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Review

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Recent advances in periodontal drug delivery systems

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Abstract

Periodontitis, a disease involving supportive structures of the teeth prevails in all groups, ethnicities, races and both genders. The relationship between bacterial plaque and the development of periodontal disease and caries is well established. 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) has recently gained interest. These products provide a long-term, effective treatment at the site of infection at much smaller doses. Biodegradable polymers are extensively employed in periodontal drug delivery devices because of their abundant source, lack of toxicity, and high tissue compatibility. A major advantage of natural polymers is that they do not affect periodontal tissue regeneration. Amongst various natural polymers, chitosan, a deacetylated product of chitin is widely used in drug delivery devices. Since it exhibits favourable biological properties such as non-toxicity, biocompatibility, biodegradability and wound healing traits, it has attracted great attention in the pharmaceutical and biomedical fields. The conventional treatment consists of tooth surface mechanical cleaning and root planning, associated or not to the systemic use of high concentrations of antibiotics, but with reduced effectiveness, and adverse effects. The patient compliance to the therapeutic is committed too. In the last decades, the treatment has been optimized for the use of drug delivery systems to the periodontal pocket, with the advantage of delivering the drug in the specific site, sustaining and/or controlling the drug concentration. Recently, the use of new drug delivery systems has been receiving great interest. 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 diseases, Periodontal pocket, Delivery systems, Periodontal pocket delivery

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Introduction

Gingivitis and periodontitis are the two major forms of inflammatory diseases affecting the periodontium. Gingivitis is inflammation of the gingiva that does not result in clinical attachment loss. Periodontitis is inflammation of the gingival and the adjacent attachment apparatus and is characterized by loss of connective tissue attachment and alveolar bone. Each of these diseases may be subclassified based upon etiology, clinical presentation, or associated complicating factors. Gingivitis is a reversible disease. Therapy is aimed primarily at reduction of etiologic factors to reduce or eliminate inflammation, thereby allowing gingival tissues to heal. Appropriate supportive periodontal maintenance that includes personal and professional care is important in preventing re-initiation of inflammation. Therapeutic approaches for periodontitis fall into two major categories: 1) anti-infective treatment, which is designed to halt the progression of periodontal attachment loss by removing etiologic factors; and 2) regenerative therapy, which includes anti-infective treatment and is intended to restore structures destroyed by disease. Essential to both treatment approaches is the inclusion of periodontal maintenance procedures. Inflammation of the periodontium may result from many causes (eg, bacteria, trauma). However, most forms of gingivitis and periodontitis result from the accumulation of tooth-adherent microorganisms. Prominent risk factors for development of chronic periodontitis include the presence of specific subgingival bacteria, tobacco use, diabetes Furthermore, there is evidence that other factors can contribute to periodontal disease pathogenesis: environmental, genetic, and systemic (eg, diabetes). Periodontitis is a chronic bacterial infection that affects the gums and bones supporting teeth, untreated gingivitis can advance to periodontitis [1]. Gingivitis is often caused by inadequate oral hygiene. Periodontal disease can affect one tooth or many teeth. It begins when the bacteria in plaque as the disease progresses, the pockets deepen and more gum tissues and bone are destroyed. Often this destructive process has very mild symptoms. Eventually teeth become loosened and may have to be removed. Periodontal pocket provides an ideal environment for the growth of anaerobic pathogenic bacteria such as actinobacillus Actinomycetemcomitans, Bacteroides gingivalis, Bacteroides melaninogenicus subspecies intermedius, Porphyromonas gingivalis and Provetella intermedia [2].

Various approaches to treat periodentitis

Gingivitis can usually be treated simply. Plaque and tartar are removed from teeth; the inflamed tissues around a tooth usually heal quickly and completely More serious cases of periodontitis cannot be treated by routine dental procedures dental surgery may be necessary to remove plaque, tartar, and infected gums tissue. Surgical access to facilitate mechanical instrumentation of the roots has been utilized to treat chronic periodontitis for decades [3]. A surgical approach to the treatment of periodontitis is utilized in an attempt, provide better access for removal of etiologic factors, reduce deep probing depth and regenerate or reconstruct lost periodontal tissues.

