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(54) **COATING DEVICE AND METHOD FOR COATING MEDICAL DEVICE WITH BIOACTIVE PEPTIDE**

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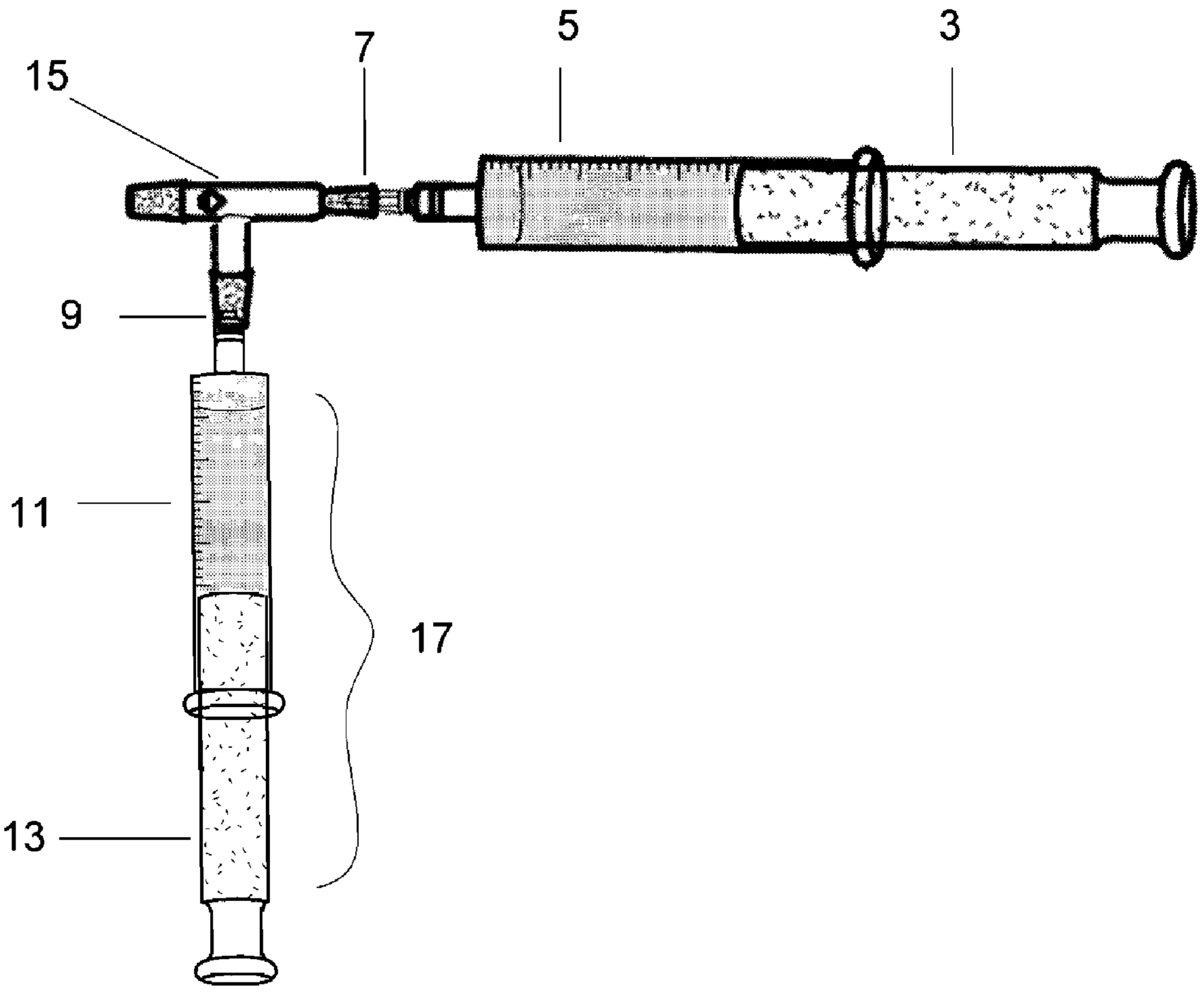
(57) **ABSTRACT**

A method for coating a medical device with a bioactive peptide comprising: providing a medical device to be coated with a bioactive peptide to a cylinder; attaching a syringe containing a bioactive peptide coating solution; introducing into the cylinder the bioactive peptide coating solution when the first valve of the connector and the second valve of the connector are open; incubating the medical device within the cylinder with the bioactive peptide coating solution; removing the bioactive peptide coating solution from the cylinder after the medical device is coated with the bioactive peptide.



