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(71) Applicant: **ALVIMEDICA VASCULAR RESEARCH B.V.** [NL/NL]; Martin Luther Kingweg 3, NL-9403 PA Assen (NL).

(72) Inventors: **MARIJNISSEN, Johannes Cornelis Maria**; Zaart 11, NL-4819 ED Breda (NL). **HEINER, Wilfred Peter**; Dora Park C-Block No. 1, Buse Sokak No. 5, Adnan Kahveci Mahallesi, Beykent-Beylikdüzü, 34524 Istanbul (TR).

(74) Agent: **VERDIJCK, Gerardus Johannes Cornelis**; Arnold + Siedsma B.V., P.O. Box 18558, NL-2502 EN The Hague (NL).

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(54) **Title**: METHOD FOR DEPOSITING A COATING MATERIAL ON A MEDICAL DEVICE AND MEDICAL DEVICE

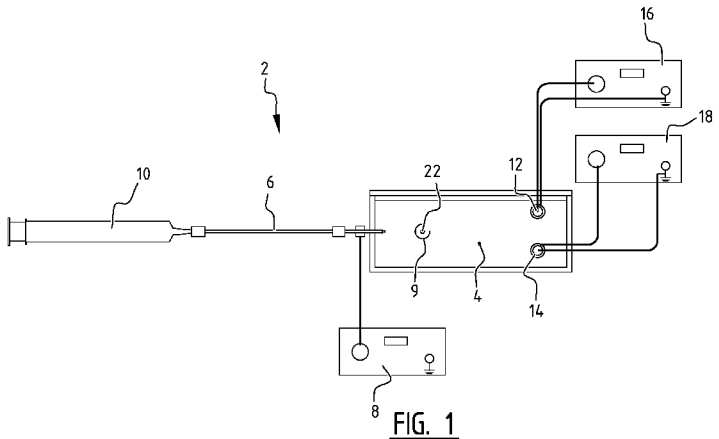

FIG. 1

(57) **Abstract**: The invention relates to a method for depositing a coating material on a medical device, a depositing system for depositing a coating on a medical device and a coated medical device. The method comprises the steps of: - providing the medical device in a spray chamber; - providing the coating material to an electrospray nozzle; - applying an electric potential to the nozzle; and - ejecting the coating material from the electrospray nozzle towards the medical device for coating a surface of the medical device; characterized in that the method further comprises - providing ions in the spray chamber to subject said surface to be coated to ions to prevent the formation of holes or cracks in the deposited coating material.

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METHOD FOR DEPOSITING A COATING MATERIAL ON A MEDICAL DEVICE AND MEDICAL DEVICE

The invention relates to a method for depositing a coating material on a medical device.

A known method for depositing a material on a target, e.g. a substrate, is electrospraying. In electrospraying, the material to be deposited is provided in a nozzle. A high voltage electric potential is applied to the nozzle, usually in the order of 1-30 kV. Due to this electric potential, the material in the nozzle obtains an electrical charge. In some cases, the electrical forces force the material out of the nozzle. Additionally or alternatively, the material is forced out mechanically, e.g. by using a syringe. The material then forms small droplets which repel each other due to their like charges. The result is a very fine spray. The target is electrically conducting and connected to ground. Therefore, the charged particles of the coating material are drawn towards the target, where they are deposited.

A related method known in the art is electrospinning. The basic principle of electrospinning is the same as for electrospraying. However, whereas in electrospraying the material is formed as spray of fine particles, in electrospinning a polymer material is used which forms very fine fibers, e.g. nanofibers, when ejected from the nozzle. The target is again electrically conducting and connected to ground to draw the fibers to the target.

Coating an electrically conducting target with an insulating coating material using conventional methods results in a coating with cracks or openings.

For example, the coating applied to a medical device, i.e. a stent or other implantable device or a catheter, needs to be free of cracks. Moreover, these devices often comprise insulating parts, which cannot be coated using the above conventional methods.

A further drawback of these known methods is that they cannot be applied to non-conductive, i.e. electrically insulating targets.

A goal of the invention is to overcome these drawbacks and provide an improved method for depositing material on a medical device.

