(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 September 2002 (06.09.2002)

PCT

(10) International Publication Number
WO 02/068000 A2

(51) International Patent Classification[7]: A61K 51/12, A61N 5/10

(21) International Application Number: PCT/US01/43517

(22) International Filing Date:
16 November 2001 (16.11.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/249,128	16 November 2000 (16.11.2000)	US
09/861,196	18 May 2001 (18.05.2001)	US
09/861,326	18 May 2001 (18.05.2001)	US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier applications:

US	09/861,196 (CIP)
Filed on	18 May 2001 (18.05.2001)
US	09/861,326 (CIP)
Filed on	18 May 2001 (18.05.2001)
US	60/249,128 (CIP)
Filed on	16 November 2000 (16.11.2000)

(71) Applicant *(for all designated States except US)*: **MICROSPHERIX LLC** [US/US]; 21283 Rockledge Lane, Boca Raton, FL 33428 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **KAPLAN, Edward, J.** [US/US]; 21283 Rockledge Lane, Boca Raton, FL 33428 (US).

(74) Agents: **PABST, Patrea, L.** et al.; Holland & Knight, LLP, Suite 2000, One Atlantic Center, 1201 West Peachtree Street, Atlanta, GA 30309-3400 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/068000 A2

(54) Title: POLYMERIC IMAGABLE BRACHYTHERAPY SEED

(57) Abstract: A brachytherapy seed that includes an imaging marker and/or a therapeutic, diagnostic or prophylactic agent such as a drug in a polymeric carrier that can be delivered to a subject upon implantation into the subject through the bore of a brachytherapy implantation needle has been developed. Because the brachytherapy seeds can be sized and shaped to fit through the bore of a brachytherapy implantation needle, they are suitable for use with brachytherapy seed implantation instruments. A drug or other therapeutically active substance or diagnostic can be included in the seed in addition to, or as an alternative to, a radioisotope. The rate of release in the implantation site can be controlled by controlling the rate of degradation and/or release at the implantation site. In the preferred embodiment, the seeds also contain a radioopaque material or other means for external imaging. Like conventional radioactive brachytherapy seeds, the seeds can be precisely implanted in many different target tissues without the need for invasive surgery. Moreover, similar to the radiation emitted from conventional brachytherapy seeds, the therapeutically active substance included within a seed can be delivered in a controlled fashion over a relatively long period of time (e.g., weeks, months, or longer periods).

POLYMERIC IMAGABLE BRACHYTHERAPY SEED

Background of the Invention

The present application claims priority to U.S. provisional application number 60/249,128 filed November 16, 2000, U.S.S.N. 09/861,326 filed May 18, 2001 and U.S.S.N. 09/861,196 filed May 18, 2001.

This application relates to imagable implantable brachytherapy devices, and methods of use thereof.

Radioactive seed therapy, commonly referred to as brachytherapy, is an established technique for treating various medical conditions, most notably prostate cancer. In a typical application of brachytherapy for treating prostate cancer, about 50-150 small seeds containing a radioisotope that emits a relatively short-acting type of radiation are surgically implanted in the diseased tissue. Because the seeds are localized near the diseased tissue, the radiation they emit is thereby concentrated on the cancerous cells and not on distantly located healthy tissue. In this respect, brachytherapy is advantageous over conventional external beam radiation.

A number of devices have been employed to implant radioactive seeds into tissues. See, e.g., U.S. Patent Nos. 2,269,963 to Wappler; 4,402,308 to Scott; 5,860,909 to Mick; and 6,007,474 to Rydell. In a typical protocol for treating prostate cancer, an implantation device having a specialized needle is inserted through the skin between the rectum and scrotum into the prostate to deliver radioactive seeds to the prostate. The needle can be repositioned or a new needle used for other sites in the prostate where seeds are to be implanted. Typically, 20-40 needles are used to deliver between about 50-150 seeds per prostate. A rectal ultrasound probe is used to track the position of the needles. Once the end of a given needle is positioned in a desired location, a

seed is forced down the bore of the needle so that it becomes lodged at that location.

As the seeds are implanted in the prostate as desired, the needles are removed from the patient. Over the ensuing several months the radiation emitted from the seeds kills the cancerous cells. Surgical removal of the seeds is usually not necessary because the type of radioisotope generally used decays over the several month period so that very little radiation is emitted from the seeds after this time.

Currently marketed radioactive seeds take the form of a capsule encapsulating a radioisotope. See, e.g., Symmetra® I-125 (Bebig GmbH, Germany); IoGold™ I-125 and IoGold™ Pd-103 (North American Scientific, Inc., Chatsworth, CA); Best® I-125 and Best® Pd-103 (Best Industries, Springfield, VA); Brachyseed® I-125 (Draximage, Inc., Canada); Intersource® Pd-103 (International Brachytherapy, Belgium); Oncoseed® I-125 (Nycomed Amersham, UK); STM 1250 I-125 (Sourcetech Medical, Carol Stream, IL); Pharmaseed® I-125 (Syncor, Woodland Hills, CA); Prostaseed™ I-125 (Urocor, Oklahoma City, OK); and I-plant® I-125 (Implant Sciences Corporation, Wakefield, MA). The capsule of these seeds is made of a biocompatible substance such as titanium or stainless steel, and is tightly sealed to prevent leaching of the radioisotope. The capsule is sized to fit down the bore of one of the needles used in the implantation device. Since most such needles are about 18 gauge, the capsule typically has a diameter of about 0.8 mm and a length of about 4.5 mm.

The two radioisotopes most commonly used in prostate brachytherapy seeds are iodine (I-125) and palladium (Pd-103). Both emit low energy irradiation and have half-life characteristics ideal for treating tumors. For example, I-125 seeds decay at a rate of 50% every 60 days, so that at typical starting doses their

radioactivity is almost exhausted after ten months. Pd-103 seeds decay even more quickly, losing half their energy every 17 days so that they are nearly inert after only 3 months.

Radioactive brachytherapy seeds may also contain other components. For example, to assist in tracking their proper placement using standard X-ray imaging techniques, seeds may contain a radiopaque marker. Markers are typically made of high atomic number (i.e., "high Z") elements or alloys or mixtures containing such elements. Examples of these include platinum, iridium, rhenium, gold, tantalum, lead, bismuth alloys, indium alloys, solder or other alloys with low melting points, tungsten, and silver. Many radiopaque markers are currently being marketed. Examples include platinum/iridium markers (Draximage, Inc. and International Brachytherapy), gold rods (Bebig GmbH), gold/copper alloy markers (North American Scientific), palladium rods (Syncor), tungsten markers (Best Industries), silver rods (Nycomed Amersham), silver spheres (International Isotopes Inc. and Urocor), and silver wire (Implant Sciences Corp.). Other radiopaque markers include polymers impregnated with various substances (see, e.g., U.S. Patent No. 6,077,880).

A number of different U.S. patents disclose technology relating to brachytherapy. For example, U.S. Patent No. 3,351,049 to Lawrence discloses the use of a low-energy X-ray-emitting interstitial implant as a brachytherapy source. In addition, U.S. Patent No. 4,323,055 to Kubiatowicz; 4,702,228 to Russell; 4,891,165 to Suthanthiran; 5,405,309 to Carden; 5,713,828 to Coniglione; 5,997,463 to Cutrer; 6,066,083 to Slater; and 6,074,337 to Tucker disclose technologies relating to brachytherapy devices.

All of these devices are permanent, however. It is an object of the present invention to provide biodegradable seeds.

It is another object of the present invention to provide a means for readily imaging implanted seeds.

It is also an object of the present invention to provide brachytherapy seeds which can be used for other purposes, for example, drug delivery.

Summary of the Invention

A brachytherapy seed that includes a drug or other therapeutically active substance that can be delivered to a subject upon implantation into the subject through the bore of a brachytherapy implantation needle has been developed. Because the brachytherapy seeds can be sized and shaped to fit through the bore of a brachytherapy implantation needle, they are suitable for use with brachytherapy seed implantation instruments such as an implant needle, a Henschke, Scott, or Mick applicator, or a similar device such as a Royal Marsden gold grain gun. A drug or other therapeutically active substance or diagnostic can be included in the seed in addition to, or as an alternative to, a radioisotope. The rate of release in the implantation site can be controlled by controlling the rate of degradation and/or release at the implantation site. In the preferred embodiment, the seeds also contain a radioopaque material or other means for external imaging. Like conventional radioactive brachytherapy seeds, the seeds can be precisely implanted in many different target tissues without the need for invasive surgery. Moreover, similar to the radiation emitted from conventional brachytherapy seeds, the therapeutically active substance included within a seed can be delivered in a controlled fashion over a relatively long period of time (e.g., weeks, months, or longer periods). Since concentrations of the therapeutically active substance will be greater at the

implantation site (e.g., the diseased tissue), any potential deleterious effect of the therapeutically active substance on healthy tissue located away from the implantation site will be reduced.

Depending on the particular application, the brachytherapy seeds offer other advantages. Among these, for example, compared to conventional systemic administration (e.g., oral or intravenous delivery) of therapeutically active substances, the brachytherapy seeds can provide higher and more consistent concentrations of a therapeutically active substance to a target tissue. They can also eliminate the need for repeated injections as well as circumvent delivery problems such as where a target tissue lacks an intact vascular supply (e.g., a target tissue whose blood flow may be compromised) or is otherwise sequestered from the blood supply (e.g., via the blood-brain barrier of the central nervous system). In some embodiments of the seeds that do not contain a radioisotope (e.g., those having only the therapeutically active substance and biodegradable component), after the therapeutically active substance is completely released and the biodegradable component is fully decomposed, no foreign device will remain at the implantation site.

