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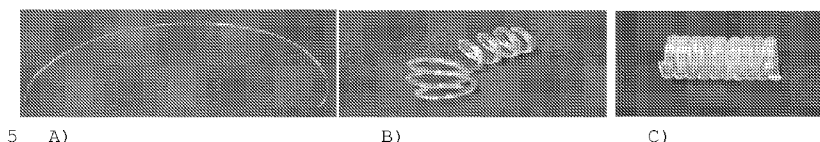


Figure 1

(57) Abstract: The present invention relates to a method for preparing an amorphous resorbable polymer material with shape memory. Further, the present invention relates to the amorphous resorbable polymer material with shape memory and furthermore to the use of the amorphous resorbable polymer material with shape memory.



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**AMORPHOUS RESORBABLE POLYMERIC NETWORK MATERIALS WITH SHAPE
MEMORY**

The present invention relates to methods for
5 preparing amorphous resorbable polymer network materials
with shape memory. Further, the present invention relates to
the amorphous resorbable polymeric network materials with
shape memory and to the use of the present amorphous
resorbable polymeric network materials with shape memory.

10 Developments in the multidisciplinary field of
tissue engineering have yielded a novel set of tissue
replacement parts and implementation strategies. Scientific
advances in biomaterials, stem cells, growth and
differentiation factors, and biomimetic environments have
15 created opportunities to synthesize tissues in the
laboratory as well as in the body from combinations of
engineered extracellular matrices ("scaffolds"), cells, and
biologically active molecules. The physical, chemical and
biological properties of these scaffold materials are
20 important in tissue engineering. Cell behaviour is
influenced by the rigidity of the substrate on which the
cells are cultured. In soft tissue engineering, the scaffold
should transmit mechanical stimuli to the cells and tissues,
and withstand repeated dynamic loadings *in vivo*. Also *in*
25 *vitro* this can be required, as mechanical stimulation of
cell-seeded tissue engineering scaffolds during cell culture
enhances the development of engineered tissues and their
function. In this respect, flexible, form-stable and
resorbable elastomeric polymer networks that allow cell
30 adhesion and proliferation are of great interest.

Resorbable polymer networks prepared from amorphous
oligomers with low glass transition temperatures (T_g s), can
for example be based on trimethylene carbonate (TMC) and/or

D,L-lactide (DLLA) oligomers, and show elastomeric properties. For example, the end-functionalization of these relatively low molecular weight polymers with (meth)acrylate- or fumarate groups yields to functionalized oligomers, or macromers, amongst others, to allow network formation.

In the lactide class, poly(D,L-lactide) (PDLLA) is known as biodegradable, thermoplastic, aliphatic polyester derived from renewable resources, such as corn starch or sugarcane. PDLLA can be used in medical applications, such as sutures, stents, dialysis media and drug delivery devices. It is also being evaluated as a material for tissue engineering. Accordingly, the racemic lactide monomer D,L-lactide (DLLA) is suitable in the methods of the present invention.

The toughness, ultimate tensile strengths and elongation at break values of flexible networks obtained in this manner significantly increase with increasing macromer molecular weights and molecular weights between crosslinks.

Shape memory polymeric materials are materials that have the ability to pass from one deformed state (temporary shape) to another state (permanent shape) induced by an external stimulus (trigger), such as a temperature or pH change, a water content modification, an electric or magnetic field, or light. As well as polymers in general, they also cover a wide range of materials with properties ranging from stable to biodegradable, from soft to hard, from hydrophilic to hydrophobic and from elastic to rigid, depending on the structural units that constitute to their structure. They can be thermoplastics and/or thermoset (covalently cross-linked) polymeric materials. They are known to be able to store up to three different shapes.

There is a continuous need in the art to further develop amorphous resorbable shape memory polymeric network materials. It is a goal of the present invention, among others, to prepare amorphous shape memory polymeric network materials that are resorbable, at least substantially. The present invention also aims at preparing resorbable flexible polymeric network materials with a glass transition temperature close to body temperature and with a sufficiently high molecular weight to have better, or equal, mechanical properties (for example, a better toughness and/or better tensile strength and/or better elongation at break). This allows the material to be implanted in its temporary shape at low temperatures (room temperature for example) when it is relatively hard and rigid, and when it heats to body temperature becomes more flexible and adopts its permanent shape. By varying the composition of the oligomer (and accordingly the composition of the macromer and network), we can tune the glass transition temperature of the networks as well as their mechanical properties.

These goals, amongst others, are met by the methods for preparing amorphous resorbable polymeric network materials with shape memory according to the present invention, which comprise: a) the preparation of polyol oligomers with a number average molecular weight higher than or equal to 900 g/mol per hydroxy-group, by polymerization of cyclic carbonates and/or cyclic esters and/or linear carbonates and/or linear esters and/or hydroxycarboxylic acids using an initiator; b) the functionalization of the polyol oligomers with at least two unsaturated groups; c) the crosslinking of the functionalized oligomers obtained in step b) using an initiator.

Polymeric network materials, also designated as polymer networks or polymer materials and also called

polymers in the context of the present invention, are large molecules composed of repeating structural units, synthesized from monomers, typically connected by covalent chemical bonds.

5 Amorphous polymeric network materials are polymers whose molecular structure lacks a definite repeating form, shape, or crystalline structure.

 Amorphous resorbable polymeric network materials are polymers that are resorbable, at least substantially.

10 Resorbable materials of the present invention can also be designated by degradable or biodegradable materials. The amorphous resorbable polymeric network materials of the present invention are not harmful to the human or animal body (biocompatible), and are therefore compatible with
15 medical applications in the body, where degradation of the networks can take place by hydrolysis and/or oxidation. These processes can be mediated by enzymes, which can be excreted by cells. It is understood that the polymeric network materials of the present invention maintain their
20 mechanical properties until it is no longer needed and then be degraded and resorbed. Typically, the backbone of the polymer is hydrolytically unstable. That is, the polymer is unstable in a water based environment. The hydrolysis can also be favorized enzymatically.