This goal is achieved with the method according to the invention for depositing a coating material on a medical device, comprising the steps of:

- providing the medical device in a spray chamber;
- providing the coating material to an electrospray nozzle;
- applying an electric potential to the nozzle; and
- ejecting the coating material from the electrospray nozzle towards the medical device for coating a surface of the medical device;

characterized in that the method further comprises

- providing ions in the spray chamber to subject said surface to be coated to ions to prevent the formation of holes or cracks in the deposited coating material.

The formation of holes or cracks occurring in conventional methods when applying an insulating coating to a conducting target is believed to be caused by a phenomenon called back ionization (sometimes called back sparking). back ionization occurs because the layers of coating material isolate the conducting target as they are build up on the target. The layers on the target therefore obtain a high charge, which can result in an electrical discharge through the deposited layers. This leads to a coating with cracks or openings.

According to the inventors, subjecting the target to ions neutralizes the charge build up in the layers of coating material. Thereby, back ionization is prevented.

On the other hand, in case of an insulating target, the ions will charge the surface of the target such that the coating material is attracted by the target's surface. When a layer of coating material is deposited, this initial charge will be at least partially neutralized. A new load of ions will attach to this first layer to again establish a net charge, on which a second layer will be deposited, and the process repeats itself.

Moreover, some of the charged particles ejected from the nozzle may be (partially) neutralized in flight by the ions in the spray chamber. Also, the charge at the surface of the target may be (partially) released through the air, since it has a certain conductivity due to the presence of the ions.

Therefore, the invention enables an electrospray or electrospinning process for insulating targets and/or depositing material.

Moreover, also in the case of an insulating target, the ions prevent back ionization. Therefore, the invention enables applying to an insulating or conducting medical device a coating free of holes or cracks.

Ejecting the material may comprise applying a high enough electric potential such that the material is ejected from the nozzle due to the electrical forces overcoming the surface tension of the liquid, i.e. without applying an additional (mechanical) force. Alternatively or additionally, a force can be applied to eject the material. For example, the nozzle comprises a piston or syringe pump for applying a pressure to expel the material from the nozzle.

In the field of the invention, the nozzle is also known as the emitter. The nozzle may for example comprise a capillary, such as a hollow needle. A capillary promotes the formation of a Taylor cone, from which the material is ejected at a sufficiently high voltage level.

The material will usually be present in a liquid, such as alcohol, tetrahydrofuran (THF), dimehtylformamide (DMF) or an isopropyl alcohol. When the charged droplets or fibres are formed, this solvent will evaporate as the droplets / fibres move away from the nozzle. This results in the creation of charged particles / fibres of the solute material.

The electric potential applied to the nozzle is preferably a high voltage. For example, a voltage over 1 kV, over 10 kV, over 20 kV or over 30 kV is used. The electrospray device may include a counter electrode, e.g. for focusing the charged particles. For example, a counter electrode ring may be used. A voltage of the same polarity as the voltage applied to the nozzle is applied to the counter electrode.

The spray chamber is preferably closable. The outlet of the nozzle is located in the chamber. For example, the chamber comprises a door to enable placing the target inside the chamber. Preferably, the chamber is substantially completely closed during use.

The spray chamber may be any suitable enclosure for the electrospray operation. In particular, the spray chamber may have any suitable size. For example, the spray chamber may comprise an entire room or a relatively small box.

Preferably, the walls of the spray chamber are electrically insulating. This prevents the ions from being drawn towards the walls of the chamber. Preferably, in such a case a counter electrode is used for forming the electrospray.

The ions are provided to the surface to be coated. In other words, the part of the surface which is to be coated is subjected to both electrospray coating and ions. Preferably, the surface to be coated is simultaneously subjected to electrospray coating and ions. In a preferred embodiment, the method comprises depositing multiple layers of the coating material on the medical device.

In a further preferred embodiment, the coating material is deposited evenly over the surface of the medical device. For example, the mass of coating material per surface area is substantially constant over the coated surface. The even distribution of the coating material can for example be inspected visually, for example using a microscope.

In a preferred embodiment, the material comprises a combination of a drug and a polymer. This is in particular advantageous for coating medical devices, such as stents, other implantable devices or catheters. Such invasive devices are often coated with a drug. For example, stents are provided with a coating comprising a drug to prevent restenosis of arteries. The coating has to be as homogeneous as possible, i.e. free of cracks and openings. The method according to the invention is in particular suitable in creating such coatings. Furthermore, the invention enables applying the coating to non-conducting parts of the medical device as well.

