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(71) Applicants: **FONDAZIONE RIMED** [IT/IT]; Via Bandiera 11, 90133 Palermo (IT). **UNIVERSITY OF PITTSBURGH - OF THE COMMONWEALTH SYSTEM OF HIGHER EDUCATION** [US/US]; 1ST Floor Gardner Steel Conference Center, 130 Thackeray Avenue, Pittsburgh, Pennsylvania 15260 (US).

(72) Inventors: **CICERONE, Carlo**; c/o Fondazione RIMED, Via Bandiera 11, 90133 Palermo (IT). **D'AMORE, An-**

tonio; c/o Fondazione RIMED, Via Bandiera 11, 90133 Palermo (IT). **FAZZARI, Marco**; C/O UNIVERSITY OF PITTSBURGH - OF THE COMMONWEALTH SYSTEM OF HIGHER EDUCATION, 1ST Floor Gardner Steel Conference Center, 130 Thackeray Avenue, Pittsburgh, Pennsylvania 15260 (US). **FREEMAN, Bruce A.**; C/O UNIVERSITY OF PITTSBURGH - OF THE COMMONWEALTH SYSTEM OF HIGHER EDUCATION, 1ST Floor Gardner Steel Conference Center, 130 Thackeray Avenue, Pittsburgh, Pennsylvania 15260 (US). **KIM, Seungil**; C/O UNIVERSITY OF PITTSBURGH - OF THE COMMONWEALTH SYSTEM OF HIGHER EDUCATION, 1ST Floor Gardner Steel Conference Center, 130 Thackeray Avenue, Pittsburgh, Pennsylvania 15260 (US). **MC-KEEL, Daniel T.**; C/O UNIVERSITY OF PITTSBURGH - OF THE COMMONWEALTH SYSTEM OF HIGHER EDUCATION, 1ST Floor Gardner Steel Conference Center, 130 Thackeray Avenue, Pittsburgh, Pennsylvania 15260 (US). **SCHOPFER, Francisco Jose**; C/O UNIVERSITY OF PITTSBURGH - OF THE COMMONWEALTH SYSTEM OF HIGHER EDUCATION, 1ST Floor Gardner Steel Conference Center, 130 Thackeray Avenue, Pittsburgh, Pennsylvania 15260 (US). **WAGNER, William R.**;

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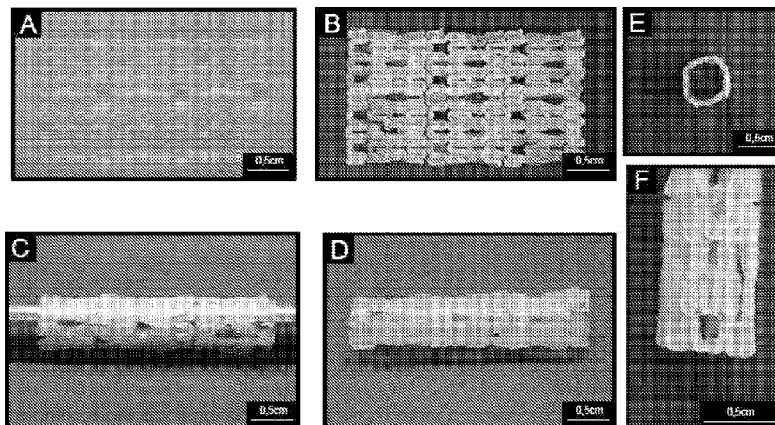


Fig. 1

(57) Abstract: The object of the present invention is an implantable medical device comprising a biodegradable shape-memory polymeric material, wherein said polymeric material is a polyurethane copolymer. Furthermore, the invention relates to the implantable medical device comprising at least one drug or a molecule with pharmacological activity.

C/O UNIVERSITY OF PITTSBURGH - OF THE COMMONWEALTH SYSTEM OF HIGHER EDUCATION,
1ST Floor Gardner Steel Conference Center, 130 Thackeray
Avenue, Pittsburgh, Pennsylvania 15260 (US).

(74) **Agent:** **DELBARBA, Andrea** et al.; C/O BUGNION
S.P.A., Viale Lancetti 17, 20158 Milano (IT).

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DESCRIPTION

IMPLANTABLE MEDICAL DEVICE

FIELD OF THE INVENTION

The object of the present invention is an implantable medical device comprising a shape-memory polymeric material.

5 BACKGROUND

Coronary heart disease (CHD) is a disorder that affects the arteries of the heart (coronary arteries), which narrow (stenosis) and reduce the blood flow to the cardiac muscle (myocardium). Coronary heart disease is subject to risk factors such as arteriosclerosis.

10 When the compromised physiological perfusion of a blocked or stenotic blood vessel is restored, extension of the time window between the onset of symptoms and surgery is an important factor, regardless of the different therapeutic approach adopted. While severe and chronic pathologies result in the grafting of a coronary artery bypass graft (CABG) with
15 autologous blood vessels or synthetic prosthetic devices, the lesions in the initial phase are generally treated with thrombolytic therapy or angioplasty, including percutaneous transluminal coronary angioplasty (PTCA). PTCA is a surgical strategy that consists of compressing a stenotic plaque against the walls of the artery by introducing and expanding a balloon
20 catheter at the blockage site.

An increasing number of randomised trials has established that PTCA is the most efficient treatment for acute myocardial infarction (AMI) if compared to intravenous thrombolytic therapy. PTCA is, in fact, capable of reducing the most serious adverse events in the short and long term, such
25 as death, non-fatal myocardial infarction, recurrent ischemia, non-fatal reinfarction or stroke. At the same time, even though a successfully implemented PTCA provides myocardial revascularisation, this procedure often needs to be repeated over time, postponing the coronary surgery to a later time. Although a previous PTCA does not alter the outcome of a

subsequent CABG, the average cost of all these heart surgery procedures contributes to increasing the overall financial burden of the treatment.

Regardless of these considerations, angioplasty continues to be the gold standard for most lesions in the initial phase.

5 Bare metal stents (BMS) represented the first generation of devices used in angioplasty. The key concept of BMS was restoring perfusion, expanding and mechanically and permanently supporting the stenotic lumen of a blood vessel through radial forces. The stent was deployed with a minimally invasive approach, positioned and expanded with a balloon
10 actuated by a catheter tip. Although this technique has demonstrated efficacy in the short term, these devices are affected by serious problems, including a significant rate of regrowth of the tunica intima (inner layer) of the blood vessels (restenosis) within one year after positioning of the stent. The introduction of drug-eluting stents (DES) capable of delivering
15 antiproliferative drugs, such as sirolimus and paclitaxel, represents the subsequent incremental evolution and has improved the efficacy of the stents.