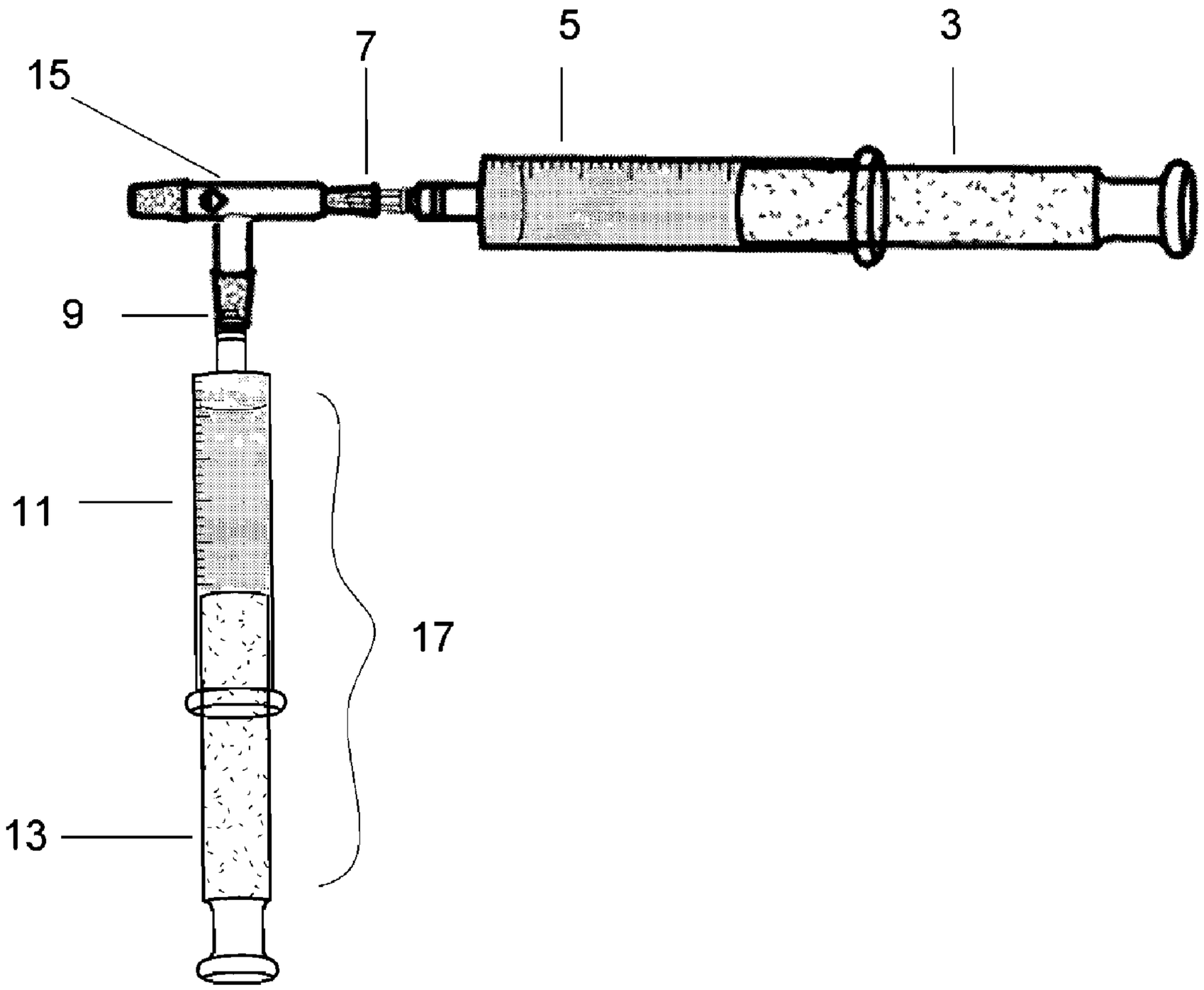


Fig. 1

COATING DEVICE AND METHOD FOR COATING MEDICAL DEVICE WITH BIOACTIVE PEPTIDE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation-in-part application of U.S. patent application Ser. No. 11/767,391, entitled "COMPOSITION AND METHOD FOR DELIVERY OF A PARTIAL AGONIST OF BMP-2 FOR ENHANCEMENT OF OSTEOGENESIS", filed on Jun. 22, 2007 which claims priority to and the benefit of the filing of U.S. Provisional Patent Application Ser. No. 60/805,594, entitled "COMPOSITION AND METHOD FOR DELIVERY OF A PARTIAL AGONIST OF BMP-2 FOR ENHANCEMENT OF OSTEOGENESIS", filed on Jun. 22, 2006, and the specification and claims thereof are incorporated herein by reference.

