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LOCAL DRUG DELIVERY APPROACHES FOR THE TREATMENT OF PERIODONTITIS

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ABSTRACT

Periodontitis is a bacterial infectious disease that results in destruction of soft and hard tissues which finally causes tooth loss. Symptoms related to the periodontal disease are inflammation in the gingival cavities, abscess and alveolar bone loss.[1] According to the WHO, 10-15% world population suffers from severe periodontitis. Different local or systemic treatments were used for the cure of periodontitis. Now days, local drug delivery is more preferred than the systemic delivery as it results in promising therapeutic outcomes by focusing on factors like targeted site specific delivery, Low dose, Hepatic first pass metabolism, decrease in GI side effects and dosing frequency. Higher occurrence of periodontitis disease in adults, adolescent and older individual is a major public health concern. Major risk factors related to the periodontal disease are smoking, poor oral hygiene, medication, age, hereditary and stress. Several evidences displayed that the periodontal diseases is associated with the various systemic diseases such as cardiovascular disease, diabetes and adverse pregnancy outcomes. The risk of cardiovascular diseases increased by 19% with periodontal diseases, which is increased to 44% amongst the individuals ages over 65 years and the individuals with severe periodontal diseases with type 2 diabetes have 3.2 times greater mortality risk as compared to the individual with no or mild periodontal diseases. Systemic drug delivery in the periodontitis disease has certain limitation that is overcome by the local drug delivery system. It provides adequate concentration of drugs at the target site. Various approaches used for local drug delivery are Oral rinses, Sub-films, chips, Gels, Ointments and Micro particles.

KEYWORDS: Periodontitis, Local drug delivery, Gels, Nanoparticles, Microparticles.

INTRODUCTION

Periodontitis is inflammatory disease caused by local bacterial infection of the periodontal cavity. It is associated with the pathological conditions like Gingivitis (Inflammation of gums), deterioration of periodontal ligament and dental cementum that leads to alveolar bone loss.

The bacteria mainly responsible for the periodontal diseases are gram negative anaerobic bacteria such as bacteroides species: B. intermedius, B. gingivalis and fusiform organisms: Actinobacillus actinomycetemcomitans, Wolinella recta and Eikenella Spp.

Bacteria release enzymes and toxins that demolish the periodontium. Recent studies and evidences suggested that the immune response of host plays important role in the destruction of periodontal structures. The Pathogenesis of periodontitis involves a complex interaction of immune and inflammatory cascades initiated by bacteria of the oral biofilm from the lipopolysaccharides present in bacteria that stimulates the inflammatory mediators such as cytokines.

Initial stage of periodontitis is Gingivitis which may or may not progress into chronic condition like cavity formation, degeneration of alveolar bone.[2]

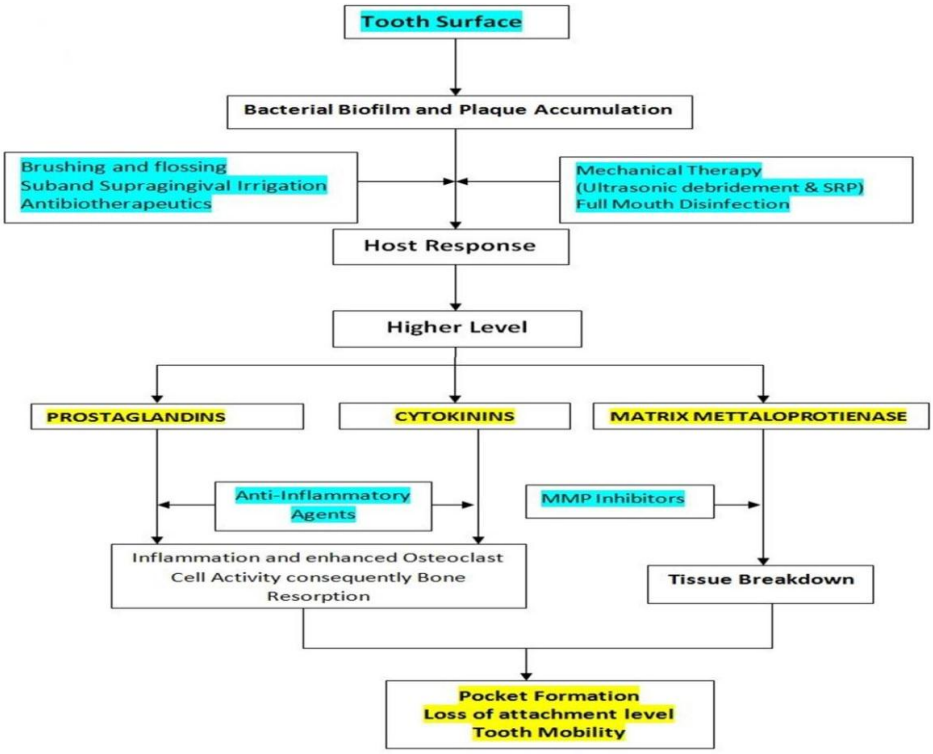

Figure 1: Schematic Diagram of Periodontitis Disease.

