SYSTEM AND DEVICE FOR TREATING PERIODONTAL DISEASES

FIELD OF THE INVENTION

The present invention relates to oral systems and implants useful in the treatment of dental diseases, more specifically periodontal diseases.

BACKGROUND OF THE INVENTION

The teeth are principally supported by the alveolar processes of the maxilla and mandible. Collagen fibers course between and insert into the cementum and alveolar bone to hold the teeth in place. The supporting structures of the teeth including the cementum, the periodontal membrane, the bone of the alveolar process, and the gums form the *periodontium*. The ability to chew normally with one's own teeth depends in part upon the health of the periodontium.

Many diseases affect the health of the periodontium and may lead to a loss of alveolar bone and the loosening of teeth. The gingival attachment to the tooth may move apically while the gingiva seemingly remains in place or becomes enlarged. This results in a loose sleeve of diseased gingiva lying against the tooth. The space between this gingiva and the tooth is called a *pocket*. The ultimate result of pocket formation, bone loss and tooth mobility is the loss of teeth.

Periodontal diseases are a very common occurrence affecting, at a conservative estimate, between 70%-90% of the world population and is the major cause of tooth loss in people over 35 years of age. Periodontal disease can be defined as an infection and inflammation of the gingiva or gums that may cause, in severe stages, to loss of the bone that support the teeth. There are varying levels of severity of the disease. The mildest cases are clinically termed *gingivitis*, while the more severe cases are clinically known as *periodontitis*.

Gingivitis is an inflammation of the gingiva (or gums) that can be associated with poor oral hygiene and/or the hormonal state of the patient. It is believed that gingivitis, if untreated, will develop into periodontitis. Periodontitis is a bacterial disease that affects the gum tissue, the tooth and the bone that surrounds the tooth. Dental professionals classify the periodontitis into five levels or "types", starting from type I that includes inflammation of the gum tissue with the presence of bleeding but without bone loss and periodontal pockets of 1-3 mm, and ending with type V, which includes severe types characterized by rapid bone loss.

The oral cavity is essentially an aerobic environment, which is perfused by saliva. In contrast, the periodontal microenvironment is more anaerobic and is perfused by a plasma filtrate, known as the "gingival crevicular fluid". The growth of microorganisms within this microenvironment has been shown to be the cause of periodontal disease (Loe, et al, J. Periodontol. 36:177 (1965); Slots, Scan. J. Dent. Res., 85:247 (1977); Socransky, S.S., J. Periodontol. 48:497-504 (1977); Axelsson, P., et al., J. Clin. Periodon. 5:133-151 (1978). Hence, the treatment of the disease is directed toward controlling this growth.

As the periodontal disease becomes more established, the periodontal microenvironment becomes more anaerobic and the flow of gingival crevice fluid increases. A review of periodontal disease, and the methods for its treatment, is provided by Goodson J.M. (In: Medical Applications of Controlled Release, Vol. II, Applications Evaluation (Langer, R.S., et al., Eds.), CRC Press, Inc., Boca Raton, FL (1984), pp.115-138. The increased flow of gingival crevice fluid, which accompanies periodontal disease, has the effect of diluting and removing therapeutic agents placed within the periodontal crevice.

Efforts to treat periodontal disease by agents, e.g. antibacterial agents, provided to the oral cavity are generally ineffective, because the periodontal pocket is substantially inaccessible. On the other hand, systemic administration of antibiotics has only variable success in treating periodontal disease (Genco, R.J., J. Periodontol. 52:545 (1981).

Antibacterial agents such as chlorhexidine and quaternary ammonium salts in the form of mouth rinses have proved to be successful in preventing periodontal disease (Loe et al., J. Periodont. Res. 5:78 (1970). These agents, however, are unable to affect the subgingival flora when administered in this form as they do not penetrate into the pockets which are the result of the disease. Hence, they cannot be used in mouth rinses to treat an established periodontal disease.

The most widely used non-pharmacological approach to date has been mechanical cleaning methods combined with surgery. Although this method has proved to be fairly successful in treating individuals, there is still a high recurrence rate.

Controlled-release pharmaceutical compositions which are capable of being inserted into the periodontal cavity and of slowly releasing an antimicrobial agent have been developed. For example, Goodson J. M. (US Patents No. 4764377 and No. 4892736) discloses the incorporation of tetracycline into non – degradable polymeric fibers which can be wrapped around the tooth and release the antibiotic into the periodontal cavity for several days. The fibers needed to be fastened in place with an adhesive and to be removed at the end of the treatment period.

Dunn, R. L. (US Patent No. 5702716) describes the incorporation of doxycycline into a gel that solidifies in the periodontal pocket. The antibiotic drug is released over several days. The solidified gel must be removed at the end of the treatment.

Degradable polymers and copolymers which have been substantially investigated as potential implant compositions include poly(lactic acid), poly(glycolic acid, poly(lactic acid)-poly(glycolic acid) copolymer), polyamides and copolymers of polyamides and polyesters. However, the biodegradation of some of these polymers and copolymers may require three to five months, which is undesirable in the case of dental therapy.

Suzuki, Y., et. al., (US Patent No. 4,569,837) discloses the use of water-

soluble polymeric substances (such as methyl cellulose, gelatin, etc.) as a polymeric matrix for a periodontal implant.

A biodegradable sustained-release composition has been described by Friedman , M. et al., (US Pat. No. 5,023,082 and EP 388220) which is capable of treating periodontal or other diseases. The composition comprises a biodegradable polymeric matrix and a bioactive agent, wherein the polymeric matrix comprises a plasticizing agent and a cross-linked, water-insoluble protein formed from a water soluble protein and a crosslinking agent. The bioactive agent include a variety of pharmaceuticals or biologicals, while in the case of treating a periodontal disease the composition would preferably contain chlorhexidine or a salt thereof.

The compositions described above have varying efficacy in reducing the bacterial load of the periodontal pocket and in reducing pocket depth. Furthermore, none of the above mentioned formulations are particularly efficacious in imparting anti-inflammatory benefits.

Various studies have been carried out on bone formation using non-steroidal anti-inflammatory drugs (NSAID) as agents affecting bone growth and bone structure. Flurbiprofen (FBP) is an example of an effective NSAID which also exhibits analgesic and anti-pyretic activity. Wechter, W. J. (EP 137668 B1) suggests the use of FBP for the inhibition or prevention of alveolar bone loss or resorption.

Jeffcoat et al (J. Perio. Res. 23:381-385, 1988) were the first investigators who demonstrated the clinical effects of FBP on the progression of periodontal disease. As evidenced by standardized radiography and reduced radiopharmaceutical uptake, treatment with FBP (100 mg/day) for two months increased bone metabolism. A study for 24 months using FBP by Williams et al (J. Dental Res. 70:468,1991) found that the FBP-treated patient group showed reduction in bone loss.

