Intrapocket Local Drug Delivery System for Periodontitis

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Abstract

Periodontitis is sort of inflammation disorder related to the tooth supportive tissue majorly occurring due to microbial infestations. In this disease, dental plaque is considered as the main cause and it is found as bio film. Plaque consists of micro-organisms which initiate inflammatory activities that ultimately leads to destruction of connective tissue, pocket formation and teeth bone loss. Varieties of drug administration or delivery systems are employed to eradicate this condition. As periodontitis is caused by the micro-organisms so antibacterial agents have been found effective in the management of periodontal infection. Mechanical removal of deposited plaque and repeated administration of antibacterial agents topically and systemically are limited due to limited or non-accessibility to causing microbes present in the periodontal pocket. Local delivery of antimicrobial has been studied for the likelihood to overcome these limitations of therapies used conventionally. The use of sustained/controlled release formulations to deliver antibacterial drugs to the site of infection is gaining interest and found to be promising delivery system. The dental inserts provide effective treatment at the infection site for prolonged duration of time at much lesser doses. This review focuses on the dental inserts for the delivery of drugs to infection site (intrapocket system), focusing on their applications, advantages and efficiency.

Keywords: Periodontitis, periodontal pocket, local delivery, dental inserts.

How to cite this article: Chaudhary R (2020): Intrapocket local drug delivery system for periodontitis, Ann Trop Med & Public Health; 23(S15): SP231548; DOI: http://doi.org/10.36295/ASRO.2020.231548

Introduction

The word periodontal means "around the tooth". Periodontitis is chronic bacterial infection that affects the teeth supporting gums and bones. Periodontal diseases can also be simple inflammation of the gum and severe disease as well if remain untreated and leads to severe bone and soft tissue damage that is present around the teeth. In the late stage, teeth are lost.[1] is sort of inflammation disorder related to the tooth supportive tissue majorly occurring due to microbial infestations. It involves progressive loss of the alveolar bone around the teeth, and if do not get treated on time will leads to the destruction and loss of teeth. Periodontitis is caused by microbes via growing on the surface of the tooth, and due to compromised immunity against these micro–organisms.[2] The main causative factor is the formation of a microbial biofilm at the gingivocervical margin, which evokes an inflammatory response in the gingival tissue, which progresses deeper into the periodontal tissue.[3] The microbes responsible for causing periodontitis are:[4]

- Porphyromonas gingivalis (Adult periodontitis)
• Prevotella intermedia
• Actinobacillus actinomycetemcomitans (Juvenile periodontitis)

As the periodontitis occurs and continues to grow, various changes have been observed like changes in the regular structure of gingival tissues, gingival blood loss and formation of periodontal pocket. The suitable environment that is required for growth of pathogenic bacteria is provided by this periodontal pocket. The warm and moist environment in periodontal pocket fasten the growth of gram negative, anaerobic bacteria. Periodontal disease includes various conditions depending upon the type of bacteria and severity of disease such as chronic periodontitis, aggressive and necrotizing periodontitis. The difference between healthy perodontium and periodontal disease is shown in Fig.1.

**Fig.1: Comparison of Healthy Periodontium and Periodontal Disease**

**Diagnosis of periodontitis**
Periodontitis is diagnosed by using visual analysis method to diagnose the soft gum tissues around the teeth using a probe and x-ray films and to determine the percent of bone loss around the teeth. Experts of periodontal disease are called as periodontists and this specific field dealing with periodontitis is known as "periodontology" or “periodontics”.[5]
Pathogenic mechanism

Tooth-associated microbial biofilms are produced by gram negative bacteria. This microbial biofilm causes chronic periodontitis that ultimately leads to damage of bone and soft tissue present around tooth. Several mediators target the alveolar bone, supporting connective tissue periodontal ligament. These mediators are released as a result of endotoxin derived from pathogens. The possible pathogenic mechanism of periodontal disease is as shown in Fig.2.

