



- (51) **International Patent Classification:**
C08F 293/00 (2006.01)
- (21) **International Application Number:**
PCT/US2013/040066
- (22) **International Filing Date:**
8 May 2013 (08.05.2013)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**
61/651,767 25 May 2012 (25.05.2012) US
- (71) **Applicant:** JOHNSON & JOHNSON VISION CARE, INC. [US/US]; 7500 Centurion Parkway, Jacksonville, Florida 32256 (US).
- (72) **Inventors:** SCALES, Charles W.; 1011 Eagle Point Drive, St. Augustine, Florida 32092 (US). MCCABE, Kevin P.; 2843 Sheephead Court, St. Augustine, Florida 32092 (US). HEALY, Brent Matthew; 1300 Shetter Avenue #8301, Jacksonville Beach, Florida 32250 (US).
- (74) **Agents:** JOHNSON, Philip S. et al.; Johnson & Johnson, One Johnson & Johnson Plaza, New Brunswick, New Jersey 08933 (US).
- (81) **Designated States** (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY,

BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

- (84) **Designated States** (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

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

[Continued on next page]

- (54) **Title:** POLYMERS AND NANOGEL MATERIALS AND METHODS FOR MAKING AND USING THE SAME

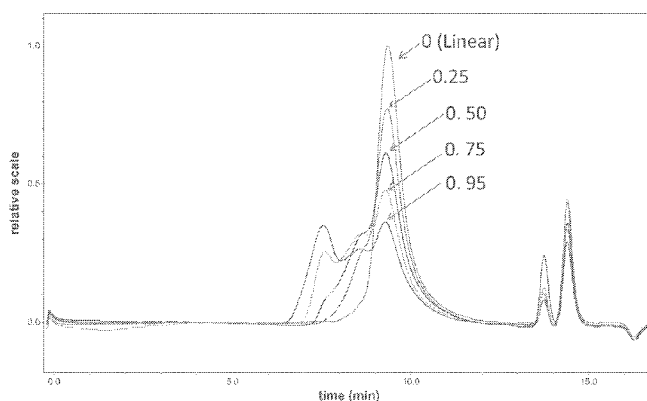


Figure 2

- (57) **Abstract:** Provided are compositions comprising a block copolymer of the following formula: [A]-B-[Q], wherein [A] is a polymer that has an affinity for a substrate; B is a linking group comprising an optionally-substituted, polyvalent linking group having a molecular weight of no more than 1000 g/mole; and [Q] comprises a semi-crosslinked, ungelled polymer derived from copolymerization of an ethylenically unsaturated monomer with a poly-functional ethylenically unsaturated monomer. Such block copolymers are cross-linked via the [Q] segment, but not macroscopically gelled. The [Q] segment is hydrophilic and has a degree of polymerization in the range of about 10 to about 10,000. The [A] segment is located at at least one terminal end of said block copolymer, comprises between about 1 and about 200 repeating units. The block copolymer is associated, via the linear substrate associative segment with a surface comprising at least one hydrophobic site, such as a silicone hydrogel. The polymers may be incorporated into a formulation from which the silicone hydrogel is made or may be contacted with the silicone hydrogel post-formation.





Published:

- *without international search report and to be republished
upon receipt of that report (Rule 48.2(g))*

POLYMERS AND NANOGEL MATERIALS AND METHODS FOR MAKING AND USING THE SAME

RELATED APPLICATIONS

This application claims priority to U.S. Provisional Patent Application No. 61/651767, filed on May 25, 2012, entitled "POLYMERS AND NANOGEL MATERIALS AND METHODS FOR MAKING AND USING THE SAME", the contents of which are incorporated by reference.

TECHNICAL FIELD

[0001] The present invention relates to block copolymers that are cross-linked but not macroscopically gelled having at least one terminal segment which can associate with a polymeric substrate. Such block copolymers can be amphiphilic or hydrophilic. Nanogel materials are also provided. These block copolymers and nanogel materials may be incorporated into a variety of substrates, including medical devices, to improve the wettability and lubricity and inhibit protein and/or lipid uptake thereof.

BACKGROUND

[0002] Contact lenses have been used commercially to improve vision since the 1950s. The first contact lenses were made of hard materials. Although these lenses are currently used, they are not widely used due to their poor initial comfort and their relatively low permeability to oxygen. Later developments in the field gave rise to soft contact lenses, based upon hydrogels. Many users find soft lenses are more comfortable, and increased comfort levels allow soft contact lens users to wear their lenses for longer hours than users of hard contact lenses.

[0003] Another class of available contact lenses is silicone hydrogel contact lenses. Silicone-containing components are combined with conventional hydrogel components to form silicone hydrogels which display increased oxygen permeability compared to conventional hydrogels. However, some silicone hydrogels display undesirably high contact angles and protein uptake compared to conventional hydrogel lenses.

[0004] Various compounds have been disclosed as suitable for treating preformed silicone hydrogel contact lenses including surface active segmented block copolymers, substantially water-soluble silicone-containing surfactants, functionalized hybrid PDMS/polar amphipathic copolymer block systems, including polydimethylsiloxane-PVP block copolymers

and (meth)acrylated polyvinylpyrrolidone. U.S. Patent Appln. Ser. No. 2011/0275734 is directed to “non-reactive, hydrophilic polymers having terminal siloxanes,” which have linear or branched hydrophilic segments. There remains a need for methods for improving the properties of contact lenses and particularly silicone hydrogel contact lenses.

SUMMARY OF THE INVENTION

[0005] Provided are compositions that impart excellent wettability and lubricity along with reduced protein and/or lipid uptake, and polymeric articles associated with the same. Methods of making and using these compositions are also disclosed. Compositions comprise a block copolymer of the following formula: [A]-B-[Q], wherein [A] is a polymer segment that has an affinity for a medical device; B is a linking group comprising an optionally-substituted, polyvalent linking group having a molecular weight of no more than 1000 g/mole; and [Q] comprises a semi-crosslinked, ungelled polymer derived from copolymerization of an ethylenically unsaturated monomer with a poly-functional ethylenically unsaturated monomer. Such block copolymers can be used as nanogel compositions that contain at least one stable, block copolymer that is cross-linked but not macroscopically gelled, comprising in said polymer's backbone, a hydrophilic segment that has a degree of polymerization of in the range of about 10 to about 10,000, and a linear substrate associating segment on at least one terminal end of said polymer, wherein said substrate associating segment comprises between about 6 and about 10,000 repeating units. Ophthalmic devices comprising a surface containing at least one hydrophobic polymeric site can be associated with said block copolymer. This association occurs via the linear substrate associative segment with the surface of the device and provides an improvement in at least one property of said ophthalmic device, such as a reduction in lipid uptake compared to only the substrate, or silicone-containing polymer, of at least about 20%. A non-limiting example of a silicone-containing polymer is a silicone hydrogel. The block copolymers can be can be amphiphilic or hydrophilic. The associative segment can be hydrophilic or hydrophobic.

[0006] Also provided are methods of inhibiting lipid uptake by silicone-containing contact lenses, the methods comprising contacting the contact lenses with a solution comprising at least one stable block copolymer comprising a hydrophilic segment having a degree of polymerization of about 10 to about 10,000 and a substrate associating segment at least one

terminal end of block copolymer, wherein said substrate associating segment comprises between about 1 and about 200 siloxy units, and said block copolymer is associated, via the substrate associating segment with a surface comprising at least one hydrophobic site of a polymer or article, such as a silicone hydrogel.

[0007] The present invention further provides a composition comprising a water soluble, block copolymer of the following formula:

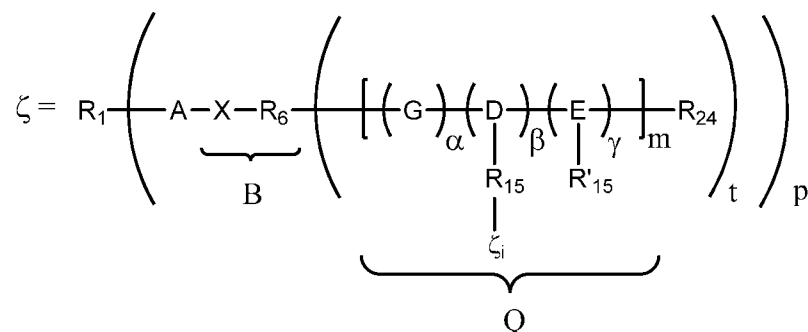
[A]-B-[Q], wherein

[A] is a segment that has an affinity for a medical device;

B is a linking group comprising an optionally-substituted, polyvalent linking group having a molecular weight of no more than 1000 g/mole; and

[Q] comprises a semi-crosslinked, ungelled segment derived from copolymerization of at least one ethylenically unsaturated monomer with a poly-functional ethylenically unsaturated monomer.

The present invention further relates to a composition comprising a water soluble, block copolymer having primary chains, ζ , represented by the formula



wherein R_1 , A, X, R_6 , G, D, E, R_{15} , R'_{15} , t, p, m, α, β, γ , are as defined herein and R_{24} is any agent capable of controlling polymerization, and in some embodiments R_{24} is selected from the group consisting of monovalent RAFT agents, ATRP agents, TERP agents and NMP agents.

BRIEF DESCRIPTION OF THE DRAWINGS

[0008] Figure 1 shows prior art performance of lipid uptake versus number average molecular weight;

[0009] Figure 2 shows the overlaid refractive index traces from GPC for a series of PDMA-siloxane block copolymers prepared with increasing amounts of crosslinker, i.e.

(XL:ζ-PC values from 0 to 0.95) according to Preparation 3 and a comparative linear PDMA-siloxane according to Preparation 4;

[0010] Figure 3 shows lipid uptake versus XL:ζ-PC for varying $DP_{nQ\text{-Segment}}$ values and a constant molar ratio of [A]:[Q] of 0.1;

[0011] Figure 4 shows lipid uptake versus XL:ζ-PC for varying $DP_{nQ\text{-Segment}}$ values and a constant molar ratio of [A]:[Q] of 0.55;

[0012] Figure 5 shows lipid uptake versus XL:ζ-PC for varying $DP_{nQ\text{-Segment}}$ values and a constant molar ratio of [A]:[Q] of 1.0;

[0013] Figure 6 shows lipid uptake versus $DP_{nQ\text{-Segment}}$ for varying XL:ζ-PC for a constant molar ratio of [A]:[Q] of 0.1;

[0014] Figure 7 shows lipid uptake versus $DP_{nQ\text{-Segment}}$ for varying XL:ζ-PC for a constant molar ratio of [A]:[Q] of 0.55;

[0015] Figure 8 shows lipid uptake versus $DP_{nQ\text{-Segment}}$ for varying XL:ζ-PC for a constant molar ratio of [A]:[Q] of 1.0;

DETAILED DESCRIPTION

[0016] Before describing several exemplary embodiments of the invention, it is to be understood that the invention is not limited to the details of construction or process steps set forth in the following description. The invention is capable of other embodiments and of being practiced or being carried out in various ways.

[0017] It has been found that despite advances made by the use of previously developed non-reactive, hydrophilic polymers having terminal siloxanes, which have linear, branched or combed hydrophilic segments, in reducing lipid and/or protein uptake and enhancing lubricity and wettability of contact lenses, a limit on improved properties is reached as molecular weight increases. FIG. 1 depicts this limit with respect to molecular weight. From the plot in Figure 1, it is apparent that for senofilcon A lenses treated with PVP-Siloxane copolymers with increasing molecular weights, the lipid uptake decreases to a minimal level of about 15 μg/lens when the hydrophilic PVP segment reaches a molecular weight of about 80 kDa. For lenses treated with PVP-Siloxane copolymers with molecular weights above 80 kDa, no additional reduction in lipid uptake on senofilcon A is observed. Surprisingly, it has been found that by employing polymer

nanogels having terminal substrate associating segments and cross-linked or “bridged” hydrophilic segments, lipid uptake can be inhibited to a greater extent as compared to the analogous non-crosslinked polymers that also comprise terminal substrate associating segments and are of comparable molecular weights. For example, Figure 1 shows that treatment of a senofilcon A contact lens with a linear, uncross-linked PDMA-siloxane copolymer and exhibiting a number average molecular weight, M_n , of about 23,000 g/mole, raised the substrate’s lipid uptake from about 30 mcg/lens to about 52 mcg/lens. Alternatively, treatment of senofilcon A with a cross-linked PDMA-siloxane material (e.g. PDMA-Sil 100-0.55-1.0) with an equivalent M_n of about 23,050 g/mole results in a remarkable drop in lipid uptake from 30.0 to about 12.5 mcg/lens.

[0018] The presence of semi-crosslinked, ungelled segments can lead to contact lenses with improved properties, for example, reduced lipid and protein uptake as well as lower friction. Also, it is thought that choice of cross-linking agent and degree of cross-linking can be tailored according to desired applications and specific substrate material.

[0019] As used herein “associated” means that the semi-crosslinked block copolymer is retained in or on the substrate without covalent bonding. Associated may include physical retention, such as entanglement or anchoring, or hydrogen bonding, van der Waals forces, dipole-dipole interactions, electrostatic attraction, and combinations of these effects. It has been surprisingly found that the association between the semi-crosslinked block copolymers and the substrate is persistent, and is maintained even with digital rubbing. When the substrate is a contact lens, the semi-crosslinked block copolymers are retained in and/or on the contact lenses through the desired wear cycle, including in embodiments where the contact lens is a reusable lens, through cleaning with a digital rub.

[0020] As used herein “associative segment” means a portion of the terminal segment of the polymer that is retained or associated in or on a surface, region, or segment of a substrate. The associative segment can be hydrophilic or hydrophobic.

[0021] As used herein “non-reactive” means the semi-crosslinked block copolymer lacks functional groups which form covalent bonds under the reaction, storage and use conditions. For example, when the hydrophilic polymer is contacted with a substrate such as a contact lens before autoclaving, very few (less than 1wt%) of the semi-crosslinked block copolymers contain residual reactive groups. Even if residual groups were present, the contacting conditions lack the

initiators necessary to catalyze free radical reactions. Thus, the semi-crosslinked block copolymer is incapable of forming covalent bonds with the substrate. It will be appreciated by those of skill in the art that while a very small number of semi-crosslinked block copolymer (less than 5 wt%, and less than 1 wt%) may have a residual reactive group, there are too few residual reactive groups to associate desirable or functional amounts of the semi-crosslinked block copolymer with the substrate. The vastly predominating effect keeping the semi-crosslinked block copolymer associated with the substrate is entrapment of at least a portion of the semi-crosslinked block copolymer.

[0022] The term “cross-linked” refers to the attachment of a polymer chain to one or more polymer chain(s) via a bridge or multiple bridges, composed of either an element, a group or a compound, that join certain carbon atoms of the chains by primary bonds, including covalent, ionic and hydrogen bonds. In various embodiments of the invention disclosed herein, cross-linking may occur via covalent bonding, ionic bonding, hydrogen bonding, or the like. An exemplary embodiment of covalent cross-linking would include the in situ formation of cross-links during a free-radical copolymerization of a mono-vinyl monomer and monomer containing multiple (i.e. 2 or more) vinyl substituents. Such a polymerization would result in the covalent cross-linking of multiple polymer chains to each other and (depending on the extent of monomer conversion and molar quantity of the cross-linker) the formation of a macroscopic gel.

[0023] Ionic cross-linking of polymer chains may occur in situ (i.e. during polymerization) or post-polymerization. The latter case may occur when an aqueous solution containing a polymeric cationic material is added to an aqueous solution containing a polymeric anionic material. Upon mixture of the two ionic polymers, polymer-polymer complexation along with small-counter-ion liberation occurs, leading to the formation of ionically cross-linked polymer-polymer complexes. The solubility of such complexes is predominately governed by the stoichiometry of positive and negative charge. Formation of such ionic cross-links between polyanionic and polycationic materials in solution is well known to those skilled in the art. The former case of ionic cross-linking may occur when a mono-vinyl monomer is copolymerized with a di-vinyl cross-linker that is composed of two ethylenically unsaturated monomers which are connected to each other via an ionic bond. Such “ionic cross-linkers” may be formed by combining an ethylenically unsaturated monomer containing an acidic (e.g. a carboxylic acid) moiety with an ethylenically unsaturated monomer containing a basic moiety (e.g. a tertiary

amine) through simple acid/base chemistry to form a monomer-monomer complex or divinyl covalent organic salt.

[0024] In the context of the disclosed invention, cross-linking via hydrogen bonding may occur when a polymer with multiple proton-donating moieties is combined in solution with a polymer with multiple proton-accepting moieties. In such embodiments, the two polymers are able to form soluble or insoluble complexes, depending on the ratio of proton-donating groups to proton-accepting groups in the complex, as well as the abundance of additional solubilizing or non-solubilizing moieties present on the polymer chains.

[0025] As used herein “nanogel” means submicron hydrogel particles which are soluble or indefinitely dispersible at room temperature in aqueous solutions. In one or more embodiments, the solutions are clear. In one embodiment the aqueous solution is at least about 50 weight % water or lens packing solution, in some embodiments at least about 70 weight %, in other embodiments at least about 90 weight %, in other embodiments at least about 99 weight %, and in other embodiments at least about 99.5 weight %.

[0026] The polymer nanogels are in a macroscopically ungelled state, making them soluble in aqueous solutions, including ophthalmic solutions and compositions. The polymers are generally in an ungelled state at the temperature at which they are associated or incorporated into the ophthalmic solution or composition. For ophthalmic devices such as contact lenses, it may not be necessary for the polymer to be ungelled once it is incorporated or associated with the contact lens. However, for ophthalmic solutions, the polymer generally remains ungelled throughout storage, and in some embodiments, use. Small quantities of gelled polymer (less than about 5 wt%) may be acceptable, and in some solutions, if the amount of gelled polymer is too great, it can be removed by processes known in the art, such as filtration.

[0027] Embodiments of polymers provided herein are randomly cross-linked among and along the hydrophilic segments of the polymers. Agents used for cross-linking are termed cross-linking agents or cross-linkers.

[0028] As used herein, “at least partially hydrophobic polymer matrices” are those which comprise repeating units derived from hydrophobic components such as hydrophobic monomers, macromers and prepolymers. Hydrophobic components are those which are not soluble in water, and which when homopolymerized or polymerized with only other hydrophobic components have contact angles with respect to, for example, ophthalmic solutions such as wetting solutions

of greater than about 90°. Examples of at least partially hydrophobic polymer matrices include contact lenses formed from PMMA, silicones, silicone hydrogels (both coated and uncoated), stents, catheters and the like. Examples of hydrophobic monomers, macromers and prepolymers are known and include monomers, macromers and prepolymers containing silicone groups, siloxane groups, unsubstituted alkyl groups, aryl groups and the like. Specific examples include silicone containing components such as monomethacryloxypropyl terminated mono-n-butyl terminated polydimethylsiloxanes (800-1000 MW) (mPDMS), monomethacryloxypropyl terminated mono-n-methyl terminated polydimethylsiloxanes, TRIS, methyl methacrylate, lauryl methacrylate, and the like.

[0029] As used herein, “stable” means that the compound does not undergo a change through a single autoclaving cycle of 121°C for 30 minutes which would deleteriously affect the desired properties of either the wetting agent or the combination of the wetting agent and polymer substrate. For example, ester bonds between the siloxane segment and the polymer segment are in some embodiments undesirable. The autoclaving may be conducted dry or in the presence of an ophthalmically compatible saline solution, such as, but not limited to borate or phosphate buffered saline.

[0030] As used herein, “near-monodisperse” means a polydispersity index (PDI) of 1.5 or less and refers to an individual primary chain degree of polymerization and/or MW within a cluster of cross-linked amphiphilic primary chains. In some embodiments, the polymers display polydispersities of less than about 1.3, and in others in the range of about 1.05 to about 1.3. It should be appreciated by those skilled in the art that the individual near-monodisperse primary chains are statistically cross-linked to one another during polymerization, and as such, the resulting amphiphilic, cross-linked, block copolymer clusters will have polydispersity values in excess of 1.5.

[0031] As used herein, “degree of polymerization” means the number of repeating units per polymer molecule or polymeric segment. For example, in one or more embodiments, the hydrophilic segment [Q] (per Formula I) can have a degree of polymerization in the range of about 10 to about 10,000 (or about 50 to about 5000, or about 300 to about 5000, or about 500 to about 2000, or about 100 to about 1000, or about 100 to about 500, or about 100 to about 300).

[0032] As used herein, “cross-linker to primary chain molar ratio” (XL:ζ-PC) refers to the number of moles of cross-linker used during preparation of the block copolymer in a ratio

with the number of moles of primary chain used in the preparation. The number of primary chains is determined by the molar amount of controlled radical polymerization (CRP) agent, or control agent, present. Specific embodiments include a cross-linker to primary chain molar ratio in the range of about 0.005 to about 10 (or about 0.1 to about 5, or about 0.1 to about 1.5, or about 0.1 to about 1.25). Exemplary CRP agents include, but are not limited to: reversible addition fragment transfer (RAFT) agents; atom transfer radical polymerization (ATRP) agents; telluride-mediated polymerization (TERP) agents; and/or nitroxide-mediated living radical polymerization (NMP) agents.

[0033] As used herein, “segment” or “block” refers to a section of polymer having repeating units with similar properties, such as composition or hydrophilicity.

[0034] As used herein, “silicone segment” refers to $-\text{[SiO]}-$. The Si atom in each $-\text{[SiO]}-$ repeating unit may be alkyl or aryl substituted, are preferably substituted with C_{1-4} alkyl, and in one embodiment are substituted with methyl groups to form a dimethylsiloxane repeating unit.

[0035] As used herein “linear silicone segment” refers to siloxane repeating units having the silicon and oxygen atoms in polymer backbone. For example, polydimethylsiloxane is an example of a linear silicone segment because $-\text{SiO}-$ groups are contained in the backbone. PolyTRIS is not a linear silicone segment, because the siloxane groups are contained pendant to the carbon-carbon backbone.

[0036] As used herein a “hydrophilic associative segment” is hydrophilic, but can associate with the substrate via hydrogen bonding or ionic bonding. For example, for lenses which comprise a proton acceptor such as DMA, NVP or PVP, the hydrophilic associative segment comprises proton donating groups. Suitable proton donating groups include 4-acrylamidobutanoic acid (ACAII) (3-acrylamidophenyl)boronic acid (APBA), or vinyl bezoic acid.

[0037] As used herein, “complexing segments” or “complexing groups” include functional group pairs that exhibit strong non-covalent interactions, e.g. alkyl or aryl boronic acids that interact strongly with diol functional groups or biotin and avidin binding. In one embodiment, the complexing segments may comprise monomers such as (4-vinylphenyl)boronic acid, (3-acrylamidophenyl)boronic acid, or (4-acrylamidophenyl)boronic acid or *N*-(2-acrylamidoethyl)-5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)pentanamide.

[0038] As used herein, “stimuli responsive components” include those which undergo a physical or chemical change in response to a change in environmental conditions. Conditions which can induce a change include pH, light, salt concentration, temperature, combinations thereof and the like. Examples of monomers which can be used to prepare stimuli responsive components include but are not limited to *N*-isopropylacrylamide, vinyl benzoic acid, or acrylamidobutanoic acid (ACAII), and the like.

[0039] As used herein “substrate” refers to an article, such as a sheet, film, tube or more complex form such as biomedical devices.

[0040] As used herein, a “biomedical device” is any article that is designed to be used while either in or on mammalian tissues or fluid. Examples of these devices include but are not limited to catheters, implants, stents, sutures, bandages, and ophthalmic devices such as intraocular lenses and contact lenses and the like.

[0041] As used herein, the term “lens” refers to ophthalmic devices that reside in or on the eye. These devices can provide optical correction, cosmetic enhancement, UV blocking and visible light or glare reduction, therapeutic effect, including wound healing, delivery of drugs or nutraceuticals, diagnostic evaluation or monitoring, or any combination thereof. The term lens includes, but is not limited to, soft contact lenses, hard contact lenses, intraocular lenses, overlay lenses, ocular inserts, and optical inserts.

[0042] As used herein, a “silicone-containing polymer” is any polymer containing silicone or siloxane repeating units. The silicone-containing polymer may be a homopolymer, such as silicone elastomers, or a copolymer such as fluoro-silicones and silicone hydrogels. As used herein, silicone hydrogel refers to a polymer comprising silicone containing repeating units and in some embodiments, a water content of at least about 10%, and in some embodiments at least about 20%.

[0043] As used herein RAFT polymerization or RAFT refers to reversible addition fragmentation-chain transfer polymerization.

[0044] As used herein “reactive components” are the components in a polymerization reaction mixture which become part of the structure of the polymer upon polymerization. Thus, reactive components include monomers and macromers which are covalently bound into the polymer network. Diluents and processing aids which do not become part of the structure of the polymer are not reactive components.

[0045] As used herein “substituted” refers to alkyl groups which may contain halogens, esters, aryls, alkenes, alkynes, ketones, aldehydes, ethers, hydroxyls, amides, amines and combinations thereof.

[0046] As used herein “free radical source” refers to any suitable method of generating free radicals such as the thermally induced homolytic scission of a suitable compound(s) (thermal initiators such as peroxides, peroxyesters, or azo compounds), the spontaneous generation from monomer (e.g., styrene), redox initiating systems, photochemical initiating systems or high energy radiation such as electron beam, X- or gamma-radiation. Chemical species known to act as “free radical sources” are commonly called initiators by those skilled in the art and will be referred to as such for the purposes of this disclosure.

[0047] As used herein “proton donating segments” or “proton donating groups” are functional groups which have the ability to donate a proton to a proton accepting segment or group under lens forming, autoclaving or storage conditions. Proton donating functional groups include alcohols, acids, primary amides, and the like.

[0048] As used herein “proton accepting segments” or “proton accepting groups” are functional groups which have the ability to accept a proton under lens forming, autoclaving or storage conditions. Proton accepting groups include amines, amides, carbonyls and the like.

