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Review Communication

REVIEW: RECENT ADVANCES IN PERIODONTAL FORMULATIONS

Mr. Prakash Sapra[1], Dr. Biraju D Patel[2], *Dr. Dhaval V Patel[3], Dr. Chetan H Borkhataria[4]

[1,3,4]B K Mody Government Pharmacy College, Rajkot, Gujarat, India.
[2]Smt. R B Patel Mahila Pharmacy College, Atkot, Gujarat, India.

***Corresponding Author:**
Dr. Dhaval V Patel, B K Mody Government Pharmacy College, Rajkot, Gujarat, India.
E-mail: drpatelrajkot@gmail.com

Abstract: *Periodontitis is an inflammatory disease of the supporting tissues of the teeth caused by infection of a periodontal pocket arising from the accumulation of subgingival plaque. Periodontal disease has been considered as a possible risk factor for other systemic diseases such as cardiovascular diseases and pre-term low birth weight infants. Aggressive forms of periodontitis can be localized or generalized. Local delivery of antimicrobial agents using controlled release systems should be considered as adjunctive to mechanical debridement for the treatment of localized forms of periodontal destruction. Systemic administration of drugs leads to therapeutic concentrations at the site of infection, but for short periods of time, forcing repeated dosing for longer periods. Local delivery of antimicrobials has been investigated for the possibility of overcoming the limitations of conventional therapy. The use of sustained release formulations to deliver anti-bacterial to the site of infection (periodontal pocket) has recently gained interest. These products provide a long-term, effective treatment at the site of infection at much smaller doses. This article reviews various types of delivery systems evaluated in practical periodontal therapy and identifies areas where further research may lead to a clinically effective intra-pocket delivery system.*

Key word: *periodontal diseases, periodontal pockets, local drug delivery system, controlled drug delivery.*

Introduction

Periodontal disease is a localized inflammatory response caused by the infection of a periodontal pocket arising from the accumulation of sub-gingival plaque. Periodontal disease has been considered as a possible risk factor for other systemic diseases such as cardiovascular diseases and pre-term low birth weight infants. Periodontal diseases are groups of infections and inflammatory conditions, including gingivitis and periodontitis that affect teeth supporting structures. These diseases occur when bacteria from dental plaque invade surrounding tissues and from the accumulation of plaque at the gingival margin, which, in turn, induces an inflammatory response. The result is the formation of pockets between gingiva and tooth that causes gingival margin retraction and the development of an ideal environment for anaerobic bacteria growth responsible for the disease. The progression of this destructive process can cause tooth loss(Luana P et al., 2004). Therapeutic approaches for periodontitis fall into two major categories: 1) anti-infective treatment, which is designed to halt the progression of periodontal attachment loss by removing etiologic factors; and 2) regenerative therapy, which includes anti-infective treatment and is intended to restore structures destroyed by disease. Recently a new approach using local delivery systems containing antimicrobial has been introduced. This produces more constant and prolonged concentration profiles. Both topical delivery system and controlled release system have been termed as local delivery. The term local delivery and site-specific delivery are sometimes used synonymously(A Bhardwaj et al., 2012).

Treatment approach for periodontal disease

Conventional periodontal therapy

The main purpose of periodontal therapy is to cure the inflamed tissue, reduce the number of pathogenic bacteria and eliminate the depth of the diseased pockets and to stop bone resorption. The conventional methods of pocket elimination are more or less mechanical and are

aimed at removal of supra and mechanical plaque and degenerated and necrotic tissue lining the gingival wall of periodontal pockets through scaling, root planning and curettage. The mechanical debridement alone often leaves behind significant number of pathogens due to possible instrumentation or ability of microorganism to penetrate into deeper tissues. Inaccessibility and recolonization of pathogens can occur after scaling and root planning. With oral hygiene, a pathogenic sub-gingival microbial may reestablish within 42-60 days after a single periodontal debridement session(Aviral K et al., 2012).

Local drug delivery

Goodson et al in 1979 first proposed the concept of controlled delivery in the treatment of periodontitis. The effectiveness of this form of therapy is that, it reaches the base of periodontal pocket and is maintained for an adequate time for the antimicrobial effect to occur. Periodontal pocket provides a natural reservoir bathed by gingival cervicular fluid that is easily accessible for the insertion of a delivery device. These delivery systems are also called sustained release, controlled - release, prolonged release, timed release, slow release, sustained action, prolonged action or extended action(Aviral K et al., 2012).