A topical pharmaceutical composition for the treatment of epidermal and muco-epidermal tissues, and designed for immediate release in said tissues, was

described by Embro W. J (WO 95/04520). The composition includes chlorhexidine and at least one non steroidal anti-inflammatory agent as the active ingredients. These active ingredients are incorporated into a gel, cream, solution or rinse and are applied topically to sites of epidermal and muco-epidermal inflammation, infection or lesion.

SUMMARY OF THE INVENTION

The present invention provides a novel pharmaceutical system and device for the treatment of diseases of the oral cavity, preferably periodontal diseases, with improved patient compliance. The term "treatment" is meant to relate to the act of providing medical aid to a subject in need thereof, and includes acute treatment in an acute phase of a disease, long term or chronic treatment in order to prevent disease progression or recurrence as well as preventive treatment given to subject, e.g. subject who may have some predisposition to develop a disease, in order to prevent disease occurrence in the first place. In the context of the invention it relates to preventing the occurrence of, preventing the development of, or preventing the worsening of diseases of the oral cavity such as periodontal diseases, or for the purposes of ameliorating such condition in such patient, either human or animal. Unless otherwise stated, the term is not limited to any particular length of time, to any therapeutic regime or to any particular dose.

In addition, the terms "device", "system", and "delivery system", are used herein interchangeably and are intended to refer to the oral delivery system of the invention.

As mentioned above, a device for the sustained delivery of water soluble drugs such as chlorhexidine salts, was described in U.S. Pat. No. 5,023,769. It has been surprisingly discovered by the inventors of the present invention that the device of U.S. Pat. No. 5,023,769 is unsuitable for the delivery of hydrophobic agents such as flurbiprofen or for the delivery of combinations of hydrophilic and hydrophobic agents.

Thus, according to a first aspect, the present invention provides an oral delivery device in a solid unit form, that is suitable for implantation into a periodontal pocket and is capable of treating periodontal diseases, where sustained drug release is desired. The pocket might be a natural one, may be caused by a disease state, or may be opened intentionally as part of the treatment (e.g. through surgery). Upon its implantation, the device of the invention is softening, swelling and changing into a soft paste that adheres to the pocket. One of the benefits of this change is the high surface area for reaction concerning the active ingredients. The term "soft" is meant to describe the state of a material of easily yielding to pressure, easily impressed, molded, or cut; not firm in resisting, malleable, elastic and/or formless.

The device of the invention comprises both a hydrophilic and a hydrophobic drug and a biodegradable or bioerodible pharmaceutically acceptable polymer which provides sustained delivery of at least one of the drugs. Preferably, the device may also comprise at least one of a crosslinking agent, a plasticizing agent a wetting agent, a suspending agent, a surfactant and a dispersing agent. The polymer, preferably water soluble protein, is compatible with a high percentage of alcohol, a water/alcohol solvent, a hydrophobic NSAID soluble in alcohol, a hydrophilic water soluble antibacterial agent, a crosslinking agent that renders the protein insoluble upon completion of the crosslinking reaction, a plasticizing agent such as glycerin and surface active agents and / or

water repelling agents.

More specifically, the invention provides an oral delivery system for the treatment of periodontal diseases, said system being in a solid form and suitable for administration to the periodontal pocket of a patient and comprising:

(i) a biodegradable or bioerodible pharmaceutically acceptable polymer;

(ii) a therapeutically effective amount of at least one antibacterial agent; and

(iii) a therapeutically effective amount of at least one anti-inflammatory agent, the relative weight ratio between the antibacterial agent and the anti-inflammatory agent ranging from about 7:1 to about 1:5.

At times, the delivery system may further comprise a cross-linking agent that is present in an amount sufficient to render said polymer water-insoluble, while permitting the release of said active agents mentioned in items (ii) and (iii) above from said delivery system.

Preferably, the system may further comprise a plasticizing agent and at least one of a wetting agent, suspending agent, surfactant and dispersing agent.

The polymer is any pharmaceutically acceptable polymer that has the ability to degrade in the oral environment safely and, consequently, disappear. In fact, the polymer is one capable to undergo biodegradation or bioerosion in the oral cavity such that it does not have to be removed from the cavity or the pocket in which it had been inserted.

Preferably, the polymer is a water-soluble protein selected from the group consisting of gelatin, collagen, albumin, an enzyme and fibrinogen, more preferably gelatin and even more preferably hydrolyzed gelatin. In the case of a water-soluble protein, the protein is cross-linked by incubation in the presence of a cross-linking agent and/or crosslinking conditions such as heat, humidity, pressure, radiation, and the same. The extent of crosslinking is such that it renders the protein water-insoluble but still permits the release of the active agents from the composition.

The polymer is preferably present at a concentration of from about 20% to about 70% and the plasticizing agent is present at a concentration of from about 1% to about 15%. In addition, the weight ratio between the bioactive agents and the

polymer in the composition, ranges from about 2:1 to about 1:3, while the weight ratio between the plasticizing agent and the polymer is from about 1:10 to about 1:2.

Upon crosslinking, a water-soluble polymer becomes insoluble in water but undergoes biodegradation or bioerosion, thus imparting to the device of the invention the capability to release the active agents in a sustained manner. When the device is placed in the periodontal pocket, it is softening and swelling, thereby adhering to the periodontal pocket. More particularly, the device degrades in the oral environment such that it does not have to be removed from the cavity or the pocket in which it has been inserted.

The in-vivo release properties of the delivery system of the invention is such, that once located in a periodontal pocket it gradually releases the anti-inflammatory agent over a period of at least 48 hours, and the antibacterial agent over a period of at least 72 hours, during which the system changes into a soft material.

In a preferred embodiment, the present invention provides a combined flurbiprofen/chlorohexidine di-gluconate oral delivery system, that forms a biodegradable solid unit dosage form which may be employed in the treatment of periodontal diseases or upon periodontal surgery for aiding the healing process and has the release properties described above. More specifically, the present invention provides a solid oral delivery system for periodontal treatment, the device comprising on a weight basis between about 5 to about 25% flurbiprofen, between about 15 to about 35% chlorhexidine di-gluconate, between about 30 to about 50% hydrolyzed gelatin, between about 2 to about 7.5% crosslinking agent, between about 0.5 to about 15% non-ionic surfactant and between about 5 to about 15% plasticizer.

In another aspect, the present invention provides an oral delivery system for the treatment of periodontal diseases, the system being in a solid unit dosage form for administration to the periodontal pocket of a patient and comprising at least two layers, each of which having a matrix comprising a water-soluble polymer

crosslinked to yield a water insoluble polymer and an active ingredient. In one of said at least two layers the active agent is an anti-bacterial agent and in another layer of said at least two layers the active agent is an anti-inflammatory agent. In a preferred embodiment of this aspect, the antibacterial agent is chlorhexidine di-gluconate and the anti-inflammatory agent is flurbiprofen.

