STM JOURNALS

Research & Reviews: A Journal of Pharmaceutical Science
ISSN: 2229-7006 (Online)
Volume 9, Issue 1
www.stmjournals.com

Advanced Local Drug Delivery Approaches for Periodontitis: A Strategic Intervention

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Abstract

Periodontal disease, one of the most prevalent oral diseases is caused by the gram negative bacterial infection of periodontal pocket identified by inflammation of subgingival plaque and degeneration of alveolar bones, teeth, dental cementum and periodontal ligaments. 80% of American adult and more than 50% of Indian community suffers from this chronic inflammatory disease depicting the severity of the disease. The objectives of the available therapies are to minimize the bacterial infection and to regenerate the damage done by infection and inflammation. The therapies involve systemic therapy, conventional therapy, as well as local therapy. Conventional therapy is further divided into two subtypes: surgical therapy and non-surgical therapy. Surgical therapy involves scale up and root planning but it leaves microorganisms behind due to the use of metallic instruments. Non-surgical therapy and systemic therapy involves the use of antibiotics but both the therapies fail as a result of the insufficient drug concentration attained at the target site. Local therapy which involves the use of novel dosage forms like gels, films, strips, fibers, nanoparticles and microparticles maintains the drug concentration at a level greater than the Minimum Inhibitory Concentration (MIC) in the gingival crevicular fluid for a prolonged period of time (10–12 days). This ultimately reduces the dosing frequency, thereby increasing patient compliance.

Keywords: *Inflammation, infection, therapy, plaque, drug*

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INTRODUCTION

Periodontal disease, an infection of periodontal pocket is caused by gram negative bacteria and is identified by symptoms like subgingival plaque, inflammation and degeneration of alveolar bones, teeth, dental cementum and periodontal ligaments [1, 2]. Gingivitis at an early stage is identified by gingival swelling of gums, bleeding, bad breath and at severe stage, it shows symptoms like degeneration and inflammation of gums, alveolar bone, and dental cementum which is commonly known as periodontitis. At the severe phase of disease, there occurs degeneration of supporting collagen and periodontal ligament and resorption of alveolar bone and gingival epithelium that finally leads to the formation of periodontal pocket.

The source of periodontal diseases are usually gram negative, facultative anaerobic bacterial species like *B. intermedius* and *B. gingivalis*; fusiform organisms: *Actinobacillus*, *actinomycetemcomitans*, *Wolinella recta* and *Eikenella spp*.; and various bacilli and cocci; spirochetes; amoebas and trichomonas.

The condition even gets worsened to a greater degree when the bacterial species releases their harmful byproducts, mainly enzymes leucotoxins, collagenases, fibrinolysins and other proteases and chemicals that cause an immune reaction by activating the immune system into the periodontal pocket. All these events occur simultaneously and eventually it leads to the loss of teeth [2].

Periodontal diseases are one of the most widespread oral diseases, where 80% of American adults and more than 50% of Indian community suffers from this chronic inflammatory disease which demonstrates the severity of the disease [3].

TREATMENT STRATEGIES

Ideal treatment strategies should focus mainly on the following:

1. It should give more or equivalent drug concentration than MIC in periodontal pocket to destroy bacterial culture.
2. It should reach deep enough in the periodontal pocket to treat periodontal disease.
3. It should give prominent effect at normal dose.
4. It should give sustained effect with constant release rate to maintain MIC.

Due to the pathological conditions existing at the periodontal pocket, it serves as a cultivating space for bacterial species. Therefore, the target of any proposed therapy should be to regenerate the damage caused by bacterial infection and to maintain the normal condition.

