LOCAL DRUG DELIVERY DEVICES USED FOR TREATING PERIODONTITIS- A REVIEW

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Abstract
Periodontitis is a disease caused by specific groups of microorganisms. Scaling and root planing is the first mode of treatment to reduce bacterial burden. Chemotherapeutic agents are used as adjuncts to improve the clinical outcomes of the treatment. Local drug delivery system does not have the side effects of systemic drugs. Controlled degradable devices offer clinicians with an additional treatment option to manage diseased sites which do not respond to standard periodontal therapy. Hence they are useful adjuncts to treat periodontal disease. This paper reviews the various local drug delivery devices used to treat periodontal disease.

INTRODUCTION
It is clear that the various forms of periodontal disease are associated with specific groups of microorganisms. This has led to the emergence of treatment strategies that are aimed at the suppression or elimination of specific periodontal pathogens. The surgical and mechanical intervention has remained the principal methods for control of the multifactorial disease process for decades. Recent advances in the development of chemotherapeutic agents have led to the increasing use of antimicrobials to suppress pathogenic flora. The use of antimetabolic agents for host modulation has also increased. Both types of chemotherapeutic agents can be used alone or along with traditional periodontal therapy to provide effective and predictable clinical improvement.1

Local delivery devices can be divided into two classes according to the duration of drug release as Sustained release devices and Controlled delivery devices. Sustained release formulations are designed to provide drug delivery for less than 24 hour. Controlled delivery systems should have a duration of drug releases that exceeds 24 hour. Intrapocket devices can be divided into two broad categories, depending on whether they are
Degradable
Non degradable

The advantage of non degradable devices is 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 advantage of degradable devices is that it reduces the number of patient’s visit and ensures compliance. A non-degradable device left in situ beyond its treatment is a potential problem as it could result in foreign body response.

FIBRES

Fibres have been developed as a non–degradable dosage form only. Fibres, 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 trapped drug into the periodontal pocket. The prototype for the use of fibre–like devices to deliver to the periodontal pocket was introduced by Goodson et al (1983), using cellulose acetate dialysis tubing. The release of the tetracycline from the cellulose acetate fibres by diffusion mechanism is rapid. Hollow fibres containing 20% (v/v) chlorhexidine, when placed into periodontal pockets, exhibited a prompt and marked reduction in signs and symptoms of periodontal disease.

The disadvantage of the hollow fibres served was that 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. Several polymers such as polycaprolactone (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. Hence monolithic fibres were essentially developed to retard the drug release. Outcomes included reduction of periodontal pathogens, reduction of bleeding on probing decrease in probing pocket depths and increase in probing attachment levels.

FILMS

The most widely used intrapocket delivery device has been the film or slab form. It has been prepared either by solvent casting or direct milling. This form enhances the physical properties. The dimensions and shape of the film can be easily controlled to correspond to the dimensions of the pocket to be treated. It can be easily and rapidly inserted to the base of pocket, totally submerged, with minimal discomfort to the patient. If the film is not more than approximately 400 μm, and physical properties provide it with sufficient adhesiveness, it will remain submerged without any interference with the patient’s eating and oral hygiene habits. Films are matrix delivery systems in which drugs are distributed throughout the polymer and release occurs by drug diffusion and/or matrix dissolution 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 in both degradable and non-degradable forms of films have been developed.

NON–DEGRADABLE FILMS

The first description of film form for intrapocket delivery appeared in 1982 and the film was made of methyl methacrylate for the intrapocket delivery of tetracycline, metronidazole, and chlorhexidine. A self-polymerizing mixture of the polymer, monomer and the appropriate drug were cured, as sheets, under high pressure and then cut into films of suitable sizes. Ethyl cellulose films showed sustained drug release and release rates were dependent on the casting solvent and drug load.
DEGRADABLE DEVICES

Many degradable devices in the form of a film have been used in studies. The ofloxacin has been tested clinically. The rapid degradation of the device and the short duration of drug exposure were distinct disadvantages. 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 are made of biodegradable polymers.

Different types of collagen-based membranes have also been tested for local drug delivery. A degradable controlled-release device based on formaldehyde cross-linked bycoprotein matrix containing chlorhexidine has been formed. Bycoprotein is a hydrolyzed gelatin of bovine origin. The release of chlorhexidine from this device and its dissolution in-vitro were shown to be dependent on the degree of protein cross linking. The nature of the chlorhexidine salt used also affected the release rate. Based on this study, the Perio Chip® (Perio products Ltd., Jerusalem, Israel) has been developed for the controlled subgingival delivery of chlorhexidine. 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 Periochip components.

