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(54) Title: BIOMATERIAL

(57) **Abrégé/Abstract:**

Biomaterial formed by crosslinking a macromer having a polymeric backbone comprising units with a 1,2-diol or 1,3-diol structure and at least two pendant chains bearing crosslinkable groups and an amphiphilic comonomer.



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(54) Title: BIOMATERIAL

(57) Abstract: Biomaterial formed by crosslinking a macromer having a polymeric backbone comprising units with a 1,2-diol or 1,3-diol structure and at least two pendant chains bearing crosslinkable groups and an amphiphilic comonomer.

WO 2006/004941 A3

RELATED APPLICATION

5 The present application is related to and claims priority to U.S. Provisional Application Serial No. 60/583,852 filed June 29, 2004, the entire contents of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

10 There are many instances in which an appropriate biomaterial is needed for use in repair of tissues and in augmentation of tissues. Applications for an appropriate biomaterial include repair of defects and conditions in a tissue caused by disease, injury, or aging, repair of congenital defects and conditions in a tissue, and augmentation of tissues to provide a desirable functional, reconstructive, or cosmetic change.

15 WO 01/68721 to BioCure, Inc. discloses a composition useful for tissue bulking that includes macromers having a backbone of a polymer having units with a 1,2-diol and/or 1,3-diol structure. Such polymers include poly(vinyl alcohol) (PVA) and hydrolyzed copolymers of vinyl acetate, for example, copolymers with vinyl chloride or N-vinylpyrrolidone. The backbone polymer contains pendant chains bearing crosslinkable groups and, optionally, other modifiers. The macromers form a hydrogel when crosslinked.

20 The hydrogel taught in WO 01/68721 is suitable for many bio-applications. However, it does not have the properties necessary for a biomaterial used as an implant in many applications. In particular it does not have properties necessary for a biomaterial undergoing the repeated stresses placed on a spinal disc nucleus, for example.

25 SUMMARY OF THE INVENTION

The invention relates to biomaterials and to compositions for forming the biomaterials. More specifically, the invention relates to biomaterials comprising a hydrogel formed from compositions including a crosslinkable macromonomer (also referred to herein as macromers) and amphiphilic comonomers. The inclusion of the comonomer provides enhanced compressibility
30 and integrity to the hydrogel.

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to biomaterials and to compositions for forming the biomaterials. More specifically, the invention relates to biomaterials having suitable properties for replacement or augmentation of certain body tissues.

5 The biomaterial can be used for bioapplications requiring a biomaterial with certain properties. Those properties generally include that the biomaterial be biocompatible and, desirably, be implantable using a minimally invasive procedure. The biomaterial is formed from a composition that is preferably injectable. The biomaterial formed in situ conforms in shape to the space into which it is injected.

10 The biomaterial should desirably be compressible, having a compression modulus between 0.2 to 40 MPa, preferably 0.5 to 3 MPa at 10-30% strain, and is fatigue resistant, up to but not limited to 50M cycles of mechanical stresses such as compression, flexion, and torsion. The biomaterial is desirably wear resistant since debris can potentially cause inflammation and pain. The biomaterial desirably has a yield load of about 1000-6000 Newtons, a 60-70% strain at
15 failure. Other features that may be desirable are the ability to withstand cyclic loading under physiologic conditions. Furthermore, it may be advantageous for the biomaterial to swell upon implantation to fill the space into which it is implanted or to provide lift. Additional potential design features include adhesion to the native tissue and recoil after compression, for example 100% after approximately 30 minutes of relaxation.

20 Besides use as a prosthetic spinal disc nucleus, other potential applications include, but are not limited to, replacement of cartilage found in joints, e.g. knee meniscus, temporomandibular joint, wrist, etc.; vertebroplasty (the augmentation or mechanical support of a compromised vertebrae); bone cement (the adhesive or material used to join bone fragments together); bone filler (the material that fills cavities in bone either permanently or temporarily as new bone fills in
25 the defect); adjunct to metal cages for spinal fixation with screws (the polymer may provide additional mechanical support); and support of fractures to non-weight bearing bones, e.g. the orbital bones of the face.

I. The Biomaterials

 The biomaterials are made using macromers similar to those described in WO 01/68721.
30 It has been discovered, however, that the addition of certain comonomers gives the biomaterials unexpected properties. The comonomers are described in detail below.

Macromers

The macromers have a backbone of a polymer comprising units with a 1,2-diol and/or 1,3-diol structure and at least two pendant chains including a crosslinkable group. The macromer backbone can optionally have other pendant chains containing modifiers.

5 Polyvinyl alcohols (PVAs) that can be used as the macromer backbone include commercially available PVAs, for example Vinol[®] 107 from Air Products (MW 22,000 to 31,000, 98 to 98.8% hydrolyzed), Polysciences 4397 (MW 25,000, 98.5% hydrolyzed), BF 14 from Chan Chun, Elvanol[®] 90-50 from DuPont and UF-120 from Unitika. Other producers are, for example, Nippon Gohsei (Gohsenol[®]), Monsanto (Gelvatol[®]), Wacker (Polyviol[®]), Kuraray, Deriki, and
 10 Shin-Etsu. In some cases it is advantageous to use Mowiol[®] products from Hoechst, in particular those of the 3-83, 4-88, 4-98, 6-88, 6-98, 8-88, 8-98, 10-98, 20-98, 26-88, and 40-88 types.

It is also possible to use copolymers of hydrolyzed or partially hydrolyzed vinyl acetate, which are obtainable, for example, as hydrolyzed ethylene-vinyl acetate (EVA), or vinyl chloride-vinyl acetate, N-vinylpyrrolidone-vinyl acetate, and maleic anhydride-vinyl acetate. If the
 15 macromer backbones are, for example, copolymers of vinyl acetate and vinylpyrrolidone, it is again possible to use commercially available copolymers, for example the commercial products available under the name Luviskol[®] from BASF. Particular examples are Luviskol VA 37 HM, Luviskol VA 37 E and Luviskol VA 28. If the macromer backbones are polyvinyl acetates, Mowilith 30 from Hoechst is particularly suitable.

