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GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- *as to applicant's entitlement to apply for and be granted a
patent (Rule 4.17(ii))*
- *as to the applicant's entitlement to claim the priority of the
earlier application (Rule 4.17(iii))*

Published:

- *with international search report (Art. 21(3))*

(54) Title: MENISCAL REPAIR ADHESIVE

(57) Abstract: A composition that includes (a) a prepolymer having at least one free isocyanate group that is capable of bonding to tissue and that cures *in vivo* upon exposure to water to form a polymer having a compressive modulus between 1.9 and 14.4 MPa and a tensile modulus between 5.0 and 30, and (b) an oil that is miscible in the prepolymer, the oil being selected from the group consisting of silicone oils, mineral oil, vegetable oils, and combinations thereof. The composition retains its integrity when delivered in an aqueous medium.



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Meniscal Repair Adhesive

CLAIM OF PRIORITY

This application claims priority to U.S. Provisional Application Serial No. 62/211,953, filed on August 31, 2015, the entire contents of which are hereby incorporated by reference.

TECHNICAL FIELD

This invention relates to repairing tissue defects and injuries such as meniscal tears.

BACKGROUND

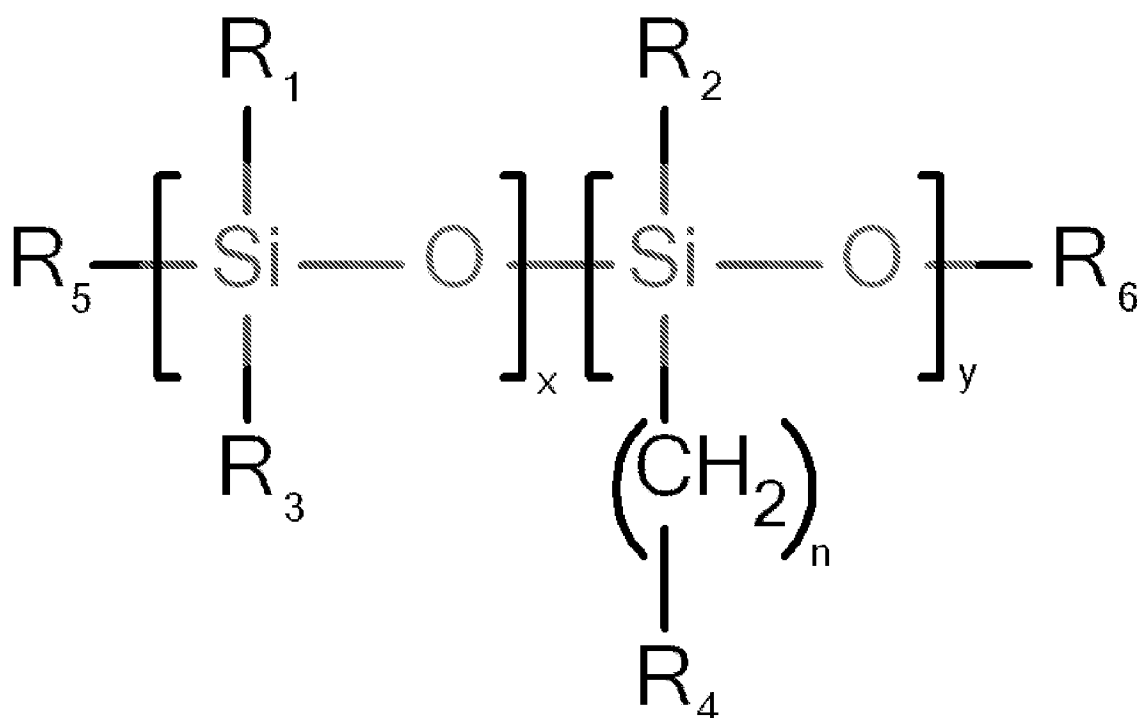
A meniscus is a C-shaped piece of cartilage located at the edge of the knee between the femur and tibia. Each knee has two menisci: one on the outer edge of the knee (lateral meniscus) and one on the inner edge of the knee (medial meniscus). A meniscal tear is a common injury that often occurs when the knee is twisted. As people age, the meniscus can also become worn and susceptible to tearing. Meniscal tears are typically treated through either open or arthroscopic surgery. In either case, the area typically is flooded with saline during the surgery.

