Periochip- a novel technology for transmucosal drug delivery system.

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ABSTRACT

PerioChip could be a second line treatment within the care and maintenance of disease. It comes within the style of an innovative, simple to insert biodegradable chip a perfect Non-antibiotic adjunct treatment to cut back pocket depth in adults with periodontal disease.. It has been demonstrated clinically to be affective and well tolerated for periodontal pockets with a depth of 5mm or more which is released slowly over a period of 7days. Periochip, is a pioneer in the field of bio degradable delivery frameworks. Periochip which is used in treatment of periodontitis is an inflammation of the periodontium that extends beyond the gingiva and destructs the connective tissue to which teeth attach. Bacteria related to plaque are wide accepted because the reason behind inflammatory odontology diseases. These are chronic, predominantly gram negative infections of the oral cavity that are initiated in the gingival and if untreated lead to alveolar bone destruction and eventual tooth loss. Conventional trans-mucosal drug delivery systems such as gels, microsphers, ointments are commonly used but they are limited in their ability to provide high transmucosal and sub-gingival drug bioavailability and sustained duration of action. These are less associated with skin irritation due to less permeation properties , that improve the water vapor permeation through the skin and do not leave sticky sensation on the site of application. Each PerioChip holds 2.5 mg of chlorhexidine gluconate in a biodegradable matrix of hydrolyzed gelatin.Many studies have shown the clinical effectiveness of dental professionals for the long-term management of adult periodontitis. The platform of periochip provides a technology of delivering any drug that can be included in the periochip formulation. The current article deals with detailed study of periochip

Keywords: Chlorhexidine,Thymoquinone, Periochip, perio-dontitis, endodontitis, adjunct, SRP, gingival.

Introduction:

PerioChip may be a second line treatment within the care and maintenance of disease.It comes in the form of an innovative, easy to insert biodegradable chip containing 2.5 mg of chlor-Hexidine Digluconate -an ideal Non-antibiotic adjunct treatment to reduce pocket depth in adults with periodontitis. It has been demonstrated clinically to be affective and well tolerated for periodontal pockets with a depth of 5mm or more. The biodegradable gelatin matrix contains 2.5 mg of chlor hexidine digluconate which is released slowly over a period of 7days.. Recently a new approach using local delivery systems containing antimicrobial has been introduced to treat periodontal diseases. There are distinct phases during a dentistry treatment arrange wherever a dentist will use this sustained unleash device.[1]

1.As an adjunct to scaling and root planning

2. periodontal maintenance therapy: repeated periodontal disease typically involves solely some teeth, where the usage of this device is good.

3.For whom surgery isn't a possibility or those that refuse surgical treatment.

4.Sustained release device may be a less invasive treatment option and it needs less time as compared to surgical treatment.

Advantages

1. Very easy and convenient to use. Take seconds to place in pocket.
2. Highly effective ,safe and well tolerated. Painless to the patient. In some instances there may be minor discomfort in the first 24 hours.
3. No restrictions on eating or oral hygiene after chip insertion.
4. All quadrants can be treated at the same visit.
5. Does not affect taste.
6. Reduces amount of pathogenic bacteria upto 100 days- 99% of subgingival microflora.
7. Systemic antibiotics can reach micro-organisms at the base of deep periodontal pockets and furcation areas, via the serum.

8. Affects tissue invasive organisms – residing within the connective tissues.
9. Eradication of periodontal pathogens colonizing the oral mucosa and other extra dental sites – the potential reservoirs of bacterial re-infection.
10. Multiple sites are treated simultaneously.
11. Less time consuming (when compared to local drug delivery).
12. A variety of drugs are available.

Disadvantages

1. Development of resistant bacterial strains.
2. Superimposed infections.
3. Uncertain patient compliance.
4. treatment is not completed in a timely fashion. Patients are numb for the SRP procedure.
5. High probability of relapse.

Dental plague:

It's highly specific variable structural entity formed by sequential colonization of microorganism on tooth surface, epithelium and restorations. Plague control is the removal of microbial plague and prevention of its accumulation on teeth an adjacent gingival tissue. It also deals with the prevention of calculus formation.[3]

Plague control types:

Mechanical plague control and chemical plague control. Available in different forms for use. Also used as antiseptic in various specialities. Highly bacteriostatic in nature. CHX is Second generation chemical plague control agent.

First generation: antibiotics , phenols ,quaternary ammonium compounds, sanguinarine.

Second generation: Bisbiguanides [Chlorhexidine]

Third generation: Delmopinol.

