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Periodontal Film for the Treatment of Periodontal Disease

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Abstract

Periodontitis is a disease associated with inflammation on the tissue around the teeth. With advances in understanding the etiology and pathogenesis of periodontal disease, attention has been focused on local drug delivery systems. In the last decades, the treatment has been optimized for the use of drug delivery systems to the periodontal pocket, with the advantage of delivering the drug in the specific site, sustaining and/or controlling the drug concentration. This review approaches the main delivery systems for the administration of drugs to the periodontal pocket. Intrapocket dental films, which could be easily placed into the periodontal pocket, and be capable of delivering therapeutic concentrations of drug for prolonged period of time at a much lower dose, hence avoiding side effects.

Keywords: Periodontitis, periodontal pocket, intrapocket dental films, delivery system

INTRODUCTION

Periodontitis is a local infection with primary bacterial etiology in the gingival crevices, which affects the structural organs surrounding the teeth such as periodontal ligament, connective tissue, and bone. The warm and moist pocket environment fasters the growth of Gram-negative, anaerobic bacteria that proliferate in the sub gingival space.

It is an inflammatory disease of bacterial origin that affects the tooth-supporting tissues. The appearance of periodontal pockets is the first clinical manifestation of periodontal diseases that offers a favourable niche with low oxygen tension for bacterial colonization. Thus, the treatment of periodontitis mainly focuses on the reduction of the total bacterial, which is the primary cause of periodontal diseases.[1]

In periodontitis, resorption of the alveolar bone, detachment of the ligament supporting the tooth and formation of lesions between teeth and junctional epithelium is observed. The tissues around a tooth that support the tooth are called periodontium which are affected during periodontits. The alveolar bone which acts as a support to the tooth gets progressively lost and the multiplication of microorganisms that grows at the junction of gums and teeth causes inflammation leading to the loss of teeth and if left untreated leading to chances of stroke and other health problems. Periodontitis arise in sulcus and cervice region between gum and tooth[2]. Anatomy of diseased tooth is shown in fig.I.

Topical applications like mouthwashes, dentifrices and gels have been successfully tried in controlling the microbial plaque. Topical agent fail to penetrate deep into periodontal pockets, hence their effectiveness is limited to supragingival areas. So to overcome all these limitations various controlled drug delivery systems, administrating therapeutic levels of antibacterial agents directly into periodontal pocket have been tested as a way to minimize total body dosage and resulting side effects and to maintain therapeutic drug levels in the gingival crevicular fluid.

Conventional treatment method by oral administration of antimicrobial agents must be given in high doses to maintain the effective concentration in gingival crevicular fluid. However, high doses of antimicrobials cause side effects, such as gastrointestinal disorders, development of resistant bacteria, and suprainfection. Thus, the drug delivery system of antimicrobial agents via intra-periodontal pockets has been invented for the possibility to overcome the clinical challenge that is encountered during the systemic administration of antimicrobials.[3]

VARIOUS APPROACHES TO TREAT PERIODONTITIS [4]

Gingivitis can usually be treated simply. Plaque and tartar are removed from teeth; the inflamed tissues around a tooth usually heal quickly and completely. More serious cases of periodontitis cannot be treated by routine dental procedures. Dental surgery may be necessary to remove plaque, tartar, and infected gums tissue. Surgical access to facilitate mechanical instrumentation of the roots has been utilized to treat chronic periodontitis for decades. Appropriate therapy for patients with periodontitis varies considerably with the extent and pattern of attachment loss, local anatomical variations, type of periodontal disease, and therapeutic objectives .

The primary objectives of therapy for patients with chronic periodontitis are to halt disease progression and to resolve inflammation. Therapy at diseased site is aimed at reducing etiologic factors below the threshold capable of producing breakdown, thereby allowing repair of the affected region. Local application into periodontal pocket could be very advantageous, both in terms of rising drug concentration directly in the action site, and in preventing systemic side effects such as gastrointestinal complaints,depression, and tachycardia. Controlled delivery of chemotherapeutic agents within periodontal pockets can alter the pathogenic flora and improve clinical signs of periodontitis .

