IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

TETRACYCLINES: A Therapeutic Paradigm in Periodontal Diseases

1. Dr. Kousain Sehar, MDS Dept of Periodontology and Implantology, BRS Dental College and Hospital Sultanpur Panchkula.
2. Dr. Nadia Irshad, MDS Dept of Paedontics and Preventive Dentistry, BRS Dental College and Hospital Sultanpur Panchkula.
3. Dr. Navneet kour, MDS Dept of Periodontology and Implantology, BRS Dental College and Hospital Sultanpur Panchkula.
4. Dr. Mir Tabish Syeed, MDS Dept of Paedontics and Preventive Dentistry, Swami Devi Dayal Hospital and Dental College, Barwala, Panchkula.
5. Dr. Manju Verma, MDS Dept of Paedontics and Preventive Dentistry, BRS Dental College and Hospital Sultanpur Panchkula.
6. Dr. Hilal Ahmad Hela, MDS Dept. of Prosthodontics, Govt Dental College and General Hospital, Srinagar.

ABSTRACT:

To complement the non-surgical therapy, there are multiple options of antimicrobials that can be locally delivered into the mucosa, such as metronidazole, chlorhexidine, minocycline, doxycycline and tetracycline. These drugs are used in periodontal pockets and can inhibit or eliminate the periodontopathogenic microorganisms as well as modulate the inflammatory response of the tissues. Antibacterial agents are used along with mechanical debridement for the management of periodontal infection. The effectiveness of all the methods are limited due to the lack of accessibility in the periodontal pocket. Periodontal pocket provides an ideal environment for the growth of anaerobic pathogenic bacteria such as Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis and Provetella intermedia.

KEY-WORDS: Antimicobials, mechanical debridement, tetracyclines

INTRODUCTION:

The aim of periodontal therapy is preserving the natural dentition by achieving a healthy functional periodontium. It involves patients motivation and oral hygiene instructions as well as mechanical removal of supra gingival and subgingival plaque and calculus deposits, correction of plaque-retentive factors such as overhangs and also risk modification factors (eg. smoking cessation). The initial treatment of periodontitis involves scaling and root planing

(SRP), mechanical debridement of surfaces and oral hygiene orientations. Periodontal disease encompasses several pathological conditions affecting the tooth supporting structures. Traditional therapies for periodontal disease included mechanical debridement for disrupting the subgingival flora and providing clean and biologically compatible root surfaces. In some instances, the complex anatomy of the root and contours of the lesion hamper the treatment and prevents sufficient reduction of the bacterial load for making the tooth surfaces biologically acceptable. In addition, the control of supragingival plaque is essential for preventing recolonization of the subgingival area with the help of periodontal pathogens. Indeed, several clinical studies have indicated that scaling and root planing, in combination with optimal oral hygiene, result in an alteration of the subgingival plaque sufficient to stop periodontal destruction in most cases. Thus, oral hygiene is of the utmost importance for clinical outcome of nonsurgical as well as surgical treatment. However, aggressive periodontitis in young patients cannot be arrested by just mechanical treatment alone. In refractory periodontitis, the persistence of pathogens in the pocket after treatment or to the production by bacteria of specific virulence factors interferes with host defense which is due to the recolonization of treated sites from bacterial reservoirs such as dentinal tubules and soft tissues. It is quite prominent that antimicrobial agents are of great interest and act as a valuable as adjuncts for mechanical therapy.

Tetracyclines provide a broad spectrum of activity against both gram positive and gram negative microorganisms and are obtained from soil actinomycetes. The first to be introduced was chlortetracycline in **1948** under the name auromycin(because of the golden yellow color of the S. aureofaciens colonies producing it.[1]

Tetracycline, minocycline and doxycycline are greatly effective in inhibition of gram-negative facultative anaerobes like Actinobacillus actinomycetemcomitans, Campylobacter rectus, Eikenella corrodens and Capnocytophaga sp. Tetracyclines have proven to be beneficial in the treatment of LAP, generalized aggressive periodontitis (GAP) and chronic periodontitis.