Antiplaque activity:

Mechanism for inhibition of plaque by CHX is mentioned as follows:

1.The effective interference of the acidic cluster of secretion glycoproteins can cut back their sorption to hydroxyapatite and formation of noninheritable investment.

2.The flexibility of microorganism to bind to tooth surface is also reduced by sorption of CHX to the extracellular polysaccharides of their capsule

3.The CHX may compete with calcium ions for acidic agglutination factors in plaque.

Antimicrobial activity:

CHX shows different effects at different concentrations

1. The agent is bacteriostatic, whereas at higher concentration it is bactericidal like cationic CHX molecule + negatively charged bacterial cell wall shows instant adsorption of CHX to Phosphate containing compounds.[2]

2.CHX binds with the phospholipids in the inner cell membrane.Leakage of the lesser molecular weight components viz. potassium ions. This is the sub lethal stage of CHX. The action can be reversed. This marks the bacteriostatic property of CHX. If the conc. Is increased and the action continues, the CHX becomes bactericidal in nature

3.Intracellular coagulation Slows down leakage of intracellular components

Cytoplasmic coagulation Irreversible cell damage (bactericidal)[4]

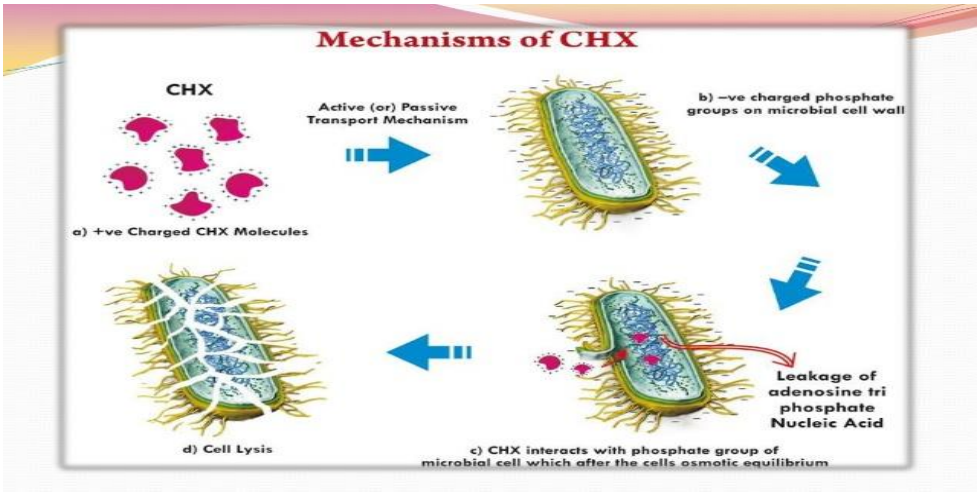

Fig1. Mechanism of CHX

The drug is poorly absorbed from gastrointestinal tract and 90% of retained drug is excreted in the faeces and remainder via urinary tract.

Method to insert periochip:

It relies solely on local anesthetic

Remove bacteria and calculus of 1/4 th mouth at a time, treatment is completed in 2-4 visits.