1. Conventional Periodontal therapy:

The purpose of periodontal treatment is to cure the inflamed tissue, reduce the number of pathogenic bacteria

and eliminate the depth of the diseased pockets and to stop bone resorption. The conventional methods of pocket elimination are more or less mechanical and are aimed at removal of supra and mechanical plaque and degenerated and necrotic tissue lining the gingival wall of periodontal pockets through scaling, root planning.

The mechanical debridement alone often leaves behind significant number of pathogens due to possible instrumentation or ability of microorganism to penetrate into deeper tissues. Inaccessibility and re-colonization of pathogens can occur after scaling and root planning. With oral hygiene, a pathogenic sub gingival microbial may re establish within 42 - 60 days after a single periodontal debridement session. Some deep periodontal pockets experience putative pathogen re-colonization by 120 - 240 days despite multiple sessions of sub gingival instrumentation and meticulous supra gingival plaque control.

2. Antibiotic Systemic therapy:

The use of antibiotics in the treatment of periodontal diseases helps to reduce or eliminate bacteria that cannot be removed by scaling and root planning**.** Chemotherapeutic agents can be administered systemically or locally. Tetracyclines, imidazole derivatives, fluoroquinolones etc., are the most favoured antibiotics.

Antimicrobials used to treat dental infections can be divided into two main categories, i.e., broad spectrum and narrow spectrum. Narrow-spectrum antimicrobials include penicillin, amoxicillin, cephalexin, macrolides and tetracyclines. These drugs are having a limited antimicrobial efficacy, as they are not effective against aerobic and anaerobic betalactamase producers, as well as other specific organisms. Systemic periodontal antimicrobial therapy is based on the premise that specific microorganism cause destructive periodontal disease and that the antimicrobial agent in the periodontal pocket can exceed the concentration necessary to kill the pathogens. With systemic antibiotic therapy there is a considerable variability in the therapeutic activity due to factors like poor absorption in the gastrointestinal tract, first pass metabolism, systemic distribution, bacterial sensitivity and resistance.Systemic antibiotics proved to help periodontal disease include amoxicillin, ciprofloxacin, metronidazole, tetracyclines/doxycyclines, erythromycin and clindamycin. One disadvantage of using systemic antibiotics is that the level needed to treat periodontal disease is high, because the concentration that reaches the periodontal tissues after systemic ingestion is low; additionally, overuse of systemic antibiotics to treat disease has contributed to an increasing level of antibiotic resistance worldwide. These disadvantages are absent with the use of locally applied antimicrobials. The increased toxic effects of these elevated dose level makes systemic administration unacceptable due to low benefit to risk ratio. Repeated long term use of systemic antibiotics is fraught with potential danger including resistant strains and super infections.

These draw backs can be markedly reduced if antimicrobial agent to be used locally. Because of the smaller dosage used and topical chemotherapy is much safer than systemic chemotherapy in avoiding the side effects of antibacterial agents.

3. Local Drug Delivery:

Locally applied antimicrobial agents (LAAs) enable targeted use of antimicrobials, with a lower dose than would be required if given systemically, and release the antimicrobial in a controlled manner at or above the minimum inhibitory concentration (MIC) over a period of several days. In addition to being effective at a lower dose, no antibiotic resistance has been found following the use of LAAs. Studies have found improved clinical parameters with the use of LAAs . Local applications (as mouth rinse, gels, tooth paste etc,) control only supra gingival microbial plaque or periodontal disease involving pocket formation and also requires high initial concentrations and multiple applications in order to provide sustained effectiveness. Local application of antibiotics has been achieved either by sub gingival irrigation or by incorporating the drug into different devices for insertion into periodontal pockets. Many drugs like chlorhexidine, tetracycline are tried as mouth rinses in the treatment of periodontal diseases. In-spite of its superior effects, chlorhexidine does not reach the periodontal pocket when administered as mouth rinse. Sub gingival irrigation of antimicrobial involves local drug delivery but not controlled release. Local drug delivery devices are of two types. In the first type, the drug delivery system is designed to deliver agent locally in the periodontal pocket but without any mechanism to retain therapeutic levels for a prolonged period of time. Such devices generally exhibit exponential increase and decrease in drug concentration at the site. Second type is the controlled release local drug delivery devices which may secure antimicrobial effect for a prolonged period of time at the diseased site, than that can be achieved by systemic or local topical applications and also bypasses the systemic complications. The controlled release delivery of antimicrobials directly into periodontal pocket has received greatest interest and appears to hold some promise in periodontal therapy. These delivery systems are produced by immobilizing antibiotic and antimicrobial agents with a carrier substance to provide controlled local release.

