(54) Title: METHODS AND DEVICES FOR OCLKING MYOCARDIAL HOLES

(57) Abstract: A biodegradable heart muscle implant is disclosed for use in plugging perforations made in a heart muscle to stimulate revascularization of damaged heart muscle regions or tissue sites. The heart muscle implants can be used directly to perforate the heart. A suturing material is also disclosed for use in heart muscle to promote or stimulate revascularization of damaged heart muscle regions or tissue. The implants and the suture materials all include impermeable portion(s) that are designed to be associated with the surface of the heart muscle and extend into the heart muscle a distance sufficient to reduce or eliminate fluid flow from the interior of the muscle. The portions that reside in the interior of the heart muscle are designed to be permeable to fluid flow and cell permeation and to act as a scaffold for revascularization of damaged heart muscle tissue.

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PATENT SPECIFICATION

TITLE: METHODS AND DEVICES FOR OCCLUDING MYOCARDIAL HOLES

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to bio-compatible plugs, implants or compositions designed to be inserted into perforations made during heart perforation surgery or percutaneous procedures and methods for making and using same.

More particularly, this invention relates to plugs, implants or compositions made of permeable, variably permeable, semi-permeable or impermeable bio-compatible materials, or combinations or mixtures thereof designed to be inserted into perforations made during heart perforation surgery to reduce or prevent fluid flow into the pericardial sac and the symptoms associated with tamponade and methods for making and using same. Such compositions, fillers, implants, cell carriers or tissue carriers can also be used to introduce pharmacologic or genetic agents into the heart muscle at any time.

2. Description of the Related Art

Heart perforation procedures have become accepted and established surgical procedures in the arsenal to treat heart disease and other cardiac ailments. However, one recently identified risk associated with this procedure is the possibility of perforating through the heart wall into the pericardial sac, resulting in tamponade. Additionally, such compositions can be used to introduce pharmacologic or genetic agents into the heart muscle at any time.

Biodegradable polymers are used in medicine as sutures and pins for fracture fixation. These materials are well suited to implantation as they can serve as a temporary scaffold to be replaced by host tissue, degrade by hydrolysis to non-toxic products, and be excreted, as described by Kulkarni, et al., J. Biomedical Materials Research, 5, 169-81 (1971); Hollinger, J. O. and G. C. Battistone, "Biodegradable

Four polymers widely used in medical applications are poly(paradoxanone) (PDS), poly(dl-lactic acid) (PLA), poly(dl-glycolic acid) (PGA), and copolymers of dl-lactic acid and dl-glycolic acid (PLG). Copolymerization enables modulation of the degradation time of the material. By changing the ratios of crystalline to amorphous polymers during polymerization, properties of the resulting material can be altered to suit the needs of the application. For example, PLA is crystalline and a higher PLA content in a PLG copolymer results in a longer degradation time, a characteristic that may be desirable where structural support for an extended period of time. Conversely, a short degradation time may be desirable if ingrowth of new tissue occurs quickly and new cells need space to proliferate within the implant.

Several patents have dealt with synthetic implants for use in reconstruction, repair and/or regeneration of tissues and/or organs and especially skeletal tissue including the following United States Patents.

U.S. Patent No. 5,631,015 discloses a sustained release parenteral composition comprising an admixture of at least one drug to be delivered in a therapeutically effective amount and a bioabsorbable polymer containing one or more lactone monomers that is a liquid at body temperature, provided in an amount effective to sustain or extend the release rate of the drug.

U.S. Patent No. 5,626,861 discloses a method for making a biodegradable composition involving mixing hydroxyapatite particles with a non-aqueous solution of a biodegradable, biocompatible polymer solvent; suspending particles of an inert water-leachable material in the solution, provided that the material is not soluble in the solution; removing the solvent; and removing the inert leachable material to yield a composite having pores.

U.S. Patent No. 5,516,532 discloses a demineralized ground bone or cartilage matrix where the phosphate content can be further reduced by treatment of the matrix with acid phosphatase, which removes residual organic phosphate. The material is
useful in a method of treatment of vesicoureteral reflux and other disorders where a bulking agent is effective in correcting the defect.

U.S. Patent No. 5,492,697 discloses a biodegradable implant for placement in nonunion bone fractures. The implant is a flat plate or disk having a thickness of between about 1 mm and about 15% of the length of the bone, interconnected micropores, and canals substantially equivalent in size and spacing to the naturally occurring Haversian canals and is incorporated herein by reference. The implant is formed from biodegradable polymers such as polylactic acid-polyglycolic acid copolymer by a gel casting technique followed by solvent extraction to precipitate the implant as a microporous solid.

U.S. Patent No. 5,366,756 discloses a porous bioabsorable surgical implant material prepared by coating particles of bioasorbable polymer with a tissue ingrowth promoter.

U.S. Patent No. 5,344,654 discloses a prosthetic device comprising a prosthesis coated with substantially pure osteogenic protein, which can be contained in a biocompatible polymer and is incorporated herein by reference.

U.S. Patent No. 5,324,519 discloses a composition comprising a liquid formulation of a biodegradable, bioerodible, biocompatible thermoplastic polymer that is insoluble in aqueous or body fluid, and a biocompatible organic solvent that is miscible or dispersible in aqueous or body fluid and dissolves the thermoplastic polymer.

U.S. Patent No. 5,286,763 discloses bioerodible polymers that degrade completely into nontoxic residues over a clinically useful period of time, including polyanhydrides, polyorthoesters, polyglycolic acid, polylactic acid and copolymers thereof, are used for the delivery of bioactive agents directly into bone and is incorporated herein by reference.

U.S. Patent Nos. 5,162,114, 5,171,574 and 4,975,526 discloses a matrix material comprising biocompatible mineral-free type I collagen, xenogenic to the host and biodegradable there within and is incorporated herein by reference.
Although these patents relate generally to various tissue scaffolds, biocompatible fillers and implants, there is a need in the art for new compositions, fillers, implants, cell carriers or tissue carriers that are adapted to simple and straightforward endovascular or open heart surgical methods to prevent or stop bleeding into the pericardial sac resulting in tamponade.
SUMMARY OF THE INVENTION

The present invention provides compositions, fillers, implants, cell carriers or tissue carriers for use in partially or completely filling or plugging holes made in the myocardium (heart muscle) during heart perforation surgery. The implants include bio-compatible compositions comprising a bio-compatible, biodegradable matrix such as a matrix composed of a protein, polymer, or combinations or mixture thereof. The compositions can also include therapeutic agents. The agents can be homogeneously or heterogeneous distributed within the matrix, encapsulated by the matrix or bonded to or on the surface(s) of the matrix. The implants can be impermeable, semi-permeable, variably permeable or highly permeable to bodily fluids, intracellular components such as proteins, platelets, or other intercellular constituents or cells or can include regions that are of different permeabilities to different classes of bodily constituents. The implants can also be non-porous, variably porous or highly porous.

The present invention also provides a filament to be used in conjunction with heart perforation surgical procedures, wherein the filament comprises a bio-compatible, biodegradable matrix such as a matrix composed of a protein, polymer, or combinations or mixture thereof. The compositions can also include therapeutic agents. The agents can be homogeneously or heterogeneous distributed within the matrix, encapsulated by the carrier or bonded to or on the surface(s) of the matrix. The filament can be impermeable, semi-permeable, or highly permeable to bodily fluids, intracellular components such as proteins, platelets, or other intercellular constituents or cells or can include regions that are of different permeabilities to different class of bodily constituents. The filament can also be non-porous, variably porous or highly porous.

The present invention also relates to a method for preventing bleeding in the pericardial sac during and after heart perforation surgery including the steps of endovascularly making a plurality of holes in the heart muscle. Once the holes are made, partially or completely filling each hole endovascularly with a composition,
filler, implant, cell carrier or tissue carrier of the present invention or a length of a filament of the present invention. The composition, filler, implant or filament can extend the entire length of the hole or any desired portion thereof.

The present invention also relates to a method of making the filaments of the present invention including extruding a composition of the present invention through a die to form a mono-filament construct.

The present invention also relates to a method for making filaments of the present invention including spinning a solution or melt of the implantable compositions of the present invention to form a multi-filament implantable string or yarn.

The present invention also provides a catheter end apparatus for delivering a length of a filament of the present invention into a hole made in the myocardium during heart perforation procedures.

The present invention provides compositions, fillers, implants or filaments including substantially impermeable regions and/or permeable regions where the implants are designed to reduce bodily fluid flow such as bleeding from a site of injury or surgery into surrounding tissues, tissues regions, organs or organ regions. The implants are preferably composed of bio-compatible polymers and especially of bio-compatible and bio-degradable polymers.

The present invention also provides methods for making compositions, fillers, implants or filaments having variable and/or differential permeability and/or variable and/or differential porosity including dispersing in a polymer matrix, or mixed matrix having a first density, at least one pore-forming agent having a second density and being insoluble in the matrix. The dispersing of the agents in the matrix is preferentially carried out under controlled conditions where the controlled conditions include air-flow and optionally temperature, pressure, gas composition and/or humidity. The dispersing is also preferably carried out using an agitation procedure that increases the porosity of the material after extraction of the pore-forming agent(s).

During or after the dispersing step, the agents are allowed to anisotropically
distribute throughout the polymer matrix or portions thereof due to the action of an external force such as gravity in excess of the normal gravitational force or for a very long time so that the normal gravitational force will have sufficient time to create a gradient in the material greater than the gradient formed by the normal gravitational force acting only for a short time. This anisotropic distribution results in formation of a portion of the composition that has reduced permeability to bodily fluids, intracellular constituents or cells compared to the remainder of the composition. Force development (anisotropic distributions of particles in the polymer matrix caused by the application of an external applied force) is preferably continued, generally with agitation, until a portion of the composition is substantially impermeable and/or non-porous. The resulting composition is then contacted with a leaching agent that leaches (dissolves) the particles from the matrix leaving voids in matrix to form a composition with homogeneous, variable and/or differential permeability and/or porosity.

This invention also provides methods for coating, adhering or affixing to at least one portion of a surface of an implant composed of a composition having a first permeability and/or porosity, a material having a homogeneous, different permeability and/or porosity to form composite implants having simple or complex differential permeabilities and/or porosities. It is preferred that the second composition be substantially impermeable to bodily fluids.