SUMMARY

In one aspect, there is described a composition that includes (a) a prepolymer having at least one free isocyanate group that is capable of bonding to tissue and that cures *in vivo* upon exposure to water to form a polymer having a compressive modulus between 1.9 and 14.4 MPa and a tensile modulus between 5.0 and 30, and (b) an oil that is miscible in the prepolymer, the oil being selected from the group consisting of silicone oils, mineral oil, vegetable oils, and combinations thereof. The composition retains its integrity when delivered in an aqueous medium.

In certain embodiments, the prepolymer may include urethane linkages, urea linkages, or a combination thereof. Examples of suitable oils include silicone oils such as polydimethylsiloxane, simethicone, and combinations thereof.

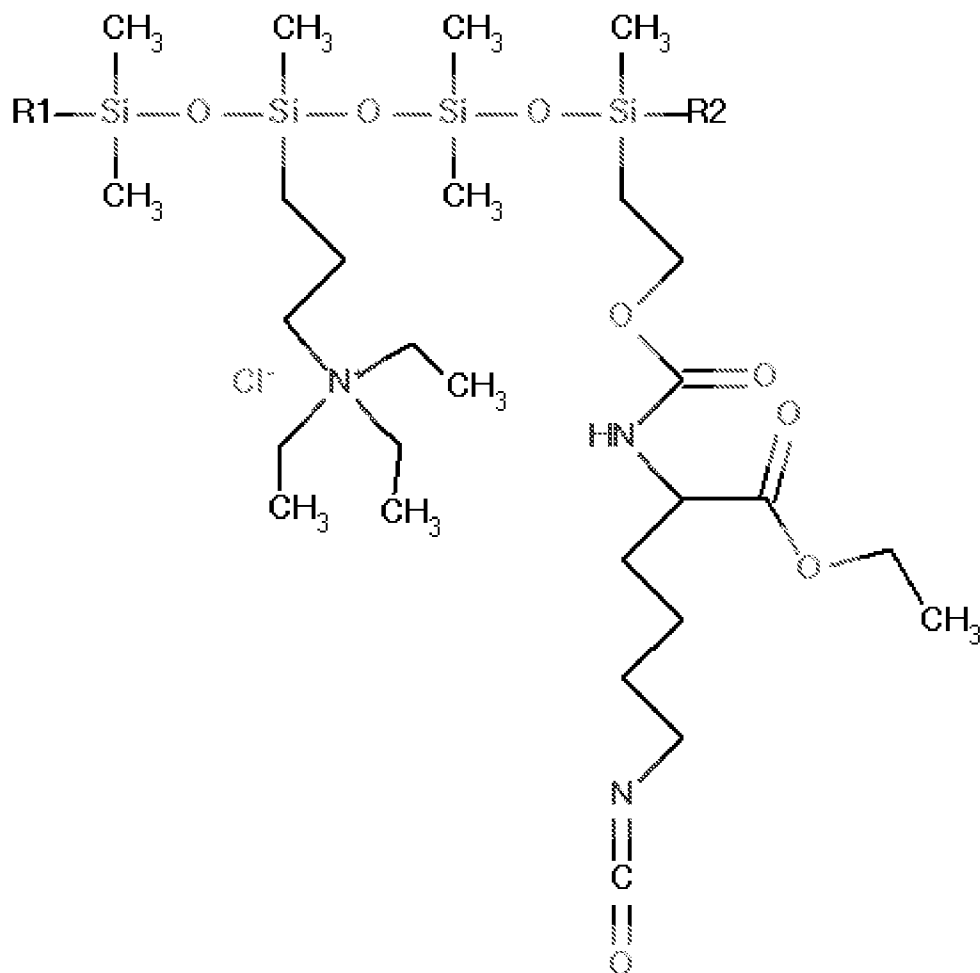
In certain embodiments, the prepolymer is a siloxane prepolymer. An example of a suitable siloxane prepolymer has the formula:



5

In this formula, n is 1 to 10; x and y, independently, are 2 to 10; R¹, R², R³, R⁵, and R⁶,
 10 independently, are selected from the group consisting of hydroxyl groups; straight chain, branched, or cyclic C₁-C₆ alkyl groups that may be substituted with one or more isocyanate groups; straight chain, branched, or cyclic C₁-C₆ fluorinated alkyl groups that may be substituted with one or more isocyanate groups; and combinations thereof; R⁴ is selected from the group consisting of -NCO, -SH, -OH, R⁷N⁺X⁻; R⁷ is a
 15 straight chain, branched, or cyclic C₁-C₆ alkyl group; and X is selected from the group consisting of F, Cl, Br, and I, with the proviso that at least one of R¹, R², R³, R⁴, R⁵, and R⁶ includes an isocyanate group.

