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MICROSPONGE DRUG DELIVERY FOR PERIODONTITIS: A REVIEW

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ABSTRACT

Periodontal disease is a chronic inflammatory disease of gum tissue of teeth, If not treated may cause mobility & loss of tooth. The current practice in treatment of periodontitis involves scaling and root planning followed by administration of systemic antibiotics or application of local antibiotics directly on gums several times as adjuncts to conventional mechanical therapy. Systemic administration of antibiotics has disadvantages like inability of drug to attain satisfactory concentration at the site of action, nausea, fever, abdominal pain, unnecessary exposure of body to high dose of drug etc. These disadvantages have led to the development of local application of antibiotics which are intended to exclusively affect bacteria within the periodontal pocket. Dosage forms like mouth washes, lotions, gel, film, strip or pastes suffer common disadvantages such as low contact time; drug is lost in the saliva, has low patient compliance, need of frequent drug application and may have ability to develop resistance to the drug. The sustain release formulation release antibacterial drug at the site of infection (periodontal pocket) and also include ease of drug delivery at site of infection, sustain release of drug into GCF (Gingival Crevicular Fluid) for desired period of time. Microsponges fulfill all these need using insoluble or slightly soluble drugs. Microsponge reduce the dose of drug and avoid unnecessary exposure to whole body by providing the sustain delivery of oral medication. The goal of this review is microsponge drug delivery is very advance and useful to deliver the drug in periodontal pocket and its therapy.

KEYWORD: Periodontal disease Periodontal Pocket, Gingival Crevicular Fluid, Microsponge.

INTRODUCTION

Human teeth and periodontal tissues[1,2,3]

The teeth's which is accessory digestive organ located in socket of alveolar process of mandible and maxillae. The alveolar processes are covered by gum. The sockets are lined by membrane which is made up of fibrous connective tissue and attached to wall of socket. Thus it anchors the teeth in position and acts as shock absorber while chewing.

Tooth structure: **Anatomy and Physiology of tooth**

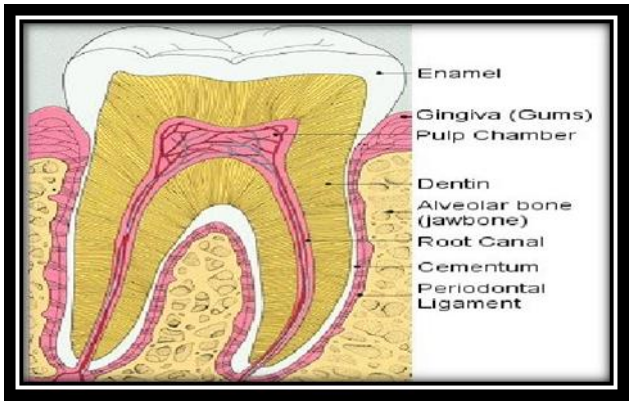


Figure 1: Tooth structure.

Major structures of tooth are Crown and Root, in this crown is visible portion and appear above the gum. Tooth is embedded in the alveolar sockets having one to three roots. The neck is constricted junction of crown and root near the gum line. Enamel, dentine and cementum are the major tissues of teeth. The pulp is composed of connective tissue. The teeth are surrounded by gingival.

Enamel: Outer covering of teeth made from inorganic material.

Dentine: present below enamel, contains calcified tissue, made from organic and inorganic material in the form of collagen fibers and calcium phosphate in bone respectively.

Cementum: It is tooth portion covering dentine at the root of tooth. It provide surface for attachment of periodontal ligament.

Dental pulp: It is inner to dentine and occupies the pulp cavity and root canal. It is composed of connective tissue blood vessel and nerves. Narrow extensions of pulp cavity, called root canal, run through the roots of the tooth.

Periodontal disease[4]

Periodontal disease is an inflammatory response due to overgrowth of anaerobic organism such as spirochetes and bacteroids cause loss of teeth. In some cases micro aerophilic organisms in the subgingival plaque may also cause periodontal diseases. If it's not treated may cause destruction of bone and soft tissue supporting to the tooth. No age group, ethnicity, race gender or socioeconomic group is immune to this disease, presenting a health problem worldwide. In the adult population it is probably responsible for the loss of more teeth than all other dental afflictions combined together. In US approx.60-70% of tooth loss occur due to periodontal disease in US. In India the disease is responsible for 80% of teeth extracted after age 30.