The films composed of polyvinylalcohol (PVA) and carboxymethylchitosan (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, 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. Chlorhexidine – loaded Diplen-Denta films were developed and used to be highly effective in patients with gingivitis and generalized periodontitis of light and medium severity.

INJECTABLE SYSTEM

Injectable systems appear to be versatile system for the delivery of antibiotic agents into the periodontal pocket. Injecting a drug delivery system into the pocket has numerous advantages. It is a simple procedure with little or no discomfort to the patient. The initial fluid nature of the formulation, which is needed to use with a syringe, would theoretically allow the formulation to gain access to the entire pocket. The formulation then forms a gel which helps in retaining the drug for required time within the pocket. They are also cost effective. All injectable systems can be considered as degradable.

GELS

Mucoadhesive metronidazole (MTZ) containing gel systems based on hydroxyethyl cellulose, carbopol 974, and polycarbophil have been used in the studies. Gel is applied subgingivally with the help of blunt cannula or syringe. The gel is only marginally effective in decreasing the anaerobic bacterial count. This may be due to the low number of bacteria susceptible to MTZ or due to presence of bacterial biofilm. The first tetracycline gel was tetracycline base loaded into the microtubular exceipient halloysite, which was coated with chitosan to further slow down drug release. Studies have suggested that locally applied controlled release doxycycline (DOX) gel may partly counteract the negative effect of smoking on periodontal healing. The safety profile, long-term retention, antimicrobial activity suggests that tetracycline containing copolymer gels represent a safe and effective biodegradable therapy for periodontitis. Growing interest in developing absorbable pharmaceutical surgical products that degrade in biologic environment to leave behind safe by-products justifies the search for novel absorbable gels. Comparative analysis of tetracycline containing dental gels:
poloxamer and monoglyceride based formulations have shown that poloxamer and monoglyceride gels, when applied subgingivally, produce a significant improved outcome in moderate to deep periodontal pockets.5

INJECTABLE GELS
Along with the solid devices, semisolid formulations have also received reasonable attention for the localized delivery of drugs. For retention in the pocket, the formulation needs to undergo a change into a sticky semi–solid or solid phase so that it will prevent the drug from being washed out of the pocket by the gingival crevicular fluid (GCF) flow. Inspite of the relatively faster release of the incorporated drug, these gels can be more easily prepared and administered. They possess higher biocompatibility and bioadhesivity, allowing adhesion to the dental pocket and they can be rapidly eliminated through normal catabolic pathways, reducing the risk of irritation 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 both tetracycline (2.5%) and metronidazole benzoate (40%), has 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. Despite the rapid drug release and poor retention of these gels, positive clinical results were obtained in moderate to deep periodontitis. Bioadhesion or mucoadhesion is a preliminary requirement for prolonged release of the drug at the site.

Chitosan, a novel biodegradable natural polymer, in a gel form (1%, w/w) with or without 15% metronidazole, had demonstrated effectiveness in the treatment of chronic periodontitis. Bioadhesive semisolid, polymeric system can be utilized as an important intra-pocket delivery vehicle because it can easily pass thorough a cannula into a periodontal pocket where it solidifies in-situ to deliver the therapeutic agent for a prolonged period. These systems exhibit a pseudo plastic flow and thermo responsive behavior, existing as a liquid at room temperature and gel at 34–37°C. Another system composed of Poloxamer 407 and Carbopol 934P and containing propolis extract were designed for the treatment of periodontal disease.

The Atrigel loaded with 10% doxycycline hyclate showed high levels of doxycycline (250 mg/ml) in the GCF for a period of seven days. The levels of 10 – 20 mg/ml were still present for three to five days after the polymer had been removed. In another study Atrigel containing 5% sanguinarine was found to be superior to the control in the treatment of adult periodontitis and the findings have been recently confirmed in a human clinical trial. Biodegradable gels are other useful prospects for the delivery of therapeutic agents into periodontal pockets. Biodegradable lactic glycolic acid gels were found to be safe and tetracycline levels observed at days 3 and 8 probably represent significant antimicrobial efficacy. Use of a clindamycin hydrochloride gel inserted into the periodontal pockets once a week for two weeks enhanced the effect of scaling and root planing on the sub gingival micro flora of adult periodontitis.3

