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(71) Applicant: BAUSCH & LOMB INCORPORATED

[US/US]; 1400 North Goodman Street, Rochester, NY 14609 (US).

(72) Inventors: AWASTHI, Alok Kumar; 36 Delancey Court,

Pittsford, NY 14534 (US). DIBELLA, Jr., James Anthony; 3551 View Pointe Drive, Macedon, NY 14502 (US). MIS, Mark R.; 1226 Rush Henrietta Townline Road, Rush, NY 14543 (US). MUSLEH, Alai; 3 Northwind Way, Rochester, NY 14624 (US). GROBE III, George L.; 2081 Lake Road, Ontario, NY 14519 (US).

(74) Agent: CARMEN, Michael E.; Ryan, Mason & Lewis,

LLP, 48 South Service Road, Suite 100, Melville, NY 11747 (US).

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(54) Title: GLYCOPHOSPHOLIPID POLYMERIC NETWORK AND USE THEREOF

(57) Abstract: A glycopospholipid polymer is disclosed. The glycopospholipid polymer comprises a reaction product of one or more glycosaminoglycans and one or more phospholipids. Also disclosed is a glycopospholipid polymeric network comprising a reaction product of one or more glycosaminoglycans, one or more phospholipids and, one or more crosslinking agents.



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## GLYCOPHOSPHOLIPID POLYMERIC NETWORK AND USE THEREOF

## BACKGROUND

**[0001]** The present invention generally relates to a glycophospholipid polymeric network and its use.

**[0002]** It is highly desirable that a contact lens be as comfortable as possible for wearers. Manufacturers of contact lenses are continually working to improve the comfort of the lenses. Nevertheless, many people who wear contact lenses still experience dryness or eye irritation throughout the day and particularly towards the end of the day. An insufficiently wetted lens at any point in time will cause significant discomfort to the lens wearer. Although wetting drops can be used as needed to alleviate such discomfort, it would certainly be desirable if such discomfort did not arise in the first place.

**[0003]** Glycosaminoglycans (GAGs) are a group of polysaccharides built of repeating disaccharide units. Due to high polarity and water affinity, they can be found in many systems of human bodies. For example, GAGs occur on the surface of cells and in the extracellular matrix of animal organisms such as skin, cartilage, and lungs.

**[0004]** GAGs each have a chemical structure including a repeating basal disaccharide structure consisting of uronic acid and hexosamine and being optionally sulfated to various degrees. GAGs are mainly classified, depending on the disaccharides constituting them, into three groups: a first group of compounds composed of chondroitin sulfate or dermatan sulfate, a second group of compounds composed of heparan sulfate or heparin, and a third group of hyaluronic acid compounds. For example, the compounds composed of chondroitin sulfate or dermatan sulfate consist of a disaccharide: uronic acid (glucuronic acid or iduronic acid) ( $\beta$ 1 $\rightarrow$ 3) N-acetylgalactosamine, the compounds composed of heparan sulfate or heparin consist of a disaccharide: uronic acid (glucuronic acid or iduronic acid) ( $\beta$ 1 $\rightarrow$ 4) N-acetylglucosamine, and the hyaluronic acid consists of a disaccharide: glucuronic acid ( $\beta$ 1 $\rightarrow$ 3)N-acetylglucosamine. In addition, the structure is highly diverse due to a combination with modification by sulfation.

**[0005]** These GAGs are known as biological materials having both physicochemical properties derived from characteristic viscoelasticity and biological properties mediated by interactions with various functional proteins, depending on the molecular size and the sulfation pattern.

**[0006]** Methacryloylethyl phosphorylcholine (MPC) polymers are known to resist both protein adsorption and cell adhesion and are widely used to construct non-biofouling surfaces in various biomedical applications in which a high level of biocompatibility is required such as coatings to significantly reduce the adhesion of common infective bacteria. The MPC unit generally contains a zwitterionic phospholipid group (i.e., phosphorylcholine (PC)) that is also present in cell membranes and possesses nonthrombogenic properties to minimize blood clot formation and minimize protein fouling due to its high biocompatibility. PC has both positive and negative charges, but overall it is electrically neutral, very polar, and has great affinity for water which makes PC materials non-stick.

**[0007]** It would be desirable to provide improved GAGs that can make a biomedical device such as a contact lens as comfortable as possible for the wearer and exhibit suitable physical and chemical properties, e.g., lubriciousness and wettability.

## SUMMARY

**[0008]** In accordance with one illustrative embodiment, a glycopospholipid polymer is provided comprising a reaction product of one or more glycosaminoglycans and one or more phospholipids.

**[0009]** In accordance with a second illustrative embodiment, a crosslinked glycopospholipid polymeric network is provided comprising one or more glycosaminoglycans crosslinked with one or more phospholipids.

**[0010]** In accordance with a third illustrative embodiment, a crosslinked glycopospholipid polymeric network is provided comprising a reaction product of one or more glycosaminoglycans, one or more phospholipids and one or more crosslinking agents.

**[0011]** In accordance with a fourth illustrative embodiment, a biomedical device having a coating on a surface thereof is provided, the coating comprising one or more

glycophospholipid polymers comprising a reaction product of one or more glycosaminoglycans and one or more phospholipids.

**[0012]** In accordance with a fifth illustrative embodiment, a packaging system for the storage of an ophthalmic device is provided comprising a sealed container containing one or more unused ophthalmic devices immersed in an aqueous packaging solution comprising one or more glycophospholipid polymers comprising a reaction product of one or more glycosaminoglycans and one or more phospholipids, wherein the solution has an osmolality of at least about 200 mOsm/kg, a pH of about 6 to about 9 and is sterilized.

**[0013]** In accordance with a sixth illustrative embodiment, a method of preparing a package comprising a storable, sterile ophthalmic device is provided, the method comprising: (a) immersing an ophthalmic device in an aqueous packaging solution comprising one or more glycophospholipid polymers comprising a reaction product of one or more glycosaminoglycans and one or more phospholipids, wherein the solution has an osmolality of at least about 200 mOsm/kg and a pH in the range of about 6 to about 9; (b) packaging the solution and the device in a manner preventing contamination of the device by microorganisms; and (c) sterilizing the packaged solution and device.

**[0014]** In accordance with a seventh illustrative embodiment, an aqueous ophthalmic composition is provided comprising one or more glycophospholipid polymers comprising a reaction product of one or more glycosaminoglycans and one or more phospholipids, wherein the aqueous ophthalmic composition has an osmolality in a range from about 200 mOsmol/kg to about 400 mOsmol/kg.

**[0015]** In accordance with an eighth illustrative embodiment, a gel composition for promoting wound healing is provided wherein the gel composition comprises one or more glycophospholipid polymers comprising a reaction product of one or more glycosaminoglycans and one or more phospholipids.

**[0016]** In accordance with a ninth illustrative embodiment, a wound dressing is provided comprising a gel composition comprising one or more glycophospholipid polymers comprising a reaction product of one or more glycosaminoglycans and one or more phospholipids.

**[0017]** The glycopospholipid polymer and crosslinked glycopospholipid polymeric network of the present invention are believed to advantageously exhibit enzymatic, oxidative and thermal degradation and thus higher stability, longer shelf life and rigidity of desired conformation. In addition, the glycopospholipid polymer and crosslinked glycopospholipid polymeric network of the present invention are also believed to exhibit suitable physical and chemical properties, e.g., oxygen permeability, lubriciousness mucoadhesivity and wettability. The glycopospholipid polymer and crosslinked glycopospholipid polymeric network of the present invention are further believed to advantageously exhibit antimicrobial activity for prolonged contact with the body by reacting one or more glycosaminoglycans with one or more phospholipids, and optional one or more crosslinking agents.

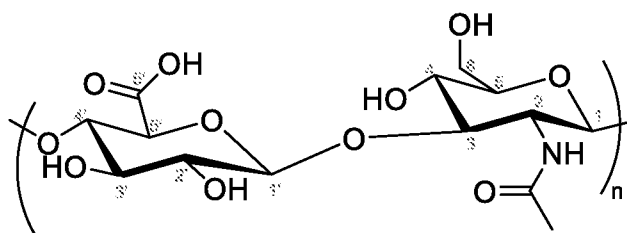
**[0018]** The glycopospholipid polymer and crosslinked glycopospholipid polymeric network of the present invention may advantageously provide improved lubricity to the surface of a biomedical device such as a contact lens. For example, the benefits of improved lubricity using glycopospholipid polymer and crosslinked glycopospholipid polymeric network of the present invention include, for example, minimizing interactions between a contact lens and its respective packaging blister, a lens surface that is more robust toward processing and handling conditions, and improved comfort upon insertion into a subject's eye, as well as reduced deposition (e.g., protein, lipid, etc.) and thus potentially reducing biofilm formation by the contact lens wearer onto the lens surface.

**[0019]** In addition, the glycopospholipid polymer and crosslinked glycopospholipid polymeric network of the present invention advantageously provide improved wettability to the surface of a biomedical device such as a contact lens. It is believed that the benefits of having improved wettability using the glycopospholipid polymer and crosslinked glycopospholipid polymeric network of the present invention include, for example, delaying evaporation of the aqueous layer of the device due to its effect like-coating on the ocular surface and moisturizing properties and thus potentially relieving dry eye symptoms.

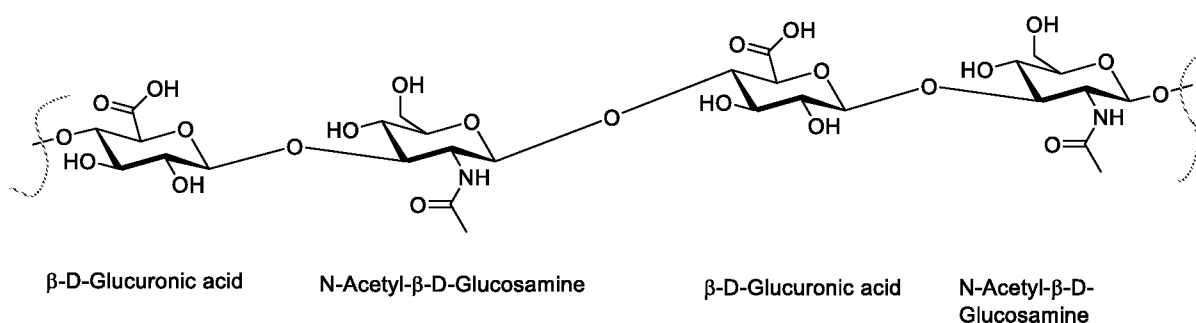
## DETAILED DESCRIPTION

**[0020]** The illustrative embodiments described herein are directed to glycopospholipid polymers and crosslinked glycopospholipid polymeric networks useful in treating the surface of a biomedical device intended for direct contact with body tissue or fluid. In general, the glycopospholipid polymers comprise a reaction product of one or more glycosaminoglycans (GAG) and one or more phospholipids. A GAG is one molecule with many alternating subunits. In general, GAGs are represented by the formula A-B-A-B-A-B, where A is an uronic acid and B is an amino sugar that is either O- or N-sulfated, where the A and B units can be heterogeneous with respect to epimeric content or sulfation. Any natural or synthetic polymer containing uronic acid can be used. Other GAGs are sulfated at different sugars. There are many different types of GAGs having commonly understood structures such as, for example, chondroitin sulfate, dermatan, heparan, heparin, dermatan sulfate, hyaluronic acid or a salt thereof, e.g., sodium hyaluronate or potassium hyaluronate, heparan sulfate, and other disaccharides such as sucrose, lactulose, lactose, maltose, trehalose, cellobiose, mannobiose and chitobiose. Glycosaminoglycans can be purchased from Sigma, and many other biochemical suppliers.

**[0021]** In one illustrative embodiment, the GAG is hyaluronic acid or a salt thereof. Hyaluronic acid is a well-known, naturally occurring, water soluble biodegradable polymer composed of two alternatively linked sugars, D-glucuronic acid and N-acetylglucosamine, linked via alternating  $\beta$ -(1,4) and  $\beta$ -(1,3) glycosidic bonds. Hyaluronic acid is a non-sulfated GAG. Hyaluronan. The polymer is hydrophilic and highly viscous in aqueous solution at relatively low solute concentrations. It often occurs naturally as the sodium salt, sodium hyaluronate. Methods of preparing commercially available hyaluronan and salts thereof are well known. Hyaluronan can be purchased from Seikagaku Company, Clear Solutions Biotech, Inc., Pharmacia Inc., Sigma Inc., and many other suppliers. Hyaluronic acid has one or more repeating units of the structure represented by the following formula:

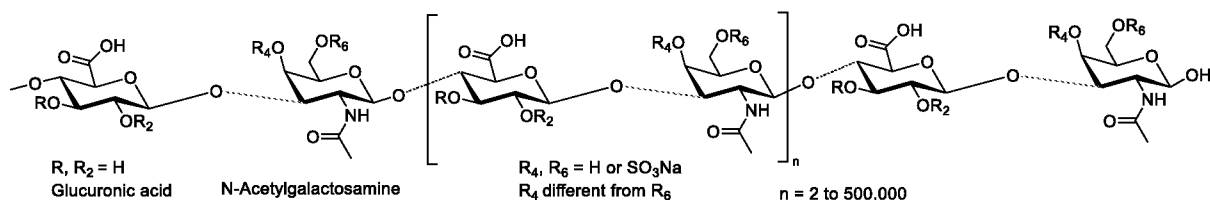


Accordingly, the repeating units in hyaluronic acid can be as follows:

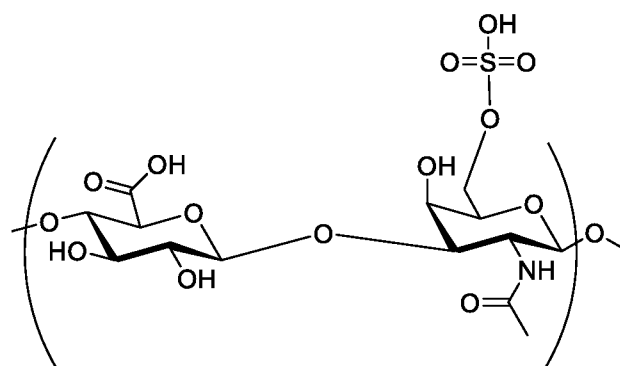


**[0022]** In general, hyaluronic acid or a salt thereof can have from about 2 to about 1,500,000 disaccharide units. In one embodiment, hyaluronic acid or a salt thereof can have a weight average molecular weight ranging from about 10,000 to about 3,000,000 Daltons (Da) in which the lower limit is from about 10,000, about 20,000, about 30,000, about 40,000, about 50,000, about 60,000, about 70,000, about 80,000, about 90,000, or about 100,000, and the upper limit is about 200,000, about 300,000, about 400,000, about 500,000, about 600,000, about 700,000, about 800,000, about 900,000, about 1,000,000, or about up to 2,800,000, where any of the lower limits can be combined with any of the upper limits.

**[0023]** In one illustrative embodiment, the GAG is chondroitin sulfate. In general, chondroitin sulfate is a linear sulfated polysaccharide composed of repeating  $\beta$ -D-glucuronic acid (GlcA) and N-acetyl- $\beta$ -D-galactosamine (GalNAc) units arranged in the sequence by GlcA-  $\beta$ (1,3)-GalNAc-  $\beta$ (1,4) glycosidic bonds. In one embodiment, chondroitin sulfate has one or more repeating units of the structure represented by the following formula:



**[0024]** In one illustrative embodiment, chondroitin sulfate has one or more repeating units of the structure represented by the following formula:

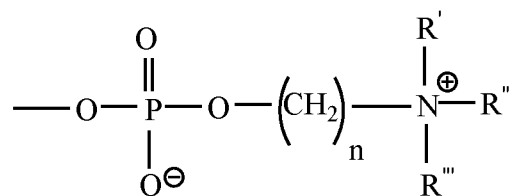


**[0025]** In general, chondroitin sulfate can have from about 2 to about 1,500,000 repeating units. In one embodiment, chondroitin sulfate can have a weight average molecular weight ranging from about 10,000 to about 3,000,000 Da in which the lower limit is from about 5,000, 10,000, about 20,000, about 30,000, about 40,000, about 50,000, about 60,000, about 70,000, about 80,000, about 90,000, or about 100,000, and the upper limit is about 200,000, about 300,000, about 400,000, about 500,000, about 600,000, about 700,000, about 800,000, about 900,000, about 1,000,000, or about 3,000,000 where any of the lower limits can be combined with any of the upper limits or any of the upper limits can be combined with any of the upper limits.

**[0026]** Suitable phospholipids for reacting with the one or more GAGs include, for example, phosphorylcholine, phosphorylhistidine, phosphorylproline, phosphorylserine,  $\alpha$ -phosphatidylcholine,  $\alpha$ -phosphatidylethanolamine,  $\alpha$ -phosphatidyl-L-serine,  $\alpha$ -phosphatidylinositol,  $\alpha$ -phosphatidic acid,  $\alpha$ -phosphatidyl-DL-glycerol,  $\alpha$ -lysophosphatidylcholine, sn-glycero-3-phosphatidylcholine (GPC) (also choline alfoscerate)

derived from soybean phosphatidylcholine sphingomyelin, and cardiolipin. The phospholipids described herein are either commercially available or can be made by techniques well known in the art, see, e.g., Park et al., “*Facile Syntheses of L- $\alpha$ -Glycerophosphorylcholine*”, Bull. Korean Chem. Soc. 2010, Vol. 31, No. pp. 9 2689-2691.

