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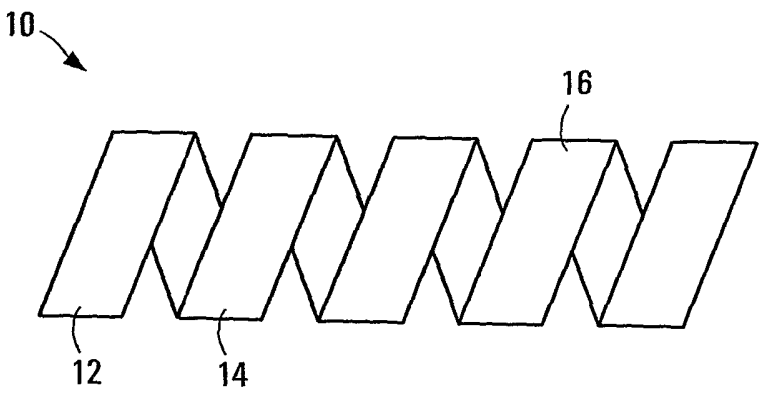
(54) Title: POLYMERIC STENT AND METHOD OF MANUFACTURE



(57) Abstract: A stent formed of polymeric material, useful for the expansion of a lumen and the delivery of one or more therapeutic agents in situ is disclosed. The stent may be multi-layered, and may change shape at a state transition temperature governed by the materials forming the layers. Methods of use and manufacture are also disclosed.

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POLYMERIC STENT AND METHOD OF MANUFACTURE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims priority from U.S. provisional patent application No. 60/478,887, filed June 16, 2003, the contents of which are hereby incorporated by reference herein.

FIELD OF THE INVENTION

[0002] The present invention relates generally to medical devices for implanting in a patient, and particularly to stents that may be self expanding, and may deliver therapeutic agents.

BACKGROUND OF THE INVENTION

[0003] Expandable medical prostheses, frequently referred to as stents, are well known and commercially available. They are, for example, disclosed generally in U.S. Patent No. 4,655,771 (Wallsten), U.S. Patent No. 5,061,275 (Wallsten *et al.*) and U.S. Patent No. 5,645,559 (Hachtmann *et al.*). Stents are used within body vessels of humans for a variety of medical applications. Examples include intravascular stents for treating stenoses, stents for maintaining openings in the urinary, biliary, tracheobronchial, oesophageal and renal tracts and inferior vena cava.

[0004] Typically, a delivery device that retains the stent in its compressed state is used to deliver the stent to a treatment site through vessels in the body. Stents tend to be designed to be flexible with a reduced radius, to enable delivery through relatively small and curved vessels. In percutaneous transluminal angioplasty, an implantable endoprosthesis is introduced through a small percutaneous puncture site, airway or port and is passed through various body vessels to the treatment site. After the stent is positioned at the treatment site, the delivery device is actuated to release the stent and the stent is mechanically expanded, usually with the aid of an inflatable balloon, to thereby expand within the body vessel. The delivery device is then detached

from the stent and removed from the patient. The stent remains in the vessel at the treatment site as an implant.

[0005] Commonly used materials for known stent filaments include Elgiloy™ and Phynox™ metal spring alloys. Other metallic materials that can be used for expandable stent filaments are 316 stainless steel, MP35N alloy and superelastic Nitinol nickel-titanium. Another expandable stent has a radiopaque clad composite structure such as shown in U.S. Patent No. 5,630,840, naming Mayer. Expandable stents can also be made of a titanium alloy.

[0006] The implantation of an intraluminal stent may cause a certain amount of acute and chronic trauma to the luminal wall while performing its function. A stent that applies a gentle radial force against the wall and that is compliant and flexible with lumen movement is preferred for use in diseased, weakened or brittle lumens. Stents are preferably capable of withstanding radially occlusive pressure from tumours, plaque and luminal recoil and remodelling.

[0007] Certain stent designs tend to be self-expanding upon insertion within a lumen. For example, EP 1287790 (Schmitt & Lentz) describes an axially flexible braided stent that is self-expandable due to the elastic memory of the braided polymer fibres. The braided fibres are shaped into a tube at or just below the melting temperature of the polymer, and then longitudinally stretched upon cooling. The stent is inserted while stretched, and once inserted the stretch tension is released, allowing for the radial expansion of the tube when inserted.

[0008] Known self expanding stents, however, typically must be constrained to be inserted. Moreover, their removal is often difficult, if not impossible.

[0009] Accordingly, there is a need for improved expandable medical stents, that simplify insertion, and may simplify removal.

SUMMARY OF THE INVENTION

[0010] A polymer that is amorphous, or is at least partially amorphous, will undergo a transition from a pliable, elastic state (at higher temperatures) to a brittle glass-like state (at lower temperatures) as it transitions through a particular temperature, referred to as the glass transition temperature (T_g). The glass transition temperature for a given polymer will vary, depending on the size and flexibility of side-chains, as well as the flexibility of the backbone linkages and the size of functional groups incorporated into the polymer backbone. Below T_g, the polymer will maintain some flexibility, and may be deformed to a new shape. However, the further the temperature below T_g the polymer is when being deformed, the greater the force needed to shape it.

[0011] Furthermore, amorphous or partially amorphous polymers, when set into a particular shape at a higher temperature, have an elastic memory or shape memory, such that when cooled and compressed into a smaller shape, the polymer will expand back to the original shape upon heating above a state transition temperature. The terms "shape memory", "elastic memory" and "memory effect" as used herein in respect of a polymer are interchangeable and refer to the characteristic of a polymer with a T_g to revert from one shape held below the T_g to a second shape when heated above the T_g, where the polymer has been previously set to the second shape above T_g.

[0012] This characteristic of amorphous or semi-crystalline polymers is employed in the self-expanding stent of the present invention. The present invention therefore provides, in one aspect, a stent. The term stent, as used herein, is intended to refer generally to expandable medical prostheses, including lengthwise extending stents, stent-grafts, grafts, filters, occlusive devices, valves or the like. The stent may be any suitable shape required to achieve the desired function as a medical prosthesis. For example, the stent may be generally tubular or generally helical.

[0013] As exemplified, the stent may be an implantable, helically tubular member which is an axially flexible and radially self-expandable structure comprising at least one polymeric layer. The stent assumes a substantially

tubular form in the expanded or non-expanded state.

[0014] Such a stent may be useful for delivering therapeutic agents and, even more particularly, multiple therapeutic agents with multiple diffusion rates. The stent may be biostable or bioabsorbable.

[0015] The invention therefore provides in one aspect a stent comprising a substrate including a polymer that is at least partially amorphous and has a glass transition temperature T_g, and a therapeutic agent included in the polymer. The stent is formed to have a first shape at a lower temperature T_2 and a second shape at a higher temperature T_1 and configured to change from the first shape to the second shape at a temperature equal to or greater than a transition temperature T_3.

[0016] Exemplary stents may be formed having multiple layers. The layers may be arranged sequentially, relative to the helical width, thereby forming an outer and one or more inner layers. In an embodiment, a multiple layered stent has an outer layer formed from an amorphous polymer with a glass transition temperature (T_g) less than the T_g of a polymer that forms at least one inner layer.

[0017] Thus, in one aspect, the present invention provides a stent including at least first and second layers. The first layer includes a first polymer that is at least partially amorphous and has a glass transition temperature T_{g1}. The second layer includes a second polymer that is at least partially amorphous and has a glass transition temperature T_{g2}. The stent is formed to have a first shape at a lower temperature T_2 and a second shape at a higher temperature T_1, and configured to change from the first shape to the second shape at a temperature equal to or greater than a transition temperature T_3, dependent at least in part on at least one of T_{g1} and T_{g2}.

[0018] In another aspect, there is provided a stent including at least first and second layers. The first layer includes a first polymer and a first therapeutic agent. The second layer includes a second polymer and a second therapeutic agent. The stent is formed to have a first shape at a lower temperature T_2 and a second shape at a higher temperature T_1.

[0019] The incorporation of one or more polymer layers into the stent may offer several advantages: the self-expansion rate can be controlled through selection of appropriate polymers; the capability of delivering the same drug at two or more different rates is provided by using polymers that degrade at different rates; the capability of delivering two or more different drugs is also provided, for example by incorporating the different drugs into the different layers; and when drugs are to be incorporated, manufacturing processes may easily be employed which do not degrade the drugs. The present invention also contemplates methods of manufacturing the stents. In one aspect, the present invention provides a method of manufacturing a stent comprising forming a strip of polymer film having a first layer including a polymer that is at least partially amorphous and has a glass transition temperature T_{g1} and a second layer including a polymer that is at least partially amorphous and has a glass transition temperature T_{g2}; and shaping the strip into a first shape at a temperature T_1, wherein $T_1 = T_{g1} + X°C$, and X is from about -20 to about +120. Additionally, the method may further comprise at a temperature T_2, shaping the strip into a second shape, wherein $T_2 = T_1 - Y°C$, and Y is from about 5 to about 80.

[0020] In another aspect, the invention provides a method of manufacturing a stent including: adding a therapeutic agent to a polymer that is at least partially amorphous and has a glass transition temperature; forming a strip of polymer film from the polymer; shaping the strip into a first shape at a temperature, wherein $T_1 = T_g + X°C$, T_g is the glass transition temperature of the polymer and X is from about -20 to about +120; and at a temperature T_2, shaping the strip into a second shape, $T_2 = T_1 - Y°C$, and Y is from about 5 to about 80.

[0021] Such stents may be useful in a variety of medical applications where a body lumen, hollow organ or other cavity is desired to be de-constricted or de-restricted. Thus, such a stent is useful *inter alia* in the treatment of blockages or potential blockages and/or the prevention of restenosis of vascular, urinary, biliary, tracheobronchial, oesophageal and renal tracts. In an embodiment, the helical shape of the stent facilitates

insertion of the stent and maintenance of the lumen in an open state.

[0022] Therefore, the invention provides in a further aspect a method of treatment or prophylaxis, to a subject in need of expansion of a lumen, comprising: introducing into the subject at site in the lumen desired to be expanded a stent comprising a first layer including a first polymer that is at least partially amorphous and a first therapeutic agent, thereby delivering the first therapeutic agent to the subject, the stent formed to have a first shape at a lower temperature T_2 and a second shape at a higher temperature T_1; and causing the stent to change to the second shape.

