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(54) **THERAPEUTIC AGENT DELIVERY DEVICE WITH CONTROLLED THERAPEUTIC AGENT RELEASE RATES**

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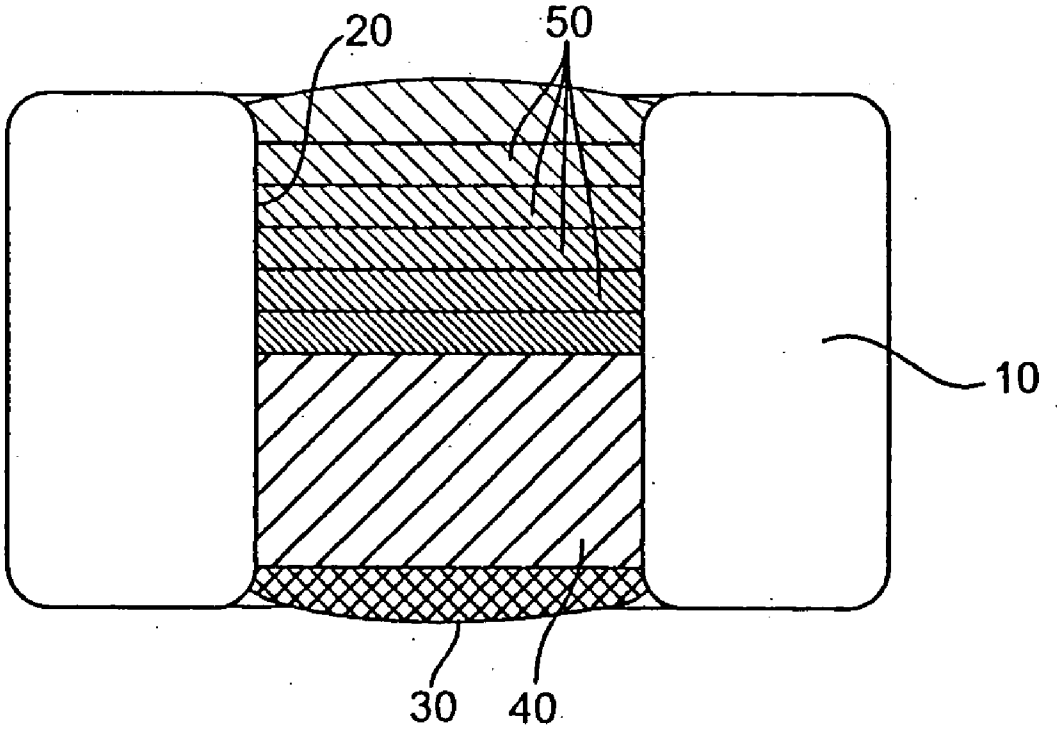
(57) **ABSTRACT**

The present invention relates to implantable medical devices for the localized delivery of therapeutic agents, such as drugs, to a patient. More particularly, the invention relates to a device having a gradient of water soluble therapeutic agents within a therapeutic agent layer and a mixing layer that allows for controlled release of the therapeutic agents.



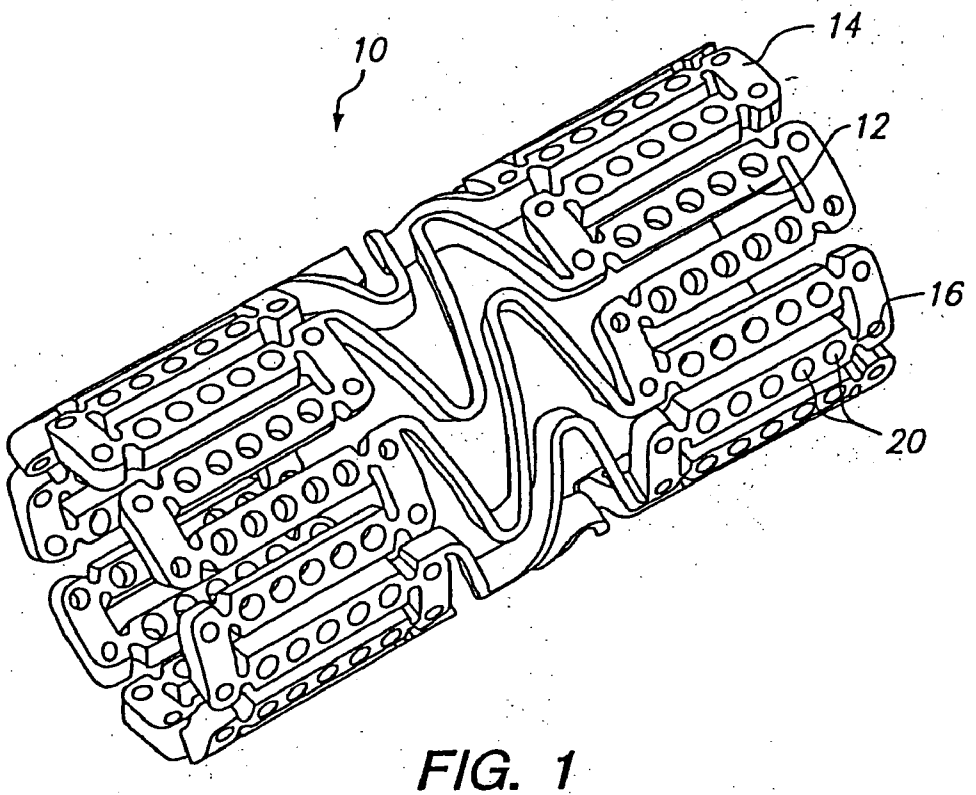


FIG. 1

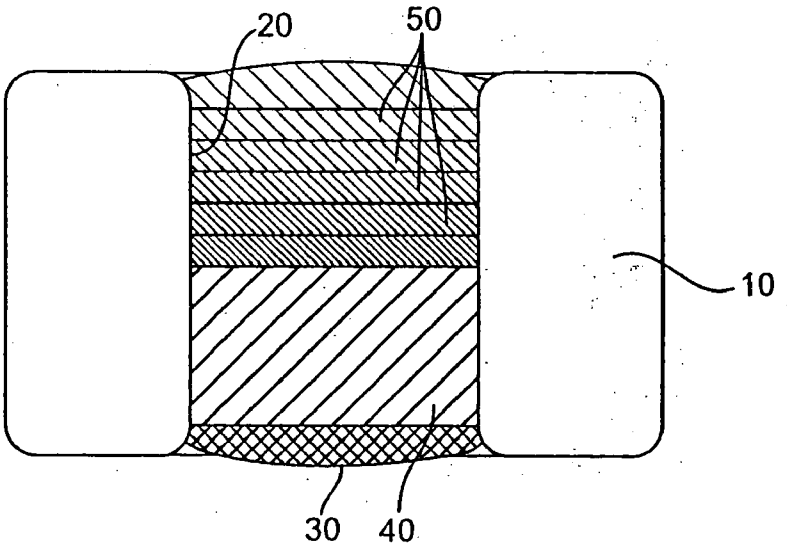


FIG. 2

THERAPEUTIC AGENT DELIVERY DEVICE WITH CONTROLLED THERAPEUTIC AGENT RELEASE RATES

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a divisional of U.S. patent application Ser. No. 10/402,893, filed Mar. 28, 2003 which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] The invention relates to a therapeutic agent delivery device which comprises a gradient of therapeutic agent within mixing layers which provides for the controlled release of water soluble therapeutic agents.

DESCRIPTION OF THE RELATED ART

[0003] Implantable medical devices are often used for delivery of a beneficial agent, such as a drug, to an organ or tissue in the body at a controlled delivery rate over an extended period of time. These devices may deliver agents to a wide variety of bodily systems to provide a wide variety of treatments.

[0004] One of the many implantable medical devices which have been used for local delivery of beneficial agents is the coronary stent. Coronary stents are typically introduced percutaneously, and transported transluminally until positioned at a desired location. These devices are then expanded either mechanically, such as by the expansion of a mandrel or balloon positioned inside the device, or expand themselves by releasing stored energy upon actuation within the body. Once expanded within the lumen, these devices, called stents, become encapsulated within the body tissue and remain a permanent implant.

[0005] Known stent designs include monofilament wire coil stents (U.S. Pat. No. 4,969,458); welded metal cages (U.S. Pat. Nos. 4,733,665 and 4,776,337); and, most prominently, thin-walled metal cylinders with axial slots formed around the circumference (U.S. Pat. Nos. 4,733,665; 4,739,762; and 4,776,337). Known construction materials for use in stents include polymers, organic fabrics and biocompatible metals, such as stainless steel, gold, silver, tantalum, titanium, and shape memory alloys, such as Nitinol.

