WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 11, 437-456. Review Article ISSN 2277– 7105

A NOVEL APPROACH TO CONTROL PERIODONTAL DISEASES: A PERIODONTAL IMPLANT

Hariom Sharma* and Kaushal K. Chandrul

School of Pharmaceutical Sciences, Shri Venkteshwara University Gajraula. (U.P)

Article Received on
21 Aug 2015,

Revised on 13 Sep 2015,
Accepted on 06 Oct 2015

***Correspondence for Author**
Hariom Sharma
School of Pharmaceutical Sciences, Shri Venkteshwara University Gajraula. (U.P).

ABSTRACT

Periodontitis is an inflammatory disease of the supporting tissues of the teeth caused by infection of a periodontal pocket arising from the accumulation of subgingival plaque. Periodontal disease has been considered as a possible risk factor for other systemic diseases such as cardiovascular diseases and pre-term low birth weight infants. Aggressive forms of periodontitis can be localized or generalized. Local delivery of antimicrobial agents using controlled release systems should be considered as adjunctive to mechanical debridement for the treatment of localized forms of periodontal destruction. 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 anti-bacterial 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. This article reviews various types of delivery systems evaluated in practical periodontal therapy and identifies areas where further research may lead to a clinically effective intra-pocket delivery system.

KEYWORD: *Periodontal diseases, periodontal pockets, local drug delivery system, controlled drug delivery.*

INTRODUCTION

Dental disease is recognized as a major public health problem the world. Numerous epidemiological studies showed that dental diseases, tooth decay and disease of the svirtually the whole world's population and is a major source of tooth loss after the age of 25years.

Dental disease do occur in all groups, ethnicities races and genders. Tooth decay while gingivitis occurs is found most often in children, as well as in adults. Periodontal disease progress with increasing age and constitute the major cause of tooth loss in adults. Pain, discomfort and other complications are associated with periodontal diseases. Hence, it is of the most importance to minimize and control diseases.[1]

Dental disease can be controlled with daily oral hygiene that plays a vital role in maintaining healthy teeth and gums. Clinical treatment in and medication are also important aids in the upkeep of a healthy oral state. Since dental diseases may be chronic, long term treatment is often necessary. In these diseases a significant pharmaceutical advantage is gained by targeting a particular drug to a desired site, thereby minimizing superfluous distribution of the drug to other body organs. Improved local pharmaceutical delivery devices which reduce the amounts of administered drug and at the same time demonstrates the same or even better clinical results, have numerous potential benefits over traditional treatments. Local treatment of periodontal disease with antibacterial agents has principally been by mouth rinses, lozenges, and to a large extent by topical application in an adhesive carrier.

Mouth washes are used to control supra gingival plaque but are very less effected against sub gingival bacteria due to an inability to penetrate to sub gingival areas .Irrigation devices are frequently employed to deliver antimicrobial agents directly to the sub gingival regions, however, due to the short duration of action, frequent applications are required.

Several therapeutic agents have proved effective controlling dental diseases and in preventing tooth decay. One of the most common agents is FLORIDE. Fluoride can be introduced systemically in the form of solid preparation, liquid preparation or as local delivery applications.

Mouth washes are used to control supra gingival plaque but are very less effected against sub gingival bacteria due to an inability to penetrate to sub gingival areas. Irrigation devices are frequently employed to deliver antimicrobial agents directly to the sub gingival regions, however, due to the short duration of action, frequent applications are required.[2]

PERIODONTAL DISEASES

Periodontal diseases may be defined as any pathologic process that affects the surrounding and supporting tissues of the teeth. Periodontal disease refers to all the diseases of the

periodontum. The vast majority of the inflammatory diseases of the periodontum result from bacterial infections .The process of inflammation is the succession of changes which occurs in a living tissue a degree when it is injured. Provided that the injury is not of such a degree as at once to destroy its structure and vitality.

Periodontitis

Periodontitis is an inflammation of the periodontium, i.e., the tissues that support the teeth. The periodontium consists of four tissues.[3]

- Gingiva, or gum tissue.
- Cementum, or outer layer of the roots of teeth.
- Alveolar bone, or the bony sockets into which the teeth are anchored.
- Periodontal ligaments (PDLs), which are the connective tissue fibers that run between the cementum and the alveolar bone.