[0023] In a further aspect, the invention provides a method for prophylaxis or treatment of a subject in need of expansion of a lumen, comprising introducing into the subject at site in the lumen desired to be expanded a stent comprising a first layer including a first polymer that is at least partially amorphous and has a glass transition temperature T_{g1} and a second layer including a second polymer that is at least partially amorphous and has a glass transition temperature T_{g2}, the stent formed to have a first shape at a lower temperature T_2 and a second shape at a higher temperature T_1 and configured to change from the first shape to the second shape at a temperature equal to or greater than a shape transition temperature T_3, and wherein the introducing is performed at a temperature below T_3 such that the stent is in the first shape; and causing the stent to change to the second shape, in part by allowing the stent to equilibrate to a temperature equal to or greater than T_3.

[0024] 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

[0025] In the figures, which illustrate, by way of example only, embodiments of the present invention,

[0026] **FIG. 1** is a side view of an stent, exemplary of an embodiment of the present invention in a first state, having helical width D_1;

[0027] **FIG. 2** is an end view of **FIG. 1**;

[0028] **FIG. 3** is a side view of the stent of **FIG. 1**, in a second state, having helical width D_2;

[0029] **FIG. 4** is an end view of **FIG. 2**;

[0030] **FIG. 5** is a process flow diagram illustrating a method of manufacturing a stent, exemplary of an embodiment of the present invention;

[0031] **FIG. 6** is a side view of a stent, exemplary of another embodiment of the present invention in a first state having helical width D_1;

[0032] **FIG. 7** is an end view of **FIG.6**;

[0033] **FIG. 8** is a side view of the stent of **FIG. 6**, in a state having helical width D_2;

[0034] **FIG. 9** is an end view of **FIG. 8**;

[0035] **FIG. 10** is a side view of a stent formed of two side-by-side layers;

[0036] **FIG. 11** is a flow diagram of a method of prophylaxis or treatment of a patient by introducing a stent into a lumen of the patient;

[0037] **FIG. 12** is a graph of the self-expansion rates of particular single - layer and double-layer stents 37°C, with a target helical width of 3 mm; and

[0038] **FIG. 13** is a representation of a catheter device comprising a balloon mechanism to deploy the helical medical stent.

DETAILED DESCRIPTION

[0039] **FIGS. 1-4**, illustrate a stent **10**, exemplary of one embodiment of the present invention. As illustrated, stent **10** includes a substrate **12** formed at

least in part, from an amorphous polymer **14**.

[0040] As will be appreciated, at the molecular level, amorphous polymers have at least a portion of the polymeric chains in a disordered state. Molecules are randomly arranged, having no long range order, rather than periodically arranged as in a crystalline material. As will be understood, such polymers therefore include polymers that are fully amorphous, partially amorphous and semi-crystalline. Amorphous polymers have a glass transition temperature T_g above which the polymer will be flexible as the polymer chains will be able to move relative to each other, and below which the polymer will be relatively brittle, since the polymer chains will tend not to move much relative to each other when the polymer is stressed. That is, below T_g, the material is solid, yet has no long-range molecular order and so is non-crystalline. In other words, the material is an amorphous solid, or a glass. Although brittle, the polymer may still be formed into another shape. The amount of force required to shape the polymer will increase the further the temperature at which the shaping is performed is below T_g. The glass transition temperature T_g is different for each polymer.

[0041] Generally, any polymer having a T_g may be used to form stent **10**. Example polymers that may be used to form stent **10** include poly-L-lactide (PLLA), poly-D-lactide (PDLA), polyglycolide (PGA), poly (lactide-co-glycolide), polydioxanone, polycaprolactone, polygluconate, polylactic acid-polyethylene oxide copolymers, modified cellulose, collagen, poly(hydroxybutyrate), polyanhydride, polyphosphoester, poly(amino acids) or related copolymers material, polyurethane including physically cross-linked ether or ester-urethanes, polyethylene, poly(ethylene terephthalate) (PET), or Nylon 6,6.

[0042] At a temperature below T_g, stent **10** is formed into its first state: a generally helical tubular shape **16** of helical width D_2 illustrated in **FIGS. 3** and **4**. At a second temperature above T_g, stent **10** is formed into its second state: a second generally helical tubular shape **18**, having a helical width D_1 illustrated in **FIGS. 1** and **2**. In the depicted embodiment, shape 16 has a generally circular cross-section. As such, the helical widths D_1 and D_2 equal

the helical diameters of the two helical shapes **16** and **18**. Moreover, $D_1/D_2 > 1$. Thus, stent **10** is capable of self-expansion from its first state to its second at a given temperature, referred to as its state-transition temperature.

[0043] Stent **10** may be formed in accordance with method **S500** illustrated in **FIG. 5**. As illustrated, in step **S502**, the substrate **12** is initially formed as a strip of polymer film.

[0044] The polymer film may be formed of one or more polymers, and may be formed using conventional methods known in the art, including solvent casting or extrusion of a polymer.

[0045] For example, a polymer to be extruded may be brought to an elevated temperature above its melting point. PLLA, for instance, may be heated to between 210° and 230°C. The polymer is then extruded at the elevated temperature into a continuous generally flat film using a suitable die, at a rate of about three to four feet per minute. The continuous film may then be cooled to or below T1, for example, by passing the film through a nucleation bath of water. The film is cut into a strip of desired width, if necessary.

[0046] In step **S504** the film is brought to a temperature and set into a helical shape having helical diameter D_1. Typically, an oven is used to heat the film. T_1 is chosen somewhere above T_g for the polymer (i.e. $T_1 = T_g +$ X°C). The value of X is from about -20 to about +120, typically from about 0 to about 30 or from about 0 to about 20. For PLLA, the oven temperature may be between about 60°C and about 90°C (preferably 70°C).

[0047] The film is maintained at temperature T_1 for a period of time necessary to set the shape having diameter D_1. The period of time required to set D_1 will vary depending on T_1, T_g and the film thickness, and may be between 30 minutes and 24 hours.

[0048] Once set at the higher temperature of T_1, in **S506** the stent is cooled to a lower temperature T_2, typically below T_g (i.e. $T_2 = T_1 - Y°C$). At this temperature, the polymer may still be deformed, and is shaped into a helix of

smaller helical width D_2, wherein $D_2 < D_1$. This reduction in diameter is usually accompanied by an increase in length, as the helical stent is stretched. The value of Y is from about 5 to about 80, and typically from about 5 to about 50, more preferably from about 5 to 30. Typically, T_2, although below T_g, is close to T_g, for example, 5 to 20°C below T_g. Usually, the closer T_2 is to T_g, the more easily the polymer can be shaped to D_2. At this smaller helical width, stent **10** is ready for use.

[0049] Finally, the film is collected onto spools of desired lengths.

[0050] Stent **10** so formed thus has two states: one having a helical shape of diameter D_2 (**FIGS. 3** and **4**); the other having a helical shape of diameter D_1 (**FIGS. 1** and **2**). As well, stent **10** will transition from its first state to its second state at or around a state transition temperature T_3. T_3 is a preferred temperature at which the stent **10** will expand, although the stent may expand above or below this temperature depending on how close T_3 is to T_g. Notably $T_1<T_3<T_2$. T_3 is related to the glass transition temperature of the polymer used to form stent **10**. T_3 may be expressed as$T_3 = T_g + Z$, where Z = -30 to +30. In the embodiment depicted in **FIGS. 1-4**, stent **10** is formed of a uniform film, made of the same polymer. In this instance, T_3 is about equal to T_g.

[0051] T_3 depends on the selected polymer and/or any additives. Preferably, it is a biologically relevant temperature. T_3 may, for example, be body temperature or below. Alternatively, the polymer may be chosen with T_g < 37°C, T_3 may be equal to T_1. If T_3 < 37°C, prior to use special storage conditions may be required, such as storage at sub-ambient temperatures (or at least equal to or lower than T_2) or storage in a constrained state.

[0052] Optionally, a therapeutic agent may be incorporated into a stent so formed. The therapeutic agent may be included with the polymer prior to extrusion. Extrusion of the film allows inclusion of a drug or agent that can withstand the extrusion temperatures. The therapeutic agent may be any agent designed to have a therapeutic or preventative effect. For example, the therapeutic agent may be a drug, an antibiotic, an anti-inflammatory agent, an anti-clotting factor, a hormone, a nucleic acid, a peptide, a cellular factor, or a

ligand for a cell surface receptor. As well, the therapeutic agent should be one that does not materially interfere with the physical or chemical properties of the polymer in which it is included.

[0053] Particular contemplated therapeutic agents include anti-proliferative agents such as sirolimus and its derivatives including everolimus, and paclitaxel and its derivatives; antithrombotic agents such as heparin, antimicrobial such as amoxicillin, chemotherapeutic agents such a spaclitaxel or doxorubicin, anti-viral agents such as ganciclovir, anti-hypertensive agents such as diuretics or verapramil or clonidine, and statins such as simvastatin.

[0054] Preferably, solvent casting, including spin casting, may be used to form film **16**, since such casting does not use high temperatures, which may degrade many therapeutic agents. Such casting may facilitate incorporate numerous additional therapeutic agents. Thus, when a therapeutic agent is to be incorporated, solvent casting is preferred to extrusion and co-extrusion, as most therapeutic agents may degrade at extrusion temperatures.

[0055] Optionally, in order to reduce T_g a plasticizer may be added to the polymer prior to forming it into a film. Generally, a plasticizer is any solid or high-boiling liquid that is miscible with the polymer in the proportions used, and when the plasticizer has a T_g, referred to as T_{gp}, then T_{gp} is lower than T_g of the polymer. Acceptable plasticizers include low molecular weight liquids or solids, for example, glycerol, polyethylene glycol, carbon disulfide or triethyl citrate.

[0056] In a second embodiment, a stent **20** may be formed of one or more polymer layers **22**, **24** as illustrated in **FIGS. 6-9.** As illustrated, layers **22** and **24** may be formed atop each other.

[0057] Layer **22** is arranged as the inner layer (closer to the axis of the helix) while layer **24** is the outer layer of the formed helix. The polymers forming the multiple layers have differing glass transition temperatures T_g. Outer layer **24**, is formed of a first polymer **28**, having a glass transition temperature T_{g1}; inner layer **22** is formed of a second polymer **26** having a different glass transition temperature T_{g2}. In the depicted embodiment, T_{g2} of

the inner layer > T_{g1} of the outer layer. For example, the stent may be formed with an outermost layer having T_{g1} of between about 25°C and 60°C, and an inner layer having a T_{g2} of between 60°C and 100°C.