[0006] Of the many problems that may be addressed through stent-based local delivery of beneficial agents, one of the most important is restenosis. Restenosis is a major complication that can arise following vascular interventions such as angioplasty and the implantation of stents. Simply defined, restenosis is a wound healing process that reduces the vessel lumen diameter by extracellular matrix deposition, neointimal hyperplasia, and vascular smooth muscle cell proliferation, and which may ultimately result in renarrowing or even reocclusion of the lumen. Despite the introduction of improved surgical techniques, devices, and pharmaceutical agents, the overall restenosis rate is still reported in the range of 25% to 50% within six to twelve months after an angioplasty procedure. To treat this condition, additional revascularization procedures are frequently required, thereby increasing trauma and risk to the patient.

[0007] One of the techniques under development to address the problem of restenosis is the use of surface coatings of various beneficial agents on stents. U.S. Pat. No. 5,716,981, for example, discloses a stent that is surface-coated with a composition comprising a polymer carrier and paclitaxel (a well-known compound that is commonly used in the treatment of cancerous tumors).

[0008] The patent offers detailed descriptions of methods for coating stent surfaces, such as spraying and dipping, as well as the desired character of the coating itself: it should "coat the stent smoothly and evenly" and "provide a uniform, predictable, prolonged release of the anti-angiogenic factor." Surface coatings, however, can provide little actual control over the release kinetics of beneficial agents. These coatings are necessarily very thin, typically 5 to 8 microns deep. The surface area of the stent, by comparison is very large, so that the entire volume of the beneficial agent has a very short diffusion path to discharge into the surrounding tissue.

[0009] Increasing the thickness of the surface coating has the beneficial effects of improving drug release kinetics including the ability to control drug release and to allow increased drug loading. However, the increased coating thickness results in increased overall thickness of the stent wall. This is undesirable for a number of reasons, including increased trauma to the vessel wall during implantation, reduced flow cross-section of the lumen after implantation, and increased vulnerability of the coating to mechanical failure or damage during expansion and implantation. Coating thickness is one of several factors that affect the release kinetics of the beneficial agent, and limitations on thickness thereby limit the range of release rates, duration of drug delivery, and the like that can be achieved.

[0010] In addition to sub-optimal release profiles, there are further problems with surface coated stents. The fixed matrix polymer carriers frequently used in the device coatings typically retain approximately 30% of the beneficial agent in the coating indefinitely. Since these beneficial agents are frequently highly cytotoxic, sub-acute and chronic problems such as chronic inflammation, late thrombosis, and late or incomplete healing of the vessel wall may occur. Additionally, the carrier polymers themselves are often highly inflammatory to the tissue of the vessel wall. On the other hand, use of biodegradable polymer carriers on stent surfaces can result in the creation of "virtual spaces" or voids between the stent and tissue of the vessel wall after the polymer carrier has degraded, which permits differential motion between the stent and adjacent tissue. Resulting problems include micro-abrasion and inflammation, stent drift, and failure to re-endothelialize the vessel wall.

[0011] Another significant problem is that expansion of the stent may stress the overlying polymeric coating causing the coating to plastically deform or even to rupture, which may therefore effect drug release kinetics or have other untoward effects. Further, expansion of such a coated stent in an atherosclerotic blood vessel will place circumferential shear forces on the polymeric coating, which may cause the coating to separate from the underlying stent surface. Such separation may again have untoward effects including embolization of coating fragments causing vascular obstruction.

[0012] In addition, it is not currently possible to deliver some drugs with a surface coating for a variety of reasons. In some cases, the drugs are sensitive to water, other compounds, or conditions in the body which degrade the

drugs. For example, some drugs lose substantially all their activity when exposed to water for a period of time. When the desired treatment time is substantially longer than the half life of the drug in water the drug cannot be delivered by know coatings. Other drugs, such as protein or peptide based therapeutic agents, lose activity when exposed to enzymes, pH changes, or other environmental conditions. And finally drugs that are highly-soluble in water tend to be released from the coatings at an undesirably high rate and do not remain localized for a therapeutically useful amount of time. These types of drugs which are sensitive to compounds or conditions in the body often cannot be delivered using surface coatings.

[0013] Accordingly, it would be desirable to provide a beneficial agent delivery device for delivery of agents, such as drugs, to a patient while protecting the agent from compounds or conditions in the body which would degrade the agent.

SUMMARY OF THE INVENTION

[0014] The present invention relates to medical device for the controlled delivery of therapeutic agents where the release of the therapeutic agent is mediated by a mixing layer.

[0015] In one of its device aspects the present invention provides for an implantable medical device comprising an implantable device body having a plurality of holes; a therapeutic agent provided in a first therapeutic agent layer and contained within the plurality of holes in the device body; and at least one mixing layer provided adjacent the first therapeutic agent layer in the plurality of holes; wherein the therapeutic agent layer and the at least one mixing layer together contain a concentration gradient of said therapeutic agent and allow for the controlled release of the therapeutic agent contained within the therapeutic agent layer and the at least one mixing layer.

[0016] In another of its device aspects the present invention provides for an implantable medical device comprising an implantable device body having a plurality of holes; a therapeutic agent within the plurality of holes in the device body provided in a therapeutic agent layer; and a mixing layer provided in the plurality of holes; wherein the therapeutic agent layer and the mixing layer contain a concentration gradient of said therapeutic agent created by delivering a mixing layer material without the therapeutic agent and liquefying a portion of the therapeutic agent layer with the mixing layer material, whereby the mixing layer has a lesser amount of therapeutic agent contained therein than the therapeutic agent layer.

[0017] The mixing layers are preferably a pharmaceutically acceptable bioresorbable matrix, more preferably pharmaceutically acceptable polymers. Even more preferably the mixing layers are selected from the group consisting of polylactic acid, polyglycolic acid, polylactic-co-glycolic acid, polylactic acid-co-caprolactone, polyethylene glycol, polyethylene oxide, poly lactic acid-block-poly ethylene glycol, poly glycolic acid-block-poly ethylene glycol, poly lactide-co-glycolide-block-poly ethylene glycol, poly ethylene glycol-block-lipid, polyvinyl pyrrolidone, poly vinyl alcohol, a glycosaminoglycan, polyorthoesters, polysaccharides, polysaccharide derivatives, polyhyaluronic acid, polyalginic acid, chitin, chitosan, chitosan derivatives, cellulose, hydroxyethylcellulose, hydroxypropylcellulose, carboxymethylcellulose, polypeptides, polylysine, polyglutamic acid, albumin, polyanhydrides, polyhydroxy alkonoates, polyhydroxy valerate, polyhydroxy butyrate, proteins, polyphosphate esters, lipids, and mixtures thereof.

[0018] The therapeutic agent layer preferably comprises the therapeutic agent and a water soluble binding agent. The water soluble binding agent is preferably selected from poly ethylene glycol, poly ethylene oxide, poly vinylpyrrolidone, poly vinyl alcohol, a glycosaminoglycan, polysaccharides, polysaccharide derivatives, poly hyaluronic acid, poly alginic acid, chitin, chitosan, chitosan derivatives, cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, poly peptides, poly lysine, poly glutamic acid, and proteins, such as albumin.

[0019] The liquefied therapeutic agent layer comprises from about 20% to about 95% therapeutic agent and from about 5% to about 70% pharmaceutically acceptable polymer preferably from about 50% to about 95% therapeutic agent and from about 5% to about 50% pharmaceutically acceptable polymer, more preferably from about 50% to about 60% therapeutic agent and from about 40% to about 50% pharmaceutically acceptable polymer.

[0020] The therapeutic agent is preferably antithrombotic agents, a antineoplastic agent, a neoplastic agent, an antiproliferative agent, an antisense compound, an immunosuppresant, an angiogenic agent, an angiogenic factor, an antiangiogenic agent, or an anti-inflammatory agent, or combinations thereof. More preferably the therapeutic agent is of 2-chlorodeoxyadenosine, bivalirudin, Resten NG, or an oliogonucleotide, or mixtures thereof.

[0021] The therapeutic agent maybe homogeneously or heterogeneously dispersed in the therapeutic agent layer and/or the mixing layer(s). The therapeutic agent may be homogeneously or heterogeneously disposed in a layer as a solid particle dispersion, encapsulated agent dispersion, an emulsion, a suspension, a liposome, niosome, or a microparticle, wherein said niosome, liposome or microparticle comprise a homogeneous or heterogeneous mixture of the therapeutic agent. When a therapeutic agent is homogeneously disposed in a therapeutic agent layer, it may be a solid-solution or a multi-phase mixture.

[0022] Optionally the liquefied bioresorbable polymer loaded into the holes does not contain the therapeutic agent.

[0023] The implantable medical device is useful in the treatment of restenosis and inflammation and is preferably a stent.