Local antimicrobial therapy in periodontitis involve direct placement of antimicrobial agents into sub gingival sites minimizing the impact of the agents on non oral body sites. Local antimicrobial agents may be personally applied as a part of home care oral hygiene regimens and/or professionally applied as part of clinic based treatment procedures. Local antimicrobial therapy in periodontitis may be further classified as providing either non-sustained or sustained sub gingival drug delivery. Non-sustained sub gingival drug delivery provides high pocket concentrations of the antimicrobial agent over an extended time period within periodontal pockets. Controlled drug release can be provided with sub gingival irrigation of an agent intrinsically substantive for both tooth surfaces or pocket placement of commercial antimicrobial fibres, gel or films.

Local application of antibiotics has been achieved either by sub gingival irrigation or by incorporating the drug into different devices for insertion into periodontal pockets .Ideally local drug delivery requires high initial concentrations and multiple applications in order to provide sustained effectiveness. Local drug delivery devices are of two types:

1. These drug delivery systems are designed to deliver drug locally in the periodontal pocket but without any mechanism to retain therapeutic levels for a prolonged period of time. Such device generally exhibits exponential increase and decrease in drug concentration at the site.
2. These are controlled release local drug delivery devices which may produce antimicrobial effect for a prolonged period of time at the diseased site. They are produced by immobilizing antimicrobial agents with carrier substances to provide controlled local release such as antimicrobial fibres, films or strips.

4) Controlled Release Local Delivery Devices:

These devices employ the controlled release technologies to assure therapeutic concentrations of the antimicrobial agents in the sub gingival area for a long period following a single application. A wide variety of specialized local delivery systems (i.e. intra-pocket devices) have been designed to maintain the drug concentration in the gingival crevicular fluid (GCF). Drug delivery systems can be classified in following three categories according to the mechanism that controlling the drug release:

(i) Solvent controlled matrix systems are based on macromolecular matrix permeability to small molecules after matrix swelling into hydrated medium.

(ii) Reservoir systems are controlled by drug diffusion across a polymeric membrane.

(iii) Chemically controlled systems in which the rate of drug release is controlled by rate of degradation of chemical bonds and erosion of the polymeric matrix.

Several studies have evaluated the use of antimicrobial/antibacterial agents in periodontal therapy such as iodine, sulphonamides, mercurials, or phenolics and antibiotics such as tetracycline, doxycycline, minocycline, metronidazole, chlorhexidine, ciprofloxacin, neomycin, kanamycin, clindamycin, azithromyicin and ofloxacin etc.

Films are most widely used intra pocket drug delivery device prepared either by solvent casting or direct milling. Bigger film either could be applied directly applied on cheek mucosa or gingival surface or can be cut into appropriate size so as to insert into site of infection. Films are matrix type of drug delivery device in which drug is distributed throughout matrix and drug release occurs by erosion, matrix dissolution or drug diffusion. This system has a several advantages than other intra pocket drug delivery devices.

Films that release drug by diffusion alone are prepared by using non-degradable water insoluble polymers, while those that release by diffusion and matrix erosion or dissolution are prepared by water soluble or biodegradable polymers. Various nonbiodegradable periodontal films of chlorhexidinediacetate, metronidazole, tetracycline and minocycline have been prepared using ethyl cellulose by solvent evaporation method. Ethyl cellulose films showed sustained drug release and release rate were dependent on the casting solvent and drug load. The use of chloroform as casting solvent significantly retarded the release rate of the drug compared to ethanol as a casting solvent. The incorporation of polyethylene glycol in the films however enhanced the release rate of the drug.