The drug may for example comprise paclitaxel or sirolumus (rapamycin) or other limus drugs, such as temsirolimus, everolymus, deforolimus, zotarolimus or biolimus.

The drug eluting coating provided on a medical device by the method according to the invention is a homogenous coating, i.e. the drug is evenly distributed over the coated surface. For example, the mass of drug per surface area is substantially constant. In particular, the coating will be substantially free of cracks and openings. This enables a homogenous release of the drug during

use of the medical device. In other words, the invention ensures optimal release kinetics of the drug eluting coating.

In a preferred embodiment according to the invention, the drug is distributed evenly over the surface of the medical device for homogeneous release of the drug during use of the medical device.

In a preferred embodiment according to the invention,
the ions in the spray chamber comprise ions having a polarity opposite to the polarity of the electric potential of the nozzle.

According to the inventors, this contributes to the neutralization of charges on the medical device, and therefore to the homogeneous building of coating layers on the medical device.

For example, when the electric potential applied to the nozzle is positive, e.g. +1kV, the ions used are negative ions, e.g. N_2^- and O_2^-.

In a further preferred embodiment, both positive and negative ions are provided.

Experiments show that surprisingly the above effects can also be reached by providing both positive and negative ions to the medical device.

In a preferred embodiment, the ions are generated by ionizing air.

The ions are for example generated using a corona discharge system. Such a system may comprise a conductor having a sharp edge, e.g. a sharp point, to which a high voltage is applied. The high electric field at the edge ionizes the air which creates a corona discharge. For example, N_2^- and O_2^- are formed.

Other types of ion sources for use in the method according to the invention include an air ionization device, as conventionally used in air purification devices, and/or a radioactive source.

In a preferred embodiment, the medical device is electrically insulating. As described above, before the invention it was not possible to coat an electrically insulating medical device using electrospraying or electrospinning.

Alternatively, the medical device is electrically conducting.

It is noted that the method of the invention does not require a conducting medical device to be grounded; it may as well be electrically insulated from ground.

In a preferred embodiment, the medical device is electrically conducting and electrically connected to ground. The inventors found that although grounding of the medical device is no longer necessary, it can be advantageous during the start of the coating process. The grounded medical device efficiently attracts the charged coating material. After the first layer of material has been deposited on the medical device, the ions will largely take over this role of providing an active surface to attract the coating material.

In an alternative embodiment, the medical device is electrically conducting and electrically insulated from ground. In conventional electrospray methods isolating the target from ground will

lead to back ionization and consequently to the formation of cracks in the coating. By providing ions according to the invention back ionization is prevented.

In a preferred embodiment, the coating material to be deposited on the medical device is electrically insulating.

In a preferred embodiment, the step of providing the ions in the spray chamber comprises providing the medical device in an atmosphere comprising the ions.

For example, the medical device is placed in a holding means, such as a clamp or platform, and the air surrounding the medical device is ionized by using an ionization device.

In an alternative embodiment, the step of providing the ions in the spray chamber comprises creating a flow or bundle of ions directed towards the medical device.

In a preferred embodiment, the ions are provided before ejecting the material towards the medical device. This is especially advantageous in the case of an insulating medical device, as it allows building up a net charge on the surface of the medical device by means of the ions before the coating material is applied.

In a preferred embodiment, the coating material comprises a polymer such that the ejected coating material forms fibers by means of electrospinning. Preferably, the polymer is chosen such that a nanofiber is created.

In an exemplary embodiment, the coating material to be deposited comprises a polymer selected from the group comprising polylactic acid (PLA),poly-L-lactide (PLLA), poly(lactic-co-glycolic acid) (PLGA), thermoplastic polyurethane (TPU), nylon and polyether block amide (PEBA or PEBAX).

The invention further relates to a medical device with layers of a coating material deposited on the device, wherein the coating is free of holes or cracks and the coating material comprises a combination of a drug and a polymer. Preferably, the coating material is deposited on the device using the method as described above.

The invention further relates to a medical device obtainable using the method described above.

