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(54) Title: TUBULAR TISSUE SUPPORT

(57) Abstract: The invention relates to a process to support and/or radially widen hollow organs of human or animal bodies using a tubular tissue support (e.g., a stent) and a tubular tissue support (e.g., a stent) usable in said process.

Tubular Tissue Support

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] The invention relates to a process to support and/or radially widen hollow organs of human or animal bodies using a tubular tissue support (*e.g.*, a stent) and a tubular tissue support (*e.g.*, a stent) usable in said process.

Relevant Background

[0002] A stent is an implant which is introduced into hollow organs, for example into veins or arteries, into bile ducts, or else into the trachea or the esophagus, in order to brace the wall radially outwards and to support it. Examples of use of stents are in coronary vessels for prophylaxis of restenosis after a percutaneous transluminal coronary angioplasty (PTCA).

[0003] Stents can be small grid structures in the form of a tube composed of metal or of polymers, often used in the context of angioplasty, in which structures in vessels are widened. In cancer treatment, stents serve to prevent closure of strictures caused by malignant tumours in respiratory passages, bile ducts or the esophagus, after these have been expanded.

[0004] Stents are usually cylindrical products composed of a type of wire mesh (wire coil design) or of tubes, which may be perforated or unperforated (slotted tube design).

[0005] A stent is subject to various requirements. First, the support has to exert large radial forces on the hollow organ requiring support. Second, the radius of the stent can be temporarily reduced, to permit its easy introduction into a hollow organ without simultaneously injuring the vessel wall or the surrounding tissue.

[0006] Two different technologies are used (Market report "US Peripheral and Vascular Stent and AAA Stent Graft Market" (Frost & Sullivan), 2001) for minimally invasive stent use:

(i) expandable-balloon stents (system composed of balloon, catheter, stent); and

(ii) self-expandable stents (system composed of introductory sheath (protective sheath), catheter, stent).

[0007] Self-expanding stents are generally composed of shape-memory materials (SM material). Shape-memory materials are materials which change their external shape upon exposure to an external stimulus. The materials are, for example, capable of controlled change in their shape when the temperature is increased above what is known as the switching temperature T_{trans}. The shape-memory effect is utilized for "spontaneous" enlargement of the diameter of the stent and/or to fix the stent at the location of use. The shape-memory effect is not a specific property of any of the materials. Rather, it is a direct result of the combination of structure and morphology and of a processing/programming technology.

[0008] In shape-memory materials, a distinction is made between a permanent and a temporary shape. The material is first converted to its permanent shape, using conventional processing methods (*e.g.*, extrusion). The material is then converted, reshaped and fixed into its desired temporary shape. This procedure is also termed programming. It is composed either of a heating, reshaping and a cooling procedure or by shaping at a relatively low temperature. The permanent shape has been held in memory, while the temporary shape is actually present. Heating of the material to a temperature higher than the transition temperature for a change of morphology (switching temperature) triggers the shape-memory effect and thus causes resumption of the permanent shape held in memory.

[0009] The shape-memory effect, which permits controlled alteration in the shape of a material by application of an external stimulus is described, for example, in the overview articles "Shape Memory Alloys," *Scientific American*, Vol. 281, 74- 82 (1979) and *Angew. Chem.*, 114, 2138-62 (2002).

[0010] An example of metallic SM materials used is nitinol, an equiatomic alloy composed of nickel and titanium (*see, e.g., J. Appl. Phys.*, 34, 1475 (1963)). However, nitinol cannot generally be used when a nickel allergy is present. The material is moreover very expensive and programmable only by complicated methods; this programming process needs comparatively high temperatures which prevent programming in the body. The SM material is therefore

programmed outside the body (*i.e.*, converted to its temporary shape). After implantation, the shape-memory effect is then triggered and the stent is expanded (*i.e.*, regains its permanent shape). Removal of the stent by again utilizing the shape-memory effect is then impossible.

[0011] In contrast, other metallic stents composed of SM materials, for example those described in U.S. Patent No. 5,197,978, also permit utilization of the shape-memory effect for stent removal. However, production of these metallic materials is very complicated and tissue compatibility is not always ensured. Inflammation and pain patterns can occur because of poor matching of the mechanical properties of the stent.

[0012] In addition metallic stents do not always open and/or close completely and uniformly over their total length and thereby bear the potential risk of injuring the surrounding tissue. Another frequent problem with metallic stents, not only in the vascular sector, is occurrence of restenosis.

[0013] The temporary stent described in U.S. Patent No. 5,716,410 is a spiral composed of a polymeric shape-memory material (SMP material). The SMP material includes an embedded heating wire. The heating wire is connected by way of a catheter shaft to an electrical control unit, the end of the shaft taking the form of a hollow tube pushed over one end of the spiral. If the implanted stent in its expanded, temporary shape is heated above the switching temperature T_{trans}, the diameter of the spiral decreases. The decrease in spiral diameter permits easy removal of the stent. A disadvantage of the spiral structure is that the radial forces are too small to expand tubular cavities. There is the danger of local mechanical pressure-overloading, and in some instances incision into the tissue because the radial forces of the spiral can be distributed merely over a very small area of contact with the tissue. Furthermore, it is difficult to secure the catheter shaft (heating element) to the heating wire of the implanted spiral because first the catheter shaft has to be pushed over one end of the spiral.

