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Dental Implants: - A Novel Approach for the Treatment of Periodontitis

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ABSTRACT:

Novel drug delivery system (NDDS) is a combination of advance technique and new dosage forms which are far better than conventional forms. The advancement in the NDDS leads to the evolution of an Implantable drug delivery system (IDDS). Dental implants designed for the treatment of periodontitis disease with aim of site specific delivery of antimicrobial agents. Periodontal disease is a microbial disease of tooth supporting tissues that results in progressive destruction of surrounding soft and hard tissue with eventual tooth mobility and exfoliation. The criteria for the treatment of periodontal disease include a local drug delivery system to target an antimicrobial agent at the infection site (periodontal pocket). Dental implants which could be placed into the periodontal pocket and be capable of delivering therapeutic concentrations of antimicrobial agent for a long-term, effective treatment at the site of infection at much smaller doses with minimal or no side effects on other body parts.

KEY WORDS: Dental Implant, Periodontitis, Local Drug Delivery System, antimicrobial agents.

I. INTRODUCTION

Novel Drug Delivery is the new branch of Pharmaceutical which is considered as best eminent technique for Targeted Drug Delivery system.[1]

Among many NDDS, Implantable drug delivery systems allow targeted and localised drug delivery and may achieve a therapeutic effect with lower concentrations of drug. As a result, this may minimise potential side-effects of therapy, while offering the opportunity for better patient compliance. This type of system also has the potential to deliver drugs which would normally be unsuitable orally because it avoids first pass metabolism and chemical degradation in the stomach and intestine, thus, increasing bioavailability.[2]

An IDDS is defined as a system in which the implant is inserted into the body by surgery. IDDS seems to be a very stronger drug delivery system, medications that are less bioavailable by the digestive tract. Example of IDDS includes Antibiotics, including NSAIDS, is mostly contraceptives, etc.[3]

Implantable drug delivery devices are particularly desirable where compliance with a prescribed drug regimen is critical. Such devices allow a drug to be delivered at a specific rate without regular physician or patient intervention.[4] Several implantable devices like fibers, films, Dental implant and gels were used.[5]

A site-specific system called Dental implants aims at delivering the active constituent at sufficient levels inside the periodontal pockets and at the same time minimizing the side effects associated with systemic drug administration.[6] Thus the Dental implant could be easily placed into periodontal pocket.[5]

Periodontal disease is considered as a major public health problem throughout the world. Good daily oral hygiene which plays a vital role in maintaining healthy gums and teeth.[7] Periodontal disease is one of the world's most prevalent chronic oral diseases affecting more than 50% of Indian community and occurs in all groups, ethnicities, races, genders and socioeconomic levels.[8]

The term Periodontitis comes from two terms "Peri' = around, "Odont" = tooth, "Itis" = inflammation.[9] The word periodontal literally means "around the tooth".[7] Periodontal diseases are infections of the structures around the teeth, which include the gums, periodontal ligament and alveolar bone.

Periodontal diseases are of two types: gingivitis and periodontitis.

Gingivitis may lead to a more serious condition called periodontitis, in which the inner gum and bone pull away from teeth and form pocket. These pockets can collect bacteria and debris, and become infected or abscessed.[10] These pockets provide an ideal environment for the growth and proliferation of aerobic and anaerobic

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pathogenic bacteria[11] Porphyromonas gingivalis, Prevotella intermedia, Fusobacterium nucleatum, Campylobacter rectus, Prevotella melaninogenica, and Actinobacillus actinomycetemcomitans etiology of periodontal diseases has been well established.[8]

One of the clinical features of the periodontal disease is the formation of periodontal pockets. Normally the gap between the gingival and the tooth is 1-3 mm deep but it usually exceeds 5mm to 10mm during diseased conditions.[12] Periodontal disease is a localized inflammatory response due to microbial infection of a periodontal pocket arising from the accumulation of plaque.[8]

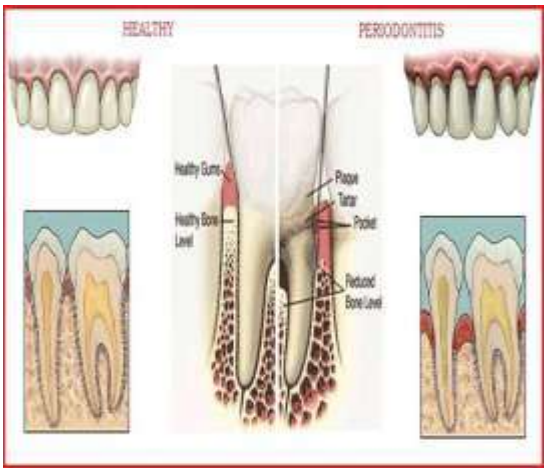

Figure 1: Representation of healthy and teeth with Periodontitis

Symptoms[13] :

- Swollen or puffy gums.
- Bright red, dusky red or purplish gums.
- Gums that feel tender when touched.
- Gums that bleed easily.
- Pink-tinged toothbrush after brushing.
- Spitting out blood when brushing or flossing your teeth.
- Bad breath.
- Pus between your teeth and gums.
- Loose teeth or loss of teeth.
- Painful chewing.
- New spaces developing between your teeth.
- Gums that pull away from your teeth (recede), making your teeth look longer than normal.
- A change in the way your teeth fit together when you bite.