The invention also relates to a depositing device configured for performing the aforementioned method for depositing a coating material on a medical device, comprising:

- an electrospray nozzle for ejecting the coating material; and
- a voltage source connected to the electrospray nozzle for applying an electric potential to the electrospray nozzle;
- a spray chamber for placing the medical device therein;

characterized in that the device further comprises

- an ion source arranged to provide ions in the spray chamber.

For example, the spray chamber encloses both the medical device and the outlet end of the nozzle. Preferably, the spray chamber is closable, preferably such that it is substantially completely closed during use. For example, the chamber comprises a door for placing the medical device inside the chamber.

As described above with respect to the method, the walls of the spray chamber preferably are electrically insulating.

For example, a holding means is provided in the spray chamber for holding the medical device in the path of the ejected material. The holding means for example comprises a platform or a clamp.

The invention further relates to the use of a device according to the invention for depositing coating material on at least a part of a medical device.

The invention further relates to a method for depositing a coating material on a target for the production of a battery. The method is the same as describe above, except that the target is a battery component instead of a medical device. In particular, the features described above with respect to preferred embodiments of the method for coating a medical device may also be applied to the method for coating a target for production of a battery.

The method for coating a target for production of a battery comprises the steps of: providing the target in a spray chamber, proving the coating material to an electrospray nozzle, applying an electric potential to the nozzle, ejecting the coating material from the electrospray nozzle towards the target for coating a surface of the target, and providing ions in the spray chamber to subject said surface to be coated to ions to prevent the formation of holes or cracks in the deposited coating material. Preferably, the method further comprises using the coated target to produce a battery. Preferably, the method comprises using the battery in a medical device, such as a catheter or a pace maker, or in a medical apparatus such as a heart monitor or diagnostic apparatus.

In a preferred embodiment of the method for coating a target for the production of a battery, the coating material comprises a polymer loaded with at least a second material, preferably in the form of nanoparticles. For example, the polymer is loaded with a metal, a ceramic or a precursor, such as chloroplatinic acid.

The same effects and advantages as described in relation to the method for coating a medical device according to the invention apply to the medical device, the device for depositing coating material, the use thereof and the method for coating a target for producing a battery.

Further details, effects and advantageous of the invention will be explained on the basis of exemplary embodiments of the invention, with reference to the accompanying figures.

- Figure 1 shows schematically a first embodiment of a device for executing the method according to the invention;

- Figure 2 shows schematically a second embodiment of a device for executing the method according to the invention;
- Figure 3 shows schematically a part of a stent;
- Figure 4 shows a detail of the stent of figure 3 when coated according to a conventional method of coating; and
- Figure 5 shows a detail of the stent of figure 3 when coated according to the method of the invention.

Device 2 (figure 1) comprises a spray chamber 4. Electrospray nozzle 6 has a needle shaped outlet in spray chamber 4. Nozzle 6 is connected to high voltage power supply 8. In this example, the voltage applied is a positive voltage of 10 kV. Counter electrode ring 9 is positioned inside chamber 4 and connected to a high voltage, which is equal or preferably lower than the voltage of nozzle 6. In this example the voltage level of counter electrode 9 is 5 kV. A stable spray will be developed between nozzle 6 and ring 9.

To push the coating material out of nozzle 6, a syringe 10 is provided.

Two ion generating devices 12, 14 are provided. Ion generating device 12 is connected to high voltage power supply 16 for generating positively charged ions. Ion generating device 14 is connected to high voltage power supply 18 for generating negatively charged ions.

Spray chamber 4 further comprises a support (not shown) on which medical device 22 is placed. In this example, medical device 22 is electrically insulating. Optionally, e.g. in the case of a conducting medical device, medical device 22 is connected to ground. For example, medical device 22 is a stent or a catheter.

To coat medical device 22, a solvent, e.g. alcohol, comprising the coating material, e.g. a polymer, is provided in syringe 10. Medical device 22 is placed on the support and spray chamber 4 is closed. Ion generating devices 12, 14 are activated by controlling power supplies 16, 18, such that both positive and negative ions are generated inside the volume of spray chamber 4. Subsequently, power supply 8 is activated, to charge the coating material. Using syringe 10, the material is forced out of nozzle 6 in the form of an electrospray. Counterelectrode ring 9 ensure the formation of a stable spray between nozzle 6 and ring 9. The coating is thereby applied on the surface of medical device 22.

