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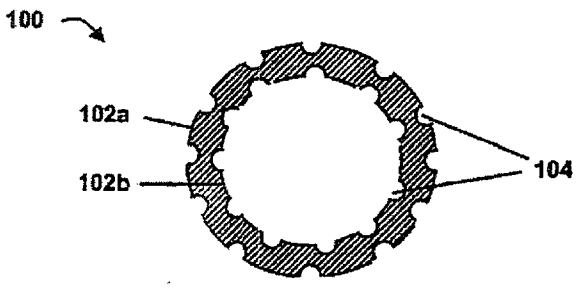
(54) **Title:** IMPLANTABLE ARTICLE, METHOD OF FORMING SAME AND METHOD FOR REDUCING THROMBOGENICITY



(57) **Abstract:** Endothelialization of a bodily fluid or tissue-contacting, particularly blood- contacting, surface may be accomplished to render that surface substantially non- thrombogenic. Thrombosis may also be mitigated or eliminated by providing an eroding layer on the surface that results in the removal of any thrombus formation as the layer erodes. An implantable device may utilize at least one surface having a plurality of nano-craters thereon that enhance or promote endothelialization. Additionally, an implantable device may have at least one first degradable layer for contacting bodily fluid or tissue and disposed about a central core, and at least one second degradable layer between the first degradable layer and the central core. The first degradable layer has a first degradation rate and the second degradable layer has a second degradation rate which degrades more slowly than the first degradable layer on contact with bodily fluid or tissue.

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IMPLANTABLE ARTICLE, METHOD OF FORMING SAME AND METHOD FOR REDUCING THROMBOGENICITY

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. Prov. Pat. App. Serial No. 60/808,558 filed May 26, 2006, which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates generally to implantable devices, such as implantable medical devices, and methods for the manufacture thereof. The invention also relates to methods for enhancing and promoting endothelialization and for minimizing thrombus formation on the surface of the implantable device.

BACKGROUND OF THE INVENTION

[0003] In recent years there has been growing interest in the use of artificial materials, particularly materials formed from polymers, for use in implantable devices that come into contact with bodily tissues or fluids particularly blood. Some examples of such devices are artificial heart valves, stents and vascular prosthesis. Progress in this area has, however, been hampered somewhat by the thrombogenicity of many polymer materials. Reference is made to M. Szycher, *J. Biomat Appln* (1998) 12: 321 in that regard.

[0004] Efforts to overcome the problems associated with thrombogenicity of polymer materials used in the production of implantable devices have not met with a great deal of success to date. Some examples of approaches that have bee attempted include heparinization (S.W. Kim, C.D. Ebert, J.Y. Lin, J.C. McRea *Am Soc Artif Internal Organs* (1983) 6: 76), physical modification of the surface (K. Webb, W. Hlady, P.A Tresco, *J. Biomed Mat Res* (1998) 41: 421-430; E.W. Merrill, *Ann NY Acad Sci* (1977) 6: 283-290) and increasing surface hydrophilicity (S.J. Sofia, E.W. Merrill, in "Polyethylene Glycol; Chemistry and Biological Applications", J.M. Harris and S. Zalipsky (eds.), *American Chemical Society* (1997) Ch. 22). Although these methods have met with some commercial viability, they are mainly useful for short-term applications, such as in catheter or in dialysis tubing. This is because many of the chemical and physical modifications of the device surfaces have limited shelf-life, both *ex vivo*

and *in vivo*. Moreover, the methods involved in the production of implantable devices using these approaches are both elaborate and intricate.

[0005] Attempts have also been made to minimize thrombus formation by promoting endothelialization of the surface of an implantable device that contacts bodily fluids or tissues in use as described, for example, in United States Patent No. 5,744,515, which relates to modification of a porous material with adhesion molecules, and U.S. Patent No. 6,379,383, which relates to deposition of the material used to form the device so as to control surface heterogenities.

SUMMARY OF THE INVENTION

[0006] Thrombus formation is a very complex process involving inter-dependent interactions between a surface of an implantable device, platelets and coagulation proteins. The present invention addresses the problem of thrombosis by endothelialization of a bodily fluid or tissue-contacting, particularly blood-contacting, surface to render that surface substantially non-thrombogenic. The invention also addresses the problem of thrombosis by providing an eroding layer on the surface that results in the removal of any thrombus formation as the layer erodes.

[0007] According to one aspect of the invention, there is provided an implantable device having at least one surface for contacting bodily fluid or tissue, said at least one surface comprising a plurality of nano-craters thereon that enhance or promote endothelialization of said at last one surface.

[0008] According to one aspect of the invention, there is provided an implantable device having at least one first degradable layer providing at least one surface of the implantable device for contacting bodily fluid or tissue and disposed about a central core, and at least one second degradable layer between said first degradable layer and the central core, wherein said first degradable layer has a first degradation rate and said second degradable layer has a second degradation rate such that said at least one first degradable layer degrades more rapidly than said at least one second degradable layer on contact with bodily fluid or tissue.

[0009] The material of the implantable device is not particularly limited. Furthermore, the nano-craters may be formed in the material that constitutes the body of the implantable

device, or may be formed in a layer that is applied to a support substrate forming the implantable device. Generally, the nano-craters will be formed in a surface layer of suitable biocompatible material applied to a support structure for the implantable device. The options for the biocompatible material forming the outer layer of the implantable device are generally known and are discussed hereafter.

[0010] The form of the implantable device is similarly not particularly limited. This may include any device that is intended to come into contact with bodily fluids or tissues, be that during in vivo applications or in vitro applications. Examples of particular devices will be provided hereafter.

[0011] According to further aspect of the invention, there is provided a method of Manufacturing an implantable device having at least one surface for contacting bodily fluid or tissue comprising: providing on said at least one surface a plurality of nano-craters that enhance or promote endothelialization of said at least one surface.

[0012] According to a further aspect of the invention, there is provided a method of reducing thrombogenicity of an implantable device having at least one surface for contacting bodily fluid or tissue, or promoting or enhancing endothelialization of an implantable device having at least one surface for contacting bodily fluid or tissue, comprising: providing on said at least one surface a plurality of nano-craters that enhance or promote endothelialization of said at least one surface.

[0013] According to another aspect of the invention, there is provided a method of manufacturing an implantable device having at least one surface for contacting bodily fluid or tissue, comprising: providing at least one first degradable layer which provides said at least one surface and which is disposed about a central core, and at least one second degradable layer between said first degradable layer and the central core, wherein said first degradable layer has a first degradation rate and second degradable layer has a second degradation rate such that said at least one first degradable layer degrades more rapidly than said at least one second degradable layer on contact with bodily fluid or tissue.

[0014] According to still another aspect of the invention, there is provided a method of reducing thrombogenicity of an implantable device having at least one surface for contacting bodily fluid or tissue, comprising: providing at least one first degradable layer which provides said at least one surface and which is disposed about a central core, and at least one second

degradable layer between said first degradable layer and the central core, wherein said first degradable layer has a first degradation rate and said second degradable layer has a second degradation rate such that said at least one first degradable layer degrades more rapidly than said at least one second degradable layer on contact with bodily fluid or tissue.

[0015] Other aspects and features of the present invention will become apparent to those of ordinary skill in the art upon review of the following description of specific embodiments of the invention in conjunction with the accompanying figures.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] In the figures, which illustrate, by way of example only, embodiments of the present invention,

[0017] **Figure 1** is a schematic representation of an implantable device having nano-craters on the surface of the device; and

[0018] **Figure 2** is a Schematic diagram of a process to form nano-craters in a surface using a mask and etching techniques;

[0019] **Figure 3** is a schematic representation of an implantable device having two degradable layers.

[0020] **Figure 4** illustrates some of the results of the number of cells correlated to pore size in a PLLA polymer.

[0021] **Figure 5** also illustrates some of the results of the number of cells correlated to pore size in a PLGA polymer sample.

[0022] **Figure 6** illustrates results correlating inter-pore distance to cell attachment and growth of the endothelial cells.

DETAILED DESCRIPTION OF THE INVENTION

[0023] When a bodily fluids-contacting or tissue-contacting, particularly blood-contacting, surface is coated with endothelial cells, it is rendered substantially non-thrombogenic. Thus, in one aspect, the reduced thrombogenicity of an implantable device is achieved by enhancing and/or promoting endothelialization of the surface of the implantable device that contacts bodily fluid or tissue.

