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Research Paper

Local drug delivery in Periodontics: A tactical entreaty

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ABSTRACT: - *Periodontitis is a silent disease. It is an inflammatory disease of the supporting tissues of the teeth caused by groups of specific microorganisms. The periodontal diseases are major cause of tooth loss for population irrespective of sex, age and races. Various treatment modalities have been tried to combat such diseases. Amidst it the most commonly employed are professional scaling polishing along with plaque control measures. In some cases, owing to limited success local applications of some antibacterial agents either by topical application or local drug delivery in periodontal pockets has been evaluated. Periodontal pockets provide natural reservoir bathed by gingival crevicular fluid that is easily accessible for the insertion of a delivery device. Controlled release delivery of antimicrobials directly into periodontal pockets has received eminent interest and appears to hold a level headed promise in periodontal therapy. It does not substitute conventional mechanical debridement but acts as an adjunct to it. The periodic use of local drug delivery in improving gingival and periodontal condition, would allow better control and management of periodontal disease. Literature reviews various drugs used for many decades in the field of Periodontology, prognosticating boosting results. This review article sheds light on the concept of local drug delivery in Periodontics and emphasizes on various drug systems available to date and rationales of using those antibacterial drugs systems through local delivery into the periodontal pockets.*

Keywords: - *Inflammatory, local drug delivery, Periodontitis, periodontal pocket, scaling and polishing*

I. INTRODUCTION

Gingival and periodontal diseases, in their various forms, have afflicted humans since the dawn of history. Periodontal diseases are considered infections of the periodontium, owing to the bacterial etiology, an immune response, and tissue destruction.[1] In 1976 Löesche *et al.* proclaimed the specific plaque hypothesis, suggesting that specific bacteria caused specific forms of periodontal diseases.[1] Since then newer treatment strategies, aiming primarily at suppression or elimination of specific periodontal diseases have been established. Putative pathogens associated with periodontal diseases are susceptible to a variety of antiseptics and antibiotics.[2, 3] Methods employed to convey antimicrobial agents into periodontal pockets have included rinsing, irrigation, systemic administration, and local application using sustained and controlled delivery devices. Success of any drug delivery system designed to target periodontal infections depends upon its ability to deliver the antimicrobial agents to the base of pocket, at a bacteriostatic or bactericidal concentration. [4] It must also facilitate retention of the medicament long enough to ensure an efficacious result. [4] Since local drug delivery can achieve the above requirements, it was thought important to critically assess the ability of these treatment methods to accomplish periodontal health. Numerous local drug transport products have undergone preliminary assessments. [3, 5, 6] but only a few methods have been evaluated in several studies. This paper addresses the potential efficacy of various delivery systems being used in Periodontics.

II. LOCAL DELIVERY AGENTS

The choice of the antimicrobial agents in periodontal diseases must be based on the bacterial etiology of the infection. There are distinct phases in a periodontal treatment plan where a dental practitioner can use a sustained release device. It can be used as an adjunct to scaling and root planing and for periodontal maintenance therapy. It has been observed that the local route of drug delivery can attain 100-fold higher concentrations of an antimicrobial agent in subgingival sites compared with a systemic drug regimen thereby

reducing the total patient dose by over 400 fold avoiding development of drug-resistant at non oral body sites. [7]

III. VARIOUS AGENTS USED

3.1. **Povidone-iodine**

The value of diluted povidone-iodine solution (final concentration 0.05% free iodine) irrigation of periodontitis lesions as an adjunct to subgingival debridement revealed reduction in gingival inflammation and 2 mm or more in gain of clinical attachment; enhanced healing pertaining to better suppression over periopathogens. [8, 9]

3.2. Tetracycline

In 1979 Goodson et al first proposed the concept of controlled delivery in the treatment of periodontitis. [4] Tetracycline are a group of closely related bacteriostatic antimicrobials.
Tetracycline-HCl in vitro displays substantivity to dentin tooth surfaces, and maintains its antimicrobial activity upon desorption [10, 11.] The first delivery devices involved hollow fibers of cellulose acetate filled with tetracycline. [12]

3.2.1. Fibers**:** The ACTISITE tetracycline fibres have been approved for the treatment of adult periodontitis by the United States Food and Drug Administration (FDA). These are non-resorbable biologically inert, 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. [13] Following application of tetracycline fibres a definite reduction in the subgingival microbiota has been observed. [14] Bio-resorbable form of fibre commercially available as PERIODONTAL PLUS AB offers the advantage of no second appointment for removal as it biodegrades within 7 days.