![Flow Chart for Pathogenesis of Periodontal Disease](image)

The periodontal pocket continues to nurture the pathogenic bacteria associated with or responsible for the disease. Immediate extensive treatment is required for this disease and failing of the same leads to tooth loss. Furthermore, in treating the disorder, the diagnosis of the infection and the removal of the periodontal pocket is regarded as first concern. The understanding of etiological and microbiological details of periodontal pocket flora have lead to advancement in therapeutic strategies managing and treating its progression.[6] As pathogenic bacteria is
responsible for causing the periodontal diseases, therefore treatment by antimicrobial agents are found to be effective against it. Bacteria like *Actinobacillus actinomycetem comitans* have the capability to penetrate the connective tissues and to reside deep into the tissue. Hence use of antimicrobials along with scaling and root planning become very much necessary to eradicate the tissue associated bacteria effectively. Antimicrobials can be given as both route that is systemically as well as locally. The main purpose of this antimicrobial therapy is to deliver desired therapeutic concentration of drug at the site of action that inhibit growth of pathogenic bacteria. The most effective and efficient way of achieving this therapeutic concentration is by systemic route where the drug acts on the sub gingival flora by reaching into the crevicular fluid. But this systemic route of administration has limitation and it may not always seem to be ideal. This limitation is due to the development of bacterial resistance. The antimicrobials delivered locally offer several advantages over systemic antimicrobials. The medications distributed locally do not display systemic toxicity. Bacterial resistance to locally administered drugs is not established and a high drug concentration is obtained and sustained at the target site for longer period of time. Local drug delivery has more patient compliance than systemic delivery as it overcomes:

- Drug toxicity
- Acquired bacterial resistance
- Drug interaction

**Local Drug Delivery Devices**

Following approaches can be employed to improve the action of drug at the required site:

- Sustained/controlled drug release system
- Site specific drug delivery system

The combination of therapeutic agent with appropriate vehicles, which are usually polymers, has developed these two methods. Polymers may be of natural or synthetic origin. But it is found that such structures do not produce promising results in clinical phase trials to demonstrate their efficacy.

**Controlled Released Drug Delivery Devices**

(1) **Reservoir device**

The reservoir unit consists of a tube which has a central compartment of drug solution. For the number of days normally one week, this dialysis tube is inserted into thr periodontal pocket. Some of the reservoir devices have no properties for controlling the rate. Such devices include tubing with hollow fibres, gels and dialysis tubing. These systems are seldom regarded as continuous release devices as numerous studies show that they are responsible for many problems like premature loss and the immediate release of therapeutic agents.

(2) **Monolithic devices**

The drug is uniformly dispersed in solid polymer matrix in the monolithic devices. The mechanism by which drug release is diffusion through matrix. Examples of polymer matrix include acrylic polymers and ethylene vinyl acetate (EVA) based fibers. Acrylic strips are normally of 0-2 mm thickness. Drug gets release over a number of days

[Annals of Tropical Medicine & Public Health](http://doi.org/10.36295/ASRO.2020.231548)
Other examples of polymers used for preparing monolithic devices include poly ethylene glycol (PEG), Hydroxy propyl methyl cellulose (HPMC), ethyl cellulose (EC) and collagen films. Bioabsorbable, biodegradable devices can be left as such once get placed which ultimately eliminates the risk of disturbing after insertion.

For designing this system, the polymer used can be obtained from natural [7], semi-synthetic [8,9] or synthetic source. The essential criteria for the selection of polymers is their biodegradation during use. Non-biodegradable systems have one limitation that they need to be removed from the action site after due drug delivery, as it may lead to irritation and inflammation of the site which in turn causes disagreement of patient. Polymers of natural origin have been considered as most promising carriers.[10] Sustained release drug delivery system based on biodegradable polymers can be used effectively in maintaining desired concentrations for prolonged period of time. Along with improving compliance, biodegradable devices are more cost effective as once they placed in the pocket, they will not require revisit to the doctor/hospital for removal and get degrade itself with time. Hence for designing useful and effective periodontal therapy, it becomes necessary to design a biodegradable polymer based drug delivery system that can maintain effective release rate pattern and drug concentration in the periodontal pocket. At the same time, it get eroded throughout the duration of treatment upto several days.