[0049] In one embodiment, the block copolymer of the present invention is a stable polymeric wetting agent and comprises a hydrophilic segment and a substrate-associative segment on at least one terminal end of the polymer. Said polymers are comprised of at least one [A] block comprising n repeat units and suitable carbon-containing groups and at least one [Q] block comprising m repeat units and suitable carbon-containing groups, whereas, [A] and [Q] are linked to each other in any order (i.e. [A] to [Q], or [Q] to [A]) via a linking group, B. As desired, a plurality of [A] and/or [Q] blocks can be used, so long as a B linking group is located between any combination of [A] and [Q] blocks. In this embodiment, A is defined as a material or polymer that has an affinity for at least a portion of a medical device, B is a linking group that comprises an optionally-substituted, polyvalent linking group with a molecular weight (MW) of no more than 1000 g/mole, and [Q] comprises a semi-crosslinked, ungelled polymer derived from the copolymerization of an ethylenically unsaturated monomer with a poly-functional ethylenically unsaturated monomer. The following structure is a generalized, non-limiting representation of an embodiment of the invention:

[A]-B-[Q]

where [Q] may or may not contain an agent capable of controlling a free radical polymerization. [A] is selected from materials that have an affinity for a given substrate or medical device. [A] may be selected from polymer and copolymer segments comprising linear or branched siloxanes, hydrophobic alkyl groups having 4-24 carbons, proton donating functional groups, proton accepting functional groups, ionic functional groups, boronic acid functionalities, stimuli responsive functionalities, combinations thereof and the like. For block copolymers with multiple A segments spaced close together, hydrophobic alkyl groups having 2 or more carbons may be suitable. In one embodiment, [A] comprises, consists or consists essentially of a polydimethylsiloxane (PDMS)-containing structure and has an affinity for medical devices which contain at least one hydrophobic material. For example, PDMS can associate with silicone hydrogel contact lenses via hydrophobic-hydrophobic interactions between the PDMS contained within [A] and that contained within the contact lens. Other embodiments of [A] include structures that comprise, consist or consist essentially of proton donating and proton accepting functional groups. In one such embodiment, [A] could comprise, consist or consist essentially of multiple proton donating functional groups, such as alcohols, and thus have an affinity for medical devices or other surfaces which proton are accepting. Conversely, [A] could comprise, consist or consist essentially of multiple proton accepting functional groups, such as amides, and thus have an affinity for medical devices or other surfaces which are proton donating. Yet in other embodiments [A] could comprise, consist or consist essentially of multiple ionic functional groups, such as carboxylates, sulfonates, ammonium salts, or phosphonium salts, and thus have an affinity for medical devices with an opposite charge to that of a given ionic group in associating segment [A]. Other embodiments of [A] could include those which comprise, consist or consist essentially of functional groups capable of undergoing complexation with other complementary functional groups on a medical device or surface; for example, [A] could comprise, consist or consist essentially of multiple boronic acid functionalities and associate with a medical device or surface which contains multiple hydroxyl groups. In an alternative embodiment, the hydroxyl groups may be comprised within [A] and be associated with a surface containing multiple boronic acid functional groups. In some embodiments, [A] is stimuli responsive and is comprised of functional groups that, when incorporated into polymeric form, cause the resulting polymer to be water-soluble or water-

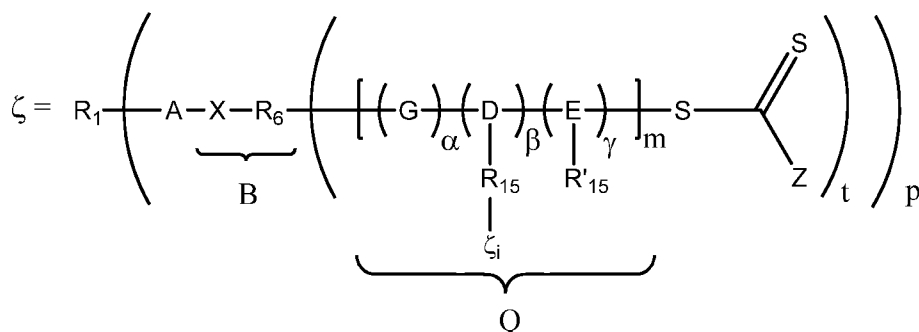
insoluble under different solution conditions. For example, [A] might comprise, consist or consist essentially of a temperature-responsive polymer or copolymer, such as poly(*N*-isopropylacrylamide) (PNIPAM), which undergoes a phase-transition in water at 32°C. Therefore, at solution temperatures below 32°C, said PNIPAM [A] block is water-soluble and hydrophilic, while at higher solution temperatures (i.e. greater than 32°C) it is water-insoluble, hydrophobic, and able to associate with a medical device or surface which contains at least one hydrophobe.

[0050] B is defined as a linking group which connects [A] and [Q] to each other in any order and can exist as any optionally substituted, polyvalent structure with a MW of less than about 1000 g/mole. Embodiments of B include optionally substituted, polyvalent aliphatic structures, optionally substituted, polyvalent aryl structures, optionally substituted, polyvalent alkylene structures, or a direct bond.

[0051] The structure [Q] is comprised of a semi-crosslinked, ungelled polymer derived from the copolymerization of an ethylenically unsaturated monomer with a poly-functional ethylenically unsaturated monomer. In one embodiment, the polymerization leading to the formation of [Q] is initiated from a carbon atom contained within structure B. In such an embodiment, the formation of a semi-crosslinked, ungelled polymer occurs and those skilled in the art will appreciate that the resultant polymer will contain multiple [A], B, and [Q] structures in a given polymer molecule due to the cross-linking that occurs between multiple propagating [A]-B-[Q] chains.

[0052] The polymeric wetting agents may beneficially be associated with the substrate in a single step, without prior pretreatment. Moreover, because the [A] segments are terminal, persistent association of the polymeric wetting agents is achieved, without covalent bonding to the lens, the requirement for special monomers like amines, carboxylates or thiols in the bulk of the substrate.

[0053] In one embodiment, the polymeric wetting agent has the general structure and primary chain designator, ζ , as shown in Formula IA.

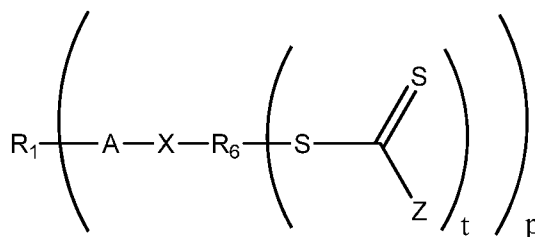


Formula I

[0054] Wherein R_6 , R_{15} , R'_{15} , X , G , D , E , Z , ζ , ζ_i , α , β , γ , n , m , t and p are defined below, and may be formed by contacting:

[0055] At least one hydrophilic monomer having the formula $H_2C=UV$,

[0056] At least one RAFT agent of Formula II having a chain transfer constant greater



than 0.1;

Formula II

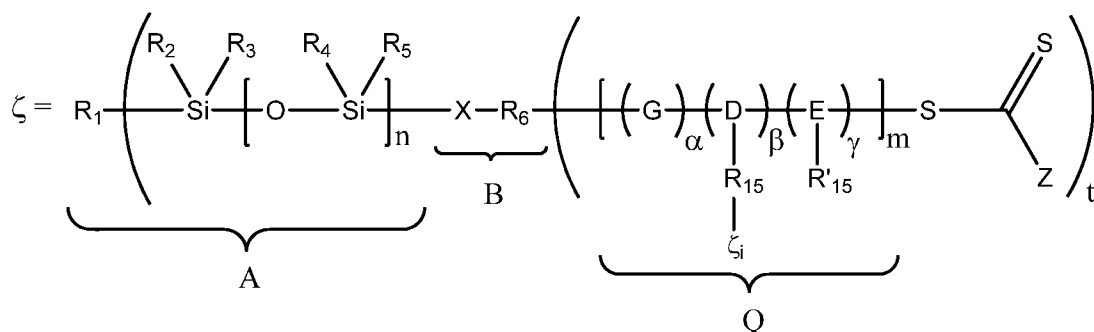
[0057] (iii) free radicals produced from a free radical source (i.e. an initiator); and

[0058] (iv) a cross-linking agent, $H_2C=UR'_{15}$

[0059] In the above formulae, A is selected from linear dialkyl or diaryl polysiloxanes having 6-1,000, 6-200, 6-60, 6-50, 6-20, 6-15 and in some embodiments, 6-12 repeating units, alkenes having 2 to 25 carbon atoms which may be optionally substituted with atoms selected from S, O, N, P and combinations thereof;

[0060] R_1 , R_6 , X , Z , t and p are defined below.

[0061] In one embodiment, that can be referred to as a hydrophobic-hydrophilic block co-polymer, where $[A]$ is a silicone or PDMS-containing polymer or oligomer, the polymeric wetting agent has the general structure and primary chain designator, ζ , as shown in Formula Ia.

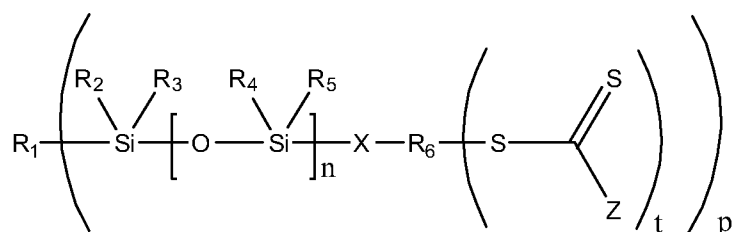


Formula Ia

[0062] Wherein R_1 through R_6 , R_{15} , R'_{15} , X , G , D , E , Z , ζ , ζ_i , α , β , γ , n , m , t and p are defined below, and may be formed by contacting:

[0063] At least one hydrophilic monomer having the formula $\text{H}_2\text{C}=\text{UV}$

[0064] At least one polysiloxane RAFT agent of Formula IIa having a chain transfer constant greater than 0.1;



Formula IIa

[0065] (iii) free radicals produced from a free radical source (i.e. an initiator); and

[0066] (iv) a cross-linking agent, $\text{H}_2\text{C}=\text{UR}'_{15}$

[0067] In the above formulae, R_1 is selected from substituted and unsubstituted C_{1-24} alkyl; in some embodiments substituted and unsubstituted C_{1-10} alkyl and in other embodiments substituted or unsubstituted C_{1-6} alkyl, C_{1-4} alkyl, methyl or n-butyl;

[0068] R_2 - R_5 are independently selected from H, C_{1-4} alkyl and C_{6-10} aryl, and combinations thereof, and in one embodiment, R_2 - R_5 are independently selected from C_1 - C_4 alkyl, and combinations thereof; and in another embodiment R_2 - R_5 are methyl;

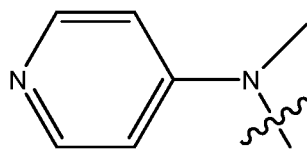
[0069] $n = \text{DP}_{\text{nA-Segment}}$ and is 6-1,000, 6-200, 6-60, 6-50, 6-20, 6-15 and in some embodiments, 6-12;

[0070] $m = DP_{nQ\text{-Segment}}$ and is 10-10,000, 50-1000, 50-500, and in some embodiments, 100-500, and X, Z, p and t are as defined below.

[0071] In polysiloxane RAFT agents of Formula II, R_6 is a free radical leaving group that initiates free radical polymerization. R_6 is selected from divalent groups consisting of optionally substituted alkylene; optionally substituted saturated, unsaturated or aromatic carbocyclic or heterocyclic rings; optionally substituted alkylthio; optionally substituted alkoxy; or optionally substituted dialkylamino. In one embodiment, R_6 is selected from optionally substituted benzyl, optionally substituted phenyl, ethanoate, optionally substituted propionate, 4-cyanopentanoate, or isobutyroate functionalities. In embodiments using the polysiloxane RAFT agents for Formula II, the % polysiloxane RAFT agent used is selected to provide the desired level of association with the substrate, but prevent gelation of the block copolymer.

[0072] X is selected from $-O-(CO)-$, $-(CO)O-$, $-NR_8-(CO)-$, $-(CO)NR_8-$, $-O-$, C_{1-12} alkylene, C_{1-4} alkylene or a direct bond, and in some embodiments R_8 is selected from H, methyl, ethyl or propyl;

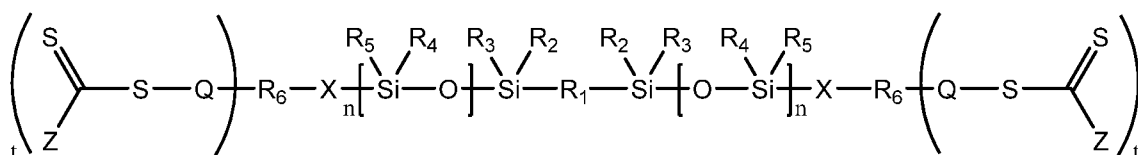
[0073] Z is selected from the group consisting of hydrogen, chlorine, fluorine, optionally substituted alkyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted alkylthio, optionally substituted alkoxy, optionally substituted alkoxy carbonyl, optionally substituted aryloxy carbonyl ($-COOR''$), carboxy ($-COOH$), optionally substituted acyloxy ($-O_2CR''$), optionally substituted carbamoyl ($-CONR''_2$), cyano ($-CN$), dialkyl- or diaryl-phosphonato [$-P(=O)(OR'')_2$], dialkyl- or diaryl-phosphinato [$-P(=O)(OR'')_2$], and a polymer chain formed by any mechanism; in other embodiments, Z may comprise a “switchable” functional group, that is sensitive to solution pH and allows one to tune the RAFT agent’s reactivity. In one embodiment, where a “Switchable” Z-group is employed, Z comprises the following non-limiting structure:



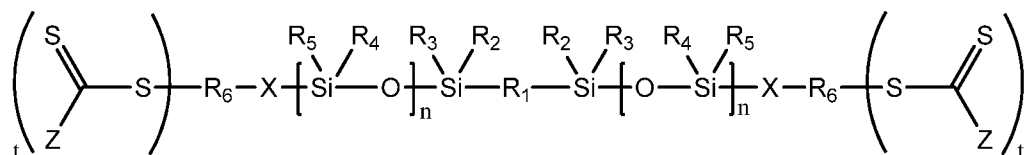
[0074]

[0075] p is 1 or an integer greater than 1, 1-5, 3-5 and in some embodiments 1 or 2.. When $p \geq 2$, then R_1 is selected from p-valent moieties derived from any of silicon, sulfur, oxygen, nitrogen, optionally substituted alkylene, optionally substituted aryl, a polymer chain, or

a combination thereof. Such an embodiment is disclosed in the following structural analogues of Formulas I and II, namely Formulas III and IV

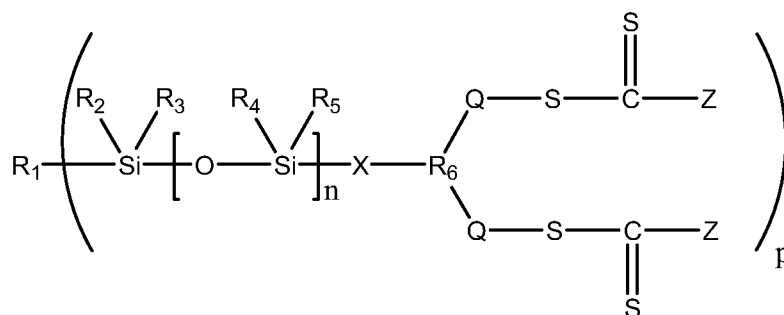


Formula III

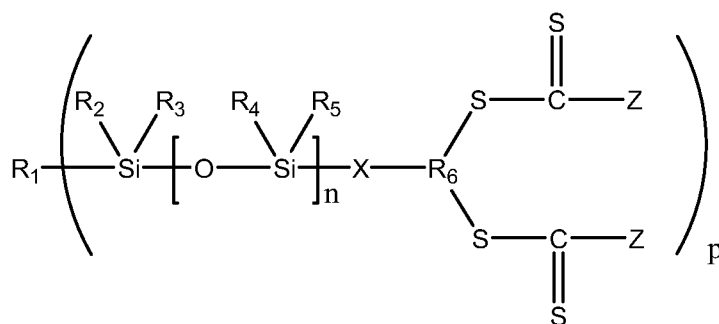


Formula IV

[0076] where R₁-R₆, X, Z, and n are defined as above and t is 1 or an integer greater than 1. When t ≥ 2, then R₆ is p-valent, and would be connected to more than one thiocarbonylthio functional group. Such an embodiment is disclosed in the following structural analogues of Formulas I and II, namely Formulas V and VI:



Formula V



Formula VI

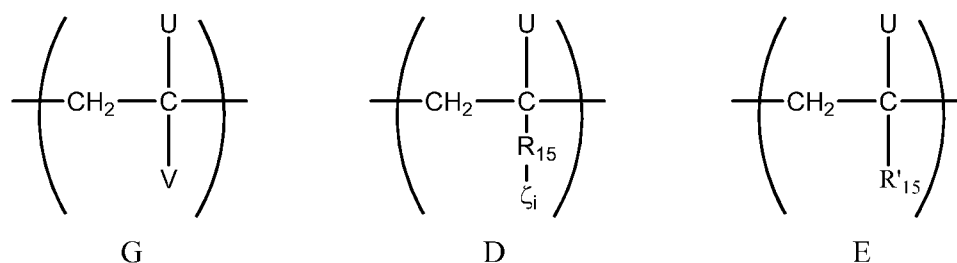
[0077] ζ_i is another primary chain that is cross-linked to a primary chain, ζ , as disclosed above. One or more ζ_i primary chains may be attached to a ζ primary chain and ζ_i primary chains may be further attached or cross-linked to additional ζ_k primary chains and so on and so forth. Those skilled in the art should appreciate the fact that the cross-linking of ζ primary chains to other ζ_i primary chains as well as the further cross-linking of ζ_i primary chains to ζ_k primary chains, and ζ_i primary chains to ζ_l primary chains, and so on and so forth, is a generalized description for the formation of statistically cross-linked block copolymers (of the form [A]-B-[Q]) that are randomly cross-linked to each other via their hydrophilic Q-segments. For the purposes of this invention, all cross-linking scenarios between hydrophilic segments of various ζ -, ζ_i -, and ζ_k ...primary chains are possible and realized and groupings of ζ -, ζ_i -, and ζ_k ...primary chain block copolymers attached to each other via cross-links, as described above, will be referred to as ζ -clusters. Without being bound to theory, the following non-limiting examples of cross-linking between ζ -primary chains can occur during formation of the semi-cross-linked ζ -clusters: ζ - ζ_i , ζ - ζ_k , ζ_k - ζ_i , ζ_i - ζ_i , ζ_k - ζ_k ...and so on and so forth. The number of ζ -primary chains that are attached to each other in a single cluster is a function of several variables, one of which includes the theoretical cross-linker to primary chain molar ratio (XL: ζ -PC). If the reactivities between the monomer and cross-linker in a given polymerization are similar, e.g. a copolymerization between *N,N*-dimethylacrylamide and *N,N'*-methylenebisacrylamide, random incorporation of cross-linker into the ζ -primary chain can be assumed. This random incorporation of potential cross-linking sites along the ζ -primary chain, as well as collision frequency of these pendant cross-linking sites with other propagating ζ -primary chains or ζ -

clusters is what is believed to govern, to a large extent, the number of ζ -clusters and the average number of primary chains per cluster.

[0078] R'_{15} is any carbon-containing structure containing at least one group capable of forming a covalent, ionic or hydrogen bond with other ζ -chains, and in one embodiment is selected from ethylenically unsaturated moiety that is linked to the primary chain, ζ , ζ_i , or ζ_k .

[0079] R_{15} is any carbon-containing structure that comprises a cross-link between two ζ -chains, and is derived from R'_{15} . R'_{15} optionally contains one or more unsaturated bonds;

[0080] The hydrophilic segment, Q, comprises statistically distributed repeating units of G, D, and E with the following formulae:



Formula VII

[0081] The terms α , β , and γ , specify the relative molar amounts (in terms of mole fraction) of G, D, and E that comprise the hydrophilic segment, Q. In some embodiments, α is equal to about 0.85 to about 0.999, about 0.92 to about 0.999, about 0.95 to about 0.999, and about 0.97 to about 0.999, while the sum of β and γ for each respective range of α would be equal to about 0.15 to about 0.001, about 0.08 to about 0.001, about 0.05 to about 0.001, and about 0.025 to about 0.001. For the purposes of the disclosed invention, the mole fraction of D in the hydrophilic segment, Q, (i.e. β) of a ζ -primary chain is intended to be maximized, compared to that of E (i.e. γ) thus maximizing the number of cross-links of Q to the Q-segments of other ζ -primary chains, i.e. very few unreacted R'_{15} moieties remain. All mole-fraction ranges of α , β , and γ are based on the relative amounts of monomer and cross-linker employed in the monomer feed of a given embodiment and assumes that the reactivity differences between vinyl-substituents on the monomer and cross-linker are minimal, i.e. near-statistical incorporation

occurs. In one embodiment, the nanogels of the present are substantially free from unreacted R'₁₅ groups. When R'₁₅ comprises a double bond, this may be confirmed via FTIR or other methods capable of detecting the presence of double bonds.

[0082] U is selected from the group consisting of hydrogen, halogen, C₁-C₄ alkyl which may be optionally substituted with hydroxyl, alkoxy, aryloxy (OR''), carboxy, acyloxy, aroyloxy (O₂CR''), alkoxy-carbonyl, aryloxy-carbonyl (CO₂R'') and combinations thereof; and in some embodiments from the group consisting of H, methyl.

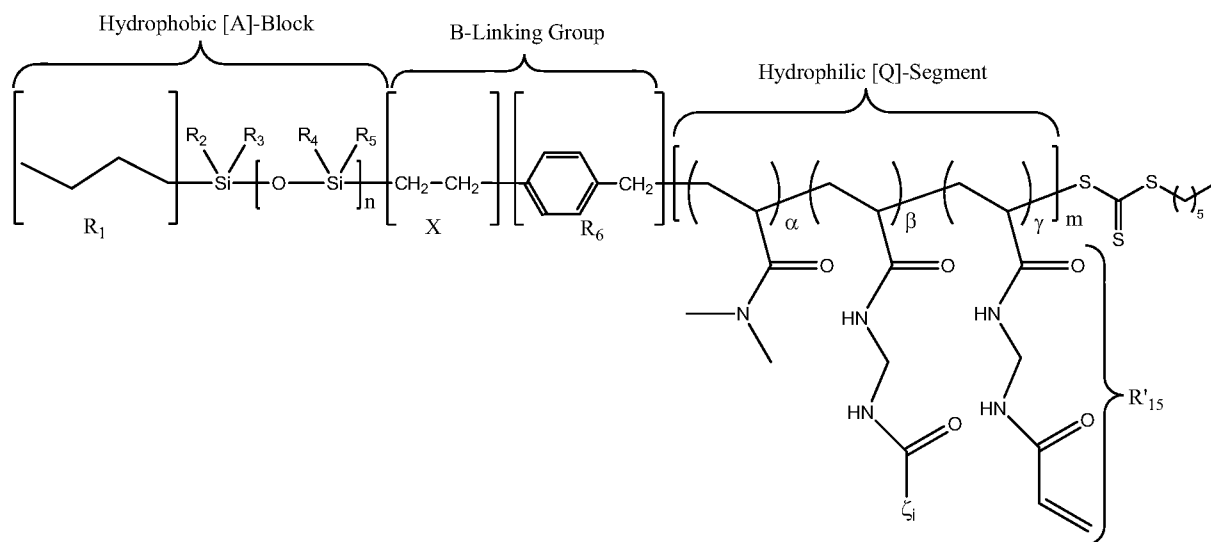
[0083] V is independently selected from the group consisting of hydrogen, R'', CO₂H, CO₂R'', COR'', CN, CONH₂, CONHR'', CONR''₂, O₂CR'', OR'' and halogen; plus cyclic and acyclic N-vinyl amides and combinations thereof;

[0084] R'' is independently selected from the group consisting of optionally substituted C₁-C₁₈ alkyl, C₂-C₁₈ alkenyl, aryl, heterocyclyl, alkaryl wherein the substituents are independently selected from the group that consists of epoxy, hydroxyl, alkoxy, acyl, acyloxy, carboxy and carboxylates, sulfonic acid and sulfonates, alkoxy- or aryloxy-carbonyl, isocyanato, cyano, silyl, halo, and dialkylamino; phosphoric acid. In one embodiment R'' is selected from the group consisting of methyl, pyrrolidonyl, -N-(CH₃)₂, -N(CH₃)-COCH₃ (N-vinyl acetamide), -CH₂CH₂-COOH, -CH₂CH₂CH₂-COOH, -CH₂CH₂CH₂CH₂-COOH, -(CH₃)₂-CH₂-SO₃H, -(CH₃)₂-CH₂-CO₂H, -CH₂CH₂CH₂-⁺N(CH₃)₂-CH₂CH₂CH₂-SO₃⁻, -CH₂CH₂CH₂-⁺N(CH₃)₂-CH₂CH₂-CO₂⁻, -CH₂CH₂CH₂-⁺N(CH₃)₂, and combinations thereof. In another embodiment V is selected from -N-(CH₃)₂.

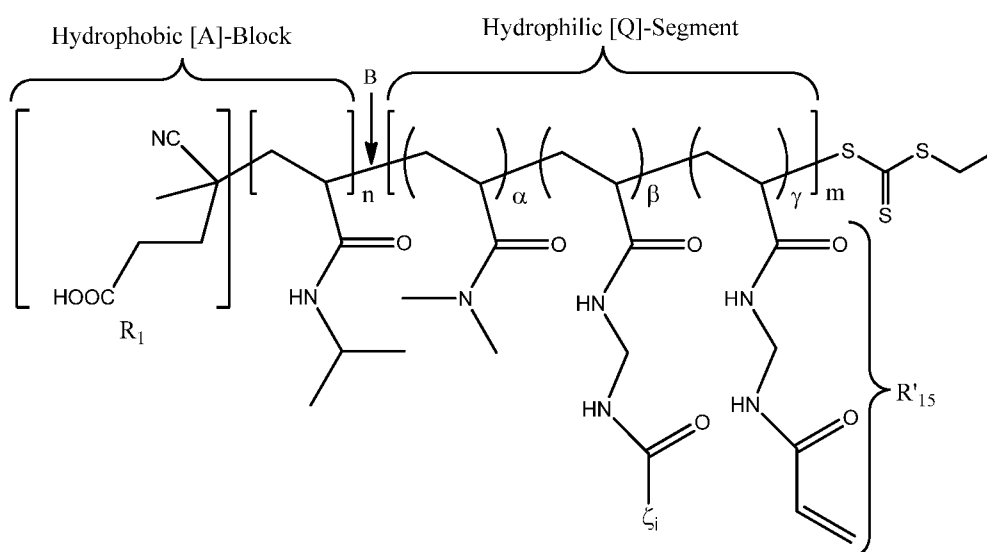
In one embodiment, the substituents R₂ through R₅ are the same. In another embodiment R₂ through R₅ are the same and are selected from methyl, ethyl or phenyl. In yet another embodiment R₂ through R₅ are the same and are selected from methyl or ethyl. In yet another embodiment each of R₂ through R₅ is methyl.

[0085] Examples of stable block copolymers are shown below in Formula VIII with substituents R₁, X and R₆ identified by brackets.

Formula XIII

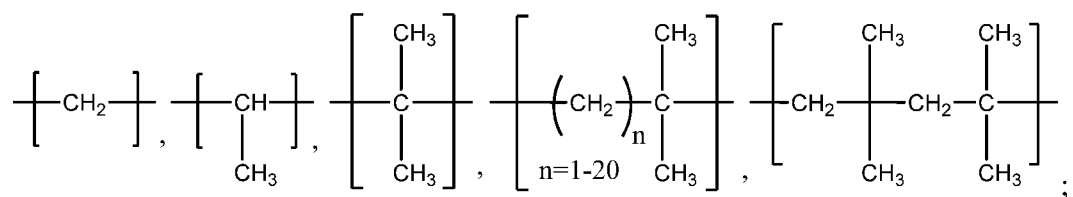


Formula XIIIa

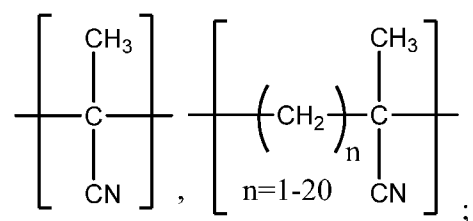


[0086] In another embodiment X is selected from ethylenyl or $-O(C=O)-$, with ethylenyl being preferred due to its hydrolytic stability.

