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REVIEW ON PERIODONTAL DRUG DELIVERY SYSTEM

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ABSTRACT

Periodontal diseases are bacterially-induced, localized chronic inflammatory disease destroying both the connective tissue and supporting bone of the teeth. Aggressive form of periodontitis can be localized and are associated with microorganism therefore treatment by local antimicrobial agents are more appropriate. Systemic administration of drugs leads to therapeutic concentration 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. This article sheds light on the drug delivery systems for treating periodontitis and risk factor related to periodontal disease.

INTRODUCTION[1]

Oral health is an important aspects of overall health status of an individual. Teeth and their supporting (periodontal) structures are of main importance to oral health. Diseases of periodontium are among the most widespread disease of mankind. Periodontium is widely affected by dental plaque diverse microbial community found on the tooth surface, embedded in matrix of polymers of bacterial and salivary origin[3]. If not removed regularly, plaque gels mineralized to forms calculus which in turn initiates the inflammatory process of periodontal disease. Initially the inflammation is confined to gingivae leading to bleeding gums. Later, other supporting structures become involved so that the small pus filled packets form around teeth and there is loss of attachment. This ultimately results in tooth mobility and tooth loss[4].

These conditions are characterized by a destruction of the periodontal ligament, a resorption of the alveolar bone and the migration of the junctional epithelium along the tooth surface. It is a localized inflammatory response caused by bacteria infection of a periodontal pocket associated with subgingival plaque. Although bacteria are the primary cause of periodontal disease, the expression of microbial pathogenic factors alone may not be sufficient to cause periodontitis. Periodontal pathogens produce harmful by-products and enzymes that break extracellular matrices as well as host cell membranes to produce nutrients for their growth.[6,7]

Therapeutic approaches for periodontitis fall into two major categories[8]

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 results from many causes (e.g. bacteria, trauma). However, most forms of gingivitis and periodontitis result from the accumulation of tooth-adherent microorganism.

Periodontal Local Drug Delivery [5]

The effectiveness of this form of the therapy is that, it reaches the base of periodontal pocket and is maintained for an adequate time for the antimicrobial effect to occur. Periodontal pocket provides a natural reservoir bathed by gingival crevicular fluid that is easily accessible for the insertion of a delivery device. Delivery systems are also called sustained release, controlled-release, prolonged release, timed release, slow release, sustained action, prolonged action or

extended action. There are distinct phases in a periodontal treatment plan where a dental practitioner can use this sustained release device.

1) As an adjunct to Scaling and Root planning.

2) Periodontal maintenance therapy: Recurrent periodontitis usually involves only a few teeth. These sites are ideal for the treatment with this device.

3) For whom surgery is not an option or those who refuse surgical treatment.

4) Sustained release device is a less invasive treatment option and it requires less time compared to surgical treatment.

Systemic or Local Antibiotic Therapy in Periodontal Disease [9]

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 may not always been ideal because of concern over the development of bacterial resistance and undesirable side effects like nausea, diarrhoea, fever , abdominal pain and pseudomembranous colitis that may be induced over long period of usage. 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. Route of administration of antibiotic can also be local by using conventional or controlled release dosages forms. The local delivery of antimicrobial therapy to periodontal tissue has the benefit of putting more drug at target site while 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. The lack of retention of antibiotic in periodontal is the main reason for these mixed results.

Controlled Release Local Delivery Devices [9]

These devices employ the controlled release technologies to assure therapeutic concentrations of the antimicrobial agents in the sub gingival area for a long period following a single application. A wide variety of specialized local delivery systems (i.e. intra pocket devices) have been designed to maintain the drug concentration in the gingival crevicular fluid (GCF)[11]. Drug

delivery systems can be classified according to the mechanism controlling drug release in following three categories[13.]

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

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

Drug Delivery Systems for Treating Periodontitis

Various drug delivery system for treating periodontitis – Fibers, Film, Injectable systems, Gels, Strips and compacts , Vesicular systems etc.

Fibers[14,15]

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 fibers 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 fibers does not provide an effective drug concentration for long periods . Compared with the less effective 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. In spite of the fact that the hollow fibers served as a good drug holding device, they permitted rapid evacuation of the drug. To retard drug release, drug- impregnated monolithic fibers 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.

