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Review Article

THERAPEUTIC STRATEGIES FOR THE TREATMENT OF PERIODONTITIS

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ABSTRACT:
Periodontitis is an inflammatory disease of the supporting tissues of the teeth caused by groups of specific microorganisms. Aggressive forms of periodontitis can be localized or generalized. The concept that localized problem sites may be treated by local drug delivery appears attractive as the antimicrobial agent is delivered within periodontal pockets and the therapy is targeted on specific pathogenic microorganisms. This review highlights the use of mucoadhesive polymers in buccal drug delivery. Advantages associated with buccal drug delivery have rendered this route of administration useful for a variety of drugs. Characterization of critical properties such as the mucoadhesive strength, drug content uniformity, and permeation rate represent the major research areas in the design of buccal films. The present review describe approaches for local prevention of bacterial infections based on antibiotic-eluting medical devices.
Key words: Periodontitis, mucoadhesive polymer, buccal film.

INTRODUCTION:

Periodontal disease is a localised inflammatory response caused by the infection of a periodontal pocket arising from the accumulation of subgingival plaque. Periodontal disease has been considered as a possible risk factor for other systemic diseases such as cardiovascular diseases and pre-term low birth weight infants. Infections by pathogenic microorganisms are of great concern in many fields, particularly in medical devices, drugs, hospital surfaces/furniture, dental restoration and surgery equipment, health care products and hygienic applications, water purification systems, textiles, food packaging and storage, major or domestic appliances, aeronautic, etc. Infectious diseases kill worldwide more people than any other single cause. The clinical signs of periodontitis are changes in the morphology of gingival tissues, bleeding upon probing as well as periodontal pocket formation. This pocket provides an ideal environment for the growth and proliferation of anaerobic pathogenic bacteria[1,2]. The microorganisms colonizing the subgingival area represent the principal etiological factor in the development of the inflammation and tissue destruction. Generally, these infections are combated with antimicrobial agents, which are susceptible to their action. Particularly problematic is the resistant microorganisms that rapid and easily mutate their genes, making difficult their elimination. For instance, Pseudomonas aeruginosa bacterium is one of the most common causes of healthcare-associated infections and is increasingly resistant to many antibiotics. Staphylococcus aureus is also a bacterium that commonly colonizes human skin and mucosa without causing severe problems. However, serious illnesses that range from mild to life-threatening can be developed if the bacteria enter the body. These include skin and wound infections, infected eczema, abscesses infections, heart valves infections or endocarditis, pneumonia and blood stream infection or bacteraemia. Some of S. aureus are resistant to the antibiotic meticillin, meticillin-resistant S. aureus, and often require different types of antibiotic to treat them.(fig.1)

The aim of current periodontal therapy is to remove the bacterial deposits from the tooth surface and to shift the pathogenic microbiota to one compatible with periodontal health. Therapeutic approaches include mechanical scaling and root planning and, in some cases, surgery. As a result of treatment, there is a decrease of gingival inflammation as well as clinical probing depth[3].

The buccal region of the oral cavity is an attractive target for administration of the drug of choice. Buccal delivery involves the administration of the desired drug through the buccal mucosal membrane lining of the oral cavity. Films as dosage forms have gained relevance in the pharmaceutical arena as novel, patient friendly, convenient products. More recently, oraly disintegrating films (or strips) have come to light, thanks to their improved mechanical properties[4]. Mucoadhesive buccal films share some of these advantages and more. Due to their small size and thickness, they have improved patient compliance, compared to tablets[3,5].

Systemically applied antimicrobials have been advocated for the treatment of severe forms of periodontitis. However, in the early 1970s, concern emerged with respect to systemic antibiotherapy for chronic infections such as periodontal disease. Indeed, side effects including hypersensitivity, gastrointestinal intolerance and the development of bacterial resistance have been described[6-8]. The local tissue concentration of a drug can be enhanced by incorporating the active agent into controlled release delivery systems to be placed directly in the periodontal pocket.

To be useful for periodontal therapy, it is desirable to have a bioerodible drug delivery system that can maintain an effective drug release rate in the periodontal pocket while simultaneously eroding throughout the duration of treatment up to several days. The advantages and recent progress in delivering a variety of compounds, specifically peptides and proteins, render the disadvantages of this route less significant. Fortunately, the enzyme activity in the buccal mucosa is relatively low compared to other mucosal routes[9].