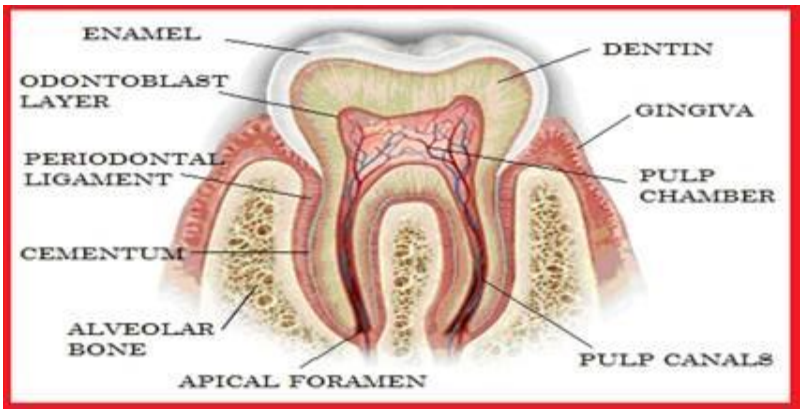

Diagram 1: Structure of a Tooth with Adjoining Tissues.

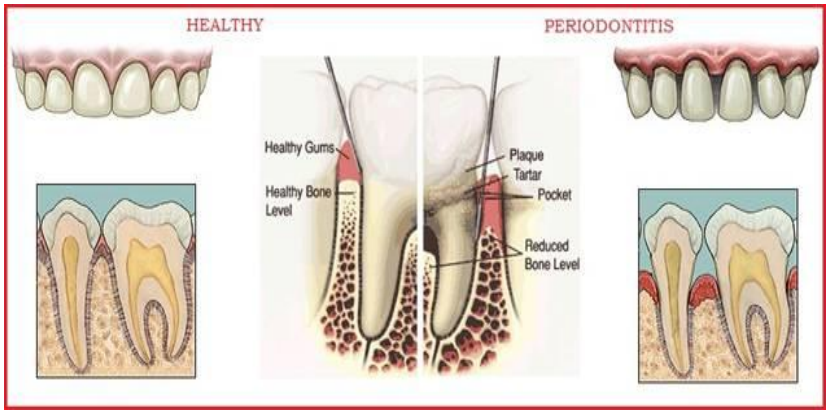

Diagram 2: Healthy and PeriodontisTooth condition: A pocket is seen clearly in peridontitis where drug can be placed directly with some Implant Device.

ETIOLOGY

The primary etiology of gingivitis is **poor or ineffective oral hygiene**, which leads to the accumulation of a mycotic and bacterial matrix at the gum line, called **dental plaque**. Other contributors are poor nutrition and underlying medical issues such as diabetes. In some people, gingivitis progresses to periodontitis with the destruction of the gingival fibers, the gum tissues separate from the tooth and deepened sulcus, called a **periodontal pocket**. **Sub gingival** micro-organisms (those that exist under the gum line) colonize the periodontal pockets and cause further inflammation in the gum tissues and progressive bone loss. Examples of secondary etiology are those things that, by definition, cause microbic plaque accumulation, such as restoration overhangs and root proximity. The excess restorative material that exceeds the natural contours of restored teeth [these are termed "overhangs"] and serves to trap microbic plaque, potentially leading to localized periodontitis. Smoking is another factor that increases the occurrence of periodontitis, directly or indirectly and may interfere with or adversely affect its treatment. More than 700 microbial species[7] 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),
- Aggregati bacter actinomycteincomitans(A.a),
- Porphyromonas gingivalis (P.g.),
- Tannerella forsythia (T.f.),
- Treponema denticola (T.d.),
- Fusobacterium nucleatum (F.n.)
- Prevotella intermedia .

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 inhibits 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. 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, diarrhea, fever, abdominal pain and pseudo membranous colitis that may be induced over long period of usage 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 .The drug can bind to tooth surface from which it is released

in active form. Therefore use of such types of drugs are beneficial in treatment of periodontal diseases.

Systemically applied antimicrobials have been advocated for the treatment of severe forms of periodontitis. However, in the early 1970s, concern emerged with respect to systemic anti biotherapy for chronic infections such as periodontal disease. Indeed, side effects including hypersensitivity, gastrointestinal intolerance and the development of bacterial resistance have been described.

Some studies also reported poor results due to the fact that the active product could not achieve an adequate concentration at the site of action and/or due to the inability of the active product to be retained locally for a sufficient period of time .These drawbacks would be markedly reduced if antimicrobial agents applied locally could be used, although unwanted effects such as gastrointestinal disturbances and development of antibiotic resistance cannot be totally ruled out.

The local tissue concentration of a drug can be enhanced by incorporating the active agent into controlled release delivery systems to be placed directly in the periodontal pocket. Such systems may have applications where systemic drugs are currently used, for instance localized juvenile periodontitis, refractory periodontitis and periodontitis with secondary systemic involvement, e.g. HIV periodontitis.

Sustained local delivery systems might also be recommended for sites considered as difficult to instrument because of depth or anatomical complexity, for example in the case of furcation defects.[4.5.6]

DIAGNOSIS OF PERIODONTITIS

A diagnosis of periodontitis is established by inspecting the soft gum tissues around the teeth with a probe (i.e a clinical examination) and by evaluating the patient's X-ray films (i.e. a radiographic examination), to determine the amount of bone loss around the teeth [Diagram 2].