Conventional Drug Delivery

The objective of conventional therapy is to reduce the bacterial flora, reduce inflammation and to stop bone resorption. Conventional drug therapy is further split into:

1. Surgical therapy, and
2. Non-surgical therapy.

1. Surgical therapy involves mechanical scaling, root planning and curettage. Surgical therapy aims at the removal of plaque and cleansing of the area damaged by periodontal infection that would result in non-favorable conditions for the growth of bacteria. In spite of the merits, such therapies can be painful and can have bacteria left at the site due to the instruments used in the therapy.
2. Non-surgical therapy involves antimicrobial/chemotherapeutic drug treatment that directly attacks the microbes giving a more pronounced effect but such therapies are unable to assess the much deeper regions of periodontal pocket [1].

Systemic Therapy [4, 5]

Systemic therapy involves antimicrobial agents like minocycline, azithromycin, moxifloxacin, doxycycline, clindamycin, metronidazole or their combinations. Such agents, when given systemically, reach the gingival area as it has good blood supply, providing effect at the periodontal pocket.

Demerits involve:

1. Low benefit/risk ratio,
2. Requirement of large dose,
3. Inability to give sustained drug release,
4. Frequent dosing,
5. Frequent chances of bacterial resistance, and
6. Inability to assess deeper areas of periodontal pocket.

Local Drug Delivery System [6, 7]

Local drug delivery involves different mechanisms and approaches to release drug in the periodontal pocket. Such systems release the drug directly into the periodontal pocket and are able to give sustained release up to 11 days. Benefits of local drug delivery into periodontal pocket are as follows:

- Directly reaches the target site.
- Improvement of patient compliance.
- Avoidance of GIT-related issues due to oral drug delivery.
- Avoidance of first pass metabolism.
- Enhanced therapeutic efficacy of the drug.
- Reduced treatment cost.
- Suitable for those patients having presystemic metabolism.
- Safer and convenient route of drug administration.
- Enhanced duration of action.
- Simple, painless and non-invasive therapy.
- Drug concentration maintained at the target site.
- Reduced side effects.
- Reduction of dosing frequency.

Limitations of local drug delivery into periodontal pocket are as follows:

- Local irritants cannot be administered.
- Dose is limited because of relatively small area.
- Presystemic metabolism occurs for drugs that degrade through peptidase and esterase.
- Administration of peptides not feasible due to the degradation by the enzyme peptidase.
- This route understood the needs for high-potency drugs.
- Manufacturing cost of the patches and devices.

Classification of Local Drug Delivery [1]

1. Based on Type of Therapy:
   - Personally applied (patient home care):
   a. Non Sustained (Oral irrigation), and
   b. Sustained (not developed till now).
   - Professionally applied (in dental office):
   a. Non Sustained (Supra and subgingival irrigation), and
   b. Sustained (Controlled release device).
2. Based on Degradability of the Device:
   - Biodegradable, and
   - Non- Biodegradable.
3. Based on Duration of Action:
   - *Sustained Released Devices*: These are the delivery systems whose actions last for less than 24 h; thereby require multiple applications. It follows the first order kinetics.
   - *Controlled Delivery Devices:* These are the delivery systems whose actions last longer than 24 h; thereby reducing the number of applications. It follows zero order kinetics.

VARIOUS APPROACHES FOR THE TREATMENT OF PERIODONTITIS

Gels [6]

Gels are semisolid dosage forms used to target antibiotics. Gels can be easily prepared, have good biocompatibility, mucoadhesiveness and patient compliance. It is widely used dosage form for local drug delivery. Gel can also be eliminated easily, so there are least chances of sensitivity reaction or irritation to the patient. Different compositions of gels containing tetracycline (2.5%), metronidazole (25%), metronidazole benzoate (40%), combination of tetracycline (2.5%) and metronidazolebenzoate (40%) made with HPMC (hydroxyl propyl methyl cellulose) had demonstrated positive clinical result but were unable to show sustained release [8–10].

Merits

- Provides controlled drug delivery,
- Enhanced bioadhesive property,
- Greater biocompatibility,
- Elimination of immune reaction, and
- Prolonged release at the target site.

Demerits

- Reduced retention, and
- Rapid drug release.

Figure 1 shows the insertion of gel.