20 The PVA preferably has a molecular weight of at least about 2,000. As an upper limit, the PVA may have a molecular weight of up to 300,000. Preferably, the PVA has a molecular weight of up to about 130,000, more preferably up to about 60,000, and especially preferably up to about 14,000.

The PVA usually has a poly(2-hydroxy)ethylene structure. The PVA may also include
 25 hydroxy groups in the form of 1,2-glycols. The PVA can be a fully hydrolyzed PVA, with all repeating groups being -CH₂-CH(OH), or a partially hydrolyzed PVA with varying proportions (1% to 25%) of pendant ester groups. PVA with pendant ester groups have repeating groups of the structure CH₂-CH(OR) where R is COCH₃ group or longer alkyls, as long as the water solubility of the PVA is preserved. The ester groups can also be substituted by acetaldehyde or
 30 butyraldehyde acetals that impart a certain degree of hydrophobicity and strength to the PVA. For an application that requires an oxidatively stable PVA, the commercially available PVA can be broken down by NaIO₄-KMnO₄ oxidation to yield a small molecular weight (2000 to 4000) PVA.

The PVA is prepared by basic or acidic, partial or virtually complete hydrolysis of polyvinyl acetate. In a preferred embodiment, the PVA comprises less than 50% of acetate units,

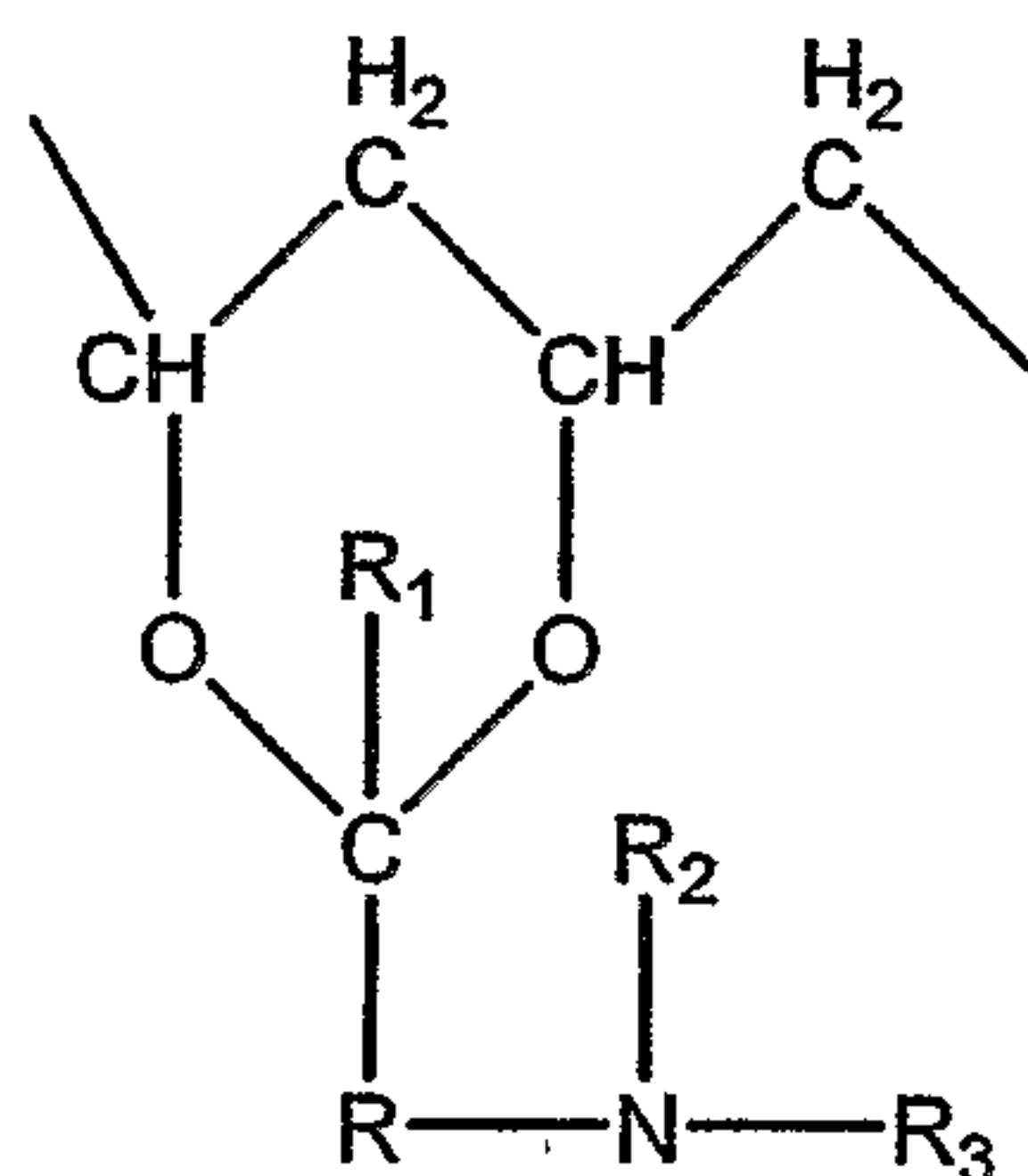
especially less than about 25% of acetate units. Preferred amounts of residual acetate units in the PVA, based on the sum of alcohol units and acetate units, are approximately from 3 to 25%.

The macromers have at least two pendant chains containing groups that can be crosslinked. Group is defined herein to include single polymerizable moieties, such as acrylates, as well as larger crosslinkable regions, such as oligomeric or polymeric regions. The crosslinkers are desirably present in an amount of from approximately 0.01 to 10 milliequivalents of crosslinker per gram of backbone (meq/g), more desirably about 0.05 to 1.5 meq/g. The macromers can contain more than one type of crosslinkable group.