Given their efficacy, DES are currently used in over 70% of coronary surgeries in the United States. Various comparative studies between BMS
20 and DES have demonstrated a significantly lower restenosis rate and an angiographic advantage in favour of DES. Various studies have assessed the safety and efficacy of sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) respectively and have reported that both these categories of DES are characterised by a lower rate of angiographic and
25 clinical restenosis if compared with BMS up to 4 years. Despite this advantage, DES are also associated with various undesired effects, including: limiting the natural process of re-endothelialization, presence of persistent fibrin deposits, stent thrombosis, under-expansion, reduction of the endothelial function, lower rate of neointimal coverage and long-term
30 dependency on anti-platelet therapy.

Drug-Eluting Balloons (DEB) represent, in turn, a treatment for coronary disease capable of overcoming most of the limitations of DES. DEB are based on a different concept of release of the drug, which occurs locally and without the prolonged mechanical support over time that is provided
5 by the rigid structure of a BMS or a DES. Release of the drug and the antiproliferative activity, which aims to inhibit the proliferation of smooth muscle cells, are maximised at the moment when the balloon is actuated, when the acute inflammatory response and platelet activation start the restenosis mechanism. This concept offers a series of clinical advantages
10 compared to PTCA, BMS and DES, including:

- (A) lower restenosis rates compared to conventional PTCA therapy;
- (B) elimination of the risks of migration of the device and damage to the endothelium, which are generally associated with a permanent implant;
- (C) stand-alone and/or possibility of being combined with the BMS implant;
- 15 (D) instantaneous and brief release of the drug compared to the use of a polymer or a degradable metal that can cause major inflammatory reactions;
- (E) reduction of the duration of antiaggregant treatment;
- (F) administration of the drug in a spatially uniform manner on the lumen of
20 the blood vessel;
- (G) potential use on lesions that, due to complex anatomies such as bifurcations or blood vessels of small diameter, cannot be treated with a semi-rigid metal stent;
- (H) furthermore, two recent randomised trials have demonstrated the
25 safety and efficacy of DES in popliteal and femoral arteries.

Despite this, a series of critical issues remain unresolved in DEB technology, including:

- (A) efficacy with drugs other than paclitaxel, repeatability of the spatial distribution and kinetics of release of the drug, excess quantity of drug on
30 the balloon with consequent systemic toxicity;

(B) efficacy as an additional therapy to BMS in the case of a lower quality of angioplasty to the standard;

(C) almost 30% of patients given a DEB require the implanting of BMS when the results are not favourable, and this compromises the possibility

5 of using DEB again in the case of further lesions;

(D) Although adoption of the DEB for peripheral arterial diseases has been partially supported by studies, further randomised clinical trials are necessary to assess the technology;

(E) It is necessary to demonstrate the advantage of the DEB compared to
10 the DES for intracoronary in-stent restenosis (ISR);

(F) Since DES can be implanted after an unsuccessful DEB treatment, the two technologies need to be further developed in order to be compatible.

There is therefore clearly a need to develop a new device that is capable of reducing the excessive quantity of drug that is administered with a
15 conventional DEB and that allows the major inflammation associated with the metal of a DES to be reduced, while continuing to provide a mechanical support after its deployment, and that allows access to anatomically complex lesions.

20 **SUMMARY OF THE INVENTION**

A first aspect of the present invention relates to an implantable medical device comprising a biodegradable shape-memory polymeric material, wherein said polymeric material is a polyurethane copolymer. Preferably, the device consists of a polyurethane copolymer.

25 The implantable medical device is preferably a stent or a polymeric film.

Preferably, the polymeric material has a glass transition temperature (T_g) of between 32°C and 42°C, preferably between 35°C and 39°C.

In one embodiment, the implantable medical device comprises at least one drug or a molecule with pharmacological activity. Preferably, said at least
30 one drug or molecule with pharmacological activity comprises at least one -NO₂ group.

Preferably, said at least one drug or molecule with pharmacological activity that comprises at least one -NO₂ group is a nitrated fatty acid (NO₂-FA).

In one embodiment, the at least one nitrated fatty acid is selected from: nitro-oleic acid (NO₂-OA), nitro-linoleic acid (NO₂-LA), nitro-conjugated
5 linoleic acid (NO₂-cLA), nitro-arachidonic acid (NO₂-AA) and combinations thereof. Preferably, said NO₂-FA is selected from: 10-nitro-oleic acid (10-NO₂-OA or CXA-10), 9-nitro-oleic acid (9-NO₂- OA), 8-nitro oleic acid (9-NO₂- OA), 7-NO₂-nonadec-7-enoic acid, 5-NO₂-eicos-5-enoic acid, 6-NO₂-eicos-5-enoic acid, 9-nitro-octadeca-9,11-dienoic acid, 12-nitro-octadeca-
10 9,11-dienoic acid, 9-nitro-12-(nitrooxy)octadec-10-enoic acid, and 12-nitro-9-(nitrooxy)octadec-10-enoic acid.

In one embodiment, said at least one drug is encapsulated in a polymeric particle for the controlled release of said at least one drug.

Preferably, the polymeric particle is a synthetic polymer, more preferably
15 selected from: polylactic-co-glycolic acid (PLGA), polylactic acid (PLA), polyglycolic acid (PGA), polycaprolactone acid (PCL), poly-sebacic acid (SA) and combinations thereof. More preferably, said synthetic polymer is PLGA or from PLA, preferably from PLGA.

A second aspect of the present invention relates to a process for preparing
20 an implantable medical device.

In one embodiment, the process comprises the steps of:

- a) providing a polymeric material;
- b) introducing the polymeric material into a mould to form structural elements, more preferably curved structural elements,
- 25 c) arranging the structural elements obtained in step b) so as to form a wall that is cylindrical in shape, preferably the structural elements are positioned on a rod, more preferably on a metal rod, wherein the structural elements are in contact with each other through at least one end thereof; and optionally
- 30 d) welding the ends of the structural elements so as to obtain the polymeric stent. Preferably, step a) comprises at least a sub-step a1) of

incorporating at least one drug or molecule with pharmacological activity into the polymeric material, said at least one drug or molecule with pharmacological activity more preferably comprising at least one -NO₂ group.