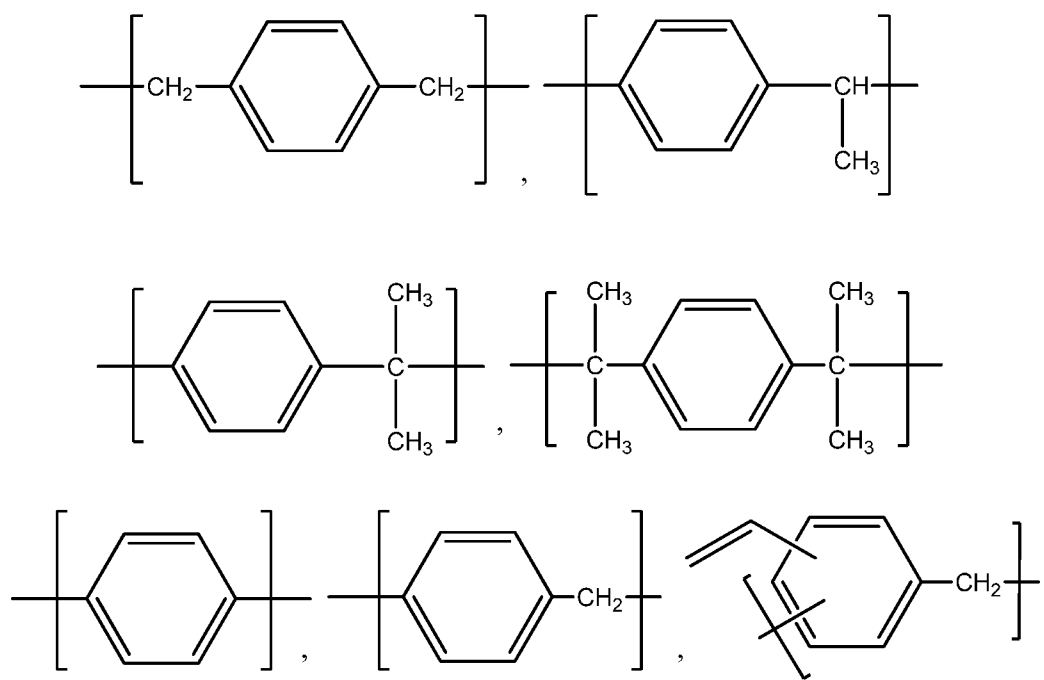
[0087] In another embodiment R_6 is an alkylene selected from:



[0088] a nitriloalkyl selected from:

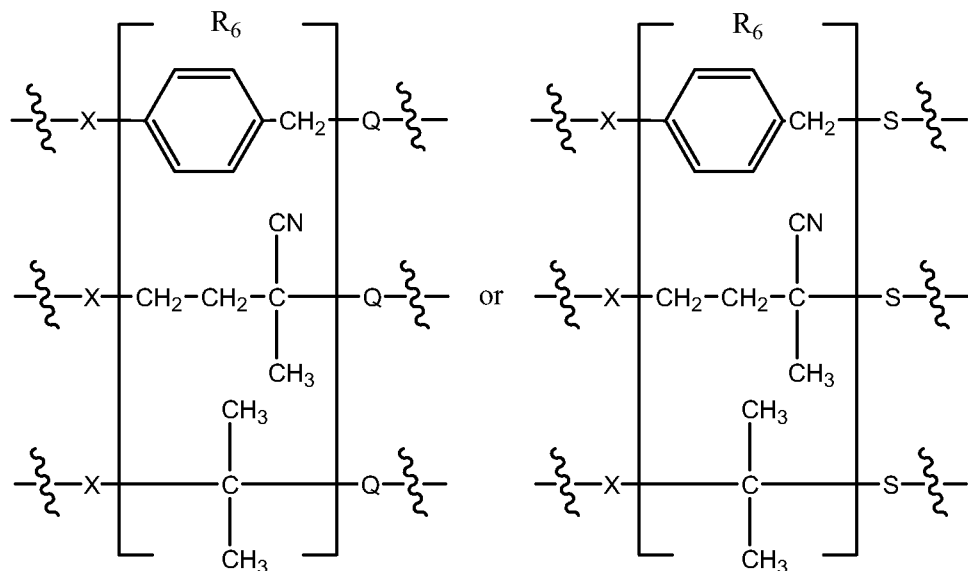


[0089] Or an aromatic group selected from:



[0090] The selection of R₆ will be influenced by the thiocarbonyl compound selected and the monomer(s) used for polymerization in the next step.

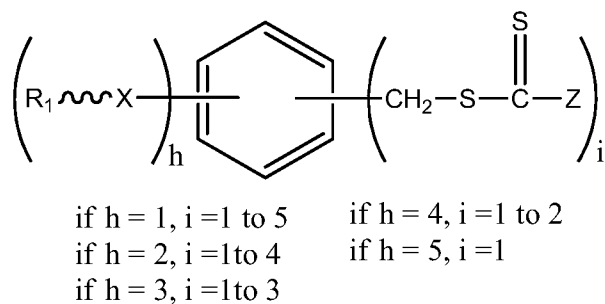
[0091] In one embodiment, R_6 is selected from the following structures, wherein Q and X are as defined above:



Formula IX

Structures of R_6 polysiloxane-functional RAFT agent (right) final copolymer (left)

[0092] In one embodiment where R_6 is p-valent it may be comprised of the following structure:



[0093] Wherein R_1 and X are as defined above and Z is selected from optionally substituted alkoxy, optionally substituted alkylthio, optionally substituted aryl, or optionally substituted benzyl. In one embodiment Z is an optionally substituted alkylthio, and in another embodiment Z is an optionally substituted alkoxy.

[0094] It should be appreciated that the substitutions described above may be combined in any combination. For example, the foregoing description includes families of

compounds having three separately defined substituent families for Z. Any of these substituent families may be combined with the substituent families disclosed for the other substituents.

[0095] The hydrophilic segment of the block copolymer generally has a degree of polymerization in the range of about 10 to about 10,000. In some embodiments, the degree of polymerization is at least about 100, or at least about 300, or even in others at least about 500. In further embodiments, the hydrophilic segment of the block copolymer has a degree of polymerization within the following ranges: about 300 to about 10,000, about 300 to about 5,000, between about 500 to about 10,000, about 500 to about 5,000 and about 500 to about 2000 and about 700 to about 2000. Degree of polymerization may be obtained from MALDI-TOF, SEC-MALLS, NMR or a combination thereof.

[0096] The hydrophilic segment, Q, for each ζ -primary chain is cross-linked or semi-cross-linked. That is, unlike previously disclosed art having only linear, branched, or combed structures, the hydrophilic segment is randomly cross-linked via covalent, ionic, or hydrogen-bonds along the block copolymer that form the hydrophilic segments. Cross-linking agents have one or more reactive or associative functionalities to react with and/or associate the amphiphilic copolymers of the present invention to one another via their hydrophilic segments. Exemplary covalent cross-linking agents include: *N,N'*-methylenebis(meth)acrylamide; *N,N'*-ethylenebis(meth)acrylamide; *N,N'*-propylenebis(meth)acrylamide; *N,N'*-butylenebis(meth)acrylamide; *N,N'*-pentamethylenebis(meth)acrylamide; *N,N'*-hexamethylenebis(meth)acrylamide; all other *N,N'*-alkylenebis(meth)acrylamides; all polyalkyleneglycoldi(meth)acrylates, including, but not limited to ethylene glycol di(meth)acrylate, triethylene glycol di(meth)acrylate, tetra-ethylene glycol di(meth)acrylate; and all polyalkyleneglycoldi(meth)acrylamides, including, but not limited to *N,N'*-(oxybis(ethane-2,1-diyl))diacrylamide *N,N'*-(((oxybis(ethane-2,1-diyl))bis(oxy))bis(ethane-2,1-diyl))diacrylamide, triallyl cyanurate (TAC), 1,3-divinylimidazolidin-2-one and 3,3''alkylenebis(1-vinylpyrrolidin-2-one), wherein the alkylene has 1-12 carbons.

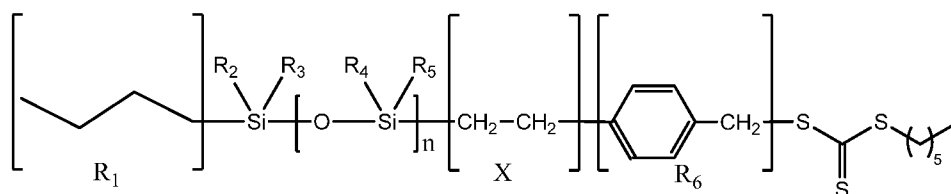
[0097] Cross-linking agents which have functionality along the backbone which can be reversibly broken or cleaved can also be used. For example, *N,N'*-cystamine di(meth)acrylamide may be used as a crosslinker. After the semi-crosslinked block copolymer is associated with the substrate, the disulfide bond in cystamine may be cleaved and reformed to create an interpenetrating network which is more intimately entangled in the substrate matrix.

[0098] The molar ratio of RAFT agent to cross-linking agent in the cross-linking reaction mixture is greater than about 0.1, greater than about 0.2, greater than about 0.3, greater than about 0.5, greater than about 0.75, greater than about 1, greater than about 2, greater than about 5 and in some cases greater than about 10. In one embodiment the cross-linking agent is free of silicone and the RAFT agent to cross-linking agent in the cross-linking reaction mixture is greater than about 0.1. In embodiments where the cross-linking agent comprises siloxane, the RAFT agent to cross-linking agent in the cross-linking reaction mixture is greater than about 0.3. A molar ratio of the molar amount of cross-linking agent to theoretical primary chains (“XL:ζ-PC”) in the cross-linking reaction mixture can be between 0.01:1.0 and 6.0:1.0, with the following non-limiting values of XL:ζ-PC being preferred: 0.1:1.0, 0.2:1.0, 0.25:1.0, 0.3:1.0, 0.4:1.0, 0.5:1.0, 0.55:1.0, 0.6:1.0, 0.7:1.0, 0.75:1.0, 0.8:1.0, 0.9:1.0, 1.0:1.0, 1.2:1.0, 1.25:1.0, 1.5:1.0, 3.0:1.0, 5.0:1.0, 7.0:1.0, or even 10.0:1.0. In some embodiments it may be desirable to select XL:ζ-PC values which provide soluble block copolymers across a wide range of temperatures and solution conditions, to allow for ready incorporation into a range of articles and solutions. For example, block copolymers comprising PDMA (poly(*N,N*-dimethyl acrylamide)) as the hydrophilic segment and a silicone segment, may desirably have an XL:ζ-PC of less than about 1.25:1 to prevent macroscopic gelling of the polymer. In other embodiments it may be desirable to select XL:ζ-PC values which provide the desired decrease in lipid uptake of the treated substrate, with increasing XL:ζ-PC values, decreasing the lipid uptake levels.

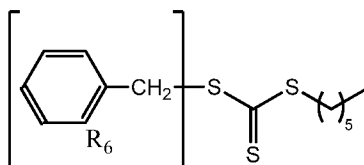
[0099] Those of skill in the art will appreciate that the number of primary chains formed in a controlled radical polymerization (CRP) system is dictated by the concentration of a controlled radical polymerization (CRP) agent or control agent. In the case of a RAFT polymerization, the control agent would be a thiocarbonylthio functional control agent. In the case of ATRP, the control agent would be a copper ligand complex. For the purposes of the invention disclosed herein, any CRP agent can be employed. In other embodiments, a CRP agent may not be required, so long as nanogel formation is possible, without macroscopic gellation.

[00100] In some embodiments of this invention, it may be desirable to change the number of associative chains per ζ-cluster, or average number of associative segments [A] per hydrophilic segment [Q], i.e. the [A]:[Q] ratio, to improve the solubility of the resulting cross-linked, ungelled, amphiphilic copolymer. This can be accomplished by using two CRP agents (i.e. an [A] segment comprising at least one CRP agent ([A]-CRP) and CRP agent that does not

contain an associative [A] segment) in the same polymerization to form the cross-linked ungelled associative block-copolymer. In one embodiment where RAFT polymerization is employed, Formula II and a silicone-free structural analogue (i.e. a CRP agent with no associative segment) are used together in the same polymerization, at a desired ratio, to yield a cross-linked, but ungelled amphiphilic copolymer with a reduced amount of silicone [A] segments per ζ -cluster or silicone [A] segments per hydrophilic [Q] segments. Formula X below details the structures for the RAFT-based CRP agents that might be used in such an embodiment to control the number of associative silicone [A] segments in each ζ -cluster.



Formula XA



Formula XB

[00101] To reduce the number of silicone [A] segments per hydrophilic [Q] segment for a given embodiment and thereby decrease the number of silicones per ζ -cluster to a desirable level, Formula XA and XB may be employed together in the formation of the final cross-linked, ungelled, block copolymers. It will be apparent to those skilled in the art that this results in the formation of ζ -clusters that contain both primary chains with substrate associative segments and primary chains without substrate associative segments. Taking into account the molar amounts of Formula XA and XB allows for the development of a theoretical term to quantify the number of substrate associative segments per hydrophilic [Q] segment, namely, the associative [A] segment to hydrophilic [Q] segment ([A]:[Q]) ratio. For embodiments where it is desirable to alter the [A]:[Q] ratio, target values in the range of 0.001:1 to 10:1 may be employed, with ranges of 0.01:1, 0.2:1, 0.25:1, 0.3:1, 0.4:1, 0.5:1, 0.55:1, 0.6:1, 0.7:1, 0.75:1, 0.8:1, 0.9:1 and even 0.99:1 being employed for embodiments where the amount of substrate associative [A] segments per hydrophilic [Q]-segment is to be reduced to below unity. For example, in

embodiments where the substrate associative [A] segment is a silicone, the amount of substrate associative silicone [A]-segments per hydrophilic [Q] segment is to be increased to above unity and ranges of 1.1:1, 1.5:1, 2.0:1.0, 3.0:1.0 or even 10.0:1.0 can be used; however, this would require a different silicone-functional RAFT agent than that proposed in Formula XA, i.e. a RAFT agent with multiple silicones would be required to exceed a [A]:[Q] ratio of 1.0. It should be apparent for those skilled in the art that a [A]:[Q] ratio of 1.0:1.0 can be reached using Formula XA above in the absence of Formula XB.

[00102] In one embodiment the hydrophilic [Q] segment may be formed from known hydrophilic monomers. Hydrophilic monomers are those which yield a clear single phase when mixed with water at 25°C at a concentration of 10 wt%. Examples of suitable families of hydrophilic monomers include vinyl amides, vinylimides, vinyl lactams, hydrophilic (meth)acrylates, (meth)acrylamides, styrenics, vinyl ethers, vinyl carbonates, vinyl carbamates, vinyl ureas and mixtures thereof.

[00103] Examples of suitable hydrophilic monomers include *N*-vinyl pyrrolidone, *N*-vinyl-2- piperidone, *N*-vinyl-2-caprolactam, *N*-vinyl-3-methyl-2- caprolactam, *N*-vinyl-3-methyl-2-piperidone, *N*-vinyl-4-methyl-2- piperidone, *N*-vinyl-4-methyl-2-caprolactam, *N*-vinyl-3-ethyl-2- pyrrolidone, *N*-vinyl-4,5-dimethyl-2-pyrrolidone, vinylimidazole, *N,N*-dimethylacrylamide, acrylamide, *N,N*-bis(2-hydroxyethyl)acrylamide, acrylonitrile, *N*-isopropyl acrylamide, vinyl acetate, (meth)acrylic acid, polyethylene glycol (meth)acrylates, 2-ethyl oxazoline, *N*-(2-hydroxypropyl) (meth)acrylamide, *N*-(2-hydroxyethyl) (meth)acrylamide, 2-methacryloyloxyethyl phosphorylcholine, 3-(dimethyl(4-vinylbenzyl)ammonio)propane-1-sulfonate (DMVBAPS), 3-((3-acrylamidopropyl)dimethylammonio)propane-1-sulfonate (AMPDAPS), 3-((3-methacrylamidopropyl)dimethylammonio)propane-1-sulfonate (MAMPDAPS), 3-((3-(acryloyloxy)propyl)dimethylammonio)propane-1-sulfonate (APDAPS), methacryloyloxy)propyl)dimethylammonio)propane-1-sulfonate (MAPDAPS), *N,N*-dimethylaminopropyl(meth)acrylamide, *N*-vinyl-*N*-methylacetamide, *N*-vinylacetamide, *N*-vinyl-*N*-methylpropionamide, *N*-vinyl-*N*-methyl-2-methylpropionamide, *N*-vinyl-2-methylpropionamide, *N*-vinyl-*N,N'*-dimethylurea, and the like, and mixtures thereof. In one embodiment the hydrophilic monomer comprises *N*-vinyl pyrrolidone, *N*-vinyl-*N*-methylacetamide, 2-methacryloyloxyethyl phosphorylcholine, (meth)acrylic acid, *N,N*-dimethylacrylamide, *N*-hydroxypropyl methacrylamide, mono-glycerol methacrylate, 2-

hydroxyethyl acrylamide, bishydroxyethyl acrylamide, and 2,3-dihydroxypropyl (meth)acrylamide and the like and mixtures thereof. In some embodiments the hydrophilic segment may also comprise charged monomers including but not limited to methacrylic acid, acrylic acid, 3-acrylamidopropionic acid (ACA1), 4-acrylamidobutanoic acid, 5-acrylamidopentanoic acid (ACA2), 3-acrylamido-3-methylbutanoic acid (AMBA), *N*-vinylloxycarbonyl- α -alanine, *N*-vinylloxycarbonyl- β -alanine (VINAL), 2-vinyl-4,4-dimethyl-2-oxazolin-5-one (VDMO), reactive sulfonate salts, including, sodium-2-(acrylamido)-2-methylpropane sulphonate (AMPS), 3-sulphopropyl (meth)acrylate potassium salt, 3-sulphopropyl (meth)acrylate sodium salt, bis 3-sulphopropyl itaconate di sodium, bis 3-sulphopropyl itaconate di potassium, vinyl sulphonate sodium salt, vinyl sulphonate salt, styrene sulfonate, sulfoethyl methacrylate, combinations thereof and the like. In embodiments where the hydrophilic segment comprises at least one charged hydrophilic monomer it may be desirable to include non-charged hydrophilic monomers as comonomers in the hydrophilic segment. In another embodiment the charged hydrophilic monomer is randomly distributed throughout the [Q] segment.

[00104] The degree of polymerization (DP) ratio of hydrophilic segments to linear substrate associative segments is between about 1:1 and about 1000:1, in other embodiments, with ratios between about 3:1 and about 200:1, between about 10:1 and about 100:1, and in other embodiments, between about 10:1 and 50:1.

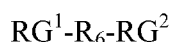
[00105] The block copolymers may be formed via a number of polymerization processes. In one embodiment the block copolymers are formed using RAFT polymerization. In other embodiments the block copolymers are formed using ATRP. While in another embodiment, the block copolymers are formed using TERP. Still yet, in some embodiments the block copolymers are formed using any known controlled radical polymerization mechanism. In another embodiment the block copolymers are formed by conventional free radical polymerization.

[00106] In one embodiment, that can be referred to as a hydrophilic-hydrophilic block copolymer or even as a biomimetic hydrophilic-hydrophilic block copolymer, a hydrophilic-hydrophilic block copolymer contains one hydrophilic block that has no affinity for the lens (i.e. a "non-associative" [Q] segment) and another hydrophilic block that has a high affinity (i.e. an "associative" [A] segment) for chemical moieties found on the surface and/or within the bulk of the lens. In one embodiment of the invention, the cross-linking of said block copolymers to each

other occurs along the backbone of the non-associative hydrophilic blocks, leaving the associative hydrophilic segments available for attachment to the surface of an article or device. Exemplary embodiments of such associative hydrophilic-hydrophilic block copolymers could include, poly(4-acrylamidobutanoic acid-block-*N,N*-dimethylacrylamide) (poly(ACAH-b-DMA)), poly((3-acrylamidophenyl)boronic acid-block-*N,N*-dimethylacrylamide) (poly(APBA-b-DMA)), and poly(3-((3-methacrylamidopropyl)dimethylammonio)propane-1-sulfonate-block-*N*-(2-hydroxypropyl)methacrylamide) (poly(MAMPDAPS-b-HPMA)), and poly(3-((3-acrylamidopropyl)dimethylammonio)propane-1-sulfonate-block-*N,N*-dimethylacrylamide) (poly(AMPDAPS-b-DMA)). Embodiments can be used to treat conventional or silicone hydrogel materials, provided the affinity of the associative blocks is tailored to the surface of the lens or device being treated. The non-associative hydrophilic block copolymers with appropriate functionality and architecture can closely mimic the behavior of bound mucins found on corneal epithelial surfaces and could be very useful in modifying the surface of a contact lens medical device to improve its lubricity, deposit uptake, and possibly comfort. Without intending to be bound by theory, it is speculated that the cross-linked nature of the non-associative hydrophilic segments could closely mimic the mucin-mucin interactions that occur through disulfide cross-linking, H-bonding, and molecular entanglement.

Polysiloxane RAFT Agent

[00107] The polysiloxane RAFT agents of Formula II may be formed by reacting at least one reactive silicone with at least one reactive group on an orthogonally reactive compound. In a subsequent or concurrent reaction, a reactive, thiocarbonylthio nucleophile is reacted with at least one other reactive group on the orthogonally reactive compound. Orthogonally reactive compounds comprise at least two reactive groups having different reactivities or reaction mechanisms such that reaction at one group can proceed to completion or near completion without reaction of at least one of the other reactive groups. Orthogonally reactive compounds have the structure:

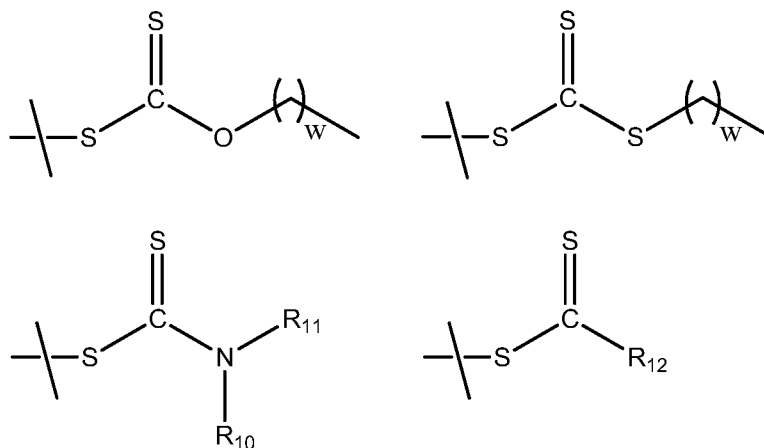


[00108] wherein R_6 is a free radical leaving group as defined above, and RG^1 and RG^2 are independently selected from paired orthogonally reactive groups such as, but not limited to, acid

halides and alkyl halides, activated esters and alkyl halides, alkyl halides and unsaturated double-bonds, and mixtures thereof and the like. Examples of alkyl halides include C₁₋₂₀ bromides, C₁₋₂₀ chlorides and C₁₋₂₀ iodides, and more specifically methyl bromide, ethyl bromide, methyl chloride, ethyl chloride, methyl iodide, ethyl iodide, benzyl bromide, benzyl chloride, or benzyl iodide.

[00109] Examples of acid halides include acetyl chloride, acetyl bromide, acetyl iodide, benzyl chloride, benzyl bromide, benzyl iodide, propionyl chloride, propionyl bromide, and propionyl iodide. Examples of unsaturated double-bonds include vinylic and allylic-double bonds. Examples of activated esters include *N*-hydroxysuccinimidyl-, *para*-nitrophenolic-, and perfluorinated phenolic carbonyl esters. Specific examples of orthogonally reactive compounds include, but are not limited to, the following: *para*-chloromethylstyrene, 4-(bromomethyl)benzoyl bromide (4-BBB), 2-bromopropanoyl bromide, and 2-bromoacetyl bromide, and combinations thereof and the like. Other combinations will be apparent to those of skill in the art.

[00110] Suitable thiocarbonylthio moieties can include xanthate esters, dithioesters, dithiocarbamates, trithiocarbonates, and the like. Specific and preferred thiocarbonylthio functional groups are shown below in the following structures:



[00111] where *w* is an integer from 1-12, R₁₀, R₁₁, and R₁₂ can be any optionally substituted alkyl or aryl group, and in some embodiments an alkyl or aryl optionally substituted with an amino group. In one embodiment, R₁₀ is C₁-C₆ alkyl (with C₁ being most preferred) and R₁₁ is a phenyl group, or a heterocyclic group. In other embodiments, R₁₀ is a C₁₋₆ alkyl and

R₁₁ is a carbon-linked aromatic heterocycle (e.g. 4-pyridinyl). In other embodiments, R₁₂ is a phenyl or benzyl, with phenyl being preferred.

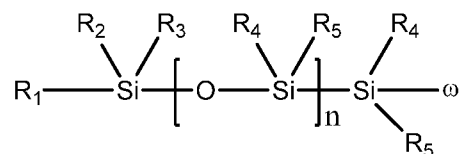
[00112] In one embodiment, the polymerization agent is at least one thiocarbonylthio-containing compound, and in one embodiment, at least one xanthate. In another embodiment, the thiocarbonylthio-containing compound is a dithiocarbamate. In another embodiment, at least one trithiocarbonate is employed. Yet, in another embodiment, a dithioester is employed.

[00113] Examples of suitable reactive thiocarbonylthio nucleophiles include, but are not limited to *O*-alkyl-xanthogenate salts, *N*-alkyl-carbamodithioate salts, *S*-alkyl-trithiocarbonate salts, *N*-alkyl-carbamodithioate salts, and phenyl, benzyl, or alkyl dithioate salts. Preferred thiocarbonylthio nucleophiles include *O*-alkyl-xanthogenate salts and *S*-alkyl-trithiocarbonate salts. Specific examples include Group I and II Alkali Metal salts of dipotassium trithiocarbonate, *O*-ethyl carbonodithioate, *O*-propyl carbonodithioate, *O*-butyl carbonodithioate, *O*-pentyl carbonodithioate, *O*-hexyl carbonodithioate, *O*-decyl carbonodithioate, *O*-dodecyl carbonodithioate, *O*-(2,3-dihydroxypropyl) carbonodithioate, ethyl carbonotrithioate, propyl carbonotrithioate, butyl carbonotrithioate, pentyl carbonotrithioate, hexyl carbonotrithioate, decyl carbonotrithioate, dodecyl carbonotrithioate, 2,3-dihydroxypropyl carbonotrithioate, methyl(phenyl)carbamodithioate, methyl(pyridin-4-yl)carbamodithioate, benzodithioate, and 2-phenylethanedithioate.

[00114] The reaction of the orthogonally reactive compound and the thiocarbonylthio nucleophile form a chain transfer agent which is bound to the substrate associative [A] segment. For illustrative purposes, the invention will be described using the reactive, linear polysiloxane for the substrate associative [A] segment. The order of these reactions is not always critical and the components may be reacted in the order described above, together in one pot, or the thiocarbonylthio nucleophile and the orthogonal reactive component may be pre-reacted to form a chain transfer agent which may then be reacted with the reactive, linear polysiloxane.

[00115] When R₁ is monovalent, the reactive linear polysiloxane is terminated on one end by R₁ (as defined above) and on the other by a group capable of reacting with at least one of the orthogonally reactive groups RG¹ and RG². For example when at least one of RG¹ or RG² is a vinyl, the polysiloxane reactive group may be a silane. In another example where at least one RG¹ or RG² is an activated ester, the polysiloxane reactive group may be a nucleophilic moiety such as a primary alcohol or amine, which may be selected from aminopropyl or hydroxypropyl.