25 An oligomer is a polymer with a low degree of polymerization. A functionalized oligomer is also designated as a macromer.

 A polyol is a hydrocarbon containing several hydroxy-groups, also called alcohol functional group, -OH. A
30 diol contains two -OH group, a triol contains three -OH groups, a tetra-ol contains four -OH group and a penta-ol contains five -OH groups.

Carbonates are hydrocarbons with at least one carbonate group $-O-C(=O)-O-$ in the hydrocarbon, such as one carbonate group, two carbonate groups, three carbonate groups.

5 Esters are hydrocarbons with at least one ester group $-COO-$ in the hydrocarbon, such as one ester group, two ester groups, three ester groups.

Hydroxycarboxylic acids are hydrocarbons with a carboxylic acids (organic function $-COOH$) comprising a
10 second organic group, a hydroxy group ($-OH$).

Cyclic molecules have a ring structure, such as aryl, or aromatic rings. Linear molecules are hydrocarbon chains, such as alkanes.

An unsaturated group is an alkenyl or alkynyl,
15 hydrocarbons with a double or a triple C-C bond. The unsaturated group can bind at the terminal or at any position in the hydrocarbon chain. An alkenyl is a rest comprising at least one double C-C bond and an alkynyl is a rest comprising at least one triple C-C bond.

20 Step b) of the methods of the present invention comprises at least two unsaturated group to functionalize each oligomer, such as two unsaturated groups or more, three unsaturated groups or more, four unsaturated groups or more, five unsaturated groups or more.

25 An initiator is a chemical substance that can start the polymerization, such as by producing radical or ionic species under mild conditions. An initiator has an active site, such as an active hydrogen to allow the polymerization to process. In step a) the initiator allows a ring-opening
30 polymerization or a polycondensation. The initiator in step c) is a radical forming initiator. The initiator in step a) and step c) may be the same initiator.

In the present invention, the number average molecular weight, usually expressed in g/mol, is used to define the size of the polyol oligomers, and accordingly to characterize the polymeric network materials. The number-
5 average molecular weight is determined experimentally by methods that count the number of polymer molecules in a sample of the polymer and is defined as the total weight of all the molecules in a polymer sample divided by the total number of moles present. The number average molecular weight
10 is commonly designated \bar{M}_n .

The number average molecular weight per hydroxy-group of the polyol oligomer is higher than, or equal to 1000 g/mol, preferably higher than, or equal to 1500 g/mol, more preferably higher than, or equal to 2000 g/mol, most
15 preferably higher than, or equal to 3000 g/mol. The number average molecular weight per hydroxy-group of the polyol oligomer is equal to, or lower than, 500000 g/mol, preferably equal to, or lower than 250000 g/mol, more preferably equal to, or lower than 150000 g/mol, most
20 preferably equal to, or lower than 50000 g/mol.

According to a preferred embodiment of the present invention, the number average molecular weight per hydroxy-group of the polyol oligomer is in the range of 1000 to 150000 g/mol, preferably 1500 to 100000 g/mol, more
25 preferably 2000 g/mol to 50000 g/mol, most preferably 5000 g/mol to 30000 g/mol.

According to the method of the present invention, the functionalization in step b) can be end-functionalization or co-polymerization. End-
30 functionalization is the functionalization of the polyol oligomers carried out with an unsaturated group (double or triple bond at one extremity of the hydrocarbon chain). Co-polymerization is polymerization, for example

polycondensation, of mixtures of different monomers and leads to polymeric products with (two or more) different structures in the polymer chain. Such mixture can be a mixture of monomers that contain double C-C bonds and
5 monomers that do not contain double C-C bonds.

According to the methods of the present invention, the polyol oligomers are chosen from the group diols, triols, tetra-ols or penta-ols. Other polyols are also of interest, such as sugar alcohols (such as maltitol,
10 sorbitol, xylitol and isomalt) or polyethylene glycol. Polyethylene glycol (PEG) is a polyether compound with many applications from industrial manufacturing to medicine. It has also been known historically as polyethylene oxide (PEO) or polyoxyethylene (POE). PEG, PEO or POE refers to an
15 oligomer or polymer of ethylene oxide. Polyethylene glycol is produced by the interaction of ethylene oxide with water, ethylene glycol or ethylene glycol oligomers. The reaction is catalyzed by acidic or basic catalysts. It is the basis of a number of laxatives (e.g., macrogol-containing
20 products) and of many skin creams.

Sterilization by autoclaving can be done with amorphous poly(lactides) and PCL-PEO co-polymers when they are crosslinked.

According to the methods of the present invention,
25 the cyclic carbonates are chosen from the group trimethylene carbonate, ethylene carbonate, propylene carbonate, diethylene glycol-bis-allyl-carbonate and derivatives thereof.

Trimethylene carbonate has the formula $(\text{CH}_2)_2\text{OCH}_2\text{CO}_2$.
30 Ethylene carbonate with the formula is also called 1,3-dioxolan-2-one. Ethylene carbonate and propylene carbonate are esters of ethylene glycol or propylene glycol, respectively, and carbonic acid. They have the formula $\text{C}_3\text{H}_4\text{O}_3$

and $C_4H_6O_3$. Diethylene glycol-bis-allyl-carbonate has the formula $C_{12}H_{18}O_7$. By derivatives thereof is to be understood as substituted trimethylene carbonate, substituted ethylene carbonate, substituted propylene carbonate, substituted diethylene glycol-bis-allyl-carbonate which can be substituted at any position, by an alkyl, alkenyl, alkynyl, aryl, cycloalkyl, cycloalkenyl, cycloalkynyl. The substituent may carry or be an organic group.

According to the methods of the present invention, the cyclic esters are chosen from the group lactones, D,L-lactide, glycolide, and derivatives thereof.