[0058] The outer layer, when above its T_{g1}, pulls the inner layer, which may be below it T_{g2}, towards an expanded state, with the inner layer acting to dampen the expansion of the stent, influencing T_3, and the rate of expansion.

[0059] Again, suitable polymers from which the layer or layers **22**, **24** of stent **20** may be formed include amorphous, partially amorphous and semi-crystalline polymers. The polymer may also be a cross-linked polymer such as generated via radiation, chemical process or physical pressure or manipulation.

[0060] Stent **20** may be formed in much the same way as stent **10** (**FIGS. 1-4**), as illustrated in **FIG. 5**. However, instead of extruding a single polymer to form a film, multiple layers may be co-extruded in step **S502**, thereby forming a multi-layer film. Interfacial bonding agents may be used to increase interlayer adhesion. For example, a solid surfactant such as Poloxamer® may be added to increase interfacial adhesion. For example, the surfactant may be added prior to extrusion. The resulting film will thus have two or more polymeric layers, atop of each other.

[0061] Alternatively, each of the multiple layers may be solvent cast. Such casting results in good interfacial adhesion. The second layer is cast from a solvent that does not dissolve the already-cast layer. For example, polyurethane used to form a first layer may be dissolved in dimethylformamide, while PET used to form a second layer may be dissolved in chloroform. The second solution may be spread on the first layer once dry, and the solvent evaporated off. Again, a surfactant may be added to the polymer solutions prior to casting. The resulting multi-layers have a strong bond between the layers.

[0062] The layers may alternatively be spin-cast using a high-speed spinning machine. Such a machine spins a solution of polymer onto a substrate and the solvent evaporates off. The films produced by this method

may be thinner than those produced by solvent casting. This method can be used to produce multi-layered polymer films. Using this method, a very thin film, for example, having a total thickness of 0.1 to 0.2 mm, can be produced which contains up to 20 different polymer layers, with good interfacial bonding between adjacent layers.

[0063] A further alternative in making the polymer film is to extrude or cast an inner layer, then solvent-cast or spin-cast a cross-linkable layer onto the inner layer. Cross-linking may then be carried out by heat, pressure, or by the use of catalysts or by photo-initiation.

[0064] As with stent **10** described above, a suitable plasticizer may be added to one or more of the polymers prior to forming multi-layered stent **20**, in order to reduce T_g, and where a plasticizer is added to more than one polymer, the same or different plasticizer may be added to each polymer.

[0065] In a preferred embodiment, a multi-layered helical stent is made by solvent casting an inner layer of PLLA in a solvent such as dichloromethane. The outer layer, such as PLGA, is made using a solvent such as acetone, which will not dissolve the PLLA. The solution is then cast onto the inner layer polymer and dried to generate a two-layered stent film. The film is then shaped helically as described above.

[0066] Once the multi-layered film is formed, it is again heated to T_1, and formed into a helical shape having helical diameter D_1. Thereafter it is cooled to T_2, and re-formed to a helical shape having diameter D_2. For multi-layer stent **20**, the definitions of T_1 and T_2 are based on the T_{g1}, T_g of the outer polymer layer.

[0067] Conveniently T_3, the temperature at which a formed stent transitions from one state to another, is influenced by the T_gs of the multiple polymers (in the case of two layers T_{g1} of the first polymer **28** and T_{g2} of the second polymer **26**). Typically, T_3 is closer to T_{g1}.

[0068] Similarly, the rate of expansion (i.e the rate at which stent **20** self-expands after its temperature has increased beyond the state transition

temperature) may depend on the combination of polymers. For example, a single polymer generally has a slow expansion rate. For example, a poly-L-lactide (PLLA) of a medium molecular weight expands to its final helical width (D_1) at 37°C in 300 hours (initial expansion of 135% occurs in 120 minutes). However, a medical device having two layers formed from, for example, PLLA and poly-lactoglycolide (PLGA), fully expands in 9 minutes at 37°C. The expansion rate may not be critical for many applications, such as for example, urological applications, in which a 24 to 48 hour expansion rate may be suitable. For other applications, such as for coronary artery applications, the expansion rate may be more critical. A skilled person will understand T_3 and the rate of expansion of the device by carefully selecting layers having particular T_g's.

[0069] Generally, the rate of expansion is related to the difference between T_3 and T_g. The higher T_3 is above T_{g1}, the faster the expansion rate. The inclusion of an inner layer having $T_{g2} > T_{g1}$ will influence the mechanical strength of the multi-layered stent **20** when in an expanded state, since the polymer of the outer layer may be above T_{g1}, and therefore lack the rigidity of the glass state. The inner layer, which may be below T_{g2}, and therefore still in a glass state, may therefore provide rigidity to the expanded stent.

[0070] Again, polymers suitable for use in one or more layers in the helical stent **20** include poly-L-lactide (PLLA), poly-D-lactide (PDLA), poly(lactide-co-glycolide), (PLGA), polyglycolide (PGA), polydioxanone, polycaprolactone, polygluconate, polylactic acid-polyethylene oxide copolymers, modified cellulose, collagen, poly(hydroxybutyrate), polyanhydride, polyphosphoester, poly(amino acids) or related copolymers material, polyurethane including physically cross-linked ether or ester-urethanes, polyethylene, poly(ethylene terephthalate) (PET), or Nylon 6,6.

[0071] In one embodiment, the medical device has at least two layers, For example, outer layer **24** may be formed from either an amorphous polymer with a T_g of between about 35°C and about 60°C, or a cross-linked polymer with a T_g of between about -10°C and about 60°C, and the second inner layer **22** is formed from either an amorphous or a semi-crystalline polymer with a T_g

of between about 60°C and about 110°C, and where semi-crystalline, a crystalline melting point of greater than 100°C. In one example, the outer layer is made from PLGA 53/47, and the inner layer is made from PLA 8.4 or PLGA 80/20. For the aforementioned PLGA copolymers, the first number given in the polymer name refers to the PLA content (53% or 80%) while the second number refers to the PGA content (47% or 20%). It is also possible to use a plasticized PLA 8.4 (or other PLA) as the outer layer, such that its T_{g2} is between 40-60°C.

[0072] The use of cross-linked polymers, especially in the outer layer **24** is useful as the T_g of a cross-linked polymer may range from below body temperature to above body temperature, such as between about -10°C and about 60°C or more particularly between about 0°C and about 40°C.

[0073] The relative thickness of the outer layer **24** and inner layer **22** can be varied, such that in different embodiments, the device, although having the same total thickness of the combined layers has a different thickness of the inner layer **22** and outer layer **24**. For a two-layer stent, ratios of the inner layer **22** to outer layer **24** may be between 3:1 and 1:1.

[0074] In alternative embodiments, stent **20** may include additional layers formed from additional polymers. Again, the layers are preferably formed atop each other. The inclusion of multiple layers, each formed from a polymer having a different glass transition temperature, allows for a fine modulation of T_3, the state transition temperature of the device, as well as the rate at which the device expands to D_1. Where additional layers are included in stent **20**, the T_g of each progressively more inward layer will be greater than the T_g of the previous more outward layer, such that the innermost layer will have the greatest T_g.

[0075] In yet further alternative embodiment, illustrated in **FIG. 10**, a two layered stent **30** may be formed with adjacent polymer layers rather than overlapping layers. As illustrated, the first layer **32** is positioned side-by-side relative to the second layer **34**, such that the two layers wind the length of the helix, and such that the first layer **32** is above, being an upper layer, the

second layer **32**, being a lower layer, relative to the longitudinal axis of the helix. Again, stent **30** is formed with a general helical shape, having a helical diameter D_1, at temperature T_1. Thereafter, it is re-formed to a general helical shape having diameter D_2, at a temperature D_2.

[0076] Stent **30** is useful for the delivery of two or more therapeutic agents, or the delivery of a single therapeutic agent at differing rates. Therefore, stent **30** may include one or more therapeutic agents. For example, each layer may contain a different therapeutic agent, or each layer may contain the same therapeutic agent, which will be dispersed at different rates depending on the polymer used to form each layer and the different T_gs of the polymers. As the layers are formed side-by-side, the therapeutic agents will be delivered in the same direction.

[0077] Stent **30** is formed as described above, using co-extrusion or solvent-casting or spin-casting. The polymers used to form each layer may be co-extruded to form a polymer strip having adjacent bands of each polymer, such that when coiled into a helix the stent will have adjacent layers that wind the length of the helix. Alternatively, the layers may be cast side-by-side, typically with a small degree of overlap at the ends of the polymer strip.

[0078] For medical applications, the polymers used to form stent **10** (or stents **20, 30**) are typically biocompatible, non-cytotoxic and non-allergenic, causing minimal irritation to the tissue when inserted in a lumen of a body.

[0079] In certain embodiments, the polymer or polymers used may be biostable, or non-biodegradable and are not degraded within the body. Such polymers are accepted to be substantially non-erodible in the sense that their erosion rates are usually of the order of years rather than months. Stent **10** (or stents **20, 30**) formed of biostable polymers is particularly useful for applications for lumen de-restriction or de-constriction over long periods of time, as for example, in coronary artery applications or urological applications, or for use with cranial aneurysms. Suitable biostable polymers include polyurethanes, poly (ether urethanes), poly (ester urethanes), polycaprolactone, plasticized PVC, polyethylene, polyethylene terephthalate,

polyvinyl acetate (PVAc), poly ethylene-co-vinyl acetate (PEVAc) or Nylon 6,6.

[0080] Stent **10** (or stents **20, 30**), when constructed of a bioabsorbable polymer provides certain advantages over known devices such as metal stents, including natural decomposition into non-toxic chemical species over a period of time. A bioabsorbable device need not be retrieved using a second procedure after its useful life in the vessel. Also, bioabsorbable polymeric stents may be manufactured at relatively low costs since vacuum-heat treatment and chemical cleaning commonly used in metal stent manufacturing are not required. However, there may be certain situations where a biostable stent is the preferred option, for example in cardiovascular applications, for added safety beyond a 6-month period.