INTRODUCTION

[0002] The present invention relates generally to the field of a system and method for coating medical devices with coating materials.

BACKGROUND OF THE INVENTION

[0003] Implantable medical devices are frequently used in a variety of reparative and regenerative medical procedures. Use of bioactive peptides in concert with these devices is one way to improve the performance of the device. However, sample preparation methods, especially with regard to the application of the peptide coating, are difficult to control but require accuracy and precision. There is a need for a coating device to apply a fine, uniform coating of onto the implantable in order to simplify the sample preparation process.

SUMMARY OF THE INVENTION

[0004] According to one embodiment of the present invention a method for coating a medical device with a bioactive peptide comprising providing a medical device to be coated with a bioactive peptide to a cylinder having a plunger that inserts into a first end of the cylinder and fits snuggly against the sides of the cylinder and at the other end of the cylinder is located a connector having a first valve that is attached to the second end of the cylinder for creating a closed cylinder when the first valve is closed; attaching a syringe containing a bioactive peptide coating solution to a second valve of the connector; introducing into the cylinder the bioactive peptide coating solution when the first valve of the connector and the second valve of the connector are open; incubating the medical device within the cylinder with the bioactive peptide coating solution; removing the bioactive peptide coating solution from the cylinder after the medical device is coated with the bioactive peptide. In a preferred embodiment the step of incubating further comprises placing the cylinder in a substantially horizontal position to increase the solution to granule contact. In another preferred embodiment the cylinder is a first syringe. In another preferred embodiment the medical device is osteoconductive material. In yet another preferred embodiment the cylinder is in a substantially vertical position during the introducing step. In another preferred embodiment the plunger of the cylinder is pushed to discharge the bioactive peptide coating solution from the cylinder. In still another preferred embodiment the bioactive peptide coating solution comprises a synthetic growth factor analogue comprising a non-growth factor heparin binding region, a linker and a sequence that binds specifically to a cell surface receptor.

[0005] Another embodiment of the present invention is a system for coating a medical device with a bioactive peptide comprising a cylinder for housing a medical device to be coated with a bioactive peptide coating solution wherein the cylinder comprises a plunger that inserts into a first end of the cylinder and fits snuggly against the sides of the cylinder and at the other end of the cylinder is located a connector having a first valve that is attached to the second end of the cylinder for creating a closed cylinder when the first valve is closed; a syringe that is attached to a second valve of the connector wherein the syringe contains a bioactive peptide coating solution that is introduced into the cylinder via the connector; and a connector having a first valve attached to the cylinder and a second valve attached to the syringe.

[0006] In yet another embodiment of the present invention comprises a kit for use in coating a medical device with a bioactive peptide comprises a bioactive peptide; a first syringe; a second syringe and a connector having a first valve and a second valve. In a preferred embodiment, the bioactive peptide comprises a synthetic growth factor analogue comprising a non-growth factor heparin binding region, a linker and a sequence that binds specifically to a cell surface receptor.

[0007] One aspect of the present invention provides an improved bioactive peptide coating method for medical devices.

[0008] Another aspect of the present invention provides for use of bioactive peptides in concert with implantable medical devices to improve the performance of the medical device.

[0009] Another aspect of the present invention provides improved methods for application of the peptide coating to medical devices.

[0010] Another aspect of the present invention provides for a method of accurately applying a bioactive peptide coating device to an implantable medical device.

[0011] Additional objects and advantages of the present invention will be apparent in the following detailed description read in conjunction with the accompanying drawing figures.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] The file of this patent contains at least one drawing executed in color. Copies of this patent with color drawing(s) will be provided by the Patent and Trademark Office upon request and payment of the necessary fee.

[0013] FIG. **1** illustrates a coating device according to one embodiment of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

[0014] One embodiment of the present invention is a coating device system. The system comprises a container, typically a cylinder, for example a syringe. The syringe is attached to a connector at one end. The connector may be a valve used to turn on, turn off, or regulate the flow of a fluid in a cylinder. The valve may be a stop cock for example a multi-way stop cock. In a preferred embodiment the multi-way stop cock is a three way stop cock valve. The cylinder may be a syringe capable of receiving a plunger with a head that is sized to fit snugly against the sides of the syringe barrel to push liquid and particles through the syringe barrel toward the tip.