Cytokines stimulates fibroblasts and epithelial cells that causes release of Prostagladins (PGE2) and Matrix metalloproteinase. Prostagladins Induces the alveolar bone resorption and matrix metalloproteinase destroys the connective tissues. Other Pro-inflammatory mediators such as Interlukin-1β and Tumor necrosis factor- α are involved in the damage of periodontium.[3]

Tetracyclines are used in the periodontitis treatment as they are active against the bacteria involved in periodontitis. They posses bacteriostatic properties and slowly act by binding to the tooth surface and inhibiting the activity of collagenase at lower concentration. Hence Preventing the Periodontal tissue destruction. Minocycline is most active antibiotics against the microorganisms associated with periodontal disease.[2]

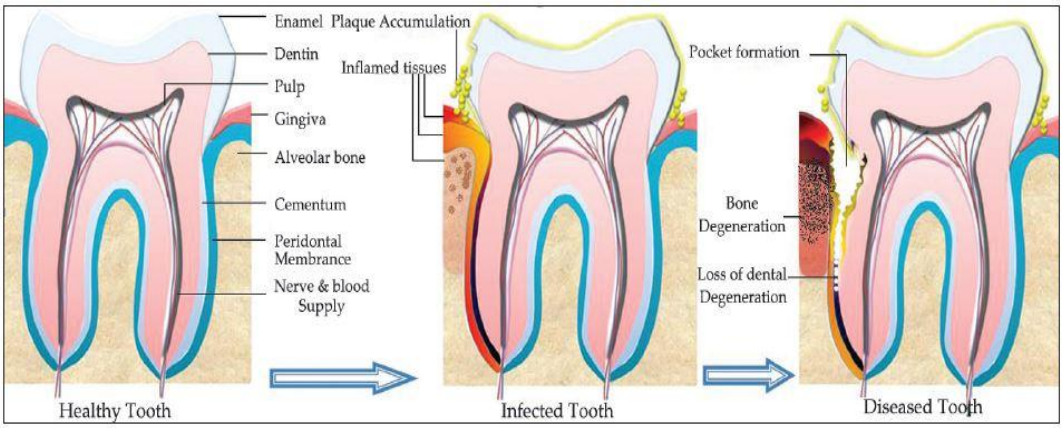

Figure 2: Periodontitis Disease.

PATHOGENESIS OF PERIODONTITIS DISEASE

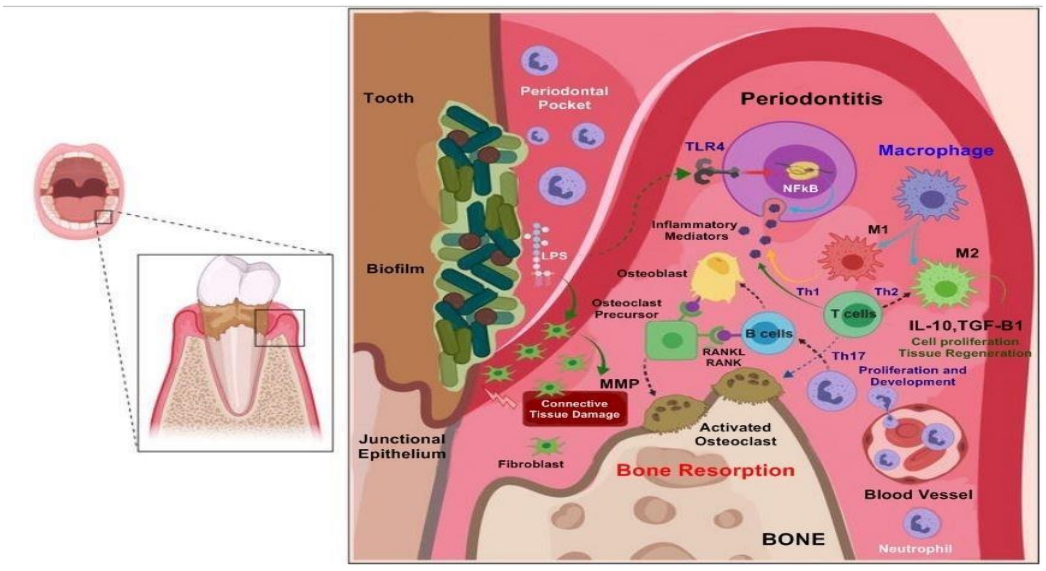

Figure 3: Pathogenesis of Periodontitis Disease.