Lactones are cyclic esters. The smaller (according to the size of their cycle) are α -acetolactone (three-membered ring with the formula $(CH_2)CO_2$), β -propiolactone (four-membered ring with the formula $(CH_2)_2CO_2$), γ -butyrolactone (five-membered ring with the formula $(CH_2)_3CO_2$), and δ -valerolactone (six-membered ring with the formula $(CH_2)_4CO_2$) and ϵ -caprolactone, also called caprolactone (seven-membered ring with the formula $(CH_2)_5CO_2$). D,L-lactide has the formula $C_6H_8O_4$. Glycolide 1,4-dioxane-2,5-dione and has the formula $C_4H_4O_4$. By derivatives thereof is to be understood as substituted lactones, substituted D,L-lactides, substituted glycolide which can be substituted at any position, by an alkyl, alkenyl, alkynyl, aryl, cycloalkyl, cycloalkenyl, cycloalkynyl. The substituent may carry or be an organic group.

According to the methods of the present invention, the linear carbonates are chosen from the group diethyl carbonate or diphenylcarbonate and derivatives thereof. Diethyl carbonate has the formula $C_5H_{10}O_3$. Diphenylcarbonate has the formula $C_{13}H_{10}O_3$.

According to the methods of the present invention, the linear esters are chosen from the group fumaric acid

monoethyl ester, fumaric acid diethylester, dimethylterephthalate, diethylterephthalate and derivatives thereof. Fumaric acid monoethyl ester, or monoethyl fumarate, has the formula $C_6H_8O_4$. Fumaric acid diethylester, or diethyl fumarate, has the formula $C_8H_{12}O_4$. Dimethylterephthalate, or terephthalic acid methyl ester, has the formula $C_{10}H_{10}O_4$. Diethylterephthalate, or terephthalic acid ethyl ester, has the formula $C_{12}H_{14}O_4$.

By derivatives thereof is to be understood as substituted linear carbonates, linear esters or linear hydroxycarboxylic monomers at any position, by an alkyl, alkenyl, alkynyl, aryl, cycloalkyl, cycloalkenyl, cycloalkynyl. The substituent may carry or be an organic group.

Oligomers comprising a double or triple bond at the end of the main chain can be obtain by ring-opening polymerization of cyclic carbonates or cyclic esters containing a pendant double bond, or by polycondensation of fumaric acid or derivatives thereof, maleic acid or derivatives thereof. Oligomers with a double or triple bond at the end of the main chain provide amorphous resorbable polymeric network materials with increased strength and toughness.

According to the methods of the present invention, the linear hydroxycarboxylic acids are any linear carboxylic acids comprising a hydroxyl group on the main hydrocarbon chain, such as α -hydroxy acids. They can be saturated or unsaturated (comprising double and or triple bonds in the carbon chain), and/or substituted or unsubstituted by alkyl, alkenyl or alkynyl. Hydroxy carboxylic acids, are a class of chemical compounds that consist of a carboxylic acid and a hydroxyl group. They may be either naturally occurring or synthetic. AHAs are well-known for their use in the

cosmetics industry. A carboxylic group is $-COOH$, an hydroxy group is the organic alcohol function $-OH$. α -hydroxy acids, or AHAs, are most commonly used in cosmetic applications are typically derived from food products including glycolic acid (from sugar cane), lactic acid (from sour milk), malic acid (from apples), citric acid (from citrus fruits) and tartaric acid (from grape wine).

According to the methods of the present invention, the polymerization in step a) is a ring-opening polymerization or polycondensation.

Ring-opening polymerization is a form of polymerization, in which the terminal end of a polymer acts as a reactive center, where further cyclic monomers join to form a larger polymer chain through propagation. The treatment of some cyclic compounds with an initiator (e.g. comprising an active hydrogen as active site) and a catalyst brings about cleavage of the ring followed by polymerization to yield oligomers or polymers. The reaction is commonly carried out under inert conditions (argon, nitrogen or vacuum) and under heating.

Polycondensation is a process by which two or more molecules join together, resulting in loss of small molecules which is often water. The type of end product resulting from a condensation polymerization is dependent on the number of functional end groups of the monomer which can react.

According to the methods of the present invention, the unsaturated end group is chosen from the group acrylate, methacrylate, fumarate, diacrylate, triacrylate. Other acrylates are also of interest.

The acrylate unit comprises one vinyl group and one ester group. A diacrylate contains two units of acrylate, a triacrylate contains three units of acrylate. The acrylate

unit is also called propenoate and has the formula $C_3H_3O_2$.
Examples of acrylates are methacrylate, also called 2-
methylprop-2-enoate with the linear formula $C_5H_8O_2$, ethylene
diacrylate with the formula $C_8H_{10}O_4$, pentaerythritol
5 triacrylate (PETA), also called 2-propenoic acid 2-
(hydroxymethyl)-2-[[(1-oxo-2-propenyl)oxy]methyl]-1,3-
propanediyl ester with the linear formula
($H_2C=CHCO_2CH_2$)₃CCH₂OH, trimethylolpropane triacrylate (TMPTA)
with the linear formula ($H_2C=CHCO_2CH_2$)₃CC₂H₅ and
10 trimethylolpropane trimethacrylate with the linear formula
[$H_2C=C(CH_3)CO_2CH_2$]₃CC₂H₅. The unsaturated end group can be
substituted, e.g. by a rest alkyl or acyl.

A fumarate has the general formula ($O_2CCH=CHCO_2$) and
can be substituted by an alkyl or acyl.

15 According to the methods of the present invention,
the crosslinking in step c) is photocrosslinking, thermal
crosslinking or redox crosslinking.

Crosslinking means that the polymeric network
materials of the invention have bonds that link polymer
20 chains in order to form a network. These networks of
polymers are also called crosslinked polymers.

Photocrosslinking is crosslinking due to
irradiation with light. Thermal crosslinking is
crosslinking allowed by a change in temperature. Redox
25 crosslinking occurs via an electrochemical reaction. Other
crosslinking reactions are also of interest such as
dimerization, Diels-Alder reaction, Michael-type additions,
metathesis, reactions with isocyanates, or any other
condensation reactions.

