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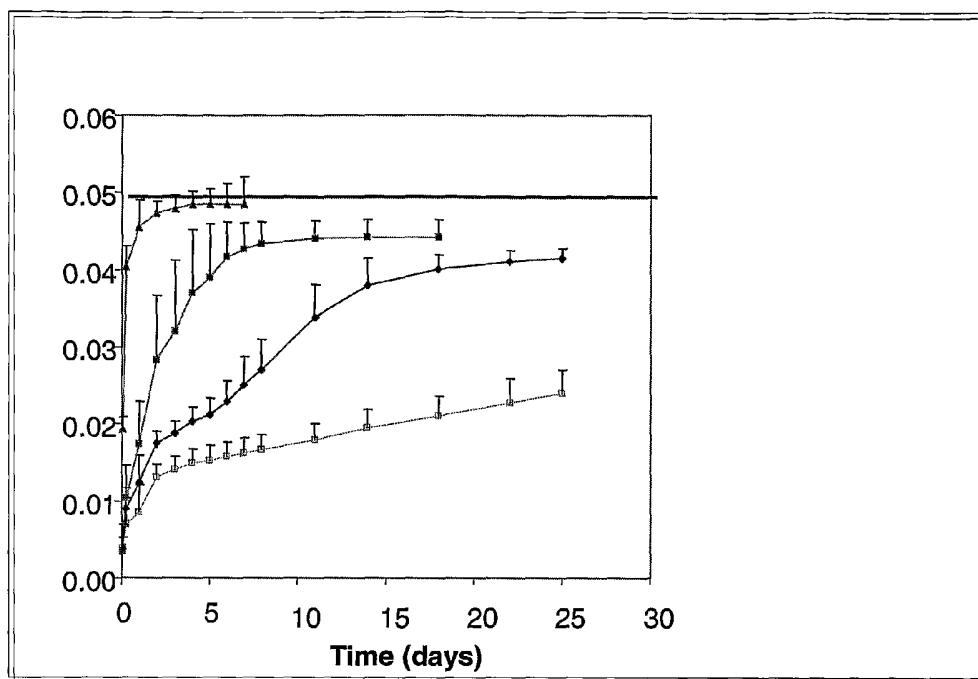
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(54) Title: POLYMER BARRIER COMPOSITIONS FOR SURGICAL WOUNDS



(57) Abstract: A composition comprising a polymer of lactic acid and glycolic acid, an elasticizing agent and a bone growth enhancing agent. The composition may be used for the preparation of a medicament for the treatment of a surgical wound.



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POLYMER BARRIER COMPOSITIONS FOR SURGICAL WOUNDS

FIELD OF THE INVENTION

- 5 This invention relates to the field of resorbable polymer barrier compositions for use in surgical applications.

BACKGROUND OF THE INVENTION

- 10 The periodontal tissues that surround teeth are composed of bone, cementum (a bony substance covering the root of the tooth), periodontal ligaments and a sheath of gingiva. In a healthy state, epithelial cells migrate coronally from the apical regions of the interface with the tooth and are lost into the saliva. Periodontitis is a disease condition caused by the accumulation of oral bacterial
- 15 between the gingival and the apical portion of the tooth. If oral hygiene is not maintained the bacteria will replicate, and accumulate to form a 'biofilm'. Once the biofilm is established, the bacteria release toxins into surrounding tissues, invoking a host immune response, including degrading enzymes in attempts to confine the bacterial invasion. This cycle continues, with Gram-negative bacteria
- 20 subsequently producing waste products from the degraded tissue that are assimilated as nutrients, furthering the host inflammatory response. As this cycle of events progresses, a chronic state of disease and inflammation state results. Chemotactic products released by the inflammatory cells activate adhesion molecules on immune cells circulating in the blood. Initially there is an influx of
- 25 polymorponuclear leukocytes, which are then followed by macrophages and lymphocytes. These cells further induce host destructive mechanisms assisting in the inflammatory wound healing processes. Neutrophils at the site of inflammation attempt to destroy the bacteria by releasing proteolytic enzymes such as neutrophilic serinases, elastase, cathepsin and the matrix
- 30 metalloproteinases including gelatinase and collagenase. In doing so, further damage to the gingival tissues results, periodontal ligaments (PDL) and crestal alveolar bone. Bone resorption is caused by the osteoblasts which are attracted to the site and stimulated by neutrophilic inflammatory mediators such as TNF-alpha

-2-

and IL-1 (*Potemba J et al. 2000. Role of bacterial proteinases in matrix destruction and modulation of host response. Periodontology 24:153-192. Hall, T and Chambers, T. 1996. Molecular aspects of osteoclast function. Inflamm. Res. 45:1-9*). In response to the degeneration of periodontal tissues around the tooth

5 host epithelial cells migrate apically in an attempt to maintain a seal between the gingiva and the tooth. As this cycle of tissue degradation progresses, apical migration also advances, resulting in reduced periodontal tissue attachment. The progressive tissue damage does not cease however, and intervention is required to stop progression, which ultimately leads to tooth loss (*Kinane DF and Lindhe J. 2000. Pathogenesis of Periodontitis. In Clinical Periodontology and Implant Dentistry 3rd edition. Lindhe, Karring, Lang, editors. Munksgaard, Copenhagen. Pp 189-225*).

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In severe cases, surgical intervention is required to remove the inflamed tissue

15 and bacteria from the periodontal pocket – this is known as debridement. Debridement alone is not successful in restoring normal periodontium. One of the main problems after surgical intervention of periodontal tissues is the rapid proliferation of junctional epithelial cells into the wound space. These cells do not have the capacity to regenerate the tissues of the periodontal area and they

20 hinder the migration of regenerating cells.

Poly(lactic-co-glycolic acid) (PLGA) is a synthetic, resorbable polymer with known applications in guided tissue regeneration. Without the inclusion of elasticizing agents, PLGA films are relatively stiff and inelastic, with a long degradation profile.

25 Under normal physiological conditions, PLGA films degrade over a 3 to 6 month period and the inclusion of medicaments in the PLGA film had little effect on degradation rates (*Andersen JM and Shive MS. 1997. Biodegradation and biocompatibility of PLA and PLGA microspheres. Adv. Drug. Del. Rev. 28:5-24; Webber WL et al., 1997. Characterization of soluble, salt-loaded degradable*

30 *PLGA films and their release of tetracycline J Biomed Mater Res. 41: 18-29; Lichun L et al. 1999. In vitro degradation of thin poly (DL-lactic-co-glycolic acid) films. J. Biomed Mater. Res 46:236-2444*). A preferred 'residence' time of a barrier film is less, and may be as little as 4-6 weeks, as evidenced by the 6-week

-3-

removal time of a non-resorbable PTFE membrane in periodontal applications. This long degradation profile of PLGA implants may have serious complications in some patients as it is well known to those skilled in the art that problems of bacterial infections are further complicated by the presence of implant material, which may act as a conduit for bacterial migration into deeper tissue regions.

SUMMARY OF THE INVENTION

10 In accordance with one aspect of the invention, there is provided a use of a polymeric barrier composition comprising a polymer of lactic acid and glycolic acid, an elasticizing agent and a bone growth enhancing agent for the preparation of a medicament for the treatment of a surgical wound. The composition may be capable of forming a film, or may be a film.

15 In accordance with another aspect of the invention, there is provided a polymeric barrier composition comprising a polymer of lactic acid and glycolic acid, an elasticizing agent and a bone growth enhancing agent. The composition may be capable of forming a film, or may be a film.

20 In accordance with another aspect of the invention, there is provided a method of preparing a polymeric barrier composition, the method comprising combining a polymer of lactic acid and glycolic acid with an elasticizing agent and a bone growth enhancing agent in an organic solvent, to form a solution or suspension, casting said solution or suspension on a form or mould, and evaporating said
25 organic solvent, causing a polymer film to remain on said form or mould.

In accordance with another aspect of the invention, there is provided a method for the treatment of a surgical wound comprising administering a polymeric barrier composition to a patient in need thereof, wherein the polymeric barrier
30 composition comprises a polymer of lactic acid and glycolic acid, an elasticizing agent and a bone growth enhancing agent. The composition may be capable of forming a film, or may be a film.

-4-

The elasticizing agent may be selected from the group consisting of MePEG, PEG, and an amphipathic diblock copolymer. The elasticizing agent may be present in a range of concentrations, from about 1% (w/w) to about 40% (w/w).

5 The bone growth enhancing agent may be a bisphosphonate. Bisphosphonates include alendronate, cimadronate, clodronate, tiludronate, etidronate, ibandronate, neridronate, olpandronate, risedronate, piridronate, pamidronate and zoledronate. The bisphosphonate is present in a concentration from about 0.1% to about 5%.

10 In accordance with another aspect of the invention, said bone growth enhancing agent is selected from the group consisting of hydroxyapatite, calcium pyrophosphate, calcium triphosphate and demineralised bone. Hydroxyapatite, calcium pyrophosphate and calcium triphosphate are examples of a more general group of calcium phosphates.

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In accordance with another aspect of the invention, said bone growth enhancing agent is a calcium phosphate.

20 In accordance with another aspect of the invention, the bone growth enhancing agent is hydroxyapatite. The bone growth enhancing agent is present in a concentration of about 20% to about 80%, or about 25%, or about 50%, or about 75%.

25 The ratio of lactic acid to glycolic acid in the polymer of lactic acid and glycolic acid is from about 50:50 (w/w) to about 95:5 (w/w). For example, the ratio of lactic acid to glycolic acid is about 50:50 (w/w), or about 85:15 (w/w) or about 95:5 (w/w).

30 The composition may further comprise an antibiotic, antiproliferative or anti-inflammatory medicament.

-5-

In accordance with another aspect of the invention, there is provided a kit for preparing a polymer barrier composition, the kit comprising a polymer of lactic acid and glycolic acid, an elasticizing agent, a bone growth enhancing agent and instructions for combining the polymer, the elasticizing agent and the bone growth enhancing agent. The composition may be capable of forming a film, or may be a film.

In accordance with another aspect of the invention, the kit may further comprise a form or mould.

In accordance with another aspect of the invention, the polymer of lactic acid and glycolic acid and/or the elasticizing agent and/or the bone growth enhancing agent may be provided solubilised or suspended in an organic solvent.

Other aspects and features of the present invention will become apparent to those ordinarily skilled in the art upon review of the following description of specific embodiments of the invention in conjunction with the accompanying figures.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a thermogram of PLGA (50/50) films containing 0%, 10%, 20%, 30% or 40% MePEG (w/w).

Figure 2 illustrates the change in the glass transition temperature (T_g) of a PLGA (50/50) film containing 0%, 10%, 20%, 30% or 40% MePEG. The open circles show the theoretical drop as determined by the Fox equation, and the closed circles show the measured T_g values.

Figure 3 illustrates the change in the glass transition temperature (T_g) of a PLGA (85/15) film containing 0%, 10%, 20%, 30% or 40% MePEG. The open circles show the theoretical drop as determined by the Fox equation, and the closed circles show the measured T_g values.

