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(54) Title: RADIOACTIVABLE COMPOSITION SUITABLE FOR FABRICATION OF IMPLANTABLE MEDICAL DEVICES

(57) Abstract

Disclosed are radioactivable compositions, preferably metal alloy compositions containing a metal having shape memory characteristics, and at least one radioactivable isotope comprising a lanthanide series element or mixtures of lanthanide series of elements or other suitable isotope. The radioactivable isotope is present in sufficient concentration (relative to other components of the composition) to deliver an effective radiation dose to a target tissue to achieve a specified therapeutic objective. One of the more advantageous and useful applications for this composition is the formation of medical devices for the treatment of coronary artery disease and the abatement of proliferation of cancer cells. In one of the preferred embodiments of this invention, a radioactivable isotope is incorporated, by isotopic beneficiated combination, with a matrix material such as a nickel/titanium alloy (e.g. *Nitinol* metal alloys), or by isotopic beneficiated combination with a biodegradable organic naturally occurring or synthetic polymer so as to form a solid solution; and, the resultant alloy or solid solution, thereafter, formed into a stent, or other suitable form, for selective and targeted delivery of therapeutic and effective amounts of low dosage forms of radiation (principally *beta* particles) to a specific site or tissue within the human body.

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TITLE OF INVENTION

RADIOACTIVABLE COMPOSITION

SUITABLE FOR FABRICATION OF IMPLANTABLE MEDICAL DEVICES

BACKGROUND OF THE INVENTION

1. ***Field Of The Invention*** - This invention relates to a composition of matter, useful articles formed from such compositions and the use of such articles in therapeutic applications responsive to radiation therapy. More specifically, this invention relates to compositions having a radioactivable naturally occurring or enriched stable isotope incorporated, by isotopically beneficiated combination, into a matrix material; and, the resultant composition, thereafter, formed into a medical device, such as a stent, or other suitable form, for selective and targeted delivery of safe and effective amounts of low dosage forms of radiation (preferably *beta* particle emissions) to a target site or mammalian tissue; and, preferably to compositions composed of an alloy having memory characteristics.

The composition of this invention can be formed into an intra-arterial stent or other complimentary device for use in the treatment of coronary peripheral artery disease or restenosis; or, alternatively, into a device useful for example in the treatment of benign prostatic hyperplasia, dysphagia, polychondritis, and cancer, particularly constrictive diseases of the esophagus, prostate, kidney or colorectal cancers.

2. ***Description Of The Prior Art*** - The target specific delivery of drugs and medical devices for the abatement and prevention disease is beginning to come of age, although not without certain limitations and problems associated with both administration and delivery. Among the medical procedures that currently use such a target specific approach is treatment of coronary artery disease by drug mediated intervention, balloon angioplasty and, more recently, intra-arterial radiation therapy. More than 1.5 million therapeutic interventional cardiology procedures are done annually worldwide. Coronary and peripheral balloon angioplasty, aimed at long term reduction of neointimal hyperplasia, has been performed for over fifteen years

but with only partial success. The latter method is limited by abrupt vessel closure, late restenosis and the inability to effectively treat acute and subacute closure. Restenosis, in which occluded coronary arteries reclose within six months after being dilated by balloon angioplasty, occurs in forty percent (40%) or more of patients, usually within six months or less, and continues to remain a serious limitation to long term success of balloon angioplasty.

It is believed that there are three mechanisms that are responsible for restenosis:

(a) elastic recoil, (vessel constriction after vascular injury)

(b) remodeling, and

(c) smooth muscle cell proliferation

Elastic recoil is generally an acute or subacute reaction. The vessel wall contracts back to its previous position after being stretched by the balloon. *Remodeling* refers to the formation of scar tissue caused by the balloon-induced injury. *Smooth muscle* cells react through healing with a cellular response to the injury by proliferating into the vessel lumen and, therefore, blocks blood flow. Another shortcoming to successful angioplasty is the natural progression of arteriosclerosis. Accordingly, there is a continuing need to improve and adapt one or more combination of the above approaches to effectively treat this disease.

Similar shortcomings are found in the treatment and recurrence of other persistent diseases, such as cancer, where temporary success (remission) is achieved, only to have the tumor reappear because of incomplete destruction or removal. For example, in oncological applications, it has been estimated that over one hundred thousand intrahepatic, renal, endotracheal, esophageal, urethral and other stenting procedures are performed annually, including non-resectable tumors of the upper part of the biliary tract. Stenting has been shown to prolong survival and improve patient comfort but in general only provides neoplastic palliation. Currently, no available medical device provides the combination or adjuvant radiation therapy and chemotherapy treatment. As with all but a few of these treatments, the non-

specificity of treatment causes the patient substantial adverse reactions, which in some cases, result in the patient refusing further treatment.

With respect to the use of targeted radiation therapy in cardiovascular applications, one approach has been to use a radioactive liquid filled balloon (containing, for example rhenium-186) for the treatment of restenosis. The preparation and filling of a balloon with a radioactive solution such as rhenium-188 is complicated by the fact that several steps are involved in the preparation of such device, and the ever present potential for bursting. The resultant balloon is subject to many of the same shortcomings and frailties of balloons currently in use in angioplasty procedures, and if and when the physical integrity thereof is compromised, (e.g. leak or rupture) the radioactive contents may leak or spill into the blood stream, or can spray onto the clinicians, technicians or nursing staff performing such procedure. Moreover, the logistical problems in filling, handling and disposing of radioactive solutions in a catheterization laboratory, or department of nuclear medicine, are tedious and considerable, and, thus, tend to favor more rational or conservative methods and devices.

Another means for the targeted radiation therapy of cardiovascular applications is the emerging use of radioactive stents. The limitations on stent design and composition (e.g. memory metal alloys), however, presents inherent limitations on both the usefulness of these devices to both treat and arrest the cause of the specific disease or disorder. For example, the first reported use of a *metallic* coronary stent involved their placement in large arteries to reduced the incidence of restenosis in 25% to 35% in a selected group of patients. As noted above, this approach does not eliminate arterial recoil in a statistically significant population receiving such treatment. It has been demonstrated in post *by-pass* patients, that treating the common reclosing of vein grafts with stents instead of angioplasty lowers the risk of complications. In such procedures, metallic stents are implanted incidental to percutaneous transluminal coronary angioplasty (PTCA) during or shortly after balloon angioplasty. Notwithstanding such remarkable progress, and the widespread acceptance of intracoronary stenting over the last few years, it does not provide a "cure" for the

patient undergoing this procedure because of the large numbers of revascularization procedures that must still be performed and the phenomena of in-stent restenosis.

For example, two clinical studies in this field have demonstrated that stents can prevent restenosis in a limited number of instances. It is further remarkable that only modest success was achieved, even though the study was biased (e.g. conducted on a selected patient population) because the patients participating therein were likely to favorable respond to such treatment, (only about 10% of the patients participating experienced reduced restenosis), and, such "success" appeared to decrease with time following intervention. Thus, despite the limited successes of current metallic stents, these devices still remain limited to use as endoluminal implants in *large occluded arteries* (over 3 mm), because of the propensity for thromboses with subsequent subacute closure, difficult placement, stiffness, migration, wall thinning, aneurysm formation, limited flexibility, compliance mismatch, medial atrophy with the potential for late vessel wall proliferation, insufficient long term patentcy data, spasm, and intrastent restenosis. Moreover, there is increasing anxiety about the application of stenting as an unrestricted (routine/elective) strategy, *See* for example discussion in ACC Expert Consensus Document, JACC 28, No. 3, Sept., 1996, pp. 782-794.

Thus, the limitations inherent in conventional (metallic) stenting, alternative therapies, and combinations of therapies, continue to be explored and evaluated, including more recently, targeted radiation therapy. The physiology of the restenotic process is recognized as a proliferation disorder. Intravascular radiation (more properly "brachytherapy"), appears to have positive results on the portion of restenosis known as remodeling and smooth muscle proliferation. Radiation is known to inhibit smooth muscle proliferation and intervene in the wound healing process. Endovascular brachytherapy, that is the use of radiation to control neointimal formation, has been successfully demonstrated in the laboratory as having potential in controlling this pathological proliferative process; and, such success has been recently confirmed in clinical studies in humans. For example, it has been shown that mild exposure to radiation effectively inhibits intimal proliferation after stent induced or balloon overstretch injury in coronary and peripheral artery disease. The activity

levels of radioactive stents are up to 10,000 times lower than the activity levels of sources used for catheter-direct source contact with the circumference of the vessel. Accordingly, this procedure is being used in trials for target vessel revascularization, for treating restenosis, and for the management of certain constrictive cancers.

