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Review Article

PERIODONTAL DRUG DELIVERY SYSTEM CONTAINING ANTIMICROBIAL AGENTS

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ABSRACT

Periodontal diseases are one of the common microbial infections in the adults. They are of two types- gingivitis and periodontitis. Periodontitis is an inflammatory disease of supporting tissue of the teeth caused by groups of micro organisms. Aggressive form of periodontitis can be localized and are associated with micro organisms therefore treatment by local antimicrobial agents are most appropriate. The main aim of antibiotic therapy is to establish a concentration of drug that inhibits the pathogenic bacteria. The local delivery of anti microbial therapy to periodontal tissue has the benefit of putting more drug at target site while minimising exposure of total body to the drug .The novel periodontal drug delivery system having controlled release should be considered as adjunctive to mechanical debridement for the treatment of periodontal disease. This article reviews novel periodontal drug delivery system containing antimicrobial agents. Further extensive comparative studies are required to optimise use of such novel drug delivery system in periodontal diseases.

Keywords: Periodontal diseases, Periodontitis, Antimicrobial agents

INTRODUCTION

Periodontal diseases are one of the common microbial infections which affect 35% of adult population in the world. Periodontal diseases are of two types- gingivitis and periodontitis. Gingivitis is a common and reversible problem which is associated with the limited inflammation of the gums. It is characterized by swelling and bleeding of the gum during brushing and nearly half of the adult population suffers from this disease. It is observed if regular brushing is discontinued and plaque is allowed to accumulate, the gingivitis will appear and untreated gingivitis can progress to chronic condition called periodontitis.

This involves general inflammation of the periodontal tissue that starts from the accumulation of sub gingival plaque and results in major damage to the soft tissue and bone. When it is not treated it results in loss of supporting structure of the tooth through resorption of alveolar bone and loss o periodontal ligament [1]. Further destruction can finally results in loss of the tooth.

The periodontal disease progress in cyclical phases of excerebration, remission and latency, a phenomenon that is closely linked to the effectiveness of the host immune response [2]. With advancement of scientific knowledge experts can distinguish among generalized, localized and aggressive periodontitis, periodontitis associated with endodontic lesion and necrotizing ulcerative periodontitis. Other factors which can aggravate condition of chronic periodontitis are sub gingival plaque, smoking and conditions associated with some immune disorder , diabetes mellitus or AIDS etc[3]. They are considered as possible risk factors in other system disease such as cardiovascular disease including coronary heart disease and stroke [3]. More than 700 microbial species have been identified in sub gingival plaque. Dental caries causing bacteria is streptococcus mutant and gingivitis is cause by *Prevotella intermedia (P.i), Campylobacter retus (C.r), Aggregatibacter actinomycteincomitans (A.a), Porphyromonas gingivalis (P.g.), Tannerella forsythia (T.f.), Treponema denticola (T.d.), Fusobacterium nucleatum (F.n.), Prevotella intermedia (P.i.), etc. [4;5;6]*

Table 1: Microbial Profiles of subgingival plaques isolated from healthy sites & diseased sites.

Microbes	Healthy sites	Gingivitis (ulcerative)	Periodontitis (early onset)	Periodontitis (localized juvenile)	Periodontitis (adult)
Facultative species					
Streptococcus sp	+++	+	+	+	+
Actinomyces sp.	+++	+	+	+	+
Veillonella sp.	+	+	+	+	+
Microaerophilic species					
A.actinomycetemocomitans	-	Not known	- to +	++	+
Capnocytophaga sp.	±	±	±	±	±
Anaerobic species					
Spirochetes	±	+++	+++	±	+++
P.gingivalis	-	±	- to ++	- to ++	-
P.intermedia	±	++	- to ++	±	- to ++
B.forsythia	±	Not known	- to ++	-	- to ++
Capnocytophaga sp	-	Not known	- to ++	-	- to ++
Fusobacteria sp.	+	++	+	±	+ to ++

- Not present ++ Levels<20%

± May be present +++ Levels >20%

+ usually present at levels <10% of flora

Prevalence of pathogens are not sufficient to cause periodontitis but host immune response also modulates progression of disease towards destruction or healing. However, over production of certain mediator, such as interleukin -1β, tumor necrosis factor alpha and prostaglandins, which leads to chronic inflammation results in tissue destruction [8]. Treatment of periodontal infections are aimed at reducing the infection in shallow to medium depth pockets with combination of non surgical scaling and root planning scaling (SRP) or surgical depth reduction of deeper pockets so that SRP dental care can maintain the health of the pockets. The current scaling and root planning is a mechanical procedure to remove subgingival calculus and plaque. Although SRP is a localized treatment but

always it does not eliminate the pathogenic bacteria present in the periodontal pockets as instruments are in accessible to them. This therapy has been reviewed [9] and it was concluded that responses to SRP are dependent upon pocket depth, skill of the practitioner, length of therapy and patient compliance.