-6-

- Figure 4 shows stress:strain curves for PLGA (85/15) films containing 0, 5%, 10%, 15% or 20% MePEG. The star series show the results for a film containing 0% MePEG, the 'x' series show the results for a film containing 5% MePEG, the grey triangle series show the results for a film containing 10% MePEG, the solid square series show the results for a film containing 15% MePEG and the solid diamond series show the results for a film containing 20% MePEG.
- Figure 5 shows a time course of MePEG loss from films of 50:50 PLGA containing 20% w/w MePEG, incubated in PBS, as determined by quantitative gel permeation chromatography.
- Figure 6 shows the change in mass of a PLGA (85/15) film containing 10% MePEG over time.
- Figure 7 shows the change in area of a PLGA (85/15) containing 10% MePEG film over time as MePEG is solublized out of the film.
- Figure 8 shows the cumulative release of tetracycline from PLGA (85/15) films including 0%, 10%, 20% or 30% MePEG. Solid diamonds show the release of tetracycline from films containing 0% MePEG, solid squares show the release of tetracycline from films containing 10% MePEG, solid triangles show the release of tetracycline from films containing 20% MePEG and the 'x' shows the release of tetracycline from films containing 30% MePEG.
- Figure 9 shows a time course of the release of alendronate from PLGA (85/15) films including 10%, 20% or 30% of amphipathic diblock copolymer. The Y axis is alendronate released in mg/mg film. The hollow square shows the results of a film lacking alendronate. The solid diamonds show the results of alendronate release in a film containing 10% amphipathic diblock copolymer, the solid squares show the results of alendronate release in a film containing 20%

-7-

amphipathic diblock copolymer, and the solid triangles show the results of alendronate release in a film containing 30% amphipathic diblock copolymer.

- 5 Figure 10 shows a bar graph illustrating the effect of alendronate on the growth of osteoblasts on PLGA (85/15)/10% amphipathic diblock copolymer films with varying concentrations of alendronate. The Y axis is the number of cells per view. The white bars show the count results on a film lacking alendronate, the black bars show the count results on a film containing 0.25% alendronate and the hatched bar shows the count results on a film containing 0.5% alendronate.
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DETAILED DESCRIPTION

- 15 The invention provides, in part, a polymeric barrier composition for use in guided tissue regeneration. The barrier composition includes a film containing of poly(lactic-co-glycolic acid), an elasticizing agent and a medicament, such as bone-growth enhancing agent. The film may be precast on a template to a suitable size and configuration for the desired application, and may include a modified surface texture to encourage or inhibit migration and/or growth of specific cell types. Further embodiments of the invention may include the inclusion of antibiotics, anti-proliferative compositions or tissue regeneration or bone growth enhancing agents, such as bisphosphonates in the polymeric film.
- 20

25 Definitions

- A 'polymeric barrier composition' as used herein refers to a composition that is, or is capable of forming an impermeable or semi-permeable barrier. The composition includes a polymer, for example a polymer of lactic acid and glycolic acid. The composition may be formed into a barrier by moulding or casting in an appropriate shape. The barrier may be a film.
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-8-

A 'polymer of lactic acid and glycolic acid' as used herein refers to a polymer including repeating linked units of lactic acid and glycolic acid monomers.

5 A 'bisphosphonate' as used herein refers to a group of medicaments characterized by a geminal bisphosphonate bond. Bisphosphonates may include alendronate, cimadronate, clodronate, tiludronate, etidronate, ibandronate, neridronate, olpandronate, risedronate, piridronate, pamidronate, zoledronate or pharmaceutically acceptable salts or derivatives thereof and mixtures thereof.

10 A therapeutically effective amount of a medicament as used herein refers to that amount of a medicament, for example, a bisphosphonate compound, that will elicit a desired therapeutic effect or response when administered in accordance with a desired treatment regimen. For example, a therapeutically effective amount of a bisphosphonate compound is an amount that, when administered to a patient or
15 test subject, decreases the rate of bone resorption in a test animal or patient. In another example, a therapeutically effective amount of a bisphosphonate, when applied to cultured bone-regenerating cells, causes the cells to respond in a manner conducive to reducing resorption of bone. In another example, a therapeutically effective amount of bisphosphonate, when administered to a
20 patient or test subject inhibits loss of bone mass at a site of periodontal surgery, or causes an increase in bone mass at a site of periodontal surgery.

The term 'treatment' as used herein refers to the administration or application of a remedy or remedies to a patient or test subject for prevention or relief of disease
25 or injury. Treatment may include medicinal applications or surgical management or therapy.

The term 'bone growth enhancing agent' as used herein refers to a composition that encourages or enhances the formation of bone or bone-like tissue. Examples
30 of bone growth enhancing agents include bisphosphonates, bone substitutes such as a calcium phosphate, demineralized bone or bioactive materials that act in a similar manner or have a similar effect.

A 'calcium phosphate' as used herein refers to a salt of calcium containing at least one phosphate group. Examples of calcium phosphates include hydroxyapatite, calcium pyrophosphate and calcium triphosphate. Other examples of a calcium phosphate may include alpha-tricalcium phosphate (.alpha.-TCP), beta- tricalcium phosphate (.beta.-TCP), tetracalcium phosphate (TTCP), monocalcium phosphate monohydrate (MCPM), monocalcium phosphate anhydrous (MCPA), dicalcium phosphate dihydrate (DCPD), dicalcium phosphate anhydrous (DCPA), octacalcium phosphate (OCP), calcium dihydrogen phosphate, calcium dihydrogen phosphate hydrate, acid calcium pyrophosphate, anhydrous calcium hydrogen phosphate, calcium hydrogen phosphate hydrate, calcium pyrophosphate, calcium triphosphate, calcium polyphosphate, calcium metaphosphate, anhydrous tricalcium phosphate, tricalcium phosphate hydrate, apatite, and fluorapatite.

A therapeutically effective amount of a bone growth enhancing agent is an amount that, when administered to a patient or test subject, inhibits further loss of bone mass, or increases bone mass. The bone growth enhancing agent may be administered locally at a site of surgical intervention, for example a site of periodontal surgery.

The term 'film' as used herein refers to a thin layer of material. A film may be impermeable or semipermeable, and may be, for example, a barrier. A film may be opaque or transparent, or semi-transparent, and may be any desired colour, or have no colour (a 'clear' film). A film may be homogeneous, or may have particulate components suspended in it. A film may further have markings, patterns or other surface features on either or both sides. These surface features may result from the materials included in the film, or may result from the process by which the film is formed. A film may be produced in a range of thicknesses depending on desired application. A film may have a uniform thickness, or the thickness may vary in different areas.

The terms 'plasticizer', 'plasticizing agent', 'elasticizer' or 'elasticizing agent', as used herein refer to a compound, for example an organic polymer, that, when

-10-

combined with the parent material, confers elasticity or elastic properties such as stretching or flexibility. Examples of elasticizing agents used herein may include methoxypolyethylene glycol (MePEG), polyethylene glycol (PEG) and amphipathic diblock copolymers.

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The term 'elasticity' as used herein refers to the tendency of a body to return to its original shape after it has been deformed. Deformation may include stretching or compression. The terms flexible, elastic, resilient or supple all refer in a literal sense to a body that is capable of withstanding stress without injury or damage. A stress is an applied force or system of forces that may strain or deform a body. To strain a structure or shape is to alter the relation between the parts of the structure or shape by applying an external force, which deforms the structure or shape. The ratio of stress/strain is commonly referred to as Young's modulus. This is an established physical parameter of elasticity, and known in the art.

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The term 'amphipathic diblock copolymer' as used herein refers to a polymer including two chains of differing polymers. One polymer is hydrophobic, and the second is hydrophilic. Examples of hydrophobic polymers may include but are not limited to polylactic acid, polylactic-co-glycolic acid, polycaprolactone, polyhydroxybutyrate and polymethylmethacrylate. Examples of hydrophilic polymers may include but are not limited to methoxypolyethylene glycol (MePEG), polyethylene glycol (PEG), polyacrylic acid and polysaccharides.

20

Preparation of polymeric barrier compositions

25

Polymeric barrier compositions may include biocompatible polymers, elasticizing agents and bone-growth enhancing agents, and in select embodiments, medicaments such as antibiotics, anti-proliferative agents or anti-inflammatory agents. An example of a biocompatible polymer is, for example PLGA. PLGA, over a range of lactic acid:glycolic acid ratios, is resorbable by the body. Further, PLGA does not substantially irritate or inflame the adjacent tissue in a surgical site where it may be used.

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-11-

As a general method, the various components of the polymeric barrier compositions are dissolved or suspended in a suitable hydrophobic, volatile organic solvent, and this solution or suspension is applied to a casting surface, and the solvent evaporated, leaving behind the polymerized film. A suitable solvent is one that is compatible with the polymers, elasticizing agents, medicaments, bone-growth enhancing agents and/or other medicaments included in the film. Suitable solvents may include, for example, dichloromethane or acetone. Methods for preparing the elasticizing agents such as amphipathic diblock copolymers are described (*Letchford K et al, 2004. Synthesis and micellar characterization of short block length methoxy poly(ethylene glycol)-block-poly(caprolactone) diblock copolymers. Colloids and Surface B: Biointerfaces 35:81-91*). In this publication, a hydrophilic polymer, for example, MePEG, was combined with a hydrophobic polymer component, for example epsilon-caprolactone. The combined polymers were heated and mixed to produce a homogenous liquid. Stannous octylate was added as a catalyst, and the polymerization reaction was allowed to proceed for at least 8 hours. The polymerization reaction was terminated by cooling to room temperature.

Methods for preparing PLGA/elasticizing agent solutions or suspensions that may be cast into a polymeric barrier composition are described in Jackson (*Jackson JK et al., 2004. Characterization of perivascular poly(lactic-co-glycolic acid) films containing paclitaxel. Int J. Pharm 283:97-109*). In this publication, PLGA of the desired lactic acid:glycolic acid ratio was combined with an elasticizer in a hydrophobic solvent. Examples of lactic acid:glycolic acid ratios include 85:15 and 50:50. Examples of an elasticizer include MePEG or an amphipathic diblock copolymer. Other examples of methods for forming polymeric barrier compositions will be known to one of skill in the art.

Casting of films

The casting surface may be a precast mould such as a 'negative' taken from a patient's jaw or teeth, or may be a precision-milled mould made from titanium or other suitable material. Alternatively, flat films with little to no surface texture may be cast on TEFLON™ moulds.

-12-

In another aspect of this invention, films, for example PLGA/MePEG films, may be cast to a fixed moulded shape other than a substantially flat surface. A precast rigid form, such as that taken from a mold of the patient's teeth and jaw before surgery may be used. Such a mould may be made from a sculptable material, for example PROVIL™ novo (Heraus), or other suitable casting polymer. After the surgeon has exposed the periodontal pocket, and removed unwanted tissue from the area, the cast of the patient's preoperative jaw may be used as a form, possibly with minor modifications as determined by the surgeon. For example, a PLGA film as described in an embodiment of this invention may be placed over the mold and moistened with water to set the three-dimensional shape. Once the film has gained a measure of rigidity, it may then be removed from the mould and placed over the exposed periodontal pocket, so that a small void is present under the film surface. This technique may thus provide a void for the bone to grow into without the need for placing infill material in the space. Other methods and techniques for manipulating such polymeric barrier compositions known to a person of skill in the art may also be used.

Grooved surfaces for use in casting a grooved film may be prepared by micromachining a grooved surface of desired pitch, width and depth on a silicon wafer. A textured surface for use in casting may be prepared by sand- blasting and acid-etching a titanium blank. A film cast using this silicon wafer and titanium mould may have a grooved first side and a textured second side. Groove width is for example, about 30 micrometers, with sides at an angle of, for example, about 125° and a pitch of, for example about 45 micrometers or about 175 micrometers. A film may be cast to have a thickness from about 50 micrometers to about 200 micrometers inclusive.

Antibiotics

In another embodiment of the invention, the polymeric barrier compositions may include medicaments such as antibacterial medicaments or antibiotics in a therapeutically effective amount, for example tetracycline at about 5%.

-13-

The release profile of the antibiotic from the polymeric barrier composition, for example a film, may be controlled by varying the amount of elasticizer; for example MePEG, in the film. This feature has the advantage of allowing the surgeon to select an optimal release profile for the required surgical site so that in areas where an increased initial dose of antibiotic may be desired, a film with a higher MePEG loading may be used to increase the concentration of the antibiotic at the initial burst phase of release.