In a second device 102 (figure 2), a bipolar ionization source 124, i.e. a source creating both positive and negative ions, is provided inside spray chamber 104. Bipolar ionization source 124 is a source as known from air purifier systems. Source 124 is connected to a power supply via cables 126.

To apply a coating to medical device 122, a solvent comprising the coating material is provided in syringe 110. Medical device 122 is placed on the support (not shown) and spray chamber 104 is closed. Source 124 is switched on, such that ions are generated inside the volume

of spray chamber 104. Subsequently, power supply 108 is activated, to charge the coating material. Counter electrode ring 109 is also brought to a high voltage, which is equal to or preferably lower than the voltage level of nozzle 6. Using syringe 110, the material is forced out of nozzle 106 in the form of an electrospray. The coating is thereby applied on the surface of medical device 122.

Stent 124 (figure 3) comprises a mesh 126. In this example mesh 126 is composed of a material comprising a metal, such as nitinol. The mesh 126 forms a tubular structure of which only a part has been shown in figure 3. The center line 128 and circumference 130 have been schematically indicated for illustrative purposes.

Figure 4 shows a detail of stent 124 when coated using a conventional method. Due to the occurrence of backsparking the coated surface shows irregularities 132, e.g. cracks or openings.

Figure 5 shows a detail of stent 124 when coated using the method of the invention. The resulting coating shows an even surface, without cracks or openings.

The present invention is by no means limited to the above described preferred embodiments thereof. The rights sought are defined by the following claims, within the scope of which many modifications can be envisaged.

CLAIMS

1. Method for depositing a coating material on a medical device, comprising the steps of:
   - providing the medical device in a spray chamber;
   - providing the coating material to an electrospray nozzle;
   - applying an electric potential to the nozzle; and
   - ejecting the coating material from the electrospray nozzle towards the medical device for coating a surface of the medical device;

   characterized in that the method further comprises
   - providing ions in the spray chamber to subject said surface to be coated to ions to prevent the formation of holes or cracks in the deposited coating material.

2. Method according to claim 1, comprising depositing multiple layers of the coating material on the medical device.

3. Method according to any of the claims 1 or 2, wherein the coating material is deposited evenly over the surface of the medical device.

4. Method according to claim 1, 2 or 3, wherein the coating material comprises a combination of a drug and a polymer.

5. Method according to claims 3 and 4, wherein the drug is distributed evenly over the surface of the medical device for homogeneous release of the drug during use of the medical device.

6. Method according to any of the preceding claims, wherein both positive and negative ions are provided.

7. Method according to any of the claims 1-6, wherein the medical device is electrically insulating.

8. Method according to any of the claims 1-6, wherein the medical device is electrically conducting and electrically insulated from ground.

9. Method according to any of the claims 1-8, the step of providing the ions in the spray chamber comprising: providing the medical device in an atmosphere comprising the ions.

10. Method according to any of the claims 1-8, the step of providing the ions in the spray chamber comprising: creating a flow or bundle of ions directed towards the medical device.

11. Method according to any of the preceding claims, wherein the ions are provided before ejecting the coating material towards the medical device.

12. Method according to any of the preceding claims, wherein the material comprises a polymer such that the ejected material forms fibers by means of electrospinning.

13. Method according to any of the preceding claims, wherein the material comprises a polymer selected from the group comprising PLA, PLLA, PLGA, TPU, Nylon and PEBAX.

14. Depositing system configured for performing the method for depositing a coating material on a medical device comprising:
- an electrospray nozzle for ejecting the coating material; and
- a voltage source connected to the electrospray nozzle for applying an electric potential to the electrospray nozzle;
- a spray chamber for placing the target medical device therein;

characterized in that the device further comprises
- an ion source arranged to provide ions in the spray chamber.

15. Medical device provided with layers of a coating material deposited on the device, wherein the coating is free of holes or cracks and the coating material comprises a combination of a drug and a polymer.