[0081] Stent **10** (or stents **20, 30**) is designed to have good collapse strength (comparable to a metal stent), longitudinal flexibility (for ease of insertion) and easy expandability, so that it may be expanded inside the vessel or cavity, and then deployed by merely deflating the balloon. The self-expansion process is unique to the helical design. Stent mechanical properties and self-expansion are directly proportional to tensile modulus of the material. The invention advantageously provides polymeric stents with the required mechanical properties capable of bracing open endoluminal structures.

[0082] In an exemplary biostable two-layered stent **10** an outer layer **24** is made from polyurethane, which may be a physically cross-linked, for example a poly(ether urethane) or a poly(ester urethane), and an inner layer **22** made from poly(ethylene terephthalate) or Nylon 6,6.

[0083] Alternatively, one or more layers stent **20** (or stent **30**) may be bioabsorbable. That is, various polymers degrade in the body but allow monomers and by-products to be absorbed. Bioabsorbable PLLA and PGA material, for example, degrade *in vivo*, through hydrolytic chain scission, to lactic acid and glycolic acid, respectively, which in turn is converted to CO_2 and then eliminated from the body by respiration.

[0084] Heterogenous degradation of semi-crystalline polymers, for example, typically occurs because such materials have amorphous and crystalline regions. Degradation occurs more rapidly at amorphous regions than at crystalline regions. This results in the product decreasing in strength faster than it decreases in mass. Totally amorphous, cross-linked polyesters show a more linear decrease in strength with mass over time as compared to a material with crystalline and amorphous regions. Degradation time may be affected by variations in chemical composition and polymer chain structures and material processing.

[0085] Suitable bioabsorbable polymers include poly-L-lactide (PLLA), poly-D-lactide (PDLA), polyglycolide (PGA), copolymers of lactide and glycolide (PLGA), polydioxanone, polygluconate, polylactic acid-polyethylene oxide copolymers, modified cellulose, collagen, poly(hydroxybutyrate), polyanhydride, polyphosphoester, poly(amino acids) or related copolymers, each of which have a characteristic degradation rate in the body. For example, PGA and polydioxanone are relatively fast-bioabsorbing materials (weeks to months) and PLLA and polycaprolactone are a relatively slow-bioabsorbing material (months to years) . Thus, a skilled person will be able to choose an appropriate bioabsorbable material, with a degradation rate that is suitable for a desired application.

[0086] It should also be noted that the collapse pressures of two-layered stents are generally lower than with single layered stents, such as by a factor of half or more.

[0087] Generally, mechanical properties of polymers increase with increasing molecular weight. For instance, the strength and tensile modulus of PLLA generally increases with increasing molecular weight. PLLA, PDLA and PGA include tensile strengths of from about 40 thousands of pounds per square inch (ksi) (276 MPa) to about 120 ksi (827 MPa); a tensile strength of 80 ksi (552 MPa) is typical and a preferred tensile strength is from about 60 ksi (414 MPa) to about 120 ksi (827 MPa). Polydixanone, polycaprolactone and polygluconate include tensile strengths of from about 15 ksi (103 MPa) to about 60 ksi (414 MPa); a tensile strength of 35 ksi (241 MPa) is typical and a

preferred tensile strength is from about 25 ksi (172 MPa) to about 45 ksi (310 MPa).

[0088] PLLA, PDLA and PGA include tensile modulus of from about 400,000 pounds per square inch (psi) (2,758 MPa) to about 2,000,000 psi (13,790 MPa); a tensile modulus of 900,000 psi (6,2606 MPa) is typical and a preferred tensile modulus is from about 700,000 psi (4,827 MPa) to about 1,200,000 psi (8,274 MPa). Polydioxanone, polycaprolactone and polygluconate include tensile modulus of from about 200,000 psi (1,379 MPa) to about 700,000 psi (4,827 MPa); a tensile modulus of 450,000 psi (3,103 MPa) is typical and a preferred tensile modulus is from about 350,000 psi (2,414 MPA) to about 550,00 psi (3,792 MPa).

[0089] A PLLA strip has a much lower tensile strength and tensile modulus than, for example, ELGILOY™ metal alloy wire which may be used to make braided stents. The tensile strength of PLLA is about 22% of the tensile strength of ELGILOY™. The tensile modulus of PLLA is about 3% of the tensile modulus of ELGILOY (registered trademark).

[0090] Stent **10** (or stents **20, 30**) is generally radiolucent and the mechanical properties of the polymers are generally lower than structural metal alloys. Bioabsorbable or biostable stents may require radiopaque markers and may have a larger profile on a delivery catheter and in a body lumen to compensate for the lower material properties.

[0091] For example, an inner layer may be unplasticized, thereby having a high T_g, and an outer layer having a lower T_g may be produced by pre-plasticizing the same or a similar polymer with acceptable plasticizers. For example, a PLLA may be plasticized with glycerol, and cast or extruded on to a PGA layer. In this instance, the level of plasticization is so high as to render the PLLA amorphous, and making it more soluble in acceptable solvents.

[0092] In one embodiment, stent **20** is used to deliver a therapeutic agent in a biphasic pattern. Stent **20** is formed from two or more layers each having a different T_g, such that the same therapeutic agent may be dissolved or dispersed in the two or more layers, so as to diffuse out at different rates. The

total amount of drug released may be manipulated by adjusting the thickness, T_g and the total area of the layer in which the drug is embedded. A skilled person, using routine experimentation, will be able to determine the appropriate amount of therapeutic agent to include in a particular layer in order to achieve a desired rate of release of the therapeutic agent, thereby delivering a particular dose of the therapeutic agent over time.

[0093] Conveniently, the innermost layer of stent **20** will release a therapeutic agent therein toward the longitudinal axis about which stent **20** winds. Similarly, the outermost layer of stent **20** will release a therapeutic agent therein away from the longitudinal axis about which stent **20** winds, and generally away from stent **20**.

[0094] Where stent **20** (or **30**) is formed of layers, if both layers are biodegradable, then the rate of biodegradation also influences the rate of drug release. In one embodiment, outer layer **24** is made from a first polymer **28** having a lower T_g and a faster degradation rate, and inner layer **22** is made from second polymer **26** having a higher T_g and a slower degradation rate. When in inserted into a lumen of a body, the outer layer **24** will generally degrade faster, leading to an initial fast rate of release of drug. Inner layer **22** will generally have a longer half-life, thereby remaining as substrate to keep the lumen open for the required length of time, while releasing drugs slowly over time.

[0095] Alternatively, a stent **20**, exemplary of an embodiment of the present invention, allows for the delivery of two or more different therapeutic agents in a controlled fashion. In one embodiment, a multi-layered stent **20** having each layer formed from a polymer impregnated with one or more therapeutic agents, different from the therapeutic agent or agents included in other layers. The degradation rate and thickness of each layer may be designed such that the therapeutic agent or agents of each layer is released from the stent **20** at a particular rate or particular time period once inserted into the lumen.

[0096] For example, in the case of cardiovascular applications, a two-

layered stent **20** is designed such that a non-proliferative drug is released initially at a faster rate from the outer layer **24**, and then much more slowly from the inner layer **22** to prevent late-stage restenosis. In addition, the inner layer **22** may be used to deliver a different type of drug, such as an anti-coagulant, to the lumen side. There are other similar applications for a bi-phasic release profile for devices of the invention that will be understood by a person skilled in the art.

[0097] In use, stent **10** (or stents **20, 30**) may be used in prophylaxis or treatment of a subject in need of expansion of a lumen, as illustrated in **FIG. 11**. Specifically, in step **S1102**, stent **10** is introduced into a lumen of a subject at a site that is desired to be expanded. The introduction is generally performed by inserting stent **10** at a temperature below T_3, while having helical width D_2. Stent **10** may be readily deployed in a lumen using a conventional catheter.

[0098] As will be appreciated, "lumen" as used herein refers to an inner open space or cavity of a tubular organ, including the cavity of a blood vessel, tubes of the gastro-intestinal tract, ducts such as the bile duct, as well as the cavity of a ureter, the tube that leads from the kidney to the bladder.

[0099] In **S1104**, once at the desired location, stent **10** is expanded. This may be done by raising the temperature of the stent **10** to T_3. If T_3 has been chosen to be at or below body temperature, the device may self-expand as its temperature equilibrates to that of the implantation site.

[00100] However, although stent **10** is designed to self-expand, an additional expansion approach may be used, such as a biphasic expansion approach, for example, by a combination of radial expansion and raised temperature. If physical expansion is used, such expansion may be by balloon or bias-mediated expansion, as is known in the art.

[00101] After the deployment, and optionally expansion if by physical expansion, any deployment and expansion aids are removed. Conveniently, when the expansion is aided by a balloon, the balloon is deflated and removed. The prosthetic device is retained in place by the tissue with which it

is in contact and its own expansion tendency.

[00102] Stent **10** may be partially expanded using a balloon and then left in place in the expanded state. Stent **10** may continue to expand to the defined final helical diameter D_1, and, if T_3 is designed to be equal to or less than 37°C, does not require heating to start the self-expansion process. This deployment of the helical stent will ensure that the blocked vessel or hollow organ is open and kept open for the duration of implantation, without complications arising from vessel or hollow organ recoiling.

[00103] Once deployed, stent **10** is generally shorter in length and larger in helical width than before deployment. For example, in one embodiment, the device may start out with a length of about 20 mm and helical width 1.5 mm and may reduce in length by about 15% and increase in helical width to about 3 mm after deployment. In comparison, an expandable metal stent generally has about the same longitudinal dimensions before loading and after deployment.

[00104] As will now be appreciated, stent **10** may be used in a variety of medical applications, including long-term and short-term implantation, where a biostable, rapidly degrading or slowly degrading bioabsorbable device is desired. Optionally, such stents may release one or more therapeutic agents at the implantation site. For example, stent **10** may be used in heart disease treatment, using bioabsorbable polymers with or without drug-carrying capacity, to prevent restenosis. Other applications include deployment of the present stents in thoracic surgery to keep airways open for patients suffering from bronchial stenosis, or in urology, to keep the ureter open.

[00105] Thus, in **S1106**, stent **10** (or stent **20, 30**) delivers one or more therapeutic agent to the site of implantation where the device incorporates such therapeutic agents dispersed in one or more polymers used to form the device, as described above.