It is hypothesized that radiation from such stents selectively interferes with the DNA replication process of the rapidly dividing smooth muscle cells. Ionizing radiation has long been known to inhibit cell proliferation, as is radiotherapy to successfully modify healing response following injury. Moreover, intrarterial radiation has been demonstrated to effectively shut down the neointimal proliferative response process following balloon angioplasty. While radiation therapy *via* stent delivery devices has and continues to be evaluated and show promise, the shortcomings associated with exposure of human tissue to radiation are all too well documented, and caution has been advised.

Notwithstanding that mild exposure to low level radiation, *via* intravascular brachytherapy, is an effective treatment in the management of a number of disease states, (e.g. coronary and peripheral artery disease, restenosis or target vessel revascularization in particular, and for the management of certain constrictive cancers), current technologies do not adequately address the hazards associated with the effects of implantation of radioactive stents, or radioactive liquid filled balloons or short-term high dose radiation therapy. Thus, uncertainties continue to remain, specifically, concerns associated with radiation safety issues, uniform radiation delivery, dose calibration, shortcomings in performance and design characteristics, (e.g. stent flexibility and radial strength, reactivity, hemorrhagic complications, clotting, risk of contamination and sterility, long term patentcy) and radioactive waste disposal problems.

In its current form and application, intrarterial irradiation presents a number of potential hazards and risks for which there appears no current or effective solution. For example, this form of radiation treatment generally involves the use of *gamma* emitting radiation therapy, and short-term ultra high-dose radiation delivery systems

delivered by an *afterloader*, permanently implantable radioactive metallic stents, and pure *beta* emitting or gamma emitting stents. In high-dose, short-term brachytherapy, the use of long-lived isotopes is the norm, and because of delays in the tortuous deployment to the targeted tissue, healthy tissue is exposed to unacceptable levels of radiation without any way to assess the risk/benefit of such treatment. The devices in current use do not yet adequately address problems associated with the effects of very high doses of localized therapy or the long-term results of permanent implantation of radioactive stents.

In the process of design and selection of materials for fabrication of acceptable delivery systems for intrarterial irradiation, a number of candidates have been evaluated, and qualified or eliminated, as the case may be. In this process, radioactive emissions of Iridium-192 have been found efficacious for brachytherapy in the prevention and treatment of restenosis. However, this isotope, and the devices utilized for endovascular afterloading-irradiation treatment with Iridium-192, have a number of the shortcomings, as discussed herein. For example, Iridium-192 is principally a low MeV *gamma* emitter, and given the high dose utilized in a typical afterloading-irradiation treatment, not only subjects the clinician/surgeon to unacceptable exposure levels of *gamma* emissions (because of the repeated contact for each procedure), but also causes unknown and unacceptable levels of irradiation of the patient's healthy tissue and cells *en route* to the target site at the distal end of an afterloading probe. In a typical procedure, the patient's healthy tissue can be exposed for anywhere from 200 seconds to 20 minutes, depending upon the length and/or the difficulty encountered in deployment to the target tissue. Moreover, should the distal end of the delivery catheter (containing the Iridium-192 wire or seed) be blocked or delayed in the tortuous journey to the target site, the endothelial membrane within the blood vessel could be overexposed to a radiation source, resulting in weakening of healthy or stenosed artery wall and concomitant cellular and tissue damage. Obviously, physicians and technicians may also receive an excessive radiation dose during a procedure. Where, as in the case of strontium-90, the isotope has a relatively long half-life, its disposal may also present a problem and/or add significant expense to the procedure (e.g.strontium-90 has half life of 28 years).

Alternative configurations of radioactive stents include the coating of the metallic stent with a radioactive material. In this alternative device configuration, the stent can be coated by ion deposition onto the surface of a stainless steel or titanium tubular or wire by conventional metal coating techniques, such as sputter coating, plating or ion deposition of a radioactive isotope (e.g. phosphorus-32 - 14.29 day half-life) onto a stainless steel surface. This approach to stent fabrication is both complex problematic. More specifically, ion deposition or implantation of the stable isotope is *line-of-sight* so that the radioactive coating does not effectively coat the entire surface of wire, and consequently the isodose/radiation field emitted from the resultant device/structure may not be uniform resulting in an ineffective treatment. Moreover, conventional stent coating techniques, such as plating, ion deposition and sputter coating may not always achieve tenacious adhesion of the isotope (e.g. phosphorus-31). Furthermore, deposited surface coatings on a stainless steel or tantalum stent consisting of phosphorus-32, or other radioisotope such as yttrium-90 and vanadium-22, as particulate matter can be shed, shear off, leach out or detach at any time during deployment and use, thus, releasing radiation and particulate matter through the blood stream to undesirable locations such as vital organs.

Notwithstanding the foregoing problems, endovascular radiation has proved to be safe and effective under certain conditions in preventing arterial reclosure after coronary intervention both in animal studies and in pilot feasibility studies in humans. The rationale for this therapy is that radiation prevents neointimal proliferation and blood vessel constriction after injury. Therapeutic radiopharmaceuticals and radioactive medical devices generally incorporate a strong beta or gamma emitting radionuclide. Beta radiation produces intensive ionization paths within a short distance of the of the radioactive isotope. Beta emitters are characterized by a sharp decline of dose rate within millimeters from the actual source. The exposure to surrounding tissue as well as the catheterization laboratory staff can be kept to a minimum. Each of these emitters require additional shielding in the catheterization laboratory and lead to whole body doses.

To summarize, uncertainties as to clinician exposure and patient risk continue to remain with devices used in the performance of intravascular brachytherapy. Thus, the concerns associated with

- radiation safety issues,
- uniform radiation delivery,
- irradiation of healthy tissue by high dose application,
- dose calibration,
- disposal of radioactive waste,
- shortcomings in performance and design characteristics of medical devices for such procedures,

have and continue to warrant a more conservative application of targeted radiation therapy for coronary and cancer treatment.

The following patent literature is representative of the prior art relative to the devices and medical procedure utilizing such devices. Each of these patents describe technologies which attempt to address one or more of the foregoing problems associated with the treatment of coronary artery disease by physical means and/or a combination of physical means coupled with radiation therapy. These patents are listed and discussed in chronological order and, thus, no significance is to be attached to the order of their discussion.

US 4,503,569 (to *C. J. Dotter*, issued March 12, 1985) describes an endovascular graft prosthesis which includes a helically wound coil having a generally tubular shape; and, which is fabricated from a memory *Nitinol* alloy.

US 4,770,725 (to *Simpson*, issued September 13, 1988) describes a nickel/titanium/niobium alloy having shaped memory transition properties. This patent is instructive as to the various transitions/phases of the alloys of this invention, and to the extent such disclosure is advantageous to the more full and complete understanding of such principles, this patent is herein incorporated by reference in its entirety.

US 5,059,166 (to *Fischell*, issued October 22, 1991) describes an intra-arterial stent for inhibition of intimal hyperplasia following balloon angioplasty. In the *Fischell* device, a radioactive inclusion is incorporated within a stent alloy or coated on the surface thereof. According to *Fischell*, the radioactive stent, (when fabricated as postulated by him), can be implanted within the affected vessel, where it presumably dispenses radiation therapy to the contiguous tissue. The *Fischell* patent is at best prophetic in its teachings and does not provide, by way of working example or otherwise, the means or methods for achievement of its stated objectives. More specifically, neither the amount of isotope, the relative proportions of the matrix materials, nor the method of incorporation thereof into a memory metal alloy, are taught, but rather left to speculation and future discovery. As is further apparent to even the casual observer, the distribution of radiation at the target site must, to be effective, provide an essential uniform radial pattern of energy emission to the surrounding tissues to prevent restenosis of the effected lumen of the treated vessel. Thus, the stent design and performance must be both exact and consistent, yet balanced by safety consideration for the healthy tissue. Accordingly, any discontinuity in manufacture will result in an unacceptable device, which cannot be compensated by asymmetric distribution of relatively intensive, long-lived radioactive materials. Thus, both uniformity in distribution, and relatively conservative doping of the memory metal alloy with radioactive substances, is required to produce both safe and effective deliver of radiation therapy *via* an intra-arterial implant (e.g. stents). The *Fischell* is manifestly deficient in how to accomplished this end.

US 5,176,617 (to *Fischell*, issued January 5, 1993 - a ***CIP*** of his earlier October 22, 199, application which matured as ***US 5,059,166***, above discussed) is directed to the use of a radioactive stent to treat cancer associated with vessels that are treatable by stenting and analogous procedures. The *Fischell* disclosure in this patent is essential the same as that of ***US 5,059,166***, and accordingly suffers from the same inadequacies.