LOCAL DRUG DELIVERY APPROACHES

1. Fibers

Fibers are thread-like and reservoir-type drug delivery systems. They are placed into the pockets circumferentially using an applicator and are sealed in place by applying cyanoacrylate adhesive. Thus the entrapped drug provides sustained release into the pocket.[4] Goodson and coworkers reported about cellulose acetate hollow fibers filled with tetracycline hydrochloride.[5] The drug simply diffused out through the reservoir system into the pocket. The single application of these fibers helped in freeing the gingival sulcus from spirochetes effectively. However, the hollow fibers allowed rapid emptying of the drug. To overcome this, matrix type of fibers was developed by incorporating the drug in molten polymers, with high temperature spinning followed by cooling.

Table 1: Fibers as Local Drug delivery system for the treatment of periodontitis.

S.No	Polymer	Drug	Inference	References
1	Alginate	Ciprofloxacin, Diclofenac sodium	Drug release from the fibers is sufficient to inhibit growth of E. coli, E. S. mutans and E. faecalis over 10 days	[6]
2	Chitosan	Tetracycline	Bleeding from Gingival pocket is reduced effectively	[7]
3	Cellulose acetate (hollow fiber)	Tetracycline	fibers on the single application will effectively eliminates spirochetes from gingival sulcus	[5]

2. Films

films are the more commonly used for intrapocket delivery. These are matrix drug delivery devices comprising of drugs distributed throughout the polymer.[8] The drugs are released by diffusion and/or matrix dissolution or erosion.[8] The methods of preparation include solvent casting and direct milling. Larger ones could either be placed in the cavity onto the cheek mucosa or surface of gingiva or be cut or punched into dimensions suitable to be inserted into the pockets. Films offer many merits like easy insertion, appropriate sizing for suiting the pockets and less discomfort to the patient Those with adequate adhesiveness and having thickness less than 400 mm are not easily dislodged by daily oral hygiene routine followed by the patient. Films composed of water-insoluble nondegradable polymers release drugs by only diffusion, whereas those made of soluble or biodegradable polymers release by diffusion and matrix erosion or dissolution.

Ethyl cellulose films have been developed incorporating a number of drugs like chlorhexidine diacetate, metronidazole, tetracycline and minocycline. Sustained release rates depending on the casting solvent and drug load were obtained.

However the disadvantage of being nonbiodegradable led to its replacement by biodegradable polymers.

Table 2: Films as Local Drug delivery system for the treatment of periodontitis.

S.No	Polymer	Drug	Inference	References
1	HPMC, Carbopol 934	Metronidazole	Burst released was observed for first 2 hours is clinically proved to be advantageous	[9]
2	Chitosan	Chlorhexidine gluconate	Both chlorhexidine and chitosan exert an antimicrobial activity against *P.gingialis*.	[10]
3	Poly(vinyl alcohol) (PVA)	Ornidazole	Good retention at the application site and maintenance of high drug concentration for long time	[11]

3. Strips

A strip can be described as thin and elongated matrix band made up of flexible polymer having a position securing mechanism, accommodating a wide range of interproximal spacing and having drugs dispersed throughout the polymer.[12] Solvent casting method and pressure melt method have been used for fabrication of strips.[13] A number of researchers have worked on strips made of acrylic polymer using single drug or combination of drugs. These strips brought significant improvement in various clinical signs by effective microbial eradication from the pockets. But there are some demerits associated with acrylic strips. Being nonbioabsorbable in nature these have to be removed after therapy, which may impair the regenerating tissue at the site. The surface of the strip dissolves due to transformation in the physical properties of acrylic strips in serum.

Table 3: Strips as Local Drug delivery system for the treatment of periodontitis.

S.No	Polymer	Drug	Inference	References
1	PCL	Minocycline	After the Day 6 of the insertion of strip Significant reductions in proportions of total Gram-negative species and Gram-negative rods and fusiforms is observed	[14]
2	HPMC	Metronidazole	The incidence of spirochetes and motile rods and gingival inflammation was remarkably reduced	[15]
3	Polyhydroxybutyric acid	Tetracycline	The proportion of spirochetes in the subgingival plaque from the pockets that were treated is decreased considerably	[16]

4 Gels

Gels are semisolid systems that widely came in lime light for the targeted delivery of antibiotics. These semisolid devices offer numerous advantages. They are comparatively easy to prepare and administer, though they have a faster drug release rate.[17] Also they are more biocompatible and bioadhesive, thus easily adhere to the mucosa in the dental pocket. The risk of irritating or allergic host reactions at the site of application is less in case of gels since they are rapidly eliminated through normal catabolic pathway.[8]

Table 4: Gels as Local Drug delivery system for the treatment of periodontitis.