30 Irradiation is the process by which an item is
exposed to radiation. The radiation of the present invention
is ultraviolet light (the ultraviolet region has a
wavelength between 1 and 400 nm), preferably at wavelengths

from 250 nm to 400 nm, more preferably 300 nm to 380nm, or visible light (400 nm to 850 nm), or any other form of radiation including microwave irradiation.

According to the methods of the present invention,
5 the initiator in step a) is a diol, a triol, a tetra-ol, a diamine, a triamine, tetra-amine, dithiol, trithiol or a tetra-thiol. A diol, triol or tetra-ol has two, three or four organic alcoholic functions -OH (also called hydroxy group), respectively. A diamine, triamine or tetra-amine has
10 two, three or four amine groups -NH- or -NH₂, respectively. A dithiol, trithiol or tetrathiol has two, three or four -SH groups, respectively.

According to a preferred embodiment of the present invention, the initiator in step a) is chosen from the group
15 1,2-ethanediol, 1,3-propanediol, 1,4-butanediol, 1,5-pentanediol, 1,6-hexanediol, 1,8-octanediol. They respectively have the chemical formula: C₂H₄(OH)₂, C₃H₆(OH)₂, C₄H₈(OH)₂, C₅H₁₀(OH)₂, C₆H₁₂(OH)₂, C₈H₁₆(OH)₂.

According to the methods of the present invention,
20 the initiator concentration in step a) is in the range 10⁻⁶ to 10⁻² mol per total mol of monomers.

According to a preferred embodiment of the present invention, step a) comprises a catalyst.

A catalyst is a chemical substance able to
25 accelerate or enhance a reaction without being consumed in the chemical reaction.

According to another preferred embodiment of the present invention, step a) comprises a catalyst which is a stannous alkyloate or a metallic compound chosen from the
30 group stannous octoate or metallic zinc. Other catalysts are also of interest, such as tin, titanium, iron, zink or calcium based catalysts.

According to the methods of the present invention, the catalyst concentration in step a) is in the range of 10^{-8} to 10^{-2} mol per total mol of the monomers.

According to the methods of the present invention,
5 the polyol oligomers in step a) are prepared from two monomers chosen from the group cyclic carbonates and/or a cyclic esters and/or linear carbonates and/or linear esters and/or hydroxycarboxylic acids with a ratio between monomers which is in the range of 0.01:100 to 100:0.01 by mol.

10 According to the methods of the present invention, the preparation of the polyol oligomers in step a) comprises: i) mixing the cyclic carbonates and/or cyclic esters and/or linear carbonates and/or linear esters and/or hydroxycarboxylic acids with the initiator at a temperature
15 in the range of 20°C to 200°C, under inert atmosphere and under stirring; ii) adding the catalyst; iii) maintaining the temperature of step a) under stirring for 15 minutes to 4 days; iv) bringing the mixture at room temperature.

The temperature range in step i) is between 20°C to
20 200°C, such as 20 °C, 25°C, 30°C, 35°C, 40°C, 45°C, 50°C, 55°C, 60°C, 65°C, 70°C, 75°C, 80°C, 85°C, 90°C, 95°C, 100°C, 105°C, 110°C, 115°C 120°C, 125°C, 130°C, 135°C, 140°C, 145°C, 150°C, 155°C, 160°C, 165°C, 170°C, 175°C, 180°C, 185°C, 190°C, 195°C, 200°C. The polymerization reaction in step a) can also be
25 done at different temperature than the temperature at which the monomers are mixed.

Stirring in step iii) is mechanical stirring, ultrasonic mixing or magnetic agitation. Stirring until homogeneity is stirring until forming a uniform mixture to
30 the naked eye.

According to the methods of the present invention, the functionalization is carried out with methacrylic anhydride or methacryloyl chloride and an amine in an

organic solvent. The solvent can be a chlorinated organic solvent.

A methacrylate group is an organic functional group with the formula $\text{CH}_2=\text{C}(\text{CH}_3)\text{COO}$. An anhydride is the group
5 $\text{O}=\text{C}-\text{O}-\text{C}=\text{O}$. Methacrylic anhydride has the formula $\text{C}_8\text{H}_{10}\text{O}_3$. Methacryloyl chloride has the formula $\text{C}_4\text{H}_5\text{ClO}$.

An amine is a chemical group comprising a $-\text{N}-$, the amine can be primary, $-\text{NH}_2$, secondary $-\text{RNH}$, or tertiary $-\text{RNR}$.

A chlorinated organic solvent is a hydrocarbon
10 containing chlorine. Examples are dichloromethane, chloroform, carbontetrachloride. Dichloromethane has the formula CH_2Cl_2 , chloroform CHCl_3 , carbontetrachloride CCl_4 .

According to the methods of the present invention, the crosslinking in step c) is photocrosslinking with
15 ultraviolet light or visible light. The ultraviolet light used in the present invention has a wavelength between 1 and 400 nm, preferably at wavelengths from 250 nm to 400 nm, more preferably 300 nm to 380nm. The visible light has a wavelength between 400 nm and 850 nm.

20 The initiator of the crosslinking can be a photoinitiator, a chemical substance that produces radical/ionic species upon exposure to light, or a thermal initiator, a chemical substance that produces the radical/ionic species with sensitivity to temperature, or a
25 redox initiator, a chemical substance that produces the radical/ionic species by a redox reaction.

According to the methods of the present invention, the initiator is chosen from the class hydroxyketone, aminoketone, phenylglyoxylate.

30 A hydroxyketone has the organic groups alcohol $-\text{OH}$ and ketone $\text{C}=\text{O}$. An aminoketone has an amine NH_2 and a ketone $\text{C}=\text{O}$. A phenylglyoxylate has an aromatic C_6H_6 hydrocarbon and an ester function $-\text{COO}-$.

According to the methods of the present invention, the photoinitiator is 2-hydroxy-4'-(2-hydroxyethoxy)-2-methylpropiophenone. 2-hydroxy-4'-(2-hydroxyethoxy)-2-methylpropiophenone has the formula $C_{12}H_{16}O_4$.