US 5,199,939 (to *Dake et al* issued April 6, 1993) describes a radioactive catheter having a flexible distal section comprising a radioactive section. The *Dake* device

reportedly is useful in the treatment of restenosis of coronary arteries following balloon angioplasty. In brief, the *Dake* device comprises a catheter having a distal end which includes both "stiffening elements" (of varying resistance) and a "segmented" distal tip comprising a plurality of cylindrical radioactive pellets longitundinally spaced along the distal section of the catheter. These pellets are separated from one another by spacers, which permit the retention of flexibility at the end of the catheter tip. The *Dake* device is apparently very "hot" and the radioactive component thereof can only remain within the vessel (at the site of treatment) for less than 30 minutes prior to its required withdrawal.

US 5,616,114 (to *Thornton, et al* issued April 1, 1997) describes a medical device that includes a catheter having a balloon tip which is inflatable with a radioactive liquid. This device is reportedly useful in the treatment of coronary artery disease by combining, in a single device, both a balloon catheter and a source of radioactive material to obviate restenosis following the distention of the blood vessels by the inflated balloon. The improvement in the *Thornton* device also includes the provision of multiple balloons, an inner balloon (or inner chamber) to contain the radioactive fluid and an outer balloon (or outer chamber) to open the occluded vessel. This multiple chambered device, thus, provides for additional containment of the radioactive substance so as to prevent release thereof into the patient should the inner balloon rupture.

US 5,674,177 (to *Hehriein et al*, issued October 7, 1997) describes a stent having a radioactive component which includes a relatively intense nuclide species that has a short half-life (less than 7 days) and a relatively low intensity nuclide species that has a relatively long half-life (more than 100 days). The *Hehriein* device also contemplates that intense nuclide species decay to form the low intensity nuclide species. In practice, the *Hehriein* device is purportedly suitable, upon implant, to deliver a high dose of radiation therapy to the vessel wall over an abbreviated period and, thereafter, a sustaining dose of radiation therapy over a prolonged period. The *Hehriein* device can be prepared by irradiation of a conventional metal stent or, alternatively, by formulation of an alloy with one or more nuclide species. With

respect to the formation of a radioactive stent from an existing metal stent, such radiation treatment can be expected to form various radioactive species, depending upon the specific alloy and its impurity content. Accordingly, the distribution of radiation from this device is at best unpredictable and subject to substantial error relative to its calibration and characterization. With respect to the *Hehriein* suggestion of formulation of alloys containing radioactive nuclide species, the *Hehriein* patent is both prophetic in its teachings and suffers from many of the same inadequacies discussed above with respect to the *Fischell* patents.

US 5,690,670 (to *Davidson*, issued November 25, 1997) describes a low modulus Ti-Nb-Zr ternary alloy having improved biocompatabiliy and other advantageous properties. More specifically, the *Davidson* alloy is suitable for the formation of diffusion hardened medical devices and components that are essentially inert upon contact with body fluids (e.g. blood) and/or placement within the human body. These alloys are also radioopaque and, thus, suitable in the fabrication of guide wires and other companion devices for translumenal medical procedures. Apparently, guide wires and other similar devices, during the placement phase of such procedures, are irradiated with X-rays and (depending upon their native composition) can produce a secondary emission (radiation) that may be harmful to the patient.

US 5,782,742 (to *Crocker et al*, issued July 21, 1998) describes a balloon catheter having an inflatable balloon which incorporates a radiation carrier. In one of the embodiments of the devices of the *Crocker* invention, a tubular metal foil is positioned on the inflatable balloon. The *Crocker* device purportedly provides for the delivery of radiation therapy to a target tissue *via* initial translumenal insertion of his device into a blood vessel, and thereafter inflation of the balloon upon its positioning at the target site. According to *Crocker,* once in place the radiation source provides continuos radiation of the target tissue. It is, however, apparent the *Crocker* device is not a permanent implant, and that the physical integrity and safety thereof is dependent upon the physical properties/durability of the balloon.

As is evident from above abbreviated description of the prior art, there is and continues to remain a number of unresolved problems associated with the use and delivery of therapeutic dosages of radiation to target tissues for the treatment and abatement of disease states. The problems associated with prior art devices, both with respect to safety and efficacy, can be attributed in large measure to both the selection of materials used in fabrication of such delivery systems, and/or the inability to adapt or combine materials into a safe and effective package for delivery of radiation therapy where it is needed.

In each instance discussed herein, the prior art has been deficient in one or more these material aspects of targeted delivery of radiation therapy; and until such shortcomings can be addressed in a coherent and comprehensive manner, the dangers inherent in radiation therapy shall and continue to prevent its widespread application for the treatment of coronary and peripheral artery disease and constrictive cancers. Thus, owing to the inherent risks associated with the aforementioned devices (e.g. for intracoronary radiation therapy or brachytherapy use), there is a continuing and unfulfilled need for a therapeutic radioactive device having both efficacy and safety for use in a clinical setting.

OBJECTS OF THE INVENTION

It is the object of this invention to remedy one or more of the above deficiencies in the prior art.

More specifically, it is the principle object of this invention to provide a composition having at least one radioactivable naturally occurring or enriched stable isotope incorporated within a biocompatible matrix material.

It is another object of this invention to provide a composition containing a radioactivatable isotope that is isotopically distributed therein, so as to effect, upon activation thereof, the emission of radiation therefrom, and from any device containing or fabricated from such composition.

It is yet another object of this invention to provide a composition containing a radioactivatable isotope that is isotopically distributed therein, suitable for fabrication of biomedical devices, including implantable biomedical devices such as intra-arterial stents.

It is still yet another object of this invention to provide a composition containing a radioactivatable isotope that is isotopically distributed therein, suitable for the targeted delivery of radiation therapy *via* an implantable biomedical devices, such as intra-arterial stents.

It is further object of this invention to provide method for the formulation of a radioactivable composition can be formed or molded into various biocompatible products and/or medical devices.

Additional objects of this invention include the fabrication of radioactivatable devices and structures from isotopically beneficiated compositions and their use in the localized, highly focused administration of radiation to a target; or, in the imaging in medical and industrial environments.

Still yet additional objects of this invention, include the use of the compositions of this invention for medical devices for delivery of combinations of radiation and companion therapies, to provide both immediate and extended treatment of the target tissue.

SUMMARY OF THE INVENTION

The above and related objects are achieved by providing an isotopically beneficiated, radioactivatable composition having both physical and nuclear properties suitable for fabrication of biocompatible medical devices, including implantable devices, such as intra-arterial stents; and, the use thereof in the targeted delivery of radiation therapy in the treatment of coronary artery disease, specifically, arterostenosis, restenosis (following balloon angioplasty) and in-stent restenosis.

In the preferred embodiments of this invention, the foregoing composition is formed from a shape memory metal, such as a nickel/titanium alloy, that contains effective amounts of the radioactivatable isotope. The effective amount of the radioactivatable element in the composition used, for example, to fabricate a medical device, is based upon several factors, including the nuclear characteristic of the element, the tolerance (phase computability) of the alloy to its presence, the amount of radiation needed to be imparted to the composition for the specific application (e.g., therapeutic or imaging), the use of the medical device, (formed from this composition), in combination with other (complimentary/companion - e.g. drug treatment), and adjuvant therapies. In the preferred embodiments of this invention, the radioactivatable composition has both physical and nuclear properties suitable for fabrication of stents useful in the radiation treatment of coronary artery disease, specifically, arterostenosis and restenosis. This preferred composition comprises a biocompatible metallic or non-metallic material having from about from about 0.05 to about 10 weight percent of radioactivable naturally occurring or enriched stable isotopes isotopically distributed therein. The isotopes selected for this composition are typically characterized as principally a *beta* particle emitter and as having a half-life of at least 24 hours and less than about 60 days. Thus, upon activation, the composition emits a therapeutic effective amount of radiation, based upon the distribution of said isotopes therein. Where the composition is in the form of a stent, the emission of radiation is essentially uniform and in a radial pattern, so as to effectively inhibit neointimal proliferation of smooth muscle tissue incidental to percutaneous transluminal coronary angioplasty (PTCA).

The radioactivatable compositions of this invention can be used to fabricate a variety of medical devices for target specific delivery of radiation therapy for the treatment of cancer; and, used in combination with companion agents and/or other devices for therapeutic and reconstructive purposes.

DESCRIPTION OF THE INVENTION
INCLUDING PREFERRED EMBODIMENTS

As indicated above, the compositions of this invention are unique in terms of their content, physical form, nuclear properties and in their selection of the appropriate combination of matrix material and radioactivatable enriched or natural stable isotopes. More specifically, it is fully appreciated that the incorporation of materials of dissimilar physical and chemical properties is generally unpredictable, and presents potential processing and stability problems, particularly where the contemplated processing conditions (both in the formation of the composition and in subsequent fabrication thereof into useful articles of commerce) are expected to be both demanding and severe.