[0024] This aspect of the invention is based on the surprising discovery that the inclusion of nano-craters on a surface of an implantable device that is intended to come into contact with bodily fluids or tissues, such as blood, advantageously improves endothelial cell attachment to the surface. The inclusion of the nano-craters therefore assists in the propagation of endothelial cells on the surface of the device. It is believed that the improved attachment and propagation of endothelial cells on the surface is a result of the nano- craters on the surface acting as foci for endothelial cell attachment. This aspect of the invention is particularly suited for manufacture of implantable devices that are intended to be in long-term contact with bodily fluids or tissues, particularly in long-term contact with blood.

[0025] In another aspect, the reduced thrombogenicity is achieved by providing a surface layer that degrades in a controlled fashion, such that any thrombus that is formed at the surface is removed as the surface layer degrades. This aspect of the invention is based on the discovery that by providing the surface with layers having different degradation rates, it is possible to remove any thrombus formed on the surface in a controlled fashion, by degradation of each successive layer. This aspect of the invention is particularly suited for manufacture of implantable devices that are intended to be in short-term contact with bodily fluids or tissues, particularly blood.

[0026] The implantable device described herein may be any device that would benefit from the reduced thrombogenicity of a surface, including by enhancement of the endothelialization of a surface or by degradation of surface that comes in contact with bodily fluid or tissue, as described below, so as to reduce or remove thrombus formation on such a surface, particularly where such a surface is a blood-contacting surface, when the device is in use.

[0027] As used herein, the term "implantable device", which may also be referred to as a "device" or a "medical device", refers to any device having at least one surface that comes in contact with bodily tissue or fluid, including blood, and includes a device for implanting in a subject's body, permanently or temporarily, long-term or short-term. The term, as used herein, also refers to any device that forms a part of an article.

[0028] It is envisaged that the device is useful not only for *in vivo* applications, but also *in vitro* applications. As such, the device is not particularly limited, but should be considered to include any device that is intended for contact with bodily fluids or tissues,

particularly blood, including conduits, grafts, valves, dialysis tubing and stents. As used herein the term "bodily fluids or tissues" includes biologically derived fluids and tissues as well as synthetic substitutes, for example artificial blood.

[0029] As used herein, the term "endothelialization" refers to the growth and/or proliferation of endothelial cells on a surface, such as the blood-contacting surface, or an implantable device. Promoting or enhancing endothelialization of a surface refers to promoting, enhancing, facilitation or increasing the attachment of, and growth of, endothelial cells on the surface.

[0030] As would be appreciated by a skilled person, the surface of a device for implantation into a subject is preferably biocompatible. The term "biocompatible" means that a substance is minimally toxic or irritating to biological tissue, such as to be sufficiently tolerated in the body without adverse effect. The surface may be formed of a material, which is different from the material that forms the surface and which is used as a support. Alternatively, the device and surface may be formed of the same material.

[0031] Suitable materials for forming the surface include biostable polymers, for example, polyethylene, polyurethane, polyolefin, or polyethylene terephthalate and degradable polymers, including degradable by chemical means or by exposure to radiation, for example, poly-lactide (PLA) including poly-L-lactide (PLLA), poly-glycolide (PGA), poly(lactide-co-glycolide) (PLGA) or polycaprolactone. In certain other embodiments, the degradable polymer may be biodegradable, meaning that the substance will readily degrade in an environment that is, or that is equivalent to, the body of a subject, for example when in contact with bodily fluid or tissue.

[0032] Other suitable materials that can be used to form an implantable device, or to provide the surface of an implantable device, are generally known in the art and examples of such materials are outlined in US Patent No. 5,744,515, which is herein incorporated by reference. For example, preferred materials include synthetic polymers, including oligomers, homopolymers, and copolymers resulting from either addition or condensation polymerization. Examples of suitable addition polymers include, but are not limited to, acrylics such as those polymerized from methyl cerylate, methyl methacrylate, acryli acid, methacrylic acid, acrylamide, hydroxyethy acrylate, hydroxyethyl methacrylate, glyceryl scrylate, glyceryl methacrylate, methacrylamide and ethacrylamide; vinyls such as styrene, vinyl chloride,

binaly pyrrolidone, polyvinyl alcohol, and vinyls acetate; polymers formed of ethylene, propylene, and tetrfluoroethylene. Examples of condensation polymers include, but are not limited to, nylons such as polycoprolactam, polylauryl lactam, polyjexamethylene adipamide, and polyexamethylene dodecanediamide, and also polyurethanes, polycarbonates, polyamides, polysulfones, poly(ethylene terephthalate), polyactic acid, polyglycolic acid, polydimethylsiloxanes, and polyetherketones.

[0033] Other suitable materials include metals and ceramics. The materials include, but are not limited to, nickel, titanium, nickel-titanium alloys such as Nitinol, stainless steel, cobalt and chromium. The ceramics include, but are not limited to, silicon nitride, silicon carbide, zirconia, and alumina, as well as glass and silica, ePTFE (Expanded polytetrafluoroethylene) is a preferred substrate material for use in fabricating implantable devices of the present invention, and particularly for fabricating vascular grafts. Suitable ePTFE is available in the form of vascular grafts from such sources as IMPRA, Inc., Tempe, Ariz. Commercially available grafts are constructed of ePTFE and supplied in sterile form in a variety of configurations, including straight, tapered and stepped configurations.

[0034] Referring to Figure1, in the depicted embodiment, device **100** is stent, with an exterior surface **102a** and an interior surface **102b** which lines the lumen of the stent, both of which have reduced thrombogenicity meaning that they have a reduced tendency to promote, induce or facilitate formation of thrombi when in contact with bodily fluid or tissue. In the case of a coronary stent, since surface **102b** contacts blood, including platelets, it is particularly important that surface **102b** be rendered less thrombogenic, as described herein.

[0035] Device **100**, in one particular variation, may comprise a polymeric stent fabricated as disclosed in U.S. Pat. App. 10/867,617 filed June 15, 2004 (U.S. Pat. Pub. 2005/0021131 A1), which is incorporated herein by reference in its entirety. The stent, as shown and described, may comprise a polymer that is at least partially amorphous and which undergoes a transition from a pliable, elastic state at a first higher temperature to a brittle glass-like state at a second lower temperature as it transitions through a particular glass transition temperature. This particular stent may be comprised of at least a first layer and a second layer where the first layer includes a first polymer that is at least partially amorphous and a second layer that is also at least partially amorphous. The stent may be formed to have a first shape at a relatively lower temperature and a second shape at a relatively higher

temperature. The inner and/or outer layer of the stent **100** may be processed to have nano-crater **104** as described herein.

[0036] A substantially uniform layer of nano-craters **104** are distributed on surface **102a** and **102b**, meaning that nano-craters **104** of substantially similar depth are distributed on the surfaces **102a** and **102b** to form a discernible layer having such nano-craters. It has advantageously been found that the provision of such nano-craters **104** enhances endothelialization of surface **102a** and **102b**, resulting in reduced thrombogenicity. The stent **100** is suitable for long-term implantation in the body of a subject.

[0037] As used herein, the term "nano-crater" means indentations or depressions provided on a surface. Generally the indentations are on the nanometer scale. In different embodiments, the nano-craters have an average diameter of between about 30 nm and about 150 nm.

[0038] The stent **100** has nano-craters **104** sufficiently distributed over surfaces **102a** and **102b** to promote or enhance endothelialization, preferably over the entirety of surface **102a** and **102b**. The nano-craters **104** may be regularly or irregularly distributed over surfaces **102a** and **102b**. In some embodiments, adjacent craters may be spaced about 200 nm or greater apart.

[0039] Such nano-craters **104** may be suitably shaped, having a regular or irregular shape, provide that endothelialization of the surfaces **102a** and **102b** having the nano-craters **104** is enhanced and/or promoted. For example, the nano-craters **104** may be hemi-spherical, hemi-cylindrical or elliptical.

[0040] The size and shape of the nano-craters **104** can be controlled to provide a unique surface morphology. By varying this surface morphology, the range of sizes that selectively promote endothelial cell attachment while not being reception to platelet attachment, can be readily ascertained.