5

DEFINITIONS

In the context of the present invention, the expression "glass transition temperature" (T_g) means the temperature at which the amorphous domains of a polymer pass from the vitreous brittle state to the deformable solid or ductile shape at atmospheric pressure. In other words, the T_g corresponds to the temperature at which the start of the segmental movement of the polymer chains occurs. When an amorphous or semi-crystalline polymer is exposed to an increasing temperature, the coefficient of expansion and the heat capacity of the polymer both increase as the temperature increases, indicating a greater molecular movement. With the increase in temperature, the effective molecular volume of the sample remains constant, therefore a higher coefficient of expansion indicates an increase of the free volume associated with the system and therefore a greater freedom of movement of the molecules.

In the context of the present invention, the term "shape-memory material" means a material capable of recovering its initial shape after reaching a predetermined temperature.

In the context of the present invention, the term "stent" means a cylindrical dilator that is introduced into the organs with lumen and is made to expand until its diameter is equal to the one of the lumen. In this manner it is possible, for example, to reduce a stenosis, exclude an aneurysm or keep the lumen open.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows A) the mould used to obtain a polymeric film with incorporated ribs to model the structural elements of the stent. B) The

structural elements are removed from the film obtained in the previous step; the geometry of the stent is dictated by the geometry of the ribs. C) The samples in B are rolled around a steel rod and arranged in a cylindrical model obtained by connecting the free edges with solvent welding. D) Processed stents. Longitudinal section E) and G).

Figure 2 shows the diagram of the process used for formation of the shape-memory stent. The initial outer diameter (OD) of the stent is 4.8 mm (A). Left for 24 hours at 37°C, the stent expanded to reach an outer diameter of 4.9 mm, which is the activated configuration (B).

Subsequently, the sample was kept for 24 hours at - 2°C inside a glass test-tube, the inner diameter of which was 3.8 mm (C). When it was released from the test-tube, the stent remained in the rest configuration with an OD of 3.9 mm at 15 minutes from the release at ambient temperature (D, E). In conclusion, the stent was maintained for 24 hours at 37°C. The final OD was 4.7 mm (F). The shape-memory stent showed a recovery of 96% at 37 °C = 4.7 (final shape) /4.9 (shape 1 - activated).

DETAILED DESCRIPTION OF THE INVENTION

A first aspect of the present invention relates to an implantable medical device formed of at least one polymeric material.

In one embodiment, said implantable medical device is a stent or a polymeric film.

Preferably, the implantable medical device has a shape defined by at least one wall that is formed or consists of the polymeric material. In one embodiment, said at least one wall comprises at least one opening, preferably a plurality of openings.

In a preferred embodiment, the implantable medical device has a tubular body. Preferably, the implantable medical device may include a network of interconnected structural elements. Figure 1D shows an example of a three-dimensional view of the device. The implementations described here are not limited to the device model shown in the Figure. 1.

The embodiments described here are easily applicable to other models and to other implantable medical devices, including, but not limited to, self-expanding stents, balloon-expandable stents, stent-grafts and grafts. The structural model of the device may have virtually any design.

- 5 In one embodiment, the device is obtained from a tube or from a polymeric sheet, by laminating and gluing the sheet to form the tube. The tube or the polymeric sheet may be formed by means of extrusion or injection-moulding.

Preferably, the device is manufactured starting from injection of the
10 polymeric material into a mould, to form the structural elements, more preferably curved structural elements, as shown in Figures 1 A and B. Preferably, the structural elements are arranged to form a wall that is cylindrical in shape, and are preferably positioned on a metal rod, as shown in Figure 1C.

- 15 In one embodiment, the device is obtained by means of welding of the ends of the structural elements with techniques known to a person skilled in the art, for example, thanks to solvent welding.

In a further embodiment, the device is obtained through injection of the polymeric material into a cylindrical mould. Preferably, when the device is
20 obtained through injection of the polymeric material into the cylindrical mould, no welding step is envisaged.

The device may therefore be attached to a balloon or to a catheter in order to be introduced into the bodily lumen.

In a preferred embodiment of the invention, the device consists at least
25 90% by weight, more preferably at least 95%, of the polymeric material.

In other words, the present invention relates to a device comprising a polymeric material with shape-memory properties so as to be self-expandable and therefore atraumatic for the vascular lumens of the body. The device may be used inside the vascular system as a means for
30 preventing restenosis of the blood vessels or as a modifier of the

intravascular flow useful in the treatment of coronary pathologies or conditions, aneurysms of the cerebral or abdominal aorta.

In one embodiment, the polymeric material is at least one shape-memory polymer.

- 5 In one embodiment, the polymeric material is at least a biodegradable and/or bioabsorbable and/or bioerodible or biostable polymer. The term biostable indicates a non-biodegradable polymer. The terms biodegradable, bioabsorbable and bioerodible are used interchangeably and refer to polymers that are able to be completely degraded and/or
- 10 eroded when exposed to bodily fluids such as blood and can be gradually reabsorbed, absorbed and/or eliminated by the organism. The processes of degradation and absorption of the polymer may be caused, for example, by hydrolysis and metabolic processes.

- In a preferred embodiment of the invention, the polymer is a
- 15 biodegradable polymer.

In one embodiment, the polymeric material comprises or consists of a copolymer, preferably a polyurethane copolymer.

- In one embodiment, the polymer is obtained through polymerisation in solution or through polymerisation in a liquid phase. Preferably, in
- 20 polymerisation in solution, in each of the synthesis phases, the reactive components involved in the polymerisation reaction are dissolved in a solvent. Preferably, in polymerisation in a liquid phase, the reactions may occur, for example, in a mixing device such as an extruder.

- In one embodiment, the polyurethane copolymer is obtained by means of
- 25 a reaction between a flexible or elastomeric segment and a diisocyanate. Preferably, the flexible or elastomeric segment is a diol.

- In one embodiment, the flexible or elastomeric segment is a polyol preferably selected from: polyester, polyether or polycarbonate. Preferably, the flexible or elastomeric segment is made to react in a
- 30 solution with a diisocyanate in the presence of a catalyst to form the polyurethane copolymer. In one embodiment, the reaction occurs at

ambient temperature, preferably between 20 and 30°C or at a temperature higher than ambient temperature, preferably in a suitable solvent and in the presence of a catalyst and/or a suitable initiator.

The resistance, tenacity and degradation rate of the polymeric material
5 and of the device can be controlled by the length of the chain and by the molar ratio between the diol and the diisocyanate, with techniques known to a person skilled in the art.