**[0027]** In one embodiment, a phosphorylcholine-containing phospholipid comprises a zwitterionic group as follow:



wherein n is an integer of 1 to 5 and R', R'' and R''' independently of each other are a C<sub>1</sub> to C<sub>8</sub> alkyl group, a C<sub>1</sub> to C<sub>8</sub> hydroxyalkyl group or a hetero atom-containing group such as histidine and proline. As one skilled in the art will readily appreciate, the foregoing phosphorylcholine-containing phospholipid will further include on or more reactive groups capable of reacting with the one or more GAGs and one or more crosslinking agents as discussed hereinbelow, e.g., hydroxyl-containing groups, epoxide-containing groups, amine-containing groups, aldehyde-containing groups, thiol-containing groups, carboxylic acid-containing groups, cyano-containing groups, halogen-containing groups, etc. Representative examples of suitable phosphorylcholine phospholipids having the foregoing zwitterionic group include, but are not limited to, glycerylphosphorylcholine, ethanaminium, 2-[[[hydroxy·2·oxiranylmethoxy]phosphinyl)oxy]·N,N,N-trimethyl,inner salt, and hydroxyethylphosphorylcholine.

**[0028]** The term “hydroxyl-containing group” should be understood to mean any group which contains a hydroxyl moiety. Representative examples of hydroxyl-containing groups for use herein include, by way of example, a hydroxy group attached directly to the rest of the molecule, i.e., --OH, or one or more hydroxy-containing groups attached to the rest of the molecule via a linking group, e.g., an alkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, aryl or an arylalkyl group and the like.

**[0029]** The term “epoxide-containing group” should be understood to mean any group which contains an epoxide moiety. Representative examples of epoxide-containing groups for use herein include, by way of example, alkylene oxides and in particular lower alkylene oxides such as ethylene oxide, propylene oxide, butylene oxide, alcohol epoxides such as glycidol, and epihalohydrins such as epichlorohydrin, epibromohydrin, epiiodohydrin, 1,2-epoxy-4-chlorobutane, 1,2-epoxy-4-bromobutane, 1,2-epoxy-4-iodobutane, 2,3-epoxy-4-chlorobutane, 2,3-epoxy-4-bromobutane, 2,3-epoxy-4-iodobutane, 2,3-epoxy-5-chloropentane, 2,3-epoxy-5-bromopentane, 1,2-epoxy-5-chloropentane, etc.; epoxy compounds such as 2,2-bis(p-1,2-epoxypropoxyphenyl)propane, 1,4-bis(1,2-epoxypropoxy)benzene, N,N'-bis(2,3-epoxypropyl)piperazine, etc.

**[0030]** The term “amine-containing group” should be understood to mean any group which contains an amine moiety. Representative examples of amine-containing groups for use herein include, by way of example, an alkyl or arylamine group such as an amine of the general formula  $-R^1NR^2R^3$  wherein  $R^1$  is a  $C_2$  to  $C_{30}$  alkylene, arylene, or cycloalkylene and  $R^2$  and  $R^3$  are independently  $C_1$  to  $C_{30}$  hydrocarbons such as, for example, alkyl groups, aryl groups, or cycloalkyl groups as defined herein.

**[0031]** The term “aldehyde-containing group” should be understood to mean any group which contains an aldehyde moiety. Representative examples of aldehyde-containing groups for use herein include, by way of example, an aldehyde group attached directly to the rest of the molecule, i.e., -CHO, or one or more aldehyde groups attached to the rest of the molecule via a linking group, e.g., an alkylene, cycloalkyl, cycloalkylalkylene, cycloalkenyl, aryl or an arylalkylene group and the like.

**[0032]** The term “thiol-containing group” should be understood to mean any group which contains a thiol moiety. Representative examples of thiol-containing groups for use herein include, by way of example, a thiol group attached directly to the rest of the molecule, i.e., -SH, or one or more thiol groups attached to the rest of the molecule via a linking group, e.g., an alkylene, cycloalkyl, cycloalkylalkylene, cycloalkenyl, aryl or an arylalkylene group and the like.

**[0033]** The term “carboxylic acid-containing group” should be understood to mean any group which contains a carboxylic acid moiety. Representative examples of carboxylic acid-containing groups for use herein include, by way of example, a carboxylic acid group attached directly to the rest of the molecule, i.e., -COOH, or one or more carboxylic acid groups attached to the rest of the molecule via a linking group, e.g., an alkylene, cycloalkyl, cycloalkylalkylene, cycloalkenyl, aryl or an arylalkylene group and the like.

**[0034]** The term “cyano-containing group” should be understood to mean any group which contains a cyano moiety. Representative examples of cyano-containing groups for use herein include, by way of example, a cyano group attached directly to the rest of the molecule, i.e., -CN, or one or more cyano groups attached to the rest of the molecule via a linking group, e.g., an alkylene, cycloalkyl, cycloalkylalkylene, cycloalkenyl, aryl or an arylalkylene group and the like.

**[0035]** The term “halogen-containing group” should be understood to mean any group which contains a halogen moiety. Representative examples of halogen-containing groups for use herein include, by way of example, a halogen group attached directly to the rest of the molecule, i.e., F, Cl, Br, I and the like, or one or more halogen groups attached to the rest of the molecule via a linking group, e.g., an alkylene, cycloalkyl, cycloalkylalkylene, cycloalkenyl, aryl or an arylalkylene group and the like.

**[0036]** Representative examples of alkyl groups for use herein include, by way of example, a straight or branched hydrocarbon chain radical containing carbon and hydrogen atoms of from 1 to about 18 carbon atoms with or without unsaturation, to the rest of the molecule, e.g., methyl, ethyl, n-propyl, 1-methylethyl (isopropyl), n-butyl, n-pentyl, etc., and the like.

**[0037]** Representative examples of alkylene groups for use herein include, by way of example, a straight or branched alkyl chain radical containing carbon and hydrogen atoms of from 1 to about 30 carbon atoms or from 1 to about 6 carbon atoms with or without unsaturation, to the rest of the molecule, e.g., methylene, ethylene, and the like.

**[0038]** Representative examples of cycloalkyl groups for use herein include, by way of example, a substituted or unsubstituted non-aromatic mono or multicyclic ring system of

about 3 to about 18 carbon atoms such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, perhydronaphthyl, adamantyl and norbornyl groups bridged cyclic group or spirobicyclic groups, e.g., spiro-(4,4)-non-2-yl and the like, optionally containing one or more heteroatoms, e.g., O and N, and the like.

**[0039]** Representative examples of cycloalkylalkyl groups for use herein include, by way of example, a substituted or unsubstituted cyclic ring-containing radical containing from about 3 to about 18 carbon atoms directly attached to the alkyl group which are then attached to the main structure of the monomer at any carbon from the alkyl group that results in the creation of a stable structure such as, for example, cyclopropylmethyl, cyclobutylethyl, cyclopentylethyl and the like, wherein the cyclic ring can optionally contain one or more heteroatoms, e.g., O and N, and the like.

**[0040]** Representative examples of cycloalkenyl groups for use herein include, by way of example, a substituted or unsubstituted cyclic ring-containing radical containing from about 3 to about 18 carbon atoms with at least one carbon-carbon double bond such as, for example, cyclopropenyl, cyclobutenyl, cyclopentenyl and the like, wherein the cyclic ring can optionally contain one or more heteroatoms, e.g., O and N, and the like.

**[0041]** Representative examples of aryl groups for use herein include, by way of example, a substituted or unsubstituted monoaromatic or polyaromatic radical containing from about 5 to about 25 carbon atoms such as, for example, phenyl, naphthyl, tetrahydronaphthyl, indenyl, biphenyl and the like, optionally containing one or more heteroatoms, e.g., O and N, and the like.

**[0042]** Representative examples of arylalkylene groups for use herein include, by way of example, a substituted or unsubstituted aryl group as defined above directly bonded to an alkylene group as defined above, e.g.,  $-\text{CH}_2\text{C}_6\text{H}_5$ ,  $-\text{C}_2\text{H}_5\text{C}_6\text{H}_5$  and the like, wherein the aryl group can optionally contain one or more heteroatoms, e.g., O and N, and the like.

**[0043]** The phospholipids for use herein are either commercially available or can be prepared by methods known in the art. For example, ethanaminium, 2-[[hydroxy-2-oxiranylmethoxy]phosphinyl)oxy)-N,N,N-trimethyl, inner salt can be prepared according to a method described in Example 11 in the J. Org. Chemistry, 67,194-199 (2002) or as in U.S.

Patent No. 7,674,782, the contents of which are incorporated by reference herein. In addition, hydroxyethylphosphorylcholine can be prepared according to Journal of the American Chemical Society, 130(23), 7357-7363 (2008), the contents of which are incorporated by reference herein, and is also commercially available from Shanghai Chemhere Co., Ltd. (Shanghai, Hong Kong).

**[0044]** In one illustrative embodiment, the reaction product of the one or more GAGs and the one or more phospholipids includes one or more crosslinking agents, e.g., to crosslink the one or more GAGs with the one or more phospholipids and form a crosslinked glycopospholipid polymeric network. The crosslinking agents for use herein can be any suitable crosslinking agent known in the art. In general, a suitable crosslinking agent is, for example, a crosslinking agent having complimentary functional groups to the one or more GAGs and the one or more phospholipids. In one embodiment, a suitable crosslinking agent includes, for example, a bi- or polyfunctional crosslinking agent. The bi- or polyfunctional crosslinking agent connects the one or more GAGs with the one or more phospholipids. In addition, the bi- or polyfunctional crosslinking agent further acts as a spacer between the one or more GAGs and the one or more phospholipids. In general, the bi- or polyfunctional crosslinking agent comprises two or more functional groups capable of reacting with functional groups of the one or more GAGs such as hyaluronic acid and the one or more phospholipids, resulting in the formation of covalent bonds.

**[0045]** Suitable bi- or polyfunctional crosslinking agents include, for example, divinyl sulfone, diepoxides, multiepoxides, dihydrazides, dihydric alcohols, polyhydric alcohols, polyhydric thiols, anhydrides, carbodiimides, polycarboxylic acids, carboxymethyl thiols, cysteine, and cysteine-like amino acids and the like. In one embodiment, a bi- or polyfunctional crosslinking agent is a bis- or polyepoxide, such as diglycidyl ether derivatives. According to an embodiment, the bi- or polyfunctional epoxide crosslinking agent comprises two or more glycidyl ether functional groups. The glycidyl ether functional groups react with primary hydroxyl groups of the hyaluronic acid or the chondroitin sulfate, resulting in the formation of ether bonds. In one embodiment, suitable bis- or polyfunctional crosslinking agents include, for example, 1,4-butanediol diglycidyl ether (BDDE), 1,2-

bis(2,3-epoxypropoxy)ethylene (EGDGE), ethylene glycol diglycidyl ether (EGDE), 1,2-ethanediol diglycidyl ether (EDDE), diepoxyoctane, 1,6-hexanediol diglycidyl ether, polypropylene glycol diglycidyl ether, polytetramethylene glycol diglycidyl ether, neopentyl glycol diglycidyl ether, polyglycerol polyglycidyl ester, diglycerol polyglycidyl ether, glycerol polyglycidyl ether, trimethylolpropane polyglycidyl ether, pentaerythritol polyglycidyl ether, sorbitol polyglycidyl ether, 1,2,7,8-diepoxyoctane, 1,3-butadiene diepoxide, pentaerythritol tetraglycidyl ether, polyepoxides and the like.

**[0046]** Suitable dihydrazide crosslinking agents include, for example, succinic acid dihydrazide, glutaric acid dihydrazide, adipic acid dihydrazide, pimelic acid dihydrazide, suberic acid dihydrazide, azelaic acid dihydrazide, sebacic acid dihydrazide, undecanedioic acid dihydrazide, dodecanedioic acid dihydrazide, brassylic acid dihydrazide, tetradecanedioic acid dihydrazide, pentadecanedioic acid dihydrazide, thapsic acid dihydrazide, octadecanedioic acid dihydrazide and the like.

**[0047]** Suitable dihydric alcohol crosslinking agents include, for example, ethylene glycol, propylene glycol, butylene glycol, diethylene glycol, dipropylene glycol, neopentyl glycol, 1,3-propanediol, hexylene glycol, pentylene glycol, heptylene glycol, octylene glycol and the like. Suitable polyhydric alcohol crosslinking agents include, for example, glycerin, pentaerythrite, xylitol, galactitol and the like. Suitable carbodiimide crosslinking agents include, for example, a compound of formula  $X-N=C=N-X$ , wherein each X independently is a  $C_1$  to  $C_6$  alkyl optionally substituted with 1-2 dialkylamino groups, or is a  $C_5$  to  $C_6$  cycloalkyl group, such as 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride, and cyclohexyl carbodiimide. Suitable anhydride crosslinking agents include, for example, methacrylic anhydride, octyl succinic anhydride and the like. In one embodiment, a suitable crosslinking agent is an aldehyde crosslinking agent such as, for example, formaldehyde, glutaraldehyde, gluronaldehyde and the like. In one embodiment, a suitable crosslinking agent includes, for example, an acid chloride, n-hydroxysuccinimide, polyethylene glycol diacrylates, polyethylene glycol diamines, ureas, diisocyanates and the like.

**[0048]** The glycophospholipid polymeric network of the present invention can be obtained by forming a solution of the one or more GAGs and the one or more phospholipids,

and optionally adding the one or more crosslinking agents when forming a crosslinked polymeric network. The solution is stirred for a suitable time sufficient to react and/or crosslink the one or more GAGs and the one or more phospholipids. In one embodiment, the reaction between the one or more GAGs and the one or more phospholipids can take place between 1°C and about 99°C, over a time period of about 2 hours to about 36 hours.

**[0049]** The solution can contain suitable one or more solvents such as, for example, water, crown-ethers, dimethyl sulphoxide (DMSO), dimethyl formamide (DMF) and other aprotic solvents.

**[0050]** In general, the amount of the one or more GAGs in the solution can range from about 0.010 to about 50 wt. %, based on the total weight of the solution. In one illustrative embodiment, the amount of the one or more GAGs in the solution can range from about 0.1 to about 5 wt. %, based on the total weight of the solution. In one illustrative embodiment, the amount of the one or more phospholipids in the solution can range from about 0.01 to about 50 wt. %, based on the total weight of the solution. In one illustrative embodiment, the amount of the one or more phospholipids in the solution can range from about 0.1 to about 5 wt. %, based on the total weight of the solution. The crosslinking agent can be added to the solution in an amount ranging from about 0.05 to about 20 wt. %, based on the total weight of the solution.

**[0051]** It will be readily understood and appreciated by those skilled in the art that the reaction product constitutes a complex mixture of compounds. For example, a reaction product of one or more GAGs, one or more phospholipids, and one or more crosslinking agents can include, by way of example, the polymer obtained from the reaction between one or more GAGs and the one or more phospholipids, the GAG crosslinked with the phospholipid, the GAG crosslinked with the GAG, the phospholipid crosslinked with the phospholipid, unreacted GAG and unreacted phospholipid. In one illustrative embodiment, a GAG crosslinked with a phospholipid can have a weight average molecular weight ranging from about 20,000 to about 6,000,000 Da in which the lower limit is from about 20,000, about 30,000, about 40,000, about 50,000, about 60,000, about 70,000, about 80,000, about 90,000, or about 100,000 Da, and the upper limit is about 200,000, about 300,000, about 400,000,

about 500,000, about 600,000, about 700,000, about 800,000, about 900,000, about 1,000,000, about 2,000,000, about 3,000,000, about 4,000,000, about 5,000,000 or up to about 6,000,000 Da where any of the lower limits can be combined with any of the upper limits. It is not necessary to isolate one or more specific components of the reaction product mixture. Indeed, the reaction product mixture can be employed as is.

**[0052]** In another illustrative embodiment, a biomedical device is provided which comprises the glycopospholipid polymer and/or the crosslinked glycopospholipid polymeric network of the present invention on the surface thereof. The glycopospholipid polymer and/or the crosslinked glycopospholipid polymeric network may be provided over the entire surface of the biomedical device or over only a portion of the biomedical device surface. The glycopospholipid polymer and/or the crosslinked glycopospholipid polymeric network may also be provided within the construct of the biomedical device. As used herein, the term “biomedical device” shall be understood to mean any article that is designed to be used while either in or on mammalian tissues or fluid, and preferably in or on human tissue or fluids. Representative examples of biomedical devices include, but are not limited to, artificial ureters, diaphragms, intrauterine devices, heart valves, catheters, denture liners, prosthetic devices, ophthalmic lens applications, where the lens is intended for direct placement in or on the eye, such as, for example, intraocular devices and contact lenses. In one embodiment, the biomedical devices are ophthalmic devices, particularly contact lenses, and most particularly contact lenses made from silicone hydrogels.

**[0053]** As used herein, the term “ophthalmic device” refers to devices that reside in or on the eye. These devices can provide optical correction, wound care, tissue repair, drug delivery, diagnostic functionality or cosmetic enhancement or effect or a combination of these properties. Useful ophthalmic devices include, but are not limited to, ophthalmic lenses such as soft contact lenses, e.g., a soft, hydrogel lens; soft, non-hydrogel lens and the like, hard contact lenses, e.g., a hard, gas permeable lens material and the like, intraocular lenses, overlay lenses, ocular inserts, optical inserts, viscoelastics and the like. As is understood by one skilled in the art, a lens is considered to be “soft” if it can be folded back upon itself without breaking.

**[0054]** The biomedical devices to be surface modified according to the present invention can be any material known in the art capable of forming a biomedical device as described above. In one embodiment, a biomedical device includes devices formed from material not hydrophilic per se. Such devices are formed from materials known in the art and include, by way of example, polysilylethanyls, polysiloxanes, perfluoropolyethers, fluorinated poly(meth)acrylates or equivalent fluorinated polymers derived, e.g., from other polymerizable carboxylic acids, polyalkyl (meth)acrylates or equivalent alkylester polymers derived from other polymerizable carboxylic acids, or fluorinated polyolefins, such as fluorinated ethylene propylene polymers, or tetrafluoroethylene, preferably in combination with a dioxol, e.g., perfluoro-2,2-dimethyl-1,3-dioxol. Representative examples of suitable bulk materials include, but are not limited to, Samfilcon, Lotrafilcon A, Neoficon, Pasificon, Telefocon, Silaficon, Fluorsilficon, Pafluficon, Silaficon, Elastofilcon, Fluoroficon or Teflon AF materials, such as Teflon AF 1600 or Teflon AF 2400 which are copolymers of about 63 to about 73 mol % of perfluoro-2,2-dimethyl-1,3-dioxol and about 37 to about 27 mol % of tetrafluoroethylene, or of about 80 to about 90 mol % of perfluoro-2,2-dimethyl-1,3-dioxol and about 20 to about 10 mol % of tetrafluoroethylene.