Systemic or local antibiotic therapy in periodontal disease

Periodontal diseases are associated with bacteria therefore treatment by antimicrobial agents are most appropriate. The main aim of antibiotic therapy is to establish a concentration of drug that inhibit pathogenic bacteria .The most effective and reliable way of achieving this concentration is by systemic route where the drug kills the sub gingival flora by reaching into the crevicular fluid [12] .But the systemic route of administration may not always been ideal because of concern over the development of bacterial resistance and undesirable side effects like nausea, diarrhoea, fever , abdominal pain and pseudomembranous colitis that may be induced over long period of usage[11]. Also there are certain drugs such as tetracycline which have been found to concentrate in crevicular fluid at higher concentration that is found in serum after the same oral dose. [13] The drug can bind to tooth surface from which it is released in active form [14].Therefore use of such types of drugs are beneficial in treatment of periodontal diseases.

Route of administration of antibiotic can also be local by using conventional or controlled release dosages forms. The local delivery of antimicrobial therapy to periodontal tissue has the benefit of putting more drug at target site while minimising exposure of total body to the drug[15].When antibiotic are applied locally, they reduces the pathogenic bacteria and provide improvement in clinical parameters and mixed response to therapy has been shown [16]. The lack of retention of antibiotic in periodontal is the main reason for these mixed results.

Local Drug Delivery of Antimicrobial Agents

Control of supra gingival microbial plaque or periodontal disease involving pocket formation can be done by local applications such as mouth rinses, gels, tooth pastes etc. Mouth rinses such as chlorhexidine and tetracycline are used in the treatment of periodontal diseases and though chlorhexidine has shown superior antimicrobial effects but it does not reach the periodontal pocket. Local application of antibiotics has been achieved either by sub gingival irrigation or by incorporating the drug into different devices for insertion into periodontal pockets .Ideally local drug delivery requires high initial concentrations and multiple applications in order to provide sustained effectiveness [16]. Local drug delivery devices are of two types:

1. These drug delivery systems are designed to deliver drug locally in the periodontal pocket but without any mechanism to retain therapeutic levels for a prolonged period of time. Such device generally exhibits exponential increase and decrease in drug concentration at the site.

2. hese are controlled release local drug delivery devices which may produce antimicrobial effect for a prolonged period of time at the diseased site. They are produced by immobilizing antimicrobial agents with a carrier substances to provide controlled local release such as antimicrobial fibers, films or strips.

Controlled Release Local Delivery Devices

These devices employ the controlled release technologies to assure therapeutic concentrations of the antimicrobial agents in the sub gingival area for a long period following a single application. A wide variety of specialized local delivery systems (i.e. intra-pocket devices) have been designed to maintain the drug concentration in the gingival cervicular fluid (GCF). Drug delivery systems can be classified according to the mechanism controlling drug release in following three categories [17]:

(i) Solvent controlled matrix systems are based on macromolecular matrix permeability to small molecules after matrix swelling into hydrated medium.

(ii) Reservoir systems are controlled by drug diffusion across a polymeric membrane.

(iii) Chemically controlled systems in which the rate of drug release is controlled by rate of degradation of chemical bonds and erosion of the polymeric matrix.

Several studies have evaluated the use of antimicrobial/antibacterial agents in periodontal therapy such as iodine, sulphonamides, mercurials, or phenolics and antibiotics such as tetracycline, doxycycline, minocycline, metronidazole, chlorhexidine, ciprofloxacin, neomycin, kanamycin, clindamycin, azithromyicin and ofloxacin etc.

DRUG DELIVERY SYSTEM FOR PERIODONTITIS

Various drug delivery system for treating periodontitis include; fibers, gels, injectable systems, microspheres/microparticles, strips, compacts, films, and nanoparticles.

