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Review Article

A Comprehensive View on Local Drug Delivery Systems in Periodontics

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Abstract

Periodontitis is a chronic inflammatory disease of soft tissue surrounding and supporting theteeth, which causes periodontal structural damage induced by specific microorganisms and requires more specific treatment. Various methods of treatments were used in the management of periodontal infections. Various effective methods like mechanical debridement of plaque, systemic and topical administration of antibacterial agents in the treatment of these conditions. There are other antimicrobials which can be locally delivered such as metronidazole, chlorhexidine, doxycycline and tetracycline. This article reviews in detail about local drug delivery system in successful management of periodontal disease.

Keywords: *Periodontitis; Local Drug Delivery Systems*

Introduction

Periodontitis is a multifactorial disease of periodontium which causes periodontal structural damage induced by specific microorganisms and modified by factors like developmental deformities of tooth, systemic conditions affecting oral tissues, socio economic factors, environmental factors [1,2]. Selection of a right antimicrobial agent with appropriate route of drug administration is the key to successful periodontal therapy. Traditional methods of non-surgical treatment of periodontitis, including scaling/root planning, do not guarantee remission of disease. These treatments are also time consuming, difficult and sometimes ineffective so, these mechanical therapy alone is not sufficient for treatment of moderate to severe periodontitis because of inaccessibility in deep periodontal pocket and depth of penetration of microorganisms into periodontal connective tissue [3].

Thus, to overcome the limitations of mechanical therapy local drug delivery into periodontal pocket is recommended. Local drug delivery system is the application of anti-microbial or anti-infective agent that would target pathogenic microorganisms by delivering it at the base of pocket yielding a stable debridement [4,5].

History

This was first proposed by Dr. Max Goodson., *et al*. in 1979. He used tetracycline in the hollow fibers.

D. Steinberg., *et al*. (1990) researched chlorhexidine as a local drug delivery agent. Nakagawa T., *et al*. (1991) used minocycline.

Ainamo., *et al*. (1992) studied 25% metronidazole gel.

Stoller., *et al*. (1998) studied doxycycline hyclate [6].

Classification

1. Based on Application-Rams and Slots 1996 [7]:
    - Personally applied (Patient self-care application):
        - Non-sustained subgingival drug delivery
        - Home oral irrigation
        - Home oral irrigation jet tips
        - Traditional jet tips
        - Oral irrigation (water pick)
        - Soft cone rubber tips (Pickpocket)
        - Sustained subgingival drug delivery.
    - Professionally applied in dental office:
        - Non-sustained subgingival drug delivery
        - Professional pocket irrigation
        - Sustained subgingival drug delivery
        - Controlled release devices
        - Hollow fibers
        - Dialysis tubing
        - Strips
        - Films.
2. Based on duration of medicament release- Greenstein and Tonetti 2000 [7]:
    - Sustained release devices
    - These devices provide drug delivery for less than 24h
    - Require multiple applications
    - Follow first-order drug kinetics
    - Controlled release devices

- Drug release is for more than 24h
- Administered only once
- Follow zero-order drug kinetics.

3. Depending on degradability [8]:
   - Non-degradable devices (First generation)
   - Degradable devices (Second generation).
4. Depending on mechanism of action- Langer and Peppas 1989: Classified controlled drug release polymeric systems [9]:
   - Diffusion controlled systems:
     - Matrices
     - Reservoirs
   - Chemically controlled systems:
     - Erodible systems
     - Pendant chain systems
   - Solvent activated systems:
     - Osmotic systems
     - Swelling controlled systems
   - Release induced by external forces.
5. Controlled release local drug delivery system classified by Kornman 1993 [10]:
   - Reservoirs without a rate controlling system like hollow fibers, gels and dialysis tubing.
   - Reservoirs with a rate controlling system like erodible polymeric matrices, micro-porouspolymer membrane, monolithic matrices and coated drug particles.
6. Depending on origin:
   - Allopathic or chemical local drug delivery.
   - Herbal or ayurvedic local drug delivery.
7. Based on their evolution, origin and forms of current usage, according to WHO, herbal medicines can be categorized into four [11]:
   - Category 1: These indigenous herbal medicines are used by local communities or region and arevery well-known by the local population through ages in context to composition, treatment and dosage.
   - Category 2: This group consists of herbal medicines in systems and is well-documented and based on long-time usage on theories and concepts that are duly accepted by the respectivecountries. Example - Ayurveda siddha and unani.
   - Category 3: This consists of modified herbal medicines which have been modified in relation totheir shape, dose, administration mode and composition. These medicines have to meet the national regulatory requirements in terms of their safety and efficacy.