[0014] U.S. Patent No. 5,964,744 describes implants, such as tubes and catheters, for the urogenital sector or gastro-intestinal tract composed of polymeric shape-memory materials which comprise a hydrophilic polymer. In an aqueous medium, the material absorbs moisture and thus softens and changes its shape. As an alternative or additionally, the material softens on heating. In the case of the ureteral stent, the effect is utilized in order to flex the straight ends of

the stent at the location of use (*e.g.*, kidneys and bladder). The result is to fix the ureteral stent at the location of use, so that the stent cannot slip during peristaltic movements of the tissue.

[0015] WO 0241929 describes tubular vessel implants with shape memory which are also suitable, for example, as bile duct stents. The material is an aliphatic, polycarbonate-based thermoplastic polyurethane with biostability.

[0016] U.S. Patent No. 6,245,103 describes bioabsorbable, self-expanding stents composed of braided filaments. In U.S. Patent No. 6,245,103 a stent is compressed by applying an external radial force. The stent is mounted on a catheter and is held in a stressed, compressed condition by an outer sheath. When the stent is expelled from this arrangement its diameter spontaneously enlarges because of the resilience of the elastic materials opposed to a shape-memory effect (which is triggered by an external stimulus, *e.g.*, a temperature increase).

[0017] Removal of an expanded stent, as indicated above, is difficult. When the stent has to be withdrawn from a tubular cavity there is a risk that the surrounding tissue will be injured by abrasion, because the stent is too large and/or has sharp edges. The shape-memory effect is therefore also used again to reduce the diameter of the stent when the stent is to be removed. Examples of removable stents composed of metals with shape-memory properties are known (*see, e.g.*, U.S. Patent No. 6,413,273; U.S. Patent No. 6,348,067; U.S. Patent No. 5,037,427; and U.S. Patent No. 5,197,978). Additionally, the shape memory polymer stents for non-vascular or vascular use known from WO 04/110313 can be removed minimal invasively and those from WO 04/110515 are biodegradable.

[0018] Known methods to support and/or radially widen hollow organs of human or animal bodies are still unsatisfactory. The dilatation with a balloon only has a limited rate of healing success, which might be negatively influenced by the short time of approximately 30 to 60 seconds the balloon can be expanded in the hollow organ. After the treatment, the hollow organ and the surrounding muscle fibers often contract again, a process known in the art as recoiling.

[0019] Stents usually do not cause the same problems as occur with balloon dilatation, but nevertheless do not have a fully satisfying healing rate. Whereas balloon dilatation has a healing rate of approximately 50%, the healing rate for stents is approximately 70 to 80%.

[0020] In addition, known stent materials usable in these processes are very restricted in that they need a high stability against the *in vivo* conditions, and have to be perfectly biocompatible. To compensate side effects of the stents, it is often necessary to give drugs orally and/or to embed drugs in the stent which can also cause side effects in turn.

[0021] It is therefore an object of the invention to avoid the disadvantages of known stent systems and, in particular, to find a process to widen hollow organs that has a high healing rate.

[0022] A further object of the invention is a stent based process to widen hollow organs that can use a wide variety of materials for the stent and that has less side effects for the patient than the known methods.

[0023] In general, the invention is directed to a process according to numbered paragraphs 1 to 13 to support and/or radially widen hollow organs of human or animal bodies and to a tubular tissue support according to numbered paragraphs 14 to 19 usable in such a process. This invention and preferred embodiments thereof will be described in the following in detail.

[0024] The invention is directed to a process to support and/or radially widen hollow organs of human or animal bodies, characterized in that it comprises the following steps (i) through (iii) in the given order:

(i) a tubular tissue support (stent) is introduced into one of said hollow organs,

(ii) the tubular tissue support is fixed in the hollow organ; and

(iii) the tubular tissue support is replaced from the position fixed in step (ii) by physical means or by (bio)chemical degradation after a retention period of 1 minute to 6 months.

[0025] Steps (i) and (ii), and in the case that step (iii) comprises a physical replacement also step (iii), are preferably done with minimally invasive techniques.

[0026] Preferably, the retention period is at least 5 minutes, in particular 30 minutes and more preferably 2 hours. If the stent is to be repositioned, the retention period can also be less than 1 minute and is only limited by the time needed to control the position of the stent.

[0027] The preferred maximum retention period is 2 months, in particular 1 month and more preferably 14 days. Very good results can also been achieved with maximum retention periods of 2 days and/or even 8 hours or less. The retention period is preferably selected to be short enough to avoid that the stent grows together with the hollow vessel. A retention period of about 8 hours is also preferable from an economic point of view as it allows for a one day ambulant treatment. If longer retention periods are necessary, it is preferred that the stent have an outer surface that is selected to reduce the tendency of the tissue support to grow together with the hollow organ. Such can be achieved, for example, by coating the tubular device with a material capable to reduce said tendency.