3.2.2. Gel: Noteworthy results were seen with Tetracycline-Serratiopeptidase-Containing Periodontal Gel Formulation along with scaling and root planing. [15] Bio erodible Injectable Poly (ortho ester) for Tetracycline Controlled Delivery formulations loaded with tetracycline 10% or 20% showed complete in vitro degradation concomitant with drug release. [16] In general, tetracycline helped in improvement of periodontal parameters.

3.3 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. [17] 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. Local levels of Doxycycline have been found to remain well above the minimum inhibitory concentration for periodontal pathogens (6.0μg/ml) through Day 7. Approximately 95% of the polymer is bio absorbed or expelled from the pocket naturally within 28 days. [18] Several studies have reported probing depth reduction and gaining clinical attachments. [19, 20]

3.4. Subgingival Minocycline

Local delivery of minocycline, a bacteriostatic antibiotic has been tried clinically via in three different modes i.e. film, microspheres, and ointment. [21, 22]

3.4.1. Film: Ethyl cellulose film containing 30% of Minocycline were tested as sustained release devices. The results indicated that the use of this device may cause complete eradication of pathogenic flora from the pocket after 14 days. [23]

3.4.2. Microsphere: A new, locally delivered, sustained release form of minocycline microspheres (ARESTIN) for subgingival placement is available. The 2% minocycline is encapsulated into bio-resorbable 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. [23]

3.4.3. Ointment: Minocycline ointment is a bio-absorbable 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. In Japan it is commercially available with 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. 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. [24]

3.5 Subgingival Chlorhexidine

The use of chlorhexidine as an antifungal and antibacterial agent has been well established. Chlorhexidine is 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. 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. 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. [25] 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.

3.5.1 Periochip: 2.5 mg Chlorhexidine Gluconate PerioChip, the controlled subgingival delivery of chlorhexidine gluconate, is a small, orange-brown, tombstone-shaped chip (4.0 x 0.5 x 0.35mm) in a biodegradable matrix of hydrolyzed gelatine and has been approved by FDA. Studies with Perio Chip showed reduction in the numbers of the putative periodontopathic organisms after placement of the chip. No overgrowth of opportunistic organisms or other adverse changes in the oral microbial ecosystem were noted. Perio Chip 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 studies compared the efficacy of scaling/root planing and combined therapy employing Chlorhexidine chips. Results indicating the number of sites with probing depth reduction were greater with combined therapy. [26, 27]

3.5.2 Periocol-CG: Periocol CG is prepared by incorporating 2.5mg chlorhexidine from a 20% chlorhexidine solution in collagen membrane. Size of the chip is 4x5 mm and thickness is 0.25 - 0.32 mm and 10 mg wt. Collagen is a natural protein, which is chemotactic for fibroblasts, enhances fibroblast attachment via its scaffold like fibrillar structure and stimulates platelet degranulation, thereby accelerating fibers and clot attachment. It has been shown to resorb after 30 days; however their coronal edge degrades within 10 days. [28]
3.5.3.Chlo-Site: Chlo-Site is an agent containing 1.5% chlorhexidine of xanthan type (Ghimas Company, Italy). Xanthan gel is a saccharide polymer, which constitutes of a three-dimensional mesh mechanism, which is biocompatible with chlorhexidine. The gel gets vanished from the pocket within l0-30 days of injection and effective concentration of chlorhexidine against microorganismsis established for at least 15 days in the region. Both chlorhexidine and gel matrix are mucoadhesive so that they stick inside the pockets and are not easily washed out by gingival fluid or saliva. It degrades spontaneously at the site of application, is well tolerated and is efficient in treatment of periodontal pockets & periimplantitis. [28]

