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A Review on “Antibacterial Intra-Pocket Dental Delivery System”

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ABSTRACT

Periodontal disease causes destruction of adjuvant structures of the teeth predominate in all groups, ethnicities, races and both genders. It is generally agreed that gram-negative anaerobic germs residing in periodontal vacuities are responsible for periodontitis. Systemic antibiotic therapy is employed in treating this disease condition, but it has limited due to the lack of accessibility to periodontopathic organisms in the periodontal pocket. Local delivery devices such as dental inserts or dental films are developed to deliver the drug locally into periodontal pits. These controlled intra-pocket devices also help in the maintenance of therapeutic drug concentration for the desired period of time. Dental films were fabricated either by using biodegradable or non-biodegradable polymers depending upon their mode of drug release. The Dental implants were evaluated for their thickness uniformity, folding endurance, weight uniformity, content uniformity, surface pH, in-vitro drug release and in-vitro antibacterial activity. This review approaches the antibacterial drug delivery systems for the administration of drugs into the periodontal cavity and also their advancements and effectiveness in periodontal therapy.

INTRODUCTION:

Periodontitis refers to an inflammatory disease with primary bacterial etiology in the gingival crevices, which affects the structural organs surrounding the teeth like the periodontal ligament, connective tissue, and bone. It is one of the world's most prevalent oral chronic disease and approximately 70 million adults suffer from this disease. Periodontitis involves progressive bone loss around the teeth, which may result in loosening and subsequent loss of teeth, and is characterized by periodontal cavity formation. Pre-existing gingivitis with the colonization of a wide range of microorganisms often triggers the emergence of periodontal disease. It is a multifactorial infection with great complexity in the mechanisms of pathogenesis. One of the clinical features of the periodontal disease is the formation of a periodontal pocket. Normally the gap between the gingiva and the tooth is 1 to 3 mm deep but it usually exceeds 5mm to 10mm during diseased condition. The warm and moist atmosphere around the pocket fosters the growth of gram-negative, anaerobic bacteria that proliferate in the subgingival space. The most commonly grown anaerobic pathogenic bacteria's that can cause periodontal diseases include *Actinobacillus actinomycetemcomitans*, *Bacteroides gingivitis*, *Bacteroides melaninogenicus subspecies intermedia*, *Porphyromonas gingivalis* and *Prevotella intermedia*. Some of the clinical signs such as gingival bleeding, bluish red thickened marginal gingiva, the bluish red vertical zone from the gingival margin to the oral mucosa and localized pain are indicative of the presence of periodontal pockets.

Effective treatment of periodontitis, as well as gingivitis, has been evolved appreciably in the last decade. The aim of dental health care is to control the population of microorganisms either by slowing or arresting of the oro-dental infections. Conventional therapy performed for periodontal disease is scaling and root planning. Systemic antibiotic therapy is also employed in treating periodontitis. The systemic administration of antibiotics leads to therapeutic concentrations at the site of infection, only for a short period of time for controlling subgingival flora. Therefore long-term antimicrobial therapy should be ensured for complete eradication of microorganisms. Antibiotics administration at higher doses are required to achieve effective concentrations in the pocket, but high doses are given for long periods of time eventually causes the development of bacterial resistance, superinfection, gastrointestinal and central nervous system disturbances. To overcome the disadvantages of systemic chemotherapy with antibiotics, local delivery of antibiotics have been investigated.

Drug targeting to the desired site contributes in minimizing the distribution of antimicrobials to other body parts or organs.

Classification for various targeted drug delivery systems developed for treating periodontal disease.