In 1976, Page & Schroeder introduced an innovative new analysis of periodontal disease based on histo- pathologic and ultra-structural features of the diseased gingival tissue. Plaque-induced periodontal lesions are divided into four stages.

1. Initial lesion

2. Early lesion
3. Established lesion.
4. Advanced lesion.

Treatment of Periodontal Infections

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 sub gingival calculus and plaque. Although SRP[10] is a localized treatment 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 and it was concluded that responses to SRP are dependent upon pocket depth, skill of the practitioner, length of therapy and patient compliance.[7]

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.

But the systemic route of administration not always was 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. 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. The drug can bind to tooth surface from which it is released in active form. Therefore uses 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.[8]

The local delivery of antimicrobial therapy to periodontal tissue has the benefit of putting more drugs at target site while minimizing exposure of total body to the drug. 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 Delive,[19] 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.[9]

The drug into different Local application of antibiotics has been achieved either by sub gingival irrigation or by incorporating devices for insertion into periodontal pockets. **The primary objectives of therapy for patients with chronic periodontitis are to halt disease progression and to resolve inflammation.** Therapy at diseased site is aimed at reducing etiologic factors below the threshold capable of producing breakdown, thereby allowing repair of the affected region. Local application into periodontal pocket could be very advantageous, both in terms of rising 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.[10]

Various Antimicrobial Agents used for treatment

Antimicrobial agent's selection in periodontal diseases must be based on the bacterial etiology of the infection. Some antimicrobial agents have been selected because of their substantivity which refers to the property of some medications that have an intrinsic ability to bind to the soft and/or hard tissue walls of the pocket. The following antibacterial agents are used for this purpose.[11]

Tetracycline

Tetracyclines are a group of broad-spectrum antimicrobial agents that were introduced into clinical practice in the late 1940s. There are now numerous compounds on the market, all based on the congeneric derivatives of the polycyclic naphthacene carboxamide. Tetracycline, doxycycline and minocycline are used extensively in the management of periodontal diseases. They are bacteriostatic antibiotics which interfere with bacterial protein synthesis and also inhibit tissue collagenase activity. They have a broad spectrum of activity inhibiting both Gram negative and Gram positive.[12]

Chlorhexidine

The use of chlorhexidine as an antifungal and antibacterial agent in dentistry is well documented. Its major application has been for the control of dental plaque. However, a number of studies have indicated that chlorhexidine is also effective in periodontitis. Chlorhexidine was primarily used in mouth-rinses and was recommended in the hygiene phase of treatment as an adjunct to tooth-brushing. Most attention, however, has been focused on the use of chlorhexidine during the operative and immediate post-operative phases of non-surgical and surgical periodontal treatment. Chlorhexidine's potential effects at these times are: (i) a surface bacteriostatic action; (ii) improved wound healing and patient preference to dressings in the immediate post-surgical phase; (iii) optimum plaque control immediately post-treatment when discomfort may compromise tooth-cleaning.[13]

Metronidazole

Among the antibiotics that have been considered for periodontal treatment, metronidazole has often been chosen because of its selective efficacy against obligate anaerobes. Metronidazole acts by inhibiting DNA synthesis. It is known to convert into a reactive reduced form and affects specifically anaerobic rods and spirochetes in the sub gingival microflora. Metronidazole, long known to be ineffective in vitro against Actinobacillus actinomycetemcomitans was marginally more effective than tetracycline in the treatment of juvenile periodontitis, a disease considered to be associated with the former organism. This emphasizes the multi infectious character of periodontal disease where in vitro tests do not necessarily reflect in vivo effect. Metronidazole has also been successful in refractory and advanced cases when used for a 1-week period. Other studies reported that adjunctive metronidazole therapy was more effective in adults with deep pockets than with less advanced periodontitis. In one study, without a thorough maintenance therapy, the beneficial effects observed in deep sites 3 months after adjunctive metronidazole were no longer apparent after 3 years. However, sites with a moderate level of disease at baseline demonstrated an improvement after 3 years which was not present after 3 months. The reason for this finding is unclear but highlights the need for clinical trials of long duration since antibiotics often produce improvements in microbiological and clinical parameters which tend to drift towards control levels with time.[14]

Histatins

The histatins are a group of small, cationic histidine-rich peptides secreted by human parotid and submandibular salivary glands. These endogenous peptides have been shown to bind to

hydroxyapatite, suggesting a role in the formation of the acquired enamel pellicle. The histatins play a major role in protecting the host oral cavity from etiologic pathogens. In particular, the histatins are antifungal and also demonstrate bactericidal and bacteriostatic effect against periodontal pathogens such as Porphyromonas gingivalis, Prevotella intermedia and Bacteroides forsythus.[15]

Ofloxacin

is a newly developed synthetic pyridine carboxylic acid (PCA) derivative. Although the earlier PCA derivatives were not active against Gram positive bacteria and anaerobes, ofloxacin can kill Gram positive bacteria and anaerobic bacteria.