3.6. Subgingival Metronidazole

Metronidazole has often been chosen because of its selective efficacy against obligate anaerobes. It acts by inhibiting DNA synthesis. After application of Elyzol 25% dental gel, Metronidazole concentrations of above100 μ/ml were measurable in the periodontal pocket for at least 8 hours and concentrations above 1 μ/ml were found at 36 hours. [29] A topical medication ELYZOL contains an oil-based Metronidazole 25% dental gel (glyceryl mono-oleate and sesame oil). It is applied in viscous consistency to the pocket, where it is liquidized by the body heat and then hardens again, forming crystals in contact with water. One study suggested better result when combined therapy was employed for probing depth reduction. [30]

IV. ANTIBIOTIC SELECTION

The most effective therapy matches the putative pathogen with an appropriate drug. Tetracyclines have often been administered to non-responsive patients, as they are broad spectrum and are effective against many periodontal pathogens including A. actinomycetemcomitans (A. a) [2, 3] However, some investigations have stated that tetracycline might not be effective in doing so. [31, 32] Currently, for A.a infections multiple drugs

such as amoxicillin and clavulanate potassium or Ciprofloxacin plus metronidazole have been employed. [3] It is apparent that no single drug is the universal drug of choice.

V. SELECTION OF APPROPRIATE DRUG CONCENTRATIONS FOR LOCAL DELIVERY

Bacteria associated with periodontal diseases are usually found in biofilms requiring considerably higher concentrations of drugs to kill bacteria in biofilms. [33, 34] In order to combat dentomicrobial infections, different antimicrobials at a variety of concentrations need to be tested against a panel of suspected pathogens. [34] Currently, the best way to determine the ideal drug concentrations is to compare in vitro and in vivo results.

VI. FUTURE PERSPECTIVES

Eradicating microorganisms from the periodontal pocket is a crucial task in treating periodontitis. For treating periodontal diseases targeting of an anti-infective agent to infection sites with effective levels for a sufficient time while concurrently evoking minimal or no side effects is needed. [35] Novel therapeutic agents are being improvised in the arena of local drug delivery system to ensure maximum benefit.

6.1. Drugs for osseous defects

6.1.1. Alendronate: Alendronate a novel bisphosphonate is a very potent inhibitor of bone resorption. Its net effect might be explained by its inhibition of osteoclasts thus affecting the bone maturation and remodelling thereby inducing bone formation. Systemically administed bisphosphonates leads to gastrointestinal disturbances but Local drug delivery avoids most of these problems, by limiting the drug to the target site; also allowing a local concentration at a much higher level than possible by systemic route. [36, 37]

6.1.2. Simvastatin: Statins like simvastatin (SMV), lovastatin, are specific competitive inhibitors of 3-hydroxy-2-methyl-glutaryl coenzyme A (HMGCoA) reductase, widely used to lower cholesterol, and for treating hyperlipidemia and arteriosclerosis. Statins modulate bone formation by increasing the expression of bone morphogenetic protein-2, inflammation, and angiogenesis. Various studies showed that SMV assists in bone regeneration as well as the anti-inflammatory effect when delivered or applied locally. [38, 39]

6.2. Okade and co-workers developed a new sub gingival release delivery system (PT-01) containing Ofloxacin for sub gingival therapy and found it to be effective in the reducing plaque scores and bleeding scores. [40]

6.3. Clarithromycin gel: A clinical study investigating the efficacy of adjunctive use of subgingivally delivered 0.5 % clarithromycin to scaling for treating chronic periodontitis smoker subjects; saw that the adjunctive use of the drug reduced the post operative gingival and periodontal parameters and enhanced the clinical outcome. This product is still under investigation and yet to be patented. [41]

6.4. Herbs for periodontitis: Various herbal formulations like Aloe Vera, Bloodroot, Chamomile, Eucalyptus neem, tulsi, propolis, cocoa husk, pomegranate, cranberry etc. are being used widely these days. [42, 43] These products have shown to improve gingival and periodontal parameters without side effects.

