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Dr. Uma Sudhakar
Professor and HOD, Department
of Periodontics, Thai
Moogambigai Dental College and
Hospital, Chennai, Tamil Nadu,
India

K Ruth Gethsie
Student-Intern, Department of
Periodontics, Thai Moogambigai
Dental College and Hospital,
Chennai, Tamil Nadu, India

H Priyanka
Student-Intern, Department Of
Periodontics, Thai Moogambigai
Dental College and Hospital,
Chennai, Tamil Nadu, India

SS Fathima Zinneerah
Student-Intern, Department Of
Periodontics, Thai Moogambigai
Dental College and Hospital,
Chennai, Tamil Nadu, India.

Corresponding Author:
K Ruth Gethsie
Student-Intern, Department of
Periodontics, Thai Moogambigai
Dental College and Hospital,
Chennai, Tamil Nadu, India

Local drug delivery drugs and systems

Dr. Uma Sudhakar, K Ruth Gethsie, H Priyanka and SS Fathima Zinneerah

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Abstract

Periodontal disease is a multifactorial disease that affects the supporting tissues resulting in destruction of supporting structure. Non surgical periodontal treatment has been a cornerstone in the management of periodontics. Local drug delivery system is the application of anti microbial or anti infective agent that would target pathogenic micro organisms by delivering it at the base of the pocket yielding a stable and good clinical outcome along with mechanical debridement. So aim of this review article is to focus upon the local drug delivery systems in the management of periodontics.

Keywords: drug, periodontics, infection, delivery.

1. Introduction

A local destructive disease like periodontitis should also be treated with local drug delivery. Local drug delivery came into existence from the 1970s, especially for its specificity in action ^[1]. Advanced development has changed the outlook and approach towards disease of periodontitis ^[2]. The host-bacteria equilibrium is shaken which provokes our immune system resulting in periodontal diseases ^[3]. Awareness and knowledge about the role of micro-organisms in periodontitis, especially how their types and colonization pattern affects the severity, clearly indicates that scaling and root planing alone won't be sufficient ^[4]. Therefore in addition to mechanical debridement, systemic antibiotics should be incorporated in the treatment plan, but it has side-effects like antibiotic resistance and super-infections hence to avoid this local drug delivery is needed ^[2]. A number of antimicrobial agents are being used as local drug delivery agent and each have been proved to be effective in reducing the infection. There are drug delivery systems which plays a major role in the efficacy of the drug. Different drug delivery systems are used for different antimicrobial agents. Many advanced trends such as micro-particulate and nano-particulate systems have emerged which delivers the drug in a more organised and controlled manner ^[4].

2. Local Drug Delivery

After the introduction of systemic drugs, the disease of periodontitis has been dealt with different types of drugs. Few dis-advantages in the systemic drugs paved the way for the introduction of local drug delivery ^[5]. Though the systemic drugs can reach the deepest micro-organisms of the pockets and furcations and even in the connective tissues and completely eradicate the pathogens not leaving any chance for re-infection, still they have their own flaws. Exposing the whole body to antibiotics to just treat the infection of the gums is unnecessary as it develops resistant bacterial strains, allergic sensitization of patients and may cause other side-effects like nausea, vomiting and gastrointestinal disturbances ^[6]. While the local drug delivery fills all the holes, less dosage of drug is sufficient enough as it is concentrated only in the site of infection and the drug is sustained in that place for a sufficient period of time. Altogether local drug delivery proves to be effective against the periodontal infection and at the same time there are no systemic side-effects ^[7].

3. Drugs

3.1 Tetracycline

- Marketed as: Actisite, Periodontal plus AB [8].
- Structure: Flexible yellow fibres which are 23 cm long and 0.5 cm of diameter [9].
- Amount: 12.7 mg of tetracycline HCL
- Duration of drug release: 10 days after insertion.
- It is also used with serratiopeptidase which has anti-inflammatory effect [10].
- Advantage: Highly effective in managing periodontal diseases.
- Disadvantage: Early degradation and it can sometimes cause candidal infection [8].

3.2 Doxycycline

- Marketed as: Atridox [8]
- 2 syringe mixing system

Advantages

- Reduces the anaerobic population in plaque.

- It also has anti-inflammatory property.
- Maintains high concentration in pockets and sustains for 7-10 days [11].

3.3 Metronidazole

- Available as: Elyzol [8]
- Dosage form: Gel
- Semi-solid suspension of metronidazole benzoate in glyceryl mono-oleate and triglyceride.
- The concentration of the drug in the pocket rises exponentially [12].
- It mainly targets anaerobes and most of the periodontal problems are caused by anaerobes [13]

3.4 Minocycline

- Marketed as: Arestin, Dentomycin or Periocline [8].
- Dosage form: Microspheres in HCL of polymer of polyglycoside-co-dl lactide
- Advantages: Marked substantivity and greater lipid solubility [13].