Clindamycin

Clindamycin has been investigated for treatment of periodontal disease in a limited number of studies. Systemic clindamycin therapy, as an adjunct to scaling, decreased the incidence of active disease from an annual rate of 8.0 to 0.5% of sites per patient. However, clindamycin did not permanently suppress sub gingival Porphyromonas gingivalis, which may explain the recurrence of disease activity in some patients. Following gel insertion of clindamycin in conjunction with sub gingival scaling, motile rods and spirochetes were not detected after 1 month. Prevotella intermedia and Porphyromonas gingivalis were eliminated or below detectable levels after 1 week post-therapy but were again detected at 12 weeks.[16]

Treatment approach for periodontal disease

Conventional periodontal therapy

The main purpose of periodontal therapy is to cure the inflamed tissue, reduce the number of pathogenic bacteria and eliminate the depth of the diseased pockets and to stop bone re sorption. The conventional methods of pocket elimination are more or less mechanical and the aimed at removal of supra and mechanical plaque and degenerated and necrotic tissue lining the gingival wall of periodontal pockets through scaling, root planning and curettage. Mechanical debridement alone often leaves behind significant number of pathogens due to possible instrumentation or ability of microorganism to penetrate into deeper tissues. Inaccessibility and re colonization of pathogens can occur after scaling and root planning. With oral hygiene, a pathogenic sub-gingival microbial may reestablish within 42-60 days after a single periodontal debridement session.

Local drug delivery Goodson et al in 1979 first proposed the concept of controlled delivery in the treatment of periodontitis. The effectiveness of this form of therapy is that, it reaches the base of periodontal pocket and is maintained for an adequate time for the antimicrobial effect to occur. Periodontal pocket provides a natural reservoir bathed by gingival cervicular fluid that is easily accessible for the insertion of a delivery device. These delivery systems are also called sustained release, controlled - release, prolonged release, timed release, slow release, sustained action, prolonged action or extended action.[17]

Classification of local drug delivery

A. Based on type of therapy

1. Personally applied (patient home care).
2. Non Sustained (Oral irrigation)
3. Sustained (not developed till now) professionally applied (in dental office).
4. Non Sustained (Supra and sub gingival irrigation)
5. Sustained (Controlled release device)

B. Based on degradability of the device

1. Biodegradable
2. Non- Biodegradable

Table 1: Non-Biodegradable polymer films.

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

Table 2 Degradable intra pocket drug delivery system in periodontal diseases

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 polyhydroxy valerate, poly lactic acid, polymer &copolymer	Direct compression	Compact	Tetracycline, Metronidazole
Poly (ε -caprolactone) Hydroxyl propylcellulose 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

C. Based on duration of action

1. Sustained released devices

These are delivery systems whose action lasts less than 24 hours therefore require multiple applications. It follows the first order kinetics.

2. Controlled delivery devices

These are the devices which follows zero order kinetics and whose actions last longer than 24 hours, thereby decreasing the number applications.

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

Fibers

Fibers, or thread-like devices, are reservoir-type systems, placed circumferentially into the pockets with an applicator and secured with cyanoacrylate adhesive for the sustained release of trapped drug into the periodontal pocket. 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. Examples are Chlorhexidine fibers and tetracycline fibers. The release of the tetracyclinefrom the cellulose acetate fibers as occurred by diffusion mechanismis rapid with approximately 95% of the drug released in the first two hours and therefore, a single application of these fibers does not provide an effective drug concentration for long periods. Compared to tetracycline delivery from hollow fibers, fibers containing 20% (v/v) chlorhexidine, when placed into periodontal pockets, exhibited a prompt and marked reduction in signs and symptoms of periodontal disease.Tetracycline fiber treatment adjunctive to scaling and root planning (SRP) showed significantly less periodontal disease recurrence (4%) compared with

SRP alone (9%), tetracycline fiber alone for 10 days (10%) and tetracycline fiber alone for 20 days (12%). This is one of the best options for delivery of drug to periodontal pockets, but they have some disadvantages such as difficulty in placing fiber in pockets, patient discomfort and at fiber removal various degree of gingival redness were observed.[18]

Strips or Implants or Films

Strips are thin and elongated matrix bands in which drugs are distributed throughout the polymer. Acrylic strips have been fabricated using a mixture of polymers, monomers and different concentrations of anti- microbial agents. Strips were fabricated either by solvent casting or pressure melt method. Strips containing tetracycline or metronidazole were found to be effective in producing changes in the sub gingival flora and improving the clinical parameters of periodontal disease. Treatment with metronidazole-loaded fibers or SRP was also associated with a slower rate of relapse of clinical parameters. The change in physical properties of acrylic strips in the serum has been reported. These strips dissolved slightly in serum, softened and were difficult to remove, leading to the risk of leaving injurious acrylic material in the periodontal pocket, which may evoke an inflammatory reaction.