[0015] The container is capable of housing a medical device referred to herein as materials to be treated. The container may be vented at one end. The container may also be a syringe barrel with an enclosed medical device which is closured with a second syringe barrel. The container in all cases houses the medical device. In a preferred embodiment the container is a syringe that is identical in shape and volume capacity to the second syringe but is not limited thereto as other volume capacities and shapes will function equivalently.

[0016] According to another embodiment, the container with the materials to be coated therein is placed in a substantially vertical position and is attached at one end to one of the valves of the connector. A syringe containing an appropriate coating solution is attached to a second of the valves of the connector. The solution is introduced into the container housing the materials to be coated. The solution fills the container from the bottom up. The coating is allowed to incubate with the material to be coated for an appropriate length of time. The coating solution is then removed by withdrawing the solution back into the syringe or by pushing the solution out of the container with the container plunger. The coated material is then removed from the container and is ready for use.

[0017] In a preferred embodiment the container is a syringe with graduated markings allowing additional materials, such as bone chips, to be added and measured.

[0018] In some cases the container may house a material which requires pre-wetting. A wetting syringe may be used, in that case, to introduce a wetting solution prior to the coating process. Similarly, a rinsing syringe may be used to introduce into the container a separate rinse for the coated device to remove residual unbound materials.

[0019] Referring now to FIG. **1**, a container **5** contains a medical device (not shown) that is the target of a bioactive peptide coating solution. The container **5** has a plunger **3** inserted into a first end. At the second end of the container **5** is attached a connector valve **7** on connector **15**. A syringe **17** having a syringe barrel **11** and a plunger **13** contains a bioactive peptide coating solution. The tip of the syringe is attached to a connector valve **9** on connector **15**. Plunger **13** forces bioactive peptide coating solution (not shown) into the container **5** containing the medical device to be coated. After incubation of the bioactive peptide solution with the medical device in container **5**, plunger **3** is depressed to discharge the bioactive peptide solution from container **5**.

EXAMPLE 1

[0020] Hydroxyapatite/tricalcium phosphate granules with nominal diameters of 1-2 mm where placed in a first 20 ml syringe barrel (referred to in example 1 as syringe A) wherein the barrel is attached to a 3-way valve connector at its tip. The plunger of the barrel is replaced with care not to compress the granules. The first 20 ml syringe barrel is placed in an upright position.

[0021] A second 20 ml syringe (referred to in example 1 as syringe B) with an attached needle is used to draw 6 ml of the peptide coating solution from a vial. The needle is removed from the second syringe containing the coating solution and the second syringe is attached to a first valve of the 3-way valve connector that is already connected to syringe A thereby connecting the syringe A to syringe B via the 3-way valve connector. The valves connected to the syringe A and syringe B are opened and the coating solution is introduced into syringe A. The material housed in syringe A is mixed with solution comprising a bioactive peptide. Both syringes are positioned on their sides to achieve improved solution-to-granule contact during incubation. The material and coating solution are incubated together for the appropriate incubation time with periodic mixing, for example 15 minutes. The syringe A is returned to a substantially vertical position. The plunger of syringe A is slowly depressed so that the plunger pushes the coating solution back into syringe B. Air from within syringe A can be pushed across the granules to improve solution removal. Syringe B is then disconnected from the connector.

[0022] The syringe plunger from syringe A can be removed and bone chips added to the desired volume (for example 5 cc). Once measured the contents of the syringe barrel can be removed into a surgical tray for final mixing and placement.

EXAMPLE 2

[0023] A small-bore ePTFE vascular graft is placed in a 10 ml syringe barrel wherein the barrel had an attached 3-way valve. A black rubber stopper was placed in the opening of the barrel. Through the stopper a venting needle is positioned with an attached 0.22 micron filter and is referred to in example 2 as syringe A.

[0024] Syringe A is placed in an upright position. Using a second 20 ml syringe (referred to in example 2 as syringe B) with an attached needle about 6 ml of the ePTFE wetting solution is drawn into syringe B. The needle is then removed from syringe B and syringe B is attached to syringe A with their female adopters in the three way stopcock. The valves attached to the syringes are opened and the wetting solution is introduced into syringe A. The wetting solution is subsequently removed from syringe A and into syringe B by pulling on the plunger of syringe B. Syringe B can be removed from the valve of the three way stop cock.