**Local intrapocket drug delivery**

The responsible pathogenic bacteria have to be known for providing an effective antimicrobial agent in the treatment of periodontal disease. The antimicrobial agent chosen must be effective against the pathogenic bacteria and no bacterial resistance develops for an appropriate period. The periodontal pocket also plays an important role in the efficacy of drug delivery systems, as it provides a convenient reservoir that allows to quickly insert drug delivery device.

The gingival crevicular fluid helps to release the drugs as it provides an effective medium that aids to release a drug from the solid dosage form type and for its delivery within the cavity of the periodontal. Because periodontal diseases are often confined to the immediate environment of the periodontal pocket, the periodontal pocket becomes a preferred site for local drug delivery care .[11] The sustained-release dosage types optimizes the therapeutic effect of antimicrobials by maintaining target concentration of drug over minimum inhibitory concentration (MIC) in a controlled manner for a prolonged period of time.[12]

**Intrapocket Drug Delivery Devices**

Intrapocket devices can be divided into two broad categories [13]

- Degradable intrapocket devices
- Non-degradable intrapocket devices.

The great benefit of patient compliance is that degradable intrapocket systems have to pay only one visit to the therapist to implant the system that minimizes non compliance with the patients.[14] The benefit of non degradable...
intrapocket devices is that the therapist monitors the withdrawal of the device at any time and thus has more control over the time the medication is exposed to the pocket environment.

Advantages of intrapocket drug delivery
- Boost enforcement and patient acceptance
- Easy exposure to disease targeting and various periodontal diseases.
- Reduce cost of the diagnosis.
- Effective route for the administration of drugs in patients that are extremely ill, pediatric and geriatric and who can not swallow.
- Fast absorption by rich blood supply as opposed to transdermal delivery.
- Prevent first pass metabolism in the liver.
- Increasing the effectiveness of the drug.
- Safe and easy distribution route
- Longer response time.
- Quick and noninvasive use

Limitations of intrapocket drug delivery
- Do not work for local irritants.
- This route cannot be used to prescribe any of the medicines responsible for either erythema, itching or local arrhythmias.
- Small dose given due to relatively limited targeted area.
- Not feasible for peptide delivery due to peptidase enzyme involvement.
- Highly potent drugs are only effective
- Often the cost of making films or insets are considered.

Factors Affecting Local Delivery of Drugs in Periodontal Pockets
To be effective, a pharmacological agent must reach its target location of action and be held there for reasonable period of time at appropriate concentration. These three parameters affect the local distribution of drug to the periodontal pocket of and also affect the selection of the correct therapeutic agent.

1) Site of Action: The first important factor to be considered is the desired site of action. As the bacteria responsible for periodontitis resides in the periodontal pocket so the desired site of action is periodontal pocket and bacteria present in junctional epithelium, connective tissue, cementum and dentine. The antibacterial agent must not only reaches the periodontal pocket but also target the bacteria residing there. It is necessary to disrupt the microbial biofilm environment in the pocket for the early penetration of the local therapeutic agent otherwise the biofilm would prevent the antimicrobial agent from spreading through the soft tissue wall.

2) Concentration: Drug should have a dose higher than Minimal Inhibitory Concentration (MIC) and less than maximum safe concentration (MSC). This is the drug’s in vitro concentration that inhibits or destroys 90% of
target species in culture. At its lowest dose the drug should be more effective. The dose which triggers adverse effect should be evaluated first and correct therapeutic dose should be determined. The therapeutic dose should be between MIC and toxic dose.

(3) **Time:** if a drug achieves an appropriate concentration at the desired site of action, it must remain at the target site for a suitable period of time to exert its pharmacological impact. Biofilm condition causes slow growth of microorganisms in periodontal pockets and it affects the effectiveness of given antibiotics. Drug kinetics must follow zero order to remain focused for longer period of time.