Fig. 1: *Insertion of Gel.*

Fibers

Fibers are thread like, reservoir type of drug delivery devices, placed into the periodontal pocket using an applicator and sealed by means of a cyanoacrylate adhesive. Fibers made up of polymers like ethyl cellulose or polyethylene can give sustained release for up to 7 days. Patients have experienced discomfort and gingival redness to various degrees but such redness can be reduced by removing the fiber after 7–10 days [2]. Hollow fibers of cellulose acetate with tetracycline HCl kept in periodontal pocket resulted in the prominent reduction of microorganisms in comparison to scaling and root planning whereas it was observed that fibers have released their 95% of drug content within 2 h [11, 12]. A number of polymers such as poly(e-caprolactone) (PCL), polyurethane, polypropylene, cellulose acetate propionate, ethyl vinyl acetate (EVA) have been tested for controlling drug release. Among the tested polymers, EVA controlled the drug release exceptionally well. Monolithic EVA fibers were also found to control the rate of the drug release and similar results were observed *in-vivo* and *in-vitro* [13–15]. EVA fibers containing 25% tetracycline hydrochloride maintained constant drug concentration in the GCF above 600 mg/ml for 10 days, representing zero-order release characteristics of fibers [8].

Merits

- Sufficient drug concentration,
- sustained release,
- Reduced dosing frequency, and
- Reduced frequency of bacterial resistance.

Demerits

- Reduced patient compliance,
- Reduced retention of the system, and
- Reduced penetration of system.

Figure 2 sows the insertion of fiber into the periodontal pocket.

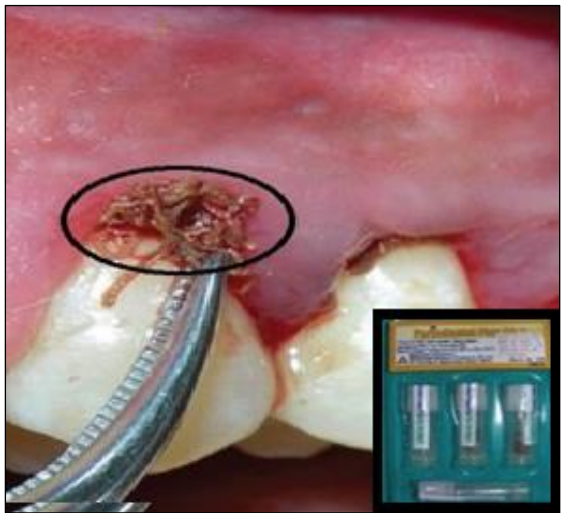

Fig. 2: *Insertion of Fiber into the Periodontal Pocket.*

Films

Films are prepared either by solvent casting method or direct milling method. Films are applied to the cavity, gingival surface, cheek mucosa or can be modified to a specific size for application in the pocket by cutting. Films are basically matrix systems in which the drug is dispersed into the matrix and gets released by diffusion or matrix erosion or dissolution. Dimensions of the film can be designed according to the pocket size. Patient feels uneasy when the size of the film is more than 400 µm. Films which release drug by diffusion have good adherence property [2]. Non-biodegradable ethyl cellulose film of chlorhexidine diacetate [16], metronidazole [17], tetracycline [18] and minocycline [19] using chloroform insolvent evaporation method have been prepared and tested clinically. These films established sustained release but rate of drug release was dependent on drug loading and the type of solvent used. For instance, chloroform comparison to ethanol as a solvent reduced the drug release rate to a greater extent [20], whereas the use of polyethylene glycol increases the drug release rate [17]. But clinical results state that using the ethyl cellulose films increases the chances of bleeding as compared to conventional therapy. There is no requirement of removing the biodegradable films after application that adds to the benefits of the film [2].

Advancements in polymer studies suggest that biopolymers like atelocollagen, (preparation of pepsin digested insoluble bovine skin collagen) can be used as a promising carrier for the transport of antibiotics. Tetracycline when incorporated with glutaraldehyde cross linked atelocollagen showed prominent level of tetracycline in GCF (gingival cervical fluid).