Oral mucosa:

1. Anatomy Of The Oral Mucosa:

The anatomy and physiology of the oral mucosa have been extensively reviewed in several publications[10,11]. Nevertheless, a brief overview in this chapter is essential. Light microscopy reveals several distinct patterns of maturation in the epithelium of the human oral mucosa based on various regions of the oral cavity. Three distinctive layers of the oral mucosa are the epithelium, basement membrane, and connective tissues. The oral cavity is lined with the epithelium, below which lies the supporting basement membrane. The basement membrane is, in turn, supported by

connective tissues (fig. 2) and (fig.3). The epithelium, as a protective layer for the tissues beneath, is divided into (a) non-keratinized surface in the mucosal lining of the soft palate, the ventral surface of the tongue, the floor of the mouth,alveolar mucosa, vestibule, lips, and cheeks, and (b) keratinized epithelium which is found in the hard palate and non-flexible regions of the oral cavity[11].

2. Oral Mucosa, A Barrier To Permeability:

The main mechanisms responsible for the penetration of various substances include simple diffusion (paracellular, transcellular), carrier-mediated diffusion, active transport, and pinocytosis or endocytosis. Recent evidence has shown that passive diffusion is the primary mechanism for the transport of drugs across the buccal mucosa, although carrier -mediated

transport has been reported to have a small role. Two routes of passive transport are available in the buccal epithelium; one involves the transport of compounds through the intercellular spaces between the cells (paracellular), and the other involves passage into and across the cells (transcellular). Depending on the nature of the permeant, i.e. the overall molecular geometry, lipophilicity, and charge, either of the transport pathways across buccal epithelium can be selected.

Determination of mucoadhesion:

Besides the important parameter of mucoadhesion strength and residence time of buccal films, the mechanical properties play a crucial role on the physical integrity of the dosage form. Several values can be obtained from a regular stress–strain curve; however, most relevant to the study of buccal films are the tensile strength, the elongation at break, and the elastic modulus, also known as Young's modulus[12]. The determination of the mechanical properties of a buccal film is usually based on the ASTM D882 method and measured using instruments such as a texture analyzer.

Young's modulus is an evaluation of the stiffness or how the film deforms in the elastic region[13]. It is defined in the initial elastic phase of deformation and is obtained from the ratio of applied stress and corresponding strain and can be computed from the slope of the stress–strain curve. It has been described that soft and weak polymers have a low tensile strength, low Young's modulus, and low elongation at break, while a soft and strong polymer exhibits a moderate tensile strength, low Young's modulus, and a high elongation at break[14,15]. Desired mechanical properties will vary depending on the formulation goals and the method chosen, but in general, some examples of behaviors obtained from stress–strain curves can be depicted, as shown in Fig. 4[16]. Tear resistance of a film is normally obtained from stress–strain curves but using very low rates of loading (displacement of 51 mm/min). It is a complex function of the film's ultimate resistance to rupture and is obtained from the maximum stress value and is reported as the correspondent force.

Finally, another test normally used and reported in the literature is the determination of the folding endurance of the film. The test is performed by repeated folding of the film at the same place until film failure. A maximum of 300 times is sometimes reported as a limit to the test[17], and the value is reported as the number of times the film can be folded prior to rupture.

Drug Delivery Via The Oral Mucosa:

Local delivery in the oral cavity has had particular applications in the treatment of toothache, periodontal diseases, and bacterial infections. Sustained-release systems, which are able to provide sustained drug concentrations in the systemic circulation due to delayed release of the drug from the formulation, are suitable dosage forms for the buccal region of the oral cavity. The lower permeability of this region compared to the sublingual site is ideal for controlled-release systems.

Drug Delivery Devices:

There are two possible approaches to improve the drug action: (i) sustained and controlled drug release to reduce or eliminate side effects by improving the therapeutic index; (ii) site-specific drug delivery to minimize systemic effects. These two strategies have been explored by the association of drugs with different vehicles, either naturals or synthetics. Drug delivery systems can be classified according to the mechanism controlling drug release. We distinguish three categories: (i) `solvent controlled' matrix systems based on macromolecular matrix permeability to small molecules after matrix swelling into hydrated medium; (ii) reservoir systems' controlled by drug diffusion across a polymeric membrane; (iii) chemically controlled systems' where the rate of drug release is controlled by the rate and extent of degradation of chemical bonds and the erosion of the polymeric matrix. For all these systems, the basic polymer can be of natural origin such as proteins[18] or collagen[19], semi-synthetic such as cellulose derivatives[20,21] or synthetic, all of which must preferably degrade during use. Natural polymers have been considered as biodegradable carriers[22]. Many polymer based systems for antibiotic delivery in the treatment of periodontal diseases have been studied and evaluated in vitro and/or in vivo.(Table-1)