Chronic Periodontitis

Appropriate therapy for patients with periodontitis varies considerably with the extent and pattern of attachment loss, local anatomical variations, type of periodontal disease, and therapeutic objectives. Periodontitis destroys the attachment apparatus of teeth resulting in periodontal pocket formation and alteration of normal osseous anatomy. The primary objectives of therapy for patients with chronic periodontitis are to halt disease progression and to resolve inflammation [4]. Therapy at a diseased site is aimed at reducing etiologic factors below the threshold capable of producing breakdown, thereby allowing repair of the affected region. Regeneration of lost periodontal structures can be enhanced by specific procedures. However, many variables responsible for complete regeneration of the periodontium are unknown and research is ongoing in this area.

Local Delivery

Local application into periodontal pocket could be very advantageous, both in terms of raising drug concentration directly in the action site, and in

preventing systemic side effects such as gastrointestinal complaints, depression, and tachycardia. Controlled delivery of chemotherapeutic agents within periodontal pockets can alter the pathogenic flora and improve clinical signs of periodontitis. Local drug delivery systems provide several benefits; the drug can be delivered to the site of disease activity at a bactericidal concentration and it can facilitate prolonged drug delivery [5]. The FDA has approved the use of an ethylene vinyl acetate fiber that contains tetracycline, a gelatin chip that contains chlorhexidine and a minocycline polymer formulation as adjuncts to scaling and root planing. The FDA has also approved doxycycline hyclate in a bioabsorbable polymer gel as a stand-alone therapy for the reduction of probing depths, bleeding upon probing, and gain of clinical attachment [6]. Local delivery systems have potential limitations and benefits. If used as a monotherapy, problems associated with local delivery can include allergic reaction, possible inability to disrupt biofilms, and failure to remove calculus. The benefits include the ease of application, selectively targeting a limited number of diseased sites that were unresponsive to conventional therapy, and possibly enhanced treatment results at specific locations. Local delivery modalities have shown beneficial clinical improvements with regard to probing depth reduction and gain in clinical attachment. Furthermore, there are limited data to suggest that local delivery of antibiotics may also be beneficial in preventing recurrent attachment loss in the absence of maintenance therapy. Utilization of antibiotics at an individual site will depend on the discretion of the treating therapist after consultation with the patient. The greatest potential of local delivery devices may be to enhance therapy at sites that do not respond to conventional treatment. Ultimately, the results of local drug delivery must be evaluated with regard to the magnitude of improvement that can be attained relative to disease severity. Conventional drug formulations for the mouth, such as toothpaste and mouthwash, have very low penetration into periodontal pocket Films appear to be a suitable dosage form to deliver drugs into periodontal pocket, because the anatomic construction of the pocket allows for relatively easy insertion of such a delivery device. Moreover, the use of biodegradable polymers can increase patient compliance, as the inserted film does not need to be removed. Commercially speaking, periodontal delivery systems are available on the US market, such as PerioChip®, consisting of across-linked gelatin matrix capable to maintain chlorhexidine concentration for up to 7 days Existing approaches for local drug delivery in periodontal pocket are often unsatisfactory due to their rapid drug release or poor biodegradability of polymeric carrier [7]. Adverse drug reactions are a greater concern and more likely to occur if drugs are distributed via systemic route. An ideal formulation should exhibit ease of delivery, good retention at application site, and controlled release of drug. Treatment with antibiotic may be necessary if infection is present introduction of locally delivered antibiotics especially for the treatment of localized disease [8]. Systemic antibiotic therapy should be reserved for juvenile periodontitis, patients with medical problems requiring antibiotic coverage, patients with severe/acute periodontal infections. Metronidazole plus amoxicillin, or ciprofloxacin have been used successfully in the treatment of advanced *Actinomycetemcomitans* [9]. Most if the dentist (71%) prescribed a combination of amoxicillin plus metronidazole, the prescription frequency and choice of combination of metronidazole and broad spectrum penicillin shows the colonization resistance by means of antibiotics and worldwide concern about the usage of antibiotics. The treatment of periodontitis usually involves a systemic regimen with antibiotics to alter the presumably pathogenic flora. Furthermore, some tetracyclines, by inhibiting collagenase, seem to diminish bone destruction. Another approach is to surgically eliminate the pocket and recontour the bone to encourage alveolar bone growth. Recently, some authors investigated the potential application of ipriflavone, a synthetic flavonoid derivative, on the healing process of experimentally injured rat perialveolar bone.This compound is usually

employed in the treatment of post-menopausal and senile osteoporosis by oral administration. Disadvantages of systemic antibiotic therapy relate to the fact that the drug is dissolved by dispersal over whole body and a small portion of total does actually reaches the subgingival microflora in periodontal pocket.s

Drug delivery systems for treating periodontits

Various drug delivery system for treating periodontits – Fibers, Film, Injectable systems, Gels, Strips and compacts , Vesicular systems etc [10].