The solvents used in synthesis in solution polymerisation of the block copolymer include, by way of example, chloroform, THF, dioxane, toluene,
10 xylene and cyclohexane. The initiators include, by way of example, ethylene glycol, propylene glycol, butandiol and polyethylene glycol. The catalysts used to facilitate synthesis of the block copolymer include, by way of example, stannous octoate and stannous trifluoromethanesulfonate.

15 In one embodiment, the device is formed of a polyurethane or consists of a polyurethane. Preferably, said device has a predetermined shape that, following a deformation, may be recovered after heating above the glass transition temperature (T_g) of the polymeric material.

In one embodiment, the glass transition temperature (T_g) of the polymeric
20 material is between 32°C and 42°C, preferably the glass transition temperature is between 35°C and 39°C.

In other words, said polymer has a glass transition temperature (T_g) and a predetermined shape with an expanded diameter after heating above the glass transition temperature (T_g). Therefore, deforming the polymeric
25 material makes it possible to return said material to its initial shape, thanks to heating of said material above the glass transition temperature (T_g).

In one embodiment, after formation of the device in its expanded configuration with a predetermined shape, when the device is heated above its glass transition temperature (T_g), the device made of shape-
30 memory material passes into a rubbery state and can be compressed to have a reduced diameter and a greater length.

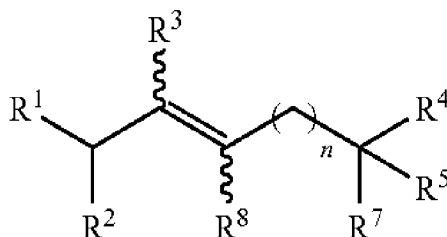
Therefore, for example, the device may be inserted into a catheter or another dispensing system for transport through the blood vessels. The device can therefore be inserted into the blood vessel and manoeuvred into the desired position, mounted on a catheter. Since the device consists
5 of a shape-memory material, it returns to its original shape and dimensions after its temperature has been returned above the T_g . The transfer of heat, given by the heat of the human or animal body into which the device is inserted, ensures that the temperature of the device rises once again above the T_g and that the device returns to a rubbery state to expand
10 radially and retract axially until it reaches the original shape and dimensions, deploying the device in the blood vessel and allowing the catheter to be extracted from the blood vessel.

In one embodiment, the device comprises at least one drug or a molecule with pharmacological activity. In other words, the device described above
15 is loaded with at least one drug. In this embodiment, the device is preferably a stent or a film eluting at least one drug.

Preferably, said at least one drug is present in a concentration between 2% and 40% relative to the weight of the polymer (p/p), more preferably between 8 and 30 % p/p, even more preferably between 10 and 20% p/p.

20 In one embodiment, the drug can comprise a nitroalkene that includes at least one carbon-carbon double bond and one nitro group. Preferably, this nitroalkene is a nitrated fatty acid, selected from the compound of Formula I, Formula II, Formula III, of Formula IV, of formula V, of Formula VI, of Formula VII, of Formula VIII and of Formula IX.

The drug is or comprises the compound of Formula I:



:

where R¹ is selected from hydrogen, C₁-C₂₄ alkyl, or C₁-C₂₄ alkynyl; R² is a hydrogen atom; R³ and R⁸ are selected independently from hydrogen,
 5 NO₂, or an electron-donating group from acyl groups, carboxylic acid, an ester, a halogen, a fluoromethyl, a -CN cyano group, sulfonyl, sulfone, sulfonic acid, a primary, secondary or tertiary amine.

When R³ or R⁸ are NO₂, the corresponding R³ or R⁸ is hydrogen;

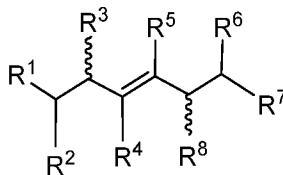
R⁷ and R⁵ are chosen independently from hydrogen, a C₁-C₄ alkyl group
 10 and R⁴ comprises a terminal group of the COOR⁶ type, where R⁶ is hydrogen, or a C₁-C₂₄ alkyl group; where n may be from 1 to 24; and when a nitroalkene such as nitrated fatty acid forms, the molecule must include the NO₂ group.

In several compounds of Formula I: R¹ is an alkyl chain of the C₁-C₂₄ type
 15 and, more specifically, C₃-C₁₄; n goes from 3 to 20; R⁴ is COOH; R⁵ and R⁷ is a hydrogen molecule.

In one embodiment, when R⁴ is -COOH; R⁵ and R⁷ are a methyl group.

In one embodiment in the compound of Formula I, R¹ is a C₁-C₂₄ alkyl and,
 more specifically, C₃-C₂₀; R² is a hydrogen molecule; R³ or R⁸ is NO₂ while
 20 the other R³ or R⁸ is a hydrogen; R⁴ is a -COOH group; R⁵ and R⁷ are hydrogen molecules.

In one embodiment, the drug is or comprises a compound of Formula II:



where R^1 is a hydrogen molecule, C_1 - C_{24} an alkyl, C_1 - C_{24} an alkenyl;

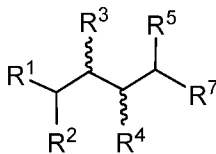
5 R^2 , R^4 , R^5 and R^6 are each a hydrogen molecule;

R^7 is a terminal group of the $R^{10}COOR^9$ type, where R^9 is a hydrogen molecule or a C_1 - C_{24} alkyl chain; R^{10} is $(CH_2)_n$ where n is greater than or equal to 1 and lower than 14. R^3 and R^8 may be independently hydrogen, oxygen, NO_2 , ONO_2 , ONO , ONO or 10- NO_2 -OA or CXA-10, and
 10 at least one of R^3 and R^8 must be NO_2 while the other R^3 or R^8 is hydrogen, ONO , ONO_2).

In several cases, Formula II has R^1 as a C_1 - C_{24} , alkyl chain, with C_3 - C_{20} alkyl;

R^9 is a hydrogen molecule; R^3 is NO_2 and R^8 is ONO_2 or R^8 is NO_2 and R^3
 15 is ONO_2 .