[0025] Using a fresh 10 ml syringe prefilled with a peptide coating solution (referred to in example 2 as syringe C), connect syringe C to syringe A with their female adopters in the three way stopcock. Introduce the coating solution in syringe C into the bottom of syringe A. Incubate the coating solution with the ePTFE for about 15 minutes with periodic mixing. Using syringe C, remove the coating solution. Remove the black rubber stopper. The coated vascular graft can be removed into a surgical tray for subsequent placement.

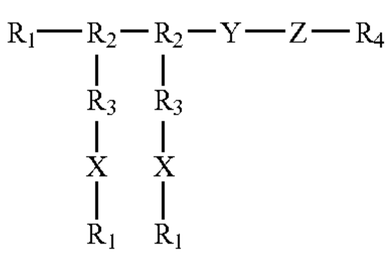
EXAMPLE 3

[0026] An ePTFE tissue patch was placed in a 20 ml syringe barrel wherein the barrel had an attached 3-way valve. A black rubber stopper was placed in the opening of the barrel. Through the stopper was placed a venting needle with an attached 0.22 micron filter. This device will be referred to as syringe A for Example 3.

[0027] Syringe A in placed in a substantially upright position. Using a separate 20 ml syringe (referred to as syringe B in example 3) with an attached needle 15 ml of the ePTFE wetting solution is withdraw into syringe B. The needle is removed and the syringe is attached to a female adopter in the three way stopcock. The valve is opened and the wetting solution is introduced into syringe A. After sufficient time to allow wetting of the material to be coated with the bioactive peptide coating solution, the wetting solution is removed by pulling on the plunger of syringe B. Syringe B is removed from the connector.

[0028] A fresh 20 ml syringe prefilled with a peptide coating solution (referred to as syringe C in example 3) is connected to syringe A with their female adopters in the three way stopcock. When the valves of the connector are in the open position, the peptide coating solution is introduced into the barrel of syringe A. The solution and the contents of syringe A are incubated for 15 minutes with periodic mixing. Using syringe C the coating solution is removed. Remove the black rubber stopper. The coated patch can be removed into a surgical tray for subsequent placement.

[0029] In one embodiment of the present invention the bioactive peptide comprises a compound of formula I



wherein:

[0030] X is a peptide chain that (i) has a minimum of three amino acid residues, (ii) has a maximum of about fifty amino acid residues, and (iii) binds specifically to a specifically to a cell surface receptor;

[0031] R_1 is independently hydrogen, such that the terminal group is NH_2, an acyl group with a linear or branched C_1 to C_{17} alkyl, aryl, heteroaryl, alkene, alkenyl or aralkyl chain including an N-terminus NH_2, NH_3^+, or NH group or a corresponding acylated derivative, or is amino acid, a dipeptide or a tripeptide with an N-terminus NH_2, NH_3^+, or NH group;

[0032] R_2 is independently a trifunctional alpha amino acid residue, wherein X is covalently bonded through a side chain of R_2;

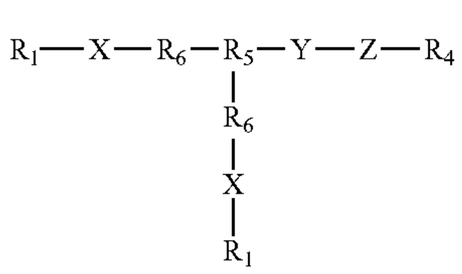
[0033] R_3 is independently a linker comprising a chain from 0 to about 15 backbone atoms covalently bonded to R_2;

[0034] R_4 is OH such that the terminal group is a carboxyl, NH_2, an acyl group with a linear or branched C_1 to C_{17} alkyl, aryl, heteroaryl, alkene, alkenyl or aralkyl chain including an N-terminus NH_2, NH_3^+, or NH group or a corresponding acylated derivative, or NH—R_1;

[0035] Y is a linker comprising a chain from 0 to about 50 backbone atoms covalently bonded to R_2 and Z; and

[0036] Z is a non-signaling peptide chain that includes a heparin binding domain comprising an amino acid sequence that comprises (i) a minimum of one heparin binding motif, (ii) a maximum of about ten heparin binding motifs, and (iii) a maximum of about thirty amino acids.