Periodontal Drug Delivery Devices can maintain an effective drug release rate in the periodontal pocket while simultaneously eroding throughout the duration of treatment up to several days. A wide variety of specialized local delivery systems (i.e. intrapocket devices) have been designed to maintain the drug in the gingival crevicular fluid (GCF) at a concentration higher than the MIC are following-

Fibers are thread like devices used for sustained release of drug into the periodontal pocket.

They can either be hollow or matrix delivery devices.Hollow fiber the open spaces within the fibers are filled with a therapeutic agent and the agent is released simply by diffusion through the reservoir wall. There is no rate control in these types of fibers. First delivery devices by Goodson were composed of cellulose acetate filled with tetracycline These fibers released 95% of the drug in the first 2 hrs and the release followed first order kinetics. Although GCF levels of tetracycline remained within the therapeutic range for 24 hrs, the study was viewed mainly as an evaluation of drug delivery. As shown by Goodson, hollow fiber systems used in periodontal pockets release drug quite rapidly. They can be qualified only marginally as sustained release devices. Studies have been conducted and have demonstrated the clinical efficacy of these fibers. However actual value in patient therapy is somewhat difficult to interpret as clinicians have found the fiber placement technique challenging. A considerable number of fibers become dislodged from the periodontal pocket during the course of 10-day treatment period. The fiber is tied around the tooth below the gingival margin so that the periodontal pocket is packed with the drug releasing material.

Strips And Compacts A controlled release strip coded PT-01 made up of polymethacrylic acid and hydroxypropylcellulose containing 10% ofloxacin has been reported in studies by Kimura et al. Data showed that ofloxacin could be found in higher concentrations than the

MIC of most periodontal bacteria in GCF over 7 days by a single application of PT-01 in the human periodontal pocket. Although the weekly application of PT-01 on days 0-35 showed some further shift in the proportion and reduction in subgingival microbial flora, no significant differences in the microbiological results between the strip group and the control groups were noticed. Consequently the authors suggested that the application of PT-01 might have a beneficial effect as an adjunct to conventional therapy.

The controlled release strips that gave long-term improvement were chlorhexidine strips[22]. Controlled trials involving chlorhexidine in ethyl cellulose strips used every 3 months in place of routine supportive periodontal therapy have shown significant clinical benefits lasting up to 2 years.Because of the non-biodegradable nature of polymeric carriers and the only temporary clinical improvements after treatment completion, no product has been marketed yet.

Injectable Systems The application of an injectable system is easy and does not take long, is without pain and is carried out with the help of a syringe. Moreover, an injectable delivery system can fill the pocket, thus reaching a large proportion of pathogens. Two types of injectable delivery systems have been assessed in the treatment of periodontal diseases, biodegradable micro particles and gels.

Microparticles Microparticles based on poly (α-hydroxyacids) such as polylactide or poly (lactide-co-glycolide)containing tetracycline have been designed for periodontal disease therapy. The in vitro release rate is influenced by the polymer choice and by the pH of the medium; the release rate is increased as the pH increases. PLGA microspheres have been suggested for the delivery of histatines. The stability of peptide release has been maintained at 100% through out release by the addition of non-ionic surfactant. In vitro release of total peptide lasts for one month. Some questions related to the retention of such formulations in the periodontal pocket need clarification.

Gels Mucoadhesive, metronidazole-containing gel systems designed for periodontal treatment based on hydroxyethylcellulose, Carbopol 974P and Polycarbophil have been described. In vitro drug release was significantly decreased with the increasing concentration of the polymer, due to both the concomitant increased viscosity of the formulation and additionally, the swelling kinetics of polycarbophil following contact with dissolution fluid.

Microcapsules They are being used for the delivery of encapsulated antibacterial agents in treating periodontal disease. These systems release the drug over a prolonged period of time in the salivary or crevicular fluid.