Brief Description of the Drawings

FIG. 1 is a schematic side view of a cylindrically shaped brachytherapy seed.

FIG. 2 is a schematic side view of a hollow tube-shaped brachytherapy seed.

FIGs. 3A-3G are schematic side views of several versions of brachytherapy seeds including a radiopaque marker.

FIG. 4A is a schematic view of a brachytherapy seed having a sealed container housing a radioisotope partially coated by a therapeutically active component and a biocompatible component.

FIG. 4B is a cross-sectional view of a brachytherapy seed having a sealed container housing a radioisotope completely coated by a therapeutically active component and a biocompatible component.

FIG. 5A is a schematic view of a flaccid chain of several brachytherapy seeds conjoined with several spacer elements.

FIG. 5B is a schematic view of a rigid cha
in of several brachytherapy seeds conjoined with several spacer elements.

Detailed Description of the Invention

A brachytherapy seed has been developed for implantation into a subject which includes a biocompatible component, a therapeutically active component that includes a non-radioactive drug, and in a preferred embodiment, a radiopaque marker. The biocompatible component is physically associated with a therapeutically active component and in contact with the marker. In a second embodiment the brachytherapy seed includes a non-metal biocompatible component, a therapeutically active component comprising a radioisotope, and a radiopaque or other diagnostic marker, the biocompatible component being (a) physically associated with a therapeutically active component and (b) in contact with the diagnostic marker, wherein the brachytherapy seed has a size and shape suitable for passing through the bore of a needle typically having an interior diameter of less than about 2.7 millimeters (10 gauge).

I. Brachytherapy Seeds.

Brachytherapy seeds typically have a size and shape suitable for passing through the bore of a needle having an interior

diameter of less than about 2.7 millimeters (10 gauge), less than about 1.4 millimeters (15 gauge), less than about 0.84 millimeters (18 gauge), or less than about 0.56 millimeters (24 gauge). In one version, the seed is shaped into a cylinder having a diameter of between about 0.5 to 3 millimeters and a length 4 to 10 millimeters, e.g., one wherein the diameter is about 0.8 millimeters and the length is about 4.5 millimeters.

II. Biodegradable Materials.

In the preferred embodiment, the biocompatible component is biodegradable. Examples of suitable materials include polymers such as polyhydroxyacids (polylactic acid, polyglycolic-lactic acid), polyanhydrides (poly(bis(p-carboxyphenoxy) propane anhydride, poly(bis(p-carboxy) methane anhydride), copolymer of poly-carboxyphenoxypropane and sebacic acid); polyorthoesters; polyhydroxyalkanoates (polyhydroxybutyric acid); and poly (isobutylcyanoacrylate). Other examples include open cell polylactic acid; co-polymers of a fatty acid dimer and sebacic acid; poly(carboxyphenoxy) hexane; poly-1,4-phenylene dipropionic acid; polyisophthalic acid; polydodecanedioic acid; or other polymers described below. See, e.g., Biomaterials Engineering and Devices: Human Applications : Fundamentals and Vascular and Carrier Applications, Donald L. Wise et al. (eds), Humana Press, 2000; Biomaterials Science : An Introduction to Materials in Medicine, Buddy D. Ratner et al. (eds.), Academic Press, 1997; and Biomaterials and Bioengineering Handbook, Donald L. Wise, Marcel Dekker, 2000.

These polymers can be obtained from sources such as Sigma Chemical Co., St. Louis, MO; Polysciences, Warrenton, PA; Aldrich, Milwaukee, WI; Fluka, Ronkonkoma, NY; and BioRad, Richmond, CA, or can be synthesized from monomers obtained from these or other suppliers using standard techniques.

Formation of Polymeric Seeds

In one embodiment, polylactic acid seeds can be fabricated using methods including solvent evaporation, hot-melt microencapsulation and spray drying. Polyanhydrides made of bis-carboxyphenoxypropane and sebacic acid or poly(fumaric-co-sebacic) can be prepared by hot-melt microencapsulation. Polystyrene seeds can be prepared by solvent evaporation. Hydrogel seeds can be prepared by dripping a polymer solution, such as alginate, chitosan, alginate/polyethylenimine (PEI) and carboxymethyl cellulose (CMC), from a reservoir though microdroplet forming device into a stirred ionic bath, as disclosed in PCT WO 93/21906.

One or more diagnostic, therapeutic or prophylactic compounds can be incorporated into the polymeric seeds either before or after formation.

Solvent Evaporation

Methods for forming seeds using solvent evaporation techniques are described in E. Mathiowitz *et al.*, *J. Scanning Microscopy*, 4:329 (1990); L.R. Beck *et al.*, *Fertil. Steril.*, 31:545 (1979); and S. Benita *et al.*, *J. Pharm. Sci.*, 73:1721 (1984). The polymer is dissolved in a volatile organic solvent, such as methylene chloride. A substance to be incorporated is added to the solution, and the mixture is suspended in an aqueous solution that contains a surface active agent such as poly(vinyl alcohol). The resulting emulsion is stirred until most of the organic solvent evaporated, leaving solid seeds. Seeds with different sizes (1-1000 μm) and morphologies can be obtained by this method. This method is useful for relatively stable polymers like polyesters and polystyrene. However, labile polymers, such as polyanhydrides, may degrade during the fabrication process due to the presence of water. For these polymers, some of the following methods

performed in completely anhydrous organic solvents are more useful.

Hot Melt Microencapsulation

Seeds can be formed from polymers such as polyesters and polyanhydrides using hot melt microencapsulation methods as described in Mathiowitz *et al.*, *Reactive Polymers*, 6:275 (1987). In this method, the use of polymers with molecular weights between 3-75,000 Daltons is preferred. In this method, the polymer first is melted and then mixed with the solid particles of a substance to be incorporated that have been sieved to less than 50 μm. The mixture is suspended in a non-miscible solvent (like silicon oil), and, with continuous stirring, heated to 5 °C above the melting point of the polymer. Once the emulsion is stabilized, it is cooled until the polymer particles solidify. The resulting seeds are washed by decantation with petroleum ether to give a free-flowing powder. Seeds with sizes between 1 and 1000 μm are obtained with this method.

Solvent Extraction

This technique is primarily designed for polyanhydrides and is described, for example, in PCT WO 93/21906, published November 11, 1993. In this method, the substance to be incorporated is dispersed or dissolved in a solution of the selected polymer in a volatile organic solvent like methylene chloride. This mixture is suspended by stirring in an organic oil, such as silicon oil, to form an emulsion. Seeds that range between 1-300 μm can be obtained by this procedure.

Spray-Drying

Methods for forming seeds using spray drying techniques are well known in the art. In this method, the polymer is dissolved in an organic solvent such as methylene chloride. A known amount of a substance to be incorporated is suspended (insoluble

agent) or co-dissolved (soluble agent) in the polymer solution. The solution or the dispersion then is spray-dried. Seeds ranging between 1 and 10 μm are obtained. This method is useful for preparing seeds for imaging of the intestinal tract. Using the method, in addition to metal compounds, diagnostic imaging agents such as gases can be incorporated into the seeds.

Phase Inversion

Seeds can be formed from polymers using a phase inversion method wherein a polymer is dissolved in a good solvent, fine particles of a substance to be incorporated, such as a drug, are mixed or dissolved in the polymer solution, and the mixture is poured into a strong non-solvent for the polymer, to spontaneously produce, under favorable conditions, polymeric seeds, wherein the polymer is either coated on the particles or the particles are dispersed in the polymer. The method can be used to produce microparticles in a wide range of sizes, including, for example, about 100 nm to about 10 μm. Exemplary polymers which can be used include polyvinylphenol and polylactic acid. Substances which can be incorporated include, for example, imaging agents such as fluorescent dyes, or biologically active molecules such as proteins or nucleic acids.

Protein Microencapsulation

Protein seeds can be formed by phase separation in a non-solvent followed by solvent removal as described in U.S. Patent No. 5,271,961 to Mathiowitz *et al.* Proteins which can be used include prolamines such as zein. Additionally, mixtures of proteins or a mixture of proteins and a bioerodable material polymeric material such as a polylactide can be used. In one embodiment, a prolamine solution and a substance to be incorporated are contacted with a second liquid of limited miscibility with the proline solvent, and the mixture is agitated to

form a dispersion. The prolamine solvent then is removed to produce stable prolamine seeds without crosslinking or heat denaturation. Other prolamines which can be used include gliadin, hordein and kafirin.

Low Temperature Casting of Seeds

Methods for very low temperature casting of controlled release seeds are described in U.S. Patent No. 5,019,400 to Gombotz *et al.* In the method, a polymer is dissolved in a solvent together with a dissolved or dispersed substance to be incorporated, and the mixture is atomized into a vessel containing a liquid non-solvent at a temperature below the freezing point of the polymer-substance solution, which freezes the polymer droplets. As the droplets and non-solvent for the polymer are warmed, the solvent in the droplets thaws and is extracted into the non-solvent, resulting in the hardening of the seeds.