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... The release of the tetracycline from the cellulose acetate fibres as occurred by diffusion mechanism is rapid with approximately 95% of the drug released in the first two hours and, therefore, a single application of these fibres does not provide an effective drug concentration for long periods . Compared with the less effective tetracycline delivery from hollow fibres, fibres containing 20% (v/v) chlorhexidine, when placed into periodontal pockets, exhibited a prompt and marked reduction in signs and symptoms of periodontal disease.

In spite of the fact that the hollow fibres served as a good drug holding device, they permitted rapid evacuation of the drug. To retard drug release, drug-impregnated monolithic fibres were developed by adding drug to molten polymers, spinning at high temperature and subsequent cooling [11]. Several polymers such as poly(e-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. In this respect, monolithic EVA fibres were found to be effective in controlling the release of encapsulated drug, and the same has been demonstrated by several in vitro and in vivo studies . Tonetti et al. reported that EVA fibres containing 25% tetracycline hydrochloride maintained a constant drug level in the GCF above 600 mg/ml throughout ten days, showing zero-order release characteristics of EVA fibres . In addition to the extensive evaluation of drug delivery kinetics from the EVA fibres, this system has undergone numerous clinical trials to test its efficacy in the treatment of periodontal diseases. A study conducted on 121 sites in 20 patients evaluated the safety and efficacy of tetracyclineloaded EVA fibres applied after scaling and root planning (SRP) for ten days. The study indicated that a significant reduction in probing depth and gain in attachment was present at one-, threeand six-month visits. A reduction in proportion of bleeding pockets was observed during the experimental period.

Tetracycline fibre treatment adjunctive to SRP showed significantly less periodontal disease recurrence (4%) compared with SRP alone (9%), tetracycline fibre alone for 10 days (10%) and tetracycline fibre alone for 20 days (12%). Studies that were wellconducted and well-controlled have demonstrated the clinical efficacy of these fibres but their actual value in patient therapy has been somewhat difficult to interpret because clinicians have found the fibre placement technique challenging. A study showed that patients experienced discomfort during fibre placement and at fibre removal various degrees of gingival redness were observed . The intricacies of winding a fibre into place, the need to retain the device within the pocket and then the removal of it after seven to ten days may limit its wide acceptance by patients and periodontists. Fibers are used for the treatment of periodontitis- Hollow fiber and monolithic.

Hollow fibers comprise of reservoirs without rate controlled delivery filled with therapeutic agent. In these the therapeutic agent is released simply by diffusion through the reservoir wall. Goodson's first delivery devices involved hollow fibers of cellulose acetate filled with tetracycline. Reduction in spirochete number and a reduction in clinical signs were produced by these fibers when placed into periodontal pocket. However the hollow fiber system released the drug very rapidly and was not very successful at sustaining the drug release. Monolithic fibers were essentially developed to

retard drug release. Monolithic fibers were made of ethylene vinyl acetate loaded with 25% tetracycline hydrochloride were placed to fill the periodontal pocket of 10 patients, which was covered with a periodontal dressing. The average concentration of tetracycline in pocket after 10 day was 643 μg/ml and the total count of pocket microflora was depressed to a level near the limit of dark field microscopy**.** In the cases presented tetracycline fiber were employed as a supplement to mechanical therapy and oral hygiene in a variety of clinical situation. Outcomes included depression of periodontal pathogens, reduction of bleeding on probing, decrease in probing pocket depths and increase in probing attachment levels [12].

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. 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. In vitro release study showed that insoluble films release drug by diffusion and soluble release drug by dissolution of the carrier.