Using these techniques, implants can be made that have complex arrays of permeabilities, either static or variable, within regions of or throughout the entire implant, to bodily fluids in general or to constituents of bodily fluids or tissues. Thus, one part of the implant could allow permeation by small molecular constituents of bodily fluids or tissues, while other parts or regions could allow permeation by all constituents of bodily fluids or tissues. Of course, the implants can be designed so that disjoint (distinct) classes of constituents are allowed to migrate through different channels in the implant.

The implants of this invention can be used to prevent tamponade as well as preventing and/or treating vascular structures that may require occlusion.
DESCRIPTION OF THE DRAWINGS

The invention can be better understood with reference to the following detailed description together with the appended illustrative drawings in which like elements are numbered the same:

Figure 1 is a cross-sectional view of a first embodiment of an implant prepared from a composition of the present invention having a single force induced variation in permeability and/or porosity;

Figure 2 is a cross-sectional view of a second embodiment of an implant prepared from a composition of the present invention having a double force induced variation in permeability and/or porosity;

Figure 3 is a cross-sectional view of another embodiment of an implant prepared from a composition of the present invention having a double force induced variation in permeability and/or porosity using two different sized pore-forming agents;

Figure 4 is a cross-sectional view of a preferred embodiment of a composite implant of the present invention prepared from a highly porous and/or permeable composition having associated with one surface an impermeable or non-porous layer;

Figure 5 is a cross-sectional view of another preferred embodiment of a composite implant of the present invention prepared from a highly porous and/or permeable composition having different pores sizes and having associated with certain surfaces thereof an impermeable or non-porous layer;

Figure 6A is a cross-sectional view of another preferred embodiment of a composite implant of the present invention prepared from a highly porous and/or permeable composition sandwiched between two single force induced variable permeable and/or porous compositions of the present invention having associated with one surface thereof an impermeable or non-porous layer;

Figure 6B is a cross-sectional view of another preferred embodiment of a composite implant of the present invention prepared from a single force induced variable permeable and/or porous composition of the present invention sandwiched
between two highly porous and/or permeable compositions and having associated with one surface thereof an impermeable or non-porous layer;

Figure 7A is a cross-sectional view of one embodiment of a two layer or component cardioplug of the present invention;

Figure 7B is a cross-sectional view of another embodiment of a two layer or component cardioplug of the present invention;

Figure 7C is a cross-sectional view of another embodiment of a two layer or component cardioplug of the present invention;

Figure 8A is a cross-sectional view of one embodiment of a three layer or component cardioplug of the present invention;

Figure 8B is a cross-sectional view of another embodiment of a three layer or component cardioplug of the present invention;

Figure 8C is a cross-sectional view of another embodiment of a three layer or component cardioplug of the present invention;

Figure 9A is a cross-sectional view of one embodiment of a three layer or component cardioplug of the present invention having a tip;

Figure 9B is a cross-sectional view of another embodiment of a three layer or component cardioplug of the present invention having a tip and barbs on the distal layer or component;

Figure 9C is a cross-sectional view of another embodiment of a three layer or component cardioplug of the present invention having a tip and barbs on all layers or components;

Figure 9D is a cross-sectional view of another embodiment of a three layer or component cardioplug of the present invention having a tip and enlarged distal and middle components;

Figure 9E is a cross-sectional view of an embodiment of a four layer or component cardioplug of the present invention having a tip and a plurality of anchoring skirts and having a christmas tree shape;

Figure 9F is a cross-sectional view of another embodiment of a four layer or
component cardioplug of the present invention having a tip and a plurality of anchoring skirts and having a reverse taper as compared to the implant of Figure 9E;

Figure 10A is a cross-sectional view of another embodiment of a cardiosuture material of the present invention;

Figure 10B is a cross-sectional view of a heart muscle section with the cardiosuture material of Figure 10A stitched therein;

Figures 11A and B depict a cardioplug of Figures 8A-C being positioned and inserted into a heart muscle perforation endovascularly; and

Figures 12A and B depict a cardioplug of Figures 9A-F being positioned inserted directly into a heart muscle endovascularly.

**DEFINITIONS**

The term animal means any organism that is a member of the animal kingdom including, without limitation, mammals including humans.

The term gradient means a change in some property over a given cross-section of a composition or article. The property can be, without limitation, the concentration of one or more compounds, physical structures, compositional make-up, permeability, porosity, or any other property of a composition or a structure. A gradient can vary smoothly, can include one or more peaks, and/or can vary continuously, discretely or discontinuously across a given cross-section. A gradient peaks when the property has relative maxima in specific regions of the composition or structure across some cross-section.

**DETAILED DESCRIPTION OF THE INVENTION**

The inventors have found that bleeding into the pericardial sac during and after heart perforation surgery can be reduced or eliminated using an implant or plug that is inserted into each hole created in the heart muscle during surgery. The compositions can be any composition known in the art provided it is compatible with the heart muscle and is capable of reducing or eliminating the flow of bodily fluids and blood from a perforation into the pericardial sac thereby reducing or eliminating a tamponade effect.
As one embodiment of this invention, prefabricated scaffolds can allow closure of transmural holes that result in tamponade, a life threatening complication of creating holes in the myocardium. There are already technologies being developed for generating holes in the myocardium by means including needles, lasers, therapeutic ultrasound, chemical and other mechanical means. These holes are developed to stimulated new blood vessel growth, and/or as a route to deliver biologic agents into the myocardium. None of these embodiments being developed include a technique to plug these holes to achieve hemostasis or to treat tamponade as a potential complication.

The inventors have demonstrated that new implants can be prepared that have homogenous, variable and/or differential permeability and/or porosity. The implants can have permeabilities to bodily fluids in general or to constituents of bodily fluids or tissues where the permeabilities are constant or vary across a desired profile of the implant or throughout the entire implant. Generally, when the term bodily fluid(s) is used in this application without further qualification, the inventors intend the term to cover any bodily fluid such as blood, plasma, mucous, or the like and/or intracellular components such as proteins, platelets, or other intercellular constituents or cells or other constituents of bodily fluids, cells or tissues.

Moreover, the implants can have porosities that also are constant or vary across a desired profile of the implant or throughout the entire implant. Implant permeability (or permeabilities to desired constituents of bodily fluids in general or to constituents of bodily fluids or tissues) can range from essentially or substantially impermeable to highly permeable to bodily fluids in general or to desired constituents of bodily fluids or tissues.

Preferably, the implants of the present invention have a surface or region of the implant that is substantially impermeable to bodily fluids so that blood flow from the injury into surrounding tissues is restricted or substantially prevented. Of course, when using bio-degradable polymer matrices, the impermeable surfaces or regions of the implant will become permeable to bodily fluids. But, by judicious selection of the
polymer matrix, the impermeable surfaces or regions can be designed to remain substantially impermeable to blood flow for a sufficient time to allow blood flow to arrest via normal processes.

The implants can also be constructed to have different regions where each region has a different permeability or permeabilities that can vary across a profile of the region where the variation in permeabilities can range from essentially or substantially impermeable to highly permeable to the same or different class of constituents of bodily fluids in general or to constituents of bodily fluids or tissues. Of course, very complex composite structures can also be prepared having very complex permeability and/or porosity characteristics. Thus, implants of this invention can be prepared where different portions, parts, sub-structures, surfaces, regions or combinations thereof have different static or variable permeations to bodily fluids in general or to constituents of bodily fluids or tissues so that the implant can direct different constituents into and out of different channels or diffusion pathways in the implant. For example, implants can be designed to channel cellular species preferentially, if not exclusively, to a first outlet via a first migration pathway in the implant and channel molecular species not only to the first outlet, but to other outlets through other migration pathways in the implant.

Moreover, the compositions of this invention can be formed not only with variable permeability and/or porosity as to a concentration of pores or void regions having one given size and/or shape, but also with variable permeability and/or porosity as to concentrations of pore sizes and/or pore shapes as well. Of course, these implants or at least the surfaces thereof should preferably be biocompatible with a target tissue site. In certain circumstances, it is also preferred that the polymeric components of the compositions be bioerodible or biodegradable as well.

The term implant includes all types of constructs for use in and/or on a living organism such as an human being. Implants, therefore, include, without limitation, tissue scaffolds, bone implants, cartilage implants, implantable drug or medication delivery systems, artificial skin, skin grafts, myocardial plugs, myocardial scaffolds,
or other attachable or implantable constructs designed to facilitate tissue or organ regeneration, repair, reconstruction, and/or growth.

The implants or the compositions from which the implants derive can be made by dispersing one or more (at least one) leachable pore-forming agent in a polymer composition, generally a polymer melt or solution, to form a polymer matrix having the particles dispersed therein. Preferably, the agents have a density or densities different from the density of the polymer composition or the resulting polymer matrix. Preferably, the agents are particles that are substantially insoluble and non-decomposable in the starting polymer composition and in the final polymer matrix. However, the pore-forming agents can also be extractable/leachable polymers that can be either soluble or insoluble in the starting or final polymer matrix.

Because the polymer composition, into which the agents are dispersed, can be a solution or a melt, the density of the polymer matrix can change somewhat during preparation. Therefore, it is preferable that the density(ies) of the agent(s) be different from the starting polymer composition and the final polymer matrix. The difference in density is what allows force-developed anisotropic distributions of the agents in the polymer matrix during matrix preparation.

The step of dispersing is effectuated preferably by mechanical or sonic agitation or other similar agitation technologies. Of course, other mixing technologies can also be used in conjunction with mechanical and/or sonic agitation. The agitation is preferably carried out under controlled conditions where the conditions to be controlled include air-flow over the surface of the mold containing the composition and optionally temperature, pressure, gas composition and/or humidity. Of course, the agitation can be carried out in a closed atmosphere where control of air flow would not be as critical. Agitation is generally continued for a time sufficient for the solid particles to be distributed in the polymeric matrix to a desired degree of dispersion.