Another example of a suitable siloxane prepolymer has the following formula:



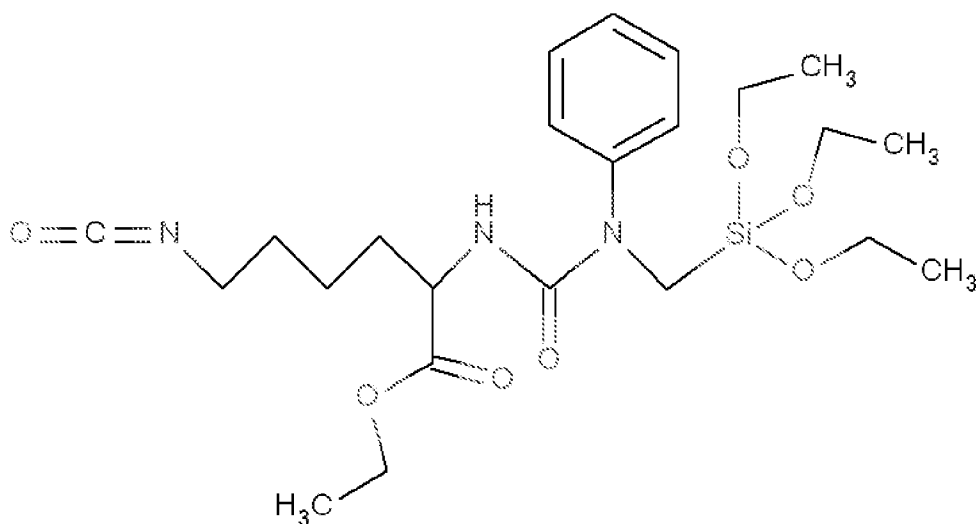
In this formula, R^1 and R^2 , independently, are selected from the group consisting of hydroxyl groups; straight chain, branched, or cyclic C_1 - C_6 alkyl groups that may be substituted with one or more isocyanate groups; straight chain, branched, or cyclic C_1 - C_6 fluorinated alkyl groups that may be substituted with one or more isocyanate groups; and combinations thereof.

In certain embodiments, the prepolymer can include the reaction product of a polyisocyanate, an active hydrogen component selected from the group consisting of polyols, polyamines, polythiols, polycarboxylic acids, and combinations thereof, and, optionally, an ionic salt or amino acid component having an average hydroxyl or amino

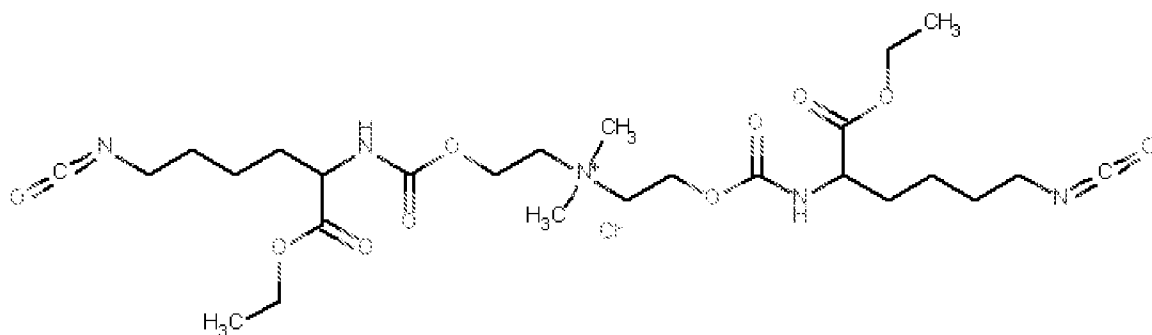
functionality, or combination thereof, of at least 1. Examples of suitable ionic salts components include ammoniates, halides, sulfonates, phosphonates, carboxylates, and combinations thereof. The composition may include at least two different prepolymers.

As used herein, the term “component” refers to single compounds, and to blends of different compounds.

Representative examples of suitable prepolymers having the following structures:



and



The composition may be used to repair a variety of tissues, including meniscal tissue, tendons, cartilage, and the like. For example, the composition may be used to repair a meniscal defect such as a tear by delivering the composition to a knee joint in an aqueous environment in the area of a meniscal defect, and allowing the composition to
5 cure in the presence of water present in the knee joint. Because the composition retains its integrity even when immersed in an aqueous environment such as the saline environment typically encountered during surgery, it remains intact and in place following delivery to the desired area of the knee joint as it cures and bonds to the meniscal tissue.

