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(54) **MEDICAL DEVICES HAVING DRUG ELUTING PROPERTIES AND METHODS OF MANUFACTURE THEREOF**

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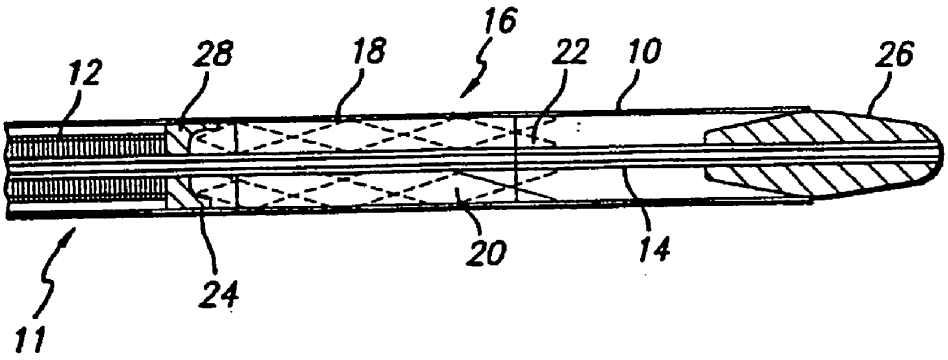
(57) **ABSTRACT**

A medical device comprises a shape memory alloy having a reverse martensitic transformation start temperature of greater than or equal to about 0° C.; and a drug coating comprising a polymeric resin and a biologically active agent. A method of manufacturing a stent comprises cold forming a shape memory alloy from a wire; heat treating the cold formed shape memory alloy at a temperatures greater than that at which a martensitic transformation can occur; and coating the stent with a drug coating comprising a biologically active agent.