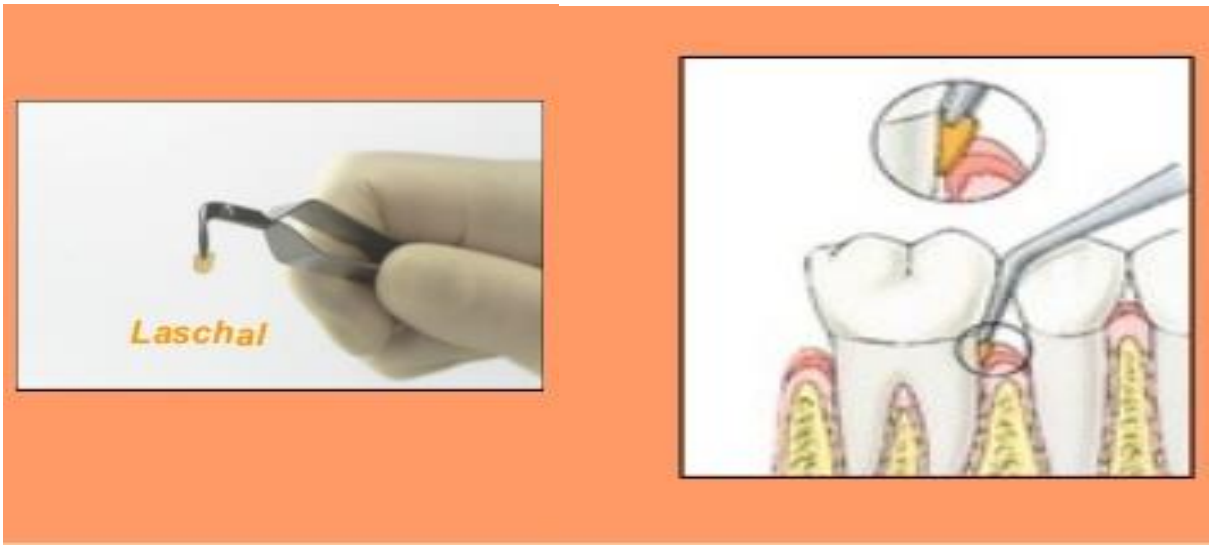

Figure 2: Insertion the locally applied periodontal pocket.

Periochip Form:

A typical Periochip of composition

Chlorhexidine chips:Chlorhexidine gluconate- 2.5 mg is supplied as a small, orange-brown, rectangular chip

Packaging: Each chip is individually packed in a separate compartment of an aluminum blister pack.

Storage: Store at 20° - 25°C with excursions allowable to 15° - 30° C (59° - 86°F)

Thymo-Quinone Chips:

Thymoquinone exhibits restrictive and disinfectant effects against each gram-positive and gram-negative microorganism, and even shows synergistic effects once combined with different antibiotics. Other studies have shown that thymoquinonehas various therapeutic effects, such as acting as a diuretic and hypotensive, attacking tumor cells, antihistamine, anti-inflammatory and analgesic properties, and antiepileptic effects. Moreover, thymoquinone exhibits chemical (nonenzymatic) metabolic activity dependent on GSH, NADPH, or NADH that may represent a "cellular switch" capable of modulating cellular antioxidant defenses[1]. Chitosan has gained attention as a drug delivery carrier as a result of it's a stable, perishable, nontoxic hydrophilic polysaccharide with extraordinary mucoadhesive properties and permeation up factors. No studies are performed to develop a dental medicine chip containing thymoquinone for the treatment of chronic periodontal disease

Mechanism of action: The bactericidal impact of the drug is because of the cationic molecule binding to further microbial complex and negatively charged microbic cell walls, thereby fixing the osmotic equilibrium of cells. It inhibits plaque formation by binding to anionic acid groups on salivary glycoproteins thus reducing pellicle formation and plaque colonization. It also binds to salivary bacteria thus interfering with their adsorption to teeth.

Clinical features after treatment: Clinical Studies In two double-blind, randomized, controlled clinical trials, 47 adult patients with disease were entered who had a minimum of 4 pockets with

searching depth of 5-8 mm that bled on probing. Patients studied were in smart general health. Diabetics were excluded from the studies. PerioChip wasn't studied in acutely septic periodontic pockets. Patients were free of supragingival calculus before baseline. In these 2 studies, the consequences of scaling and root planing (SRP) alone, and SRP followed by PerioChip treatment, were compared. All patients received full mouth SRP at baseline. If the pocket depth remained ≥ 5 mm at 3 and/or six months when initial treatment, another chip was placed into the pocket. Teeth treated with PerioChip were found to possess considerably reduced inquisitory pocket depth (PD) compared with those treated with SRP alone at nine months when initial treatment.. PerioChip treatment resulted in a exceedingly larger proportion of pockets and patients that showed an improvement in pd of 2 mm or a lot of compared with SRP alone at nine months. The variations in improvement were statistically vital once analyzed on a per patient basis ($p < 0.005$). PerioChip treatment maintained inquisitory attachment level (PAL) compared with baseline or with SRP alone at nine months. the consequences of PerioChip on bleeding upon probing haven't been established. in the 2 studies, there have been no vital changes in plaque development or periodontitis. Smokers and non-smokers were registered in these studies; though non-smokers mistreatment PerioChip demonstrated important improvement in pd, smokers incontestable a trend towards improvement that failed to reach statistical significance. This finding is per the accord that smoking could be a risk consider periodontal diseases.[5]

Formulation parameters:

Various anti-microbial drugs used in periodontal diseases-

•Tetracycline- non resorbablefibres

•Metronidazole.

•Minocycline

•Chlorhexidine chips.

•Doxycyclatehyclate in a resorbabe polymer.

Drugs other than anti-microbial agnets used in periodontal chip-

•Clotrimazole- antifungal.

• Nystatins-antifungal.