[0041] Optionally, surfaces **102a** and **102b** of the stent **100** can be chemically modified so as to further enhance or promote endothelialization, for example when implanted in a subject's body.

[0042] By way of background, it is noted that there are two ways by which an implanted device or surface can be covered with endothelial cells. In the first, called the transmural or capillary endothelialization, endothelial cells migrate into the device from tissue

that is external to (usually above or below) the implanted device. For this sort of endothelialization to occur, the device itself must be sufficiently porous to permit the endothelial cells to migrate into it. A coronary stent such as the Palmaz stent (US Patent No. 6,379,383) is an example of such a device. This type of endothelialization may be achieved by coating an implantable device with a radiation-sensitive bioerodible polymer followed by irradiation with an electron beam to generate the nano-craters, as it set out below.

[0043] The second method of endothelialization involves migration of endothelial cells longitudinally into the device (e.g., in the lumen of a stent implanted in a blood vessel) from tissue adjacent to the device. In this case, porosity of the implantable device is not required, as endothelial cell attachment occurs from within a lumen or cavity of the device. However, the number of endothelial cells that are capable of this type of attachment is lower than those that can be achieved by transmural endothelialization.

[0044] Hence, it is envisaged that while the nano-cratered surfaces will enhance selective endothelial cell attachment on non-porous devices, the production and attachment of these endothelial cells *in vivo* may be enhanced using certain growth-stimulating molecules and adhesion-promoting molecules.

[0045] As used herein, the term "growth-stimulating molecule" refers to a molecule that stimulates or induces the differentiation, growth and proliferation of endothelial cells. Growth-stimulating molecules include peptides, proteins and glycoproteins, including hormones, capable of inducing an endothelial cell to grow and divide.

[0046] As used herein, the term "adhesion-promoting molecule" refers to a molecule that promotes or encourages adhesion or attachment of an endothelial cell to a surface. Adhesion-promoting molecules include peptides, proteins and glycoproteins capable of binding a cell to a substrate or to an adjacent cell.

[0047] As such, according to certain embodiments, surfaces **102a** and **102b** of the stent **100** include growth-stimulating molecules and/or adhesion-promoting molecules dispersed therein, which facilitate enhanced production of endothelial cells and their attachment to the nano-cratered surfaces **102a** and **102b**.

[0048] Suitable growth-stimulating molecules include granulocyte colony stimulating factor (gCSF), platelet-derived endothelial cell growth factor (PD-ECGF), fibroblast-derived

endothelial cell growth factor alpha, endothelial cell growth factor beta, endothelial cell growth factor 2a and endothelial call growth factor 2b.

[0049] Suitable adhesion molecules are described in US Patent No. 5,774,515, which is herein incorporated by references. They are typically large, naturally occurring proteins or carbohydrates, with molecular weights above 100,000 daltons. In vivo, adhesion molecules are typically able to bind to specific cell surface receptors, and mechanically attached cells to the substrate or to adjacent cells. In addition to promoting cell attachment, suitable adhesion molecules can promote other cell responses including cell migration and cell differentiation (which in turn can include the formation of capillary tubes by endothelial cells).

[0050] Preferred adhesion molecules include substrate adhesion molecules (SAM's) such as the proteins laminin, fibronectin, collagen, vitronectin, and tenascin, and adhesion peptides or functional synthetic analogs derived from SAM's. Other suitable adhesion molecules include cell-to-cell adhesion molecules (CAM's) such as N-cadherin and P-cadherin.

[0051] Parent (i.e., native) adhesion proteins typically have one or more active peptide domains that bind to cell surface receptors and which domains produce the cell attachment, migration, and differentiation effects of the parent adhesion proteins. .These domains consist of specific amino acid sequences, several of which have been synthesized and reported to promote the adhesion of endothelial cells. These domains and functional analogs of these domains are termed "adhesion peptides". In different embodiments, adhesion molecules are adhesion peptides and desirably, adhesion peptides have about 3 to about 30 amino acid residues in their amino acid sequences.

[0052] Adhesion peptides from fibronectin include, but are not limited to, RGD (arg-gly-asp) [SEQ ID NO.:1], REDV (arg-glu-asp-val) [SEQ ID NO.:2], and C/H-V (WQPPRARI or trp-gln-pro-pro-arg-ala-arg-ile) [SEQ ID NO.:3]. Adhesion peptides from laminin include, but are not limited to, YIGSR (tyr-ile-gly-ser-arg) [SEQ ID NO.:4] and SIKVAV (ser-ile-lys-val-ala-val) [SEQ ID NO.:5] and F-9 (RYVVLPRPVCFEKGMNYTVR or arg-tyr-val-val-leu-pro-arg-pro-val-cys-phe-glu-lys-gly-met-asn-tyr-thr-val-arg) [SEQ ID NO.:6]. Adhesion peptides from type IV collagen include, but are not limited to, Hep-III (GEFYFDLRLKGDK or gly-glu-phe-tyr-phe-asp-leu-arg-leu-lys-gly-asp-lys) [SEQ ID NO.:7].

[0053] While it is believed that nano-craters can selectively promote endothelialization, it is possible that platelet attachment to the nano-cratered surface may also be enhanced, leading to the undesirable effect of clot formation. To minimize any such effect, an anti-thrombotic molecule may be included on the surfaces **102a** and **102b** of the stent **100** by any suitable means, in amounts sufficient to minimize any platelet attachment during the process of endothelialization.

[0054] As used herein, an "anti-thrombotic molecule" is a molecule that reduces or prevents the formation of thrombi or clots on the surface of an implantable device that contacts bodily fluid or tissue, including when implanted in a subject's body. Anti-thrombotic molecules include, without limitation, heparin, and small molecules, such as benzamidine compounds, bicyclic pyrimidine compounds, nitro compounds, thio acid compounds, and proteins and peptides, including tissue-type plaminogen activator (t-PA), protein S and protein C.

[0055] The implantable device may be formed entirely from a single material and standard methods know in the art may be used to fashion the device. For example, a mold may be used, and a liquid polymer may be poured into the mold. This methods used will depend on the particular material used and the particular medical device that is to be formed.

[0056] In the case of the stent **100**, the device may be formed by rolling a sheet or film of material, or by winding a thin strip of material into a helix, as is known in the art. In this way, the nano-craters may be readily formed on each side of the sheet or strip, as discussed below, prior to rolling or winding to form the stent.

[0057] The implantable device may also be formed from a substrate material and another material applied to the substrate material to form a bodily fluid or tissue contracting surface by any suitable means, for example, by spin-coating from a solution or suspension, and the nano-craters are subsequently introduced into the surface. This surface layer should have sufficient thickness to introduce nano-craters having depth sufficient to enhance or promote endothelialization.

[0058] Without intending to particularly limit the method by which the nano-craters **104** are introduced to the surfaces **102a** and **102b** of the stent **100**, the following illustration of two possible approaches for forming the nano-craters 104 are provided.

[0059] The nano-craters **104** may be introduced through controlled degradation of the surfaces **102a** and **102b** of the stent **100**, as depicted in Figure 2. According to this approach, discrete portions of surfaces **102a** and **102b**, both of which are formed from a degradable polymer, are etched using a degradative process, for example, by exposing the polymer surface to electron beam radiation or by treating with a chemical that will degrade the surface, for example, strong alkali.

[0060] The technique of masking certain areas of the surface **102a** and **102b** may be employed to define areas of degradation. A higher density material, for example a silicon-based polymer or an acrylic polymer, may be patterned over surface **102a** and **102b** in which the nano-craters **104** are to be introduced, in a pattern that defines the desired distribution and depth of the nano-craters. For example, a focused ion beam may be used to form the desired pattern in the mask material which is layered on the degradable surface **102a** and **102b**.

[0061] After exposure to the etching means that degrade the unmasked regions of surface **102a** and **102b**, for example radiation or chemical means, the surface material in the degraded areas may then be leached out using water or solvent in which the degraded portions of the surface material are soluble, but which will not dissolve the non-degraded regions of the surface. The mask material may then be subsequently removed, for example by dissolution in a suitable solvent that dissolves the mask material but not the polymer surface **102a** and **102b**.