[0028] It has been found that a higher healing rate is achieved if the stent is only used for a short time as described above instead of the long retention times commonly used and that were thought to be necessary to avoid recoiling or restenosis. In most cases, the stents were left in the hollow organ for the whole lifetime of the patient and they grew together with the organ or had irreversibly fixed anchor groups. Only if the side effects of such a stent became too severe was it removed surgically, in most case by conventional (invasive) operation techniques.

[0029] The short retention time of the invention is long enough to avoid recoiling and restenosis, but is short enough to diminish side effects that adversely influence the healing process. Although the inventive process includes an additional removal step, the advantages of the invention overcompensate this effort for many applications.

[0030] Another advantage of the invention is that it does not need to have a long term stability under *in vivo* conditions. As such, it can be produced from a broader range of materials.

Preferably, the materials selected for the invention are less expensive and/or have less side effects than the materials of known stents.

[0031] Even if side effects may be caused by the stent of the invention, such will have minimal or no prohibitive effect for its use in the inventive process because it is possible to give highly potent drugs to the patient that effectively treat said side effects because such drugs only have to be given for a short time (*i.e.*, during stent retention). As an example concerning the risk of thromboses, drugs can be given to the patient that effectively inhibit blood coagulation (and not only acetyl salicic acid (*e.g.*, Aspirin®, ASS®)), that are suitable for long term treatment.

[0032] As discussed above, the process of the invention is less critical than known processes concerning the material of the stent. Nevertheless the stent should have a weak tendency to grow together with the hollow organ because the stent has to be removed according to a preferred embodiment of the invention and should not injure the organ on removal. It has been found to be less harmful, and therefore to be a preferred embodiment if the stent has a closed outer surface and to be particularly preferred if it has a smooth outer surface.

[0033] The same advantages concerning a short retention in step (iii), in particular that the stent does not grow together with the vessel, were found for another preferred embodiment of the invention: during repositioning of the stent to another position in the hollow organ. The repositioning is not only useful for the correction within a few minutes, but may also be used to consecutively widen more than one stenosis in the blood vessel without the need to replace the stent or even pull it outwards the patients body. Such is both very economical and also reduces the risk of infection.

[0034] In a preferred process of the invention, the implanted tissue support is heated at the end of step (iii) to a temperature below the transition temperature T_{trans} until softening occurs and then undergoes minimally invasive withdrawal from the hollow organ. Preferably, the softening point of the polymer is below the transition temperature by from approximately 0.5 to approximately 10° C, particularly preferably from approximately 1 to approximately 5° C. For this process it is also possible to make use of polymers which have no or only weak shape-memory properties. According to this process, the diameter of the stent is retained, and therefore also is the

flow of body fluid. As such, the organ is subjected to very little thermal stress because only very slight heating of the stent is sufficient for softening to occur. For the purposes of the process, the stents are generally composed of one or more polymeric hydrocarbons, particularly of elastomers. For example, polymers can be used from the urethanes, polyethers, polyesters, polycarbonates, and polyamides series. The polymers can also have shape-memory properties (SMP materials).

[0035] In another preferred embodiment of the invention, the tissue support is reshaped at the end of step (iii) before replacement from the position determined in step (ii). The change in shape of the stent is done in a way to facilitate its removal, namely a decrease in radius and preferably via a shape memory effect. A stent useful for this preferred embodiment is described in WO 04/110313 (pp. 5-30) which is expressly incorporated herein by reference in its entirety .

[0036] In a further preferred embodiment of the invention, the stent is degradable, in particular biodegradable. The stent useful in this embodiment may only degrade to a certain extend during step (iii) and may also have sufficient stability for the whole time, so that is has to be removed or can be repositioned in the above described way. Such a stent is composed only of a different kind of material without changing the principal handling described above. On the other hand, it is particularly preferred in the embodiment using a degradable stent, if the degradation of the stent is essentially completed during the duration of step (iii) and therefore no physical removement is necessary. In the context of the invention essentially completed means, that the mass of the stent has reduced to less than approximately 50 weight-% (wt-%) of the original mass, preferably less than approximately 90 wt-% and particularly preferred to less than approximately 95 wt-% of the original mass. The material of the stent should be selected to avoid side effects for the patient that might be caused by the degradation products. In addition it should be degraded without separation of macroscopic parts. A stent useful for this preferred embodiment is described in WO 04/110515 (pp. 6-26), in the examples and the claims, that is herewith incorporated by reference.

[0037] The hollow organ treated according to the invention can be any organ where a stent can be applied usefully, and therefore can be vascular or non-vascular. The advantages of

the invention, in particular the high healing rate and the reduction of side effects, are particularly pronounced for the treatment of blood vessels, in particular coronary vessels.

[0038] The stents usable in the process preferably include a polymer and, in particular, preferably include a polymer in the form of shape-memory material (shape memory polymer, SMP). For the purposes of the invention, the polymers preferably can be thermoplastics, blends and/or networks. Composites composed of a polymer, in particular a SMP, with inorganic particles, filaments, wires or grids are also suitable.

