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Contemporary Proposals in the Treatment of Periodentitis: A Review

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Abstract

Periodontitis is an inflammatory disease destroying tooth-supporting tissues due to diverse microflora. Basic treatment includes scaling and root planning, with mechanical therapy limited by physical and biochemical factors. Antimicrobial agents, delivered nonsurgically, enhance treatment. Controlled release systems like fibers and nanoparticles offer effective, low-cost, and long-term treatment solutions. Periodontitis, linked to systemic diseases, is treated with localized antimicrobial delivery systems for sustained, effective therapy. Local delivery of antimicrobials using sustained-release formulations offers long-term, effective treatment for periodontal pockets. Biodegradable polymers, especially chitosan, are favored for their safety, compatibility, and support of tissue regeneration.

Key words: Periodontitis, controlled release, antimicrobial agent

INTRODUCTION

Periodontal disease encompasses various conditions marked by gum, ligament, bone, and cementum degeneration due to bacterial infection in periodontal pockets. Bacteria alone may not suffice for periodontitis, as they produce enzymes damaging tissues and eliciting host responses. Gingivitis precedes periodontitis, where inflammation spreads deeper, causing swelling, bleeding, and eventual pocket formation fostering microbial growth.[1] This periodontal pocket provides ideal conditions for the proliferation of microorganisms: primarily Gram negative, facultative anaerobic species. Prominent amongst these are Bacteroides spp.: B. intermedius and B. gingivalis; fusiform organisms: Actinobacillus actinomycetemcomitans, Wolinella recta and Eikenella spp.; and various bacilli and cocci; spirochetes; amoebas and trichomonads[2]

Periodontal disease (PD) is an immune-inflammatory condition causing soft tissue attachment loss and alveolar bone resorption due to pathogenic microorganisms. It affects over 743 million globally, impacting oral functions, self-confidence, systemic health, and overall well-being significantly, making it the sixth most prevalent chronic disease worldwide.[3]

Initially an inflammatory reaction in the gingival tissue (gingivitis), untreated periodontitis extends to the periodontal ligament, cementum, and alveolar bone, forming pockets conducive to anaerobic pathogens (e.g., Porphyromonas gingivalis, Prevotella intermedia, Aggregatibacter actinomycetemcomitans, Fusobacterium nucleatum).[4]

Various studies have revealed that LDD into the periodontal pockets can provide higher therapeutic concentrations of the antibiotic compared to the systemic administration. Local antibiotics including, tetracycline (TET), doxycycline (DOX), minocycline (MIN), metronidazole (MTZ), chlorhexidine (CHX), clarithromycin (CLM), azithromycin (AZM), moxifloxacin (MXF), clindamycin (CLI), and satranidazole (SZ) are presently being used in various drug delivery systems such as irrigations, fibres, films, injectable, gels, strips, compacts, vesicular liposomes, microparticles, and nanoparticle systems in the management of periodontal disease.[5]

Treatment for stages I, II, and III of periodontitis includes patient education for better oral hygiene, managing factors like diabetes, cardiovascular disease, and quitting smoking, along with subgingival cleaning by a clinician. Stage IV necessitates surgical correction of bone defects and multidisciplinary approaches like occlusal trauma control, orthodontics, and prosthetic rehabilitation.[6]

Table 1. Stages of Periodontitis with associated therapy and the studied adjunctive therapeutical agents with relative LDDSs[6]

periodentitis	Therapy	Studied Adjunctive Therapeutical Agents	LDDSforAdjunctive Therapeutic Agents
Stage I, II, III	SRP, motivation and education for Stage I, II, III Stage IV domiciliary oral hygiene, correction of bad habits (ex. Smoking), control of systemic diseases (ex. Diabetes).	Anti-bacterial andanti-septic drugs (tetracyclines,metronidazole, azithromycin, metronidazole, chlorhexidine), inflammationmodulators (statins, lipoxin, aspirin, erythropoietin), natural agents (TP, curcumin, TGEC, mangosteen)	Fibers, Strips and Films, Microparticles, Nanosystems, Gels.
Stage IV	SRP, motivation and education for domiciliary oral hygiene, correction of bad habits (ex. Smoking), control of systemic diseases (ex. Diabetes), surgical correction of bone defects.	Antibiotic (amoxicillin), alveolar bone and tissue repairing agents (inhibitor SP600125, BMP-2, rhAm, GAL, MSCs)	Membranes, Scaffolds.

Treatment approach for periodontal disease

Conventional periodontal therapy

Periodontal therapy aims to heal inflamed tissue, reduce pathogenic bacteria, and eliminate diseased pocket depth to halt bone loss. Conventional methods like scaling, root planing, and curettage mechanically remove plaque and necrotic tissue, but residual pathogens can persist due to deep tissue penetration and re-establishment within 42-60 days despite treatment.