Films They are matrix delivery systems in which the drug is distributed through out the polymer and drug release occurs by diffusion and/or matrix dissolution or erosion. The dimensions and shape of the film can be controlled to correspond to the dimensions of the pocket where the film is to be inserted. It can be rapidly inserted into the pocket with minimal pain to the patient[23]. It can be totally submerged in the pocket and can be inserted to the base of the pocket. If the thickness of the film is reduced to less than 400 micrometer, it carries sufficient adhesiveness, thus not interfering with the oral hygiene of the patient. Both degradable and non-biodegradable films have been developed. The films that release drug by diffusion alone are prepared using water insoluble or non-degradable polymers whereas those that release drug by diffusion and matrix erosion use soluble or biodegradable polymers in the matrix.

Non-degradable films The first descriptions of an intra pocket, non-biodegradable matrix delivery device was made by Addy and coworkers in 1982. They described the use of matrix films of polymethacrylates for the intrapocket delivery of tetracycline, metronidazole and chlorhexidine[24]. Suitable sized films were prepared. In vitro release profile and duration of drug release was studied and was shown to be dependent on the drug loading in the delivery systems.

It also depended on the nature of drug incorporated. Films containing 30% w/w chlorhexidine, tetracycline and metronidazole released 57.0, 40.0 and 96% of the drug load. They further described formulations delivering in vitro therapeutic levels of all three drugs over a 14-day trial period. Clinical assessment of films containing 30% w/w drug have shown metronidazole containing strips to be more effective but no evaluation of in vivo drug release rates was done. In later studies these systems were found to be associated with slower rate of relapse of clinical parameters and have not yet been developed commercially. Ethyl cellulose matrix films for intrapocket drug delivery have been described. These films were made by casting ethanol or chloroform solutions of the polymer into molds and allowing the solvent to evaporate.

The appropriate drug and plasticizing agent were incorporated into the solution prior to casting. The dried films were then cut into desired shapes. Films containing chlorhexidine, metronidazole and minocycline have been developed and tested to various degrees. The release of the therapeutic agent from these films is dependent on the solvent used,

the presence of the plasticizer, the nature and concentration of the drug in the film. Films cast from ethanol solutions containing 5% w/w chlorhexidine released 95% of the drug over a period of 10 days, whereas chloroform-cast films released 20% of drug load over a 205-dayperiod. This could be due to the differential solubility of the drug in the casting solvents. Drug release from chloroform-cast films was modified by the addition of PEG to the formulation. Golomb et al., described metronidazole-bearing films cast with PEG 3000 and concluded that the amount of crystalline water bound to the surface of the films increased with the inclusion of PEG[25].

It was further suggested that enhanced release of drug was due to improved water binding to the surface of the matrix films containing PEG. Stabholz et al. assessed the efficacy of periodic treatment with chlorhexidine-containing films in a 2-year study of maintenance of periodontal pocket[26]. Treatment showed significantly lower incidence of bleeding on probing, pocket depths and attachment levels when compared to the conventional maintenance treatment.The limitations of such delivery devices include the removal and replacement as they do not degrade. On the other hand, less expertise is required than for scaling and plaque removal.

Degradable/Soluble films These systems dissolve or erode in the gingival crevice so that removal after treatment is not required. Drug release occurs by erosion or dissolution and drug diffusion through the matrix. Sustained release profile can be obtained by appropriate manipulation of one or more release mechanisms.

A number of biodegradable polymers are used for the delivery of antimicrobial agents in the

treatment of periodontal diseases. Some of these polymers are hydroxyl propyl cellulose,

polyesters, cross-linked collagens and protein films. Device erosion probably accounts for the more gradual release seen from the device from 2 to 24 hours.

Main advantages and potential disadvantages of controlled delivery systems (CDS) for the treatment of periodontitis.

Advantages Of Controlled Delivery System

- Maintenance of drug levels in a therapeutically desirable range.
- Reduction or elimination of harmful side effects of drugs.
- Protection from degradation of drugs with short in vivo half-lives.
- Improved patient compliance.
- Improved drug administration in geographic areas with low medical supervision.
- Permits localization of the drug for a prolonged period of time.

Disadvantages of controlled delivery system

- Toxicity or lack of biocompatibility of the polymer material.
- Pain caused by the presence of the implant.
- Production of harmful by-products from a polymer if it is biodegradable.
- Need of surgical procedure to implant the device in the appropriate location.
- Expense of a particular polymer-drug formulation.