6.4.1. Herbal Combinations: Along with individual herbs, herbal combinations can help to combat periodontitis symptoms and can improve the oral hygiene. [44]

6.5. Colloidal drug carriers include micelles, emulsions, liposomes and nanoparticles (nanospheres and nanocapsules). Liposomes and nanoparticles are largely used due to ease and simplicity of preparation**.** Colloidal carriers increase the specificity towards tissues, improve the bioavailability of drugs and protect them against enzyme inactivation. [45]

6.6. Local delivery of growth factors: Platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and pyridinoline cross-linked carboxyterminal telopeptide of Type I collagen (ICTP) are mediators involved in mitogenesis, angiogenesis, bone turnover and are essential for wound regeneration of periodontal tissues. [46, 47] Fibroblast growth factor is effectively introduction in local drug delivery. To regenerate periodontal tissues, a sandwich membrane composed of a collagen sponge scaffold and gelatin microspheres containing basic fibroblast growth factor (bFGF) in a controlled-release system was developed. [48]

6.7. Nanoparticles: The recent success of many polymeric depot delivery systems has encouraged further research to develop new systems for use in regional therapy. Nanoparticles, owing to their small size, penetrate

regions that may be inaccessible to other delivery systems. They reduce the frequency of administration and provide uniform distribution of the active agent over an extended period. Various studies have assessed efficacy of nanoparticles in periodontal diseases. Namely, Dung et al using Antisense oligonucleotide- loaded chitosantripolyphosphate (TPP) nanoparticles, Pinon et al using Triclosan-loaded polymeric (PLGA, PLA and cellulose acetate phthalate) nanoparticles and Moulari et. al, using Harungana madagascariensis leaf (HLE)-loaded PLGA nanoparticles. [23]

VII. CONCLUSION

New formulations and novel-controlled delivery system will continue to be explored. One of the most persistent problems faced by the formulation technologist is that many drugs do not reach the target areas in the therapeutic concentrations intended. By the development of novel drug delivery systems, a more site-specified and controlled drug delivery systems was made possible, thereby dose and side effects can be reduced which ensures better patient compliance. There is no single universal drug that would be effective in all situations. Therefore, at non-responsive sites, bacterial and antibiotic sensitivity testing may be necessary to determine putative pathogens and their susceptibility to specific antimicrobial agents. Local drug delivery systems usually do not provide a benefit beyond what is achievable with conventional scaling and root planing.

In conclusion, hence antimicrobial drug as site-specific dental formulations into periodontal pocket proves to be a viable alternative to conventional periodontal therapy. Obviously, its clinical use in the fast-growing field is promising.