Hydrogel Seeds

Seeds made of gel-type polymers, such as alginate, are produced through traditional ionic gelation techniques. The polymer first is dissolved in an aqueous solution, mixed with a substance to be incorporated, and then extruded through a microdroplet forming device, which in some instances employs a flow of nitrogen gas to break off the droplet. A slowly stirred ionic hardening bath is positioned below the extruding device to catch the forming microdroplets. The seeds are left to incubate in the bath for twenty to thirty minutes in order to allow sufficient time for gelation to occur. Particle size is controlled by using various size extruders or varying either the nitrogen gas or polymer solution flow rates.

Chitosan seeds can be prepared by dissolving the polymer in acidic solution and crosslinking it with tripolyphosphate. Carboxymethyl cellulose (CMC) seeds can be prepared by

dissolving the polymer in acid solution and precipitating the microsphere with lead ions. Alginate/polyethylene imide (PEI) can be prepared in order to reduce the amount of carboxylic groups on the alginate microcapsule. The advantage of these systems is the ability to further modify their surface properties by the use of different chemistries. In the case of negatively charged polymers (e.g., alginate, CMC), positively charged ligands (e.g., polylysine, polyethyleneimine) of different molecular weights can be ionically attached.

Fluidized Bed

Particles, including seeds, can be formed and/or coated using fluidized bed techniques. One process is the Wurster air-suspension coating process for the coating of particles and seeds. The process consists of supporting the particles in a vertical column of heated air while the particles pass an atomizing nozzle that applies the coating material in the form of a spray. Enteric and film coating of seeds by this process typically requires approximately 30 minutes. Suitable coating materials include, but are not limited to, cellulose acetate phthalate, ethylcellulose, hydroxypropyl methylcellylose, polyethylene glycol, and zein.

The Wurster apparatus provides controlled cyclic movement of the suspended particles by a rising stream of warm air, the humidity, temperature, and velocity of the air regulated. An air-suspended or fluidized bed of particles has a random movement. If seeds move in and out of a coating zone in a random manner, the coating can be applies only at a slow rate. The Wurster apparatus, however, provides better drying and eventually a more uniform coating by imparting a controlled cyclic movement without or with less randomness. A support grid at the bottom of the vertical column typically includes a course screen, e.g., 10 mesh, and a fine screen, e.g., 200 mesh. The fine screen offers considerably more

resistance to the air flow than the coarse screen; thus, the greater amount of air flows through the coarse screen. The air flowing through coarse screen lifts the seeds upward in the column. As the velocity of the air stream is reduced due to diffusion of the stream and resistance of the seeds, the upward movement of the seeds ceases. Then the seeds enter the region of a still lower velocity air stream above the fine screen, where they dry and gently settle. As the dried and partially coated seeds approach the grid, they are again introduced into the higher-velocity air stream the coarse screen and enter into another cycle.

Below the grid support for the coarse screen, the coating fluid is dispersed by atomization under pressure. A compressed-air inlet is connected to the atomizing the solution or slurry of the coating material. The seeds, which are suspended above the coarse screen, have little contact with each other, so the coating fluid is readily distributed onto the surface of the seeds in the moving bed. As the cyclic movement of the seeds continues, the seeds are presented many times in many different positions to the atomized spray; therefore, a uniform coating is built up on the seeds. Coating is controlled by the weight of the coated seeds, formulation of the coating, temperature, time, and air velocity. Particle sizes can vary from about 50 μm to about 2 mm or greater.

III. Therapeutic and Diagnostic Agents

Polymers can be used to form, or to coat, drug delivery devices such as seeds or seeds containing any of a wide range of therapeutic and diagnostic agents. Any of a wide range of materials can be incorporated into the seeds including organic compounds, inorganic compounds, proteins, polysaccharides, and nucleic acids, such as DNA, using standard techniques. Any of a wide range of therapeutic, diagnostic and prophylactic materials can be incorporated into the seeds,including organic compounds,

inorganic compounds, proteins, polysaccharides, and nucleic acids, such as DNA, using standard techniques.

The non-radioactive drug can take the form of stimulating and growth factors; gene vectors; viral vectors; anti-angiogenesis agents; cytostatic, cytotoxic, and cytocidal agents; transforming agents; apoptosis-inducing agents; radiosensitizers; radioprotectants; hormones; enzymes; antibiotics; antiviral agents; mitogens; cytokines; anti-inflammatory agents; immunotoxins; antibodies; or antigens. For example, the non-radioactive therapeutic can be an anti-neoplastic agent such as paclitaxel, 5-fluorouracil, or cisplatin. It can also be a radiosensitizing agent such as 5- fluorouracil, etanidazole, tirapazamine, BUdR, or IudR.

Many different therapeutically active substances have been associated with biocompatible materials for use in drug delivery systems apart from brachytherapy seeds. These include, for example, adriamycin (Moritera et al., Invest. Ophthal. Vis. Sci. 33:3125-30, 1992); bupivicaine (Park et al., J. Controlled Release 52:179-189, 1998); camptothecin (Weingart et al., Int. J. Cancer 62:1-5, 1995); carboplatin (Chen et al., Drug Delivery 4:301-11, 1997); carmustine (Brem et al., J. Neurosurg 74:441-6, 1991; and U.S. Patent Nos. 4,789,724 and 5,179,189); cefazolin (Park et al., J. Controlled Rel. 52:179-189, 1998); cisplatin (Yapp et al., IJROBP 39:497-504, 1997); cortisone (Tamargo et al., J. Neurooncol. 9:131-8, 1990); cyclosporine (Sanchez et al., Drug Delivery 2:21-8, 1995); daunorubicin (Dash et al., J. Pharmacol. Tox. Meth. 40:1-12, 1999); dexamethasone (Reinhard et al., J Contr. Rel. 16:331-340, 1991); dopamine (During et al., Ann. Neurol. 25:351-6, 1989); etanidazole (Yapp et al., Radiotherapy Oncol. 53:77-84, 1999); 5-fluorouracil (Menei et al., Cancer 86:325-30, 1999); fluconazole (Miyamoto et al., Curr. Eye Res. 16:930-5, 1997); 4-hydroxycyclophosphamide (Judy et al., J. Neurosurg. 82:481-6, 1995); ganciclovir (Kunou et

al., J. Controlled Rel. 37:143-150, 1995); gentamicin (Laurentin et al., J. Orthopaed. Res. 11:256-62, 1993); heparin (Tamargo et al., J Neurooncol. 9:131-8, 1990); interleukin-12 (Kuriakose et al., Head & Neck 22:57-63, 2000); naproxen (Conforti et al., J. Pharm. Pharmacol. 48:468-73, 1996); nerve growth factor (Camerata et al., Neurosurgery 30:313-19, 1992); retroviral vector producer cells to transfer a cytotoxic gene product (Beer et al., Adv. Drug Deliver. Rev. 27:59-66, 1997); taxol (Park et al., J. Controlled Rel. 52:179-189, 1998; and Harper, E et al., Clin. Cancer Res., 5:4242-4248, 1999); tetanus toxoid (Alonso et al., Vaccine 12:299-306, 1994); tetracaine hydrochloride (Ramirez et al., J. Microencap. 16:105-15, 1999); tirapazamine (Yuan et al., Radiation Oncol. Investig. 7:218-30, 1999); thyrotropin-releasing hormone (Kubek et al., Brain Res. 809:189-97, 1998); and vaccines (Chattaraj et al., J. Controlled Rel. 58:223-32, 1999). Other therapeutically active substances that can be combined with a biocompatible component include: anesthetics, angiogenesis inhibitors (e.g., Lau D.H. et al., Cancer Biother. Radiopharm. 14:31-6,1999), antibiotics (e.g., Bahk J.Y. et al., J. Urol. 163:1560-4, 2000; and Miyamoto H. et al., Current Eye Research 16:930-5, 1997), antibodies (e.g., Gomez S.M. et al., Biotechnol. Prog. 15:238-44, 1999), anticoagulants (e.g., Tamargo R.J. et al., J. Neurooncol. 9:131-138, 1990), antigens (e.g., Machluf M. et al., J. Pharm. Sci. 89:1550-57, 2000), anti-inflammatory agents (e.g., Reinhard C.S. et al., J. Controlled Release 16:331-40, 1991; and Tamargo R.J. et al., J. Neurosurg. 74: 956-61, 1991), antivirals, apoptosis-inhibiting agents (e.g., Macias D. et al., Anat. Embryol. (Berl) 193:533-41, 1996), cytokines (e.g., Edelman E.R. et al., Biomaterials 12:619-26, 1991), cytotoxic agents (e.g., Brem H. et al., J. Neurosurg. 80:283-90, 1994; Brem H. et al., J. Neurosurg. 80:283-90, 1994; Brem H. et al., Lancet 345:1008-12, 1995;Ewend M.G. et al., Cancer Res. 56:5217-23, 1996; Fung L.K. et al., Cancer

Res. 58:672-85, 1998; Grossman S. et al., J. Neurosurg. 76:640-47, 1992; Kong Q. et al., J. Surgical Oncology 69:76-82, 1998; Shikani A.H. et al., Laryngoscope 110:907-17, 2000; Straw R.C. et al., J. Orthop. Res. 12:871-7, 1994; Tamargo R.J. et al., Cancer Research 53:329-33, 1993; Valtonen S. et al., Neurosurgery 41:44-9, 1997; Walter K.A. et al., Cancer Research 54:2207-12, 1994; Yapp D.T.T. et al., IJROBP 39:497-504, 1997; Yapp D.T.T. et al., Anti-Cancer Drugs 9:791-796, 1998; Yapp D.T.T. et al., IJROBP 42:413-20, 1998; and Yoshida M. et al., Biomaterials 10:16-22, 1989), enzymes (e.g., Park T.G. et al., J. Control Release 55:181-91, 1998), gene vectors (e.g., Hao T. et al., J. Control Release 69:249-59, 2000; and Maheshwari A. et al., Mol. Ther. 2:121-30, 2000), hormones (e.g., Rosa G.D. et al., J. Control Release 69:283-95, 2000), immunosuppressants (e.g., Sanchez A. et al., Drug Delivery 2:21-8, 1995), mitogens (e.g., Ertl B. et al., J. Drug Target 8:173-84, 2000), neurotransmitters (e.g., During M.J. et al., Ann Neurology 25:351-6, 1989), radioprotectants (e.g., Monig H. et al., Strahlenther Onkol. 166:235-41, 1990), radiosensitizers (e.g., Williams J.A. et al., IJROBP 42:631-39, 1998; and Cardinale R.M. et al., Radiat. Oncol. Invest. 6:63-70, 1998), stimulating and growth factors, transforming agents (e.g., Hong L. et al., Tissue Eng. 6:331-40, 2000), and viral vectors.