Examples of other antibiotics that may be used in this embodiment include tetracyclines such as minocycline, doxycycline, oxytetracycline, demeclocycline, or methacycline which may be preferred for periodontal applications. Alternatively, other antibiotics may be used such as penicillins, cephalosporins, aminoglycosides, erythromycins and related antibiotics, vancomycin, polypeptide antibiotics or sulfonamides. Dosage ranges and preferred applications are specific to the antibiotic selected, and examples of such may be found, for example, in the Merck Manual of Diagnosis and Therapy, 15th edition (Merck Sharp & Dohme Research Laboratories, Rahway NJ)

Antiproliferative agents

In another embodiment of the invention, the polymeric barrier composition may include medicaments such as antiproliferative medicaments. An antiproliferative agent is an agent that exerts an inhibitory effect on cell proliferation. The antiproliferative agent may have a cytostatic effect, where cell growth may be slowed or stopped, or a cytotoxic effect wherein cells are killed, by apoptosis or other biological mechanisms. Antiproliferative drugs may include antimetabolites such as methotrexate; anticancer drugs such as estramustine, platinum containing compounds, or 5-fluorouracil; microtubule inhibitors such as paclitaxel, colchicine or vinca alkaloids including vincristine and vinblastine; topoisomerase inhibitors such as camptothecin, etoposide, doxorubicin, mitoxantrone; DNA intercalating agents such as anthracyclines; oxygen-radical producing agents such as naphthoquinones; and antiangiogenic agents such as paclitaxel, thalidomide, VEGF related antibodies or statins; or derivatives of any of these

-14-

In an alternate embodiment, the antiproliferative agent may be applied to an outer surface boundary of the cast polymeric barrier composition, for example a film. The antiproliferative medicament may be preferentially deposited as a border of about 1-2 mm width on the 'outer' side of the film (not facing the tooth), to inhibit
5 epithelial cell and gingival fibroblast proliferation in a controlled manner. As epithelial cell growth over and around periodontal barriers is a problem in many settings, this temporary inhibition of growth at the boundaries may prevent the invasion of the epithelial cells around the membrane and into the periodontal pocket. This selective inhibition of cell growth may further give the osteoblasts
10 more time to develop a bone or bone-like tissue barrier to epithelial cell infiltration around the film into the pocket. This improvement may be achieved by dissolving or suspending the antiproliferative medicament in a small volume of suitable solvent and pipetting or painting a thin bead of the drug solution on boundary regions of the non-channeled or outer side of the membrane. The solvent may
15 further help to incorporate the antiproliferative medicament by partially dissolving the outer boundary region and allow medicament penetration into the matrix of the film.

Anti-inflammatory agents

20 In another embodiment, anti-inflammatory agents may be incorporated into the polymeric barrier composition for release in a controlled manner over time. Inhibition of the inflammation that underlies periodontal disease and accompanies surgical repair of the damaged tissue and bone would be advantageous. Examples of suitable medicaments may include those that inhibit leukocyte
25 activation or migration into the area, inhibit the production of cytokines, chemokines or chemotactic mediators that exacerbate inflammation and osteoclast activity, or inhibit the production or action of metalloproteinases.

Other elasticizing agents

30 Other elasticizing agents may be incorporated into the polymeric barrier composition to enhance elasticity. In an alternate embodiment, an amphipathic diblock copolymer for manufactured from methoxypolyethyleneglycol-block-poly-lactic acid was included with PLGA and a bone-growth enhancing agent.

Uses of a polymeric barrier composition

Controlled wound healing and regeneration of the connective tissue and bone at the wound site is the goal of guided tissue regeneration (GTR) techniques and methods. Preventing the invasion of the wound space by unwanted cells is important to encourage bone regeneration. Use of guided regeneration techniques in, for example, periodontal surgical applications reduces or eliminates the invasion of, for example, epithelial cells and gingival fibroblasts. Physical barriers may be placed over and/or around the wound site to prevent such invasive ingrowth. Use of a resorbable barrier eliminates the need for a second surgical procedure several weeks after the initial surgery to remove the barrier so that healing may be completed.

A resorbable barrier is one that includes material that is able to be dissolved and/or assimilated in the body. The material may be digested or otherwise acted upon by enzymes or cells in the body of the host animal and be broken down into constitutive molecules, which are then metabolized or further processed for metabolism. For example, PLGA films are broken down to the constitutive lactic acid and glycolic acids.

The length of time that a barrier should remain at the surgical site may vary depending on the site, surgeon preference, rate of healing and other factors that may influence the surgical repair. A barrier that is resorbed too quickly may permit ingrowth of unwanted cells, while a barrier that is resorbed too slowly may prevent healing of the site.

In some situations, a surgeon may want to maintain a void or space around the wound site – this may be described as a wound space. The presence of such a wound space may permit bone or bone-like tissue to grow into the space as the wound heals. If the barrier is too rigid, it may not be effectively shaped to the desired wound space and may permit the invasion of unwanted cells. If the barrier is too flexible, a wound space may not be maintained for sufficient time following surgery to permit bone or bone-like tissue to fill in.

-16-

As osteoblasts proliferate and migrate up the inner surface channels of the grooved PLGA film, these cells may lay down calcified nodules and begin to form layers on the inner surface of the film. These layers may form a stiffening structure so that as the film, for example a PLGA/MePEG film degrades, this layer
5 of bone or bone-like tissue becomes structural, allowing growth of bone and/or bone-like tissue on the inner side (facing the tooth) into the wound space. This new bone/bone-like tissue may serve as an additional barrier to unwanted cells such as epithelial cells and gingival fibroblasts migrating from the gingival flap side of the interface.

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In one embodiment, incorporation of a bone growth enhancing agent into the film provides controlled release of these agents at the surgical site, enabling a higher localized concentration than otherwise possible through systemic administration of these medicaments. For example, alendronate is released from the film in a
15 controlled, time-dependent manner.

Properties of the polymeric barrier compositions

As the polymeric barrier composition, for example a PLGA/MePEG film, absorbs water and swell, it increases in rigidity. In one embodiment, this swelling may
20 further seal the outer boundary of the film, so that epithelial cells and gingival fibroblasts may be prevented from growing or migrating around the film and invading the wound space. Swollen films maintain the feature of aligned osteoblastic cell growth along the residual channels on the films. The resulting swelling may further promote the formation of the rough, swollen surface that
25 encourages the attachment but discourages the migration of epithelial cells.

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The degradation rate of the film is dependent on the ratio of lactic acid to glycolic acid in the copolymer, and on the molecular weight of the starting polymer. Degradation may further be affected by the concentration of the elasticizing agent, for example, MePEG, in the film. The PLGA polymer may, for example, have a lactic acid:glycolic acid ratio from about 50:50 (w/w) to about 85:15 (w/w), inclusive. In alternate embodiments, the lactic acid:glycolic acid ratio may be, for example, about 55:45, or about 60:40, or about 65:35, or about 70:30, or about

-17-

75:25, or about 80:20 or about 85:15, inclusive, or any integer ratio in between. In an alternative embodiment, the lactic acid:glycolic acid may be as great as 95:5.

5 The concentration of elasticizing agent, for example MePEG, may be about 5%, or about 10%, or about 15%, or about 20%, or about 25%, or about 30%, or about 35%, or about 40%. In alternative embodiments, the elasticizer concentration may be from about 1% to about 40% inclusive, and any integer in between, inclusive.

10 These polymeric barrier compositions provide, for example films, that have the feature of being flexible and elastic once cast, but become more rigid upon exposure to water.

15 The polymeric barrier compositions may include biocompatible polymers, elasticizing agents and bone-growth enhancing agents, and in select embodiments, medicaments such as antibiotics, anti-proliferative agents or anti-inflammatory agents. An example of a biocompatible polymer is PLGA. PLGA, over a range of lactic acid:glycolic acid ratios, is resorbable by the body. Further, PLGA does not substantially irritate or inflame the adjacent tissue in a surgical site
20 where it may be used.

Varying the elasticizing agent and/or the concentration of the elasticizing agent in the polymeric barrier composition provides for another method to alter the elasticity and rate of change in rigidity in the resulting film, offering an advantage
25 to the surgeon. Increasing the concentration of the elasticizing agent, for example MePEG in a film, for example a PLGA film, increases the elasticity (as measured by Young's modulus) and decreases the glass transition temperature. A therapeutically effective amount or concentration of elasticizing agent for a film for use in a particular surgical procedure may be dependent on both the specific
30 needs of the surgical procedure and the preference of the surgeon. Glass transition temperature is dependent on the concentration of the elasticizer, and may be calculated using, for example, the Fox equation. Other methods of determining a desired concentration will be known to those of skill in the art. For

-18-

example, in a surgical site that is difficult to access (such as the very back of the jaw) where more time and manipulation may be needed to fit and mould a film around the base of the tooth of interest, a film with a higher elasticizing agent concentration may be selected to provide a film that maintained elasticity for a longer period of time. Other excipients, medicaments or materials known in the art may also be incorporated into the polymer barrier compositions to provide altered elastic properties. Properties of the excipient and/or elasticizing agent, such as molecular weight may enable further manipulation and control of the elasticity and handling of the film. For example, higher molecular weight MePEG or PEG may reduce the glass transition temperature of the polymeric barrier composition, resulting in reduced elasticity.

In another embodiment, incorporation of bone-growth enhancing agents such as hydroxyapatite or calcium phosphate microparticles into the polymeric barrier composition provides enhanced structural rigidity of the resulting film, but the film does not become inflexible and brittle. This was unexpected, as a suspension of insoluble, inorganic material in a hydrophobic organic solvent/polymer mixture would have been expected to aggregate and not remain homogeneously distributed throughout the resulting film. When films were cast using such a suspension, the microparticles remained homogeneously dispersed throughout the film. More surprisingly, the presence of microparticles did not adversely affect channel formation when the films were cast on grooved templates. The resulting films were flexible and had well formed channels with clear evidence of uniformly distributed microparticles along the channel sides without interference of channel structure. These films were found to have unusual properties in that instead of being purely elastic (i.e. returning to the original shape after stretching or manipulation), they could be shaped around forms and when the form was removed they retained much of the shape of the form without returning to the original flat film shape. This feature was unexpected and is advantageous in the application of such films in a clinical setting, as a surgeon may have more control over the shape and positioning of the film at a surgical site and may cast a film to a desired three-dimensional shape.

-19-

In a further investigation of hydroxyapatite loading of the films, PLGA/MePEG films were produced ratios of 75% hydroxyapatite, 2.5% MePEG and 22.5% PLGA. It was found that these 75% hydroxyapatite films retained a flexible structure, although elasticity was reduced compared to films that did not include hydroxyapatite or other microparticulates. These films could be readily formed without breakage of the film structure. The films were still slightly elastic under mild stretching, and inclusion of 75% hydroxyapatite did not interfere with channel formation when casting. As observed with other PLGA/MePEG films, the hydroxyapatite-containing films became more rigid when water was introduced around the film. This characteristic of these hydroxyapatite-containing films enables the manufacture of grooved films with various levels of elasticity/rigidity.

Furthermore, the inclusion of hydroxyapatite or other bone-compatible material may promote the rapid formation of bone by the osteoblasts growing up the grooved channels. Not only might such cells adhere to such material, the material offers a readily available source of calcium for mineralization and bone formation. The hydroxyapatite (or other microparticulate matter) may further offer scaffold type properties such that the periodontal space or void may remain empty or clot filled, without collapse of the film into the space. Another advantage of the inclusion of insoluble microparticles is that they may form a physical barrier to epithelial cell ingrowth through a polymeric barrier composition film that may degrade prior to effective bone formation.

An additional embodiment may incorporate hydroxyapatite particles in combination with at least one bisphosphonate medicament (hydroxyapatite particles coated with the medicament, for example) in the polymer barrier compositions of this invention.