The polysiloxane may be selected from C₁-C₄ polyalkyl and polyaryl siloxanes. Examples of suitable polysiloxanes include polydimethylsiloxane, polydiethylsiloxane, polydiphenylsiloxanes and copolymers thereof. The reactive linear polysiloxane may be selected from compounds of the formula:

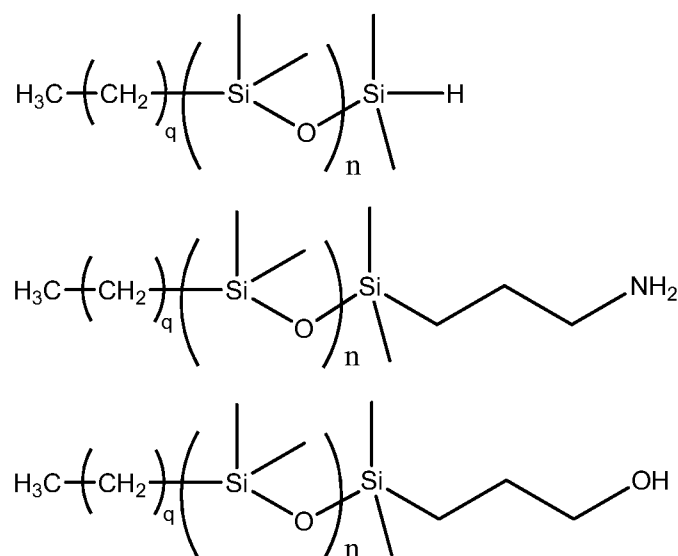


Formula XI

[00116] Wherein R₁ through R₅ are defined as above, and n is about 6-about 200, about 6-about 60, about 6-about 50, about 6-about 20, about 6-about 15, about 6-about 12 and in some embodiments about 10-about 12 siloxane repeating units. For example, it will be appreciated that in some embodiments *n* may represent a range. For example reactive linear polysiloxane where *n* is 10 may contain polysiloxanes, and in some embodiments polydialkyl siloxanes, and in another embodiment, polydimethylsiloxanes having repeating units ranging from 8 to 12, centered around 10. In some embodiments R₁ is a C₁₋₄ alkyl group and R₂ through R₅ are methyl. In another embodiment R₁ is selected from methyl, ethyl, propyl, or butyl.

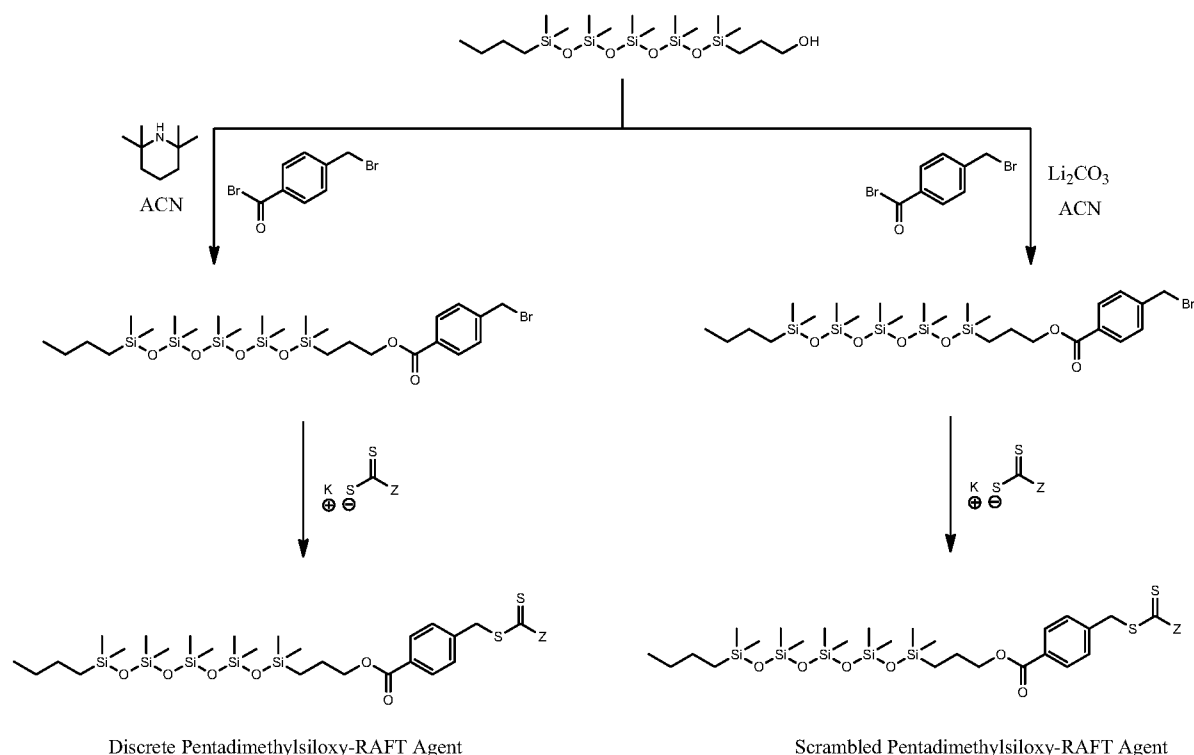
[00117] ω is independently selected from H, unsubstituted C₁₋₁₂ alkyl, C₁₋₁₂ alkyl substituted with hydroxyl, amino and the like, and in some embodiments, ω is selected from unsubstituted C₁₋₄ alkyl, C₁₋₄ alkyl substituted with hydroxyl, amino and the like and combinations thereof.

[00118] Specific examples of reactive linear polysiloxanes include



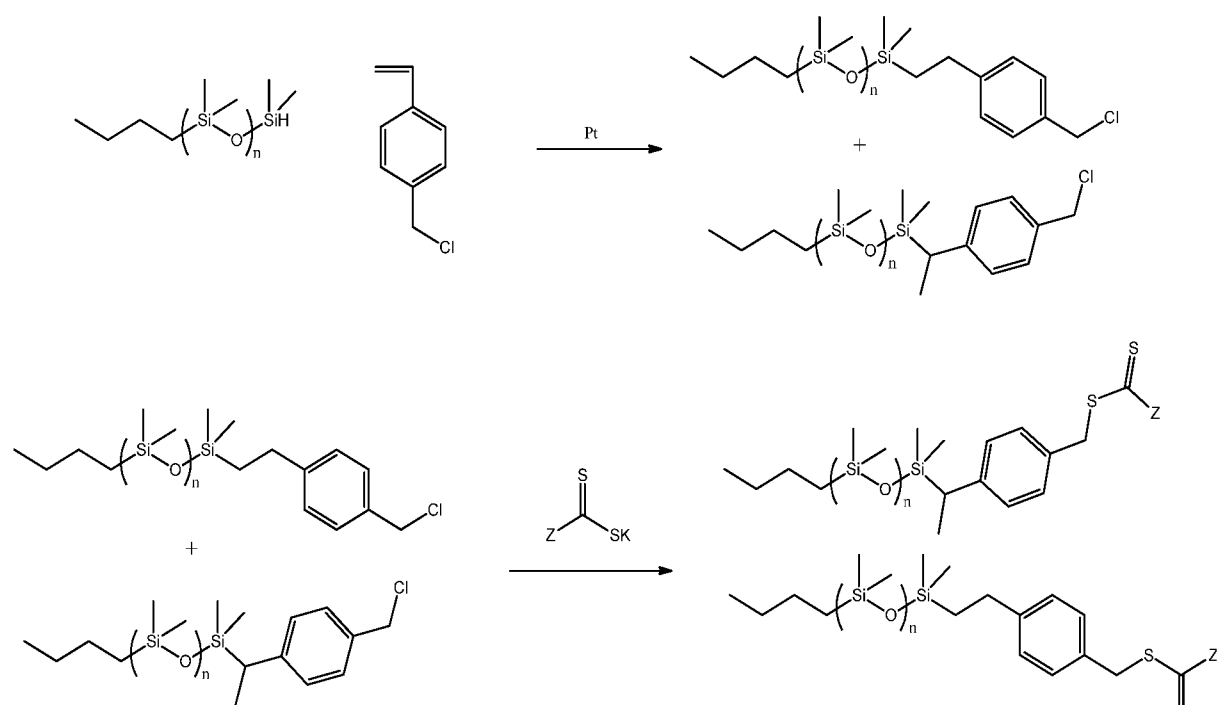
[00119] In one embodiment q is 0 to 9, 0 to 5, and in some embodiments 0- 3, and in some embodiments 0 or 3.

[00120] When the polysiloxane-functional RAFT agent is prepared via esterification or amidation with an orthogonally reactive compound containing both an acid halide and an alkyl halide (e.g. 4-BBB), the reaction may be conducted in the presence of at least one acid scavenger. This is depicted in Reaction Scheme I, below. Acid scavengers include carbonate salts, such as Na_2CO_3 or Li_2CO_3 , tertiary amines, such as triethylamine (TEA), or a non-nucleophilic hindered secondary amine, such as 2,2,6,6-tetramethylpiperidine (TMP). To prevent uncontrolled scrambling of the polysiloxane during the reaction, TMP is preferred over carbonate salts. Also, in some embodiments, TMP is preferred over TEA due to its low reactivity with alkyl halides and acid halides. Sterically-hindered tertiary amines, such as ethyl-di(2-methylpropyl)amine, may also be used, so long as their reactivity with alkyl and acid halides is very low.



Reaction Scheme I

[00121] When the polysiloxane-functional RAFT agent is prepared via hydrosilylation chemistry with an orthogonally reactive compound containing a reactive double bond and an alkyl halide (e.g. 1-(chloromethyl)-4-vinylbenzene), the reaction is conducted in the presence of a Pt catalyst, such as Karstedt's Catalyst. This reaction pathway, shown below in Reaction Scheme II, is preferred to esterification or amidiation, due to the fact that the number of required reaction steps is lower and the scrambling of the polysiloxane is mitigated. Furthermore, the final product of this reaction pathway yields a more hydrolytically stable linkage (i.e. X) between R_6 and the polydialkylsiloxane chain. In the final RAFT polymer, this yields a pure carbon-containing divalent linkage between the polydialkylsiloxane segment and the polymer.



Reaction Scheme II

[00122] The number of polydialkylsiloxane groups and thiocarbonylthio-moieties that are reacted with the orthogonally-reactive compound depends upon the nature of the reactive silicone, the nature and number of the specific functional groups on the orthogonally-reactive component, and the reactive nature of the thiocarbonylthio nucleophile used to form the final compound of interest, namely the polydialkylsiloxane-functional RAFT agent. For example, if a hydroxypropyl-terminal n-butylpolydimethylsiloxane is reacted with 4-(bromomethyl)benzoyl bromide (4-BBB) in the presence of TMP (see Reaction Scheme I), one skilled in the art would expect to observe ester formation between the hydroxypropyl-terminal n-butyl polydimethylsiloxane and the acid bromide of 4-BBB. One would not expect a thiocarbonylthio nucleophilic salt to react with the acid chloride on 4-BBB; but instead, displacement of the acid bromide on the 4-BBB by said thiocarbonylthio nucleophilic salt would be anticipated. If an orthogonally-reactive compound containing one acid halide and two alkyl halides was employed instead of 4-BBB, e.g. 3,5-bis(bromomethyl)benzoyl bromide, one would expect to obtain a polydialkylsiloxane-functional RAFT agent containing two separate, but covalently attached, thiocarbonylthio moieties. When polymerized in the presence of a hydrophilic monomer, this

specific polysiloxane-functional RAFT agent would yield a polymeric structure containing a single polysiloxane segment at one end of the chain and two hydrophilic segments at the opposite end. Analogous synthetic pathways that employ above-mentioned hydrosilylation chemistry and lead to structures with two or more hydrophilic segments and one linear silicone segment, or structures with two or more linear silicone segments and one hydrophilic segment would be understood by those skilled in the art to be suitable.

[00123] The reaction may be conducted at temperatures ranging from 0° C to about 100° C. In one embodiment the reaction is conducted at about ambient temperature. The reaction may be conducted for times from about 1 min to about 24 hours, and in some embodiments from about 1 hour to about 3 hours. The product of the reaction is a polysiloxane RAFT agent or silicone-functional [A]-CRP agent.

[00124] The reaction may be conducted neat or in at least one polar aprotic solvent which is capable of dissolving the functional polysiloxane, thiocarbonyl compound and the orthogonally reactive compound and the intermediates formed by their reaction. Suitable solvents include acetonitrile, acetone, DMF, NMP and combinations thereof and the like.

[00125] In one embodiment the polydimethylsiloxane RAFT agent is contacted with an appropriately selected monomer, a free radical initiating species (i.e. a free radical initiator such as CGI-819 or AIBN), and optionally, a solvent that is capable of solvating all reactants and products used in and resulting from the reaction, respectively. Reaction times for this step are from about 1 minute to about 12 hours and in some embodiments from about 1 to about 6 hours. Reaction temperatures include those between about 0° C and about 150° C.

Polymerization Conditions

[00126] The number average molecular weight of each ζ -primary chain, $M_{n_{\zeta-PC}}$, in a given polymerization produced from contacting a polysiloxane-functional RAFT agent or associative [A]-CRP agent, and a non-silicone-functional RAFT agent (when required), with at least one hydrophilic monomer, free radical initiator, and cross-linking agent can be targeted using the following equation:

$$M_{n_{\zeta-PC}} = M_{n_M} + M_{n_{XL}} + \varepsilon + \phi$$

where

$$M_{n_M} = \frac{[M]}{([CTA_{Silicone}] + [CTA_{Std}])} \cdot X \cdot MW_{monomer} \quad M_{n_{XL}} = \frac{[XL]}{([CTA_{Silicone}] + [CTA_{Std}])} \cdot \frac{X}{\psi} \cdot MW_{XL}$$

$$\varepsilon = \frac{[CTA_{Silicone}]}{([CTA_{Silicone}] + [CTA_{Std}])} \cdot MW_{CTA_{Silicone}} \quad \phi = \frac{[CTA_{Std}]}{([CTA_{Silicone}] + [CTA_{Std}])} \cdot MW_{CTA_{Std}}$$

[00127] M_{n_M} , $M_{n_{XL}}$, ε , and ϕ represent the individual contributions of molecular weight for the monomer, cross-linker, silicone-functional RAFT agent, and non-silicone-functional RAFT agent that (when summed) are equal to the number average molecular weight of a ζ -primary chain, i.e. $M_{n_{\zeta-PC}}$. ψ is the number of reactive functional groups on the crosslinker, $[M]$ is the reactive monomer concentration, $[XL]$ is the cross-linker concentration, X is the extent of conversion in fractional form, $[CTA_{Silicone}]$ is the concentration of silicone-functional RAFT agent, $[CTA_{Std}]$ is the concentration of non-silicone RAFT agent, if used, and $MW_{monomer}$, MW_{XL} , $MW_{CTA_{Silicone}}$, and $MW_{CTA_{Std}}$ are the molecular weights of reactive monomer, cross-linker, silicone-functional RAFT agent, and non-silicone RAFT agent, respectively.

[00128] Rearrangement of the equation gives the predicted degree of polymerization (DP) for the hydrophilic polymer segment, $DP_{Q-Segment}$, at a given monomer conversion. If X is unity (i.e. the polymerization reaches 100 % conversion), and $MW_{CTA_{Silicone}}$ and $MW_{CTA_{Std}}$ are neglected in the calculation because they are not part of the Q-segment, the equation reduces to an expression that predicts the target number average DP for the hydrophilic Q-segment, $DP_{n_{Q-Segment}}$, within a single ζ -primary chain that would be obtained for a given polymerization that reaches 100 % conversion:

$$M_{n_{Q-Segment}} = M_{n_M} + M_{n_{XL}}$$

Solving for $DP_{n_{Q-Segment}}$ gives:

$$DP_{n_{Q-segment}} = \frac{M_{n_M}}{MW_M} + \frac{M_{n_{XL}}}{\frac{MW_{XL}}{\psi}} = DP_{n_M} + \frac{DP_{n_{XL}}}{\psi}$$

$$DP_{n_{Q-segment}} = \frac{[M]}{([CTA_{Silicone}] + [CTA_{Std}])} + \frac{[XL]}{([CTA_{Silicone}] + [CTA_{Std}])} \cdot \frac{1}{\psi}$$

Equation 2.

[00129] It should be apparent to those of skill in the art that while these equations do predict the number average molecular weight of a ζ -primary chain, $M_{n\zeta-PC}$, and the number average degree of polymerization of the hydrophilic [Q] segment, namely, $DP_{nQ-Segment}$, it does not predict the total DP or overall average molecular weight of the ζ -cluster, which is formed due to the participation of the cross-linker in the RAFT polymerization and the fact that ζ -primary chains become randomly cross-linked to each other and to other growing ζ -clusters.. The MW of a given ζ -cluster is much higher than that of an individual ζ -primary chain found within that ζ -cluster and may or may not be an exact multiple of the average $M_{n\zeta-PC}$ for a given polymerization.

[00130] One target $DP_{nQ-Segment}$ is in the range of about 10 to 10,000, with 50 to 1500 being preferred, 50 to 1000 being preferred, and 50-500 being most preferred.

[00131] Polymerization conditions for the polymerization of the hydrophilic monomer in the presence of the appropriate polydialkylsiloxane RAFT agent and cross-linking agent to form the block copolymer are selected based upon the initiator system used and to provide the desired balance between chain growth and termination. Other polymerization components, such as solvents, initiator and additives may also be selected such that they have a low transfer constant toward the propagating radical. and are fully miscible with all other polymerization components

[00132] The cross-linker may be added to the polymerization solution at the beginning of the reaction or withheld until a later point in the reaction to manipulate the architecture of the resulting nanogel material in a way that gives a desired structure or property. Alternatively, the reactive groups on the cross-linker may be selected such that incorporation into the propagating polymer backbones is less random and thus forms polymeric nanogels that have a less evenly distributed cross-link density. If a polymeric nanogel with more “blocky” incorporation of the cross-linker is desired, a crosslinker with a different reactivity to that of the propagating mono-vinyl monomer may be used. For example, a dimethacrylated cross-linker may be employed in the formation of a nanogel with an acrylamido, mono-vinyl monomer. For some embodiments that exploit CRP, this would result in a “tapered” incorporation of the cross-linker into the Q-segment backbone, i.e. one end of each Q-segment would be richer in divinyl monomer than the other. Alternatively, for embodiments where a random distribution of the cross-linker throughout the Q segment is desired, the cross-linker may be selected so that both of its reactive sites have

similar reactivities (or identical functional groups) to that of the propagating mono-vinyl monomer. In some embodiments, cross-linkers containing functional groups with different reactivities, e.g. 2-(acryloyloxy)ethyl methacrylate or *N*-(2-acrylamidoethyl)methacrylamide, may be employed. Those skilled in the art would expect such structures to also incorporate across each Q-segment in a less-random fashion to that of an analogous system which contains matched reactivities for all reactive functional groups.

[00133] In embodiments where the block copolymer is made via RAFT, the initiating system is chosen such that under the reaction conditions there is no substantial adverse interaction of the initiator or the initiating radicals with the transfer agent. The initiator should also have the requisite solubility in the reaction medium or monomer mixture. The initiator is selected based upon the hydrophilic monomer selected. For example, where free radical reactive hydrophilic monomers are used, the initiator may be any initiator capable of providing a radical source, such as photoinitiators, thermal initiators, redox initiators and gamma initiators. Suitable photoinitiators include the UV and visible photoinitiators described below. Thermal initiators are chosen to have an appropriate half life at the temperature of polymerization. These initiators can include one or more of the following compounds: 2,2'-azobis(isobutyronitrile), 2,2'-azobis(2-cyano-2-butane), dimethyl 2,2'-azobisdimethylisobutyrate 4,4'-azobis(4-cyanopentanoic acid), 1,1'-azobis(cyclohexanecarbonitrile, 2-(*t*-butylazo)-2-cyanopropane, 2,2'-azobis[2-methyl-*N*-(1,1)-bis(hydroxymethyl)-2-hydroxyethyl] propionamide, 2,2'-azobis[2-methyl-*N*-hydroxyethyl]-propionamide, 2,2'-azobis(*N,N'*-dimethyleneisobutyramidine) dihydrochloride, 2,2'-azobis (2-amidinopropane)dihydrochloride, 2,2'-azobis(*N,N'*-dimethyleneisobutyramine), 2,2'-azobis(2-methyl-*N*-[1,1-bis(hydroxymethyl)-2-hydroxyethyl] propionamide), 2,2'-azobis(2-methyl-*N*-[1,1-bis(hydroxymethyl)ethyl] propionamide), 2,2'-azobis[2-methyl-*N*-(2-hydroxyethyl) propionamide], 2,2'-azobis(isobutyramide)dihydrate, 2,2'-azobis(2,2,4-trimethylpentane), 2,2'-azobis(2-methylpropane), *t*-butyl peroxyacetate, *t*-butyl peroxybenzoate, *t*-butyl peroxyoctoate, *t*-butyl peroxyneodecanoate, *t*-butylperoxy isobutyrate, *t*-amyl peroxy pivalate, *t*-butyl peroxy pivalate, di-isopropyl peroxydicarbonate, dicyclohexyl peroxydicarbonate, dicumyl peroxide, dibenzoyl peroxide, dilauroyl peroxide, potassium peroxydisulfate, ammonium peroxydisulfate, di-*t*-butyl hyponitrite, dicumyl hyponitrite. In one embodiment, the thermal initiator is selected from initiators that generate free radicals at

moderately elevated temperatures, such as lauryl peroxide, benzoyl peroxide, isopropyl percarbonate, azobisisobutyronitrile combinations thereof, and the like.

[00134] Examples of redox initiators include combinations of the following oxidants and reductants:

[00135] oxidants: potassium peroxydisulfate, hydrogen peroxide, t-butyl hydroperoxide.

[00136] reductants: iron (II), titanium (III), potassium thiosulfite, potassium bisulfate.

[00137] In one embodiment, the initiator is selected from photoinitiators which have the requisite solubility in the reaction medium or monomer mixture and have an appropriate quantum yield for radical production under the conditions of the polymerization. Examples include benzoin derivatives, benzophenone, acyl phosphine oxides, and photo-redox systems. In another embodiment the initiator is selected from visible initiators selected from 1-hydroxycyclohexyl phenyl ketone, 2-hydroxy-2-methyl-1-phenyl-propan-1-one, bis(2,6-dimethoxybenzoyl)-2,4,4-trimethylpentyl phosphine oxide (DMBAPO), bis(2,4,6-trimethylbenzoyl)-phenyl phosphineoxide (Irgacure 819), 2,4,6-trimethylbenzoyldiphenyl phosphine oxide and 2,4,6-trimethylbenzoyl diphenylphosphine oxide, benzoin methyl ester and a combination of camphorquinone and ethyl 4-(N,N-dimethylamino)benzoate, combinations thereof and the like. In another embodiment the initiator comprises at least one phosphine oxide containing photoinitiator, and in another embodiment, bis(2,4,6-trimethylbenzoyl)-phenyl phosphineoxide. When a photoinitiator is used, the reaction mixture is irradiated using radiation in the activating wavelength for the selected photoinitiator.

[00138] The polymerization may be conducted in solution, suspension or emulsion, under batch, continuous or feed mode. In one embodiment the process is conducted by adding polymerization agent to the reaction mixture containing the polysiloxane terminated chain transfer agent. Other conditions may be used and are known in the art.

Block Copolymer

[00139] The block copolymers provided herein may be purified via known means such as solvent precipitation and/or subsequent solvent extractions or by dialysis or related purification techniques such as, but not limited to tangential flow filtration (TFF).

[00140] The block copolymers provided herein have at least one terminal substrate associative chain and, in some embodiments where RAFT polymerization is used and where the RAFT agent is not removed prior to use, a RAFT polymerization agent at the terminal end.

[00141] Frequently the RAFT polymerization agents are not thermally or hydrolytically stable, and thus it is a benefit of embodiments of the present invention that the RAFT polymerization agents are at the terminal end as they may be readily cleaved or replaced prior to incorporation into the polymer substrates. Prior to their end-use, the block copolymers may be isolated and employed in a subsequent “chain-extension” polymerization with an additional suitable monomer. Alternatively, the RAFT polymerization agent may be left on the block copolymer and either cleaved during incorporation into the polymer substrate or during use (if the RAFT and/or its degradants are non-toxic, non-irritating). In one embodiment the RAFT polymerization agent is removed prior to incorporating the block copolymers into the substrates, or the solutions to be contacted with the substrates. Suitable processes for removing the end groups include, but are not limited to reaction with amines, such as disclosed in US7109276, US6794486, US7807755, US2007232783, US2010137548, US5385996, and US5874511. Other end-group removal techniques, such as thermolysis or radical reduction, may be employed in some embodiments as well.

[00142] In one embodiment, the block copolymers have the structure represented in Formula I, above.

In another embodiment, the block copolymers may be formed using conventional free radical reactions. In this embodiment the block copolymers may be formed by the free radical reaction of at least one hydrophilic monomer and an azo-type macro initiator with a hydrophobic segment having a molecular weight between about 300 and about 1800 via processes disclosed in US2010/0099829 and co-filed application USSN 61/482,260.

Hydrophobic or Partially Hydrophobic Substrates

[00143] The block copolymers disclosed herein may be non-covalently associated with a variety of hydrophobic, partially hydrophobic, hydrophilic, or amphiphilic substrates, such as polymeric articles formed from polysiloxanes, silicone hydrogels, conventional hydrogels, polymethyl methacrylate, polyethylene, polypropylene, polycarbonate, polyethylene terephthalate, polytetrafluoroethylene, glass, metal and mixtures and copolymers thereof and the like. The

association occurs, provided there is sufficient affinity between the functional groups contained within the [A] block of the block copolymer and those found on or within a given substrate. Examples of substrates which may be treated to associate the block copolymers of the present invention therewith include polymers and metals used for implantable devices, sutures, graft substrates, punctal plugs, catheters, stents, wound dressings, surgical instruments, ophthalmic devices and the like.

[00144] Additional examples of at least partially hydrophobic polymer matrices include highly crosslinked ultra high molecular weight polyethylene (UHMWPE), which is used for implantable devices, such as joint replacements, are made typically has a molecular weight of at least about 400,000, and in some embodiments from about 1,000,000 to about 10,000,000 as defined by a melt index (ASTM D-1238) of essentially 0 and reduced specific gravity of greater than 8 and in some embodiments between about 25 and 30.

[00145] Absorbable polymers suitable for use as yarns in making sutures and wound dressings include but are not limited to aliphatic polyesters which include but are not limited to homopolymers and copolymers of lactide (which includes lactic acid d-,l-and meso lactide), glycolide (including glycolic acid), ϵ -caprolactone, p-dioxanone (1,4-dioxan-2-one), trimethylene carbonate (1,3-dioxan-2-one), alkyl derivatives of trimethylene carbonate, δ -valerolactone, β -butyrolactone, γ -butyrolactone, ϵ -decalactone, hydroxybutyrate, hydroxyvalerate, 1,4-dioxepan-2-one (including its dimer 1,5,8,12-tetraoxacyclotetradecane-7,14-dione), 1,5-dioxepan-2-one, 6,6-dimethyl-1,4-dioxan-2-one and polymer blends thereof.