According to another aspect, the present invention provides an implant device, preferably a periodontal implant device, formed from the system of the invention and to the use of said device in treating periodontal or other oral diseases which require prolonged drug release. In a preferred embodiment, the device comprises the flurbiprofen/chlorohexidine di-gluconate combination described above.

In another aspect, the present invention also provides for the use of an oral delivery system as defined above in the preparation of an agent adapted for oral administration for the treatment of a condition of the oral cavity. The invention is further directed to a method of treating periodontal disease by placing the device herein described into a periodontal pocket or implanting the device in an oral pocket or gap before and/or after periodontal surgery, such that the device releases the drugs that are effective in reducing the pocket depth or in aiding the healing process after periodontal surgery.

BRIEF DESCRIPTION OF THE DRAWINGS

In order to understand the invention and to see how it may be carried out in practice, some preferred embodiments will now be described, by way of non-limiting example only, with reference to the accompanying drawings, in which:

Fig. 1 schematically shows a flow chart for the preparation of a bi-layer device.

Fig. 2 schematically shows a flow chart for the preparation of a tri-layer film.

Fig. 3 schematically shows a flow chart for the preparation of a precursor solution for the device of the invention (termed "Chip plus").

Fig. 4 shows a graph that compares the pocket depth reduction, determined by PPD (Probing Pocket Depth), between the device of the invention (termed "Chip plus") that contains chlorhexidine digluconate and flurbiprofen and a device (termed "Periochip) that contains only chlorhexidine digluconate as the active ingredient.

Fig. 5 shows the in-vivo release profile of CHG and FBP in gingival cervicular fluid from Chip plus and Periochip.

Fig. 6 shows the in vitro release profile of CHG from Chip plus and Periochip in protease solution.

Fig. 7 shows the in vitro release profile of CHG from several batches of Chip plus and Periochip in buffer tris+10% AcN.

Fig. 8 shows the in vitro release profile of FBP from several batches of Chip plus in buffer tris+10% AcN.

DETAILED DESCRIPTION OF THE INVENTION

The oral delivery device of the present invention may be in the form of films, pellets, granules, or any other convenient shape for the task at hand. Typically, the device is a film formed through the solidification of liquid, precursor solutions. When dried to produce the solid devices (i.e. implants) of the present invention, they may be used as inserts to oral cavities. Most preferably, the implants are in the form of a film and may be used as an insert into periodontal pockets, or as an implant before and/or after periodontal surgery for improving/enhancing/aiding the healing process and allowing the sustained drug delivery at the desired location. The term "film" as used in the present invention denotes a thin sheet or strip of flexible material comprising the system of the invention.

Examples of pharmaceutically acceptable polymers that may be used in

the device of the invention include but are not limited to water-soluble proteins, cellulose derivatives such as cellulose acetate, methylcellulose, HPMC (hydroxypropyl methylcellulose), carboxymethyl cellulose (CMC), hydroxyethyl cellulose (HEC), carbomer, PVP (polyvinylpyrrolidone), acacia gum, guar gum, polyvinyl alcohol, polyhydroxyethyl metacrylate, polyhydroxymethyl metacrylate polyacrylic acid, polyacryl amide, polyethylene glycol, starch sodium alginate, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyanhydride, polyortho esters and the like.

Proteins have been found useful as the basis for drug delivery systems since their degradation products are harmless amino acids and their biodegradation is facile in many parts of the body. Useful proteins for drug delivery include proteins derived from connective tissue such as collagen and gelatin, and proteins of the albumin class that may be derived from milk, serum, or from vegetable sources, with gelatin and hydrolyzed gelatin being the most preferable. Byco™ (a trademark of Croda Colloids, Ltd.) have been found to be the most preferred proteins for use in the device of the present invention.

Proteins tend to be water-soluble. In a water-soluble form the protein is less useful for sustained release of a drug. It is therefore desirable to render the protein insoluble while maintaining its ability to biodegrade through proteases in the body. This insolubilization of the protein may be achieved by making insoluble salts of the protein, insoluble complexes of the protein or most preferably by crosslinking the protein. Since proteins in general contain lysine and arginine residues carrying amino reactive groups and serine, threonine and tyrosine carrying hydroxyl side chains, one preferable and well accepted method of crosslinking proteins is with aldehydes or dialdehydes. Formaldehyde and more preferably glutaraldehyde are well known in the art in methods of crosslinking proteins.

In addition to chemical crosslinking agents, physical means capable of producing crosslinking in proteins may be employed. Examples of such physical means are heat, humidity, pressure or radiation.

The crosslinked protein is rendered water-insoluble but its ability to be degraded by proteases in the body is maintained. The amount of crosslinking can be controlled by the ratio of the crosslinking agent to the protein side groups with which it is to react. The more heavily crosslinked the protein the less soluble it will be and the more slowly it will be biodegraded by protease enzymes. For example, the preferable amount of glutaraldehyde for crosslinking hydrolyzed gelatin has been found to be the amount that is stoicheometric with the amino side chains in the protein. The crosslinked protein can be designed to degrade over a convenient time span, most preferably between about 4 to about 10 days.

The incorporation of the drugs in the delivery system must be uniform so as to keep tight control over the dosing level. If one chooses crosslinked protein because of its delivery, degradation, and non toxic by-product properties, one is faced with a problem of incorporating non water soluble drugs into such a system. When all the components are dissolved in a solution, the mixture of the components upon solidification is considerably more intimate and the control of the drug delivery from the crosslinked protein is much enhanced.

Many drugs that are not soluble to any extent in aqueous solutions are soluble in alcohol solutions. Alcohols which are compatible with the aqueous solutions of the proteins are preferably ethanol, isopropanol and n-propanol, with ethanol being the most preferable. Proteins of low molecular weight and a relatively high proportion of hydrophobic side groups do not precipitate from aqueous solution when a certain proportion of alcohol is added. A preferable protein with regards to this property is hydrolyzed gelatin with an average molecular weight less than 20,000 and most preferably less than 13,000 but higher than 1000. This protein is stable in solutions that contain over 50% ethanol, allowing the incorporation of water insoluble drugs that are soluble in alcohol. When using the hydrolyzed gelatin as the matrix for drug delivery and using glutaraldehyde as the crosslinking agent, it was found that the preferred ethanol to water ratios are between 1.2 and 2.5.