Local drug delivery systems	Injectable drug delivery systems	Nano drug delivery systems	Miscellaneous
Fibers	Biodegradable microparticles	Nanopores	Drug delivery using ultrasound
Dental corns	Gels	Nanotubes	Gene delivery using bubble liposomes for periodontal therapy
Films		Nanospheres	Polymeric micelles
Periodontal chips		Nanorods	Liquid crystals
Strips or compacts		Nanowires	Nanoparticles
		Nanoshells	Industrial lab on chip delivery
		Quantum dots	Nanogenerators
		Dendrimers	Nanorobots
		Liposomes	
		Fullerenes	
		Nanocapsules	

Dental films

Dental films (periodontal films) are the far more widely used form of intra-pocket delivery devices which are prepared either by solvent casting or direct milling methods. Films of various polymers have been made for the controlled release of antimicrobials. Depending upon the nature of polymers we can prepare both biodegradable and non-degradable films. Periodontal films that release drugs by diffusion alone are prepared using water insoluble non-degradable polymers, whereas those that release by diffusion and matrix erosion or dissolution use soluble or biodegradable polymers.

In the form of films, we can directly place the drug into the pocket so as to attain therapeutic drug levels in the gingival crevicular fluid and thus reduce the adverse effects of an antibacterial agent on other non-oral body parts. Films are matrix delivery systems in which drugs are distributed throughout the polymer and release occurs by drug diffusion and/or matrix dissolution or erosion. This dosage form has several advantageous physical properties for intra-pocket use. The dimensions and shape of the films can be easily controlled according to the dimensions of the pocket to be treated. It can be rapidly inserted into the base of the pocket with minimal discomfort to the patient. The convenient size of the film or sheet may be 0.1-0.5 mm in thickness, 0.5-3 mm in width, and 5-50 mm in length and it has sufficient adhesiveness, it will remain submerged without any noticeable interference with the patient's oral hygiene habits. Once a film is inserted in the periodontal pocket, the polymer adheres, swells, expands, and reaches narrow crevices and furcations of the cavity, carrying therapeutic agent throughout the cavity. This provides most desirable and advanced treatment for dental diseases. Although this type of drug delivery is still young, it has attracted much attention and has proved to be a most promising alternative method of treatment. There is great potential in the treatment offered by local drug delivery devices in the field of both pharmacies as well as dentistry.

Various polymers used for the preparation of dental films:

(I) Synthetic polymers:

1. Cellulose derivatives.

Eg; Methylcellulose, Ethylcellulose, Hydroxyethylcellulose, Hydroxyl propyl cellulose, Hydroxypropyl methyl cellulose, Sodium Carboxymethylcellulose.

2. Poly (Acrylic acid) polymers.

Eg; Carbomers, Polycarbophil.

3. Polyhydroxy ethyl methyl acrylate.

4. Polyethylene oxide.

5. Polyvinylpyrrolidone.

6. Polyvinyl alcohol.

(II) Natural polymers:

1. Tragacanth.
2. Sodium alginate.
3. Guar gum.
4. Xanthan gum.
5. Soluble starch.
6. Gelatin.
7. Chitosan.

Methods:

Preparation of dental implants:

The method used for the preparation of dental implants was solvent casting technique. Dental inserts were prepared by dissolving polymer and copolymer alone and in combination with suitable solvents or in solvent mixtures. Plasticizers provide good strength to films and therefore added to the preparation with respect to the concentration of polymer. Consequently, polymer and copolymer were dissolved in the suitable solvent, containing a plasticizer. Into this, a drug of required concentration was added and stirred the polymeric solution homogeneously by using a magnetic stirrer. After complete mixing, the solution was poured into a clean Petri dish (Anumbra® area 60.8 so cm approximately) placed on a horizontal plane. The solvent was allowed to evaporate slowly by inverting a glass funnel with a cotton plug closed in the stem of the funnel on Petri dish at 24° for 24 h. After complete evaporation of a solvent, cast films were obtained. Dental films were then cut into pieces of 0.5×0.5 cm and wrapped in an aluminum foil and stored in desiccators at the relative humidity at room temperature in a dark place until further use.

Evaluation of the films

Periodontal films were evaluated for physical characteristics as follows.

Thickness uniformity

The thickness of each film at different positions was measured using screw gauge (thickness tester) and the average was calculated.