Agitation, unlike conventional mixing, causes the particles to oscillate at a frequency corresponding to a frequency of the agitation. The oscillation will also have an amplitude and direction corresponding to an amplitude and direction of the
agitation. This oscillation of the particles generally causes formation of a larger void volume than a volume of the particle itself, which is the minimum void volume that will be left behind after particle extraction. Depending on the frequency, direction and amplitude of agitation, the voids left behind after particle extraction can be substantially spherical or non-spherical (elongate, rod-like, tube-like, irregular shaped, ellipsoidal, or the like).

If the composition is subjected to an external force other than agitation, then a variation in the distribution of particles throughout the composition can be achieved. The external force can be static or variable and can be applied before, during, intermittently and/or after agitation. The difference in density is what allows force developed anisotropic distributions of the particles in the polymer matrix to be achieved. Of course, gravity is always acting on the composition during its preparation and a small particle gradient induced by gravity may result during any formation procedure. However, using the present methods, the gradients in particle concentrations can be facilitated by either inducing a greater gravitational force, allowing normal gravity to act for a long period of time without mixing type agitation or allowing other applied forces such as centripetal force.

The gradient in porosity, permeability and/or pores in the composition can be abrupt, peaked or smooth depending on the nature of implant desired. Implants with abrupt changes in pore volume include implants having an impermeable layer and a permeable layer, a non-porous layer and a porous layer or a non-porous, impermeable layer and a porous, permeable layer or combinations and mixtures thereof. Note that the permeability and porosity are different properties that can be varied dependently or independently. Implants with smoothly varying or changing permeability and/or porosity include compositions where: (a) the permeability changes from substantially impermeable to substantially permeable to a given bodily fluid in general or to constituents of bodily fluids or tissues including cells over a given cross-sectional profile of the composition; (b) the porosity changes from substantially non-porous to substantially porous over a given cross-sectional profile of the composition; or (c) the
porosity and permeability change over a given cross-sectional profile of the composition. Compositions can also be prepared having permeabilities and porosities that vary in such a way that across a given cross-sectional profile the permeability and/or porosity include regions with reduced permeability and/or porosity and regions with enhanced permeability and/or porosity where the peaking is caused by periodic application of an external force using centrifugation or spinning.

Moreover, the compositions can be subjected to a combination of forces so that variations in two or more dimensions can be induced in the compositions. Thus, the composition can be placed in a cylindrical mold so that the mold can be spun to achieve a radial anisotropic distribution of the particles at the same time as gravity is causing or inducing an anisotropic distribution of particles in an axial direction.

Once the desired degree of dispersion is obtained, agitation can be stopped and the composition allowed to stand so that gravity and/or (an)other applied force(s) can act on the composition to affect a segregation or variation in the concentration of the solid particles in the final polymeric matrix. For example, the mold containing the composition could be subjected to centripetal force by spinning the mold in a centrifuge or other similar device. Centripetal force will cause a radial anisotropic distribution of the particles dispersed in the matrix. The degree of anisotropy will depend on the magnitude of the centripetal force and on a period of time that the applied force acts on the composition. Other factors that control the degree and rate of segregation or anisotropic distribution of the particles are the viscosity of the polymer matrix, the temperature of the polymer matrix, the size and shape of the particles, or the like.

Of course, if a solvent(s) is (are) used to make a polymer solution, then during agitation and subsequent segregation or force development, a certain amount of solvent will be removed from the polymer composition. However, to ensure more complete removal of solvent, the compositions are generally subjected to a reduced pressure environment with or without heating for a time sufficient to ensure substantial removal of solvent. Additionally, the temperature can be held constant, then ramped to a new
temperature and held, with or without the composition being subjected to a reduced pressure environment.

Once a desired degree of segregation or variation in the concentration of particles in the protein and/or polymer matrix has been achieved, and if necessary a desired degree of solvent removal has been achieved, then the composition is contacted with a leaching reagent that removes the particles from the polymer matrix leaving voids or pores therein to form a composition having variable permeability and/or porosity. The resulting composition will have a variation in the concentration of pores substantially identical to the variation in the concentration of the particles, provided the leaching agent does not adversely effect the polymer matrix by causing voids to collapse or otherwise change shape.

After leaching, the matrix is dried for a sufficient amount of time to remove any leaching medium that may be occupying the pores. Preferably, the matrix is air-dried for a time sufficient to result in a desired dryness, generally between about 8 and 48 hours and preferably for about twenty-four hours. Optionally, the matrix can then be vacuum-dried for a time sufficient to result in a given state of dryness, generally between about 8 and 72 hours and preferably for about forty-eight hours. Additionally, the composition can be subjected to heating during the drying or solvent removal process.

Additionally, the compositions of the present invention can be subjected to post-formation (after preparation and leaching) cross-linking reactions such as chemical, oxidative processing or radiation curing. Preferably, the cross-linking forms biodegradable cross-links such as cross-linking with a biodegradable polyl or a polyacid.

The compositions, fillers, implants, cell carriers or tissue carriers of the present invention are prepared using either biodegradable or bioerodible materials, meaning that the composition substantially or completely dissolves over a period of time when exposed to aqueous environments including biological fluids found in animal or human bodies. During the time in which the composition, filler, implant, cell carrier or tissue
carrier dissolve, growing tissue can permeate the composition, filler, implant, cell carrier or tissue carrier through pores in the composition thereby providing a scaffold into which rapid tissue regeneration can occur. The compositions, fillers, implants, cell carriers or tissue carriers are particularly well suited for use in damaged or diseased tissue areas to promote repair or regeneration. Because the compositions, fillers, implants, cell carriers or tissue carriers are preferably biodegradable, the carriers or implants provide interim support to the injured or damaged tissue site.

**Proteins, Polymers and Polymeric Compositions**

Suitable polymers for use in the present invention include, without limitation, proteins and/or biocompatible polymers that are preferably bioerodible by normal erosion activities within the body and/or biodegradable by normal degradation activities in the body or by action of a specific degrading reagent in and/or within the compositions or injected into the compositions. Such polymeric substances include polyesters, polyamides, polypeptides and/or polysaccharides or the like.

Non-limiting examples of suitable biocompatible, biodegradable polymers, include polylactides, polyglycolides, polycaprolactones, polyanhydrides, polyamides, polyurethanes, polyetheramides, polyorthoesters, polydioxanones, polycetals, polyketals, polycarbonates, polyorthocarbonates, polyphosphazenes, polyhydroxybutyrates, polyhydroxvvalerates, polyalkylene oxalates, polyalkylene succinates, poly(malic acid), poly(amine acids), poly(methyl vinyl ether), poly(maleic anhydride), chitin, chitosan, and copolymers, terpolymers, or higher poly-monomer polymers thereof or combinations or mixtures thereof. Certain preferred biodegradable polymers are degraded by hydrolysis.

Typically, the polymers will either be surface erodible polymers such as polyanhydrides or bulk erodible polymers such as polyorthoesters. Poly(l-lactic acid) (PILA), poly(dl-lactic acid) (PLA), poly(glycolic acid) (PGA), polycaprolactones, copolymers, terpolymer, higher poly-monomer polymers thereof, or combinations or mixtures thereof are preferred biocompatible, biodegradable polymers. The preferred biodegradable copolymers are lactic acid and glycolic acid copolymers sometimes
referred to as poly(dl-lactic-co-glycolic acid) (PLG). The co-monomer
(lactide:glycolide) ratios of the poly(DL-lactic-co-glycolic acid) can be between about
100:0 to about 0:100, 90:10 to 10:90; 80:20 to 20:80; 70:30 to 30:70; 60:40 to 40:60
or 50:50 lactic acid to glycolic acid, with ratios of 70:30 to 30:70; 60:40 to 40:60 or
50:50 being preferred. Most preferably, the co-monomer ratios are between about
85:15 and about 50:50 lactic acid to glycolic acid. Blends of PLA with PLG,
preferably about 85:15 to about 50:50 PLG to PLA, are also used to prepare polymer
materials.

PLA, PILA, PGA, PLG and combinations or mixtures or blends thereof are
among the synthetic polymers approved for human clinical use. They are presently
utilized as surgical suture materials and in controlled release devices, as well as in
other medical and pharmaceutical applications. They are biocompatible and their
degradation products are low molecular weight compounds, such as lactic acid and
glycolic acid, which enter into normal metabolic pathways. Furthermore, copolymers
of poly(lactic-co-glycolic acid) offer the advantage of a large spectrum of degradation
rates from a few days to years by simply varying the copolymer ratio of lactic acid to
glycolic acid.

Non-limiting examples of suitable proteins include, without limitations, fibrins,
estins and/or collagens or other structural proteins.

To enhance bio-degradation of the polymers used in biological applications, the
compositions of the present invention can also include the addition of enzymes that can
facilitate the biodegradation of the polymers used in the composition. Preferred
enzymes or similar reagents are proteases or hydrolases with ester-hydrolyzing
capabilities. Such enzymes include, without limitation, proteinase K, bromelaine,
pronase E, cellulase, dextranase, elastase, plasmin streptokinase, trypsin, chymotrypsin,
papain, chymopapain, collagenase, subtilisin, clostridiopeptidase A, ficin,
carboxypeptidase A, pectinase, pectinesterase, an oxidoreductase, an oxidase or the
like. The inclusion of an appropriate amount of such a degradation enhancing agent
can be used to regulate implant duration.
Suitable Solvents

Suitable polymers can be combined with suitable organic solvents to form polymeric solutions. The solubility or miscibility of a polymer in a particular solvent will vary according to factors such as crystallinity, hydrophilicity, capacity for hydrogen-bonding and molecular weight of the polymer. Consequently, the molecular weight and the concentration of the polymer in the solvent are adjusted to achieve desired miscibility and/or viscosity. Preferred polymers are those that have a low degree of crystallinity, a low degree of hydrogen-bonding, low solubility in water, and high solubility in organic solvents.

In general, the polymers are dissolved in a suitable organic solvent. Of course, the solvent should not adversely affect the polymer or the particulate solids and preferably should be a volatile organic solvent. The relative amount of solvent will have a minimal effect on the structure of the produced materials, but will affect the solvent evaporation time.