Tetracyclines can be divided into:

GROUP I	**GROUP II**	**GROUP III**
Chlortetracycline	Deneclocyclines	Doxycyclines
Oxytetracyclines	Methacycline	Minocyclines
Tetracyclines	Lymecycline	

They are similar chemically and therefore possess similar antibacterial spectra and have cross hypersensitivity. When resistance or hypersensitivity occurs to tetracycline, it wil occur to all in the group.[1]

MODE OF ACTION:

Tetracyclines are bacteriostatic in nature and require access to inside of the bacterial cell. Within the cell, tetracycline binds specifically to 30S sub-unit of ribosome. There is also evidence that tetracycline may cause alterations in bacterial cytoplasmic membrane, facilitating leakage of nucleotides and other compounds from the cell. Absorption of tetracycline from the gastrointestinal tract is fairly rapid but is reduced if the drug is taken with milk or with substances containing calcium, magnesium, iron or aluminium as it results in chelate formation.

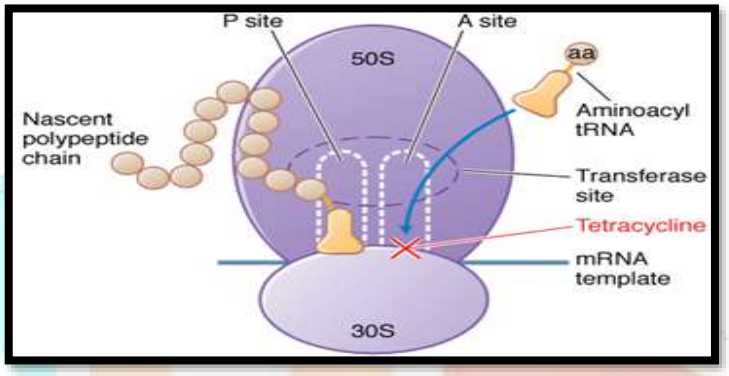

FIG:1 MODE OF ACTION OF TETRACYCLINE

Tetracyclines are effective in treating periodontal diseases because their concentration in the gingival crevice is 2 to 10 times that in serum. This allows a high drug concentration to be delivered into the periodontal pockets. The GCF concentration achieved by tetracycline is 4-8 µg/ml and plasma concentration achieved is 1.9-2.5 µg/ml. Doxycycline GCF levels reach 1.2-8.1 µg/ml while the same for minocycline is 6.0 µg/ml. Plasma concentration achieved by doxycycline and minocycline is 2.1-2.9 µg/ml and 2.6-3.3 µg/ml respectively.[2]

Apart from antibacterial activity, tetracycline also exhibits additional pharmacological properties, which include

i) Collagenase inhibition-

Tetracycline has anti-collagenase property but this activity appears to be related to the source of enzyme and tetracycline used. Tetracycline is less active against fibroblast-type collagenase and most active against neutrophil derived collagenase.

Interstetial collagenases are proteinase type enzymes which degrade connective tissue. Theses enzymes are derived from fibroblasts, epithelial cells, macrophages and neutrophils and MMP-8.

Tetracycline inhibition of collagenases may relate to the drugs ability to:

1. Bind with calcium and zinc ions. Zinc are located at the active site of the enzyme whilst calcium are on exogenous co-factor.

2. Scavenge reactive oxygen radicals produced by PMNS. These oxygen radicals activate latent collagenases.

   Inhibition of collagenases may further result in anti-proteolytic effects such as inactivation of ∝-1 proteinase inhibitor and neutrophil elastase.[3]

ii) Anti-oxidative property-

Tetracycline can scavenge reactive oxygen radicals (e.g., hypochlorous acid and hydroxyl groups) produced by polymorphonuclear neutrophils (PMNs) which have been found to activate latent collagenase. Thus tetracyclines can prevent the oxidative activation of latent collagenase.

iii) Anti-proteolytic property-

Tetracycline inhibition of neutrophil collagenase may also prevent other proteolytic events because neutrophil collagenase (MMP-8) as well as neutrophil-derived reactive oxygen species, i.e., hypochlorous acid, hydrogen peroxide and hydroxyl radicals can 20degrade and inactivate α -1 proteinase inhibitor.[3]

iv) Inhibition of bone resorption –

Tetracycline inhibits osteoblast collagenase and may also have a modifying effect on osteoclasts. Tetracyclines inhibit bone resorption induced by parathyroid hormone, prostaglandins of the E series and bacterial endotoxins. This action may be related to the anti-proteolytic property of a drug having modifying effect on osteoclasts. Osteoclast mediated bone resorption is facilitated by collagenase secreted osteoblasts.

v) Anti-inflammatory action-

Tetracycline can suppress PMN activity, in particular, by scavenging action on reactive oxygen metabolites. The drug may block eicosanoid synthesis (especially PGE2) by inhibiting phospholipase A2 activity.