**[0055]** In another illustrative embodiment, a biomedical device includes a device formed from material hydrophilic per se, since reactive groups, e.g., carboxy, carbamoyl, sulfate, sulfonate, phosphate, amine, ammonium or hydroxy groups, are inherently present in the material and therefore also at the surface of a biomedical device manufactured therefrom. Such devices are formed from materials known in the art and include, by way of example, polyhydroxyethyl acrylate, polyhydroxyethyl methacrylate, polyvinyl pyrrolidone (PVP), polyacrylic acid, polymethacrylic acid, polyacrylamide, polydimethylacrylamide (DMA), polyvinyl alcohol and the like and copolymers thereof, e.g., from two or more monomers selected from hydroxyethyl acrylate, hydroxyethyl methacrylate, N-vinyl pyrrolidone, acrylic acid, methacrylic acid, acrylamide, dimethyl acrylamide, vinyl alcohol and the like. Representative examples of suitable bulk materials include, but are not limited to, Polymacon, Teficon, Methafilcon, Deltafilcon, Buficon, Phemfilcon, Ocufilecon, Focofilcon, Etafilecon, Heficon, Vificon, Tetrafilcon, Perfilcon, Droxifilcon, Dimefilecon, Isofilecon, Maficon,

Nelfilcon, Atafilcon and the like. Examples of other suitable bulk materials include Balafilcon A, Hilafilcon A, Alphafilcon A, Bilafilcon B, Samfilcon and the like.

**[0056]** In another illustrative embodiment, a biomedical device to be surface modified according to the present invention include a device which is formed from material which are amphiphilic segmented copolymers containing at least one hydrophobic segment and at least one hydrophilic segment which are linked through a bond or a bridge member.

**[0057]** It is particularly useful to employ biocompatible materials herein including both soft and rigid materials commonly used for ophthalmic lenses, including contact lenses. In general, non-hydrogel materials are hydrophobic polymeric materials that do not contain water in their equilibrium state. Typical non-hydrogel materials comprise silicone acrylics, such as those formed bulky silicone monomer (e.g., tris(trimethylsiloxy)silylpropyl methacrylate, commonly known as "TRIS" monomer), methacrylate end-capped poly(dimethylsiloxane) prepolymer, or silicones having fluoroalkyl side groups (polysiloxanes and polysilylethanes are also commonly known as silicone polymers).

**[0058]** On the other hand, hydrogel materials comprise hydrated, crosslinked polymeric systems containing water in an equilibrium state. Hydrogel materials contain about 5 wt. % water or more (up to, for example, about 80 wt. %). The preferred hydrogel materials, include silicone hydrogel materials. In one preferred embodiment, materials include vinyl functionalized polydimethylsiloxanes copolymerized with hydrophilic monomers as well as fluorinated methacrylates and methacrylate functionalized fluorinated polyethylene oxides copolymerized with hydrophilic monomers. Representative examples of suitable materials for use herein include those disclosed in U.S. Patent Nos. 5,310,779; 5,387,662; 5,449,729; 5,512,205; 5,610,252; 5,616,757; 5,708,094; 5,710,302; 5,714,557; 5,908,906; 7,915,323 and 8,420,711, the contents of which are incorporated by reference herein.

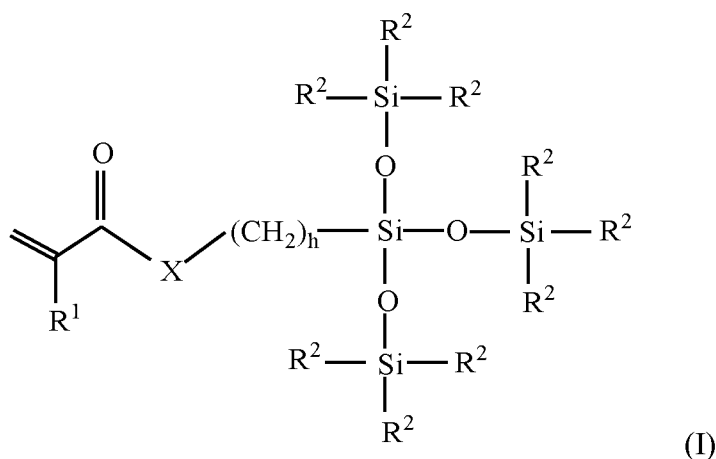
**[0059]** In one illustrative embodiment, hydrogel materials for biomedical devices, such as contact lenses, can contain a hydrophilic monomer such as one or more unsaturated carboxylic acids, vinyl lactams, amides, polymerizable amines, vinyl carbonates, vinyl carbamates, oxazolone monomers, copolymers thereof and the like and mixtures thereof.

Useful amides include acrylamides such as N,N-dimethylacrylamide and N,N-dimethylmethacrylamide. Useful vinyl lactams include cyclic lactams such as N-vinyl-2-pyrrolidone. Examples of other hydrophilic monomers include hydrophilic prepolymers such as poly(alkene glycols) functionalized with polymerizable groups. Examples of useful functionalized poly(alkene glycols) include poly(diethylene glycols) of varying chain length containing monomethacrylate or dimethacrylate end caps. In a preferred embodiment, the poly(alkene glycol) polymer contains at least two alkene glycol monomeric units. Still further examples are the hydrophilic vinyl carbonate or vinyl carbamate monomers disclosed in U.S. Patent No. 5,070,215, and the hydrophilic oxazolone monomers disclosed in U.S. Patent No. 4,910,277. Other suitable hydrophilic monomers will be apparent to one skilled in the art. In another embodiment, a hydrogel material can contain a siloxane-containing monomer and at least one of the aforementioned hydrophilic monomers and/or prepolymers.

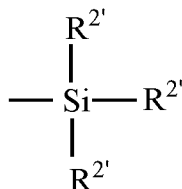
**[0060]** Non-limited examples of hydrophobic monomers are C<sub>1</sub>-C<sub>20</sub> alkyl and C<sub>3</sub>-C<sub>20</sub> cycloalkyl (meth)acrylates, substituted and unsubstituted aryl (meth)acrylates (wherein the aryl group comprises 6 to 36 carbon atoms), (meth) acrylonitrile, styrene, lower alkyl styrene, lower alky vinyl ethers, and C<sub>2</sub>-C<sub>10</sub> perfluoroalkyl (meth)acrylates and correspondingly partially fluorinate (meth)acrylates.

**[0061]** A wide variety of materials can be used herein, and silicone hydrogel contact lens materials are particularly preferred. Silicone hydrogels generally have a water content greater than about 5 wt. % and more commonly between about 10 to about 80 wt. %. Such materials are usually prepared by polymerizing a mixture containing at least one silicone-containing monomer and at least one hydrophilic monomer. Typically, either the silicone-containing monomer or the hydrophilic monomer functions as a crosslinking agent (a crosslinker being defined as a monomer having multiple polymerizable functionalities) or a separate crosslinker may be employed. Applicable silicone-containing monomers for use in the formation of silicone hydrogels are well known in the art and numerous examples are provided in U.S. Patent Nos. 4,136,250; 4,153,641; 4,740,533; 5,034,461; 5,070,215; 5,260,000; 5,310,779; and 5,358,995.

**[0062]** Representative examples of applicable silicon-containing monomers include bulky polysiloxanylalkyl(meth)acrylic monomers. An example of a bulky polysiloxanylalkyl(meth)acrylic monomer is represented by the structure of Formula I:

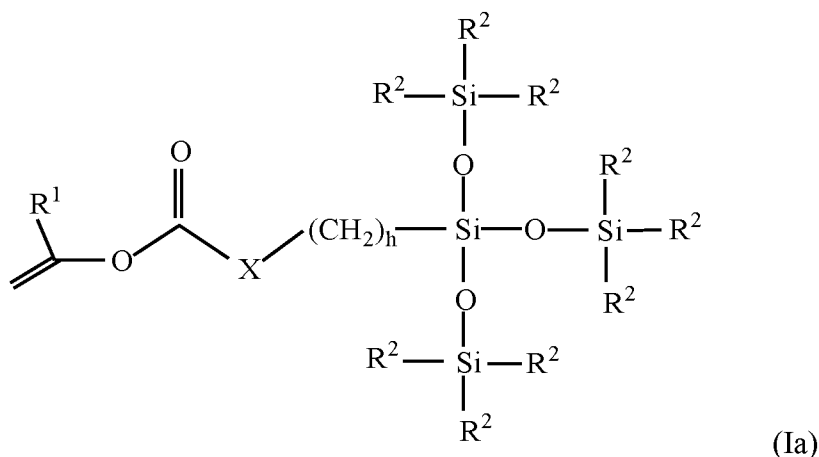


wherein X denotes —O— or —NR— wherein R denotes hydrogen or a C<sub>1</sub>-C<sub>4</sub> alkyl; each R<sup>1</sup> independently denotes hydrogen or methyl; each R<sup>2</sup> independently denotes a lower alkyl radical, phenyl radical or a group represented by

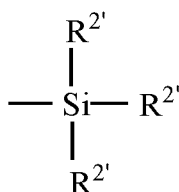


wherein each R<sup>2'</sup> independently denotes a lower alkyl or phenyl radical; and h is 1 to 10.

**[0063]** Representative examples of other applicable silicon-containing monomers include, but are not limited to, bulky polysiloxanylalkyl carbamate monomers as generally depicted in Formula Ia:



wherein X denotes  $\text{-NR-}$ ; wherein R denotes hydrogen or a  $\text{C}_1\text{-C}_4$  alkyl;  $\text{R}^1$  denotes hydrogen or methyl; each  $\text{R}^2$  independently denotes a lower alkyl radical, phenyl radical or a group represented by



wherein each  $\text{R}^{2'}$  independently denotes a lower alkyl or phenyl radical; and h is 1 to 10, and the like.

**[0064]** Examples of bulky monomers are 3-methacryloyloxypropyltris(trimethylsiloxy)silane or tris(trimethylsiloxy)silylpropyl methacrylate, sometimes referred to as TRIS and tris(trimethylsiloxy)silylpropyl vinyl carbamate, sometimes referred to as TRIS-VC and the like and mixtures thereof.

**[0065]** Such bulky monomers may be copolymerized with a silicone macromonomer, which is a poly(organosiloxane) capped with an unsaturated group at two or more ends of the molecule. U.S. Patent No. 4,153,641 discloses, for example, various unsaturated groups such as acryloxy or methacryloxy groups.

**[0066]** Another class of representative silicone-containing monomers includes, but is not limited to, silicone-containing vinyl carbonate or vinyl carbamate monomers such as, for example, 1,3-bis[4-vinyloxy-carbonyloxy]but-1-yl]tetramethyl-disiloxane; 3-

(trimethylsilyl)propyl vinyl carbonate; 3-(vinylloxycarbonylthio)propyl-[tris(trimethylsiloxy)silane]; 3-[tris(trimethylsiloxy)silyl]propyl vinyl carbamate; 3-[tris(trimethylsiloxy)silyl]propyl allyl carbamate; 3-[tris(trimethylsiloxy)silyl]propyl vinyl carbonate; t-butyl dimethylsiloxyethyl vinyl carbonate; trimethylsilylethyl vinyl carbonate; trimethylsilylmethyl vinyl carbonate and the like and mixtures thereof.

**[0067]** Another class of silicon-containing monomers includes polyurethane-polysiloxane macromonomers (also sometimes referred to as prepolymers), which may have hard-soft-hard blocks like traditional urethane elastomers. They may be end-capped with a hydrophilic monomer such as HEMA. Examples of such silicone urethanes are disclosed in a variety of publications, including Lai, Yu-Chin, "The Role of Bulky Polysiloxanylalkyl Methacryates in Polyurethane-Polysiloxane Hydrogels," *Journal of Applied Polymer Science*, Vol. 60, 1193-1199 (1996). PCT Published Application No. WO 96/31792 discloses examples of such monomers, which disclosure is hereby incorporated by reference in its entirety. Further examples of silicone urethane monomers are represented by Formulae II and III:



wherein:

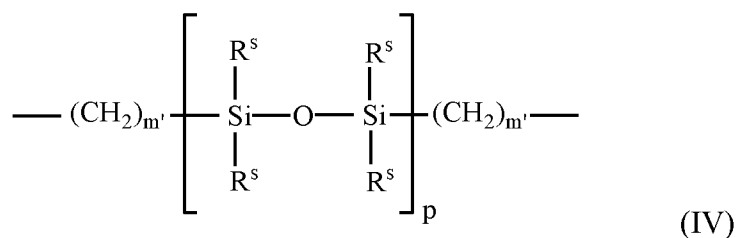
D independently denotes an alkyl diradical, an alkyl cycloalkyl diradical, a cycloalkyl diradical, an aryl diradical or an alkylaryl diradical having 6 to about 30 carbon atoms;

G independently denotes an alkyl diradical, a cycloalkyl diradical, an alkyl cycloalkyl diradical, an aryl diradical or an alkylaryl diradical having 1 to about 40 carbon atoms and which may contain ether, thio or amine linkages in the main chain;

\* denotes a urethane or ureido linkage;

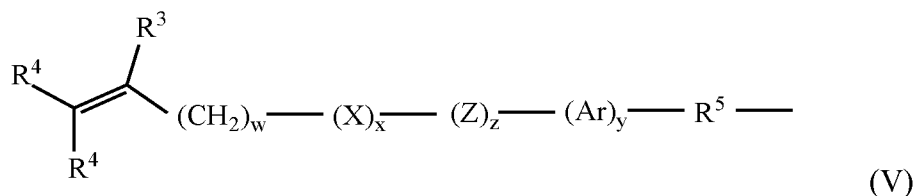
a is at least 1;

A independently denotes a divalent polymeric radical of Formula IV:



wherein each  $\text{R}^s$  independently denotes an alkyl or fluoro-substituted alkyl group having 1 to about 10 carbon atoms which may contain ether linkages between the carbon atoms;  $m'$  is at least 1; and  $p$  is a number that provides a moiety weight of about 400 to about 10,000;

each of  $\text{E}$  and  $\text{E}'$  independently denotes a polymerizable unsaturated organic radical represented by Formula V:



wherein:  $\text{R}^3$  is hydrogen or methyl;

$\text{R}^4$  is hydrogen, an alkyl radical having 1 to 6 carbon atoms, or a  $\text{---CO---Y---R}^6$  radical wherein  $\text{Y}$  is  $\text{---O---}$ ,  $\text{---S---}$  or  $\text{---NH---}$ ;

$\text{R}^5$  is a divalent alkylene radical having 1 to about 10 carbon atoms;

$\text{R}^6$  is a alkyl radical having 1 to about 12 carbon atoms;

$\text{X}$  denotes  $\text{---CO---}$  or  $\text{---OCO---}$ ;

$\text{Z}$  denotes  $\text{---O---}$  or  $\text{---NH---}$ ;

$\text{Ar}$  denotes an aromatic radical having about 6 to about 30 carbon atoms;

$w$  is 0 to 6;  $x$  is 0 or 1;  $y$  is 0 or 1; and  $z$  is 0 or 1.



5,310,779; 5,449,729 and 5,512,205 are also useful substrates in accordance with the invention. The silane macromonomer may be a silicon-containing vinyl carbonate or vinyl carbamate or a polyurethane-polysiloxane having one or more hard-soft-hard blocks and end-capped with a hydrophilic monomer.

**[0070]** Another class of representative silicone-containing monomers includes fluorinated monomers. Such monomers have been used in the formation of fluorosilicone hydrogels to reduce the accumulation of deposits on contact lenses made therefrom, as disclosed in, for example, U.S. Patent Nos. 4,954,587; 5,010,141; 5,079,319 and 7,994,356. Also, the use of silicone-containing monomers having certain fluorinated side groups, i.e.,  $-(CF_2)-H$ , have been found to improve compatibility between the hydrophilic and silicone-containing monomeric units. See, e.g., U.S. Patent Nos. 5,321,108 and 5,387,662.

**[0071]** The above silicone materials are merely exemplary, and other materials for use as substrates that can benefit by being coated with the hydrophilic coating composition according to the present invention and have been disclosed in various publications and are being continuously developed for use in contact lenses and other medical devices can also be used. For example, a biomedical device can be formed from at least a cationic monomer such as cationic silicone-containing monomer or cationic fluorinated silicone-containing monomers.

**[0072]** Contact lenses for application of the present invention can be manufactured employing various conventional techniques, to yield a shaped article having the desired posterior and anterior lens surfaces. Spincasting methods are disclosed in U.S. Patent Nos. 3,408,429 and 3,660,545; and static casting methods are disclosed in U.S. Patent Nos. 4,113,224, 4,197,266 and 5,271,876. Curing of the monomeric mixture may be followed by a machining operation in order to provide a contact lens having a desired final configuration. As an example, U.S. Patent No. 4,555,732 discloses a process in which an excess of a monomeric mixture is cured by spincasting in a mold to form a shaped article having an anterior lens surface and a relatively large thickness. The posterior surface of the cured spincast article is subsequently lathe cut to provide a contact lens having the desired thickness

and posterior lens surface. Further machining operations may follow the lathe cutting of the lens surface, for example, edge-finishing operations.