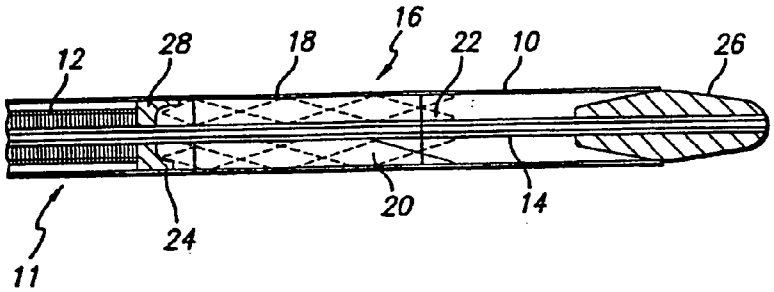


FIG. 1

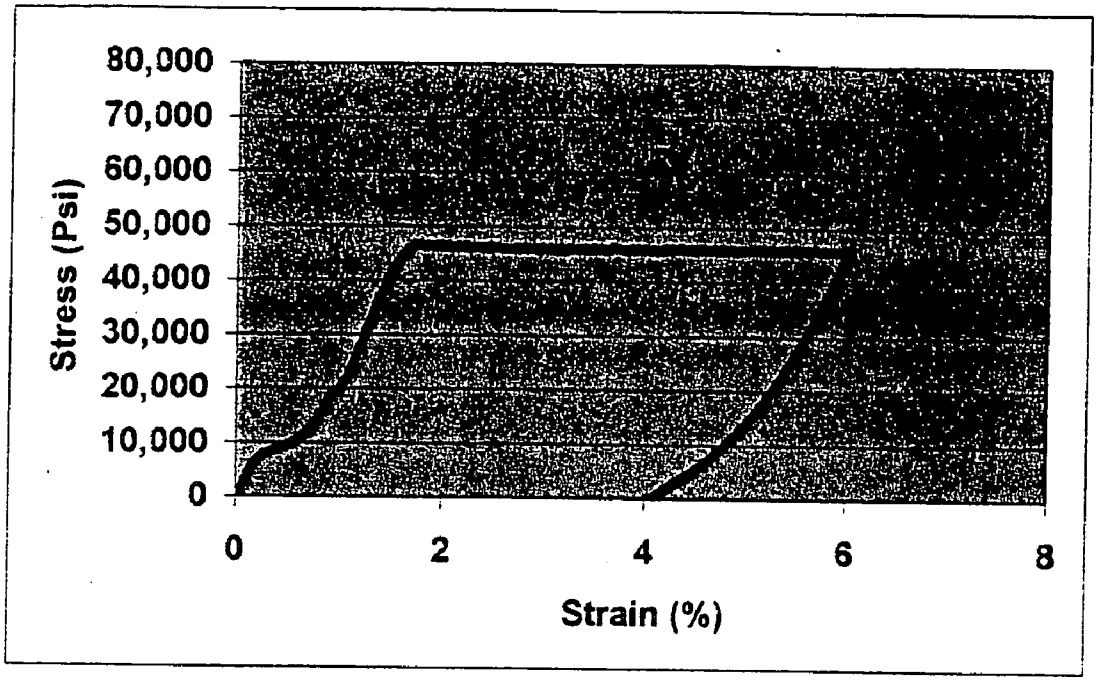


Fig. 2

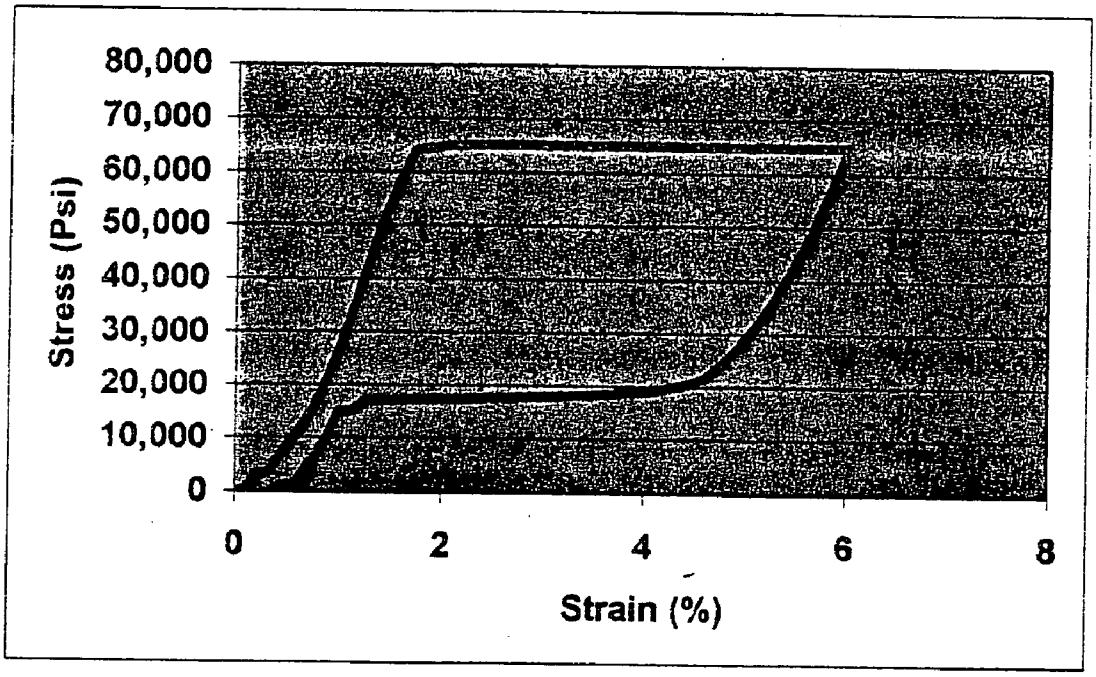


Fig. 3

MEDICAL DEVICES HAVING DRUG ELUTING PROPERTIES AND METHODS OF MANUFACTURE THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application Serial No. 60/459,392 filed 31 Mar. 2003.

BACKGROUND

[0002] The present disclosure relates to medical devices having drug eluting properties and methods of manufacture thereof.

[0003] Vascular diseases caused by the progressive blockage of the blood vessels often leads to hypertension, ischemic injury, stroke, or myocardial infarction. Atherosclerotic lesions, which limit or obstruct blood flow, are the major cause of vascular disease. Balloon angioplasty is a medical procedure whose purpose is to increase blood flow through an artery and it is used as a predominant treatment for vessel stenosis. The increasing use of this procedure is attributable to its relatively high success rate and its minimal invasiveness compared with coronary bypass or vascular surgery. A limitation associated with balloon angioplasty is the abrupt or progressive post-procedural re-closure of the vessel or restenosis.

[0004] The difficulties associated with balloon angioplasty have facilitated the use of medical devices such as stents and stent technology in most coronary or vascular interventions. The use of such medical devices has significantly reduced the restenosis rate from about 40% after balloon angioplasty alone, to about less than 15% when balloon angioplasty is followed by a subsequent placement of a medical device such as a stent. While contractive remodeling of the vessel is the primary mechanism that leads to restenosis after balloon angioplasty, the restenosis after stent placement is associated with neointimal hyperplasia, which assumed to be caused by vessel injury during stent placement. The in-stent restenosis process occurs first with platelet accumulation on the stent surface. Smooth muscle begins to migrate to the site of the platelet accumulation and proliferate in response to the inflammation. Extracellular matrix finally deposits on the site during the later stages of the healing process. The platelet accumulation and development of extracellular matrix is detrimental to the functioning of the artery.