- Category 4: Imported products with an herbal medicine base include all the imported herbal medicines (raw materials and products). The national authority of the importing country shouldhave safety and efficacy data.

8. Based on types of local drug delivery system [12]:
   - Fibers
   - Films
   - Strips
   - Gels
   - Vesicular liposomal systems
   - Microparticle systems
   - Nanoparticle systems.

Ideal requirements of local drug delivery system [7]:

1. Should deliver drug at a microbiologically effective concentration
2. It should not affect the commensal microflora of periodontal pocket and should act against periodontal pathogens
3. Should be safe without any adverse effects
4. Should have prolonged shelf life
5. Should be economical
6. Should be both biodegradable and biocompatible
7. Drug must show *in vitro* activity against the organisms
8. Should not develop bacterial resistance
9. It should retain at the proximity of periodontal pocket after placement
10. Should sustain the concentration of delivered drug in the pocket for sufficient time and concentration to be clinically effective.

Pharmacokinetics of LDD drug [13]:

- **Site of action**: Local drug delivery targets microbes deep into the connective tissue of periodontal pocket altered and exposed cementum of radicular dentin.
- **Adequate concentration**: It has been proved by various experimental studies that Minimuminhibitory concentration (MIC) of antimicrobial agent should be at least 50 times higher than for bacteria growing under planktonic condition. It is ensuring adequate concentration andenhancing its efficacy at the local site subgingivally.
- **Sufficient duration:** Duration of action is dependent upon the mechanism by which the antimicrobial agent inhibits or destroys target bacteria, bactericidal or bacteriostatic pathway.
- **Substantivity:** Substantivity refers to the property of an antimicrobial to bind to oral surfaces (mucosa and teeth) and its slow release at effective doses that guarantees the persistence of antimicrobial activity.

It was estimated that half-life of a drug delivered into a periodontal pocket is about a minute.

Therefore, the addition of local drug delivery agents into various vesicle or devices prior toplacement into periodontal pocket enhances its substantivity.

Indications [14]:

- Localized periodontal pockets with probing pocket depth > 5 mm, after completion ofsuccessful phase I therapy.
- Medically compromised patients where surgical therapy is contraindicated or not suggested.
- As an adjunct to mechanical debridement.
- In patients suffering from recurrent or refractory periodontitis.

Contraindications [14]:

- Patients with known hypersensitivity reaction to any components of the LDD systems to be used.
- As a replacement to scaling and root planning during initial periodontal therapy and maintenance.
- In pregnant or lactating patients.
- Patients susceptible to infective endocarditis to avoid the risk of bacteremia.
- As a replacement for surgical periodontal therapy in cases indicated for periodontal surgery.
- As a replacement for systemic antibiotic therapy, where systemic administration is indicated.
- Patients with known hypersensitivity to the antimicrobials used.
- Patients susceptible to bacterial endocarditis who are contraindicated for subgingival irrigation devices to avoid the risk of bacteremia.
- Delivery of antimicrobials using ultrasonic devices is contraindicated in asthmatics, infective conditions such as AIDS, tuberculosis and those with cardiac pacemakers.

Advantages [7,14]:

- Improved patient compliance.
- Small doses can be administered.
- Improved pharmacokinetics.
- Improved drug access to the site of disease.
- Attains a 100-fold higher concentration of antimicrobial agents in subgingival sites.
- The concentration of the drug in periodontal pocket is not affected by the fluctuations in plasma levels.
- The technique is suitable for agents which cannot be given systemically, such as chlorhexidine.
- Small doses can be administered.
- Lowers the total drug dosage.
- No risk of emergence of resistant microorganism.
- Drug can reach the site of action in adequate concentration.
- Maintenance the drug level for a sufficient period of time.
- Superinfection and drug resistance are rare.
- Reduction in frequency of drug administration.