**[0073]** Typically, an organic diluent is included in the initial monomeric mixture in order to minimize phase separation of polymerized products produced by polymerization of the monomeric mixture and to lower the glass transition temperature of the reacting polymeric mixture, which allows for a more efficient curing process and ultimately results in a more uniformly polymerized product. Sufficient uniformity of the initial monomeric mixture and the polymerized product is of particular importance for silicone hydrogels, primarily due to the inclusion of silicone-containing monomers which may tend to separate from the hydrophilic comonomer.

**[0074]** Suitable organic diluents include, for example, monohydric alcohols such as C<sub>6</sub>-C<sub>10</sub> straight-chained aliphatic monohydric alcohols, e.g., n-hexanol and n-nonanol; diols such as ethylene glycol; polyols such as glycerin; ethers such as diethylene glycol monoethyl ether; ketones such as methyl ethyl ketone; esters such as methyl enanthate; and hydrocarbons such as toluene. Preferably, the organic diluent is sufficiently volatile to facilitate its removal from a cured article by evaporation at or near ambient pressure.

**[0075]** Generally, the diluent may be included at about 5 to about 60 percent by weight of the monomeric mixture, with about 10 to about 50 percent by weight being especially preferred. If necessary, the cured lens may be subjected to solvent removal, which can be accomplished by evaporation at or near ambient pressure or under vacuum. An elevated temperature can be employed to shorten the time necessary to evaporate the diluent.

**[0076]** Following removal of the organic diluent, the lens can then be subjected to mold release and optional machining operations. The machining step includes, for example, buffing or polishing a lens edge and/or surface. Generally, such machining processes may be performed before or after the article is released from a mold part. As an example, the lens may be dry released from the mold by employing vacuum tweezers to lift the lens from the mold.

**[0077]** As one skilled in the art will readily appreciate, biomedical device surface functional groups of the biomedical device according to the present invention may be

inherently present at the surface of the device. However, if the biomedical device contains too few or no functional groups, the surface of the device can be modified by known techniques, for example, plasma chemical methods (see, for example, WO 94/06485), or conventional functionalization with groups such as -OH, or -CO<sub>2</sub>H. Suitable biomedical device surface functional groups of the biomedical device include a wide variety of groups well known to the skilled artisan. Representative examples of such functional groups include, but are not limited to, hydroxy groups, cis 1,2-diols, cis 1,3-diols,  $\alpha$  hydroxy acid groups (e.g., sialic acid, salicylic acid), carboxylic acids, di-carboxylic acids, catechols, silanols, silicates and the like.

**[0078]** In one illustrative embodiment, the foregoing biomedical devices are subjected to an oxidative surface treatment such as corona discharge or plasma oxidation followed by treatment with the glycopospholipid polymer and/or the crosslinked glycopospholipid polymeric network of the present invention. For example, a biomedical device such as a silicone hydrogel formulation containing hydrophilic polymers, such as poly(N,N-dimethylacrylamide) or poly(N-vinylpyrrolidinone), is subjected to an oxidative surface treatment to form at least silicates on the surface of the lens and then the lens is treated with an aqueous solution containing the glycopospholipid polymer and/or the crosslinked glycopospholipid polymeric network of the present invention to render a lubricious, stable, highly wettable surface coating. The complexation treatment is advantageously performed under autoclave conditions (sterilization conditions).

**[0079]** The standard process such as a plasma process (also referred to as “electrical glow discharge processes”) provides a thin, durable surface upon the biomedical device prior to binding the glycopospholipid polymer and/or the crosslinked glycopospholipid polymeric network to at least a portion of the surface thereof. Examples of such plasma processes are provided in U.S. Patent Nos. 4,143,949; 4,312,575; and 5,464,667.

**[0080]** Although plasma processes are generally well known in the art, a brief overview is provided below. Plasma surface treatments involve passing an electrical discharge through a gas at low pressure. The electrical discharge may be at radio frequency (typically 13.56 MHz), although microwave and other frequencies can be used. Electrical

discharges produce ultraviolet (UV) radiation, in addition to being absorbed by atoms and molecules in their gas state, resulting in energetic electrons and ions, atoms (ground and excited states), molecules, and radicals. Thus, a plasma is a complex mixture of atoms and molecules in both ground and excited states, which reach a steady state after the discharge is begun. The circulating electrical field causes these excited atoms and molecules to collide with one another as well as the walls of the chamber and the surface of the material being treated.

**[0081]** The deposition of a coating from a plasma onto the surface of a material has been shown to be possible from high-energy plasmas without the assistance of sputtering (sputter-assisted deposition). Monomers can be deposited from the gas phase and polymerized in a low-pressure atmosphere (e.g., about 0.005 to about 5 torr, or about 0.001 to about 1 torr) onto a substrate utilizing continuous or pulsed plasmas, suitably as high as about 1000 watts. A modulated plasma, for example, may be applied about 100 milliseconds on then off. In addition, liquid nitrogen cooling has been utilized to condense vapors out of the gas phase onto a substrate and subsequently use the plasma to chemically react these materials with the substrate. However, plasmas do not require the use of external cooling or heating to cause the deposition. Low or high wattage (e.g., about 5 to about 1000, or about 20 to about 500 watts) plasmas can coat even the most chemical-resistant substrates, including silicones.

**[0082]** After initiation by a low energy discharge, collisions between energetic free electrons present in the plasma cause the formation of ions, excited molecules, and free-radicals. Such species, once formed, can react with themselves in the gas phase as well as with further ground-state molecules. The plasma treatment may be understood as an energy dependent process involving energetic gas molecules. For chemical reactions to take place at the surface of the lens, one needs the required species (element or molecule) in terms of charge state and particle energy. Radio frequency plasmas generally produce a distribution of energetic species. Typically, the “particle energy” refers to the average of the so-called Boltzman-style distribution of energy for the energetic species. In a low-density plasma, the electron energy distribution can be related by the ratio of the electric field strength sustaining the plasma to the discharge pressure ( $E/p$ ). The plasma power density  $P$  is a function of the

wattage, pressure, flow rates of gases, etc., as will be appreciated by the skilled artisan. Background information on plasma technology, hereby incorporated by reference, includes the following: A. T. Bell, Proc. Intl. Conf. Phenom. Ioniz. Gases, "*Chemical Reaction in Nonequilibrium Plasmas*", 19-33 (1977); J. M. Tibbitt, R. Jensen, A. T. Bell, M. Shen, *Macromolecules*, "A Model for the Kinetics of Plasma Polymerization", 3, 648-653 (1977); J. M. Tibbitt, M. Shen, A. T. Bell, *J. Macromol. Sci.-Chem.*, "*Structural Characterization of Plasma-Polymerized Hydrocarbons*", A10, 1623-1648 (1976); C. P. Ho, H. Yasuda, *J. Biomed. Mater. Res.*, "*Ultrathin coating of plasma polymer of methane applied on the surface of silicone contact lenses*", 22, 919-937 (1988); H. Kobayashi, A. T. Bell, M. Shen, *Macromolecules*, "*Plasma Polymerization of Saturated and Unsaturated Hydrocarbons*", 3, 277-283 (1974); R. Y. Chen, U.S. Pat. No., 4,143,949, Mar. 13, 1979, "*Process for Putting a Hydrophilic Coating on a Hydrophobic Contact lens*"; and H. Yasuda, H. C. Marsh, M. O. Bumgarner, N. Morosoff, *J. of Appl. Poly. Sci.*, "*Polymerization of Organic Compounds in an Electroless Glow Discharge. VI. Acetylene with Unusual Co-monomers*", 19, 2845-2858 (1975).

**[0083]** Based on this previous work in the field of plasma technology, the effects of changing pressure and discharge power on the rate of plasma modification can be understood. The rate generally decreases as the pressure is increased. Thus, as pressure increases the value of  $E/p$ , the ratio of the electric field strength sustaining the plasma to the gas pressure decreases and causes a decrease in the average electron energy. The decrease in electron energy in turn causes a reduction in the rate coefficient of all electron-molecule collision processes. A further consequence of an increase in pressure is a decrease in electron density. Providing that the pressure is held constant, there should be a linear relationship between electron density and power.

**[0084]** In practice, contact lenses are surface-treated by placing them, in their unhydrated state, within an electric glow discharge reaction vessel (e.g., a vacuum chamber). Such reaction vessels are commercially available. The lenses may be supported within the vessel on an aluminum tray (which acts as an electrode) or with other support devices designed to adjust the position of the lenses. The use of a specialized support devices which

permit the surface treatment of both sides of a lens are known in the art and may be used herein.

**[0085]** As mentioned above, the surface of the lens, for example, a silicone hydrogel continuous-wear lens is initially treated, e.g., oxidized, by the use of a plasma to render the subsequent glycopospholipid polymer and/or the crosslinked glycopospholipid polymeric network surface deposition more adherent to the lens. Such a plasma treatment of the lens may be accomplished in an atmosphere composed of a suitable media, e.g., an oxidizing media such as oxygen, air, water, peroxide, O<sub>2</sub> (oxygen gas), etc., or appropriate combinations thereof, typically at an electric discharge frequency of about 13.56 Mhz, preferably between about 20 to about 500 watts at a pressure of about 0.1 to about 1.0 torr, preferably for about 10 seconds to about 10 minutes or more, more preferably about 1 to about 10 minutes. It is preferred that a relatively “strong” plasma is utilized in this step, for example, ambient air drawn through a five percent (5%) hydrogen peroxide solution. Those skilled in the art will know other methods of improving or promoting adhesion for bonding of the subsequent glycopospholipid polymer and/or the crosslinked glycopospholipid polymeric network layer.

**[0086]** The biomedical device is then subjected to a surface treatment in accordance with the present invention. In general, the biomedical device such as a wettable silicone-based hydrogel lens is contacted with a solution containing at least one or more of the glycopospholipid polymer and/or the crosslinked glycopospholipid polymeric network of the present invention, whereby the glycopospholipid polymer and/or the crosslinked glycopospholipid polymeric network forms a complex with the plurality of biomedical device surface functional groups on the surface of the biomedical device. The biomedical devices can either be contacted with the solution containing at least the glycopospholipid polymer and/or the crosslinked glycopospholipid polymeric network directly in the mold assembly or the biomedical device can be released from the mold assembly and then contacted with the solution. The solutions can be water-based solutions containing the glycopospholipid polymer and/or the crosslinked glycopospholipid polymeric network and

render a lubricious, stable, highly wettable surface. The complexation treatment is advantageously performed under autoclave conditions.

**[0087]** The solutions generally include compositions for direct instillation in the eye, including eye drop solutions and contact lens treating solutions distilled directly in the eye such as for rewetting a contact lens while worn as well as those that also qualify as a multi-purpose solution. Ophthalmic compositions also include compositions instilled indirectly in the eye, such as contact lens treating solutions for treating the contact lens prior to the lens being inserted on the eye or a packaging solution for storing the lens.

**[0088]** The ophthalmically acceptable solutions according to the present invention are physiologically compatible. Specifically, the compositions must be “ophthalmically safe” for use with a contact lens, meaning that a contact lens treated with the solution is generally suitable and safe for direct placement on the eye without rinsing, that is, the solution is safe and comfortable for daily contact with the eye via a contact lens that has been wetted with the solution. An ophthalmically safe composition has a tonicity and pH that is compatible with the eye and comprises materials, and amounts thereof, that are non-cytotoxic according to ISO (International Standards Organization) standards and U.S. FDA regulations. The compositions should be sterile in that the absence of microbial contaminants in the product prior to release must be statistically demonstrated to the degree necessary for such products.

**[0089]** In general, the one or more of the glycopospholipid polymer and/or the crosslinked glycopospholipid polymeric network of the present invention can be present in the ophthalmic solution in an amount ranging from about 0.001 to about 10% w/w. In one illustrative embodiment, the one or more of the glycopospholipid polymer and/or the crosslinked glycopospholipid polymeric network of the present invention can be present in the ophthalmic solution in an amount ranging from about 0.1 to about 2% w/w.

**[0090]** The ophthalmic solutions may be in the form of drops and are useful as a component of a contact lens cleaning, disinfecting or conditioning composition containing such materials. In one embodiment, the compositions and/or solutions of the present invention may be formulated as a “multi-purpose solution”. A multi-purpose solution is useful for cleaning, disinfecting, storing, and rinsing a lens, particularly soft contact lenses.

Multi-purpose solutions do not exclude the possibility that some wearers, for example, wearers particularly sensitive to chemical disinfectants or other chemical agents, may prefer to rinse or wet a contact lens with another solution, for example, a sterile saline solution prior to insertion of the lens. The term “multi-purpose solution” also does not exclude the possibility of periodic cleaners not used on a daily basis or supplemental cleaners for further removing proteins, for example, enzyme cleaners, which are typically used on a weekly basis. By the term “cleaning” is meant that the solution contains one or more agents in sufficient concentrations to loosen and remove loosely held lens deposits and other contaminants on the surface of a contact lens, which may be used in conjunction with digital manipulation (e.g., manual rubbing of the lens with a solution) or with an accessory device that agitates the solution in contact with the lens, for example, a mechanical cleaning aid.

**[0091]** Traditionally, multi-purpose solutions on the market have required a regimen involving mechanical rubbing of the lens with the multi-purpose solution, in order to provide the required disinfection and cleaning. Such a regimen is required under governmental regulatory authorities (e.g., the FDA or U.S. Food & Drug Administration (FDA)) for a Chemical Disinfection System that does not qualify as a Chemical Disinfecting Solution. In one embodiment of the present invention, it is possible to formulate a cleaning and disinfecting product that, on one hand, is able to provide improved cleaning and disinfection in the absence of a rubbing regimen and, on the other hand, is gentle enough to be used as a wetting agent, e.g. as an eye drop. For example, a product qualifying as a Chemical Disinfecting Solution must meet biocidal performance criteria established by the US FDA for Contact Lens Care Products (May 1, 1997) which criteria does not involve rubbing of the lenses. In one embodiment of the present invention, a composition is formulated to meet the requirements of the FDA or ISO Stand-Alone Procedure for contact lens disinfecting products. Similarly, the compositions of the present invention can be formulated to provide enhanced cleaning without the use of a rubbing regimen. Such formulations may ensure higher patient compliance and greater universal appeal than traditional multi-purpose disinfecting and cleaning products. A multi-purpose solution can have a viscosity of less than

about 75 cps, or from about 1 to about 50 cps, or from about 1 to about 25 cps or at least about 95 percent weight by volume water in the total composition.

**[0092]** The aqueous ophthalmic solutions may contain, in addition to the one or more of the glycopospholipid polymer and/or the crosslinked glycopospholipid polymeric network of the present invention, one or more antimicrobial agents, preservatives and the like. The compositions generally include a primary antimicrobial agent. Antimicrobial agents suitable for use in the present invention include chemicals that derive their antimicrobial activity through a chemical or physiochemical interaction with the microbial organisms. These agents may be used alone or in combination.

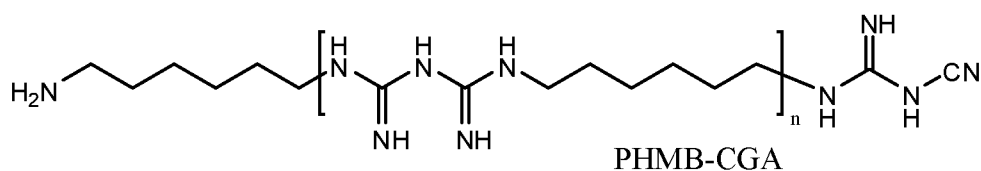
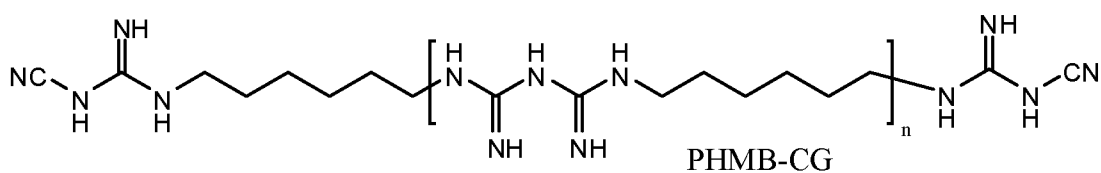
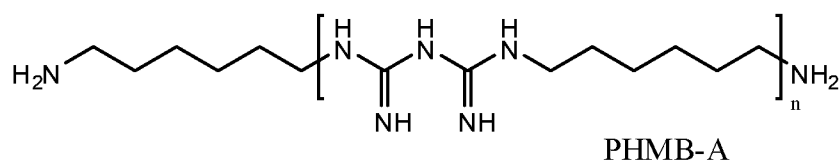
**[0093]** Suitable known ophthalmically acceptable antimicrobial agents include, but are not limited to, a biguanide or a salt or free base thereof, quaternary ammonium compound or a salt thereof or free base thereof; terpene or derivative thereof, a branched, glycerol monoalkyl ether, a branched, glycerol monoalkyl amine, a branched, glycerol monoalkyl sulphide, a fatty acid monoester, wherein the fatty acid monoester comprises an aliphatic fatty acid portion having six to fourteen carbon atoms, and an aliphatic hydroxyl portion, amidoamine compound, and the like and combinations thereof.

**[0094]** Suitable biguanide antimicrobial agents for use in the ophthalmic compositions can be any biguanide or salt thereof known in the art. Representative biguanides include non-polymeric biguanides, polymeric biguanides, salts thereof, free bases thereof and the like and mixtures thereof. Representative non-polymeric biguanides are the bis(biguanides), such as alexidine, chlorhexidine, salts of alexidine, e.g., alexidine HCl, salts of chlorhexidine, alexidine free base, and the like and mixtures thereof. The salts of alexidine and chlorhexidine can be either organic or inorganic and are typically disinfecting nitrates, acetates, phosphates, sulfates, halides and the like.