Causes[14]:

Periodontitis is caused by microorganisms that adhere on the tooth's surfaces, along with an overly aggressive immune response against these microorganisms.

The invisible, sticky film called plaque mainly composed of bacteria stays on the teeth for more than two or three days, can harden under the gumline into tartar (calculus). Tartar makes plaque more difficult to remove and acts as a reservoir for bacteria.

The Longer that plaque and tartar remain on the teeth, the more damage they can cause. Initially irritation and inflammation occurs at the gingiva, which eventually causes pockets to develop between the gums and teeth that fill with plaque, tartar and bacteria. In time, these pockets become deeper and more bacteria accumulate which causes infection and eventually leads to loss of tissue and bone.

II. LOCAL DRUG DELIVERY[15]

Goodson et al., in 1979 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. Periodontal pocket provides a natural reservoir bathed by gingival cervicular fluid that is easily accessible for the insertion of a delivery device. These delivery systems are also called sustained release, controlled-release, prolonged release, timed release, slow release, sustained action, prolonged action or extended action.

Classification of local drug delivery

A. **Based on type of therapy**

- Personally applied (patient home care)
  - Non Sustained (Oral irrigation)
  - Sustained (not developed till now)
- Professionally applied (in dental office)
  - Non Sustained (Supra and subgingival irrigation)
  - Sustained (Controlled release device)

B. **Based on degradability of the device**

- Biodegradable
- Non- Biodegradable

C. **Based on duration of action**

- **Sustained released devices:** These are delivery systems whose action lasts less than 24 hours therefore require multiple applications. It follows the first order kinetics.
- **Controlled delivery devices:** These are the devices which follows zero order kinetics and whose actions last longer than 24 hours, thereby decreasing the number applications.

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Various drug delivery systems for treating periodontitis are Fibers, Injectable systems, Gels, Strips and compacts, Vesicular systems, Micro-particle system, Nanoparticle system, Films etc.

Drugs commonly employed in the Dental implants[16]:

Some therapeutic agents which are flexible 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.

III. FACTORS AFFECTING LOCAL DELIVERY OF DRUGS IN PERIODONTAL POCKETS[17]

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.

- **Site of Action:**

As the bacteria responsible for periodontitis lives 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 living 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.

- **Concentration:**

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

- **Time:**

Once the drug reaches to the site of action in an appropriate concentration, it must stay at the target site for a suitable period of time to exert its pharmacological effect. Biofilm condition causes slow growth of microorganisms in the periodontal pockets and it affects the effectiveness of given antibiotics. Drug kinetics must follow zero order to remain focused for longer duration.

IV. PREPARATION METHODS[16]

- **Solvent casting technique:**

For casting the films glass moulds were used. In a beaker, Polymers were dissolved in solvent and plasticizer using magnetic stirrer to get different concentration of polymeric solutions. Required amount of drug 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 at edge and was placed on the mould at room temperature for 24h. After complete evaporation of solvent, cast film was formed. Inverted funnel was continuously kept on the glass mould to control drying rate. The prepared cast films were lined with butter paper and stored in a desiccator.

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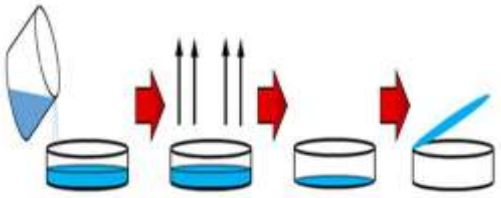

Figure 2: Solvent Casting Method

➢ **Semisolid casting method:**

In this method, first of all a solution of water soluble film forming polymer is prepared. Then obtained 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.

➢ **Solid dispersion extrusion:**

In solid dispersion extrusion method, an immiscible component is extruding with drugs and then solid dispersions are prepared. Finally the solid dispersions are shaped into films by means of dies.

➢ **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.