[0062] To illustrate, in one example, PLGA, PLLA, PGA, polycaprolactone or poluethylene may be employed to form the stent **100** or surfaces **102a** and **102b** of the stent **100**, both of which degrade in the dry state under electron-beam irradiation.

[0063] Thus, the degree of degradation may be controlled using the well-known effects of attenuation with depths of an incident electron beam. The depth of penetration of the incident electron beam is generally proportional to the electron energy or the accelerating voltage being used. This depth-dose distribution is determined by the absorption mechanism of mono-energetic electron beams having electron energy, eV, for a material of density p. The higher the density of a given material, the grater the attenuation effect on the electron beam. This attenuation effect will result in a varying radiation dose across the thickness of the surface and patterned higher density material, resulting in a variation of molecular weight of the polymer across the thickness of the surface.

[0064] An example of utilizing an incident electron beam for patterning a surface of a polymeric sample may include use of electron beam lithography, which is typically used in the semiconductor electronics industry for patterning integrated circuits and biosensors. Generally, a polymeric substrate having a radiation-sensitive film or resist may be placed in a vacuum chamber of a scanning- electron microscope and exposed by an electron beam under digital control. Because the beam width may be adjusted to range from a few picometers to several nanometers, an etched pattern may be formed by the beam across the polymer surface.

[0065] This variation of molecular weight across the thickness of the surface will result in differing degradation rates at areas masked with the higher density material than those not asked. When these non-masked degraded sections are exposed to water (or another suitable solvent), the leaching of low-molecular weight, water-soluble oligomers from the water-insoluble not-degraded regions of the surface will result in well-defined craters of known lateral dimensions and depth. Thus, the size and shape of the nano-craters **104** may be accurately controlled by this method, for example by controlling the does of the radiation, and the density of the material used to mask, as well as the pattern in which the masking material is applied. This results in a unique surface morphology, as discussed above, that selectively promotes endothelial cell attachment, while not being receptive to platelet attachment.

[0066] Alternatively, chemical means can be used with the above-described masking method to produce nano-craters at the surfaces **102a** and **102b**. For example, sodium hydroxide may be used to dissolve PLA in regions that are not protected by the alkali-resistant mask material, and the dissolved material may then be rinsed away in water to form nano-craters **104**. The mask may be removed as described above.

[0067] The nano-craters **104** may alternatively be formed on the surfaces **102a** and **102b** of the stent **100** by including nano-particles that are leachable from the surfaces **102a** and **102b**.

[0068] A "nano-particle" is any granular or particulate material in which the particulates have dimensions in the nano-metre range. The nano-particles may be irregularly shaped, or may be of well-defined size and shape, and may be leached from the surface leaving behind nano-craters corresponding to the size and shape of the nano-particles.

[0069] The nano-particles may be formed of any granular or particulate material which can be embedded in the material used to form surface **102a** and **102b**, which will not dissolve

in or become irreversibly bound to the material, and which can then be subsequently leached from the material. For example, the nano-particles can be formed from an inorganic salt, such as sodium chloride, form gelatin, sugar, chitosan, or polyvinyl pyrrolidone.

[0070] The nano-particles may be suspended in a dilute solution of a polymer being used to form the implantable device or more preferably, the surface of the implantable device which may then be spin-coated onto the substrate of the device at a desired thickness. The thickness will usually be in the micrometer range. By casting a very thin layer containing the nano-particles, it is possible to form a layer of polymer on an implantable device that has nano-craters only at the surface.

[0071] Subsequently, these particles on the surface are either leached out upon exposure to water or another suitable solvent, or are eroded once the device comes in contact with bodily fluid or tissue, for example when stent **100** is implanted, leaving behind a surface with well defined nano-craters **104** of know dimensions. Advantageously, the dimensions of the nano-craters **104** may be varied by varying the size and shape of the nano-particles dispersed in the polymer.

[0072] If the bodily fluid-contacting or tissue-contacting surface of the implantable device is to contain adhesion-promoting molecules, the nano-craters may be created, for example by irradiation, and concurrently the surface may be modified to release adhesion-promoting molecules and/or growth-stimulating molecules, for example into a lumen or cavity of the implantable device. Te adhesion-promoting molecules and/or growth-stimulating molecules may be assed to a polymer used to form the implantable device or the surface of the implantable device prior to coating the polymer on the substrate of the implantable device, and forming nano-craters.

[0073] However, adhesion-promoting molecules and growth-stimulating molecules may typically be proteins, which are sensitive biomolecules that may be denatured by addition to a liquid polymer, or when subjected to high intensity radiation. Thus, the adhesion-promoting molecules and/or growth-stimulating molecules may first be encapsulated in nano-particles of well-defined size and shape as it known in the art, for example, as described in US Patent No. 6,589,562 which is herein fully incorporated by reference. The nano-particles may be leached out as discussed above, leaving behind the nano-craters and simultaneously releasing the adhesion-promoting molecules and/or growth-stimulating molecules, for example

into a lumen. The nano-particles, when containing adhesion-promoting molecules and/or growth-stimulating molecules for delivery to bodily fluid or tissue comprise a material that is soluble in bodily fluid or tissue, for example, gelatin.

[0074] An anti-thrombotic molecule may be included in the nano-crated surface of an implantable device in a similar manner.

[0075] In an alternative embodiment, an implantable device with reduced thrombogenicity is achieved by providing the device with a surface that will degrade in a layered fashion when it contacts bodily fluid or tissue. This embodiment is useful for applications in which the device will be in contact with bodily fluid or tissue for a relatively short period of time, for example, a catheter or dialysis tubing that is in such contact for less than 24 hours. Preferably, the layers degrade relatively quickly, so as to prevent the formation of thrombi. This means that the degradation time for a given layer upon contacting bodily fluid or tissue may be, for example, between about 5 minutes and about 1 hour.

[0076] Thus, with reference to Figure 3, in an illustrative embodiment, a stent **100'** has first degradable layers **106a** and **106b** disposed about a central core **110**, and which layers provide surfaces **102'a** and **102'b** that comes into contact with bodily fluid or tissue, including blood, and second degradable layers **108a** and **108b**, between layers **106a** and **106b**, respectively, and the central core **110** of stent **100'**. In the depicted embodiment, the stent **100'** has a first surface **102'a**, which forms the exterior surface of the stent and an interior surface **102'b** which defines the lumen of the stent.

[0077] The second degradable layers **108a** and **108b** are the inner layer relative to the outer surfaces **102a'** and **102'b**, respectively, and have a slower degradation rate than the first degradable layers **106a** and **106b**. Therefore, on contact with bodily fluid or tissue, there is a peeling effect resulting from successive degradation of first degradable layers **106a** and **106b** followed by degradation of the second degradable layers **108a** and **108b**, and any thrombus formation on surface 102'a and 102'b is removed as the layers erode.

[0078] As mentioned above, the stent **100'** may also be configured and comprised in the manner as shown and described in U.S. Pat. App. 10/867,617, which has been incorporated above by reference in its entirety. In one variation, the stent **100'** configured as disclosed in U.S. Pat. App. 10/867,617 may comprise the central core **110** having the multiple degradable

layers disposed thereon. In other variations, it may be possible to have the multiple degradable layers correspond to the multiple layers comprising the stent structure.

[0079] The degradable layers **106a** and **106b** and **108a** and **108b** may be formed from any biodegrable polymers that are generally known in the art and described above and hereafter. For example, suitable polymers include polylactic acid (PLA) and polyglycolic acid (PGA) and copolymers of PLA and PGA (PLGA). These polymers may be amorphous or semi-crysalline.

[0080] For example, in one embodiment layers 106a and 106b may comprise PLA and the layers **108a** and **108b** may comprise PLGA, particularly PLDA 80/20; PLGA 75/25; or PLGA 53/47, wherein the numbers in the copolymer represent the percentage of PLA and PGA by weight, respectively, included in the copolymer.

[0081] Preferably, the thickness of each layers **106a** and **106b** and **108a** and **108b** is in the micrometer or sub-micrometer range, for example about 0.5 μm to about 10 μm.