OINTMENT
Antimicrobial ointments which are commercially available are of two types. Minocycline – containing Dentomycin® (Cyanamid international, Lederle Division, Wayne NJ, and Sunstar, Osaka, Japan) which does not appear to have any sustained release properties. The second commercially available system Elyzol® (Dumex, Copenhagen, Denmark) is a formulation consisting of a water–free mixture of melted glycerol monooleate and metro diazole benzoate for which a triglyceride, sesame oil, has been added to lower the melting point in order to improve the flow properties of the gel in the syringe. When the

http://mutagens.co.in
mixture comes into contact with water, it sets in a liquid crystalline state. The formulation contains 25% metronidazole as 40% w/w metronidazole benzoate.¹

**ROOT CONDITIONING GELS**

Tetracycline or a mixture of tetracycline and citric acid gels have been used in moderate pockets, using a 5-minute burnishing technique to burnish the gel into the roots subgingivally, with or without root planing. Tetracycline plus citric acid had been used to attain attachment gain. An adverse effect caused by the low pH of citric acid is that it delays wound healing. Beneficial effects of the acidic gel is that it can cause elimination or diminution of surface smear layer resulting from incomplete removal or translocation of dentin, plaque, calculus and cementum following root planing. Surface demineralization may occur and this could enhance new attachment by detoxifying the root. Non-root planed surfaces showed altered morphology, indicating potential chemical dissolution of the surface and demineralization.³

**ANTI–INFLAMMATORY GELS**

Studies have supported the positive role of anti–inflammatory agents in the treatment of periodontal disease. Williams and co-workers have investigated the effect of topical application of a non steroidal anti–inflammatory drug flurbiprofen on periodontal disease progression in beagle dogs. Dogs treated with 0.3 mg flurbiprofen applied to the gingival margin daily shows considerably less tooth loss than untreated control dogs over the 7-month study.³

**STRIPS AND COMPACTS**

Acrylic strips have been fabricated using a mixture of polymers, monomers and different concentrations of antimicrobial agents. Strips were fabricated either by solvent casting or pressure melt method. Strips containing tetracycline, metronidazole (MTZ) or chlorhexidine demonstrated a decrease in number of motile rods, notably spirochetes. In a later development, the evaluation of amoxicillin–clavulanic acid loaded acrylic strips is reported. Tissue adhesive implants were made using n-buty1-2-cyanoacrylate as a drug trapping material and slowly release the drug when used in the structure of a biodegradable local drug delivery device.

**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. It shows interactions between liposomes made up of phosphatidylinositol (PI) and biofilms. The potential of lectin – bearing liposome systems as a targeting system for the control of gingivitis and dental plaque has been used. The delivery of triclosan and chlorhexidine was studied for several liposomal compositions involving cationic as well as anionic lipids.

**MICRO PARTICLE SYSTEM**

Micro particles based system with polyalphahydroxyl acids such as polylactide (PLA) or polylactide–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 digluconate and their association or inclusion complex with methylated–beta–cyclodextrin (HPBCD) were prepared with single emulsion, solvent evaporation technique. 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 substance 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 pocket. Tetracycline-containing microcapsules in Pluronic F127 were reported to form gel at body temperature and hold the microcapsules in the periodontal pocket for the required 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, crystallity and pH of the medium. Recently, the controlled delivery of doxycycline for up to 11 days was achieved through novel biodegradable microspheres prepared by w/o/w double emulsion technique.

**Local application into the periodontal pocket has following advantages:**
It can be delivered to the site of disease activity at a bactericidal concentration. It can facilitate prolonged action of the drug. It can prevent many systemic side effects like gastrointestinal complaints, depression, and tachycardia. It can alter the pathogenic flora. It could act as potent therapy to treat selective sites that do not respond to conventional treatment, ease of application and possibly enhanced treatment results when used as an adjunct to scaling and root planing. It may prevent recurrent attachment loss. Biodegradable local drug delivery systems can increase patient compliance.

**Potential limitations are:**
If used as a monotherapy, there could be a possibility of inability to disrupt biofilms, allergic reactions and failure to remove local factors. With the existing systems concerns have been raised regarding the drug release rate which might be more rapid than anticipated or the poor biodegradability of the polymer.

**REFERENCES**