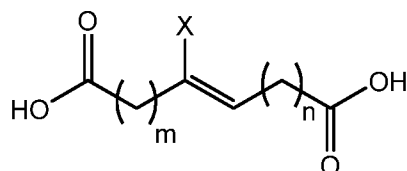
In a further embodiment, the drug is or comprises a compound of Formula III:



20 Where R^1 is a hydrogen molecule, a C_1 - C_{24} alkyl or alkenyl chain; R^2 and R^5 are each a hydrogen group; R^7 is an $R^{10}COOR^9$ terminal group, where R^9 is a hydrogen or a C_1 - C_{24} alkyl chain; R^{10} is $(CH_2)_n$ with n greater than or equal to 1 and lower than 14. R^3 and R^4 may be independently NO_2 , ONO , ONO_2 , NO , 10- NO_2 -OA, where at least R^3 or R^4 must be NO_2 and
 25 the other R^3 or R^4 must be hydrogen, ONO or ONO_2 .

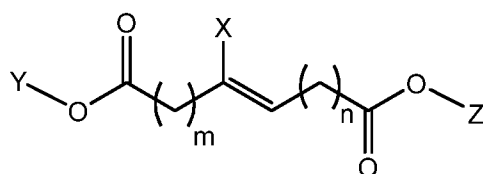
In several cases of the compound of Formula III, R¹ is a C₁-C₂₄ alkyl group, more specifically with alkyl between C₃-C₂₀; R⁶ is a hydrogen molecule; R³ is NO₂ and R⁴ is ONO₂ or R⁴ is NO₂ and R³ is ONO₂.

In another illustrative formula, the drug is or comprises a compound
5 of Formula IV:



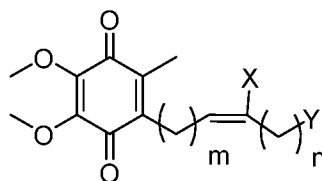
where X is an electron-donating group from an alkyl group, a carboxylic acid, an ester, a halogen, a fluoromethyl, a -CN cyano group, sulfonyl, sulfonic acid, sulfone, or a primary, secondary or tertiary amine or
10 an -NO₂, both m and n go from 1 to 10. In several cases, X is -NO₂.

In a further embodiment, the drug is or comprises a compound of Formula V:



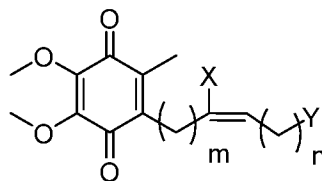
where X is an electron-donor from an alkyl group, a carboxylic acid,
15 an ester, a halogen, a fluoromethyl, a -CN cyano group, sulfonyl, sulfonic acid, sulfone, or a primary, secondary or tertiary amine or an -NO₂; Y and Z are independently hydrogen or alkyl chains from C₁ to C₁₀; m and n go from 1 to 10.

In certain cases, the drug comprises a quinone, as in the following cases:

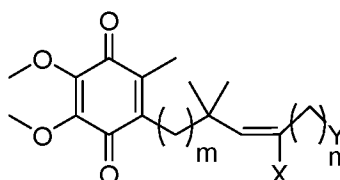


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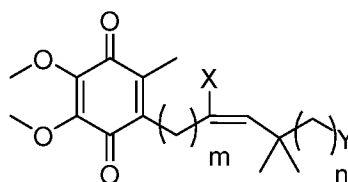
Formula VI,



Formula VII,



Formula VIII, or



Formula IX

where X is an electron-donor. The term “electron-donor” indicates the tendency of a substituent agent to attract valence electrons from surrounding atoms, just as electronegative substituents do with vicinal atoms. Examples of electron-donating groups are the following: aldehyde (-COH), acyl (-COR), carboxylic acid (-COOH), ester (-COOR), halides (-Cl, F, -Br, etc.), fluoromethyl (-CF₃), fluoroalkyl (-CF_nH_{2-n}R), cyano (-CN), sulfoxide (-SOR), sulfonyl (-SO₂R), sulfonate (SO₃R), 1st, 2nd and 3rd ammonium (-NR₃⁺), and nitro (-NO₂) where R may be a hydrogen, methyl, alkyl from C₂ to C₆, alkene or alkyne. In certain cases, the electron-donating groups may have a value of σ (bonding value between valence electrons) of around 0.2, and in certain cases may, on the other hand, form a dipole, or be a nitro, ammonio or sulfonic group. Generally, Y is a terminal group that inhibits enzymatic hydroxylation of the omega-terminal

groups, oxidation and reduction of the chain to which the Y is bonded; m and n may be between 1 and 10. In certain other cases, Y consists of a hydrogen molecule.

In a preferred embodiment of the invention, the drug comprises at least one -NO₂ group. Preferably, said at least one drug is a fatty acid that comprises at least one -NO₂ group, or a nitrated fatty acid (NO₂-FA). In a preferred embodiment, the at least one nitrated fatty acid is selected from nitro-oleic acid (NO₂-OA), nitro-linoleic acid (NO₂-LA), nitro-conjugated linoleic acid (NO₂-cLA) and nitro-arachidonic acid (NO₂-AA). In a preferred embodiment, the fatty acid is nitro-oleic acid (NO₂-OA), preferably selected from: 10-nitro-oleic acid (10-NO₂-OA or CXA-10), 9-nitro-oleic acid (9-NO₂-OA), 8-nitro oleic acid (8-NO₂-OA), 7-NO₂-nonadec-7-enoic acid, 5-NO₂-eicos-5-enoic acid, 6-NO₂-eicos-5-enoic acid, 9-nitro-octadeca-9,11-dienoic acid, 12-nitro-octadeca-9,11-dienoic acid, 9-nitro-12-(nitrooxy)octadec-10-enoic acid, and 12-nitro-9-(nitrooxy)octadec-10-enoic acid.

In this case, the stereochemistry of the carbon-carbon bond in the double bond may have a cis or trans configuration.

In one embodiment, the device comprises a second drug suitable for the treatment or the prevention of a vascular pathology, preferably coronary.

In one embodiment, the at least one drug is mixed with the flexible or elastomeric segment or with the diisocyanate in the reaction to obtain the copolymer as described above. Preferably, the at least one drug is mixed with the flexible or elastomeric segment, preferably with the diol, before the start of the reaction to obtain the copolymer, to obtain a drug-diol solution.

In one embodiment, the drug-diol solution is mixed, preferably through mechanical stirring, in order to obtain particles with a diameter of between 0.1 and 0.8 µm, preferably with a diameter lower than 0.7 µm, even more preferably lower than 0.6 µm.

In a further embodiment, the at least one drug is mixed with polymeric particles for a controlled release of the at least one drug. In other words, the at least one drug, preferably a drug comprising at least one NO₂ group, is encapsulated in a polymeric particle for the controlled release of said at least one drug.