Uniformity of weight

Film (size of 1 cm²) was taken from different areas of the film. The weight variation of each film was calculated.

Estimation of percentage moisture loss

About 20 films of different concentrations of size (7 × 2 mm) are weighed accurately and placed in desiccators for 3 consecutive days and then reweighed. % moisture loss was calculated by using a formula:

$$\text{Moisture Loss} = (\text{initial wt.} - \text{final wt.} / \text{initial wt.}) \times 100.$$

Folding endurance studies

The folding endurance of the films was determined by repeatedly folding one film at the same place till it broke or folded up to 350 times, which is considered as an indication to reveal good film properties. The film was folded a number of times at the same place without breaking gave the value of the folding endurance. This test was repeated on all the films for five times.

Surface pH

An acidic or alkaline pH may cause irritation to the periodontal mucosa. Therefore the surface pH of the films was determined to avoid possible in vivo side effects due to change in pH of the film. The film to be tested was placed in a Petri dish and was moistened with 0.5 ml of pH 6.6 buffer and kept for 1 hr. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibrating for 1 min.

Swelling Index

The studies for Swelling Index of the films were conducted in simulated salivary fluid of pH 6.6. The film sample (1×1cm²) was weighed and placed in a preweighed stainless steel wire sieve of approximately 800 μm mesh. The mesh containing the film sample was then

submerged into 15 ml of the simulated salivary medium contained in a porcelain dish. At definite time intervals, the stainless steel mesh was removed, excess moisture removed by carefully wiping with absorbent tissue and reweighed. The increase in weight of the film was determined at each time interval until a constant weight was observed. The degree of swelling was calculated using the formula:

$$S.I = (wt - w_0) / w_0$$

Where S.I is the Swelling Index, wt is the weight of film at time t and w₀ is the weight of the film at time 0.

Drug content uniformity

The drug-loaded films of known weight (7 × 2 mm) were dissolved in 10 ml of 2% aqueous lactic acid, suitably diluted and the amount of drug present was estimated by UV/VIS spectrophotometer (Shimadzu).

In Vitro Drug Release Studies

The pH of gingival fluid lies between 6.5 – 6.8, phosphate buffer pH 6.6 was used as simulated gingival fluid. Also, since the film should be immobile in the periodontal pocket, a static dissolution model was adopted for the dissolution studies. Sets of three films of known weight and dimension were placed separately in small sealed test tubes containing 1.0 ml of phosphate buffer (pH 6.6) and kept at 37 ± 0.5 °C for 24 h. The buffer was then drained off and replaced with a fresh 1.0 ml of buffer. The concentration of drug was determined by UV/VIS spectrophotometer (Shimadzu).

Mass Balance Study

Following the in-vitro release studies, the test films were further analyzed for the drug content left in the film. Each film was dissolved in lactic acid 2% v/v and diluted suitably. The absorbance was measured by UV/VIS spectrophotometer (Shimadzu). The amount of drug released into the dissolution medium and the residual content in the films were accounted and compared for the actual drug content.

In-vitro Drug Permeation Studies

For the permeation studies, the bovine periodontal mucosa was used as the model membrane. The periodontal mucosa of the freshly sacrificed cattle was procured from the local slaughterhouse and used in within two hours of slaughter. The mucosa was excised and trimmed evenly from the sides. The epithelium was separated from the underlying connective tissue by the surgical method and the delipidated membrane was allowed to equilibrate approximately for one hour in receptor buffer to gain the lost elasticity. The Franz cells that have the surface area of 3.14 cm^2 were used and the receptor compartment had a capacity of approximately 15 ml. The receptor compartment was filled with pH 6.6 phosphate buffer. The epithelial mucosa was exposed to donor compartment, while the opposite side was bathed with receptor solution. A static permeation model was adopted throughout the study. To mimic the body condition during the experiment, the temperature was maintained as $37 \pm 0.5^\circ\text{C}$ with an external constant water circulator. Sink conditions were maintained. A 1 cm^2 film under study was placed in intimate contact with the excised epithelium, was applied to the donor compartment of the prepared Franz diffusion cell. At a predetermined time, like 1, 2, 3, 4, 5, 6, 7, 8, 24 and 48 hours, 0.5 ml of the sample were withdrawn and the cell was refilled with the same amount of the fresh receptor solution. Withdrawn samples should be analyzed spectrophotometrically. Each permeation experiments were replicated three times and from the concentration of the drug the withdrawn solution, the amount of drug permeated to the receptor compartment was calculated.