[00146] Non-absorbable polymer materials such as but are not limited to, polyamides (polyhexamethylene adipamide (nylon 66), polyhexamethylene sebacamide (nylon 610), polycapramide (nylon 6), polydodecanamide (nylon 12) and polyhexamethylene isophthalamide (nylon 61) copolymers and blends thereof), polyesters (e.g. polyethylene terephthalate, polybutyl terephthalate, copolymers and blends thereof), fluoropolymers (e.g. polytetrafluoroethylene and polyvinylidene fluoride) polyolefins (e.g. polypropylene including isotactic and syndiotactic polypropylene and blends thereof, as well as, blends composed predominately of isotactic or syndiotactic polypropylene blended with heterotactic polypropylene (such as are described in U.S. Patent 4,557,264 issued December 10, 1985 assigned to Ethicon, Inc. hereby incorporated by reference) and polyethylene (such as is described in U.S. Patent 4,557,264 issued December 10, 1985 assigned to Ethicon, Inc. and combinations thereof).

[00147] The body of the punctal plugs may be made of any suitable biocompatible polymer including, without limitation, silicone, silicone blends, silicone co-polymers, such as, for example, hydrophilic monomers of pHEMA (polyhydroxyethylmethacrylate), polyethylene glycol, polyvinylpyrrolidone, and glycerol. Other suitable biocompatible materials include, for example fluorinated polymers, such as, for example, polytetrafluoroethylene ("PTFE"), polyvinylidene fluoride ("PVDF"), and teflon; polypropylene; polyethylene; nylon; and ethylene vinyl alcohol ("EVA").

[00148] Polymeric parts of ultrasonic surgical instruments may be made from polyimides, fluora ethylene propene (FEP Teflon), PTFE Teflon, silicone rubber, EPDM rubber, any of which may be filled with materials such as Teflon or graphite or unfilled. Examples are disclosed in US20050192610 and US 6458142. For these embodiments, the block copolymer may be mixed with a solvent that swells the at least partially hydrophobic polymer matrix and then contacted with the polymer matrix.

[00149] In one embodiment, the block copolymers are associated with preformed articles including silicone ophthalmic devices such as lenses or punctal plugs, silicone hydrogel articles, such as silicone hydrogel lenses. In this embodiment it is believed that the terminal polysiloxane associates with the substrate which comprises hydrophobic polymer components. In this embodiment, the block copolymer is dissolved in a solvent which also swells the substrate. The polymer substrate is contacted with a solution comprising the block copolymer. When the substrate is a silicone hydrogel article, such as a contact lens, suitable solvents include packing solution, storing solution and cleaning solutions. Using this embodiment as an example, the silicone hydrogel lens is placed in a packing solution comprising the block copolymer. The block copolymer is present in the solution in amounts between about 0.001 and about 10%, in some embodiments between about 0.005 and about 2% and in other embodiments between about 0.01 and about 0.5 weight %, based upon all components in the solution.

[00150] The packing solutions may be any water-based solution that is used for the storage of contact lenses. Typical solutions include, without limitation, saline solutions, other buffered solutions, and deionized water. The preferred aqueous solution is saline solution containing salts including, without limitation, sodium chloride, sodium borate, sodium phosphate, sodium hydrogenphosphate, sodium dihydrogenphosphate, or the corresponding potassium salts of the same. These ingredients are generally combined to form buffered

solutions that include an acid and its conjugate base, so that addition of acids and bases cause only a relatively small change in pH. The buffered solutions may additionally include 2-(N-morpholino)ethanesulfonic acid (MES), sodium hydroxide, 2,2-bis(hydroxymethyl)-2,2',2''-nitrilotriethanol, n-tris(hydroxymethyl)methyl-2-aminoethanesulfonic acid, citric acid, sodium citrate, sodium carbonate, sodium bicarbonate, acetic acid, sodium acetate, ethylenediamine tetraacetic acid and the like and combinations thereof. Preferably, the solution is a borate buffered or phosphate buffered saline solution. The solutions may also include known additional components such as viscosity adjusting agents, antimicrobial agents, wetting agents, anti-stick agents, preservatives, polyelectrolytes, stabilizers, chelants, antioxidants, combinations thereof and the like.

[00151] The block copolymer may also be associated with the lens using organic solvents (with or without water as a co-solvent). In one embodiment, an organic solvent is used to both swell the medical device, e.g. a contact lens medical device, and dissolve the block copolymer so that it may be imbibed. Suitable solvents may be selected to swell the medical device, to dissolve the block copolymer or both. In another embodiment the solvents may also be biocompatible so as to simplify manufacturing. The substrate is contacted with the block copolymer under conditions sufficient to incorporate a lubricious and surface-wetting effective amount of the block copolymer. As used herein, a lubricious effective amount, is an amount necessary to impart a level of lubricity which may be felt manually (such as by rubbing the device between one's fingers) or when the device is used. Additionally, as used herein, a surface-wetting effective amount is an amount necessary to impart a level of increased wettability to the lens, as determined via known contact angle measurement techniques (i.e. sessile drop, captive bubble, or dynamic contact angle measurements). It has been found that in one embodiment, where the device is a soft contact lens, amounts of block copolymer as little as 50 ppm provide improved lens "feel" and lowered surface contact angles, as measured by sessile drop. Amounts of block copolymer greater than about 50 ppm, and more preferably amounts greater than about 100 ppm in the processing packaging, storing or cleaning solution, add a more pronounced improvement in feel. Thus, in this embodiment, the block copolymer may included in a solution in concentrations up to about 50,000 ppm, in some embodiments between about 10 and 5000 ppm, and in some embodiments between about 10 and about 2000ppm. In one embodiment the solution comprising the block copolymer is free from visible haze (clear). The

packaged lens may be heat treated to increase the amount of block copolymer which permeates and becomes entangled in the lens. Suitable heat treatments, include, but are not limited to conventional heat sterilization cycles, which include temperatures of about 120°C for times of about 20 minutes and may be conducted in an autoclave. If heat sterilization is not used, the packaged lens may be separately heat treated. Suitable temperatures for separate heat treatment include at least about 40°C, and preferably between about 50°C and the boiling point of the solution. Suitable heat treatment times include at least about 10 minutes. It will be appreciated that higher temperatures will require less treatment time.

[00152] It is a benefit of the present invention that the step of associating the semi-crosslinked block copolymer with the desired substrate may be conducted in a single step without pretreatment, covalent reaction or tie layers. However, in some embodiments it may be desirable to contact the substrate/semi-crosslinked block copolymer construct with an additional polymer or nanogel to form a layered coating. The additional polymer may be linear, branched or crosslinked, and may have associating groups located at an end of the polymer, or throughout the polymer. Each additional polymer comprises groups which are capable of associating or reacting with groups contained in the polymer of the preceding layer. Thus, for substrates which were initially treated with a semi-crosslinked block copolymer comprising proton donating groups in the [Q] segment, the addition polymer would comprise, consist or consist essentially of proton receiving groups. Several alternating layers of WSC and additional polymer may be applied. Examples of polymers comprising proton receiving groups include but are not limited to poly-*N*-vinyl pyrrolidone, poly-*N*-vinyl-2-piperidone, poly-*N*-vinyl-2-caprolactam, poly-*N*-vinyl-3-methyl-2-caprolactam, poly-*N*-vinyl-3-methyl-2-piperidone, poly-*N*-vinyl-4-methyl-2-piperidone, poly-*N*-vinyl-4-methyl-2-caprolactam, poly-*N*-vinyl-3-ethyl-2-pyrrolidone, and poly-*N*-vinyl-4,5-dimethyl-2-pyrrolidone, polyvinylimidazole, poly-*N,N*-dimethylacrylamide, polyvinyl alcohol, polyethylene-oxide, poly-2-ethyl-oxazoline, heparin polysaccharides, polysaccharides, mixtures and copolymers (including block or random, branched, multichain, comb-shaped or star shaped) thereof, Polymers and copolymers of Poly-*N*-vinylpyrrolidone (PVP) and poly-*N,N*-dimethylacrylamide may be used.

[00153] The second solution may be any of the solutions described above for contacting the substrates with the semi-crosslinked block copolymer. The at least one second polymer may be present in the solution in concentrations up to about 50,000 ppm, between about 10 and 5000

ppm, or between about 10 and about 2000ppm. Because both polymers are non-ionic, the additional treating steps may be done at pH between about 6 and 8 and in some embodiments at about 7.

[00154] Many silicone hydrogel materials are known and may be used, including but not limited to senofilcon, galyfilcon, lotrafilcon A and lotrafilcon B, delefilcon, balafilcon, comfilcon, osmofilcon, enfilcon, filcon II, filcon IV and the like. Almost any silicone hydrogel polymer can be treated using the block copolymers provided herein, including but not limited to those disclosed in US6,637,929, WO03/022321, WO03/022322, US5,260,000, US5,034,461, US6,867,245, WO2008/061992, US 5,760,100, US7,553,880, US20100048847, US2006/0063852.

[00155] Similar processes may be used for substrates made from polymers other than silicone hydrogels. The primary change will be in the selection of the solvent, which should solubilize the polymer and swell the substrate. Mixtures of solvents maybe used, and additional components, such as surfactants may be included if desired. For example where the article is a silicone article such as a silicone contact lens or a silicone punctal plug, the block copolymer may be dissolved in a solvent such as aliphatic alcohols, water and mixtures thereof. Specific examples include isopropanol, n-propanol and the like, at the concentrations described above.

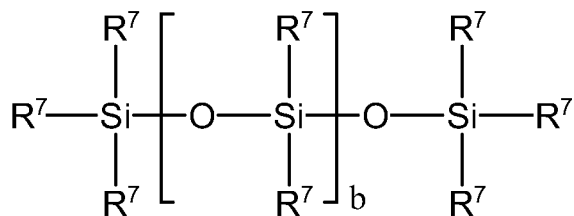
[00156] In another embodiment, the block copolymer may be included in the reaction mixture from which the polymeric article is made. In such an embodiment, effective amounts of block copolymer might include quantities from about 0.1 % to 50 % of the total weight of all lens components, with quantities from about 1 % to 20 % being more preferred, and quantities from about 2 % to 15 % being most preferred. For example, where the article is a silicone hydrogel contact lens, the block copolymer may be included, in amounts up to about 20 weight% in the contact lens reaction mixture with one or more silicone-containing components and one or more hydrophilic components. The silicone-containing components and hydrophilic components used to make the polymers disclosed herein can be any of the known components used in the prior art to make silicone hydrogels. These terms, specifically silicone-containing component and hydrophilic component, are not mutually exclusive, in that, the silicone-containing component can be somewhat hydrophilic and the hydrophilic component can comprise some silicone, because the silicone-containing component can have hydrophilic groups and the hydrophilic components can have silicone groups.

[00157] One advantage of the block copolymers disclosed herein is in embodiments where the block copolymer is formed by RAFT, the molecular weight (MW) and molecular weight distribution (MWD) may be readily controlled depending on the requirements of manufacture for the chosen article. For example, in one embodiment where the block copolymer is incorporated into a low viscosity reactive monomer mix, such as those used to form cast molded contact lenses, the MW of the block copolymer may be kept below about 100,000 g/mol. In one embodiment where controlled polymerization is used, the polydispersity of the ζ -primary chains is less than about 1.3. The ζ -cluster will have polydispersity values greater than 1.3. Having lower MW block copolymer allows addition of a higher concentration of the block copolymers according to embodiments of the present invention compared to commercially available polymers, such as PVP. Conventional polymers, such as PVP, have higher polydispersities, which can result in extremely viscous monomer mixes that tend to have processing issues due to stringiness.

[00158] The use of RAFT to prepare the nanogels of the present invention allows for the formation of nano-sized gels without the formation of macroscopically gelled polymer. In addition to this, such nanogels exhibit significantly lowered viscosities, when compared to the same linear polymers with equivalent molecular weights. As mentioned above, high molecular weight polymers with lower viscosities can be desirable for a variety of process applications, including minimizing the viscosity and “stringiness” of a given reactive monomer mix formulation.

[00159] A silicone-containing component is one that contains at least one [-Si-O-] group, in a monomer, macromer or prepolymer. In one embodiment, the Si and attached O are present in the silicone-containing component in an amount greater than 20 weight percent, and in another embodiment greater than 30 weight percent of the total molecular weight of the silicone-containing component. Useful silicone-containing components comprise polymerizable functional groups such as (meth)acrylate, (meth)acrylamide, N-vinyl lactam, N-vinylamide, and styryl functional groups. Examples of silicone-containing components which are useful may be found in U.S. Pat. Nos. 3,808,178; 4,120,570; 4,136,250; 4,153,641; 4,740,533; 5,034,461 5,760,100, 4,139,513, 5,998,498, US2006/0063852 and 5,070,215, and EP080539. All of the patents cited herein are hereby incorporated in their entireties by reference. These references disclose many examples of olefinic silicone-containing components.

[00160] Suitable silicone-containing components include compounds of the following formula:



Formula XII

[00161] where R^7 is independently selected from monovalent reactive groups, monovalent alkyl groups, or monovalent aryl groups, any of the foregoing which may further comprise functionality selected from hydroxy, amino, oxa, carboxy, alkyl carboxy, alkoxy, amido, carbamate, carbonate, halogen or combinations thereof; and monovalent siloxane chains comprising 1-100 Si-O repeat units which may further comprise functionality selected from alkyl, hydroxy, amino, oxa, carboxy, alkyl carboxy, alkoxy, amido, carbamate, halogen or combinations thereof;

[00162] where $b = 0$ to 500, where it is understood that when b is other than 0, b is a distribution having a mode equal to a stated value;

[00163] wherein at least one R^7 comprises a monovalent reactive group, and in some embodiments between one and 3 R^7 comprise monovalent reactive groups.

[00164] As used herein “monovalent reactive groups” are groups that can undergo free radical and/or cationic polymerization. Non-limiting examples of free radical reactive groups include (meth)acrylates, styryls, vinyls, vinyl ethers, substituted or unsubstituted C_{1-6} alkyl(meth)acrylates, (meth)acrylamides, C_{1-6} alkyl(meth)acrylamides, N-vinyl lactams, N-vinyl amides, C_{2-12} alkenyls, C_{2-12} alkenylphenyls, C_{2-12} alkenyl naphthyls, C_{2-6} alkenylphenyl C_{1-6} alkyls, O-vinyl carbamates and O-vinyl carbonates. Suitable substituents on said C_{1-6} alkyls include ethers, hydroxyls, carboxyls, halogens and combinations thereof. Non-limiting examples of cationic reactive groups include vinyl ethers or epoxide groups and mixtures thereof. In one embodiment the free radical reactive groups comprises (meth)acrylate, acryloxy, (meth)acrylamide, and mixtures thereof.

[00165] Suitable monovalent alkyl and aryl groups include unsubstituted monovalent C_1 to C_{16} alkyl groups, C_6 - C_{14} aryl groups, such as substituted and unsubstituted methyl, ethyl, propyl,

butyl, 2-hydroxypropyl, propoxypropyl, polyethyleneoxypropyl, combinations thereof and the like.

[00166] In one embodiment R^7 is selected from C_{1-6} alkyl(meth)acrylates, and C_{1-6} alkyl(meth)acrylamides, which may be unsubstituted or substituted with hydroxyl, alkylene ether or a combination thereof. In another embodiment R^7 is selected from propyl(meth)acrylates and propyl (meth)acrylamides, wherein said propyl may be optionally substituted with hydroxyl, alkylene ether or a combination thereof.

[00167] In one embodiment b is zero, one R^7 is a monovalent reactive group, and at least 3 R^7 are selected from monovalent alkyl groups having one to 16 carbon atoms, and in another embodiment from monovalent alkyl groups having one to 6 carbon atoms. Non-limiting examples of silicone components of this embodiment include 2-methyl-, 2-hydroxy-3-[3-[1,3,3,3-tetramethyl-1-[(trimethylsilyl)oxy]disiloxanyl]propoxy]propyl ester ("SiGMA"),

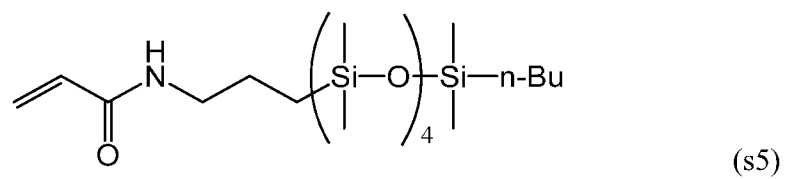
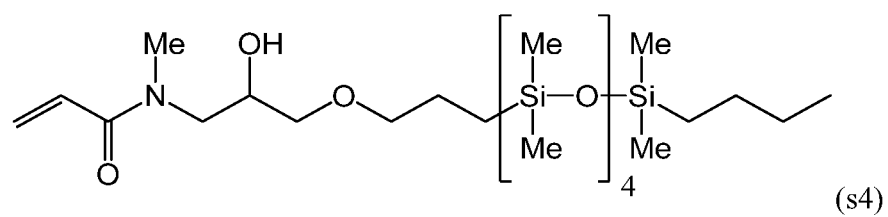
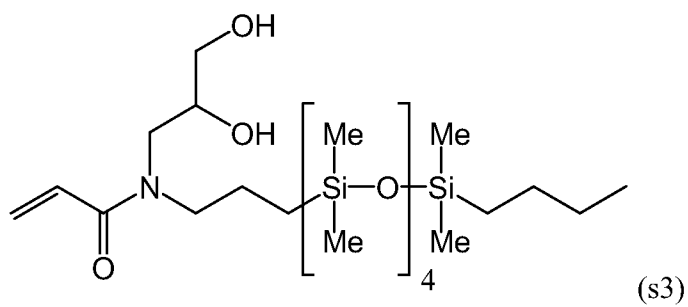
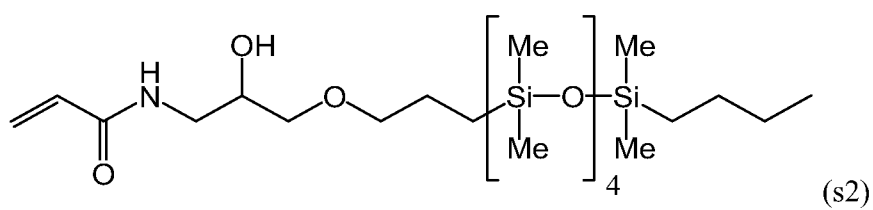
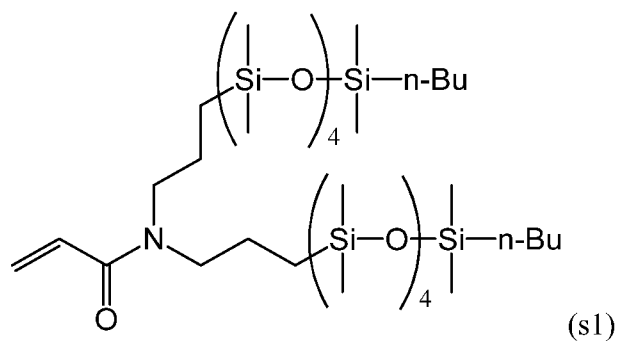
[00168] 2-hydroxy-3-methacryloxypropyloxypropyl-tris(trimethylsiloxy)silane,

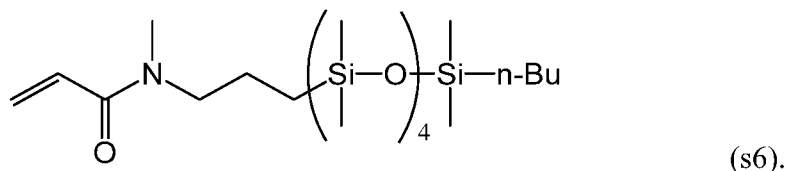
[00169] 3-methacryloxypropyltris(trimethylsiloxy)silane ("TRIS"),

[00170] 3-methacryloxypropylbis(trimethylsiloxy)methylsilane and

[00171] 3-methacryloxypropylpentamethyl disiloxane.

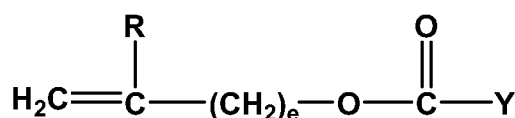
In another embodiment, b is 2 to 20, 3 to 15 or in some embodiments 3 to 10; at least one terminal R^7 comprises a monovalent reactive group and the remaining R^7 are selected from monovalent alkyl groups having 1 to 16 carbon atoms, and in another embodiment from monovalent alkyl groups having 1 to 6 carbon atoms. In yet another embodiment, b is 3 to 15, one terminal R^7 comprises a monovalent reactive group selected from substituted or unsubstituted C_{1-6} alkyl(meth)acrylates, substituted or unsubstituted C_{1-6} alkyl(meth)acrylamides, the other terminal R^7 comprises a monovalent alkyl group having 1 to 6 carbon atoms and the remaining R^7 comprise monovalent alkyl group having 1 to 3 carbon atoms. Non-limiting examples of silicone components of this embodiment include (mono-(2-hydroxy-3-methacryloxypropyl)-propyl ether terminated polydimethylsiloxane (400-1000 MW)) ("OH-mPDMS"), monomethacryloxypropyl terminated mono-n-butyl terminated polydimethylsiloxanes (800-1000 MW), ("mPDMS"), *N*-(2,3-dihydroxypropane)-*N'*-(propyl tetra(dimethylsiloxy) dimethylbutylsilane)acrylamide methacryamide silicones of the following formulae (s1) through (s6);





[00172] In another embodiment b is 5 to 400 or from 10 to 300, both terminal R^7 comprise monovalent reactive groups and the remaining R^7 are independently selected from monovalent alkyl groups having 1 to 18 carbon atoms which may have ether linkages between carbon atoms and may further comprise halogen.

[00173] In another embodiment, one to four R^7 comprises a vinyl carbonate or carbamate of the formula:

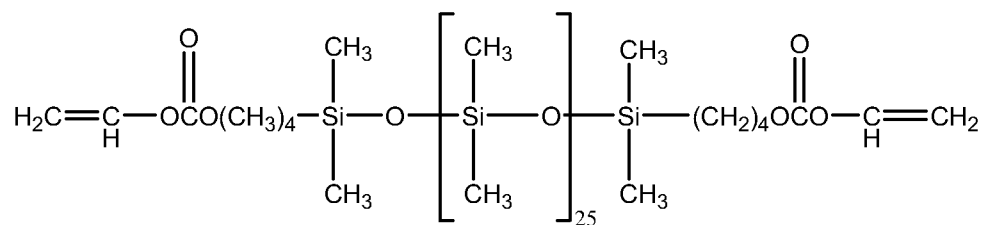


Formula XIII

[00174] wherein: Y denotes O-, S- or NH-;

[00175] R denotes hydrogen or methyl; and q is 0 or 1.

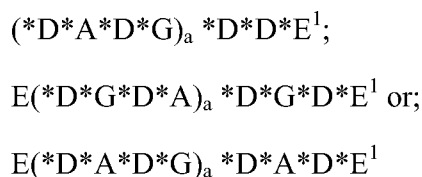
[00176] The silicone-containing vinyl carbonate or vinyl carbamate monomers specifically include: 1,3-bis[4-(vinylloxycarbonyloxy)but-1-yl]tetramethyl-disiloxane; 3-(vinylloxycarbonylthio) propyl-[tris (trimethylsiloxy)silane]; 3-[tris(trimethylsiloxy)silyl] propyl allyl carbamate; 3-[tris(trimethylsiloxy)silyl] propyl vinyl carbamate; trimethylsilylethyl vinyl carbonate; trimethylsilylmethyl vinyl carbonate, and



[00177] Where biomedical devices with modulus below about 200 are desired, only one R^7 shall comprise a monovalent reactive group and no more than two of the remaining R^7 groups will comprise monovalent siloxane groups.

[00178] In one embodiment, where a silicone hydrogel lens is desired, the lens will be made from a reaction mixture comprising at least about 20 weight % and in some embodiments between about 20 and 70%wt silicone-containing components based on total weight of reactive monomer components from which the polymer is made.

[00179] Another class of silicone-containing components includes polyurethane macromers of the following formulae:



Formulae XIV-XVI

[00180] wherein:

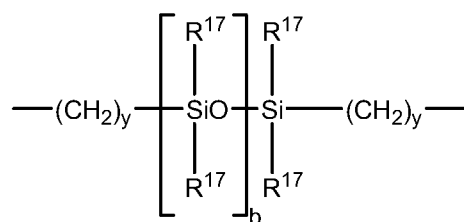
[00181] D denotes an alkyl diradical, an alkyl cycloalkyl diradical, a cycloalkyl diradical, an aryl diradical or an alkylaryl diradical having 6 to 30 carbon atoms,

[00182] G denotes an alkyl diradical, a cycloalkyl diradical, an alkyl cycloalkyl diradical, an aryl diradical or an alkylaryl diradical having 1 to 40 carbon atoms and which may contain ether, thio or amine linkages in the main chain;

[00183] * denotes a urethane or ureido linkage;

[00184] a is at least 1;

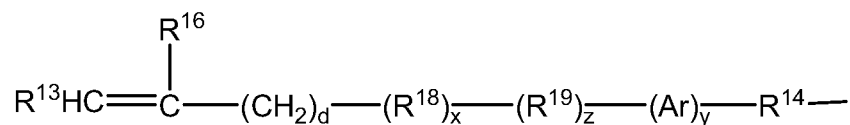
[00185] A denotes a divalent polymeric radical of formula:



Formula XVII

[00186] R^{17} independently denotes an alkyl or fluoro-substituted alkyl group having 1 to 10 carbon atoms which may contain ether linkages between carbon atoms; y is at least 1; and b

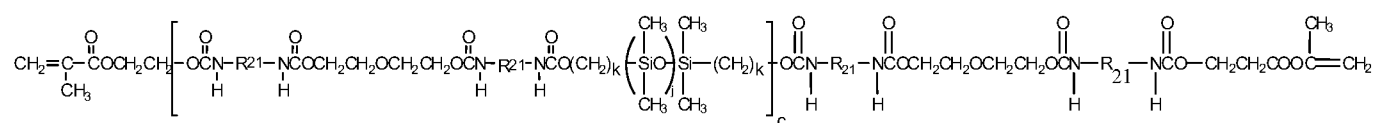
provides a moiety weight of 400 to 10,000; each of E and E¹ independently denotes a polymerizable unsaturated organic radical represented by formula:



Formula XVIII

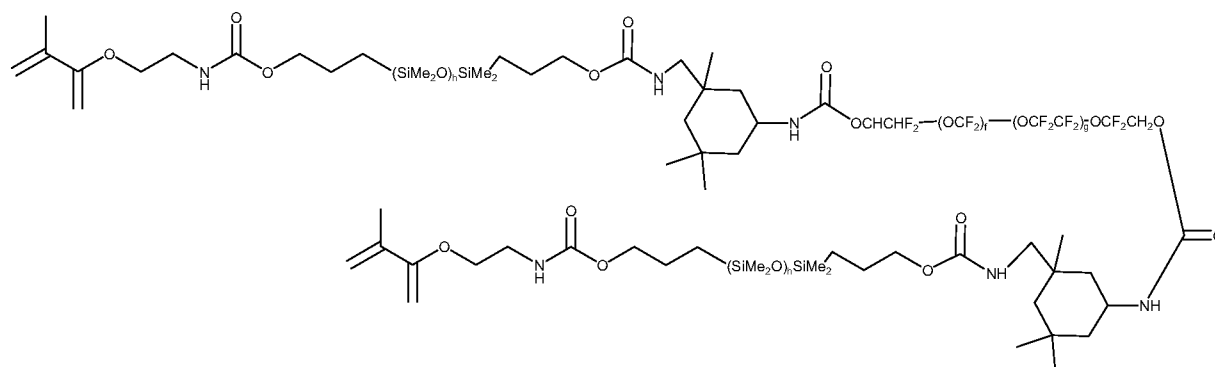
[00187] wherein: R¹⁶ is hydrogen or methyl; R¹³ is hydrogen, an alkyl radical having 1 to 6 carbon atoms, or a —CO—Y—R²⁰ radical wherein Y is —O—, —S— or —NH—; R²⁰ is a C₁₋₆ monovalent alkyl, and in some embodiments an unsubstituted C₁₋₃ alkyl; R¹⁴ is a divalent radical having 1 to 12 carbon atoms; R¹⁴ is a divalent radical having 1 to 12 carbon atoms; R¹⁸ denotes —CO— or —OCO—; R¹⁹ denotes —O— or —NH—; Ar denotes an aromatic radical having 6 to 30 carbon atoms; d is 0 to 6; x is 0 or 1; y is 0 or 1; and z is 0 or 1.