Gelatin obtained from fish was crosslinked to sustain the release of chlorhexidine diacetate or chlorhexidine HCl which showed 4 to 80 h of release, dependent on the type of the polymer and on the degree of cross-linking [21, 22].

Figure 3 shows the insertion of film and chip into the periodontal pocket.

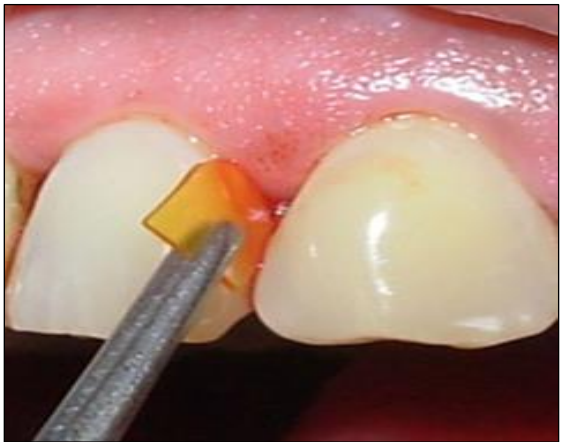

Fig. 3: *Insertion of Film and Chip into the Periodontal Pocket.*

Strips

Strips are thin elongated matrix system containing drugs that are distributed uniformly in the polymer. It is mainly made up of elastic polymers possessing a wide range of interproximal space [23, 24]. Metronidazole strips were found to be effective in the treatment of the subgingival flora [23]. Acrylic strips when in contact with the serum, effectively eradicate the microbials from the pocket but such strips were found to alter its

physical properties when in contact with the serum which limits the use of such strips. There are even chances of disruption of such material during its preparation which may cause the risk of leaving behind the traces into the periodontal pocket and thereby provoking the inflammatory response [25]. In order to overcome the above said complications, bioabsorbable strips were prepared that are biocompatible and biodegradable in nature incorporating the moieties like tetracycline, chlorhexidine and doxycycline [26, 27]. Other natural and synthetic polymers include PCL, ethyl cellulose, polyhydroxybutyric acid, hydroxypropyl cellulose, polymethylmethacrylate, poly (D, L-lactide/glycolide) and Hydroxypropyl methylcellulose [6]. Green catechin containing hydroxy cellulose strips when administered in the pockets of the patients once a week continued to give release for 8 weeks; showed a decrease in the pocket depth and were effective against *P. gingivalis* and *Prevotella spp*. with an MIC of 1.0 mg/ml [28].

Microparticles

Microparticles are free flowing, solid spherical polymeric structures of particle size ranging between 1 and 1000 µm. The drug is homogenously dispersed in the polymeric matrix for controlled and sustained release at the target site. They show good retention property in the pocket and thereby maintain the therapeutic level of drug in the pocket and improve efficacy of the treatment [29]. It also provides sustained release and enhanced bioavailability and thereby provides improved patient compliance by reducing the frequency of administration [30]; e.g. Chitosan containing metronidazole loaded microparticles provides sustained drug release [31], chitosan microspheres containing minocycline hydrochloride reduces periodontal depths and causes a significant reduction in bleeding on probing at 6 months [32]. Doxycycline microspheres prepared in PLGA and PCL provide controlled release *in vitro* as well as *in vivo*. It provides burst effect initially and followed by controlled release up to 11 days with good clinical results such as probing pocket depth. Plaque index [33]. Naproxen and succinyl sulphathiazolein poly phosphazenes microspheres provide satisfactory therapeutic levels in periodontal pocket for eradication of periodontal microbes [34]. Combination of PLGA and Zein containing tetracycline forms monolithic biodegradable microparticulate system in which there occurs hydrodrophobic interaction between Zein and drug that was confirmed by C(NMR) and X-ray diffraction studies [35]. Microparticulate system can be prepared from non-biodegradable and degradable polymers. Biodegradable polymers are generally preferred as they are biodegradable and biocompatible in nature [36]. The chlorhexidine loaded PLGA microspheres modulates the release profile and encapsulation due to complexation. It shows good release profile for at least 2 week period and suitable for targeting antimicrobial agents [37].