Solvents that may be used to make polymeric compositions of the invention include, without limitation, N-methyl-2-pyrrolidone, 2-pyrrolidone, C2 to C6 alkanols, propylene glycol, acetone, alkyl esters such as methyl acetate, ethyl acetate, ethyl lactate, alkyl ketones such as methyl ethyl ketone, dialkylamides such as dimethylformamide, dimethyl sulfoxide, dimethyl sulfone, tetrahydrofuran, cyclic alkyl amides such as caprolactam, decyymethylsulfoxide, oleic acid, propylene carbonate, aromatic amides such as N,N-diethyl-m-toluamide, and 1-dodecylazacycloheptan-2-one. Preferred solvents according to the invention include N-methyl-2-pyrrolidone, 2-pyrrolidone, dimethyl sulfoxide, acetone, and propylene carbonate. Other preferred solvents are simple ketones such as acetone, chlorinated hydrocarbons such as methylene chloride, chloroform, methylethylketone, or the like.

Pore-Forming Agents

Suitable pore-forming agents include any substance, combination or mixture of substances that are insoluble or substantially insoluble in the polymeric composition or final polymer matrix (after solvent removal or after cooling) and can be removed
from the polymer matrix leaving pores, voids or spaces in the matrix using any technique well-known in the art such as leaching with one or more leaching agents. Of course, the removal process should not significantly adversely affect the polymer matrix and should not significantly cause the polymer matrix to coalesce closing off or collapsing the volume occupied by the pore-forming agent or agents.

Suitable pore-forming agents for use in the present invention are preferably biocompatible, soluble in body fluids or capable of being biodegraded or bio-assimilated in the body and relatively non-toxic. Non-limiting examples of suitable pore-forming agents, include: mono, di, tri and polysaccharides including erythrose, arabinose, xylose, ribose, lyxose, glucose, mannose, gulose, idose, talose, altrose, allose, sorbose, tagotose, fructose, sucrose, lactose, maltose, meliboise, cellobiose, trehalose, raffinose, melitose, or the like; amino acids; solid hydrocarbons and hydrocarbons containing one or more hetero atoms, including naphthylene, benzoic acid, stearic acid or the like; carboxylic acids salts such as alkali metal salts including halide salts (fluorides, chlorides, bromides and iodides), carbonate salts, carboxylic acid salts, perchlorate salts or the like, alkaline metal salts such as including halide salts (fluorides, chlorides, bromides and iodides), carbonate salts, carboxylic acid salts, perchlorate salts or the like, ammonium salts including halide salts (fluorides, chlorides, bromides and iodides), carbonate salts, carboxylic acid salts, perchlorate salts or the like, phosphonium salts including halide salts (fluorides, chlorides, bromides and iodides), carbonate salts, carboxylic acid salts, perchlorate salts or the like, polymers such as hydroxylpropylcellulose, carboxymethylcellulose, polyethylene glycol, polyvinylpyrrolidone, or the like.

Besides the compounds noted above, suitable pore-forming agents include compounds that decompose upon heating, being subjected to strong electric or magnetic fields or compounds that can be selectively melted by sonic or microwave energy or that can be decomposed by exposure to radiation or other ionizing energy sources. A requirement for the pore-forming agents in any of the applications to which the compositions of the present invention can be used is that the substances must be
insoluble or substantially insoluble in the starting polymer composition or in the final polymeric matrix.

Again, a requirement for any pore-forming agent is that the agent must not have appreciable solubility (preferably little to no solubility) in the polymer matrix or its precursor solution or melt and must be soluble (preferably very soluble) in a solvent in which the polymer matrix does not have appreciable solubility (preferably little to no solubility). However, the solvent can cause the polymer matrix to swell as long as the matrix does not substantially or significantly rearrange during the leaching process to either collapse forming pores or melt pores together.

The matrix is not considered to be significantly rearranged, if the pore-forming agent is removed with less than 35% loss in pore volume, i.e., no more than 35% of volume originally occupied by pore-forming agent(s) is lost during leaching assuming 100% leaching efficiency. The 35% target should be reduced appropriately for less than complete leaching efficiency. Thus, if leaching efficiency is only 85%, then not significantly rearranged means that no more than 35% of the 85% pore volume is loss during leaching. The matrix is not considered to be substantially rearranged, if the pore-forming is removed with less than 15% loss in potential pore volume. Preferably, the rearrangement or loss in potential pore volume due to leaching should be less than 10% and particularly less than 5%.

The concentration of pore-forming agent relative to polymer in the composition will vary according to the degree of pore-formation desired. Generally, this concentration will range from about 0.01g to about 200g of pore-forming agent per gram of polymer. Preferably, this concentration will range from about 10g to about 150g of pore-forming agent per gram of polymer. More particularly, this concentration will range from about 50g to about 150g of pore-forming agent per gram of polymer. Most particularly, this concentration will range from about 50g to about 125g of pore-forming agent per gram of polymer. And, most preferably, this concentration should be at least 50g of pore-forming agent to polymer, with the upper limit being the point at which no more agent can be incorporated into the polymer matrix.
Particle Leaching

The resulting polymeric matrix with the solid particles distributed variably therein is then leached to remove the dispersed solid particles. The leaching step is generally accomplished by immersing the matrix in a leach agent, which is preferably a liquid in which the particles are soluble. Leaching is continued for a sufficient amount of time to allow leaching of substantially all of the particles, but which does not dissolve or detrimentally alter the polymer matrix.

For compositions composed of water insoluble or substantially water insoluble polymers or polymer mixtures, the preferred leaching agent is water, most preferably distilled-deionized water, which does not dissolve the polymer nor cause measurable hydrolysis of the polymer within the time required for processing. Preferably, the particle is leached out of the material in a vessel containing distilled-deionized water for a period of eight to about seventy-two hours with about forty-eight hours being preferred for a polymer such as PLGA or about eight to about 120 hours and preferably about ninety-six hours for PLG, and the water is changed approximately every hour to twelve hours. The vessel can be placed in a heated water bath or incubator and shaken to enhance particle leaching. Most preferably, the vessel of water is placed in a water bath heated to approximately 37°C and can be shaken at approximately 100 rpm to enhance the leaching process.

Alternatively, the matrix with the pore-forming agent therein can be inserted into the tissue site, and leaching of the particles can occur after or during implantation. Thus, if the particles are leachable in bodily fluids in general or to constituents of bodily fluids or tissues, then the permeability and/or porosity of the implant can be controlled by the rate of leaching and biodegradation. Moreover, the leaching solution can be blood and/or a fluid circulated within a catheter bearing the implant. Furthermore, the particles can be bio-degradable agents activated by leaching or medication activated by leaching.

Permeability of the Polymer Matrix

Removal of the particles creates a polymer material having a plurality of pores,
spaces or voids in the material formerly occupied and/or formed by the particles. Of course, these pores, spaces or voids can be either isotropically or anisotropically distributed throughout the matrix so that the matrix has substantially uniform, differential or variable permeation to components of complex fluid mixtures such as bodily fluids in general or to constituents of bodily fluids or tissues, complex reaction mixtures or complex mixtures in general. Moreover, these voids can be connected to form large interconnected cavities, channels, or other similar structures. Of course, the voids can also be isolated and disconnected. Thus, the compositions can be highly porous yet relatively impermeable to relatively non-porous and relatively permeable to highly porous and permeable.

In fact, the composition can have regions where the permeation or migration propensity of the composition to a given range of materials is very low to zero (i.e., less than about 20%, preferably less than about 10%, particularly less than about 5% and especially less than 1% with 0% being an ultimate goal) or very high (i.e., greater than about 50%, preferably greater than about 70%, particularly greater than about 80% and especially greater than 90%, with 100% permeation being an ultimate goal).

Such permeation can be measured either as to a particular component or using its hydraulic permeability given by the formula (Darcy's law) of equation (1):

\[ K = \frac{h \Delta V}{A \Delta P \Delta t} \]  

(1)

where \( K \) is the permeability, \( h \) is the height of the object being tested, \( \Delta V \) is the volume change in the solution in contact with the object, \( A \) is the surface area of the object, \( \Delta P \) is the pressure differential, and \( \Delta t \) is the time. Darcy's law is designed to measure the permeation of a material to water, but the same principal can be used to define a permeability for other solvents or for constituents in a solution.

In the case of the implants of the present invention, the permeable part(s) of the implant should have a hydraulic permeability \( K \) greater than or equal to about 1x10^{-11}, preferably greater than or equal to about 1x10^{-9}, particularly greater than or equal to about 1x10^{-7} and especially greater than or equal to about 1x10^{-5}. Alternatively, the
impermeable part(s) of the implants of the present invention should have a hydraulic permeability less than about $1 \times 10^{-13}$, preferably less than or equal to about $1 \times 10^{-15}$, particularly less than or equal to about $1 \times 10^{-17}$ and especially less than about $1 \times 10^{-19}$.

Moreover, to attain a permeability sufficient to allow macromolecular and cellular components of bodily fluids to permeate the implant, the implant or region thereof should have at least 20% of the pores in an interconnected state, preferably at least 30% of the pores in an interconnected state, particularly at least 40% of the pores in an interconnected state and especially at least 50% of the pores in an interconnected state. By interconnected state, the inventors mean that the pores are connected in such a way as to allow a given class of material to migrate from one pore into an interconnected pore. Generally, permeability increases when the number of interconnected pores increases.

**Porosity of the Polymer Matrix**

The size and/or quantity of a pore-forming agent incorporated in the polymer matrix, the distribution of the pore-forming agent within the polymer matrix, the frequency, direction and magnitude of agitation, among other factors, influence pore size and porosity of the polymer matrix. Where the implant is employed for the purpose of cardiac tissue regeneration or revascularization, as for example, to promote guided regeneration or revascularization of cardiac tissue, it is preferred that the diameter of the pores in the matrix be effective to enhance growth of blood vessels and heart muscle cells into the matrix.

Porosity is generally measured by the formula equation (2): 

$$Porosity = \frac{V_v}{V_t} * 100$$  \hspace{1cm} (2)

where $V_v$ is the void volume and $V_t$ is the total volume.

Preferably, the size of the pores and porosity of the matrix of the implant are distributed and interconnected to an extent sufficient to facilitate the diffusion of nutrients and other growth-promoting substances such as growth factors, to cells that
have grown into the matrix. Of course, for those regions of the implants where diffusion is not desired, then the porosity should be relatively low or the pores should be unconnected. That is, the implant could have a high porosity and yet have low permeability to bodily fluids in general or to constituents of bodily fluids or tissues including water or the implant could have low porosity and in turn low permeability to bodily fluids in general or to constituents of bodily fluids or tissues.