10 The details of one or more embodiments of the invention are set forth in the description below. Other features, objects, and advantages of the invention will be apparent from the description and from the claims.

DETAILED DESCRIPTION

The compositions include (a) a prepolymer having at least one free isocyanate
15 group that is capable of bonding to tissue and that cures *in vivo* upon exposure to water to form a polymer having a compressive modulus between 1.9 and 14.4 MPa and a tensile modulus between 5.0 and 30, and (b) an oil that is miscible in the prepolymer, the oil being selected from the group consisting of silicone oils, mineral oil, vegetable oils, and combinations thereof. The composition retains its integrity when delivered in an aqueous
20 medium.

Because the compositions retain their integrity even when delivered in an aqueous environment, e.g., a saline solution, they remain intact and in place following delivery to the desired area of the tissue during surgery as the prepolymer cures and bonds to the tissue. In addition, the cured compositions are capable of withstanding the tensile, shear,
25 and compressive forces to which they are exposed, e.g., within the knee joint. The specific cure times, viscosities, and mechanical properties can be tailored as necessary for individual applications.

Because the prepolymer includes at least one isocyanate group, it can bond to tissue, e.g., meniscal tissue, by reacting with surface groups on the tissue. In some cases,

the release of controlled amounts of gas can create a scaffold-like structure and/or a textured surface that facilitates potential cell attachment and tissue regrowth through the cured polymer.

The oil in the composition contributes to the ability of the composition to retain its integrity when delivered in an aqueous environment. The oil may also perform the function of a defoaming agent.

In some embodiments, the compositions include siloxane prepolymers having the formula recited in the Summary of the Invention. Such prepolymers may be prepared e.g., by reacting alkoxy silanes and isocyanate-functional organosilanes.

Suitable alkoxy silane reactants have the formula: $(R^1R^2R^3)\text{-Si-CH}_2\text{-Z}$ where (i) Z is an -OH , -SH , -NCO , or -NHR^4 group. R^4 is a hydrogen, an alkyl group (e.g., a $\text{C}_1\text{-C}_6$ alkyl group), or an aryl group (e.g., having at least one ring such as a phenyl group). Each R^1 , R^2 , and R^3 , independently, is H, an alkoxy group (e.g., a $\text{C}_1\text{-C}_6$ alkoxy group), an alkyl group (e.g., a $\text{C}_1\text{-C}_6$ alkyl group), a heteroalkyl group other than an alkoxy group (e.g., an alkyl amido or amido group), an aryl group (e.g., a phenyl group), or a heteroaryl group (e.g., a pyrrolyl, furyl, or pyridinyl group), with the proviso that at least two of R^1 , R^2 , and R^3 are alkoxy groups. The alkyl groups may be straight chain, branched, or cyclic alkyl groups.

Suitable isocyanate-functional organosilane reactants have at least one free isocyanate group and at least one terminal silane group having the formula: $(R^5R^6R^7)\text{-Si-}$ where each R^5 , R^6 , and R^7 , independently, is H, an alkoxy group (e.g., a $\text{C}_1\text{-C}_6$ alkoxy group), an alkyl group (e.g., a $\text{C}_1\text{-C}_6$ alkyl group), a heteroalkyl group other than an alkoxy group (e.g., an alkyl amido or amido group), an aryl group (e.g., a phenyl group), or a heteroaryl group (e.g., a pyrrolyl, furyl, or pyridinyl group).

In some embodiments, the compositions include prepolymers prepared by reacting a polyisocyanate and an active hydrogen component. Examples of suitable active hydrogen components include hydroxyl-functional components, amine-functional components, thiol-functional components, carboxylic acid-functional components, and combinations thereof. In some embodiments, some or all of the functional groups may be primary groups.

One class of suitable active hydrogen components includes multi-functional alcohols selected from glycerol, di-glycerol, erythritol, pentaerythritol, xylitol, arabitol, fucitol, ribitol, sorbitol, mannitol, and combinations thereof. Also suitable are hydroxyalkyl derivatives and esters of any of these alcohols such as ethoxylated pentaerythritol.