**Dental Inserts**

Dental films are the most widely used form of dental inserts which are easy to fabricate and which show effective results. Films are the implantable devices in which drug is encapsulated in a manner that it is distributed throughout the polymer matrix. Controlled release of drug occurs through diffusion, dissolution or erosion mechanism. The release pattern of drug depends on type of polymer used to formulate the film. An ideal film should be flexible, smooth and elastic in nature. Film needs to be properly solid enough to withstand breakage due to pressure exerted by mouth. This also needs to have sufficient muco-adhesive properties to remain in the pocket for the desired duration of action. For certain cases, if film swelling occurs, it should not be too severe or it will not cause discomfort. There are many benefits to this dosage form for intrapocket delivery. With minimal pain to the patient it can be conveniently inserted deeper into the periodontal cavity. If the films thickness is less than 400mm and has adequate adhesive properties, it will stay in the pocket without any visible interference or irritation with the oral hygiene habits of the patient. Films releasing drugs by diffusion alone are prepared using water-insoluble, non-degradable polymers [15], whereas films releasing drugs by diffusion and matrix erosion or dissolution are made using soluble or biodegradable polymers.[16]

The advantages of such a device include
1. Simple insertion procedure for the patient.
2. Optimum measurements which agree well with the pocket measurements resulting no discomfort.
3. Minimum pain on insertion into pocket.[17-20]

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Product</th>
<th>Dosage form</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Actisite</td>
<td>Fiber</td>
</tr>
<tr>
<td>2</td>
<td>Atridox</td>
<td>Biodegradable mix in syringe</td>
</tr>
</tbody>
</table>

**Table No.1: Commercially available dental products for local drug delivery**
<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Arestin</td>
<td>Biodegradable powder in syringe</td>
</tr>
<tr>
<td>4</td>
<td>Periochip</td>
<td>Biodegradable insert</td>
</tr>
<tr>
<td>5</td>
<td>Periochip</td>
<td>Film</td>
</tr>
<tr>
<td>6</td>
<td>Elyzol</td>
<td>Gel</td>
</tr>
</tbody>
</table>

**Methods of preparation:**
The various methods which can be employed for preparing films are:

- Solvent casting method
- Melt fabrication method
- *In situ* polymerization method

1. **Solvent casting method**
The most commonly used method for preparing dental films is solvent casting method. In this method, weighed quantity of polymer is added in suitable solvent and dissolved with continuous stirring and a plasticizer is added to it. An accurately weighed amount of drug is incorporated into this solution and mixed properly. After complete mixing, the solution is poured in clean glass petri plates and left undisturbed for 24-48 hrs at room temperature for allowing the solvent to evaporate. After complete evaporation of solvent, films are produced which are then cut into required size, wrapped properly and stored in a dessicator for further evaluation studies. For preparing cross-linked films a suitable cross-linking agent like glutaraldehyde may be incorporated into the polymer solution. This method is ideal for making films containing heat sensitive APIs.

2. **Melt fabrication method**
The drug and other excipients are first combined at a dry state in this process. Heating process ends and the mixture is melted. The molten mass is extruded from the extruder for hot melting. The benefit of this method over others is that the solvent is completely removed. At room temperature the films are allowed to cool and cut to the desired size.

3. **In situ polymerization method**
A liquid monomer or pre-polymer is polymerized inside a suitable mould. The mechanism of release from monolithic devices is based on drug diffusion via polymer matrix. Regulated rate release can be accomplished by manipulating the device, using the ideal monomer, cross-linking agent, plasticizer and appropriate co-polymers.
Characterization of the films

The prepared films are subjected to the preliminary evaluation testing. Films with any defects are excluded from further research. Specific characterization properties such as thickness uniformity, weight uniformity, percentage loss of moisture, folding endurance, surface pH, swelling index and drug content uniformity of the prepared films were determined using appropriate methods.[21-24]

1. Thickness uniformity

Every film’s thickness is determined by using a screw gauge (thickness tester) at different film positions and the average is calculated.

2. Uniformity of weight

Film of specific dimensions is taken and weighed carefully. The weight variation of each film is calculated.

3. Folding endurance studies

The film’s folding endurance is determined to know film’s power. It is measured by repeated folding at the same point of one selected film until it splits or folds up to 350 times, which is considered sufficient to reveal good film properties. Around the same point the film is folded number of times without breaking gives the value of the folding endurance.