[0039] That the stents usable in the process include a polymer, in particular a SMP, means that the stents are on the one hand composed of a polymer, in particular a SMP, but on the other hand the stents can also comprise an underlying structure composed for example of a plastic or metallic material, embedded or coated with an SMP material. The underlying structure preferably is made of a biodegradable material, in the case of metallic materials (*e.g.*, of biodegradable metals such as magnesium or magnesium alloys).

[0040] Stents comprising polymer materials, in particular SMP materials, use the polymer material to determine the mechanical properties of the stent. Given that the materials described below are used for this purpose, good tissue compatibility is ensured. Furthermore, as described above, minimally invasive implantation and in turn removal of these stents is facilitated. The polymer materials, in particular the SMP materials, have relatively good processibility and therefore make the production process easier. Finally, the polymer materials, in particular the SMP materials, can also be coated or compounded with other substances, thus permitting further functionalization.

[0041] The uses envisaged for the stents determine their form (*e.g.*, type of surface (microstructuring) or the presence of coatings, etc.).

[0042] For example, the surface of the stent has been formed so as to be compatible with the physiological environment at the location of use, via suitable coating (*e.g.*, hydrogel coating) or surface microstructuring. Parameters such as pH and the number of microbes present have to be considered as a function of the location of use during design of the stent. Endothelial

cells are then used to colonize the surface, and this can be promoted, if appropriate, by suitably modifying the surface (*e.g.*, coating). The result is that growth of endothelial cells gradually covers the stent. Finally, degradation (usually hydrolytic degradation) begins and the stent degrades in contact with soft tissue. Given the degradation behavior described above (particle-free degradation, mechanical stability being unimpaired by degradation over a long period), the stent nevertheless continues to exert the desired supportive action.

[0043] In another alternative, the stent is intended to remain outside the endothelial layer after fitting. Such can be achieved by suitable measures, including selection of the appropriate surface, pigment selection for the SMP materials, etc.

[0044] Suitable materials for the stents of the invention are as follows:

[0045] For the purposes of the invention, SMP materials are materials which by virtue of their chemical and physical structure are capable of carrying out controlled changes of shape. The materials have, besides their actual permanent shape, another shape which can be impressed temporarily on the material. These materials are characterized by two structural features: crosslinking points (physical or covalent) and switching segments.

[0046] SMPs with a thermally induced shape-memory effect have at least one switching segment with a transition temperature in the form of a switching temperature. The switching segments form temporary crosslinking sites which separate on heating above the transition temperature and form again on cooling. The transition temperature can be a glass transition temperature of amorphous regions or a melting point of crystalline regions. The general term T_{trans} is used below for this temperature.

[0047] Above T_{trans}, the material is in the amorphous condition and is elastic. If, therefore, a specimen is heated above the transition temperature T_{trans}, deformed in the flexible condition, and then cooled again below the transition temperature, the chain segments are fixed in the deformed condition by virtue of freezing of degrees of freedom (programming). Temporary crosslinking sites (non-covalent) are formed, making it impossible for the specimen to revert to its original shape, irrespective of whether any external load is applied. On reheating to a temperature

above the transition temperature, these temporary crosslinking sites are again separated and the specimen reverts to its original shape. The temporary shape can be produced again by renewed programming. The precision with which the original shape is regained is termed the recovery ratio.

[0048] In photo-switchable SMPs, the function of the switching segment is assumed by photoreactive groups which can be linked to one another reversibly by irradiation with light. In this case, the programming of a temporary shape and regeneration of the permanent shape takes place by virtue of irradiation with no need for any temperature change.

[0049] In principle, all SMP materials can be used to produce stents. By way of example, reference may be made here to the materials and the production processes described in the following documents: DE 10208211 A1, DE 10215858 A1, DE 10217351 A1, DE 10217350 A1, DE 10228120 A1, DE 10253391 A1, DE 10300271 A1, DE 10316573 A1, EP 99934294 A1 and EP 99908402 A1, each of which applications are expressly incorporated herein by reference in their entirety.

[0050] To produce the stents usable in the process, thermoplastic elastomers can be used. Suitable thermoplastic elastomers preferably feature at least two transition temperatures. The higher transition temperature can be attributed to the physical crosslinking points which determine the permanent shape of the stent. The lower transition temperature at which the shape-memory effect can be triggered can be attributed to the switching segments (switching temperature, T_{trans}). The switching temperature of suitable thermoplastic elastomers is typically from approximately 3 to approximately 20° C above body temperature.

[0051] Examples of thermoplastic elastomers are multiblock copolymers. Preferred multiblock copolymers are composed of blocks (macrodiols) composed of α,ω-diol polymers of poly(ε-caprolactone) (PCL), poly(ethylene glycol) (PEG), poly(pentadecalactone), poly(ethylene oxide), poly(propylene oxide), poly(propylene glycol), poly(tetrahydrofuran), poly(dioxanone), poly(lactide), poly(glycolide) and poly(lactide-ran-glycolide) or of α,ω-diol copolymers of the monomers on which the abovementioned compounds are based, in a range of molecular weight M_n of

from approximately 250 to approximately 500,000 g/mol. Two different macrodiols are linked with the aid of a suitable bifunctional coupling reagent (specifically an aliphatic or aromatic diisocyanate or diacyl chloride or phosgene) to give a thermoplastic elastomer with molecular weights M_n in the range from approximately 500 to approximately 50,000,000 g/mol. In a phase-segregated polymer, a phase with at least one thermal transition (glass transition or melt transition) can be allocated in each of the blocks of the abovementioned polymer, independently of the other block.