[00106] Typically, the diffusion of a drug through an amorphous or partially amorphous polymer is influenced by the T_g of the polymer; the diffusion rate of a drug is higher in polymers of lower T_g.

[00107] Of course, stents **10, 20 or 30** in the various embodiments as described above may be packaged for sale and sold with or without instructions for use.

[00108] Although the embodiments described herein relate to helical stents, a skilled person will appreciate that the invention is not so limited, and that the multi-layered polymeric stents and stents including therapeutic agents having the self-expansion properties described herein may be formed into shapes other than a helix, including a tubular shape.

[00109] Embodiments of the invention may be further appreciated, in light of the following non-limiting examples.

EXAMPLES

[00110] ***Example 1: Manufacture of the Stent***

[00111] A strip of polymer film is made by the usual methods (solvent-casting or extrusion). Next, the strip is coiled into a helical shape and set into this shape (helical width is D_1) at a higher temperature (T_1). The choice of T_1 depends on the T_g of the polymer: the general rule is to select T_1 such that T_1 is from T_g to about T_g + 40°C. Once set at the higher temperature (T_1), the stent is usually made into a helix of smaller helical width (D_2); the ratio of D_1/D_2 is generally greater than 1, such as from 6 to 2) at a lower temperature (T_2): again, T_2 may range from T_1 less from about 5 to 80°C.

[00112] At this lower helical width, the stent may be deployed easily using a conventional catheter. Once inside the body vessel or cavity, the stent may be expanded by using both pressure and a raised temperature (this temperature is usually between T_1 and T_2 and is referred to as T_3, i.e. $T_1>T_3>T_2$). Under these conditions, the stent expands quickly first due to the physical expansion method and then more slowly due to the self-expansion properties of the stent, to the helical width set at T_1.

[00113] After the initial expansion, the balloon is deflated and withdrawn. The stent is retained in place by the tissue it is in contact with, and its own

expansion tendency.

[00114] Generally, the stent, in use, is initially expanded by a balloon and then allowed to self-expand at body temperature. The expansion rate at body temperature is generally slower than at T_3, where T_g is below body temperature. **FIGS. 1-4** provide a diagrammatic representation of the stent with helical widths D_1 and D_2.

[00115] ***Example 2: Generation of multi-layered stent***

[00116] The preferred configuration of the stent is a multi-layered helical stent, in which the outer layer(s) are made of an amorphous polymer with a T_g between 40°C and 60°C, while the inner layer is made of an amorphous or semi-crystalline polymer with a higher T_g (60-100°C), and crystalline melting point greater than 100°C. This ensures rapid expandability.

[00117] To make a two-layered stent, the following procedure is adopted.

[00118] The inner layer (made from PLA, for example) is made by casting the polymer (with or without drug) from a solution in dichloromethane. A standard solution coater is used for this purpose. Next, a solution of the outer-layer polymer (typically a PLGA) is made in a solvent that does not dissolve the inner polymer that is already cast. An example of such a solvent is acetone. This solution is then cast onto the inner layer polymer, and dried to make the two-layer stent film. The film is then shaped into a helical stent using procedures already outlined above.

[00119] The two layers, if made from biodegradable polymers, will degrade at different rates, which may be used to advantage. For instance, in preventing restenosis, it appears that rapid neo-intimal cell proliferation occurs in the first 2-4 weeks. Thus the outer layer may be programmed to degrade over this period, releasing all the drug content in the same time period. The second layer may then be programmed to degrade at a much slower rate, to prevent later stage restenosis. It may also be used to deliver another drug, such as an anti-coagulant.

[00120] With a two (or multiple) layered system, the polymers may be on top of each other or side-by-side. The outer layer has a lower T_g than the inner layer or layers. In this case, the range of T_1 is usually from the T_g of the outer layer to about T_g + 40°C. If the T_g of the outer polymer is close to 37°C, then the expansion rate is rapid at body temperature. In this instance, T_3 may be 37°C. Such is the case with PLGA 53/47, or a 50/50 copolymer of PLA and PGA, whose T_g is approximately 37-38°C.

[00121] Table 1 provides representative values for T_1, T_2 and T_3. Poly ethylene glycol was used as a plasticizer where indicated.

Table 1: T_1, T_2 and T_3 values

POLYMER	T1	T2	T3
PLLA8.4 (T_g = 65°C) Single-layer	50°C 70°C	25°C 40°C	37°C 45°C (faster) or 37°C
PLGA 80/20 (T_g = 51°C) Single-layer	50°C 70°C	25°C 40°C	37°C 45°C (faster) or 37°C
PLLA8.4/plasticized PLGA 80/20 (T_g = 44°C)	37°C	25°C	37°C
PLGA 80/20/plasticized PLGA80/20/ (T_g = 44°C)	50°C	25°C	37°C

[00122] ***Example 3: Stent expansion***

[00123] **FIG. 12** is a graphical representation showing expansion rate data of for single-layer and double-layer stents at 37°C.

[00124] ***Example 4: Use of the stent***

[00125] **FIG. 13** is a representation of the stent being placed *in situ*.

[00126] ***Example 5: Therapeutic agent delivery***

[00127] One or more polymers in the stent may be impregnated with a therapeutic agent or drug. Examples of such agents include anti-proliferative

agents such as sirolimus and its derivatives including everolimus and paclitaxel and its derivatives; anti-thrombotic agents such as heparin; antibiotics such as amoxicillin; chemotherapeutic agents such a paclitaxel or doxorubicin; anti-viral agents such as ganciclovir; and anti-hypertensive agents such as diuretics or verapramil or clonidine.

[00128] While the helical shape herein described is preferred, it is possible to provide a fully tube-like stent which may be stretched to a lower helical width at a temperature greater than the T_g of any one of the polymers. This may require higher forces. The helical width may then be expanded at T_3 to provide a functional stent.

[00129] ***Example 6: Bilayer stents***

[00130] For a biostable PET/Poly vinyl acetate (PVA) stent, where T_g of PVA (outer layer) = 28°C and T_g of PET (inner layer) = +60°C, and where T_1 = 37°C and T_2 =25°C, a self-expanding stent having a PET layer with thickness = 0.18mm; PVA thickness = 0.07 to 0.15 mm.

[00131] An extruded sheet of PET, 0.18mm thick, is used as the inner layer. On to this is cast a PVA film, using a solution of PVA in dichloromethane. The thickness of the cast layer of PVA is about 0.10mm. This bilayer film is set into a helical stent of helical width 3mm at 37°C for 1 hour and the lower helical width of 1mm is set at 25°C. This stent can be balloon-expanded and then self-expand at 37C.

[00132] As will now be appreciated, the above describe embodiments are susceptible to many modifications. For example, an exemplary stent could be formed of a non-helical shape. An exemplary stent could be formed of having a generally cylindrical shape, two differing shapes at two temperatures, or an undefined shape at one temperature. Similarly, exemplary stents could be formed of third, fourth and additional layers, between first and second layers. Each or some of the multiple layers could include a therapeutic agent as described.

[00133] 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. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations of any two or more of the steps or features.

WHAT IS CLAIMED IS:

1. A stent comprising first and second layers, said first layer including a first polymer that is at least partially amorphous and has a glass transition temperature T_{g1}, said second layer including a second polymer that is at least partially amorphous and has a glass transition temperature T_{g2}, said stent formed to have a first shape at a lower temperature T_2 and a second shape at a higher temperature T_1, and configured to change from said first shape to said second shape at a temperature equal to or greater than a transition temperature T_3, dependent at least in part on at least one of T_{g1} and T_{g2}.

2. The stent of claim 1, further comprising at least one additional third layer including a third polymer that is at least partially amorphous and has a glass transition temperature T_{g3}.

3. The stent of claim 1 or claim 2, wherein $T_3 \leq 37°C$.

4. The stent of any one of claims 1 to 3, wherein said first polymer comprises a therapeutic agent.

5. The stent of claim 4, wherein said therapeutic agent is selected from the group consisting of a drug, an antibiotic, an anti-inflammatory agent, an anti-clotting factor, a hormone, a nucleic acid, a peptide, a cellular factor, a ligand for a cell surface receptor, an anti-proliferative agent, an anti-thrombotic agent, an antimicrobial agent, an anti-viral agent, a chemotherapeutic agent, and an anti-hypertensive agent.

6. The stent of claim 4 or claim 5, wherein said first polymer and said second polymer each comprise a different therapeutic agent.

7. The stent of any one of claims 1 to 6, wherein said first layer is an outer layer and said second layer is an inner layer such that said outer layer is spaced farther from a central longitudinal axis of said stent than said inner layer, and $T_{g1} < T_{g2}$.

8. The stent of claim 7, wherein T_{g1} is between about 25°C to about 60°C and T_{g2} is between about 60°C to about 100°C.

9. A stent comprising first and second layers, said first layer including a first polymer and a first therapeutic agent, said second layer including a second polymer and a second therapeutic agent, said stent formed to have a first shape at a lower temperature T_2 and a second shape at a higher temperature T_1.

10. The stent of claim 9, wherein said first therapeutic agent and said second therapeutic agent are independently selected from the group consisting of a drug, an antibiotic, an anti-inflammatory agent, an anti-clotting factor, a hormone, a nucleic acid, a peptide, a cellular factor, a ligand for a cell surface receptor, an anti-proliferative agent, an anti-thrombotic agent, an antimicrobial agent, an anti-viral agent, a chemotherapeutic agent, and an anti-hypertensive agent.

11. The stent of any one of claims 1 to 10, wherein said first shape is a generally helical shape having helical width D_2 and said second shape is a generally helical shape having helical width D_1, and wherein $D_1 > D_2$.

12. The stent of any one of claims 1 to 11, wherein said first polymer is cross-linked.

13. The stent of any one of claims 1 to 12, wherein said first layer is an upper layer and said second layer is a lower layer, such that said upper layer is generally parallel to said lower layer, and said upper layer and said lower layer traverse the length of the stent prior to said stent being formed into said first shape.

14. The stent of any one of claims 1 to 12, wherein said first layer is an outer layer and said second layer is an inner layer such that said outer layer is spaced farther from a central longitudinal axis of said stent than said inner

layer.

15. The stent of any one of claims 7, 8 and 12, wherein the ratio of thickness of said inner layer to said outer layer is between about 3:1 to about 1:3.

