy.[20] The first was tetracycline base loaded into the microtubular excepient halloysite, which was coated with chitosan to further retard drug release. The syringeability of this formulation at various temperatures was evaluated to ensure ease of delivery to periodontal pocket. A stability study was performed to examine change in thermoresponsivity over time.[21] In addition, lidocaine release from gels was evaluated using a release apparatus stimulating buccal condition. The results indicated that an increase in carbopol

concentration significantly increased gel compressibility, hardness and adhesiveness factors that affect ease of gel removal from container, ease of gel application onto mucosal membrane, and gel bioadhesion. Characterization of tetracycline containing bioadhesive polymer network designed for the treatment of periodontal disease and result shows that effect of increasing drug concentrations on the rheological and textural properties was dependent on PVP concentration. Locally applied controlled release DOX gel may partly counteract the negative effect of smoking on periodontal healing. The safety profile, longer-term retention, antimicrobial activity suggests that tetracycline containing copolymer gels represents a safe and effective bioerodible therapy for periodontitis. Growing interest in developing absorbable pharmaceutical surgical products that degrade in biologic environment to safe by products and leaves the residual mass at application site justified the search fir novel absorbable gels. Comparative analysis of tetracycline containing dental gels: poloxamer and monoglyceride based formulations have been done which shows that poloxamer and monoglyceride gels, when applied subgingivally, produce a significant improved outcome in moderate to deep periodontal pockets.[22]

Injectable Gels

Together with the solid devices, semisolid formulations also receive reasonable attention for the localised delivery of antibiotics.[23] Semisolid or gel formulations can indeed have some advantages. In spite of the relatively faster release of the incorporated drug, gels can be more easily prepared and administered. Moreover, they possess a higher biocompatibility and bioadhesivity, allowing adhesion to the mucosa in the dental pocket and, finally, they can be rapidly eliminated through normal catabolic pathways, decreasing the risk of irritative or allergic host reactions at the application site. Various oleogels and hydrogels for the delivery of tetracycline (2.5%), metronidazole (25%), metronidazole benzoate (40%), as well as a combination of tetracycline (2.5%) and metronidazole benzoate (40%), have been tested and satisfactory results have been achieved. The gels composed of cellulose derivatives such as hydroxypropylmethyl cellulose[24] and hydroxyethyl cellulose[25-27] do not appear to have sustained release properties. Surprisingly, despite the rapid drug release and poor retention of these gels, positive clinical results in moderate to deep periodontitis were obtained.

Bioadhesion or mucoadhesion is a preliminary requirement for prolonged release of the drug at the site.[28] The retention time, as determined by fluorescein release, was found to be significantly higher for chitosan gel as compared to xanthan gum and poly(- ethylene oxide) gel.[29] 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.[30] Bioadhesive semisolid, polymeric system can be utilised 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 pseudoplastic flow and thermoresponsive behaviour, existing as a liquid at room temperature and gel at 34–37^{0}C.[31]

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.[12] Acrylic strips have been fabricated using a mixture of polymers, monomers and different concentrations of ant microbial agents. Strips were fabricated either by solvent 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 amoxycillin-clavulainic acid loaded acrylic strips is reported. Highest level of antibacterial agent was released during the first 24 hours 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. Tissue adhesive implants were made

using n-butyl-2-cyanoacrylate as a drug trapping material and slowly release 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 immediate therapeutic level of drug in pocket, followed by marked fall in release by day two.[32] Chlorhexidine slow release devise has been made and it is antibacterial effect has been evaluated by agar diffusion test.