4. Percentage moisture loss

The films of various concentrations are correctly weighed and then held in desiccators for 3 consecutive days and then reweighed. Therefore the percentage loss of moisture is determined.

% moisture loss is calculated by using formula:
\[
\% \text{Moisture loss} = \frac{(\text{initial wt} - \text{final wt})}{\text{initial wt}} \times 100.
\]

5. Surface pH

The pH of the surface is known to be the main factor influencing the drug activity. Surface pH of the films is chosen to examine potential side effects due to changes in pH in vivo as an acid or alkaline pH may cause discomfort to the periodontal mucosa. The film to be screened is put in a petri-plate, moistened with 0.5ml phosphate buffer 6.6 and held for 1 hour as such. The pH is noted after bringing the pH meter electrode into contact with the formulation surface and allowing for a balancing period of 1 min.

6. Swelling Index

The film swelling index test is carried out in pH 6.6 simulated salivary fluid. The film sample is weighed and put in a pre-weighted roughly 800micrometer mesh stainless steel wire sieve. The film sample mesh was then immersed in 15ml of the simulated salivary fluid in a china dish. The stainless steel mesh is replaced at specific time intervals, excess moisture removed by carefully cleaning and reweighing it with absorbent tissue. Increase in the film weight is measured at each interval of time until a constant weight is observed.

The degree of swelling is calculated by using the formula:
\[
S.I = \frac{(Wt - W0)}{W0}
\]
Where, S.I is the swelling Index
Wt is the weight of film at time t
W0 is the weight of the film at time 0.

7. Drug content uniformity
The drug-loaded films of known weight are dissolved in solvent medium, samples are extracted at different time intervals, diluted appropriately with the same solvent and the amount of drug present is carefully measured by UV/VIS spectrophotometer.

8. In vitro Drug Release Studies
The pH of gingival fluid varies from 6.5 – 6.8, so pH 6.8 phosphate buffer is used as simulated gingival fluid. In addition, because the film should be immobile in the periodontal pocket, a static dissolution model is adopted for the dissolution studies. Sets of three films of known weight and dimensions are separately placed in small sealed test tubes containing 5ml of phosphate buffer with pH 6.8 and held for 24 hours at 37 ± 0.5 °C. Then 1ml of buffer solution is pipetted out and replaced by 1.0 ml of fresh buffer. After that the concentration of released drug is determined by UV/VIS spectrophotometer.

9. Stability studies
The stability of polymer dental films filled entirely with drug is tested at various temperatures. Three sets (12 strips in each set) weigh the films of scale (7mm × 2 mm). The films are individually wrapped in aluminum foil as well as in butter paper and placed in petri plates. These containers are kept at different temperature conditions such as room temperature (27 ± 2°C), oven temperature (40 ± 2°C) and in a refrigerator (5–8 ± 2°C) for specific period of time. For any physical changes such as color, shape, flexibility or texture, all polymeric films are examined and the drug content is measured at an interval of 1 week. In addition, the volume of drug in the film is spectrophotometrically measured. The drug sample solutions are further screened to detect any potential spectral changes.[25-26]

Conclusion
The most important step in the treatment of periodontitis is complete elimination of the micro organisms from the periodontal pocket. Mouth rinsing and irrigation were the old forms of treatment used which have a range of drawbacks. These mouth rinsing and irrigation restrictions have inspired work to develop alternative drug delivery systems. Advancement in delivery technology have led to the necessary controlled release of drugs. The criteria for the treatment of periodontal disease include a local drug delivery system to target an anti-infective agent at the infection site (periodontal pocket) and to retain its effective localized concentration at effective leves for a reasonable period of time. This method along with concerted intervention, also prove helpful in preventing antibiotic resistance from occurring. Thus, site-specific drug delivery can address the drawbacks faced by systemic antimicrobial administration for periodontitis where the medication is diluted several times until it reaches the appropriate site of action. It can be therefore concluded that the antimicrobial drug is an important alternative to traditional periodontal treatment as site-specific dental formulations in the periodontal pocket.
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http://doi.org/10.36295/ASRO.2020.231548