[0082] In stent **100'**, the central core **110** may comprise a different material than layers **106a**, **106b**, **108a** and **108b**, and the material comprising the respective layers may be applied to central core **110**. Alternatively, stent **100'** may be formed of a single polymeric material but having first and second degradable layers of different average molecular weights of the polymer than found in central core **110**, so as to form the discrete layer **106a**, **106b**, **108a**, and **108b** about central core **110**, as described below.

[0083] Without intending to particularly limit the method by which the degradable layers **106a** and **106b** and **108a** and **108b** hading varying degradation rates are provided on the central core **110**, the following illustration of two possible approaches for forming the degradable layers are provided.

[0084] Polymers having different degradation rates can be selected and applied successively such that the layers **108a** and **108b** comprise a polymer with a slower degradation rate. A polymer with a faster degradation rate is selected for layers **106a** and **106b** such that layer **106a** and **106b** degrade more rapidly and remove any thrombus that may have formed on the surfaces **102'a** and **102'b**, respectively.

[0085] A skilled person will appreciate that a layered device having first and second degradable layers may comprise additional degradable layers, and that the degradation rate of each degradable layer increases with each successively inward layer such that the outer-most

layer degrades more quickly and that the inner-most layer degrades most slowly. For example, in one particular embodiment, a layered device may comprise the following layers disposed about a central core: PLA; PLGA 80/20; PLGA 75/25; and PLGA 53/47 in the given order with PLGA 53/47 being the outer-most layer.

[0086] The suitable number of layers to be applied can be readily determined and will depend on the degradation rates of the layers and the particular type of device and its intended use, including the intended duration of contact with bodily fluid or tissue.

[0087] Each of such layers may be spin-coated or solvent cast on to a substrate material forming the implantable device, using a solution or suspension containing, for example, about 10 to about 40% polymer by weight. As will be appreciated, other suitable means of applying thin layers of a polymer to a substrate may also be employed, for example, vapour deposition.

[0088] Alternatively, controlled degradation of a surface of an implantable device may be effected, for example, using radiation such as electron beam radiation. This method utilizes the attenuation effect of electron beam radiation within an irradiated material.

[0089] To illustrate, a single biodegradable material may be applied to the surface of an implantable device as described above and then irradiated to provide layers having different average molecular weights of the biodegradable material, and therefore varying degradation rates.

[0090] The suitable thickness of the material to be applied will typically be in the micrometer range, for example about 1 micron to about 20 microns, and can be readily determined. The desired thickness will depend on the particular polymer used and on the particular type of device and its intended use, including the intended duration of contact with bodily fluid and tissue.

[0091] The mechanism of attenuation, as discussed above, can be described as the loss of energy of the accelerating electrons. The depth of penetration is proportional to the electron energy or the accelerating voltage, and is attenuated in a manner proportional to the density of the material being penetrated. This attenuation effect will result in a varying radiation does through the depth of the material as the beam is attenuated as it travels deeper into the material, with the exterior surface receiving the strongest does of radiation. This will result in a variation of molecular weight in the surface material as a function of penetration depth or

material thickness. This variation of molecular weight through the depth of the material will in turn result in different degradation rates of the material coated on the device, thereby providing the first degradable layer, which due to the higher radiation does will have a lower molecular weight and will degrade faster then the underlying second degradable layer. This will result in a 'layer peeling' effect across the thickness of the polymer when in contact with bodily fluid or tissue.

[0092] The above-described devices can provide an implantable device having reduced thrombogenicity on contact with bodily fluid or tissue, for example when implanted, as compared to that typically observed with implantable medical devices. Standard surgical methods for implanting medical devices are known in the art. The method of implantation and duration of implantation will depend on the type of implantable device used, for example, a stent or a valve, the purpose of implantation and the disorder or condition that is to be treated with the implantable medical device. Thus, a method for reducing thrombogenicity, and for enhancing or promoting endothelialization, of an implantable device having at least one surface for contacting bodily fluid or tissue is contemplated.

[0093] The method comprises providing on the at least one surface a plurality of nano-craters that enhance or promote endothelialization of the at least one surface.

[0094] Alternatively the method comprises providing at least one first degradable layer which provides said at least one surface and which is disposed about a central core, and at least one second degradable layer between said first degradable layer and the central core, wherein said first degradable layer has a first degradation rate and said second degradable layer has a second degradation rate such that said at least one first degradable layer degrades more rapidly then said at least one second degradable layer so as to remove any thrombus that may be formed on said at least one surface.

[0095] All documents referred to herein are fully incorporated by reference.

[0096] Although various embodiments of the invention are disclosed herein, many adaptations and modifications may be made within the scope of the invention in accordance with the common general knowledge of those skilled in this art. Such modifications include the substitution of know equivalents for any aspect of the invention in order to achieve the same result in substantially the same way. All technical and scientific terms used herein have

the same meaning as commonly understood by one of ordinary skill in the art of this invention, unless defined otherwise.

EXAMPLE 1

[0097] For the following examples, each polymer was first dissolved in chloroform. Nano-sized salt particles were ground and sieved, and then dispersed in the polymer solution with constant stirring until the particles were visually uniformly dispersed. The polymer concentration was chosen such that it had sufficiently high viscosity to maintain a stable dispersion. The dispersion was then cast as a film of required thickness using a coater. The film was dried in an oven at 37°C, and then left at room temperature for several days in a dry environment. The dried films were immersed in water for 14days, with constant exchange of the water. The salt nano-particles were thus leached out, and the resulting film was dried again at 37°C and at room temperature.

[0098] Control films were prepared as pure polymer films without any surface modification.

[0099] PLLA and PLGL films having nano-craters in the surface were obtained by leaching out incorporated nano-particles of NaCl, as indicated in Table 1.

[0100] The best result were obtained with PLLA polymer surfaces prepared by incorporation and leaching out of salt particles (<90 Micron Diameter). Rapid endothelial cell attachment was seen with these surfaces, with significant coverage of the surface by cells.

[0101] Although early attachment of cells to the PLGA polymer film was observed, the results obtained with PLGA did not result in significant endothelialization of the polymer film. This is likely due to the molecular weight of PLGA chosen, or the ratio of lactide to glycolide in the copolymer, resulting in a polymer that degraded under the conditions used to leach the salt particles, and confirms that the degradation properties of the polymer and dissolution rate of the leachable salt particle can affect the formation of nano-craters. The resulting craters were therefore likely too large and improperly formed to promote confluent growth and attachment of the cells. This problem can be solved by varying the PLGA used to select a more stable form of PLGA and to increase the rate of leaching of salt particles, such that the PLGA is not degraded during the leaching process.

Table 1: Results of Endothelialization of Nano-Cratered Surfaces.

Material	Sample Preparation	Surface Treatment	Cell Seeding (cells/sq cm)	First endothrlial call attachment	Result at days 4/5
Control PLLA	Polymer + Solvent PLLA	NIL	20000	36 hours	Day 5 approximately 20% confluency
Contold PLGA	Polymer + Solvent PLGA 80:20	NIL	As Above	36 hours	Day 5 approximately 40% confluency
PLLA with Nanocraters	Polymer + Solvent PLLA	Leached NaCl 99% purity <90 Microns 1% concentration Leaching period 15 days.	As Above	2 hours	At Day 4 about 70% confluency Seen.
PLGA with nanocraters	Polymer + Solvent PLGA 80:20	Leached NaCl 990% Purity <90 microns 1% concentration Leaching period 15 days.	As Above	6 hours	At Day 4 about 5% confluency Seen.

EXAMPLE 2

[0102] In another example of a method for modifying a surface of a polymer for implantation within a patient body, porogen leaching of surfaces may be utilized to yield a surface which enhances endothelial cell growth over a defined range of surface features. In this particular example, surface pores were created by filling polymers such as Poly caprolactone (PCL), Poly L-lactide (PLLA), Poly (lactide-co-glycolide), etc. (although any of the other suitable polymers described herein may be utilized) with leaching agents of sugar and gelatin.

[0103] The sugar and gelatin particles ranged in size from 20 to 90 microns in diameter (although particles as small as 5 microns may also be utilized) where the average particle sizes typically ranged from 20, 45, and 90 microns. The leaching agents were added in concentrations ranging from 1 to 10% by weight in the polymer.

More particularly, the leaching agents were added in concentrations ranging from 1%, 5%, and 10% by weight in the polymer.