Evaluation Of Local Delivery Devices In Periodontics:

Studies dealing with local delivery devices vary considerably in regards to the selection of patients, the treatments provided, the duration of the study and the microbiological and clinical parameters used.

Experimental Design:

There are surprisingly few studies that demonstrate clinical efficacy using controlled release local delivery systems in periodontitis patients.The experimental designs for some clinical trials that used controlled release locally delivered antimicrobials. Comparison between reports is not straightforward sincetheir treatment patterns differ widely. In some studies the device is used as the only treatment for each site, but more commonly they are used adjunctively. Similarly, the control sites to which the device effects are compared vary in type or may be absent.

Microbiological evaluation:

In recent years, it has been accepted that a variety of suspected pathogens have been important etiological factors in the breakdown of periodontal tissues. These pathogens include anaerobic Gram negative species such as Porphyromonas gingivalis (Pg), Prevotella intermedia (Pi), Bacteroides forsythus (Bf), Fusobacterium nucleatum (Fn), Selenomonas and Campylobacter species and facultatively anaerobic Gram negative rods such as Actinobacillus actinomycetemcomitans (Aa) and Eikenella corrodens (Ec). The effects of controlled local therapies on the microflora appear to be transient. This may be due to inadequate supragingival plaque control as several studies have shown that treated sites are rapidly recolonized unless good oral hygiene is maintained[27].

CONCLUSION:

Most reports regarding the recent periodontal literature on medical treatment have involved tetracyclines, metronidazole, or chlorhexidine. Although these therapeutic agents have been selected according to current knowledge of bacteria involved in periodontal diseases, the outcome of interest to manufacturers, regulatory agencies, practitioners, and patients is the clinical efficacy. These therapeutic systems have shown strong efficacy against periodontal microorganisms; however, it has been difficult to correlate the therapeutic improvements with microbiological results. Indeed, the type of microbial assay can dramatically influence the results observed with different therapies. It is very likely therefore that these agents in such high concentrations exert multiple effects on the local environment, only one of which may be related to antimicrobial activity.

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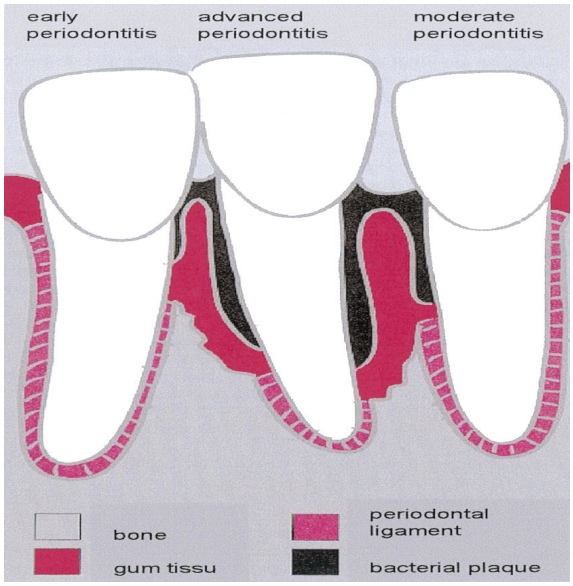

Fig. 1: Bacteria in subgingival plaque have caused a periodontal pocket to develop, inflaming surrounding tissue and causing loss of alveolar bone

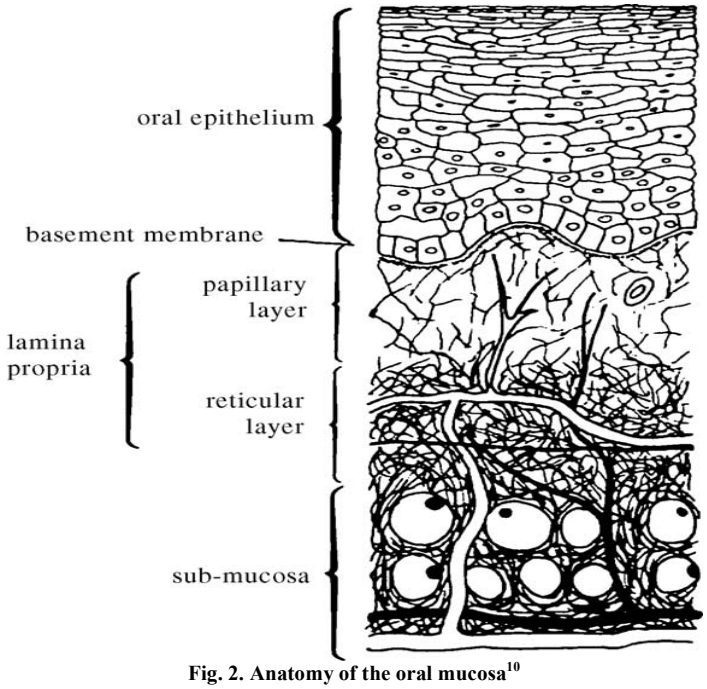

Fig. 2. Anatomy of the oral mucosa[10]