Diagnostic compounds can be magnetic (detectable by MRI), radioopaque (detectable by x-ray), fluorescent (detectable by fluorescent techniques) or ultrasound detectable. These materials are commerically available, as are the systems for detection and measurements.

Radiopaque marker 30 can be made of any substance that can be detected by conventional X-ray imaging techniques. See, e.g., Fundamentals of Diagnostic Radiology, 2d edition, William E. Brant and Clyde A. Helms (eds.), Lippincott, Williams and

Wilkins, 1999; Physical Principles of Medical Imaging, 2d ed., Perry Jr. Sprawls, Medical Physic Publishing, 1995; Elements of Modern X-ray Physics, Jens Als-Nielsen and Des McMorrow, Wiley & Sons, 2001; X-ray and Neutron Reflectivity: Principles and Applications, J. Daillant et al., Springer-Verlag, 1999; Methods of X-ray and Neutron Scattering in Polymer Science, Ryoong-Joon J. Roe, Oxford University Press, 2000; and Principles of Radiographic Imaging: An Art & A Science, Richard R. Carlton, Delmar Publishers, 2000. Many such substances that can be used as marker 30 are known including, most notably, high atomic number (i.e., "high Z") elements or alloys or mixtures containing such elements. Examples of these include platinum, iridium, rhenium, gold, tantalum, bismuth alloys, indium alloys, solder or other alloys, tungsten and silver. Many currently used radiopaque markers that might be adapted include platinum/iridium markers from Draximage, Inc.; and International Brachytherapy; gold rods from Bebig GmbH; gold/copper alloy markers from North American Scientific, palladium rods from Syncor; tungsten markers from Best Industries; silver rods from Nycomed Amersham; silver spheres from International Isotopes Inc, and Urocor, and silver wire from Implant Sciences Corp. Other radiopaque markers include polymers impregnated with various substances (see, e.g., U.S. Patent Nos. 6,077,880; 6,077,880; and 5,746,998). Radiopaque polymers are described in European Patent Application 894, 503 filed May 8, 1997; European Patent Application 1,016,423 filed December 29, 1999; and published PCT application WO 9605872 filed August 21, 1995. Those radiopaque polymers that are biodegradable are preferred in applications where it is desired to have the implant degrade over time in the implantation site.

Examples of radiopaque markers include platinum, iridium, rhenium, gold, tantalum, bismuth, indium, tungsten, silver, or a radiopaque polymer. Suitable radioisotopes include ^{125}I and ^{103}Pd.

Sometimes combinations of agents may provide enhanced results. For example, in preferred embodiment, a radiosensitizing agent such as 5- FU, etanidazole, tirapazamine, BUdR, can be used in combination with IUdR. Various combinations of substances are known to be more effective when used in combination than when used alone. See, e.g, Brem et al., J. Neurosurg. 80:283-290, 1994; Ewend et al., Cancer Res. 56:5217-5223, 1996; Cardinale, Radiation Oncol. Investig. 6:63-70, 1998; Yapp et al., Radiotherapy and Oncol. 53:77-84, 1999; Yapp, IJROBP 39:497-504, 1997; Yuan et al., Radiation Oncol. Investig. 7:218-230, 1999; and Menei et al., Cancer 86:325-330, 1999.

IV. Method of Implantation

The method of making a brachytherapy seed for implantation into a subject includes the steps of: (a) providing a non-metal biocompatible component and a therapeutically diagnostic or prophylactic (method to include here as "therepeutically active") active component, optimally further including an imaging agent; (b) physically associating the biocompatible component and the therapeutically active component to form a combination product; and (c) forming the combination product into a seed having a size and shape suitable for passing through the bore of a needle having an interior diameter of less than about 2.7 millimeters (10 gauge), less than about 1.4 millimeters (15 gauge), or less than about 0.84 millimeters (18 gauge), or less than about 0.56 millimeters (24 gauge).

Referring to the drawings there are illustrated various different embodiments of the brachytherapy seeds of the invention.

In FIG.1, there is shown a brachytherapy seed 10 composed of a biocompatible component 12 associated with a therapeutically active component 14 (schematically shown as small circles or spheres). As illustrated, the therapeutically active component 14 is present as a plurality of small particles dispersed throughout a matrix consisting of the biocompatible component 12. The mixture of the components 12 and 14 is formed into the cylindrically shaped brachytherapy seed 10.

The brachytherapy seed 10 shown in FIG. 1 has a size and shape suitable for passing through the bore of a brachytherapy implantation needle. Although the bore can be any size compatible with brachytherapy methods, in order to minimize damage to tissue, the bore preferably has an interior diameter of between about 0.01 and 10 mm (e.g., 0.009, 0.01, 0.02, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 4, 5, 6, 7, 8, 9, 10, or 11 mm). For use with 10 gauge or less brachytherapy implantation needles, seed 10 has a size and shape that can pass through a bore having a diameter of less than about 2.7 millimeters (i.e., the interior diameter of a standard 10 gauge brachytherapy implantation needle). For smaller needles such as 15 and 18 gauge needles, seed 10 has a size and shape that can pass through bores having an interior diameter of less than about 1.4 millimeters (e.g., 1.40, 1.39, 1.38, 1.37, 1.36, 1.35, or 1.34 mm) or less than about 0.84 millimeters (e.g., 0.86, 0.85, 0.84, 0.83, 0.82, 0.81, 0.80 mm), respectively.

Although there is no lower limit as to how small any dimension of seed 10 can be, in many applications, those that are not able to pass through bores smaller than 0.3 mm are preferred. For example, in many applications where it is desirable for the implanted brachytherapy seeds to maintain their orientation in

the tissue, the seed 10 should be large enough to stay lodged at the site of implantation in the desired orientation for a relatively long period, larger seeds are preferred. In some cases, the selection of materials for use in the seed 10 will affect its size. For instance, in versions of the seed 10 where the biocompatible component 12 is a stainless steel or titanium capsule, the walls of the capsule may need to be greater than a certain minimum size in order to maintain the structural integrity of the seed 10. In addition, in some applications, the seed 10 should also be large enough to carry a sufficient amount of the therapeutically active component 14 to be therapeutically active (i.e., a therapeutically effective amount or an amount that exerts a desired medically beneficial effect). In order to facilitate the passage of seed 10 through the bore of a needle while preventing jamming of the brachytherapy implantation needle bore (e.g., caused by clumping of several seeds), it is also preferred that the diameter of seed 10 be just slightly less than the diameter of the bore of the needle (e.g., 0.5-5 % less).

For use with the needles used in many conventional brachytherapy seed implantation devices, brachytherapy seeds shaped into a cylinder (or rod) having a diameter of between about 0.8 to 3 millimeters and a length of between about 4 to 10 millimeters are preferred. Because many conventional brachytherapy seed applicators make use of brachytherapy implantation needles about 17 to 18 gauge in size, cylindrically shaped brachytherapy seeds having a diameter of between about 0.8 and 1.1 mm and a length greater than the diameter (e.g., 2-10 mm) are preferred for use with such applicators. In particular, because many conventional brachytherapy seed applicators are designed to accept conventional radioactive brachytherapy seeds that have a diameter of about 0.8 millimeters and a length of

about 4.5 millimeters, brachytherapy seeds of similar size are especially preferred.

Brachytherapy seeds are not limited to those being cylindrical in shape (e.g., seed 10 shown in FIG. 1), but rather can be any shape suitable for passing through the bore of a needle. For example, in many cases, seeds can be cuboid, spheroid, ovoid, ellipsoid, irregularly shaped, etc. The ends of the seeds can be rounded, squared, tapered, conical, convex, concave, scalloped, angular, or otherwise-shaped. The brachytherapy seeds can be solid as shown in FIG. 1, and have one or more cavities or pores (e.g., to increase the surface area of the seed exposed to the target tissue). As one example, as illustrated in FIG. 2, a brachytherapy seed 10 is shaped into a hollow tube 18 having a cylindrical cavity 20. In preferred versions of seed 10, cylindrical cavity 20 is sized to accept and envelop a standard-sized brachytherapy seed (e.g., one having a diameter of about 0.8 mm and a length of about 4.5 mm). For use, the seed 10 can be placed over the standard-sized brachytherapy seed, and introduced into the bore of a needle (sized to accept the enveloped seed) for implantation into a target tissue. The seed 10 shown in FIG. 2 can also be used alone without being placed over a standard-sized brachytherapy seed, e.g., to increase the surface area exposed in the site of implantation. Hollow tube 18 can have any wall thickness or length suitable for wholly or partially enveloping a standard-sized brachytherapy seed and passing through the bore of a needle. Preferably it has a wall thickness between about 0.01 and 0.1 mm and a length of between about 1 to 4.5 mm .