Figure 4 shows the insertion of microparticles into the periodontal pocket.

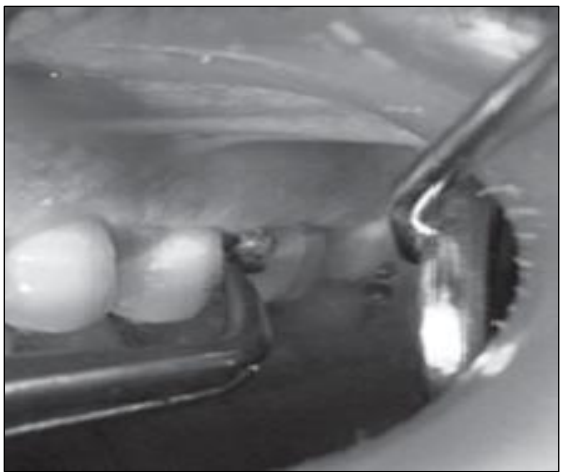

Fig. 4: *Insertion of Microparticles into the Periodontal Pocket.*

Nanoparticulate System

Nanoparticulates are the dispersed solid particles of size range about 10–1000 nm. The drug is either dissolved, entrapped, encapsulated or attached to a nanoparticle matrix [30]. Nanoparticles provide control release rate, enhanced stability, sustained release of drug, reduced frequency of administration and can access to unreachable sites like the periodontal pocket regions [37]. Calcium sulphate bone cement beads incorporating tetracycline nanoparticles by ionic gelation method were developed [36].

The NPs were prepared using Poly (D,L-lactide-co-glycolide) (PLGA), poly(D,L-lactide) (PLA) and cellulose acetate phthalate (CAP) by emulsification-diffusion process. A preliminary *in-vivo* study with induced periodontitis in dogs demonstrated that tetracycline loaded NPs penetrate through the junctional epithelium [38]. *Harungana madagascariensis* leaf extract (HLE) loaded in PLGA NPs showed optimized antibacterial activity [39, 40].

CONCLUSION

Periodontal disease is not easy to treat by one or many therapies, because every therapy comes with certain advantages and certain drawbacks. For improvement of patient treatment, it is advisable to use combination of therapies like using gels in periodontal pocket and scale up and root planning. It is necessary to choose patient relevant therapy according to the growth of disease and condition of patient. Local drug delivery has shown most promising results with high level of patient compliance. Care should be taken that proper therapy is being chosen with proper combination and use of drugs. Antibiotics like chlorhexidine HCl, tetracycline, minocycline, moxifloxacin, ofloxacin and doxycycline are used in combination. Newer approach for the future therapies should aim at regenerating the damage done to teeth, alveolar bone and cavity as well as periodontal pocket. The difficulty is in achieving adequate drug concentration greater than the MIC at the periodontal pocket without creating drug resistance.