Fibers

Fibers or thread like devices which are of reservoir type and are used for sustained release of drug into the periodontal pocket. They can either be hollow or matrix delivery devices. The reservoirs without rate control delivery include devices such as hollow fibers filled with a therapeutic drug in which the drug is released simply by diffusion through the reservoir wall [18]. First delivery devices by Goodson were composed of cellulose acetate filled with tetracycline [19]. These fibers released 95% of the drug in the first 2 hrs and the release followed first order kinetic and therapeutic concentration was maintained for 24hrs.These fibres served as a good drug holding device but there was no rate control in these types of fibers and they permitted rapid evacuation of the drug. To sustain the drug release, Goodson evaluated the delivery of tetracycline incorporated into different polymers such as polyethylene, polypropylene, polycaprolactone, polyurethane, cellulose acetate propionate and ethylene vinyl acetate (EVA) [20]. EVA was found to be flexible and to allow drug delivery for up to 9 days in vitro. The EVA fibers containing 25% tetracycline hydrochloride commercialized under the trademark Actisite. Examples of the drugs used in fiber are chlorhexidine and tetracycline etc.

Injectable drug delivery systems

Injectable systems are used for the delivery of antibiotic agents into the periodontal pocket. An injectable delivery system fills the periodontal pocket easily with therapeutic agent and reaches to a large population of pathogens inside the pocket. This application can be rapidly carried out without causing pain using a syringe. The cost of the therapy is also less as compared to devices that need time to be placed in the pocket. Two types of injectable drug delivery systems have been studied in periodontal diseases- biodegradable microparticles and gels.

Microparticles/Microspheres

These are controlled release drug delivery system which comprises of drug-containing microparticles or microspheres, between 10 and 500 microns in size, suspended in a pharmaceutically acceptable carrier medium, and are capable of maintaining an effective level of drug in the periodontal pocket for a period of one to thirty days. Non-biodegradable as well as biodegradable materials have been investigated for the preparation of microspheres. Baker et al. [21] produced a biodegradable microparticles system containing tetracycline. This system consists of poly (1actide-co-glycolide) (PLGA) micro particles in a thermo reversible gel base that is injected into the periodontal pocket in a liquid form which gels at body temperature. The release of drug from this system is quite rapid and the biodegradation of the poly (1actide-co-glycolide) microparticles occurs over a long period of several months. The poly (1actide-co-glycolide) system has been used with other second generation tetracycline antibiotics also. Recently the controlled delivery of doxycycline was achieved through novel biodegradable microspheres prepared by w/o/w double emulsion technique using the blends of PLGA and PCL in different ratios. The formulation showed significant results in vivo and also with respect to microbiological and clinical parameters studied for up to three months [22]. PLGA microspheres containing minocycline were evaluated alone or as an adjunct to scaling and root planning in adult

periodontitis [23]. The minocycline local delivery system, both with or without scaling and root planning achieved a significant reduction in Porphyromonas *gingivalis* for one month after therapy.

Gels

Semisolid or gel formulations can be easily administered and have relatively faster drug release at the site of application. They are also bioadhesive and biocompatible with oral mucosa .Gel systems containing metronidazole designed for periodontal treatment and based on hydroxyethylcellulose, Carbopol 974P and Polycarbophil have been studied [24]. In vitro drug release was significantly decreased as the concentration of each polymeric component was increased. Bioadhesive semi-solid systems based on hydroxyethylcellulose (HEC) and polyvinylpyrrolidone (PVP) containing tetracycline were studied for mechanical properties and drug release rate [25]. An injectable lipid-like vehicle based on glycerol monooleate and sesame oil containing 25% metronidazole (Elyzolw) (Dumearma, Copenhagen, Denmark) has become available with supportive evidence of efficacy. This product is syringed into the pocket area where the initially thixotropic carrier thickens into a gel. Two other semi-solid lipid-like formulations based on poly (oxyethylene-co-oxypropylene) (poloxamer) and glycerol monooleate were developed for tetracycline release by Esposito *et al.* [26]. Gel formulations containing 2% minocycline have been commercialized under several trademarks; Perioclinew (Sunstar Co. Ltd., Osaka, Japan) [27, 28] and Dentomycinw (Lederle Laboratories, UK) [29]. The gel is composed of hydroxyethylcellulose, aminoalkyl-methacrylate copolymer, triacetine, and magnesium chloride and glycerynum concentratum. Another injectabe biodegradable delivery system containing 10% doxycycline on a biodegradable polyester poly (DL-lactide) dissolved in a biocompatible solvent N-methyl-2-pyrrolidone (NMP) [29, 30] was also studied. The viscosity of delivery system is so that it can pass through a cannula into a periodontal pocket where it solidified to deliver the therapeutic agent over seven days. A mucoadhesive gel formulation based on 4% carbopol containing 1% clindamycin hydrochloride was evaluated in vivo on microbial flora of periodontal pockets deeper than 5mm [31]. 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 evaluated.

