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Microspheres in Periodontal Theraphy

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ABSTRACT

Controlled drug delivery technology is concerned with the systematic release of a pharmaceutical agent to maintain a therapeutic level of the drug in the body for a sustained period of time. This may be achieved by incorporating the therapeutic agent into a degradable polymer vehicle, releasing the agent continuously as the matrix erodes. Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers having a particle size ranging from 1-1000 µm. So incorporating these microspheres in periodontal therapy as an adjunct to surgical and nonsurgical periodontal therapy should be considered. This review discusses the use of microspheres in periodontal therapy.

KEYWORDS : Microspheres, doxycycline, Minocycline, Periodontal therapy.

INTRODUCTION:

With advances in biotechnology, genomics and combinatorial chemistry a wide variety of new and more potent therapeutics are being created. Corresponding to the problems encountered in drug delivery, the need for safer and more effective methods and devices for drug delivery are needed.[1]

Indeed drug delivery system should be designed in the manner to provide therapeutic agent in the needed amount, at the right time to the proper location in the body, in a manner that optimize efficacy, increase compliance and minimizes side effects. The control release dosage form maintains relatively constant drug level in the plasma by releasing the drug at a predetermined rate for an extended period of time.[1]

One such form of controlled release drug dosage "microspheres" as carriers of drug becomes an approach of controlled release dosage form in novel drug delivery system. Microspheres are defined as "Monolithic sphere or therapeutic agent distributed throughout the matrix either as molecular dispersion of particles. It has a particle size of (1-1000nm).[2]

MICROSPHERES IN PERIODONTAL THERAPY:

A local drug delivery system consists of a drug reservoir and limiting elements that control the rate of medicament release. The success of any delivery system designed to target periodontal infection depends on the ability to deliver the antimicrobial into base of the pocket at a bacteriostatic or bactericidal concentration. The most popular and important bioabsorbable polymers used in formulating microspheres for developing controlled drug delivery system are aliphatic polysters, such as poly-e-caprolactone(PCL), poly(3-hydroxybutyrate), polyglycolic acid (PGA) polylactic acid-co-glycoliacid(PLGA) which provides a wide range of degradation rates, from months to years, depending on the composition and molecular weight.[3]

Drugs like doxycycline, Minocycline, tetracycline has shown to improve probing depth and improvement in clinical attachment loss. This is presumably due to decrease in gingival inflammation by modulating the inflammatory response and suppressing the microbiota. The use of these medications has shown the improved outcome in periodontal maintenance.

The first local drug delivery product available was an ethylene/vinyl acetate copolymer fibers (diameter 0.5mm) containing tetracycline 12.7 mg per inches. When packed into a periodontal pocket it showed good tolerance by oral tissue. These fibers yield tetracycline concentration in excess of 1300µg/ml in gingival crevicular fluid (GCF) which is much higher than 4-8 µg/ml that is provided by systemic dose of tetracycline. Therapeutic levels of tetracycline persist in GCF for 3-21 days following local drug delivery. Disadvantages of the fiber included the length of time required for placement less than 10 min/ tooth and second patient appointment. Fluorescent light and scanning electron microscopy showed superficial penetration of tetracycline with minor penetration into dentinal tubules, few areas of demineralized root surfaces and reduction in subgingival microflora.[4]

Sustained subgingival delivery provides retention of antimicrobial agent over an extended time period within periodontal pockets. Controlled drug release can be provided with subgingival irrigation (aqueous tetracycline) or pocket placement of commercially available antimicrobial fibers, gel or films.[5]

FDA APPROVED LOCAL DRUGS:

ANTIMICROBIAL AGENT	FDA CLEARANCE	DOSAGE FORM
12% Minocycline microspheres	Yes	Biodegradable powder in syringe
10% Doxycycline gel	Yes	Biodegradable mixture in syringe
25% Metronidazole gel	No	Biodegradable mixture in syringe
Chlorhexidine (2.5 mg) in gelatin matrix	Yes	Biodegradable device

Table 1 :FDA approved local drugs; US Food and Drug administration

LOCAL DELIVERY OF DOXYCYCLINE MICROSPHERES

Doxycycline Polymer Atridox is a biodegradable gel containing 10% (w/w) doxycycline, 33% (w/w) poly-DL-lactide, and 57% (w/w) Nmethyl-2-- pyrrolidone. 22 The medicament is supplied in two syringes that must be mixed together chair side for 25 repetitions (approximately 30 seconds). The mixed solution is placed into one syringe to which a 23-gauge canula is attached and is placed to the depth of the pocket. The solution is expressed until it overfills the pocket and begins to set. Upon contact with the moist environment, the N-methyl-2-pyrrolidone solvent diffuses out as the liquid poly-DL-lactide rapidly solidifies. The residual polymer can then be packed into the pocket using the underside of a curette. Treatment areas should not be brushed or flossed for 1 week, and the patient is prescribed chlorhexidine mouth rinse twice a day. Resistance with doxycycline is lower than with tetracycline. In patients with adult periodontitis, natural resistance is 4.2% of the anaerobic subgingival bacteria.[7]