[0024] The bioresorbable polymers, binding agents of the individual layers may be the same or different. In one embodiment, the polymers used in the therapeutic agent layer is different than the polymer used in the mixing layer. The polymers and binging agents of the individual layers maybe liquefied by dissolution of the materials in a solvent or by maintaining the materials at a temperature that is higher than their melting points, or glass transition temperatures.

[0025] The implantable medical device may optionally further comprise a barrier layer, wherein the barrier layer is located adjacent the therapeutic agent layer. The barrier layer is formed by loading into the plurality of holes an

amount of a liquefied biocompatible polymer, which amount is sufficient to form a barrier layer, wherein the barrier layer is located adjacent the therapeutic agent layer.

[0026] In one of its method aspects the present invention provides for an method for preparing an implantable medical device as described herein above, which method comprises:

[0027] a) providing an implantable medical device with a plurality of holes;

[0028] b) loading into the plurality of holes an amount of a liquefied therapeutic agent, which amount is sufficient to form a therapeutic agent layer;

[0029] c) allowing said liquefied therapeutic agent layer to at least partially solidify;

[0030] d) loading into the plurality of holes an amount of a liquefied bioresorbable polymer which amount is sufficient to liquefy a portion of the therapeutic agent layer, thereby allowing a portion of the therapeutic agent layer to be disposed within a mixing layer;

[0031] e) allowing said liquefied bioresorbable polymer and said portion of the therapeutic agent layer to solidify;

wherein an amount of therapeutic agent contained within the mixing layer upon solidification is smaller than an amount of therapeutic agent contained in the therapeutic agent layer and further wherein steps d and e may optionally be repeated to form multiple mixing layers.

BRIEF DESCRIPTION OF THE DRAWING FIGURES

[0032] The invention will now be described in greater detail with reference to the preferred embodiments illustrated in the accompanying drawings, in which like elements bear like reference numerals, and wherein:

[0033] **FIG. 1** is a perspective view of a therapeutic agent delivery device in the form of an expandable stent.

[0034] **FIG. 2** is a cross sectional view of a portion of a therapeutic agent delivery device having a beneficial agent contained in an opening in layers.

DETAILED DESCRIPTION OF THE INVENTION

[0035] The present invention relates to a delivery device for delivery of water soluble therapeutic agents to a patient. More particularly, the invention relates to a medical device having therapeutic agents protected from premature release into a patient by one or more mixing layers. Details for the device design, therapeutic agents, therapeutic agent layers, and mixing layers may also be found in U.S. patent application Ser. No. 10/253,020, filed on Sep. 23, 2002, incorporated herein by reference in its entirety. First, the following terms, as used herein, shall have the following meanings:

[0036] The term "beneficial agent" as used herein is intended to have its broadest possible interpretation and is used to include any therapeutic agent or drug, as well as inactive agents such as barrier layers, carrier layers, therapeutic layers or mixing layers.

[0037] The terms "drug" and "therapeutic agent" are used interchangeably to refer to any therapeutically active substance that is delivered to a bodily conduit of a living being to produce a desired, usually beneficial, effect. The present invention is particularly well suited for the delivery of antineoplastic, angiogenic factors, immuno-suppressants, and antiproliferatives (anti-restenosis agents) such as paclitaxel, Rapamycin or 2-chlorodeoxyadenosine, for example, and antithrombins such as heparin, for example.

[0038] The therapeutic agents used in the present invention include classical low molecular weight therapeutic agents commonly referred to as drugs including all classes of action as exemplified by, but not limited to: antineoplastic, immuno-suppressants, antiproliferatives, antithrombins, antiplatelet, antilipid, anti-inflammatory, angiogenic, anti-angiogenic, vitamins, ACE inhibitors, vasoactive substances, antimitotics, metello-proteinase inhibitors, NO donors, estradiols, anti-sclerosing agents, alone or in combination. Therapeutic agent also includes higher molecular weight substances with drug like effects on target tissue sometimes called biologic agents including but not limited to: peptides, lipids, protein drugs, protein conjugates drugs, enzymes, oligonucleotides, ribozymes, genetic material, prions, virus, bacteria, and eucaryotic cells such as endothelial cells, monocyte/macrophages or vascular smooth muscle cells to name but a few examples. The therapeutic agent may also be a pro-drug, which metabolizes into the desired drug when administered to a host. In addition, the therapeutic agents may be pre-formulated as a microcapsules, microspheres, microbubbles, liposomes, niosomes, emulsions, dispersions or the like before it is incorporated into the therapeutic layer. The therapeutic agent may also be radioactive isotopes or agents activated by some other form of energy such as light or ultrasonic energy, or by other circulating molecules that can be systemically administered.

[0039] A water soluble drug is one that has a solubility of greater than 1.0 mg/mL in water at body temperature.

[0040] The term "matrix" or "biocompatible matrix" are used interchangeably to refer to a medium or material that, upon implantation in a subject, does not elicit a detrimental response sufficient to result in the rejection of the matrix. The matrix typically does not provide any therapeutic responses itself, though the matrix may contain or surround a therapeutic agent, and/or modulate the release of the therapeutic agent into the body. A matrix is also a medium that may simply provide support, structural integrity or structural barriers. The matrix may be polymeric, non-polymeric, hydrophobic, hydrophilic, lipophilic, amphiphilic, and the like.

[0041] The term "bioresorbable" refers to a matrix, as defined herein, that can be broken down by either chemical or physical process, upon interaction with a physiological environment. The matrix can erode or dissolve. A bioresorbable matrix serves a temporary function in the body, such as drug delivery, and is then degraded or broken into components that are metabolizable or excretable, over a period of time from minutes to years, preferably less than one year, while maintaining any requisite structural integrity in that same time period.

[0042] The term "pharmaceutically acceptable" refers to a matrix or an additive, as defined herein, that is not toxic to the host or patient. When in reference to a matrix, it provides the appropriate storage and/or delivery of therapeutic, activating or deactivating agents, as defined herein, and does not interfere with the effectiveness or the biological activity of the agent.

[0043] The term "mixing layer" refers to a matrix layer which is adjacent a therapeutic agent layer. Before the mixing layer is introduced to the device, the mixing layer preferably contains no therapeutic agent, or it contains a therapeutic agent which is different from the therapeutic agent of the therapeutic agent layer. The mixing layer is introduced in a liquefied state and may mix with the therapeutic agent layer causing the mixing layer to incorporate a portion of the adjacent therapeutic agent layer once the layer has at least partially solidified. The mixing layer may also serve to control the rate at which a drug is released into the reaction environment. The release rate can be controlled by the rate of erosion or dissolution of the mixing layer or by the rate of diffusion of the therapeutic agent from within the mixing and therapeutic agent layers. The mixing layer is preferably bioresorbable.

[0044] The term "erosion" refers to the process by which the components of a medium or matrix are bioresorbed and/or degraded and/or broken down by either chemical or physical processes. For example in reference to polymers, erosion can occur by cleavage or hydrolysis of the polymer chains, such that the molecular weight of the polymer is lowered. The polymer of lower molecular weight will have greater solubility in water and is therefore dissolved away. In another example, erosion occurs by physically breaking apart upon interaction with a physiological environment.

[0045] The term "erosion rate" is a measure of the amount of time it takes for the erosion process to occur and is usually report in unit area per unit time.

[0046] The term "degrade" or "deactivate" refers to any process that causes an active component, such as a therapeutic agent, to become unable, or less able, to perform the action which it was intended to perform when incorporated in the device.

[0047] The term "polymer" refers to molecules formed from the chemical union of two or more repeating units, called monomers. Accordingly, included within the term "polymer" may be, for example, dimers, trimers and oligomers. The polymer may be synthetic, naturally-occurring or semisynthetic. In preferred form, the term "polymer" refers to molecules which typically have a M_w greater than about 3000 and preferably greater than about 10,000 and a M_w that is less than about 10 million, preferably less than about a million and more preferably less than about 200,000. Examples of polymers include but are not limited to, poly-α-hydroxy acid esters such as, polylactic acid, polyglycolic acid, polylactic-co-glycolic acid, polylactic acid-co-caprolactone; polyethylene glycol and polyethylene oxide, polyvinyl pyrrolidone, polyorthoesters; polysaccharides and polysaccharide derivatives such as polyhyaluronic acid, polyalginic acid, chitin, chitosan, chitosan derivatives, cellulose, hydroxyethylcellulose, hydroxypropylcellulose, carboxymethylcellulose; polypeptides, and proteins such as polylysine, polyglutamic acid, albumin; polyanhydrides; polyhydroxy alkonoates such as polyhydroxy valerate, polyhydroxy butyrate, and the like.