Strips and compacts

Strips are comprises of polymers and active ingredients in form of thin and flexible band for the treatment of periodontal disease. The strips can be applied directly to the lesion region to be treated and so that the active ingredient can be concentrated at the desired site. These strips are useful for the treatment of plaques and inflammation beneath the gingival margin. Strips containing 25%w/w tetracycline hydrochloride or metronidazole in poly (hydroxybutyric acid) (PHBA) as a biodegradable polymer matrix showed sustained release over 4±5 days with a significant burst effect on first day [32]. First controlled release strip containing ofloxacin using poly (methacrylic acid) and hydroxypropyl-cellulose as polymer has been reported by Kimura et al [33]. The controlled release chlorhexidine strips gave the most interesting and long-term clinical improvement [34]. Larsen studied in vitro release of doxycycline from different bioabsorbable materials and acrylic strips [35]. Noguchi and co-workers produced hydroxypropyl cellulose strips containing chlorhexidine and tetracycline. These strips bioerode and release their drugs within twenty-four hours. Although they are effective in reducing pathogenic bacteria when applied three times over seven days but their drug delivery is not really prolonged.

Films

They are matrix delivery systems in which the drug is distributed throughout the polymer and drug release occurs by diffusion and/or matrix dissolution or erosion. The size and shape of the film can be controlled according to the dimensions of the pocket where the film is to be inserted and should be easily placed with minimal pain to the patient. A periodontal film should be non toxic, non interfering and should have sufficient adhesiveness. Both degradable and non-biodegradable films have been developed. The films that release drug by diffusion alone are prepared using water insoluble or non-degradable polymers [36, 37], whereas those that release drug by diffusion and matrix erosion use soluble [39] or biodegradable polymers in the matrix [40,41]. Films containing antibiotics such as tetracycline, doxycycline, minocycline, metronidazole, ciprofloxacin, neomycin, kanamycin, ofloxacin and clindamycin have been studied.

Non-biodegradable films

The first descriptions of an intra pocket, non-biodegradable matrix delivery device was made by Addy et al [42]. They described the use of matrix films of polymethacrylates for the intrapocket delivery of tetracycline, metronidazole and chlorhexidine. The drug release from the film was studied and was shown to be dependent on the drug loading and nature of drug incorporated in the delivery system. Films containing 30% w/ w chlorhexidine, tetracycline and metronidazole released 57%, 40% and 96% of the drug load. Ethyl cellulose matrix films for periodontal drug delivery have been described [43]. These films were made by casting ethanol or chloroform solutions of the polymer into moulds and allowing the solvent to evaporate. Films containing chlorhexidine (44], metronidazole [45] and minocycline [46] have been developed and evaluated. The release of the therapeutic agent from these films is dependent on the solvent and the plasticizer used and the nature and concentration of the drug. Clorhexidine films (5%w/w) cast from ethanol solutions released 95% of the drug over a period of 10 days, whereas chloroform-cast films released 20% of drug load over a 205-day period [47]. This could be due to the differential solubility of the drug in the casting solvent. Golomb *et al.* [48] studied metronidazole films cast with PEG 3000 and concluded that enhanced release of drug was due to improved water binding to the surface of the matrix films containing PEG. Stabholz et al. [49] assessed the efficacy of periodic treatment with chlorhexidine-containing films in a 2-year study of maintenance of periodontal pocket. Treatment showed significantly lower incidence of bleeding on probing, pocket depths and attachment levels when compared to the conventional maintenance treatment [50]. The limitations of such delivery devices are the removal and replacement as they do not degrade. On the other hand, less expertise is required than for scaling and plaque removal.

Table 2: Non-degradable intra-pocket drug delivery system in periodontal diseases [51].

