LOCAL DRUG DELIVERY SYSTEMS IN PERIODONTAL DISEASES - A REVIEW

Type of manuscript: Review article
Running title: Local drug delivery systems in periodontal diseases.

Lakshya Rani. S,
Graduate student,
Saveetha Dental College, Saveetha University,
Saveetha Institute of Medical and Technical Sciences,
Chennai, Tamilnadu, India.

Gopinath.P
Assistant professor,
Department of Microbiology
Saveetha Dental College and Hospitals
Saveetha Institute of Medical Sciences and Technology,
Chennai, Tamilnadu, India.

Corresponding Author:
Gopinath.P
Assistant professor,
Department of Microbiology,
Saveetha Dental College and Hospitals
Saveetha Institute of Medical Sciences and Technology,
Chennai- 600077, Tamilnadu, India.
Total number of words: 1912

***Abstract*: Periodontitis is an inflammatory disease of gums involving the degeneration of periodontal ligaments, creation of periodontal pocket and resorption of alveolar bone, resulting in the disruption of the support structure of teeth. According to WHO, 10–15% of the global population suffers from severe periodontitis. The disease results from the growth of a diverse microflora (especially anaerobes) in the pockets and release of toxins, enzymes and stimulation of body's immune response. Various local or systemic approaches were used for an effective treatment of periodontitis. Currently, controlled local drug delivery approach is more favorable as compared to systemic approach because it mainly focuses on improving the therapeutic outcomes by achieving factors like site-specific delivery, low dose requirement, bypass of firstpass metabolism, reduction in gastrointestinal side effects and decrease in dosing frequency. Overall it provides a safe and effective mode of treatment, which enhances patient compliance. Complete eradication of the organisms from the sites was not achieved by using various surgical and mechanical treatments. So a number of polymer-based delivery systems like fibers, films, chips, strips, microparticles, nanoparticles and nanofibers made from a variety of natural and synthetic materials have been successfully tested to deliver a variety of drugs. These systems are biocompatible and biodegradable, completely fill the pockets, and have strong retention on the target site due to excellent mucoadhesion properties. The review summarizes various available drugs and penetration level of drugs in the treatment of periodontitis.**

***Keywords*: Periodontitis, microparticles, nanofibres, mucoadhesion, drug delivery system**

INTRODUCTION:

Periodontal disease is a pathological conditions affecting the supporting tooth structures. It includes two conditions, they are chronic periodontitis, aggressive periodontitis, systemic disease-associated periodontitis and necrotizing periodontitis.[1] It has been known that periodontitis is a condition which occurs due to local bacterial infection with pathogenic microflora which is present within the periodontal pocket. The local bacteria is the primary etiological factor which causes direct and indirect destruction of the host supporting tissues. The microflora which is found in the periodontitis is composed mainly of gram negative anaerobic bacteria[2].

Traditional therapies for periodontal disease have included mechanical debridement to disrupt the subgingival flora and provide clean, smooth and biologically compatible root surfaces. Unfortunately, in some instances, the complex anatomy of the root and the contours of the lesion may hamper the treatment and prevent sufficient reduction of the bacterial load to make the tooth surface biologically acceptable.[3]It also has been shown that patients who fail to achieve acceptable plaque control during or after subgingival treatment frequently suffer from recurrent periodontitis. Thus, oral hygiene is of the utmost importance for the clinical outcome of non-surgical as well as surgical treatment[4].The persistence of pathogens in the pocket after treatment or to the production by the bacteria of specific virulence factors interfering with the host defense is the reason for the disease to reccur.It also

could be due to the recolonization of treated sites from bacterial reservoirs such as dentinal tubules and soft tissues. Therefore , it is evident that pharmacological therapy are of great interest and may be valuable as adjuncts to mechanical therapy[5].