vi) Conditioning agent-

Pre-treatment of dentin with tetracycline enhances fibroblast attachment and colonization.

vii) Property of substantivity

viii) **Sub-inhibitory concentrations** have been shown to reduce adherence and co-aggregation of species including P. gingivalis and P. intermedia.

ix) Fibroblast attachment-

In vitro studies have shown that pretreatment of root surfaces with tetracyclines enhances fibroblast attachment and colonization. The drug can also bind to demineralize dentin. However, its uncertain whether these actions of tetracycline on dentin are due to a chemical modifications properties of the

dentinal surfaces or due to the release of matrix components from the dentin such as type I collagen, proteoglycans, osteonectin or growth factors.[3]

Tetracyclines have been used in the treatment of localized juvenile Periodontitis, generalized juvenile periodontitis, early onset periodontitis, and adult periodontitis. The different mechanisms of bacterial resistance to tetracyclines are either by acquisition of R-plasmid which carry genes which are resistant to antibiotics (Plasmid is extra-chromosomal genetic material that can replicate independently and freely in cytoplasm) or by acquisition of transposon-associated genetic material (Transposon are DNA segments that cannot self-replicate but can self-transfer between plasmids or from plasmid to chromosomes; during this transfer or co-integration, transposon can replicate, and the each new plasmid contains r-gene, which results in resistance). Also, efflux pump is another mechanism of resistance (Efflux pumps are cytoplasmic membrane transport proteins, which protect bacterial cell from foreign chemical invasion and are regulated by a number of genes) and lastly by resistance genes, which encode ribosomal protection proteins. These proteins release ribosome-bound tetracycline and, at the same time, increase the apparent dissociation constant of the tetracycline ribosome interaction, thereby reducing the possibility of a further interaction between the ribosome and the released drug. Currently, 38 tetracycline resistance genes have been identified, of which 23 encode efflux pumps, 11 encode ribosomal protection proteins, 3 encode inactivating enzymes, and 1 is of unknown function.

When tetracyclines are taken orally considerations must be given both to the potential unwanted effectsand to interactions with other drugs that are taken concurrently. Such problems are minimized however when the drugs are incorporated into controlled slow release formulations which are currently being researched and marketed for intraoral use. **Goodson et al**, observed that tetracycline filled hollow fibers placed in the gingival sulcus have dramatic effect both on the periodontal flora and clinical manifestation of disease. Of theoretical importance was the observation that virtual elimination of spirochetes from the gingival sulcus is possible by a single placement of tetracycline filled hollow fibers and spirochetes once eliminated from a site do not recolonize despite the persistence of viable organisms.

Lindhe et al in his experiments demonstrated that use of tetracycline filled hollow fiber devices markedly changes the composition of the subgingival flora of initially diseased periodontal sites. Pavia et al showed that tetracycline and its derivatives minocycline, oxytetracycline and chlortetracycline strongly adsorb to tooth surfaces retaining their antibacterial activity and are quite effective in treating chronic periodontitis. Thomas et al compared the effects of tetracycline fibers plus scaling and root planing versus scaling and root planing alone. In 2004 Rodrigues et al compared antibiotic resistance profile with local and systemic tetracycline and observed that there are less chances of bacterial resistance with locally delivered tetracyclines. Local drug delivery with tetracycline fibers has also a role to play in the treatment of peri-implantitis sites as observed in microbiological studies.

PHARMACOLOGY

PHARMACOKINETICS:

Tetracyclines are usually administered orally since injections are painful. Local application may also have been used in the periodontal treatment regimes. The oral administration of tetracycline results in the detachable serum levels within 30 minutes with peak concentration achieved after 1-3 hours. The half- life of tetracycline HCL is about 8 hours. Longer half- life of 18 hours for doxycycline hyclate and 16 hours for minocycline permit a lower initial dose and less frequent dosing than for tetracycline HCL. Doxycycline is excreted mainly in feces, the other drugs are excreted through urine.[4]

FIG:2 TETRACYCLINE HCL

Tetracycline is adequately but incomplelety absorbed 75% from the stomach abnd upper duodenum in the fasting state. Multivalent cations chelate tetracycline and inhibit absorption. Patients should avoid the concurrent consumption of antacids, dairy produvts and iron. The capsule has to be taken half an hour before or two hours after the meal.

DOSE: 250 mg four times a day.