The advantages of such a device include ease of insertion, dimensions that confirms well with the dimensions of the pocket and minimum pain on insertion. With the realization that pocket bacteria accumulate as biofilms, studies are now being directed towards eliminating /killing biofilms concentration rather then planktonic (fluid phase) counterparts. Intraperiodontal pocket drug delivery has emerged as a novel paradigm for the future research [13]. Some natural biodegradable polymers have been used for controlled release of antibacterial agents in the treatment of periodontitis. Sustained release devices composed of across-linked fish gelatin (Byco protein) containing chlorhexidine diacetate or chlorhexidine hydrochloride have been developed by Steinberg et al. The in vitro release profile of chlorhexidine from such degradable films is dependent on the amount of chlorhexidine incorporated into the film, by the cross-link density of the polymer and by the chlorhexidine salt used. The time of total drug release is short and varies from 4 to 80 h. Among synthetic biodegradable polymers used as films for controlled release of antimicrobial agents, systems based on poly (ortho esters) have also been studied for the delivery of metronidazole. The in vitro study showed the influence of drug loading, film thickness and oleic acid content on drug release rate and profile. This dosage form has several advantageous physical properties for intra-pocket use. 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 [14]. Non-biodegradable ethyl cellulose based films for the delivery of chlorhexidine diacetate, metronidazole, tetracycline and minocycline have been developed by solvent evaporation method and clinically tested. Ethyl cellulose films showed sustained drug release and release rates were dependent on the casting solvent and drug load. The use of chloroform as the casting solvent significantly retarded the release rate of the drug compared to ethanol as the casting solvent. The incorporation of polyethylene glycol in the

films, however, enhanced the release rate of the drugs. Published clinical findings also confirmed that the treatment with drug-loaded ethyl cellulose films produced significantly greater improvements in the incidence of bleeding on probing, probing depths and attachment levels when compared to the conventional maintenance treatment. In contrast to the non-degradable systems discussed above, the films made up of degradable polymers erode or dissolve in the gingival crevice so that removal after treatment is not required. Natural and synthetic biopolymers play a pivotal part in drug delivery to periodontal pocket. Amongst natural biopolymers, atelocollagen, a pepsindigested preparation of insoluble bovine skin collagen, has been investigated as a possible carrier material for antibacterial agents in periodontal disease. Prolonged concentration of tetracycline in GCF could be maintained for at least ten days by incorporating the drug in glutaraldehyde cross-linked atelocollagen. Application of these films resulted in a significant improvement in clinical parameters. Another natural polymer, gelatin (Byco1 protein), obtained from fish, was cross-linked and used as a sustained release device for the delivery of chlorhexidine diacetate or chlorhexidine hydrochloride. In vitro drug release from such degradable films varied from 4 to 80 hours, depending on the amount of drug and cross-link density of the polymer. More recently, a film composed of cross-linked hydrolysed gelatin and glycerine for local delivery of chlorhexidine digluconate has been developed and commercialised under the tradename Periochip. The system showed an initial burst effect, whereby 40% of chlorhexidine was released in the first 24 hours, followed by a constant slower release over about seven days. This film has the advantage over other biodegradable films in which it remains inside the pocket with no additional aids for retention because of the adhesive nature of the Periochip1 components . The novel natural polymer chitosan is also utilised as a polymeric matrix in the form of film enriched with taurine (antioxidant agent). Taurine enhances the wound healing ability of chitosan and could be considered beneficial in tissue repair in destructive diseases like periodontitis. Furthermore, Perugini et al. carried the periodontal delivery of ipriflavone in a new chitosan/PLGA film delivery system. Monolayer films made of ipriflavone-loaded PLGA micromatrices in a chitosan film were compared with multilayer films composed of chitosan/PLGA/chitosan (three layers). In vitro experiments demonstrated that the composite micromatricial films represent a suitable dosage form to prolong ipriflavone release for 20 days. In another study, a two-layered film utilising mucoadhesive chitosan and biodegradable PCL was prepared. The film containing chitosan:PCL in the ratio of 1:0.625 had the best tensile properties and the slowest metronidazole release rate. In vivo evaluation of this film revealed that metronidazole concentration in saliva over six hours ranged from 5 to 15 mg/ml, which was within (and at the top end higher than) the reported range of minimum inhibitory concentration for metronidazole. A significant in vitro:in vivo correlation under the adopted experimental conditions was also obtained. The distinguishable films composed of poly(vinyl alcohol) (PVA) and carboxymethyl-chitosan (CMCS) were prepared by blending/ casting methods, and loaded with ornidazole as a periodontal drug delivery system. The blended films were found to be biocompatible, showed pH-responsive swelling, had a good retention at the application site and maintained high drug concentration at least for five days.