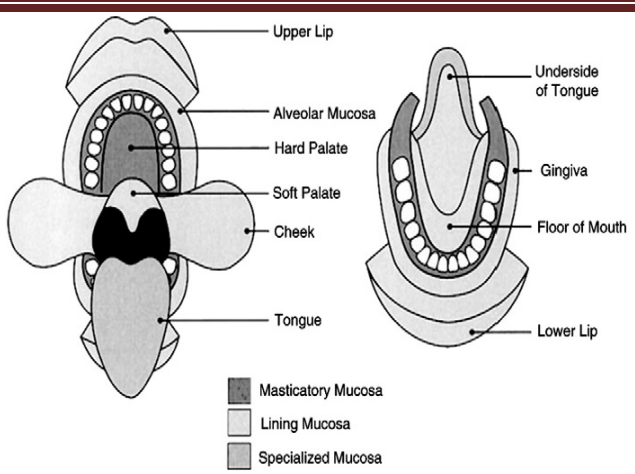

Fig. 3. Schematic representation of the different linings of mucosa in mouth[10]

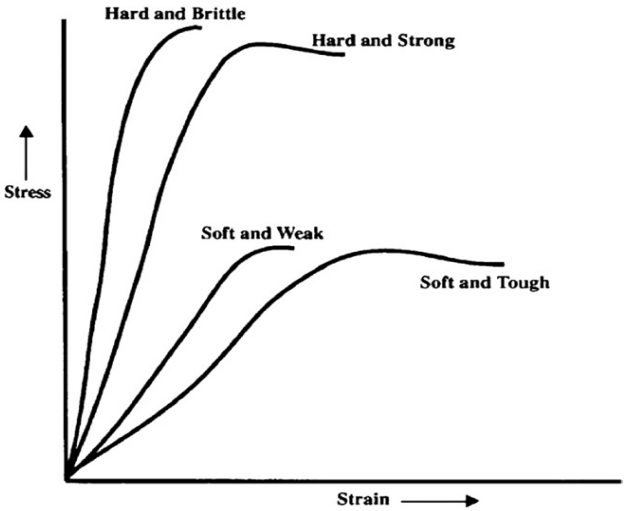

Fig. 4. Examples of behaviors observed in stress–strain curves in polymeric films[16]

Table-1: Summary Of Some Investigated Intra-Pocket Delivery Systems:

System	Polymer	Drug Incorporated
Fibres	Cellulose Acetate	Tetracycline Hcl
	Ethylene Vinyl Acetate	Tetracycline Hcl
Strip	Polyethylmetha Acrylate (Acrylic)	Metronidazole
	Ethyl Cellulose	Chlorhexidine
Films	Ethyl Cellulose	Metronidazole
	Cross-Linked Atelocollagen	Tetracycline
	Gelatin (Bycow Protein)	Chlorhexidine Diacetate
	Chitosan	Taurine
	Chitosan + Plga	Iproflavone
	Chitosan + Pcl	Metronidazole
	Polyvinyl Alcohol + Carboxymethyl Chitosan	Ornidazole
	Plga	Amoxycillin + Metronidazole
	Poly(Ortho Ester)	Metronidazole
	Pcl	Minocycline
Gels	Hydroxyethyl Cellulose + Polyvinylpyrrolidone	Tetracycline
	Chitosan	Metronidazole
	Poly(Dl-Lactide) + N-Methyl 2-Pyrrolidone	Doxycycline Hyclate
	Glycerol Monooleate + Sesame Oil	Metronidazole
Microparticles	Pluronic F 127	Tetracycline
	Plga + Pcl	Doxycycline
Nanoparticles	Chitosan	Antisense Oligonucleotide
	Cellulose Acetate Phthalate	Triclosan
Injectable semi-solid system	POE 1 Mg(OH)2	Tetracycline HCl

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