[0005] To battle restenosis, medical devices such as stents often encapsulate drugs or are coated with drugs in order to inhibit or minimize various stages of undesirable cell activity. The pharmacological characteristics of the drugs proposed as coatings for the attenuation of such undesirable cell activity include but are not limited to anti-inflammation, anti-proliferation, immuno-suppressive and anti-migration properties. Examples of such drugs include SIROLIMUS, EVEROLIMUS, ABT 578, PACLITAXEL, DEXAMETHASONE and MYCOPHENOLIC ACID.

[0006] Drug coatings generally comprise biologically active agents and polymers. The biologically active agent may be physically blended or encapsulated into a bio- at various rates post procedurally. Since the polymers utilized in drug coatings generally have glass transition temperatures around room temperature (i.e., about 23° C.) they can be designed and fabricated to have sufficient flexibility at temperatures higher than room temperature. However, when cooled to temperatures below the glass transition temperature they are easily embrittled and suffer permanent damage thus rendering them unusable or ineffective.

[0007] Some of the alloys used in the manufacture of self-expanding medical devices such as stents (upon which are applied the drug coatings) can be shape memory alloys having a reverse martensitic transformation start temperature (A_s) of about 0° C. with an austenite transformation finish temperature (A_f) of about 20° C. to 30° C. Because of the superelastic properties displayed by these alloys at temperatures greater than or equal to about A_f, loading a self-expanding medical device into a delivery system at or near ambient temperature is highly challenging as the device often displays a tendency to recover its expanded shape just like a regular spring. To minimize this spring-like phenomena and to achieve free or enhanced loading characteristics into a delivery system, a self-expanding device is generally first cooled to a temperature below its A_s temperature, which is also below the ambient temperature. As stated above, this low temperature deformation of the device promotes embrittlement of the drug coating, which often leads to undesirable ruptures or mechanical degradation in the coating.

SUMMARY

[0008] In one embodiment, a medical device comprises a shape memory alloy having a reverse martensitic transformation start temperature of greater than or equal to about 0° C.; and a drug coating comprising a polymeric resin and a biologically active agent.

[0009] In another embodiment, the medical device is an implantable stent.

[0010] In yet another embodiment, a nickel-titanium alloy composition comprises about 55.5 wt % of nickel based on the total composition of the alloy.

[0011] In yet another embodiment, a nickel-titanium-niobium alloy composition comprises about 48 wt % nickel and about 14 wt % niobium based on the total composition of the alloy.

[0012] In yet another embodiment, a method of manufacturing a stent comprises cold forming a shape memory alloy from a wire; heat treating the cold formed shape memory alloy at a temperatures greater than that at which a martensitic transformation can occur; and coating the stent with a drug coating comprising a biologically active agent.

[0013] In yet another embodiment, a method of manufacturing a stent comprises laser cutting, water jet cutting, electrode discharge machining (EDM), chemically, electrochemically or photo-chemically etching a nickel-titanium alloy having about 55.5 wt % of nickel or a nickel-titanium-niobium alloy having about 48 wt % nickel and about 14 wt % niobium from a tube, wherein the weight percents are based on the total weight of the composition; heat treating the alloy at a temperatures greater than that at which a

BRIEF DESCRIPTION OF THE FIGURES

[0014] **FIG. 1** represents a cross-sectional view of the end of a catheter illustrating a stent to be implanted;

[0015] **FIG. 2** is a graphical representation of a tensile stress-strain curve of Ti-55.5 wt % Ni tested at 10° C.; and

[0016] **FIG. 3** is a graphical representation of a tensile stress-strain curve of Ti-55.5 wt % Ni tested at 37° C.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[0017] Disclosed herein is a medical device coated with a drug coating comprising a polymeric resin and a biologically active agent, wherein the medical device is manufactured from an alloy having a reverse martensitic transformation start temperature A_s of greater than or equal to about 0° C., preferably greater than or equal to about 10° C. and further wherein the polymeric resin also has a glass transition temperature (T_g) of less than or equal to about A_s. The use of an alloy having an A_s of greater than or equal to about 0° C. in conjunction with a drug coating wherein the polymer has a T_g is less than or equal to about A_s, advantageously allows the medical device to be used at temperatures that are generally lower than sub-ambient temperatures without any permanent deformation and embrittlement of the polymeric resin. Additionally, since the alloy used in the medical device has an A_s greater than or equal to about 0° C., the need to cool the medical device to temperatures below 0° C. to minimize the "spring-like behavior" is reduced, thereby easing the loading of the device onto the delivery system improving the performance of the medical device post-procedurally.