[00188] In one embodiment the silicone-containing component comprises a polyurethane macromer represented by the following formula:



Formula XIX

[00189] wherein R²¹ is a diradical of a diisocyanate after removal of the isocyanate group, such as the diradical of isophorone diisocyanate c is 1-5, k is 3-4 and j is 10-200 or 10-100. Another suitable silicone containing macromer is compound of formula XIX (in which f + g is a number in the range of 10 to 30 h is a number in the range of 20-30, 22-26 or 25) formed by the reaction of fluoroether, hydroxy-terminated polydimethylsiloxane, isophorone diisocyanate and isocyanatoethylmethacrylate.



Formula XX

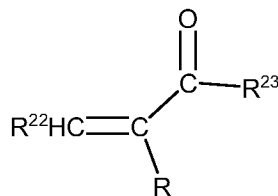
[00190] Other silicone-containing components suitable for use include those described in WO 96/31792 such as macromers containing polysiloxane, polyalkylene ether, diisocyanate, polyfluorinated hydrocarbon, polyfluorinated ether and polysaccharide groups. Another class of suitable silicone-containing components includes silicone containing macromers made via GTP, such as those disclosed in U.S. Pat. Nos. 5,314,960, 5,331,067, 5,244,981, 5,371,147 and 6,367,929. U.S. Pat. Nos. 5,321,108; 5,387,662 and 5,539,016 describe polysiloxanes with a polar fluorinated graft or side group having a hydrogen atom attached to a terminal difluoro-substituted carbon atom. US 2002/0016383 describe hydrophilic siloxanyl methacrylates containing ether and siloxanyl linkages and crosslinkable monomers containing polyether and polysiloxanyl groups. Any of the foregoing polysiloxanes can also be used as the silicone-containing component.

[00191] In one embodiment of the present invention where a modulus of less than about 120 psi is desired, the majority of the mass fraction of the silicone-containing components used in the lens formulation should contain only one polymerizable functional group (“monofunctional silicone containing component”). In this embodiment, to insure the desired balance of oxygen transmissibility and modulus it is preferred that all components having more than one polymerizable functional group (“multifunctional components”) make up no more than 10 mmol/100 g of the reactive components, and preferably no more than 7 mmol/100 g of the reactive components.

[00192] In another embodiment, the reaction mixtures are substantially free of silicone containing components which contain trimethylsiloxy groups.

[00193] The silicone containing components may be present in amounts up to about 85 weight %, and in some embodiments between about 10 and about 80 and in other embodiments between about 20 and about 70 weight %, based upon all reactive components.

[00194] Hydrophilic components include those which are capable of providing at least about 20% and in some embodiments at least about 25% water content to the resulting lens when combined with the remaining reactive components. Suitable hydrophilic components include hydrophilic monomers, prepolymers and polymers and may be present in amounts between about 10 to about 60 weight % based upon the weight of all reactive components, in some embodiments about 15 to about 50 weight %, and in other embodiments between about 20 to about 40 weight %. The hydrophilic monomers that may be used to make the polymers have at least one polymerizable double bond and at least one hydrophilic functional group. Examples of polymerizable double bonds include acrylic, methacrylic, acrylamido, methacrylamido, fumaric, maleic, styryl, isopropenylphenyl, *O*-vinylcarbonate, *O*-vinylcarbamate, allylic, *O*-vinylacetyl and *N*-vinyl lactam and *N*-vinylamido double bonds. Such hydrophilic monomers may themselves be used as crosslinking agents. “Acrylic-type” or “acrylic-containing” monomers are those monomers containing the acrylic group



Formula XXI

[00195] wherein R is H or CH₃, R²² is H, alkyl or carbonyl, and R²³ is O or N, which are also known to polymerize readily, such as *N,N*-dimethylacrylamide (DMA), 2-hydroxyethyl (meth)acrylate, glycerol methacrylate, 2-hydroxyethyl methacrylamide, polyethyleneglycol monomethacrylate, methacrylic acid, acrylic acid, mixtures thereof and the like.

[00196] Hydrophilic vinyl-containing monomers which may be incorporated into the hydrogels include monomers such as *N*-vinyl lactams (e.g. *N*-vinyl pyrrolidone (NVP), *N*-vinyl-2- piperidone, *N*-vinyl-2-caprolactam, *N*-vinyl-3-methyl-2- caprolactam, *N*-vinyl-3-methyl-2- piperidone, *N*-vinyl-4-methyl-2- piperidone, *N*-vinyl-4-methyl-2-caprolactam, *N*-vinyl-3-ethyl-2- pyrrolidone, *N*-vinyl-4,5-dimethyl-2-pyrrolidone); *N*-vinyl-*N*-methyl acetamide, *N*-vinyl-*N*-ethyl acetamide, *N*-vinyl-*N*-ethyl formamide, *N*-vinyl formamide, *N*-2-hydroxyethyl vinyl carbamate,

N-carboxy- β -alanine *N*-vinyl ester, vinylimidazole with NVP being preferred in one embodiment.

[00197] Additional hydrophilic monomers which may be used include acrylamide, *N,N*-bis(2-hydroxyethyl)acrylamide, acrylonitrile, *N*-isopropyl acrylamide, vinyl acetate, (meth)acrylic acid, polyethylene glycol (meth)acrylates, 2-ethyl oxazoline, *N*-(2-hydroxypropyl) (meth)acrylamide, *N*-(2-hydroxyethyl) (meth)acrylamide, 2-methacryloyloxyethyl phosphorylcholine, 3-(dimethyl(4-vinylbenzyl)ammonio)propane-1-sulfonate (DMVBAPS), 3-((3-acrylamidopropyl)dimethylammonio)propane-1-sulfonate (AMPDAPS), 3-((3-methacrylamidopropyl)dimethylammonio)propane-1-sulfonate (MAMPDAPS), 3-((3-acryloyloxy)propyl)dimethylammonio)propane-1-sulfonate (APDAPS), methacryloyloxy)propyl)dimethylammonio)propane-1-sulfonate (MAPDAPS), *N*-vinyl-*N*-methylacetamide, *N*-vinylacetamide, *N*-vinyl-*N*-methylpropionamide, *N*-vinyl-*N*-methyl-2-methylpropionamide, *N*-vinyl-2-methylpropionamide, *N*-vinyl-*N,N'*-dimethylurea, and the like, and mixtures thereof. In one embodiment suitable hydrophilic monomers comprise *N*-vinyl pyrrolidone, *N*-vinyl-*N*-methylacetamide, 2-methacryloyloxyethyl phosphorylcholine, (meth)acrylic acid, *N,N*-dimethylacrylamide, *N*-hydroxypropyl methacrylamide, mono-glycerol methacrylate, 2-hydroxyethyl acrylamide, bis(2-hydroxyethyl) acrylamide, and 2,3-dihydroxypropyl (meth)acrylamide and the like and mixtures thereof.

[00198] In some embodiments the hydrophilic monomers may also comprise charged monomers including but not limited to methacrylic acid, acrylic acid, 3-acrylamidopropionic acid (ACA1), 4-acrylamidobutanoic acid, 5-acrylamidopentanoic acid (ACA2), 3-acrylamido-3-methylbutanoic acid (AMBA), *N*-vinylloxycarbonyl- α -alanine, *N*-vinylloxycarbonyl- β -alanine (VINAL), 2-vinyl-4,4-dimethyl-2-oxazolin-5-one (VDMO), reactive sulfonate salts, including, sodium-2-(acrylamido)-2-methylpropane sulphonate (AMPS), 3-sulphopropyl (meth)acrylate potassium salt, 3-sulphopropyl (meth)acrylate sodium salt, bis 3- sulphopropyl itaconate di sodium, bis 3- sulphopropyl itaconate di potassium, vinyl sulphonate sodium salt, vinyl sulphonate salt, styrene sulfonate, sulfoethyl methacrylate, combinations thereof and the like.

[00199] Other hydrophilic monomers that can be employed include polyoxyethylene polyols having one or more of the terminal hydroxyl groups replaced with a functional group containing a polymerizable double bond. Examples include polyethylene glycol with one or more of the terminal hydroxyl groups replaced with a functional group containing a

polymerizable double bond. Examples include polyethylene glycol reacted with one or more molar equivalents of an end-capping group such as isocyanatoethyl methacrylate ("IEM"), methacrylic anhydride, methacryloyl chloride, vinylbenzoyl chloride, or the like, to produce a polyethylene polyol having one or more terminal polymerizable olefinic groups bonded to the polyethylene polyol through linking moieties such as carbamate or ester groups.

[00200] Still further examples are the hydrophilic vinyl carbonate or vinyl carbamate monomers disclosed in U.S. Pat. No. 5,070,215, and the hydrophilic oxazolone monomers disclosed in U.S. Pat. No. 4,190,277. Other suitable hydrophilic monomers will be apparent to one skilled in the art.

[00201] In one embodiment the hydrophilic monomers which may be incorporated into the polymers disclosed herein include hydrophilic monomers such as *N,N*-dimethyl acrylamide (DMA), 2-hydroxyethyl acrylate, glycerol methacrylate, 2-hydroxyethyl methacrylamide, *N*-vinylpyrrolidone (NVP), *N*-vinyl methacrylamide, HEMA, and polyethyleneglycol monomethacrylate.

[00202] In another embodiment the hydrophilic monomers include DMA, NVP, HEMA and mixtures thereof.

[00203] The reactive mixtures used to form substrates such as contact lenses may also comprise as hydrophilic components one or more polymeric wetting agents. As used herein, such polymeric wetting agents used in reaction mixtures refers to substances having a weight average molecular weight of no less than about 5,000 Daltons, wherein said substances upon incorporation to silicone hydrogel formulations, increase the wettability of the cured silicone hydrogels. In one embodiment the weight average molecular weight of these polymeric wetting agents is greater than about 30,000; in another between about 150,000 to about 2,000,000 Daltons, in yet another between about 300,000 to about 1,800,000 Daltons, and in yet another about 500,000 to about 1,500,000 Daltons.

[00204] Alternatively, the molecular weight of polymeric wetting agents can be also expressed by the K-value, based on kinematic viscosity measurements, as described in Encyclopedia of Polymer Science and Engineering, *N*-Vinyl Amide Polymers, Second edition, Vol. 17, pgs. 198-257, John Wiley & Sons Inc. When expressed in this manner, hydrophilic monomers having K-values of greater than about 46 and in one embodiment between about 46 and about 150. Suitable amounts of polymeric wetting agents in reaction mixtures include from

about 1 to about 20 weight percent, in some embodiments about 5 to about 20 percent, in other embodiments about 6 to about 17 percent, all based upon the total of all reactive components.

[00205] Examples of polymeric wetting agents include but are not limited to polyamides, polylactones, polyimides, polylactams and functionalized polyamides, polylactones, polyimides, polylactams, such as DMA functionalized by copolymerizing DMA with a lesser molar amount of a hydroxyl-functional monomer such as HEMA, and then reacting the hydroxyl groups of the resulting copolymer with materials containing radical polymerizable groups, such as isocyanatoethylmethacrylate or methacryloyl chloride. Polymeric wetting agents made from DMA or *N*-vinyl pyrrolidone with glycidyl methacrylate may also be used. The glycidyl methacrylate ring can be opened to give a diol which may be used in conjunction with other hydrophilic prepolymer in a mixed system to increase the compatibility of the component in the reactive mixture. In one embodiment the polymeric wetting agents contain at least one cyclic moiety in their backbone, such as but not limited to, a cyclic amide or cyclic imide. Polymeric wetting agents include but are not limited to poly-*N*-vinyl pyrrolidone, poly-*N*-vinyl-2-piperidone, poly-*N*-vinyl-2-caprolactam, poly-*N*-vinyl-3-methyl-2-caprolactam, poly-*N*-vinyl-3-methyl-2-piperidone, poly-*N*-vinyl-4-methyl-2-piperidone, poly-*N*-vinyl-4-methyl-2-caprolactam, poly-*N*-vinyl-3-ethyl-2-pyrrolidone, and poly-*N*-vinyl-4,5-dimethyl-2-pyrrolidone, polyvinylimidazole, poly-*N,N*-dimethylacrylamide, polyvinyl alcohol, polyacrylic acid, polyethylene-oxide, poly-2-ethyl-oxazoline, heparin polysaccharides, polysaccharides, mixtures and copolymers (including block or random, branched, multichain, comb-shaped or star shaped) thereof, where poly-*N*-vinylpyrrolidone (PVP) is particularly preferred in one embodiment. Copolymers might also be used such as graft copolymers of PVP.

[00206] The polymeric wetting agents used in reaction mixtures also provide improved wettability, and particularly improved in vivo wettability to the medical devices. Without being bound by any theory, it is believed that the polymeric wetting agents are hydrogen bond receivers which in aqueous environments, hydrogen bond to water, thus becoming effectively more hydrophilic. The absence of water facilitates the incorporation of the polymeric wetting agents in the reaction mixture. Aside from the specifically named polymeric wetting agents, it is expected that any polymer will be useful provided that when said polymer is added to a formulation, the polymer (a) does not substantially phase separate from the reaction mixture and

(b) imparts wettability to the resulting cured polymer network. In some embodiments it is preferred that the polymeric wetting agents be soluble in the diluent at reaction temperatures.

[00207] Compatibilizing agents may also be used. In some embodiments the compatibilizing component may be any functionalized silicone containing monomer, macromer or prepolymer which, when polymerized and/or formed into a final article is compatible with the selected hydrophilic components. The compatibility test disclosed in WO03/022321 may be used to select suitable compatibilizing agents. In some embodiments, a silicone monomer, prepolymer or macromer which also comprises hydroxyl groups is included in the reaction mixture. Examples include 3-methacryloxy-2-hydroxypropyloxy)propylbis(trimethylsiloxy)methylsilane, mono-(3-methacryloxy-2-hydroxypropyloxy)propyl terminated, mono-butyl terminated polydimethylsiloxane (MW 1100), hydroxyl functionalized silicone containing GTP macromers, hydroxyl functionalized macromers comprising polydimethyl siloxanes, combinations thereof and the like. In another embodiment, the polymeric wettings may be used as compatibilizing components.

[00208] The hydroxyl containing component may also act as a cross-linking agent during the formation of substrates such as contact lenses.

[00209] With respect to making substrates such as contact lenses, it is generally necessary to add one or more cross-linking agents, also referred to as cross-linking monomers, to the reaction mixture, such as ethylene glycol dimethacrylate ("EGDMA"), trimethylolpropane trimethacrylate ("TMPTMA"), glycerol trimethacrylate, polyethylene glycol dimethacrylate (wherein the polyethylene glycol preferably has a molecular weight up to, e.g., about 5000), and other poly(meth)acrylate esters, such as the end-capped polyoxyethylene polyols described above containing two or more terminal methacrylate moieties. The cross-linking agents are used in the usual amounts, e.g., from about 0.000415 to about 0.0156 mole per 100 grams of reactive components in the reaction mixture. Alternatively, if the hydrophilic monomers and/or the silicone containing monomers act as the cross-linking agent, the addition of a crosslinking agent to the reaction mixture is optional. Examples of hydrophilic monomers which can act as the crosslinking agent and when present do not require the addition of an additional crosslinking agent to the reaction mixture include polyoxyethylene polyols described above containing two or more terminal methacrylate moieties.

[00210] An example of a silicone containing monomer which can act as a crosslinking agent and, when present, does not require the addition of a crosslinking monomer to the reaction mixture includes α , ω -bismethacryloylpropyl polydimethylsiloxane.

[00211] The reaction mixture may contain additional components such as, but not limited to, UV absorbers, photochromic compounds, pharmaceutical and nutraceutical compounds, antimicrobial compounds, reactive tints, pigments, copolymerizable and nonpolymerizable dyes, release agents and combinations thereof.

[00212] Generally the reactive components are mixed in a diluent to form a reaction mixture. Suitable diluents are known in the art. For silicone hydrogels suitable diluents are disclosed in WO 03/022321, US6,020,445 the disclosure of which is incorporated herein by reference.

[00213] Classes of suitable diluents for silicone hydrogel reaction mixtures include alcohols having 2 to 20 carbons, amides having 10 to 20 carbon atoms derived from primary amines and carboxylic acids having 8 to 20 carbon atoms. In some embodiments primary and tertiary alcohols are preferred. Preferred classes include alcohols having 5 to 20 carbons and carboxylic acids having 10 to 20 carbon atoms.

[00214] Specific diluents which may be used include 1-ethoxy-2-propanol, diisopropylaminoethanol, isopropanol, 3,7-dimethyl-3-octanol, 1-decanol, 1-dodecanol, 1-octanol, 1-pentanol, 2-pentanol, 1-hexanol, 2-hexanol, 2-octanol, 3-methyl-3-pentanol, tert-amyl alcohol, tert-butanol, 2-butanol, 1-butanol, 2-methyl-2-pentanol, 2-propanol, 1-propanol, ethanol, 2-ethyl-1-butanol, (3-acetoxy-2-hydroxypropyloxy)propylbis(trimethylsiloxy) methylsilane, 1-tert-butoxy-2-propanol, 3,3-dimethyl-2-butanol, tert-butoxyethanol, 2-octyl-1-dodecanol, decanoic acid, octanoic acid, dodecanoic acid, 2-(diisopropylamino)ethanol mixtures thereof and the like.

[00215] Preferred diluents include 3,7-dimethyl-3-octanol, 1-dodecanol, 1-decanol, 1-octanol, 1-pentanol, 1-hexanol, 2-hexanol, 2-octanol, 3-methyl-3-pentanol, 2-pentanol, t-amyl alcohol, tert-butanol, 2-butanol, 1-butanol, 2-methyl-2-pentanol, 2-ethyl-1-butanol, ethanol, 3,3-dimethyl-2-butanol, 2-octyl-1-dodecanol, decanoic acid, octanoic acid, dodecanoic acid, mixtures thereof and the like.

[00216] More preferred diluents include 3,7-dimethyl-3-octanol, 1-dodecanol, 1-decanol, 1-octanol, 1-pentanol, 1-hexanol, 2-hexanol, 2-octanol, 1-dodecanol, 3-methyl-3-pentanol, 1-

pentanol, 2-pentanol, t-amyl alcohol, tert-butanol, 2-butanol, 1-butanol, 2-methyl-2-pentanol, 2-ethyl-1-butanol, 3,3-dimethyl-2-butanol, 2-octyl-1-dodecanol, mixtures thereof and the like.

[00217] Suitable diluents for non-silicone containing reaction mixtures include glycerin, ethylene glycol, ethanol, methanol, ethyl acetate, methylene chloride, polyethylene glycol, polypropylene glycol, low molecular weight PVP, such as disclosed in US 4,018,853, US 4,680,336 and US 5,039,459, including, but not limited to boric acid esters of dihydric alcohols, combinations thereof and the like.

[00218] Mixtures of diluents may be used. The diluents may be used in amounts up to about 55% by weight of the total of all components in the reaction mixture. More preferably the diluent is used in amounts less than about 45% and more preferably in amounts between about 15 and about 40% by weight of the total of all components in the reaction mixture.

[00219] A polymerization initiator is preferably included in the reaction mixture used to form substrates such as contact lenses. The polymerization initiators includes compounds such as lauryl peroxide, benzoyl peroxide, isopropyl percarbonate, azobisisobutyronitrile, and the like, that generate free radicals at moderately elevated temperatures, and photoinitiator systems such as aromatic alpha-hydroxy ketones, alkoxyoxybenzoines, acetophenones, acylphosphine oxides, bisacylphosphine oxides, and a tertiary amine plus a diketone, mixtures thereof and the like. Illustrative examples of photoinitiators are 1-hydroxycyclohexyl phenyl ketone, 2-hydroxy-2-methyl-1-phenyl-propan-1-one, bis(2,6-dimethoxybenzoyl)-2,4,4-trimethylpentyl phosphine oxide (DMBAPO), bis(2,4,6-trimethylbenzoyl)-phenyl phosphineoxide (Irgacure 819), 2,4,6-trimethylbenzoyldiphenyl phosphine oxide and 2,4,6-trimethylbenzoyl diphenylphosphine oxide, benzoin methyl ester and a combination of camphorquinone and ethyl 4-(N,N-dimethylamino)benzoate. Commercially available visible light initiator systems include Irgacure 819, Irgacure 1700, Irgacure 1800, Irgacure 819, Irgacure 1850 (all from Ciba Specialty Chemicals) and Lucirin TPO initiator (available from BASF). Commercially available UV photoinitiators include Darocur 1173 and Darocur 2959 (Ciba Specialty Chemicals). These and other photoinitiators which may be used are disclosed in Volume III, Photoinitiators for Free Radical Cationic & Anionic Photopolymerization, 2nd Edition by J.V. Crivello & K. Dietliker; edited by G. Bradley; John Wiley and Sons; New York; 1998, which is incorporated herein by reference. The initiator is used in the reaction mixture in effective amounts to initiate photopolymerization of the reaction mixture, e.g., from about 0.1 to about 2 parts by weight per

100 parts of reactive monomer. Polymerization of the reaction mixture can be initiated using the appropriate choice of heat or visible or ultraviolet light or other means depending on the polymerization initiator used. Alternatively, initiation can be conducted without a photoinitiator using, for example, e-beam. However, when a photoinitiator is used, the preferred initiators are bisacylphosphine oxides, such as bis(2,4,6-trimethylbenzoyl)-phenyl phosphine oxide (Irgacure 819®) or a combination of 1-hydroxycyclohexyl phenyl ketone and bis(2,6-dimethoxybenzoyl)-2,4,4-trimethylpentyl phosphine oxide (DMBAPO), and the preferred method of polymerization initiation is visible light. The most preferred is bis(2,4,6-trimethylbenzoyl)-phenyl phosphine oxide (Irgacure 819®).

[00220] The preferred range of silicone-containing monomer present in the reaction mixture is from about 5 to 95 weight percent, more preferably about 30 to 85 weight percent, and most preferably about 45 to 75 weight percent of the reactive components in the reaction mixture. The preferred range of hydrophilic monomer present is from about 5 to 80 weight percent, more preferably about 10 to 60 weight percent, and most preferably about 20 to 50 weight percent of the reactive components in the reaction mixture. The preferred range of diluent present is from about 2 to 70 weight percent, more preferably about 5 to 50 weight percent, and most preferably about 15 to 40 weight percent of the total reaction mixture (including reactive and nonreactive components).

[00221] The reaction mixtures can be formed by any of the methods known to those skilled in the art, such as shaking or stirring, and used to form polymeric articles or devices by known methods.

[00222] For example, the biomedical devices may be prepared by mixing reactive components and the diluent(s) with a polymerization initiator and curing by appropriate conditions to form a product that can be subsequently formed into the appropriate shape by lathing, cutting and the like. Alternatively, the reaction mixture may be placed in a mold and subsequently cured into the appropriate article.

[00223] Various processes are known for processing the reaction mixture in the production of contact lenses, including spincasting and static casting. Spincasting methods are disclosed in U.S. Pat. Nos. 3,408,429 and 3,660,545, and static casting methods are disclosed in U.S. Pat. Nos. 4,113,224 and 4,197,266. The preferred method for producing contact lenses is by the molding of the silicone hydrogels, which is economical, and enables precise control over

the final shape of the hydrated lens. For this method, the reaction mixture is placed in a mold having the shape of the final desired silicone hydrogel, i.e., water-swollen polymer, and the reaction mixture is subjected to conditions whereby the monomers polymerize, to thereby produce a polymer/diluent mixture in the shape of the final desired product. Then, this polymer/diluent mixture is treated with a solvent to remove the diluent and ultimately replace it with water, producing a silicone hydrogel having a final size and shape which are quite similar to the size and shape of the original molded polymer/diluent article. This method can be used to form contact lenses and is further described in U.S. Pat. Nos. 4,495,313; 4,680,336; 4,889,664; and 5,039,459, incorporated herein by reference.

[00224] Biomedical devices, and particularly ophthalmic lenses, have a balance of properties which makes them particularly useful. Such properties include clarity, water content, oxygen permeability and contact angle. The incorporation of at least one block copolymer according to embodiments of the present invention provides articles having very desirable wettability/contact angles with solutions and improved biometric performance as evidenced by reduced lipocalin, lipid and mucin uptake levels. Silicone hydrogel contact lenses incorporating the block copolymers will display contact angles of less than about 60° and in some embodiments less than about 40°, and decreases in contact angle of 40% and in some embodiments 50% or more. Lipid uptake can be lowered by 50% or more and silicone hydrogel lenses having about 12 µg, 10 µg, or even 5 µg or less may be produced. In one embodiment, the biomedical devices are contact lenses having a water content of greater than about 17%, preferably greater than about 20% and more preferably greater than about 25%.

[00225] Suitable oxygen permeabilities for silicone containing lenses are preferably greater than about 40 barrer and more preferably greater than about 60 barrer.

[00226] In some embodiments the articles of the present invention have combinations of the above described oxygen permeability, water content and contact angle. All combinations of the above ranges are deemed to be within the present invention.

[00227] The non-limiting examples below further describe this invention.

[00228] Wettability of lenses can be determined using a sessile drop technique measured using KRUSS DSA-100 TM instrument at room temperature and using DI water as probe solution. The lenses to be tested (3-5/sample) were rinsed in DI water to remove carry over from packing solution. Each test lens was placed on blotting lint free wipes which were dampened

with packing solution. Both sides of the lens were contacted with the wipe to remove surface water without drying the lens. To ensure proper flattening, lenses were placed “bowl side down” on the convex surface on contact lens plastic moulds. The plastic mould and the lens were placed in the sessile drop instrument holder, ensuring proper central syringe alignment and that the syringe corresponds to the assigned liquid. A 3 to 4 microliter of DI water drop was formed on the syringe tip using DSA 100-Drop Shape Analysis software ensuring the liquid drop was hanging away from the lens. The drop was released smoothly on the lens surface by moving the needle down. The needle was withdrawn away immediately after dispensing the drop. The liquid drop was allowed to equilibrate on the lens for 5 to 10 seconds and the contact angle was computed based on the contact angle measured between the drop image and the lens surface.

[00229] The water content may be measured as follows: lenses to be tested were allowed to sit in packing solution for 24 hours. Each of three test lens were removed from packing solution using a sponge tipped swab and placed on blotting wipes which have been dampened with packing solution. Both sides of the lens were contacted with the wipe. Using tweezers, the test lens were placed in a weighing pan and weighed. The two more sets of samples were prepared and weighed as above. The pan was weighed three times and the average is the wet weight.