[0048] The term "lipid", as used herein, refers to a matrix that comprises preferably non-polymeric small organic, synthetic or naturally-occurring, compounds which are generally amphipathic and biocompatible. The lipids typically comprise a hydrophilic component and a hydrophobic component. Exemplary lipids include, for example, fatty acids, fatty acid esters, neutral fats, phospholipids, glycolipids, aliphatic alcohols, waxes, terpenes, steroids and surfactants. Term lipid is also meant to include derivatives of lipids. More specifically the term lipids includes but is not limited to phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, sphingomyelin as well as synthetic phospholipids such as dimyristoyl phosphatidylcholine, dipalmitoyl phosphatidylcholine, distearoyl phosphatidylcholine, distearoyl phosphatidylglycerol, dipalmitoyl phosphatidylglycerol, dimyristoyl phosphatidylserine, distearoyl phosphatidylserine and dipalmitoyl phosphatidylserine.

[0049] The term "additives" refers to pharmaceutically acceptable compounds, materials, and compositions that may be included in a matrix along with a therapeutic agent. An additive may be encapsulated in or on or around a matrix. It may be homogeneously or heterogeneously disposed, as defined herein, in the matrix. Some examples of additives are pharmaceutically acceptable excipients, adjuvants, carriers, antioxidants, preservatives, buffers, antacids, and the like, such as those disclosed in Remington: The Science and Practice of Pharmacy, Gennaro, ed., Mack Publishing Co., Easton, Pa., 19th ed., 1995.

[0050] The term "holes" refers to holes of any shape and includes both through-openings and recesses.

[0051] The term "reaction environment" or "environment" refers to the area between a tissue surface abutting the device and the first intact layer of beneficial agent within a hole in the medical device.

[0052] The term "liquefied" is used herein to define a component which is put in a liquid state either by heating the component to a temperature higher than its melting point, or glass transition temperature, or by dissolving the component in a solvent. The typical liquefied materials of the present invention will have a viscosity of less than about 13,000 centipoise, and preferably less about 10,000 centipoise.

[0053] The term "homogeneously disposed" or "homogeneously dispersed" refers to a mixture in which each of the components are uniformly dispersed within the matrix.

[0054] The term "heterogeneously disposed" or "heterogeneously dispersed" refers to a mixture in which the components are not mixed uniformly into a matrix.

[0055] The term "solid solution" refers to a homogeneously dispersed mixture of two or more substances. A component that is mixed uniformly in a matrix in such a manner that the component is macroscopically indistinguishable from the matrix itself. An example of a solid solution is a metal alloy, such as brass.

[0056] The term "multi-phase mixture" refers to a mixture of two or more substances in which at least one component is macroscopically distinguishable from the matrix itself. An example of a multi-phase mixture is a macro emulsion.

Implantable Medical Devices with Holes

[0057] **FIG. 1** illustrates a medical device **10** according to the present invention in the form of a stent design with large, non-deforming struts **12** and links **14**, which can contain holes **20** without compromising the mechanical properties of the struts or links, or the device as a whole. The non-deforming struts **12** and links **14** may be achieved by the use of ductile hinges **16** which are described in detail in U.S. Pat.

No. 6,241,762 which is incorporated hereby by reference in its entirety. The holes **20** serve as large, protected reservoirs for delivering various beneficial agents to the device implantation site.

[**0058**] The relatively large, protected openings **20**, as described above, make the expandable medical device of the present invention particularly suitable for delivering larger molecules or genetic or cellular agents, such as, for example, protein drugs, enzymes, antibodies, antisense oligonucleotides, ribozymes, gene/vector constructs, and cells (including but not limited to cultures of a patient's own endothelial cells). Many of these types of agents are biodegradable or fragile, have a very short or no shelf life, must be prepared at the time of use, or cannot be pre-loaded into delivery devices such as stents during the manufacture thereof for some other reason. The large holes **20** in the expandable device of the present invention form protected areas or receptors to facilitate the loading of such an agent either at the time of use or prior to use, and to protect the agent from abrasion and extrusion during delivery and implantation.

[**0059**] The volume of beneficial agent that can be delivered using holes **20** is about 3 to 10 times greater than the volume of a 5 micron coating covering a stent with the same stent/vessel wall coverage ratio. This much larger beneficial agent capacity provides several advantages. The larger capacity can be used to deliver multi-drug combinations, each with independent release profiles, for improved efficacy. Also, larger capacity can be used to provide larger quantities of less aggressive drugs and to achieve clinical efficacy without the undesirable side-effects of more potent drugs, such as retarded healing of the endothelial layer.

[**0060**] Holes also decrease the surface area of the beneficial agent bearing compounds to which the vessel wall surface is exposed. For typical devices with beneficial agent openings, this exposure decreases by a factors ranging from about 6:1 to 8:1, by comparison with surface coated stents. This dramatically reduces the exposure of vessel wall tissue to polymer carriers and other agents that can cause inflammation, while simultaneously increasing the quantity of beneficial agent delivered, and improving control of release kinetics.

[**0061**] **FIG. 2** shows a cross section of a medical device **10** in which one or more beneficial agents have been loaded into the opening **20** in discrete layers **30**. Examples of some methods of creating such layers and arrangements of layers are described in U.S. patent application Ser. No. 09/948,989, filed on Sep. 7, 2001, which is incorporated herein by reference in its entirety.

[**0062**] According to one example, the total depth of the opening **20** is about 125 to about 140 microns, and the typical layer thickness would be about 2 to about 50 microns, preferably about 12 microns. Each typical layer is thus individually about twice as thick as the typical coating applied to surface-coated stents. There would be at least two and preferably about ten to twelve such layers in a typical opening, with a total beneficial agent thickness about 4 to 28 times greater than a typical surface coating. According to one preferred embodiment of the present invention, the openings have an area of at least 5×10^{-6} square inches, and preferably at least 7×10^{-6} square inches.

[**0063**] Since each layer is created independently, individual chemical compositions and pharmacokinetic properties can be imparted to each layer. Numerous useful arrangements of such layers can be formed, some of which will be described below. Each of the layers may include one or more agents in the same or different proportions from layer to layer. The layers may be solid, porous, or filled with other drugs or excipients.

[**0064**] **FIG. 2** shows an arrangement of layers provided in a through opening **20** which include a barrier layer **30**, one or more therapeutic agent layers **40**, and a plurality of mixing layers **50**. The barrier layer **30** substantially prevents delivery of the therapeutic agent in the therapeutic agent layers and the mixing layers from being delivered to a side of the device **10** adjacent the barrier layer. The therapeutic agent layer **40** and the mixing layers **50** are loaded sequentially into the medical device opening **20**, such that a concentration gradient of therapeutic agent is present with a highest concentration of therapeutic agent at the interior layers closer to the barrier layer and a lowest concentration of therapeutic agent at the exterior mixing layers. The combination of therapeutic agent layer and mixing agent layers allows a water soluble therapeutic agent to be delivered over an extended time period of time. The time period for delivery can be modulated from minutes, to hours, to days. Preferably the time period for delivery is greater than 1 day, more preferably greater than 3 days.

[**0065**] In one embodiment the layers are loaded into the medical device by first loading the therapeutic agent layer, **40**, into the holes of the medical device in a liquefied state. The therapeutic agent layer is then allowed to solidify. A first mixing layer, **50**, is then loaded into the holes within the medical device in a liquefied state. When the liquid mixing layer, **50**, comes into contact with the therapeutic agent layer, **40**, a portion of the therapeutic agent layer is liquefied allowing a co-mingling of some of the components of each of the two layers. When the mixing layer solidifies, there is therapeutic agent within the mixing layer.

[**0066**] Optionally, a second mixing layer is then loaded into the holes within the medical device in a liquefied state. When the second liquid mixing layer comes into contact with the first mixing layer, a portion of the first mixing layer is liquefied allowing a co-mingling of some of the components of each of the two layers. When the mixing layer solidifies, there is an amount of therapeutic agent within the second mixing layer that is less than the amount of therapeutic agent in the first mixing layer. Subsequent additions of mixing layers results in the formation of multiple mixing layers with decreasing amounts of therapeutic agent. The gradient of therapeutic agent incorporated in a mixing layers adjacent the therapeutic agent layer is especially advantageous for the delivery of water soluble drugs such as a 2-chlorodeoxyadenosine.

[**0067**] An example of a binding agent is Poly vinylpyrrolidone. The polymers of the therapeutic agent layer may be the same as or different from the polymer of the mixing layers. The polymer can be liquefied by maintaining the material at a temperature that is greater than its melting point, or glass transition temperature, or by dissolution in a solvent.