Film[8]

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

Injectable Drug Delivery System [9]

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

Gels[16,17]

Semisolid or gel formulations can be easily administered and have relatively faster drug release at the site of application. They are also bioadhesive and biocompatible with oral mucosa .Gel systems containing metronidazole designed for periodontal treatment and based on hydroxyethylcellulose, Carbopol 974P and Polycarbophil have been studied. In vitro drug release was significantly decreased as the concentration of each polymeric component was increased. Bioadhesive semi-solid systems based on hydroxyethylcellulose (HEC) and polyvinylpyrrolidone (PVP) containing tetracycline were studied for mechanical properties and drug release rate. An injectable lipid-like vehicle based on glycerol monooleate and sesame oil containing 25% metronidazole has become available with supportive evidence of efficacy. This product is syringed into the pocket area where the initially thixotropic carrier thickens into a gel. Two other semi-solid lipid-like formulations based on poly (oxyethylene-co-oxypropylene) (poloxamer) and glycerol monooleate were developed for tetracycline release. Gel formulations

containing 2% minocycline have been commercialized under several trademarks. The gel is composed of hydroxyethylcellulose, aminoalkyl-methacrylate copolymer, triacetine, and magnesium chloride and glycerynum concentratum. Another injectabe biodegradable delivery system containing 10% doxycycline on a biodegradable polyester poly dissolved in a biocompatible solvent N-methyl-2-pyrrolidone (NMP) was also studied. The viscosity of delivery system is so that it can pass through a cannula into a periodontal pocket where it solidified to deliver the therapeutic agent over seven days. A mucoadhesive gel formulation based on 4% carbopol containing 1% clindamycin hydrochloride was evaluated in vivo on microbial flora of periodontal pockets deeper than 5mm [31]. Various oleogels and hydrogels for the delivery of tetracycline (2.5%), metronidazole (25%), metronidazole benzoate (40%) as well as a combination of tetracycline (2.5%) and metronidazole benzoate (40%) have been evaluated.

Strips and Compacts [18,19]

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. 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. Chlorhexidine slow release devise has been made and it is antibacterial effect has been evaluated by agar diffusion test.

icroparticles [20]

Microparticles based system of biodegradable poly alpha hydroxy acids such as poly lactide (PLA) or poly (lactide-co-glycolide) PLGA containing tetracycline has been designed for periodontal disease therapy. PLGA microspheres containing minocycline have been formulated and have been used for the elimination of Porphyromonas gingivalis from the periodontal pocket.

Microparticles of poly (dl-lactic-coglycolic acid) (PLGA) containing chlorhexidine free base, chlorhexidine di gluconate and their association or inclusion complex with methylated-beta cyclodextrin (HPBCD) were prepared with single emulsion, solvent evaporation technique. 18 Non- biodegradable as well as biodegradable materials have been investigated for the preparation of microspheres. These materials include the polymers of natural origin, modified natural substances and synthetic polymers. They could preferably be formulated as a chip or could be part of a dental paste formulation, or otherwise be directly injected into the periodontal cavity. Tetracycline-containing microcapsules in Pluronic F127 were reported to form gel at body temperature and hold the microcapsules in the periodontal pocket for the duration of treatment. PLGA microcapsules and microspheres have been proposed for the delivery of tetracycline and histatins. These microparticulate systems provide stability to the encapsulated drug. The in vitro drug release from such systems depends upon the polymer (Lactide:Glycolide) ratio, molecular weight, crystallinity and pH of the medium. Some questions, however, related to the retention of such formulations in the periodontal pocket need clarification.

Vesicular Systems [21]

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. 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. The delivery of triclosan and chlorhexidine was studied for several liposomal compositions involving cationic as well as anionic lipids. The anti-oralis immunoliposomes showed the greatest affinity. oralis and affinity was unaffected by net charge on the lipid bilayer or by the number of antibodies conjugated to the liposomal surface.

Risk Factor [22]

1. Microorganisms and Periodontal Disease [23,25]

The oral bacterial microbiome includes over 700 different phylotypes, with approximately 400 species found in subgingival plaque. Subgingival plaque from deepened periodontal pockets is dominated by gram-negative anaerobic rods and spirochetes.