5 According to the methods of the present invention, the methods further comprise a step b2) between step b) and step c) of compression molding or extrusion or injection molding or casting of the functionalized oligomer obtained in step b). The process of casting can also be solvent
10 casting.

Compression molding is a method of molding in which the molding material, generally preheated, is first placed in an open, (heated) mold cavity. The mold is closed with a top force or plug member, pressure is applied to force the
15 material into contact with all mold areas, while heat and pressure are maintained until the molding material has cured. Extrusion is a process used to create objects of a fixed cross-sectional profile. A material is pushed or drawn through a die of the desired cross-section. The main
20 advantages of this process over other manufacturing processes are its ability to create very complex cross-sections. It also forms finished parts with an excellent surface finish. Injection molding is a manufacturing process for producing parts of polymer materials. The material is
25 fed into a heated barrel, mixed, and forced into a mold cavity where it cools and hardens to the configuration of the mold cavity. After a product is designed, molds are made in usually either steel or aluminium, and precision-machined to form the features of the desired part. Injection molding
30 is widely used for manufacturing a variety of parts. Casting is a process for forming thermoplastic articles by dipping a male mold into a liquid polymer, a solution or dispersion of

the polymer and drawing off the solvent (if any present) to leave a layer of plastic film adhering to the mold.

According to the methods of the present invention, the shape changes in the polymer network material are
5 induced by stimuli chosen from the group thermal, electric, pH, magnetic stimuli, light or gamma irradiation, or water content modification.

According to another aspect of the present invention, amorphous polymeric materials with shape memory
10 are obtainable by the methods of the present invention.

According to another aspect, the amorphous polymeric network materials with shape memory of the present invention are used for coating surfaces, as a protective layer for thermal insulation and/or for anti-oxidation insulation, for
15 the manufacture of packaging materials.

According to yet another aspect, the amorphous polymeric network materials with shape memory of the present invention are used for preparing medical devices.

According to still another aspect of the present invention, the amorphous polymeric network materials with shape memory are used to prepare implants, used in tissue engineering, or drug delivery.
20

The present invention is further described by the figure and Examples herewith. The Examples illustrate the present invention and do not aim to limit its scope.
25

Figure 1: Photo-crosslinked network prepared from a DLLA(0.6):TMC(0.4) oligomers with number average molecular weight of approximately 30000g/mol displaying shape memory behaviour. A) Shape at 10 °C (Temporary shape); B) Shape at 37 °C after 20 s; C) Shape at 37 °C after 100 s (Permanent shape).

10

Examples

15 Example 1

A series of poly(D,L-lactide-co-trimethylene carbonate) diols and their corresponding homopolymers, *i.e.* oligomeric Poly(DLLA) and Poly(TMC) diols, are synthesized by ring opening polymerization of DLLA and TMC using 1,6-hexanediol as an initiator and SnOct₂ as a catalyst. The composition in the oligomeric copolymers (TMC:DLLA molar ratio) is varied from 0 to 1 in steps of 0.2. The employed monomer feed compositions and the amounts of initiator are shown in Table 1. In a typical reaction, the required amounts of TMC or 20 DLLA or their mixtures along with the initiator, are charged into a 250 mL three necked round bottom flask equipped with magnetic stirrer under the flow of nitrogen (Table 1). The number average molecular weight of oligomers can be varied by adjusting the monomer to initiator molar ratio. The flask 30 is then evacuated and purged with nitrogen several times and heated to 130 °C under a nitrogen atmosphere. To the homogenous mixture, SnOct₂ (2×10^{-4} mole of monomers) is charged immediately and the reaction is continued for 3 days

at this temperature. Upon completion of the reaction, the mixture is cooled to room temperature, dissolved in chloroform and precipitated in an excess of cold ethanol to remove unreacted TMC or DLLA. The purified oligomers are then dried in a vacuum oven for 2 days at 30 °C.

Hydroxyl-group terminated (co)polymeric oligomers, with targeted number average molecular weights of 30000 g/mol (designated by 30k) were prepared. Copolymeric oligomers containing 40 mol% TMC oligomers with number average molecular weights of 5000 and 10000 g/mol (designated by 5k and 10k, respectively) were also prepared.

Table 1. Polymerization recipes for preparing oligomeric PDLA and PTMC diols and copolymer oligomeric diols with intended number average molecular weights of 5000, 10000, and 30000 g/mol.

Intended oligomer composition and number average molecular weight	mol TMC : mol DLLA	Initiator ($\times 10^4$) (mol)
DLLA 30k	0:0.13	5.07
DLLA(0.8):TMC(0.2) 30k	0.03:0.11	6.68
DLLA(0.6):TMC(0.4) 30k	0.098:0.146	10.4
DLLA(0.4):TMC(0.6) 30k	0.10:0.07	6.76
DLLA(0.2):TMC(0.8) 30k	0.147:0.036	6.76
TMC 30k	0.24:0	8.12
DLLA(0.6):TMC(0.4) 5k	0.097:0.146	63.46
DLLA(0.6):TMC(0.4) 10k	0.097:0.146	31.3

The synthesized diols are subsequently methacrylate-endcapped. This reaction is carried out using methacrylic anhydride in the presence of triethyl amine (TEA). The oligomers, methacrylic anhydride, and TEA are measured out in 1:4:4 molar ratios. The pre-dried oligomer is charged

into a 3-necked round bottom flask under nitrogen atmosphere containing 100 mL of anhydrous dichloromethane. After dissolution of the oligomer, methacrylic anhydride and TEA are charged into the flask. The reaction is allowed to proceed for 7 days at room temperature. Purification is done by precipitation in cold excess ethanol. The precipitated macromer is then vacuum dried for 2 days at room temperature and stored at -20 °C.