Synthetic biodegradable polymers have also been evaluated for sustained release of drug in the periodontal pocket. The combination of amoxycillin and metronidazole in the carrier polymer PLGA showed not only an extended spectrum of antimicrobial activity but also a synergistic effect against E. limosum, which had been reported to be resistant to metronidazole in earlier studies. The films showed a sustained in vitro release for a period of 16 days and the in vivo drug concentrations were maintained above the MIC value for the entire period of the release studies. By contrast, PLGA films containing tetracycline hydrochloride showed poor retention in the

periodontal pockets with incomplete release of tetracycline. This effect could be attributed to the hydrophobic nature of PLGA matrix and the difference in physicochemical properties of the drugs. Another biodegradable polymer poly(ortho esters) was also explored for the controlled delivery of metronidazole; however, no study on patients has been reported. Higashi et al. prepared films of water-soluble polymer Eudragit S1 and non-water-soluble polymer Eudragit L1 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. Kyun and co-workers showed that by embedding minocycline in PCL it is feasible to obtain sustained release of the drug within the periodontal pocket for seven days and should be a useful tool for the elimination of pathogenic microflora from periodontal pocket or reducing inflammation in periodontal disease. Dedein et al. performed a clinico-laboratory study for the treatment of periodontal diseases using chlorhexidine-loaded Diplen-Denta films. The new treatment was found to be highly effective in patients with catarrhal gingivitis and generalised periodontitis of light and medium severity .

Injectable System

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. These systems allow easy application of therapeutic agent using a syringe. They are also cost saving.

Gels

Mucoadhesive, MTZ 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 [15]. 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 [16]. 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 [17].

Injectable Gels

Together with the solid devices, semisolid formulations also receive reasonable attention for

the localised delivery of antibiotics. 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 and hydroxyethyl cellulose 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 [18]. 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. 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 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 8C. Tetracycline-loaded bioadhesive semisolid, polymeric system based upon hydroxyethyl cellulose- and polyvinylpyrrolidone- and metronidazole-loaded systems based upon Carbopol 974P, hydroxyethyl cellulose and polycarbophil are reported. Another such system composed of Poloxamer 407 and Carbopol 934P and containing propolis extract were designed for the treatment of periodontal disease. The release of the propolis was controlled by the relaxation of polymer chains and the greatest mucoadhesion was noted for the formulation containing 60:1 ratio of Poloxamer 407:Carbopol 934P. Another injectable biodegradable gel based on poly(DL-lactide) dissolved in a biocompatible solvent N-methyl-2-pyrrolidone (NMP) (Atrigel1) was widely studied . The Atrigel1 loaded with 10% doxycycline hyclate showed high levels of doxycycline (250 mg/ml) in the GCF for a period of seven days. Interestingly, levels of 10–20 mg/ml were still present for three to five days after the polymer had been removed. It is possibly because of minute particles of polymer remaining within the pockets or because of the substantive effects of tetracyclines within the periodontal pocket-adjacent-tooth-surface environment. In another study, Atrigel1 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. The semisolid system based on water-free mixtures of lipids, such as glycerol monooleate (monoglyceride) and sesame oil (triglyceride), is characterised by a solid–gel transition and become semisolid on contact with gingival fluid in the periodontal pocket. The system is based on the ability of glycerides to form liquid crystals, that is, reverse hexagonals on contact with water. The reverse hexagonal form has more favourable sustained release properties, compared with the initial cubic form. The matrix is degraded by neutrophils and bacterial lipase in the GCF . 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.

Strips and Compacts

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, MTZ 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[19]. 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 [20]. 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 [21]. The delivery of triclosan and chlorhexidine was studied for several liposomal compositions involving cationic as well as anionic lipids [22]. 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 .

Microparticle System

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-co-glycolic 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 [23]. Non-biodegradable as well as biodegradable materials have beeninvestigated 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-containingmicrocapsules in Pluronic F127were reported to formgel at body temperature and hold the microcapsules in the periodontal pocket for the duration of treatment. PLGAmicrocapsules 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. Recently, the controlled delivery of doxycycline for up to 11 days was

achieved through novel biodegradablemicrospheres prepared by w/o/w double emulsion technique using the Theformulationwas also effective in vivo andsignificant resultswere obtained with respect to microbiological and clinical parameters for up to three months .