•Amlexanox-anti-inflammatory

•Thymoquinone-anti-inflammatory.

Excipients used in periodontal chip

Excipients used in the formulation of dental film other than active drug include solvents, plasticizers, permeation enhancers and polymers .

Polymers used are of 2 types :

a) Biodegradable polymers ex: chitosan.
b) Non-Biodegradable polymers ex: ethyl cellulose.

•Chitosan- biodegradable polymer

•Methylene chloride- solvent

•Polyvinylpyrrolidone-solvent/polymer.

•Lactic acid solution-biodegradable polymer.

•Sodium benzoate- preservative.

•Glycerol- plasticizer, humectant.

•Poly lactic-co-glycolic acid- water soluble polymer.

•Acetic acid- solvent.

•Water.- solvent.

Types	Example
Natural	Carbohydrates, Starch, Cellulose, Lignin, Poly amino acid.
Synthetic	Silk, Protein, Cotton and Linen.
Non -Synthetic	PVC, Polypropylene, Rubber and Nylon.
Biodegradable	CO2, NO2, Water and Biomass.

Table 01: List of polymers used in preparation of Periodontal Chip.

Permeation Enhancers

These are compounds which promote gum permeability by altering the periodontium stratum as a barrier to the flux of a desired penetrant .

A large number of compounds have been investigated for their ability to enhance stratum permeability. These may be conveniently class yers of periodontium to achieve penetration enhancement under the following mainheadings:

Solvents: Water, Alcohols (methanol and ethanol), Alkyl methyl sulfoxides-(dimethylsulfoxide), Dimethylacetamide and dimethylformamide

Miscellaneous solvents (propylene-glycol, glycerol, isopropyl-palmitate)

Surfactants: Commonly used surfactants are:

Anionic-surfactants-(Dioctyl-sulphosuccinate)Sodium-laurylsulphate,Decodecyl-methyl-sulphoxide)

Nonionic-surfactant-(PluronicF127,PluronicF68).

Preparation:

Preparation of chip by solvent casting method

- Glass moulds are used for casting of films/chips. Formulations is designed in such a way using different drug/polymer ratio based on the drug release from the film.

- Ethyl celluose was taken as the main non- biodegradable polymer. films were prepared by dissolving ethyl cellulose in chloroform solution, using dibutyl phthlate and peg 400 as plasticizers in a beaker using magnetic stirrer to get different concentrations of polymeric solutions. then the selected drug is added to the polymeric solution and mixed homogenously magnetic stirrer in a closed beaker.
- After proper mixing the solution was poured into labelled glass moulds placed in horizontal plane.
- The solvent was allowed to evaporate slowly by inverting the glass funnel with the cotton plug closed into the stem of the funnel at room temperature for 24 hours.
- After complete evaporation of solvent, cast films obtained, which are then cut into pieces of (10X6mm), wrapped in aluminium foil and stored in a dessicator at room temp in a dark place for further evaluation of studies to be performed.

Preparation of chip by direct milling method:

- Selected drug was dissolved and added to chitosan that had been soaked in 1% acetic acid overnight using PEG 400 as plasticizer. Both ingredients were sonicated to form a homogenous mixture and poured into a uniquely designed rectangular glass mold lined with aluminum foil. After drying overnight at room temperature, the resultant film was cut into small rectangular chips 0.5 × 0.5 sqcm in size. A content uniformity check was conducted on some chips in an exceedingly random fashion to affirm the amount of drug administered in each chip. The chips were then keep in sterile vials and kept at temperature.[6]

Preparation methods of periochip:

A) Solvent casting:

- Among many techniques of film producing, solvent casting is possible, preferred and doubtless wide used methodology principally because of the easy producing process and low value of process.
- The manufacturing procedure of thin films with the solvent casting method along with the quality control parameters in each step is illustrated below.