A solid device for insertion into a body crevice needs to be rigid enough to

be inserted against a certain amount of back pressure exhibited by the frictional forces on the device when being inserted, but flexible enough so as not to break and flexible enough to conform to the contour of the crevice. Therefore, in order to improve the flexibility of the device of the invention, a plasticizing agent or mixture of such agents is added. The type and the amount of the plasticizer will control the flexibility of the composition. Examples of suitable plasticizers include but are not limited to phthalates such as dimethyl phthalate, dibutyl phthalate, diethyl phthalate; dibutyl sebacate, triethyl citrate, tributyl citrate, acetylated monoglyceride, acetyl tributyl citrate, triacetin, benzyl benzoate, glycol derivatives such as glycerol, polyethylene glycols, propylene glycol butyl and/or glycol esters of fatty acids, refined mineral oils, oleic acid, castor oil, corn oil, camphor and and sugar alcohols such as sorbitol. Preferred plasticizers are sorbitol and glycerin with glycerin being the most preferred plasticizer. The preferred amount of plasticizer is between 1 and 15% and most preferably between 4 and 10%. Further plastic properties of the crosslinked protein are determined by the moisture content of the composition.

The device of the invention may also contain at least one of a wetting agent, solubilizing agent suspending agent, surfactant, and dispersing agent, or a combination thereof, in addition to the plasticizer.

Examples of suitable wetting agents include, but are not limited to, poloxamer, polyoxyethylene ethers, polyoxyethylene sorbitan fatty acid esters (polysorbates), polyoxymethylene stearate, sodium lauryl sulfate, sorbitan fatty acid esters, benzalkonium chloride, polyethoxylated castor oil, docusate sodium.

Examples of suitable suspending agents include but are not limited to, alginic acid, bentonite, carbomer, carboxymethylcellulose, carboxymethylcellulose calcium, hydroxyethylcellulose, hydroxypropyl cellulose, microcrystalline cellulose, colloidal silicon dioxide, dextrin, gelatin, guar gum, xanthan gum, kaolin, magnesium aluminum silicate, maltitol, medium chain triglycerides, methylcellulose, polyoxyethylene sorbitan fatty acid esters (polysorbates), povidone (PVP), propylene glycol alginate, sodium alginate,

sorbitan fatty acid esters, and tragacanth.

When preparing the device of the invention, it may be advantageous to include surface active agents, preferably non-ionic surfactants, in order to enhance the solubilization of the components and to stabilize the solutions. The surface active agent may be present in amounts that vary from 0 to about 20% of the delivery device. Examples of suitable surfactants include but are not limited to, anionic surfactants such as polysorbate 80 (Tween 80), anionic emulsifying wax (Crodex A), and sodium lauryl sulfate; cationic, such as cetrimide; nonionic, such as polyoxyethylene sorbitan fatty acid esters (polysorbates) and sorbitan fatty acid esters.

Examples of suitable dispersing agents include but are not limited to, poloxamer, polyoxyethylene sorbitan fatty acid esters (polysorbates) and sorbitan fatty acid esters.

A variety of pharmacological agents may be incorporated into the system of the invention and thus into the devices described herein. The requirements are that the drug is soluble in alcohol so that it is compatible with the precursor solution. According to the present invention, more than one pharmacological agent is incorporated into the device. The agents may be of the same therapeutic category (e.g. two or more anti-inflammatory drugs, or two or more anti-bacterial drugs) or of different therapeutic categories (e.g. one or more anti-bacterial drug and one or more anti-fungal drug, or one or more anti-inflammatory drug and one or more anti-neoplastic drug, or one or more anti-bacterial drug and one or more anti-inflammatory drug). The amount of drugs to be incorporated into the composition depends on the intended therapeutic use and can be determined by one skilled in the art. The drugs can be present in the composition from 1 to 70% (w/w) most preferably between 15 and 60% (w/w).

Suitable drugs which can be administered using the device of the present invention include the following groups:

- anti-inflammatory agents, including steroidal anti-inflammatory agents such as dexamethasone, budesonide, beclomethasone, and hydrocortisone; and

non-steroidal anti-inflammatory agents (NSAIDs) such as carprofen, diclofenac, fenbufen, fenclozic acid, fenoprofen, flufenamic acid, flurbiprofen, ibuprofen, indomethacin, indoprofen, ketoprofen, lonazolac, loxoprofen, meclofenamic acid, mefanamic acid, naproxen, proprionic acids, salicylic acids, sulindac, tolmetin, meloxicam, oxicams, piroxicam, tenoxicam, etodolac and oxaprozin; (please confirm that you wish to mention steroidal anti-inflammatory agents)

- anti-bacterial agents such as sulfonamides, phenolics, quaternary ammonium salts, chlorhexidine and salts thereof, antibiotics such as penicillins, cephalosporins, tetracycline, doxycycline, chloramphenicol, and erythromycin;
- anti pain agents for the control of pain from a localized site in the body, for example morphine, codeine, etc.

A particularly preferred combination of pharmacological agents used in the device of the invention will include an anti-inflammatory agent together with an antibacterial agent. An example of a preferred combination includes flurbiprofen and chlorhexidine di-gluconate.

The above mentioned components are mixed in a suitable solvent in any ratio which is capable of producing a liquid composition, which forms, upon drying, a sustained-release composition. The components may be mixed as liquids or as solids to be dissolved in a suitable solvent. Suitable solvents include water, ethanol and water-ethanol mixtures.

The device of the present invention is prepared in solid form by pouring the liquid composition into molds which may then be dried, thus forming the implant of the present invention. It is preferable to use a protein concentration range which results in the formation of a liquid composition having acceptable pourability, and which is capable of releasing the active agents upon its drying into the solid, sustained-release form.

The particular form into which the composition is cast will depend upon its intended use. Thus, for example, if the implant is designed to be used in the treatment of periodontal (or other dental) disease by insertion into the periodontal cavity, then the implant will preferably be cast into a film or film-like sheet.

In order to be inserted into a patient's periodontal pocket to treat periodontal or other disease, the implant should preferably be a film having a thickness which ranges from 0.01-1.0 millimeters, and preferably having a thickness of between 0.2 and 0.6 millimeters. In order to be inserted in the periodontal pocket, it is preferable that the implant shape be oval, and/or torpedo (i.e., bullet) and/or rod-like.

Although the width and length of the implant may vary depending upon the size of the periodontal pocket of the recipient patient, it is preferable to use implants having a width of between 1-5 millimeters, and preferably between 3-5 millimeters. It is preferable to employ implants having a length of between 3-10 millimeters, and most preferable to employ implants having a length of between 4-6 millimeters. Typically, an implant of the invention has a length of about 5 mm, a width of about 3.8-4.5 mm and a thickness of about 0.35-0.55 mm.

The implants of the present invention may be individually produced or may be obtained (i.e., cut, ground, etc.) from a larger material (i.e., a block, or film-like sheet).

In addition to its use in the treatment of periodontal disease, the device of present invention may be used in a variety of alternative dental applications. For example, it may be used in the treatment and/or prevention of pericoronitis, to assist with root canal sterilization, to facilitate the healing of gums after tooth extraction and to treat or prevent the problem of "dry socket" or to prevent infection incident to tooth implants.