Nanoparticulate 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 [11]. 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. The polymer-based nanoparticles were prepared via micellar polymerisation, which resulted in a well dispersible white powder material with particle size in the range of 50–180 nm. These nanoparticles are suitable for incorporation into a hydrogel matrix and to design new drug delivery devices for dental applications. Moulari et al. investigated the in vitro bactericidal activity of the Harungana madagascariensis leaf extract (HLE) on the oral bacterial strains largely implicated in dental caries and gingivitis infections. HLE-loaded PLGA nanoparticles were prepared using interfacial polymer deposition following the solvent diffusion method. Incorporation of the HLE into a colloidal carrier improved its antibacterial performance and diminution of the bactericidal concentration was observed. Shefer and Shefer patented a controlled release system useful for site-specific delivery of biologically active ingredients over an extended period of time. This system is a multi-component release system comprising biodegradable nanoparticles having bioadhesive properties encapsulated within a moisture sensitive microparticle. The bioadhesive properties of the nanoparticles are attributed to the positively charged surfactant entrapped on the particle surface. The multi-component release system can be incorporated into any suitable oral hygiene product including gels, chewing gums, toothpaste and mouthwash for the treatment and prevention of periodontal disease. 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 [24]. In an attempt to obtain a novel delivery system adequate for the treatment of periodontal disease, triclosan-loaded polymeric (PLGA, PLA and cellulose acetate phthalate) nanoparticles were prepared by emulsification–diffusion process. A preliminary in vivo study in dogs with induced periodontal defects suggested that triclosan-loaded nanoparticles penetrate through the junctional epithelium [25]. With the emergence and increase of microbial resistance to multiple antibiotics, the antibiotic-free delivery systems for periodontal infections have been tried. The problem of antibiotic resistance has led to resurgence in the use of Ag-based antiseptics that may be linked to broad-spectrum activity and far lower propensity to induce microbial resistance than antibiotics. Ag nanoparticles can be used as effective growth inhibitors in various microorganisms, making them applicable to treat periodontal diseases. Another approach is antimicrobial enzymes covalently attached to nanoparticles to generate antibiotic-free treatment for microbial infections. Satishkumar *et al.* developed a system in which hen-egg lysozyme

(antimicrobial enzyme) was covalently attached to two types of polystyrene latex nanoparticles: positively charged, containing aliphatic amines surface group; and negatively charged, containing sulphate and chloromethyl surface group. These particles were showing lower activity compared to free enzyme, but can be explored for targeted antimicrobial activity.

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 [11].

Surgical treatment for periodontal diseases:

Bone\Tissue grafts: - It is the method employed mostly to replace or speed up the formation of new cells of bone or gingiva, which is destroyed in periodontitis. The grafting also helps to prevent the gum tissue from growing into the area of the bone, allowing the gum and the bone to grow again. This technique is known as Guided Tissue Regeneration (GTR) [26].

Flap Surgery: - This is next step of tissue grafting and is used when the periodontal pockets are still seen even after the use of medications and tooth-cleaning techniques. This involves removal of the calculus and lifting back the gums. The gums are sutured back in place so that the tissue can re-grow and fit around the tooth. The success rate is very low in this type of surgery, because the gums have lost the stiffness and very rarely gain it again [26].

Periodontal Maintenance Procedures

Periodic monitoring of periodontal status and appropriate maintenance procedures should be part of the long-term treatment plan for managing chronic periodontitis. Although experimental studies have demonstrated very successful treatment outcomes when patients are professionally maintained at 2-week intervals, such a program is impractical for most chronic periodontitis patients. Therefore, to maximize successful therapeutic outcomes, patients must maintain effective daily plaque control. It also appears that in-office periodontal maintenance at 3 to 4 month intervals can be effective in maintaining most patients.