Disadvantages [7,14]:

- Time consuming and laborious.
- Difficulty in placing into the deeper part of the pockets of the furcations lesions.

- Does not have any effect on adjacent or near-by structures such as tonsils, buccal mucosa so may cause chances of reinfection.
- In the presence of generalized pockets, other periodontal therapies should be used.
- Personal application of antimicrobial agents by patients as a part of their home self-care procedure is compromised.

Various local drug delivery systems

Locally delivered drug is formulated by inserting them into a vehicle in the form of fibers, gels, strips, among others to improve its bioavailability at the site. Most likely, the drug should have a resorbable vehicle so that there is no need to remove the vehicle after insertion [15,16].

Vehicle	Chemical agent used	Commercial Name
Fibres	Tetracycline	Actisite Periodontal Plus AB
Films	Minocycline	
Gels	Tetracycline Satranidazole	
	Metronidazole	Elyzol
	Chlorhexidine	Chlo-site
Injectable Form	Doxycycline	Atridox
Microspheres	Minocycline	Arestin
Ointments	Minocycline	Dentomycin, Periocline
Chips	Chlorhexidine	Periochip Periocol-CG
Mouth rinse	Chlorhexidine	
Varnish	Chlorhexidine	
Inserts	Ofloxacin	PT-01

Chemical agents used in drug delivery

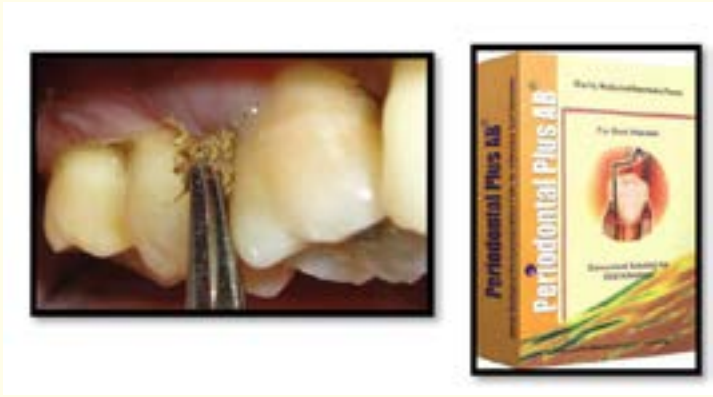
Tetracycline fibres

Actisite: These are non-resorbable biological inert, normally considered as safe, plastic copolymer (ethylene and vinyl-acetate) loaded with 25% w/w tetracycline HCL powder packaged as a thread of 0.5 mm in diameter and 23 cm in length. When delivered into the periodontal pocket, it is well tolerated by oral tissues and for 10 days it sustains tetracycline concentrations.

Recently bio-resorbable tetracycline fibers has been developed with base of collagen films, which is commercially available as periodontal plus AB. It has an advantage of no further appointment for removal as it biodegrades within 7 days [6].

Minocycline

Minocycline HCL, a semi synthetic tetracycline is one of the most active antibiotics against microorganisms associated with periodontitis. It has a significant antimicrobial activity against a wide range of organisms as well as an anti-collagenase effect [6].



There are three modes of local application are available:

- Film
- Microspheres
- Ointment.

Film

Ethyl cellulose films contains 30% of minocycline which totally eradicates pathogenic flora from the periodontal pocket after 14 days [4].

Microspheres

Arestin

A new, locally delivered, sustained release form of minocycline microspheres (ARESTIN) for subgingival placement is available. The 2% minocycline is encapsulated into bio-resorbable microspheres in a gel carrier and has resorption time of 21 days. The gingival crevicular fluid (GCF) hydrolyses the polymer and releases minocycline for a period of 14 days or longer before resorbing completely [4].