The pendant chains are attached via the hydroxyl groups of the backbone. Desirably, the pendant chains having crosslinkable groups are attached via cyclic acetal linkages to the 1,2-diol or 1,3-diol hydroxyl groups. Desirable crosslinkable groups include (meth)acrylamide, (meth)acrylate, styryl, vinyl ester, vinyl ketone, vinyl ethers, etc. Particularly desirable are ethylenically unsaturated functional groups. A particularly desirable crosslinker is N-acryloyl-aminoacetaldehyde dimethylacetal (NAAADA) in an amount of between about 6 and 21 crosslinkers per macromer.

Specific macromers that are suitable for use in the compositions are disclosed in U.S. Patent Nos. 5,508,317, 5,665,840, 5,807,927, 5,849,841, 5,932,674, 5,939,489, and 6,011,077.

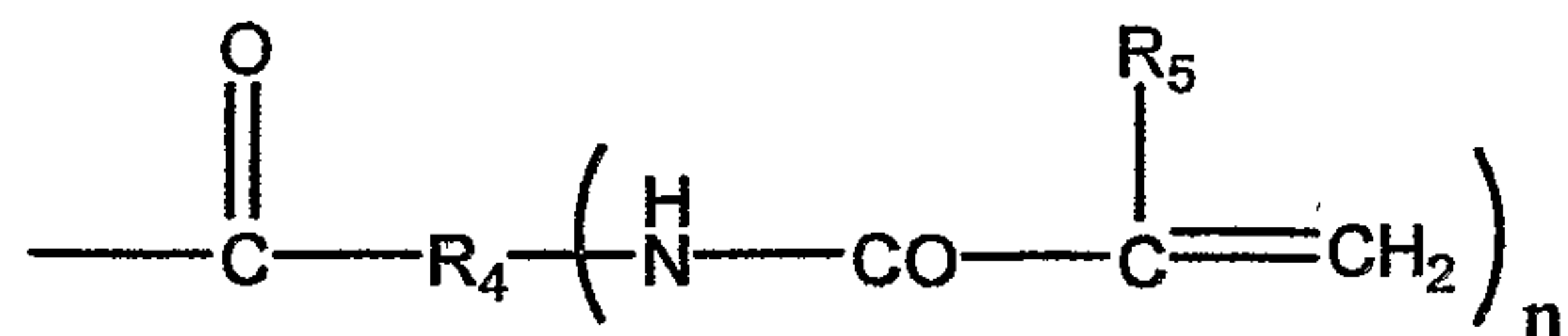
In one embodiment, units containing a crosslinkable group conform, in particular, to the formula I



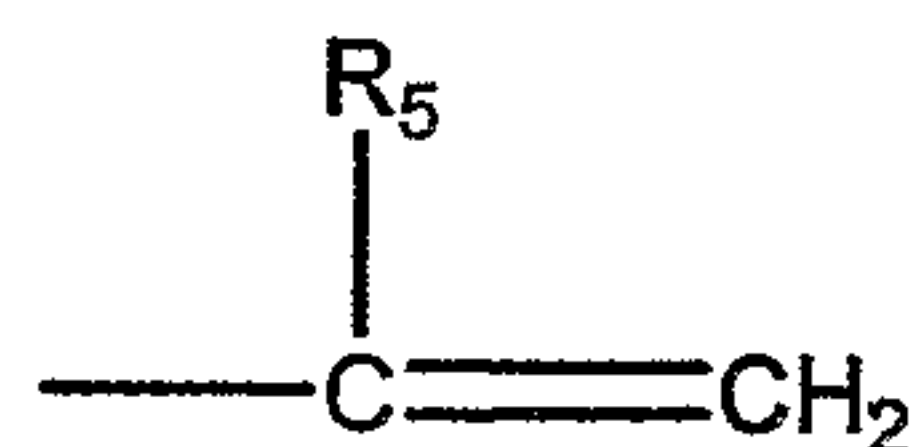
in which R is a linear or branched C₁-C₈ alkylene or a linear or branched C₁-C₁₂ alkane. Suitable alkylene examples include octylene, hexylene, pentylene, butylene, propylene, ethylene, methylene, 2-propylene, 2-butylene and 3-pentylene. Preferably lower alkylene R has up to 6 and especially preferably up to 4 carbon atoms. The groups ethylene and butylene are especially preferred. Alkanes include, in particular, methane, ethane, n- or isopropane, n-, sec- or tert-butane, n- or isopentane, hexane, heptane, or octane. Preferred groups contain one to four carbon atoms, in particular one carbon atom.

R₁ is hydrogen, a C₁-C₆ alkyl or a cycloalkyl, for example, methyl, ethyl, propyl or butyl and R₂ is hydrogen or a C₁-C₆ alkyl, for example, methyl, ethyl, propyl or butyl. R₁ and R₂ are preferably each hydrogen.

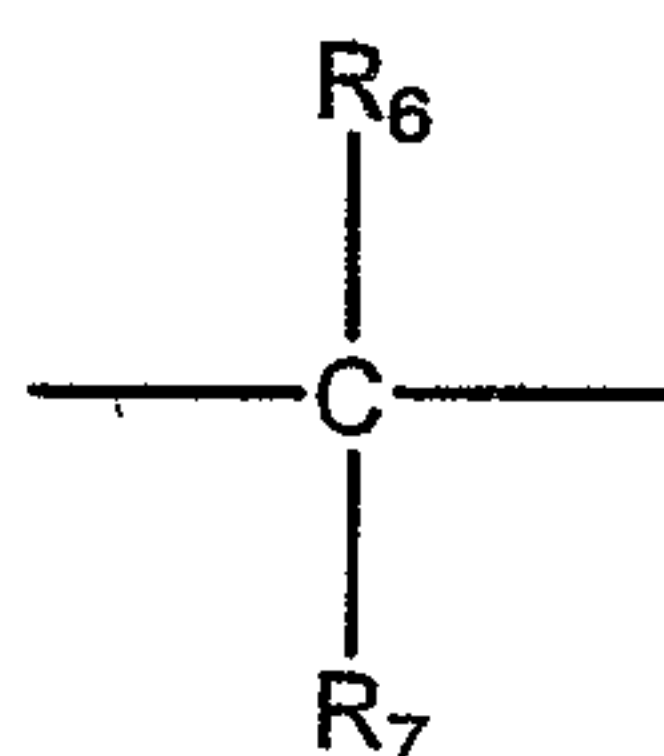
R₃ is an olefinically unsaturated electron attracting copolymerizable radical having up to 25 carbon atoms. In one embodiment, R₃ has the structure



where R₄ is the



group if n=zero, or the



10

bridge if n=1;