Another class of suitable active hydrogen components includes hydroxyalkyl derivatives of C₃-C₁₀ carboxylic or dicarboxylic acids (e.g., dimethylol propionic acid, dimethylol butyric acid, and combinations thereof), and hydroxyalkyl derivatives of C₃-C₁₀ hydrocarbons (e.g., trimethylol propane).

The active hydrogen component can also be a hydroxalkyl amine (e.g., triethanolamine), a di-, tri-, or tetralkylene glycol, or combination thereof. Also suitable are hydroxyl-functional compounds selected from saccharides (e.g., glucose, fructose, sucrose, or lactose), oligosaccharides, polysaccharides, esters thereof, and combinations thereof.

The active hydrogen component can also be a polyamine or polyetheramine, e.g., Jeffamine.

An ionic salt or amino acid may also be included as a reactant in preparing the prepolymer. Suitable ionic salt reactants include one or more hydroxyl and/or amino functional groups. Consequently, they are able to react with isocyanate-functional components in the reaction mixture, and thereby become covalently incorporated in the prepolymer. Examples of suitable salts include ammoniates, halides, sulfonates, phosphonates, carboxylates, and combinations thereof. Specific examples include ammonium halides (e.g., ethyl triethanol ammonium chloride), choline halides (e.g., choline chloride), and combinations thereof. Examples of suitable amino acids include lysine, l-arginine, and combinations thereof.

The composition may further include a catalyst. Examples of suitable catalysts include tertiary amines (e.g., aliphatic tertiary amines), organometallic compounds (e.g., bismuth salts and zirconium chelates), platinum, and palladium. Specific examples include 1,4-diazabicyclo[2.2.2]octane ("DABCO"), 2,2'-dimorpholine diethyl ether ("DMDEE"), dibutyltin dilaurate ("DBTDL"), bismuth 2-ethylhexanoate, bismuth

neodecanoate, and combinations thereof. The amount of catalyst is selected based upon the particular reactants.

The composition may also include rheology-modifying agents such as a solvent and/or a non-volatile diluent. Examples of suitable solvents include dimethylsulfoxide (DMSO), dimethylformamide (DMF), tetrahydrofuran (THF), glyme, and combinations thereof. Examples of suitable non-volatile diluents include dimethylsulfoxide (DMSO), propylene carbonate, diglyme, polyethylene glycol diacetates, polyethylene glycol dicarbonates, dimethylisobutyl sebacate, ethyl pyruvate, triacetin, triethylene glycol and combinations thereof. A single reagent can perform multiple roles. Thus, for example, DMSO can function as both a solvent and a non-volatile diluent. The amount of the rheology modifying agent is selected based upon the constituents of the composition and the particular application for which it is being used.

The composition may also include antioxidants (e.g., BHT and BHA), water scavengers (e.g., acyl and aryl halides, and anhydrides), Bronsted acids, protonic acids (e.g., sulfuric or hydrochloric acid), and the like. The acids may also function as catalysts.

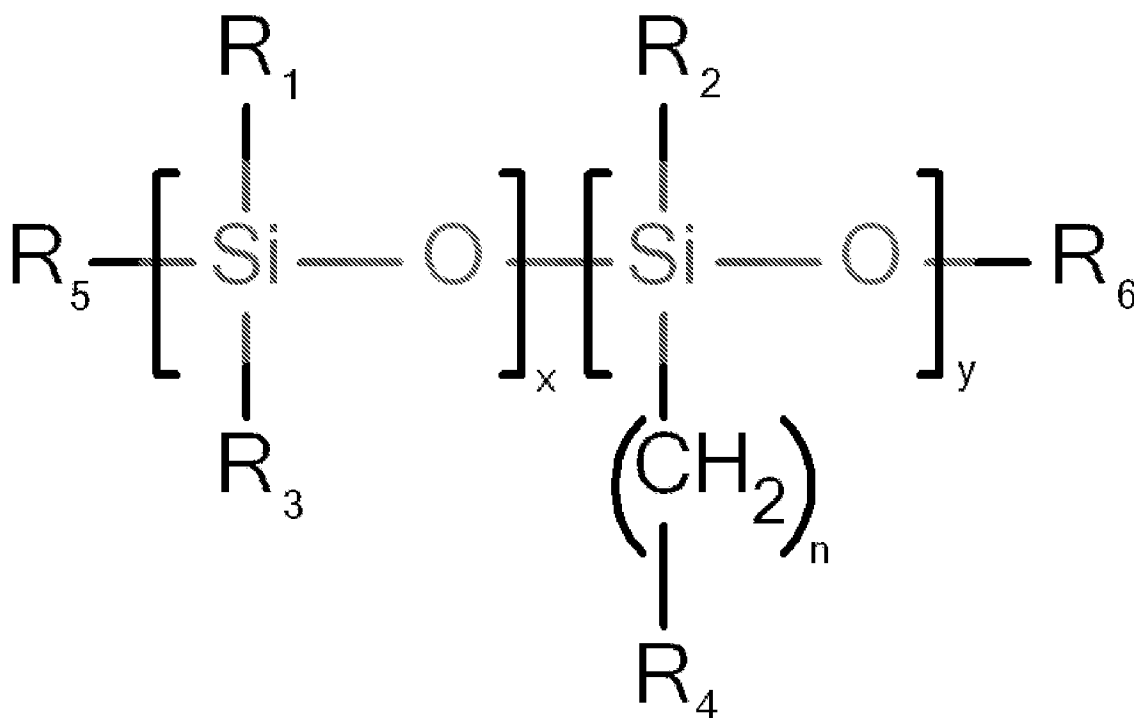
The composition may also include a colorant to help a surgeon visualize the composition during application to the meniscal tissue. An example of a suitable colorant is beta-carotene.