16. Medical device obtainable using the method of any of the claims 1-13.

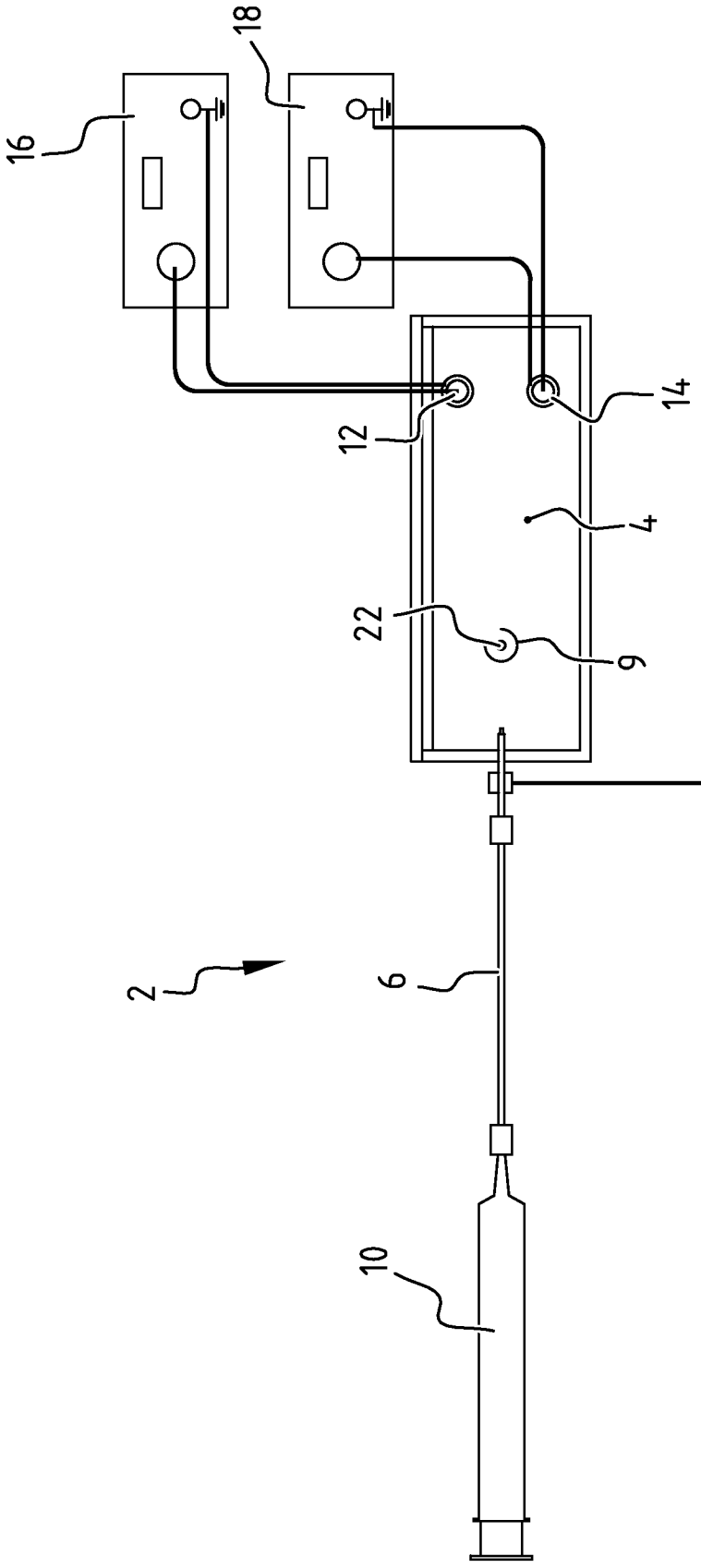

FIG. 1

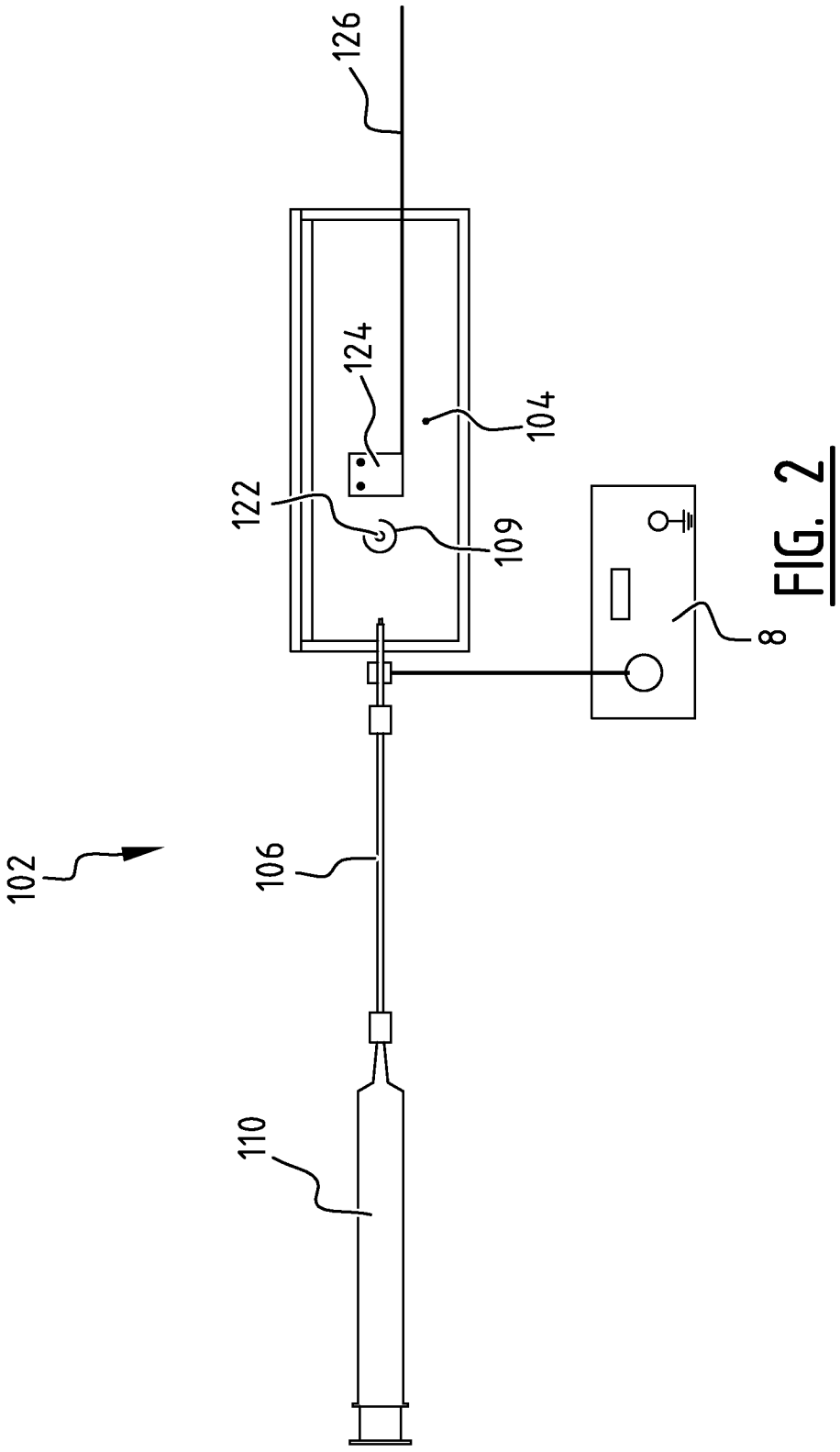

FIG. 2

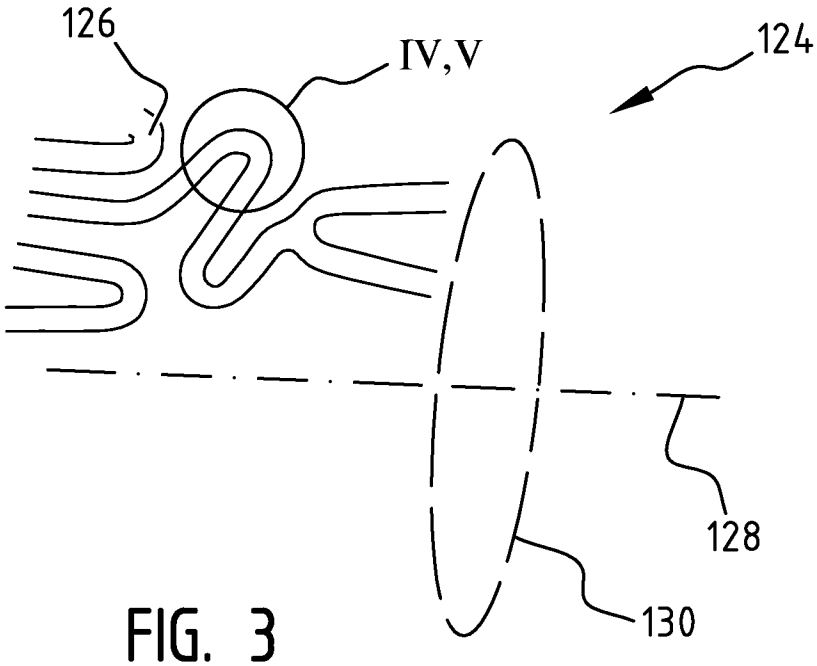

FIG. 3

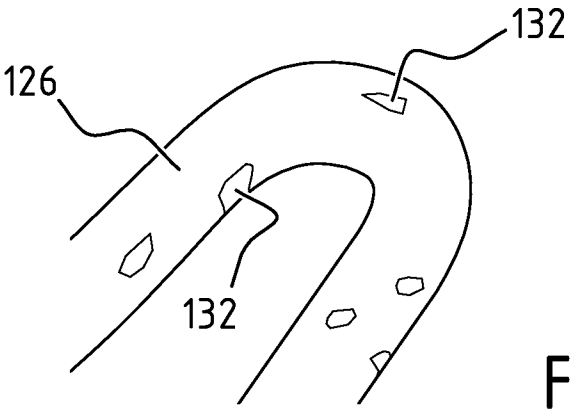

FIG. 4

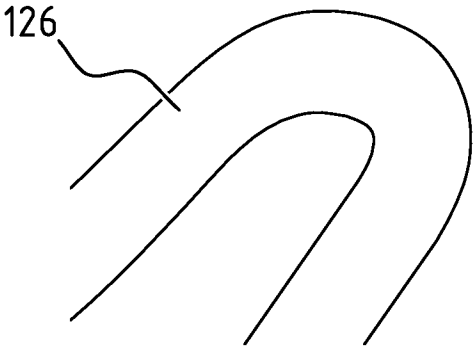

FIG. 5

INTERNATIONAL SEARCH REPORT

International application No
PCT/NL2014/050324

A. CLASSIFICATION OF SUBJECT MATTER
INV. B05D1/04
ADD. B05B5/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
B05D B05B

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	GB 1 493 285 A (ALFO AG; GEMA AG) 30 November 1977 (1977-11-30) page 2, left-hand column, line 64 - page 3, right-hand column, line 94; figures	1,6-14, 16 2-5