In alternate embodiments, other materials may be included in the polymeric barrier compositions, for example PLGA/MePEG films, to control mechanical properties. Inorganic salts, for example, sodium chloride may be suspended in the films when casting. Other examples of such materials may include calcium phosphates, calcium salts or materials compatible with bone formation, for

-20-

example demineralized bone fragments, for example calcium triphosphate, or other materials with properties similar to hydroxyapatite. In an alternate embodiment, these bone-enhancing or bone-compatible materials may also be incorporated on the surface of the films after casting. A surface coating of bioactive material may attract osteoblasts, and also supply the osteoblasts with an enhanced supply of calcium phosphate for localized bone deposition. Methods of surface application of the bioactive material to the channeled or grooved side of the film will be familiar to those of skill in the art. For example, the bioactive material may be distributed on the surface and 'set in' by subsequent exposure to a compatible solvent, so that the surface is partially solubilized and the particles embedded in the film matrix on one side of the film only, providing an optimized surface for osteoblast adherence, growth and replication. In an alternative embodiment, the bioactive material may be suspended in the PLGA/MePEG casting solution in a compatible solvent before casting, so that the bioactive material is uniformly incorporated throughout the film. Other examples of bioactive materials may include compounds such as talc, beryllium or silica; components of the extracellular matrix (such as fibronectin), polymers such as poly-lysine, tet-ammonium end terminated polymers, cationic polymers such as chitosan, inflammatory cytokines, chemotactic molecules, growth factors, fibrin/fibrinogen or other coagulation inducing molecules such as thrombin, inflammatory microcrystals such as sodium urate or calcium pyrophosphate, or silicates. Derivatives or analogues of these materials are also included in this definition.

Other embodiments

Film casting and thickness

The optimal groove dimensions and thickness of the polymeric barrier compositions, for example a film, may be determined by one of skill in the art. For example, a film may have a thickness from about 25 micrometers to about 250 micrometers. For example, a film may have a thickness from about 25 micrometers to about 75 micrometers, or from about 50 micrometers to about 100 micrometers, or from about 75 micrometers to about 125 micrometers, or from

-21-

about 100 micrometers to about 150 micrometers, or from about 125 micrometers to about 175 micrometers, or from about 150 micrometers to about 200 micrometers, or from about 175 micrometers to about 225 micrometers, or from about 200 micrometers to about 250 micrometers, or from about 225 micrometers to about 275 micrometers. A film may also be cast for example, with a different thickness around the edge from that of the rest of the film, for example a thinner edge extending from about 1 to about 5 millimeters in from the edge.

Smooth, rough or grooved surfaces with a variety of groove dimensions may be replicated on, for example, PLGA-MePEG films, using methods such as obtaining a negative impression of a desired surface texture, for example a sandblasted acid-etched surface, or a precision-milled grooved surface on a casting form, followed by film casting on the form. A method of solvent casting for replicating the desired topography was successful in the embodiments presented herein, however other methods will be known to those skilled in the art. The use of a channeled surface on the inside or 'tooth' side of, for example, a PLGA/MePEG film may facilitate the accelerated bone cell growth along the inside surface of the film, forming new bone or bone-like tissue. The layers of new bone or bone-like on the inner surface of the film may have a stiffening effect, so that as the, for example, PLGA/MePEG film degrades, these new layers become structural, further facilitating bone or bone-like tissue growth on the inner side and into the wound space, and remain as a structural barrier to epithelial cell and gingival fibroblast growth found on the outer side of the film.

In alternate embodiments, the polymeric barrier composition, for example a film, integrates with the surrounding tissues and, upon water adsorption, swells and seals the contact area at the surgical site, providing a barrier to exclude bacteria, epithelial cells and gingival fibroblasts from the wound space. In alternate embodiments, upon water absorption and subsequent swelling, the film loses elasticity and may be of sufficient strength and rigidity to withstand soft tissue contraction at the surgical site and maintain the wound space volume for the bone-regenerating cells.

-22-

Kits

A kit is a set of reagents and instructions for using the set of reagents to perform a task or produce a product. For example, a kit for making a polymeric barrier film according to one embodiment of the invention may include predetermined or premeasured quantities of an lactic acid:glycolic acid polymer, elasticizing agent and bone growth enhancing agents, either dry or solubilized or suspended in a suitable solvent, and instructions for combining the set of reagents in an appropriate manner. The instructions may further include instructions for casting a film and evaporating the solvent to produce a film.

In an alternative embodiment, the solvent may be supplied separately and the instructions may provide details as to the volume required to produce a film with particular concentrations of elasticizing agent and/or bone growth enhancing agent. In an alternative embodiment, the kit may also include moulds or forms suitable for casting the film.

Aspects of the invention are illustrated by the following non-limiting examples.

Example 1**Methods and Materials**

PLGA 85/15 (inherent viscosity = 0.61dL/g) and 50/50 (inherent viscosity= 0.66dL/g) were obtained from Birmingham Polymers (Birmingham, AL). Methoxypolyethylene glycol (MePEG), molecular weight 350, was obtained from Union Carbide (Danbury, CT). Alendronate (sodium salt) was obtained from Sigma (St. Louis, MO). All solvents were HPLC grade and obtained from Fisher Scientific.

Poly(D,L lactic acid) /MePEG amphipathic diblock copolymer was synthesized in the laboratory and were composed of MePEG copolymerized with polylactic acid, according to the methods of Letchford (*Letchford K et al, 2004. Synthesis and micellar characterization of short block length methoxy poly(ethylene glycol)-block-poly(caprolactone) diblock copolymers. Colloids and Surface B:*

-23-

Biointerfaces 35:81-91)) using MePEG MW 2000 g/mol and weight percentages of D,L-lactic acid and MePEG of 40:60. Briefly, MePEG, was combined with polylactic acid and the combined polymers were heated and mixed to produce a homogenous liquid. Stannous octylate was added as a catalyst, and the polymerization reaction was allowed to proceed for at least 8 hours. The polymerization reaction was terminated by cooling to room temperature.

Film casting

Polymer solutions for film casting were made by dissolving the appropriate amount of polymers (PLGA (85/15 or 50/50) and MePEG or amphipathic diblock copolymer) in dichloromethane. Alendronate, tetracycline or other medicaments may also be incorporated in the film casting solution. Solutions were allowed to stand with intermittent gentle agitation, usually about 1 hour.

For stress-strain determinations, 1 cm x 2.5 cm TEFLON™ strips were cut and attached to glass microscope slides to provide a surface for the films to form. Two hundred microlitres of the desired polymer solution was applied to each strip and the solvent allowed to evaporate.

For polymer miscibility, medicament release and mass loss studies, the same method was used, except that 80 ul of the desired polymer/medicament solution was applied onto 0.8 cm x 0.8 cm TEFLON™ strips and the solvent allowed to evaporate.

Films with grooved surfaces were cast using PROVIL™ novo (Heraeus Kulzer, USA) forms made so that the resulting membrane were 15mm diameter and 1mm thick. Both the dissolved polymer solution and the negative material were precooled to -20°C, and 1 ml applied to the casting form. Solvent was allowed to evaporate at -20°C.

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Film thickness ranged from about 50 micrometers to about 200 micrometers.

Replication of surface topographies on epoxy & PLGA

Original grooved surfaces were patterned on silicon wafers by micromachining (Brunette DM. *Spreading and orientation of epithelial cells on grooved substrata. ExpCell Res* 1986;167:203–17). The two types of grooved surfaces used were 30 micrometers deep, with sloping walls that met the floor of the groove at 125°. Groove width was also constant at 30 micrometers but two widths of ridge were used - 45 or 175 micrometers. The surface originals of the coarsely blasted and acid etched commercially pure titanium ((SLA) were prepared by Institut Straumann AG, Waldenberg, Switzerland).

Negative surface impressions

Impressions of the grooved, SLA and glass surfaces were made using polyvinylsiloxane impression material (PROVIL™ novo Light; Heraeus Kulzer, Dormagen, Germany). Vinyl polysiloxane negative replicas were then used as templates to cast epoxy-resin (EPO-TEK 302-3; Epoxy Technology, Belrica, MA) positive replicas of these surfaces. Epoxy resin replicas were polymerised at 60°C for 4 days and left to cool. All replicas were thoroughly cleaned before titanium coating. The cleaning procedure involved ultrasonication in a detergent (7X, ICN Biomedicals, Inc., Costa Mesa, CA), and then replicas were sputter coated (Randex 3140 Sputtering System, Palo Alto, CA) with 50nm of Ti on both sides.

Fluorescent time-lapse digital cinematography

The movement of fluorescently labelled cells was documented by time-lapse digital videomicrography. Suspended cells were stained with cell tracker orange molecular probe (Invitrogen, Carlsbad, USA) at a concentration of 0.0004% for 30 min then plated on each surface at a concentration (40,000 cells/ml) for 22 h. Individual surfaces were secured with silicon grease on glass slides and sealed in a previously sterilised Pentz chamber (Bachofer, Reutlingen, Germany). Cell growth medium was added through the silicone rubber seal by sterile syringe. The Pentz chamber was placed on a stage incubator (Bachofer) that was held at 37°C and perfused with 5% CO₂ throughout the experiment. Images were taken automatically at 5 min intervals over a period of 12 h with a digital video camera

-25-

(Q imaging, Retisa 1300) connected to a computer running Northern Eclipse software (Empix Imaging Inc., Mississauga, Canada).

Cell proliferation

- 5 Cells were cultured and plated on the PLGA membranes as previously described and seeded at a concentration of 10,000 cells/mL for 1, 3 and 5 days . All samples were then rinsed with 0.01M PBS buffer and stained with propidium iodide. Cells were imaged with an epifluorescent microscope (Axioscop, Zeiss, Germany) equipped with a rhodamine filter and images were captured digitally with Northern
10 Eclipse software (Empix). Twenty images were taken from two samples and the number of cells per unit area were counted manually. One-way ANOVA and Bonferoni post-hoc statistical test were used at each time point to find significant differences in cell number among different surfaces. The significance level was set at 0.05.

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Example 2

Miscibility of polymers determined by Differential Scanning Calorimetry - Effect of the addition of MePEG on the glass transition temperature of the PLGA.

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- Differential scanning calorimetry (DSC) was performed using a Perkin Elmer Pyris 1 calorimeter. Approximately 10 mg of films having a range of MePEG concentrations ranging from 0-40% were placed in a crimped aluminium DSC pan. Each sample was heated to 80°C, then rapidly cooled to -80°C at 200°C per
25 minute, and then heated at a rate of 40°C per minute.

- The glass transition temperature (T_g) is a measure of the temperature below which molecules have low mobility. A polymer is more rigid below its T_g, and can become more flexible above the T_g. Theoretical T_g values for a polymer blend
30 (such as MePEG in PLGA) may be calculated using the Fox equation:

$$1/T_g(\text{combined polymer}) = A/T_g(\text{MePEG}) + B/T_g(\text{PLGA})$$

where:

A = weight fraction of MePEG, and

B =weight fraction of PLGA.

(Rosen, S. 1993. *Fundamental principles of polymeric materials* 2nd edition. Wiley, New York)

The addition of MePEG to both 50:50 and 85:15 PLGA copolymers caused a concentration dependant decrease in the Tg value of the blended mixture. Representative thermograms for the 50:50 PLGA copolymer blended with increasing amounts of MePEG are shown in Figure 1. The endothermic characteristic of the glass transition temperature is seen to decrease with increasing MePEG concentration.

Figure 2 illustrates the effect of increasing MePEG on the Tg value in the 50:50 PLGA copolymer, and Figure 3 illustrates the effect of increasing MePEG concentration on the Tg value in the 85:15 PLGA copolymer. In both figures the measured drop (open circle series) in Tg approximately matched the theoretical drop (closed circle series) as determined by the Fox equation for full miscibility.