According to this invention, radionuclides are combined with other substances (e.g. formable matrix materials, such as metal alloys or structural polymer compounds) to produce an isotopically beneficiated composition that can be fabricated into a shielded, sterile therapeutic radioactive device for shipment to the site of use in a form ready for use, preferably a radioactive stent. Thus, complicated or tedious formulation procedures, as well as unnecessary risk or exposure to radiation, at the site of use are avoided.

In the fabrication of medical products, (which come in contact with human tissue, e.g. implantable devices), such as are contemplated herein, extreme care must be exercised to avoid materials that can evoke adverse tissue reaction (immune response), and/or toxic effects. Accordingly, the resultant product should avoid the formation a new compound that can evoke the type of response that can be detrimental to the patient. Thus, the selection of compatible combinations of materials for the compositions of this invention, are dictated by practical considerations which favor the utilization of acceptable/approved (FDA) materials; and, yet permit additions of an isotope without adversely affecting both their processing characteristics, biocompatability and measurable radiation doses variability. Those products to which the improvements of this invention are most appropriately applied are those in which the preparation of a

radiation emitting device is not straightforward, or where the resultant radiation delivery system requires tedious preparation.

Moreover, in the adaptation of memory metal alloys to this invention, the relative stoichiometry of the alloy components, as is the processing history, is of critical importance to control of the physical properties of the resultant product. Accordingly, the efficacious modification of a matrix material, such as an alloy, by the inclusion of a radiaocativatable isotope, is unpredictable because such properties are recognized as dependent upon the precise proportions of the major components of the matrix material and, thus, must be undertaken with extreme care. Moreover, the nuclear properties of the isotope (e.g. stability) are also, to a degree, dependent upon their interaction with the other (major) components of the composition, under the processing conditions required for their combination, and can, thus, also produce unexpected and unpredictable results. For example, in one of the more advantageous uses of the composition of this invention, the composition is drawn as a fine wire or filament, and thereafter woven or braided into a tubular shape or a mesh. The resultant wire and/or filament prepared from the compositions of this invention, remains essentially unaltered in its physical properties and formability, thereby permitting the fashioning of structures commonly used in various environments and procedures, specifically, medical devices and other know items, which can benefit from the addition of a radioactivable matter.

In each instance, the resultant device and/or item is thereafter activated by exposure in a nuclear reactor by N-gamma or other reaction from a neutron source such as a nuclear reactor, or by a proton beam in an accelerator or a cyclotron, so as to energize the radioactivable substance within the composition prior to use, and thereby cause short range emission of low level radiation (preferable *beta* particles) from the device and/or item, over a finite period (half life) depending upon the specific radioactivable substance of choice.

In a preferred embodiment of this invention, the radioactivable substance is selected from the isotopic forms of the lanthanide series of elements in the periodic table of

elements, and most preferably from a group consisting essentially of lutetium-177, samarium-153, cerium-137, 141 or 143, terbium-161, holmium-166, erbium-166 or 172, thulium-172, ytterbium-169, ytrium-90, actinium-225, astatine-211, cerium-137, dysprosium-165, erbium-169, gadolinium-148, 159, holmium-166, iodine-124, titanium-45, rhodium-105, palladium-103, rhenium-186, 188, scandium-47, samarium-153, strontium-89, thulium-172, vanadium-48, ytterbium-169, ytrium-90, silver-111; or a combination thereof. The aforementioned lanthanides, especially lutetium-177 is particularly preferred and is known for its chemical versatility and therapeutic value.

In brief, one or more radioactivatable isotopes can be combined in the appropriate proportions with a biocompatible metal or a biocompatible polymer (hereinafter also "matrix material" or "matrix"), and the resultant mixture processed by mechanical means such as melt mixing or twin screw extrusion so as to form a isotopically beneficiated composition. This composition, in the case of the metal alloy, is typically vacuum arc melted and thereafter progressively cooled (annealed) to form a product that can be fabricated into useful shapes and articles of manufacture. Similarly, the composition, in the case of a polymer, can be melt mixed, extruded or solution blended and thereafter can be recovered as compound, extruded, solvent cast, or drawn through a spinneret as a fiber, from which useful shapes and articles can be manufactured. The biocompatible polymer can typically comprise any readily processable organic and/or organometallic polymerizable substance having the requisite physical and processing characteristics to accept the isotope, at the appropriate concentration, and yet resist the activation energy required to energize isotope, incident to its use. These materials typically include the same polymeric materials currently available and in use in the medical devices in the catherization laboratory, specifically, the polyurethanes, polyamides, polyvinyl chloride, methylmethacrylate and the their various combinations (e.g. graft and block copolymers).

In sharp contrast to the prior art, the resultant product is virtually free from leaching or flaking (as is the case of medical devices coated with radioactive phosphorus-32), and

exhibit precise control of the radiation dose, (e.g. low radiation dose, and shallow tissue penetration) and, thus, provide for substantial improvement in the means of therapeutic delivery of radiation to mammalian tissue. Moreover, where the medical device is the radioactive stent, it can be prepared several days or weeks in advance by precalibration (producing a higher level of radiation that decays to the desired delivered doses) and shipped and stored until needed for use. At the time of receipt and/or prior to implantation by the hospital, the radioactive stent should be and remain active for at least 24 hours up to about 10 days.

The isotopically beneficiated composition (and the medical devices formed from these materials), retains its native desirable physical and chemical properties of the metal and polymer matrix material, respectively; and, thus, these metal and polymer compositions are preferably selected from known metals (including alloys) and polymers that are known to be useful in the fabrication of medical products and devices.

In the preferred embodiments of this invention, the radionuclides that can be used in the present invention, will be alpha, beta or Auger emitters of therapeutic value and with a half life sufficiently long to make the activation, preparation and shipment of the radioactivatable devices practical. Therefore, radionuclides with a half-life of at least 24 hours are preferred. By contrast, deeply penetrating gamma emitters and high energy beta emitters or long lived radioisotopes, utilizing present delivery systems, are impractical. Similarly, radioactivatable elements, such as calcium, utilizing present delivery systems, are potentially undesirable because they chemically react when in direct contact with blood. Likewise, radionuclides that require long irradiation times are also inexpedient and can give rise to undesirable long lived or gamma emitting radioisotopes that result from impurities within the nickel, titanium or chromium matrix. Moreover, to the extent a relatively large quantity of the enriched stable isotope is required (in excess of the amount that can be effectively "dissolved" within the matrix without phase separation and/or material alteration of processing conditions), the materials balance of the matrix will be adversely affected resulting in an unacceptable temperature transition temperature and, thus, the resulting

intra-arterial deployment of the device being affected. Moreover, if the natural or enriched stable isotope is incompatible with the matrix material in terms of, say melt temperature, it is obviously cannot be used. Similarly, enriched or natural stable isotopes that give rise to long lived radionuclides are also generally considered of marginal value for this critical application. Accordingly, the radioisotopes of choice that possess the requisite desirable characteristics (short nuclear reactor or cyclotron activation time, small amount of radioactivatable stable isotope required within the carrier matrix, a beta emitter with preferably a small gamma emission for imaging purposes, compatibility with mammalian tissue and blood, desirable half life, e.g. more than 24 hours but less than 60 days) necessarily requires considerable thought to arrive at a preferred selection.

In the preferred embodiments of this invention, the isotopically beneficiated composition comprises a metal or metal alloy of nickel and titanium containing from about 0.01 to about 10 weight percent of one or more isotopes from the lanthanide series of elements. The relative weight ratio of nickel and titanium in the composition is preferable the same as typically used in the so-called "Nitinol" or "memory metal" family of alloys prepared from these materials. In the context of this invention, the alloy is proportioned and processed (annealed) to have memory effects at or slightly below the temperature of the environment of intended use (e.g. memory metal effects @ 33°C for use in intralumenal environment of human body). Thus, the novel isotopically beneficiated shape memory metal alloys, preferably a ternary alloy, are produced so that when activated, both emit radiation and yet retain their otherwise native and desirable combination of physical and therapeutic properties.