Aetiology of periodontal diseases[4]

In healthy gum the normal gap between gingival and tooth is 0 to 2mm. During perioodontitis, collagens and bacterial enzyme destroy the connective tissue and periodontal ligaments. Hence there is formation of periodontal pocket having depth 5mm.The conventional aim is removal of subgingival plaque and necrotic tissue linining the gingival wall of pocket.

Microorganisms associated with periodontal infections

In oral cavity more than 400 species of aerobic and anaerobic bacteria are colonizes. These organism reside in the teeth, GCF, mucus membranes, dorsum of tongue and saliva. Studies have indicated a strong association of microorganism of Actinobacillus, Bacteroids, porphyromonas, Prevotella, Wolinella and Capnocytophagas species in periodontitis of all stages.

Dental infection may occur due to -

- Introduction of pathogen from extra oral origin,
- Change in balance of indigenous flora,
- With the entry of bacteria into the normally sterile vital pulp of tooth.

Table No. 1: Microorganisms associated with periodontal infections.

Aerobic bacteria	Anaerobic bacteria
Gram positive cocci *streptococcus species* Gram-positive bacilli *Lactobacillus spp* Gram negative cocci-bacilli *Actinobacillus spp* *Actinobacillus actinomycetemcomita* Gram-negative rods *Pseudomonas spp* *Enterobacteriaceae*	Gram positive cocci *Veillonella spp* *Actinomyces spp* *Lactobacillus spp* Spirochetes *Treponema socranskii* Gram positive bacilli Gram-negative bacilli *Bacteroides spp*

Sign and symptoms[5]

- Loss and sensitive teeth
- Leave metallic taste in mouth and bad smell
- Pocket is formed between teeth and gum
- Red or tumor occur at gum
- Bleeding occur at gum

Rational for local intrapocket delivery of antimicrobial drugs[5]

The periodontal pocket is natural reservoir bathed by Gingival Crevicular Fluid (GCF). GCF is inflammatory secretion collected at gingival margin. it helps in easy insertion of device. It acts as leaching medium for release of drug from dosage form and for its distribution. Moreover, the periodontal diseases are localized to the immediate environment of the pocket. It is natural site for treatment with local sustains release system. The sustain release dosage form give maximum therapeutic effect of antimicrobial by maintaining constant plasma drug concentration over MIC for prolong period of time in controlled manner.

Types of periodontitis

A. Mild Periodontitis (gingivitis)

Gingival gets red, shiny, soft, swollen, causes separation of gum from teeth by forming pocket filled with plaque. Toxins produced by bacteria present in plaque irritate the gum.

B. Moderate Periodontitis

The toxins gives chronic inflammatory response in which body in essence turns on itself and then bone and tissues that give support to the are broken down. It is characterized by puffy, bleeding gum bone loss and with pocket depth up to 5mm.

C. Advanced Periodontitis

It is the major stage shows swollen, bleeding gum, bone loss, gum recessi on and pocket depth 6mm which is hard to treat. Teeth may get loose due to loss of bone and tissue. It may leads to loss of tooth due to inadequate support.

D. Refractory Periodontitis

This stage results in tooth loss due to loss of bone and destruction of tissue and bone supporting to the teeth.

Systemic or local antibiotic therapy in periodontal disease[6,7]

Periodontal diseases most commonly occurred due to bacteria, hence antimicrobial are most effective. The main aim of antibiotic therapy is to establish a concentration of drug which inhibits growth of bacteria. Mostly it is achieved by systemic route where drug kill gingival flora by reaching into GCF. But systemic route is not preferred as it develops bacterial resistance, fever, nausea, diarrhea and abdominal pain.

Route of administration of antibiotic can also be local by using conventional or controlled release dosage form. It is more advantageous than systemic as more rich at the site of infection by minimizing exposure to whole body.

Local Drug Delivery of Antimicrobial Agents

Periodontal disease can be controlled by local applications such as mouth rinses, gel, tooth paste etc. Mouth rinses, mouth irrigation does not reach the periodontal pocket. Ideally local drug delivery requires high initial concentration and multiple applications in order to provide sustain action.