V. EVALUATION OF DENTAL IMPLANTS

➢ **Weight Uniformity:**

The weight Uniformity test was carried out by weighing 6 implants cut from different places of the same formulation (size of 8x2 mm^2) and their individual weights were determined by using the electronic balance. The mean value was calculated.[18]

➢ **Thickness:**

The thickness of the implant was measured by screw gauge with least count of 0.01mm. An average of 6 values determined at 6 different points on the implants was calculated.[19]

➢ **Surface pH:**

Dental implants were allowed to swell for 3 hour on the surface of the agar plate, prepared by dissolving 2% (w/v) agar in double distilled water under stirring and then pouring the solution into the petridish to solidify at room temperature. The surface pH was measured by means of pH paper placed on the surface of the swollen implants. The mean of 6 readings was recorded. [20]

➢ **Folding Endurance:**

The folding endurance or flexibility of the implants was determined by repeatedly folding the implants at the same place until it breaks. The number of times the implants folded without breaking as considered as folding endurance.[21]

➢ **Tensile Strength**

Tensile strength of the films was determined with Universal strength testing machine. The sensitivity of the machine is 1 gram. The test film of specific size (4 x 1 cm^2) was fixed between these cell grips and force was gradually applied till the film breaks. Tensile strength was calculated by using formula[22, 23]

$$\text{Tensile strength} = \frac{\text{Force at break (N)}}{\text{Initial cross sectional area of implants } (mm^2)}$$

➢ **Percentage Moisture Loss:**

The percentage moisture loss test was carried out to check physical stability or integrity of the implants. 6 Implants of known weight and size (8x2 mm^2) were placed in a desiccator containing anhydrous calcium chloride. After 3 days, the implants were taken out, re-weighed and calculated percentage moisture loss using the following formula.[18, 24]

$$\%\text{Moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \text{ X } 100$$

➢ **Percentage Moisture Absorption**

The percentage moisture absorption test was carried out to check of known size were

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weighed and placed in a dessicator containing 100 ml of saturated solution of aluminium chloride and 79.5% humidity was maintained. After three days the inserts were taken out and reweighed. The percentage moisture absorption was calculated using the formula.[25]

$$\%\text{Moisture Absorption} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \text{ X } 100$$

➢ **Drug Content Uniformity**

The prepared periodontal films formulations were analyzed for drug content by taking films of known size (8x2 mm^2) from each batch and individually dissolved in 10 ml of pH 6.8 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 then diluted to 10 ml with pH 6.8 phosphate buffer in a 10 ml volumetric flask. Drug concentrations were determined by taking six readings, using a UV Visible Spectrophotometer.[26]

➢ **In-vitro Drug Release:**

The pH of gingival fluid lies in between 6.5 to 6.8. Phosphate buffer pH 6.8 solution were used which were similar to the pH of saliva. Since the implants should be immobile in the periodontal pocket, a static dissolution method was adopted for the dissolution studies. Implants of size (8x2 mm^2) were taken separately into small test tubes sealed with aluminium foil containing 10 ml simulated saliva (pH 6.8) and kept at 37^oC. The temperature was maintained at 37^oC by keeping the test tube in dissolution apparatus with temperature control. The sample was withdrawn and replaced with fresh 1 ml of pH 6.8 at a predetermined time intervals up to 24 hours. The concentration of drug in the buffer was measured by using a UV-Visible Spectrophotometer.[27, 28]

➢ **In-vitro antibacterial activity:**

The implants (size of 5x5 mm^2) were taken for the study; 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 poured into sterile Petri plates. After solidification, 0.1 ml of microbial suspension of S.aureus and E.coli of known concentration was spread on media. The implants were placed over the medium and the plates incubated for 48 hours at 37^oC. Then the zone of inhibition was measured.[8, 29]

➢ **Accelerated stability studies:**

Stability of pharmaceutical preparation can be defined as the "capability of particular formulation in a specific system to remain within its physical, chemical, micro-biological, therapeutic and toxicological specifications throughout its shelf life". The purpose of stability testing is to provide evidence on how the quality of a substance or drug product varies with time under the influence of variety of environmental factors such as temperature, humidity, and light, enabling recommended storage conditions re-test periods and shelf-lives to be established.

ICH Guidelines:

Long-term testing 25 ± 2^oC/60% ± 5% RH for 12 months.

Accelerated testing 40 ± 2^oC/75% ± 5% RH for 6 months.

Procedure:

The drug loaded Dental implants were subjected to short term stability testing. The implants were wrapped in aluminium foil, and placed in petriplate which were kept in a stability chamber maintained at 40 ± 2^oC and 75 ± 5% RH for 45 days[11] after 45 the implants were evaluated for physicochemical parameters and drug release.

VI. CONCLUSION:

Complete elimination of the microorganism from the periodontal pocket is the most important step in treatment of periodontitis. Advancement in the technology has led to the development of implantable drug delivery system. Dental implants for the treatment of periodontitis were developed. Dental Implant once implanted into the periodontal pocket it shows its effect for long period of time. It releases the drug with a sustained manner for a long constant period of time. It shows its effect at a targeted site and by-pass the systemic route, with lower dose of drug are better alternative to systemic therapy in the treatment of periodontitis. Local drug delivery is designed to deliver the drug locally into the periodontal pocket and can improve the periodontal health. When compared to systemic antimicrobials the local drug delivery will reduce the developing drug resistance bacterial strain which is of current world concern. Therefore it can be concluded that the antimicrobial drug is an important alternative to traditional periodontal treatment as site-specific Dental implants in the periodontal pocket.

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