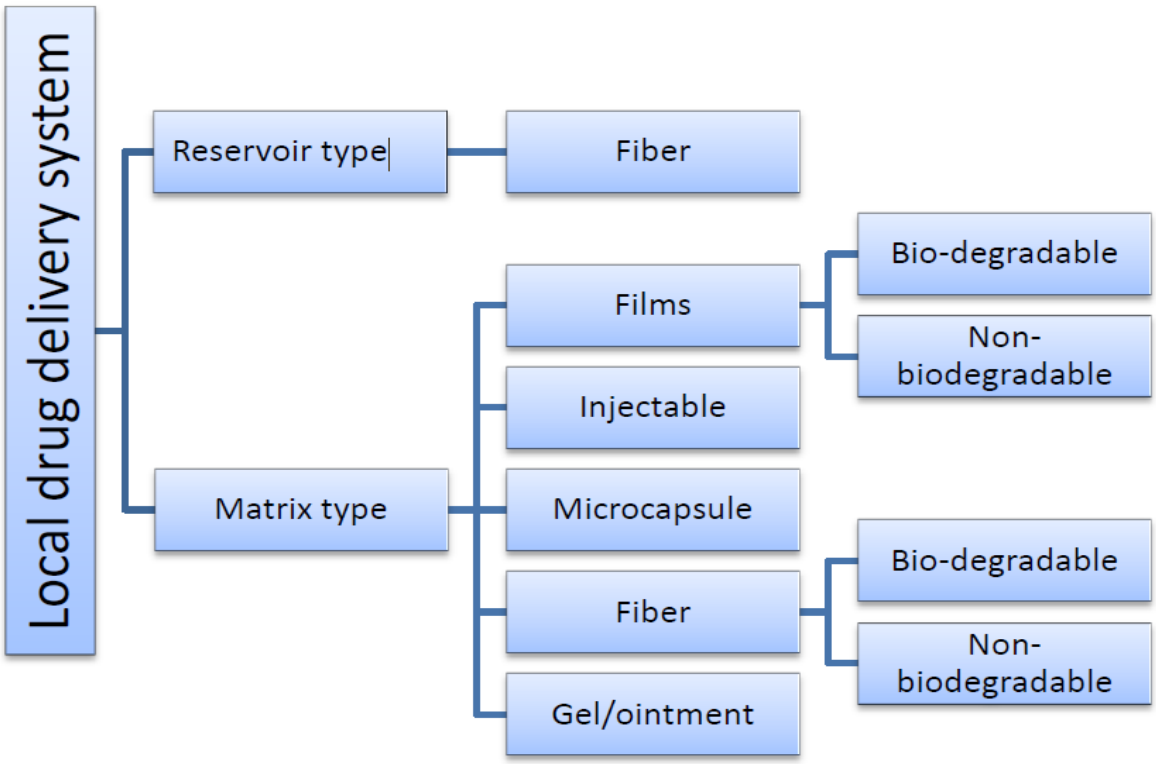

Figure 1: Local sustained delivery systems (LSDS) for the treatment of periodontal pocket diseases.

Classification of local drug delivery

A. Based on type of therapy

- Personally applied (patient home care).
  - → Non Sustained (Oral irrigation)
  - → Sustained (not developed till now)
- Professionally applied (in dental office).
  - → Non Sustained (Supra and subgingival irrigation)
  - → Sustained (Controlled release device)

B. Based on degradability of the device

- Biodegradable

- Non- Biodegradable

C. Based on duration of action

- Sustained released devices - These are delivery systems whose action lasts less than 24 hours therefore require multiple applications. It follows the first order kinetics.
- Controlled delivery devices - These are the devices which follows zero order kinetics and whose actions last longer than 24 hours, thereby decreasing the number applications(Aviral K et al., 2012).

Various drug delivery systems for treating periodontitis are Fibers, Film, Injectable systems, Gels, Strips and compacts, Vesicular systems, Micro-particle system, Nanoparticle system etc.