Generally, the pores in the implants can range in diameter from about 1μ to about 1000μ. However, larger and smaller pores can also be formed in the polymer matrix using larger or smaller particulate materials. Preferably, the pores size ranges from about 50 to about 500 microns, more preferably between about 50 to about 400 microns, and most preferably between about 75 to about 300 microns. Of course, the implants of the present invention can have pores size distributions that are mono-modal, bi-modal or polymodal depending on the number of different pore-forming agents used and their particle size distributions and on agitation amplitude, direction and frequency.

It is further preferred that the degree of porosity of the matrix provides an implant that is capable of substantially maintaining structural integrity for a desired period of time without breakage or fracturing during use in those regions of the implant where permeation is preferred and remains substantially impermeable for a desired period of time to prevent swelling due to bleeding from an injured surface into and through the implant. The two periods of time can be the same or different. Through judicious choices of pore-forming agents and polymers that have different densities, a differential polymer composition can also be achieved during applied force material migration and segregation.

The size or diameter of the pores formed in the matrix may be modified by the size and/or distribution of the pore-forming agent within the polymer matrix. For example, pore-forming agents that are relatively insoluble in the polymer mixture, may be selectively included in the composition according to particle size to generate pores having a diameter that corresponds to the size of the pore-forming agent. Pore-forming
agents that are soluble in the polymer mixture may vary the pore size and porosity of the polymer matrix according to the pattern of distribution and/or aggregation within the mixture and resulting polymer matrix. Again, the amplitude, direction and frequency of agitation will also affect the size and shape of the pores formed by the particles, especially rigid particles and particles insoluble in the polymer matrix.

It is further preferred that the matrix has a porosity between about 1 and about 99%, preferably between about 50 and about 99%, and particularly between about 75% and 99% in order to provide optimum cell and tissue ingrowth into the matrix and optimum structural integrity. Pore diameter and distribution within the polymer matrix may be measured, for example, according to scanning electron microscopy methods by examination of cross-sections of the polymer matrix. Porosity of the polymer matrix may be measured according to any suitable method, as for example, mercury intrusion porosimetry, specific gravity or density comparisons, calculation from scanning electronic microscopy photographs, and the like. Additionally, porosity may be calculated according to the proportion or percent of water-soluble material included in the polymer composition. For example, a composition, which contains about 30% polymer and about 70% water-soluble components will generate a polymer matrix having a porosity of about 70%.

Of course, because the present implants have homogeneous, heterogeneous, variable permeability and/or porosity, the exact permeation and/or porosity of a given part or portion of the composition or object made therefrom can be varied from substantially impermeable and/or non-porous to highly to completely permeable and/or porous to a given material or class of materials.

For heart muscle applications, the implant size, shape and composition must be tailored to withstand the action of the heart muscle itself so that the implants or fillers are not ejected into the ventricle or atrial chambers during systole. Thus, the implants or fillers should be resilient, fatigue resistant and not subject to fragmenting into pieces after implantation. The implant shape can assist in this matter by having a large and small end where the large end is in the heart muscle while the small end is at or near
the interior surface of the heart. By at or near, the inventors mean that the end can be flush with the interior wall of the ventricle or atrium, or can be slightly protruding from or recessed in the heart muscle either in a hole made during perforation or by direct injection of the implant. Additionally, the implant can be constructed with barbs, lips, or other protrusions that act to anchor the implant in the heart muscle to reduce or prevent implant loss into the ventricle or atrium of the heart during heart pumping action.

**Incorporation of Other Materials Including Biologically-Active Agents**

The implants of this invention may further contain other materials such as fillers to improve the strength of the polymer matrices, materials that will aid in degradation, anti-degradants such as anti-oxidants and anti-ozonants, biologically-active agents, colorants, chromophores or light activated (fluorescent or phosphorescent) tags or any other material that may alter or change one or more properties of the compositions.

The addition of bioactive agents can provide the implants with biological, physiological or therapeutic effects in animals and humans. Generally, such agents can be applied to the matrix after formation by dip or spray application. Additionally, the agents can be chemically or ionically bound to sites in the matrix. Preferably, these sites are bio-degradable so that the agent can be released during biodegradation of the matrix.

Bioactive agents can be added, for example, to enhance cell growth and tissue regeneration, tissue revascularization, angiogenesis of heart tissue, tissue repair, or other medications targeted specifically for heart tissue and/or conditions. The agent may also stimulate other desired biological or physiological activities within an animal, including humans. The biologically-active agent is preferably incorporated into the matrix, and subsequently released into surrounding tissue or tissue fluids and to the pertinent body tissues or organs.

Biologically-active agents that may be used alone or in combination in the present compositions and/or implants include medicaments, drugs, or any suitable biologically-, physiologically- or pharmacologically-active substance that is capable
of providing local or systemic biological or physiological activity in an animal, including a human, and that is capable of being released from the matrix into an adjacent or surrounding tissue or bodily fluid. The composite material can be used not only as cardioplug after a heart perforation procedure, as a heart perforation apparatus, or as a suture, but also for drug delivery to the heart or as a part of a heart repair process. Examples of materials that can be incorporated include antibiotics, beta-blockers, anti-coagulants, angiogenic factors, revascularization promoters, hypertensive medications, or any other pharmaceutical agent with specific, systemic or local heart activity.

If the biologically-active agent(s) are to be added to the polymer composition during preparation, then the agent(s) are preferably either insoluble or substantially insoluble in the leaching media. If the biologically-active agent(s) are to added to the polymer matrix after leaching of the pore-forming agent(s), then the biologically-active agent(s) can simply be applied to the matrix by standard dip or spray techniques followed by drying. Alternatively, the polymer matrix after removal of the pore-forming can also be treated with reagents that generate functional groups in the polymeric matrix to which biologically active agents can be chemically or physically attached. For chemically bound biologically active agents, the chemical bonding should be such that body enzyme systems or other active agents in bodily fluids can attack the bond and release the biologically active agent. Moreover, the biologically-active agent(s) can be covalently or ionically bound to sites in the matrix or otherwise complexed to or associated with site in the matrix, where complexed to or associated with means sites in the matrix that the biologically active agent interacts with site in the matrix in a combination of ionic interactions, apolar interactions, van der waal interactions, hydrogen bonding interactions and/or covalent interactions.

Suitable biologically-active agents also include substances useful in preventing infection at the implant site, as for example, antiviral, antibacterial, antiparasitic, antifungal substances and combinations thereof. The agent may further be a substance capable of acting as a stimulant, sedative, hypnotic, analgesic, anticonvulsant, and the
like. The implants of this invention can contain large numbers of biologically-active agents either singly or in combination. Examples of these biologically-active agents include, but are not limited to: (1) anti-inflammatory agents such as hydrocortisone, prednisone, fludrotisone, triamcinolone, dexamethasone, betamethasone and the like; (2) anti-bacterial agents such as penicillins, cephalosporins, vancomycin, bacitracin, polymyxins, tetracyclines, chloramphenicol, erythromycin, streptomycin, and the like; (3) antiparasitic agents such as quinacrine, chloroquine, quinine, and the like; (4) antifungal agents such as nystatin, gentamicin, miconazole, tolnaftate, undecyclic acid and its salts, and the like; (5) antiviral agents such as vidarabine, acyclovir, ribarivin, amantadine hydrochloride, iododeoxyuridine, dideoxyuridine, interferons and the like; (6) antineoplastic agents such as methotrexate, taxanes, 5-fluorouracil, bleomycin, tumor necrosis factor, tumor specific antibodies conjugated to toxins, and the like; (7) analgesic agents such as salicylic acid, salicylate esters and salts, acetaminophen, ibuprofen, morphine, phenylbutazone, indomethacin, sulindac, tolmetin, zomepirac, and the like; (8) local anaesthetics such as cocaine, benzocaine, novocaine, lidocaine, and the like; (9) vaccines such as hepatitis, influenza, measles, mumps, rubella, hemophilus, diphtheria, tetanus, rabies, polio, and the like; (10) central nervous system agents such as tranquilizers, sedatives, anti-depressants, hypnotics, B-adrenergic blocking agents, dopamine, and the like; (11) growth factors such as colony stimulating factor, epidermal growth factor, erythropoietin, fibroblast growth factor, neural growth factor, human growth hormone, platelet derived growth factor, insulin-like growth factor, and the like; (12) hormones such as progesterone, estrogen, testosterone, follicle stimulating hormone, chorionic gonadotrophin, insulin, endorphins, somatotropins and the like; (13) antihistamines such as diphenhydramine, chlorphenamine, chlorcyclizine, promethazine, cimetidine, terfenadine, and the like; (14) cardiovascular agents such as verapamil hydrochloride, digitalis, streptokinase, nitroglycerine paparefine, disopyramide phosphate, isosorbide dinitrate, and the like; (15) anti-ulcer agents such as cimetidine hydrochloride, isopropamide iodide, propantheline bromide, and the like; (16) bronchodilators such as metaproterenal
sulfate, aminophylline, albuterol, and the like; (17) vasodilators such as theophylline, niacin, nicotinate esters, amyl nitrate, minoxidil, diazoxide, nifedipine; (18) antiphoretic gradients angiogenic factors; and the like.

As the implants biodegrades and/or bioerodes, the biologically-active agent may be released from the matrix into the adjacent tissue fluids. Preferably, the biologically-active agent is released into the surrounding tissue fluids at a controlled rate. For example, the polymer matrix may be formulated to degrade after an effective and/or substantial amount of the biologically-active agent is released from the matrix. Release of a biologically-active agent having a low solubility in water, as for example a peptide or protein, may require the degradation of a substantial part of the polymer matrix to expose the agent directly to the surrounding tissue fluids. Thus, the release of the biologically-active agent from the matrix may be varied by, for example, the solubility of the biologically-active agent in water, the distribution of the biologically-active agent within the matrix, or the size, shape, porosity, solubility and biodegradability of the polymer matrix, among other factors.