Controlled Release Local Delivery Devices

Controlled release technologies assure therapeutic concentrations of the antimicrobial agents in the sub gingival area for a long period.

Various drug delivery systems for treating periodontitis include; fibers, gel, injectable systems, microspheres/micro particles, strips, compacts, films, and nanoparticles.[6,7]

The advantages of controlled release intra pocket devices are regulated dosage to the target sites Patient compliance, quicker reattachment of periodontal tissues to the tooth due to gradual decrease in size of the device inside the pocket, total release of the loaded drug in the

device, thereby effecting a more accurately regulated dosage to the target sites. Though it has above advantages some major disadvantage of controlled release intra pocket devices are like generates painful foreign body response, if any remnant of the device left behind in the pocket, removal of device can be painful, the drug evacuation from these devices has always been found to be incomplete and any remnant of the device left behind in the pocket cause several tissue reactions.

Microsponge[8]

Won introduced Microsponge technology in 1987. It is porous sphereical, non collapsible structures structure with interconnected void spaces with size range 5-300 µm and have capacity entrap wide range of active ingredients like emollients, fragrances, essential oil, sunscreen and anti-infective etc. Further, these porous microspheres with active ingredients can be incorporated in to formulations such as creams, lotions and powders.

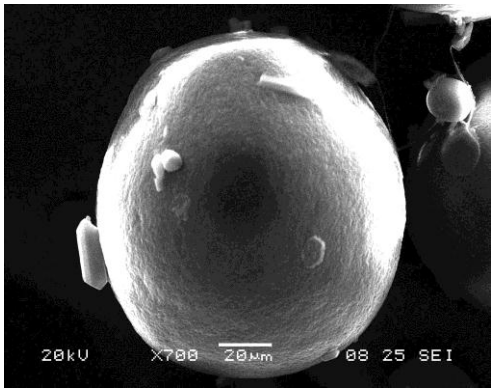


Figure No 2: SEM photogrph of microsponge.

Characteristics[10]

- Stable over pH range of 1 to11.
- Stable at temp up to 130°C.
- Compatible with most vehicle and ingredient.
- Self sterilizing as their pore size is 0.25mm where bacteria cannot penetrate.
- High payload (50 to 60%)
- Non-irritating, non-mutagenic, non-allergic and nontoxic.

Advantages[10,11]

- Prolonged release up to 12hrs
- Reduced irritation and better tolerance hence improved patient compliance

- Improved thermal, physical and chemical stability
- Incorporation of immiscible products
- Improve efficacy in treatment
- Used for topical and recently for oral administration

Characteristics of active ingredients[10]

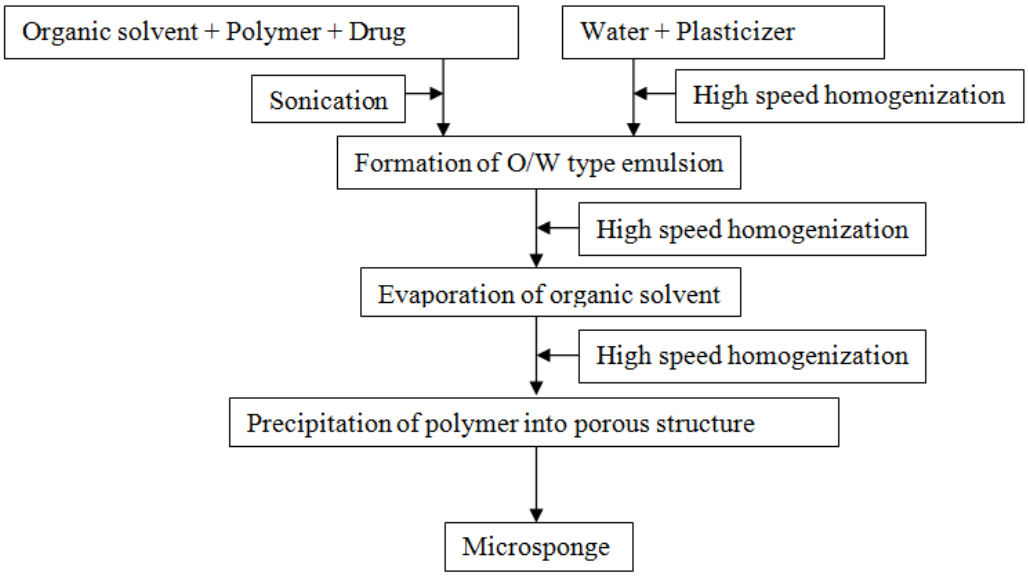
Active ingredients entrapped in microsponge must meet following requirement