Vesicular Systems

Vesicular liposomal systems are designed to mimic the bio-membranes in terms of structure and bio-behaviour, and hence are investigated intensively for targeting periodontal biofilms. Jones and Kaszuba reported interactions between liposomes made up of phosphatidylinositol (PI) and bacterial biofilms. The targeting of liposomes was thought to be because of the interaction of the polyhydroxy groups of liposomes with surface polymers of the bacterial glycol-calyx. Succinylated Concanavalin-A (lectin)-bearing liposomes (proteoliposomes) have been found to be effective for the delivery of triclosan to periodontal biofilms. In vitro and in vivo studies have revealed that, even after a very short exposure, the proteoliposomes are retained by the bacteria eventually delivering triclosan into the cellular interiors. The potential of lectin-bearing liposome systems as a targeting system for the control of gingivitis and dental plaque has been extensively studied by Vyas *et al.*[33] The delivery of triclosan and chlorhexidine was studied for several liposomal compositions involving cationic as well as anionic lipids.[34] Robinson and co-workers reported further on the affinity and specificity of immunoliposomes to reduce dental plaque. The anti-oralis immunoliposomes showed the greatest affinity for S. oralis and affinity was unaffected by net charge on the lipid bilayer or by the number of antibodies conjugated to the liposomal surface.

Nanoparticle System

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 is being 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 areas 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 polyethyleneglycol dimethacrylate (PEGDMA) could be used as a drug delivery system for dental applications.

Miscellaneous: low-dose antibiotic

Recently, there has been interest in the use of low-dose antibiotics. The dose is so low that the drug does not act to kill bacteria, but rather to change the way the body responds to infection. Production of the enzyme collagenase is essential because older gingival tissues are replaced with new tissues. In periodontal disease there is an overproduction of collagenase, causing the destruction of healthy gum tissue. An interesting effect of low-dose antibiotics is that they not only kill the bacteria that may cause periodontal disease but also reduce the body's production of collagenase, an enzyme that destroys gingival tissues. The antibiotic doxycycline was found to combat these enzymes, even in doses so small that there was no antibiotic effect. The advantages of smaller doses are that there is a great reduction in the chances of formation of resistant bacterial strains and side effects. Periostat is a capsule of 20 mg of doxycycline, and clinical studies have shown that patients who take two capsules daily have a reduction in clinical inflammation. The

daily 40-mg dose is so low as not to qualify as an antibiotic, and there is no known effect on the pocket bacteria. Thus, Periostat must be used in conjunction with other therapies that address bacterial removal.[35]

CONCLUSION

Eradication of microorganisms from the periodontal pocket is the most important step in treating periodontitis. The limitations of mouth rinsing and irrigation have prompted research for the development of alternative delivery systems. Recently, advances in delivery technology have resulted in the controlled release of drugs. The requirements for treating periodontal disease include a means for targeting an anti-infective agent to infection sites and sustaining its localized concentration at effective levels for a sufficient time while concurrently evoking minimal or no side effects. This article has discussed the various local drug delivery devices used in treating periodontitis. From that following conclusions can be made: local drug delivery system is used effectively in controlling tissue associated bacteria, it eradicates the periodontal pathogens for several weeks, local drug delivery system is effective for treating single rooted teeth than multi rooted teeth and mode of treatment for shallow periodontal pockets and recurrent periodontal disease.

Table 1: Microbial species associated with various clinical forms of periodontitis[4]

Species	Adult	Refractory	Localized Aggressive	Early Onset
Actinobacillus	++	++	+++	++
Actinomycetemcomitans				
Porphyromonas gingivalis	+++	++	o	+++
Prevotella intermedia	+++	+++	++	+++
Tannerella forsythia	+++	++	o	++
Fusobacterium nucleatum	+++	++	+	++
Eubacterium species	++	+	NE	+
Campylobacter rectus	++	+	+	++
Treponema species	+++	++	++	+++
Candida species	NE	o	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