S.No	Polymer	Drug	Inference	References
1	Pluronic	Moxifloxacin	0.4% moxifloxacin gel showing particular inhibition of P. gingivalis and seem to be safe	[18]
2	Chitosan	Metronidazole	Chitosan gels seem to be beneficial in providing significant improvements in clinical periodontal parameters both individually and in combination with metronidazole	[11]
3	Lactic-glycolic acid	Tetracycline	significant antimicrobial efficacy and fall in count of bleeding on probing sites is observed	[19]

4. Micro particle

Solid spherical polymeric structures (1–1000 mm) containing drug dispersed throughout the polymeric matrix are known as microspheres. They are free-flowing powders and provide sustained and controlled drug release at target site. Many nonbiodegradable and biodegradable materials including polymers from natural and synthetic origin have been used. They can be used to form chip, dental paste or can be directly injected into the pocket.[4] Microparticles put forth a number of advantages like shielding of unstable drug before and after administration, controlled drug release, improved patient compliance, sustained therapeutic effect, enhanced bioavailability and decreased frequency and intensity of adverse effects.[17]

Table 5: Micro particles as Local Drug delivery system for the treatment of periodontitis.

S.No	Polymer	Drug	Inference	References
1	Chitosan	Metronidazole	Preferable drug release profile was obtained from hydrogels containing metronidazole loaded microparticles	[20]
2	Gelatin	Doxycycline	Local drug delivery of doxycycline microspheres significantly reduced P. gingivalis in periodontal pockets	[21]
3	PDLGA	Hydroxyapatite (HA), Ofloxacin	spherical, Biocompatible and porous microspheres active against S. aureus and E. coli	[22]

5. **Nanoparticles**

They are particulate dispersions or solid particles having size range from 10–1000 nm. The drug is dissolved, entrapped, encapsulated, or attached to a nanoparticle matrix.[17] They are highly dispersible in aqueous medium, offer controlled release rate and enhanced stability. Because of their small size, nanoparticles can access sites unreachable for other devices, like the periodontal pocket regions below the gum line. A uniform drug distribution for prolonged time period is obtained thus decreasing the dosage frequency.[23]

Table 6: Nanoparticles as Local Drug delivery system for the treatment of periodontitis.

S.No	Polymer	Drug	Inference	References
1	Polymersomes	Metronidazole, Doxycycline	Polymersomes are useful drug delivery systems for antibiotics into host cells, decreased count of P.gingivalis	[24]
2	PDLGA	Harungana madagascariensis leaf extract	The bactericidal effect of the extract is enhanced by PLG nanoparticles	[25]
3	2-hydroxyethyl methacrylate (HEMA)	Tetracycline nanoparticles in Calcium sulfate beads	Cytocompatible CaSO4-Tet NP composite beads could be valuable in declining bacterial count at the infection site.	[26]

MARKETED PREPARATIONS AVAILABLE FOR THE TREATMENT OF PERIODONTITIS

S.No	Product Name	Dosage Form	Drug	Manufacturer
1	Actisite®	Nonbiodegradable fibers	Tetracycline hydrochloride	ALZA Corporation, Palo Alto, CA 94304 USA
2	ATRIDOX ®	Gel	doxycycline hyclate	Atrix labs, Ft., Collins
3	DENTOMYCIN	Gel	Minocycline hydrochloride dihydrate	Henry Schein UK Holdings Ltd.
4	Atrigel ®	Gel	Doxycycline	Atridox (Atrix Lab)
5	Periochip®	Chip	Chlorhexidine digluconate	Dexcel Pharma Technologies ltd., Jerusalem, Israel.
6	Periochip	Films	Chlorhexidine/tetracycline	Perioproducts Ltd.
7	Elyzol®	Biodegrable mixture in syringe	Metronidazole	Dumex corp. Co Denmark

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CONCLUSION

With the increment in understanding of periodontal disease and the drug administration methods, various targeted delivery systems have been designed contributing in eradication of the systemic side effects of antibiotics. These include fibers, strips, films, chips, microparticles, nanoparticles and nanofibers.

A shift from nonbiodegradable polymers to a variety of biodegradable polymers has helped in achieving biocompatible sustained release formulations, reduced the dosage frequency and thus minimized the chances of bacterial resistance. These devices along with the root planking and scaling procedures provide an effective treatment for the disease. However, the nanoscale intrapocket devices are still emerging as a promising opportunity for novel, low dose and efficient treatment.

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