Advantages [5]

- This route is more possible for direct access to target diseases.
- This may reduce oral healthcare treatment cost.
- It offers avoidance of GI tract problems of oral drug administration.
- It can serve as a reliable route for drug administration in very ill patient who are not able to swallow.
- It can offer increase therapeutic efficacy of the drug.
- It can show improved patient acceptance and compliance.
- This is safe and convenient route.
- It can produce longer duration of action.
- It offers non-invasive, painless, and simple application.
- It is useful in controlling and monitoring the desired drug levels in the site.
- It is a useful means of delivery of drug to the oral cavity that is not absorbed into the gastro intestinal system.
- It bypasses hepatic first pass metabolism, therapy offering a greater bioavailability and reduction in dosage.

Disadvantages

- This route is not feasible for local irritants.
- The drug and other excipients used in the formulation possessing either erythema, itching, or local arrhythmia cannot be delivered by this route.
- Dose is limited because of relatively small area.
- Pre systemic metabolism may occur by the enzymes like peptidase and esterase.
- This route is not feasible for peptide delivery due to peptidase.
- This route understood the needs for high-potency drugs.
- It should be devoid of irritancy or a sensitization.
- Manufacturing cost should be taken inconsideration.

DRUGS COMMONLY EMPLOYED IN FILMS

Some therapeutic agents which are amenable to delivery by this means and are potentially of value for periodontal therapy, include (but are not limited to) antimicrobial/antibacterial agents such as iodine, sulfonamides, mercurials, bisbiguanides, or phenolics; antibiotics such as tetracycline, neomycin, kanamycin,

metronidazole, clindamycin; anti inflammatory agents such as aspirin, naproxen, ibuprofen, flurbiprofen, indomethacin, eugenol, or hydrocortisone; immune-suppressive or stimulatory agents such as methotrexate or levamasole; dentinal desensitizing agents such as strontium chloride or sodium fluoride; odor masking agents such as peppermint oil; immune reagents such as immunoglobulin or antigens; local anaesthetic agents such as lidocaine or benzocaine; nutritional agents such as amino acids essential fats, and vitamin C; antioxidants such as alphatocopherol and butylatedhydroxy toluene; lipopolysaccharide complexing agents such as polymyxin; or peroxides such as urea peroxide.

The choice of the antimicrobial agents in periodontal diseases must be based on the bacterial etiology of the infection. Some antimicrobial agents have been selected because of their substantivity which refers to the property of some medications that have an intrinsic ability to bind to the soft and/or hard tissue walls of the pocket.[6]

PREPARATION METHODS

- **Solvent casting technique:**

Glass moulds were used for casting the films. Polymers were dissolved in solvent and plasticizer in a beaker using magnetic stirrer to get different concentration of polymeric solutions. Into these solutions drug of required concentration was added. After complete mixing, the solution was poured into a clean glass mould placed on a horizontal plane. The solvent was allowed to evaporate slowly by inverting a glass funnel with a cotton plug in the stem of the funnel was placed on the mould at room temperature for 24 h. After complete evaporation of solvent, cast film was obtained. Inverted funnel was continuously kept on the mould to control drying rate. The prepared cast films were lined with butter paper and stored in a dessicator. To accommodate different variables, batches of cast films were prepared.[7]

- **Semisolid casting method:**

In this method, first of all a solution of water soluble film forming polymer is prepared. Then resulting solution is added to a solution of acid insoluble polymer. Then approximate amount of plasticizer is added so that a gel mass is obtained. Finally the gel mass is casted into the films or ribbon by using heat controlled drums. The thickness of film is about 0.015- 0.05 inches. The ratio of the acid insoluble polymers to film forming polymer should be 1:4.

- **Hot melt extrusion:**

In present method the mass is prepared first under the control of temperature and steering speed. Afterwards, the film is coated and dried in a drying tunnel; once again the temperature, air circulation and line speed are controlled. Then follows a slitting and in the last step the films are punched, pouched and sealed. [8]

- **Solid dispersion extrusion:**

In solid dispersion extrusion method immiscible components is extrude with drugs and then solid dispersions are prepared. Finally the solid dispersions are shaped into films by means of dies.[9]

- **Rolling method:**

In this method, suspension or solution containing drug is rolled on a carrier. The solution or suspension should have a specific rheological consideration. Solvent mainly used is water as well as a mixture of water and alcohol. Film is dried on the rollers and cut into desired shapes and sizes.[10]

EVALUATION

1. Thickness uniformity:

The thickness of each periodontal film was measured using the screw gauge at different 6 positions of the film, and the average was calculated.