[0104] The leaching agents were then leached out with water from the polymer for a period of 10 to 12 days and the surface porosity was characterized by a scanning electron microscope (SEM) for crater dimensions and inter-crater spacing. With the physical characteristics determined, the surfaces of the polymer were then exposed to endothelial cells over an 11 day period, at the end of which the cells attached to the surface were counted and correlated to the surface features.

[0105] Figure 4 illustrates some of the results of the number of cells correlated to pore size in a PLLA polymer sample at day 9, which is representative of the results. Figure 5 also illustrates some of the results of the number of cells correlated to pore size in a PLGA polymer sample (specifically PLGA 80/20) also at day 9. In both the PLLA and PLGA polymers, each sample was prepared utilizing the methods described above. Generally, endothelial cell growth appeared better on PLGA 80/20 samples than on PLLA samples. Moreover, both gelatin and sugar porogens appear to act similarly and regardless of the porogen used, cell growth appears inversely dependent on pore size. However, gelatin appeared to be optimal for use as a porogen in the size range of about 5 to 40 microns at concentrations of about 5 to 10% in the starting solution. The PCL samples, also prepared as described above, showed growth of endothelial cells although the growth did not appear dependent on pore size in the range studied.

[0106] Generally, endothelial cell attachment and proliferation is higher at lower crater sizes (between about 5-10 microns) and decreases with higher crater size up to about 90 microns; however, compared to controls (no craters), all the samples showed enhanced endothelial cell attachment.

[0107] By changing the concentration of the particles in the polymer (prior to leaching), mentioned above as 1%, 5%, and 10% concentrations, the inter-pore distances along the polymer surfaces were varied from an average of about 50 microns to 250 microns. As illustrated by the results in Figure 6, an inter-pore

distance ranging from about 50 to 100 microns and more preferably between 50 to 80 microns appeared optimal for attachment and growth of the endothelial cells.

[0108] Accordingly, endothelial cell growth appears to correlate inversely to pore size on surfaces of PLLA and PLGA samples, but not to PCL samples. As pore size is decreased (e.g., down to about 5 to 10 microns), endothelial cell growth is increased. However, at all pore sizes, PCL showed good endothelial cell growth on its surface.

EXAMPLE 3

[0109] As mentioned above, chemicals such as sodium hydroxide may be used to dissolve PLA in regions unprotected by an alkali-resistant mask material where the dissolved material may be rinsed away in water to form nano-craters. In another example, the polymer surface may be first irradiated prior to etching with the sodium hydroxide to enhance the etching process.

[0110] In this example, samples of PLGA, PCL, and PLLA (other suitable polymers described above may alternatively be utilized) were first irradiated with an electron beam and then etched using the sodium hydroxide, as described above, for a period of 16 hours to create surface features. The average surface roughness of the samples was measured using an atomic force microscope (AFM) and the etched samples were then exposed to endothelial cells. Growth was quantified over a period of 15 days and the irradiated and etched samples were compared to control samples after 4 days, 8 days, and 15 days. Table 2 shows a comparison of the results for sample roughness between the irradiated and control samples where the MTS value is an indication of the number of active cells.

Table 2: Results of Comparison For Irradiated and Control Samples With Respect to Sample Roughness and Cell Growth.

	AFM Avg surface Roughness (Scan Size 50μm)	Static Contact Angle	MTS Average Absorbance after 4 days	MTS Average Absorbance after 8 days	MTS Average Absorbance after 15 days
PLGA Control	3.3 ± 1	73.2 ± 1	0.51	0.37	0.26
PLGA Modified	93 ± 3	57.4 ± 2	0.57	0.29	0.45
PLLA Control	646 ± 9	94.2 ± 2	0.40	0.29	0.40
PLLA Modified	333 ± 27	63.4 ± 1	0.51	0.17	0.27
PCL Control	259± 20	80.2± 3	0.39	0.24	0.28
PCL Modified	390 ± 16	61.8 ± 1	0.53	0.38	0.39
* Modified = Ebeam with 2.5Mrads + 16hours 0.1N NaOH immersion					

[0111] Generally, irradiating samples prior to etching with sodium hydroxide gives surface features that are rougher than control samples. Table 3 shows a comparison of the results for the irradiated and control samples with respect to live cell growth and total cell growth.

Table 3: Results of Comparison For Irradiated and Control Samples With Respect to Live Cell Growth and Total Cell Growth.

	Hemocytometer Avg Live Cells Count after 4 day	Hemocytometer Avg total Cells Count after 4 day	Hemocytometer Avg Live Cells Count after 8 day	Hemocytometer Avg total Cells Count after 8 day	Hemocytometer Avg Live Cells Count after 15 day	Hemocytometer Avg total Cells Count after 15 day
PLGA Control	5400	9600	9300	15800	9400	22700
PLGA Modified	8800	12800	9700	17800	17800	31400
PLLA Control	5300	9000	3800	4900	13500	27700
PLLA Modified	6500	8800	3300	4800	13600	27400
PCL Control	4400	9200	1530	3800	3060	12000
PCL Modified	4100	7600	9830	14200	5300	23400
* Modified = Ebeam with 2.5Mrads + 16hours 0.1N NaOH immersion						

[0112] Generally, the surface-modified samples show enhanced endothelial cell growth for PLGA and PCL samples except for PLLA samples. The endothelial cell growth also appeared to correlate well with overall surface roughness of PLGA and PCL samples where endothelial cell growth increases as surface roughness increases.

[0113] As can be understood by one skilled in the art, many modifications to the exemplary embodiments described herein are possible. The invention, rather, is intended to encompass all such modification within its scope, as defined by the claims.

CLAIMS

What is claimed is:

1. An implantable device having at least one surface for contacting bodily fluid or tissue, said at least one surface comprising a plurality of nano-craters thereon that enhance or promote endothelialization of said at least one surface.

2. The implantable device of claim 1, wherein said at least one surface comprises a polymer selected from the group consisting of polyglycolide, poly-lactide, poly-co-glycolactive and polycaprolactone.

3. The implantable device of claim 1, further comprising an adhesion-promoting molecule in said at least one surface.

4. The implantable device of claim 3, wherein the adhesion-promoting molecule is selected from the group consisting of laminin, fibronactin, collagen, vitronectin, tenascin, N-cadherin, P-cadherin and a peptide.

5. The implantable device of claim 1, further comprising a growth-stimulating molecule in said at least one surface.

6. The implantable device of claim 5, wherein the growth-stimulating molecule is selected from the group consisting of granulocyte colony stimulating factor, platelet-derived endothelial call growth factor, fibroblast-derived endothelial call growth factor, NB41 endothelial cell growth factor, endothelial cell growth factor alpha, endothelial cell growth factor beta, endothelial call growth factor 2a and endothelial cell growth factor 2b.

7. The implantable device of claim 1, further comprising an anti-thrombotic molecule in said at least one surface.

8. The implantable device of claim 7, wherein the anti-thrombotic molecule is selected from the group consisting of heparin, a benzamidine compound, a bicyclic pyrimidine compound, a nitro compound, a thio acid compound, a protein, and a peptide.

9. The implantable device of claim 7, wherein the anti-thrombotic molecule is selected from the group consisting of tissue-type plasminogen activator, protein S and protein C.

10. The implantable device of claim 1, wherein the implantable device is selected from the group consisting of a stent, a graft, a conduit, a valve and dialysis tubing.

11. The implantable device of claim 1, wherein a size of the nano-craters is inversely proportional to the endothelialization of the at least one surface whereby a relatively smaller size of the nano-craters is correlated to increased endothelialization.

12. The implantable device of claim 1, further comprising a leaching agent suitable for creating the plurality of nano-craters, wherein the leaching agent is selected from the group consisting of inorganic salt, form gelatin, sugar, chitosan, and polyvinyl pyrrolidone.

13. The implantable device of claim 12, wherein the leaching agent is included in a concentration ranging from 1 to 10% by weight.

14. The implantable device of claim 1, wherein a size of each nano-crater ranges from 5 to 90 microns in diameter.

15. The implantable device of claim 1, wherein a distance between each nano-craters ranges from 50 to 100 microns.

16. The implantable device of claim 15, wherein the distance between each nano-crater ranges from 50 to 80 microns.

17. The implantable device of claim 1, wherein the at least one surface defines a roughness which is correlated to the endothelialization.