[0052] Particular preference is given to multiblock copolymers composed of macrodiols based on pentadecalactone (PDL) and ε-caprolactone (PCL) and a diisocyanate. The switching temperature, in this case a melting point, can be adjusted by way of the block length of the PCL in the range from about approximately 30 to approximately 55° C. The physical crosslinking points for fixing of the permanent shape of the stent are formed by a second crystalline phase whose melting point is in the range from approximately 87 to approximately 95° C. Blends composed of multiblock copolymers are also suitable. Controlled adjustment of the transition temperatures is possible via the mixing ratio.

[0053] It is also possible to use polymer networks to produce the stents. Suitable polymer networks feature covalent crosslinking points and at least one switching segment with at least one transition temperature. The covalent crosslinking points determine the permanent shape of the stent.

[0054] To produce a covalent polymer network, one of the macrodiols described above is crosslinked with the aid of a multifunctional coupling reagent. This coupling reagent can be an at least trifunctional, low-molecular-weight compound, or a polyfunctional polymer. If it is a polymer, it can be a star-shaped polymer with at least three arms, a graft polymer having at least two side chains, a hyperbranched polymer, or a dendritic structure. In the case of the low-molecular-weight (and also the polymeric) compounds, the end groups have to be capable of reaction with the diols. Specifically, isocyanate groups can be used for this purpose (*i.e.*, to make polyurethane networks).

[0055] Particular preference is given to amorphous polyurethane networks composed of triols and/or tetrols and diisocyanate. Star-shaped prepolymers, such as oligo[(rac-lactate)-co-glycolate]triol or –tetrol are prepared via ring-opening copolymerization of rac-dilactide and

diglycolide in the melt of the monomers using hydroxy-functional initiators, with addition of dibutyltin(IV) oxide (DBTO) as catalyst. Initiators used for the ring-opening polymerization reaction are ethylene glycol, 1,1,1-tris(hydroxymethyl)ethane and pentaerythritol. Oligo(lactate-co-hydroxycaproate)tetrols and oligo(lactatehydroxyethoxyacetate)tetrols and [oligo(propylene glycol)-block-oligo(rac-lactate)-co-glycolate)]triols are produced analogously. The inventive networks can be obtained simply via reaction of the prepolymers with diisocyanate (*e.g.*, with an isomer mixture composed of 2,2,4- and 2,4,4-trimethylhexane 1,6-diisocyanate (TMDI), in asolution such as in dichloromethane followed by subsequent drying).

[0056] The macrodiols described above can moreover be functionalized to give corresponding α,ω-divinyl compounds, which can be crosslinked thermally or photochemically. The functionalization preferably permits covalent linkage of the macromonomers via reactions which give no by-products. This functionalization is preferably rendered available via ethylenically unsaturated units, particularly preferably via acrylate groups and methacrylate groups, particular preference being given to the latter. Specifically, the reaction here to give α,ω-macrodimethacrylates or macrodiacrylates can be carried out via the reaction with the corresponding acyl chlorides in the presence of a suitable base. The networks are obtained via crosslinking of the end-group-functionalized macromonomers. This crosslinking can be achieved by irradiation of the melt, comprising the end-group-functionalized macromonomer component and, if appropriate, a low-molecular-weight comonomer as explained below. Suitable process conditions for this are irradiation of the mixture in the melt, preferably at temperatures in the range from approximately 40 to approximately 100° C, with light whose wavelength is preferably from approximately 300 to approximately 500 nm. An alternative possibility is thermal crosslinking if a corresponding initiator system is used.

[0057] If the macromonomers described above are crosslinked, the products are networks with a uniform structure if only one type of macromonomer is used. If two types of monomer are used, AB-type networks are obtained. These AB-type networks can also be obtained if the functionalized macromonomers are copolymerized with suitable low-molecular-weight or oligomeric compounds. If the macromonomers have been functionalized with acrylate groups or with methacrylate groups, suitable compounds which can be copolymerized are low-

molecular-weight acrylates, methacrylates, diacrylates or dimethacrylates. Preferred compounds of this type are acrylates such as butyl acrylate or hexyl acrylate, and methacrylates such as methyl methacrylate and hydroxyethyl methacrylate.

[0058] The amount of these compounds that can be copolymerized with the macromonomers, based on the network composed of macromonomer and of the low-molecular-weight compound, can be from approximately 5 to approximately 70% by weight, preferably from approximately 15 to approximately 60% by weight. Incorporation of varying amounts of the low-molecular-weight compound takes place via addition of corresponding amounts of compound to the mixture requiring crosslinking. The amount of the low-molecular-weight compound incorporated into the network corresponds to the amount present in the crosslinking mixture.