Preferably, said polymeric particle is a microparticle consisting of at least one polymer. Preferably, said at least one polymer is a synthetic polymer, more preferably selected from: polylactic-co-glycolic acid (PLGA), polylactic acid (PLA), polyglycolic acid (PGA), polycaprolactone acid (PCL), poly-sebacic acid (SA) and combinations thereof.

In a preferred embodiment, said polymeric particle is a polymeric microparticle consisting of a PLGA or from PLA, preferably from PLGA.

In a further embodiment, said polymeric particle is a polymeric microparticle consisting of at least one natural polymer known to a person skilled in the art.

In one embodiment, the at least one drug is mixed with the polymeric particles. Preferably, the at least one drug is mixed with at least one solvent, preferably an aqueous solvent, to obtain an aqueous solution. Preferably, the polymeric particles are mixed to obtain an oily solution.

The aqueous solution and the oily solution are preferably mixed with each other to obtain a drug-polymeric particles solution.

In one embodiment, the drug-polymeric particles solution is mixed, preferably through mechanical stirring, in order to obtain particles with a diameter between 5 and 15 µm, preferably with a diameter lower than 12 µm, even more preferably lower than 10 µm.

In one embodiment, the drug-polymeric particles solution is mixed with the polyol to obtain the polymeric material as described in detail above.

The Applicant has developed an implantable medical device, such as for example a stent or a polymeric film with advantageous features. In fact, the polymeric material that characterises the device makes it possible to incorporate at least one drug to be administered, to incorporate

microparticles for the controlled release of drugs, to be mixed with the drug, to mechanically support and anchor itself to the wall of the blood vessel thanks to expansion of the diameter that may be obtained thanks to its shape-memory properties. Furthermore, use of the polymeric material is compatible with conventional techniques of moulding polymers or of knitting and, as such, may be combined with any stent geometry commercially available.

The choice to use and to incorporate into the device at least one drug with an NO₂ group makes it possible to inhibit the production and the gene expression of vasoconstriction mediators and to increase the concentration of nitric oxide (NO) in the blood vessel. In fact, the at least one drug with at least one NO₂ group allows a direct production of NO, an increase of the expression of eNOS and a direct activation of eNOS thanks to the phosphorylation of the serine-1177. In addition, the administration of the at least one drug described above allows a significant improvement of the angiogenesis at local level.

Furthermore, the loaded drug is released through diffusion or degradation of the shape-memory matrix. The release profile can be adjusted by the correlation of the physical-chemical characteristics of the loaded drug, the shape-memory polymer and the release medium.

A second aspect of the present invention relates to a process for preparing an implantable medical device.

In one embodiment, the process comprises the steps of:

- a) providing a polymeric material;
- b) introducing the polymeric material into a mould to form structural elements, more preferably curved structural elements,
- c) arranging the structural elements obtained in step b) so as to form a wall that is cylindrical in shape, preferably the structural elements are positioned on a rod, more preferably on a metal rod, wherein the structural elements are in contact with each other through at least one end thereof; and optionally

d) welding the ends of the structural elements so as to obtain the implantable medical device.

In one embodiment, step d) of welding occurs thanks to solvent welding.

In one embodiment, in step a), the polymeric material is obtained through
5 polymerisation in solution or through polymerisation in a liquid phase.
Preferably, in polymerisation in solution, in each of the synthesis phases,
the reactive components involved in the polymerisation reaction are
dissolved in a solvent. Preferably, in polymerisation in a liquid phase, the
reactions may occur, for example, in a mixing device such as an extruder.

10 In one embodiment, the polymeric material is at least one shape-memory
polymer.

In a preferred embodiment of the invention, the polymer is a
biodegradable polymer.

In one embodiment, the polymeric material comprises or consists of a
15 copolymer, preferably a polyurethane copolymer.

In one embodiment, the polyurethane copolymer is obtained by means of
a reaction between a flexible or elastomeric segment and a diisocyanate.
Preferably, the flexible or elastomeric segment is a diol.

In one embodiment, the flexible or elastomeric segment is a polyol
20 preferably selected from: polyester, polyether or polycarbonate.
Preferably, the flexible or elastomeric segment is made to react in a
solution with a diisocyanate in the presence of a catalyst to form the
polyurethane copolymer. In one embodiment, the reaction occurs at
ambient temperature, preferably between 20 and 30°C or at a temperature
25 higher than ambient temperature, preferably in a suitable solvent and in
the presence of a catalyst and/or a suitable initiator.

The resistance, tenacity and degradation rate of the polymeric material
and of the device can be controlled by the length of the chain and by the
molar ratio between the diol and the diisocyanate, with techniques known
30 to a person skilled in the art.

The solvents used in synthesis in solution polymerisation of the block

copolymer include, by way of example, chloroform, THF, dioxane, toluene, xylene and cyclohexane. The initiators include, by way of example, ethylene glycol, propylene glycol, butandiol and polyethylene glycol. The catalysts used to facilitate synthesis of the block copolymer include, by way of example, stannous octoate and stannous trifluoromethanesulfonate.

In one embodiment, step a) comprises at least a sub-step a1) of incorporating at least one drug or molecule with pharmacological activity into the polymeric material.

- 10 In a preferred embodiment of the invention, the drug is at least one drug, preferably at least a fatty acid that comprises at least one -NO₂ group. Preferably, said at least one drug is a fatty acid that comprises at least one -NO₂ group, or a nitrated fatty acid (NO₂-FA). In a preferred embodiment, the at least one nitrated fatty acid is selected from nitro-oleic acid (NO₂-OA), nitro-linoleic acid (NO₂-LA), nitro-conjugated linoleic acid (NO₂-cLA) and nitro-arachidonic acid (NO₂-AA). In a preferred embodiment, the fatty acid is nitro-oleic acid (NO₂-OA), preferably 10-nitro-oleic acid (10-NO₂-OA or CXA-10), 9-nitro-oleic acid (9-NO₂-OA), 8-nitro oleic acid (9-NO₂-OA), 7-NO₂-nonadec-7-enoic acid, 5-NO₂-eicos-5-enoic acid, 6-NO₂-eicos-5-enoic acid, 9-nitro-octadeca-9,11-dienoic acid, 12-nitro-octadeca-9,11-dienoic acid, 9-nitro-12-(nitrooxy)octadec-10-enoic acid, 12-nitro-9-(nitrooxy)octadec-10-enoic acid.

- 25 In one embodiment, in sub-step a1) the at least one drug is mixed with the flexible or elastomeric segment or with the diisocyanate in the reaction to obtain the copolymer as described above. Preferably, the at least one drug is mixed with the flexible or elastomeric segment, preferably with the diol, before the start of the reaction to obtain the copolymer, to obtain a drug-diol solution.