A further preferred usage of the delivery device is as an adjunct treatment to periodontal surgery where it is inserted into the periodontal pockets both before and after the periodontal surgery.

The invention will now be further described with reference to the following non-limiting examples.

EXAMPLES

Example 1

The liquid precursor compositions in Table 1 below were prepared according to the following procedure: the hydrolyzed gelatin was completely dissolved in chlorhexidine di-gluconate (CHG) solution in water, then the solution of the plasticizer (glycerin) in ethanol, the crosslinking agent (GA), the solution of the surfactant (Tween 80) in ethanol and the solution of the flurbiprofen (FBP) in ethanol were added. Each component was added after completely dissolving the former one. The mixing was carried out by a mechanical stirrer at 500 RPM, at room temperature. The liquid precursors were then poured into a leveled mold to obtain a solid film after drying at 22◦C for 48 hours.

Table 1

Formulation No.	500-3	500-4	500-5	500-8	500-16
Ingredients	gr.				
BYCO E [1]	50.0	50.0	25.0	25.0	22.5
GLYCERIN	5.0	5.0	5.0	5.0	2.5
GA(25%)[2]	2.0	3.0	2.0	4.0	4.0
TWEEN 80	15.0	10.0	5.0	5.0	5.0
CHG(20%)[3]	125.0	125.0	63.5	63.5	62.5
FBP[4]	10.0	10.0	2.5	2.5	2.5
P.W[5]	43.0	52.0	30.5	28.5	91.0
ETHANOL	40.0	35.0	15.0	15.0	10.0
TOTAL	290.0	290.0	148.5	148.5	200.0
GA/BYCO(%)	1.0	1.5	2.0	4.0	4.4

(1) BYCO E- type of hydrolyzed gelatin
(2) GA (25%)- 25% aqueous solution of glutaraldehyde
(3) CHG(20%)-20% aqueous solution of chlorhexidine di-gluconate
(4) FBP-Flurbiprofen
(5) P.W.- pure water

Example 2

The liquid precursor compositions listed in Table 2 were prepared as in Example 1, except that the solutions of Tween 80 and FBP in ethanol were mixed together before adding to the liquid precursor.

Table 2

Formulation No.	500-9	500-10
Ingredients	gr	gr
BYCO E	25.0	22.5
GA(25%)	4.0	4.0
TWEEN 80	10.0	10.0
CHG(20%)	63.5	63.5
FBP	2.5	5.0
Pure water	28.5	41.0
ETHANOL	15.0	12.5
TOTAL	148.5	158.5

Example 3

The liquid precursor compositions showed in Table 3 were prepared in a manner similar to that described in Example 1.Triethyl citrate was used as plasticizer instead of glycerin.

Table 3

Formulation	555-7
Ingredients	gr.
BYCO E	22.5
T.E.C	4.5
GA(25%)	2.0
TWEEN 80	5.0
CHG(20%)	62.5
FBP	5.0
P.W	30.5
ETHANOL	15.0
TOTAL	142.5
GA/BYCO(%)	2.2

T.E.C-triethyl citrate

Example 4

The liquid precursor compositions showed in Table 4 below were prepared according to the following procedure:

Hydrolyzed gelatin was dissolved in pure water using a mechanical stirrer (500 rpm) at room temperature. After complete dissolution, all the remaining components were added to the hydrolyzed gelatin solution. Each component was added after complete dissolving the former one. The crosslinking agent was added in two distinct portions. The liquid precursors were then poured into a leveled mold to obtain a solid film after drying at 22÷C for 48 hours.

Table 4

Formulation	500-17	500-18
Ingredients		
BYCO E	22.5	22.5
GLYCERIN	2.5	2.5
GA(25%)	4.0	4.0
TWEEN 80	5.0	5.0
CHG(20%)	62.5	62.5
FBP	2.5	2.5
P.W	91.0	91.0
ETHANOL	10.0	10.0
TOTAL	200.0	200.0

Example 5

The liquid precursor compositions showed in Table 5 were prepared. In all formulations tannic acid was used as the crosslinking agent instead of GA. The preparation process was the same as that described in Example 4. Whereas in the liquid precursor of 500-34 tannic acid was added in a powder form, the solutions of tannic acid in pure water were used in both liquid precursor compositions of 500-35 and 500-38.

Table 5

Formulation	500-34	500-35	500-38
Ingredients			
BYCO E	4.5	4.5	3.6
Glycerin	0.5	0.5	0.3
Tannic Acid	0.3	2.0	0.5
Tween 80	1.0	0.5	0.7
CHG(20%)	2.5	12.5	13.0
FBP	1.5	1.5	
P.W	13.5	23.5	10.8
ETHANOL	2	6	
TOTAL	25.8	51.0	28.9
TA/BYCO(%)	0.1	0.4	0.1

Example 6

The purpose of this experiment was to check the effect of a hydrophobic polymeric component, namely Eudragit L-100-55, in the formulation as an appropriate phase for FBP which is a hydrophobic active agent. The liquid precursor composition showed in Table 6 was used to form the drug delivery solid implants of 500-42. The preparation process was the same as that described for Example 4. An ethanolic solution of Eudragit L-100-55 which included also Tween 80 and FBP was prepared prior to addition to the liquid precursor.

Table 6

Formulation	500-42
Ingredients	
BYCO E	6.0
Eudragit L100-55	2.0
GA(25%)	1.2
CHG(20%)	25.0
FBP	3.0
TWEEN 80	2.0
ETHANOL	12.0
P.W	22.8
TOTAL	74.0
GA/BYCO(%)	104.2

Example 7

The liquid precursor compositions showed in Table 7 were prepared and used to form the drug delivery solid implants of 500-47 to 500-53. The preparation process was the same as that described for Example 4. In this example the hydrolyzed gelatin was dissolved in a mixture of water and ethanol.

Table 7

Formulation	500-47	500-48	500-49	500-50	500-51	500-52	500-53
Ingredients	gr	gr	gr	gr	gr	gr	gr
BYCO E	5	5	2.5	2.5	3	3	3
GLYCERIN	1	1	0.5	0.5	0.4	0.8	0.8
GA(25%)	1	2	1.3	1.3	1.6	1.8	1.8
TWEEN 80	1.6	1.6	0	0.7	0.3	0	0.3
CHG(20%)	20	20	12.5	12.5	12.5	13	13.5
FBP	2.4	2.4	2	1.5	1.5	1.6	1.7
P.W	46.5	48	24.4	24.4	30.4	54	29.7
ETHANOL	12.5	10.5	11.25	9.25	9.5	9.5	9.5
TOTAL	90	90.5	54.45	52.65	59.2	83.7	60.3
GA/BYCO	5	10	13	13	13	15	15

Example 8

The liquid precursor composition showed in Table 8 was prepared and used to form the drug delivery solid implants of 500-67. The preparation process was the same as that described for Example 4. In this Example the chlorhexidine (CHX) dihydrochloride was used as the antibacterial agent instead of chlorhexidine digluconate.