Ointment

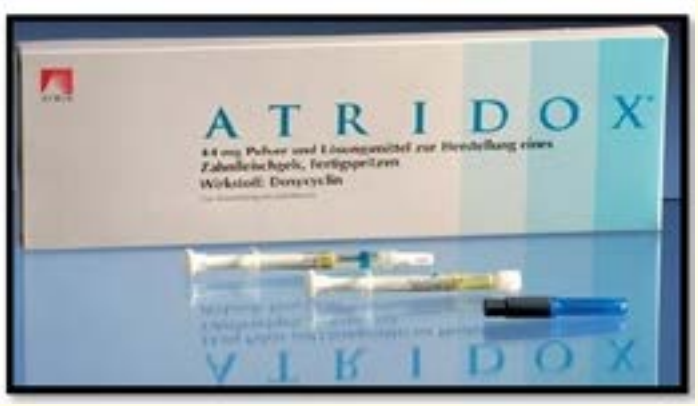
This is 2% minocycline hydrochloride in a matrix of hydroxyethyl-cellulose, amino alkyl methacrylate, triacetin and glycerine. The concentration of minocycline in the periodontal pocket is about 1300 µg/ml of gingival crevicular fluid, 1 hr after single topical application of 0.05 ml ointment and is reduced to 90 µg/ml after 7 hrs [4].

It is available by the trade name dentomycin and periocline in European Union and Japan, respectively.

Doxycycline

Atridox

Doxycycline is a bacteriostatic agent. Its effective against the matrix metalloproteinase (MMP's) and has the ability to down-regulate matrix metalloproteinase (MMP's). MMP's are the periodontal biomarkers causing the destruction of periodontal connective tissue. Atridox (42.5 mg doxycycline) is the only subgingival controlled-release local drug delivery system, a commercially available product of doxycycline composed of a two syringe mixing system. Local levels of doxycycline have been found to remain well above the MIC for periodontal pathogens (6.0 µg/ml) for the 7 days. Within 28 days the 95% of the polymer of atridox is bio absorbed or expelled from the periodontal pocket. The efficiency of 10% doxycycline hyclate as a local delivery antimicrobial agent for achieving probing depth reduction and gaining clinical attachment. It is a liquid biodegradable system that hardens when placed in the periodontal pocket [4].



Metronidazole

Elyzol

It is a nitro imidazole compound. It is bactericidal in nature to anaerobic organism. It acts at the site by disrupting bacterial DNA synthesis. After delivery of Elyzol (25% Metronidazole), concentrations of above 100 µg/ml of drug in GCF were measurable in the periodontal pocket for at least 8 hrs and concentrations above 1 µ/ml were found after 36 hrs. It is delivered in viscous consistency to the pocket, where it is liquidized by the body heat and then hardens again and forming crystals in contact with GCF or saliva [4,6].

Chlorhexidine

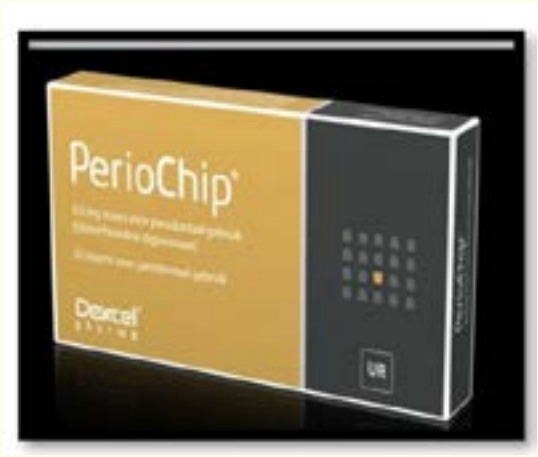
Chlorhexidine belongs to the family of biguanide, it is commonly used as an antifungal and antibacterial agent. It is mostly active against gram positive group of organisms. It is bacteriostatic at low and bactericidal at high concentrations. Chlorhexidine is being used in mouth rinses, chlorhexidine has only a short-lived effect on the pocket flora [6].

It is available in the forms of

- Mouth rinses
- Gels
- Varnishes
- Chips.