[0059] The macromonomers to be used according to the invention are described below:

[0060] Networks with varying crosslinking densities (or segment lengths) and mechanical properties can be achieved by varying the molecular weight of the macrodiols. The number-average molecular weight of the macromonomers requiring covalent crosslinking, determined via GPC analysis, is preferably from approximately 2,000 to approximately 30,000 g/mol, preferably from approximately 5,000 to approximately 20,000 g/mol and particularly preferably from approximately 7,500 to approximately 15,000 g/mol. The macromonomers requiring covalent crosslinking preferably have a methacrylate group at both ends of the macromonomer chain. This type of functionalization permits crosslinking of the macromonomers by simple photoinitiation (irradiation).

[0061] The macromonomers are preferably polyester macromonomers, particularly preferably polyester macromonomers based on ε-caprolactone. Other possible polyester macromonomers are based on lactide units, glycolide units, p-dioxanone units and mixtures of these and mixtures with ε-caprolactone units, particular preference being given here to polyester macromonomers having caprolactone units. Other preferred polyester macromonomers are poly(caprolactone-co-glycolide) and poly(caprolactone-co-lactide). The transition temperature can be adjusted by way of the quantitative proportion of the comonomers, as also can the degradation rate.

[0062] The macromonomers to be used according to the invention are particularly preferably polyesters, comprising the crosslinkable end groups. A particularly preferred polyester to be used according to the invention is a polyester based on ε-caprolactone or pentadecalactone, for which the statements made above concerning molecular weight are applicable. This type of polyester macromonomer, functionalized at the ends, preferably with methacrylate groups, can be prepared via simple syntheses known to the person skilled in the art. These networks, ignoring the other substantive polymeric component of the invention, exhibit semicrystalline properties, and their melting point of the polyester component (which can be determined by DSC measurements) depends on the type of polyester component used and is moreover also controllable thereby. This temperature (T_m 1) for segments based on caprolactone units is known to be from approximately 30 to approximately 60° C, depending on the molar mass of the macromonomer.

[0063] One preferred network with a melting point as switching temperature is based on the macromonomer poly(caprolactone-co-glycolide) dimethacrylate. The macromonomer can be reacted as it stands, or can be copolymerized with n-butyl acrylate to give the AB network. The permanent shape of the stent is determined by covalent crosslinking points. The network features a crystalline phase whose melting point is capable of controlled adjustment by way of example via the comonomer ratio of caprolactone to glycolide in the range from approximately 20 to approximately 57° C. The function of n-butyl acrylate as comonomer can by way of example be to optimize the mechanical properties of the stent.

[0064] Another preferred network with a glass transition temperature as switching temperature is obtained from an ABA triblock dimethacrylate as macromonomer, characterized by a central block composed of polypropylene oxide and by end blocks A, composed of poly(rac-lactide). The amorphous networks have a very wide switching temperature range.

[0065] To produce stents with two shapes in memory and which can also be used in the process of the invention, suitable networks have two transition temperatures, an example being interpenetrating networks (IPNs). For example, the covalent network can be based on poly(caprolactone) dimethacrylate as macromonomer; the interpenetrating component can be a

multiblock copolymer composed of macrodiols based on pentadecalactone (PDL) and ε-caprolactone (PCL) and on a diisocyanate. The permanent shape of the material is determined via the covalent crosslinking points. The two transition temperatures (*i.e.*, the melting points of the crystalline phases) can be utilized as switching temperatures for a respective temporary shape. The lower switching temperature T_{trans} 1 can be adjusted by way of the block length of the PCL in the range from about approximately 30 to approximately 55° C. The upper switching temperature T_{trans} 2 is in the range from approximately 87 to approximately 95° C. SMP materials with two or more temporary shapes have been disclosed in U.S. Patent No. 6,388,043.

[0066] It is also possible to use photosensitive networks to produce the stents usable in the present invention. Suitable photosensitive networks are amorphous and feature covalent crosslinking points, which determine the permanent shape of the stent. Another feature is a photoreactive component, or a reversibly light-switchable unit, which determines the temporary shape of the stent.

[0067] In the case of the photosensitive polymers, a suitable network is used which comprises photosensitive substituents along the amorphous chain segments. On UV irradiation, these groups are capable of entering into covalent bonds with one another. If the material is deformed and irradiated with light of a suitable wavelength λ1, the original network is additionally crosslinked. The crosslinking achieves temporary fixing of the material in the deformed condition (programming). Renewed irradiation with light of another wavelength λ2 can in turn release the crosslinking and thus restore the original shape of the material (regeneration) because the photo-crosslinking is reversible. This type of photochemical cycle can be repeated as often as desired. The basis for the photosensitive materials is a wide-mesh polymer network which, as stated above, is transparent with respect to the radiation intended to trigger the alteration of shape (*i.e.*, preferably forming a UV-transparent matrix). According to the invention, preference is given to networks of the invention based on low-molecular-weight acrylates and methacrylates which can be polymerized by a free-radical route, in particular C1-C6 (meth)acrylates and hydroxy derivatives, preference being given to hydroxyethyl acrylate, hydroxypropyl methacrylate, hydroxypropyl acrylate, poly(ethylene glycol) methacrylate and n-butyl acrylate; n-butyl acrylate and hydroxyethyl methacrylate are preferably used.