18. A method of reducing thrombogenicity of an implantable device by promoting or enhancing endothelialization of the implantable device having at least one surface for contacting bodily fluid or tissue, comprising: providing on said at least one surface a plurality of nano-craters that enhance or promote endothelialization of said at least one surface.

19. The method of claim 18, wherein the implantable device is selected from the group consisting of a stent, a graft, a conduit, a valve and dialysis tubing.

20. The method of claim 18, wherein said at least one surface comprises a polymer selected from the group consisting of polyglycolide, poly-lactide and poly-co-glycolactide.

21. The method of claim 18, further comprising irradiating said at least one surface to degrade portions of the surface prior to providing on said at least one surface a plurality of nano-craters.

22. The method of claim 21, further comprising etching the nano-craters with sodium hydroxide.

23. The method of claim 18, wherein providing comprises incorporating a plurality of leachable nano-particles in said at least one surface.

24. The method of claim 23, wherein incorporating comprises adding the leachable nano-particles in a concentration ranging from 1 to 10% by weight.

25. The method of claim 18, wherein providing comprises providing nano-craters ranging in diameter from 5 to 90 microns.

26. The method of claim 18, wherein providing comprises providing nano-craters having a distance between each nano-crater ranging from 50 to 100 microns.

27. The method of claim 18, wherein providing comprises providing the at least one surface having a roughened surface correlated to enhance endothelialization.

28. The method of claim 18, further comprising including an adhesion-promoting molecule in said at least one surface.

29. The method of claim 28, wherein the adhesion-promoting molecule is selected from the group consisting of laminin, fibronactin, collagen, vitronectin, tenascin, N-cadherin. P-cadherin and a peptide.

30. The method of claim 18, further comprising including a growth-stimulating molecule in said at least one surface.

31. The method of claim 30, wherein the growth-stimulating molecule is selected from the group consisting of granulocyte colony stimulating factor, platelet-derived endothelial cell growth factor, fibroblast-derived endothelial cell growth factor, NB41 endothelial cell growth factor. Endothelial call growth factor alpha.

Endothelial cell growth factor beta, endothelial cell growth factor 2a and endothelial cell growth factor 2b.

32. The method of claim 18, further comprising including an anti-thrombotic molecule in said at least one surface.

33. The method of claim 32, wherein the anti-thrombotic molecule is selected from the group consisting of heparin, a benzamidine compound, a bicyclic pyrimidine compound, a nitro compound, a thio acid compound, a protein, and a peptide.

34. The method of claim 33, wherein the anti-thrombotic molecule is a tissue-type selected from the group consisting of plasminogen activator, protein S and protein C.

35. An implantable device comprising:

at least one first degradable layer providing at least one surface of the implantable device for contacting bodily fluid or tissue and disposed about a central core; and

at least one second degradable layer between said first degradable layer and the central core, wherein said first degradable layer has a first degradation rate and said second degradable layer has a second degradation rate such that said at least one first degradable layer degrades more rapidly then said at least one second degradable layer on contact with bodily fluid or tissue.

36. The implantable device of claim 35, wherein the first degradable layer comprises a different material than the second degradable layer.

37. The implantable device of claim 35, wherein the second degradable layer comprises PLA and the first degradable layer comprises PLGA.

38. The implantable device of claim 35, wherein the first degradable layer comprises a polymer selected from the group consisting of PLGA 80/20, PLGA 75/25, and PLGA 53/47.

39. The implantable device of claim 35, further comprising:

at least one third degradable layer between the at least one second degradable layer and the central core and having a third degradation rate slower than the second degradation rate; and

at least one fourth degradable layer between the at least one third degradable layer and the central core and having a fourth degradation rate slower than the third degradation rate.

40. The implantable device of claim 39, wherein the first degradable layer comprises PLGA 53/47, the second degradable layer comprises PLGA 75/25, the

third degradable layer comprises PLGA 80/20, and the fourth degradable layer comprises PLA.

41. The implantable device of claim 35, wherein the implantable device is selected from the group consisting of a stent, a graft, a conduit, and a valve or dialysis tubing.

42. A method of reducing thrombogenicity of an implantable device having at least one surface for contacting bodily fluid or tissue, comprising:

providing at least one first degradable layer which provides said at least one surface and which is disposed about a central core, and at least one second degradable layer between said first degradable layer and the central core,

wherein said first degradable layer has a first degradation rate and said second degradable layer has a second degradation rate such that said at least one first degradable layer degrades more rapidly than said at least one second degradable layer on contact with bodily fluid or tissue.

43. The method of claim 42, wherein the implantable device is selected from the group consisting of a stent, a graft, a conduit, a valve, and dialysis tubing.

44. The method of claim 42, wherein providing comprises providing the first degradable layer having a different material than the second degradable layer.

45. The method of claim 42, wherein providing comprises providing the first degradable layer made from a polymer selected from the group consisting of PGA, PLA and PGLA.

46. The method of claim 42, wherein providing comprises providing the first degradable layer made from PLA and the second degradable layer made from PLGA.

47. The method of claim 42, wherein providing comprises providing the second material made from a polymer selected from the group consisting of PLGA 80/20, PLGA 75/25, and PLGA 53/47.

48. The method of claim 42, wherein the device further comprises:

at least one third degradable layer between the at least one second degradable layer and the central core and having a third degradation rate slower than the second degradation rate; and

at least one fourth degradable layer between the at least one third degradable layer and the central core and having a fourth degradation rate slower than the third degradation rate.

49. The method of claim 48, wherein the first degradable layer comprises PLDA 53/47, the second degradable layer comprises PLGA 75/25, the third degradable layer comprises PLGA 80/20 and the fourth degradable layer comprises PLA.