REFERENCES

1. Sapra P, *et al*. Review: Recent Advances in Periodontal Formulations. *Int J Pharm Chem Anal*. 2014; 1(1): 65–74p.
2. Jain N, *et al.* Recent Approaches for the Treatment of Periodontitis. *Drug Discov Today*. 2008; 13(2): 932–943p.
3. Nair S, *et al.* Intraperiodontal Pocket: An Ideal Route for Local Antimicrobial Drug Delivery. *J Adv Pharm Tech Res.* 2012; 3(1): 9–15p.
4. Slots J. Systemic Antibiotics in Periodontics. *J Periodontol.* 2004; 75(11): 1553–65p.
5. Slots J, van Winkelhoff AJ. Antimicrobial Therapy in Periodontics. *J Calif Dent Assoc*. 1993; 21(11): 51–6p.
6. Joshi D, *et al*. Advanced Drug Delivery Approaches against Periodontitis. *Drug Deliv.* 2014; 1–15p.
7. Aslani Abolfazl, Malekpour Negar. Design, Formulation and Evaluation of Periodontal Propolis Mucoadhesive Gel. *Dent Res J*. 2016; 13(6): 484–493p.
8. Hayashi K, *et al.* Clinical and Microbiological Effects of Controlled Release Local Delivery of Minocycline on Periodontitis in Dogs. *Am J Vet Res.* 1998; 59: 464–467p.
9. Graca MA, *et al.* A Randomized Controlled Trial of a 2% Minocycline Gel as an Adjunct to Non-Surgical Periodontal Treatment, Using a Design with Multiple Matching Criteria. *J Clin Periodontol*. 1997; 24: 249–253p.
10. Addy M, Langeroudi M. Comparison of the Immediate Effects on the Subgingival Microflora of Acrylic Strips Containing 40% Chlorhexidine, Metronidazole or Tetracycline. *J Clin Periodontol*. 1984; 11: 379–386p.
11. Lindhe J, *et al.* Local Tetracycline Delivery Using Hollow Fibre Devices in Periodontal Therapy. *J Clin Periodontol.* 1979; 6: 141–149p.
12. Goodson JM, *et al.* Periodontal Disease Treatment by Local Drug Delivery. *J Periodontol*. 1985; 56: 265–272p.
13. Goodson JM, *et al.* Multicenter Evaluation of Tetracycline Fibre Therapy. I. Experimental Design, Methods, and Baseline Data. *J Periodontol Res.* 1991; 26: 371–379p.
14. Newman MG, *et al.* A 6-Month Multicenter Evaluation of Adjunctive Tetracycline Fibre Therapy Used in Conjunction with Scaling and Root Planning in Maintenance Patients: Clinical Results. *J Periodontol.* 1994; 65: 685–691p.
15. Tonetti M, *et al.* Zero-Order Delivery with Periodontal Placement of Tetracycline-Loaded Ethylene Vinyl Acetate Fibres. *J Periodontol Res*. 1990; 25: 243–249p.
16. Friedman M, Golomb G. New Sustained Release Dosage Form of Chlorhexidine for Dental Use. *J Periodontol Res.* 17: 323-328p.