The first challenge in treating periodontitis is a timely and proper diagnosis. Disease diagnosis and treatment in its earliest stages will prevent future breakdown. Because the disease is painless, patients rarely seek care[1,2]. Thus, it is not uncommon for the disease to go undiagnosed until progression has reached moderate to advanced degrees of severity, characterized by obvious radiographic bone loss and/or tooth mobility[3,4].The second challenge is diagnosing and properly controlling all the factors contributing to this disease. Such factors include smoking, diabetes, stress, genetic factors, occlusal trauma, and patient compliance. Due to its numerous and complex contributing factors, successful management of chronic periodontitis can be very challenging[5]. Thus, it is imperative that clinicians are aware of risk factors contributing to the patient's susceptibility to disease, response to existing disease, and potential response to therapy before initiating a treatment plan[1,3,4]. The third challenge in the treatment of chronic periodontitis involves the long-term maintenance of the periodontium. This phase of therapy is known as supportive periodontal therapy, or periodontal maintenance. The challenge during this phase of therapy is focused on maintaining patient motivation and compliance, management of all risk factors, and finally making the appropriate decisions regarding retreatment, when indicated[1,2,4].

SYSTEMIC ADMINISTRATION OF DRUGS

Systemic antibitoic therapy should be reserved for juvinile periodontitis ,patients with medical history requiring antibiotic coverage,patients with severe and acute periodontal infection[6].Metronidazole in combination with amoxicillin or ciprofloxacin have been used sucessfully for the treatment of advanced Actinomycetemcomitans.The combination of metronidazole with broad spectrum antibiotics shows colonization resistance by means of antibiotics.The treatment of periodontitis usually ivolves the systemic regimen with antibiotics which alter the pathogenic flora.Furthermore ,some tertracyclines ,by inhibiting collangenase,seem to diminsh bone destruction.Another approach is to surgically eliminatee the pocket and recontour the bone to encourage alveolar growth.Synthetic flavonoid derative is employed in the senile osteoporosis[6,7] .

DRUG DELIVERY SYSTEM

Drug delivery refers to approaches,formulations,technologies and systems for transporting pharmaceutical compound in the body as needed to safely achieve therapeutic effect.It is concept heavily intergrated with dosage form and route of adminstration[8].Current efforts in the area of drug delivery include the development of targeted delivery in which the drug is only active in the targeted area and sustained release formulations in which drug is released over a period of time in a controlled manner from a formulation,avoid the the host defence mechanisms and circulate to its intended site of action.Types of sustained release formulations include liposomes ,drug loaded biodegradable microspheres and drug polymer conjugates[9].

Tetracycline

Goodson et al in 1979 first proposed the concept of controlled delivery in the treatment of periodontitis[7]. The first delivery devices involved hollow fibers of cellulose acetate filled with tetracycline. Tetracyclines are a group of closely related bacteriostatic antimicrobials. They have been frequently used in treating refractory periodontitis, including localized aggressive periodontitis[8].

Fibers: The ACTISITE tetracycline fibres have been approved for the treatment of adult periodontitis both by the United States Food and Drug Administration (FDA) and by the European Union's regulatory agencies. These are non-resorbable biologically inert, generally considered as safe, plastic copolymer (ethylene and vinyl-acetate) loaded with 25% w/w tetracycline HCI powder packaged as a thread of 0.5 mm in diameter and 23 cm in length. It maintains constant concentrations of active drug in the crevicular fluid in excess of 1000 µg/mL for a period of 10 days[9]. Following application of tetracycline fibres a definite reduction in the subgingival microbiota has been observed. Recently bioresorbable tetracycline fiber has been developed with base of collagen film, which is commercially available as PERIODONTAL PLUS AB. It offers the advantage of no second appointment for removal as it biodegrades within 7 days[8,9].

Gel

Tetracycline-Serratiopeptidase-Containing Periodontal Gel Formulation has shown statistically significant results along with scaling and root planing. Bioerodible Injectable Poly (ortho ester) for Tetracycline Controlled Delivery formulations loaded with tetracycline 10% or 20% showed complete in vitro degradation concomitant with drug release[10].In general, the data indicates that tetracycline fibers used as a monotherapy without adjunctive scaling and root planing were effective at reducing probing depths, in gaining clinical attachment and reducing monitored bacteria though the results of monotherapy were not significantly different when compared to scaling and root planing.Tetracycline fibers have shown a better result when used as an adjunct to scaling and root planing in patients with refractory periodontitis than in patients with adult periodontitis.Similarly, other investigations and several case reports have indicated better results when combined therapy was used at non-responsive sites.[11]

Subgingival Doxycycline

Doxycycline is a bacteriostatic agent and has the ability to downregulate MMP's a family of zinc dependent enzymes that are capable of degrading a variety extracellular matrix molecules including collagens[12].