These data demonstrate the miscibility of the blended components in the film. At temperatures below the T_g, the polymer tends to be stiff and the inclusion of MePEG decreases the T_g to around or below 37°C, and the film become more flexible and easy to apply to a surgical site

Example 3

Stress – Strain determinations. Effect of the addition of MePEG on the stress strain properties of PLGA: the induction of flexibility by the introduction of MePEG.

For elasticity determinations, rectangular films were cast as described above. Measurement of stress and strain was performed using published methods (Jackson, JK et al. 2002. *Paclitaxel loaded crosslinked hyaluronic acid films for the prevention of post surgical adhesions. Pharm Res.* 19:411-417). Briefly, films

-27-

were clamped at the short ends and suspended vertically and perpendicular to the optical path of a microscope having a calibrated eyepiece micrometer. The thickness of the film was measured using a digital micrometer (Mitutoyo, Japan) and the length of the film between the clamps was measured using calipers. A reference mark was made on the film and the eyepiece focused on this mark. Increasing mass was applied to the lower end of the film and the extension of the film was measured using the eyepiece micrometer.

Stress was determined as the force applied per unit area:

$$(9.81 \times \text{mass applied (kg)} / \text{width} \times \text{thickness (m}^2\text{)}) \text{ N/m}^2$$

Strain was determined as the change in film length:

(extension)/original length (m).

Films made from PLGA alone were found to be brittle and fractured, rather than stretch, when mass was applied. The addition of MePEG in increasing amounts to the PLGA films increased the ability of the film to stretch without breaking when weight was applied, resulting in films with increased elasticity and flexibility. The addition of increasing amounts of MePEG to PLGA resulted in films that were increasingly elastic, with a concentration dependant reduction in the gradient of the stress:strain curve, shown in Figure 4.

Example 4

Release of MePEG from PLGA films.

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Sample films (0.8 cm x 0.8 cm) formulated with 80% w/w PLGA (50/50) with 20% w/w MePEG were placed in 14 mL PBS in a culture tube and oscillated at 150 rpm in a 37°C incubator. The supernatant was replaced with fresh PBS at regular intervals and oscillation continued at 37°C to maintain sink conditions. At various timepoints the supernatant was completely removed and the film dried at 30°C under a stream of nitrogen gas. Once completely dry, the film was dissolved in 1 ml of chloroform and the amount of MePEG remaining in the film was quantified by gel permeation chromatography.

-28-

Quantitative gel permeation chromatography (GPC) was performed on the film samples at ambient temperature using a Shimadzu LC-10 AD HPLC pump, a Shimadzu RID-6A refractive index detector coupled to a 50 Angstrom Plgel column (Hewlett Packard). The mobile phase was chloroform with a flow rate of 1 ml/min. The injection volume of the polymer sample was 50 uL at a polymer concentration of approximately 0.25% (w/v). Components of the film samples were detected by refractive index detection and the peak areas were used to determine the amount of MePEG remaining in the films at each time point. Stock solutions containing PLGA or MePEG in the 0-5 mg/ml concentration range were analyzed by GPC and peak areas were used to create separate calibration curves for each polymer. The change in the MePEG peak areas for films on subsequent days of the experiment was expressed as weight percentages relative to the day 0 film.

Two distinct peaks were observed in the chromatogram. The early peak arose from the higher molecular weight PLGA copolymer and the later peak from the low molecular weight MePEG polymer. A set of standards including various weight ratios of PLGA and MePEG gave a quantitative calibration curve for each polymer with correlation coefficients greater than 0.98. These calibration graphs were then used to quantitate the residual amount of each polymer in the incubation tubes at times up to 72 hours. MePEG was solubilized from the PLGA films rapidly for the first 8 hours as shown in Figure 5. This was followed by a slower, more sustained release of MePEG over the following 64 hours.

Example 5

PLGA/MePeg films swell in PBS.

PLGA (85/15)/MePEG films (90% PLGA (85/15)/10% MePEG 350) with one grooved surface were cast on PROVIL™ forms as described above, with 30µm deep, 30µm wide channels and a pitch of 45 µm on one side. The mass and dimensions (thickness and area) were measured and recorded for each film sample. The films were then placed in sterile PBS at 37°C, removed at various time points and swabbed dry with tissue (to remove surface water) and the mass

-29-

and dimensions measured and recorded. The time dependent change in both mass and area are shown in Figures 6 and 7 respectively..

Example 6

5 **Release of tetracycline from PLGA/MePEG films.**

Drug release experiments were performed as follows: 10 mg film including PLGA (85/15) with MePEG at 0%, 10%, 20% or 30% (w/w). Film samples containing 5% (w/w) tetracycline were placed in 16 ml test tubes and 15 ml of 10mM phosphate buffered saline (PBS) was pipetted on top. The tubes were capped and incubated at 37°C with end over end rotation at 8 rpm. At various timepoints, the entire volume of buffer was removed and the concentration of tetracycline present was analysed by UV/VIS absorbance spectroscopy..

15 Tetracycline was released into the buffer in a linear manner (Figure 8). The addition of increasing amounts of MePEG in the PLGA films caused a concentration dependent increase in the release rate of the drug from the films.

The release profile of antibiotic from the film is advantageous for treatment of the periodontal pocket. An initial burst of antibiotic release occurs over the first few days, followed by a sustained release over the life of the film. This profile creates a high initial concentration of the antibiotic locally in the periodontal pocket to prevent the growth of residual and influxing bacteria at the most critical time - before the wound has sealed up. This is followed by the maintenance of lower concentrations, which may be sufficient to prevent growth of the smaller numbers of bacteria able to invade the area as time progresses.

Example 7

30 **Stiffening and degradation of PLGA/MePEG films in rodent models.**

Wistar rats weighing 400 - 500 g were purchased from the Animal Care Center of the University of British Columbia. All procedures involving animals were approved by the Animal Care Committee of the University of British Columbia.

-30-

The animals (n=15) were anesthetized with 1.5% halothane in oxygen and a 1 cm distal segment of the left external carotid artery exposed, and a PLGA (85/15)/MePEG 10% film applied. The area was perfused with a small amount of sterile isotonic saline and the film sutured in place. At this point, the films retained their original elasticity/flexibility that facilitated placement on the artery. The films were monitored for stiffness and rigidity for 10-15 minutes, and the wound subsequently closed. Stiffer films had lost their elasticity to some degree at this point and were less deformable. 5 animals were sacrificed at 2 weeks post-implantation, 5 at 4 weeks post-implantation, and the remaining 5 sacrificed at 12 weeks post-implantation, and the residual films assessed for resorption, degradation, and general condition.

The films showed significant signs of stiffening after just 5 to 10 minutes of placement at the surgical site. As films stiffen, less deformation occurs when films are manipulated manually. Animals assessed at 2 weeks had significant whole film sections remaining in place, while animals treated for 4 weeks had some minor residual traces of PLGA films left at the surgical site but essentially the film was fully degraded at this time. Animals treated for 12 weeks were free of any sign of residual films. No toxicity or adverse effects were noted in the animals treated with these films.

PLGA films including elasticizing agents such as methoxypolyethylene glycol (MePEG), for example, demonstrate a shorter degradation profile, and greater elasticity than those of PLGA alone. PLGA/MePEG films degrade over a 4 to 6 week period. When placed in rats, the PLGA/MePEG films were substantially resorbed within 4 weeks. This faster degradation profile offered by the inclusion and rapid dissolution of MePEG accelerates water-induced hydrolytic PLGA degradation by allowing extensive water penetration into the film in a homogenous manner. This homogeneity arises from the homogeneous dispersion of the MePEG elasticizing agent.

-31-

Example 8**Growth of osteoblasts on 30µm grooved PLGA (85/15) /MePEG films (90% PLGA/10% MePEG).**

- 5 Osteogenic cells from newborn rat calvaria were isolated as described (*Bellows CG et al., 1986. Mineralized bone nodules formed in vitro from enzymatically released rat calvaria cell populations. Calcif. Tissue Int. 38:143-54; Hasegawa S et al., 1985. Mechanical stretching increases the number of cultured bone cells synthesizing DNA and alters their pattern of protein synthesis. Calcif Tissue Int*
- 10 *37:4431-6*). Briefly, osteoblast like cell populations were isolated, by timed enzymatic digestion, from the frontal, parietal and occipital bones of newborn (24–36 h old) Sprague-Dawley rates. Primary cultures were subcultured by trypsinisation (0.25% trypsin, 0.1 glucose, citrate-silane buffer, pH 7.8) and maintained in minimal essential medium (α-MEM, (Stem Cell Technologies Inc.,
- 15 Vancouver, Canada)) containing additions of 15% fetal calf serum (Cansera International Inc., Rexdale, Canada) and antibiotics (penicillin G, Sigma, St. Louis, USA), 100 mg/mL; gentamicin (Sigma), 50 mg/mL; amphotericin B (Fungizone, Gibco, Grand Island, NY, USA), 3 mg/mL) in a humidified atmosphere with 5% CO₂ at 37 °C.
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- When the cells were between passage 5 and 11 they were used for aligned growth experiments. Grooved (30 micrometers deep, 45 micrometer or 175 micrometer pitch) PLGA/MePEG films (90% PLGA (85/15), 10% MePEG, 0.8 cm x 0.8 cm) with were placed on plastic cell culture dishes (3 cm diameter) and glow
- 25 discharged for sterilization (*Baier, BE and Meyer, AE. Implant surface preparation. Int J Oral Maxillofac Implant 1988; 37:431-; Wieland, M et al. Use of Ti-coated replicas to investigate the effects on fibroblast shape of surfaces with varying roughness and constant chemical composition. J Biomed Mater Res 2002; 60:434-44: herein incorporated by reference*). Cells at 40,000/ ml media were
- 30 then pipetted on top of the films so that a 0.3 cm depth covering was achieved. Cells and film were then incubated under normal cell culture conditions for 1 day and then the cells were observed by stereo microscopy with a digital camera attachment. The osteoblasts adhered well to the PLGA/MePEG films and

-32-

proliferated in a random manner on non-grooved sections of the films. In the grooved areas of the films, the cells adhered to the base of the channels and grew in a directional manner.

- 5 Osteoblasts on the grooved surfaces migrated in the direction of the groove and were not noticeably affected by the pitch width. Osteoblasts appeared more elongated on the grooved surfaces with a narrow pitch (45 micrometers) in which more cells were found in the grooves compared to those cultured on the grooves with a wider pitch (175 micrometers), where more cells were found on the ridges.
- 10 On both surfaces, osteoblasts were polarized with lamellipodia and ruffling at the leading edge of the cell. Osteoblast numbers increased over a 5 day growth period on both the tissue culture plastic as well as the PLGA film surfaces.

- These data illustrate the compatibility of osteoblasts with the films described herein, and further illustrate that bisphosphonates may be released in a controlled manner at a dose that enhances osteoblast proliferation. In vivo, such films may increase the rate of bone deposition in the periodontal space.
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Example 9

- 20 **Growth of epithelial cells on 30um non-grooved PLGA (85/15) /MePEG films (90% PLGA/10% MePEG).**

- Epithelial cells were isolated from porcine periodontal ligament and cultured as described (*Brunette, EM et al., 1976. Culture origin of epithelium-like and fibroblast-like cells from porcine periodontal ligament explants and cell suspensions. Arch Oral Biol 21:393-400*). Briefly, cells were maintained in a-MEM (Stem Cell Technologies Inc.,) supplemented with 15% fetal bovine serum (Medicorp, Montreal, Canada), antibiotics (penicillin G—Sigma, St. Louis, USA), 100 mg/mL; gentamicin (Sigma), 50 mg/mL; amphotericin B (Fungizone—Gibco), 3 mg/mL) in a humidified atmosphere with 5% CO₂ at 37 °C. Confluent layers trypsinised (0.25% Trypsin, 0.1 glucose, citrate—silane buffer, pH 7.8) and seeded on all surfaces at a concentration of 20,000 cells/ml for 24 h.
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-33-

When the cells were between passages 5 and 11 they were used for aligned growth experiments. Grooved (30 micrometers deep, 45micrometer or 175 micrometer pitch) PLGA/MePEG films (90% PLGA (85/15), 10% MePEG, 0.8 cm x 0.8 cm) with were placed on plastic cell culture dishes (3 cm diameter) and glow discharged for sterilization as described above. Cells at 40,000/ ml media were then pipetted on top of the films so that a 0.3 cm depth covering was achieved. Cells and film were then incubated under normal cell culture conditions for 1 day and then the cells were observed by stereo microscopy with a digital camera attachment. The epithelial cells adhered well to the PLGA/MePEG films. Epithelial cells on rough surfaces exhibited strikingly different morphology to those cultured on the smooth surfaces. The majority of cells were well spread, but stellate, and conformed to the shape of the pits on the SLA surface. A decrease in proliferation is observed on the sandblasted and acid-etched surface, relative to the smooth surface. Epithelial cells on the SLA surface did not exhibit detectable cell movement in any direction.