**[0095]** Representative polymeric biguanides include polymeric hexamethylene biguanides (PHMB) (commercially available from Zeneca, Wilmington, Del.), their polymers and water-soluble salts. In one embodiment, water-soluble polymeric biguanides for use herein can have a number average molecular weight of at least about 1,000 or a number average molecular weight from about 1,000 to about 50,000. Suitable water-soluble salts of

the free bases include, but are not limited to, hydrochloride, borate, acetate, gluconate, sulfonate, tartrate and citrate salts. Generally, the hexamethylene biguanide polymers, also referred to as polyaminopropyl biguanide (PAPB), have number average molecular weights of up to about 100,000. Such compounds are known and are disclosed in U.S. Pat. No. 4,758,595 which is incorporated herein by reference.

[0096] PHMB is best described as a polymeric biguanide composition comprising at least three and preferably at least six biguanide polymers, which we refer to as PHMB-A, PHMB-CG and PHMB-CGA, the general chemical structures of which are depicted below.



[0097] For each of these polymers, “n” represents the average number of repeating groups. Actually, a distribution of polymer length would exist for each of the polymers shown. The prior synthetic routes to PHMB provided a polymeric biguanide composition with about 50% by weight of the polymeric composition as PHMB-CGA, that is, having a cyanoguanidino end cap on one end and an amine on the other end, about 25% by weight PHMB-A and about 25% by weight PHMB-CG. Given this approximate weight ratio of the three major PHMB polymers above, the percentage of cyanoguanidino end caps is also about 50% of the total number of terminal groups. In this application we refer to this conventional polymeric biguanide composition as poly(hexamethylene biguanide) or PHMB.

**[0098]** A polymeric biguanide composition comprising less than 18 mole % of terminal amine groups as measured by <sup>13</sup>CNMR can also be used. The polymeric biguanide composition can also be characterized by a relative increase in the molar concentration of terminal guanidine groups or terminal cyanoguardino groups. For example, in one embodiment, the biguanide composition comprises less than about 18 mole % of terminal amine groups and about 40 mol% or greater of terminal guanidine groups. In another embodiment, the biguanide composition comprises less than about 18 mole % of terminal amine groups and about 55 mol% or greater of terminal guanidine groups.

**[0099]** In this application, this biguanide composition is referred to as PHMB-CG\*. Polymeric biguanide compositions are also referred to in the generic sense as “hexamethylene biguanides”, which one of ordinary skill in the art would recognize to include both PHMB as well as PHMB-CG\*.

**[00100]** Representative examples of suitable quaternary ammonium compounds for use in the ophthalmic compositions of the present invention include, but are not limited to, poly[(dimethyliminio)-2-butene-1,4-diyl chloride] and [4-tris(2-hydroxyethyl)ammonio]-2-butenyl-w-[tris(2-hydroxyethyl)ammonio]-dichloride (chemical registry no. 75345-27-6) generally available as Polyquaternium 1 under the tradename ONAMER<sup>®</sup> M (Stepan Company, Northfield, Ill), and the like and mixtures thereof.

**[00101]** Suitable terpene antimicrobial agents for use in the ophthalmic compositions of the present invention include any monoterpene, sesquiterpene and/or diterpene or derivatives thereof. Acyclic, monocyclic and/or bicyclic mono-, sesqui- and/or diterpenes, and those with higher numbers of rings, can be used. A “derivative” of a terpene as used herein shall be understood to mean a terpene hydrocarbon having one or more functional groups such as terpene alcohols, terpene ethers, terpene esters, terpene aldehydes, terpene ketones and the like and combinations thereof. Here, both the trans and also the cis isomers are suitable. The terpenes as well as the terpene moiety in the derivative can contain from 6 to about 100 carbon atoms and preferably from about 10 to about 25 carbon atoms.

**[00102]** Representative examples of suitable terpene alcohol antimicrobial agents include verbenol, transpinocarveol, cis-2-pinanol, nopol, isoborneol, carbeol, piperitol,

thymol,  $\alpha$ -terpineol, terpinen-4-ol, menthol, 1,8-terpin, dihydro-terpineol, nerol, geraniol, linalool, citronellol, hydroxycitronellol, 3,7-dimethyl octanol, dihydro-myrcenol, tetrahydro-alloocimanol, perillalcohol, falcarindiol and the like and mixtures thereof.

**[00103]** Representative examples of suitable terpene ether and terpene ester antimicrobial agents include 1,8-cineole, 1,4-cineole, isobornyl methylether, rose pyran,  $\alpha$ -terpinyl methyl ether, menthofuran, trans-anethole, methyl chavicol, allocimene diepoxide, limonene mono-epoxide, isobornyl acetate, nonyl acetate,  $\alpha$ -terpinyl acetate, linalyl acetate, geranyl acetate, citronellyl acetate, dihydro-terpinyl acetate, meryl acetate and the like and mixtures thereof.

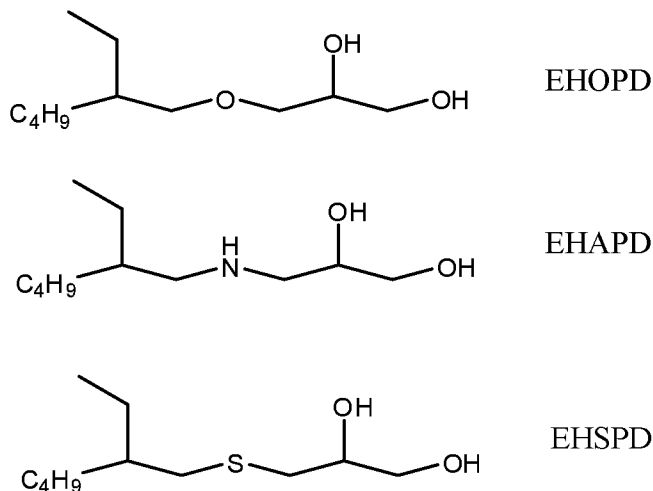
**[00104]** Representative examples of terpene aldehyde and terpene ketone antimicrobial agents include myrtenal, campholenic aldehyde, perillaldehyde, citronellal, citral, hydroxy citronellal, camphor, verbenone, carvenone, dihydro-carvone, carvone, piperitone, menthone, geranyl acetone, pseudo-ionone,  $\alpha$ -ionine, iso-pseudo-methyl ionone, n-pseudo-methyl ionone, iso-methyl ionone, n-methyl ionone and the like and mixtures thereof. Any other terpene hydrocarbons having functional groups known in the art may be used herein in the inventive composition.

**[00105]** In one illustrative embodiment, suitable terpenes or derivatives thereof as antimicrobial agents include, but are not limited to, tricyclene,  $\alpha$ -pinene, terpinolene, carveol, amyl alcohol, nerol,  $\beta$ -santalol, citral, pinene, nerol, b-ionone, caryophyllen (from cloves), guaiol, anisaldehyde, cedrol, linalool, d-limonene (orange oil, lemon oil), longifolene, anisyl alcohol, patchouli alcohol,  $\alpha$ -cadinene, 1,8-cineole,  $p$ -cymene, 3-carene,  $p$ -8-mentane, trans-menthone, borneol,  $\alpha$ -fenchol, isoamyl acetate, terpin, cinnamic aldehyde, ionone, geraniol (from roses and other flowers), myrcene (from bayberry wax, oil of bay and verbena), nerol, citronellol, carvacrol, eugenol, carvone,  $\alpha$ -terpineol, anethole, camphor, menthol, limonene, nerolidol, farnesol, phytol, carotene (vitamin A<sub>1</sub>), squalene, thymol, tocotrienol, perillyl alcohol, borneol, simene, carene, terpenene, linalool, 1-terpene-4-ol, zingiberene (from ginger) and the like and mixtures thereof.

**[00106]** In one illustrative embodiment, the compound of component (ii) of the ophthalmic composition comprises a branched, glycerol monoalkyl ether. In another

embodiment, the compound of component (ii) of the ophthalmic composition comprises a branched, glycerol monoalkyl amine. In another embodiment, the compound of component (ii) of the ophthalmic composition comprises a branched, glycerol monoalkyl sulphide. In still another embodiment, the compound of component (ii) of the ophthalmic composition comprises any one mixture of a branched, glycerol monoalkyl ether, a branched, glycerol monoalkyl amine or a branched, glycerol monoalkyl sulphide.

**[00107]** In one illustrative embodiment, the branched, glycerol monoalkyl ether for use in the ophthalmic compositions of the present invention is 3-[(2-ethylhexyl)oxy]-1,2-propanediol (EHOPD). In another embodiment, the branched, glycerol monoalkyl amine is 3-[(2-ethylhexyl)amino]-1,2-propanediol (EHAPD). In another embodiment, the branched, glycerol monoalkyl sulphide is 3-[(2-ethylhexyl)thio]-1,2-propanediol (EHSPD). In still another embodiment, the ophthalmic composition comprises any one mixture of EHOPD, EHAPD and EHSPD. The chemical structures of EHOPD, EHAPD and EHSPD are provided below.



**[00108]** EHOPD is also referred to as octoxyglycerin and is sold under the tradename Sensiva® SC50 (Schülke & Mayr). EHOPD is a branched, glycerol monoalkyl ether known to be gentle to the skin, and to exhibit antimicrobial activity against a variety of Gram-positive bacteria such as *Micrococcus luteus*, *Corynebacterium aquaticum*, *Corynebacterium flavescens*, *Corynebacterium callunae*, and *Corynebacterium nephredi*. Accordingly, EHOPD is used in various skin deodorant preparations at concentrations between about 0.2

and 3 percent by weight. EHAPD can be prepared from 2-ethylhexylamine and 2,3-epoxy-1-propanediol using chemistry well known to those of ordinary skill in the art. EHSPD can be prepared from 2-ethylhexylthiol and 2,3-epoxy-1-propanediol using chemistry well known to those of ordinary skill in the art.

**[00109]** Suitable fatty acid monoester for use in the ophthalmic compositions of the present invention include those fatty acid monoesters comprising an aliphatic fatty acid portion having six to fourteen carbon atoms, and an aliphatic hydroxyl portion.

**[00110]** The term “aliphatic” refers to a straight or branched, saturated or unsaturated hydrocarbon having six to fourteen carbon atoms. In one embodiment, the aliphatic fatty acid portion is a straight chain, saturated or unsaturated hydrocarbon with eight to ten carbons. In another embodiment, the aliphatic fatty acid portion is a branched chain, saturated or unsaturated hydrocarbon with eight to ten carbons.

**[00111]** The aliphatic hydroxyl portion of the fatty acid monoester can be any aliphatic compound with at least one hydroxyl group. In many of the embodiments, the aliphatic hydroxyl portion will have from three to nine carbons. The aliphatic hydroxyl portion can include, but is not limited to, propylene glycol, glycerol, a polyalkylene glycol, e.g., polyethylene glycol or polypropylene glycol, a cyclic polyol, e.g., sorbitan, glucose, mannose, sucrose, fructose, fucose and inositol and derivatives thereof, and a linear polyol, e.g., mannitol and sorbitol and derivatives thereof and the like and mixtures thereof.

**[00112]** Representative examples of suitable amidoamines for use in the ophthalmic compositions of the present inventions include those amidoamines of the general formula:

$R^{15}-(OCH_2CH_2)_m-X-(CH_2)_n-Y$  wherein  $R^{15}$  is a  $C_6-C_{30}$  saturated or unsaturated hydrocarbon including by way of example, a straight or branched, substituted or unsubstituted alkyl, alkylaryl, or alkoxyaryl group;  $m$  is zero to 16;  $n$  is 2 to 16;  $X$  is  $-C(O)-NR^{16}-$  or  $-R^{16}N-C(O)-$ ;  $Y$  is  $-N(R^{17})_2$  wherein each of  $R^{16}$  and  $R^{17}$  independently are hydrogen, a  $C_1-C_8$  saturated or unsaturated alkyl or hydroxyalkyl, or a pharmaceutically acceptable salt thereof.

**[00113]** Some of the amidoamines utilized in the present invention are available from commercial sources. For example, myristamidopropyl dimethylamine is available from Alcon Inc. (Fort Worth, Tx.) under the tradename Aldox<sup>®</sup>; lauramidopropyl dimethylamine is

available from Inolex Chemical Company (Philadelphia, Pa.) under the tradename LEXAMINE<sup>®</sup> L-13; and stearamidopropyl dimethylamine is also from Inolex Chemical Company as LEXAMINE<sup>®</sup> S-13. The above-described amidoamines can be synthesized in accordance with known techniques, including those described in U.S. Patent No. 5,573,726.

**[00114]** The amount of the primary antimicrobial agent may vary depending on the specific agent employed. For the aforementioned organic nitrogen-containing agent, typically, such agents are present in concentrations ranging from about 0.00001 to about 0.5 wt. %, or from about 0.00003 to about 0.05 wt. %. For sorbic acid, higher amounts may be required, typically about 0.01 to about 1 wt. %, or from about 0.1 to about 0.5 wt. %. It is preferred that the antimicrobial agent is used in an amount that will at least partially reduce the microorganism population in the formulations employed. If desired, the antimicrobial agent may be employed in a disinfecting amount, which will reduce the microbial bioburden by at least two log orders in four hours and more preferably by one log order in one hour. Most preferably, a disinfecting amount is an amount which will eliminate the microbial burden on a contact lens when used in regimen for the recommended soaking time (FDA Chemical Disinfection Efficacy Test-July, 1985 Contact Lens Solution Draft Guidelines).

**[00115]** The aqueous solutions may further contain one or more other components that are commonly present in ophthalmic solutions, for example, surfactants, tonicity adjusting agents; buffering agents; chelating agents; pH adjusting agents, viscosity modifying agents, and demulcents and the like as discussed hereinabove, and which aid in making ophthalmic compositions more comfortable to the user and/or more effective for their intended use.

**[00116]** The pH of the solutions and/or compositions according to the present invention may be maintained within the range of pH of about 4.0 to about 9.0, or about 5.0 to about 8.0, or about 6.0 to about 8.0, or about 6.5 to about 7.8. In one embodiment, pH values of greater than or equal to about 7 at most.

**[00117]** In one illustrative embodiment, the biomedical device is transferred to an individual lens package containing a buffered saline solution containing at least one or more of the glycophospholipid polymer and/or the crosslinked glycophospholipid polymeric network of the present invention. Generally, a packaging system for the storage of an

ophthalmic device according to the present invention includes at least a sealed container containing one or more unused ophthalmic devices immersed in an aqueous packaging solution. In one embodiment, the sealed container is a hermetically sealed blister-pack, in which a concave well containing an ophthalmic device such as a contact lens is covered by a metal or plastic sheet adapted for peeling in order to open the blister-pack. The sealed container may be any suitable generally inert packaging material providing a reasonable degree of protection to the lens, preferably a plastic material such as polyalkylene, PVC, polyamide, and the like.

**[00118]** The amount of the one or more glycopospholipid polymer and/or the crosslinked glycopospholipid polymeric network employed in a packaging solution for storing an ophthalmic device in a packaging system of the present invention is an amount effective to improve the surface properties of the ophthalmic device. It is believed that the glycopospholipid polymer and/or the crosslinked glycopospholipid polymeric network enhances initial and extended comfort when a contact lens, packaged in the solution and then removed from the packaging system, is placed on the eye for wearing. In one illustrative embodiment, the concentration of the one or more glycopospholipid polymer and/or the crosslinked glycopospholipid polymeric network in the packaging solution will range from about 0.01 to about 20 % w/w. In one illustrative embodiment, the concentration of the one or more glycopospholipid polymer and/or the crosslinked glycopospholipid polymeric network present in the packaging solution will range from about 0.02 to about 0.1 % w/w.

**[00119]** The packaging solutions according to the present invention are physiologically compatible. Specifically, the solution must be “ophthalmically safe” for use with a lens such as a contact lens, meaning that a contact lens treated with the solution is generally suitable and safe for direct placement on the eye without rinsing, that is, the solution is safe and comfortable for daily contact with the eye via a contact lens that has been wetted with the solution. An ophthalmically safe solution has a tonicity and pH that is compatible with the eye and includes materials, and amounts thereof, that are non-cytotoxic according to ISO standards and U.S. Food & Drug Administration (FDA) regulations.

**[00120]** The packaging solution should also be sterile in that the absence of microbial contaminants in the product prior to release must be statistically demonstrated to the degree necessary for such products. The liquid media useful in the present invention are selected to have no substantial detrimental effect on the lens being treated or cared for and to allow or even facilitate the present lens treatment or treatments. In one embodiment, the liquid media is aqueous-based. A particularly useful aqueous liquid medium is that derived from saline, for example, a conventional saline solution or a conventional buffered saline solution.

**[00121]** The pH of the packaging solutions should be maintained within the range of about 6 to about 9, or from about 6.5 to about 7.8. Suitable buffers may be added, such as boric acid, sodium borate, potassium citrate, citric acid, sodium bicarbonate, TRIS and various mixed phosphate buffers (including combinations of  $\text{Na}_2\text{HPO}_4$ ,  $\text{NaH}_2\text{PO}_4$  and  $\text{KH}_2\text{PO}_4$ ) and mixtures thereof. Generally, buffers will be used in amounts ranging from about 0.05 to about 2.5 percent by weight of the solution. In one embodiment, buffers will be used in amounts ranging from about 0.1 to about 1.5 percent by weight of the solution. In one embodiment, the packaging solutions of this invention will contain a borate buffer, e.g., a borate buffer containing one or more of boric acid, sodium borate, potassium tetraborate, potassium metaborate or mixtures thereof. In another embodiment, the packaging solutions of this invention will contain a phosphate buffer.

**[00122]** Typically, the packaging solutions are also adjusted with tonicity agents, to approximate the osmotic pressure of normal lacrimal fluids which is equivalent to a 0.9 percent solution of sodium chloride or 2.5 percent of glycerol solution. The packaging solutions are made substantially isotonic with physiological saline used alone or in combination, otherwise if simply blended with sterile water and made hypotonic or made hypertonic the lenses will lose their desirable optical parameters. Correspondingly, excess saline may result in the formation of a hypertonic solution which will cause stinging and eye irritation.