[**0068**] Some examples of hydrophobic, bioresorbable matrix materials for the mixing layer are lipids, fatty acid esters, such as glycerides. The erosion rate is controlled by varying the hydrophilic-lipophilic balance (HLB). The poly-

mers of the individual mixing layers may be the same or different. These polymers can be liquefied by maintaining the material at a temperature that is greater than its melting point, or glass transition temperature, or by dissolution in a solvent.

[0069] Bioerosion of the mixing layers may induce the release of the therapeutic agent from either the mixing layer or the therapeutic agent layer. However, in some embodiments, the mixing layer remains essentially intact, and the therapeutic agent is released into the reaction environment by diffusing from the therapeutic agent layer and through the mixing layers.

Therapeutic Layer Formulations

[0070] The therapeutic agent layers of the present invention may consist of the therapeutic agent alone or a therapeutic agent in combination with a bioresorbable matrix. The matrix of the therapeutic agent layers can be made from pharmaceutically acceptable polymers, such as those typically used in medical devices. This polymer may also be referred to as a binding agent. Typically, when a lesser amount of matrix material is used relative to the amount of drug, for example 5-50% polymer to 95-50% drug, the material is called a binding agent.

[0071] Polymers useful in the therapeutic agent layer as either a matrix material or a binding agent are well known and include but are not limited to poly-α-hydroxy acid esters such as, polylactic acid, polyglycolic acid, polylactic-co-glycolic acid, polylactic acid-co-caprolactone; polyethylene glycol and polyethylene oxide; poly vinyl alcohol, polyvinyl pyrrolidone; polyorthoesters; polysaccharides and polysaccharide derivatives such as polyhyaluronic acid, a glycosaminoglycan, polyalginic acid, chitin, chitosan, chitosan derivatives, cellulose, hydroxyethylcellulose, hydroxypropylcellulose, carboxymethylcellulose; polypeptides, and proteins such as polylysine, polyglutamic acid, albumin; polyanhydrides; polyhydroxy alkonoates such as polyhydroxy valerate, polyhydroxy butyrate, and the like, and copolymers thereof. Particularly useful polymers include poly ethylene glycol, poly ethylene oxide, poly vinylpyrrolidone, poly vinyl alcohol, polysaccharides and their derivatives, poly hyaluronic acid, poly alginic acid, chitin, chitosan, chitosan derivatives, cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, poly peptides, poly lysine, poly glutamic acid, and proteins. These polymers and copolymers can be prepared by methods well known in the art (see, for example, Rempp and Merril: Polymer Synthesis, 1998, John Wiley and Sons) in or can be used as purchased from Alkermes, in Cambridge, Mass. or Birmingham Polymer Inc., in Birmingham, Ala.

[0072] The preferred polymer for use in the therapeutic layer of the present invention is poly vinylpyrrolidone (PVP). The rate at which the polymer resorbs is determined by the selection of the subsequently loaded mixing layers.

Therapeutic Agent Formulations

[0073] Some drugs that are useful in the present invention are low molecular weight synthetic oligonucleotides and polypeptides, such as 2-chlorodeoxyadenosine, restinase, or restin NG.

[0074] Typical formulations for therapeutic agents incorporated in these medical devices are well known to those skilled in the art and include but are not limited to solid particle dispersions, encapsulated agent dispersions, and emulsions, suspensions, liposomes or microparticles, wherein said liposome or microparticle comprise a homogeneous or heterogeneous mixture of the therapeutic agent.

[0075] The amount of the drug that is present in the device, and that is required to achieve a therapeutic effect, depends on many factors, such as the minimum necessary dosage of the particular drug, the condition to be treated, the chosen location of the inserted device, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

[0076] The appropriate dosage level of the therapeutic agent, for more traditional routes of administration, are known to one skilled in the art. These conventional dosage levels correspond to the upper range of dosage levels for compositions, including a physiologically active substance and traditional penetration enhancer. However, because the delivery of the active substance occurs at the site where the drug is required, dosage levels significantly lower than a conventional dosage level may be used with success. Ultimately, the percentage of therapeutic agent in the composition is determined by the required effective dosage, the therapeutic activity of the particular formulation, and the desired release profile. In general, the active substance will be present in the composition in an amount from about 0.0001% to about 99%, more preferably about 0.01% to about 80% by weight of the total composition depending upon the particular substance employed. However, generally the amount will range from about 0.05% to about 75% by weight of the total composition.

Mixing Layer Formulations

[0077] The mixing layers of the present invention are comprised of a bioresorbable matrix and optionally contain additional additives, therapeutic agents, activating agents, deactivating agents, and the like as described in U.S. patent application Ser. No. 10/253,020. In addition to the polymer materials described above, the mixing layer may also be comprised of pharmaceutically acceptable lipids or lipid derivatives, which are well known in the art and include but are not limited to fatty acids, fatty acid esters, lysolipids, phosphocholines, (Avanti Polar Lipids, Alabaster, Ala.), including 1-alkyl-2-acetoyl-sn-glycero 3-phosphocholines, and 1-alkyl-2-hydroxy-sn-glycero 3-phosphocholines; phosphatidylcholine with both saturated and unsaturated lipids, including dioleoylphosphatidylcholine; dimyristoyl-phosphatidylcholine; dipentadecanoylphosphatidylcholine; dilauroylphosphatidyl-choline; dipalmitoylphosphatidyl-choline (DPPC); distearoylphosphatidylcholine (DSPC); and diarachidonylphosphatidylcholine (DAPC); phosphatidyl-ethanolamines, such as dioleoylphosphatidylethanolamine, dipahnitoyl-phosphatidylethanolamine (DPPE) and distearoylphosphatidylefhanolamine (DSPE); phosphatidylserine; phosphatidylglycerols, including distearoylphosphatidylglycerol (DSPG); phosphatidylinositol; sphingolipids such as sphingomyelin; glucolipids; sulfatides; glycosphingolipids; phosphatidic acids, such as dipahmitoylphosphatidic acid (DPPA) and distearoylphosphatidic acid (DSPA); palmitic acid; stearic acid; arachidonic acid; oleic acid; lipids bearing polymers, such as chitin, hyaluronic acid, polyvinylpyrrolidone or polyethylene glycol (PEG), also referred to herein as "pegylated lipids", with

preferred lipids bearing polymers including DPPE-PEG (DPPE-PEG), which refers to the lipid DPPE having a PEG polymer attached thereto, including, for example, DPPE-PEG5000, which refers to DPPE having attached thereto a PEG polymer having a mean average molecular weight of about 5000; lipids bearing sulfonated mono-, di-, oligo- or polysaccharides; cholesterol, cholesterol sulfate and cholesterol hemisuccinate; tocopherol hemisuccinate; lipids with ether and ester-linked fatty acids; polymerized lipids (a wide variety of which are well known in the art); diacetyl phosphate; dicetyl phosphate; stearylamine; cardiolipin; phospholipids with short chain fatty acids of about 6 to about 8 carbons in length; synthetic phospholipids with asymmetric acyl chains, such as, for example, one acyl chain of about 6 carbons and another acyl chain of about 12 carbons; ceramides; non-ionic liposomes including niosomes such as polyoxyethylene fatty acid esters, polyoxyethylene fatty alcohols, polyoxyethylene fatty alcohol ethers, polyoxyethylated sorbitan fatty acid esters, glycerol polyethylene glycol oxystearate, glycerol polyethylene glycol ricinoleate, ethoxylated soybean sterols, ethoxylated castor oil, polyoxyethylene-polyoxypropylene polymers, and polyoxyethylene fatty acid stearates; sterol aliphatic acid esters including cholesterol sulfate, cholesterol butyrate, cholesterol isobutyrate, cholesterol palmitate, cholesterol stearate, lanosterol acetate, ergosterol palmitate, and phytosterol n-butyrate; sterol esters of sugar acids including cholesterol glucuronide, lanosterol glucuronide, 7-dehydrocholesterol glucuronide, ergosterol glucuronide, cholesterol gluconate, lanosterol gluconate, and ergosterol gluconate; esters of sugar acids and alcohols including lauryl glucuronide, stearoyl glucuronide, myristoyl glucuronide, lauryl gluconate, myristoyl gluconate, and stearoyl gluconate; esters of sugars and aliphatic acids including sucrose diacetate hexaisobutyrate (SAIB), sucrose laurate, fructose laurate, sucrose palritate, sucrose stearate, glucuronic acid, gluconic acid and polyuronic acid; saponins including sarsasapogenin, smilagenin, hederagenin, oleanolic acid, and digitoxigenin; glycerol dilaurate, glycerol trilaurate, glycerol monolaurate, glycerol dipalmitate, glycerol and glycerol esters including glycerol tripalmitate, glycerol monopalmitate, glycerol distearate, glycerol tristearate, glycerol monostearate, glycerol monomyristate, glycerol dimyristate, glycerol trimyristate; long chain alcohols including n-decyl alcohol, lauryl alcohol, myristyl alcohol, cetyl alcohol, and n-octadecyl alcohol; 1,2-dioleoyl-sn-glycerol; 1,2-dipalmitoyl-sn-3-succinylglycerol; 1,3-dipalmitoyl-2-succinylglycerol; 1-hexadecyl-2-palmitoylglycerophosphoethanolamine and palmitoylhomocysteine, and/or combinations thereof.