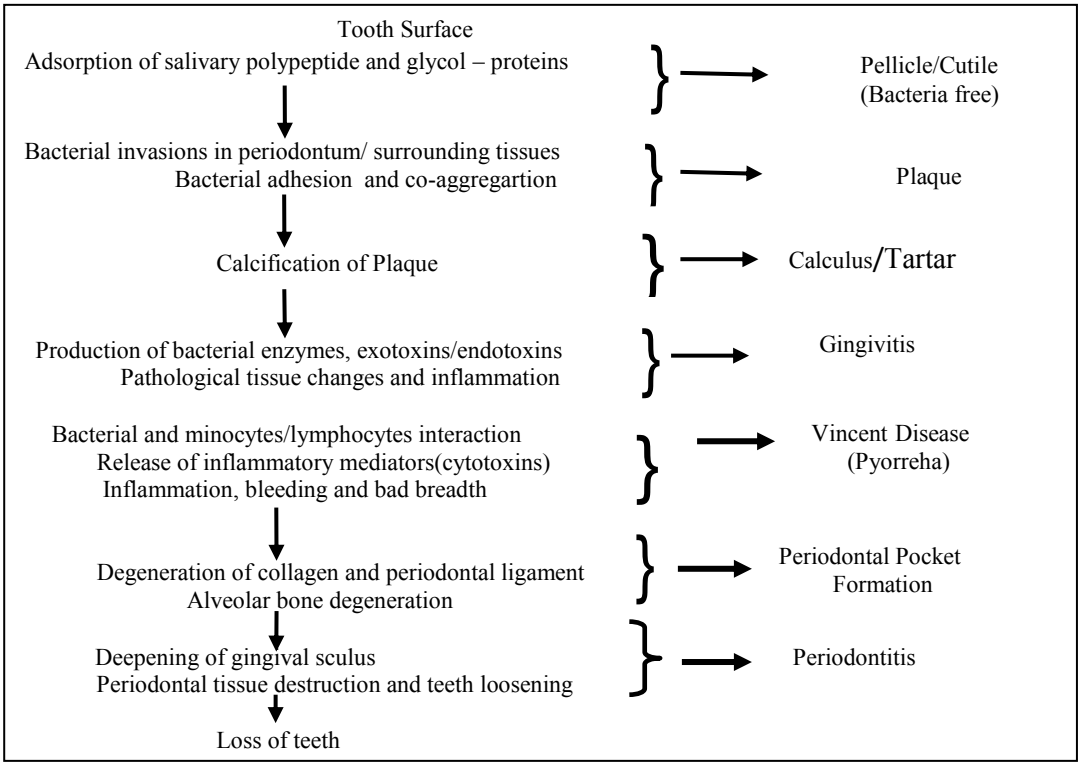

Figure 1: Flow chart representing pathogenesis of periodontal diseases. Formation of bacterial plaque; calcification of plaque; pathological and immunological manifestations resulting in gingivitis and periodontitis

Table 2: Summary of some investigated local controlled delivery systems[12, 13]

System	Polymer matrix	Drug Incorporated
Fibers	Cellulose acetate	Tetracycline HCl
		Chlorhexidine
	Ethylene vinyl acetate	Tetracycline HCl
	Poly(e-caprolactone) (PCL)	Tetracycline HCl
Strip	Polyethylmetha acrylate (acrylic)	Tetracycline HCl
		Metronidazole
	Hydroxypropyl cellulose	Chlorhexidine, tetracycline
		Doxycycline
	HPC + methacrylic acid Ofloxacin	
	Polyhydroxybutyric acid	Tetracycline HCl
	Polylactide-co-glycolic acid (PLGA)	Tetracycline HCl
		Chlorhexidine
	Ethyl cellulose	Chlorhexidine
Films	Ethyl cellulose	Metronidazole, Minocycline
		Tetracycline HCl
	Cross-linked atelocollagen	Tetracycline
	Gelatin (BycoW protein)	Chlorhexidine diacetate
	Cross-linked gelatin + glycerine	Chlorhexidine digluconate
	Chitosan	Taurine
	Chitosan + PLGA	Iproflavone
	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
	Glycerol monooleate + sesame oil	Metronidazole
	PLGA	Tetracycline
Microparticle	Pluronic F 127	Tetracycline
	PLGA	Tetracycline
		Histatin peptides
	PLGA + PCL	Doxycycline
Nanoparticles	PLGA	Harungana madagascariensis
		leaf extract
	Chitosan	Antisense oligonucleotide
	Cellulose acetate phthalate	Triclosan
	PLGA	Triclosan
Vesicular System	Phosphatidylinositol	Triclosan
	Immunoliposomes	Anti-oralis
Other system	Poly(ethylene-co-vinyl acetate)	Acyclovir
		Chlorhexidine

Table 3: List of commercial periodontal products presented in various dosage forms[36]