A number of embodiments of the invention have been described. Nevertheless, it will be understood that various modifications may be made without departing from the spirit and scope of the invention. Accordingly, other embodiments are within the scope of the following claims.

WHAT IS CLAIMED IS:

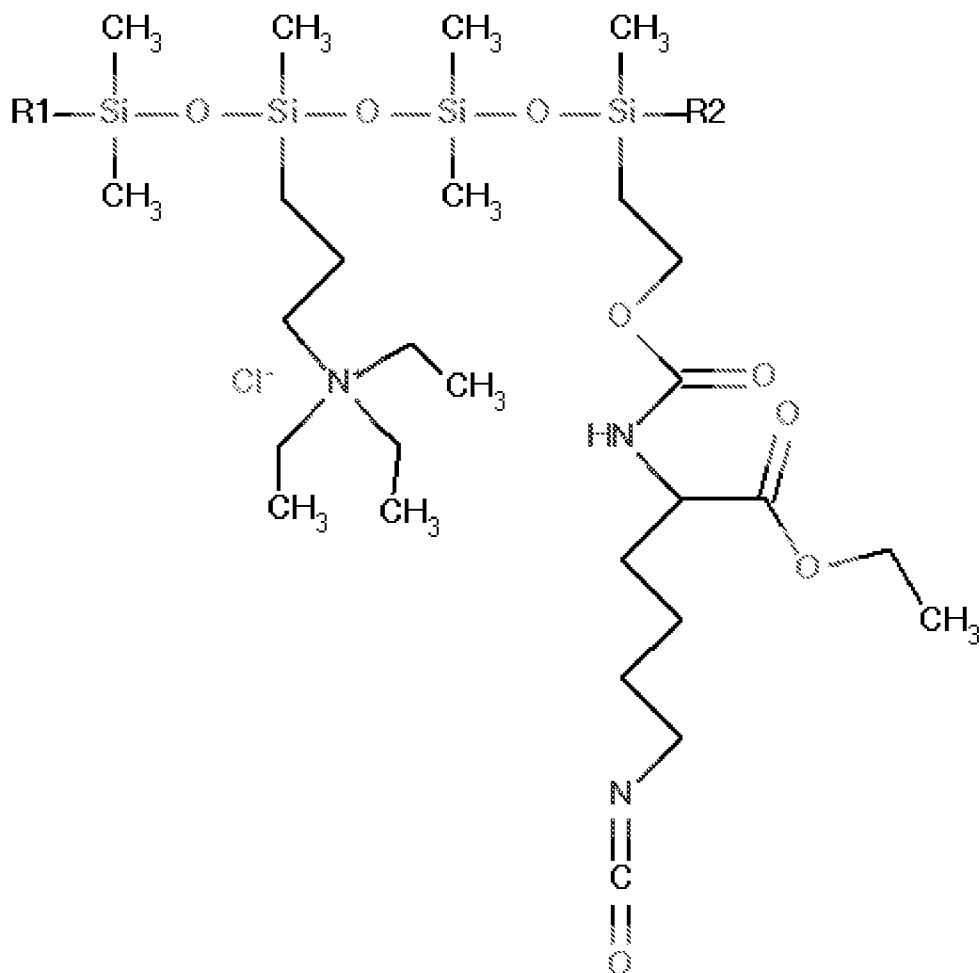
- 1 1. A composition comprising:
 - 2 (a) a prepolymer having at least one free isocyanate group that is capable of bonding
 - 3 to tissue and that cures *in vivo* upon exposure to water to form a polymer having a
 - 4 compressive modulus between 1.9 and 14.4 MPa and a tensile modulus between 5.0
 - 5 and 30, and
 - 6 (b) an oil that is miscible in the prepolymer, the oil being selected from the group
 - 7 consisting of silicone oils, mineral oil, vegetable oils, and combinations thereof,
 - 8 wherein the composition retains its integrity when delivered in an aqueous medium.
- 1 2. A composition according to claim 1 wherein the prepolymer comprises linkages
- 2 selected from the group consisting of urea linkages, urethane linkages, and
- 3 combinations thereof.
- 1 3. A composition according to claim 1 wherein the prepolymer is a siloxane prepolymer.