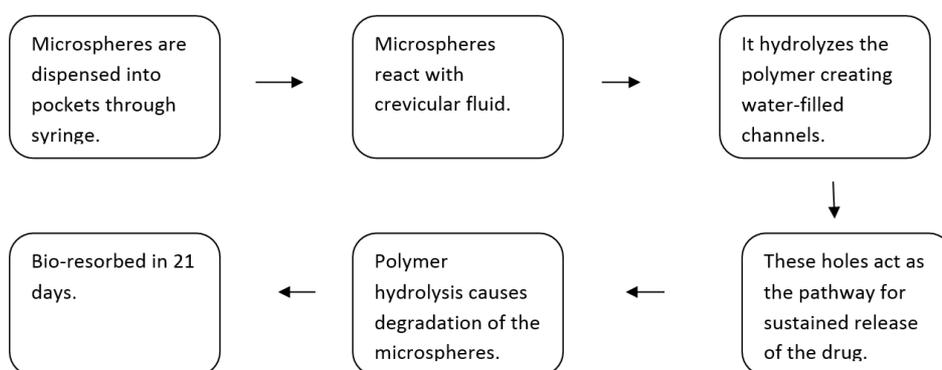


Fig 1: Mechanism of delivery

3.5 Chlorhexidine

- Available as: Periochip, Chlosite, Periochol [8].
- Dosage forms: Gels, chips.
- Composition: 34% Chlorhexidine in gelatine matrix
- Structure: Length – 5mm, Width – 4mm. 4.5 mg of Chlorhexidine gluconate
- Indication: In pockets more than 5mm of depth [14].

Table 1: Release of chlorhexidine

Duration	Chlorhexidine Concentration in GCF
First 48 hours after insertion	800-1000 ppm
Next 6 days	100-500 ppm

3.6 Ofloxacin

- Available as: Ofloxacin inserts PT – 01
- Has both fast and sustained release of drug.
- First it has initial early release phase which is 12Mg/ml and after 3-7 days of insertion the concentration is 2 Mg/ml [8].

3.7 Azithromycin

- Broad antimicrobial spectrum of action.
- Dosage form: Gel [13].

4. Drug Delivery Systems

These systems help in delivering the antimicrobial agent into the periodontal pocket with a consistent release of constant concentration to have a proper control over the infections. Based on the duration of action, these devices are categorized into sustained release devices and controlled release devices. In sustained release the drug is delivered for only less than 24 hours hence it required multiple applications of the drug whereas in controlled delivery the drug is delivered for more than 24 hours hence one time application is mostly sufficient enough to get the desirable results [15].

4.1 Fibres

Table 2: Types of fibres and their features [15]

Drug Delivery Device	Duration of Delivery	Mechanism of Delivery	Structure and Composition	Advantages
1A. Hollow fibres	Sustained	Simple diffusion	Cellulose acetate fibres filled with tetracycline hydrochloride.	• Single use helps in freeing gingival sulcus from spirochetes.
1B. Monolithic fibres	Sustained	Simple diffusion	<ul style="list-style-type: none"> • Incorporation of drugs in molten state. • Then high temperature followed by cooling. 	• Retards drug release

4.2 Gels

It is a semisolid type of drug delivery system that helps in delivering the antibiotics right in the target sites. Its biocompatible and bio-adhesive ability helps in proper adherence to the mucosa of the pocket. Gels are easily manufactured and it is easy to use^[15]. The allergic reactions are not much of a concern as the gels are eliminated rapidly by the catabolic pathway. Hydrogels are 3D cross linked structures of ionic interaction and hydrogen bonding. It has many advantages such as good structural integrity and cellular organisation^[16].

4.3 Films

It is the most commonly used local drug delivery system for intra-pocket therapy. The drugs are placed in a matrix of polymer from which it is delivered by diffusion and/or erosion of matrix or by its dissolution. It is prepared by solvent casting and direct milling. The suitable sized films are used or the films are cut into suitable dimensions to be properly placed in the surface of gingiva^[15]. If the thickness is less than 400Mm the films would not get displaced easily and would not cause any inconvenience during routine oral hygiene procedures. The films which are water-soluble and bio-degradable undergo dissolution or erosion of the matrix dispersing out the drugs whereas in the case of water-insoluble films, the drugs are released by diffusion process. Most commonly used drugs within the films are chlorhexidine diacetate, metronidazole, tetracycline and minocycline. Periochip is made up of cross-linked hydrolysed gelatine and glycerine and contains the antimicrobial agent which is the chlorhexidine digluconate. In the first 24 hours of insertion, 40% of chlorhexidine is released by diffusion which is followed by slow drug release which is for about 7 days of insertion where the delivery is by the enzymatic degradation

of the films^[17].

Table 3: Advantages of films and their types

Drug Delivery Device	Advantages
Films	<ul style="list-style-type: none"> • Easy insertion • Appropriate sizing for suiting the pockets • Totally submerged with less discomfort.
A. Periochip	<ul style="list-style-type: none"> • Film components are adhesive in nature. • Remarkable results in periodontal health status.
B. Periocol-CG	<ul style="list-style-type: none"> • Collagen is chemotactic to fibroblasts thus enhances fibroblast attachment. • Stimulates platelet degranulation • Accelerates fibres and clot attachment.