2. Estimation of percentage moisture loss:

6 films of different concentrations of size (7×4 mm) were weighed accurately, and then, they were kept in desiccators for 3 consecutive days and then reweighed. The percentage moisture loss was calculated by the formula;

Moisture loss = (initial weight – final weight/initial weight) ×100

3. Uniformity of weight:

Periodontal film pieces (size of 7×4 mm) were taken from different areas of film. The weight variation of each film was calculated.

4. *In vitro* drug release studies:

Since the pH of gingival fluid lies between 6.5 and 6.8, phosphate buffer pH 6.6 was used as the simulated gingival fluid. The *in vitro* drug release was performed using a keshary–Chien (K-C) diffusion cell. Phosphate buffer pH 6.6 was used as a receptor solution as a dissolution medium. The volume of diffusion cell was 10 ml. The prepared periodontal film (7×4 mm) was firmly pressed onto the centre of the semi permeable membrane, and then, the membrane was mounted in the donor compartment. The donor compartment was then placed in a position such that the surface of membrane just touches the receptor fluid surface. The whole assembly was fixed on a hot plate magnetic stirrer, and the solution in the receptor compartment was continuously stirred at 100 rpm using magnetic beads and the temperature was maintained at 37±1°C. The diffusion was carried out for 24 h and 1 ml of the receptor fluid was withdrawn at predetermined time interval and replaced immediately with the same volume of fresh dissolution media to maintain sink conditions. The samples were analyzed for drug release at 216 nm and 226 nm using ultraviolet (UV) visible spectrophotometer after suitable dilution with diffusion media.

5. Drug content uniformity:

The prepared film formulations were analyzed for drug content by taking film (size of 7×4 mm) from each batch and individually dissolved in 5 ml of pH 6.6 phosphate buffer in a beaker. The dispersion was kept in the dark place for overnight. The dispersion was filtered. 0.1 ml of the filtered solution was diluted to 10 ml with pH 6.6 phosphate buffer in a 10 ml volumetric flask. Drug concentrations were determined by taking three readings,

using a UV visible spectrophotometer at 216 nm and 226nm.

6. Tensile strength:

The tensile strength was determined by the apparatus designed. A small film (7×4 mm) was cut on a glass plate with a sharp blade. The instrument was designed such that it had a horizontal wooden platform with fixed scale and attachments for two clips that hold periodontal film under test. Of the two clips, one was fixed and another was movable. Weights were hanged to one end of the pulley and the other end of the pulley was attached to movable clip. The wooden platform was such fitted that it would not dislocate while the test is running. To determine elongation and tensile strength, the film was pulled by means of a pulley system. Weights were gradually added to the pan to increase the pulling force till the film was broken. Percentage elongation and tensile strength were calculated using the following formulae;

Tensile strength = Load at breakage/ Film thickness **x** Film width

% Elongation = Increase in length x 100 / Original length

7. Swelling index:

Swelling index of the drug-loaded films was determined by placing the film (area 7×4 mm) in the Petridis containing about 10.0 ml of phosphate buffer pH 6.6, and before placing the film in the Petridis, its initial weight was calculated and increase in weight due to swelling was determined by weighing the film at predetermined time interval.

8. Folding endurance:

The folding endurance value for all periodontal films was >200; it indicates that all formulations had ideal periodontal film properties.

9. Surface pH:

Surface pH of all the formulations was determined. All the formulations were found to have a pH between 6 and 7. This reveals that the prepared periodontal films would not alter the pH of the gingival fluid in the periodontal pocket and therefore may not cause any irritation.

10. Aging:

Optimized medicated films were subjected to stability testing. Films were placed in a glass beaker lined with aluminium foil and kept in a humidity chamber maintained at 40 + 2°C and 75 + 5% RH for 1 month. Changes in the appearance and drug content of the stored films were investigated after storage. The data presented were the mean of 3 determinations.