REFERENCES

[1]. Haffajee AD, Socransky SS. Microbial etiological agents of destructive periodontal diseases. Periodontol 2000 1994:5:78-111.
[2]. Winkelhoff AJ, Rams TE, Slots J. Systemic antibiotic therapy in periodontics. Periodontol 2000 1996; 10:47-78.
[3]. Drisko CH. Non-surgical therapy: Pharmacotherapeutics. Ann Periodontol 1996; 1: 491-518.
[4]. Goodson JM. Controlled drug delivery: A new means of treatment of dental diseases. Compend Cont Educ Dent 1985; 6: 27-36.
[5]. Soskolne WA. Subgingival delivery of therapeutic agents in the treatment of periodontal diseases. Crit Rev Oral Biol Med 1997;8: 164-174.
[6]. Rams TE, Slots J. Local delivery of antimicrobial agents in the periodontal pocket. Periodontol 2000 1996; 10:139-159.
[7]. Goodson J. Antimicrobial strategies for treatment of periodontal diseases. Periodontol 2000: 1994; 5:142-168.
[8]. Christersson LA, Rosling BG, Dunford RG, Wikesjo UME, Zamhon JJ, Genco RJ. Monitoring of subgingival Bacteroides gingiualis and Actinobacillus actinomyceterncomitans in the management of advanced periodontitis. Adv Dent Res 1988: 2: 382-388.
[9]. Rosling BG, Slots 1, Christersson LA, Grondahl HG, Genco RJ. Topical antimicrobial therapy and diagnosis of subgingiva1 bacteria in the management of inflammatory periodontal disease. J Clin Periodontol 1986: 13: 975-981.
[10]. Baker PJ, Evans RT, Coburn RA, Genco RJ. Tetracycline and its derivatives strongly bind to and are released from the tooth surface in active form. J Periodontol 1983: 54:580-585
[11]. Wikesjo UME, Baker PJ, Christersson LA, Genco RJ, Lyall RM, Hic S, DiFlorio RM, Terranova W. A biochemical approach to periodontal regeneration: tetracycline treatment conditions dentin surfaces. J Periodont Res 1986:21:322-329
[12]. Goodson JM, Offenbacher S, Farr DH, Hogan PE. Periodontal disease treatment by local drug delivery. J Periodontol 1985; 4: 265-272.
[13]. Maurizio S, Tonetti. The topical use of antibiotics in periodontal pockets., in: N.P. Lang, T. Karring, J. Lindhe (Eds.), Proceedings of the Second European Workshop on Periodontology, Quintessence, London, 1997, pp. 109-132.
[14]. Lowenguth RA, Chin I, Caton JG, Cobb CM, Drisko CL, Killoy WJ et al. Evaluation of periodontal treatment using controlled release tetracycline fibers. J Periodonol 1995; 66:700-707.
[15]. Maheshwari M, Miglani G, Mali A, Paradkar A, Yamamura S, Kadam S. Development of Tetracycline-Serratiopeptidase-Containing Periodontal Gel: Formulation and Preliminary Clinical Study; AAPS Pharm Sci Tech 2006; 7 (3) Article 76:E162-171.
[16]. Schwach K, Loup PJ, Castioni N, Mombelli A, Baehni P, Barr J et al. Bioerodible Injectable Poly(ortho ester) for Tetracycline Controlled Delivery to Periodontal Pockets: Preliminary Trial in Humans; AAPS Pharm Sci 2002; 4 (4) article 20:1-7.
[17]. Preshow PM. Host response modulation in Periodontics. Periodontol 2000:2008; 48:92-110.
[18]. Polson AM, Garrett S, Stoller NH, Bandt CL, Hanes PJ, Killoy WJ et al. Multi-center comparative evaluation of subgingivally delivered sanguinarine and doxycycline in the treatment of Periodontitis. II. Clinical results. J Periodontol 1997; 68:119- 126.
[19]. Borden LC, Walker CB, Stone C, Mankodi S., Godowski K.C., Southard H. Microbiota effects following sustained release subgingival delivery of doxycycline. J Dent Res 1997; 76(Spec. Issue): 153 (Abstr. 1114).
[20]. Garrett S, Adams D, Bandt C, Beiswanger B, Bogle BC, Caton J et al. Two multicenter clinical trials of subgingival doxycycline in the treatment of Periodontitis. J Dent Res 1997; 76(Spec. Issue):153 (Abstr. 1113).
[21]. Akula S, Chava V. Minocyclines in periodontal therapy; J Indian Soc Periodontol 2000; 3: 49-51.
[22]. Vandekerckhove BN, Quirynen M, V Steenberghe. The use of locally delivered minocycline in the treatment of chronic periodontitis- A review of the literature. J Clin Periodontol 1998; 25: 964-968.
[23]. Pragati S, Ashok S, Kuldeep S. Recent advances in periodontal drug delivery systems. Int J Drug Del 2009; 1: 1-14.
[24]. Van Steenebergh D, Bercy P, Kohl J. Subgingival Minocycline Hydrochloride ointment in moderate to severe chronic adult periodontitis a randomised double blind, vehicle controlled multicenter study. J Periodontol 1993; 64:637-644.
[25]. Abdellaouia KS, Castionib NV, Gurnya R. Local delivery of antimicrobial agents for the treatment of periodontal diseases. Eur J Pharm Biopharm; 2000: 83-99.
[26]. Jeffcoat M, Bray KS, Cianico SG, Dentino AR, Fine DH, Gordon JM, et al. Adjunctive use of a subgingival controlled-release Chlorhexidine chip reduces probing depth and improves attachment level compared with scaling and root planing alone. J Periodontol 1998; 69:989-997.
[27]. Soskolne WA, Heasman PA, Stabholz A, Smart GJ, Palmer M, Flashner M, et al. Sustained local delivery of Chlorhexidine in the treatment of Periodontitis: a multicenter study. J Periodontol 1997; 68:32-38.