- It should be miscible in monomer
- It should be inert to monomers
- It should be water immiscible or slightly soluble in water

Preparation of microsponges[9,12]

There are two methods have been used for preparation of microsponges are as follows.

a. Quasi emulsion solvent diffusion method



b. Liquid liquid suspensions polymerization[8]

Other method for preparation of microsponges is liquid liquid suspensions polymerization.

Steps involved in preparation of microsponge:

- Dissolve monomers along with active ingredients in a suitable solvent.
- Disperse solution of monomer in the aqueous phase containing additives (surfactant, suspending agent, etc. to aid in formation of suspension).
- Initiation of polymerization by temperature or irradiation.

Programmable parameters[9,10]

Several parameters of microsponge can be changed during production to obtain desire size sphere. It includes-

A. particle size

Affect release rate of active ingredient. The smaller the particle size, the slower the rate of release.

B. Pore Diameter and Volume

It determines the amount of active ingredient which can be entrapped in the microsponge.

C. Resiliency

Increased cross-linking leads to decrease in release rate. Monomer Composition, Selection of the monomer depends upon the active ingredient and vehicle into which it is dispersed.

Release modulation[10]

The microsponge particles contains interconnected voids because of this active ingredients are free to travel in and out from the particles and into the vehicle until equilibrium is reached. After application of product to oral mucosa actives present in the formulation gets absorb first into oral mucosa causes depletion of active in the vehicle and there is disturbance of equilibrium. Actives present in the microsponge starts to dissolve in vehicle to attain equilibrium. This will start a flow of active from the microsponge particles into vehicle and free from it to the oral mucosa until the vehicle is dried.

Physical characterization of microsponges

Fourier Transform Infrared Spectroscopy (FTIR) study[11]

Drug-Excipients compatibility study was carried out using FTIR spectrophotometer. The IR spectrum of drug was recorded using FTIR spectrophotometer with diffuse reflectance principle. Sample preparation include mixing the sample with Potassium bromide (KBr), triturating in glass mortar. The mixture was compressed to form a disc and finally placing in the sample holder. The spectrum was scanned over a frequency range 4000-400 cm-1. The infrared absorption spectra of pure drug, physical mixture of (drug and polymer) and microsponge formulation were obtained.

The Powder X-Ray Diffraction (PXRD)[12]

The powder X-ray diffraction (PXRD) patterns were recorded using X-ray diffractometer employing Cu Kα radiation (1.542 Å) with a voltage of 30 kV and a current of 30 mA. Samples were scanned from 5° and 50° 2θ.

Particle size[11]

The particle size can be determined by using microscope or any other suitable method. The average particle size was expressed in terms of µm. The particle size can also be determined by using an optical microscope. Particle larger than 30µm can impart gritty feeling and hence particles of sizes between 10 to25 µm are preferred for final preparation.

Differential scanning calorimetry[12]

Thermal properties can be recorded by using DSC. Samples (5 mg each) were heated in hermetically sealed aluminium pan at a heating rate of 10°C/min over a range of room temperature to 100°C under a nitrogen atmosphere (flow rate of 50 ml/min).

Drug content and entrapment efficiency[12]

The drug content and entrapment efficiency were calculated using equation

Actual drug content (%) = M_{act} / M_{ms} x 100

Entrapment efficiency (%) = M_{act} / M_{the} x 100

Where M_{act} is the actual MB content in weighed quantity of microsponges, M_{ms} is the weighed quantity of powder of microsponges and M_{the} is the theoretical amount of MB in the microsponges calculated from the quantity added in the process.

Scanning electron microscope[12]

Morphology of microsponge can be studied by using scanning electron microscope (SEM).

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