Different types of synthetic biodegradable polymers such as polyhydroxybutyric acid (PHBA) and polylactide co-glycolic acid (PLGA) have been evaluated as a matrix for sustained delivery of tetracycline. PHBA strips containing 25% tetracycline showed sustained release over four to five days with a significant burst effect at day one (P B , whereas, PLGA strips containing 25% tetracycline (25 TTC–PLGA) released therapeutic concentrations of the drug for ten days. Several bio absorbable dental materials like hemostatic gauze made of oxidized regenerated cellulose, a collagen wound dressing and a fibrin sealant have been investigated by Larsen et al. for their potential use as carrier materials for doxycycline.[19]

Films are most widely used Intra-pocket drug delivery device prepared either by solvent casting or direct milling. Bigger films either could be applied directly on chiek mucosa or gingival surface or can be cut into appropriate size so as to insert into the site of infection which drug is distributed throughout the matrix and drug release occur by erosion, matrix dissolution or drug diffusion. This system has a several advantages than other intra pocket drug delivery devices. Adhesiveness will remain submerged into periodontal pocket without interfering with the patient's oral hygiene habit. Films that release drug by diffusion alone are prepared by using non-degradable water insoluble polymers, while those that release by diffusion and matrix erosion or dissolution are prepared by water soluble or biodegradable

polymers. (TABLE 2). Various non-biodegradable periodontal films of chlorhexidine diacetate, metronidazole, tetracycline and minocycline have been prepared using ethyl cellulose by Ethyl cellulose films showed sustained drug release and release rate were dependent on the casting solvent and drug load. The use of chloroform as casting solvent significantly retarded the release rate of the drug compared to ethanol as a casting solvent. The incorporation of polyethylene glycol in the films however enhanced the release rate of the drug(S Pragati et al., 2009). More recently, a film prepared and commercialized and it composed of crossed linked hydrolysed gelatin and glycerine for local delivery of chlorhexidine digluconate(P A Heasman et al., 2001).Higashi et al. prepared films of water-soluble polymer EudragitS® 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(K Higashi et al., 1991). 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 (K D Kyun et al., 1990solvent evaporation method (TABLE 1).[20]

Injectable gel

Along with solid devices, semi-solid devices also attain a reasonable attention for localized delivery of anti-microbial agents. Release rate of the drug from gel is faster as compared to other formulations. These types of the formulations can be easily prepared and administered. Various hydrogels and oleo gels for the delivery of metronidazole (25%), tetracycline (2.5%), and combination of tetracycline (2.5%) and metronidazole benzoate (40%) have been prepared, tested and satisfactory results were obtained. Gels composed of hydroxylpropylmethyl cellulose and hydroxyethyl cellulose and do not having sustained release properties. In-spite of their rapid drug release and poor retention time, they obtained positive clinical results for treatment of periodontitis. Mucoadhesion or bio adhesion is the prime requirement for delivery of drug to the site of infection. The chitosan gel (1%w/w) incorporated with or without 15% metronidazole was found to be effective in treatment of periodontitis. Semi solid bio adhesive polymeric system can be utilized as vehicle for intra pocket drug delivery because it can easily pass through cannula into periodontal pocket where it easily solidified in-situ to deliver therapeutic agent for prolonged period. These types of systems exhibit pseudo plastic flow and thermo responsive behavior, existing as a liquid at

room temperature and gel at 34-37 oc. Tetracycline loaded semisolid bio-adhesive polymeric system based on hydroxyl ethycellulose and polyvinylpyrollidine and metronidazole loaded system based on carbopol 934p, hydroxyl ethylcellulose and polycarophil are reported.[21]

Micro particulate system

Both biodegradable as well as non-biodegradable polymeric materials have been investigated for the preparation of microspheres. These materials include the polymers of natural origin, modified natural substances and synthetic substances. Micro particles based system of biodegradable poly alpha hydroxyl acids such as poly lactide (PLA) or poly (lactide-co-glycolide) PLGA microsphere containing tetracycline has been designed for periodontal therapy and study shows that microsphere could enhance tetracycline delivery to periodontal pocket by enhancing drug encapsulated efficiency, release quantity and sustained release period compared to uncoated ones. Tetracycline containing microcapsule in pluronic F127 was reported to form gel at body temperature and hold the microsphere in the periodontal pocket for duration of treatment. The in-vitro drug release from such system depends upon the polymer (lactide:glycolide) ratio, molecular weight, crystallinity 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 using the blends of PLGA and PCL in different ratios. The formulation was also effective in vivo and significant results were obtained with respect to microbiological and clinical parameters for up to three months.