Table 8

Formulation	500-67
Ingredients	gr
Byco E	3.2
GLYCERIN	0.5
GA(25%)	0.8
TWEEN 80	0.1
CHXHcl	2.5
FBP	1.5
P.W	10.8
ETHANOL	9.2
TOTAL	28.6
GA/BYCO	6.25

Example 9

The effect of GA/hydrolyzed gelatin ratio was determined by preparing the liquid precursor compositions shown in Table 9.

Table 9

Formulation	500 -72	500-73	500-74	500-75
Ingredients	gr	gr	gr	gr
BYCO M	5.7	5.4	5.2	5.3
GLYCERIN	0.9	0.8	0.8	0.8
GA(25%)	1.8	2.2	2.8	2.4
TWEEN 80	0.2	0.2	0.2	0.2
CHG(20%)	24.2	23.3	23.3	23.3
FBP	2.7	2.6	2.6	2.6
P.W	18.4	19.5	17.2	19.5
ETHANOL	8.8	9.6	9.2	12.1
TOTAL	62.7	63.6	61.3	66.2
GA/BYCO	7.89	10.19	13.46	11.32

Example 10: Bilayer film: A lamination film forming process

A bi-layer laminated film forming process has been provided where each layer contains either CHG or FBP. The formulations of both layers are shown in Table 10. The liquid precursor composition of each layer was prepared according to the scheme in **Fig. 1**. The liquid precursor of layer I was first poured into a leveled mold to obtain a solid film after drying at 22◦C for 48 hours. Then the liquid precursor II was poured onto the solid film of the layer I to obtain a bi-layer laminated solid film after additional drying at 22◦C for 48 hours.

Table 10

Formulation	500-94-I	500-94-II	500-95-I	500-95-II	500-96-I	500-96-II
Ingredients						
BYCO E	2.4	1.2	2.4	1.2	2.4	1.2
GLYCERIN	0.36	0.18	0.36	0.18	0.36	0.18
GA(25%)	1.3	0.6	1.3	0.6	1.3	0
TWEEN 80	1	0.15	0	0.15	0	0.15
CHG(20%)	15	0	15	0	15	0
FBP	0	1.7	0	1.7	0	1.7
P.W	20.2	24.9	20.2	24.9	20.2	24.9
ETANOL	0	0	0	0	0	0
TOTAL	40.26	28.73	39.26	28.73	39.26	28.13
GA/BYCO	13.54	12.50	13.54	12.50	13.54	0.00

Example 11

A tri-layer laminated film forming process has been developed where the outer layers (layer I and layer II) contain CHG whereas the intermediate layer contains FBP. The preparation process of the liquid processor of the outer layers was the same. The formulations of all layers are shown in Table 11. The preparation process of the laminated film of layer I and II was performed as described in Scheme 1. The layer III was then laminated onto solid film of bi-layer (I and II) on the side of the layer II, by pouring the liquid precursor of layer III and subsequently drying at 22÷C for 48 hours. The entire process is described in **Fig. 2**.

Table 11: Three layered film

Formulation	500-109-I	500-109-II	500-109-III
Ingredients	gr	gr	gr
BYCO E	1	1	1
GLYCERIN	0.15	0.15	0.15
GA(25%)	0.32	0.32	0.32
TWEEN 80	0	0.1	0
CHG(20%)	2.74	7.4	2.74
FBP	0	1.44	0
P.W	14.76	9	14.76
ETHANOL	0	5.2	0
TOTAL	18.97	24.61	18.97
GA/BYCO	8.00	8.00	8.00

Example 12: Scaled up production process

The production of the implant device of the invention was scaled up to 2Kg and 6Kg. The production process was carried out as follows:

Hydrolyzed gelatin was dissolved in an aqueous/alcohol solvent and the solution was mixed for 45min. Glycerin was added and the mixing was continued for 15 min. Chlorohexidine digluconate solution-20% was added and mixing was continued for 15 min. Glutaraldehyde solution 10% was added and the solution was mixed for 15 min.

Flurbiprofen in an alcoholic solubilizer mixture was added and the mixing of the resulting mixture was continued for further 15 min. The formulations of the precursors are shown in Tables 12I and 12II for the scale up to 2Kg and 6Kg respectively. The preparation process of the precursor solution is shown in **Fig. 3**.

Table 12I: scale-up to 2 kg

Formulation		
	W(g)	W(%)
BYCO	180.0	9.2
Glycerin	27.0	1.4
GA (25%)	56.0	2.9
Tween 80	5.0	0.3
CHG(20%)	765.0	39.0
FBP	85.0	4.3
EtOH	309.0	15.8
H_2O	533.0	27.2
TOTAL	1960.0	100.0
GA/BYCO	0.078	0.078
glycerin/Byco	0.150	0.150

Table 12 II: Scale up to about 6 Kg

Formulation		
	W(gr)	W(%)
BYCO	480.0	8.4
Glycerin	82.0	1.4
GA (25%)	150.0	2.6
Tween 80	13.0	0.2
CHG(20%)	2040.0	35.7
FBP	230.0	4.0
EtOH	940.0	14.7
H_2O	1785.0	33.0
TOTAL	5720.0	100.0
GA/BYCO	0.078	0.078
glycerin/Byco	0.171	0.171

Example 13: In-Vivo efficacy trial

The efficacy of the device of the invention was indicated by probing pocket depths (PPD) for all teeth using a standard 15mm, North Carolina periodontal probe. The pocket depth was recorded before and after inserting the device and the % change (reduction) was calculated. At the target sites scaling and root planing was followed by placement of a FBP/CHG implant of the invention, consisting of 2.5 mg of chlorhexidine di-gluconate and 1.5 mg flurbiprofen formulated in a biodegradable cross-linked fish gelatin matrix. The probing pocket depth (mm) and reduction in pocket depth upon the treatment (%) are shown in Table 13.

A comparison test was carried out between the efficacy of the device of the present invention, termed hereinafter *Chip Plus,* and comprising 2.5 mg of chlorhexidine digluconate and 1.5 mg flurbiprofen and that of a device containing only 2.5 mg chlorhexidine digluconate, termed hereinafter *PerioChip* and prepared according to the procedure described in US 5,023,082. The results are demonstrated in **Fig. 4**. The data show that a significant reduction in pocket depth is obtained upon using Chip Plus than PerioChip during a comparable period of treatment. In fact it was not clinically necessary to use Chip Plus over 3 months of treatment, while the pockets that received PerioChip, remained >5 mm in depth after 3 and 6 months of treatment.