16. The stent of any one of claims 1 to 15, wherein said first polymer is biostable.

17. The stent of claim 16, wherein said second polymer is biostable.

18. The stent of claim 17, wherein said first polymer and said second polymer are independently selected from the group consisting of polyethylene, polypropylene, poly ethylene terephthalate (PET), polyurethane poly (ether urethane), poly (ester urethane), poly vinyl chloride, polyvinyl acetate (PVAc), poly(ethylene-co-vinyl acetate) (PEVAc), polycaprolactone and Nylon 6,6.

19. The stent of any one of claims 1 to 15, wherein said first polymer is bioabsorbable.

20. The stent of claim 19, wherein said second polymer is bioabsorbable.

21. The stent of claim 20, wherein said first polymer and said second polymer are independently selected from the group consisting of poly-L-lactide (PLLA), poly-D-lactide (PDLA), polyglycolide (PGA), poly lactide-co-glycolide (PLGA), polydioxanone, polygluconate, polylactic acid-polyethylene oxide copolymer, modified cellulose, collagen, poly(hydroxybutyrate), polyanhydride, polyphosphoester and poly-amino acid.

22. The stent of any one of claims 7, 8, 14, 15, 20 and 21, wherein said outer layer degrades at a different rate than said inner layer.

23. The stent of any one of claims 9 to 22, wherein said stent extends along a helical axis, and said first layer forms an exterior layer of said stent,

and said second layer forms an interior layer of said stent, so that said first therapeutic agent is released away from said axis, and said second therapeutic agent is released toward said axis.

24. A method of manufacturing a stent comprising:

forming a strip of polymer film having a first layer including a polymer that is at least partially amorphous and has a glass transition temperature T_{g1} and a second layer including a polymer that is at least partially amorphous and has a glass transition temperature T_{g2};

shaping the strip into a first shape at a temperature T_1, wherein $T_1 = T_{g1} + X°C$, and X is from about -20 to about +120.

25. The method of claim 24, further comprising:

at a temperature T_2, shaping the strip into a second shape, wherein $T_2 = T_1 - Y°C$, and Y is from about 5 to about 80.

26. The method of claim 25, wherein said shaping the strip into a first shape comprises coiling the strip into a helix shape having a helical width D_1, and wherein said shaping the strip into a second shape comprises compressing the strip into a helix shape having helical width D_2, wherein $D_2 < D_1$.

27. The method of any one of claims 24 to 26, further comprising adding a plasticizer to said first polymer prior to forming said strip of polymer film.

28. The method of claim 27, further comprising adding a plasticizer to said second polymer prior to forming said strip of polymer film.

29. The method of any one of claims 24 to 28, wherein said first layer is an outer layer and said second layer is an inner layer such that said outer layer is spaced farther from a central longitudinal axis of said stent than said inner layer, and $T_{g1} < T_{g2}$.

30. The method of any one of claims 24 to 29, wherein said polymer film is

formed by co-extruding said first layer and said second layer.

31. The method of any one of claims 24 to 29, wherein said polymer film is formed by solvent-casting said first layer and said second layer.

32. The method of any one of claims 24 to 29, wherein said polymer film is formed by spin-casting said first layer and said second layer.

33. The method of claim 31 or claim 32, wherein the solvent used to cast said second layer does not dissolve said first layer.

34. The method of any one of claims 31 to 33, further comprising adding a therapeutic agent to said first polymer prior to casting.

35. The method of claim 34, wherein said therapeutic agent is selected from the group consisting of a drug, an antibiotic, an anti-inflammatory agent, an anti-clotting factor, a hormone, a nucleic acid, a peptide, a cellular factor, a ligand for a cell surface receptor, an anti-proliferative agent, an anti-thrombotic agent, an antimicrobial agent, an anti-viral agent, a chemotherapeutic agent, and an anti-hypertensive agent.

36. The method of claim 34 or claim 35, further comprising adding a therapeutic agent to said second polymer prior to casting.

37. The method of claim 36, wherein a different therapeutic agent is added to each of said first polymer and said second polymer prior to casting.

38. The method of any one of claims 24 to 37, wherein said first polymer is biostable.

39. The method of claim 38, wherein said second polymer is biostable.

40. The method of claim 39, wherein said first polymer and said second are independently selected from the group consisting of polyethylene,

polypropylene, poly ethylene terephthalate (PET), polyurethane poly (ether urethane), poly (ester urethane), poly vinyl chloride, polyvinyl acetate (PVAc), poly(ethylene-co-vinyl acetate) (PEVAc), polycaprolactone and Nylon 6,6.

41. The method of any one of claims 24 to 37, wherein said first polymer is bioabsorbable.

42. The method of claim 41, wherein said second polymer is bioabsorbable.

43. The method of claim 42, wherein said first polymer and said second polymer are independently selected from the group consisting of poly-L-lactide (PLLA), poly-D-lactide (PDLA), polyglycolide (PGA), poly lactide-co-glycolide (PLGA), polydioxanone, polygluconate, polylactic acid-polyethylene oxide copolymer, modified cellulose, collagen, poly(hydroxybutyrate), polyanhydride, polyphosphoester and poly-amino acid.

44. The method of any one of claims 41 to 43, wherein said first polymer degrades at a different rate from said second polymer.

45. A method of treatment or prophylaxis, to a subject in need of expansion of a lumen, comprising:

introducing into the subject at site in the lumen desired to be expanded a stent comprising a first layer including a first polymer that is at least partially amorphous and a first therapeutic agent, thereby delivering said first therapeutic agent to said subject, said stent formed to have a first shape at a lower temperature T_2 and a second shape at a higher temperature T_1; and

causing said stent to change to said second shape.

46. The method of claim 45, wherein said stent comprises a second layer including a second polymer that is at least partially amorphous and a second therapeutic agent.

47. A method for prophylaxis or treatment of a subject in need of

expansion of a lumen, comprising:

introducing into the subject at site in the lumen desired to be expanded a stent comprising a first layer including a first polymer that is at least partially amorphous and has a glass transition temperature T_{g1} and a second layer including a second polymer that is at least partially amorphous and has a glass transition temperature T_{g2}, said stent formed to have a first shape at a lower temperature T_2 and a second shape at a higher temperature T_1 and configured to change from said first shape to said second shape at a temperature equal to or greater than a shape transition temperature T_3, and wherein said introducing is performed at a temperature below T_3 such that said stent is in said first shape; and

causing said stent to change to said second shape, in part by allowing said stent to equilibrate to a temperature equal to or greater than T_3.

48. The method of claim 47, further comprising delivering a first therapeutic agent to said subject, wherein said first therapeutic agent is included in said first layer of said stent.

49. The method of claim 48 further comprising delivering a second therapeutic agent to said subject, wherein said second therapeutic agent is included in said second layer of said stent.

50. The method of any one of claims 45 to 49, wherein said first shape is a generally helical shape having helical width D_2 and said second shape is a generally helical shape having helical width D_1, and wherein $D_1 > D_2$.

51. The method of any one of claims 45, 46 and 48 to 50, wherein said first therapeutic agent is independently selected from the group consisting of a drug, an antibiotic, an anti-inflammatory agent, an anti-clotting factor, a hormone, a nucleic acid, a peptide, a cellular factor, or a ligand for a cell surface receptor, an anti-proliferative agent, an anti-thrombotic agent, an antimicrobial agent, an anti-viral agent, a chemotherapeutic agent, and an anti-hypertensive agent.

52. The method of claim 46 or claim 49, wherein said second therapeutic agent is independently selected from the group consisting of a drug, an antibiotic, an anti-inflammatory agent, an anti-clotting factor, a hormone, a nucleic acid, a peptide, a cellular factor, or a ligand for a cell surface receptor, an anti-proliferative agent, an anti-thrombotic agent, an antimicrobial agent, an anti-viral agent, and an anti-hypertensive agent.

53. The method of any one of claims 46, 49 and 52, comprising delivering a therapeutic agent to a subject in a biphasic manner, wherein said first therapeutic agent and said second therapeutic agent are the same and said therapeutic agent has a different diffusion rate from said first layer than from said second layer.

54. The method of any one of claims 45 to 53, wherein the stent is biostable.

55. The method of any one of claims 45 to 53, wherein the stent is bioabsorbable.

56. The method of any one of claims 46, 49, 52 and 53, wherein said stent extends along a helical axis, and said first layer forms an exterior layer of said stent, and said second layer forms an interior layer of said stent, and said method further comprises releasing said first therapeutic agent away from said axis, and releasing said second therapeutic agent toward said axis.

57. A stent comprising a substrate including a polymer that is at least partially amorphous and has a glass transition temperature T_g, and a therapeutic agent included in said polymer, said stent formed to have a first shape at a lower temperature T_2 and a second shape at a higher temperature T_1 and configured to change from said first shape to said second shape at a temperature equal to or greater than a transition temperature T_3.

58. The stent of claim 57, wherein said first shape is a generally helical shape having helical width D_2 and said second shape is a generally helical

shape having helical width D_1, and wherein $D_1 > D_2$.

59. The stent of claim 57 or claim 58, wherein said polymer is cross-linked.

60. The stent of any one of claims 57 to 59, wherein $T_3 \leq 37°C$.

61. The stent of any one of claims 57 to 60, wherein said polymer is biostable.

62. The stent of claim 61, wherein said polymer is selected from the group consisting of polyethylene, polypropylene, poly ethylene terephthalate (PET), polyurethane poly (ether urethane), poly (ester urethane), poly vinyl chloride, polyvinyl acetate (PVAc), poly(ethylene-co-vinyl acetate) (PEVAc), polycaprolactone and Nylon 6,6.

63. The stent of any one of claims 57 to 60, wherein said polymer is bioabsorbable.

64. The stent of claim 63, wherein said polymer is selected from the group consisting of poly-L-lactide (PLLA), poly-D-lactide (PDLA), polyglycolide (PGA), poly lactide-co-glycolide (PLGA), polydioxanone, polygluconate, polylactic acid-polyethylene oxide copolymer, modified cellulose, collagen, poly(hydroxybutyrate), polyanhydride, polyphosphoester and poly-amino acid.