The only FDA approved 10% doxycycline in a gel system ATRIDOX (42.5 mg doxycycline) is a subgingival controlled-release product composed of a 2 syringe mixing system. Doxycycline levels in GCF peaked to 1,500 - 2000 µg/mL in 2 hours following

treatment with ATRIDOX. These levels remained above 1000 µg/mL through 18 hours, at which time the levels began to decline gradually[13].

Local levels of doxycycline have been found to remain well above the minimum inhibitory concentration for periodontal pathogens (6.0 µg/mL) through Day 7. Approximately 95% of the polymer is bio absorbed or expelled from the pocket naturally within 28 days.Several studies have reported the efficacy of 10% doxycycline hyclate as a local delivery antimicrobial agent for attaining probing depth reduction and gaining clinical attachment[12,13]

Subgingival Minocycline

Local delivery of minocycline, a bacteriostatic antibiotic has been tried clinically via in three different modes i.e. film, microspheres, and ointment

Film; Ethyl cellulose film containing 30% of Minocycline were tested as sustained release devices. The results of this study indicated that the use of this device may cause complete eradication of pathogenic flora from the pocket after 14 days[14]

Microsphere: The FDA recently approved a new, locally delivered, sustained-release form of minocycline microspheres (ARESTIN) for subgingival placement. The 2% minocycline is encapsulated into bioresorbable microspheres (20-60µm in diameter) in a gel carrier and has resorption time of 21 days. Gingival crevicular fluid hydrolyses the polymer and releases minocycline for a period of 14 days or longer before resorbing completely[12,7].

Ointment: Minocycline ointment is a bioabsorbable sustained delivery system consisting of 2% minocycline hydrochloride in a matrix of hydroxyethyl-cellulose, aminoalkyl-methacrylate, triacetine and glycerine. Dentomycin (2% Minocycline gel) has received regulatory approval for the treatment of periodontitis in the European Union. The same product is available in Japan with the name Periocline. The concentration of minocycline in the periodontal pocket is about 1300µg/ml, 1 hr after single topical application of 0.05 ml ointment (1mg of minocycline) and is reduced to 90µg/ml after 7 hrs[15]

Results have shown that the combination of ointment with scaling and root planing was significantly better than scaling and root planing alone in pockets > 7mm[13].

Subgingival Chlorhexidine

The use of chlorhexidine as an antifungal and antibacterial agent has been well established. Chlorhexidine is being used in mouth rinses and is highly recommended in the hygiene phase of treatment as an adjunct to tooth brushing. The major application has been for the control of dental plaque and gingivitis. Its mechanism of action relates to reduction in pellicle formation, alteration of bacterial adherence to teeth and an alteration of bacterial cell walls causing lysis[16]

Its antibacterial action is due to an increase of the cellular membrane permeability followed by the coagulation of intracellular cytoplasmic macromolecules. Because chlorhexidine is highly cationic, it exhibits high substantivity[17].

The long term efficacy of chlorhexidine on the periodontal pocket flora is dependent on the duration of exposure. However, intracrevicular irrigation of the periodontal pocket with chlorhexidine has only a short lived effect on the pocket flora.6 Chlorhexidine is available in the form of mouthrinses, Gels, varnishes, and chip to be used as a local drug delivery agent for the treatment of periodontal diseases[18]

Periochip

2.5 mg Chlorhexidine Gluconate PerioChip, the controlled subgingival delivery of chlorhexidine gluconate, is a small, orangebrown, tombstone-shaped chip (4.0x 0.5x 0.35mm) in a biodegradable matrix of hydrolyzed gelatin and has been approved by FDA.[19,20]

Studies with PerioChip showed reduction in the numbers of the putative periodontopathic organisms Porphyromonas gingivalis, Prevotella intermedia, Bacteroides forsythus, and Campylobacter rectus after placement of the chip. No overgrowth of opportunistic organisms or other adverse changes in the oral microbial ecosystem were noted[21,22].