2. Tobacco Smoking [26]

Tobacco smoking exerts a substantial destructive effect on the periodontal tissues and increases the rate of periodontal disease progression. Smokers with periodontal disease seem to show less signs of clinical inflammation and gingival bleeding compared to nonsmokers. That could be explained by the fact that nicotine exerts local vasoconstriction, reducing blood flow, edema, and clinical signs of inflammation.

3. Diabetes Mellitus [27,28]

One of the important oral signs of diabetes is gingivitis and periodontitis. Patients with undiagnosed or poorly controlled diabetes mellitus type 1 or type 2 are at higher risk for periodontal disease. Periodontitis also progresses more rapidly in poorly controlled diabetics, and early age of onset of the disease is seen as a risk factor for more severe diseases.

4.Cardiovascular Disease [29,30]

Patients at risk for infective endocarditis may require antibiotic cover prior to dental procedures likely to cause bacteraemia's. People diagnosed with acute cerebrovascular ischaemia, particularly non-haemorrhagic stroke,were found to be more likely to have a periodontal infection.

5. Drug-Induced Disorders [31]

Some medications significantly decrease salivary flow. These include antihypertensives, narcotic analgesics, some tranquilizers and sedatives, antihistamines, and antimetabolites. Other drugs, particularly those in liquid or chewable form that contain added sugar, alter the pH and composition of plaque, making it more able to adhere to tooth surfaces.

6. Stress [32,33]

Stress is associated with poor oral hygiene, increased glucocorticoid secretion that can depress immune function, increased insulin resistance, and potentially increased risk of periodontitis. Studies have found some periodontal disease indicators such as tooth loss and gingival bleeding to be associated with work stress and financial strain.

7. Obesity [34]

Obesity has been reported to be an important risk factor for periodontal disease.

Younger people may have different dietary patterns than older study participants. Research in dietary trends in adolescent's ages from 11 to 18 reveals a significant decrease in raw fruit and nonpotato vegetables, which are sources of vitamin C. In addition, adolescents have decreased their calcium intake and increased their intake of soft drinks and noncitrus juices. This is important to oral health because low dietary intake of calcium and vitamin C has been associated with periodontal disease.

Current status of intra-pocket delivery devices in periodontics [8]

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.