10 **Example 2**

The photo-crosslinking process is carried out by UV light (365 nm) using Irgacure 2959 as a photoinitiator. The photoinitiator (2 wt% of the macromer) is dissolved in chloroform (1 mL/g macromer) and then added to the macromer. The mixture is then gently heated and stirred manually until a homogenous mixture is obtained. The solvent is subsequently evaporated by applying vacuum. The mixture is then slightly heated to soften it and shaped by compression molding. The sheets were then heated to 75 °C and irradiated for 500 sec under a blanket of nitrogen gas. The distance between the film and UV lamps was 10 cm. The films were carefully taken out from the mould and punched into the desired shapes. Several of the specimens were extracted using chloroform. In these cases, network strips were immersed in an excess of chloroform for 24 h. During the extraction, the strips were regularly moved with tweezers. After 24 h, the extraction media was replaced with fresh chloroform and small amounts of methanol were gradually added to the chloroform to shrink the specimens without forming cracks or defects. The shrunk samples were then transferred to a vacuum oven and dried for 36 hours at 40 °C and 0.2 Bar.

Example 3

Macromers based on PTMC and PDLLA homopolymeric oligomers and the TMC and DLLA copolymeric oligomers, which form
 5 covalently crosslinked networks upon photo-initiated radical polymerization, were prepared by the two step process of example 1.

These macromers, formed by functionalization of the hydroxyl-group terminated TMC and DLLA oligomers using
 10 methacrylic anhydride, were then crosslinked according to the photo-polymerization process of example 2. Table 2 gives an overview of the properties of the macromers and the obtained networks. Tables 3 to 6 give an overview of the thermal and mechanical properties of the prepared networks.

15

Table 2.Characterization of the synthesized macromers and their corresponding networks

Macromer	TMC:DLLA ^{a)}	Macromer M _n (g/mol)	Degree of swelling ^{b)} (%)	Sol fraction ^{b)} (%)
DLLA 30k	0:100	28200	18.27(2.15)	26.7(4.3)
DLLA(0.8):TMC(0.2) 30k	20:80	27000	13.95(0.5)	23.83(2.32)
DLLA(0.6):TMC(0.4) 30k	40:60	27000	12.4(0.18)	14.26(0.8)
DLLA(0.4):TMC(0.6) 30k	60:40	29000	9.11(0.06)	10.10(1.6)
DLLA(0.2):TMC(0.8) 30k	80:20	28000	7.6(0.35)	12.33(2.6)
TMC 30k	0:100	27000	14 (0.09)	22.3(0.9)
DLLA(0.6):TMC(0.4) 5k	40:60	n.d. ^{c)}	4.6(0.56)	7.2 (0.53)
DLLA(0.6):TMC(0.4) 10k	40:60	n.d. ^{c)}	3.5(0.11)	15.5 (0.96)

a) molar ratios of the monomers in the feed

b) measurements of the degree of swelling and the sol fraction were conducted using chloroform. Values between parentheses are standard deviations.

c) n.d. = not determined

5

Table 3. Glass transition temperatures of the different networks as determined by DSC and DMA

Macromer	Tg ^{a)} (°C)	Tg ^{b)} (°C)	Tg ^{c)} (°C)
DLLA 30k	50.5	51.0	51.0
DLLA (0.8) :TMC (0.2) 30k	37.0	39.0	42.0
DLLA (0.6) :TMC (0.4) 30k	21.0	26.0	29.0
DLLA (0.4) :TMC (0.6) 30k	10.3	11.0	15.9
DLLA (0.2) :TMC (0.8) 30k	-5.3	-1.0	0.3
TMC 30k	16.3	-13.0	-12.8
DLLA (0.6) :TMC (0.4) 5k	17.2	24.0	n.d. ^{d)}
DLLA (0.6) :TMC (0.4) 10k	19.0	26.0	n.d. ^{d)}

a) Tg determined by differential scanning calorimetry (DSC) on non-extracted specimens

10 b) Tg determined by DSC on specimens extracted using dichloromethane

c) Tg determined by dynamic mechanical analysis (temperature at which $\tan\delta$ reaches a maximum value).

d) n.d. = not determined

15 Differential scanning experiments were conducted at a heating rate of 10 °C per minute using a PerkinElmer Pyris DSC. Temperature scans were done between -40 °C and 90 °C, after first heating the specimens to 90 °C and then cooling to -40 °C at 5 °C per minute.

20

Table 4. Dynamic mechanical analysis of the prepared photocrosslinked networks showing the rigidity of the materials at the different temperatures.

Macromer and network composition	E' at 23 °C (MPa)	E' at 37 °C (MPa)	E' at 10 °C below Tg (MPa)	E' at 10 °C above Tg (MPa)
DLLA 30k	1510	1323	1428	11.7
DLLA (0.8) : TMC (0.2) 30k	1450	1150	1363	10.9
DLLA (0.6) : TMC (0.4) 30k	515	4.39	1060	6.8
DLLA (0.4) : TMC (0.6) 30k	9,50	3.3	1000	10.7
DLLA (0.2) : TMC (0.8) 30k	9,69	2.9	956	8.4
TMC 30k	8,43	3.1	97	8.1

5 Dynamic mechanical analysis (DMA)

The dynamic mechanical thermal properties of extracted photocrosslinked networks measuring $5 \times 20 \times 0.5 \text{ mm}^3$, were determined using a PerkinElmer DMA 7 operating in the tensile mode. Storage modulus and loss tangent values ($\tan \delta$) were determined between $-50 \text{ }^\circ\text{C}$ and $100 \text{ }^\circ\text{C}$ at a heating rate of $2 \text{ }^\circ\text{C}/\text{min}$. The static strain was 200 mN.

Table 5. Mechanical properties of photo-crosslinked networks prepared from macromers with number average molecular weights of approximately 30000 g/mol after extraction and drying determined by tensile testing at room temperature (23 °C). Values between parentheses are standard deviations.