Example 14: The in vivo release profile

The objective of this experiment was to determine the release profile of both CHG and FBP in periodontal pocket in-vivo. The Chip Plus was inserted into a periodontal pocket of 5 mm or more in 5 volunteers (12 pockets). The gingival cervicular fluid (GCF) was collected by inserting Periopaer Gingival collection Strips (HARCO Company Inc.) into the pocket for a predetermined time interval. The GCF sampling was carried out prior to Chip insertion for a zero time sample and at one hour, 24 hours, 2 days, 3 days, 6 days, 8 days, and 10

days. The paper strip was inserted into the pocket for thirty seconds. The volume of GCF in the paper strip was measured using a Periotron 6000 (Siemans Company Inc.) The Periotron 6000 was calibrated prior to and during trial. The concentration of both FBP as well as CHG was determined by extraction from the paper strip and determination in an HPLC analysis developed for this project. A comparison between the release profile of Chip Plus and PerioChip for CHG release has been drawn. The results of the In vivo release of both FBP as well as CHG (for both PerioChip and Chip Plus) are shown in Table 14 and **Fig. 5**.

Table 13: In Vivo release of FBP and CHG

	PerioChip		ChipPlus	Chip Plus
Time(hr.)	CHG(ppm)	Time(hr.)	CHG(ppm)	FBP (ppm)
1	1162	1	8948	7382
24	515.8	24	1816	877
48	841	48	186	59
72	482	72	125	36
144	127.1	96	30	
192	103	168	7	
240	69.4			

Table 14: Probing pocket depth (mm) and reduction (%) upon treatment with Chip Plus

Patient # 1	Pocket depth (mm) at time = 0	Pocket depth (mm) after 3 months	Pocket depth (mm) after 5 months	Reduction(%)
	5	2	<2	60
	5	2	<2	60
	6	2	<2	67
	7	6	5	29
	7	3	2	57

Patient # 2	Pocket depth (mm) at time = 0	Pocket depth (mm) after 2 months	Reduction(%)
	6	3	50

Patient # 11	Pocket depth (mm) at time = 0	Pocket depth (mm) after 1 month	Reduction(%)
	7	4.5	36
	5	2	60

Patient # 12	Pocket depth (mm) at time = 0	Pocket depth (mm) after 2 months	Reduction(%)
	7	4	43

Patient # 14	Pocket depth (mm) at time = 0	Pocket depth (mm) after 1 month	Reduction(%)
	5	3	40
	6	3	50
	7	3	57
	7	2	71
	7	3	57

Patient # 15	Pocket depth (mm) at time = 0	Pocket depth (mm) after 3 months	Reduction(%)
	5	2	60
	5	1	80
	6	1	83

Example 15: The in vitro release-protease method for CHG

Chip Plus and PerioChip were placed into a test tube with a protease solution of fixed activity and incubated for one, three, eight and twenty four hours. At each time point the protease solution is removed for analysis and fresh protease solution is added to the Chip. CHG released from the chip is then determined in the sample of each time point by extraction and spectrophotometric method. The results of CHG release from Chip Plus as compared to that of PerioChip are shown in **Fig.6**.

Example 16: In vitro release of CHG –Dissolution method

The release of CHG from both Chip Plus and PerioChip was determined using a dissolution method at 37÷C. The dissolution test was performed in a 900 ml water containing 2% Tween 80. 5 chips were placed in each vessel containing 900 ml of the dissolution medium. The basket speed was set at 100 rpm. The amount of CHG released from the chips at each point of time was determined using an HPLC method. The results are summarized in Table 15 and shown in **Fig.7**.

Table 15: CHG- In Vitro release of Chip Plus from different batches, compared to PerioChip

	Periochip	Chip Plus, batch1	Chip Plus, batch2	Chip Plus, batch3	Chip Plus, batch4	Chip Plus, batch5
Time(hr.)	CHG(%)	CHG(%)	CHG(%)	CHG(%)	CHG(%)	CHG(%)
0	0	0	0	0	0	0
1	50.2	16.9	15.6	14.9	14.4	18.9
3	59.5	20.8	22.8	21.2	22.1	28.6
6	62.3	38.1	43	39.9	46.1	52.6
24	68.9	85	84.7	83.7	92.9	91.4

Example 16: In vitro release of FBP

The release of FBP from Chip Plus was determined using a dissolution method at 37◦C. The dissolution test was performed in a 900 ml water containing 2% Tween 80. Five chips were placed in each vessel containing 900 ml of the dissolution medium. The basket speed was set at 100 rpm. The amount of FBP released from the chips at each point of time was determined using an HPLC method. The results of release profile from different batches are summarized in Table 16 and shown in **Fig. 8**.

Table 16: In vitro release of Flurbiprofen from several batches of Chip Plus

	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5
Time(hr.)	FBP(%)	FBP(%)	FBP(%)	FBP(%)	FBP(%)
0	0	0	0	0	0
1	9.7	8.1	8.2	11.3	13.2
3	25	28.7	28.1	29.8	40.1
6	53.5	58.9	47.9	57	67.3
24	92.7	92.2	79.6	93.1	97.2

CLAIMS:

1. An oral delivery system for the treatment of periodontal disease, said system being in a solid unit dosage form for administration to a patient, comprising:

(i) a biodegradable or bioerodible pharmaceutically acceptable polymer;

(ii) a therapeutically effective amount of at least one antibacterial agent; and

(iii) a therapeutically effective amount of at least one anti-inflammatory agent, the relative weight ratio between the antibacterial agent and the anti-inflammatory agent ranging from about 7:1 to about 1:5.

2. The system of Claim 1 further comprising a cross-linking agent present in an amount sufficient to render said polymer water-insoluble, while permitting the release of said active agents from said delivery system.

3. The system of Claim 1 or 2 further comprising a plasticizing agent and at least one of a wetting agent, a suspending agent, a surfactant and a dispersing agent.

4. The system of anyone of Claims 1 to 3 adapted for administration to a periodontal pocket.

5. The system of Claim 4 having in-vivo release properties that yield to reducing the periodontal pocket depth of a patient.

6. The system of Claim 4, being such that it biodegrades in the periodontal pocket thereby becoming soft and adhering to the periodontal pocket.

7. The system of Claim 4 that once located in a periodontal pocket gradually releases said anti-inflammatory agent over a period of at least about 48 hours, and said antibacterial agent over a period of at least about 72 hours, during which said system changes into a soft material.

8. The system of anyone of Claims 1 to 7 wherein said polymer is selected from water-soluble protein, cellulose or cellulose derivative, starch or starch derivative, glyceryl monostearate, carbomer, PVP (polyvinylpyrrolidone), gum, acacia gum, guar gum, polyvinyl alcohol, polyhydroxyethyl metacrylate, polyhydroxymethyl metacrylate polyacrylic acid, polyacryl amide, polyethylene glycols, polylactic acid,

polyglycolic acid, copolymers of polylactic acid and polyglycolic acid, polyanhydrides and polyorthoesters.

9. The system of anyone of Claims 1 to 8 wherein said anti-inflammatory agent is a non-steroidal anti-inflammatory agent (NSAID).