PHARMACODYNAMICS:

After absorption, tetracyclines are widely distributed in the body tissue and fluids. They can also pass through placenta and occur in low doses in breast milk. Selective distribution results in the accumulation of tetracycline by adsorption into bone crystal lattice. If tetracycline is administered during fetal development or permanent tooth formation, permanent discolouration and inadequate calcification of deciduous and permanent teeth are commonly seen.

SPECTRUM OF ACTIVITY:

All tetracyclines are bacteriostatic at recommended doses, although they can be come bactericidal when given in higher concentrations. Strict anaerobic bacteria are susceptible to tetracyclines although some black pigmented bacteroides have been reported to be minocycline resistant.

Gram negative facultative rods are also sensitive to tetracyclines. Some strains of Actinobacillus Actinomycetemcomitans and Eikenella corrodens are tetracycline resistant. Tetracyclines are also effective against a few viruses, such as Mycoplasma, Chlamydia, Rickettsia and Legionella.

EFFICACY/ CLINICAL USE:

Efficacy studies both systemic and topical applications have compared tetracyclines with both non-surgical and surgical management and as an adjunct to conventional periodontal treatment. In adult periodontitis, systemic tetracycline is no substitute for scaling or root planning and has a little advantage when used as an adjunct to these procedures.

Systemic tetracyclines appear to be more useful in the management of localized periodontitis, aggressive and refractory periodontitis. In localised periodontitis, the prime pathogen is difficult to eliminate by mechanical debridement alone because of its ability to invade gingival connective tissues. A 3-6 week course of tetracycline of 1g/day will halt the progression of aggressive periodontitis adjunct to non-surgical or surgical management. Tetracycline medications should be continued 1 week after obtaining negative culture results to minimize the chances of recolonization.

Cases of refractory periodontitis also benefit from a 2 week course of systemic therapy of 250 mg q.d.s. however. Long term tetracycline therapy can lead to the development of resistant organisms and also clinical and bacterial status characteristic of the disease from approximately 6 months after the cessation of dosage.

Resistance to tetracycline develops slowly in graded manner. Its concentrating mechanism becomes less efficient or the bacteria require the capacity to pump iy out. Another mechanism is the plasmid mediated synthesis of protection protein which protects the ribosomal binding site from tetracycline.

COMMON ADVERSE EFFECTS OF TETRACYCLINES:

1. Gastrointestinal tract: nausea, vomiting, irritative diarrhea.
2. Photosensitivity: phototoxic skin reaction resembling sunburn.
3. CNS: vestibular toxicity with minocycline
4. Bone: tetracycline deposit at sites of newly deposited bone which can cause discolouration, decreased fibula growth in children.
5. Teeth: it is deposited at the active calcifications, discolouration is concentration dependent.
6. Candida overgrowth
7. Pregnancy and lactation: tetracyclines are present in the milk of breast feeding women and have toxic effects on developing foetus.[1,4]

LOCAL DELIVERY OF TETRACYCLINES

A. IRRIGATION WITH TETRACYCLINES:

Despite reports of substantivity and antimicrobial efficacy of tetracyclines, mixed result shave been reviewed on the tetracycline irrigation. Subgingival irrigation with 2cc of tetracycline HCL (50mg/ml) following scaling and root planning with repeated every 2 weeks for 24 weeks failed to show significant improvement in clinical and microbiologic parameters when compared with scaling and root planning alone.

Following a subgingival irrigation for 5 minutes with a much higher concentration of 50% tetracycline HCL solution retains its activity for 16 days. It was concluded that the degree of anti-microbial activity is proportional to the concentration of tetracycline used for irrigation.

Limitations of irrigation therapy includes a restricted size of the delivery system due to the low volume of GCF, and a higher clearance rate of the drug from the periodontal pocket due to a high turnover rate of GCF.[4,5]

B. SUBGINGIVAL DELIVERY OF TETRACYCLINES:

The relatively low toxicity and higher substantivity of tetracyclines have encouraged investigators to test a variety of delivery devices. Sulcular administration of an antibiotic through a controlled release delivery system ha sthe advantage of directly reaching the target area at the base of the periodontal pocket at low doses at concentration higher enough to achieve a possible reduction in the emergence of resistant bacteria.