Polymers used	Technique used	Form	Drugs Incorporated
Polyethylmethacrylate	Moulding and compression	Film	Chlorhexidine, tetracycline, metronidazole
Ethyl cellulose	Casting from ethanol or Chloroform	Film	Chlorhexidine, metronidazole, tetracycline, minocycline
Ethylene vinyl acetate	Heat extrusion	Fiber	Tetracycline
Ethyl methacrylate/ Chlorotrimethyl ammonium methyl methacrylate	Cast from ethanol: water mixture	Film	Clindamycin

Degradable/Soluble films

These systems dissolve or erode in the gingival crevice so that removal after treatment is not required. Drug release occurs by erosion or dissolution. Friedman and Steinberg studied cross-linked gelatin delivery systems containing chlorhexidine diacetate or chlorhexidine hydrochloride which was first biodegradable delivery systems but polymer degradation kinetics was very slow

compared to the drug releases [52]. Maze *et al.* Studied 25% (w/w) tetracycline in resorbable poly (1actide-co-glycolide) strips [53]. Higashi *et al.* prepared films of water-soluble polymer eudragit S and non-water-soluble polymer eudragit L for the delivery of clindamycin. An *in vitro* release study showed that insoluble films release drug by diffusion and soluble films release drug by dissolution of the carrier [54].Minabe *et al.* [55] synthesized a tetracycline immobilized cross-linked collagen fiber. Similar to the cross-linked gelatin systems mentioned earlier, the cross-linking agents react to cause insolubility of the collagen and gelatin thus making the collagen and/or gelatin very slow to erode. The cross-linking agents (such as gluteraldehyde or formaldehyde) may also cause biocompatibility problems in the periodontal pocket. More recently, a newly film composed of cross linked hydrolyzed gelatin and glycerine for local delivery of chlorhexidine digluconate has been developed and commercialized under the trademark Periochip [56]. This biodegradable film showed an initial burst effect in the first 24 h, whereby 40% of chlorhexidine was released, probably due to diffusion followed by a constant slower release over about 7 days.

Table 3: Degradable intra pocket drug delivery system in periodontal disease. [51]

Polymers used	Techniques used	Form	Drugs used
Hydroxypropylcellulose	Cast from ethanol solutions	Film	Tetracycline, Clorhexidine
Byco Protein	Cast from ethanol-water mixture cross linked with gluteraldehyde	Film	Tetracycline, Clorhexidine
Hydroxypropylcellulose. Methacrylic acid, copolymer S	-	Film	Ofloxacin
Polyhydroxybutyric acid polyhydroxyvalerate, poly lactic acid, polymer &copolymer	Direct compression	Compact	Tetracycline, Metronidazole
Poly (ε -caprolactone) hydroxypropylcellulose Polyethylene glycol	Heat extrusion	Fiber	Tetracycline
Poly (ε-caprolactone)	Casting from dichloromethane	Film	Clorhexidine
Methacrylic acid (methylmethacrylate mixture copolymer)	Cast from ethanol-water	Film	Clindamycin
PLGA	Solvent evaporation	Film	Tetracycline
PLGA	Phase separation	Microspheres	Minocycline

Nanoparticles

Nanoparticles have several advantages as they have extremely small size and can penetrate areas (extracellular and intracellular areas) such as gingival fluid, bacterial cells, from the gingival sulcus to the underlying connective tissue and to the periodontal pocket areas below the gum line that may be inaccessible to other delivery system [57]. They also have more favourable drug pharmacokinetics [58] and stability as compared with microparticles and other drug delivery system. These systems reduce the frequency of administration and further provide a uniform distribution of the active agent over an extended period of time [59]. Antisense oligonucleotide-loaded chitosan-tripolyphosphate (TPP) nanoparticles were prepared and evaluated. Chitosan/oligonucleotide-TPP nanoparticles, which were prepared by adding TPP after the formation of chitosan/oligonucleotide complex showed the sustained release of oligonucleotides and are suitable for the local therapeutic application in periodontal diseases [60]. Biocompatible nanoparticles composed of 2-hydroxyethyl methacrylate (HEMA) and polyethyleneglycol dimethacrylate (PEGDMA) could be used as a drug delivery system for periodontal applications. The polymer-based nanoparticles were prepared by using micellar polymerisation, which resulted in a well dispersible powder material with particle size in the range of 50–180 nm. These nanoparticles are used as hydrogel matrix and in form of new drug delivery devices for dental applications [61].

CONCLUSION

The review of studies suggested that the local controlled delivery devices are useful adjunct to conventional surgical or non-surgical treatments but are no substitute for these measures. Local controlled delivery systems containing antibacterial agents can be used effectively in recurrent and refractory periodontitis. To be useful for periodontal therapy, it is desirable to

use a biodegradable or bioerodable drug delivery system that can maintain an effective drug release rate in the periodontal pocket while it should simultaneously erode throughout the duration of treatment . Through there are large number of studies performed but there is insufficient comparative data to support any one of the local delivery systems as superior to another and so further comparative studies are required to optimise use of such novel drug delivery system.

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