11. *In-vitro* antibacterial studies:

80 ml of nutrient agar media was prepared and sterilized at 15 lb pressure for 20 min in an autoclave. Under aseptic condition 20 ml of nutrient agar media was transferred into 4 sterile petri plates. After solidification 0.1 ml of microbial suspension of both E.coli & S.aureus of known concentration was spread on the media. Wells were prepared by using a sterile borer of diameter 6 mm and the samples were added in each well separately. The optimized film and the standard drug solution sample were tested. The plates were then incubated at 37°C for 48 hrs. Then the zone of inhibition was measured & compared.

FUTURE STRATEGIC APPROACHES

Although the attention towards treating bacterial infections has yielded many successful delivery devices, concerted efforts in developing ideal intra-pocket periodontal systems are still needed. Currently available formulations suffer from several disadvantages including: requirement of mechanical bonding of delivery system to a tooth surface, requirement for the removal of non-biodegradable delivery systems, lack of penetration into deeper regions of periodontal pocket and poor patient compliance. To improve the usefulness of intra-pocket delivery systems, the aims of treatment with antibacterial agents must be clearly defined. Treatment for one to three days appears to be sufficient to alleviate the signs and symptoms of periodontal disease, but not to prevent re colonisation and reoccurrence of the condition. It may be that the most effective treatment is achieved with a combination of delivery systems. Initial treatment with a short-acting biodegradable system may be useful to provide a bactericidal concentration of the antibacterial agent within the periodontal pocket. Subsequent prolonged delivery of antibacterial agents to the area surrounding the pocket opening may then prevent pocket re colonisation from the oral cavity by the suppression of marginal plaque.

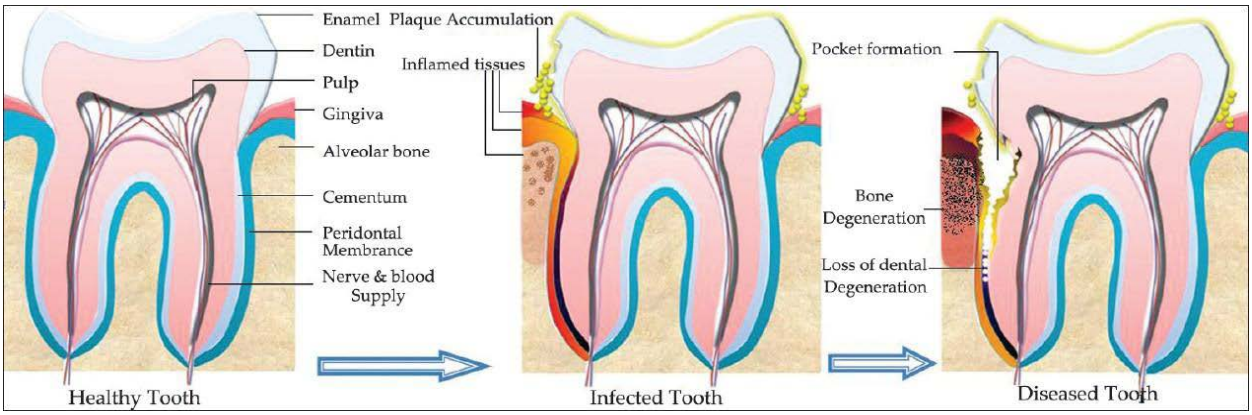

Fig.I: Anatomy of healthy, infected and diseased teeth

CONCLUSION

From the review of advances in periodontal drug delivery system it can be said that biodegradable, mucoadhesive nanoparticle has an immense opportunity for designing of novel, controlled release, low dose, intra pocket drug delivery device. These devices are proving to be more effective, more convenient and easy to use than regular systemic administration of medicines. There is an inclination amongst dental practitioners to stop the empirical use of systemic antibiotics for the treatment of common dental afflictions. This development definitely paves the way for future patenting of novel, commercially feasible and physiologically acceptable intra-pocket-targeted drug delivery systems.

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