Example 10

PLGA/MePEG films containing calcium pyrophosphate or hydroxyapatite microparticles.

PLGA/MePEG films including 50% hydroxyapatite or calcium pyrophosphate microparticles (w/w) were produced as described above. After dissolution of PLGA and MePEG, 100 mg of either calcium pyrophosphate (monoclinic form) or 100mg of hydroxyapatite (30 um diameter) were subsequently added to the solution with vortexing. The resulting film solution was applied to the forms as described. The final composition of the resulting films was 45% (w/w) PLGA (85/15), 5 % (w/w) MePEG and 50% (w/w) microparticles of either hydroxyapatite or calcium pyrophosphate. The resulting films were flexible and had well formed channels with clear evidence of uniformly distributed microparticles along the channel sides without interference of channel structure. Additionally, these films demonstrated a 'memory' characteristic. The films, when cast around a PROVIL™ form, retained the shape of the form when removed and did not return to the original flat dimension. The cast films were flexible but did not exhibit the

-34-

same elasticity as PLGA/MePEG films lacking hydroxyapatite or calcium pyrophosphate microparticles.

5 PLGA/MePEG films with increased hydroxyapatite (22.5% w/w PLGA (85/15), 2.5% MePEG (mw 325), 75% hydroxyapatite) were produced as described above. The resulting films also demonstrated a flexible structure (with more rigidity than the 50% hydroxyapatite film) and were mouldable (using precast forms) without breakage of the film structure. Moderate elasticity was retained with the shift in the hydroxyapatite/PLGA/MePEG ratio. Inclusion of increased hydroxyapatite
10 microparticles did not interfere with groove formation, and the films also became increasingly rigid when exposed to an aqueous environment.

Example 11

Release of bis-phosphonate from PLGA/amphipathic diblock 15 copolymer films.

Drug-loaded films were synthesized and cast as above but incorporated 5% w/w of alendronate (a bis-phosphonate), premixed with dichloromethane, before adding the dichloromethane to dissolve the PLGA (85/15) and amphipathic diblock
20 copolymer. 10 mg film samples including 5% (w/w) alendronate were placed in 16 ml test tubes and 15 ml of 10mM phosphate buffered saline (PBS, pH 7.4) was pipetted on top. The tubes were capped and incubated at 37°C with end over end rotation at 8 rpm. At various timepoints, the entire volume of buffer was removed and the concentration of alendronate present in the buffer was analysed by HPLC
25 (C18: 1 ml/minute flow of 1 mM Na₂EDTA;MeOH pH 6.5, fluorescamine derivitization and detection using fluorescence analysis).

Alendronate was released into the buffer in a linear manner (Figure 9). The addition of increasing amounts of amphipathic diblock copolymer in the PLGA film
30 caused a concentration dependent increase in the release rate of the drug from the films.

-35-

Example 12**Growth of osteoblasts on alendronate containing PLGA/diblock films.**

- 5 PLGA (85/15): 10% amphipathic diblock copolymer films containing 0.25% or 0.5% alendronate were synthesized and cast as described above. Osteoblast cells were cultured and seeded on the films as described above. Cells that adhered to the films were later imaged and counted with an epifluorescent microscope, following propidium iodide staining.
- 10 After 24 hours, cells adhered strongly to all films except those containing 0.5% Alendronate. Alendronate at 0.25 % greatly enhanced the adhesion of osteoblasts to the film after both 3 and 7 days incubation. After 7 days the apparent inhibitory effect of alendronate on cell growth was reversed (Figure 10).
- 15 At high concentrations, alendronate causes a temporary inhibition of osteoblast proliferation, but is not cytotoxic at these concentrations, as the cells recovered and demonstrated proliferation by 7 days. At lower concentrations the proliferation of osteoblasts was enhanced.
- 20 Inclusion of at least one bisphosphonate, for example alendronate, in the PLGA or PLGA/MePEG films offers another method of enhancing bone growth around treated teeth. The medicament may be incorporated and cast in the films. Such bisphosphonate-enhanced films provide a controlled release of the medicament (Figure 9). The localized release of alendronate from the film enhanced
- 25 proliferation of osteoblasts. Higher concentrations of alendronate appeared to initially suppress osteoblast proliferation, however proliferation was observed at later times (Figure 10). These results demonstrate that use of these alendronate-containing films are effective in enhancing osteoblast growth.
- 30 While specific embodiments of the invention have been described and illustrated, such embodiments should be considered illustrative of the invention only and not as limiting the invention as construed in accordance with the accompanying claims.

-36-

What is claimed is:

1. Use of a polymeric barrier composition comprising:
a polymer of lactic acid and glycolic acid;
5 an elasticizing agent; and,
a bone growth enhancing agent,
for the preparation of a medicament for the treatment of a surgical wound.
2. The use of claim 1 wherein said composition is capable of forming a film.
- 10 3. The use of claim 1 wherein said composition is a film.
4. The use of any one of claims 1 to 3 wherein said elasticizing agent is selected from the group consisting of MePEG, PEG, and an amphipathic diblock
15 copolymer.
5. The use of any of claims 1 to 4 wherein said elasticizing agent is present in a concentration from about 1% (w/w) to about 40% (w/w).
- 20 6. The use of any one of claims 1 to 5 wherein said bone growth enhancing agent is a bisphosphonate.
7. The use of claim 6 wherein said bisphosphonate is selected from the group consisting of alendronate, cimidronate, clodronate, tiludronate, etidronate,
25 ibandronate, neridronate, olpandronate, risedronate, piridronate, pamidronate and zoledronate.
8. The use of claim 7 wherein said bisphosphonate is alendronate.
- 30 9. The use of claims 8 or 9 wherein said bisphosphonate is present in a concentration from about 0.1% to about 5%.

-37-

10. The use of any of one of claims 1 to 5 wherein said bone growth enhancing agent is selected from the group consisting of hydroxyapatite, calcium pyrophosphate, calcium triphosphate and demineralised bone.
- 5 11. The use of claim 10 wherein said bone growth enhancing agent is hydroxyapatite.
12. The use of any of claims 1 to 11 wherein said bone growth enhancing agent is present in a concentration of about 20% to about 80%.
- 10 13. The use of claim 12 wherein said bone growth enhancing agent is present in a concentration of about 25%.
14. The use of claim 12 wherein said bone growth enhancing agent is present
- 15 15. The use of claim 12 wherein said bone growth enhancing agent is present in a concentration of about 50%.
16. The use of claim 12 wherein said bone growth enhancing agent is present in a concentration of about 75%.
- 20 16. The use of any of claims 1 to 15 wherein the ratio of lactic acid to glycolic acid in said polymer of lactic acid and glycolic acid is from about 50:50 (w/w) to about 95:5 (w/w).
17. The use of any of claims 1 to 15 wherein the ratio of lactic acid to glycolic
- 25 18. The use of any of claims 1 to 15 wherein the ratio of lactic acid to glycolic acid in said polymer of lactic acid and glycolic acid is about 50/50 (w/w).
19. The use of any of claims 1 to 15 wherein the ratio of lactic acid to glycolic acid in said polymer of lactic acid and glycolic acid is about 85/15 (w/w).
- 30 19. The use of any of claims 1 to 18 further comprising an antiproliferative agent.

-38-

20. The use of any of claims 1 to 19 further comprising an anti-inflammatory agent.
21. The use of claim 1 wherein said polymer of lactic acid and glycolic acid is PLGA, said elasticizing agent is MePEG and said bone growth enhancing agent is hydroxyapatite.
22. A polymeric barrier composition comprising:
a polymer of lactic acid and glycolic acid;
an elasticizing agent; and,
a bone growth enhancing agent.
23. The composition of claim 22 wherein said composition is capable of forming a film.
24. The composition of claim 22 wherein said composition is a film.
25. The composition of claim 22 wherein said elasticizing agent is selected from the group comprising MePEG, PEG and an amphipathic diblock copolymer.
26. The composition of any of claims 22 to 25 wherein said elasticizing agent is present in a concentration from about 1% (w/w) to about 40% (w/w).
27. The composition of any of claims 22 to 26 wherein said bone growth enhancing agent is a bisphosphonate.
28. The composition of claim 27 wherein said bisphosphonate is selected from the group consisting of alendronate, cimidronate, clodronate, tiludronate, etidronate, ibandronate, neridronate, olpandronate, risedronate, piridronate, pamidronate and zoledronate.
29. The composition of claim 28 wherein said bisphosphonate is alendronate.

-39-

30. The composition of any of claims 27 or 28 or 29 wherein said bisphosphonate is present in a concentration from about 0.1% to about 5%.

5 31. The composition of claim 22 to 26 wherein said bone growth enhancing agent is selected from the group consisting of hydroxyapatite, calcium pyrophosphate, calcium triphosphate and demineralised bone.

32. The composition of claim 31 wherein said bone growth enhancing agent is hydroxyapatite.

10

33. The composition of any of claims 11 to 32 wherein said bone growth enhancing agent is present in a concentration of about 20% to about 80%.

15

34. The composition of claim 33 wherein said bone growth enhancing agent is present in a concentration of about 25%.

35. The composition of claim 33 wherein said bone growth enhancing agent is present in a concentration of about 50%.

20

36. The composition of claim 33 wherein said bone growth enhancing agent is present in a concentration of about 75%.

25

37. The composition of any of claims 22 to 36 wherein the ratio of lactic acid to glycolic acid in said polymer of lactic acid and glycolic acid is from about 50:50 (w/w) to about 95:5 (w/w).

38. The composition of any of claims 22 to 36 wherein the ratio of lactic acid to glycolic acid in said polymer of lactic acid and glycolic acid is about 50:50 (w/w).

30

39. The composition of any of claims 22 to 36 wherein the ratio of lactic acid to glycolic acid in said polymer of lactic acid and glycolic acid is about 85:15 (w/w).

-40-

40. The composition of any of claims 22 to 39 further comprising an antiproliferative agent.

5 41. The composition of any of claims 22 to 40 further comprising an anti-inflammatory agent.

42. The composition of claim 22 wherein the polymer of lactic acid and glycolic acid is PLGA, the elasticizing agent is MePEG and the bone growth enhancing agent is hydroxyapatite.

10

43. A method of preparing a polymer film, the method comprising:
combining a polymer of lactic acid and glycolic acid with an elasticizing agent and a bone growth enhancing agent in an organic solvent, to form a solution or suspension;

15

casting said solution or suspension on a form or mould; and,
evaporating said organic solvent, causing a polymer film to remain on said form or mould.

20

44. A kit for preparing a polymer film, the kit comprising:
a polymer of lactic acid and glycolic acid;
an elasticizing agent;
a bone growth enhancing agent; and,
instructions for preparing said polymer film.