- The rheologic properties of the polymeric mixture ought to be taken into consideration since they have an effect on the drying rate.
- The film thickness, the morphology as well as the content uniformity of the films is evaluated. The mixing process could introduce the air bubbles into the liquid inadvertently; therefore, de-aeration is a pre-requisite to obtain a homogeneous product. After casting the solution into a suitable substrate, they are left for drying to allow the solvent to evaporate, which just leaves a polymeric film with a drug on it.
- After the entire drying of the film, it's take appropriate form and size depending upon the desired dosage of the shaped strip.
- Majority of the cases, the strips are rolled and stored for a certain time before cutting, which is known as ‘roll-stock’ in an industry. However, a film should not be exposed for too long time since it is prone for being damaged.
- Several advantages like higher physical properties, straightforward and low value process, and glorious uniformity of thickness are determined with the film obtained by solvent- casting.
- However, this process possess some limitation. For instance, a chemical compound thin film prepared by solvent casting methodology was brittle upon storage, as marked by decrease within the % elongation because of evaporation or loss of the residual solvent within the film over time.
- Another issue under scrutiny associated with this method is the requirement of using organic solvents. The presence of organic solvent system is a serious problem because it causes a hazard to health and environment.
- As a result, strict laws are adopted by several countries relating to the utilization of an organic solvent.
- Therefore, sufficient endeavor should be invested to optimize the various parameters such as the speed of casting, drying time, and final thickness of the dried strip, which may affect the production of films from commercial scale output.

Evaluation parameters:

1. Thickness of the film: The thickness of patches was measured at three completely different places employing a micrometer and average values were calculated.

Uniformity of weight of the films

Film (size of 10x5 mm2) is taken from completely different areas of film. Then the weight variation of every film is calculated.

2. Folding endurance:

Folding endurance was firm by repeatedly folding one film at an equivalent place until it poor. the amount of times the film may be collapsable at an equivalent place while not breaking/cracking gave the worth of folding endurance .

3. Tensile strength of the films:

In order to work out the strength, the compound patch was force by suggests that of a machine system; weights were step by step extra to the pan to extend the actuation force until the patch was brokenThe strength was calculated to all or any formulations and expressed in N/mm^2.

Tensile strength of the film can be determined by Universal Strength Testing Machine.It consist of 2 load cell grips, the lower one is fixed and the upper one is movable. The test film of specific size 4*1cmsq was fixed between these cell grips and force was gradually applied till the film breaks.

Tensile Stength= (Load At Break) (Original width) / Original Thickness.

4. Drug content uniformity of films

Content uniformity was determined by taking previously weighed film in a clean volumetric flask and warm buffer solution (370C) was added in small portions. The flask was kept in the shaker for 4 hours and then the final volume was adjusted to 100 ml with the buffer. The flask was kept undisturbed for one hour and 5 ml of the supernatant portion was taken in a 25 ml volumetric flask and diluted to 5 times in buffer. The turbid solution was centrifuged and the absorbance was read at absorption maximum 284 nm. on an U.V. spectrophotometer.

5. Moisture loss

The 20 films of different concentrations are weighed accurately and then they are kept in desiccators for 3 days and then reweighed and by using the formula % moisture loss was calculated.

6. Surface pH :

Periodontal films were left to swell for one hour on the surface of the agar plate, ready by dissolving a pair of (w/v) agar in warm double water beneath stirring and so gushing the answer into the petridish to gelling / solidify at temperature. The surface hydrogen ion concentration was measured by suggests that of hydrogen ion concentration paper placed on the surface of the swollen film. The mean of 3 readings was recorded.

7. Viscosity:

Aqueous solutions containing each compound and softener were ready within the same concentration as that of films. Brookfield viscosimeter (LVDV-E model) connected to the helipath spindle variety eighteen was used. The consistence was measured at twenty revolutions per minute at temperature. The recorded values were the mean of 5 determinations.

8. In-vitro study: The pH of gingival fluid lies between 6.5 – 6.8, phosphate buffer pH 6.8 was used as simulated gingival fluid. Also, since the film ought to be immobile within the periodontic pocket, a static dissolution model was adopted for the dissolution studies**.** Films of known weight were placed individually in small test tubes sealed with foil containing 1.0 cubic centimeter of phosphate buffer (pH 6.8) and unbroken at 37 0Cfor twenty four hours. The temperature was maintained at 37 0C by keeping the beaker on magnetic stirrer with temperature management. The buffer was then drained off at the interval of two hours and replaced with a recent 1.0 cubic centimeter of buffer.The concentration of drug decided by ultraviolet spectrophotometer at 284 nm the procedure was continued for forty eight hours. Studies were performed and also the mean additive percentage of drug was calculated **.**

In vitro antibacterial activity: Sterilized culture medium medium was ready by autoclaving underneath antiseptic condition and transfer the medium to sterile Petri plates. once solidification

of culture medium medium, created a field with 0.1 cubic centimeter microorganism i.e. S. aureus and E. coli in separate Petri plates, over that the films were placed and incubate for forty eight hrs at 37° C. measure the zone of inhibition using "Hi Antibiotic Zone Scale". Same procedure is followed by substitution the films over following plates and measures the zone of inhibition

9 . In-vivo study:

In-vivo study of optimized film formulation was performed on male white rabbits.