Periochip

A small chip composed of biodegradable hydrolyzed gelatin matrix, comprised of 34% chlorhexidine cross-linked with glutaraldehyde and also containing glycerine and water. The chip is 5 mm long, 4 mm wide with 2.5 mg of chlorhexidine gluconate. The chip releases chlorhexidine *in vitro* in a biphasic manner, at first releasing approximately 40% of the chlorhexidine within the first 24 hrs and later releasing the remaining chlorhexidine in an almost linear fashion for 7 - 10 days [4].



Periocol-CG

It is prepared by incorporating 2.5 mg chlorhexidine from a 20% chlorhexidine solution in collagen membrane. Size of the chip is 4 x 5 mm and the thickness of the chip is 0.25 - 0.32 mm. Weight of thechips: 10 mg wt. It resorbs after 30 days and their coronal edge degrades within 10 days [4].

CHLO-Site

It is an agent containing 1.5% chlorhexidine of xanthan type (Xanthan gel - saccharide polymer). The chlosite gel disappears from the pocket within 10 - 30 days of injection and effective concentration of chlorhexidine against microorganisms is established for at least 15 days in the region. It adheres inside the pockets and are not easily washed away by gingival fluid or saliva. It is very efficientin treatment of periodontal pocket and peri-implantitis [4,6].

Satranidazole (SZ)

It is an another antibiotic that belongs to the 5-nitroimidazole. Satranidazole gel, when used as an adjunct with scaling and root planing in the management of periodontitis, achieves significantly better and improved clinical and microbiological results than mechanical periodontal treatment alone [17].

Ofloxacin

Ofloxacin is a fluoroquinolone derivatives. Fluoroquinolones are highly effective against gram positive and gram negative bacteria both *in vivo* and *in vitro*.

PT-01

PT-01 a controlled-release insert, was developed for topical chemotherapy in periodontal disease. It is a soluble insert that consists of fast release and sustained-release parts containing 10% ofloxacin (OFLX) as an antibacterial agent and showed a constant drug level of above 2 mg/ml (Minimum MIC for most pathogenic organisms) which could be sustained for up to 7 days. The controlled release system exhibited a biphasic pattern with a rapid early release phase peaking at approximately 12 µg/ml and stabilizing at approximately 2 µg/ml from day 3 to 7 following insertion [18]. The PT-01 was found to be effective in the reduction of supra gingival plaque, reduction in the plaque index, reduction in bleeding on probing [19].

Herbal agents used in local drug delivery system

Recently, usage of the herbal product has increased because of they are moderately safe nature of herbal extracts; many herbal products and their components are being used for treating periodontitis in the form of local drugs delivery. Some of them are listed below.

Neem

Neem leaf extract can help in reducing bacterial load in dental plaque levels that cause the initiation and progression of periodontitis. It is evaluated that bioactive materials available in neem leads to the presence of gallotannins during the early stages of plaque formation that could effectively decrease the bacterial load in dental plaque and help removal of plaque from the tooth surface and oral cavity through the aggregate formation. Additionally, the effective inhibition of glucosyl transferase activity and the reduced bacterial adhesion to saliva-coated hydroxyl appetite suggest some potential antiplaque activity [20].

Aloe vera

Aloe vera is most commonly used medicinal cactus plant that belongs to the Liliaceae family. More than 300 species of aloe plants exist in the world, but only two species have been studied for local drug delivery, which are *Aloe barbadensis* and *Aloe arborescence*. Aloe vera is having anti-inflammatory, antibacterial, antioxidant, antiviral and antifungal actions and also produces hypoglycemic effects. It is effective in reducing gingival bleeding, inflammation and swelling. It is a powerful healing promoter and can be used following tooth extractions also [21].

Lemon grass

It is a popular medicinal plant. This plant is most commonly used in teas, cosmetics and folk medicine for its antiseptic, antiemetic, antirheumatic, analgesic and antipyretic properties. Its chemical components like phenol and flavonoid substances were reported to show many *in-vitro* and *in-vivo* biological activities such as antioxidant, anti-inflammatory and anti-mutagenic activities. At a favourable concentration of 2% lemongrass, essential oil appears to be an effective local drug delivery agent as an adjunct to mechanical nonsurgical periodontal therapy [22].