[0037] In another embodiment the bioactive peptide comprises a compound of formula II comprising:



II

wherein:

[0038] X is a peptide chain that (i) has a minimum of three amino acid residues, (ii) has a maximum of about fifty amino acid residues, and (iii) binds specifically to a specifically to a cell surface receptor;

[0039] R_1 is independently hydrogen, such that the terminal group is NH_2, an acyl group with a linear or branched C_1 to C_{17} alkyl, aryl, heteroaryl, alkene, alkenyl or aralkyl chain including an N-terminus NH_2, NH_3^+, or NH group or a corresponding acylated derivative, or is amino acid, a dipeptide or a tripeptide with an N-terminus NH_2, NH_3^+, or NH group;

[0040] R_6 is independently a linker comprising a chain from 0 to about 15 backbone atoms covalently bonded to R_3 when the linker is greater than 0 atoms;

[0041] R_5 is a trifunctional alpha amino acid residue, wherein X is covalently bonded through a side chain of R_3;

[0042] R_4 is OH such that the terminal group is a carboxyl, NH_2, an acyl group with a linear or branched C_1 to C_{17} alkyl, aryl, heteroaryl, alkene, alkenyl or aralkyl chain including an N-terminus NH_2, NH_3^+, or NH group or a corresponding acylated derivative, or NH—R_1;

[0043] Y is a linker comprising a chain from 0 to about 50 backbone atoms covalently bonded to R_5 and Z; and

[0044] Z is a non-signaling peptide chain that includes a heparin binding domain comprising an amino acid sequence that comprises (i) a minimum of one heparin binding motif, (ii) a maximum of about ten heparin binding motifs, and (iii) a maximum of about thirty amino acids.

[0045] In another embodiment the bioactive peptide comprises a synthetic growth factor analogue comprising a non-growth factor heparin binding region, a linker and a sequence that binds specifically to a cell surface receptor.

[0046] The present invention has been described in terms of preferred embodiments, however, it will be appreciated that various modifications and improvements may be made to the described embodiments without departing from the scope of the invention. The entire disclosures of all references, applications, patents, and publications cited above and/or in the attachments, and of the corresponding application(s), are hereby incorporated by reference.

What is claimed is:

1. A method for coating a medical device with a bioactive peptide comprising:

providing a medical device to be coated with a bioactive peptide to a cylinder having a plunger that inserts into a first end of the cylinder and fits snuggly against the sides of the cylinder and at the other end of the cylinder is located a connector having a first valve that is attached to the second end of the cylinder for creating a closed cylinder when the first valve is closed;

attaching a syringe containing a bioactive peptide coating solution to a second valve of the connector;

introducing into the cylinder the bioactive peptide coating solution when the first valve of the connector and the second valve of the connector are open;

incubating the medical device within the cylinder with the bioactive peptide coating solution;

removing the bioactive peptide coating solution from the cylinder after the medical device is coated with the bioactive peptide.

2. The method of claim **1** wherein the step of incubating further comprises placing the cylinder in a substantially horizontal position to increase the solution to granule contact.

3. The method of claim **1** wherein the cylinder is a first syringe.

4. The method of claim **1** wherein the medical device is osteoconductive material.

5. The method of claim **1** wherein the cylinder is in a substantially vertical position during the introducing step.

6. The method of claim **1** wherein the plunger of the cylinder is pushed to discharge the bioactive peptide coating solution from the cylinder.

7. The method of claim **1** wherein the bioactive peptide coating solution comprises a synthetic growth factor analogue comprising a non-growth factor heparin binding region, a linker and a sequence that binds specifically to a cell surface receptor.

8. A system for coating a medical device with a bioactive peptide comprising:

a cylinder for housing a medical device to be coated with a bioactive peptide coating solution wherein the cylinder comprises a plunger that inserts into a first end of the cylinder and fits snuggly against the sides of the cylinder and at the other end of the cylinder is located a connector having a first valve that is attached to the second end of the cylinder for creating a closed cylinder when the first valve is closed;

a syringe that is attached to a second valve of the connector wherein the syringe contains a bioactive peptide coating solution that is introduced into the cylinder via the connector; and

a connector having a first valve attached to the cylinder and a second valve attached to the syringe.

9. A kit for use in coating a medical device with a bioactive peptide comprising:

a bioactive peptide;

a first syringe;

a second syringe and

a connector having a first valve and a second valve.

10. The kit of claim **9** wherein the bioactive peptide comprises a synthetic growth factor analogue comprising a non-growth factor heparin binding region, a linker and a sequence that binds specifically to a cell surface receptor.

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