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 Corp.Co Denmark
Periochip®	Chlorhexidene	Biodegradable device	Dexcel Pharma Inc Jerusalem
Periochop®	Chlorhexidene /Tetracycline	Film	Perioproducts Ltd.
Periochip®	Gluconate	Inserts	Perioproducts Ltd.
Gluconate®	Metronidazole	Inserts	Perioproducts Ltd.
Elyzol®	Minocycline	Gel	Dumex pharma
Atrigel®	Doxycycline	Gel	Atridox (atridox lab)

REFERENCES

1. American Academy of Periodontology (2000), "Proceedings of the International Workshop for the classification of periodontal diseases", ***Ann. Periodontal.***, in press.
2. Haffajee, AD and Socransky, SS (1986), "Attachment level changes in destructive periodontal diseases", ***J. Clin. Periodonto,*** 13, 461–472.
3. Vyas, SP *et al.* (2005), "Controlled and targeted drug delivery strategies towards intraperiodontal pocket diseases", ***J. Clin. Pharm. Ther***, 25, 21–42.
4. Moore, WEC, Moore and LVH (1994), "The bacteria of periodontal diseases", ***Periodontology*** 2000, 66±77.
5. Slots, J and Rams, TE (1990) "Antibiotics in periodontal therapy: advantages and disadvantages", ***J. Clin. Periodontol***., 17, 479–493.
6. Van Wachem, PB; Van Luyn, MJA; Nieuwenhuis, P; Koerten, HK; Olde Damink, L; Ten Hoopen, H and Feijen, J (1991), "In vivo degradation of processed dermal sheep collagen evaluated with transmission electron microscopy", ***Biomaterials***, 12 , 215±223.
7. Steinberg, D; Friedman, M; Soskolne, and Sela, MN (1990), "A new degradable controlled release device for treatment of periodontal disease", In vitro release study**,** ***J. Periodontol***, 61, 393±398.
8. Minabe, M; Uematsu, A; Nishijima, K; Tomomatsu, E; Tamura, T; Hori, T; Umemoto, T and Hino,T(1989), "Application of a local drug delivery system to periodontal therapy", "Development of collagen preparations with immobilized tetracycline", ***J. Periodontol***, 60, 113±117.
9. Loesche, WJ; Giordano, J; Soehren, S; Hutchinson, R; Rau, CF; Walsh, L; Schork, A; Arbor, A and Mich, D (1996), "Nonsurgical treatment of patients with periodontal disease", ***Oral Surg. Oral Med. Oral Pathol. Endod,*** 81, 533±543.
10. Paquette, DW; Waters, GS; Stefanidou, VL; Lawrence, HP; Friden, PM; O'Connor, SM; Sperati, JD; Oppenheim, FG ; Hutchens, LH and Williams, RC (1997), "Inhibition of experimental gingivitis in beagle dogs with topical salivary histatins", ***J. Clin. Periodontol***, 24, 216±222.
11. McLeod, AD; Tolentino, L and Tozer, TN (1994), "Glucocorticoid-dextran conjugates as potential prodrugs for colon-specific delivery: steady-state pharmacokinetics in the rat", ***Biopharm. Drug Disposition,*** 15,151±161.
12. Jain, N; Jain, G; Javed, S and Iqbal, Z (2008), "Recent approaches for the treatment of periodontitis",***Drug Discovery Today*** , 13, 21-22.
13. K Schwach-abdellaoui, N and Vivien-castioni, R (2000), "Gurny Local delivery of antimicrobial agents for the treatment of periodontal diseases", ***European Journal of Pharmaceutics and Biopharmaceutics,*** 50, 83±99.