4. A composition according to claim 3 wherein the siloxane prepolymer has the formula:



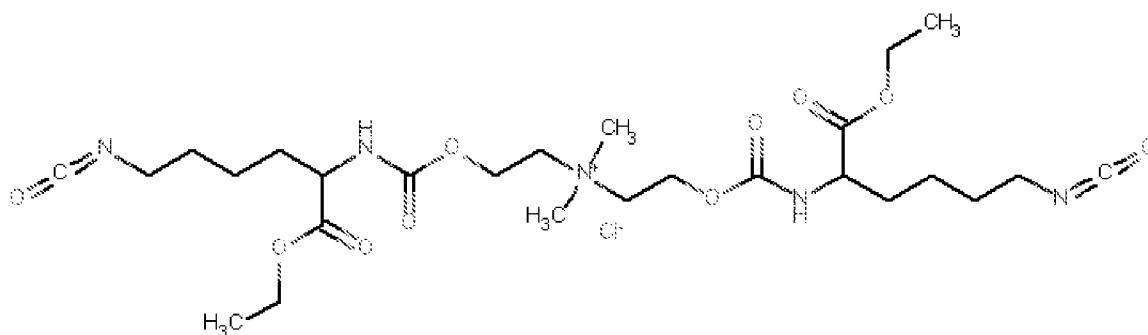
where n is 1 to 10; x and y, independently, are 2 to 10; R^1 , R^2 , R^3 , R^5 , and R^6 , independently, are selected from the group consisting of hydroxyl groups; straight chain, branched, or cyclic C_1 - C_6 alkyl groups that may be substituted with one or more isocyanate groups; straight chain, branched, or cyclic C_1 - C_6 fluorinated alkyl groups that may be substituted with one or more isocyanate groups; and combinations thereof; R^4 is selected from the group consisting of $-NCO$, $-SH$, $-OH$, $R^7N^+X^-$; R^7 is a straight chain, branched, or cyclic C_1 - C_6 alkyl group; and X is selected from the group consisting of F, Cl, Br, and I, with the proviso that at least one of R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 includes an isocyanate group.

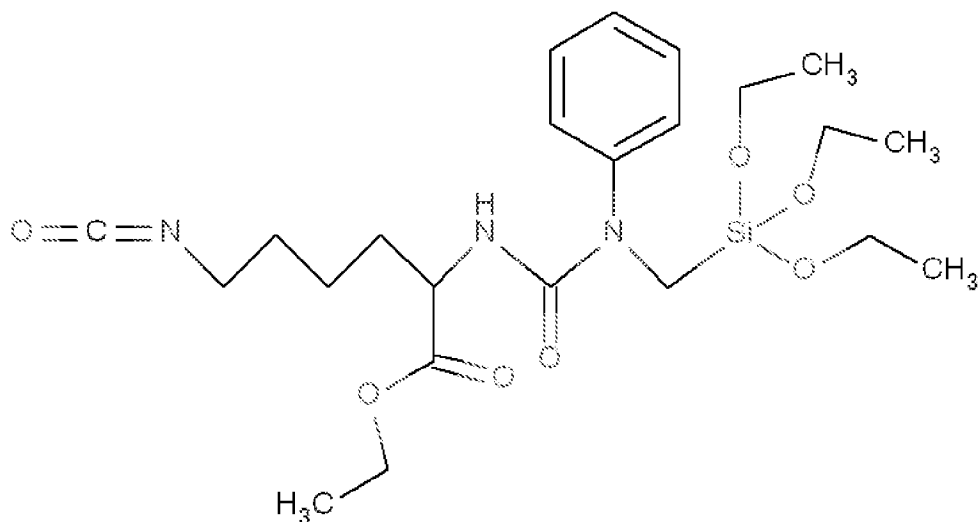
5. A composition according to claim 3 wherein the siloxane prepolymer has the formula:



where R^1 and R^2 , independently, are selected from the group consisting of hydroxyl groups; straight chain, branched, or cyclic C_1 - C_6 alkyl groups that may be substituted with one or more isocyanate groups; straight chain, branched, or cyclic C_1 - C_6 fluorinated alkyl groups that may be substituted with one or more isocyanate groups; and combinations thereof.

6. A composition according to claim 1 wherein the prepolymer comprises the reaction product of a polyisocyanate and an active hydrogen component selected from the group consisting of polyols, polyamines, polythiols, polycarboxylic acids, and combinations thereof.
7. A composition according to claim 1 wherein the prepolymer comprises the reaction product of (a) a polyisocyanate, (b) an active hydrogen component selected from the group consisting of polyols, polyamines, polythiols, polycarboxylic acids, and combinations thereof, and (c) an ionic salt or amino acid component having an average hydroxyl or amino functionality, or combination thereof, of at least 1.
8. A composition according to claim 7 wherein the ionic salt component is selected from the group consisting of ammoniates, halides, sulfonates, phosphonates, carboxylates, and combinations thereof.
9. A composition according to claim 1 wherein the composition comprises at least two different prepolymers.
10. A composition according to claim 8 wherein the prepolymers are selected from the group of compounds having the formulae:





and combinations thereof.

11. A composition according to claim 1 wherein the oil comprises a silicone oil.

12. A composition according to claim 11 wherein the silicone oil is selected from the group consisting of polydimethylsiloxane, simethicone, and combinations thereof.

13. A composition according to claim 1 wherein the tissue is selected from the group consisting of meniscal tissue, cartilage, tendons, and combinations thereof.

14. A method of repairing a defect in meniscal tissue comprising delivering a composition according to claim 1 to the knee joint in an aqueous environment in the area of the meniscal defect, and allowing the composition to cure and bond to the meniscal tissue.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/049561**A. CLASSIFICATION OF SUBJECT MATTER****A61L 27/18(2006.01)i, C07F 7/08(2006.01)i, C07C 265/14(2006.01)i**

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61L 27/18; C08G 18/10; C08J 9/12; A61F 13/02; C08L 75/04; C08G 77/04; C08L 83/04; C08G 18/00; C07C 269/02; C08F 2/46; C08G 69/26; C07F 7/08; C07C 265/14

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

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal) & keywords: silioxane, prepolymer, water, isocyanate, oil

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2011-0015292 A1 (RADHAKRISHNAN, BINDUSHREE et al.) 20 January 2011 See abstract; paragraphs [0017]-[0058]; and claims 1-13,16-24.	1-2,6-10
Y		3-5,11-13
Y	US 2010-0029802 A1 (MEHRABI, MANSOUR et al.) 4 February 2010 See abstract; paragraphs [0005]-[0106]; and claims 1-36.	3-5,11-13
X	WO 00-04069 A1 (RATHOR AG et al.) 27 January 2000 See abstract; claims 1-13.	1
X	US 2009-0005716 A1 (ABUZAINA, FERASS et al.) 1 January 2009 See abstract; paragraphs [0025]-[0028]; and claims 1-18.	1
A	US 2006-0142526 A1 (LAI, YU-CHIN et al.) 29 June 2006 See the whole document.	1-13



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

08 December 2016 (08.12.2016)

Date of mailing of the international search report

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Name and mailing address of the ISA/KR

International Application Division

Korean Intellectual Property Office

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INTERNATIONAL SEARCH REPORTInternational application No.
PCT/US2016/049561**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. ☒ Claims Nos.: 14
because they relate to subject matter not required to be searched by this Authority, namely:
Claim 14 pertains to a method for treatment of the human body and thus relates to a subject-matter which this International Searching Authority is not required, under PCT Article 17(2)(a)(i) and PCT Rule 39.1(iv), to search.
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 all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers 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/US2016/049561

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2011-0015292 A1	20/01/2011	EP 2274357 A2 JP 2011-516634 A WO 2009-117665 A2 WO 2009-117665 A3	19/01/2011 26/05/2011 24/09/2009 08/04/2010
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