[0018] The medical device may be a stent, a covered stent or stent graft, a needle, a curved needle, bone staples, a vena cava filter, a suture or anchor-like mechanism, or the like. In one exemplary embodiment, the medical device is an implantable stent. A stent as defined herein may be either a solid, hollow, or porous implantable device, which is coated with or encapsulate the drug coating(s). Since the stent may be hollow, solid or porous, the drug coating(s) may be applied to the outer surface, the inner surface, both surfaces of the stent, on selective locations on the stent, for example a different coating could be applied to the ends of a stent compared to its middle portion

[0019] The figure illustrates one embodiment of a catheter having an implantable stent. In the figure, the distal end of a catheter **11** having a stent **16** carried within it for implantation into the body of a patient. The proximal end of the catheter **11** is connected to a suitable delivery mechanisms and the catheter **11** is of sufficient length to reach the point of implantation of the stent **16** from the introduction point into the body. The catheter **11** includes an outer sheath **10**, a middle tube **12** which may be formed of a compressed spring, and a flexible (e.g., polyamide) inner tube **14**. A stent **16** for implantation into a patient is carried within the outer sheath **10**. The stent **16** is generally manufactured from a shape memory alloy frame **18**, which is formed in a criss-cross pattern, which may be laser cut. One or both ends of the stent **16** may be left uncovered as illustrated at **22** and **24** to provide anchoring within the vessel where the stent **16** is to be implanted.

[0020] [illegible] tip **26** has a rounded end and is gradually sloped to aid in the movement of the catheter through the body vessel. The atraumatic tip **26** is radiopaque so that its location may be monitored by appropriate equipment during the surgical procedure. The inner tube **14** is hollow so as to accommodate a guide wire, which is commonly placed in the vessel prior to insertion of the catheter, although a solid inner section and be used without a guide wire. Inner tube **14** has sufficient kink resistance to engage the vascular anatomy without binding during placement and withdrawal of the delivery system. In addition, inner tube **14** is of sufficient size and strength to allow saline injections without rupture.

[0021] A generally cup-shaped element **28** is provided within the catheter **11** adjacent the rear end of the stent **16** and is attached to the end of the spring **12** by appropriate means, e.g., the cup element **28** may be plastic wherein the spring **12** is molded into its base, or the cup element **28** may be stainless steel wherein the spring **12** is secured by welding or the like. The open end of the cup element **28** serves to compress the end **24** of the stent **16** in order to provide a secure interface between the stent **16** and the spring **12**. Alternatively, instead of a cup shape, the element **28** could be formed of a simple disk having either a flat or slightly concave surface for contacting the end **24** of the stent **16**.

[0022] The alloys used in the medical devices are preferably shape memory alloys having an A_s greater than or equal to about 0° C. The medical devices may be self expanding or thermally expanding. It is desirable for a self expanding medical device to have the A_s of the shape memory alloy be greater than or equal to about 10° C., preferably greater than or equal to about 15° C., preferably greater than or equal to about 20° C., and more preferably greater than or equal to about 23° C. In another embodiment, the shape memory alloys used in the self-expanding medical devices have an A_f temperature of about 25° C. to about 37° C. Within this range it is generally desirable to have an A_f temperature of greater than or equal to about 28° C., preferably greater than or equal to about 30° C. Also desirable within this range is an A_f temperature of less than or equal to about 36° C., preferably less than or equal to about 35° C.

[0023] If the medical device is thermally expanding, then it is preferable for the shape memory alloys to have an A_s greater than or equal to about 35° C. When a medical device is thermally expanding such as is achieved by the use of a hot saline solution, it may be desirable to have an A_f temperature of less than or equal to about 50° C.

[0024] It is generally desirable to use shape memory alloys having pseudo-elastic properties, and which are formable into complex shapes and geometries without the creation of cracks or fractures. It is also generally desirable to use shape memory alloys, which permit large plastic deformations during fabrication of the medical device before the desired pseudoelastic properties are established and wherein the pseudoelastic properties are developed after fabrication.

[0025] Shape memory alloys that may be used in the medical devices are generally nickel titanium alloys. Suitable examples of nickel titanium alloys are nickel-titanium-niobium, nickel-titanium-copper, nickel-titanium-iron, nickel-titanium-hafiiium, nickel-titanium-palladium, nickel-[illegible]

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