PerioChip releases chlorhexidine in vitro in a biphasic manner, initially releasing approximately 40% of the chlorhexidine within the first 24 hours, and then releasing the remaining chlorhexidine in an almost linear fashion for 7–10 days. Several large clinical trials were completed which compared the efficacy of scaling/root planing and combined therapy employing Chlorhexidine chips[19,23]. The differences between therapies were statistically significant, but may not be clinically relevant. Furthermore, the number of sites with probing depth reduction was greater with combined therapy[24,25].

Strips And Compacts

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[20,21]. 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.This modified therapeutic method has been proved to be more effective than any conventional pharmacotherapy[22,23].

Acrylic strips have been fabricated using the mixture of polymers,monomers and different concentrations of any antimicrobial agents.They were fabricated either by solvent casting or pressure melt method.strips containing metronidazole, tetracycline and chlorhexidine demonstrated a decrease in number of motile spirochete rods.In a later development ,the evaluation of amoxycillin-clavulainic acid loaded acrylic strips is reported[26,27].

Once a strip is placed in periodontal cavity, the polymer swells, expands, and reaches narrow crevices and furcations of the treated cavity, carrying active agent throughout the cavity. This provides most desirable efficacy at treatment site.Highest level of antibacterial agent was released during the first 24 hrs 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 strip[27,28]

Conclusion

From the Advancements in the periodontal drug delivery systems and its penetration level in the tissues ,it can be said that the antibiotic free ,mucoadhesive ,biodegradable nanoparticles technology has an immense oppurtunity for designing a novel,low dose and effective diffusion and effective treatment[25,27]

Nanodentistry will make possible the maintance of comprehensive oral health by employing nanomaterials,biotechnology,including tissue engineering and dental nanorobotics.Although this technology is at an early stage,it has already made a significant clinical and commercial impact[2,3].

However local drug deliveries has more drug efficacy and reduce the potential of developing anti- biotic resistance and have greater range of success in treating periodontal diseases

REFERENCES

1. GencoRJ,EvansRT,Ellison SA.(1969)Review of dental research in microbiology with emphesis on periodontal research.Journal of American Dental Association,78,1016-1023.

2. Slots J.(1979) Subgingivalmicroflora and periodontal disease.Journal of Clinical Periodontology,6,351-354.

3. UnsallE,WalsamTF,Walsh TF.(1994)Influence of a single application of subgingivalchlorhexidine gel or tetracycline paste on the clinical parameter of adult periodontitis.Journal of Clinical Periodontology,21,351-355.

4. NakgawaT,YamadaS,OosukaY,et al.(1991)Clinical and microbiological study of minocycline delivery(Periocycline).Bulletin of the
tokoyo Dental College,32,63-69.

5. K.SKornman,Contolled release local delivery antimicrobials in periodontitis.Prospects for the future,J.Periodontol.64(1993) 353-361.

6. K.Schwach-Addellaoui,N.Vivien-Castioni,R.Gurny, Local delivery of antimicrobial agents for the treatment of periodontal diseases
50(2000) 83-89.

7. J. M. Goodson, P. E. Hogan, and and S. L. Dunham,Clinical Responses Following Periodontal Treatment by Local Drug Delivery ,Journal of Periodontology, November 1985, Vol. 56, No. 11s , Pages 81-87.

8. P,R.cortesi, F.Ce.Epositorvellati,E.Menegatti,C.Nastruzzi,Biodegradablemicroparticles for sustained delivery of tetracycline to the periodontal pocket:formulatory and drug release studies,J.Microencapsulation 14 (1997) 175-187.