C. TETRACYCLINE 40% IN PETROLATUM:

As an example of the use of high concentrations of tetracyclines is of 40% mixture of tetracycline in petrolatum in the periodontal pocket. However, no adjunctive clinical benefits to localized and adult periodontitis patients were seen when this formulation was used.[5]

D. TETRACYCLINE CONTAINING FIBERS:

Goodson et al in 1979 first proposed the concept of controlled delivery in the treatment of periodontitis. It has been observed that the local route of drug delivery can attain 100-fold higher concentrations of an antimicrobial agent at subgingival sites compared with a systemic drug regimen. Thus reducing the patient dose by over 400 fold, thereby reducing the potential problems with use of systemic antibiotic drug regimens and the development of drug-resistant microbial populations at non oral body sites. These can be safely used in medically compromised patients for whom surgery is not an option and contraindicated in patients with known hypersensitivity to the antimicrobial used, asthmatics and infective conditions such as AIDS, Tuberculosis.

FIBRES:

Monolithic Tetracycline containing fibers, using different acrylics like Polyethylene, Polypropylene, Polycaprolactone, Polyurethane cellulose propionate and Ethylene Vinyl Acetate (EVA) were first developed and tested by Goodson

ACTISITE tetracycline fibres are approved for treating adult periodontitis by the United States Food and Drug Administration (FDA). It is non-resorbable biologically inert, safe, plastic copolymer (ethylene and vinyl-acetate) loaded with 25% w/w tetracycline HCL powder packaged as a thread of 0.5 mm in diameter and 23 cm in length, maintaining constant concentrations of active drug in the crevicular fluid in excess of 1000 µg/ml for a time period of 10 days. Actisite is used as an adjunct to SRP, showing significantly greater reduction in probing depths, bleeding on probing and significant reduction in A. a and P. gingivalis level. Bio-resorbable form of fibre is commercially available as PERIODONTAL PLUS AB which offers an advantage of no second appointment for its removal as it biodegrades within 7 days.

FIG:3 ACTISITE

A new generation of semi-synthetic tetracycline compounds called glycyclines has recently been developed which are effective not only against tetracycline-sensitive bacteria, but also against tetracycline-resistant gram-positive and negative microorganisms.

The delivery device is provided individually packaged as a thread of 0.5 mm in diameter and 23 cm in length applied to fill the pocket for 1 week to 10 days. During the therapeutic period, the device has been shown to maintain active effect in crevicular fluid in excess of 1000 ug/ml for a period of 10 days. –**TONETTI et al, 1990**.[6]

A series of investigations has been reported that the tetracycline can be retrieved in substantial concentration within the soft tissue walls of the pocket and on the root surfaces exposed to subgingival plaque environment. – **Ciancio et al, 1992.**[7]

INDICATIONS OF TETRACYCLINE FIBERS:

1. If the active periodontitis is confined to a few local sites at the reevaluation, 4 to 6 weeks after scaling and root planning.
2. When localized, recurrent active sites are found in the maintenance visit in localised aggressive periodontitis.
3. In acute periodontal abscess, the fibre acts as a drain while releasing high doses of tetracycline.
4. In ailing or failing implants.[8]

DISDAVANTAGES OF NON-BIODEGRADABLE FIBRE:

1. Length of time required for placement.
2. Considerable learning curve required to gain proficiency at placement and the need for second appointment 10 days after the placement for the removal of fibers.
3. Placement of fibre around 12 or more teeth resulted in oral candidiasis.
4. Lack of penetration of the drug into deeper periodontal tissues.
5. Inability of the agent to reach non periodontal sites such as cheeks, tonsils and tongue which are the potential sources of reinfection.

TETRACYCLINE-SERRATIOPEPTIDASE CONTAINING PERIODONTAL GEL FORMULATIONS:

The Gel is applied sublingually with the help of a blunt cannula and syringe. The safety profile, longer-term retention, antimicrobial activity suggests that tetracycline containing copolymer gels represents a safe and effective therapy for periodontitis. Comparative analysis of tetracycline containing dental gels: poloxamer and monoglyceride based formulations have been done which shows that when applied subgingivally produce a significant improved outcome in moderate to deep periodontal pockets.[9]

The semisolid formulations also receive reasonable attention for the local delivery of antibiotics. In spite of the faster release of the incorporated drug, gels are more easily prepared and administered. They possess higher biocompatibility and bioadhesivity which allows adhesion of the mucosa in pocket and finally, they are rapidly eliminated through catabolic pathways, thereby decreasing the risk of allergic host reactions at the application site. Various oleogels and hydrogels for the delivery of tetracycline (2.5%), metronidazole (25%-Elyzol dental gel), metronidazole benzoate (40%), have been tested with satisfactory results. Elyzol have been applied in viscous consistency to the pocket, where it is liquidized by the body heat and then hardens again forming crystal in contacts with water. After the application of Elyzol 25% dental gel, metronidazole concentrations of above 100 µ/ml were measurable in the periodontal pocket for at least 8 hours and concentrations above 1 µ/ml were found at 36 hours.