4.4 Microparticulate System

Polyalphanhydroxy acids such as polylactide or polylactide-co-glycolide (PLGA) are used with the antimicrobial agents in the micro-particles system. Tetracycline, minocycline, chlorhexidine digluconate are used along the microspheres.^[18] Dosage form: Chip, dental paste or injection.

Advantages:

- Improved patient compliance.
- Highly stable system
- Delivers optimum concentration of the drug.^[15]
- Sustained therapeutic effect
- Enhanced bioavailability
- Decrease in the potential of adverse effects.^[18]

4.5 Implants, Injectable Systems, Vesicular Systems, Strips and Compacts

Table 4: Implants, injectable systems, vesicular systems, strips and compact.

Drug Delivery Device	Mechanism of Delivery	Structure and Composition	Advantages
Implants	Formulation is placed in the pocket by a syringe and then the implant is formed ^[18] .	Poly (DL-lactide) [PLA] and poly (DL-lactide-co-glycolide) [PLGA] are potential polymer candidates.	<ul style="list-style-type: none"> • Ease of administration. • Low cost^[18].
Injectable systems	Application is done without pain using a syringe ^[19] .	Antibiotic agents	<ul style="list-style-type: none"> • Cost saving • It fills the pocket hence reaching large proportion of pathogens. • Easy application^[19].
Vesicular systems	The proteoliposomes are retained by the bacteria eventually delivering triclosan into the cellular interiors ^[15] .	Succinylated concanavalin-A (lectin) bearing liposomes helps in delivering triclosan to periodontal biofilms.	<ul style="list-style-type: none"> • Affinity and specificity of immunoliposomes to reduce dental plaque^[15].
Strips and compacts	Flexible polymer having a position occurring mechanism having inter-proximal spacing through which drugs are dispersed ^[20]	Acrylic strips fabricated using monomers and polymers and different concentrations of anti-microbial agents.	<ul style="list-style-type: none"> • Effect persists even after 3 weeks of removal of the strips. • Causes decrease in number of spirochetes^[20].

4.6 Nanoparticulate System

Controlled slow-drug release has been the most desired drug delivery pattern.^[18] More than the microspheres and emulsion-based delivery systems, their superiority in dispersion in aqueous medium their controlled release rate and increased stability proves them to be highly effective. Nanoparticles are generally very small in size hence even the deepest pockets which are mostly unreachable for the other

delivery systems, is easily accessible here. As the drugs are delivered in a slow and sustained manner for extended period of time, the drug is equally distributed and thus there is a decrease in the frequency of administration. Their absorption and bio-availability capacity is so high that a large dose of drug is not necessary anymore. To improve the therapeutic effect, nanoparticles are combined with hydrogels.^[21]

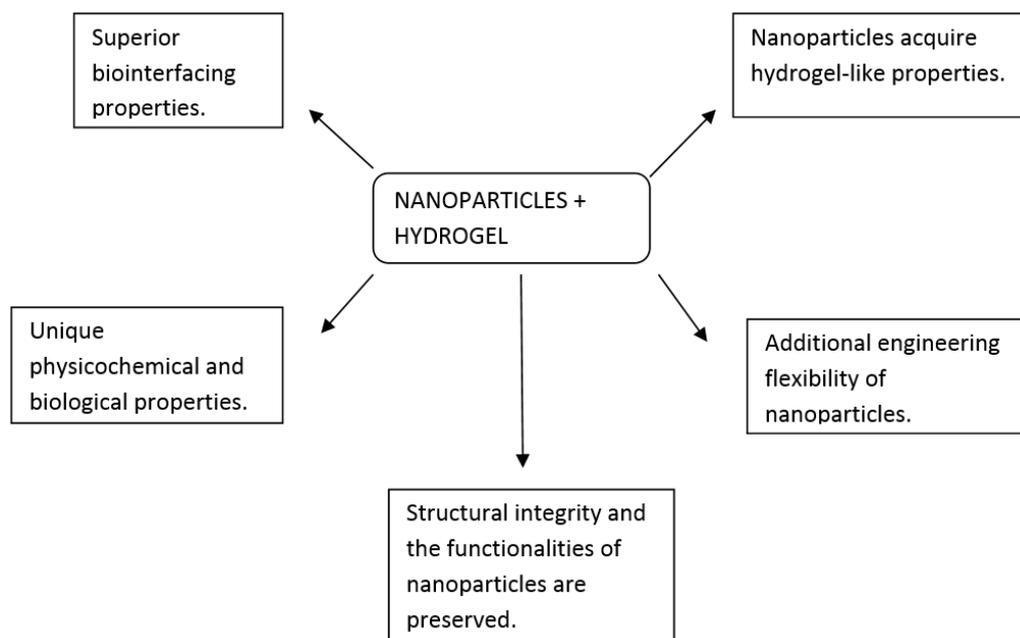


Fig 2: Advantages of Nanoparticles and hydrogel ^[21]

5. Conclusion

Various antimicrobial agents are available with different advantages and different mode of delivery. Suitable antibiotic agent should be selected in suitable dosage form based on the necessity of the patient for successful results. Awareness should be increased among the dental students to use these local drug deliveries in their regular clinical practise.

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