R₅ is hydrogen or C₁-C₄ alkyl, for example, n-butyl, n- or isopropyl, ethyl, or methyl; n is zero or 1, preferably zero; and

R₆ and R₇, independently of one another, are hydrogen, a linear or branched C₁-C₈ alkyl, aryl or cyclohexyl, for example one of the following: octyl, hexyl, pentyl, butyl, propyl, ethyl, methyl, 2-propyl, 2-butyl or 3-pentyl. R₆ is preferably hydrogen or the CH₃ group, and R₇ is preferably a C₁-C₄ alkyl group. R₆ and R₇ as aryl are preferably phenyl.

In another embodiment, R₃ is an olefinically unsaturated acyl group of formula R₈-CO-, in which R₈ is an olefinically unsaturated copolymerizable group having from 2 to 24 carbon atoms, preferably from 2 to 8 carbon atoms, especially preferably from 2 to 4 carbon atoms. The olefinically unsaturated copolymerizable radical R₈ having from 2 to 24 carbon atoms is preferably alkenyl having from 2 to 24 carbon atoms, especially alkenyl having from 2 to 8 carbon atoms and especially preferably alkenyl having from 2 to 4 carbon atoms, for example ethenyl, 2-propenyl, 3-propenyl, 2-butenyl, hexenyl, octenyl or dodecenyl. The groups ethenyl

and 2-propenyl are preferred, so that the group $-\text{CO}-\text{R}_8$ is the acyl radical of acrylic or methacrylic acid.

In another embodiment, the group R_3 is a radical of formula



5 wherein p and q are zero or one and

R_9 and R_{10} are each independently lower alkylene having from 2 to 8 carbon atoms, arylene having from 6 to 12 carbon atoms, a saturated divalent cycloaliphatic group having from 6 to 10 carbon atoms, arylenealkylene or alkylenearylene having from 7 to 14 carbon atoms or arylenealkylenearylene having from 13 to 16 carbon atoms, and

10 R_8 is as defined above.

Lower alkylene R_9 or R_{10} preferably has from 2 to 6 carbon atoms and is especially straight-chained. Suitable examples include propylene, butylene, hexylene, dimethylethylene and, especially preferably, ethylene.

15 Arylene R_9 or R_{10} is preferably phenylene that is unsubstituted or is substituted by lower alkyl or lower alkoxy, especially 1,3-phenylene or 1,4-phenylene or methyl-1,4-phenylene.

A saturated divalent cycloaliphatic group R_9 or R_{10} is preferably cyclohexylene or cyclohexylene-lower alkylene, for example cyclohexylenemethylene, that is unsubstituted or is substituted by one or more methyl groups, such as, for example, trimethylcyclohexylenemethylene, for example the divalent isophorone radical.

20 The arylene unit of alkylenearylene or arylenealkylene R_9 or R_{10} is preferably phenylene, unsubstituted or substituted by lower alkyl or lower alkoxy, and the alkylene unit thereof is preferably lower alkylene, such as methylene or ethylene, especially methylene. Such radicals R_9 or R_{10} are therefore preferably phenylenemethylene or methylenephenylene.

25 Arylenealkylenearylene R_9 or R_{10} is preferably phenylene-lower alkylene-phenylene having up to 4 carbon atoms in the alkylene unit, for example phenyleneethylenephenylene.

The groups R_9 and R_{10} are each independently preferably lower alkylene having from 2 to 6 carbon atoms, phenylene, unsubstituted or substituted by lower alkyl, cyclohexylene or cyclohexylene-lower alkylene, unsubstituted or substituted by lower alkyl, phenylene-lower alkylene, lower alkylene-phenylene or phenylene-lower alkylene-phenylene.

30 The group $-\text{R}_9\text{-NH-CO-O-}$ is present when q is one and absent when q is zero. Macromers in which q is zero are preferred.

The group $-\text{CO-NH-(R}_9\text{-NH-CO-O)}_q\text{-R}_{10}\text{-O-}$ is present when p is one and absent when p is zero. Macromers in which p is zero are preferred.

In macromers in which p is one, q is preferably zero. Macromers in which p is one, q is zero, and R₁₀ is lower alkylene are especially preferred.

All of the above groups can be monosubstituted or polysubstituted, examples of suitable substituents being the following: C₁-C₄ alkyl, such as methyl, ethyl or propyl, -COOH, -OH, -SH, C₁-C₄ alkoxy (such as methoxy, ethoxy, propoxy, butoxy, or isobutoxy), -NO₂, -NH₂, -NH(C₁-C₄), -NH-CO-NH₂, -N(C₁-C₄ alkyl)₂, phenyl (unsubstituted or substituted by, for example, -OH or halogen, such as Cl, Br or especially I), -S(C₁-C₄ alkyl), a 5- or 6-membered heterocyclic ring, such as, in particular, indole or imidazole, -NH-C(NH)-NH₂, phenoxyphenyl (unsubstituted or substituted by, for example, -OH or halogen, such as Cl, Br or especially I), an olefinic group, such as ethylene or vinyl, and CO-NH-C(NH)-NH₂.