Fibers:

Fibers, or thread-like devices, are reservoir-type systems, placed circumferentially into the pockets with an applicator and secured with cyanoacrylate adhesive for the sustained release of trapped drug into the periodontal pocket. Several polymers such as poly (e-caprolactone) (PCL), polyurethane, polypropylene, cellulose acetate propionate and ethyl vinyl acetate (EVA) have been investigated as matrices for the delivery of drug to the periodontal pocket. Examples are Chlorhexidine fibers and tetracycline fibers. The release of the tetracyclinefrom the cellulose acetate fibers as occurred by diffusion mechanismis rapid with approximately 95% of the drug released in the first two hours and therefore, a single application of these fibers does not provide an effective drug concentration for long periods(J M Goodson et al., 1985). Compared to tetracycline delivery from hollow fibers, fibers containing 20% (v/v) chlorhexidine, when placed into periodontal pockets, exhibited a prompt and marked reduction in signs and symptoms of periodontal disease(J Coventry and H N Newman, 1982).Tetracycline fiber treatment adjunctive to scaling and root planning (SRP) showed significantly less periodontal disease recurrence (4%) compared with SRP alone (9%), tetracycline fiber alone for 10 days (10%) and tetracycline fiber alone for 20 days (12%)(B S Michalowicz et al., 1995). This is one of the best options for delivery of drug to periodontal pockets, but they have some disadvantages such as difficulty in placing fiber in pockets, patient discomfort and at fiber removal various degree of gingival redness were observed(B N Vandekerckhove, 1997).

Strips:

Strips are thin and elongated matrix bands in which drugs are distributed throughout the polymer. Acrylic strips have been fabricated using a mixture of polymers, monomers and different concentrations of anti- microbial agents. Strips were fabricated either by solvent casting or pressure melt method. Strips containing tetracycline or metronidazole were found to be effective in producing changes in the sub gingival flora and improving the clinical parameters of periodontal disease(M Addy et al., 1988). Treatment with metronidazole-loaded fibers or SRP was also associated with a slower rate of relapse of clinical parameters. The change in physical properties of acrylic strips in the serum has been reported. These strips dissolved slightly in serum, softened and were difficult to remove, leading to the risk of leaving injurious acrylic material in the periodontal pocket, which may evoke an inflammatory reaction(T Larsen, 1990). Different types of synthetic biodegradable polymers such as polyhydroxybutyric acid (PHBA) and polylactide co-glycolic acid (PLGA) have been evaluated as a matrix for sustained delivery of tetracycline. PHBA strips containing 25% tetracycline showed sustained release over four to five days with a significant burst effect at day one (P B Deasy et al., 1989), whereas, PLGA strips containing 25% tetracycline (25 TTC–PLGA) released therapeutic concentrations of the drug for ten days(G I Maze et al., 1995).Several bioabsorbable dental materials like haemostatic gauze made of oxidized regenerated cellulose (Surgicel®), a collagen wound dressing (CollaCote®) and a fibrin sealant (Tissel®) have been investigated by Larsen et al. for their potential use as carrier materials for doxycycline. Surgicel® produced a relatively higher antibacterial activity compared to intermediate for Tissel® and lower for CollaCote®(T Larsen, 1990). In the field of herbal drug delivery, recently, green tea catechin showed a bactericidal effect against

Porphyromonasgingivalis and Prevotella sp. in vitro with an MIC of 1.0 mg/ml. The application of green tea catechin through an intra-pocket delivery system using slow release cellulose strips was effective in improving the periodontal status(M Hirasawa et al., 2002).

Films:

Films are most widely used intra pocket drug delivery device prepared either by solvent casting or direct milling. Bigger film either could be applied directly applied on cheek mucosa or gingival surface or can be cut into appropriate size so as to insert into site of infection. Films are matrix type of drug delivery device in which drug is distributed throughout matrix and drug release occurs by erosion, matrix dissolution or drug diffusion. This system has a several advantages than other intra pocket drug delivery devices(W A Soskolne, 1997).Film having thickness less than 400µm and sufficient adhesiveness will remain submerged into periodontal pocket without interfering with the patient's oral hygiene habit. Films that release drug by diffusion alone are prepared by using non-degradable water insoluble polymers, while those that release by diffusion and matrix erosion or dissolution are prepared by water soluble or biodegradable polymers(M Minabe et al., 1989, E M Augusta et al., 1989). Various non-biodegradable periodontal films of chlorhexidine diacetate, metronidazole, tetracycline and minocycline have been prepared using ethyl cellulose by solvent evaporation method. Ethyl cellulose films showed sustained drug release and release rate were dependent on the casting solvent and drug load. The use of chloroform as casting solvent significantly retarded the release rate of the drug compared to ethanol as a casting solvent. The incorporation of polyethylene glycol in the films however enhanced the release rate of the drug(S Pragati et al., 2009). More recently, a film under the trade name Periochip® prepared and commercialized and it composed of crossed linked hydrolysed gelatin and glycerine for local delivery of chlorhexidine digluconate(P A Heasman et al., 2001).*Higashi et al.* prepared films of water-soluble polymer EudragitS® and non-water-soluble polymer Eudragit L®for the delivery of clindamycin. An in vitro release study showed that insoluble films release drug by diffusion and soluble films release drug by dissolution of the carrier(K Higashi et al., 1991). *Kyun* and co-workers showed that by embedding minocycline in PCL it is feasible to obtain sustained release of the drug within the periodontal pocket for seven days and should be a useful tool for the elimination of pathogenic microflora from periodontal pocket or reducing inflammation in periodontal disease(K D Kyun et al., 1990).