[00230] The dry weight was measured by placing the sample pans in a vacuum oven which has been preheated to 60°C for 30 minutes. Vacuum was applied until at least 0.4 inches Hg is attained. The vacuum valve and pump were turned off and the lenses were dried for four hours. The purge valve was opened and the oven was allowed reach atmospheric pressure. The pans were removed and weighed. The water content was calculated as follows:

Wet weight = combined wet weight of pan and lenses – weight of weighing pan

Dry weight = combined dry weight of pan and lens – weight of weighing pan

$$\% \text{ water content} = \frac{(\text{wet weight} - \text{dry weight})}{\text{wet weight}} \times 100$$

[00231] The average and standard deviation of the water content are calculated for the samples are reported.

[00232] Oxygen permeability (Dk) may be determined by the polarographic method generally described in ISO 18369-4:2006(E), but with the following variations. The measurement is conducted at an environment containing 2.1% oxygen. This environment is

created by equipping the test chamber with nitrogen and air inputs set at the appropriate ratio, for example 1800 ml/min of nitrogen and 200 ml/min of air. The t/Dk is calculated using the adjusted pO_2 . Borate buffered saline was used. The dark current was measured by using a pure humidified nitrogen environment instead of applying MMA lenses. The lenses were not blotted before measuring. Four lenses with uniform thickness in the measurement area were stacked instead of using lenses of varied thickness. The L/Dk of 4 samples with significantly different thickness values are measured and plotted against the thickness. The inverse of the regressed slope is the preliminary Dk of the sample. If the preliminary Dk of the sample is less than 90 barrer, then an edge correction of $(1 + (5.88(CT \text{ in cm})))$ is applied to the preliminary L/Dk values. If the preliminary Dk of the sample is greater than 90 barrer, then an edge correction of $(1 + (3.56(CT \text{ in cm})))$ is applied to the preliminary L/Dk values. The edge corrected L/Dk of the 4 samples are plotted against the thickness. The inverse of the regressed slope is the Dk of the sample. A curved sensor was used in place of a flat sensor. The resulting Dk value is reported in barrers.

[00233] Lipocalin uptake can be measured using the following solution and method. The lipocalin solution contained B Lactoglobulin (Lipocalin) from bovine milk (Sigma, L3908) solubilized at a concentration of 2 mg/ml in phosphate saline buffer (Sigma, D8662) supplemented by sodium bicarbonate at 1.37g/l and D-Glucose at 0.1 g/l.

[00234] Three lenses for each example were tested using the lipocalin solution, and three were tested using PBS as a control solution. The test lenses were blotted on sterile gauze to remove packing solution and aseptically transferred, using sterile forceps, into sterile, 24 well cell culture plates (one lens per well) each well containing 2 ml of lipocalin solution. Each lens was fully immersed in the solution. Control lenses were prepared using PBS as soak solution instead of lipocalin. The plates containing the lenses immersed in lipocalin solution as well as plates containing control lenses immersed in PBS, were parafilmed to prevent evaporation and dehydration, placed onto an orbital shaker and incubated at 35°C, with agitation at 100 rpm for 72 hours. After the 72 hour incubation period the lenses were rinsed 3 to 5 times by dipping lenses into three (3) separate vials containing approximately 200 ml volume of PBS. The lenses were blotted on a paper towel to remove excess PBS solution and transferred into sterile 24 well plates each well containing 1 ml of PBS solution.

[00235] Lipocalin uptake can be determined using on-lens bicinchoninic acid method using QP-BCA kit (Sigma, QP-BCA) following the procedure described by the manufacturer (the standards prep is described in the kit) and is calculated by subtracting the optical density measured on PBS soaked lenses (background) from the optical density determined on lenses soaked in lipocalin solution. Optical density was measured using a SynergyII Micro-plate reader capable for reading optical density at 562 nm.

[00236] Mucin uptake can be measured using the following solution and method. The Mucin solution contained Mucins from bovine submaxillary glands (Sigma, M3895-type 1-S) solubilized at a concentration of 2 mg/ml in phosphate saline buffer (Sigma, D8662) supplemented by sodium bicarbonate at 1.37g/l and D-Glucose at 0.1 g/l.

[00237] Three lenses for each example were tested using Mucin solution, and three were tested using PBS as a control solution. The test lenses were blotted on sterile gauze to remove packing solution and aseptically transferred, using sterile forceps, into sterile, 24 well cell culture plates (one lens per well) each well containing 2 ml of Mucin solution. Each lens was fully immersed in the solution. Control lenses were prepared using PBS as soak solution instead of lipocalin.

[00238] The plates containing the lenses immersed in Mucin as well as plates containing control lenses immersed in PBS were parafilmmed to prevent evaporation and dehydration, placed onto an orbital shaker and incubated at 35°C, with agitation at 100 rpm for 72 hours. After the 72 hour incubation period the lenses were rinsed 3 to 5 times by dipping lenses into three (3) separate vials containing approximately 200 ml volume of PBS. The lenses were blotted on a paper towel to remove excess PBS solution and transferred into sterile 24 well plates each well containing 1 ml of PBS solution.

[00239] Mucin uptake can be determined using on-lens bicinchoninic acid method using QP-BCA kit (Sigma, QP-BCA) following the procedure described by the manufacturer (the standards prep is described in the kit) and is calculated by subtracting the optical density measured on PBS soaked lenses (background) from the optical density determined on lenses soaked in Mucin solution. Optical density was measured using a SynergyII Micro-plate reader capable for reading optical density at 562nm.

[00240] Cell viability can be evaluated in vitro using a reconstituted corneal epithelium tissue construct. The tissue construct was a full thickness corneal epithelium (corneal epithelium

tissue from Skinethics) reconstituted and grown in vitro on a polycarbonate insert at the air liquid interface to form a fully stratified epithelial construct.

[00241] For the evaluation of lenses a punch biopsy (0.5 cm^2) of the lens was applied topically onto the tissue followed by a 24-hour incubation at 37°C , 5 % CO_2 . The lens biopsy was removed, and tissue was washed with PBS. Cell viability was then measured using the MTT colorimetric assay (Mosman, T. Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays. *J. Immunol. Methods*, 65; 55-63 (1983)): tissues were incubated in the presence of MTT for 3 hours at 37°C , 5 % CO_2 , followed by extraction of the tissues in isopropyl alcohol. Absorbance of the isopropyl alcohol extracts was then measured at 550 nm using a microplate reader. Results were expressed as a percentage of the PBS control (tissues treated with PBS versus lens-treated tissues).

[00242] For the evaluation of solutions 30 μg of solution was applied topically onto the tissue. The rest of the cell viability was as described for lenses. Each evaluation was done in triplicate.

[00243] Lipid uptake was measured as follows:

[00244] A standard curve was set up for each lens type under investigation. Tagged cholesterol (cholesterol labeled with NBD ([7-nitrobenz-2-oxa-1,3-diazol-4-yl], CH-NBD; Avanti, Alabaster, AL)) was solubilized in a stock solution of 1 mg /mL lipid in methanol at 35°C . Aliquots were taken from this stock to make standard curves in phosphate-buffered saline (PBS) at pH 7.4 in a concentration range from 0 to 100 micg /mL.

[00245] One milliliter of standard at each concentration was placed in the well of a 24-well cell culture plate. 10 lenses of each type were placed in another 24-well plate and soaked alongside the standard curve samples in 1 mL of a concentration of 20 micg /ml of CH-NBD. Another set of lenses (5 lenses) were soaked in PBS without lipids to correct for any autofluorescence produced by the lens itself. All concentrations were made up in phosphate buffered saline (PBS) at pH 7.4. Standard curves, test plates (containing lenses soaked in CH-NBD) and control plates (containing lenses soaked in PBS) were all wrapped in aluminum foil to maintain darkness and were incubated for 24 hours, with agitation at 35°C . After 24 hours the standard curve, test plates and control plates were removed from the incubator. The standard curve plates were immediately read on a micro-plate fluorescence reader (Synergy HT)).

[00246] The lenses from the test and control plates were rinsed by dipping each individual lens 3 to 5 times in 3 consecutive vials containing approximately 100 ml of PBS to ensure that only bound lipid would be determined without lipids carryover. The lenses were then placed in a fresh 24-well plate containing 1 mL of PBS in each well and read on the fluorescence reader. After the test samples were read, the PBS was removed, and 1 mL of a fresh solution of CH-NBD were placed on the lenses in the same concentrations as previously mentioned and placed back in the incubator at 35°C, with rocking, until the next period. This procedure was repeated for 15 days until complete saturation of lipids on lenses. Only the lipid amount obtained at saturation was reported.

[00247] Lysozyme uptake can be measured as follows: The lysozyme solution used for the lysozyme uptake testing contained lysozyme from chicken egg white (Sigma, L7651) solubilized at a concentration of 2 mg/ml in phosphate saline buffer supplemented by Sodium bicarbonate at 1.37g/l and D-Glucose at 0.1 g/l.

[00248] The lipocalin solution contained B Lactoglobulin (Lipocalin) from bovine milk (Sigma, L3908) solubilized at a concentration of 2 mg/ml in phosphate saline buffer supplemented by Sodium bicarbonate at 1.37g/l and D-Glucose at 0.1 g/l.

[00249] Three lenses for each example were tested using each protein solution, and three were tested using PBS as a control solution. The test lenses were blotted on sterile gauze to remove packing solution and aseptically transferred, using sterile forceps, into sterile, 24 well cell culture plates (one lens per well) each well containing 2 ml of lysozyme solution. Each lens was fully immersed in the solution. 2 ml of the lysozyme solution was placed in a well without a contact lens as a control.

[00250] The plates containing the lenses and the control plates containing only protein solution and the lenses in the PBS, were parafilmed to prevent evaporation and dehydration, placed onto an orbital shaker and incubated at 35°C, with agitation at 100 rpm for 72 hours. After the 72 hour incubation period the lenses were rinsed 3 to 5 times by dipping lenses into three (3) separate vials containing approximately 200 ml volume of PBS. The lenses were blotted on a paper towel to remove excess PBS solution and transferred into sterile conical tubes (1 lens per tube), each tube containing a volume of PBS determined based upon an estimate of lysozyme uptake expected based upon on each lens composition. The lysozyme concentration in each tube to be tested needs to be within the albumin standards range as described by the

manufacturer (0.05 microgram to 30 micrograms). Samples known to uptake a level of lysozyme lower than 100 µg per lens were diluted 5 times. Samples known to uptake levels of lysozyme higher than 500 µg per lens (such as etafilcon A lenses) are diluted 20 times.

[00251] 1 ml aliquot of PBS was used for all samples other than etafilcon. 20ml were used for etafilcon A lens. Each control lens was identically processed, except that the well plates contained PBS instead of either lysozyme or lipocalin solution.

[00252] Lysozyme and lipocalin uptake was determined using on-lens bicinchoninic acid method using QP-BCA kit (Sigma, QP-BCA) following the procedure described by the manufacturer (the standards prep is described in the kit) and is calculated by subtracting the optical density measured on PBS soaked lenses (background) from the optical density determined on lenses soaked in lysozyme solution.

[00253] Optical density can be measured using a SynergyII Micro-plate reader capable for reading optical density at 562nm.

[00254] The following abbreviations will be used throughout the Preparations and Examples and have the following meanings.

[00255] ACA1 3-acrylamidopropionic acid;

[00256] ACA2 5-acrylamidopentanoic acid;

[00257] 4-BBB 4-(bromomethyl)benzoyl bromide (Sigma-Aldrich);

[00258] DMA *N,N*-dimethylacrylamide

[00259] Irgacure-819 bis(2,4,6-trimethylbenzoyl)-phenylphosphineoxide (Ciba Specialty Chemicals);

[00260] KXpotassium O-ethyl xanthogenate;

[00261] mPDMS monomethacryloxypropyl terminated mono-n-butyl terminated polydimethylsiloxanes (800-1000 MW);

[00262] NaHTTC sodium hexyltrithiocarbonate;

[00263] HBTTTC *S*-hexyl-*S'*-benzyl-trithiocarbonate

[00264] XG1996TTC *S*-hexyl-*S'*-4-(2-(n-butylpolydimethylsiloxydimethylsilyl)ethyl)benzyl carbonotrithioate;

[00265] nBPDMS-H 3-(n-butyltetramethylsiloxydimethylsilyl) propanol

[00266] MBA *N,N'*-methylenebisacrylamide

[00267] NVP N-vinylpyrrolidone (Acros Chemical), further purified via vacuum distillation;

[00268] NRPTHP polysiloxane terminated block copolymer comparison produced in Preparation 3;

[00269] PTHPWCL polysiloxane terminated block copolymer with cross-links produced in Preparation 3;

[00270] HO-mPDMS mono-(2-hydroxy-3-methacryloxypropyl)-propyl ether terminated polydimethylsiloxane (400-1000 MW));

[00271] SBX 3-(n-butyltetramethylsiloxymethyl)silylpropyl 4-((ethoxycarbonothioylthio)methyl)benzoate;

[00272] SiGMA 2-methyl-,2-hydroxy-3-[3-[1,3,3,3-tetramethyl-1-[(trimethylsilyl)oxy]disiloxanyl]propoxy]propyl ester;

[00273] TRIS-VC tris(trimethylsiloxy)silylpropyl vinyl carbamate;

[00274] V₂D₂₅ a silicone-containing vinyl carbonate describe at col. 4, lines 33-42 of US5,260,000

[00275] XG-1996 4-(2-(n-butylpolydimethylsiloxymethyl)silyl)ethyl)benzyl chloride, MW ~ 1000;

[00276] XG1996HTTC *S*-hexyl-*S'*-4-(2-(n-butylpolydimethylsiloxymethyl)silyl)ethyl)benzyl carbonotrithioate (preparation 1); and

[00277] D3O 3,7-dimethyl-3-octanol

[00278] Borate buffer is an ophthalmic solution containing the following components

component	Wt%
Deionized Water	98.48
Sodium Chloride	0.44
Boric Acid	0.89
Sodium Borate Decahydrate	0.17
Ethylenediamine Tetraacetate (EDTA)	0.01

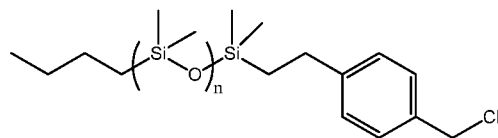
[00279]

[00280] **Preparation 1 Synthesis of Silicone-Functional macro-RAFT Agent:** *S*-hexyl-*S'*-4-(2-(n-butylpolydimethylsiloxymethyl)silyl)ethyl)benzyl carbonotrithioate (XG1996TTC).

[00281] XG-1996 (shown in Formula XX below, MW distribution centered around about 1000 g/mole, which corresponds to an average repeat, m of 10-12), (10 g, 10 moles), was dissolved in approx. 250 mL of acetone in a 1 L round bottom flask. Sodium

hexyltrithiocarbonate (NaHTTC) was dissolved in 100 mL acetone and added to the reaction mixture. The reaction mixture was stirred overnight. A white solid precipitated out of the bright yellow solution. Acetone was removed via rotary-evaporation, and the crude product was partitioned between 250 mL DI water and 250 mL hexane. The hexane layer was separated out and the aqueous layer was extracted with hexane (3 x 200mL). All organic layers were combined, washed with brine (250mL) and dried over Na₂SO₄. The crude product in hexane was passed over a silica gel plug to remove cloudiness. Hexane was removed via rotary-evaporation leaving the product *S*-hexyl-*S*'-4-(2-(*n*-butylpolydimethylsiloxysilyl)ethyl)benzyl carbonotrithioate (XG1996HTTC) in the form of a clear yellow oil. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 0.00-0.05 (m, 60H), 0.52 (t, 2H), 0.83-0.91 (m, 8H), 1.22-1.44 (m, 10H), 1.63-1.73 (m, 2H), 2.61 (t, 2H), 3.34 (t, 2H), 4.56 (s, 2H), 7.14 (d, 2H), 7.21 (d, 2H).

[00282] XG-1996: -(2-(*n*-butylpolydimethylsiloxydimethylsilyl) ethyl) benzyl chloride
MW ~ 1000 g/mole



Formula XX

[00283] **Preparation 2 Synthesis of Standard, Non-Silicone RAFT Agent:** *S*-hexyl-*S*'benzyl-trithiocarbonate (HBTTC)

[00284] Sodium in kerosene (Sigma Aldrich batch # 13322HH) was added in pieces slowly under nitrogen to 20mL of methanol to form sodium methoxide. The resulting solution was added to a flask containing 1-hexanethiol (Sigma Aldrich batch # 09818LE) in several aliquots. Carbon disulfide (Sigma Aldrich batch # 04897JJ) was added drop-wise via syringe. The solution turned yellow immediately. The solution was allowed to react for 15 minutes. Benzyl bromide (Sigma Aldrich batch # 14714PD) was then added dropwise via syringe. A precipitate formed immediately. The reaction was allowed to proceed for two hours. A yellow oil eventually formed at the bottom of the flask. The methanol was roto-vapped off and the product was separated from the sodium salt with deionized water and hexane. The aqueous layer was approximately 50mL and was extracted three times with 50mL of hexane. The hexane was combined, dried over Na₂SO₄ and reduced to dryness via rotary evaporation. ¹H NMR (300

MHz, CDCl₃): δ (ppm) 0.875-1.125 (t, 3H), 1.25-1.63 (m, 6H), 1.63-1.95 (m, 2H), 3.25-3.63 (t, 2H), 4.63-4.8 (s, 2H), 7.25-7.5 (m, 5H),

[00285] **Preparation 3:** *Synthesis of polyDMA-Based Polysiloxane Terminated Block Copolymer With Cross-Links PTHPWCL in the Presence of XG1996TTC and HBTTC*

[00286] A series of PDMA-based PTHPWCLs was prepared with variations in the target DP_{nQ-Segment}, cross-linking agent to ζ -primary chain ratio (XL: ζ -PC), and ratio of silicone segment to hydrophilic Q-segment ([A]:[Q]) *via* RAFT polymerization.

[00287] DMA was obtained from Jarchem and further purified *via* vacuum distillation. XG1996TTC was synthesized according to Preparation 1, HBTTC was synthesized according to Preparation 2 above. Irigacure 819 was dissolved in n-propanol at a concentration of 10mg/mL.

[00288] For the synthesis of Example A, the polymerization solution was prepared by dissolving 30 g of DMA, 0.101 g XG1996TTC, 0.260 g HBTTC, and 0.017 g CGI-819 into 30 g of n-propanol in a 20 mL amber glass vial. Next, 0.157 g *N,N'*-methylenebisacrylamide was added to the polymerization solution. The resulting solution was stirred under ambient conditions until homogeneous. The amber vial containing the final polymerization solution was sealed with a rubber septum and purged for 20 minutes with N₂ to remove O₂ from the solution. Finally the sealed jar was placed in an N₂ glove-box for storage.

[00289] The polymerization solution was cured to a conversion, ρ , of 0.96 or 96 % under an N₂ atmosphere with 4 standard Phillips TL 20W/03 RS bulbs at intensity of 2.0 mW/cm² for 45 minutes. Prior to curing, the polymerization solution was poured into an 80 mm diameter crystallization dish, which was then placed on a reflective glass surface.

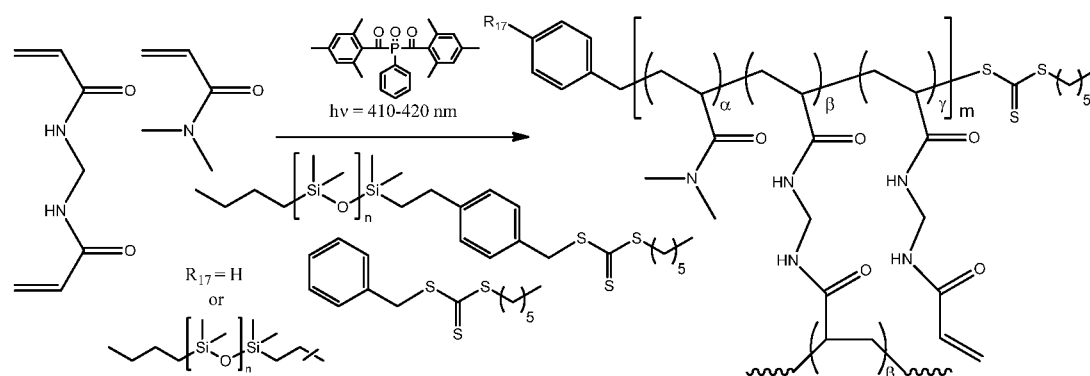
[00290] After curing, the resulting highly viscous polymerized material was diluted with 5mL of ethanol. The polymerized solution was stirred then added drop-wise to 500 mL of vigorously stirring cold diethyl ether to precipitate product. The precipitated polymer was dried *in vacuo* for several hours.

[00291] Examples B-P were prepared in accordance with Example A with ingredient amounts adjusted to meet the desired target DP_{nQ-Segment}, XL: ζ -PC ratio, and [A]:[Q] ratio as listed in Table 1. Specific amounts used in the preparation of each example may be found below in Table 2. The monomer conversions, ρ , for specific examples are shown in Table 1.

[00292] The resulting polymers were analyzed for MW and MWD via SEC-RI. Figure 2 shows the Size Exclusion Chromatography with Refractive Index (SEC-RI) results for Examples

A-P of cross-linked PDMA-siloxanes and comparison for a comparative linear PDMA-siloxane according to Preparation 3. Degree of polymerization of the hydrophilic segment was measured along with polydispersity index.

[00293] The generalized synthesis of PTHPWCLs via RAFT polymerization is shown below:



[00294] The resulting molecular weights and polydispersity index (PDI) and conversions (ρ) are provided in Table 1.

TABLE 1

Example	DP _{nQ-Segment}	XL:ζ-PC	[A]:[Q]	M _n (g/mole)	M _w (g/mole)	PDI	ρ
A	300	1.00	0.10	53,030	195,400	3.7	0.96
B	100	0.10	0.55	12,570	13,830	1.1	0.95
C	300	0.55	0.55	44,040	74,960	1.7	0.97
D	500	0.55	1.00	52,640	112,700	2.1	0.98
E	300	0.55	0.55	45,180	77,390	1.7	0.97
F	100	0.55	0.10	16,890	25,120	1.5	0.94
G	500	0.10	0.55	45,260	55,790	1.2	0.96
H	300	0.55	0.55	46,640	75,740	1.6	0.96
I	300	1.00	1.00	238,600	841,500	3.5	1.00
J	500	1.00	0.55	104,400	303,300	2.9	1.00
K	100	1.00	0.55	157,300	756,800	4.8	1.00
L	300	0.10	0.10	29,210	32,690	1.1	0.97
M	500	0.55	0.10	49,870	78,140	1.6	0.94
N	100	0.55	1.00	23,050	54,610	2.4	0.97
O	300	0.10	1.00	31,720	38,510	1.2	0.98
P	100	1.25	0.1	43,270	450,100	10.4	0.94

Table 2

Sample Name	DP _{nQ-Segment}	XL:ζ-PC	[A]:[Q]	MBA (g)	DMA (g)	CGI (mg)	n-Prop (g)	CTA _{Silicone} (mg)	CTA _{Standard} (mg)
A	300	1.00	0.10	0.157	30	17.0	30	101	260
B	100	0.10	0.55	0.049	30	50.8	30	1668	388
C	300	0.55	0.55	0.086	30	17.0	30	557	130
D	500	0.55	1.00	0.051	30	10.2	30	607	0
E	300	0.55	0.55	0.086	30	17.0	30	557	130
F	100	0.55	0.10	0.260	30	51.0	30	305	780
G	500	0.10	0.55	0.010	30	10.2	30	333	78
H	300	0.55	0.55	0.086	30	17.0	30	557	130
I	300	1.00	1.00	0.156	30	17.0	30	1013	0
J	500	1.00	0.55	0.094	30	10.2	30	334	78
K	100	1.00	0.55	0.470	30	51.2	30	1683	392
L	300	0.10	0.10	0.015	30	17.0	30	101	259
M	500	0.55	0.10	0.051	30	10.2	30	61	155
N	100	0.55	1.00	0.260	30	51.0	30	3047	0
O	300	0.10	1.00	0.015	30	17.0	30	1010	0
P	100	1.25	0.1	0.59	30	51.5	30	308	788

[00295] **Preparation 4a-c**

[00296] **COMPARATIVE:** *Synthesis of polyDMA-Based Polysiloxane Terminated Polymers NRPTHF.*

[00297] **Preparations 19-21** Synthesis of PDMA-Based Non-Reactive Polysiloxane Terminated Hydrophilic Polymer NRPTHF Varied MW Series via RAFT Polymerization in the Presence of XG1996TTC

[00298] A series of DMA-containing NRPTHFs having different molecular weights was prepared using the components in the amounts listed in Table 3, below and the following procedure. For all preparations, the length of the silicone segment was held constant at 10-12 repeat units, i.e. all polymers were made from the same lot of XG1996HTTC from Preparation 5. Three ratios of DMA:XG1996HTTC ratios were targeted in order to vary the molecular weight of the hydrophilic polymer, including 300, 600, and 1000.

[00299] Distilled DMA was added to an amber 120mL glass jar. Next, diluents (either D3O or pentanol), XG1996HTTC, and Irgacure-819 were added to the monomer and warmed and stirred to ensure homogeneity. The amber jars containing the final polymerization solutions were placed in an N₂ atmosphere and purged for 20 minutes with N₂ to remove O₂ from the solution. The jar was sealed and placed in an N₂ glove-box until use.

[00300] The polymers were analyzed for MW and MWD via SEC-MALLS, described below. The results are shown in Table 14, below.

[00301] Table 3

Preparation#	4a	4b	4c
DP	300	600	1000
Materials	(g)	(g)	(g)
XG1996HTTC	9.67	0.58	0.290
DMA	250.0	30.0	25.0
CGI-819	0.176	0.0021	0.0053
D3O	0.0	30.0	25.0
Pentanol	250.0	0	0.0

[00302] Table 4

Prep#	Sample Type	Mn (g/mole)	Mw (g/mole)	PDI
4a	PDMA-Sil	23,720	27,790	1.17
4b	PDMA-Sil	44,830	49,480	1.10
4c	PDMA-Sil	92,180	102,700	1.11

Comparative Examples 1-3

Three senofilcon lenses were removed from their packages and transferred glass vials containing packing solution containing 500 ppm of the non-reactive polysiloxane terminated hydrophilic polymer (“NRPTHP”) produced in Preparations 4a-c. The lenses were re-packaged in the NRPTHP packing solution, autoclaved at 121°C for 28 minutes and, after sterilization, were allowed to soak in the NRPTHP packing solution at ambient temperature for at least 24 hours. The sessile drop contact angle of the lenses were measured and are reported in Table 5.

Table 5

Ex#	Prep		DP	Lipid Uptake ($\mu\text{g}/\text{lens}$)	Contact Angle ($^{\circ}$)
CE1	4a	PDMA-Sil-23K	222	52.1 (6.6)	55.7 (5.0)
CE2	4b	PDMA-Sil-44K	434	35.5 (7.8)	50.5 (1.7)
CE3	4c	PDMA-Sil-92K	918	14.1 (3.0)	43.7 (3.4)

Examples – A-P

[00303] For each Example, production quality senofilcon A lenses were removed from their packages and transferred to glass vials containing packing solution containing the polysiloxane terminated block copolymer with cross-links (“PTHPWCL”) produced in Preparation 2 a concentration of 5000 ppm in a 30/70 volume/volume IPA/Borate Buffer mixture. The lenses were re-packaged in the PTHPWCL packing solution, allowed to soak in the PTHPWCL packing solution at ambient temperature for at least 24 hours. Treated lenses were then repackaged in fresh packing solution and were subsequently sterilized at 124°C for 30 minutes.