Table 1-List of commercial periodontal products presented in various dosage forms [27]

Product	Antimicrobial Agent	Dosage form	Manufacturer
Actinide®	Tetracycline	Non resorbable fiber	Alzacorp
Arestin®	Minocycline	Bio degradable powder in syringe	Oropharma corp Warminster
Atridox®	Doxycycline	Biodegrable mix in syringe	Atrix labs, Ft, Collins, co.
Dentamycin e ®/	Minocycline	Biodegrable mix in syringe	Sunstar corp., Tokyo, Japan
Elyzol®	Metronidazole	Biodegrable mixture in syringe	Dumex corp. Co Denmark.
Periochip®	Chlorhexidine	Biodegradable device	Dexcel Pharma Inc, Jerusalem,
Periochip®	Chlorhexidine /tetracycline	Films	Perioproducts Ltd.
Periochip®	Perioproducts Ltd.	Insert	Gluconate
Gluconate®	Perioproducts Ltd	Insert	Metronidazole
Elyzol®	Dumex pharma	Gel	Minocycline
Atrigel ®	Atridox (atrix Lab)	Gel	Doxycycline

Current status of intra-pocket delivery devices in periodontics

With the current availability of number of intra-pocket delivery systems containing antimicrobials for periodontal therapy, questions can be raised about the role of intra-pocket delivery devices in periodontics. Firstly, if intra-pocket delivery systems can deliver equivalent clinical results to SRP, should the use of these therapies be considered in place of SRP? Better still, how will antimicrobials be incorporated into treatment strategies with or without mechanical intervention? Lastly, to be considered are the physical properties of delivery system, which may influence the acceptance by the patient and professional community. Most reports on the local delivery concepts have appeared in the periodontal literature but there are surprisingly few studies that demonstrate the clinical efficacy using intra-pocket delivery systems in periodontitis patients. Despite the large number of studies, there are insufficient comparative data to support any one of the local delivery systems as superior to another because their treatment patterns differ widely. Great variability from site to site has been repeatedly noted by investigators showing that the same system could not work equally in all sites and in all patients. Many studies have failed to show real and clinically meaningful effects provided by the intra-pocket drug delivery systems when used as stand-alone monotherapies. Other studies have demonstrated that these systems have beneficial effects in terms of probing depth reduction; however, the statistical significance reached in these studies was not always clinically significant.

The strategic approaches with associated challenges and achievements towards the formation of periodontal drug delivery system [29-32]

Challenges Goals achieved

Strategy 1: systemic delivery devices

- Low benefit to risk ratio, ingestion of large drug doses
- Inadequate drug concentration at periodontal site
- Rapid/non-sustained drug release
- Poor patient compliance: frequent administration
- No penetration of delivery system
- No adhesion/retention into periodontal pocket
- High incidence of bacterial resistance

Strategy 2: local mouth rinses and dental irrigation

- Inadequate drug concentration at periodontal site Drug dose is reduced
- Rapid/non-sustained drug release Systemic toxicity is decreased
- Poor patient compliance: frequent administration
- No penetration of delivery system
- No adhesion/retention into periodontal pocket
- High incidence of bacterial resistance

Strategy 3: non-biodegradable, intrapocket fibres, strips, films and microparticles

- Poor patient compliance: discomfort during the placement
- of device, at least two visits to therapist is required and development of foreign body response, if left in situ Adequate drug concentration at periodontal site
- Poor penetration of system/drug Prolonged/sustain drug release
- Poor retention of system into periodontal pocket Less frequent administration
- Low incidence of bacterial resistance

Strategy 4: biodegradable, intra-pocket fibres, strips, films and microparticles

- Poor patient compliance: discomfort during placement Visit to therapist is reduced
- Poor penetration of system/drug No foreign body response
- Poor retention of system into periodontal pocket
- Low incidence of bacterial resistance

Strategy 5: biodegradable nanoparticles

- Poor retention of system into periodontal pocket Placement is easier
- Low incidence of bacterial resistance Good penetration due to nano-sized particles

Strategy 6: Mucoadhesive, biodegradable nanoparticles

- Low incidence of bacterial resistance Good retention of system

Strategy 7: antibiotic-free, mucoadhesive, biodegradable nanoparticles

- Bacterial resistance does not develop

Conclusion

From the preceding review of the recent advances in periodontal drug delivery systems it can be said that the antibiotic-free, mucoadhesive, biodegradable nanoparticles technology has an immense opportunity for the designing of a novel, low-dose and effective treatment method by the use of the intra-pocket controlled device..These devices are proving to be more convenient, easy-to-use and more effective than the regular drugs and medicines which act systemically. These devices also do not probe the risk of overdose or systemic overload, simple for formulation, affordable and easily available

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