FIG:4 ELYZOL-25%

2% minocycline HCL in a matrix of 20 mg hydroxyethyl cellulose, 25 mg magnesium chloride, 10 mg eudragit, 60 mg triacetine, and 0.5 gm glycerine available as yellow coloured ointment Dentomycin in European Union. It is commercially available in Japan with name Periocline. The concentration of minocycline in the periodontal pocket is 1300 µg/ml, 1 hr after single topical application of 0.05 ml ointment (1 mg of minocycline) and is reduced to 90 µg/ml after 7 hrs. Results have shown that the combination of ointment with scaling and root planing was significantly better than scaling and root planning.

The only FDA approved gel system is 8.5% Doxycycline w/w (42.5 mg Doxycycline) dissolved in 37% poly (DLlactide) (PLA)+63% N-methyl-2-pyrrolidon (NMP) ATRIDOX available as 2 syringe mixing system. Doxycycline level in GCF was seen to be peaked upto 1,500-2000 µg/ml in 2 hours along with the treatment of ATRIDOX. The levels remained above 1000 µg/ml per 18 hours. 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 and show significant improvement in chronic periodontitis. Approximately 95% of the polymer is bio absorbed or expelled from the pocket naturally within 28 days.[9]

BIOERODIBLE INJECTABLES POLY(ORTHO ESTER) FOR TETRACTYCLINE CONTROLLED DELIVERY TO PERIODONTAL POCKETS:

Poly (ortho ester) is a bioerodible injectable and adhesive semi solid polymer containing tetracycline free base which allows direct injection in the periodontal pockets and shows sustained release and almost constant vitro release of phosphate buffer, ph of 7.4 at 37 degree celcius for 14 days.

POEs is able to degrade predominantly by surface erosion and then to sustain drug release for days to weeks depending on their physiochemical properties related to the percentage of lactic acid in the polymeric backbone. Increase in the lactic acid content in the polymer tended to increase the drug release rate and reduce the initial lag time.

Tetracycline release from the bioerodible delivery system occurs predominantly by surface erosion of the polymeric matrix leading to kinetics which can be zero order. These formulations loaded with tetracycline 10% or 20% showed complete in vitro degradation concomitant with drug release.[10]

CONCLUSION:

Local drug delivery systems have the advantage of avoiding the harmful effects of systemic administration including development of resistant flora, suppression of normal flora, poor patient compliance.

These locally applied antimicrobial agents into the periodontal pockets may further suppress the periodontal pathogens thereby augment the effect of conventional mechanical therapy.

REFERENCES:

1. K.D. Tripath; Essentials of Medical Pharmacology; 4th Edition.
2. Clay B Walker; Selected antimicrobial agents; Mechanism of action, side effects and drug interaction. Periodontal 2000;1996;10;12-28.
3. R.A. Seymour and P.A. Heasman; Pharmacological control of periodontal disease. 2 Antimicrobial agents. J. Dent. 1995;23;5-14.
4. Mea A. Weinberg, Michael Bral; Tetracycline and its Analogues; A Therapetuic Paradigm in Periodontal Diseases.Crit Rev Oral Biol Med 1998;9;3;322-332.
5. J Max Goodson; Antimicrobial strategies for treatment of periodontal diseases. Periodontal 2000,1994;5; 142-168.
6. Tonetti M, Cugini M & Goodson J; Zero order delivery with periodontal placement of tetracycline loaded ethylene vinylacetate fiber. J Periodontal Research 1990;25;243-249.
7. Ciancio S, Cobb C, Leung M; Tissue concentration & localization of tetracycline following site specific tetracycline therapy. J Periodontal 1992;63;849-853
8. Maria Perno; Pharmacotherapy in Periodontaol Therapy; Access, special supplemental issue, September-October 2001
9. Manish Maheshwari, Gunjan Miglani, Amita Mali et al; Development of Tetracycline-Serratiopeptidase-Containing Periodontal Gel: Formulation and Preliminary Clinical Study; AAPS PharmSci 2006;7(3) article 76.
10. K. Schwach, P.J. Loup, Castioni et al; Bioerodible Injectable Poly (ortho ester) for Tetracycline Controlled Delivery to Periodontal Pockets: Preliminary Trial in Humans; AAPS PharmSci 2002;4(4) article 20.