Implantable Medical Devices

The preferred compositions of this invention are preferably formed from superelastic materials (e.g. nickel/titanium alloy); and, are intended for the fabrication of radioactive wire, tube or mesh and, as such, are especially suited for various designs of medical implant used in the treatment of cardiovascular or oncological disease. The method of manufacture of the compositions of this invention, thus, involves

combining radioactivatable additions of a stable or enriched isotope and a nickel/titanium alloy to a near stoichiometric nickel titanium or nickel chromium alloy, so as to alter the atomic percent ratio of the Ti and Al or the Ni and Cr to what has been found to be an effective alloy. In one of the preferred embodiments of this invention, a stable isotope such as lutetium-176, or other inclusion which may be optionally coupled with additions of other radioactivatable dopants or combination of dopants selected from a group consisting of natural or enriched stable isotopes or combination of stable isotopes thereof, are made in approximate concentrations of between .0025 and 10 atomic percent.

A preferred composition for the foregoing superelastic composition of this invention can be approximated by the following expression wherein the proportion/ratio of the components of the matrix (e.g. alloy) can be adjusted relative to the amount of isotope that is present therein:

Ti--i Ni (48--51) Lu (.0025--10)

Ni--i Cr (48--51) Lu (.0025--10)

Ti (x) Ni (y) Me (z) - (x+y+z)

in which Me is at least one natural or enriched stable isotope that when irradiated gives rise to a radioactive isotope, when present in approximate concentrations of between .0025 and 10 atomic percent.

In the preferred embodiments of this invention "Me" is selected based upon both practical criteria and functional constraints that are dictated by its environment of intended use. For example, it is generally preferable to select a radioactivatable isotope that requires relatively little activation energy to form the corresponding radioactive analogue having a half-life time within the preferred parameters (at least 24 hours and less than 10 days) of this invention. Moreover, the nuclear response of the preferred radioactivatable isotope to low activation energy generally favors the formation a single isotope having primarily beta particle emission without giving rise to other isotopes whose nuclear properties emit gamma radiation or that have extended life times. Lutetium is the model for the preferred radioactivatable isotope

of this invention. More specifically, lutetium is characterized by low energy beta emissions, short half life and due to a very wide cross section in Barns, ease of activation at low power (neutron flux rate) in a nuclear reactor. The incorporation of this enriched stable isotope within a metal or shape memory alloy, while at very low percentage, does not an appreciate effect upon shape memory characteristics, and is yet sufficient for activation thereof in a nuclear reactor. Although interstitial Lutetium atoms have a larger size (Z=71) and could theoretically alter the lattice structure of *Nitinol* alloys, empirical data appear to indicate essentially no substantial change in the alloys modulus of elasticity and dispersivity at the optimum Lutetium concentration (0.05-0.1%), thus retaining the original *Nitinol* alloys properties and stents fabricated from this novel ternary alloy. At the preferred concentration contemplated herein (0.01 to about 10 weight percent), the lutetium doped nickel/titanium alloys from a meltable, castable, weldable, bondable, magnetic or non-magnetic cohesive composition that can be activated and made radioactive, whilst resistant to corrosion or reactivity in blood over a wide range of acid strengths.

With its wide cross-section, lutetium results in rapid activation in a low-power nuclear reactor with short irradiation time at a low flux rate. By being able to use a short irradiation time at relatively low flux rates, production costs are reduced. Furthermore, when utilizing a natural or highly enriched stable isotopic form of lutetium-176, the formation of undesirable long lived isotopes such as high energy beta emitters or deeply penetrating gamma emitters is avoided. The advantages of a lutetium-176 doped composition are, thus, indeed both significant and unexpected. Since only less than 10% of an enriched stable isotope is required as a part of the device, (and in the case of some isotopes such as lutetium-176, preferably as low as 0.10 percent), the neutron penalty is low, the irradiation time in the reactor may be brief, the shortened irradiation time reduces the possibility of giving rise to undesirable long lived radioisotopes which can result from inorganic impurities, the reactor core size may be minimal, the irradiation flux requirement can be reduced, and the nuclear waste disposal volumes would be small. Further advantage occurs by the addition of a quantity of one or more of an isotopically enriched elements. When exposed to radiation in a reactor, such a material, preformed or post formed, produces

only short half-life radioisotopes. Another advantage of this radioactive material is reduced nuclear waste disposal problems as a result of much shorter isolation time and decay requirements. As *beta* emitting radioisotopes travel only a short distance, radionuclides of this type are most desirable, in particular where there is only a weak gamma facilitating device visualization and calibration. In another preferred embodiment, the maximum soft tissue penetration of short lived lutetium-177 (6.67 day half life) is 0.15 millimeters.

Only short reactor irradiation time is, thus, required for the preferred Lutetium doped compositions of this invention to achieved desired levels of radioactivity, preferably between 20 microcuries and 50 millicuries, when activating isotopically enriched or natural lutetium. On the other hand, if nickel titanium or chrome nickel is activated to yield, say,vanadium-22, long lived radioactive impurities and high energy gamma emitters have been known to arise. Unlike most other radioisotopes, such as yttrium-90 produced from yttrium-89 wire, much higher specific activities can be achieved utilizing lutetium-177 without giving rise to undesirable radioisotopes.

Utilizing the foregoing selection criteria, this invention also provides a unique range of radioactive alloys for the preferred compositions of this invention, wherein there is provided either a single enriched stable isotope or combination of enriched stable isotope or isotopes, including tellurium, germanium, iodine, monoisotopic yttrium or other element, which may be a natural or isotopically enriched form of an element. For example, an alloy may optionally be doped with a combination of beneficiated stable isotopes, including preferably lutetium-176, samarium-152, strontium-88, yttrium, or other natural or enriched stable isotopes. Depending upon the relative concentration of isotopes and the environmental constraints imposed by the anticipated use, the composition shall only require relatively short nuclear reactor irradiation time at low neutron flux rates to achieved desired levels of radioactivity, preferably between 20 microcuries and 50 millicuries, when activating a unique alloy containing isotopically enriched or natural lutetium.

A short irradiation time, typical of enriched stable isotopes with wide cross sections, and in particular, the preferred ternary alloy of this invention, for *Nitinol* doped with lutetium-176, avoids the formation of undesirable long-lived radioisotopes such as that which could occur when irradiating form deep penetrating long lived gamma emitting impurities in metallic stents such as cobalt-60, titanium-44, and other radioisotopes arising from activation of impurities found in stainless steel or nickel. Thus, the use of high purity nickel, titanium and lutetium is highly recommended and for certain applications can be critical.

Because of the impurities typically found in metal alloys, organic polymer based compositions may have certain advantages; and, to the extent that "memory" can be engineered into such polymeric materials, would be the system of choice. Typically, polymer composition of this invention can be prepared by an admixture of a biocompatible resin and an enriched stable isotope, or combination of isotopes, preferably lutetium-176 so as to yield radioactive lutetium-177 (6.71 day half life), which is produced by neutron capture irradiation from isotopically enriched (70-75%) lutetium-176. As above noted, and once again emphasized, radioactive lutetium-177 is principally a beta emitter, most energy deposited only penetrates a few millimeters into contiguous tissue, ~0.15mm (78.2% at 497.3 keV, 12.2% at 176 keV and 9.5% at 384.3 keV); and, exhibits a weak gamma (11% at 208.4 keV and 6.5% at 112.9). Radioactive lutetium-177 decays to metastable hafnium-177. Further, the incorporation into the polymer of lutetium-177 takes advantage of the inherent safety advantages of a short lived, short range, low-dose beta radiation emitter by incorporating the polymer-encapsulable lutetium-177. This isotope has a weak but measurable gamma emission, so as to overcome the problem of dose calibration.

The incorporation of radiation into a shape memory stent, a bioerodable stent or a shape memory biodegradable extends beyond simply the restricted focus of mechanical metallic stents, by providing precise therapeutic and physical targeting unavailable with systemically administered drugs; and, a platform for the delivery of therapeutic drugs for combination or adjuvant therapy.

In alternative embodiments of this invention, an enriched stable isotope, preferably lutetium, (which typically exhibits spontaneous infiltration properties under a given set of processing conditions) can be induced to infiltrate a metal or alloy when combined or contacted with a matrix metal having either a physical form or affinity for the isotope so as to be receptive to spontaneous infiltration properties of the Lutetium. It is known, for example, that when an infiltration enhancer and/or an infiltration enhancer precursor and/or an infiltrating atmosphere are in communication with a filler material or a preform, at least at some point during the process, and a metal which, under the process conditions, ordinarily would not exhibit spontaneous infiltration, is combined with (e.g., mixed with and/or exposed to) a matrix which does exhibit spontaneous infiltration behavior under the same processing conditions, the combination of metals will spontaneously infiltrate the filler material or preform.