Green tea

Green tea is an effective local drug delivery agent as it contains a number of bioactive chemicals such as flavonoids, including catechins and their derivatives. Green tea is rich in therapeutic effects such as antioxidant, anticollagenase, anti-inflammatory, anti-caries, anti-fungal, antiviral and antibacterial effects. Mageed MJ., *et al*. found that the antimicrobial effects of green tea extracts on *Porphyromonas gingivalis*, and he found that alcoholic green tea extract was able to inhibit *Porphyromonas gingivalis* [23].

Tea tree oil

Tea tree oil (TTO) is derived from the paperbark tea tree. TTO has a broad-spectrum antimicrobial, antifungal, antiviral, antioxidant and anti-inflammatory effect. Elgendy EA suggested that TTO is effective and successful as an adjunctive treatment of scaling and root planing on the clinical parameters [24].

Curcumin

Turmeric (*Curcuma longa*) is an Indian spice derived from the rhizomes, a perennial member of the Zingiberaceae family. It is rich in curcuminoids such as curcumin (diferuloylmethane), demethoxycurcumin and bisdemethoxycurcumin as well as volatile oils (turmerone, atlantone and zingiberene), sugars, proteins and resins. Curcumin exhibits anti-inflammatory, antioxidant, anticarcinogenic, antiviral and antimicrobial activities. Curcumin modulates the inflammatory response by down-regulating the activity of cyclooxygenase-2, lipoxygenase and inducible nitric oxide synthase enzymes and inhibits the production of the inflammatory cytokines.

Oak

Oak is a species from the Fagacea family. Oak is rich in hemostatic, anti-bacterial, anti-inflammatory, antinociceptive and anti-oxidant effects and has been traditionally used for the treatment of gastric ulcers, superficial injuries and local inflammation. Oak has been evaluated as a local drug delivery agent in periodontal diseases [14].

Coriander

Coriander sativum is from the Umbelliferae family was used in Iranian folk medicine as a carminative and spasmolytic agent. It is effective local drug delivery agent as it has anti-inflammatory, analgesic, anti-bacterial and antioxidant activities. *C. sativum* extract has tannins also. Yaghini J conducted a randomized, double blinded controlled trial to evaluate the clinical effects of subgingival application of herbal gel (extracts of oak and coriander) in periodontal pockets. Results showed statistically significantimprovements in periodontal indices ($P = < 0.05$) [25].

Babul

Babul has cyanogenic glycosides in addition to several enzymes such as oxidases, peroxidases, and pectinases that have shown to inhibit microbial growth. Its bark contains tannins (24 - 42%) which have analgesic and anti-inflammatory properties.

Bakul

One of the major pharmacologically active ingredients lupeol is present in bakul has anti-inflammatoryand anti-microbial properties [26].

Pomegranate

Pomegranate has active compounds containing polyphenolic flavonoids (e.g. Punicalagins and ellagic acid) are believed to prevent gingivitis, including reduction of oxidative stress in the oral cavity, antioxidant activity, anti-inflammatory effects and anti-bacterial effects. So, rinsing with pomegranate lowers the activity of alfa glucuronidase, an enzyme that breaks down sucrose while it increased the

activities of ceruloplasmin, an antioxidant enzyme. Gomes., *et al*. (2016) did a study to evaluate the antimicrobial activity of pomegranate glycolic extract (PGE) against the periodontal pathogen *Porphyromonas gingivalis* by using *Galleria mellonella* as *in-vivo* model and results were significant [27].

Conclusion

The review of studies suggested that the local drug delivery devices are a useful and productive adjunct to conventional surgical or non-surgical periodontal therapy but are no substitute for these measures. Controlled release delivery drug systems containing antibacterial, anti-inflammatory, antioxidant properties can be indicated effectively in the management of periodontitis. The local drug delivery provides a better improved outcome in periodontal conditions. Various chemical and herbal products are evaluated in local drug delivery systems with controlled release properties. It aims to minimize drug degradation and loss, prevent harmful adverse effects and increase drug bioavailability at the site of the lesion. However, the drug fails to completely replace the conventional scaling and root planning. Thus, the benefit of these drug as monotherapy is questionable.

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