Preferred substituents are lower alkyl, which here, as elsewhere in this description, is preferably C₁-C₄ alkyl, C₁-C₄ alkoxy, COOH, SH, -NH₂, -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)₂ or halogen. Particular preference is given to C₁-C₄ alkyl, C₁-C₄ alkoxy, COOH and SH.

For the purposes of this invention, cycloalkyl is, in particular, cycloalkyl, and aryl is, in particular, phenyl, unsubstituted or substituted as described above.

One particularly preferred macromer has a PVA backbone (14 kDa, 17% acetate incorporation) modified with 0.45 meq/g N-acrylamidoacetaldehyde dimethyl acetal (NAAADA) pendant polymerizable groups (about 6.3 crosslinks per chain). Another particularly preferred macromer has a PVA backbone (14 kDa, 17% acetate incorporation) modified with 1.07 meq/g N-acrylamidoacetaldehyde dimethyl acetal (NAAADA) pendant polymerizable groups (about 15 crosslinks per chain).

Comonomers

WO 01/68721 describes the addition of comonomers that are hydrophilic or hydrophobic to change the characteristics of the hydrogel. Surprisingly, it has been found that the inclusion of an amphiphilic comonomer adds certain qualities such as improving the yield load of the material.

As used herein, the term amphiphilic means that one portion of the molecule is hydrophilic and one portion of the molecule is hydrophobic. In one embodiment, the hydrophilic portion is water soluble and the hydrophobic portion is not water soluble. The monomer as a whole is preferably wholly or partially water soluble. Examples of useful amphiphilic comonomers are diacetone acrylamide (DAA), N-vinyl caprolactam, N-(butoxymethyl)acrylamide, N-acrylmorpholine, crotonamide, N,N-dimethyl acrylamide, N-octadecylacrylamide, and acrylamide.

When the amphiphilic comonomers are copolymerized with the macromers described above, a hydrogel results that is more cohesive and has higher compressive strength than a

hydrogel not containing the amphiphilic comonomer. Desirably, the comonomer is included in an amount ranging from about 5 to 95 weight percent, most preferably 40-60 weight percent (where weight percent is the percent by weight of the total solution).

Crosslinking Initiators

5 The ethylenically unsaturated groups of the macromer and comonomer can be crosslinked via free radical initiated polymerization, including via photoinitiation, redox initiation, and thermal initiation. Systems employing these means of initiation are well known to those skilled in the art.

10 In one embodiment, a two part redox system is employed. One part of the system contains a reducing agent. Examples of reducing agents are ferrous salts (such as ferrous gluconate dihydrate, ferrous lactate dihydrate, or ferrous acetate), cuprous salts, cerous salts, cobaltous salts, permanganate, manganous salts, and tertiary amines such as N,N,N,N-tetramethylethylene diamine (TMEDA). The other half of the solution contains an oxidizing agent such as hydrogen peroxide, t-butyl hydroperoxide, t-butyl peroxide, benzoyl peroxide, cumyl peroxide, potassium
15 persulfate, or ammonium persulfate.

Either or both of the redox solutions can contain macromer, or it may be in a third solution. The solutions containing reductant and oxidant are combined to initiate the crosslinking. Ascorbate, for example, can be used as a coreductant to recycle the reductant and reduce the amount needed. This can reduce the toxicity of a ferrous based system.

20 Thermal initiation can be accomplished using ammonium persulfate as the crosslinking initiator and optionally using N,N,N,N-tetramethylethylene diamine (TMEDA), which is an amine accelerator.

The desired amounts of the components will be determined by concerns related to gelation speed, toxicity, extent of gelation desired, and stability.

25 Modifier Groups

The macromers can include further modifier groups and crosslinkable groups. Some such groups are described in U.S. Patent Nos. 5,508,317, 5,665,840, 5,807,927, 5,849,841, 5,932,674, 5,939,489, and 6,011,077 and include hydrophobic modifiers such as acetaldehyde diethyl acetal (AADA), butyraldehyde, and acetaldehyde or hydrophilic modifiers such as N-(2,2-dimethoxy-ethyl) succinamic acid, amino acetaldehyde dimethyl acetal, and aminobutyraldehyde dimethyl
30 acetal. These groups may be attached to the macromer backbone, or to other monomeric units included in the backbone. Crosslinkable groups and optional modifier groups can be bonded to the macromer backbone in various ways, for example through a certain percentage of the 1,3-diol units being modified to give a 1,3-dioxane, which contains a crosslinkable group, or a further

modifier, in the 2-position. Modifiers include those to modify the hydrophobicity, active agents or groups to allow attachment of active agents, photoinitiators, modifiers to enhance or reduce adhesiveness, modifiers to impart thermoresponsiveness, modifiers to impart other types of responsiveness, and additional crosslinking groups.

5 Attaching a cellular adhesion promoter to the macromers can enhance cellular attachment or adhesiveness of the composition. These agents are well known to those skilled in the art and include carboxymethyl dextran, proteoglycans, collagen, gelatin, glucosaminoglycans, fibronectin, lectins, polycations, and natural or synthetic biological cell adhesion agents such as RGD peptides.

10 Having pendant ester groups that are substituted by acetaldehyde or butyraldehyde acetals, for example, can increase the hydrophobicity of the macromers and the formed hydrogel. One particularly useful hydrophobic modifying group is acetaldehyde diethyl acetal (AADA) present in an amount from about 0 to 4 milliequivalents per gram (meq/ g) of PVA.

15 Hydrophilic modifiers such as $-\text{COOH}$ in the form of N-(2,2-dimethoxy-ethyl) succinamic acid in an amount from about 0 to 2 meq / g PVA can be added to the composition to enhance performance of the composition, such as swelling.

It may also be desirable to include on the macromer a molecule that allows visualization of the formed hydrogel. Examples include dyes and molecules visualizable by magnetic resonance imaging.