The biologically-active agent may also be a substance, or metabolic precursor thereof, which is capable of promoting growth and survival of cells and tissues, or augmenting the activity of functioning cells, as for example, blood cells, neurons, muscle, bone marrow, bone cells and tissues, and the like. For example, the biologically-active agent may be a nerve growth promoting substance, for example, a ganglioside, phosphatidylserine, a nerve growth factor, brain-derived neurotrophic factor, a fibroblast growth factor, and the like.

To promote tissue growth, the biologically-active agent may be either a hard or soft tissue promoting substance or combinations thereof. Suitable peptides and/or tissue growth promoting agents include, for example, a heart tissue or angiogenesis growth promoting substance such as growth factors, such as fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), or a combination thereof, and the like. Angiogenic factors suitable for use in the present invention include a variety of known growth factors, such as fibroblast growth factors (FGF's), particularly including
basic FGF (bFGF) and acidic FGF (aFGF); epidermal growth factor (EGF); platelet-derived growth factor (PDGF); vascular endothelial growth factor (VEGF); and the like. The phrases "FGF polypeptide," "VEGF polypeptide," "EGF polypeptide," and "PDGF polypeptide" are defined to include natural and recombinant forms of the full length proteins as well as fragments, analogs, mimetics, and other related molecules having similar or identical angiogenic activity when administered transmurally as described herein.


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**Cardioplug and Implantation of Cardioplug**

Cardioplug are implants designed to be inserted in holes made in the heart or to be directly inserted into the heart to make and plug the hole simultaneously. These holes are surgically made in the heart in an attempt to revascularize a damaged part of
the heart. One risk associated with this type of surgery is the possibility that the holes or perforations will pierce through the heart allowing blood and/or fluid flow into the pericardial sac surrounding the heart resulting in a tamponade complication. The cardioplasts of this invention can be of any shape with elongated shape being preferred such as a cylindrical shape, polygonal shape, or the like form-fit into the holes in the heart. The cardioplasts preferably have an impermeable distal portion or end so the fluid flow is reduced from the hole into the pericardial sac, if the hole extended into the pericardial sac, with the remainder of the plug being permeable. Alternatively, the cardioplasts can have impermeable proximal and distal portions or ends so the fluid flow is reduced from the hole into either the pericardial sac or the interior of the heart, with the middle portion being permeable.

The impermeable portions of the cardioplasts or implants can be porous or non-porous depending on the nature of the implant desired. Because the implants are bioerodible or biodegradable, implants with non-porous and impermeable top portions are preferred. However, in applications where the surgeon desires that the implants bioerode rapidly, then impermeable porous top portions may be preferred. Impermeable, porous compositions are generally closed foams where the pores are totally embedded within the matrix with no or little inter-penetration of pores.

Similarly, the permeable portions of the implants can have a high porosity or a low permeability. However, generally the bottom portion will be both highly porous and highly permeable. The bottom portion, which is also biodegradable, is designed to act as a scaffold for heart tissue repair, scar tissue formation, regeneration and revascularization.

In certain embodiments, the distal portion is impermeable and is inserted into the hole first to reduce or substantially eliminated bodily fluid flow out of the hole. Moreover, the implants can be a three layer structure where a permeable portion is sandwiched between two impermeable portions, one on top and one on bottom. This tri-layered arrangement reduces or substantially eliminates fluid flow into and out of the holes after heart perforation surgery.
The implants can be inserted in a variety of ways depending on the way in which the heart perforation surgery is performed. If the surgery is performed endovascularly, then the implants can be held at the tip of an endovascular instrument that inserts the implant into a perforation made by a second endoscopic instrument. If open heart surgery is performed, then the implants can simply be inserted into the holes by the surgeon either manually or using an insertion tool.

Alternatively, the implants can be forceably inserted into the heart so that the perforation is accomplished using the implant itself. A preferred design for implant for use in forceable insertion would be for the distal portion of the implant to be tipped and be formed of a biodegradable composition than has a high stiffness. The tip and high stiffness act to aid in implant insertion. Again, the implant can be a single composition or a multi-layered composite such as bi or tri-layered implants.

Another use of the compositions of the present invention is as a suture that can be sewn into the heart muscle to induce revascularization of heart muscles or damaged heart regions. The suture material can be designed with alternating permeable and impermeable regions separated so that when the material is sewn into the heart muscle the impermeable regions will be associated with the outside of the heart, while the permeable regions will be associated with the interior of the heart. Thus, the suture structure prevents tamponade, while promoting revascularization of the heart area by providing a scaffold for heart regeneration.

The plugs of the present invention are ideally suited for use in the myocardial revascularization procedures described in U.S. Pat. Nos. 6,165,188, 6,143,276, 6,126,654, 6,102,926, 6,088,613, 6,030,377, 5,999,678, 5,941,893, 5,931,834, and 5,807,384 incorporated herein by reference.

Detailed Description of Figures -- Implant with Varying Permeability and Porosity

Referring now to Figure 1, one embodiment of an implant or filler of the present invention, generally 100, can be seen to comprise a polymer matrix 102 having dispersed therein pores 104. The pores 104 increase in number or frequency from a
distal end or portion 106 to a proximal end or portion 108 of the implant 100. For cardioplasts, the distal portion or end 106 is preferably associated with the part of the implant that first enters a heart perforation or enters the heart if direct injection is used. However, the implant can be oriented in the site of tissue injury or surgical removal or formation with either the distal end or portion 106 or with the proximal end or portion 108 positioned in the interior of the injured site.

It should be recognized that the permeability and/or porosity of the implant 100 can change from across a profile 110 including the distal end portion 106 and the proximal end portion 108. This variation is the result of an applied force acting on pore-forming agents during the preparation of the composition out of which the implant 100 was formed. It should also be recognized that as a density or frequency of pores increases, the pores may not represent a single void as shown in Figure 1, but adjacent pores may have points and/or areas of contact. When individual pores have points or areas of contact, then the volume of the resulting void area is the sum of the interconnected pores. Such interconnections can yield macro-voids and even regular or irregular channel-like structures in the matrix. If the manner of agitation is such that pore volume is increase relative to the actual volume of each pore-forming particle, then the tendency of macro-void or channel formation generally increases.

Preferably, as shown in Figure 1, the distal end or portion 106 of the plug 100 is substantially pore free or impermeable. Of course, the portion 106 can also simply be less porous (fewer pores) than the proximal portion 108. Moreover, the composition can be such that the biodegradability (the rate at which bio-degradation occurs) can be different across the profile 110. This result can be achieved by using two different polymers having different densities in the preparation of the composition so that the applied force induces not only a variation in particle density in the matrix, but also induces a variation in the composition of the matrix due to differential sedimentation of the different polymers used to make the compositions.

Referring next to Figure 2, another embodiment of an implant of the present invention, generally 200, can be seen to comprise a polymer matrix 202 having
dispersed therein pores 204. The implant 200 further includes a distal end portion or
region 206, a proximal end portion or region 208, a left side portion or region 210 and
a right side portion or region 212. Unlike the implant 100 of Figure 1, the implant 200
is the result of a preparation of a composition of the present invention in which two
applied forces were used to induce a two dimensional variable distribution of pores in
the matrix. Thus, the pore density varies not only from the distal end portion to
proximal end portion, but also from left to right. It should be recognized that the
composition from which the implant 200 was prepared used a static force like gravity
and a radial force like centripetal force to induce the two dimensional variation in pore
density. The implant 200 has a substantially impervious or impermeable top or less
permeable upper region and a less permeable (fewer pores) central region 214. This
composition can also be made with different polymers so that the resulting
composition will not only have a two dimension variation in pore density, but also a
two dimensional variation in composition.

Referring now to Figure 3, yet another embodiment of a implant made from a
composition of the present invention, generally 300, can be seen to comprise a polymer
matrix 302 having dispersed therein a first type of pore 304 having a first size and a
second type of pore 306 having a second pore size. The implant 300 further includes
a distal end portion or region 308, a proximal end portion or region 310 and a central
region 312. The implant 300 derives from a composition in which two different sizes
of a given pore forming agent was used. The implant 300 illustrates a matrix 302
where two forces act along mutually perpendicular axes, i.e., gravity acting up and
down coupled with spinning about a central axis 314 of the implant. Of course, the
two forces do not have to act in a perpendicular arrangement for it is possible to spin
the composition along any axis so that the angle between the centripetal and
gravitational force vectors can be substantially zero degrees (parallel) or substantially
180° (perpendicular). Such an orientation can be easily accomplished by attaching the
machinery that spins and agitates the composition as it is being prepared and force is
being developed on a platform that can be rotated through 180°.
It should be recognized that size and shape of the particles may affect the time it takes for force developed variations in the distribution of particles and/or different density polymers in the compositions. Thus, smooth and symmetric particles will generally move through the matrix at a faster rate under a developing force than will irregular, rough particles.

Moreover, larger particles will generally migrate under the action of an applied force (force-develop) faster than smaller particles provided the particles have similar density, smoothness and shape characteristics. The duration of application of the developing force will also depend on the viscosity of the matrix that in turn will depend on solvent, if any, concentration and/or temperature. For example, raising the temperature of the composition will decrease development time.

Looking next at Figures 4 and 5, two composite implant structures of the present invention, generally 400 and 500. The composite implant 400 includes a first part 402 composed of a polymer matrix 404 having dispersed therein pores 406. Preferably, the pores 406 are dispersed uniformly or homogeneously throughout the matrix 404 as shown in the figure, but the pores can be distributed in any manner by the processes taught herein. It should be recognized that although the pores 406 are shown as circles of a given diameter, in actuality the pores will be of a given range of particle sizes and shapes depending on the nature of the particles used and the size distribution of the particles used.