Referring again to FIGs 1 and 2, biocompatible component 12 can be composed of any material suitable for implantation in a target tissue in an animal subject (e.g., a mammal such as a human patient) that can be associated with therapeutically active

component 14 such that all or part of the therapeutically active component 14 will be delivered to the target tissue when the brachytherapy seed 10 is introduced into the implantation site, as discussed above. For ease of use, ease of manufacture, and for therapeutic advantages, it is preferred that the biocompatible component 12 be biodegradable (i.e., made of a substance other than titanium or stainless steel).

A skilled artisan can select the particular composition of the component 12 that is most suited for a given application. For example, where the seed 10 is intended to be used to slowly deliver the therapeutically active component 14 when implanted in a target tissue, a biocompatible and biodegradable material made up of a chemical composition of a polymer known to degrade at a desired rate when placed under conditions similar to those encountered in the implantation site can be selected for use as component 12. Various characteristics of such biodegradable components are described, e.g., in Biomaterials Engineering and Devices: Human Applications : Fundamentals and Vascular and Carrier Applications; Biomaterials Science : An Introduction to Materials in Medicine; and Biomaterials and Bioengineering Handbook, supra. For example, by selecting an appropriate material for use as the biocompatible component 12 of the brachytherapy seed 10, the duration of release of the therapeutically active component 14 from seed 10 can be varied from less than about an hour to more than about several months (e.g., 10 min., 30 min., 1 h., 2 h., 3 h., 6 h., 12 h., 1 day, 2 days, 3 days, 1 week, 2 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 1 year, 2 years, or 3 years). Biocompatible component 12 is not limited to being biodegradable. For example, in some cases, component 12 can also be made of a non-biodegradable material such as stainless steel or titanium. In this

case, biocompatible component 12 can be coated or otherwise associated with therapeutically active component 14, such that component 14 will be delivered to a target tissue into which seed 10 is implanted. For instance, component 12 might take the form of a porous stainless steel or titanium cylinder having a plurality of pores through its outer surface, such pores being filled with or otherwise in communication with the component 14 such that the component 14 can diffuse from the seed 10 into the environment surrounding the seed 10 (e.g., a target tissue).

These can be tested for suitability in a given application by conventional clinical testing. For example, a test composition can be fashioned into a brachytherapy seed and implanted in a laboratory animal in a selected target tissue. The effects of the implanted compositions on the animal can then be monitored over a period of time. Those that prove to be biocompatible (e.g., not causing an undesired response such as calcification or an allergic response) and have a desired rate of degradation and delivery of a therapeutically active component (if included in the test seed) can thus be identified.

As discussed above, the therapeutically active component 14 is a material that can (a) be implanted in a target tissue of an animal subject (e.g., a mammal such as a human patient) to exert an effect on the animal's physiology, and (b) be associated with the biocompatible component 12 in the brachytherapy seed 10.

Myriad different substances can be used as the therapeutically active component 14. See, e.g., Physician's Desk Reference, The Merck Index, and USP DI® 2000 published by U.S. Pharmacopeia. For example, the therapeutically active component 14 can include a small molecule drug (e.g., a non-peptide or non-nucleic acid-based molecule with a molecular weight generally less than 5 kDa) such as a chemical with known anti-cancer properties. It can also

include a biologic such as a polypeptide (e.g., an antibody or a cytokine) or nucleic acid (e.g., an expression vector).

For example, where the seed 10 is intended to be used as a primary treatment for prostate cancer, the therapeutically active substance 14 can include a anti-neoplastic drug such as paclitaxel (taxol), cisplatin, or 5-fluorouracil; or a hormone such as leuprolide. As another example, where the seed 10 is intended to be used as an adjuvant to radiation treatment for prostate cancer, the therapeutically active substance 14 can include a radio-sensitizing agent such as tirapazamine, BUdR, IUdR, or etanidazole. Because brachytherapy seed 10 allows *in situ* drug delivery to a tissue, the therapeutically active substance 14 may include a drug that is usually considered too toxic to treat a given condition if given systemically, e.g., tirapazamine or camptothecin.

In a preferred embodiment in which the brachytherapy seed contains radionuclide, the seed is coated with a non-radioactive biodegradable coating which degrades at a rate slower than that which allows the radioactivity to leach out, so that radioactivity is not released – i.e., the radioactivity has already fully decayed.

As indicated in the above description of the brachytherapy seed 10 shown in FIGs. 1 and 2, the biocompatible component 12 is associated with the therapeutically active component 14. As used herein, when referring to the biocompatible component 12 and the therapeutically active component 14, the phrase "associated with" means physically contacting. Thus, in the seed 10, the association of the biocompatible component 12 with the therapeutically active component 14 can take many forms. For example, the biocompatible component 12 and the therapeutically active component 14 can be combined into a mixture as shown in FIGs. 1 and 2. This mixture can have a uniform or non-uniform distribution of components 12 and 14.

The brachytherapy seed 10 shown in FIG. 1 is an example of a uniform mixture of components 12 and 14. The brachytherapy seed 10 of this example can be made by simply mixing together the biocompatible component 12 and the therapeutically active component 14 to form a combination product and then forming the product into the desired size and shape, e.g., using a mold.

Although the brachytherapy seeds shown in FIGs. 1 and 2 include mixtures of discrete particles dispersed through a matrix consisting of the therapeutically active component 14, in other versions of brachytherapy seed 10, components 12 and 14 are combined in a single particle or in a larger mass without discrete particles (e.g., a pellet the size and shape of brachytherapy seed 10). For example, biocompatible component 12 and therapeutically active component 14 can be dissolved into a liquid and then dried or cured to form seeds or a larger pellet made up of a homogeneous distribution of both components 12 and 14. (see, e.g., Ramirez et al., J. Microencapsulation 16:105, 1999).

The skilled artisan can select the desired size according to the properties desired and particular properties of the microsphere constituents. In one variation of this, the seeds are also made to include magnetic elements. The seeds can then be molded or compressed together into the desired shape and sized of brachytherapy seed 10. The larger pellet can likewise be sculpted, extruded, molded or compressed into the desired shape and size of brachytherapy seed 10. Alternatively, the liquid mixture of components 12 and 14 can be poured into a mold defining the shape and size of brachytherapy seed 10, and then cured in the mold. Brachytherapy seeds having components 12 and 14 combined in a single particle or in a larger mass (rather than discrete particles of each) are advantageous for delivering the

therapeutically active component 14 into a target tissue over longer time periods.

In other embodiments of seed 10, components 12 and 14 are not necessarily homogeneously mixed in the seed 10. Rather they can be positioned in different areas of the seed 10. For example, components 12 and 14 can separately be fashioned into discrete sections, strips, coils, tubes, etc. The discrete sections, strips, coils, tubes, etc. of the component 12 can then be combined (e.g., by molding together, adhering, structurally interlocking, etc.) with the discrete sections, strips, coils, tubes, etc. of the component 14 to form the seed 10. In another embodiment, the seed 10 shown in FIG. 2 can be modified by filling the cylindrical cavity 20 with a hydrogel, including a therapeutically active substance, and capping off the ends of the hollow tube 18.

The foregoing combination products (i.e., at least one biocompatible component mixed with at least one therapeutically active component) can be used in the brachytherapy seeds by forming them into a size and shape suitable for passing through the bore of a needle such as one in a conventional brachytherapy seed implantation device.

Referring now to FIGs. 3A-F, in others embodiments of the invention, a brachytherapy seed 10 includes a biocompatible component 12 associated with a therapeutically active component 14, and a radiopaque marker 30 attached to the biocompatible component 12 and/or the therapeutically active component 14. Radiopaque marker 30 allows for the position of brachytherapy seed 10 to be determined using standard X-ray imaging techniques (e.g., fluoroscopy) after seed 10 has been implanted in a target tissue. Proper positioning of seed 10 and spacing of a plurality of brachytherapy seeds in a given target tissue is important for

ensuring that the therapeutically active component 14 is delivered adequately to the site of the disease in the target tissue.

As indicated above, radiopaque marker 30 is attached to seed 10 via the biocompatible component 12 and/or the therapeutically active component 14. The exact manner in which radiopaque marker 30 is attached to seed 10 can is not critical so long as (a) the seed 10 can be passed through the bore of a brachytherapy implantation needle and (b) the attachment allows the position of seed 10 to be readily detected by X-ray imaging. A description of some different examples of how marker 30 can be associated with seed is presented in FIGs. 3A-F. In the embodiment shown in FIG. 3A, the radiopaque marker 30 in the form of a ribbon, filament, strip, thread, or wire is placed in the center and along the length of cylindrical seed 10. In FIG. 3B, the radiopaque marker 30 takes the form of two end caps placed at both ends of cylindrical seed 10. In the embodiment illustrated in FIG. 3C, the radiopaque marker 30 is a coil made of a radiopaque substance running through the length of cylindrical seed 10 as shown. In FIG. 3D, the radiopaque marker 30 takes the form of two beads or pellets placed at two locations along cylindrical seed 10. In the embodiment shown in FIG. 3E, the radiopaque marker 30 takes the form of two bands or rings placed at two locations along the outer surface of cylindrical seed 10. In the seed 10 shown in FIG. 3F, the radiopaque marker 30 takes the form of a mesh formed into cylindrical shape. In the seed 10 shown in FIG. 3G, the radiopaque marker 30 is dispersed throughout the seed in a stippled pattern.