20 Contrast Agents

The biomaterial can include a contrast agent, which is a biocompatible material capable of being monitored by, for example, radiography. The contrast agent can be water soluble or water insoluble. Examples of water soluble contrast agents include metrizamide, iopamidol, iothalamate sodium, iodomide sodium, and meglumine. Iodinated liquid contrast agents include 25 Omnipaque®, Visipaque®, and Hypaque-76®. Examples of water insoluble contrast agents are tantalum, tantalum oxide, barium sulfate, gold, tungsten, and platinum. These are commonly available as particles preferably having a size of about 10 μm or less. Coated-fibers, such as tantalum-coated Dacron fibers can also be used.

30 The contrast agent is incorporated temporarily or permanently in the biomaterial. Both solid and liquid contrast agents can be simply mixed with a solution of the liquid composition prior to crosslinking of the macromers and comonomers. Liquid contrast agent can be mixed at a concentration of about 10 to 80 volume percent, more desirably about 20 to 50 volume percent. Solid contrast agents are desirably included in an amount of about 5 to 40 weight percent, more preferably about 5 to 20 weight percent.

Active Agents

The biomaterial can include an effective amount of one or more biologically or structurally active agents. It may be desirable to deliver the active agent from the formed hydrogel. Biologically active agents that it may be desirable to deliver include prophylactic, therapeutic, and diagnostic agents including organic and inorganic molecules and cells (collectively referred to herein as an "active agent" or "drug"). A wide variety of active agents can be incorporated into the hydrogel. Release of the incorporated additive from the hydrogel is achieved by diffusion of the agent from the hydrogel, degradation of the hydrogel, and/or degradation of a chemical link coupling the agent to the polymer. In this context, an "effective amount" refers to the amount of active agent required to obtain the desired effect.

Examples of active agents that can be incorporated include, but are not limited to, anti-angiogenic agents, growth factors, chemotherapeutic agents, radiation delivery devices, such as radioactive seeds for brachytherapy, gene therapy compositions, analgesics for the treatment of pain, for example ibuprofen, acetaminophen, and acetylsalicylic acid; antibiotics for the treatment of infection, for example tetracyclines and penicillin and derivatives; and additives for the treatment of infection, for example silver ions, silver (metallic), and copper (metallic).

Chemotherapeutic agents that can be incorporated include water soluble chemotherapeutic agents, such as cisplatin (platinol), doxorubicin (adriamycin, rubex), or mitomycin C (mutamycin). Other chemotherapeutic agents include iodinated fatty acid ethyl esters of poppy seed oil, such as lipiodol.

Cells can be incorporated into the composition, including cells to encourage tissue growth or cells to secrete a desired active agent. For example, cells that can be incorporated include stem cells, autologous nucleus pulposus cells, transplanted autologous nucleus pulposus cells, autologous tissue, fibroblast cells, chondrocyte cells, notochordal cells, allograft tissue and cells, and xenograft tissue and cells.

It may be advantageous to incorporate material of biological origin or biological material derived from synthetic methods of manufacture such as proteins, polypeptides, polysaccharides, proteoglycans, and growth factors.

It may be desirable to include additives to improve the swelling and space-filling properties of the biomaterial, for example, dehydrated spheres, fibers, etc., hydrophilic polymers, such as AMPS, etc., or hydrocolloids, such as agar, alginates, carboxymethylcellulose, gelatin, guar gum, gum arabic, pectin, starch, and xanthum gum.

Other additives that may prove advantageous are additives to improve the adhesive properties of the biomaterial, including positively charged polymers, such as Quat, etc., PVA

~~modified with positive-charged moieties~~ attached to the backbone, cyanoacrylates, PVA modified with cyanoacrylate moieties attached to the backbone, chitosan, and mussel-based adhesives.

Incorporation of additives to improve the toughness properties of the biomaterial may prove desirable such as low modulus spheres, fibers, etc that act as "crack arrestors" and high modulus spheres, fibers, etc that act as "reinforcing" agents.

Active agents can be incorporated into the composition simply by mixing the agent with the composition prior to administration. The active agent will then be entrapped in the hydrogel that is formed upon administration of the composition. Active agents can be incorporated into preformed articles through encapsulation and other methods known in the art and discussed further below. The active agent can be in compound form or can be in the form of degradable or nondegradable nano or microspheres. In some cases, it may be possible and desirable to attach the active agent to the macromer or to the preformed article. The active agent may also be coated onto the surface of the preformed article. The active agent may be released from the macromer or hydrogel over time or in response to an environmental condition.

15 Other Additives

It may be desirable to include a peroxide stabilizer in redox initiated systems. Examples of peroxide stabilizers are Dequest® products from Solutia Inc., such as for example Dequest® 2010 and Dequest® 2060S. These are phosphonates and chelants that offer stabilization of peroxide systems. Dequest® 2060S is diethylenetriamine penta(methylene phosphonic acid). These can be added in amounts as recommended by the manufacturer.

20 II. Methods of Making and Using the Biomaterials

In one embodiment of the method for making the biomaterials, the amphiphilic comonomer is mixed with the macromer in the desired concentrations for each and proportion to each other. The mixture is then exposed to conditions to encourage polymerization. For example, thermal initiation can be used, wherein a thermal initiator such as ammonium persulfate is included in the solution and the solution is then heated. Redox polymerization can be used wherein a reducing agent is included in one part and an oxidant is included in the second part, and polymerization occurs when the parts are combined.

According to the general method of use, an effective amount of the composition is administered to the desired administration site. In one embodiment, the macromer and comonomer are crosslinked in situ. In another embodiment, the macromer and comonomer are formed into a hydrogel prior to administration. The composition may be administered over a number of treatment sessions.

An especially advantageous use of the biomaterial is in situ crosslinking of the biomaterial, wherein the liquid precursors are delivered via minimally invasive techniques.