10 . In-vivo drug release study:

In vivo tests were performed on film formulation chosen on the idea of the results of in vitro test. The films were placed on the buccal mucosa of the animal. a rectangular.Piece of the film was introduced to the cavity by finger and adhered to the lower facet of the cavity facing the gum. uptake and drinking was prohibited throughout the primary three hours.After application, spit samples (one.0 mL) were collected sporadically at every time purpose of the experiment. spit samples were centrifuged at 5,000 revolutions per minute for ten min to separate any solid parts.The supernatant was transferred to centrifuge tubes and also the tubes were vortex mixed with phosphate buffer 6.8 for 2 min and centrifuged at 13,000 revolutions per minute for ten min. The supernatant is taken and add phosphate buffer 6.8 and analysed with the ultraviolet spectrophotometer for drug content

Marketed products:

The market products of periochip used for treatment of periodontics contain Sustained release therapy by Chlorhexidine, minocycline, tetracycline, Doxycycline, Metronidazole.

FDA APPROVED BRAND PRODUCTS: ***Periostat, atridox,periochip***

Chlorhexidine topical is sold as Betasept, Biopatch, Calgon Vesta, ChloraPrep One-Step, Dyna-Hex, Hibiclens, Hibistat Towelette, Scrub Care Exidine, Spectrum-4 among others.

Chlorhexidine gluconate mouth rinse is sold as **Paroex, Peridex, PerioChip,** Periogard among others.

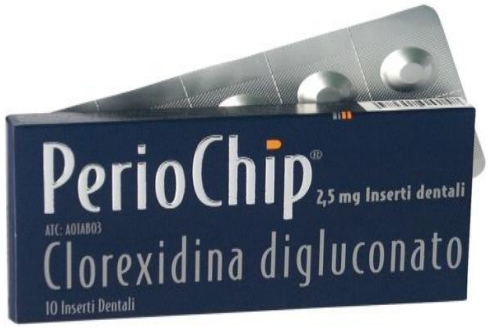

Fig 3.Marketed Formulations

Future development of technology:

- The platform of periochip provides a technology of delivering any drug that can be included in the peiochip in the formulation to the subgingival environment.
- Drugs that can be used for treatment of periodontal diseases include antibacterial, anti inflammatory and immuno modulatory agents and drugs that may influence bone resorption.
- A chip that can provide the controlled releases non-steroidal anti-inflammatory drugs to the sub gingival environment is being developed.[7]
- The formulation of a drug into various films has been popular in recent years. Several undesirable drawbacks associated with conventional dosage forms such as inconvenience of administration, lower bioavailability and patient non-compliance have pushed the development of novel polymeric thin films as a drug delivery platform. This drug delivery platform is being under surveillance from both start-up and established pharmaceutical companies. The companies strive to design a wide range of thin films for oral, buccal, sublingual, ocular and transdermal routes. Therefore, as an alternative to conventional dosage forms, polymeric thin films are expected to stand out as a dosage form to overcome the limitations posed by existing dosage forms. The film dosage form encounters several challenges during the phases of formulation development and manufacture. Such issues should be addressed to optimize the overall formulation even after transferring to large-scale manufacturing. The future looks very promising for the film technology in the time to come as new technologies are rapidly introduced to prepare thin films.

Conclusion:

It has been proven that a link exist between periodontal disease and cardiovascular disease. Periodontal disease It is a risk factor for the future development of cardio-vascular disease. The prevention and treatment of periodontal disease reduce the risk of cardio-vascular disease. The films were capable of inhibiting the growth of S. aureus and E. coli strains commonly found in periodontal disease. Films were developed to a satisfactory level in terms of drug content, drug release, mechanical properties and microbiological evaluation. On the basis of in vitro characterization of study it was concluded that periochip could be incorporated in a slow characterization it was concluded that periochip could be incorporated in a slow release chitosan chip for the treatment of periodontitis. A detailed investigation is required to establish in-vivo efficiency of periochip. Drugs that can be used for treatment of periodontal diseases include antibacterial, anti inflammatory and immuno-modulatory agents and drugs that may influence bone resorption. The formulation of a drug into various films has been popular in recent years. Development of novel polymeric thin films as a drug delivery platform helps to avoid Several undesirable drawbacks associated with conventional dosage forms such as inconvenience of administration, lower bioavailability and patient non-compliance. The future looks very promising for the film technology in the time to come as new technologies are rapidly introduced to prepare thin periochips.

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