In-vitro Antibacterial Activity

The procedure follows agar diffusion assay method. *P. gingivalis* should be inoculated directly with clinical material or a broth that has been previously inoculated from clinical material. Inoculated plates should be streaked to obtain isolated colonies, immediately placed in an anaerobic atmosphere and incubated at $35-37^\circ\text{C}$ for 18-48 hrs. The samples were tested at different concentration. Sterile PGA plates were prepared and 0.1 ml of the inoculums of test organism was spread uniformly. Wells were prepared by using a sterile borer of diameter 6 mm and the samples (sample A and B) at different concentration ($5\mu\text{l}$, $10\mu\text{l}$, $15\mu\text{l}$ and $20\mu\text{l}$) were added in each well separately. Sample A is the optimized F5 film and sample B is the blank film. The plates were incubated at $35-37^\circ\text{C}$ for 18-48 hrs, a period of time sufficient for the growth. The zone of inhibition of microbial growth around the well was measured in cm and statistical analysis was performed.

Scanning Electron Microscopy (SEM)

The morphology and surface topography of the optimized film were examined by SEM (Joel jsm-6490la analytical SE). Spherical samples (5 mm²) were mounted on the SEM sample stab using a double sided sticking tape. The samples were coated with gold (200 Å) under reduced pressure (0.001torr) for 2 min using an ion sputtering device (model JFC-1100 E, Jeol, Japan). The gold-coated samples were observed under the SEM at room temperature and photomicrographs of suitable magnifications were obtained.

Stability studies

The stability of the entire drug loaded polymer films was studied at different temperatures using the reported procedure. The films of size (7×2mm) were weighed in three sets (12 films in each set). The films were wrapped individually in aluminum foil and also in butter paper and placed in Petri dishes. These containers were stored at room temperature (27 ± 2°C), and in a refrigerator (5–8 ± 2°C) for a period of 45 days. All the polymeric films were observed for any physical changes, such as color, appearance, flexibility, or texture, and the % drug release was estimated at an interval of one week.

List of marketed periodontal products presented in various dosage forms:

Product	Antimicrobial agent	Dosage form	Manufacturer
Actinide	Tetracycline	Non-resorbable fibre	Alzacorp
Arestin	Minocycline	Bio-degradable powder in syringe	Oropharma corp, Warminster
Atridox	Doxycycline	Bio-degradable mix in syringe	Atrix Labs, ft, Collins, Co.
Atrigel	Doxycycline	Gel	Atrix Labs
Dentamycine	Minocycline	Bio-degradable mix in syringe	Sunstar Corp, Tokyo, Japan
Elyzol	Metronidazole	Bio-degradable mix in syringe	Dumex corp. Co Denmark
Elyzol	Minocycline	Gel	Dumex pharma
Periochip	Chlorhexidine	Bio-degradable device	Dexcel Pharma Inc, Jerusalem
Periochip	Chlorhexidine/tetracycline	Films	Perioproduts Ltd.
Periochip	Gluconate	Insert	Perioproduts Ltd.
Gluconate	Metronidazole	Insert	Perioproduts Ltd.