[28]. NandaKumar P.K. Local Drug Delivery-Periocol in Periodontics. Trends Biomater Artif Organs 2006; 19(2); 74-80.
[29]. Chhina K, Bhatnagar R. Local drug delivery. Indian J Dent Sci 2012; 4: 166-69.
[30]. Greenstein G, Polson A. The Role of Local Drug Delivery in the Management of Periodontal Diseases: A Comprehensive Review. J Periodontol 1998; 69:507-520.
[31]. Miller HR Lange DE, Muller RE Failure of adjunctive minocycline- HCL to eliminate oral Actinobacillus actinomycetemcomitans. J Clin Periodontol 1993; 20: 498-504.
[32]. Van Winkelhoff AJ, Rodenburg JR Goene RJ, Abbas F, Winkel EG, de Graaff J. Metronidazole plus amoxycillin in the treatment of Actinobacillus actinomycetemcomitans associated with Periodontitis. J Clin Periodontol 1989; 16: 128-131.
[33]. Wilson M. Susceptibility of oral bacterial biofilms to antimicrobial agents. J Med Microbio! 1996; 44: 79-87.
[34]. Caufield PW, Allen DN, Childers NK. In vitro susceptibilities of suspected periodontopathic anaerobes as determined by membrane transfer assay. Antimicrob Agents Chemo 1987; 31: 1989-1993.
[35]. Venkatesh A, Ramamurthy J. Local drug delivery systems in the treatment of periodontitis – An Overview. Int J Pharm Pharm Sci, 2012; 4: 30-37.
[36]. Veena HR, Prasad D., Evaluation of an aminobisphosphonate (alendronate) in the management of periodontal osseous defects, 2010 Jan; 14(1):40-45.
[37]. Binderman I,Adut M,Yaffe A.Effectiveness of local delivery of Alendronate in reducing alveolar bone loss following periodontal surgery in rats.J Periodontol 2000;71:1236-40
[38]. Avani R. Pradeep, Manojkumar S. Thorat, Clinical Effect of Subgingivally Delivered Simvastatin in the Treatment of Patients With Chronic Periodontitis: A Randomized Clinical Trial, J Periodontol 2010;81:214-222
[39]. Morris MS, Lee Y, Lavin MT, et al. Injectable simvastatin in periodontal defects and alveolar ridges: Pilot studies. J Periodontol 2008; 79:1465-1473.
[40]. Shah N. Local delivery of antimicrobial agents in periodontal therapy. J Indian Soc Periodontol 1999; 2:26-29.
[41]. Agarwal E, Pradeep AR, Bajaj P, Naik SB. Efficacy of local drug delivery of 0.5 % clarithromycin gel as an adjunct to nonsurgical periodontal therapy in the treatment of chronic periodontitis subjects among smokers – A randomized controlled clinical trial. DOI: 10.1902/jop.2012.110600.
[42]. Kukreja BJ, Dodwad V. Herbal Mouthwashes – A Gift Of Nature: Int J Pharm Bio Sci 2012; 3: 46-52.
[43]. Bansal S, Rastogi S, Bajpai M. Mechanical, Chemical and Herbal Aspects of Periodontitis: A Review. Int J Pharm Sci Res 2012; 3(5): 1260-1267.
[44]. P.Dwarakanadha Reddy, T.Satyanarayana.D, SwarnaLatha, M.Purushothaman Local Drug Delivery of Herbs for Treatment of Periodontitis. JITPS 2010, Vol.1 (5), 144-151.
[45]. Prajapati J, Patel H, Agrawal YK. Targeted drug delivery for central nervous system: a review. Int J Pharm Pharm Sci 2012; 4(3): 32-38.
[46]. Cooke JW, Sarment DP, Whitesman LA, Miller SE, Jin Q, Lynch SE, Giannobile WV. Effect of rhPDGF-BB delivery on mediators of periodontal wound repair. Tissue Eng. 2006 Jun; 12(6):1441-50.
[47]. Pinheiro ML, Feres-Filho EJ, Graves DT, Takiya CM, Elsas MI, Elsas PP, Luz RA. Quantification and localization of platelet-derived growth factor in gingiva of periodontitis patients. J. Periodontol 2003; 74: 323.
[48]. Nakahara T, Nakamura T, Kobayashi E, Inoue M, Shigeno K et.al. Novel Approach to Regeneration of Periodontal Tissues Based on in Situ Tissue Engineering: Effects of Controlled Release of Basic Fibroblast Growth Factor from a Sandwich Membrane. Tissue Engineering 2003, 9(1): 153-162.