A particularly preferred embodiment of a brachytherapy seed having a radiopaque marker is one in which the radiopaque markers is a polymer. In one version of this embodiment, radiopaque polymers are combined with a biocompatible

component and a therapeutically active component to form a brachytherapy seed that can be visualized by X-ray imaging. Alternatively, the radiopaque polymer can serve as the biocompatible component. For example, seeds made of a radiopaque polymer are co-mingled with seeds containing a biocompatible component and seeds containing (e.g., encapsulating) a therapeutically active component (or seeds containing both a biocompatible component and a therapeutically active component). The co-mingled seeds are then molded into a radiopaque brachytherapy seed. As another example, the radiopaque polymer, the biocompatible component, and the therapeutically active component can be mixed together into a liquid, and the liquid can be cured to form a solid pellet that can be sculpted, molded, compressed, or otherwise made into the size and shape of a brachytherapy seed. An advantage of preparing a radiopaque brachytherapy seed in this manner is that, after implantation, the entire seed can be visualized by X-ray imaging rather than only a portion of a seed (e.g., as occurs with seeds utilizing conventional markers).

Referring now to FIGs. 4A and 4 B, a brachytherapy seed 10 includes a biocompatible component 12 associated with a therapeutically active component 14, and a sealed container 40 housing a radioisotope 42. Sealed container 40 is at least partially coated (e.g., partially coated in the version shown in FIG. 4A, and completely coated in the version shown in FIG. 4B) by the biocompatible component 12 and/or the therapeutically active component 14. Sealed container 40 is similar in some respects to those employed in conventional radioactive brachytherapy seeds (e.g., those lacking a biocompatible component 12 associated with a therapeutically active component 14). To prevent leaching of radioisotope 42 after seed 10 is implanted into a target tissue,

sealed container 40 is made of a non-biodegradable substance such as titanium or stainless steel. Further, radioisotope 42 is hermetically sealed within container 40.

The exact shape of sealed container 40 is not critical as long as it can be at least partially coated with component 12 and/or 14 to form a brachytherapy seed that can fit through the bore of a brachytherapy implantation needle. It can thus vary in shape from cylindrical (as shown in FIG. 4), cuboid, spheroid, ovoid, ellipsoid, irregularly shaped, etc. Of more importance is the size of sealed container 40. Because the brachytherapy seed 10 containing both the sealed container 40 and the biocompatible component 12 and/or therapeutically active component 14 must fit through the bore of a brachytherapy implantation needle, container 40 must be smaller than the overall size of seed 10. In the example shown in FIG. 4B, sealed container 40 is a cylindrical cannister placed down the center of the length of the rod-shaped seed 10 in a coaxial fashion. Thus, where the seed 10 has a diameter of about 0.8 mm and a length of about 4.5 mm, the sealed container will have a diameter less than 0.8 mm and a length less than 4.5 mm, and rather than having only a single sealed container 40 included within brachytherapy seed 10, there can be two or more such containers housing the radioisotope 42.

The therapeutically active agent 14 in seed 10 including the sealed container 40 can be any of those agents described above. Preferably, however, agent 14 is selected to provide an enhanced effect when used in combination with the radioisotope 42 to treat a particular diseased tissue, as discussed above.

Radioisotope 42 can be any substance that emits electromagnetic radiation (e.g., gamma-rays or X-rays), beta-particles or alpha-particles and is suitable for use in brachytherapy seed 10. Examples of such substances include

those that decay principally by electron capture followed by X-ray emission such as palladium-103 and iodine-125; isotopes that decay by the emission of beta-particles such as gold-198, gold-199, yttrium-90, and phosphorus-32; isotopes that decay with the emission of both beta-particles and gamma-rays such as iridium-192; and isotopes that decay with the emission of alpha-particles such as americium-241. Also useful is gadolinium-157, e..g, for use in boron-neutron capture therapy, and californium-252, rhenium-188, samarium-153, indium-111, ytterbium-169, and holmium-166. For the treatment of prostate cancer, palladium-103 and iodine-125 are preferred as these have been the subject of much clinical investigation for the treatment of the disease. The amount of radioactivity of radioisotope 42 can vary widely. For example, when using palladium-103 or iodine-125, an exemplary amount to treat prostate cancer is respectively about 1.5 mCi and 0.33 mCi per seed if about 50-150 seeds are used at the time of implantation. In other applications the radioactivity per seed can range from about 0.01 mCi to May 1, 2001 about 100 mCi.

In one embodiment, radioisotope 42 can be mixed with and then configured into seeds, or it can be encapsulated by the biocompatible component to form seeds. The radioactive seeds can be molded or otherwise sized and shaped into a brachytherapy seed suitable for implantation via a brachytherapy implantation device. In one version of this embodiment, the biocompatible component is biodegradable such that the radioisotope contained by this component is gradually released from the seed. Alternatively, the biocompatible component and radioisotope can be mixed together and configured as an amorphous pellet having the size and shape of a brachytherapy seed suitable for implantation via a brachytherapy implantation device.

In another embodiment illustrated in FIGs. 5A and 5B, a plurality of brachytherapy seeds 10 may be conjoined into a chain 50 using a plurality of spacers 52 to connect the plurality of seeds 10. In the embodiments shown in FIGs. 5A and 5B, a spacer 52 is used to connect two adjacent seeds 10. Spacer 52 can have any size suitable for use with brachytherapy seed 10. Where a plurality of spacers are used in one chain 50, the length of each spacer 52 can be the same or different from the other spacers 52. For many applications the length of spacer 52 will vary from between about 0.5 mm to about 50 mm. In many cases, it is important to minimize the bunching or straying of seeds 10 to avoid over- or under-dosing of the target tissue by the therapeutically active component 14 and/or radioisotope 42. Thus, the length of spacer 52 should be selected accordingly.

Spacer 52 can be made of a biocompatible material that can be used to join two brachytherapy seeds. See, e.g., U.S. Patent No. 6,010,446. The biocompatible material can be either biodegradable or non-biodegradable. For example, spacer 52 can be made of catgut or a like material. Spacers designed for use with conventional radioactive brachytherapy seeds can be used in chain 50. For example, Ethicon, Inc. (Cincinnati, OH) manufactures the PG 910 non-sterile autoclavable spacer for Indigo (Cincinnati, OH) that is sold in conjunction with an Express Seed Cartridge. In addition, Medical Device Technologies, Inc. (Gainesville, FL) distributes a pre-sterilized 5.5 mm long absorbable pre-cut spacer that is made of collagen (Look®, model number 1514b). Materials for use as the spacer 52 are also manufactured by Surgical Specialties Corp. (Reading PA). Where spacer 52 is made of a relatively flexible material, the chain 50 can be relatively flaccid as shown in Fig. 5A. Where spacer 52 is made

of an inflexible material, chain 50 will be rigid as shown in FIG. 5B.

In some embodiments, the spacer 52 may include a radiopaque substance (e.g., a high Z material or radiopaque polymer described above), so that spacer 52 serves both to facilitate locating an implanted brachytherapy seed by X-ray imaging as well as to physically join together (and/or control the distance between) two or more seeds.

Spacer 52 can be connected to seed 10 by any means known. For example, spacer 52 can be connected to seed 10 by direct attachment such as by gluing, crimping, or melting. Spacer 52 can be attached to any portion of the seed 10. For rod or cylinder-shaped seeds 10, to facilitate implantation, it is generally preferred that spacer 52 be attached to the ends of the seeds 10 that the ends would be adjacent to one another when the chain 50 is inserted into the barrel of a brachytherapy implantation needle. Spacer 52 and seed 10, however, need not be physically attached to each other. Rather they can also be associated with each other by placing each with within the lumen of a tube. The tube can be used to load a brachytherapy seed implantation device with a plurality of spacers 52 and seeds 10 in any sequence. For example, the brachytherapy seed implantation device can be loaded with one (or 2, 3, 4, 5, or more) spacer 52 being interposed between every two seeds 10. Similarly, the brachytherapy seed implantation device can be loaded with one (or 2, 3, 4, 5, or more) seed 10 being interposed between every two spacers 52.

The brachytherapy seeds are implanted into a target tissue within a subject (e.g., a human patient or a non-human animal) by adapting known methods for implanting conventional radioactive brachytherapy seeds into a tissue. For example, the brachytherapy seeds can be implanted using one or more

implantation needles; Henschke, Scott, or Mick applicators; or a Royal Marsden gold grain gun (H. J. Hodt et al., British J. Radiology, pp. 419-421, 1952). A number of suitable implantation devices are described in, e.g., U.S. Patent Nos. 2,269,963; 4,402,308; 5,860,909; and 6,007,474.

In many applications, to treat a given target tissue with a therapeutic agent it is desirable (or even ideal) to fully saturate the target tissue with the therapeutic agent, while avoiding under- or over-dosing the target tissue. This can be achieved by implanting the brachytherapy seeds into a target tissue using a brachytherapy implantation device so that a precise number of seeds can be implanted in precise locations within the target tissue. By previously calculating the rate of diffusion of the therapeutically active substance under experimental conditions (e.g., using tissue from animal models), an appropriate dosage can be delivered to the target tissue. Because use of brachytherapy implantation devices allows the brachytherapy seeds to be implanted in any number of different desired locations and/or patterns in a tissue, this method is advantageous over methods where a drug or drug impregnated matrix is simply placed on the surface of a tissue or manually inserted into a surgically dissected tissue.