9. R.Jeyanthi,A.Akiyama,F.D.Roberts,J.VanHamont,P.Friden,One-month controlled release of an antimicrobial peptide from biodegreaable poly(lactide/glycolide)microspheres for the treatment of periodontitis,Proc.Int.Symp.Controlled Release Bioact.Mater.24(1997) 883-884.

10. A.A.Jones,K.S.Kornman,D.A.Newbold,M.A.Manwell,Clinical and microbiological effects of contolled release locally delivered minocycline in periodontitis,J.Periodontol.65(1994) 1058-1066.

11. AmitBhardwaj,Shalu V Bhardwaj,RuchiPandey,Advances in periodontal drug delivery systems ,20 March 2012.

12. Jones SD,WoolfsonDA,BrownFA,MichealJ,NeillO.Mucoadhesive,syringeable drug delivery systems for contolled application of metronidazole to periodontal pocket.Invitro release kinetics,syringeability,mechanical and mucoadhesive properties
J.Contr.rEL.2002;49(1):71-79.

13. Finkelman RD, Williams RC. Local delivery of chemotherapeutic agents in periodontal therapy:Has it's time arrived. 1998; 25: 943-946.

14.Marjorie K. Jeffcoat, Kimberly S. Bray, Sebastian G. Ciancio, Andrew R. Dentino, Daniel H. Fine, Jeffrey M, Kent G. Palcanis, Howard M. Proskin, Richard D. Finkelman, and and Moshe Flashner ,Journal of Periodontology, September 1998, Vol. 69, No. 9 Pages 989-997.

15. Pinon SE, Ganem QA, Alonso PV, QuintanarGD. Preparation and characterization of triclosan nanoparticles for periodontal treatment. Int J Pharm 2005;294:217-32.

16. CouvreurP,DubernetC,PuisieuxF.Controlled drug delivery with nanoparticles:current possibilities and future trends.Eur J Pharm Biopharm1995;41:2-13.

17. Papadogiannis DY, Lakes RS, Papadogiannis Y, Palaghias G, Helvatjoglu-Antoinades M. The effect of temperature on viscoelasticproperties of nano-hybrid composites. Dent Mater. 2008;24:257–266.

18. Duan R, Xia F, Jiang L.ACS Nano. Constructing tunablenanopores and their application in drug delivery.2013 Oct 22;7(10):8344-9.

19. NyborgWL.Biological effects of ultrasound:development of safety guidelines,Part II general review.Ultrasound Med Biol2001:27:301-333.

20. Alipour,M.;Halwani,M.;Omri,A.;Suntres,Z.E.Antimicrobial effectiveness of liposomal polymyxin B against resistant Gram-negative bacterial stains.Int.J.Pharm.2008,355,293-8.

21 Zhong Lin Wang,JinhuiSong, PiezoelectricNanogenerators Based on Zinc oxide Nanowires Arrays,14 April 2006,Vol 312 no.5771pp. 242-246.

22. Saravanan KR,VijayalakshmiR.Nanotechnology in dentistry.Ind J Dent Res.2006;17;62-65.

23. SudeepKothari,G.Gnanaranjan and PreetiKothiyal,Periodontalchip:An adjunct to Conventional Surgical Treatment,vol.2(6),411-421.

24. Shah R. Local Drug Delivery. Dental Dialogue. 2006;32(3):82-5.

25. Kornman KS. Controlled release local delivery-Antimicrobials in periodontics. Prospects for the future. J Periodontol.1993;64:782-91.

26. Kalsi R, Vandana KL, Prakash S. Effect of local drug delivery in chronic periodon- titis patients: A meta-analysis. J Indian Soc Periodontol. 2011;15(4):304-9.

27. Greenstein G, Tonetti M. The role of controlled drug delivery for periodontitis. The Research, Science and Therapy Committee of the References American Academy of Periodontology. J Periodontl. 2000;71(1):125-40.

28. RamsTE, Slots J. Local delivery of antimicrobial agents in the periodontal pocket. Periodontology 2000. 1996;10:139-59.

29.. Dodwad V, Vaish S, Chhokra M, Mahajan A. Magic Bullet to treat Periodontitis: A targeted approach. J Pharm Biomed Sci. 2012;20(20):1-5.