[0078] If desired, a cationic lipid may be used, such as, for example, N-[1-(2,3-dioleoyloxy)propyl]-N,N,N-trimethylammonium chloride (DOTMA), 1,2-dioleoyloxy-3-(trimethylammonio)propane (DOTAP); and 1,2-dioleoyl-3-(4'-trimethylammonio)butanoyl-sn-glycerol (DOTB). If a cationic lipid is employed in the lipid compositions, the molar ratio of cationic lipid to non-cationic lipid may be, for example, from about 1:1000 to about 1:100. Preferably, the molar ratio of cationic lipid to non-cationic lipid may be from about 1:2 to about 1:10, with a ratio of from about 1:1 to about 1:2.5 being preferred. Even more preferably, the molar ratio of cationic lipid to non-cationic lipid may be about 1:1.

[0079] These lipid materials are well known in the art and can be used as purchased from Avanti, Burnaby, B.C. Canada.

[0080] The preferred lipids for use in the present invention are phosphatidyl-choline, phosphatidylethanolamine, phosphatidylserine, sphingomyelin as well as synthetic phospholipids such as dimyristoyl phosphatidylcholine, dipalmitoyl phosphatidylcholine, distearoyl phosphatidylcholine, distearoyl phosphatidyl-glycerol, dipalmitoyl phosphatidylglycerol, dimyristoyl phosphatidylserine, distearoyl phosphatidylserine and dipalmitoyl phosphatidylserine.

[0081] The rate at which the bioresorbable matrix resorbs is determined by the choice of lipid, the molecular weight, and the ratio of the chosen materials.

[0082] The mixing layer can resorb by either chemical mechanisms such as chemical interactions, dissolution in water, hydrolysis, or reaction with enzymes, or by physical erosion mechanisms.

Composite Matrix of Therapeutic Agent and Mixing Layers

[0083] Because of the methods used to make the implantable devices of the present invention, the therapeutic agent that is first incorporated in the therapeutic agent layer is ultimately found throughout the therapeutic agent layer and the mixing layers. Each layer is introduced into the holes of the device while in a liquefied state and then is allowed to solidify. A layer previously solidified within the wells is partially liquefied again when a new liquefied layer is introduced on top of the existing solid layer. This allows for the materials of these two layers to mix. The concentration of a therapeutic agent in a later applied layer is going to be smaller than the concentration of therapeutic agent in the previously formed layers. This layer method allows for a concentration gradient of therapeutic agent to be formed in the layers within the medical device.

[0084] The mixing layer and the therapeutic agent layer, into which the therapeutic agent is homogeneously or heterogeneously dispersed, may each be a homogeneous or heterogeneous mixture. For example, if the polymers of the mixing layer and the polymers of the therapeutic agent layer are mutually miscible, then the material contained within the holes of the implantable medical device will be a solid solution, or a one phase mixture, comprising each of these polymers. Examples of polymer systems that can form a one phase homogeneous mixture include but are not limited to 1) polyvinyl pyrrolidone and poly vinyl alcohol, 2) polyvinyl pyrrolidone and polyethylene glycol, 3) polyvinyl pyrrolidone and polyalginate, and 4) polyvinyl pyrrolidone and carboxymethylcellulose.

[0085] If the polymers comprising the mixing layer and therapeutic agent layer are only slightly miscible or are immiscible, then the material contained within the holes of the implantable medical device will be a two phase (or phase separated) mixture comprising each of these polymers. The two phase mixture may be

[0086] i) phase domains of the mixing layer polymer dispersed in a continuous phase of the therapeutic agent layer polymer;

[0087] ii) phase domains of the therapeutic agent layer polymer dispersed in a continuous phase of the mixing layer polymer; or

[0088] iii) two co-continuous phases each of the mixing layer polymer and the therapeutic agent layer polymer.

[0089] The type of two-phase mixture is determined by judicious choice of polymer for each layer, and the percentage of each polymer that dissolves in the solvent used to introduce the mixing layer(s). Examples of polymer systems that can form a multi-phase homogeneous mixture include but are not limited to 1) 50% by volume of polylactide and 50% by volume of poly vinylpyrrolidone 2) Poly(lactide-co-glycolide) and polyethylene oxide, and 3) poly DL-lactide and polyethylene oxide.

[0090] Additionally, two phase mixtures can be prepared such that one phase is a homogeneous mixture of a first weight ratio of mixing layer polymer and therapeutic agent layer polymer and a second phase is a is a homogeneous mixture of a second weight ratio of the same mixing layer polymer and therapeutic agent layer polymer. Generally, to achieve phase separation and a resulting two phase mixture, one phase will consist largely of mixing layer polymer and a second phase will consist largely of therapeutic agent layer polymer.

[0091] The therapeutic agent maybe homogeneously or heterogeneously disposed within the homogeneous or heterogeneous matrix formed by the polymers of the mixing layer and the therapeutic agent layer. For example, if the therapeutic agent is fully soluble in each of the mixing layer and therapeutic agent layer polymers, then the distribution of the therapeutic agent will be controlled by the relative solubility of the agent in each polymer and the relative miscibility of the polymers in each other as well as their respective volume proportions. If the desired amount of therapeutic agent exceeds the solubility in either or both of the mixing layer or the therapeutic agent layer, then the therapeutic agent can theoretically be found in four separate phases within the final composite matrix.

[0092] 1) homogeneously dissolved in the mixing layer polymer;

[0093] 2) dispersed as a second phase within the mixing layer polymer;

[0094] 3) homogeneously dissolved in the therapeutic agent layer polymer which is itself in a continuous or non-continuous phase with respect to the therapeutic agent layer; or

[0095] 4) dispersed as a second phase within the therapeutic agent layer polymer.

[0096] The distribution of the therapeutic agent, and thus the kinetic release profile, may be controlled by the selection of the molecular weight of the polymer, the solubility of the polymer and the volume percentage of each of the polymers used within the mixing and the therapeutic agent layers.

[0097] Any of the specific polymers or chemicals listed as a useful matrix material for the mixing layer may also be used in the therapeutic agent layer as a binder and vise-versa. Generally, the material chosen as a binding agent in therapeutic agent layer has different physical properties than the material used as the matrix in the mixing layers. This may be accomplished by using two different chemicals or polymers. Alternatively, the same type of polymer maybe used as long as the physical properties, such as solubility, or hydrophobicity, hydrophilicity or melting point or glass transition temperature can be altered by changing the polymers molecular weight or by adding additional components or additives, such as co-polymers, elasticizers, plasticizers and the like.

[0098] The therapeutic agent, which can be heterogeneously or homogeneously dispersed in the therapeutic agent layer and/or the mixing layer, can be a drug, or a drug formulated into a microcapsule, niosome, liposome, microbubble, microsphere, or the like. In addition, the mixing layer may contain more than one therapeutic agent. For example, a water sensitive drugs, such as a limus, or any other drug that must be administered through intravenous, intramuscular, or subcutaneously, could be incorporated in a hydrophobic matrix such as SAIB, or fatty acid ester.

[0099] Bioresorbable polymers may also be used to form barrier layers that resorb at a rate that can be predetermined base on the composition and that contain no therapeutic agent.

[0100] In one embodiment, the mixing layers, **50**, of the present invention are essentially hydrophobic and are bioresorbed at a rate that can be selected based on the polymers that are chosen in the formulation. The therapeutic agent layer, **40**, is comprised of about 50% to about 60% of a therapeutic agent and about 40% to about 50% of a pharmaceutically acceptable bioresorbable polymer that acts primarily as a binding agent.

Uses for Implantable Medical Devices

[0101] Although the present invention has been describe with reference to a medical device in the form of a stent, the medical devices of the present invention can also be medical devices of other shapes useful for site-specific and time-release delivery of drugs to the body and other organs and tissues. The drugs may be delivered to the vasculature including the coronary and peripheral vessels for a variety of therapies, and to other lumens in the body including the esophagus, urethera, and the bile duct. The drugs may increase lumen diameter, create occlusions, or deliver the drug for other reasons.

[0102] Medical devices and stents, as described herein, are useful for the prevention of amelioration of restenosis, particularly after percutaneous transluminal coronary angioplasty and intraluminal stent placement. In addition to the timed or sustained release of anti-restenosis agents, other agents such as anti-inflammatory agents may be incorporated in to the multi-layers incorporated in the plurality of holes within the device. This allows for site-specific treatment or prevention any complications routinely associated with stent placement that are known to occur at very specific times after the placement occurs.