CONCLUSION

One of the major problems associated with periodontitis is that many drugs do not reach the specific sites in the therapeutic concentrations. Intra-pocket delivery systems have several greater advantages and prove to be much safer, less time consuming and more site specific than any other conventional therapy. The core advantage of dental inserts is that it requires the only lesser amount of drug to achieve effective concentration at the site. The periodontal mucosa offers several advantages for controlled drug delivery for longer periods of time. Almost all the drug loaded dental films were found to be flexible and demonstrated satisfactory physicochemical characteristics. However further, elaborated investigation is required to establish the potential benefits and in-vivo efficiency of these films.

REFERENCES

1. Sreeja C Nair, Anoop KR. Intraperitoneal pocket-An ideal root for local antibacterial drug delivery. *Adv Pharm Technol Res* 2012; 3(1):9-15.
2. Dr. Vandana Gupta, Dr. Nandini Bhaskar et al. Local Drug Delivery in Periodontics - An Update. *Heal Talk* July-August 2013: Volume 05 Issue 06.
3. Vineetha V. C, Manju Maria Mathews. Development and evaluation of dental films containing an antibacterial agent for the treatment of periodontitis. *International Journal of Pharmacy and Pharmaceutical Sciences* 2015: Vol 7, Issue 3.
4. Vaishali Potnis, Suchita Dhamne, and Ajit Mane. Formulation and Evaluation of Dental Films for the Treatment of Periodontal Diseases. *IJPPR* September 2016: Vol.:7, Issue: 2.
5. Gaurav Tiwari. Biodegradable monolithic periodontal films for controlled delivery of metronidazole to periodontal pocket. *International journal of pharma and biosciences* 2010: v1 (2).
6. G. Harini, G. Kaarthikeyan. Advanced drug delivery systems in treating periodontal diseases-a review. *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)* Feb. 2014: Volume 13, Issue 1, Ver. VIII PP 27-32.
7. Umadevi S, BeethaRohini, Nithyapriya, Sasidharan. Formulation and evaluation of ciprofloxacin dental films for periodontitis. *Journal of Chemical and Pharmaceutical Research* 2012: 4(6):2964-2971.
8. V. S. Mastiholimath et al. Formulation and evaluation of ornidazole dental formulation and evaluation of ornidazole dental implants for periodontitis. *Indian Journal of Pharmaceutical Sciences* January - February 2006.
9. Borude A. D, Mahale N. B. Formulation, and evaluation of dental implant of moxifloxacin HCl for the treatment of periodontitis. *IJPBS* oct-dec 2013: Volume 3, Issue 4:49-55.
10. Vicky Kaplish, Manpreet Kaur Walia, S.L. Hari Kumar. Local drug delivery systems in the treatment of periodontitis: A review. *Pharmacophore* 2013: Vol. 4 (2), 39-49.
11. Goodson JM. Controlled drug delivery-A new means of treatment of dental diseases. *Compend Cont Educ Dent* 1985;6(1).
12. Sudeep Kothari, Gnanaranjan G, Preeti Kothiyal. Formulation and evaluation of erythromycin dental implants for periodontitis. *Int J Drug Res Tech* 2012;2(5):407-10.
13. Seth AK, Agarwal GP, Saini TR. Evaluation of free films. *Indian Drugs* 1985; 23(2):45-7.
14. Sreeja C Nair, Anoop KR. Design and in vitro evaluation of controlled release satranidazole subgingival films for periodontitis therapy. *Int J Pharm Sci Rev Res* 2014; 24(1):8-14.
15. Navneet Singh, Rishabha Malviya, Mayank Bansal, Pramod Kumar Sharma. Formulation and evaluation of different polymer based periodontal film of Ofloxacin. *Pharm Lett* 2010; 2(3):297-303.
16. Pragati S, Ashok S, Kuldeep S. Recent advances in periodontal drug delivery systems. *International Journal of Drug Delivery* 1(2009); 1-14.

17. Vivekanand Prajapati, Mayank Bansal, Pramod Kumar Sharma. Mucoadhesive Buccal Patches and Use of Natural Polymer in Its Preparation – A Review. International Journal of PharmTech Research April-June 2012; Vol.4, No.2, pp 582-589.