14. Jain, N; Gaurav, K; Javed, S; Iqbal, Z; Talegaokar, S; Ahmad, FJ and Khar, RK (2008), "Recent approaches for the treatment of periodontitis", ***Drug. Discov. Today***, 1 (21-22), 932-943.
15. Soskolne, WA et al. (1997), "Subgingival delivery of therapeutic agents in the treatment of periodontal diseases", ***Crit. Rev. Oral Biol. Med***, 8, 164–174.
16. Medlicott, NJ (1994), "Delivery systems for the administration of the drugs to the periodontal pocket", ***Adv. Drug Deliv. Rev***, 13, 181–203.
17. Vyas, SP; Sihorkar, V and Mishra, V (2000), "Controlled and targeted drug delivery strategies towards Intraperiodontal pocket disease", ***J.Clin Pharm Ther***, 25 (1), 21-42.
18. Esposito, P; Cortesi, R; Cervellati, F; Menegatti, E and Nastruzzi, C (1997), "Biodegradable microparticles for sustained delivery of tetracycline to the periodontal pocket: formulatory and drug release studies", ***J. Microencapsulation,*** 14, 175±187.
19. Pragati, S; Ashok, S and Kuldeep, S (2009), "Recent advances in periodontal drug delivery systems", ***International journal of drug delivery,*** 1, 1-14.
20. Tomasi, C and Jan, LW (2004), "Locally delivered doxycycline improves the healing following non surgical periodontal therapy in smokers", ***J. of Clin. Periodontology***, 31, 589-595.
21. Kelly, HM; Deasy, PB; Ziaka, E and Cleffey, N (2004), "Formulation and preliminary in vivo dog studies of a novel drug delivery for the treatment of periodontitis", ***Int. J. Pharm,*** 15 (1), 167 – 183.
22. Esposito, E; Carrota, V; Scabbia, A; Trombelli, L; Antena, PD and Menegatti, E (1996), "Comparative analysis of tetracycline containing dental gels: poloxamer and monoglyceride based formulations", ***Int. J. Phar***, (142), 9-23.
23. Stolze, K and Stellfeld, M (1992), "Systemic absorption of metronidazole after application of a metronidazole 25% dental gel," ***J. Clin. Periodontol***, 19, 693–697.
24. Paquette, DW *et al.* (1997), "Inhibition of experimental gingivitis in beagle dogs with topical salivary histatins", ***J. Clin. Periodontol***, 24, 216–222
25. Nakagawa, T *et al.* (1991), "Clinical and microbiological study of local minocycline delivery (PERIOCLINER) following scaling and root planning in recurrent periodontal pockets", ***Bull. Tokyo Dent. Coll***, 32, 63–70.
26. Hayashi, K. et al. (1998), "Clinical and microbiological effects of controlled release local delivery of minocycline on periodontitis in dogs", ***Am. J. Vet. Res***, 59, 464–467.
27. Graca, MA *et al.* (1997), "A randomized controlled trial of a 2%minocycline gel as an adjunct to non-surgical periodontal treatment, using a design with multiple matching criteria", ***J. Clin. Periodontol,*** 24, 249–253.
28. Pattnaik, S *et al*. (2007), "Periodontal muco-adhesive formulations for the treatment of infectious periodontal diseases", ***Curr. Drug Deliv***, 4, 303–323.
29. Needleman, IG and Smales, FC (1995), "In vitro assessment of bioadhesion for periodontal and buccal drug delivery", ***Biomaterials*** ,16, 617–624.
30. Akncbay, H *et al.* (2007), "Application of chitosan gel in the treatment of chronic periodontitis"***, J. Biomed. Mater. Res. B Appl. Biomater***, 80, 290–296.
31. Jones, D.S. *et al.* (1996), "Development and mechanical characterization of bioadhesive semi-solid, polymeric systems containing tetracycline for the treatment of periodontal diseases", ***Pharm. Res***, 13, 1734–1738.
32. Mastiholimath, VS; Dandagi, PM; Gadad, AP; Patil, MB and Manvi, FV (2006), "Formulation and evaluation of ornidazole dental implants for periodontitis", ***Indian J. Pham Sci.***, 68(1), 68-71.
33. Vyas, SP *et al.* (2001), "Preparation, characterization and in vitro antimicrobial activity of metronidazole bearing lectinized liposomes for intra-periodontal pocket delivery", ***Pharmazie***, 56, 554–560.
34. Jones, MN *et al.* (1997), "The interaction of phospholipid liposomes with bacteria and their use in the delivery of bactericides",***J. Drug Target***, 5, 25–34.
35. Goodson, JM *et al.* (1983) Monolithic tetracycline-containing fibres for controlled delivery to periodontal pockets. J. Periodontol., (54), 575–579.
36. Carranza, GM and Fermim, AC (2004), ***"Clinical Periodontology***", 9th Ed., Saunders, 676- 683.

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