Development of bacterial resistance to doxycycline was studied using the Atridox system. The authors validated the development of short-term resistance (7-21 days); however, no long-term change (90-180 days) in the proportion of doxycycline resistant bacteria in the subgingival flora was noted. [8]

The first study, published by Polson et al. in 1997, suggests that for PD reduction and gaining CAL, doxycycline hyclate (DH) applied in a vehicle carrier was superior to sanguinarine and the vehicle alone. [9]

LOCAL DELIVERY OF MINOCYCLINE MICROSPHERES

A non–FDA-cleared ointment product of 2% (wt/wt) minocycline hydrochloride known as Dentamycine (Wyeth, United Kingdom) or PerioCline (Sunstar, Japan) and marketed in a number of countries.

A minocycline microsphere system **Arestin**; (Johnson and Johnson, USA) has been approved by the FDA. The Arestin microspheres are bio-adhesive, bioresorbable, allow for sustained release, and are administered as a powder. Each sphere measures 20–60 microns in diameter. The sphere is a bio-absorbable polymer of polyglycolide-co-dl lactide, which is hydrolyzed into CO_2 and H_2O. Arestin is delivered to sites of 5 mm or greater through a cartridge (containing 1 mg of minocycline hydrochloride) attached to a handle. The tip is removed from the cartridge and placed subgingivally, and the handle is depressed to express the Arestin from the cartridge. The antibiotic maintains therapeutic drug levels and remains in the pocket for 14 days. This configuration of material allows placement to the depths of most pockets and while the material cannot conform to the shape of the pocket as well as Atridox gel, it is still easier to use than the solid Actisitefibers.[10]

Arestin is indicated as an adjunct to SRP procedures for reduction of pocket depth in patients with adult periodontitis. Arestin may be used as part of a periodontal maintenance program, which includes good oral hygiene and SRP. (In subjects with chronic adult periodontitis, the application of minocycline microspheres three times over the course of 9 months (at baseline and at 3 and 6 months) resulted in an average of 0.25 mm improvement above average probing depth reductions seen with SRP alone at month 9. When the data are stratified in accordance with severity of baseline probing depths, there are 20% improvements in mild sites, 40% in moderately diseased sites, and 100% in severely diseased sites compared with SRP alone. SRP plus Arestin resulted in a greater percentage of pockets showing a change of pocket depths are compared with SRP alone at 9 months. The data also show that for pockets of 5 to 7 mm at baseline, greater reductions in pocket depths occurred in pockets that were deeper at baseline. SRP plus Arestin produced significantly greater pocket depth reductions than SRP alone at 6 and 9 months.[10]

LOCAL DRUG DELIVERYOF MOXIFLOXACIN MICROSPHERES

Moxifloxacin is fourth-generation fluroquinilone antibiotic with a broad antimicrobial activity against aerobic and anaerobic bacteria. It exerts a bactericidal effect by specifically inhibiting adenosine triphosphate-dependent topoisomerase IV and topoisomerase II(DNA gyrase). Moxifloxacin exerts excellent antibacterial activity against a wide range of putative periodontal pathogens, including Poryphyromonas gingivalis, Tannerella forsythia, Prevotella fusobacterium nucleatum, Aggregatibacter actinomycetemcomitans, Actinomyces species and Peptostreptococous species. Its bactericidal activity against biofim embedded P. gingivalis and AA was found to be superior to clindamycin, metronidazole, doxycycline. Soft tissue penetration of moxifloxacin has helped its improvised action against intracellular periodontal pathogens. Used adjunctively with scaling and root planning has provided superior out comes compared to scaling and root planning with systemic administration of doxycycline or scaling and root planning alone.[11]

LOCAL DRUG DELIVERY OF IBUPROFEN MICROSPHERES

Ibuprofen is a non-steroidal anti-inflammatory drug, which possess analgesic and mild antipyretic action, because of its short half life (1-3 hours) it was selected as model in this study3. Its activity is more than indomethacin, naproxen and other NSAIDS. Ibuprofen mediating the inflammation by acting on cyclooxygenase and it inhibit the lipoxygenase pathway, these decreases the production of leukotrienes by the leukocytes and the synovial cells. It also masks T cell suppressing the production of rheumatoid factors. Most frequent adverse effects occurring with ibuprofen are gastro intestinal disturbance; peptic ulceration and gastrointestinal bleeding have been reported. Hypersensitivity reaction, abnormalities of liver function including intestinal nephritis or the nephritic syndrome are rare. Sustained drug delivery of ibuprofen will reduce these toxicities considerably by maintaining a low and constant level of drug in the blood.[12]

CONCLUSION:

It can be concluded that within the limits, the application of locally-delivered microspheres as an adjunct to scaling and root planing could provide additional benefits. The controlled delivery devices are a useful adjunct to conventional surgical or non-surgical treatments, but are no substitute for these measures. In particular, controlled delivery systems are of interest as an adjunct for recurrent and refractory periodontitis.

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