25

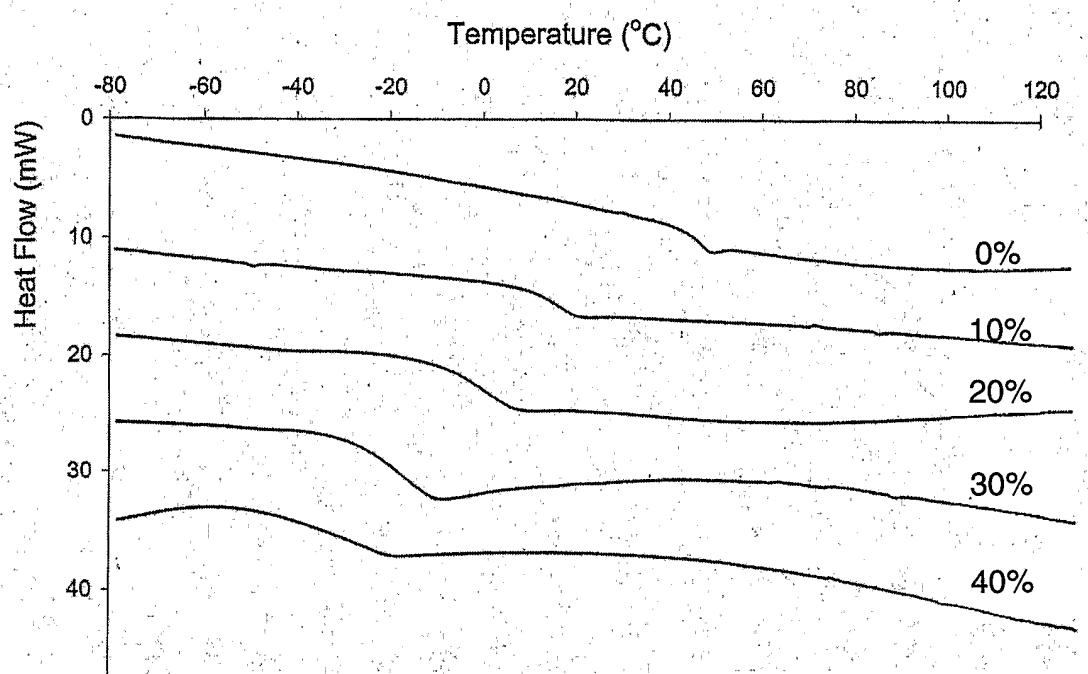
45. A method for the treatment of a surgical wound comprising: administering a polymeric barrier composition to a patient in need thereof, wherein the polymeric barrier composition comprises:

30

a polymer of lactic acid and glycolic acid;
an elasticizing agent; and,
a bone growth enhancing agent.