The materials and processes of this invention are especially useful for the preparation of radioactive shape memory alloys that transition at or near body temperature and relates to a process for preparing and forming novel, medically useful radioactively beneficiated compositions for the forming of biocompatable implantable stents therefrom. In use, the devices provide localized, sustained release of a uniform, short-lived, low-level radiation dose. Unlike gamma emitters, the radiation is confined so that very limited radiation is delivered to nearby healthy tissue. Thus, the radioactive stents of this invention provide a novel, clinically practical approach to the prevention of restenosis after angioplasty and the treatment of certain cancers. Lutetium-177 further provides radioopacity and may also be imaged using various nuclear medicine modalities including single photon emission computed tomography, gamma camera, scinitigraphy, PET, or alternatively, autoradiography, fluoroscopy or X-ray.

The radioactivable composition used in this invention can be converted into a tube, a wire or mesh, and may be braided, woven, knitted, or wound together, or laminated, wherein the enriched stable isotope is uniformly dispersed and incorporated throughout the radiation delivery component of the medical device (e.g. stent). Where the medical device is a stent, it is contemplated that such device can be utilized intra-arterially or interstitially in its non-radioactive state. The composition of the

present invention is particularly well suited for the preparation of radioactivatable stents and radioactive meshes that may be easily handled for use in the treatment of vascular disease, cancer, benign prostatic hyperplasia and other diseases. The device fabricated from the composition of this invention may be activated by irradiation/neutron bombardment in a nuclear reactor, or by proton or electron beam in a cyclotron or accelerator, resulting in a radioactive stent. This radioactivation produces a stent having the radioactive complex in a stable, solid form that retains its physical integrity during insertion and residence at the target site.

The radionuclide selection criteria, as above described herein, results in a radioactive stent that can be stored indefinitely and readily disposed of with practical consideration being given to the half life of the radionuclide. This intended period of storage is practically limited by the half life of the radioisotope. In the case of Lu-177, for example, the desired period of storage would range from 0 days to about 20 days. Thus, the radioactive stent could be shipped to end users of the product and could be implanted with very little additional preparation time or effort than a conventional non-radioactive stent.

The radioactivatable stent can include or be coated with other components (hereinafter "companion substances"), if desired. Useful therapeutic compounds that can be associated with the stent and, thus, delivered at a controlled release rate, include anti-proliferative drugs such as GP IIb-IIIa platelet inhibitors, benign prostatic hyperplasia inhibitors, chemical stabilizers such as ascorbic acid, gentisic acid and for the diffusion of anti-telomerase compounds and anti-neoplastic drugs including cytarabine, doxorubicin vincristine and cisplatin. A radiolytically stable biocompatible radioactive polymeric gel for use as an arterial or body passageway paving material or coating is also contemplated for use with the products formed from the composition of this invention. These companion substances, together with the radionuclide, may be incorporated within a biosorbable polymer matrix such as a hydrogel, a lactide, polyglycolic acid, a poly(beta-hydroxybutyric acid), poly-DL lactic acid, containing a radioactivatable substance for combination or adjuvant therapy. Thus, a stent made of these materials, or coated with these substances,

would provide combination therapy by both emitting radiation and delivery of a therapeutic substance *in-situ*. It is emphasized that the co-application of such therapy is not simply accretive, but rather enables the more efficacious treatment of the physiologic condition or disease state by permitting an initial radiation treatment to shock or arrest the undesirable physiological processes, and thereafter deliver of a sustaining therapy (possible at a lower dosage) to the site specific target for treatment.

Biodegradable Radioactive Stents

In this preferred embodiment of the invention, the radioactive stent is principally comprised of any one of the following polymers or copolymers compounds or hydrogels: lactides, glycosides, caprolactones, oxyalkanes, polyurethanes, and ultra high molecular weight polyethylene. These compounds or hydrogels can contain a radiation emitter such as lutetium-177, samarium-153, cerium-137, 141 or 143, terbium-161, holmium-166, erbium-166 or 172, thulium-172, ytterbium-169, ytrium-90, actinium-225, astatine-211, cerium-137, dysprosium-165, erbium-169, gadolinium-148, 159, holmium-166, iodine-124, titanium-45,rhodium-105, palladium-103, rhenium-186, 188,scandium-47, samarium-153, strontium-89, thulium-172, vanadium-48, ytterbium-169, ytrium-90, silver-111; or a combination thereof or other radioisotope with a half life of less than two months, preferably one that principally emits a short lived alpha, preferably a beta emitter or an Auger electron.

A biodegradable radioactive stent, prepared from the compositions of this invention, safely degrades within the bloodstream over a period of weeks or months. In one such preferred embodiment, the radioactive biodegradable stent will undergo progressive erosion and/or decomposition into harmless materials and the radioactive component of the short lived radioisotope will have decayed to ultralow, safe levels and thus overcomes mechanical limitations and permanency associated with metallic stents. These devices, thus, provide a "scaffold" for remodeling the vessel as well as a pharmacokinetically acceptable vehicle for sustained local drug delivery, and as such can provide an alternative to prevent restenosis and acute closure post PTCA.

This invention also relates to the development of these devices as a means of improved deployment and as a vehicle for local therapeutic drug delivery incorporating an exogenous radioactive polymer that is biodegradable and which acts as a biological conduit so as to further reduce restenosis and proliferative oncological disease. A drug loaded polymeric stent formed by either coating a therapeutic drug onto the surface structure of an intravascular stent, or may be incorporated into the polymer, prior to forming the stent. The radioactive stent may also incorporate copolymeric compositions and other agents that promote adherence of the stent to passageway tissue, thus, insuring proper retention at the target site.

An implantable deformable polymeric stent, made from the radioactive polymers of this invention, exhibit enhanced mechanical and processing properties in response to polymer modification by activation, and thus enable the incorporation of a organometallic (such as an organotitanate, an organozirconate or an organovandate) additive as a processing aid for enhanced linking of the organic and inorganic radioactivatable component, while providing uniform and selective radiation delivery to the target tissue..

In a preferred embodiment relating to the radioactive biodegradable stent, the material safely disintegrates/dissolves within a few weeks or months. Similarly, biodegradable terpolymers or hydrogels containing a short lived radioisotope exhibit controlled bioerodability and bioresorption degrading over time into harmless materials. These polymers, terpolymers, homopolymers, copolymers, oligomers, or a blend thereof such as a poly (DL-lactide-co-glycolide) and selected monomers, oligomers or terpolymers, may be used to form a radioactive stent providing sustained, site specific adjunctive drug delivery. The group of radioactive polymers includes selected lactides and shape memory plastics. Other radioactive, bioabsorble polymers suitable for this purpose include lactides polyglycolic acid, polyorthoesters, (utilized for the sustained release of contraceptive steroids), glycosides, polyanhydrides, phosphazines, caprolactones, oxyalkanes, trimethylene carbonate, paradioxanone, polyacryl starches, triethyleneglycol monomethylacrylate, hydrogels, polyurethanes, and other potentially radioactive terpolymers which undergo

decomposition bioerodable and bioabsorbable terpolymers including polyglycolic acid, poly(2-hydroxyethyl methacrylate), poly L-lactic acid, poly (e. caprolactam), poly (DL-lactide-co-glycolide) high molecular weight poly-L-lactic acid poly L-lactide, polyglycolic/poly-L-Lactic acid, polyglactin, polydioxanone, polyglyconate, e-caprolactone, polyhydroxybutyrate valarate, covalently immobilized poly(2-hydroethylmethacrylate)-gelatin composite polymer, polyethylene terephthalate (PET polyanhydride), ethyl terminated oligomers of lactic acid, difunctional polyurethane, and radioactive copolymers of any combination of the aforementioned materials such as 50/50 (poly) D,L-lactide-co-glycoside.

The radioactive stent of the present invention is a useful device to improve upon current success rates in recanalizing acutely occluded body passageways or conduits, stabilizing vessel patentcy. More specifically, this radioactive polymer stent is of therapeutic value in preventing endovascular restenosis after transluminal percutaneous angioplasty. Radioopaque polymeric materials for endovascular brachytherapy are also disclosed.

The subject of this invention can also be used to provide adjuvant or combination therapy and to provide palliation and adjuvant therapy for malignant esophageal, laryngeal, gastrointestinal and biliary stenoses and/or obstructions that have traditionally been treated with surgical bypass or comfort care measures only.

Fabrication of Medical Device

The product of this invention can be converted into a radioactive tube, strand, fiber, thread, mesh, film, coil or polymer coated wire and may be braided, woven, knitted, crocheted, wound, (or any combination of the aforementioned procedures, preferably knitted, braided and woven) multilayered, molded, extruded, cast, welded, bonded, glued, high frequency or ultrasonic welded or heat sealed into a predetermined shape constituting a stent, in which a natural or enriched stable isotope is uniformly dispersed in particle form and incorporated throughout the stent material. A compressed radioactivatable stent can be prepared by knitting, weaving, braiding or a

combined method thereof of a biostable or biodegradable polymeric fiber, filament or a combination of a polymer fiber or filament and a wire.