- 30 In one embodiment, the drug-diol solution is mixed, preferably through mechanical stirring, in order to obtain particles with a diameter of between

0.1 and 0.8 μm , preferably with a diameter lower than 0.7 μm , even more preferably lower than 0.6 μm .

In a further embodiment, in sub-step a1) the at least one drug is mixed with polymeric particles for a controlled release of the at least one drug. In
5 other words, the at least one drug, preferably a drug comprising at least one NO_2 group, is encapsulated in a polymeric particle for the controlled release of said at least one drug.

Preferably, said polymeric particle is a microparticle consisting of at least one polymer. Preferably, said at least one polymer is a synthetic polymer,
10 more preferably selected from: polylactic-co-glycolic acid (PLGA), polylactic acid (PLA), polyglycolic acid (PGA), polycaprolactone acid (PCL), poly-sebacic acid (SA) and combinations thereof.

In a preferred embodiment, said polymeric particle is a polymeric microparticle consisting of a PLGA or from PLA, preferably from PLGA.

15 In a further embodiment, said polymeric particle is a polymeric microparticle consisting of at least one natural polymer known to a person skilled in the art.

In one embodiment, the at least one drug is mixed with the polymeric particles. Preferably, the at least one drug is mixed with at least one
20 solvent, preferably an aqueous solvent, to obtain an aqueous solution. Preferably, the polymeric particles are mixed to obtain an oily solution.

The aqueous solution and the oily solution are preferably mixed with each other to obtain a drug-polymeric particles solution.

In one embodiment, the drug-polymeric particles solution is mixed,
25 preferably through mechanical stirring, in order to obtain particles with a diameter between 5 and 15 μm , preferably with a diameter lower than 12 μm , even more preferably lower than 10 μm .

In one embodiment, the drug-polymeric particles solution is mixed with the polyol to obtain the polymeric material as described in detail above.

A third aspect of the present invention relates to a method for the treatment or prevention of a vascular pathology in an individual. In one embodiment, said pathology is a coronary pathology.

In one embodiment, the method provides for at least one step of
5 implanting the medical device described above in detail in an individual suffering from or at risk of suffering from a vascular pathology, preferably a coronary pathology.

EXAMPLE

10 1. The NO₂-FA is encapsulated in PLGA microparticles.

Microparticles were formulated by means of a double-emulsion process that comprises the mixing of two solutions, one aqueous and the other oily. The drug was mixed in the starting aqueous solution, ensuring a load between 10 and 20%. Mixing took place by means of a vortex to obtain
15 particles with a diameter lower than 10 μm . The combination of the diameter of the particles and the choice of starting polymer, said PLGA, has an effect on the release time of the drug. Once formulated, the microparticles were incorporated into the solution necessary to manufacture the stent itself.

20 2. The drug can be dissolved in the solution for the stent without a microparticle carrier.

A drug-polymer solution was prepared and vortexed to obtain particles with a diameter lower than 0.5 μm . Once the drug-polymer solution had been formulated, it was used in the manufacturing process of the stent
25 itself.

CLAIMS

1. An implantable medical device comprising a biodegradable shape-memory polymeric material, wherein said polymeric material is a polyurethane copolymer.

5

2. The device according to claim 1, wherein the device consists at least 90% by weight of a polyurethane copolymer.

3. The device according to claim 1 or 2, wherein the device is a stent or is
10 a polymeric film.

4. The device according to any one of claims 1-3, wherein the polymeric material has a glass transition temperature (T_g) of between 32°C and 42°C, preferably between 35°C and 39°C.

15

5. The device according to any one of claims 1-4, comprising at least one drug or a molecule with pharmacological activity, wherein said at least one drug or molecule with pharmacological activity comprises at least one -NO₂ group.

20

6. The device according to claim 5, wherein said at least one drug or molecule with pharmacological activity comprising at least one -NO₂ group is a nitrated fatty acid (NO₂-FA).

25 7. The device according to claim 6, wherein the at least one nitrated fatty acid is selected from: nitro-oleic acid (NO₂-OA), nitro-linoleic acid (NO₂-LA), nitro-conjugated linoleic acid (NO₂-cLA), nitro-arachidonic acid (NO₂-AA) and combinations thereof.

30

8. The device according to claim 6 or 7, wherein said NO₂-FA is nitro-oleic acid (NO₂-OA); it is preferably selected from: 10-nitro-oleic acid (10-NO₂-OA or CXA-10), 9-nitro-oleic acid (9-NO₂- OA), 8-nitro oleic acid (9-NO₂-OA), 7-NO₂-nonadec-7-enoic acid, 5-NO₂-eicos-5-enoic acid, 6-NO₂-eicos-5-enoic acid, 9-nitro-octadeca-9,11-dienoic acid, 12-nitro-octadeca-9,11-dienoic acid, 9-nitro-12-(nitrooxy)octadec-10-enoic acid, and 12-nitro-9-(nitrooxy)octadec-10-enoic acid.

9. The device according to any one of claims 5-8, wherein said at least one drug is encapsulated in a polymeric particle for the controlled release of said at least one drug.

10. The device according to claim 9, wherein the polymeric particle is a synthetic polymer, preferably selected from: polylactic-co-glycolic acid (PLGA), polylactic acid (PLA), polyglycolic acid (PGA), polycaprolactone acid (PCL), poly-sebacic acid (SA) and combinations thereof.

11. A process for preparing an implantable medical device, comprising the steps of:

- a) providing a polymeric material;
 - b) introducing the polymeric material into a mould to form structural elements, preferably curved structural elements,
 - c) arranging the structural elements obtained in step b) so as to form a wall, preferably cylindrical in shape,
 - wherein the structural elements are in contact with each other through at least one end thereof; and optionally
 - d) welding the ends of the structural elements so as to obtain the implantable medical device,
- wherein the polymeric material is a polyurethane copolymer.

12. The process according to claim 11, wherein step a) comprises at least a sub-step a1) of incorporating at least one drug or molecule with pharmacological activity into the polymeric material, said at least one drug or molecule with pharmacological activity preferably comprising at least one -NO₂ group.

13. The process according to claim 12, wherein said at least one drug or molecule with pharmacological activity is a nitrated fatty acid (NO₂-FA), preferably selected from: nitro-oleic acid (NO₂-OA), nitro-linoleic acid (NO₂-LA), nitro-conjugated linoleic acid (NO₂-cLA), nitro-arachidonic acid (NO₂-AA) and combinations thereof.