Nanoparticulate system

Up to now only micro particle or polymer based hydrogel have been applied in dentistry, recently intensive research performed all over the world to improve the effectiveness of delivery system. Various advantages of nano-particulate system compared to micro particle, microsphere and emulsion based delivery system includes increased stability, controlled release rate, high dispersibility in an aqueous medium. Because of their small size nanoparticles penetrate deeper regions that may be inaccessible to other delivery system, such as periodontal pocket area below the gum line. These reduce the frequency of administration and further provide a uniform distribution of the active agents over an extended period of time.*Moulari et al* investigated antibacterial effect of Harunganamadagascariensis leaf extract (HLE) by using the poly (D,L-lactide-co glycolide) nanoparticles (PLG-NP) prepared by interfacial polymer deposition following the solvent diffusion method, and concluded that

incorporation of the HLE into a colloidal carrier optimized its antibacterial performance. *Dung et al* prepared and evaluated antisense oligonucleotide loaded chitosan nanoparticles. Oligonucleotide formed complex with chitosan and then chitosan/oligomer-TPP nanoparticles prepared by adding TPP after the formation of chitosan/nucleotide complex and study shows that sustained release of oligonucleotide from chitosan nanoparticles may be suitable for the local therapeutic application in periodontal diseases.In an attempt to obtain a novel delivery system adequate for the treatment of periodontal disease, the nanoparticles were prepared using poly (D,L-lactide-co-glycolide) (PLGA), poly(D,L-lactide) (PLA) and cellulose acetate phthalate (CAP)by emulsification-diffusion process.A preliminary in vivo study in dogs with induced periodontal defects suggested that TCS-loaded NPs penetrate through the junctional epithelium.[22]

Vesicular system

Vyas et al have prepared and investigated in vitro antimicrobial activity of metronidazole bearing lectinized liposomes for intra-periodontal pocket delivery.

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

Product	Antimicrobial agents	Dosage form	Manufacturer
Atrigel®	Doxycycline	Gel	Atridox (atrix Lab)
Elyzol®	Metronidazole	Gel	Dumexpharma
Periochip®	Chlorhexidine gluconate	Films	Adrian Pharmaceuticals, LLC
Periochip®	Chlorhexidine gluconate	Biodegradable device	DexcelPharmaInc, Jerusalem,
Dentomycine®	Minocycline	Biodegradable mix in syringe	Sunstar corp., Tokyo, Japan
Arestin®	Minocycline	Microsphere	Oropharmacorp
Actisite®	Tetracycline	Non resorbable fiber	Alza Corp. Palo Alto, CA, USA
OnSite®	Antibiotics	Fiber	Alza Corp. Palo Alto, CA, USA

Some investigated intra-pocket delivery systems

Table 4: Some intra-pocket delivery system

System	Polymer matrix	Drug Incorporated	References
Strip	Ethyl cellulose	Chlorhexidine	(M Friedman and G Golomb, 2006)
	Hydroxypropyl cellulose + methacrylic acid	Ofloxacin	K Higashi et al., 1990
	Polyhydroxybutyric acid	Tetracycline HCl	P B Deasy et al., 1989
	Polylactide-co-glycolic acid (PLGA)	Tetracycline HCl	(G I Maze et al., 1995)
	Hydroxypropyl cellulose	Chlorhexidine, tetracycline	(T Noguchi et al., 1984)
	Polyethylmetha acrylate (acrylic)	Tetracycline HCl	(M Addy and Langeroudi., 1984

Fibers	Poly(e-caprolactone) (PCL)		(M Tonetti et al., 1990)
	Cellulose cetate	Tetracycline HCl	(J M Goodson et al., 1979

Periodontal Chip or Periodontal Implant

A pharmaceutical composition which is applied to a periodontal pocket or paradentium for the purpose of treating periodontal diseases. The pharmaceutical composition, which is provided in the form of gel, sheet, film or bar-like formulation, releases a controlled and effective amount of an active ingredient at the periodontal pocket or paradentium. Strips which comprise polymers and active ingredients for treatment of periodontal diseases have been developed. These strips are said useful for the treatment of plaques and inflammation beneath the gingival margin. The strips can be applied directly to the lesional region to be treated, and therefore, the active ingredient can be concentrated to the desired site selectively. This modified therapeutic method has been proved to be more effective than any conventional pharmacotherapy. The formulations comprise a mixture of an active ingredient and a homogeneous polymer base. Accordingly, where such formulation is designed to contain two or more active ingredients which differ from each other in terms of pharmacological activity and therapeutically effective dose, it has been impossible to prepare the formulation in which each of the plural ingredients may release independently and provide its suitable concentration as desired. The strip which comprises a soluble polymer as a base or carrier permits a rapid release of an active ingredient.