Local drug delivery

In 1979, Goodson et al introduced controlled delivery for treating periodontitis. This therapy effectively targets the base of periodontal pockets, ensuring sustained antimicrobial action. Utilizing gingival crevicular fluid, these systems, known by various names like sustained release or prolonged action, offer reliable access and extended efficacy.

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[7,8,9]

Table 2 Commercialized Conventional treatments for dental diseases.10

Brand Name	Dosage Form	Active	Base	Dose	Manufacturer
Periostat	Tablet, Capsule	Doxycyclinehyclate	-	20mg	Alliance, Galderma, Collagenex
Elyzol	Suspension Gel	Metronidazole benzoate	Glycerylmonooleate and sesame oil	25%	Dumex Corp. co, Denmark
Atrisorb	Guided tissue regeneration resorbable membrane	Doxycycline	PLA in N-methyl-2-pyrolidone	4%	Atrix laboratories
Actisite	Non- resorbable fibers	Tetracycline	Ethylene vinyl acetate polymer	12.7 mg/9 inches	Alzacorp
Periopatch	Patches	Sambucusnigra, Echinacea purpurea,	Ethylcellulose,polyacrylic acid, acacia, hydroxypropyl cellulose	-	Izun Pharmaceuticals

Systamic administration of antibiotics:

Systemic antibiotic therapy is selectively recommended for juvenile periodontitis, patients needing antibiotic coverage due to medical conditions, and those with severe periodontal infections. Successful treatments include metronidazole combined with amoxicillin or ciprofloxacin for advanced Actinobacillus actinomycetemcomitans infections. Antibiotics altering pathogenic flora are typically used, and tetracyclines may reduce bone destruction by inhibiting collagenase. Surgical methods involve pocket elimination and bone recontouring to foster alveolar growth. Synthetic flavonoid derivatives are used in senile osteoporosis treatment.

Gels:

Semisolid or gel formulations offer advantages in delivering drugs locally to periodontal pockets. They exhibit higher biocompatibility and bioadhesivity, adhering effectively to dental pockets. They are eliminated quickly through natural pathways, reducing the risk of anaphylactic reactions. Gels containing tetracycline, metronidazole, or their combinations have shown satisfactory treatment outcomes.[11]

Fibres:

Fibres, like thread-like devices, are used in periodontal pockets for sustained drug release. Initially, hollow fibres effectively held drugs but allowed rapid evacuation. To slow release, drug- impregnated monolithic fibres were developed by incorporating drugs into molten polymers, spun at high temperatures, and cooled. Various polymers like PCL, polyurethane, polypropylene, cellulose acetate propionate, EVA, and chitosan are explored for drug delivery to periodontal pockets.

Films:

A challenge in treating periodontal infections is the rapid dilution and elimination of topically applied drugs by saliva. Implantable thin films address this by being applied onto oral mucosa or gingival surfaces, designed for controlled drug release through diffusion or matrix erosion, offering ease of use and minimal interference with oral hygiene. Degradable polymer films dissolve or erode in the gingival crevice, eliminating the need for removal after treatment unlike non-degradable systems. Films combining poly (vinyl alcohol) (PVA) and carboxymethyl-chitosan (CMCS) were fabricated using blending/casting methods, loaded with ornidazole for periodontal drug delivery. These films proved biocompatible, exhibited pH-responsive swelling, effectively retained drug at the application site, and sustained high drug concentrations for at least five days.[9,10,11]

Injectable System

Injectable systems are ideal for delivering antibiotics into the periodontal pocket. They are quick, painless, and cost-effective compared to other devices. These systems efficiently fill the pocket,

targeting a large number of pathogens and allowing easy application of therapeutic agents using a syringe. Injectable hydrogels deliver cells and therapeutic agents for periodontal treatment, encapsulating drugs and targeting diseased sites minimally invasively. They transition to gel after injection via chemical or physical cross-linking.[12]

Nanoparticles

Metal nanoparticles, including silver, copper oxide, and zinc oxide, have strong antimicrobial properties. Silver nanoparticles disrupt bacterial DNA and membrane proteins, increasing cell permeability. Copper oxide fights resistant bacteria, and zinc oxide inhibits biofilms. Other nanoparticles, like silica and casein phosphopeptide, show significant antimicrobial and enamel remineralization effects. Quaternary ammonium nanoparticles also inhibit bacteria in composites. Chitosan membrane composites with bioactive glass nanoparticles (50nm) are non-cytotoxic, enhancing cell proliferation, stem cell activity, and tooth mineralization, aiding periodontal bone regeneration by inhibiting soft tissue growth. Similarly, PLGA nanocomposites with chitosan-58S- bioactive glass and high porosity show strong potential for bone regeneration.[13]

The main polymers used for the preparation of nanocarriers are differentiated in three groups:

- Natural polymers (chitosan, dextran, alginate and other polysaccharides, hyaluronic acid, gelatin, poly (amino acids), etc.)
- Degradable synthetic polymers (polyesters, polyolefin resins, polyamides, polyamines, etc.)[4]

Nanogenerators:

Nanogenerators convert mechanical or thermal energy from small physical changes into electricity. Piezoelectric nanogenerators use zinc oxide (ZnO) nanowires to generate electric current through bending and releasing motions. ZnO is both piezoelectric and semiconducting, making it suitable for implantable devices. Its biocompatibility and ability to be synthesized on organic substrates ensure that the nanogenerator is safe for biomedical applications. These features enable energy harvesting for low-power, implantable technologies.[14]

Strips

The stips were fabricated either by solvent casting or pressure melt method. Flexible polymer strips, often made from acrylic, secure in place and accommodate interproximal spacing; they are loaded with antimicrobial agents.[11]Thin elongated strips are intra-pocket delivery devices made of flexible polymers, but they often fail to fit properly between teeth. The film, composed of 60-90% polycaprolactone I and II in a 1:1 to 4:1 ratio, delivers antibiotics like minocycline and doxycycline. It is designed for easy insertion and long-term retention.[12,15,16]

Liposomes

Liposomes' lipid bilayer carries antimicrobial agents and adsorbs on tooth enamel's hydroxyapatite due to the dental pellicle. This pellicle, formed by salivary proteins, provides protection but also facilitates bacterial attachment. Positively charged liposomes adsorb better, mimicking the protective action of the pellicle on dental enamel. Liposomes aggregate with salivary compounds, but coating them with negatively charged pectin increases retention by over 40%. Pectin-coated liposomes show higher retention on enamel due to their affinity for calcium in hydroxyapatite's

hydration layer. This binding, likely via calcium bridges, enhances adhesion compared to uncoated liposomes. Studies show increased adsorption of negatively charged liposomes in artificial saliva, and liposomes with Triclosan and Chlorhexidine have superior delivery to biofilms.[17,18,19,20]

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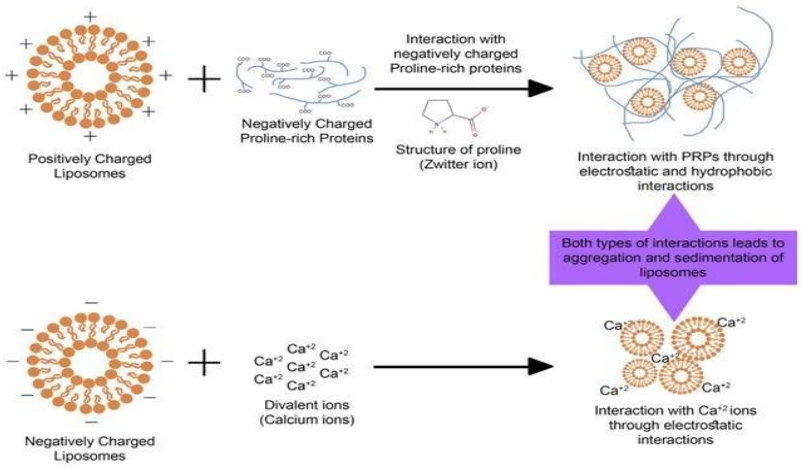

Fig. 1. Aggregation of liposomes with salivary components[7,8]

Microspheres:

Microspheres are solid particles (1-1000 µm) made from biodegradable materials like polymers, waxes, gums, and proteins. Drugs are encapsulated or dispersed within the polymer, gradually releasing at the target site. Microcapsules have a drug core with a polymer coat. They provide sustained and controlled drug release.

Advantages

- Prolong and constant therapeutic effect
- Easily injected due to their spherical shape and small size
- Reduce dosing frequency
- Reduction in the intensity of adverse effect
- Improved patient compliance.
- Enhanced bioavailability

Disadvantages

- Release rate may vary from variable factors like food and rate of transit through the gut.
- Difference in the release rate from one dose to another.
- Generally, contain a higher drug load and thus may cause toxicit.[13,14.21,22]

CONCLUSION

Advances in periodontitis understanding and drug administration have led to local drug delivery systems like fibers, strips, films, chips, microparticles, and nanoparticles. These systems reduce systemic antibiotic side effects, minimize bacterial resistance, and increase therapeutic efficacy with biocompatible, controlled-release formulations, reducing dose frequency. Dental treatments focus on rebalancing the oral microenvironment and eradicating pathogens. Conventional treatments, like films, fibers, and hydrogels, help but require surgical intervention for complete plaque removal. Novel treatments like nanobubble water, gene therapy, probiotics, and photodynamic therapy show promise for better biofilm disruption. Further studies are needed for clinical application.

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