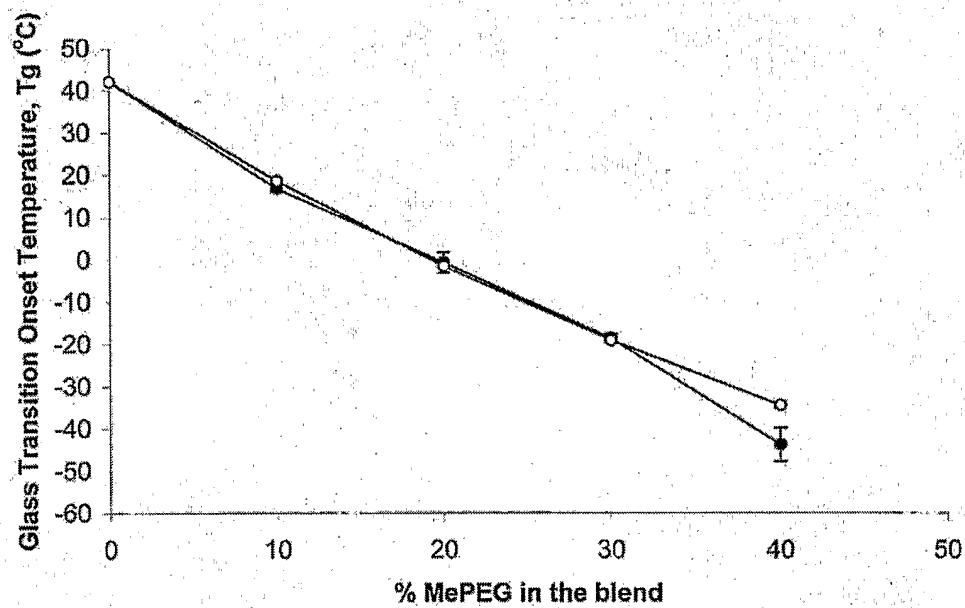
1/10

Figure 1



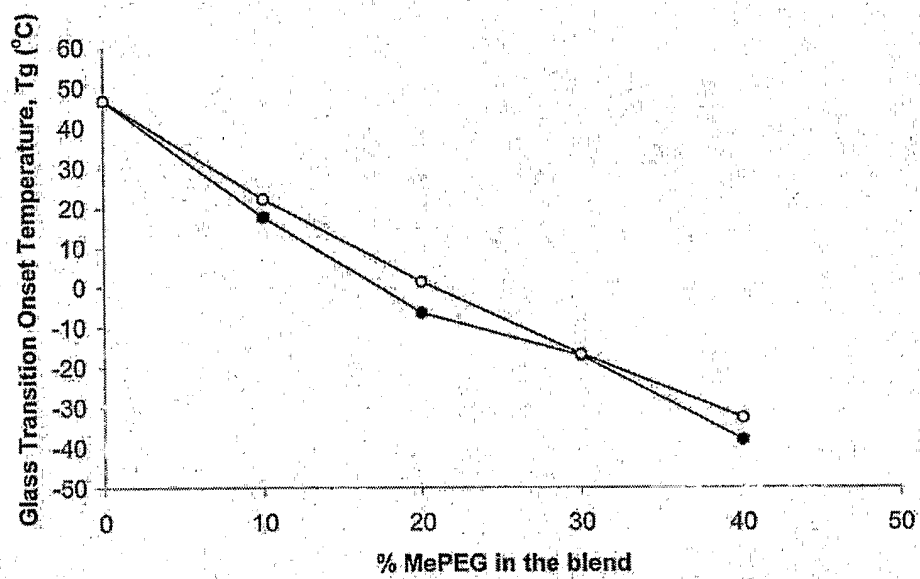
2/10

Figure 2



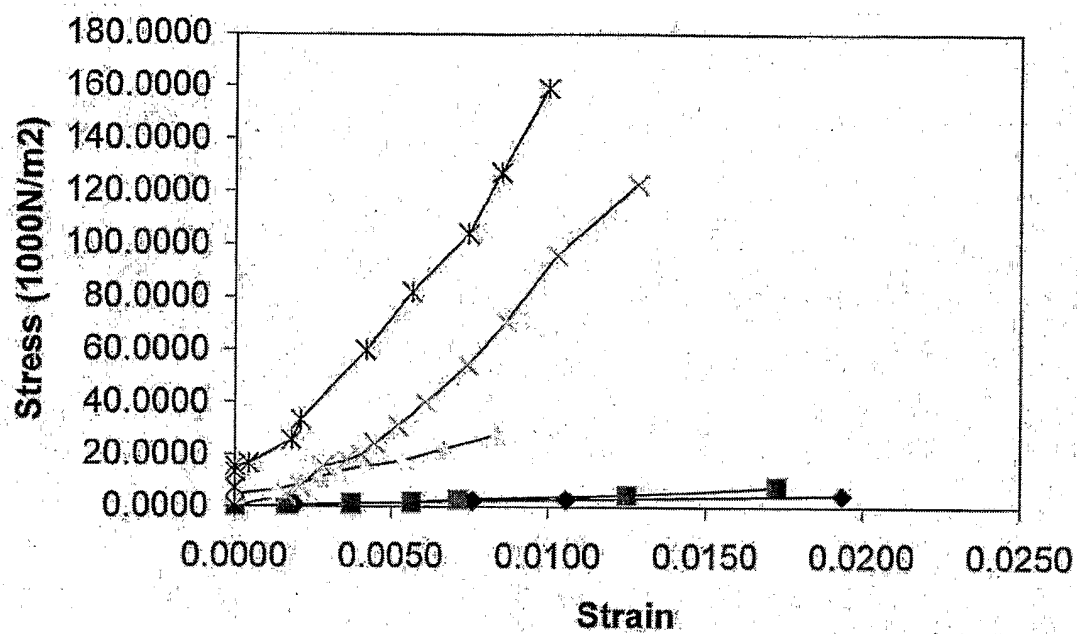
3/10

Figure 3



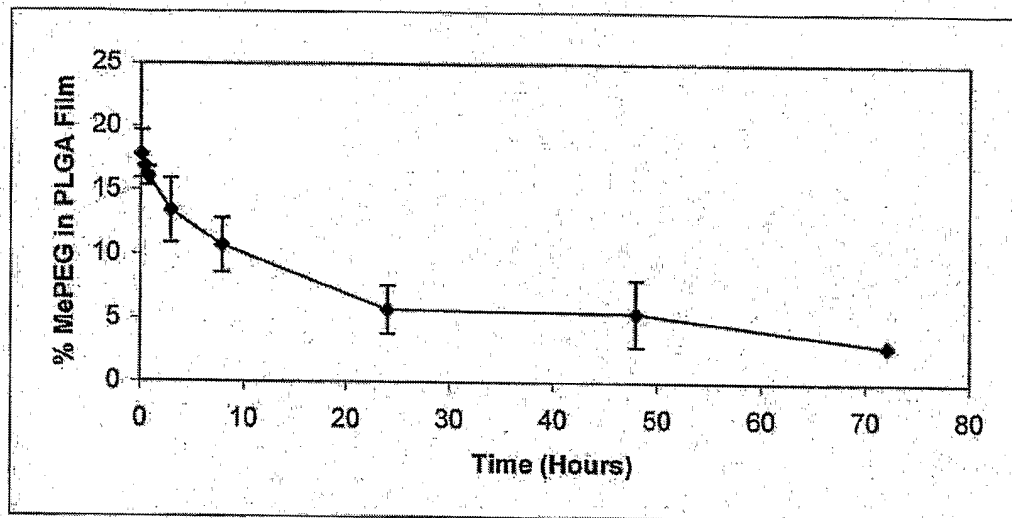
4/10

Figure 4



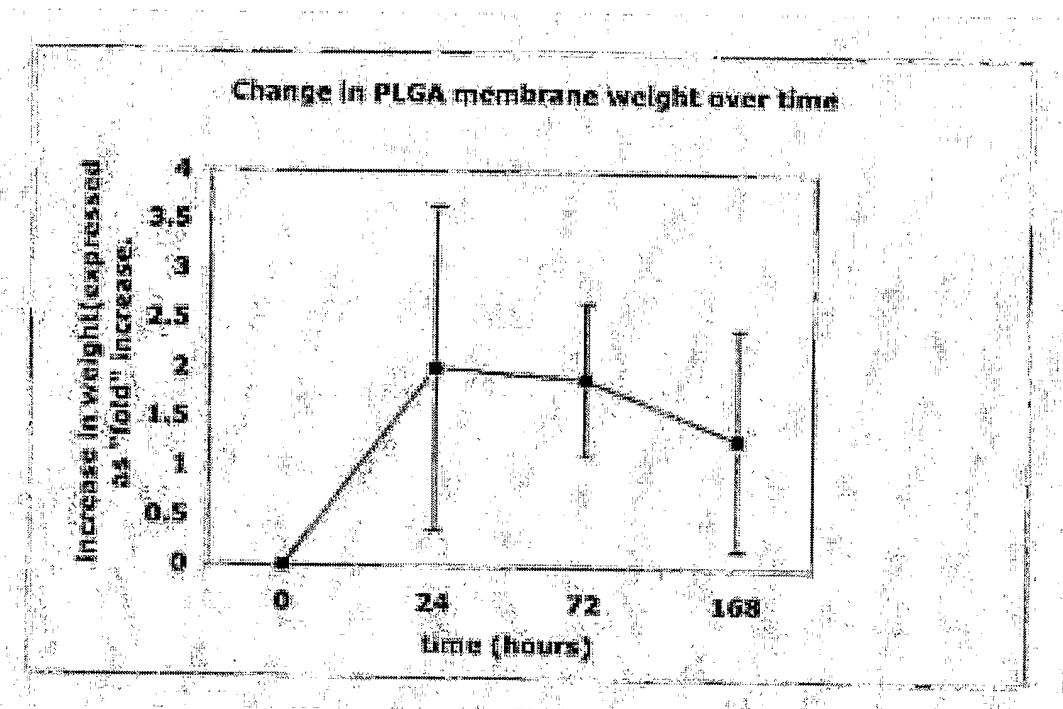
5/10

Figure 5



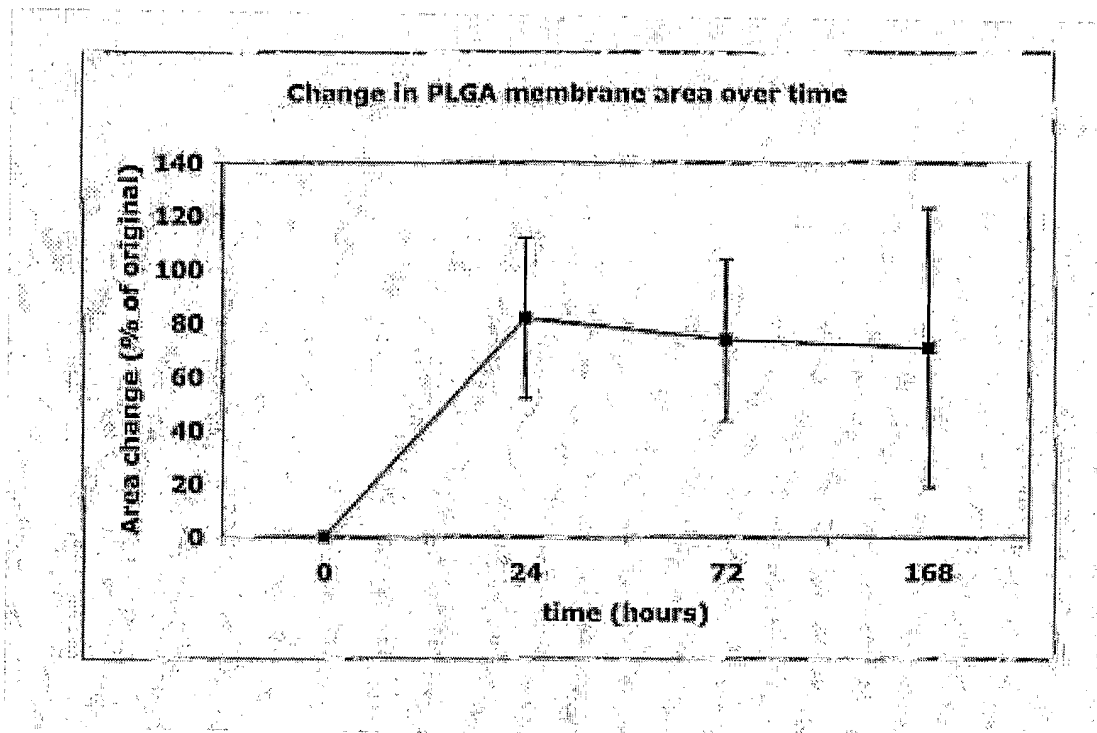
6/10

Figure 6



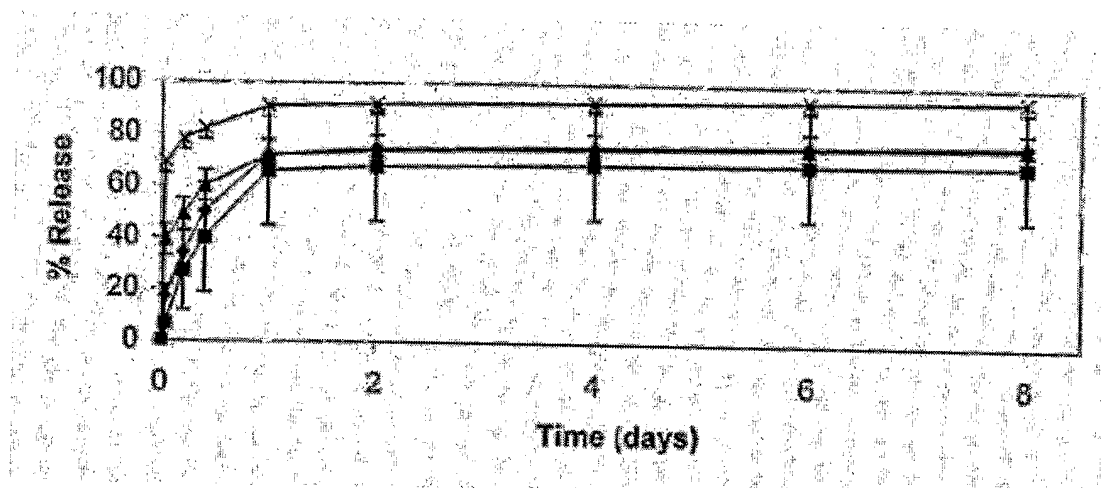
7/10

Figure 7



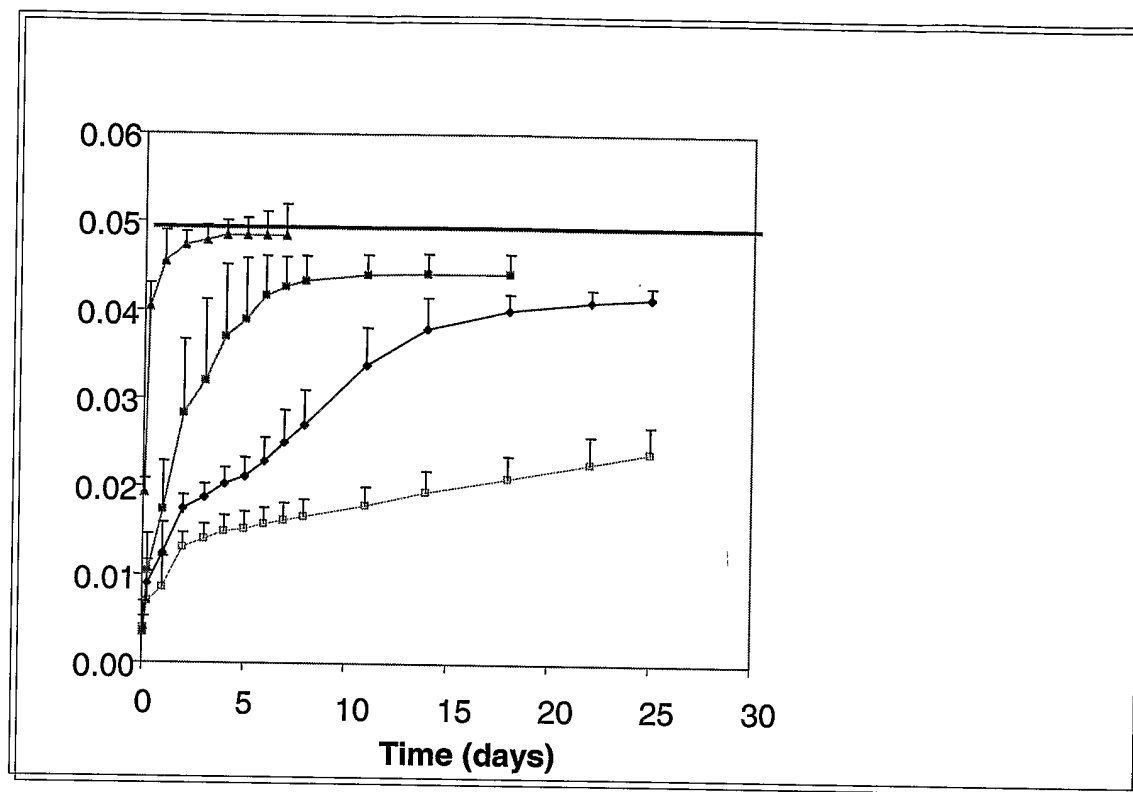
8/10

Figure 8



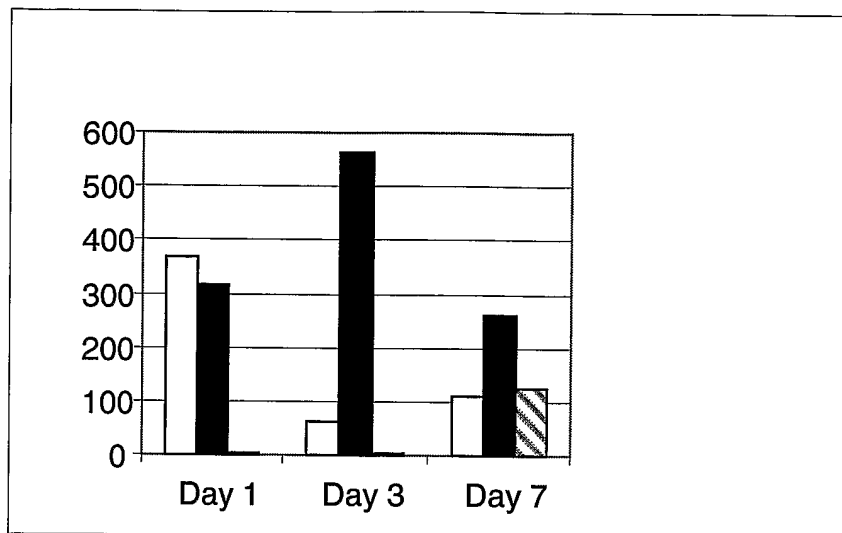
9/10

Figure 9



10/10

Figure 10



INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2005/001631

A. CLASSIFICATION OF SUBJECT MATTER IPC: A61L 31/06 (2006.01), A61L 31/04 (2006.01), A61L 31/14 (2006.01)		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC(7): A61L		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used) Scopus, NCBI/PubMed, Delphion, Canadian Patent Database, USPTO		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<i>International Journal of Pharmaceutics</i> , vol. 283, 2004, pp. 97-109 (JACKSON ET AL.) *cited in the application* • see the entire document	1-45
Y	<i>Journal of Cranio-Maxillofacial Surgery</i> , vol. 28, 2000, pp. 294-299 (MIKI ET AL.) • see the entire document	1-45
Y	<i>Materials Research Society Symposium-Proceedings</i> , vol. 550, 1999, pp.155-160 (MARRA ET AL.) • see the entire document	1-45
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "I" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed		"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family
Date of the actual completion of the international search 24 November 2005 (24-11-2005)		Date of mailing of the international search report 8 February 2006 (08-02-2006)
Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001(819)953-2476		Authorized officer Ryan Jaecques (819) 953-6570

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2005/0001631

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP 1 163 135 A2 (TAKAI CHEMICAL COMPANY LTD.) 27 June 1989 • see abstract	22-26, 31-39, 43 and 44

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2005/001631

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons :

1. ☒ Claim Nos. : 45

because they relate to subject matter not required to be searched by this Authority, namely :

Claim 45 relates to a method of medical treatment of the human body as defined under Rule 39.1(iv) PCT. The search has thus been carried out based on the alleged effects of the composition when used in the treatment of surgical wounds.

2. ☐ Claim Nos. :

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically :

3. ☐ Claim Nos. :

because they are dependant claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows :

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos. :

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos. :

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/CA2005/0001631

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
JP01163135A2	27-06-1989	JP05037967B4	07-06-1993