65. The stent of any one of claims 57 to 64, wherein said therapeutic agent is selected from the group consisting of a drug, an antibiotic, an anti-inflammatory agent, an anti-clotting factor, a hormone, a nucleic acid, a peptide, a cellular factor, a ligand for a cell surface receptor, an anti-proliferative agent, an anti-thrombotic agent, an antimicrobial agent, an anti-viral agent, a chemotherapeutic agent, and an anti-hypertensive agent.

66. A method of manufacturing a stent comprising:

adding a therapeutic agent to a polymer that is at least partially amorphous and has a glass transition temperature;

forming a strip of polymer film from said polymer;

shaping the strip into a first shape at a temperature T_1, wherein $T_1 = T_g + X°C$, T_g is the glass transition temperature of the polymer and X is from about -20 to about +120; and

at a temperature T_2, shaping the strip into a second shape, $T_2 = T_1 - Y°C$, and Y is from about 5 to about 80.

67. The method of claim 66, wherein said shaping the strip into a first shape comprises coiling the strip into a helix shape having a helical width D_1, and wherein said shaping the strip into a second shape comprises compressing the strip into a helix shape having helical width D_2, wherein $D_2 < D_1$.

68. The method of claim 66 or claim 67, further comprising adding a plasticizer to said polymer prior to forming said strip of polymer film.

69. The method of any one of claims 66 to 68, wherein said polymer film is formed by extruding said layer.

70. The method of any one of claims 66 to 68, wherein said polymer film is formed by solvent-casting said layer.

71. The method of any one of claims 66 to 68, wherein said polymer film is formed by spin-casting said layer.

72. The method of any one of claims 66 to 71, wherein said therapeutic agent is selected from the group consisting of a drug, an antibiotic, an anti-inflammatory agent, an anti-clotting factor, a hormone, a nucleic acid, a peptide, a cellular factor, a ligand for a cell surface receptor, an anti-proliferative agent, an anti-thrombotic agent, an antimicrobial agent, an anti-viral agent, a chemotherapeutic agent, and an anti-hypertensive agent.

73. The method of any one of claims 66 to 72, wherein said polymer is biostable.

74. The method of claim 73, wherein said polymer is selected from the group consisting of polyethylene, polypropylene, poly ethylene terephthalate (PET), polyurethane poly (ether urethane), poly (ester urethane), poly vinyl chloride, polyvinyl acetate (PVAc), poly(ethylene-co-vinyl acetate) (PEVAc), polycaprolactone and Nylon 6,6.

75. The method of claim any one of claims 66 to 72, wherein said polymer is bioabsorbable.

76. The method of claim 75, wherein said polymer is independently selected from the group consisting of poly-L-lactide (PLLA), poly-D-lactide (PDLA), polyglycolide (PGA), poly lactide-co-glycolide (PLGA), polydioxanone, polygluconate, polylactic acid-polyethylene oxide copolymer, modified cellulose, collagen, poly(hydroxybutyrate), polyanhydride, polyphosphoester and poly-amino acid.

77. The method of any one of claims 24 to 44 or claims 66 to 76, wherein X is from about 0 to about 40.

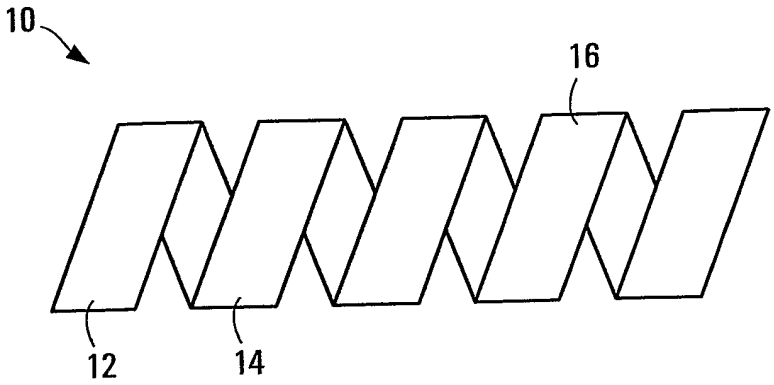

FIG. 1

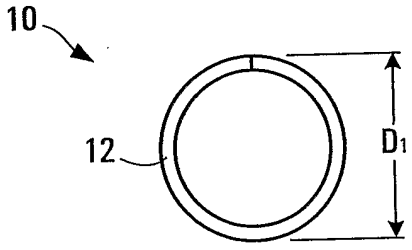

FIG. 2

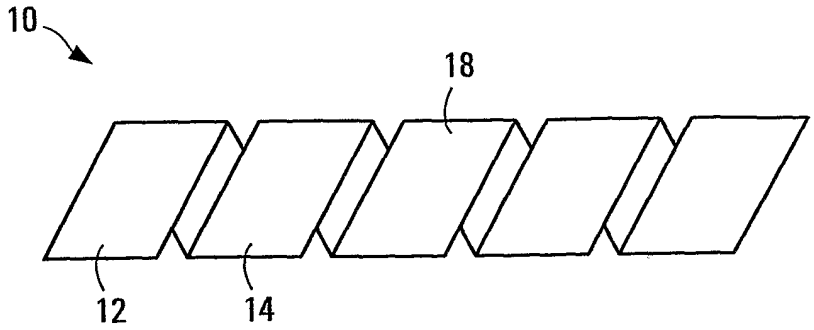

FIG. 3

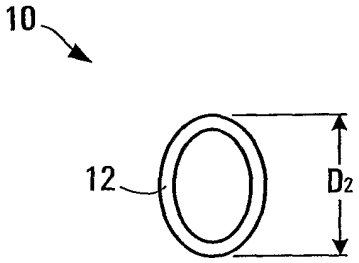

FIG. 4

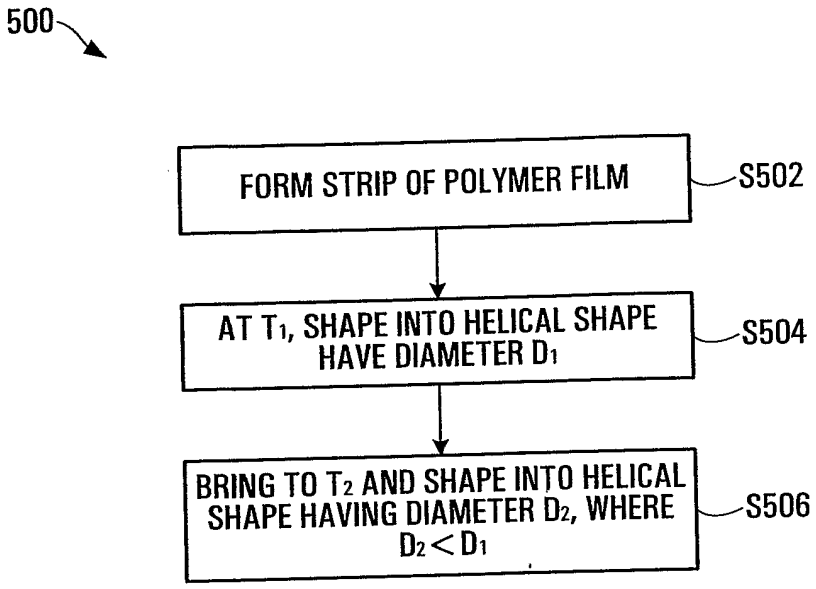
500
FORM STRIP OF POLYMER FILM
S502
AT T1, SHAPE INTO HELICAL SHAPE HAVE DIAMETER D1
S504
BRING TO T2 AND SHAPE INTO HELICAL SHAPE HAVING DIAMETER D2, WHERE D2 < D1
S506