Macromer and network composition	E-modulus (MPa)	Tensile strength (MPa)	Elongation at break (%)
DLLA	2730 (102)	49.1 (3.14)	2.7 (0.6)
DLLA (0.8) : TMC (0.2)	2450 (162)	44 (0.45)	2.6 (0.5)
DLLA (0.6) : TMC (0.4)	763 (42.5) 1380 (33) ^{a)}	15.1 (1.53) 18.2 (2.5) ^{a)}	418 (58) 431 (70) ^{a)}
DLLA (0.4) : TMC (0.6)	3.63 (0.23)	13.6 (1.35)	696 (62)
DLLA (0.2) : TMC (0.8)	5.31 (0.4)	3.43 (0.85)	289 (37)
TMC	4.5 (0.2)	3.9 (0.3)	800 (163)

a) Tensile test conducted at 20 °C

Tensile testing

10 Testing was done according to ASTM D882-91, narrow strips (5×100×0.5 mm³) were tested using a Zwick Z020 tensile tester at room temperature. The crosshead speed was 50 mm/min and the grip to grip separation was 50 mm. The Young's modulus values, elongations at break and the maximal tensile
15 strengths of the photocrosslinked specimens were determined from the stress-strain curves.

Table 6. Mechanical properties of photo-crosslinked networks prepared from macromers with different number average molecular weights of approximately 30000, 10000 and 5000 g/mol after extraction and drying determined by tensile testing at room temperature (23 °C) and by dynamic mechanical analysis. Values between parentheses are standard deviations.

Macromer and network composition	E-modulus (MPa)	Tensile strength (MPa)	Elongation at break (%)	E' at 37 °C (MPa)
DLLA (0.6) :TMC (0.4) 5k	1340 (153)	21.2 (1.77)	192 (24)	3.8
DLLA (0.6) :TMC (0.4) 10k	1240 (148)	24.5 (2.71)	197 (91)	4.4
DLLA (0.6) :TMC (0.4) 30k	763 (42.5)	15.1 (1.53)	418 (58)	4.4

The mechanical properties of the polymer network materials of the present invention are significantly better than the materials known up to date: the tensile strength and elongation at break values are equal or higher in the polymer network material of the present invention.

15

Example 4

The amorphous photo-crosslinked networks display shape memory properties. For instance, when a network is prepared from a DLLA(0.6):TMC(0.4) macromer with number average molecular weight of approximately 30000g/mol in the shape of a spring by photo-crosslinking using a transparent mould,

20

the specimen can be deformed to a linear shape by heating the spring to above the glass transition temperature, stretching the specimen and cooling the stretched specimen to below the glass transition temperature. This specimen
5 maintains its temporary shape while it is kept at temperatures below the glass transition temperatures. As Figure 1 shows, heating the specimen to 37 °C, which is 11 °C above the glass transition temperature measured by DSC, rapidly returns the specimen to its original (spring) shape.

10

The shape memory polymers investigated here present an amorphous crosslinked network. Amorphous resorbable networks with glass transition temperatures below or close to body temperature are most suited for biomedical applications
15 where the loading conditions are relatively low.

CLAIMS

1. Method for preparing amorphous resorbable polymeric network materials with shape memory comprising:

- 5 a) the preparation of polyol oligomers with a number average molecular weight higher than or equal to 900 g/mol per hydroxy-group, by polymerization of cyclic carbonates and/or a cyclic esters and/or linear carbonates
10 and/or linear esters and/or hydroxycarboxylic acids using an initiator;
- b) the functionalization of the polyol oligomers with at least two unsaturated group;
- 15 c) the crosslinking of the functionalized oligomers obtained in step b) using an initiator;

2. Method for preparing amorphous resorbable polymeric network materials with shape memory according to
20 claim 1, wherein the number average molecular weight per hydroxy-group of the polyol oligomers of step a) is in the range 1000 to 150000 g/mol, preferably 1500 to 100000 g/mol, more preferably 2000 g/mol to 50000 g/mol, most preferably
25 5000 g/mol to 30000 g/mol.

3. Method for preparing amorphous resorbable polymeric network materials with shape memory according to claim 1 or 2, wherein the functionalization in step b) is
30 end-functionalization or co-polymerization.

4. Method for preparing amorphous resorbable polymeric network materials with shape memory according to

any one of claims 1 to 3, wherein the polyol oligomers are chosen from the group diols, triols, tetra-ols or penta-ols.

5 5. Method for preparing amorphous resorbable polymeric network materials with shape memory according to any one of claims 1 to 4, wherein the cyclic carbonates are chosen from the group trimethylene carbonate, ethylene carbonate, propylene carbonate, diethylene glycol-bis-allyl-carbonate and derivatives thereof.

10

6. Method for preparing amorphous resorbable polymeric network materials with shape memory according to any one of claims 1 to 5, wherein the linear carbonates are chosen from the group diethyl carbonate, diphenyl carbonate and derivatives thereof.

15

7. Method for preparing amorphous resorbable polymeric network materials with shape memory according to any one of claims 1 to 6, wherein cyclic esters are chosen from the group lactones, D,L-lactide, glycolide and derivatives thereof.

20

8. Method for preparing amorphous resorbable polymeric network materials with shape memory according to any one of claims 1 to 7, wherein the linear esters are chosen from the group fumaric acid monoethyl ester, fumaric acid diethyl ester, dimethylterephthalate, diethyl terephthalate and derivatives thereof.

25

9. Method for preparing amorphous resorbable polymeric network materials with shape memory according to any one of claims 1 to 8, wherein the polymerization in step a) is a ring-opening polymerization or polycondensation.

30

10. Method for preparing amorphous resorbable polymeric network materials with shape memory according to any one of claims 1 to 9, wherein the unsaturated end group
5 is chosen from the group acrylate, methacrylate, fumarate, diacrylate, triacrylate.

11. Method for preparing amorphous resorbable polymeric network materials with shape memory according to
10 any one of claims 1 to 10, wherein the crosslinking in step c) is photocrosslinking, thermal crosslinking or redox crosslinking.

12. Method for preparing amorphous resorbable polymeric network materials with shape memory according to
15 any one of claims 1 to 11, wherein the initiator in step a) is a diol, a triol, a tetra-ol, an diamine, a triamine, a tetra-amine, a dithiol, a trithiol, or a tetra-thiol.