I claim:

1. A brachytherapy seed for implantation into a subject comprising

(a) a non-radionuclide imaging marker, and

(b) a polymeric carrier, wherein the polymer is biocompatible, and

wherein the brachytherapy seed has a size and shape suitable for passing through the bore of a needle having an interior diameter of less than about 2.7 millimeters (10 gauge).

2. The brachytherapy seed of claim 1 further comprising an agent selected from the group consisting of non-radionuclide therapeutic, prophylactic and diagnostic agents.

3. The brachytherapy seed of claim 1 or 2 wherein the imaging marker is detectable by X-ray, fluorescence, infrared, ultrasound, magnetic detection, or MRI.

4. The brachytherapy seed of claim 1 or 2, wherein said size and shape is suitable for passing through the bore of a needle having an interior diameter of less than about 1.4 millimeters (15 gauge).

5. The brachytherapy seed of claim 1 or 2, wherein the seed is shaped into a cylinder having a diameter of between about 0.5 to 3 millimeters and a length 4 to 10 millimeters.

6. The brachytherapy seed of claim 1 or 2, wherein the polymeric carrier is biodegradable.

7. The brachytherapy seed of claim 2, wherein the agent is selected from the group consisting of proteins, polysaccharides, nucleic acids, and other non-polymeric drug molecules.

8. The brachytherapy seed of claim 7 wherein the agent is selected from the group consisting of: stimulating and growth factors; gene vectors; viral vectors; anti-angiogenesis agents; cytostatic, cytotoxic, and cytocidal agents; transforming agents; apoptosis-inducing agents; radiosensitizers; radioprotectants;

hormones; enzymes; antibiotics; antiviral agents; mitogens; cytokines; anti-inflammatory agents; immunotoxins; antibodies; and antigens.

9. The brachytherapy seed of claim 2, wherein the therapeutic agent is an anti-neoplastic agent.

10. The brachytherapy seed of claim 1 or 2, further comprising a radioactive agent.

11. The brachytherapy seed of claim 10 further comprising a radiosensitizing agent.

12. The brachytherapy seed of claim 11, wherein the radiosensitizing agent is selected from the group consisting of: 5-fluorouracil, etanidazole, tirapazamine, BUdR, and IUdR.

13. The brachytherapy seed of claim 1 or 2 wherein the imaging marker is a radiopaque marker comprising a substance selected from the group consisting of: platinum, iridium, rhenium, gold, tantalum, bismuth, indium, tungsten, silver, and radiopaque polymers.

14. The brachytherapy seed of claim 1 or 2 comprising a therapeutic radionuclide.

15. The brachytherapy seed of claim 14 wherein the seeds is coated with a biodegradable polymeric material that degrades after the radionuclide has decayed and is no longer radioactive.

16. A method of making a brachytherapy seed for implantation into a subject comprising mixing a polymeric carrier with a non-radioactive imaging agent to form a bachytherapy seed, as defined by any of claims 1-14.

17. A method for administering a therapeutically active component to a target tissue in a subject, the method comprising administering the brachytherapy seed of any of claims 2-14.

18. The method of claim 17, wherein the target tissue is a diseased tissue, preferably prostrate tissue.

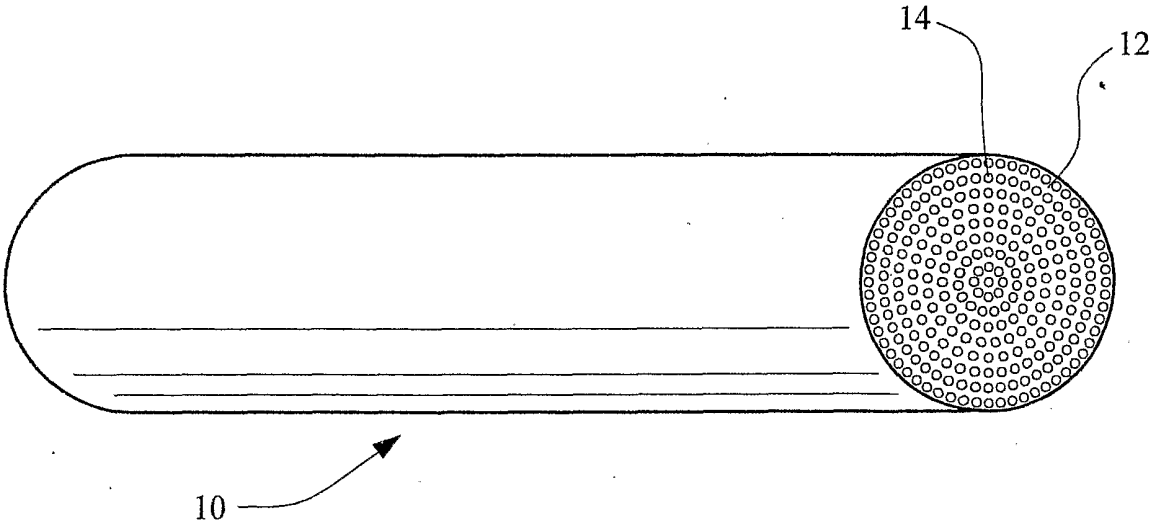


FIG. 1

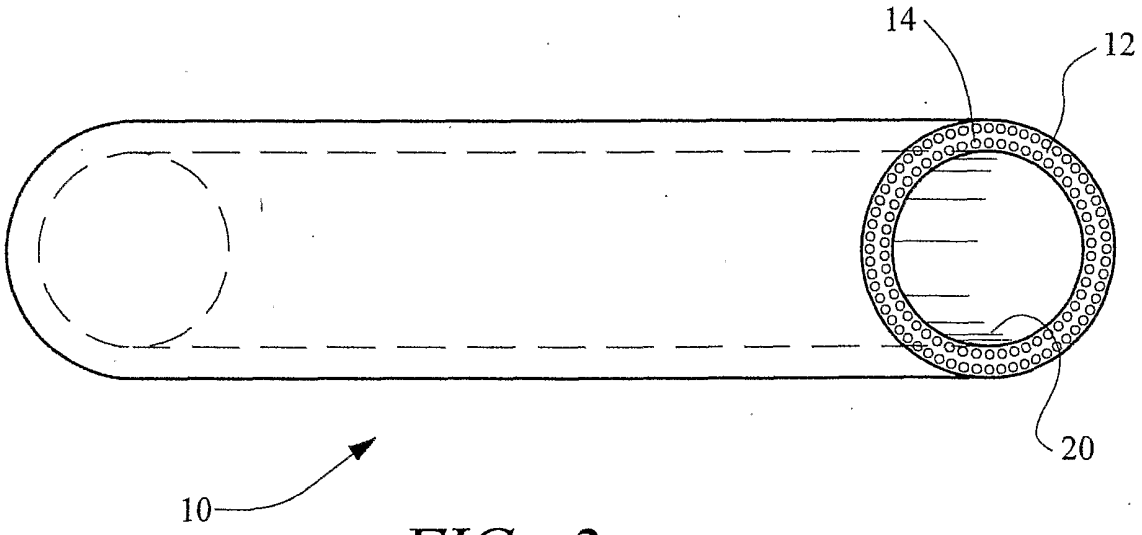


FIG. 2

FIG. 3A

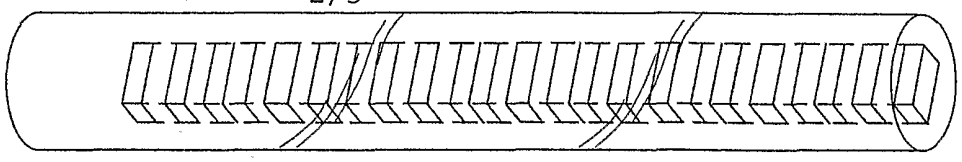


FIG. 3B

FIG. 3C

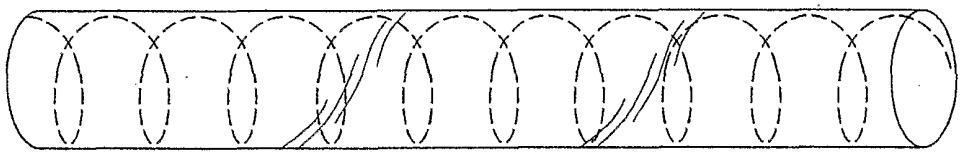


FIG. 3D

FIG. 3E

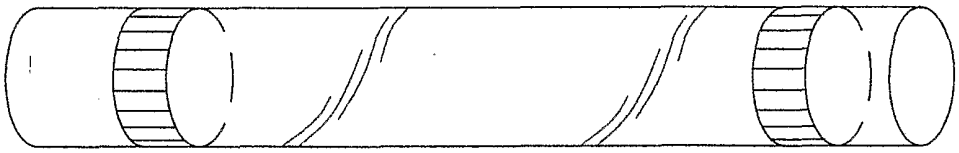


FIG. 3F

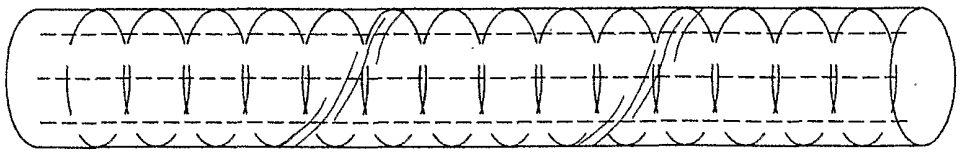
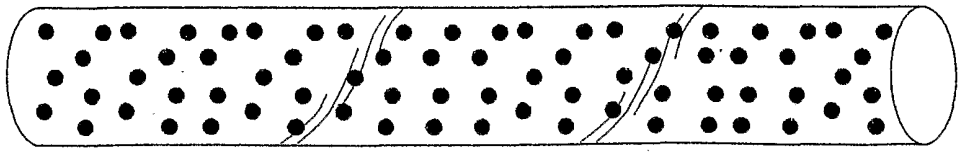