Injectable gel:

Along with solid devices, semi-solid devices also attain a reasonable attention for localized delivery of anti-microbial agents(K Stoltze and Stellfeld., 1992). Release rate of the drug from gel is faster as compared to other formulations. These types of the formulations can be easily prepared and administered. Various hydrogels and oleogels for the delivery of metronidazole (25%), tetracycline (2.5%), and combination of tetracycline (2.5%) and metronidazole benzoate (40%) have been prepared, tested and satisfactory results were obtained. Gels composed of hydroxylpropylmethyl cellulose and hydroxyethyl cellulose and do not having sustained release properties. In-spite of their rapid drug release and poor retention time, they obtained positive clinical results for treatment of periodontitis. Mucoadhesion or bioadhesion is the prime requirement for delivery of drug to the site of infection(S Pattnaik et al., 2007). The chitosan gel (1%w/w) incorporated with or without 15% metronidazole was found to be effective in treatment of periodontitis(H Akncbay and Senel., 2007).Semi solid bioadhesive polymeric system can be utilized as vehicle for intra pocket drug delivery because it can easily pass through cannula into periodontal pocket where it easily solidified in-situ to deliver therapeutic agent for prolonged period. These types of systems exhibit pseudoplastic flow and thermoresponsive behavior, existing as a liquid at room temperature and gel at 34-37 ^{o}c. Tetracycline loaded semisolid bio-adhesive polymeric system based on hydroxyl ethycellulose and polyvinylpyrollidine and metronidazole loaded system based on carbopol 934p, hydroxyl ethylcellulose and polycarophil are reported(D SJones et al., 1996, D S Jones et al., 1997b).Another injectable biodegradable gel based on poly (DL- lactide) dissolved in biocompatible solvent N-methyl-2-pyrrolidone (Atrigel®) loaded with 10% doxycycline hyclate showed high level doxycline (250µg/ml) in the GCF for a

period of 7 days(A M Polson et al., 1997a). Biodegradable gels are other useful prospects for the delivery of therapeutic agents into periodontal pockets. *Maze et al.,* prepared lactic-glycolic acid gel loaded with 35% tetracycline and Based upon the reduction in probing depths and % of sites bleeding on probing at 8 days relative to pretreatment, and the absence of any serious adverse events, it is concluded that these bioerodible gels are safe, and since the bacteriostatic range for most putative periodontopathogens is in the 2-10 micrograms/ml range, the tetracycline levels observed at days 3 and 8 likely represent significant antimicrobial efficacy(G I Maze et al., 1996).

Microparticulate system:

Both biodegradable as well as non-biodegradable polymeric materials have been investigated for the preparation of microspheres.These materials include the polymers of natural origin, modified natural substances and synthetic substances. Microparticles based system of biodegradable poly alpha hydroxyl acids such as poly lactide (PLA) or poly (lactide-co-glycolide) PLGA microsphere containing tetracycline has been designed for periodontal therapy and study shows that microsphere could enhance tetracycline delivery to periodontal pocket by enhancing drug encapsulated efficiency, release quantity and sustained release period compared to uncoated ones(D Z Liu et al., 2004). Tetracycline containing microcapsule in pluronic F127 was reported to form gel at body temperature and hold the microsphere in the periodontal pocket for duration of treatment. The in-vitro drug release from such system depends upon the polymer (lactide:glycolide) ratio, molecular weight, crystallinity and pH of the medium. Recently, the controlled delivery of doxycycline for up to 11 days was achieved through novel biodegradable microspheres prepared by w/o/w double emulsion technique using the blends of PLGA and PCL in different ratios. The formulation was also effective in vivo and significant results were obtained with respect to microbiological and clinical parameters for up to three months(R C Mundargi et al., 2007b).