5 The macromer/ comonomer solution is thoroughly mixed with other components, such as a contrast agent, an initiator, and any additional accelerator or catalytic agents. The solution is then drawn up in a 10ml Luer-lok syringe with care being taken to expel any air bubbles. A blunt needle of about 18 Gauge is attached to the syringe. The macromer and comonomer solution is then delivered under fluoroscopic guidance until the space has been filled to the desired level. The macromer/ comonomer solution will then preferably cross-link into the formed hydrogel within 2-15 minutes post injection.

10 In an alternative delivery method a twin syringe applicator connected to a common 18 Gauge needle or mixing tip can be used. A macromer/ comonomer solution is prepared containing an initiator and optionally a contrast agent and is drawn in to a 5 ml Luer-Lok syringe and attached to the twin syringe applicator. A second solution is prepared with the accelerator/catalytic species and optional contrast agent, drawn into another 5ml Luer-Lok syringe and attached to the twin syringe applicator. The two solutions are simultaneously delivered into the space under fluoroscopic guidance until the space has been filled to the desired level. The macromers/ comonomers will then preferably cross-link in to the formed polymer within 2 to 15 minutes post injection.

20 The viscosity of the composition is, within wide limits, not critical, but the solution should preferably be a flowable solution that can be delivered through an appropriately sized catheter or syringe needle. For delivery through a microcatheter, a viscosity in the range of about 10 to 50 cp is desirable. The viscosity can be substantially higher for delivery through a syringe needle, such as, for example 20 to 300 cp without mechanical assistance or 100 to 500 cp with mechanical assistance. The viscosity will generally be controlled by the molecular weight of the macromers, the solids content of the solution, and the type and amount of contrast agent present (if any). The solids content of the solution will preferably range from about 2 percent by weight to about 30 percent by weight, desirably from about 6 to 12 percent by weight.

25 The crosslinking initiator is mixed with the macromer and comonomer composition before administration, during administration, or after administration. For example, a redox system can be mixed with the composition at the time of administration. In one embodiment, the crosslinking initiator may be present at the site of administration. For example, the initiator could be a substance, such as charged blood components, present at the site. Macromers and comonomers can be used that crosslink when they contact each other. These can be mixed before, during, or after administration. In one embodiment, the crosslinking initiator is an applied stimulus, such as

light or heat, which causes crosslinking. Suitable initiators are known for thermal, photo, and redox initiated polymerization. In a redox initiated system employing ferrous ion, peroxide, and ascorbate, the desired amounts of the components will be determined by concerns related to gelation speed, toxicity, extent of gelation desired, and stability.

5 It may be desirable, if initiator is added before administration, to use a system that provides delayed crosslinking so that the composition does not gel too early. Moreover, using delayed curing, the composition can assume or be formed into a desired shape before complete curing has occurred.

10 In some embodiments, the composition should be injected before substantial crosslinking of the macromers has occurred. This allows the macromers to continue crosslinking in situ and prevents blockage of the syringe needle or catheter with gelled polymer. In addition, such in situ crosslinking may allow anchoring of the hydrogel to host tissue by covalently bonding with collagen molecules present within the host tissue.

15 Since the compositions preferably comprise no undesired low molecular weight constituents, the crosslinked hydrogel products also comprise no such constituents. The bulking and coating agents obtainable by the compositions are therefore distinguished, in an advantageous embodiment, by the fact that they are extremely clean.

20 In another embodiment, the composition can be formed into a hydrogel article prior to implantation. The preformed article can be implanted similarly to how solid implants are presently implanted.

The examples below serve to further illustrate the invention, to provide those of ordinary skill in the art with a complete disclosure and description of how the compounds, compositions, articles, devices, and/or methods claimed herein are made and evaluated, and are not intended to limit the scope of the invention. In the examples, unless expressly stated otherwise, amounts and percentages are by weight, temperature is in degrees Celsius or is at ambient temperature, and pressure is at or near atmospheric.

Example 1: Prior Art

30 PVA (mw = 14,000) was modified with 0.45 mmol/g of N-acryloyl-aminoacetaldehyde dimethylacetal (NAAADA) as crosslinker (6.3 xl/ chain). 10g of a 20% (w/w) modified-PVA solution in water was mixed with 1g of a 10% (w/w) solution of ammonium persulfate and then added to one barrel of a dual syringe applicator fitted with a 2 cm long mixing tip. Separately, 10 g of a 20% (w/w) aqueous modified-PVA solution was mixed with 50 µl of N,N,N,N-tetramethylethylene diamine (TMEDA) then placed in the second barrel of the dual syringe applicator. The mixture was injected into a disc mold wherein a hydrogel was quickly formed in

about 20 seconds at room temperature. The hydrogel was transparent, soft, and compressible but brittle.

Example 2

5 The same modified PVA was used as in Example 1. The comonomer diacetone acrylamide (DAA) (4.2 g) was dissolved in 20 g of a 30% (w/w) modified-PVA solution and 0.8 g of a 2% Irgacure photoinitiator solution. The solution was dispensed into a disc mold then irradiated with a UV light source for 3×90 seconds. The hydrogel was opaque, firm and tough yet compressible.

Example 3

10 The same modified PVA was used as in Example 1. 2.5 g of the comonomer DAA was slowly dissolved in 10 g of a 20% (w/w) modified-PVA solution. 3 g of the resulting solution was mixed with 0.3 g of a 10% (w/w) solution of ammonium persulfate then added to one barrel of a dual syringe applicator fitted with a 2 cm long mixing tip. Another 3 g of the modified-PVA-DAA solution was mixed with 15 μ l of TMEDA then placed in the second barrel of the dual
15 syringe applicator. The mixture was injected to a disc mold wherein a polymer formed in about 2.5 minutes at room temperature. The disc was opaque, firm, and compressible.