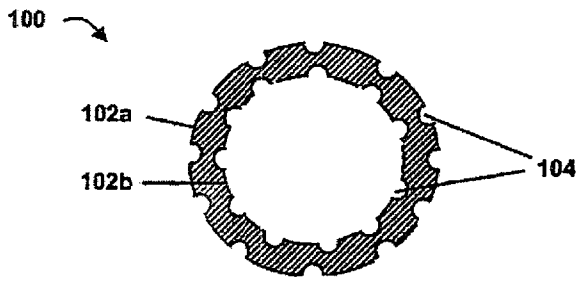

FIGURE 1

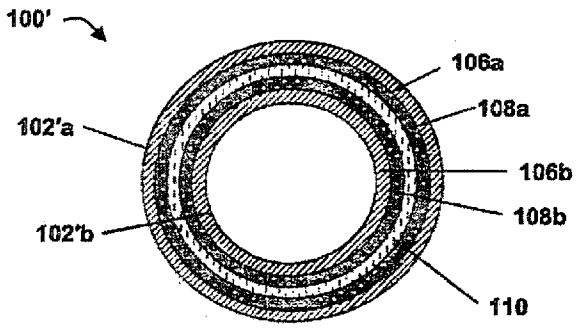

FIGURE 3

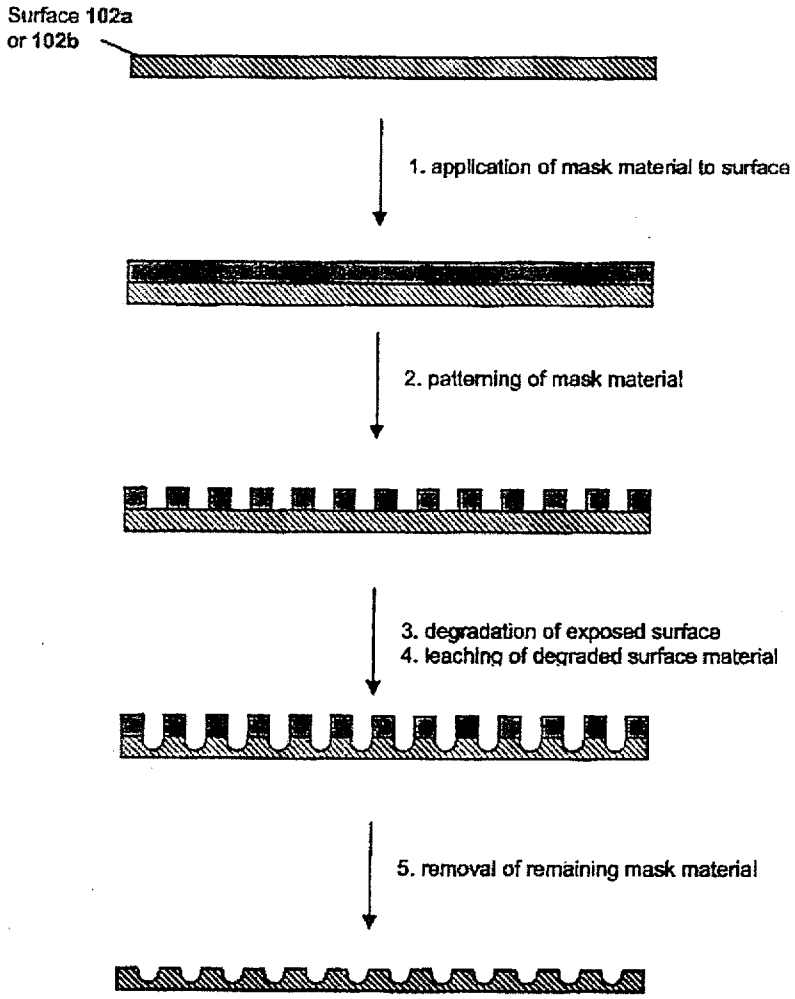
Surface 102a
or 102b
1. application of mask material to surface
2. patterning of mask material
3. degradation of exposed surface
4. leaching of degraded surface material
5. removal of remaining mask material

FIGURE 2

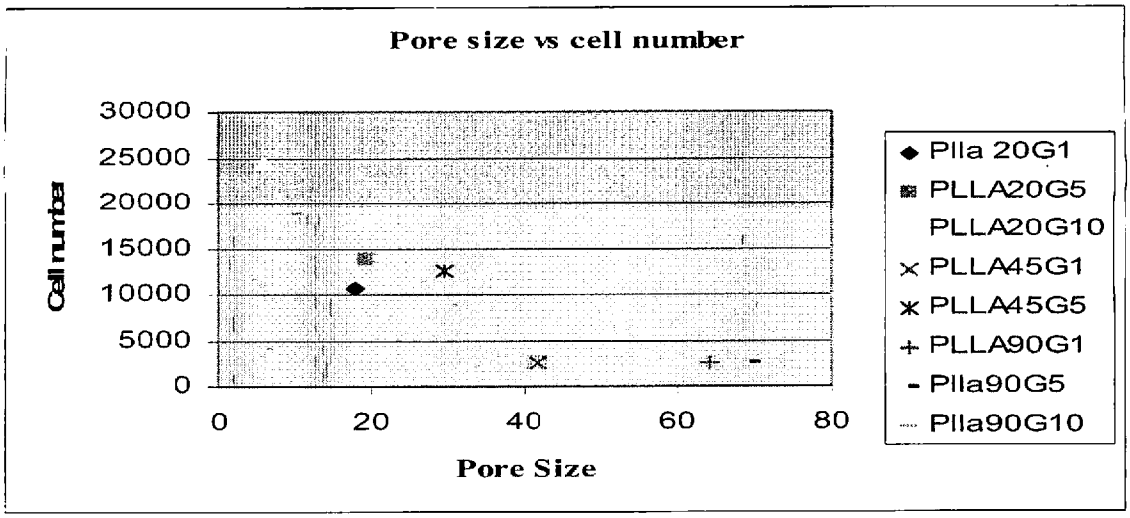

FIGURE 4

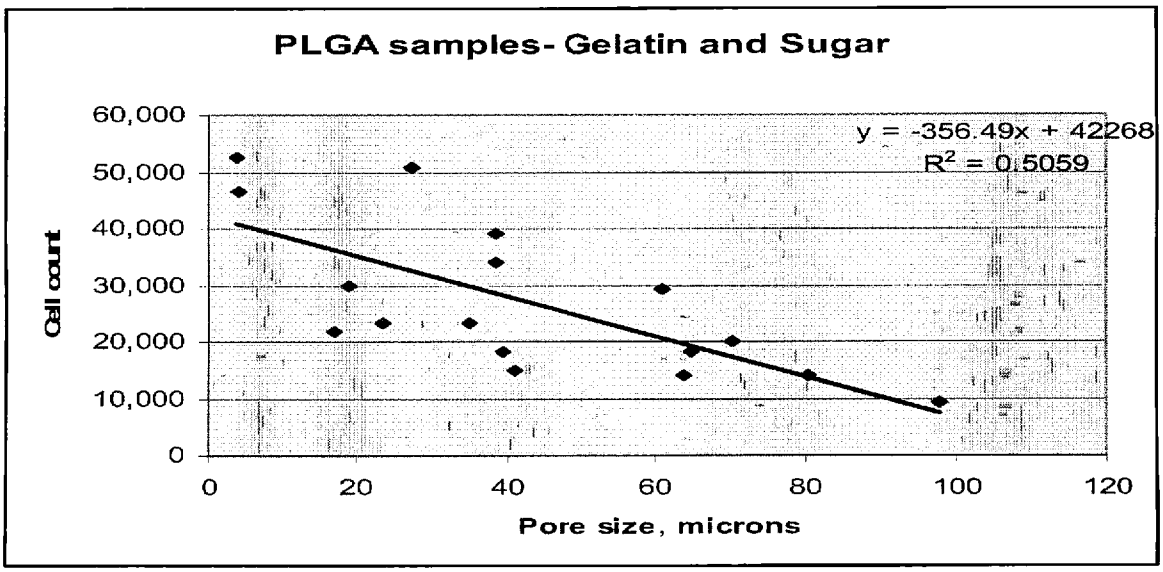

FIGURE 5

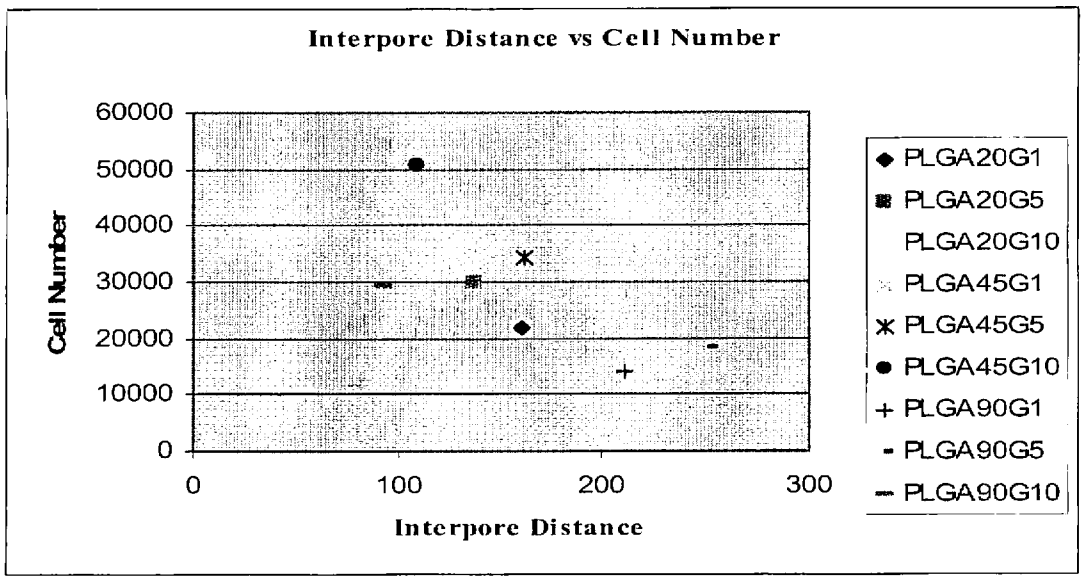
Interpore Distance vs Cell Number
Cell Number
60000
50000
40000
30000
20000
10000
0
0
100
200
300
Interpore Distance
PLGA20G1
PLGA20G5
PLGA20G10
PLGA45G1
PLGA45G5
PLGA45G10
PLGA90G1
PLGA90G5
PLGA90G10

FIGURE 6