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Local Drug Delivery Systems in Periodontal Treatment: A Review

Manjunath SH[1], Austin Howard Jones[2], Mahesh Gabhane[3]
[1]PhD Research scholar, Pacific university, Udaipur, Rajasthan, India
[2]Professor, Dept. of Periodontogy, Pacific Dental College & Hospital, Debari, Udaipur, Rajasthan, India
[3]Reader, Dept of Oral Pathology, SMBT Dental College & Hospital, Sangamner, Maharashtra, India

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***Corresponding author**
Manjunath SH

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Abstract: Periodontal Diseases are heterogeneous group of diseases, proven to be caused by pathological microorganisms that organize to form a plaque associated biofilm on the tooth surface. The destruction of Periodontium is a result of interaction between microorganism and specific host defense mechanism. Removal of this biofilm by mechanical instrumentation is essential. Scaling and Root planing is the first mode of treatment to reduce bacterial burden. Mechanical instrumentation has some limitations 1) in case of unfavorable anatomy of the tooth, 2) in situations like intraoral microbial translocation,3) in presence of tissue invasive organisms and 4) when there is bacterial invasion into dentinal tubules. To overcome this, Antimicrobials both systemically and locally acting were used in adjunct to mechanical therapy. To overcome the adverse effects of systemic antimicrobial agents such as drug toxicity, drug interaction, acquired bacterial resistance and patient's compliance local drug delivery system has been developed. Local drug delivery system does not have the side effects of systemic drugs. The use of sustained release formulations to deliver antimicrobials to the site of periodontal infections is gaining interest. These products provide long term, effective treatment at the site of infection at much smaller doses. This review approaches the main delivery systems for the administrations of the drug to the periodontal pocket, their usefulness as well as advancement of these systems effectiveness in the periodontal therapy.
Keywords: Periodontal Diseases, Periodontal Pocket, Local Drug Delivery

INTRODUCTION

Periodontal disease is a term which involves several pathological conditions range from simple gum inflammation to serious disease that results in major damage to the soft tissue and bone that support the teeth. Periodontal diseases include conditions such as chronic periodontitis, aggressive periodontitis, systemic disease-associated periodontitis and necrotizing periodontitis [1].

Periodontal pocket provides ideal conditions for the proliferation of microorganisms: primarily Gram negative, facultative anaerobic species. The microflora found in periodontitis is complex and composed mainly of Gram negative anaerobic bacteria [2].

Advances in the understanding of the aetiology, epidemiology and microbiology of the periodontal pocket flora have revolutionized the therapeutic strategies for the management of periodontal disease progression [3].

Goodson *et al.* in [4] 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.

Ideal requirements for local antimicrobial agents [4]

- Must deliver the drug to the base of pocket.
- Must have microbiologically effective concentrations in the pocket.
- Should sustain the concentration of the drug in the pocket for
- sufficient period of time & at a concentration to be clinically effective
- Less undesirable side effects

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 [5].

Local delivery of antimicrobial therapy to periodontal pockets has the benefit of administering

- More drugs at the target site
- Minimizing the exposure of total body to the drug
- Sustained release of antimicrobial in the periodontal Pockets

Indications	Contra-indications
Isolated periodontal pockets (>5mm), with successful phase 1 therapy	Periodontal patients with known hypersensitivity reaction to any of the antimicrobials used for periodontal therapy
Periodontal patients who are medically compromised where surgical therapy is Contraindicative.	With local delivery of Metronidazole preparations, contraindicated in alcoholics
In combination with mechanical debridement or alone.	Patients susceptible to infective endocarditis are contraindicated for irrigation devices to avoid the Risk of bacteremia.
In-patients who are suffering from recurrent or Refractory periodontitis.	Delivery of antimicrobial agents using ultrasonic scalers is contraindicated in asthmatics, infective conditions (AIDS, TB) and those with cardiac pacemakers
During periodontal regenerative procedures.	

Drug Delivery Devices [6]

There are two possible approaches to improve the drug action

- Sustained (are designed to provide drug delivery for less than 24 hour) and controlled (Controlled delivery systems should have a duration of drug releases that exceeds 24 hour) drug release to reduce or eliminate side effects by improving the therapeutic index.
- Site specific drug delivery to minimize systemic effects.
- Intrapocket devices can be divided into two broad categories, depending on whether they are Biodegradable and Non-Biodegradable

Various drug delivery devices for local drug delivery

- Fibers
- Strips and compacts
- Film
- Injectable systems
- Gels
- Vesicular liposomal systems
- Microparticle system
- Nanoparticle system

Fibers

Fibers are placed circumferentially around the tooth. There are Hollow fibers and Ethylene vinyl acetate fibers.

Hollow fibers -Released tetracycline at a first order rate with 95% of the drug released in the first 2 hrs – GCF - remained in the therapeutic range for 24 h and some effects on spirochetes. Study should be viewed primarily as an evaluation of drug delivery. Ethylene vinyl acetate fibers Tetracycline incorporated into different polymers (1) Polyethylene, (2) Polypropylene, (3) Polycaprolactone, (4) Polyurethane, (5) Cellulose acetate propionate and (6) Ethylene vinyl acetate (EVA) [7].