17. Golomb G, *et al.* Sustained Release Device Containing Metronidazole for Periodontal Use. *J Dent Res.* 1984; 63(9): 1149–1153p.
18. Azoury R, *et al*. Nuclear Magnetic Resonance Study of an Ethyl Cellulose Sustained-Release Delivery System II. Release Rate Behaviour of Tetracycline. *J. Pharm Sci*. 1988; 77: 428–431p.
19. Elkayama R, *et al.* Sustained Release Device Containing Minocycline for Local Treatment of Periodontal Disease. *J Control Release.* 1988; 7(3): 231–236p.
20. Minabe M, *et al.* Application of a Local Drug Delivery System to Periodontal Therapy. I. Development of Collagen Preparations with Immobilized Tetracycline. *J Periodontol.* 1989; 60(2): 113–117p.
21. Steinberg D, *et al.* A New Degradable Controlled Release Device for Treatment of Periodontal Disease: *in vitro* Release Study. *J Periodontol.* 1990; 61(7): 393–398p.
22. Goffin G. Efficacy of Sustained Local Delivery of Chlorhexidine Periochip as an Adjuvant to Scaling and Root Planning in the Treatment of Chronic Periodontal Disease. *Int Dent Rev.* 1998; 18: 1–18p.
23. Addy M, *et al.* Use of Antimicrobial Containing Acrylic Strips in the Treatment of Chronic Periodontitis Disease. A Three-Month Follow-Up Study. *J Periodontol.* 1998; 59: 557–564p.
24. Larsen T, *et al. In vitro* Release of Doxycycline from Bioabsorbable Materials and Acrylic Strips. *J Periodontol.* 1990; 61: 30–34p.
25. Noguchi T, *et al.* New Method for Local Drug Delivery Using Resorbable Base Material in Periodontal Therapy. *Bull Tokyo Med Dent Univ.* 1984; 31: 145–153p.
26. Taner IL, *et al.* Comparison of the Antibacterial Effects on Subgingival Microflora of Two Different Resorbabale Base Materials Containing Doxycycline. *J Nihon Univ Sch Dent*. 1994; 36: 183–190p.
27. Hirasawa M, *et al.* Improvement of Periodontal Status by Green Tea Catechin Using a Local Delivery System: A Clinical Pilot Study. *J Periodontol Res.* 2002; 37: 433–438p.
28. Jayaprakash S, *et al.* Preparation and Evaluation of Biodegradable Microspheres of Methotrexate. *Asian J Pharm.* 2009; 3: 26–29p.
29. Pichayakorn W, Boonme P. Evaluation of Cross-Linked Chitosan Microparticles Containing Metronidazole for Periodontits Treatment. *Mater Sci Eng C*. 2013; 33: 1197–1202p.
30. Yue Isaac C, *et al.* A Novel Polymeric Chlorhexidine Delivery Device for the Treatment of Periodontal Disease. *Biomaterials*. 2004; 25(17): 3743–3750p.
31. Zingale J, *et al.* The Effectiveness of Scaling and Root Planning with Adjunctive Time-Release Minocycline Using an Open and Closed Approach for the Treatment of Periodontitis. *Gen Dent.* 2011; 60: 300–305p.
32. Mundargi SS, *et al.* Development and Evaluation of Novel Biodegradable Microspheres Based on Poly(D,Llactide-co-Glycolide) and Poly(Epsilon-Caprolactone) for Controlled Delivery of Doxycycline in the Treatment of Human Periodontal Pocket: *in vitro* and *in vivo* Studies. *J Control Release.* 2007; 119: 59–68p.
33. Wang W, *et al.* Microencapsulation Using Natural Polysaccharides for Drug Delivery and Cell Implantation. *J Mat Chem.* 2006; 16: 3252–3267p.
34. Garg T, *et al.* Scaffold: A Novel Carrier for Cell and Drug Delivery. *Crit Rev Ther Drug Carrier Syst.* 2012b; 29: 1–63p.
35. Garg T, *et al*. Stimuli-Sensitive Hydrogels: An Excellent Carrier for Drug and Cell Delivery. *Crit Rev Ther Drug Carrier Syst*. 2013; 30: 369–409p.
36. Sindhura Reddy N, *et al.* Tetracycline Nanoparticles Loaded Calcium Sulfate Composite Beads for Periodontal Management. *Biochim Biophys Acta (BBA) Gen Subj*. 2014; 1840(6): 2080–2090p.
37. Kong LX, *et al.* Nanotechnology and its Role in the Management of Periodontal Diseases. *Periodontol.* 2006; 40: 184–196p.
38. Piñón SE, *et al*. Preparation and Characterization of Triclosan

Nanoparticles for Periodontal Treatment. *Int J Pharm*. 2005; 294: 217–232p.
39. Moulari, *et al.* Potentiation of the Bactericidal Activity of Harunganamadagascariensis Lam. ex Poir. (Hypericaceae) Leaf Extract against Oral Bacteria Using Poly (D, Llactide-co-Glycolide) Nanoparticles: *in vitro* Study. *Acta Odontol Scand.* 2006; 64: 152–158p.
40. Goodson JM, *et al.* Multicenter Evaluation of Tetracycline Fibre Therapy. I. Experimental Design, Methods, and Baseline Data. *J Periodontol Res.* 1991; 26: 361–370p.

Cite this Article
Shivani Patel, Jaimini Gandhi, Harita Naik *et al.* Advanced Local Drug Delivery Approaches for Periodontitis: A Strategic Intervention. *Research & Reviews: A Journal of Pharmaceutical Science*. 2018; 9(1): 4–11p.