REFERENCES

1. Bindra J, Soni RK, Sood M. Prevalence of Periodontal Diseases in Urban and Rural areas of Ludhiana, Punjab. Indian Journal of Community Medicine. 2005; 30(4) :2005.
2. Rozier RG. Dental Public Health. In Wallace RB ed, Public Health and Preventive Medicine, Washington. Prentice Hall International Inc. 1998; 1091-1112.
3. Marsh PD, Bradshaw DJ. Dental Plaque as a Biofilm. J Ind Microbiol 1995; 15(3): 169-175.
4. Spolsky V. Epidemiology of Gingival and Periodontal Diseases. In Carranza N, Dyson J eds, Clinical Periodontology, New York; WB Saunders Company. 1996; 61-81.
5. Kaplish V, Walia MK and Hari Kumar SL. Local Drug Delivery Systems In The Treatment Of Periodontitis: A Review. An International Research Journal Pharm. 2013; 5(3): 39-49
6.American Academy of Periodontology (2000), "Proceedings of the International Workshop for the classification of periodontal diseases", Ann. Periodontal., in press.
7. Haffajee AD, Socransky SS. "Attachment level changes in destructive periodontal diseases", J. Clin. Periodonto.1986; 13: 461–472.
8. Pragati S, Ashok S, Kuldeep S. Recent advances in periodontal drug delivery systems. International Journal of Drug Delivery. 2009; 1-14.
9. Raheja I, Kohli K. Periodontal Drug Delivery System Containing Antimicrobial Agents. International Journal of Pharmacy and Pharmaceutical Sciences . 2013; 5(3).
10. Southard LG. et al, Subgingival controlled release of antimicrobial agents. International journal of Antimicrobial agents.1998; 9:239-253
11. 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.
12. 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
13. Abdellaoui KS, Vivien-Castioni N, Gurny R. Local delivery of antimicrobial agents for the treatment of periodontal diseases. European Journal of Pharmaceutics and Biopharmaceutics 2000; 50: 83-99.
14. Kornman KS, Controlled release local delivery antimicrobials in periodontics. Prospects for the future, J. Periodontal. 1993; 64: 782-791.
15. Goodson JM, Holborow D, DunnRL, Hogan P, Dunham S. Monolithic tetracycline containing fibers for controlled delivery to periodontal pockets. J. Periodontol. 1983; 54:575-579.
16. Jones DS, Woolfson AD, Djokic J, Coulter WA.Development and mechanical characterization of bioadhesive semi-solid, polymeric systems containing tetracycline for the treatment of periodontal diseases, Pharm. Res. 1996;13:1734-1738.
17. Esposito P, Carotta V, Scabbia A, Trombelli L, D'Antona P, Menegatti E, Nastruzzi C. Comparative analysis of tetracycline containing dental gels: poloxamer and monoglyceride based
formulations, Int. J. Pharm. 1990;142: 9-23
18. Eskanderi MM, Ozturk OG, Eskandari HG, Balli E and Yilmaz C. Cyanoacrylate adhesive
provides efficient local drug delivery. Clin. Orthop Releat Res 2006; (12): 45-55.
19. Mastiholimath VS, Dandagi PM, Gadad AP, Patil MB and Manvi FV. Formulation and evaluation of ornidazole dental implants for periodontitis . Indian J. Pham Sci. 2006 ;68(1): 68-71.
20. Yoe IC, Poff J, Cortes ME, Simisterra RD, Faris CB, Hildgen P, Langer R, Shastri VP. A novel
polymeric chlorhexidine device for treatment of periodontal disease. Biomaterials. 2004 : 25 (17): 3743 –3750.
21. Vyas SP et al. Preparation, Characterization and In-Vitro Antimicrobial Activity of Metronidazole Bearing Lectinized Liposomes For Intra- Periodontal Pocket Delivery. Pharmazie 2001;56:554–560.
22. Yousef AA. Risk Factors of Periodontal Disease: Review of the Literature. Hindawi Publishing Corporation International Journal of Dentistry , 2014.
23. BerezowAB, Darveau RP. "Microbial shift and periodontitis," Periodontology 2011; 55(5): 36–47.

24. Haffajee AD, Socransky SS, "Microbial etiological agents of destructive periodontal diseases," Periodontology. 2000; 5: 78–111.
25. Moore WE, Moore LV, "The bacteria of periodontal diseases," Periodontology 2000; 5: 66–77.
26. Zini A, Sgan-Cohen HD, Marcenes W. "Socio-economic position, smoking, and plaque: a pathway to severe chronic periodontitis," Journal of Clinical Periodontology. 2011; 38(3): 229–235.
27. Thorstensson H, Hugoson A. "Periodontal disease experience in adult long-duration insulin-dependent diabetics," Journal of Clinical Periodontology. 1993; 20(5): 352–358.
28. Pucher J, Stewart J. "Periodontal disease and diabetes mellitus," Current Diabetes Reports. 2004; 4(1): 46–50.
29. Mattila K, Vesanen M, Valtonen V et al. "Effect of treating periodontitis on Creactive protein levels: a pilot study," BMC Infectious Diseases. 2002; 2(30).
30. Kinane DF, Lowe GDO. "How periodontal disease may contribute to cardiovascular disease," Periodontology. 2000; 23(1): 121–126.
31. Rees TD, Levine RA. "Systematic drugs as a risk factor for periodontal disease initiation and progression," Compendium. 1995; 16(1): 20, 22, 26, 42.
32. Akhter R, Hannan MA, Okhubo R, Morita M. "Relationship between stress factor and periodontal disease in a rural area population in Japan," European Journal of Medical Research. 2005; 10(8): 352–357.
33. Merchant AT, Pitiphat W, Ahmed B, Kawachi I, Joshipura K. "A prospective study of social support, anger expression and risk of periodontitis in men," Journal of the American Dental Association. 2003; 134(12): 1591–1596.
34. Chaffee BW, Weston SJ. "Association between chronic periodontal disease and obesity: a systematic review and meta-analysis," Journal of Periodontology. 2010; 81(12): 1708–1724.