Example 4

PVA (mw = 14,000) was modified with 0.55 mmol/g of NAAADA and 3 mmol/g acetaldehyde dimethyl acetal (a hydrophobic modifier). 20 g of the comonomer DAA was slowly
20 dissolved in 20g of a 23% (w/w) modified-PVA solution. To 3 g of the resulting solution was added 0.3 g of a 10% ammonium persulfate solution. Upon thorough mixing, 15 μ l of TMEDA was added, mixed for approximately 5 seconds, then delivered to a disc mold, resulting in the quick formation of a polymer. The disc was opaque-white, very firm and compressible.

Example 5

25 The same modified PVA was used as in Example 4. 2.0 g of the comonomer DAA was dissolved in 10 g of a 23% (w/w) modified-PVA solution and 0.45 g of a 2% Irgacure photoinitiator solution. The solution was dispensed in to a disc mold then irradiated with a UV light source for 3×90 seconds. The resulting hydrogel was opaque-white, very firm and compressible.

Example 6

30 PVA (mw = 31,000) was modified with 0.55 mmol/g of NAAADA and 3 mmol/g acetaldehyde dimethyl acetal. 20g of the comonomer DAA was slowly dissolved in 20 g of a 19% (w/w) PVA solution. 0.3 g of a 10% ammonium persulfate solution and 30 mg of N,N-dimethylacrylamide were added to 3 g of the resulting solution. Upon thorough mixing, 15 μ L of

TMEDA was added, mixed for approximately 5 seconds, then delivered in to a disc mold. The resulting hydrogel was opaque-white, very firm, and compressible.

Example 7

PVA (mw = 14,000) was modified with 1.07 mmol/g of N-acryloyl-aminoacetaldehyde dimethylacetal (NAAADA) as crosslinker and 2.7 mmol/g of acetaldehyde diethyl acetal (AADA). 20 g of comonomer DAA was slowly dissolved in 20 g of a 24% (w/w) PVA solution. 50 mg of ammonium persulfate was dissolved in 5 g of the resulting solution. 20 μ m TMEDA was added and mixed for 20 seconds, then delivered into a disc mold. The resulting hydrogel was opaque-white and had a compression yield load of 4800 N.

Example 8

PVA (mw = 14,000) was modified with 1.07 mmol/g of N-acryloyl-aminoacetaldehyde dimethylacetal (NAAADA) as crosslinker, 2.7 mmol/g of l acetaldehyde diethyl acetal (AADA), and 0.5 mmol/ g of amino acetaldehyde diethyl acetal. 20 g of comonomer DAA was slowly dissolved in 20 g of a 24% (w/w) PVA solution. 25 mg of ammonium persulfate was dissolved in 5 g of the resulting solution. 20 μ l TMEDA was added and mixed for 20 seconds, then delivered into a disc mold. The resulting hydrogel was slightly opaque and had a compression yield load of 4600 N.

Example 9

PVA (mw = 14,000) was modified with 1.07 mmol/g of N-acryloyl-aminoacetaldehyde dimethylacetal (NAAADA) as crosslinker, 2.5 mmol/g of acetaldehyde diethyl acetal (AADA), and 1.0 mmol/ g of N-(2,2-dimethoxy-ethyl)succinamic acid. 14 g of comonomer DAA was slowly dissolved in 20 g of a 24% (w/w) PVA solution. 25 mg of ammonium persulfate was dissolved in 5 g of the resulting solution. 20 μ l TMEDA was added and mixed for 20 seconds, then delivered into a disc mold. The resulting hydrogel was translucent and has a compression yield load of 2700 N.

The following chart compares the results of examples 7-9:

EX	hydrophobic modifier	hydrophilic modifier	yield load
7	2.7 mmol/g acetaldehyde diethyl acetal (AADA)		4800 N
8	2.7 mmol/g acetaldehyde diethyl acetal (AADA)	0.5 mmol/ g aminoacetaldehydediethyl acetal	4600 N
9	2.5 mmol/g acetaldehyde diethyl acetal (AADA)	1.0 mmol/ g N-(2,2-dimethoxy-ethyl)succinamic acid.	2700 N

Example 10: Comparison of Comonomer Concentration

The following chart compares the effect of comonomer concentration on yield load. The comonomer was diacetone acrylamide (DAA).

PVA:DAA	yield load
1:1	4289
1:0.7	2385
1:0.6	1294
1:0.5	1015

- 5 Modifications and variations of the present invention will be apparent to those skilled in the art from the forgoing detailed description. All modifications and variations are intended to be encompassed by the following claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety.

CLAIMS

What is claimed is:

1. A biomaterial comprising a hydrogel formed from a macromer having a polymeric backbone comprising units with a 1,2-diol or 1,3-diol structure and at least two pendant chains bearing crosslinkable groups and an amphiphilic comonomer.
2. The biomaterial of claim 1, wherein the hydrogel has a yield load between about 1000 to 6000 Newtons.
3. The biomaterial of claim 1, wherein the hydrogel has a compression modulus between about 0.2 and 40 MPa at 10-30% strain
4. The biomaterial of claim 1, wherein the comonomer is selected from the group consisting of diacetone acrylamide (DAA), N-vinyl caprolactam, N-(butoxymethyl)acrylamide, N-acroyl morpholine, crotonamide, N,N-dimethyl acrylamide, N-octadecylacrylamide, and acrylamide.
5. The biomaterial of claim 1, wherein the comonomer is diacetone acrylamide (DAA) at a concentration between about 40-60% by weight.
6. The biomaterials of claim 1, wherein the macromer has a poly(vinyl alcohol) backbone having a molecular weight of between about 2000 and 60,000 and the pendant chains bearing crosslinkable groups are N-acrylamidoacetaldehyde dimethyl acetal (NAAADA) in an amount of about 6 to 21 crosslinkers per PVA.
7. The biomaterial of claim 1, wherein the PVA backbone further is modified with a hydrophobic or hydrophilic modifier.
8. The biomaterial of claim 7, wherein the hydrophobic modifier is acetaldehyde diethyl acetal (AADA) present in an amount from about 0 to 4 milliequivalents per gram (meq/ g) of PVA.