10. The system of anyone of Claims 1 to 9 in the form of a film.

11. The system of Claim 10, wherein said film is from about 3 to about 6 mm in length and from about 1 to about 5 mm in width and from about 0.01 to about 1.0 mm in thickness.

12. The system of Claim 8 wherein said water-soluble protein is selected from the group consisting of gelatin, collagen, albumin, an enzyme and fibrinogen.

13. The system of Claim 12 wherein said water-soluble protein is gelatin.

14. The system of Claim 13 wherein said gelatin is hydrolyzed gelatin.

15. The system of anyone of Claims 1 to 14 wherein said polymer is cross-linked by a curing process in the presence of a cross-linking agent, wherein said curing process is selected from the group consisting of heat, humidity, pressure, radiation, and the vapors of a cross-linking agent.

16. The system of Claim 15 wherein the cross-linking renders said protein water-insoluble, while permitting gradual release of the active agents from said system.

17. The system of anyone of Claims 1 to 16 wherein said polymer is present at a concentration of from about 20% to about 70%.

18. The system of Claim 3 wherein said plasticizing agent is selected from glycol derivatives, phthalates, citrate derivatives, benzoates, butyl or glycol esters of fatty acids, refined mineral oils, camphor, oleic acid, castor oil, corn oil and sugar alcohols.

19. The system of Claim 18 wherein said glycol derivative is glycerin.

20. The system of Claim 3 wherein said plasticizing agent is present at a concentration of from about 1% to about 15%.

21. The system of anyone of Claims 1 to 20 wherein said antibacterial agent is selected from the group consisting of penicillin, cephalosporin, tetracycline, oxytetracycline, chlortetracycline, metronidazole, chloramphenicol, streptomycin,

neomycin, a sulfonamide, a phenolic compound, a mercurial, a quarternary ammonium compound, doxycycline and chlorhexidine or salts thereof.

22. The system of Claim 9 wherein said non-steroidal anti- inflammatory agent is selected from the group consisting of flurbiprofen, carprofen, diclofenac, fenbufen, fenclozic acid, fenoprofen, flufenamic acid, ibuprofen, indomethacin, indoprofen, ketoprofen, lonazolac, loxoprofen, meclofenamic acid, mefanamic acid, naproxen, proprionic acids, salicylic acids, sulindac, tolmetin, meloxicam, oxicams, piroxicam, tenoxicam, etodolac and oxaprozin.

23. The system of anyone of Claims 1 to 22 wherein said therapeutically effective agents and said polymer are present at a relative weight ratio which ranges from about 2:1 to about 1:3.

24. The system of Claim 3 wherein said plasticizing agent and said polymer are present at a relative weight ratio which ranges from about 1:10 to about 1:2.

25. The system of anyone of Claims 1 to 24, wherein said periodontal disease is periodontitis.

26. An oral delivery system for the treatment of periodontal diseases, said system being in a solid unit dosage form for administration to a patient and comprising at least two layers, each of which having a matrix comprising a biodegradable or bioerodible pharmaceutically acceptable polymer and an active ingredient, in one of said at least two layers said active agent being an anti-bacterial agent and in another layer of said at least two layers said active agent being an anti-inflammatory agent, said system once in the oral cavity gradually releases the active agents from said layers.

27. The system of Claim 26 wherein said antibacterial agent is chlorhexidine di-gluconate and said anti-inflammatory agent is flurbiprofen.

28. The system of Claim 26 or 27 wherein said polymer is a protein.

29. The system of Claim 28 wherein said protein is hydrolyzed gelatin.

30. The system of Claim 26 wherein said polymer is crosslinked in the presence of glutaraldehyde to yield a water-insoluble polymer.

31. The system of anyone of Claims 26 to 31 in the form of a film.

32. An oral delivery system according to claim 1 for the treatment of periodontal diseases, said system being in a single solid unit dosage form for administration to the periodontal pocket of a patient for changing in said pocket within a soft form, the system comprising on a weight basis, between about 5 to about 25% flurbiprofen, between about 15 to about 35% chlorhexidine di-gluconate, between about 30 to about 50% hydrolyzed gelatin and between about 2 to about 7.5% crosslinking agent.

33. The system of Claim 32, further comprising between about 0.5 to about 15% surfactant and between about 5 to about 15% plasticizer.

34. The system of Claim 32 or 33, having in-vivo release properties that yield to reducing of the periodontal pocket depth of a patient.

35. The system of anyone of Claims 32 to 34 in the form of a film.

36. A periodontal implant comprising the system of anyone of Claims 1 to 25.

37. A periodontal implant comprising the system of anyone of Claims 26 to 31.

38. A periodontal implant comprising the system of anyone of Claims 32 to 35.

39. A method for the treatment of periodontal disease comprising administering to a patient in need of such treatment the delivery system of Claim 1.

40. The method of Claim 39 wherein said system is implanted into a periodontal pocket.

41. The method of Claim 39 wherein said treatment is an adjunct treatment to periodontal surgery, where said system is inserted into a periodontal pocket before and/or after the periodontal surgery.

42. A method for the treatment of periodontal disease comprising administering to a patient in need of such treatment a delivery system being in a solid unit dosage form, said system comprising:

(a) a biodegradable or bioerodible pharmaceutically acceptable polymer;

(b) a therapeutically effective amount of at least one antibacterial agent; and

(c) a therapeutically effective amount of at least one anti-inflammatory agent, the relative weight ratio between the antibacterial agent and the anti-inflammatory agent ranging from about 7:1 to about 1:5.

43. The method of Claim 42, wherein said delivery system further comprises a cross-linking agent present in an amount sufficient to render said polymer water-insoluble, while permitting the release of said active agents from said delivery system.

44. A method for administering an active agent to the oral cavity, said method comprising the administration of a delivery system being in a solid unit dosage form, the system comprising:

(a) a biodegradable or bioerodible pharmaceutically acceptable polymer;

(b) a therapeutically effective amount of at least one antibacterial agent; and

(c) a therapeutically effective amount of at least one anti-inflammatory agent, the relative weight ratio between the antibacterial agent and the anti-inflammatory agent ranging from about 7:1 to about 1:5.

45. The method of Claim 44, wherein said system further comprises a cross-linking agent present in an amount sufficient to render said polymer water-insoluble, while permitting the release of said active agents from said delivery system.

46. The method of claim 44, wherein said delivery system is in the form of a film.

47. Use of an oral delivery system according to claim 1 in the preparation of an agent adapted for oral administration for the treatment of a condition of the oral cavity.

48. Use according to claim 47, wherein said delivery system further contains a cross-linking agent.

49. Use according to Claim 47, for the treatment of periodontal disease.

50. Use according to Claim 47, for use in a dental surgery.

51. Use according to claim 47 wherein said delivery system is in the form of a film.