X	EP 0 437 383 A1 (RENAULT S.A. [FR]) 17 July 1991 (1991-07-17) column 2, line 6 - column 3, line 54; figures	1-3,5-8, 10,14
X	US 3 323 934 A (POINT, MARCEL A. R.) 6 June 1967 (1967-06-06) column 4, line 29 - column 5, line 44; figure 2	1-3,5,9, 10,14
X	US 3 130 067 A (BULGIN, DOUGLAS) 21 April 1964 (1964-04-21) the whole document	1-3,7, 9-11,14

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
22 July 2014	30/07/2014

Name and mailing address of the ISA/	Authorized officer
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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/NL2014/050324

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 103 44 135 A1 (FORSCHUNGSZENTRUM KARLSRUHE GMBH [DE]) 4 May 2005 (2005-05-04) paragraph [0042] - paragraph [0055]; figure 5	1-3,7, 9-11,14
X	EP 1 595 845 A1 (RIKEN [JP]; FUENCE CO LTD [JP]) 16 November 2005 (2005-11-16) paragraph [0063] - paragraph [0078]; figures 1-8	1-3,7, 9-11,14
X	WO 93/07465 A1 (TSI INC [US]) 15 April 1993 (1993-04-15) page 8, line 22 - page 17, line 31; figures	1-3, 9-11,14
X	US 2006/267156 A1 (MEAGLEY, ROBERT P. [US]) 30 November 2006 (2006-11-30) paragraph [0020] - paragraph [0025]; figure 4	1,7,14
X	WO 2009/046093 A2 (EXOGENESIS CORP [US]; KIRKPATRICK SEAN R [US]; SVRLUGA RICHARD C [US]) 9 April 2009 (2009-04-09)	16
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