[0068] The comonomer used to produce the polymeric networks of the invention include a component which is responsible for the crosslinking of the segments. The chemical nature of this component depends on the nature of the monomers.

[0069] For the preferred networks based on the acrylate monomers described above as preferred, suitable crosslinking agents are bifunctional acrylate compounds which have suitable reactivity with the starting materials for the chain segments, so that they can be reacted together. These crosslinking agents include short, bifunctional crosslinking agents (*e.g.*, ethylene diacrylate), low-molecular-weight bi- or polyfunctional crosslinking agents, oligomeric, linear diacrylate crosslinking agents (*e.g.*, poly(oxyethylene) diacrylates or poly(oxypropylene) diacrylates) and branched oligomers or polymers having acrylate end groups.

[0070] The inventive network can further include a photoreactive component (group) which is concomitantly responsible for triggering the controllable alteration of shape. This photoreactive group is a unit which, via excitation by suitable light, preferably UV radiation, can react reversibly (with a second photoreactive group) to generate or separate covalent bonds. Preferred photoreactive groups are those capable of reversible photodimerization. Preferred photoreactive components used in the photosensitive networks are various cinnamates (CA) and cinnamylacylates (GM).

[0071] It is known that cinnamic acid and its derivatives dimerize under UV light of approximately 300 nm, forming a cyclobutane. If the dimers are irradiated with UV light of smaller wavelength, approximately 240 nm, they can be cleaved again. The absorption maxima can be shifted by substituents on the phenyl ring, but always remain within the UV region. Other derivatives capable of photodimerization are 1,3-diphenyl-2-propene-1-one (chalkone), cinnamylacylic acid, 4-methylcoumarin, various ortho-substituted cinnamic acids, cinnamyloxysilanes (silyl ethers of cinnamyl alcohol).

[0072] Photodimerization of cinnamic acid and of similar derivatives is a [2+2] cycloaddition of the double bonds to give a cyclobutane derivative. The E-isomers, and also the Z-isomers, are capable of entering into this reaction. Under irradiation, E/Z-isomerization competes with the cycloaddition reaction. However, E/Z-isomerization is inhibited in the

crystalline state. The various possible arrangements of the isomers with respect to one another theoretically permit 11 different stereoisomeric products (truxillic acids, truxinic acids). For the reaction, the required separation of the double bonds of two cinnamic acid groups is about 4 Å.

[0073] The networks that are preferred materials for the stent of the process feature the following properties:

[0074] Overall, the networks are good SMP materials with high recovery values, meaning that a high percentage, usually above approximately 90%, of the original shape is regained even on repeated passage through a cycle of changes of shape. Nor does any disadvantageous loss of mechanical properties occur here.

[0075] As far as the abovementioned materials are based on aliphatic polyesters, the SMP materials used are hydrolyzable or biodegradable. Surprisingly, it has been found that on the one hand these materials decompose in a biocompatible manner (*i.e.*, giving non-toxic degradation products) while on the other hand the mechanical integrity of the stent is retained during the degradation process, ensuring sufficiently long functionality of the stent.

[0076] Polymers for the inventive process preferably have a transition temperature in the range from approximately 20 to approximately 70° C, preferably in the range from approximately 30 to approximately 50° C, and particularly preferred in the range from approximately 35 to approximately 45° C.

[0077] Known methods known can be used to control the temperature in the tissue support during introduction and removal from the organ, in particular to set the transition temperature. In one particular embodiment of the process, the temperature in the tissue support can be controlled via a heating element (*e.g.*, a wire) leading into the polymer. However, prferably no heating element is embedded into the SMP material.

[0078] To establish the transition temperature of stents composed of SMP material, it is possible to trigger the shape-memory effect not only thermally with the aid of a heatable medium

but also via use of IR or NIR radiation, via application of an oscillating electrical field, via VIS (visible) and/or via UV irradiation. An example of IR radiation is electromagnetic radiation in the range from approximately 2.5 to approximately 25 μm, preferably in the range from approximately 4.0 to approximately 7.0 μm. An example of NIR (near infrared) radiation is electromagnetic radiation in the range from approximately 700 to approximately 2500 nm, preferably in the range from approximately 700 to approximately 1600 nm. An example of UV radiation is electromagnetic radiation in the range from approximately 200 to approximately 500 nm, preferably in the range from approximately 250 to approximately 350 nm. The radiation source can be introduced, for example, in the form of a probe into the stent.

[0079] The shape of the tube of the inventive tissue supports corresponds to the shape of the tissue requiring support. Accordingly, they can have a straight or curved shape. The tube length of the inventive stents is generally in the range from approximately 1 to approximately 15 cm, their diameter being in the range from approximately 1 to approximately 15 mm.