FIG. 5

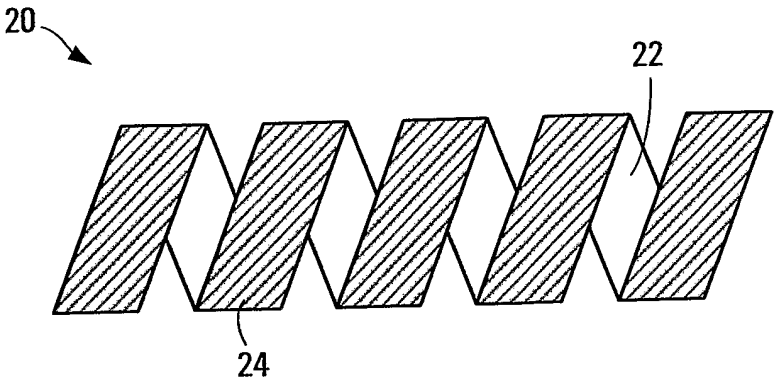

FIG. 6

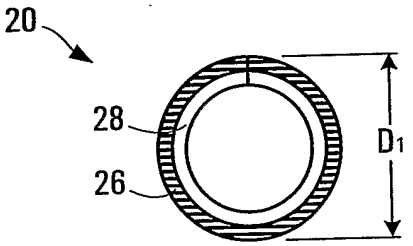

FIG. 2

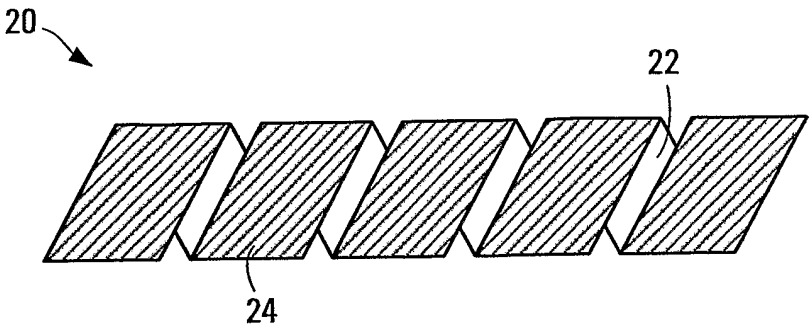

FIG. 8

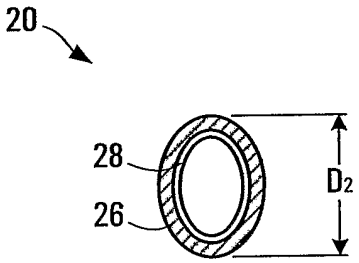

FIG. 9

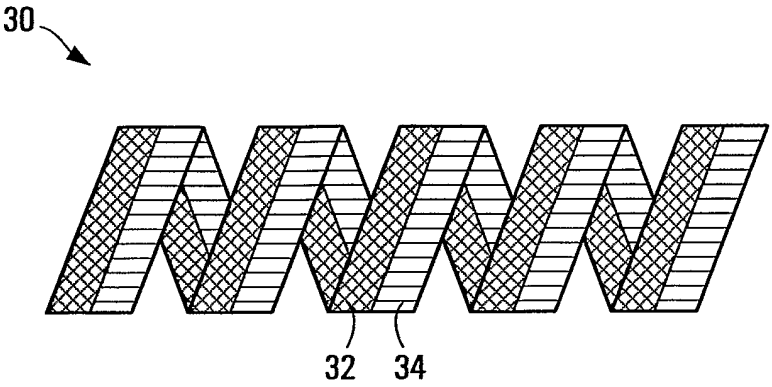
30
32
34

FIG. 10

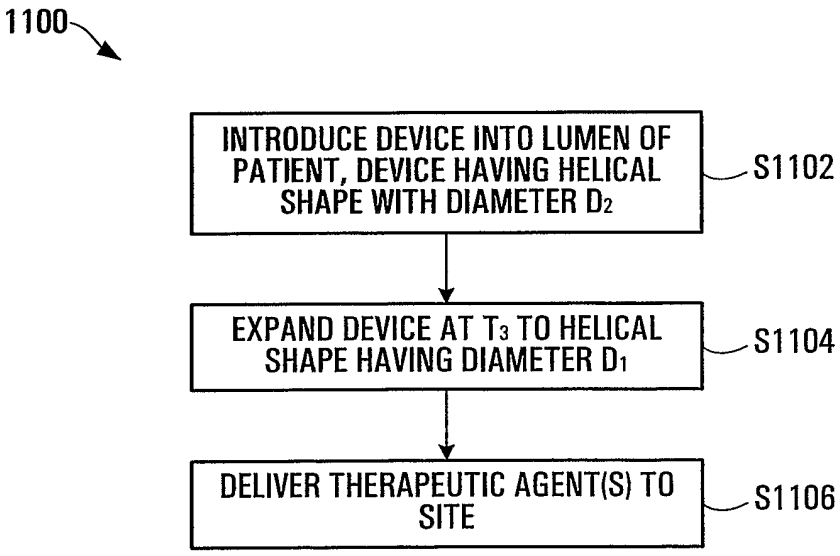
1100
INTRODUCE DEVICE INTO LUMEN OF PATIENT, DEVICE HAVING HELICAL SHAPE WITH DIAMETER D2
S1102
EXPAND DEVICE AT T3 TO HELICAL SHAPE HAVING DIAMETER D1
S1104
DELIVER THERAPEUTIC AGENT(S) TO SITE
S1106

FIG. 11

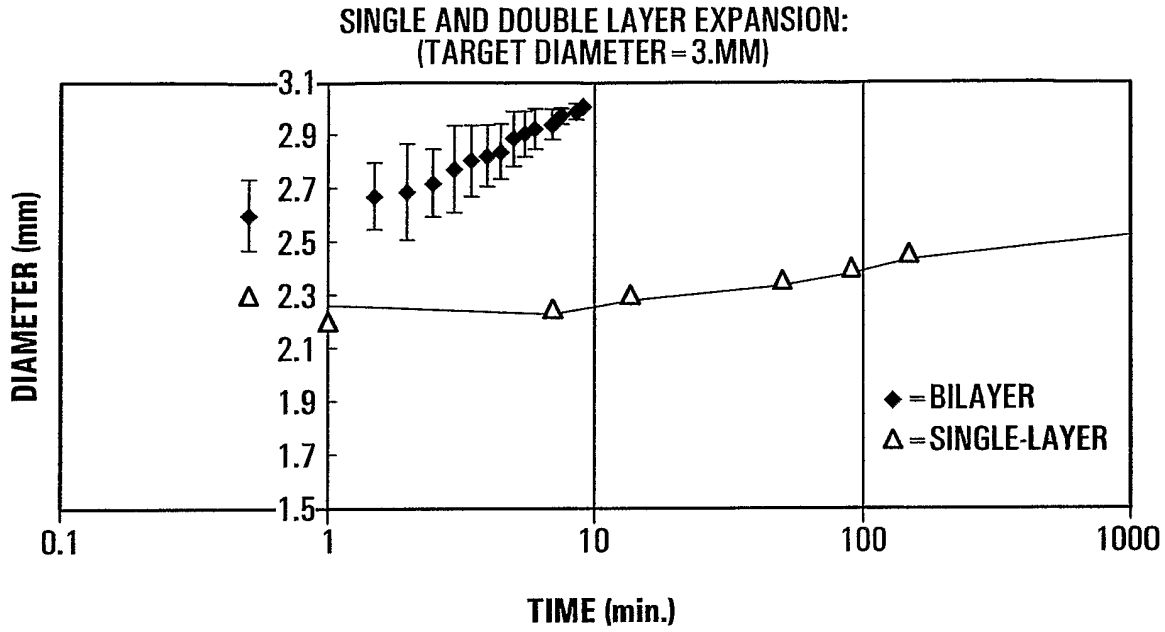
SINGLE AND DOUBLE LAYER EXPANSION:
(TARGET DIAMETER = 3.MM)
DIAMETER (mm)
3.1
2.9
2.7
2.5
2.3
2.1
1.9
1.7
1.5
0.1
1
10
100
1000
TIME (min.)
◆ = BILAYER
△ = SINGLE-LAYER

FIG. 12

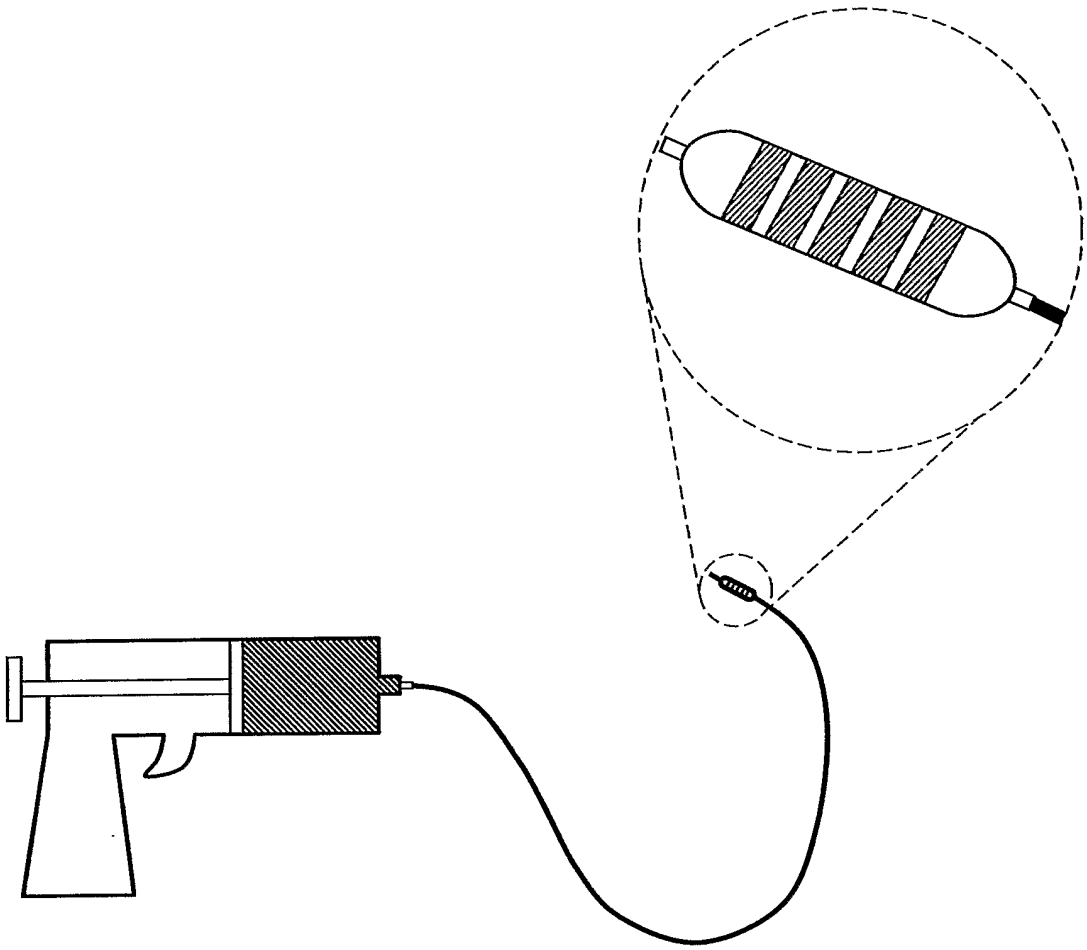

FIG. 13

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SG2004/000180

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: A61F 2/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
DWPI IPC: A61M, A61B, A61F & +keywords: stent, polymer and similar terms

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,954,744 A (PHAN et al) 21 September 1999 Abstract and figures 3A, 3B and 3C	45, 57-63, 65
A	US 6,364,904 B1 (SMITH) 2 April 2002 Figures 23-35 and column 9 line 59 to column 10 line 14	
A	WO 1999/042528 A2 (MNEMOSCIENCE GMBH) 26 August 1999 Page 26 lines 24 to page 27 line 6	
A	US 2002/0077693 A1 (BARCLAY et al) 20 June 2002 Abstract	

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 July 2004	28 JUL 2004
Name and mailing address of the ISA/AU	Authorized officer
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	**MARK COX** Telephone No : (02) 6283 2178

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SG2004/000180

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6,338,739 B1 (DATTA et al) 15 January 2002 Abstract	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/SG2004/000180

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
US	5954744	AU	55900/98	AU	59783/96	CA	2222892
		CN	1192668	EP	0831754	US	5603722
		US	5674242	WO	9639103	WO	9820928
WO	9942528	AU	33084/99	BR	9908339	CA	2316945
		EP	1062278	HU	0102138	PL	342996
		US	6388043	US	2003055198		
US	6364904	EP	1200015	US	2002065550	US	2004024446
		WO	0101886				
US	2002077693	AU	31058/02	AU	54153/01	CA	2351917
		EP	1343436	US	6585760	US	2002082682
		US	2003028245	WO	0249544	WO	02093674
US	6338739	EP	1110561	JP	2001333975	US	2002019661
		US	2002143388	US	2003045924	US	2003144730

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

END OF ANNEX