**[00123]** Suitable tonicity adjusting agents include, for example, sodium and potassium chloride, dextrose, glycerin, calcium and magnesium chloride and the like and mixtures thereof. These tonicity adjusting agents are typically used individually in amounts ranging

from about 0.01 to about 2.5% w/v. In one illustrative embodiment, the tonicity adjusting agents are used in amounts ranging from about 0.2 to about 1.5% w/v. The tonicity agent will be employed in an amount to provide a final osmotic value of at least about 200 mOsm/kg. In one illustrative embodiment, the tonicity adjusting agents are used in an amount to provide a final osmotic value of from about 200 to about 400 mOsm/kg. In one illustrative embodiment, the tonicity adjusting agents are used in an amount to provide a final osmotic value of from about 250 to about 350 mOsm/kg. In one illustrative embodiment, the tonicity adjusting agents are used in an amount to provide a final osmotic value of from about 280 to about 320 mOsm/kg.

**[00124]** If desired, one or more additional components can be included in the packaging solution. Such additional component or components are chosen to impart or provide at least one beneficial or desired property to the packaging solution. In general, the additional components may be selected from components which are conventionally used in one or more ophthalmic device care compositions. Suitable additional components include, for example, cleaning agents, wetting agents, nutrient agents, sequestering agents, viscosity builders, contact lens conditioning agents, antioxidants, and the like and mixtures thereof. These additional components may each be included in the packaging solutions in an amount effective to impart or provide the beneficial or desired property to the packaging solutions. For example, such additional components may be included in the packaging solutions in amounts similar to the amounts of such components used in other, e.g., conventional, contact lens care products.

**[00125]** Suitable sequestering agents include, for example, disodium ethylene diamine tetraacetate, alkali metal hexametaphosphate, citric acid, sodium citrate and the like and mixtures thereof.

**[00126]** Suitable viscosity builders include, for example, hydroxyethyl cellulose, hydroxymethyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol and the like and mixtures thereof.

**[00127]** Suitable antioxidants include, for example, sodium metabisulfite, sodium thiosulfate, N-acetylcysteine, butylated hydroxyanisole, butylated hydroxytoluene and the like and mixtures thereof.

**[00128]** The method of packaging and storing a biomedical device such as a contact lens according to the present invention includes at least packaging a biomedical device immersed in the aqueous packaging solution described above. The method may include immersing the biomedical device in an aqueous packaging solution prior to delivery to the customer/wearer, directly following manufacture of the contact lens. Alternately, the packaging and storing in the packaging solution may occur at an intermediate point before delivery to the ultimate customer (wearer) but following manufacture and transportation of the lens in a dry state, wherein the dry lens is hydrated by immersing the lens in the packaging solution. Consequently, a package for delivery to a customer may include a sealed container containing one or more unused contact lenses immersed in an aqueous packaging solution according to the present invention.

**[00129]** In one illustrative embodiment, the steps leading to the present ophthalmic device packaging system includes (1) molding a biomedical device in a mold comprising at least a first and second mold portion, (2) hydrating and cleaning the biomedical device in a container comprising at least one of the mold portions, (3) introducing the packaging solution with the one or more crosslinked polymeric networks into the container with the biomedical device supported therein, and (4) sealing the container. In one embodiment, the method also includes the step of sterilizing the contents of the container. Sterilization may take place prior to, or most conveniently after, sealing of the container and may be effected by any suitable method known in the art, e.g., heat sterilized by autoclaving of the sealed container at temperatures of about 120°C or higher, or sterilized by other known techniques such as UV, beta or gamma radiation or sterile filtration.

**[00130]** In another illustrative embodiment, the glycopospholipid polymer and/or the crosslinked glycopospholipid polymeric network of the present invention can be in a gel formulation. As will readily be understood by those skilled in the field of formulations, a gel is a semisolid, suspension-type system. Accordingly, in one embodiment, a gel formulation

can include one or more of the glycopospholipid polymer and/or the crosslinked glycopospholipid polymeric network of the present invention and one or more gel forming agents. Gel forming agents for use herein can be any gelling agent typically used in the art for semi solid gel dosage forms. As used herein, the term “gelling agent” is intended to mean a compound used to render a liquid vehicle into a jelly-like vehicle. Exemplary gelling agents include, by way of example and without limitation, synthetic macromolecules, cellulose derivatives (e.g., carboxymethylcellulose and hydroxypropylmethyl-cellulose) and natural gums (e.g., tragacanth). The synthetic macromolecules include carbomers (e.g., Carbomer 910, 934, 934P, 940, 941, and 1342), which are high molecular weight water-soluble polymers of acrylic acid crosslinked with allyl ethers of sucrose and/or pentaerythritol. Carbomers have different viscosities depending on their polymeric composition. Gelling agents may be selected from any of synthetic or semi-synthetic polymeric materials, polyacrylate copolymers, cellulose derivatives and polymethyl vinyl ether/maleic anhydride copolymers. Various grades of Carbopol such as, for example, Carbopol 934, 940, 941, 974, 980, 981, 1342, 5984, ETD2020, ETD 2050, and Ultrez 10 (available from Noveon of Cleveland, Ohio) can be used in the present invention. The present invention preferably includes Carbopol 980 as a gelling agent. A Carbopol is a carbomer. Generally, carbomers are synthetic high molecular weight polymer of acrylic acid that are cross linked with either allylsucrose or allylethers of pentaerythritol.

**[00131]** The gelation mechanism depends on neutralization of the carboxylic acid moiety to form a soluble salt. The polymer is hydrophilic and produces sparkling clear gels when neutralized. Carbomer gels possess good thermal stability in that gel viscosity and yield value are essentially unaffected by temperature. As a topical product, carbomer gels possess optimum rheological properties. The inherent pseudo plastic flow permits immediate recovery of viscosity when shear is terminated and the high yield value and quick break make it ideal for dispensing. In the present pharmaceutical formulations, carbomer gels are used as a suspending or viscosity increasing agent. An aqueous solution of Carbopol is acidic in nature due to the presence of free carboxylic acid residues. Neutralization of this solution crosslinks and gelatinizes the polymer to form a viscous integral structure of desired viscosity.

The amount of gelling agents varies widely and will ordinarily range from about 0.1% to about 10% w/w.

**[00132]** The gel compositions can be incorporated into wound dressings (e.g., bandages, adhesive bandages, transdermal patches). Generally, in these embodiments, the gel compositions are embedded within puffs, gauzes, fleeces, gels, powders, sponges, or other materials that are associated with a second layer to form a wound dressing. Absorption enhancers can also be used to increase the flux of the composition, and particularly the therapeutic protein within the composition, across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the therapeutic protein in a polymer matrix or gel.

**[00133]** In illustrative embodiments, the second layer of a wound dressing can be an elastomeric layer, vapor-permeable film, waterproof film, a woven or nonwoven fabric, mesh, or the like. The composition containing layer and second layer can be bonded using any suitable method (e.g., the application of adhesives, such as pressure sensitive adhesives, hot melt adhesives, curable adhesives; the application of heat or pressure, such as in lamination; a physical attachment through the use of stitching, studs, other fasteners; or the like).

**[00134]** Wound dressings may include adhesives for attachment to the skin or other tissue. Although any adhesive suitable for forming a bond with the skin or other tissue can be used, in certain embodiments a pressure sensitive adhesive is used. Pressure sensitive adhesives are generally defined as adhesives that adhere to a substrate when a light pressure is applied but leave little to no residue when removed. Pressure sensitive adhesives include solvent in solution adhesives, hot melt adhesives, aqueous emulsion adhesives, calenderable adhesives, and radiation curable adhesives.

**[00135]** The most commonly used elastomers in pressure sensitive adhesives can include natural rubbers, styrene-butadiene latexes, polyisobutylene, butyl rubbers, acrylics, and silicones. In particular embodiments, acrylic polymer or silicone-based pressure sensitive adhesives can be used. Acrylic polymers can often have a low level of allergenicity, be cleanly removable from skin, possess a low odor, and exhibit low rates of mechanical and

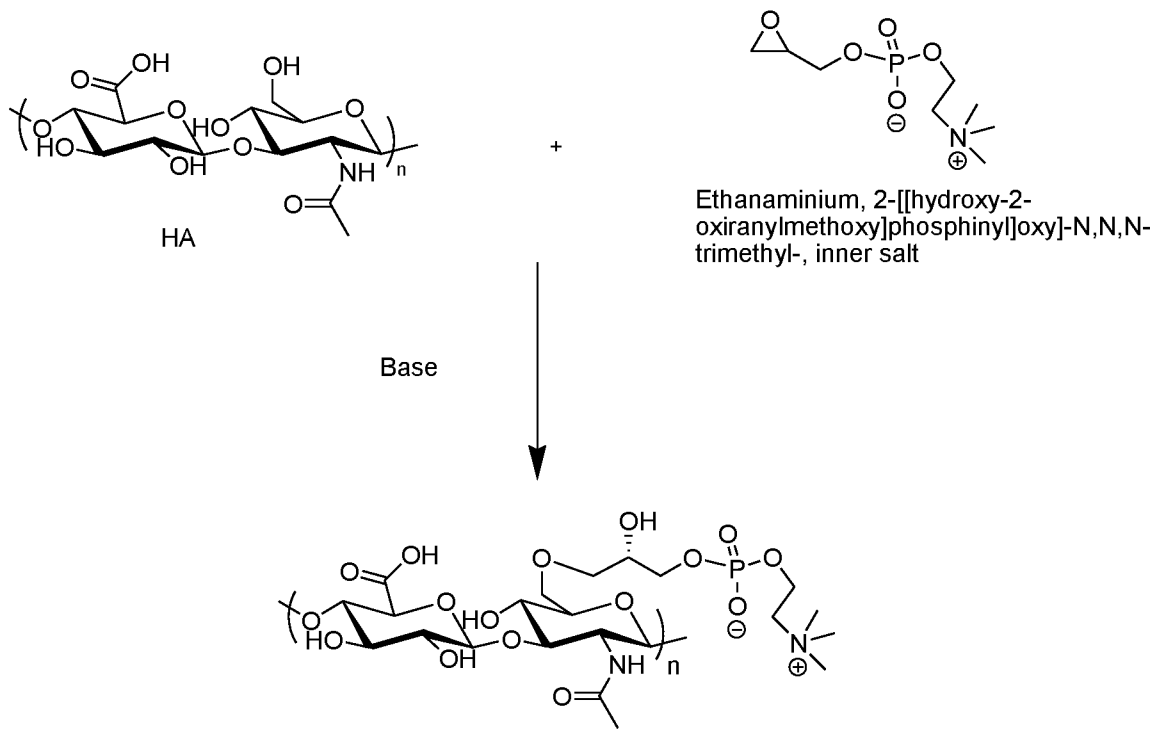
chemical irritation. Medical grade silicone pressure sensitive adhesives can be chosen for their biocompatibility.

**[00136]** Amongst the factors that influence the suitability of a pressure sensitive adhesive for use in wound dressings of particular embodiments is the absence of skin irritating components, sufficient cohesive strength such that the adhesive can be cleanly removed from the skin, ability to accommodate skin movement without excessive mechanical skin irritation, and good resistance to body fluids.

**[00137]** The following examples are provided to enable one skilled in the art to practice the invention and are merely illustrative. The examples should not be read as limiting the scope of the invention as defined in the claims.

#### EXAMPLE 1

**[00138]** Preparation of a glyphospholipid polymer of hyaluronic acid (HA) and a phosphorylcholine following the general reaction scheme 1:

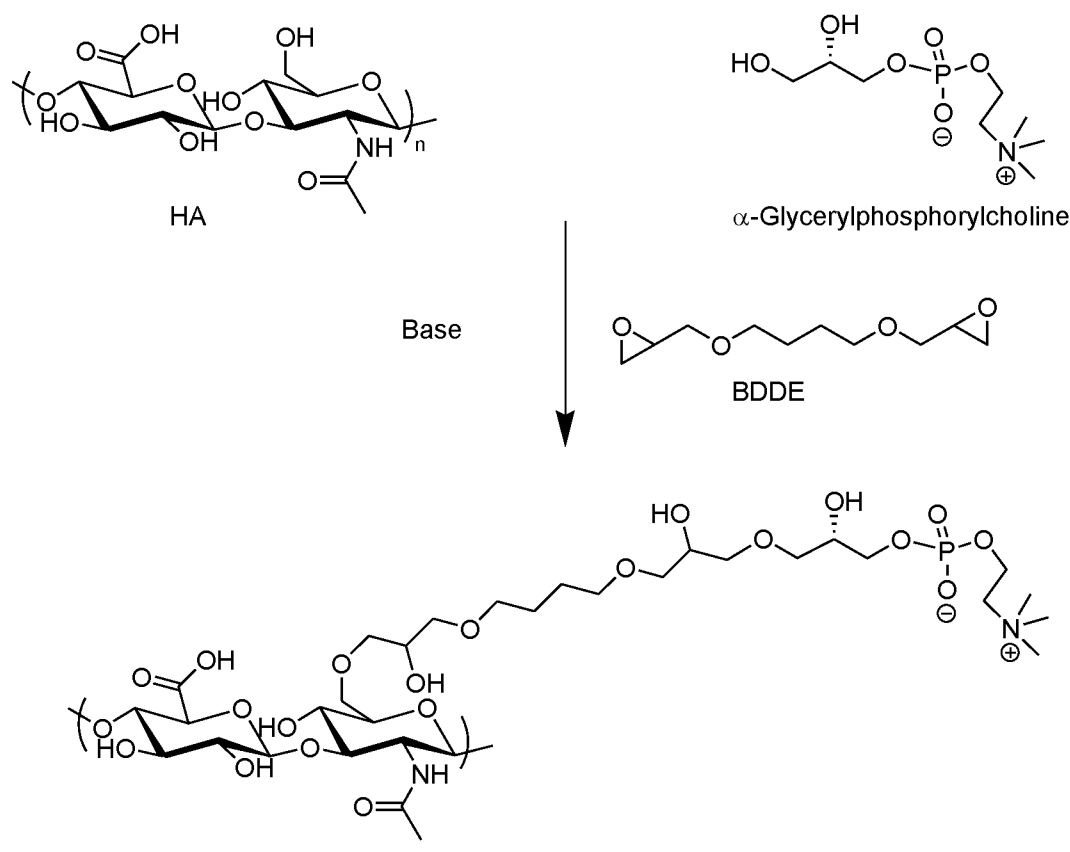


wherein n is 100.

**[00139]** To a 100 mL round bottom flask fitted with magnetic stirrer was added 60 mL of (reverse-osmosis) water and 3.00 g of HA (7.44 mmol based on disaccharide unit), and 1.00 g, (4.2 mmol) ethanaminium, 2-[[hydroxy-2-oxiranylmethoxy]phosphinyl)oxy)-N,N,N-trimethyl, inner salt prepared by following the method described in Example 11 in the J. Org. Chemistry, 2002, 67,194-199, the contents of which are incorporated by reference herein. The solution was then stirred for 15 hours to ensure complete dissolution of materials to provide a clear solution having a pH of approximately 7. The pH of the solution was adjusted to 8.09 with 0.25 g of a 10 wt. % solution of sodium hydroxide. After 4.5 hours the pH was at 8.82 and after 7 hours the pH rose to 9.07. The reaction mixture was stirred for an additional 15 hours and the pH rose to 9.6. The reaction mixture was then poured into 900 mL of ethanol to yield a precipitate and filtered. The solid was washed with 3 x 100 mL of ethanol and dried under high vacuum for 24 hours to yield 2.8 g (85 % yield) of a white solid.

#### EXAMPLE 2

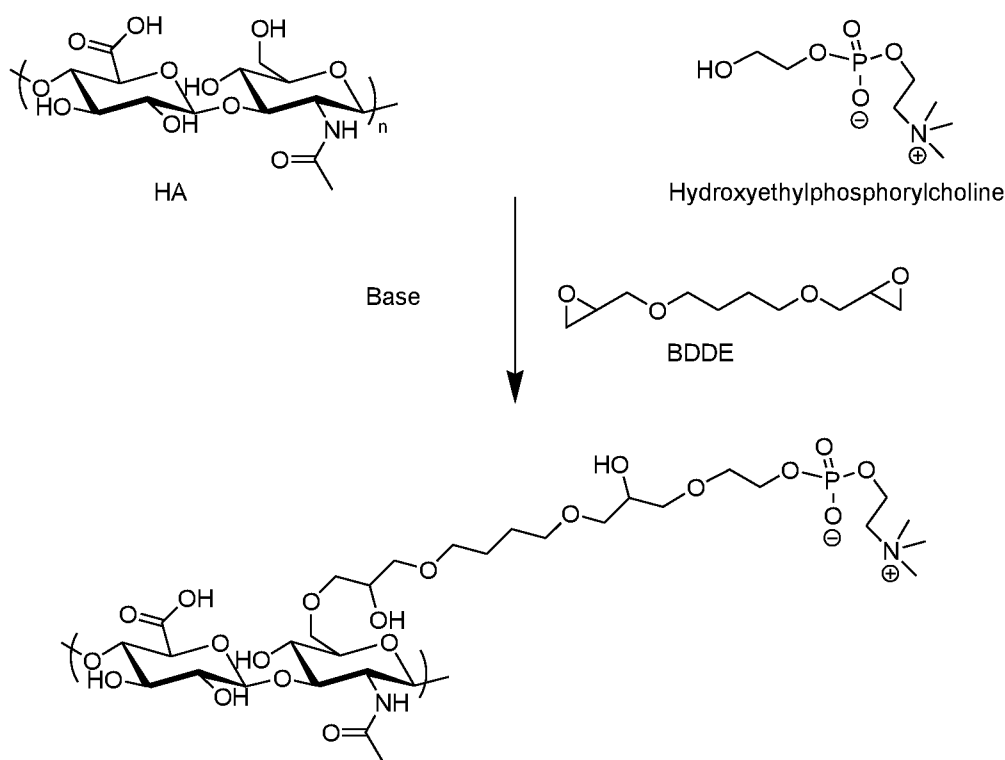
**[00140]** Preparation of a crosslinked polymeric network of HA and glycerylphosphorylcholine with 1,4-butanediol diglycidyl ether (BDDE) following the general reaction scheme 2:



**[00141]** To a 100 mL round bottom flask fitted with magnetic stirrer was added 60 mL of (reverse-osmosis) water and 3.00 g of HA (7.44 mmol based on disaccharide unit), and 3.00 g, (11.7 mmol), of glycerylphosphorylcholine (purchased from Lipoid). The solution was then stirred for 15 hours to ensure complete dissolution of materials to provide a clear solution having a pH of 6.65. To this solution was added 1.2 mL of BDDE (6.25 mmol). After 15 minutes of stirring, the pH of the slightly hazy solution was adjusted to 8.5 with 0.2 g of a 10 wt. % solution of sodium hydroxide. After 24 hours the reaction mixture was then poured into 900 mL of ethanol to yield a precipitate and filtered. The solid was washed with 3 x 100 mL of ethanol and dried under high vacuum for 24 hours to yield 4.6 g (77 % yield) of a white solid. Integration by NMR of the inner methylene groups of the attached BDDE against the methyl groups of the acetamide indicate 2.90 mole % BDDE functionalized.