Advantages of periodontal chip

1. Relatively small amounts of the drug can produce a high concentration in the periodontal pocket.
2. Minimal side effects
3. Less potential of inducing resistant bacterial strains in other parts of the body.
4. Controlled release devices can maintain a high concentration of the drug for an extended period.
5. Reduces potential problems with patient compliance.
6. May employ antimicrobial agents not suitable for systemic administration, such as various broad spectrum antiseptic solutions.

Preparation of Periodontal Chip

Periodontal chips are prepared by solvent casting technique. Glass moulds are used for casting of the films. Formulations are designed using different polymers and copolymers in

different ratios. Films are prepared by dissolving polymer alone and with copolymers in suitable solvent, using Dibutyl phthalate and PEG-400 as plasticizers. The drug is added in to the polymeric solution and mixed homogenously using magnetic stirrer in a closed beaker. After complete mixing 10 ml of the solution was poured into the clean levelled glass moulds of 15 sq. cm. The solvent is allowed to evaporate slowly by inverting a glass funnel with a cotton plug closed into the stem of the funnel at room temperature for 24 hours. After complete evaporation of solvent, cast films are obtained, which are then cut into pieces of 7×2 mm, wrapped in an aluminium foil and can be stored in a desiccator at room temperature in a dark place for further evaluation studies.

Evaluation Parameters of the Periodontal chip

Various parameters for which Periodontal chips can be evaluated are.

1. ***Thickness uniformity of the films***

Thickness of the film can be measured using digital screw gauge at different areas of the film and the average is calculated.

2. ***Uniformity of weight of the films***

Film (size of 7x2 mm2) is taken from different areas of film. Then the weight variation of each film can be calculated.

3. ***Surface pH***

Periodontal films are left to swell for 1 hour on the surface of the agar plate, prepared by dissolving 2% (w/v) agar in warmed double distilled water with constant stirring and poured into the Petri dish to solidify at room temperature. The surface pH can be measured by means of pH paper placed on the surface of the swollen film.

4. Viscosity

Viscosity can be measured by using Brookfield viscometer. Aqueous solutions containing both polymers and plasticizers are prepared in the same concentration as that of films. Viscosity can be measured at 20 rpm at room temperature using the viscometer attached to the helipath spindle.

5. ***Folding endurance***

As described by Khanna *et al*., the folding endurance of the films can be determined by repeatedly folding the film at the same place up to 300 times till it broke or folded, which is considered satisfactory to reveal good film properties.

6. *Drug content uniformity of films*

Film (size of 7x2 mm2) is taken from different areas of the film and placed into a 10 ml volumetric flask, in to which 10 ml of suitable solvent is added and kept aside till the film is completely dissolved. Withdraw the sample and suitably dilute it. The absorbance of the solution is measured. The polymeric solution without drug served as blank.

7. *Tensile strength of the films*

Tensile strength of the films can be determined by Universal strength testing machine. It consists of two load cell grips, the lower one is fixed and upper one is movable. The test film of specific size (4 × 1 cm2) was fixed between these cell grips and force was gradually applied till the film breaks. The tensile strength of the film was taken directly from the dial reading in kilograms.

8. *In vitro drug release*

Static dissolution method can be used to study the drug release from the periodontal chip. Films of known weight and dimensions (size of 7×2 mm2) are placed separately into small test tubes containing 1 ml of simulated saliva. The test tubes were sealed with aluminium foil and kept at 37°C for 24 hours. The medium is drained off and replaced with fresh 1 ml of the simulated saliva after 24 hours. The concentration of drug in the medium is measured. The procedure can be repeated for 10 days.

9. *In vitro antibacterial activity*

The films (size of 2x2 mm2) are taken for the study. Prepare and sterilize nutrient agar medium by autoclaving under aseptic condition and transfer the medium to sterile Petri plates. After solidification of nutrient agar medium, made a lawn with 0.1 ml microorganism i.e. S. aureus and E. coli in separate Petri plates, over that the films were placed and incubate for 48 hrs at 37^0 C. Measure the zone of inhibition using "Hi Antibiotic Zone Scale". Same procedure is followed by replacing the films over the next plates and measures the zone of inhibition.

CONCLUSION

From the preceding review of the recent advances in periodontal drug delivery systems it can be said that technology of formulation of periodontal chip 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.