14. The process according to claim 12 or 13, wherein said at least one drug or molecule with pharmacological activity is encapsulated in a polymeric particle for the controlled release of said at least one drug, preferably selected from: polylactic-co-glycolic acid (PLGA), polylactic acid (PLA), polyglycolic acid (PGA), polycaprolactone acid (PCL), poly-sebacic acid (SA) and combinations thereof.

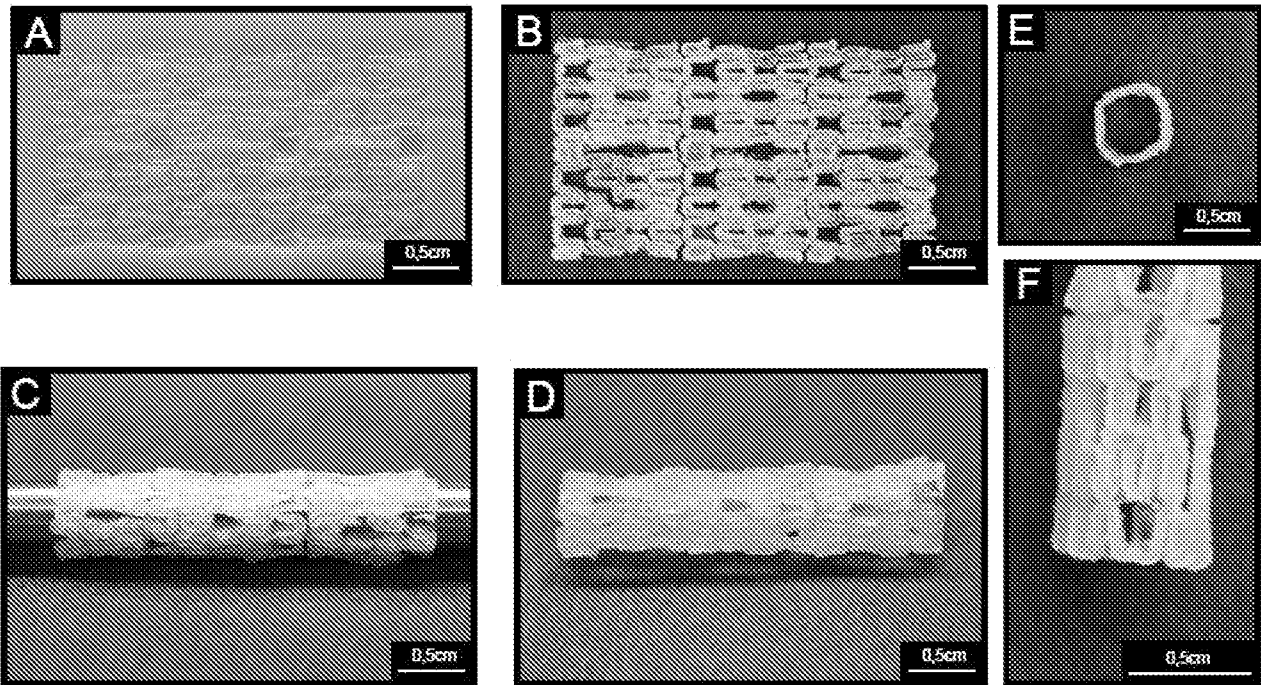


Fig. 1

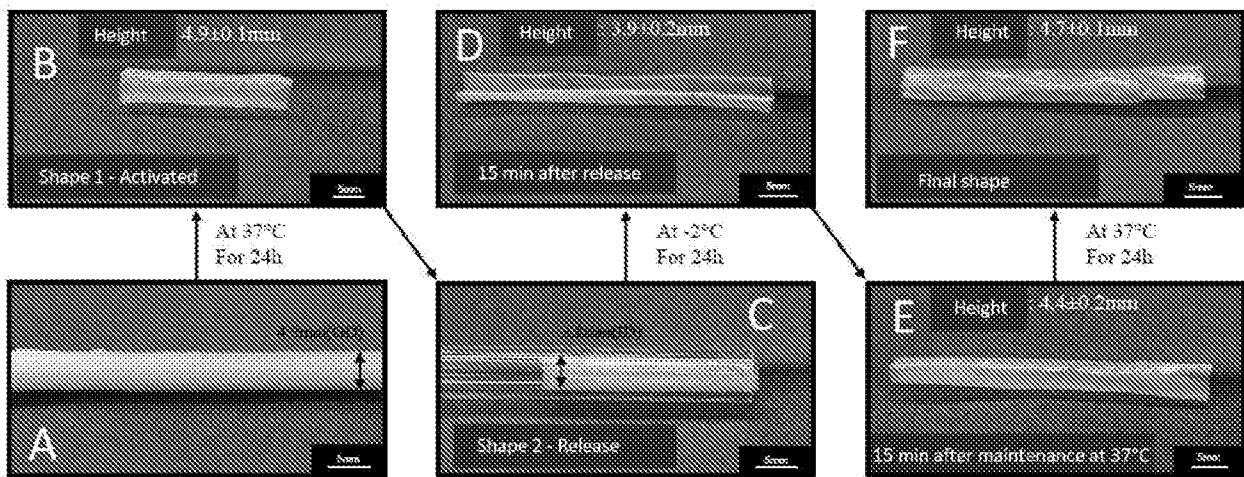


Fig. 2

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2024/055161

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61L27/18 A61L27/26 A61L27/34
ADD.

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)

A61L

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	WEI ZHAO ET AL: "Shape memory polymers and their composites in biomedical applications", MATERIALS SCIENCE AND ENGINEERING C, vol. 97, 1 April 2019 (2019-04-01), pages 864-883, XP055734002, CH ISSN: 0928-4931, DOI: 10.1016/j.msec.2018.12.054	1-4, 9-11,14
Y	the whole document	5-8,12, 13
Y	US 2020/171214 A1 (DIETZ MAX [DE]) 4 June 2020 (2020-06-04) claims 35-60; examples 1-14	5-8,12, 13



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

8 July 2024

Date of mailing of the international search report

19/07/2024

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2

NL - 2280 HV Rijswijk

Tel. (+31-70) 340-2040,

Fax: (+31-70) 340-3016

Authorized officer

Burtan, M

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2024/055161

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2020171214 A1	04-06-2020	EP 3648806 A1	13-05-2020
		US 2020171214 A1	04-06-2020
		WO 2019008192 A1	10-01-2019