A transluminally placed endovascular prosthesis, which may be in the shape of a helically wound coil having a generally tubular shape, is made of a shape memory polymer tube or solid having a transition temperature in the range of 36° C. After placement within a body blood vessel, and upon the prosthesis reaching its transition temperature, the prosthesis expands so as to become firmly anchored to the inside wall of the body blood vessel. Upon expansion, the diameter of the lumen of the prosthesis is approximately equal to the diameter of the body blood vessel passageway. The prosthesis may also be used in other body passageways.

Radioactive Hydrogel Coatings

In one of the alternative forms of the medical device of this invention, a biocompatible radioactive gel stent coating that resists radiolysis and syneresis and methods of manufacture, is also contemplated. This gel may be used to coat a metal or polymer stent and may be similarly activated in a reactor, cyclotron or accelerator. Such a radioactive coating would have emission characteristics similar to an integrally cast radioactive alloy.

Accordingly, the stent may be coated with a radioactive/radioactivatable hydrogel which may contain a minimally platelet activating, anti-thrombolytic or anti-proliferative agent as a platform for the delivery of a drug to further inhibit the proliferation of neointima. The coating of an intravascular radioactive stent with a hydrogel is a means of precisely targeted high dose drug delivery with a sustained biological half life. Therapeutic drugs that may be delivered at a controlled release rate include anti-proliferative drugs such as GP IIb-IIIa platelet inhibitors, anti-neoplastics, benign prostatic hyperplasia inhibitors, chemical stabilizers such as ascorbic acid, gentisic acid and for the diffusion of anti-telomerase compounds and anti-neoplastic drugs including cytarabine, doxorubicin vincristine and cisplatin. A radiolytically stable biocompatible radioactive polymeric gel for use as an arterial or body passageway paving material or coating is also claimed.

In a preferred embodiment the stent may also be coated with the aforementioned gel which contains a minimally platelet activating , anti-thrombolytic or anti-proliferative agent such as a nitric oxide donor, or may be the platform for the delivery of a drug to further inhibit the proliferation of neointima. Thus, a radioactive stent may be coated with heparin, coumadin, dexamethasone, ticoplidine, nitric oxide, other pharmaceutical agent or a biologically active substance so as to enable the delayed release of a pharmaceutical or a recombinant compound and to further reduce the risk of thromboses in combination with intrarterial brachytherapy. Alternatively, the polymer may contain any of the aforementioned agents by incorporating mixing said agent into the polymer prior to production of the finished shape.

Organometallic Chelators

Organometallic chelators can be used in combination with the isotopes to link various other substances to such isotopes to provided combination therapies. Typically this involves obtaining a polymer with improved dispersion and cohesive bonding of additive components comprised of the aforementioned applicable polymers (including other polymers that may be substituted are polyanhydride polymer such as polyethylene terephthalate (PET), polyurethanes, polyethylene oxide, ultra high molecular weight polyethylene, polynorbornene, or a copolymer such as fluorine-acryl-styrene-urethane-silicone, 2-[2'-iodobenzoyl]-ethyl methylacrylate and hydrogels containing azoaromatic moieties), and the use of titanium, zirconium, vanadium or iodine organometallic coupling and processing agents as an aqueous solution or a powder such as an organotitanate to enable combining of different biodegradable polymers with a radioisotope. The aforementioned chelate, or mixtures thereof, may be used to link radioisotopes, such as lutetium, samarium or other activatable isotope and/or substance or drug to a range of polymers, so as to cross-link and enhance dispersive and siccative properties or to improve the adhesion between the organic and inorganic components, improving flowability and reducing voids in precursors. In another preferred embodiment, linkers or chelators may be incorporated to improve binding. They have been shown to be especially useful in immobilizing enzyme composites that prefer a non-aqueous, hydrophobic

environment and the like. Such compounds maintain high activity even when applied to a filler such as a hydrogel containing water. The cross-linking reaction modifies the inorganic surface by forming a monomolecular organic complex layer due to a cross-linking reaction between the organotitanate, or other organometal, and the polymer causing complete dispersion of the radioactive particles or fibers. The organometallic may be used to surface treat a polytetrafluorethylene surface to improve the binding characteristics to drug compounds.

EXAMPLES

The Examples which follow further define describe and illustrate a number of the preferred embodiments of this invention. The apparatus used in the preparation of the radioactivatable compositions, and their subsequent fabrication into products (e.g. wire mesh, etc.) from which medical devices can be fabricated, are standard or as hereinabove described. Parts and percentages appearing in such Examples are by weight, unless otherwise indicated.

EXAMPLE 1

Preparation of Radioactivatable Nickel-Titanium-Lutetium Ternary Alloy

A radioactivatable ternary alloy charge comprising 53.1 weight percent nickel, 0.1 weight percent lutetium, and 44.8 weight percent titanium weighing 50 grams is placed in a crucible. Prior to melting, deoxidization is performed by striking a movable arc onto a zirconium getter source. The alloy charge is vacuum arc melted and flipped three times at 1,750° C to form a button. The resulting alloy is cast in a second copper crucible at the or about the same temperature into a 5/8 inch diameter rod under an inert atmosphere.

EXAMPLE 2

Preparation of Radioactivatable Nickel-Titanium-Lutetium Ternary Wire

The resulting 0.480"X2.75" rough rod of Example 1 is machined on a lathe to achieve a smooth, clean surface and is inserted into a stainless steel tube. The ends of the stainless steel tube are welded closed. The assembly is hot swaged using progressive

steel dies at 500° C so as to convert the sample to an 1/8" rod whereupon the stainless steel is peeled off the Ni-Ti-Lu sample. In order to render the rod and the resulting wire ductile, it was necessary to heat the wire to about 500° C. The final annealing temperature causes a shift in the transition temperature for the radioactivatable alloy of this given composition. The rod is subsequently hot drawn into wire using twenty progressive tungsten carbide and diamond dies, annealing for 30 minutes after each pass. The wire is reduced in diameter to 0.015 inch and varying lengths were annealed at temperatures ranging from 450° C to 600° C.

EXAMPLE 3

Treatment of Shape Memory Nickel-Titanium-Lutetium Ternary Wire

The wire formed according to the process of Example 2 is thereafter annealed. Annealing of the radioactivatable alloy is done at a high temperature well above the Af. On cooling the material stays austenite until the Ms temperature is reached. Further cooling causes the austenite state to transform to martensite with the transformation being complete at Mf. On heating the martensite is stable until the As is reached. Further heating causes the martensite state to transform with the transformation being complete at the Af. If the heating or cooling of the radioactivatable alloy is stopped before the transformation is complete the amount of each phase present will be stable. Between the Ms and As the radioactivatable alloy can exist in either phase or combination of phases depending upon the thermal treatment history. Thus the ingot temperatures were: Mf=2° C, Ms=27° C, As=46 C and Af=75° C.

For the production of radioactivatable shape memory *Nitinol* wire, the wire is preferably 100% austenitic (were it is to be formed into a knitted or braided tube-stent). Thus, the wire is heated above the Af and was kept above the Ms until the tubular shape was produced. The device is thereafter cooled below the Mf and kept below the Af for forming.

As the radioactive stent heats above the As to the Af, it will take the original knitted or braided shape. The Af is near mammalian body temperature, (37° C). Ninety to ninety-five percent (90-95%) transformation may be considered acceptable. However, the As should be as high as possible before insertion is completed with about a 5-10% transformation occurring before insertion is completed. Transformation may be restrained by sheathing. The transformation temperature, (Af), may be adjusted by adjusting the alloying elements but the Af-As tends to be fixed.

EXAMPLE 4

Shape Memory Nickel-Titanium-Lutetium Ternary Wire

In another example, radioactivatable NiTiLu wire of 0.019" diameter, of Example 2, annealed at 520° C, completed its memory response at 36.1° C. in water (as measured with a thermocouple). Thus, as the radioactivatable alloy is warmed by body heat, (which is above the temperature transition range), it expands and regains its permanent shape; and, in the case of a radioactive implantable medical device, such as stent, displaces surrounding tissue in the process.

EXAMPLE 5

Electron Microprobe Analysis Traverse Across Wire Samples

Electron microprobe analyses were performed on the wire of Example 2 to confirm that the distribution of the activatable lanthanide concentration is relatively consistent within the NiTi matrix. One tenth of one percent (1/10%) of activatable lanthanide was added initially and it was expected that some of this material would volatilize or adhere to the crucible, resulting in about a 6-8% target and traverses across the wire samples and final wire samples at over a thousand points confirmed this assumption. Scanning electron microscopy of the wire reveals lutetium striations along the length and circumference of the wire indicating essentially istopical distribution therein.