REFERENCES

1. The American Academy of Periodontology (AAP) (2004), *J. Periodontal*., 2004; 75: 1553-65.
2. Armitage GC. Development of a classification system for Periodontal diseases and conditions. Ann Periodontal., 1999; 4(1): 1–6.
3. Pejčić Ana et al: Antibiotic in the management of periodontal disease. Acta Facult tatis Naissensis., 2010; 27(2): 85-92
4. Van Dyke TE, Sheilesh D. Risk factors for periodontitis. J IntSanz M., van Winkelhoff AJ. Periodontal infections: understanding the complexity consensus of the Seventh European Workshop on Periodontology. J Clin Periodontol., 2011; 38(Suppl 11): 3-6.
5. Sanz M., van Winkelhoff AJ. Periodontal infections: Understanding the complexity consensus of the Seventh European Workshop on Periodontology. J Clin Periodontol., 2011; 38(Suppl 11): 3-6.
6. Nishihara T, Koneke T. Microbial etiology of periodontitis. Periodontol., 2004; 36: 14–26.
7. Paster BJ, Boches SK, Galvin J et al. Bacterial diversity in human Sub gingival plaque. J Bacteriology 2001; 183 (12):3770-6. 8. Feng Z, Weinberg A., Role of bacteria in health and disease of Periodontal tissues. Periodontol., 2000., 2006; 40: 50-76.
8. Madianos PN, Bobetsis YA, Kinane DF. Generation of inflammatory Stimuli: how bacteria set up inflammatory responses in the gingival. J Clin Periodontol., 2005; 32(Suppl 6): 57-71.
9. Sbordone L, Ramaglia L, Gulleta J. Recolonization of subgingival microflora after scaling and root planning in human periodontitis. J Periodontal., 1990; 61: 579-584.
10. Slots J, Pallasch TJ. Dentist role in halting antimicrobial Resistance. J Dent Res., 1996; 75: 1338-1341.
11. Southard Lee G. et al, Subgingival controlled release of antimicrobial agents. International journal of Antimicrobial agents., 1998; 9: 239-253.
12. Herrera D, Alonso B, León R, Roldan S, Sanz M. Antimicrobial therapy in periodontitis: the use of systemic antimicrobials against the subgingival biofilm. J Clin Periodontol., 2008; 35: 45-66.

13. Baker PJ, Evans RT, Slots J, Genco RJ. Susceptibility of human oral anaerobic bacteria to antibiotics suitable for topical use. J Clin Periodontol., 1985; 12: 201-08.
14. Herrera D, Alonso B, León R, Roldan S, Sanz M. Antimicrobial therapy in periodontitis: the use of systemic antimicrobials against the subgingival biofilm. J Clin Periodontol., 2008; 35: 45-66
15. Baker PJ, Evans RT, Slots J, Genco RJ. Susceptibility of human oral anaerobic bacteria to antibiotics suitable for topical use. J Clin Periodontol., 1985; 12: 201-08.
16. Baker PJ, Evans RT, Coburn RA, et al. Tetracycline and its derivatives strongly bind to and are released from the tooth surface in active form. J Periodontal., 1983; 54: 580-5.
17. J.M. Goodson, A. Haffajee, S.S. Socransky, Periodontal therapy by local delivery of tetracycline, J. Clin. Periodontol., 1979: 83-92.
18. Friedman M., Golomb G. New sustained release dosage form of chlorhexidine for dental use. Journal of periodontal Research., 1982; 17: 323-328.
19. P.B. Deasy, A.E.M. Collins, D.J. Maccarthy, R.J. Russell, Use of strips containing tetracycline hydrochloride or metrondazole for the treatment of advanced periodontal disease, J. Pharm. Pharmacol., 1989; 41: 694-699.
20. Higashi K., Marisaki K., Hayashi S., et al. Local ofloxacin delivery using a controlled release insert (PT-01) in human periodontal pocket. Journal of periodontal research., 1990; 25: 1-5.
21. E.Sauvetre, Y. Glupczynsky, E. Yourassowsky, M. Pourtois, The effect of clindamycin gel insert in periodontal pockets, as observed on smears and cultures, Infection., 1993; 21: 245-247.
22. D. Steinberg, M. Friedman, A. Soskolne, M.N. Sela , A new degradable controlled release device for treatment of periodontal disease. In vitro release study, J. Periodontol., 1990; 61: 393-398.
23. Addy M., Langeroudi M. Comparison of the immediate effects on the subgingival flora of acrylic strips containing 40% chlorhexidine, metronidazole or tetracycline. Journal of Clinical periodontology., 1984; 11: 179-186.
24. Natalie et al, Delivery system for the administration of drugs to the periodontal pockets, Advanced drug delivery review, 1994; 13: 181-203.
25. Belsen, David J, Parthasarathy, V (2011), "Formulation and in-vitro evaluation of Bio-degradable polymer based Sparfloxacin Periodontal chip*", RJPBCS*., 2011; 2(3): 319-325.