[0103] The methods for loading beneficial agents into openings in an expandable medical device may include known techniques such as dipping and coating and also known piezoelectric micro-jetting techniques. Micro-injection devices may be used to deliver precise amounts of one or more liquid beneficial agents including mixing layers, therapeutic agent layers, and any other layers to precise locations on the expandable medical device in a known manner. The beneficial agents may also be loaded by manual injection devices.

EXAMPLES

[0104] In the examples below, the following abbreviations have the following meanings. If an abbreviation is not defined, it has its generally accepted meaning.

[0105] mL=milliliters

[0106] M=Molar

[0107] wt.=weight

[0108] vol.=volume

[0109] μL=microliters

[0110] μm=micrometers

[0111] nm=nanometers

[0112] DMSO=Dimethyl sulfoxide

[0113] NMP=N-methylpyrrolidone

[0114] DMAC=Dimethyl acetamide

Example 1

Formulation Comprising a Gradient of a Therapeutic Agent within the Mixing Layers

[0115] A first mixture of poly(lactide-co-glycolide) (PLGA) (Birmingham Polymers, Inc), lactide:glycolide::85:15, (M_v>100,000 Daltons) 7% wt. and a suitable organic solvent, such as DMSO, NMP, or DMAC 93% wt. is prepared. The mixture is loaded dropwise into holes in the stent, then the solvent is evaporated to begin formation of the barrier layer. A second barrier layer is laid over the first by the same method of filling polymer solution into the hole followed by solvent evaporation. The process is continued until five individual layers have been laid down to form the barrier layer.

[0116] A second mixture of 2-chlorodeoxyadenosine, 50% solids basis, and poly vinylpyrrolidone (PVP), 50% solids basis, in a suitable organic solvent, such as DMSO, is introduced into holes in the stent over the barrier layer. The solvent is evaporated to form a drug filled therapeutic agent layer. The filling and evaporation procedure is repeated until the hole is filled to about 50% of its total volume with drug in therapeutic agent layer layered on top of the barrier layer.

[0117] Three layers of a third solution, of poly(lactide-co-glycolide) (PLGA), lactide:glycolide::50:50, (M_v≅80,000 Daltons) 8% wt. and a suitable organic solvent, such as DMSO, are then laid down over the therapeutic agent layer to form three mixing layers. When each of the mixing layers is loaded into the stent, a portion of the layer beneath is incorporated in the new layer. In this way multiple mixing layers are formed containing a concentration gradient of therapeutic agent.

[0118] Following implantation of the filled stent in vivo, the 2-chlorodeoxyadenosine contained within the stent is delivered slowly over a time period of about 1 to about 8 days. The barrier layer prevents the therapeutic agent from being delivered out the barrier layer side of holes in the stent.

Example 2

Measurement of Drug Release Rates from a Medical Device with Multiple Therapeutic Agent Layers

[0119] A solution of phosphate buffered saline (PBS) is prepared by dissolving five "Phosphate Buffered Saline Tablets" (Sigma-Aldrich Co., catalog #P-4417) in 1000 mL deionized water to provide a solution with a pH of 7.4, 0.01 M in phosphate buffer, 0.0027 M in potassium chloride and 0.137 M in sodium chloride. This PBS solution is used as a Release Solution.

[0120] The elution rate of drug from the multilayered stent of Example 1 is determined in a standard sink condition experiment.

[0121] A first 10 mL screw capped vial is charged with release solution, 3 mL, then placed in a shaking water bath held at 37° C. until temperature has equilibrated. The above stent containing a concentration gradient of drug in the mixing layers is placed into the release solution, shaking at 60 cycles per minute commenced, and the stent is held immersed in the release solution for a period of time. The stent is then placed in a second screw capped vial is charged with release solution, 3 mL, at 37° C., and held for a period of time. The first release solution is called sample #1. From time to time, the stent is removed from release solution in one vial and placed into fresh solution in the next vial to generate a series of samples containing varying amounts of drug eluted from the stent.

[0122] The amount of drug in a given release solution sample is determined by High Pressure Liquid Chromatography (HPLC). The following conditions are used:

[0123] Analysis Column: Sym. C_{18} (5 μm, 3.9×150 mm, Waters Corp., Mass.)

[0124] Mobile phase: Water/Acetonitrile::55% vol./45% vol.

[0125] Flow Rate: 1 mL/minute

[0126] Temperature: 25° C.

[0127] Detection wavelength: 227 nm

[0128] Injection volume: 50 μL

[0129] Retention time: 10.5 minutes

[0130] By comparison with a calibration curve generated from known stock solutions, the amount of drug eluted into the release solution during any time period of the experiment can be calculated.

[0131] Methods and results for measuring release profiles are published in A. Finkelstein et al., "The Conor Medsystems Stent: A programmable Drug Delivery Device," TCT 2001 Conference, Washington, D.C., September 2001.

[0132] While the invention has been described in detail with reference to the preferred embodiments thereof, it will be apparent to one skilled in the art that various changes and modifications can be made and equivalents employed, without departing from the present invention.

1. An implantable medical device comprising:

an implantable device body having a plurality of holes;

a therapeutic agent provided in a first therapeutic agent layer and contained within the plurality of holes in the device body;

at least one mixing layer provided adjacent the first therapeutic agent layer in the plurality of holes, the at least one mixing layer including said therapeutic agent;

wherein the therapeutic agent layer and the at least one mixing layer together contain a concentration gradient of said therapeutic agent and allow for the controlled release of the therapeutic agent contained within the therapeutic agent layer and the at least one mixing layer; and

wherein the at least one mixing layer is formed by delivery of a polymer without the therapeutic agent to the holes, and further wherein the mixing layer acquires therapeutic agent when a portion of one of said therapeutic agent layer and said at least one mixing layer is in a liquid state.

2. The implantable medical device of claim 1, wherein the at least one mixing layer is a pharmaceutically acceptable bioresorbable matrix that allows the therapeutic agent contained within the therapeutic agent layer and the at least one mixing layer to be released as the matrix resorbs.

3. The implantable medical device of claim 2, wherein said pharmaceutically acceptable bioresorbable matrix comprises at least one pharmaceutically acceptable polymer.

4. The implantable medical device of claim 3, wherein said pharmaceutically acceptable polymer is selected from the group consisting of polylactic acid, polyglycolic acid, polylactic-co-glycolic acid, polylactic acid-co-caprolactone, polyethylene glycol, polyethylene oxide, poly lactic acid-block-poly ethylene glycol, poly glycolic acid-block-poly ethylene glycol, poly lactide-co-glycolide-block-poly ethylene glycol, poly ethylene glycol-block-lipid, polyvinyl pyrrolidone, poly vinyl alcohol, a glycosaminoglycan, polyorthoesters, polysaccharides, polysaccharide derivatives, polyhyaluronic acid, polyalginic acid, chitin, chitosan, chitosan derivatives, cellulose, hydroxyethylcellulose, hydroxypropylcellulose, carboxymethylcellulose, polypeptides, polylysine, polyglutamic acid, albumin, polyanhydrides, polyhydroxy alkonoates, polyhydroxy valerate, polyhydroxy butyrate, proteins, polyphosphate esters, lipids, and mixtures thereof.

5. The implantable medical device of claim 1, wherein the therapeutic agent layer comprises the therapeutic agent and a water soluble binding agent.

6. The implantable medical device of claim 5, wherein the binding agent is a pharmaceutically acceptable polymer selected from the group consisting of poly ethylene glycol, poly ethylene oxide, poly vinylpyrrolidone, poly vinyl alcohol, a glycosaminoglycan, polysaccharides, polysaccharide derivatives, poly hyaluronic acid, poly alginic acid, chitin, chitosan, chitosan derivatives, cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, poly peptides, poly lysine, poly glutamic acid, and proteins.

7. The implantable medical device of claim 5, wherein the at least one mixing layer includes a polymer different from the water soluble binding agent

8. The implantable medical device of claim 7, wherein the at least one mixing layer includes a plurality of mixing layers formed by sequential delivery of a substantially identical composition to the implantable medical device for each of the layers which take on the concentration gradient in the plurality of holes.

9. The implantable medical device of claim 5, wherein said therapeutic agent is homogeneously dispersed as a solid solution in said therapeutic agent layer.

10. The implantable medical device of claim 5, wherein said therapeutic agent is homogeneously dispersed as multiphase mixture in said therapeutic agent layer.

11. The implantable medical device of claim 5, wherein said therapeutic agent is heterogeneously disposed in said therapeutic agent layer.