13. Method for preparing amorphous resorbable polymeric network materials with shape memory according to
20 any one of claims 1 to 12, wherein the initiator in step a) is chosen from the group 1,2-ethanediol, 1,3-propanediol, 1,4-butanediol, 1,5-pentanediol, 1,6-hexanediol, 1,8-
25 octanediol.

14. Method for preparing amorphous resorbable polymeric network materials with shape memory according to
any one of claims 1 to 13, wherein the initiator in step a)
30 is in the range 10^{-6} to 10^{-2} mol per total mol of monomers.

15. Method for preparing amorphous resorbable polymeric network materials with shape memory according to

any one of claims 1 to 14, wherein step a) comprises a catalyst.

16. Method for preparing amorphous resorbable polymeric network materials with shape memory according to any one of claims 1 to 15, wherein step a) comprises a catalyst which is a stannous alkyloate or a metallic compound chosen from the group stannous octoate or metallic zinc.

10

17. Method for preparing amorphous resorbable polymeric network materials with shape memory according to claim 15 or 16, wherein the catalyst concentration in step a) is in the range of 10^{-8} to 10^{-2} mol per total mol of the monomers.

15

18. Method for preparing amorphous resorbable polymeric network materials with shape memory according to any one of claims 1 to 17, wherein the polyol oligomers in step a) are prepared from two monomers chosen from the group cyclic carbonates and/or a cyclic esters and/or linear carbonates and/or linear esters and/or hydroxycarboxylic acids with a ratio between monomers which is in the range of 0.01:100 to 100:0.01 by mol.

20
25

19. Method for preparing amorphous resorbable polymeric network materials with shape memory according to any one of claims 1 to 18, wherein the preparation of the polyol oligomers in step a) comprises:

30

- i) mixing the cyclic carbonates and/or cyclic esters and/or linear carbonates and/or linear esters and/or hydroxycarboxylic acids with the initiator at a temperature

in the range of 20°C to 200°C, under inert atmosphere and under stirring;

ii) optionally adding a catalyst;

iii) maintaining the temperature of step a)

5 under stirring for 15 minutes to 4 days;

iv) bringing the mixture at room temperature.

20. Method for preparing amorphous resorbable polymeric network materials with shape memory according to
10 any one of claims 1 to 19, wherein the functionalization is carried out with methacrylic anhydride or methacryloyl chloride and an amine in an organic solvent

21. Method for preparing amorphous resorbable polymeric network materials with shape memory according to
15 any one of claims 1 to 20, wherein the crosslinking in step c) is a photocrosslinking obtained with ultraviolet light or visible light.

22. Method for preparing amorphous resorbable polymeric network materials with shape memory according to
20 any one of claims 1 to 21, wherein the initiator in step c) is chosen from the class hydroxyketone, aminoketone, phenylglyoxylate.

23. Method for preparing amorphous resorbable polymeric network materials with shape memory according to
25 any one of claims 1 to 22, wherein the initiator in step c) is 2-hydroxy-4'-(2-hydroxyethoxy)-2-methylpropiophenone.

24. Method for preparing amorphous resorbable polymeric network materials with shape memory according to
30 any one of claims 1 to 23, wherein the method further

comprises a step b1) between step b) and c) of compression molding or extrusion or injection molding or casting of the functionalized oligomer.

5 25. Method for preparing amorphous resorbable polymeric network materials with shape memory according to any one of claims 1 to 24, wherein shape changes are induced by stimuli chosen from the group thermal, electric, pH, magnetic stimuli, light or gamma irradiation, water content
10 modification.

 26. Amorphous resorbable polymeric network materials with shape memory obtainable by any one of claims 1 to 25.

15 27. Use of the amorphous resorbable polymeric network materials with shape memory as defined in claim 26 for coating surfaces, as a protective layer for thermal insulation and/or for anti-oxidation insulation, for the manufacture of packaging materials.

20 28. Use of the amorphous resorbable polymeric network materials with shape memory as defined in claim 26 for preparing medical devices.

25 29. Use of the amorphous resorbable polymeric network materials with shape memory as defined in claim 26 for preparing implants, used in tissue engineering, or drug delivery.

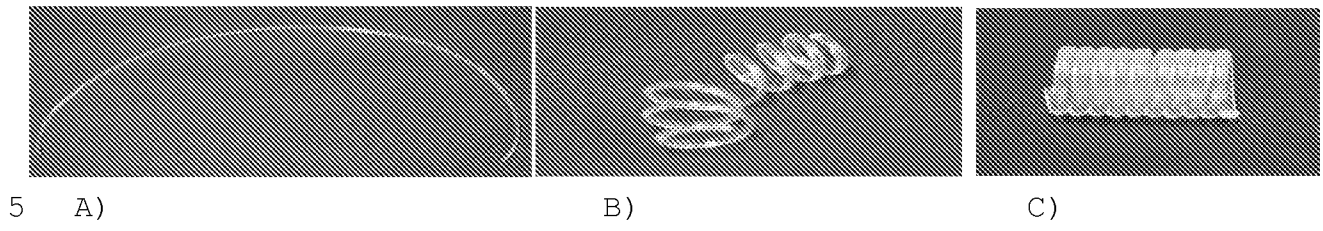


Figure 1

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/057075

A. CLASSIFICATION OF SUBJECT MATTER

INV. C08F299/04 C08J3/24 C08G63/91 C09D167/06 A61L27/58
A61L27/18

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)

C08F C08J C08G C09D 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 practical, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	EP 1 801 140 A1 (MNEMOSCIENCE GMBH [DE]) 27 June 2007 (2007-06-27)	1-26,28, 29
A	paragraph [0021] - paragraph [0024] paragraphs [0029], [0032], [0039] paragraph [0041] - paragraph [0043] paragraphs [0051], [0054]; claims	27
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A	paragraphs [0008], [0027], [0033]; claims; examples	27
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Further documents are listed in the continuation of Box C.

See patent family annex.

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"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.

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2010/057075

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	page 8, line 20 - line 24; claims; examples	27
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