Nanoparticulate system:

Up to now only microparticle or polymer based hydrogel have been applied in dentistry, recently intensive research performed all over the world to improve the effectiveness of delivery system. Various advantages of nano-particulate system compared to microparticle, microsphere and emulsion based delivery system includes increased stability, controlled release rate, high dispersibility in an aqueous medium. Because of their small size nanoparticles penetrate deeper regions that may be inaccessible to other delivery system, such as periodontal pocket area below the gum line. These reduce the frequency of administration and further provide a uniform distribution of the active agents over an extended period of time(L X Kong et al., 2006).*Moulari et al* investigated antibacterial effect of Harunganamadagascariensis leaf extract (HLE) by using the poly (D,L-lactide-co glycolide) nanoparticles (PLG-NP) prepared by interfacial polymer deposition following the solvent diffusion method, and concluded that incorporation of the HLE into a colloidal carrier optimized its antibacterial performance(B Moulari et al., 2006).*Dung et al* prepared and evaluated antisense oligonucleotide loaded chitosan nanoparticles. Oligonucleotide formed complex with chitosan and then chitosan/oligomer-TPP nanoparticles prepared by adding TPP after the formation of chitosan/nucleotide complex and study shows that sustained release of oligonucleotide from chitosan nanoparticles may be suitable for the local therapeutic application in periodontal diseases(T H Dung et al., 2007).In an attempt to obtain a novel delivery system adequate for the treatment of periodontal disease, the nanoparticles 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 in dogs with induced periodontal defects suggested that TCS-loaded NPs penetrate through the junctional epithelium(S E Piñón et al., 2005).

Vesicular system:

Vyas et al have prepared and investigated in vitro antimicrobial activity of metronidazole bearing lectinized liposomes for intra-periodontal pocket delivery. These lectinized liposomes

were found to retain the ligand binding activity of surface coated concanavalin A (Con-A) as demonstrated by bovine submaxillary mucin (BSM) binding assay. The Con-A coating was found to be stable in simulated salivary fluids (SSF, pH 7.2) and under various pH conditions. In vitro targeting studies of lectinized liposomes with gram-negative bacilli (Streptococcus mutans) that harbor in the periodontal pocket (biofilm) demonstrated nearly 100% bacterial growth inhibition (% BGI). These observations suggest that liposomes coated with lectin (Con-A) were able to maintain the sugar affinity and specificity of the associated ligand and could be targeted to the surface 'glyco-calyx' of bacterial bio-film(S P Vyas et al., 2001).The delivery of triclosan and chlorhexidine was studied for several liposomal compositions involving cationic as well as anionic lipids (M N Jones et al., 1997). *Robinson et al* investigated specificity and affinity of immunoliposome targeting to oral bacteria to reduce dental plaque. The anti-oralisimmunoliposomes showed the greatest affinity for S. oralis and affinity was unaffected by net charge on the lipid bilayer or by the number of antibodies conjugated to the liposomal surface(A M Robinson et al., 1998).

Table 1:

List of commercial periodontal products presented in various dosage forms

Product	Antimicrobial agents	Dosage form	Manufacturer
Atrigel®	Doxycycline	gel	Atridox (atrix Lab)
Elyzol®	Metronidazole	gel	Dumexpharma
Periochip®	Chlorhexidine gluconate	Films	Adrian Pharmaceuticals, LLC
Periochip®	Chlorhexidine gluconate	Biodegradable device	DexcelPharmaInc, Jerusalem,
Dentomycine®	Minocycline	Biodegrable mix in syringe	Sunstar corp., Tokyo, Japan
Arestin®	Minocycline	microsphere	Oropharmacorp Warminster
Actisite®	Tetracycline	Non resorbable fiber	Alza Corp. Palo Alto, CA, USA
OnSite®	Antibiotics	fiber	Alza Corp. Palo Alto, CA, USA

Table 2:

Summary of some investigated intra-pocket delivery systems

System	Polymer matrix	Drug incorporated	References
Strip	Ethyl cellulose	Chlorhexidine	(M Friedman and G Golomb, 2006)
	Hydroxypropyl cellulose + methacrylic acid	Ofloxacin	(K Higashi et al., 1990)
	Polyhydroxybutyric acid	Tetracycline HCl	(P B Deasy et al., 1989)
	Polylactide-co-glycolic acid (PLGA)	Tetracycline HCl	(G I Maze et al., 1995)
		Chlorhexidine	(M Paolantonio et al., 2008)
	Hydroxypropyl cellulose	Chlorhexidine, tetracycline	(T Noguchi et al., 1984)
		Doxycycline	(I L Taner et al., 1994)
	Polyethylmetha acrylate (acrylic)	Tetracycline HCl	(M Addy and Langeroudi., 1984)
		Metronidazole	(M Addy et al., 1988)
Fibers	Poly(e-caprolactone) (PCL)	Tetracycline HCl	(M Tonetti et al., 1990)
	Cellulose acetate	Tetracycline HCl	(J M Goodson et al., 1979)

		Chlorhexidine	(J Coventry and Newman., 1982)
	Ethylene vinyl acetate	Tetracycline HCl	(M Tonetti et al., 1990)
Gels	PLGA	Tetracycline	(G I Maze et al., 1996)
	Chitosan	Metronidazole	(H Akncbay and Senel., 2007)
	Glycerol monooleate + sesame oil	Metronidazole	(U Noyan et al., 1997)
	Hydroxyethyl cellulose + polyvinylpyrrolidone	Tetracycline	(D S Jones et al., 1996)
	Poly(DL-lactide) + N-methyl 2-pyrrolidone	Saguinarium	(A M Polson et al., 1996)
		Doxycycline hyclate	(A M Polson et al., 1997b)
	Hydroxyethyl cellulose + polycarbophil	Metronidazole	(D S Jones et al., 1997a)
	Poloxamer 407 + Carbopol 934P	Propolis	(M L Bruschi et al., 2007)
Films	PCL	Minocycline	(K D Kyun et al., 1990)
	Ethyl cellulose	Metronidazole	(G Golomb et al., 1984)
		Minocycline	(R Elkayama et al., 1988)
	Eudragit L® and Eudragit S®	Clindamycin	(K Higashi et al., 1991)
	Cross-linked atelocollagen	Tetracycline HCl	(M Minabe et al., 1989)
	Gelatin (Byco® protein)	Chlorhexidine diacetate	(D Steinberg et al., 1990)
	PLGA	Tetracycline HCl	(R K Agarwal et al., 1993)
		Amoxycillin + metronidazole	(A Ahuja et al., 2006)
	Polyvinyl alcohol + carboxymethyl chitosan	Ornidazole	(L C Wang et al., 2007)
	Chitosan	Taurine	(N Ozmeriç et al., 2000)
	Chitosan + PCL	Metronidazole	(A H El-Kamel et al., 2007)
	Chitosan + PLGA	Iproflavone	(P Perugini et al., 2003)
Vesicular system	Immunoliposomes	Anti-oralis	(M N Jones et al., 1997)
	Phosphatidylinositol	Triclosan	(M N Jones and Kaszuba., 1994)
Nanoparticles	PLGA	Triclosan	(S E Piñón et al., 2005)
	PLGA	Harunganamadagascariensis leaf extract	(B Moulari et al., 2006)
	Cellulose acetate phthalate	Triclosan	(S E Piñón et al., 2005)
	Chitosan	Antisense oligonucleotide	(T H Dung et al., 2007)
Microparticles	PLGA + PCL	Doxycycline	(R C Mundargi et al., 2007a)
	Pluronic F 127	Tetracycline	(R W Baker and Park., 1988)
	PLGA	Tetracycline	(E Esposito et al., 1997)

Conclusion

From the review of advances in periodontal drug delivery system it can be said that biodegradable, mucoadhesive nanoparticle has an immense opportunity for designing of novel, controlled release, low dose, intra pocket drug delivery device. These devices are proving to be more effective, more convenient and easy to use than regular systemic administration of medicines. There is an inclination amongst dental practitioners to stop the empirical use of systemic antibiotics for the treatment of common dental afflictions. This development definitely paves the way for future patenting of novel, commercially feasible and physiologically acceptable intra-pocket-targeted drug delivery systems.

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