Strips and compacts

Larsen – studied in vitro release of doxycycline from different bioabsorbable materials and acrylic strips Acrylic strip and Colla Cote decreased to low levels of both concentration and residual antibacterial activity in a few days Compacts-Compacts based on PHBA containing tetracycline hydrochloride, 50% (w/w) of tetracycline, the mean drug concentration obtained was in the therapeutic range over the 10 days

Films

Developed by Higashi *et al.* [11] for the delivery of clindamycin. Made of – Eudragit L and Eudragit S, two water soluble poly (methacrylic acid-co-methyl methacrylate), and – Eudragit RL - non-water soluble polymer poly (ethyl methacrylate-co-chlorotrimethyl ammonium methyl methacrylate),

A far more widely used form of intra-pocket delivery device has been in the shape of film, prepared either by solvent casting or direct milling. Films are matrix delivery systems in which drugs are distributed throughout the polymer and release occurs by drug diffusion and/or matrix dissolution or erosion. This dosage form has several advantageous physical properties for intra-pocket use[8]. The dimensions and shape of the films can be easily controlled according to the dimensions of the pocket to be treated.

Sustained release devices composed of a cross linked fish gelatin containing chlorhexidine diacetate or chlorhexidine hydrochloride – developed by Steinberg *et al*. [12] Time of total drug release is short & varies from 4 - 80 hrs. Films based on synthetic biodegradable polymers – poly (lactide-co-glycolide) (PLGA) containing tetracycline. Incomplete release of

tetracycline; – only 30-60% of total tetracycline - released - R.K. Agarwal *et al*. [13]. New film composed of cross-linked hydrolyzed gelatin and glycerin for local delivery of chlorhexidine digluconate has been developed and commercialized under the trademark Periochip - G. Goffin [14]

Injectable systems

Attractive for the delivery of antibiotic agents into the periodontal pocket ,Easily and rapidly carried out, without pain, by using a syringe and Cost of the therapy is considerably reduced compared to devices that need time to be placed and secured.

Gels

Gels are Mucoadhesive, various drugs have been developed in gel forms, and they are 1. Metronidazole- containing gel 2. Tetracycline containing gel 3. Gel containing 1% clindamycin hydrochloride 4. Gel formulation based on 2.5% hydroxy propylmethyl cellulose containing 0.125% histatin etc.

Tetracycline gel - Bioadhesive semi-solid systems based on a) Hydroxyethyl cellulose (HEC) and b)Polyvinyl pyrrolidone (PVP).Increased concentrations of HEC decreased the rate of release of tetracycline, due to the concomitant increase in product viscosity and the subsequent decreased rate of penetration of dissolution fluid into the formulation.

Comparative analysis of tetracycline containing dental gels: poloxamer and monoglyceride based formulations have been done which shows that poloxamer and monoglyceride gels, when applied subgingivally, produce a significant improved outcome in moderate to deep periodontal pockets[9].

Vesicular liposomal systems

Vesicular liposomal systems are designed to mimic the bio-membranes in terms of structure and bio-behavior, and hence are investigated intensively for targeting periodontal biofilms. The anti-oralis immunoliposomes 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

It shows interactions between liposomes made up of phosphatidylinositol and biofilms. The potential of lectin – bearing liposome systems as a targeting system for the control of gingivitis and dental plaque has been used. The delivery of tricolosan and chlorhexidine was studied for several liposomal compositions involving cationic as well as anionic lipids.

Micro particle system

Based on biodegradable poly(a-hydroxyacids) a) poly(lactide) (PLA) or b)poly(lactide-co-glycolide) (PLGA) – P. Esposito *et al*. [9] Tetracycline release rate is influenced by the – polymer choice (lactide/glycolide ratio) – polymer molecular weight and crystallinity) – pH of the medium, Tetracycline release rate is increased as the pH increases. PLGA microspheres - proposed for delivery of histatins. PLGA microspheres containing minocycline were evaluated alone or as an adjunct to scaling and root planing, in comparison to scaling and root planing alone or to no subgingival treatment in adult periodontitis [10].

Nanoparticle system

Nanoparticles, owing to their small size, penetrate regions that may be inaccessible to other delivery systems, such as the periodontal pocket areas below the gum line. These systems reduce the frequency of administration and further provide a uniform distribution of the active agent over an extended period of time. Modern drug delivery systems are designed for targeted controlled slow drug release. Up to now polymer or micro particle-based hydrogels have been applied in dentistry, which can affect the rate of release because of their structure. Recently, intensive research is being performed all over the world to improve the effectiveness of delivery systems. The Nano particulate system provides several advantages as compared with microspheres, micro particles and emulsion-based delivery systems, including high dispensability in an aqueous medium, controlled release rate and increased stability.

Limitations

Limitation are 1) Not feasible for local irritants – Drug and other excipients used in the formulation processing either erythema, itching, or local arrhythmia cannot be delivered by this route 2) Dose is limited because of relatively small area 3) Presystolic metabolism may occur by the enzymes like peptidase and esterase 4) Should be devoid of irritancy or a sensitization 5) Manufacturing cost of the patches or devices should be taken in consideration

CONCLUSION

Effectiveness of SRP may be enhanced with antiseptics and antibiotics 1) Medication - released over 1 to 3 weeks and helps eliminate the disease causing bacteria with a high concentration of a drug or antiseptic – Gives the gum tissue more time and a better chance to heal without the disease causing bacteria present 2) Useful adjunct to conventional surgical or nonsurgical treatments, – but are no substitute for these measures 3) Controlled delivery systems are of interest as an adjunct for recurrent and refractory periodontitis

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