[0080] Minimally invasive insertion of a stent into a hollow organ according to steps (i) and (ii) of the inventive process can, for example, be described as follows:

1. The stent, provided on a temperature-controllable balloon catheter, undergoes minimally invasive introduction into the tubular, non-vascular organ;

2. The fitted stent is heated by means of a catheter above its T_{trans} (balloon fills with warm water (liquid) or gas), or is irradiated with light of wavelength smaller than 300 nm. The stent expands and widens during this process; and

3. The stent now has its permanent shape (expanded) and the balloon catheter can be removed.

[0081] For example, the stents usable for the process can be shaped (*i.e.*, "programmed") as follows before step(i) is performed:

1. The stent gains its permanent shape in a manner known per se, for example via injection moulding or extrusion.

2. The stent in its permanent shape is heated to a temperature greater than T_{trans}, thus producing the temporary shape.

3. During the programming process, the inventive stent in its temporary shape is converted to a diameter which is smaller than the original diameter.

4. The stent is cooled to a temperature smaller than T_{trans}, is drawn out of the production process with the aid of a guide wire or of a guide thread and can be assembled onto a suitable catheter.

[0082] Although the invention has been described and illustrated with a certain degree of particularity, it is understood that the present disclosure has been made only by way of example, and that numerous changes in the conditions and order of steps can be resorted to by those skilled in the art without departing from the spirit and scope of the invention.

CLAIMS

1. A tubular tissue support usable in a process, wherein the process comprises the following steps (i) through (iii) in the given order:

(i) a tubular tissue support (stent) is introduced into one of said hollow organs,

(ii) the tubular tissue support is fixed in the hollow organ and

(iii) the tubular tissue support is replaced from the position fixed in step (ii) by physical means or by (bio)chemical degradation after a retention period of 1 minute to 6 months.

2. The tissue support according to claim 1, comprising at least a shape memory polymer.

3. The tissue support according to any of claims 1 or 2 that has a closed outer surface.

4. The tissue support according to any of claims 1 to 3 that has a smooth outer surface.

5. The tissue support according to any of claims 1 to 4, wherein the outer surface is selected to reduce the tendency, that the tissue support growth together with the hollow organ.

6. The tissue support according to claim 5, wherein the tissue support comprises a tubular device that is coated with a material capable to reduce the tendency, that the tissue support growth together with the hollow organ.

7. Process to support and/or radially widen hollow organs of human or animal bodies, characterized in that it comprises the following steps (i) through (iii) in the given order:

(i) a tubular tissue support (stent) is introduced into one of said hollow organs,

(ii) the tubular tissue support is fixed in the hollow organ and

(iii) the tubular tissue support is replaced from the position fixed in step (ii) by physical means or by (bio)chemical degradation after a retention period of 1 minute to 6 months.

8. The process according to claim 7, wherein in step (iii) the tissue support is replaced after a retention period of 8 hours to 14 days.

9. The process according to claim 7 or 8, wherein in step (iii) the tissue support is replaced from the hollow organ.

10. The process according to claim 7, 8 or 9, wherein step (iii) the tissue support is repositioned to another position in the hollow organ.

11. The process according to claim 7, 8, 9 or 10, wherein a drug is given to the patient that inhibits blood coagulation.

12. The process according to claim 7, 8, 9, 10 or 11, wherein the tissue support is softened at the end of step (iii) before replacement from the position determined in step (ii).

13. The process according to claim 12, wherein the change in hardness is a shape memory effect.

14. The process according to claim 7, 8, 9, 10, 11, 12 or 13, wherein the tissue support is reshaped at the end of step (iii) before replacement from the position determined in step (ii).

15. The process according to claim 14, wherein the radius of the tissue support is decreased at the end of step (iii) before replacement from the position determined in step (ii).

16. The process according to any of claims 14 or 15, wherein the change in shape is a shape memory effect.

17. The process according to any of claims 7 to 16, wherein the tissue support is degraded in step (iii).

18. The process according to any of claims 7 to 17, wherein the hollow organ is a blood vessel.

19. The process according to any of claims 7 to 17, wherein the hollow organ is a coronary blood vessel.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/007301

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61F2/82
ADD. A61F2/02

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)
A61F

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 practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/110313 A (MNEMOSCIENCE GMBH [DE]; SIMON PETER [DE]; KRATZ KARL [DE]; LENDLEIN AN) 23 December 2004 (2004-12-23) page 1, paragraph 1 - page 38, paragraph 1; figures 1-3	1-6
X	US 2002/142119 A1 (SEWARD KIRK P [US] ET AL) 3 October 2002 (2002-10-03) paragraphs [0077] - [0080]; figures 12,13	1-4
X	WO 2006/086304 A (WILSON COOK MEDICAL INC [US]; RUCKER BRIAN K [US]) 17 August 2006 (2006-08-17) paragraphs [0023], [0032]	1,3-5

☐ 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 document 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	Date of mailing of the international search report
3 December 2007	13/12/2007

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2007/007301

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 7-19
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2007/007301

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004110313 A	23-12-2004	BR PI0411437 A	18-07-2006
		CA 2527976 A1	23-12-2004
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