FIG. 3G



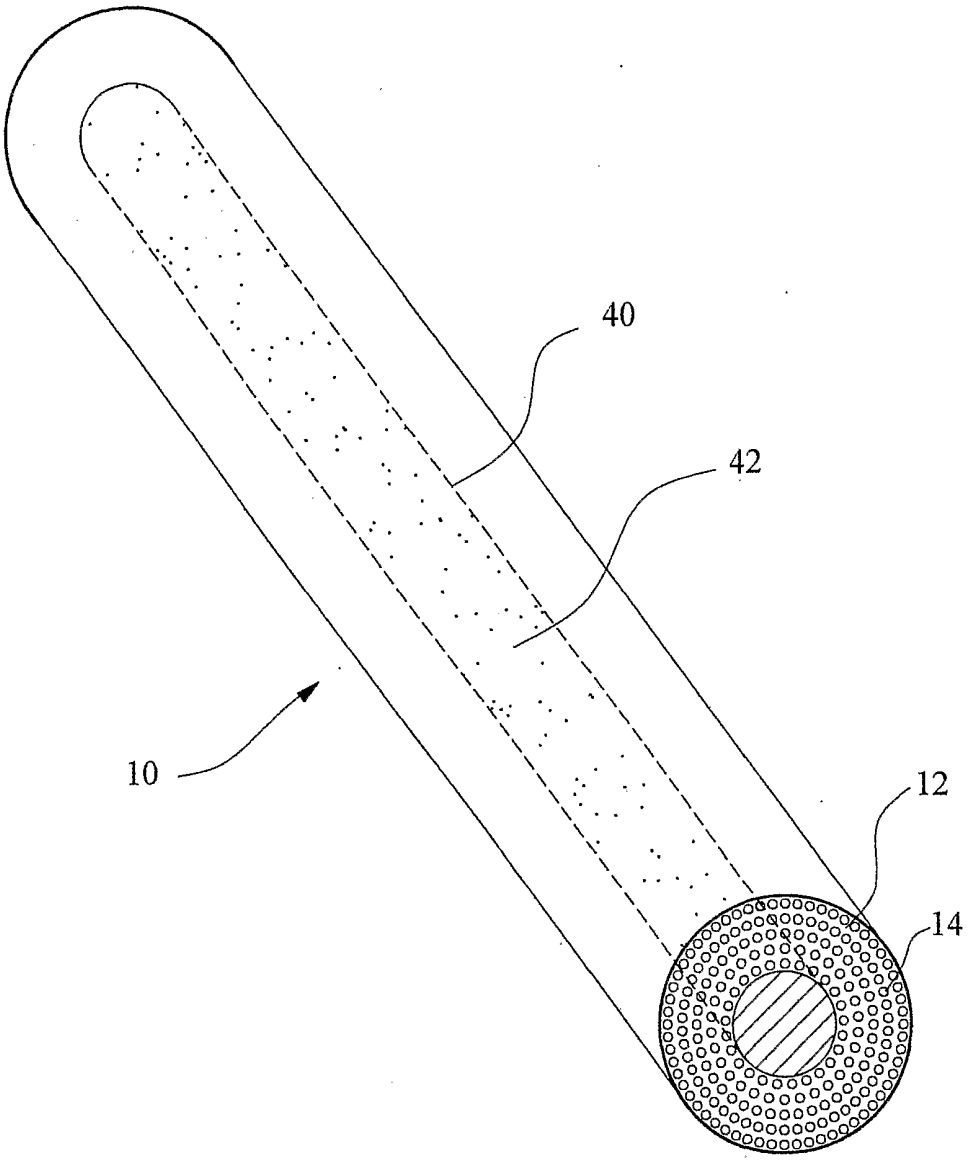


FIG. 4A

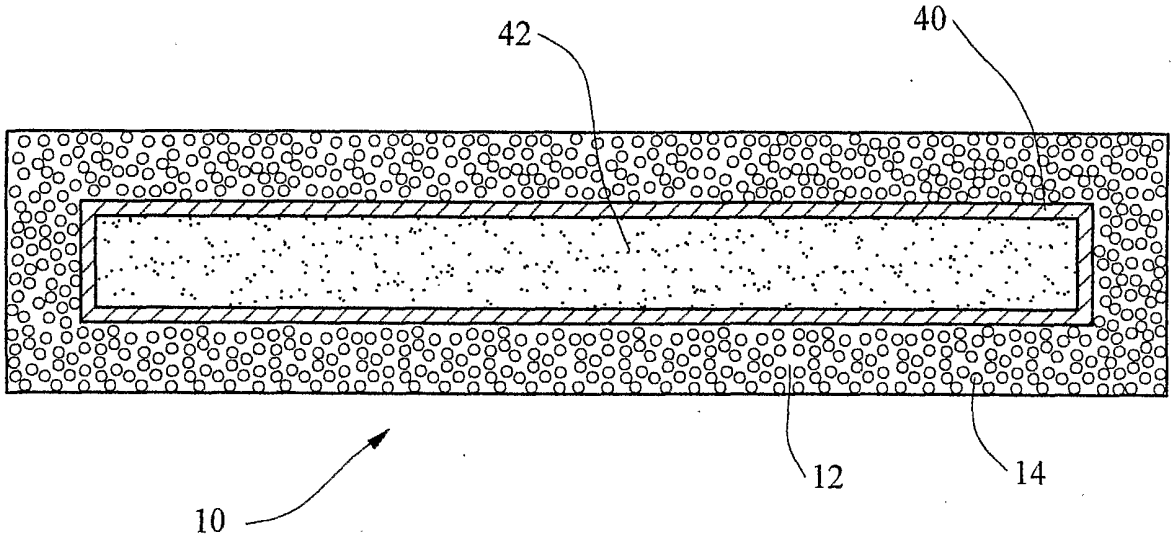


FIG. 4B

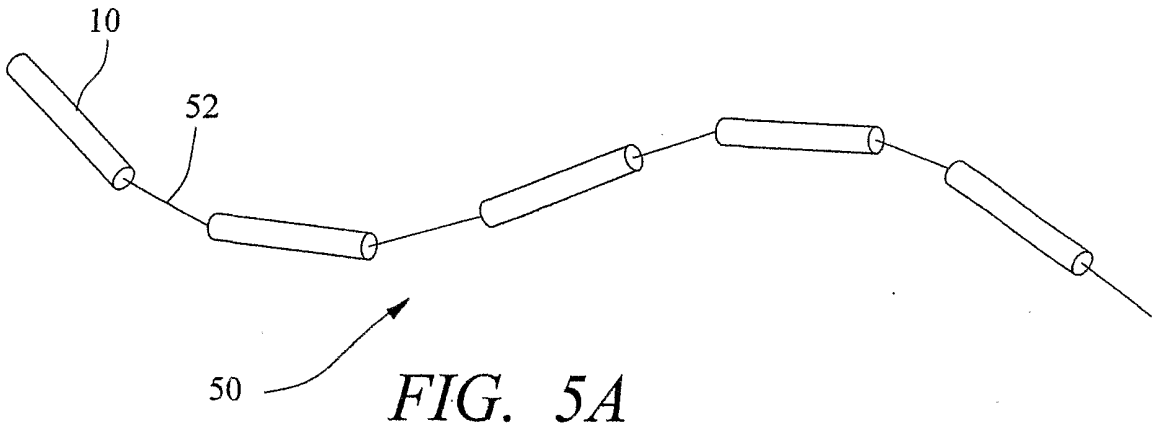


FIG. 5A

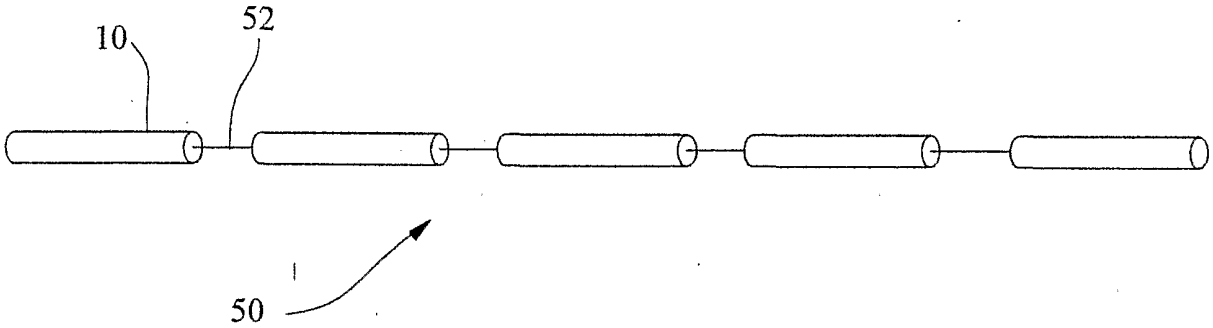


FIG. 5B