EXAMPLE 6

Neutron Activation Analysis and Quality Evaluation of Radioactivatable Shape Memory Nickel-Titanium-Lutetium (Ternary Alloy) Wire

A 0.0058" (260 mm length) wire sample of the radioactivatable alloy of Example 1 (53.1 weight percent nickel 0.1 weight percent lutetium, and 44.8 weight percent titanium) weighing 27.8 mg. -containing approximately 0.0278 mg. of lutetium - is placed in a quartz glass protected with aluminum foil. The tube is placed into an aluminum capsule holder, pressure sealed using an inert gas and welded shut. The capsule is inserted into a reactor channel position by hydraulic means and activated by neutron activation in a 10 mW nuclear reactor. The activated sample is retrieved and the following results obtained:

Results:

At Calibration: 82.0 microcuries

Radionuclidic Purity 98.12% of Lu-177, E=208 keV

Neutron Flux Rate: $5X10^{12}$ n/cm^2. sec.

Position: 19-5X

Irradiation Time: 11 hours

Decay Time Allowed: 48 Hours

Uniformity of Radiation Delivery Along the Wire Was Demonstrated By Autoradiography

EXAMPLE 7

Neutron Activation Analysis and Quality Evaluation of Radioactivatable Shape Memory Nickel-Titanium-Lutetium (Ternary Alloy) Wire

A 0.0058" (314 mm length) wire sample of the radioactivatable alloy of Example 1 (53.1 weight percent nickel 0.1 weight percent lutetium, and 44.8 weight percent titanium) weighing 33.4 mg. -containing approximately 0.0334 mg. of lutetium - is placed in a quartz glass protected with aluminum foil. The tube is placed into an aluminum capsule holder, pressure sealed using an inert gas and welded shut. The capsule is inserted into a reactor channel position by hydraulic means and activated by

neutron activation in a 10 mW nuclear reactor. The activated sample is retrieved and the following results obtained:

Results:

Activity at Calibration: 1,620 microcuries

Radionuclidic Purity 91.68% of Lu-177, E=208 keV

Neutron Flux Rate: $5X10^{13}$ n/cm^2. sec.

Position: 1-4-6

Irradiation Time: 6 hours

Decay Time Allowed: 16 Hours

Uniformity of Radiation Delivery Along the Wire Was Demonstrated By Autoradiography

EXAMPLE 8

Neutron Activation Analysis and Quality Evaluation of Radioactivatable Shape Memory Nickel-Titanium-Lutetium (Ternary Alloy) Wire

A 0.0058" (365 mm length) wire sample of the alloy of Example 1 (53.1 weight percent nickel 0.1 weight percent lutetium, and 44.8 weight percent titanium) weighing 38.0 mg. -containing approximately <0.038 mg. Of lutetium - is placed in a quartz glass protected with aluminum foil. The tube is placed into an aluminum holder, pressure sealed using an inert gas and welded shut, and inserted into a reactor channel by hydraulic means and activated by neutron activation in a 10 mW nuclear reactor. The activated sample is retrieved and the following results obtained:

Results:

Activity at Calibration: 809 microcuries

Radionuclidic Purity 93.07% of Lu-177, E=208 keV

Neutron Flux Rate: $2.63X10^{13}$ n/cm^2. sec.

Reactor Position: B3-8Y

Irradiation Time: 9.5 hours

Decay Time Allowed: 48 Hours

The foregoing data confirms the attainment of the activity (10, 20, 50, 100 microcuries) or even greater in reactor position of higher flux rates within the RP10 or other nuclear reactor. The radiation isodose, determined by autoradiography, is deemed to be uniform along the length of the activated NiTiLu wire samples. There is no observable physical changes in the activated NiTiLu wire samples as a result of irradiation by neutron activation.

As is evident from the foregoing description, including the foregoing examples, the physical and nuclear properties of the medical devices, (e.g. stents), fabricated from the radioactively beneficiated compositions of this invention, appear to be highly efficacious for the fabrication of medical devices for intralumenal stenting for the targeted delivery of radiation therapy; the prevention of secondary failure of such procedure due to late endovascular restenosis; and, can also be used for the treatment of proliferative cancers. Their apparent advantages over traditional devices for targeted radiation therapy is attributable, in part, to the enhanced safety of such medical device in the hands of the clinician, the reduction in exposure of healthy patient tissues to radiation in the deployment thereof within the body and the control over radiation dose permitted from the shallow particle emission characteristics, and relatively short half-life times.

WHAT IS CLAIMED IS:

1. A radioactivatable composition comprising:

(a) a matrix material selected from the group consisting essentially of a metal, an organometallic material, an organic material and mixtures thereof, and

(b) radioactivable naturally occurring or enriched stable isotopes isotopically distributed therein,

said composition comprising from about from about 0.05 to about 10 weight percent of radioactivable naturally occurring or enriched stable isotopes isotopically distributed within said matrix material, and further characterized as being formable into structural shapes and articles that can be placed in contact with human tissue without eliciting an immune or toxic response.

2. The radioactivatable composition of Claim 1, wherein the radioactivable naturally occurring or enriched stable isotopes is selected from the group consisting essentially of lutetium-177, samarium-153, cerium-137, 141 or 143, terbium-161, holmium-166, erbium-166 or 172, thulium-172, ytterbium-169, ytrium-90, actinium-225, astatine-211, cerium-137, dysprosium-165, erbium-169, gadolinium-148, 159, holmium-166, iodine-124,titanium-45,rhodium-105,palladium-103, rhenium-186, 188,scandium-47, samarium-153,strontium-89, thulium-172,vanadium-48, ytterbium-169, ytrium-90,silver-111; and combinations thereof.

3. The radioactivatable composition of Claim 1, wherein the radioactivable naturally occurring or enriched stable isotopes is being characterized as principally a *beta* particle emitter and having a half-life of least 24 hours and less than about 60 days, with the further proviso that when activated within the composition, said composition emits a therapeutic effective amount of radiation, based upon the distribution of said isotopes therein.

4. The radioactivatable composition of Claim 1, wherein the matrix material is a metal alloy containing nickel and titanium and has shaped memory characteristics.

5. The radioactivatable composition of Claim 1, wherein the matrix material is either organometallic material or an organic material and further characterized as being selected from the group consisting of a structural polymer and a biodegradable polymer.

6. A method for forming a medical device for targeted delivery of radiation therapy, comprising:

(a) providing a radioactivatable composition having a

(i) a matrix material selected from the group consisting essentially of a metal, an organometallic material, an organic material and mixtures thereof, and

(ii) a radioactivable naturally occurring or enriched stable isotopes isotopically distributed therein,

said composition comprising from about from about 0.05 to about 10 weight percent of radioactivable naturally occurring or enriched stable isotopes isotopically distributed within said matrix material, and further characterized as being formable into structural shapes and articles that can be placed in contact with human tissue without eliciting an immune or toxic response; and

(b) subjecting said radioactivatable composition to activating energy effective amounts of radiation, whereby said radioactivable naturally occurring or enriched stable isotopes are rendered radioactive and thereby caused to emit radiation for a period determined by the half-life of said isotopes.

7. A medical device for target specific delivery of radiation therapy to site tissue that is responsive to radiation therapy, comprising:

(a) a shaped member fabricated from a radioactivatable composition comprising:

(i) a matrix material selected from the group consisting essentially of a metal, an organometallic material, an organic material and mixtures thereof, and

(ii) a radioactivable naturally occurring or enriched stable isotopes isotopically distributed therein,

said composition comprising from about from about 0.05 to about 10 weight percent of radioactivable naturally occurring or enriched stable isotopes isotopically distributed within said matrix material, and further characterized as being formable into structural shapes and articles that can be placed in contact with human tissue without eliciting an immune or toxic response.

(b) means for the adaptation of said shaped member to a delivery system to effect placement of said shaped member at a target site so as to administer radiation therapy at said target site with said shaped member.

8. An radioactivatable composition having both physical and nuclear properties suitable for fabrication of stents useful in the radiation treatment of coronary artery disease, specifically, arterostenosis and restenosis,

said composition comprising a biocompatible metallic or non-metallic material having from about from about 0.05 to about 10 weight percent of radioactivable naturally occurring or enriched stable isotopes isotopically distributed therein,

said isotopes being characterized as principally a *beta* particle emitter and having a half-life of least 24 hours and less than about 60 days,

with the further proviso that when activated, said composition emits a therapeutic effective amount of radiation, based upon the distribution of said isotopes therein.