The implant 400 further includes a second part 408 composed of a coating or layer 410 composed of the same or different material that is either impervious or impermeable or has a different permeability than the permeability of the first part 402. This composite structure can be prepared by coating a uniformly permeable material or composition made by any procedure known in the art or by coating a composition of the present invention with a material having a different permeability and/or porosity. Preferably, the layer 410 is substantially impervious, non-porous or impermeable so that the final composition will be impermeable on one surface and permeable on other surfaces. Of course, the layer 410 could extend over only a portion of a surface 412.
The composite implant 500 includes a first part 502 composed of a polymer matrix 504 having dispersed therein a first set of pores 506 and a second set of pores 508. Preferably, the pores 506 and 508 are dispersed uniformly throughout the matrix 504 as shown in the figure, but can be dispersed throughout the matrix in any manner according to the processes taught herein. It should be recognized that although the pores 506 and 508 are shown as circles of a given diameter, in actuality the pores will be of a given range of particle sizes and shapes depending on the nature of the particles used and the particles size distribution of the particles used.

The composite implant 500 further includes a second part 510 composed of a coating or layer 512 composed of the same or different material that is either impervious or impermeable or has a different permeability than the permeability of the first part 502. The layer 512 extends over a bottom surface 514 of the first part 502 and up onto a portion 516 of side surfaces 518 and 520 of the first part 502 of the implant 500. Of course, if the composite implant 500 is cylindrical in shape, then the side surfaces 518 and 520 are actually only a single contiguous surface.

Again, this composite structure can be prepared by coating a uniformly permeable material or composition made by any procedure known in the art or by coating a composition of the present invention with a material having a different permeability and/or porosity. Preferably, the layer 512 is substantially impervious, non-porous or impermeable so that the final composite will be impermeable on one surface and permeable on other surfaces.

Referring now to Figures 6A and B, two complex composite implants of the present invention are shown generally as 600. The composite implant 600 of Figure 6A includes a first component 602, a second component 604, a third component 606 and an optional fourth component 608. These components can be adhesively bonded together or integrally fused to each other, where integrally fused means that an exchange of material across the interface has occurred, or one material can simply be coated onto another material. Thus, the optional fourth component 608 could simply represent a coating or layer over surfaces of other components. The component 602
includes a polymer matrix 610 having dispersed therein pores 612. The component 604 includes a polymer matrix 614 having dispersed therein pores 616. The component 606 includes a polymer matrix 618 having dispersed therein pores 620.

The components 602 and 606 have variable permeability and/or porosity formed using a single applied force such as gravity, while component 604 has uniform porosity and/or permeability. Thus, by sandwiching component 604 between components 602 and 606, the composite 600 has a more porous interior region 622 to allow the diffusion of larger species quickly into this area with diffusion into adjacent areas varying with the distance from a bottom 624 of the composite 600.

Alternatively, as shown in Figure 6B, the components 602 and 606 are now compositions that have a uniform permeability and/or porosity and the component 604 interposed therebetween has a variable permeability and/or porosity. The optional component 608 of the composite implants 600 of Figures 6A and B can comprise a substantially impervious, non-porous and/or impermeable layer or coating deposited on a surface of the implants 600 or any portion thereof. In both Figures 6A and B, the component 608 extends over all of the other components.

Looking at Figures 4-6, it should be clear that many different composite implants can be constructed to facilitate uni-directional, bi-directional or multi-directional channeling of different biological species and/or biologically active agents in the implant through different parts of the composite to either act to selectively direct certain biological agents to one tissue site and other agents to other tissue sites. Thus, composites could be designed to direct growth factors to all tissues in contact with permeable areas of a composite, while directing antibiotics to one tissue site and not other tissue sites.

Even more complex structures can be constructed, if the composition comprising the separate components are force-developed in a more complex manner. Thus, the component compositions could first be gravity developed, then centripetally developed along one axis and then along another axis. Moreover, if some of the pore forming agents are electrically active (charged ion pairs), then electrical developing
can be performed on the electrically active agents after gravity and/or centripetal developing have been performed. This same procedure could be used for magnetically active agents (agent that will move when subjected to an external magnetic field). Again, it must be emphasized that electrically and magnetically mobile pore-forming agents must be capable of being leached from the matrix after development. In the case of ion pairs, generally water leaching will remove these species. In the case of magnetically active agents, if the agents can be leached by acid, base or chelating solutions that do not significantly decompose the polymer matrix, then the agents can be used in the present invention to make a composition having variable permeability and/or porosity.

**Detailed Description of Figures – Cardioplug and Suture Structures**

Referring now to Figure 7A, one embodiment of a cardioplug 700 of this invention has a cylindrical shape and includes a top impermeable, non-porous portion 702 and a bottom permeable, porous portion 704, where the top portion 702 is designed to be inserted into a heart perforation or hole so that it will reduce or substantially prevent fluid flow from the hole into the pericardial sac, if the hole perforates through the heart surface.

Referring now to Figure 7B, another embodiment of a cardioplug 710 of this invention has a cylindrical shape and includes a top impermeable, porous portion 712 and a bottom permeable, highly porous portion 714, where the top portion 712 is designed to be inserted into a heart perforation or hole so that it will reduce or substantially prevent fluid flow from the hole into the pericardial sac, if the hole perforates through the heart surface.

Referring now to Figure 7C, another embodiment of a cardioplug 720 of this invention has a cylindrical shape and includes a top impermeable, porous portion 722 and a bottom permeable, moderately porous portion 724, where the top portion 722 is designed to be inserted into a heart perforation or hole so that it will reduce or substantially prevent fluid flow from the hole into the pericardial sac, if the hole perforates through the heart surface. Referring now to Figure 8A, another
embodiment of a cardioplug 800 of this invention has a cylindrical shape and includes a top impermeable, non-porous portion 802, a middle permeable, porous portion 804 and a bottom impermeable, non-porous portion 806. The top portion 802 is designed to be inserted into a heart perforation or hole so that it will reduce or substantially prevent fluid flow from the hole into the pericardial sac, if the hole perforates through the heart surface, while the bottom portion 806 is designed to be associated with the surface of the heart where the perforation was made.

Referring now to Figure 8B, another embodiment of a cardioplug 810 of this invention has a cylindrical shape and includes a top impermeable, porous portion 812, a middle highly permeable, porous portion 814 and a bottom impermeable, non-porous portion 816. The top portion 812 is designed to be inserted into a heart perforation or hole so that it will reduce or substantially prevent fluid flow from the hole into the pericardial sac, if the hole perforates through the heart surface, while the bottom portion 816 is designed to be associated with the surface of the heart where the perforation was made.

Referring now to Figure 8C, another embodiment of a cardioplug 820 of this invention has a cylindrical shape and includes a top impermeable, porous portion 822, a middle highly permeable, porous portion 824 and a bottom permeable, porous portion 826. The top portion 822 is designed to be inserted into a heart perforation or hole so that it will reduce or substantially prevent fluid flow from the hole into the pericardial sac, if the hole perforates through the heart surface, while the bottom portion 826 is designed to be associated with the surface of the heart where the perforation was made.

Referring now to Figures 9A-C, three embodiments of a cardioplug 900 of this invention is preferentially cylindrically shaped and includes a distal impermeable portion 902 having a pointed tip 904, a middle permeable portion 906 and a proximal impermeable portion 908. The distal portion 902 is designed to be inserted directly into a desired region of a heart where the pointed tip 904 is preferably made of a polymer matrix having a greater hardness than the middle or proximal portions or segments 906 and 908, so that it can penetrate the heart muscle. The distal and
proximal portions 902 and 908 are designed to reduce or substantially prevent fluid flow. Looking at Figure 9B, in this embodiment of the cardioplug 900 also includes barbs 910. The cardioplug 900 is shown with four barbs 910 associated with the distal segment 902. Of course, the number and exact location of the barbs 910 on the segment 902 is a matter of design expedience. Looking at Figure 9C, in this embodiment of the cardioplug 900 includes barbs 910 associated with each segment 902, 906 and 908. Again, the number and exact location of the barbs 910 is a matter of choice and design expedience. The barbs 910 are designed anchor the implant 900 in the heart muscle during implantation. Because the barbs 910 are angled away from the tip 904, the barbs 910 will flex inward toward the implant 900 during implantation and spring out somewhat, depending on the matrix, to anchor the implant 900. Regardless of whether the barbs spring out somewhat, the barbs will act to hold the implant in place much as barbs on a fishing hook anchor the hook.

Looking now at Figure 9D-F, several embodiments of tipped cardioplug 900 are shown. In the embodiment of Figure 9D, the distal segment 902 is enlarged, while the middle portion 906 tapers to the proximal portion 908. The distal portion 902 also includes an anchor rim 909. The rim 909 is designed to reduce any tendency for the implant 900 to be expelled from the heart after implantation during normal heart action. In the embodiment of Figure 9E, the distal segment 902 is narrow and the middle segment has two parts 906a and 906b. Each segment 902, 906a, 906b and 908 all taper, being smaller at the distal end 912 and larger at the proximal end 914. This implant 900 also includes skirts 910, which act to anchor the implant after implantation. In the embodiment of Figure 9F, the distal segment 902 is flares at its proximal end 912 and the middle segment has two parts 906a and 906b. The segments 906a, 906b and 908 all taper, being larger at the distal end 912 and smaller at the proximal end 914. This implant 900 also includes skirts 910, which act to anchor the implant after implantation.

It should be recognized that the embodiments shown above can have a variety of properties provided that the material that is associated with the external surface of
the heart reduces or does not permit fluid flow out of the heart and into the pericardial sac for some period of time. Because the plugs are biodegradable or bioerodible, they will disappear over time. By varying the composition of the polymer matrix of each portion, as is well-known in the art, the rate of biodegradation or erosion can be controlled. Still the rate must be sufficiently slow to allow the hole to seal with new tissue or at least for the bleeding process to be arrested through regular bodily functions. Preferably, the material associated with the external or exterior surface of the heart should have a slower rate of bioerosion and generally should persist for at least six hours to about a week, preferably for at least one day to about three days and particularly for at least one day to about two days.

Referring now to Figures 10A and B, a cardiosuture material 1000 of this invention is shown to be a filament or string like shape and comprises alternating portions or segments 1002 and 1004. The segments 1002 are shown here as being impermeable and porous, while the segments 1004 are shown as being permeable and porous. The impermeable portions 1002 have a length $l_1$ and the permeable portions 1004 have a length $l_2$.