## EXAMPLE 3

[00142] Preparation of a crosslinked polymeric network of HA and hydroxyethylphosphorylcholine with BDDE following the general reaction scheme 3:

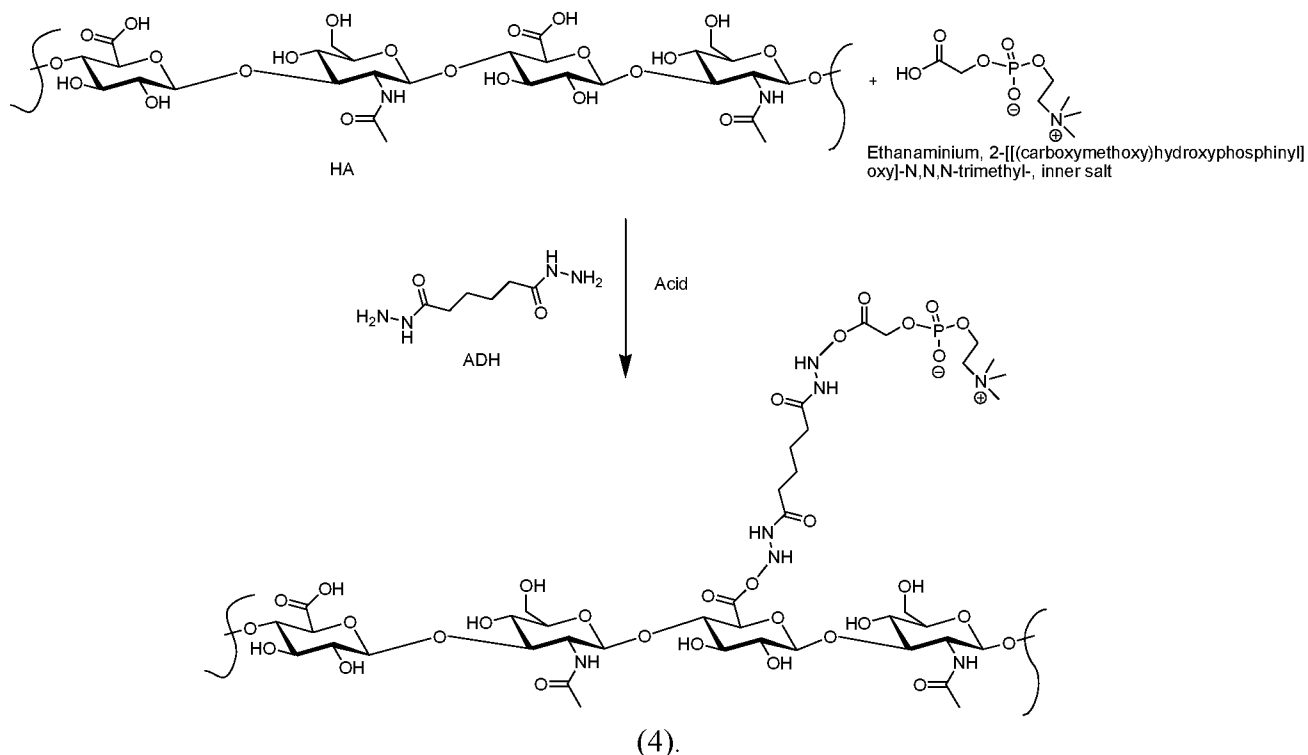


[00143] To a 100 mL round bottom flask fitted with magnetic stirrer was added 60 mL of (reverse-osmosis) water and 3.00 g of HA (7.44 mmol based on disaccharide unit), and 3.00 g, (13.1 mmol), of hydroxyethylphosphorylcholine (purchased from Shanghai Chemhere Co., Ltd.). The solution was then stirred for 15 hours to ensure complete dissolution of materials to provide a clear solution having a pH of 6.65. To this solution was added 1.2 mL of BDDE (6.25 mmol). After 15 minutes of stirring, the pH of the slightly hazy solution was adjusted to 8.5 with 0.2 g of a 10 wt. % solution of sodium hydroxide. After 24 hours the reaction mixture was then poured into 900 mL of ethanol to yield a precipitate and filtered. The solid was washed with 3 x 100 mL of ethanol and dried under high vacuum for 24 hours to yield 4.9 (77 % yield) of a white solid. Integration by NMR of the inner methylene groups

of the attached BDDE against the methyl groups of the acetamide indicate 3.2 mole % BDDE functionalized.

#### EXAMPLE 4

**[00144]** Preparation of a crosslinked polymeric network of HA and Ethanaminium, 2-[[[(carboxymethoxy)hydroxyphosphinyl]oxy]-N,N,N-trimethyl, inner salt with adipic acid dihydrazide (ADH) following the general reaction scheme 4:



**[00145]** In a 50 mL Erlenmeyer flask fitted with a stir bar added 31.9 mL of (reverse-osmosis) water along with 1.50 g HA, (3.72 mmol based on disaccharide unit). In a separate Erlenmeyer flask fitted with stir bar added 31.9 mL of (reverse-osmosis) water and 0.170 g, (0.706 mmol) ethanaminium, 2-[[[hydroxy-2-oxiranylmethoxy]phosphinyl]oxy]-N,N,N-trimethyl, inner salt. Both solutions were stirred for 15 hours to ensure complete dissolution of materials. To each solution was added 0.075 g, (0.389 mmol), N-(3-

dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in 0.5 mL of (reverse-osmosis) water. Each container was rinsed with 0.5ml (reverse-osmosis) water. The solutions were allowed to stir for 5 minutes then added to a 100 mL round bottom flask fitted with stir bar. The flasks were rinsed with 2 mL each (reverse-osmosis) water. To this solution was added 0.062 g (0.353 mmol) of ADH, in 0.5ml of (reverse-osmosis) water. The pH was adjusted from 7.08 to 4.54 with 6.08 g 0.1 N HCl. After 40 minutes pH was adjusted from 6.15 to 4.53 with 3.49 g 0.1 N HCl. After 6 hours the pH was at 4.65 and after 24 hours the pH was adjusted from 4.65 to 7.36 with 0.425 g of 10 wt. % sodium hydroxide. The solution was dialyzed using molecular weight cut-off (MWCO) 3500 in PBS buffer, (1.0 mM), along with 100 mM sodium chloride changing out the dialysis bath every 3 hours. A total of six exchanges were done. The third and fourth exchanges were in 50 mM NaCl and 1mM PBS buffer. The last two exchanges being done in (reverse-osmosis) water only. Solution was lyophilized for 3 days to give 2.70 g of fluffy white solid, (78 % yield). Integration by NMR of the inner methylene groups of the attached ADH against the methyl groups of the acetamide indicate 4.75 mole % ADH functionalized.

#### EXAMPLE 5

**[00146]** A packaging solution is made by mixing the following components in the respective amounts listed in Table 1.

TABLE 1

Ingredients	Parts
Trizma HCl	0.627
Trizma Base	0.116
Sodium Chloride	0.577
Purified Water, USP	98.680
Crosslinked HA-PC of Example 1, 2, 3 or 4	0.010 to 1.000
pH	3 to 6.2
Osmolality	200 to 400

## EXAMPLE 6

[00147] A packaging solution is made by mixing the following components in the respective amounts listed in Table 2.

TABLE 2

Ingredients	Parts
Trizma HCl	0.627
Trizma Base	0.116
Sodium Chloride	0.577
Purified Water, USP	98.680
Crosslinked HA-PC of Example 1, 2, 3 or 4	0.010 to 1.000
Comfort Agents	0.010 to 5.000
pH	3 to 6.2
Osmolality	200 to 400

## EXAMPLE 7

[00148] A packaging solution is made by mixing the following components in the respective amounts listed in Table 3.

TABLE 3

Ingredients	Parts
Citric Acid, Anhydrous	11.320
Sodium Citrate	62.220
Sodium Chloride	26.460
Purified Water, USP	100.000
Crosslinked HA-PC of Example 1, 2, 3 or 4	0.010 to 1.000
pH	3 to 6.2
Osmolality	200 to 400

## EXAMPLE 8

[00149] A packaging solution is made by mixing the following components in the respective amounts listed in Table 4.

TABLE 4

Ingredients	Parts
Citric Acid, Anhydrous	11.320
Sodium Citrate	62.220
Sodium Chloride	26.460
Purified Water, USP	100.000
Crosslinked HA-PC of Example 1, 2, 3 or 4	0.010 to 1.000
Comfort Agents	0.010 to 5.000
pH	3.0 to 6.2
Osmolality	200 to 400

EXAMPLE 9

[00150] A packaging solution is made by mixing the following components in the respective amounts listed in Table 5.

TABLE 5

Ingredients	Parts
MOPS Sodium Salt	0.560
MOPS or 3-(N-morpholino)propanesulfonic acid	0.520
Sodium Chloride	0.630
Purified Water, USP	98.280
Crosslinked HA-PC of Example 1, 2, 3 or 4	0.010 to 1.000
pH	6.5 to 7.9
Osmolality	200 to 400

EXAMPLE 10

[00151] A packaging solution is made by mixing the following components in the respective amounts listed in Table 6.

TABLE 6

Ingredients	Parts
MOPS Sodium Salt	0.560
MOPS or 3-(N-morpholino)propane sulfonic acid	0.520
Sodium Chloride	0.630
Purified Water, USP	98.280
Crosslinked HA-PC of Example 1, 2, 3 or 4	0.010 to 1.000
Comfort Agents	0.010 to 5.000
pH	6.5 to 7.9
Osmolality	200 to 400

## EXAMPLE 11

[00152] A packaging solution is made by mixing the following components in the respective amounts listed in Table 7.

TABLE 7

Ingredients	Parts
Monobasic sodium phosphate monohydrate	0.015
Dibasic sodium phosphate anhydrous	0.065
Sodium Chloride	0.999
Purified Water, USP	99.040
Crosslinked HA-PC of Example 1, 2, 3 or 4	0.010 to 1.000
pH	6.0 to 8
Osmolality	200 to 400

## EXAMPLE 12

[00153] A packaging solution is made by mixing the following components in the respective amounts listed in Table 8.

TABLE 8

Ingredients	Parts
Monobasic sodium phosphate monohydrate	0.015
Dibasic sodium phosphate anhydrous	0.065
Sodium Chloride	0.999
Purified Water, USP	99.040
Crosslinked HA-PC of Example 1, 2, 3 or 4	0.010 to 1.000
Comfort Agents	0.010 to 5.000
pH	6.0 to 8
Osmolality	200 to 400

EXAMPLE 13

**[00154]** A packaging solution is made by mixing the following components in the respective amounts listed in Table 9.

TABLE 9

Ingredients	Parts
Sodium Borate	0.610
Boric Acid	0.098
Sodium Chloride	0.886
Purified Water, USP	98.406
Crosslinked HA-PC of Example 1, 2, 3 or 4	0.010 to 1.000
pH	7 to 9
Osmolality	200 to 400

EXAMPLE 14

**[00155]** A packaging solution is made by mixing the following components in the respective amounts listed in Table 10.

TABLE 10

Ingredients	Parts
Sodium Borate	0.610
Boric Acid	0.098
Sodium Chloride	0.886
Purified Water, USP	98.406
Crosslinked HA-PC of Example 1, 2, 3 or 4	0.010 to 1.000
Comfort Agents	0.010 to 5.000
pH	7 to 9
Osmolality	200 to 400

EXAMPLE 15

[00156] A packaging solution is made by mixing the following components in the respective amounts listed in Table 11.

TABLE 11

Ingredients	Parts
Monobasic sodium phosphate monohydrate	0.014
Dibasic sodium phosphate anhydrous	0.059
Sodium Chloride	0.810
Poloxamine 1107	0.450
Purified Water, USP	98.560
Crosslinked HA-PC of Example 1	0.100

[00157] Autoclave degradation was studied and did not show any statistically significant changes in pH, viscosity and osmolality even after 3 autoclave cycles as shown below in Table 12:

TABLE 12

Solution Properties of Example 15		
pH	Before Filtration	17.31
	After Filtration	7.30
	1x Autoclave	7.25
	2x Autoclave	7.10
	3x Autoclave	6.97
Viscosity	Before Filtration	1.18
	After Filtration	1.21
	1x Autoclave	1.16
	2x Autoclave	1.11
	3x Autoclave	1.09
Osmolality	Before Filtration	269
	After Filtration	267
	1x Autoclave	281
	2x Autoclave	282
	3x Autoclave	283

## EXAMPLE 16

**[00158]** Contact lenses made of Balafilcon A are cast and processed under standard manufacturing procedures. Balafilcon A is a copolymer comprised of 3-[tris(trimethylsiloxy)silyl] propyl vinyl carbamate, N-vinyl-2-pyrrolidone (NVP), 1,3-bis[4-vinyloxycarbonyloxy)but-1-yl]polydimethylsiloxane and N-vinyloxycarbonyl alanine. All Balafilcon A lenses are air-plasma treated prior to exposure to the crosslinked polymeric network.

**[00159]** For coating with the crosslinked polymeric network of Example 1, each lens is placed in a polypropylene blister package containing 3.8-mL of a 100 or 250 ppm (w/v) solution of the crosslinked polymeric network dissolved in an appropriate buffer system, e.g., a phosphate-buffered saline system (PBS), a borate-buffered saline (BBS) with or without

containing 300 ppm EDTA. The blister packages are sealed with foil lidstock and autoclaved at 121°C for 30 minutes.

#### EXAMPLE 17

**[00160]** Contact lenses made of Balafilcon A are cast and processed under standard manufacturing procedures. Balafilcon A is a copolymer comprised of 3-[tris(trimethylsiloxy)silyl] propyl vinyl carbamate, N-vinyl-2-pyrrolidone (NVP), 1,3-bis[4-vinyloxycarbonyloxy)but-1-yl]polydimethylsiloxane and N-vinyloxycarbonyl alanine. All Balafilcon A lenses are air-plasma treated prior to exposure to the crosslinked polymeric network.

**[00161]** For coating with the crosslinked polymeric network of Example 2, each lens is placed in a polypropylene blister package containing 3.8-mL of a 100 or 250 ppm (w/v) solution of the crosslinked polymeric network dissolved in an appropriate buffer system, e.g., a PBS, a BBS with or without containing 300 ppm EDTA. The blister packages are sealed with foil lidstock and autoclaved at 121°C for 30 minutes.

**[00162]** It will be understood that various modifications may be made to the embodiments disclosed herein. Therefore, the above description should not be construed as limiting, but merely as exemplifications of preferred embodiments. For example, the functions described above and implemented as the best mode for operating the present invention are for illustration purposes only. Other arrangements and methods may be implemented by those skilled in the art without departing from the scope and spirit of this invention. Moreover, those skilled in the art will envision other modifications within the scope and spirit of the features and advantages appended hereto.

WHAT IS CLAIMED IS:

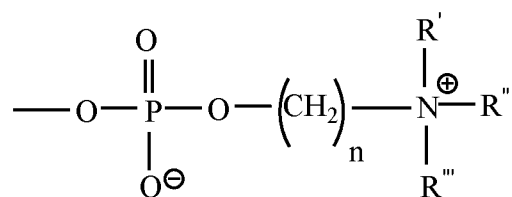
1. A glycopospholipid polymer comprising a reaction product of one or more glycosaminoglycans and one or more phospholipids.

2. The glycopospholipid polymer according to claim 1, wherein the one or more glycosaminoglycans are selected from the group consisting of chondroitin, chondroitin sulfate, dermatan, dermatan sulfate, heparin, heparan sulfate, hyaluronan, hyaluronic acid, sucrose, lactulose, lactose, maltose, trehalose, cellobiose, mannobiose and chitobiose.

3. The glycopospholipid polymer according to claims 1 or 2, wherein the one or more phospholipids are selected from the group consisting of phosphorylcholine, phosphorylhistidine, phosphorylproline, phosphorylserine,  $\alpha$ -phosphatidylcholine,  $\alpha$ -phosphatidylethanolamine,  $\alpha$ -phosphatidyl-L-serine,  $\alpha$ -phosphatidylinositol,  $\alpha$ -phosphatidic acid,  $\alpha$ -phosphatidyl-DL-glycerol,  $\alpha$ -lysophosphatidylcholine, sphingomyelin, and cardiolipin.

4. The glycopospholipid polymer according to claims 1-3, wherein the one or more glycosaminoglycans are hyaluronic acid and the one or more phospholipids comprises phosphorylcholine.

5. The glycopospholipid polymer according to claims 1-4, wherein the one or more phospholipids are a phosphorylcholine-containing phospholipid represented by the following structure:



wherein n is an integer of 1 to 5 and R', R'' and R''' independently of each other are a C<sub>1</sub> to C<sub>8</sub> alkyl group, a C<sub>1</sub> to C<sub>8</sub> hydroxyalkyl group or a hetero atom-containing group.