12. The implantable medical device of claim 5, wherein said therapeutic agent is homogeneously or heterogeneously disposed in said therapeutic agent layer as a solid particle dispersion, encapsulated agent dispersion, an emulsion, a suspension, a liposome, niosome, or a microparticle, wherein said niosome, liposome or microparticle comprise a homogeneous or heterogeneous mixture of the therapeutic agent.

13. The implantable medical device of claim 4, wherein said therapeutic agent from the therapeutic agent layer is homogeneously dispersed as a solid solution in said at least one mixing layer.

14. The implantable medical device of claim 4, wherein said therapeutic agent is homogeneously dispersed as multiphase mixture in said at least one mixing layer.

15. The implantable medical device of claim 4, wherein said therapeutic agent from the therapeutic agent layer is heterogeneously disposed in said at least one mixing layer.

16. The implantable medical device of claim 16, wherein said therapeutic agent from the therapeutic agent layer is homogeneously or heterogeneously disposed in said at least one mixing layer as a solid particle dispersion, encapsulated agent dispersion, an emulsion, a suspension, a liposome, niosome, or a microparticle, wherein said niosome, liposome or microparticle comprise a homogeneous or heterogeneous mixture of the therapeutic agent.

17. The implantable medical device of claim 1, wherein the therapeutic agent is selected from the group consisting of antithrombotic agents, antineoplastic agents, neoplastic agents, antiproliferative agents, antisense compounds, immunosuppresants, angiogenic agents, angiogenic factors, antiangiogenic agents, and anti-inflammatory agents, or combinations thereof.

18. The implantable medical device of claim 1, wherein the therapeutic agent is selected from the group consisting of 2-chlorodeoxyadenosine, bivalirudin, Resten NG, and an oliogonucleotide.

19. The implantable medical device of claim 1, wherein said therapeutic agent is an agent selected for treatment of restenosis or inflammation.

20. The implantable medical device of claim 1, wherein the implantable medical device is a stent.

21. An implantable medical device comprising:

an implantable device body having a plurality of holes;

a therapeutic agent within the plurality of holes in the device body provided in a therapeutic agent layer; and

a mixing layer provided in the plurality of holes, the mixing layer including said therapeutic agent;

wherein the therapeutic agent layer and the mixing layer contain a concentration gradient of said therapeutic agent created by delivering a mixing layer material without the therapeutic agent and liquefying a portion of one of the therapeutic agent layer and the mixing layer with the other of the therapeutic layer and the mixing layer material, whereby the mixing layer has a smaller amount concentration of therapeutic agent contained therein than the therapeutic agent layer.

22. The implantable medical device of claim 21, wherein the mixing layer is a pharmaceutically acceptable bioresorb-

able matrix that allows the therapeutic agent contained within the therapeutic agent layer and the mixing layer to be released as the matrix resorbs.

23. The implantable medical device of claim 22, wherein said bioresorbable matrix comprises at least one pharmaceutically acceptable polymer.

24. The implantable medical device of claim 23, wherein said pharmaceutically acceptable polymer is selected from the group consisting of polylactic acid, polyglycolic acid, polylactic-co-glycolic acid, polylactic acid-co-caprolactone, polyethylene glycol, polyethylene oxide, poly lactic acid-block-poly ethylene glycol, poly glycolic acid-block-poly ethylene glycol, poly lactide-co-glycolide-block-poly ethylene glycol, poly ethylene glycol-block-lipid, polyvinyl pyrrolidone, poly vinyl alcohol, a glycosaminoglycan, polyorthoesters, polysaccharides, polysaccharide derivatives, polyhyaluronic acid, polyalginic acid, chitin, chitosan, chitosan derivatives, cellulose, hydroxyethylcellulose, hydroxypropylcellulose, carboxymethylcellulose, polypeptides, polylysine, polyglutamic acid, albumin, polyanhydrides, polyhydroxy alkonoates, polyhydroxy valerate, polyhydroxy butyrate, proteins, polyphosphate esters, lipids, and mixtures thereof.

25. The implantable medical device of claim 23, wherein the therapeutic agent layer comprises at least one pharmaceutically acceptable polymer different from the pharmaceutically acceptable polymer of the mixing layer.

26. The implantable medical device of claim 21, wherein the therapeutic agent layer comprises the therapeutic agent and a water soluble binding agent.

27. The implantable medical device of claim 26, wherein the binding agent is a pharmaceutically acceptable polymer selected from the group consisting of poly ethylene glycol, poly ethylene oxide, poly vinylpyrrolidone, poly vinyl alcohol, a glycosaminoglycan, polysaccharides, polysaccharide derivatives, poly hyaluronic acid, poly alginic acid, chitin, chitosan, chitosan derivatives, cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, poly peptides, poly lysine, poly glutamic acid, and proteins.

28. The implantable medical device of claim 26, wherein said therapeutic agent is homogeneously dispersed as a solid solution in said therapeutic agent layer.

29. The implantable medical device of claim 26, wherein said therapeutic agent is homogeneously dispersed as multi-phase mixture in said therapeutic agent layer.

30. The implantable medical device of claim 26, wherein said therapeutic agent is heterogeneously disposed in said therapeutic agent layer.

31. The implantable medical device of claim 30, wherein said therapeutic agent is homogeneously or heterogeneously disposed in said therapeutic agent layer as a solid particle dispersion, encapsulated agent dispersion, an emulsion, a suspension, a liposome, niosome, or a microparticle, wherein said niosome, liposome or microparticle comprise a homogeneous or heterogeneous mixture of the therapeutic agent.

32. The implantable medical device of claim 26, wherein said therapeutic agent from the therapeutic agent layer is homogeneously dispersed as a solid solution in said mixing layer.

33. The implantable medical device of claim 26, wherein said therapeutic agent from the therapeutic agent layer is homogeneously dispersed as multi-phase mixture in said mixing layer.

34. The implantable medical device of claim 26, wherein said therapeutic agent from the therapeutic agent layer is heterogeneously disposed in said mixing layer.

35. The implantable medical device of claim 34, wherein said therapeutic agent from the therapeutic agent layer is homogeneously or heterogeneously disposed in said mixing layer as a solid particle dispersion, encapsulated agent dispersion, an emulsion, a suspension, a liposome, niosome, or a microparticle, wherein said niosome, liposome or microparticle comprise a homogeneous or heterogeneous mixture of the therapeutic agent.

36. The implantable medical device of claim 21, wherein the therapeutic agent is selected from the group consisting of antithrombotic agents, antineoplastic agents, neoplastic agents, antiproliferative agents, antisense compounds, immunosuppresants, angiogenic agents, angiogenic factors, antiangiogenic agents, and anti-inflammatory agents, or combinations thereof.

37. The implantable medical device of claim 21, wherein the therapeutic agent is selected from the group consisting of 2-chlorodeoxyadenosine, bivalirudin, Resten NG, and an oliogonucleotide.

38. The implantable medical device of claim 21, wherein said therapeutic agent is an agent selected for treatment of restenosis or inflammation.

39. The implantable medical device of claim 21, wherein the implantable medical device is a stent.

40. An implantable medical device comprising:

an implantable device body having a plurality of holes;

a therapeutic agent provided in a first therapeutic agent layer and contained within the plurality of holes in the device body; and

at least one mixing layer provided adjacent the first therapeutic agent layer in the plurality of holes, the at least one mixing layer including said therapeutic agent;

wherein the first therapeutic agent layer and the at least one mixing layer together contain a concentration gradient of said therapeutic agent and allow for the controlled release of the therapeutic agent contained within the therapeutic agent layer and the at least one mixing layer; and

wherein the concentration gradient of the therapeutic agent in the holes has a highest concentration of therapeutic agent at an interior of the holes and a lowest concentration of therapeutic agent at an exterior of the holes.

41. The implantable medical device of claim 40, wherein said therapeutic agent is an agent selected for treatment of restenosis or inflammation.

42. The implantable medical device of claim 40, wherein the implantable medical device is a stent.

43. The implantable medical device of claim 40, wherein said therapeutic agent is homogeneously dispersed as a solid solution in said therapeutic agent layer.

44. The implantable medical device of claim 40, wherein said therapeutic agent is homogeneously dispersed as multi-phase mixture in said therapeutic agent layer.

45. The implantable medical device of claim 40, wherein said therapeutic agent is heterogeneously disposed in said therapeutic agent layer.

46. An implantable medical device comprising:

an implantable device body having a plurality of holes;

a barrier layer of PLGA formed in the plurality of holes;

a therapeutic agent layer formed in the plurality of holes adjacent the barrier layer, the therapeutic agent layer comprising a therapeutic agent and PLGA; and

a mixing layer formed in the plurality of holes adjacent the therapeutic agent layer, wherein the mixing layer comprises PLGA and a concentration gradient of the therapeutic agent.

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