The lengths $l_1$ and $l_2$ can be adjusted so that when the suture material 1000 is sewn into the heart muscle 1006 either endovascularly or during open-heart surgery, the impermeable segments 1002 become associated with the exterior 1008 of the heart muscle 1006 and portions thereof 1010 extend from the surface 1012 of the heart muscle into its interior 1014 a distance $d$ sufficient to reduce or substantially reduce or prevent fluid flow out of the suture sites. By exterior of the heart muscle, the inventors mean either the outer surfaces of the heart muscle that would be accessible via an open-heart procedure or the surfaces of the ventricles or atria. The permeable segments 1004 are designed to be associated with the interior 1014 of the heart muscle 1006 and act as scaffolding for heart regeneration and revascularization. Generally, the lengths $l_1$ and $l_2$ are similar, but not equal with the length $l_1$ being generally larger than the length $l_2$. The lengths $l_1$ and $l_2$ are generally between about 1 mm and about 20 mm, preferably between about 2 mm and about 10 mm and particularly about 5 mm.
and about 10 mm. Generally, the distance \( d \) is on the order of about 1 mm to about 5 mm, preferably about 1 mm to about 3 mm and particularly about 1 mm to about 2 mm.

Of course, the porosity of the segments or portions can be any desired porosity provided that the segments 1002 are impermeable and the segments 1004 are permeable. Moreover, the permeability of the segments can vary provided that a middle section of the impermeable segments remains substantially impermeable. Thus, the filament can be manufactured in such a way that the permeability of the composition varies smoothly from impermeable to permeable to form alternating portions that have no definite line of demarcation separating the portions; provided that the impermeable portions are of sufficient length to act as an effective barrier to fluid flow from the interior or the heart muscle to an exterior of the heart muscle. Either configuration can be made using well known extrusion processing where one simply varies or starts and stops the amount of pore forming agent being added to the polymers during extrusion. The formed filament can then be subjected to further processing such as vibronic agitation to increase pore volume or the like.

Furthermore, the cross-sectional shape of the filament can be of any desired shape including, without limitation, circular, oval, flat (ribbon-shaped), triangular, rectangular, pentagonal, hexagonal, etc. or any other desired cross-sectional shape.

**Detailed Description of Figures – Implantation of Cardioplugs/Sutures**

Referring now to Figures 11A-B, a cardioplug implant 1100 having a top portion 1102, middle portion 1104 and a bottom portion 1106 is shown being inserted into a hole 1108 created in a heart region 1110 endovascularly. The implant 1100 is positioned in an end 1112 of an endoscopic tool 1114 against a plugger 1116 attached to a plugger guide 1118 for pushing the plugger 1116 in and out and pushing the implant 1100 into the hole 1108. The top and bottom portions 1102 and 1106 are substantially impermeable to bodily fluids, while the middle portion 1104 is substantially permeable to bodily fluids including cells. The hole 1108 is shown to have penetrated through an exterior surface 1120 of the heart region 1110 and into a
pericardial sac 1122 surrounding the heart region 1110. In Figure 11B, the implant 1100 is inserted into the hole 1108 so that the top portion 1102 protrudes a small distance beyond the surface 1120, the middle portion 1104 is positioned in the heart muscle region 1110 and the bottom portion 1106 protrudes a small distance beyond an interior surface 1124 of the heart region 1110. If the perforation is made during open heart surgery, then the cardioplugs are inserted into the heart from its exterior so that a small amount of the impermeable part of the plug protrudes above the outer surface of the heart. It should be recognized that the endoscope used to make the holes and fill them can be any endoscopic tool that has a heart perforation unit and a plug insertion unit.

Referring now to Figures 12A-B, a cardioplug implant 1200 having a distal portion 1202, middle portions 1204a and 1204b and a proximal portion 1206 is shown being inserted into a heart region 1210 endovascularly. The implant 1200 is positioned in an end 1212 of an endoscopic tool 1214 against a plunger 1216 attached to a plunger guide 1218 for pushing the plunger 1216 in and out, which pushes the implant 1200 into the heart region 1210. The distal and proximal portions 1202 and 1206 are substantially impermeable to bodily fluids, while the middle portions 1204a&b are substantially permeable to bodily fluids including cells. The site 1208 of the heart region 1210 where the implant 1200 will inserted includes an interior surface 1220, an exterior surface 1222, which is surrounded by a pericardial sac 1224. In Figure 12B, the implant 1200 is inserted into the site 1208 so that the proximal portion 1206 protrudes a small distance below the interior surface 1220, the middle portions 1204a&B are positioned in the heart region 1210 and the distal portion 1202 is positioned a small distance below the exterior surface 1222 of the heart region 1210. If perforations are made during open heart surgery, then the cardioplugs are inserted into the heart from its exterior so that a small amount of the impermeable part of the plug protrudes above the exterior surface of the heart. It should be recognized that the endoscope used to make the holes and fill them can be any endoscopic tool that has a heart perforation unit and a plug insertion unit.
While this invention has been described fully and completely, it should be understood that, within the scope of the appended claims, the invention may be practiced otherwise than as specifically described. Although the invention has been disclosed with reference to its preferred embodiments, from reading this description those of skill in the art may appreciate changes and modification that may be made that do not depart from the scope and spirit of the invention as described above and claimed hereafter.
We claim:

1. A cardioimplant comprising:
   a distal end;
   a distal segment including a first biodegradable, biocompatible polymer matrix having a first permeability to bodily fluids;
   a proximal end; and
   a proximal segment including a second biodegradable, biocompatible polymer matrix having a second permeability to bodily fluids; and
   where the polymer matrices are the same or different and the permeabilities are different.

2. The cardioimplant of claim 1, wherein the first permeability is substantially impermeable to bodily fluids and the second permeability is permeable to bodily fluids.

3. The cardioimplant of claim 2, wherein the second permeability is highly permeable of bodily fluids.

4. The cardioimplant of claim 2, wherein the second permeability comprises a permeability gradient, which changes from permeable where the second segment contacts the first segment to highly permeable.

5. The cardioimplant of claim 1, wherein the first permeability comprises a first permeability gradient and the second permeability comprises a second permeability gradient, where the first permeability gradient changes from impermeable to bodily fluids to highly permeable to bodily fluids and the second permeability gradient changes from highly permeable to bodily fluids where the two segments contact to impermeable at the proximal end of the implant.
6. The cardioimplant of claim 1, wherein the first matrix further includes a first bio-active agent and the second matrix further includes a second bio-active agent, where the two bio-active agents are same or different.

7. The cardioimplant of claim 6, wherein the first and second bio-active agents are selected from the group consisting of basic FGF (bFGF) and acidic FGF (aFGF); epidermal growth factor (EGF); platelet-derived growth factor (PDGF); vascular endothelial growth factor (VEGF); FGF polypeptide, VEGF polypeptide, EGF polypeptide, PDGF polypeptide, and mixtures and combinations thereof.

8. The cardioimplant of claim 1, further comprising a third segment including a third bio-degradable, bio-compatible polymer matrix having a third permeability to bodily fluids, wherein the second segment is interposed between the first and third segments.

9. The cardioimplant of claim 8, wherein the third permeability is substantially impermeable to bodily fluids.

10. The cardioimplant of claim 2, further comprising alternating segments of the first and second polymer matrix.

11. The cardioimplant of claim 1, wherein a top part of the first segment tapers to a point.

12. The cardioimplant of claim 1, further comprising a tissue anchoring member.

13. The cardioimplant of claim 12, wherein the tissue anchoring member is a barb, a skirt or a flare protruding from an outer surface of the cardioimplant.
14. A cardiosuture material comprising a filament including alternating first and second segments, where the first segments comprise a first biodegradable, biocompatible polymer matrix and the second segments comprise a second biodegradable, biocompatible polymer matrix.

15. The material of claim 14, wherein the first matrix is substantially impermeable to bodily fluids and the second matrix is permeable to bodily fluids.

16. The composition of claim 14, wherein the second polymer has a permeability gradient which changes from permeable where the second segments contacts the first segments to highly permeable in a central region of the second segments.

17. The composition of claim 14, wherein the first polymer has a first permeability gradient and the second polymer has a second permeability gradient, wherein the gradients change from impermeable to bodily fluids in a central region of the first portions to highly permeable to bodily fluids in a central region of the second segments.

18. A method comprising the steps of:

forming a hole in a heart muscle at a given site; and

inserting into the hole a cardioimplant comprising:

a distal end;

a distal segment including a first biodegradable, biocompatible polymer matrix having a first permeability to bodily fluids;

a proximal end; and

a proximal segment including a second biodegradable, biocompatible polymer matrix having a second permeability to bodily fluids; and

where the polymer matrices are the same or different; the permeabilities are different and the distal end enters the hole, and the proximal end is associated with an
interior surface of the site.

19. The method of claim 18, wherein the first permeability is substantially impermeable to bodily fluids.

20. The method of claim 18, wherein the second permeability is permeable to bodily fluids.

21. The method of claim 20, wherein the proximal segment further includes a bio-active agent to promote revascularization of the site.

22. A method comprising the step of:
   inserting directly into a site of a heart muscle a cardioimplant comprising:
      a distal end tapering to a point;
      a distal segment including a first biodegradable, biocompatible polymer matrix having a first permeability to bodily fluids;
      a proximal end; and
      a proximal segment including a second biodegradable, biocompatible polymer matrix having a second permeability to bodily fluids; and
   where the polymer matrices are the same or different; the permeabilities are different and the distal end enters the heart muscle.

23. A method comprising the step of:
   sewing into a site of a heart muscle a cardiosuture material comprising:
      a filament including alternating first and second segments, where the first segments comprise a first biodegradable, biocompatible polymer matrix having a first permeability and the second segments comprise a second biodegradable, biocompatible polymer matrix having a second permeability,
where the first segments are designed to be extend from an exterior of the site
to an exterior surface of the site and the second segments are designed to be embedded
in an interior of the heart muscle of the site.

24. The method of claim 23, wherein the first permeability is substantially
impermeable to bodily fluids and reduces blood flow from the interior of the site to the
exterior of the site.

25. The method of claim 24, wherein the first segments extend from the exterior of
the site into the interior of the site.

26. The method of claim 23, wherein the second permeability is highly permeable
to bodily fluids and promotes site revascularization.

27. The method of claim 26, wherein the second segments further include a bio-
active agent to promote revascularization of the heart muscle.