6. The glycophospholipid polymeric network according to claims 1-5, wherein the reaction product comprises:

about 0.01 to about 50 wt. %, based on the total weight of the reaction product, of the one or more glycosaminoglycans; and

about 0.01 to about 50 wt. %, based on the total weight of the reaction product, of the one or more phospholipids.

7. The glycophospholipid polymer according to claims 1-6, wherein the reaction product of the one or more glycosaminoglycans and the one or more phospholipids further comprises one or more first crosslinking agents.

8. The glycophospholipid polymer according to claim 7, wherein the one or more first crosslinking agents comprise a bi- or polyfunctional crosslinking agent comprising two or more functional groups capable of reacting with functional groups of the one or more glycosaminoglycans and the one or more phospholipids.

9. The glycophospholipid polymer according to claim 7, wherein the one or more first crosslinking agents comprise a bi- or polyfunctional crosslinking agent comprising a bis- or polyfunctional crosslinking agent selected from the group consisting of 1,4-butanediol diglycidyl ether, 1,2-bis(2,3-epoxypropoxy)ethylene, ethylene glycol diglycidyl ether, 1,2-ethanediol diglycidyl ether, diepoxyoctane, 1,6-hexanediol diglycidyl ether, polypropylene glycol diglycidyl ether, polytetramethylene glycol diglycidyl ether, neopentyl glycol diglycidyl ether, polyglycerol polyglycidyl ester, diglycerol polyglycidyl ether, glycerol polyglycidyl ether, trimethylolpropane polyglycidyl ether, pentaerythritol polyglyglycidyl ether, sorbitol polyglycidyl ether, 1,2,7,8-diepoxyoctane, 1,3-butadiene diepoxide, pentaerythritol tetraglycidyl ether, and a polyepoxide.

10. The glycopospholipid polymer according to claim 7, wherein the one or more first crosslinking agents comprise a dihydrazide crosslinking agent selected from the group consisting of succinic acid dihydrazide, glutaric acid dihydrazide, adipic acid dihydrazide, pimelic acid dihydrazide, suberic acid dihydrazide, azelaic acid dihydrazide, sebacic acid dihydrazide, undecanedioic acid dihydrazide, dodecanedioic acid dihydrazide, brassylic acid dihydrazide, tetradecanedioic acid dihydrazide, pentadecanedioic acid dihydrazide, thapsic acid dihydrazide, and octadecanedioic acid dihydrazide.

11. The glycopospholipid polymer according to claim 7, wherein the one or more first crosslinking agents comprise a dihydric alcohol crosslinking agent selected from the group consisting of ethylene glycol, propylene glycol, butylene glycol diethylene glycol, dipropylene glycol, neopentyl glycol, 1,3-propanediol, hexylene glycol, pentylene glycol, heptylene glycol, and octylene glycol.

12. The glycopospholipid polymer according to claim 7, wherein the one or more first crosslinking agents comprise a polyhydric alcohol crosslinking agent selected from the group consisting of glycerin, pentaerythrite, xylitol, and galactitol.

13. The glycopospholipid polymer according to claim 7, wherein the one or more first crosslinking agents comprise a carbodiimide crosslinking agent of formula  $X-N=C=N-X$ , wherein each X independently is a  $C_1$  to  $C_6$  alkyl optionally substituted with 1-2 dialkylamino groups, or is a  $C_5$  to  $C_6$  cycloalkyl group.

14. The glycopospholipid polymer according to claim 7, wherein the one or more first crosslinking agents are selected from the group consisting of methacrylic anhydride, octeyl succinic anhydride, formaldehyde, gluteraldehyde, gluraraldehyde, acid chloride, n-hydroxysuccinimide, polyethylene glycol diacrylates, polyethylene glycol diamines, divinyl sulfone, a urea, a diisocyanate.

15. The glycopospholipid polymer according to claim 7, wherein one or more additional glycosaminoglycans are crosslinked with the reaction product with one or more second crosslinking agents.

16. The glycopospholipid polymer according to claim 15, wherein the one or more second crosslinking agents are the same as the first crosslinking agent.

17. The glycopospholipid polymer according to claim 16, wherein the one or more second crosslinking agents are different than the first crosslinking agent.

18. The glycopospholipid polymer according to claims 7-17, wherein the reaction product comprises:

about 0.01 to about 50 wt. %, based on the total weight of the reaction product, of the one or more glycosaminoglycans;

about 0.01 to about 50 wt. %, based on the total weight of the reaction product, of the one or more phospholipids; and

about 0.05 to about 10 wt. %, based on the total weight of the reaction product, of one or more first crosslinking agents.

19. The glycopospholipid polymer according to claims 7-17, wherein the reaction product comprises:

about 0.1 to about 5 wt. %, based on the total weight of the reaction product, of the one or more glycosaminoglycans;

about 0.1 to about 5 wt. %, based on the total weight of the reaction product, of the one or more phospholipids; and

about 0.05 to about 10 wt. %, based on the total weight of the reaction product, of one or more crosslinking agents.

20. The glycopospholipid polymer according to claims 1-6, wherein the reaction product comprises the one or more glycosaminoglycans crosslinked with the one or more phospholipids.

21. The glycopospholipid polymer according to claim 20, wherein the one or more glycosaminoglycans crosslinked with the one or more phospholipids has a weight average molecular weight ranging from about 20,000 to about 6,000,000 Da.

22. A biomedical device having a coating on a surface thereof, the coating comprising one or more of the glycopospholipid polymer according to claims 1-21.

23. The biomedical device according to claim 22, wherein the biomedical device is an ophthalmic lens.

24. The biomedical device according to claim 23, wherein the ophthalmic lens is a contact lens or an intraocular lens.

25. A packaging system for the storage of an ophthalmic device comprising a sealed container containing one or more unused ophthalmic devices immersed in an aqueous packaging solution comprising one or more of the glycopospholipid polymers according to claims 1-21, wherein the solution has an osmolality of at least about 200 mOsm/kg, a pH of about 6 to about 9 and is sterilized.

26. The packaging system according to claim 25, wherein the one or more unused ophthalmic devices are a contact lens.

27. A method of preparing a package comprising a storable, sterile ophthalmic device, the method comprising:

(a) immersing an ophthalmic device in an aqueous packaging solution comprising one or more of the glycopospholipid polymers according to claims 1-21, wherein the solution has an osmolality of at least about 200 mOsm/kg and a pH in the range of about 6 to about 9;

(b) packaging the solution and the device in a manner preventing contamination of the device by microorganisms; and

(c) sterilizing the packaged solution and device.

28. The method according to claim 27, wherein the ophthalmic device is a contact lens.

29. An aqueous ophthalmic composition comprising one or more of the glycopospholipid polymers according to claims 1-21, wherein the aqueous ophthalmic composition has an osmolality in a range from about 200 mOsmol/kg to about 400 mOsmol/kg.

30. The aqueous ophthalmic composition according to claim 29, in the form of an eye care or a contact lens care product selected from the group consisting of eye drops, contact lens preservative solution, contact lens cleaning solution, and contact lens multi-purpose solution.

31. The aqueous ophthalmic composition according to claim 29, in the form a multi-purpose solution or rewetting drops.

32. A gel composition for promoting wound healing wherein the gel composition comprises one or more of the glycopospholipid polymers according to claims 1-21.

33. A wound dressing comprising the gel composition according to claim 32.

**AMENDED CLAIMS**  
**received by the International Bureau on 19 August 2020 (19.08.20)**

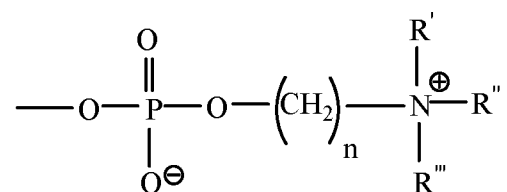
1. A glycopospholipid polymer comprising a reaction product of one or more glycosaminoglycans, one or more phospholipids and one or more first crosslinking agents.

2. The glycopospholipid polymer according to claim 1, wherein the one or more glycosaminoglycans are selected from the group consisting of chondroitin, chondroitin sulfate, dermatan, dermatan sulfate, heparin, heparan sulfate, hyaluronan, hyaluronic acid, sucrose, lactulose, lactose, maltose, trehalose, cellobiose, mannobiose and chitobiose.

3. The glycopospholipid polymer according to claims 1 or 2, wherein the one or more phospholipids are selected from the group consisting of phosphorylcholine, phosphorylhistidine, phosphorylproline, phosphorylserine,  $\alpha$ -phosphatidylcholine,  $\alpha$ -phosphatidylethanolamine,  $\alpha$ -phosphatidyl-L-serine,  $\alpha$ -phosphatidylinositol,  $\alpha$ -phosphatidic acid,  $\alpha$ -phosphatidyl-DL-glycerol,  $\alpha$ -lysophosphatidylcholine, sphingomyelin, and cardiolipin.

4. The glycopospholipid polymer according to claims 1-3, wherein the one or more glycosaminoglycans are hyaluronic acid and the one or more phospholipids comprises phosphorylcholine.

5. The glycopospholipid polymer according to claims 1-4, wherein the one or more phospholipids are a phosphorylcholine-containing phospholipid represented by the following structure:



wherein n is an integer of 1 to 5 and R', R'' and R''' independently of each other are a C<sub>1</sub> to C<sub>8</sub> alkyl group, a C<sub>1</sub> to C<sub>8</sub> hydroxyalkyl group or a hetero atom-containing group.

6. The glycopospholipid polymeric network according to claims 1-5, wherein the reaction product comprises:

about 0.01 to about 50 wt. %, based on the total weight of the reaction product, of the one or more glycosaminoglycans; and

about 0.01 to about 50 wt. %, based on the total weight of the reaction product, of the one or more phospholipids.

8. The glycopospholipid polymer according to claims 1-6, wherein the one or more first crosslinking agents comprise a bi- or polyfunctional crosslinking agent comprising two or more functional groups capable of reacting with functional groups of the one or more glycosaminoglycans and the one or more phospholipids.

9. The glycopospholipid polymer according to claims 1-6, wherein the one or more first crosslinking agents comprise a bi- or polyfunctional crosslinking agent comprising a bis- or polyfunctional crosslinking agent selected from the group consisting of 1,4-butanediol diglycidyl ether, 1,2-bis(2,3-epoxypropoxy)ethylene, ethylene glycol diglycidyl ether, 1,2-ethanediol diglycidyl ether, diepoxyoctane, 1,6-hexanediol diglycidyl ether, polypropylene glycol diglycidyl ether, polytetramethylene glycol diglycidyl ether, neopentyl glycol diglycidyl ether, polyglycerol polyglycidyl ester, diglycerol polyglycidyl ether, glycerol polyglycidyl ether, trimethylolpropane polyglycidyl ether, pentaerythritol polyglyglycidyl ether, sorbitol polyglycidyl ether, 1,2,7,8-diepoxyoctane, 1,3-butadiene diepoxide, pentaerythritol tetraglycidyl ether, and a polyepoxide.

10. The glycopospholipid polymer according to claims 1-6, wherein the one or more first crosslinking agents comprise a dihydrazide crosslinking agent selected from the group consisting of succinic acid dihydrazide, glutaric acid dihydrazide, adipic acid dihydrazide, pimelic acid dihydrazide, suberic acid dihydrazide, azelaic acid dihydrazide, sebacic acid dihydrazide, undecanedioic acid dihydrazide, dodecanedioic acid dihydrazide, brassylic acid dihydrazide, tetradecanedioic acid dihydrazide, pentadecanedioic acid dihydrazide, thapsic acid dihydrazide, and octadecanedioic acid dihydrazide.

11. The glycopospholipid polymer according to claims 1-6, wherein the one or more first crosslinking agents comprise a dihydric alcohol crosslinking agent selected from the group consisting of ethylene glycol, propylene glycol, butylene glycol diethylene glycol, dipropylene

glycol, neopentyl glycol, 1,3-propanediol, hexylene glycol, pentylene glycol, heptylene glycol, and octylene glycol.

12. The glycophospholipid polymer according to claims 1-6, wherein the one or more first crosslinking agents comprise a polyhydric alcohol crosslinking agent selected from the group consisting of glycerin, pentaerythrite, xylitol, and galactitol.

13. The glycophospholipid polymer according to claims 1-6, wherein the one or more first crosslinking agents comprise a carbodiimide crosslinking agent of formula  $X-N=C=N-X$ , wherein each X independently is a  $C_1$  to  $C_6$  alkyl optionally substituted with 1-2 dialkylamino groups, or is a  $C_5$  to  $C_6$  cycloalkyl group.

14. The glycophospholipid polymer according to claims 1-6, wherein the one or more first crosslinking agents are selected from the group consisting of methacrylic anhydride, octeoyl succinic anhydride, formaldehyde, gluteraldehyde, gluraraldehyde, acid chloride, n-hydroxysuccinimide, polyethylene glycol diacrylates, polyethylene glycol diamines, divinyl sulfone, a urea, a diisocyanate.

15. The glycophospholipid polymer according to claims 1-6, wherein one or more additional glycosaminoglycans are crosslinked with the reaction product with one or more second crosslinking agents.

16. The glycophospholipid polymer according to claim 15, wherein the one or more second crosslinking agents are the same as the first crosslinking agent.

17. The glycophospholipid polymer according to claim 15, wherein the one or more second crosslinking agents are different than the first crosslinking agent.

18. The glycophospholipid polymer according to claims 1-6 and 8-17, wherein the reaction product comprises:

about 0.01 to about 50 wt. %, based on the total weight of the reaction product, of the one or more glycosaminoglycans;

about 0.01 to about 50 wt. %, based on the total weight of the reaction product, of the one or more phospholipids; and

about 0.05 to about 10 wt. %, based on the total weight of the reaction product, of one or more first crosslinking agents.

19. The glycopospholipid polymer according to claims 1-6 and 8-17, wherein the reaction product comprises:

about 0.1 to about 5 wt. %, based on the total weight of the reaction product, of the one or more glycosaminoglycans;

about 0.1 to about 5 wt. %, based on the total weight of the reaction product, of the one or more phospholipids; and

about 0.05 to about 10 wt. %, based on the total weight of the reaction product, of one or more crosslinking agents.

20. The glycopospholipid polymer according to claims 1-14, wherein the reaction product comprises the one or more glycosaminoglycans and the one or more phospholipids are crosslinked with the one or more first crosslinking agents.

21. The glycopospholipid polymer according to claim 20, wherein the crosslinked reaction product has a weight average molecular weight ranging from about 20,000 to about 6,000,000 Da.

22. A biomedical device having a coating on a surface thereof, the coating comprising one or more of the glycopospholipid polymers according to claims 1-6 and 8-21.

23. The biomedical device according to claim 22, wherein the biomedical device is an ophthalmic lens.

24. The biomedical device according to claim 23, wherein the ophthalmic lens is a contact lens or an intraocular lens.

25. A packaging system for the storage of an ophthalmic device comprising a sealed container containing one or more unused ophthalmic devices immersed in an aqueous packaging solution comprising one or more of the glycopospholipid polymers according to claims 1-6 and 8-21, wherein the solution has an osmolality of at least about 200 mOsm/kg, a pH of about 6 to about 9 and is sterilized.

26. The packaging system according to claim 25, wherein the one or more unused ophthalmic devices are a contact lens.

27. A method of preparing a package comprising a storable, sterile ophthalmic device, the method comprising:

(a) immersing an ophthalmic device in an aqueous packaging solution comprising one or more of the glycopospholipid polymers according to claims 1-6 and 8-21, wherein the solution has an osmolality of at least about 200 mOsm/kg and a pH in the range of about 6 to about 9;

(b) packaging the solution and the device in a manner preventing contamination of the device by microorganisms; and

(c) sterilizing the packaged solution and device.

28. The method according to claim 27, wherein the ophthalmic device is a contact lens.

29. An aqueous ophthalmic composition comprising one or more of the glycopospholipid polymers according to claims 1-6 and 8-21, wherein the aqueous ophthalmic composition has an osmolality in a range from about 200 mOsmol/kg to about 400 mOsmol/kg.

30. The aqueous ophthalmic composition according to claim 29, in the form of an eye care or a contact lens care product selected from the group consisting of eye drops, contact lens preservative solution, contact lens cleaning solution, and contact lens multi-purpose solution.

31. The aqueous ophthalmic composition according to claim 29, in the form a multi-purpose solution or rewetting drops.

32. A gel composition for promoting wound healing wherein the gel composition comprises one or more of the glycophospholipid polymers comprising a reaction product of one or more glycosaminoglycans and one or more phospholipids.

33. A wound dressing comprising the gel composition according to claim 32.

# INTERNATIONAL SEARCH REPORT

International application No PCT/US2020/022022
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<b>A. CLASSIFICATION OF SUBJECT MATTER</b> INV. C08B37/00 C08B37/08 B65B25/00 C11D3/00 ADD.				
According to International Patent Classification (IPC) or to both national classification and IPC				
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) C08B B65B C11D				
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched				
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, BIOSIS, COMPENDEX, WPI Data				
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>				
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
X	WO 2008/063520 A1 (YISSUM RES DEV CO [IL]; MORRIA BIOPHARMACEUTICALS INC [US] ET AL.) 29 May 2008 (2008-05-29) paragraphs [0121], [0129], [0132]; claims; table 1 -----	1-6, 22-24		
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<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none;"><input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C.</td> <td style="width: 50%; border: none;"><input checked="" type="checkbox"/> See patent family annex.</td> </tr> </table>			<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C.	<input checked="" type="checkbox"/> See patent family annex.
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C.	<input checked="" type="checkbox"/> 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	Date of mailing of the international search report			
8 June 2020	19/06/2020			
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer  Vaccaro, Eleonora			

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PCT/US2020/022022

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