Example	DP _{nQ-Segment}	XL:ζ-PC	[A]:[Q]	M _n (g/mole)	M _w (g/mole)	PDI	Lipid Uptake ($\mu\text{g}/\text{lens}$)*
A	300	1.00	0.10	53,030	195,400	3.7	9.5
B	100	0.10	0.55	12,570	13,830	1.1	15.4
C	300	0.55	0.55	44,040	74,960	1.7	12.8
D	500	0.55	1.00	52,640	112,700	2.1	12.8
E	300	0.55	0.55	45,180	77,390	1.7	12.2
F	100	0.55	0.10	16,890	25,120	1.5	12.4
G	500	0.10	0.55	45,260	55,790	1.2	14.4
H	300	0.55	0.55	46,640	75,740	1.6	12.6
I	300	1.00	1.00	238,600	841,500	3.5	9.5
J	500	1.00	0.55	104,400	303,300	2.9	8.4
K	100	1.00	0.55	157,300	756,800	4.8	8.4
L	300	0.10	0.10	29,210	32,690	1.1	15.7
M	500	0.55	0.10	49,870	78,140	1.6	12.7
N	100	0.55	1.00	23,050	54,610	2.4	12.5
O	300	0.10	1.00	31,720	38,510	1.2	15.1
P	100	1.25	0.1	43,270	450,100	10.4	5.2

*Lipid Uptake = CH-NBD uptake. A pooled standard deviation of ± 0.4 $\mu\text{g}/\text{lens}$ can be used to assess statistical significance.

[00304] FIGS. 3, 4, and 5 show that lipid uptake decreases significantly as the XL:ζ-PC increases for all ratios of [A]:[Q] and target DP_{nQ-segment} values.

[00305] FIGS. 6, 7, and 8 also show that lipid uptake decreases significantly as the XL:ζ-PC increases for all ratios of [A]:[Q]. Figures 6-8 also show that the DP_{nQ-segment} does not have as big an impact on the lipid uptake of lenses treated with the block copolymers as the ratio of cross-linker to primary chain XL:ζ-PC does. This suggests that a tight mesh is desired.

[00306] FIGS. 9, 10, and 11 show lipid uptake surface responses for varying degrees of polymerization and ratios of [A]:[Q] for constant ratios of cross-linking agent to primary chain, XL:ζ-PC.

[00307] From these figures, it is seen that the use of higher amounts of cross-linker to form the nanogel materials of this invention leads to structures that, when used to treat a contact lens medical device, drastically lower the device's lipid and protein uptake profile.

[00308] Reference throughout this specification to "one embodiment," "certain embodiments," "one or more embodiments" or "an embodiment" means that a particular feature, structure, material, or characteristic described in connection with the embodiment is included in at least one embodiment of the invention. Thus, the appearances of the phrases such as "in one or more embodiments," "in certain embodiments," "in one embodiment" or "in an embodiment" in various places throughout this specification are not necessarily referring to the same embodiment of the invention. Furthermore, the particular features, structures, materials, or characteristics may be combined in any suitable manner in one or more embodiments.

[00309] Although the invention herein has been described with reference to particular embodiments, it is to be understood that these embodiments are merely illustrative of the principles and applications of the present invention. It will be apparent to those skilled in the art that various modifications and variations can be made to the method and apparatus of the present invention without departing from the spirit and scope of the invention. Thus, it is intended that the present invention include modifications and variations that are within the scope of the appended claims and their equivalents.

What is claimed is:

1. A composition comprising a water soluble, block copolymer of the following formula:
[A]-B-[Q], wherein
[A] is a segment that has an affinity for a medical device;
B is a linking group comprising an optionally-substituted, polyvalent linking group having a molecular weight of no more than 1000 g/mole; and
[Q] comprises a semi-crosslinked, ungelled segment derived from copolymerization of at least one ethylenically unsaturated monomer with a poly-functional ethylenically unsaturated monomer.
2. The composition of claim 1, wherein:
the block copolymer is stable, water soluble and cross-linked but not macroscopically gelled,
[Q] comprises a plurality of crosslinked primary polymer chains each having a degree of polymerization in the range of about 10 to about 10,000, and
[A] comprises a linear substrate associative segment on at least one terminal end of said block copolymer, wherein said substrate associative segment comprises between about 1 and about 1000 repeating units, and said block copolymer is associated, via the linear substrate associative segment with a surface of the medical device.
3. The composition of claim 2, wherein said substrate associative segment is selected from the group consisting of a hydrophobic segment, a hydrophilic substrate associative segment, a proton donating segment, a proton accepting segment, an ionic segment, a complexing segment, and a stimuli responsive segment.
4. The composition of claim 3, wherein the hydrophobic segment comprises siloxy groups.
5. The composition of claim 3, wherein the proton donating segment comprises one or more alcohols.
6. The composition of claim 3, wherein the proton accepting segment comprises one or more amides.
7. The composition of claim 3, wherein the ionic segment comprises one or more of the following: a carboxylate, a sulfonate, an ammonium salt, and a phosphonium salt.
8. The composition of claim 3, wherein the complexing segment comprises one or more boronic acid functionalities and/or hydroxyl functionalities.

9. The composition of claim 3, wherein the stimuli responsive segment comprises a polymer selected from the group consisting of temperature-responsive polymers, pH responsive polymers, electrolyte responsive polymers, light responsive polymers and mixtures thereof.
10. The composition of claim 9, wherein the temperature-responsive polymer is poly(*N*-isopropylacrylamide) (PNIPAM).
11. A composition comprising an amphiphilic nanogel material comprising one or more cross-linked copolymers, wherein said copolymer comprises one or more hydrophilic segments having a degree of polymerization in the range of about 10 to about 10,000, and wherein said one or more hydrophilic segments contains a linear silicone segment on at least one terminal end, wherein said linear silicone segment comprises between about 1 and about 200 siloxy units, and said amphiphilic nanogel material associates via the linear silicone segment, with a surface comprising at least one partially hydrophobic substrate.
12. The composition of claim 11 wherein said hydrophilic segment of said nanogel has a degree of polymerization in the range of about 50 to about 5,000.
13. The composition of claim 11 wherein said hydrophilic segment of said nanogel has a degree of polymerization in the range of about 100 to about 1000.
14. The composition of claim 11 wherein said hydrophilic segment of said nanogel has a degree of polymerization in the range of about 100 to about 500.
15. The composition of claim 11 wherein said hydrophilic segment of said nanogel has a degree of polymerization in the range of about 100 to about 300.
16. The composition of claim 11 wherein the hydrophilic segment and the linear silicone segment are present in said nanogel in a weight ratio, based upon the degree of polymerization, in the range of about 1:1 to about 500:1.
17. The composition of claim 16 wherein the weight ratio of the hydrophilic segment to the linear silicone segment, based upon degree of polymerization, is in the range of about 1:1 to about 200:1.
18. The composition of claim 17 wherein the weight ratio of the hydrophilic segment to the linear silicone segment, based upon degree of polymerization is in the range of about 1:1 to about 10:1.

19. The composition of claim 11 wherein said hydrophilic segment has a cross-linker to primary chain molar ratio in the range of about 0.01 to about 1.5.
20. The composition of claim 11 wherein said hydrophilic segment is cross-linked to other hydrophilic segments of said amphiphilic copolymer having polydispersity indices (PDIs) of less than about 1.5.
21. The composition of claim 20 wherein said hydrophilic segment is cross-linked by covalent bonding, ionic bonding, hydrogen bonding, or a combination thereof.
22. The composition of claim 11 wherein said silicone segment comprises polydialkylsiloxane, polydiarylsiloxane, and mixtures thereof.
23. The composition of claim 22 wherein said alkyl is selected from C₁-C₄ alkyl.
24. The composition of claim 22 wherein said polydialkylsiloxane comprises polydimethylsiloxane or polydiethylsiloxane.
25. The composition of claim 11 wherein said hydrophilic segment is formed from monomers selected from the group consisting of vinyl amides, vinyl lactones, vinylimides, vinyl lactams, hydrophilic (meth)acrylates, (meth)acrylamides, and mixtures thereof.
26. The composition of claim 20 wherein said hydrophilic segment is cross-linked by a cross-linking agent selected from the group consisting of an *N,N'*-alkylenebis(meth)acrylamide, an polyalkyleneglycoldi(meth)acrylate, an polyalkyleneglycoldi(meth)acrylamide, and combinations thereof.
27. The composition of claim 11 wherein the surface comprising at least one partially hydrophobic substrate comprises a silicone hydrogel which comprises a contact angle of no more than about 50° after said surface has been treated with said amphiphilic nanogel material.
28. A method of making a stable, block copolymer that is cross-linked but not macroscopically gelled, the method comprising:
 - (a) reacting a terminally-functionalized polydialkylsiloxane with a functional moiety capable of controlling the polymerization of unsaturated monomers to form a polysiloxane-functional controlled radical polymerization (CRP) agent;
 - (b) contacting the polysiloxane-functional CRP agent with at least one hydrophilic monomer, a free radical initiator, a cross-linking agent, and, optionally, a solvent;

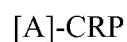
- (c) polymerizing the at least one hydrophilic monomer in the presence of the polysiloxane-functional CRP agent to form a hydrophilic segment on the polysiloxane-functional CRP agent, such that an active portion of the CRP compound is on a terminal end of said hydrophilic segment and a silicone segment is on an opposite terminus; and
 - (d) cross-linking the hydrophilic segment during polymerization.
29. The method of claim 28 wherein said CRP agent is a reversible addition fragment transfer (RAFT) agent.
30. The method of claim 28 wherein said CRP agent is an atom transfer radical polymerization (ATRP) agent
31. The method of claim 28 wherein said CRP agent is a telluride-mediated polymerization (TERP) agent
32. The method of claim 28 wherein said CRP agent is a nitroxide-mediated living radical polymerization (NMP) agent.
33. The composition of claim 11 wherein said block copolymer is formed by
- (a) reacting a hydroxyl alkyl terminated polydialkylsiloxane with 4-(bromomethyl)benzoyl bromide in the presence of at least one hindered non-nucleophilic amine and subsequently reacting a thiocarbonylthio anion to form a polysiloxane-functional RAFT agent having a silicone segment and a dithio compound on one terminus of said silicone segment;
 - (b) contacting the polysiloxane-functional RAFT agent with at least one hydrophilic monomer, a free radical initiator, a cross-linking agent, and an optional solvent;
 - (c) polymerizing said at least one hydrophilic monomer in the presence of the polysiloxane-functional RAFT agent to form a hydrophilic segment on the polysiloxane-functional RAFT agent, such that the dithio compound is on a terminal end of said hydrophilic segment and the silicone segment is on an opposite terminus; and
 - (d) cross-linking the hydrophilic segment during polymerization with a cross-linking agent.
34. The composition of claim 11 wherein said block copolymer is formed by

- (a) reacting a silane-terminated polydialkylsiloxane with 1-(chloromethyl)-4-vinylbenzene in the presence of a platinum catalyst and subsequently reacting a thiocarbonylthio anion to form a polysiloxane-functional RAFT agent having a silicone segment and a thiocarbonylthio compound on one terminus of said silicone segment;
 - (b) contacting the polysiloxane-functional RAFT agent with at least one hydrophilic monomer, a free radical initiator, a cross-linking agent, and an optional solvent; and
 - (c) polymerizing at least one hydrophilic monomer in the presence of the polysiloxane-functional RAFT agent to form a hydrophilic segment on the polysiloxane-function RAFT agent, such that the dithio compound is on a terminal end of said hydrophilic segment and the silicone segment is on the opposite terminus; and
 - (d) cross-linking the hydrophilic segment during polymerization.
35. A process comprising contacting a silicone-containing contact lens with a solution comprising at least one stable block copolymer that is cross-linked but not macroscopically gelled in an amount effective to inhibit lipid uptake by the lens comprising in said polymer's backbone, a hydrophilic segment that has a degree of polymerization in the range of about 10 to about 10,000, and a linear substrate associative segment on at least one terminal end of said block copolymer, wherein said substrate associative segment comprises between about 1 and about 200 repeating units, under contacting conditions suitable to associate said block copolymer with said silicone-containing contact lens.
36. The process of claim 35 wherein said contact lens comprises a silicone hydrogel contact lens.
37. The process of claim 35 wherein said hydrophilic segment has a cross-linker to primary chain molar ratio in the range of about 0.01 to about 1.5.
38. The process of claim 35 wherein said effective amount is at least about 10 ppm.
39. The process of claim 35 wherein said effective amount is in the range of about 10 ppm to about 10,000 ppm.

40. The process of claim 35 wherein the lipid uptake by the lens is no more than about 10 $\mu\text{g}/\text{lens}$.
41. A process comprising:
 - (a) forming a reaction mixture comprising at least one silicone-containing component, at least and at least one stable block copolymer that is cross-linked but not macroscopically gelled, comprising in said polymer's backbone, a hydrophilic segment that has a degree of polymerization in the range of about 10 to about 10,000, and a linear silicone segment on at least one terminal end of said block copolymer, wherein said silicone segment comprises between about 1 and about 200 siloxy units, and
 - (b) curing said reaction mixture to form a contact lens.
42. The process of claim 41 wherein said reaction mixture further comprises at least one hydrophilic component.
43. The process of claim 41 wherein said reaction mixture comprises about 0.1 to about 50 wt% of the block copolymer.
44. The process of claim 43 wherein said reaction mixture comprises about 1 to about 20 wt% of the block copolymer.
45. The process of claim 44 wherein said reaction mixture comprises about 2 to about 15 wt% of the block copolymer.
46. An ophthalmic device comprising a silicone-containing polymer and at least one stable, block copolymer that is cross-linked but not macroscopically gelled comprising in said block copolymer's backbone, a hydrophilic segment that has a degree of polymerization in the range of about 10 to about 10,000, and a linear substrate associative segment on at least one terminal end of said block copolymer, wherein said silicone segment comprises between about 1 and about 200 siloxy units, wherein said block copolymer is associated, via the linear substrate associative segment with a surface comprising at least one hydrophobic site and provides said ophthalmic device with a reduction in lipid uptake compared to the silicone-containing polymer of at least about 20%.
47. The ophthalmic device of claim 46 wherein said lipid uptake is less than about 12 $\mu\text{g}/\text{lens}$.
48. The ophthalmic device of claim 47 wherein said lipid uptake is about 10 $\mu\text{g}/\text{lens}$ or less.

49. The ophthalmic device of claim 46 wherein said hydrophilic segment has a cross-linker to primary chain molar ratio in the range of about 0.01 to about 1.5.
50. The ophthalmic device of claim 46 wherein said at least one stable block copolymer comprises 6 to 60 siloxy repeat units.
51. The ophthalmic device of claim 46 wherein said hydrophilic segment of said block copolymer has a degree of polymerization in the range of about 50 to about 5,000.
52. The ophthalmic device of claim 51 wherein said hydrophilic segment of said block copolymer has a degree of polymerization in the range of about 100 to about 1000.
53. The ophthalmic device of claim 46 wherein hydrophilic segment and the linear substrate associative segment comprising a linear silicone are present in said block copolymer in a weight ratio, based upon the degree of polymerization, in the range of about 1:1 and about 500:1.
54. The ophthalmic device of claim 53 wherein the weight ratio of hydrophilic segment to the linear silicone, based upon degree of polymerization is in the range of about 1:1 and about 200:1.
55. The ophthalmic device of claim 46 wherein said at least one stable block copolymer comprises 6 to 60 siloxy repeat units.
56. The ophthalmic device of claim 55 wherein said at least one stable block copolymer comprises 6 to 20 siloxy repeat units.
57. An ophthalmic solution comprising at least one stable block copolymer that is cross-linked but not macroscopically gelled comprising in said polymer's backbone, a hydrophilic segment having a degree of polymerization in the range of about 10 to about 10,000, and a linear substrate associative segment on at least one terminal end of said polymer, wherein said linear substrate associative segment comprises between about 1 and about 200 siloxy units, wherein said block copolymer is present in an amount effective to reduce lipid uptake of an ophthalmic device contacted with said solution and said ophthalmic solution is transparent.
58. The ophthalmic solution of claim 57 wherein said hydrophilic segment has a cross-linker to primary chain molar ratio in the range of about 0.01 to about 1.5.
59. The ophthalmic solution of claim 57 wherein said at least one stable block copolymer comprises 6 to 60 siloxy repeat units.

60. The ophthalmic solution of claim 59 wherein said at least one stable block copolymer comprises 6 to 20 siloxy repeat units.
61. The ophthalmic solution of claim 57 wherein said at least one stable block copolymer is present in an amount in the range of about 0.005 and about 2 weight %.
62. The ophthalmic solution of claim 61 wherein said at least one stable block copolymer is present in an amount in the range of about 0.01 and about 0.5 weight %.
63. The ophthalmic solution of claim 57 wherein said hydrophilic segment of said block copolymer has a degree of polymerization in the range of about 50 to about 1,000.
64. The ophthalmic solution of claim 63 wherein said hydrophilic segment of said block copolymer has a degree of polymerization in the range of about 100 to about 500.
65. The ophthalmic solution of claim 57 wherein the hydrophilic segment and the linear substrate associative segment comprising a linear silicone segment are present in said block copolymer in a weight ratio, based upon the degree of polymerization, in the range of about 1:1 to about 500:1.
66. The ophthalmic solution of claim 65 wherein the weight ratio of the hydrophilic segment to the linear silicone segment, based upon degree of polymerization is in the range of about 1:1 to about 200:1.
67. The ophthalmic solution of claim 57 wherein said ophthalmic device is a contact lens formed from a reaction mixture comprising at least one hydrophobic component.
68. The ophthalmic solution of claim 58 where said contact lens comprises a silicone hydrogen.
69. The ophthalmic solution of claim 68 wherein said contact lens is uncoated.
70. A method of making a stable, block copolymer that is cross-linked but not macroscopically gelled, the method comprising:
- (a) contacting (i) a macro controlled radical polymerization (CRP) agent having a formula

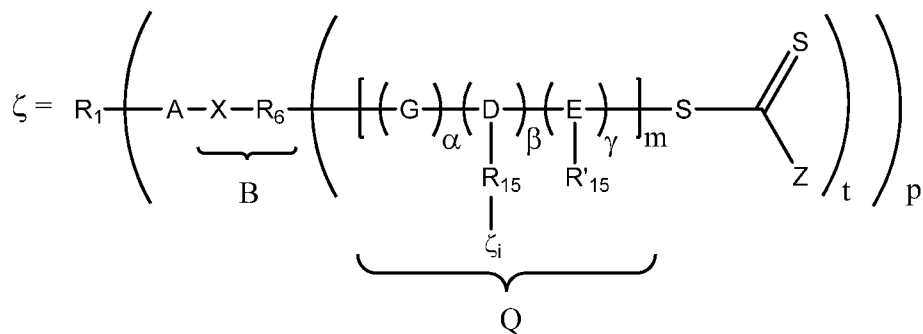


wherein [A] is polymer segment that has an affinity for a medical device and CRP is functional terminal moiety capable of controlling the polymerization of unsaturated monomers with (ii) at least one hydrophilic monomer, a free radical initiator, a cross-linking agent, and, optionally, a solvent;

- (b) polymerizing the at least one hydrophilic monomer in the presence of the [A]-CRP agent to form a hydrophilic segment on the [A]-CRP agent, such that an active portion of the macro CRP agent is on a terminal end of said hydrophilic segment and the [A] segment is on an opposite terminus; and
 - (c) cross-linking the hydrophilic segment during or after polymerization.
71. A method of making a stable, block copolymer that is cross-linked but not macroscopically gelled, the method comprising:
- (a) contacting a substrate associative polymeric free radical initiator with at least one hydrophilic monomer, a monomer that is capable of both propagation and chain transfer, and optionally, a solvent;
 - (b) initiating polymerization of at least one hydrophilic monomer and a monomer capable of both propagation and chain transfer to form a hydrophilic segment on at least one terminus of the substrate associative polymer; and
 - (c) cross-linking the hydrophilic segment during polymerization via monomeric chain transfer.
72. The process of claim 35, wherein said contact lens is not pretreated prior to said contacting step.
73. The process of claim 35, further comprising contacting said contact lens with a second solution comprising a second polymer under conditions suitable to bond or associate said second polymer with said block copolymer.
74. The process of claim 73, wherein said second polymer is selected from the group consisting of linear, branched or crosslinked polymers comprising group capable of bonding to or associating with said block copolymer.
75. The process of claim 74, wherein said block copolymer comprises proton donating groups in said hydrophilic segment and said second polymer comprises proton receiving groups.
76. The process of claim 75 wherein said second polymer is selected from the group consisting of poly-*N*-vinyl pyrrolidone, poly-*N*-vinyl-2- piperidone, poly-*N*-vinyl-2-caprolactam, poly-*N*-vinyl-3-methyl-2-caprolactam, poly-*N*-vinyl-3-methyl-2-piperidone,

poly-*N*-vinyl-4-methyl-2-piperidone, poly-*N*-vinyl-4-methyl-2-caprolactam, poly-*N*-vinyl-3-ethyl-2-pyrrolidone, and poly-*N*-vinyl-4,5-dimethyl-2-pyrrolidone, polyvinylimidazole, poly-*N,N*-dimethylacrylamide, polyvinyl alcohol, polyethylene-oxide, poly-2-ethyl-oxazoline, heparin polysaccharides, polysaccharides, and mixtures and copolymers thereof.

77. The process of claim 74, wherein said block copolymer comprises proton receiving groups in said hydrophilic segment and said second polymer comprises proton donating groups.
78. The process of claim 74 wherein said at least one second polymer is present in the solution in concentrations up to about 50,000 ppm.
79. The process of claim 74 wherein said at least one second polymer is present in the solution in concentrations between about 10 and 5000 ppm.
80. The process of claim 74 wherein said second contacting step is conducted at a pH between about 6 and about 8.
81. The composition of claim 1 wherein block copolymer has primary chains, ζ , represented by the formula



wherein

R_1 is selected from the group consisting of substituted and unsubstituted C_{1-24} alkyl;

A is selected from the group consisting of linear dialkyl or diaryl polysiloxanes having 6-1,000 repeating units, and alkenes having 2 to 25 carbon atoms which may be optionally substituted with atoms selected from S, O, N, P and combinations thereof;

R_6 is a free radical leaving group that initiates free radical polymerization;

X is selected from $-\text{O}-(\text{CO})-$, $-(\text{CO})\text{O}-$, $-\text{NR}_8-(\text{CO})-$, $-(\text{CO})\text{NR}_8-$, $-\text{O}-$, C_{1-12} alkylene, C_{1-4} alkylene or a direct bond;

G is a polymerization residue of at least one hydrophilic monomer;

D is a polymerization residue comprising at least one reactive group, R'_{15}

E is a polymerization residue comprising R_{15} a residue of a crosslinker which has polymerized with another polymer segment ζ_i

α , β , γ are relative molar amounts (in mole fraction) of G, D, and E;

Z is selected from the group consisting of hydrogen, chlorine, fluorine, optionally substituted alkyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted alkylthio, optionally substituted alkoxy, optionally substituted alkoxycarbonyl, optionally substituted aryloxycarbonyl ($-\text{COOR}''$), carboxy ($-\text{COOH}$), optionally substituted acyloxy ($-\text{O}_2\text{CR}''$), optionally substituted carbamoyl ($-\text{CONR}''_2$), cyano ($-\text{CN}$), dialkyl- or diaryl-phosphonato [$-\text{P}(=\text{O})(\text{OR}'')_2$], dialkyl- or diaryl-phosphinato [$-\text{P}(=\text{O})(\text{OR}'')_2$], and a polymer chain formed by any mechanism;

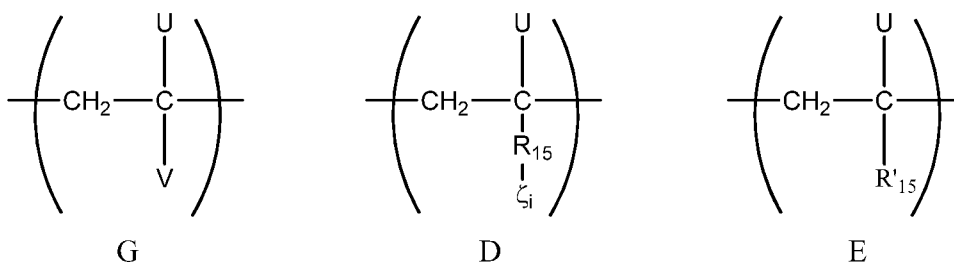
ζ_i is another primary chain that is cross-linked to a primary chain, ζ ,

t is 1 or an integer greater than 1; and p is 1 or an integer greater than 1.

82. The composition of claim 81 wherein G is a residue of at least one hydrophilic monomer selected from the group consisting of *N*-vinyl pyrrolidone, *N*-vinyl-2- piperidone, *N*-vinyl-2-caprolactam, *N*-vinyl-3-methyl-2- caprolactam, *N*-vinyl-3-methyl-2-piperidone, *N*-vinyl-4-methyl-2- piperidone, *N*-vinyl-4-methyl-2-caprolactam, *N*-vinyl-3-ethyl-2- pyrrolidone, *N*-vinyl-4,5-dimethyl-2-pyrrolidone, vinylimidazole, *N,N*-dimethylacrylamide, acrylamide, *N,N*-bis(2-hydroxyethyl)acrylamide, acrylonitrile, *N*-isopropyl acrylamide, vinyl acetate, (meth)acrylic acid, polyethylene glycol (meth)acrylates, 2-ethyl oxazoline, *N*-(2-hydroxypropyl) (meth)acrylamide, *N*-(2-hydroxyethyl) (meth)acrylamide, 2-methacryloyloxyethyl phosphorylcholine, 3-(dimethyl(4-vinylbenzyl)ammonio)propane-1-sulfonate (DMVBAPS), 3-((3-acrylamidopropyl)dimethylammonio)propane-1-sulfonate (AMPDAPS), 3-((3-methacrylamidopropyl)dimethylammonio)propane-1-sulfonate (MAMPDAPS), 3-((3-(acryloyloxy)propyl)dimethylammonio)propane-1-sulfonate (APDAPS), methacryloyloxy)propyl)dimethylammonio)propane-1-sulfonate (MAPDAPS), *N,N*-dimethylaminopropyl(meth)acrylamide, *N*-vinyl-*N*-methylacetamide, *N*-vinylacetamide, *N*-vinyl-*N*-methylpropionamide, *N*-vinyl-*N*-methyl-2-

methylpropionamide, *N*-vinyl-2-methylpropionamide, *N*-vinyl-*N,N'*-dimethylurea, and the like, and mixtures thereof.

83. The composition of claim 81 wherein G is a residue of at least one hydrophilic monomer selected from the group consisting of *N*-vinyl pyrrolidone, *N*-vinyl-*N*-methylacetamide, 2-methacryloyloxyethyl phosphorylcholine, (meth)acrylic acid, *N,N*-dimethylacrylamide, *N*-hydroxypropyl methacrylamide, mono-glycerol methacrylate, 2-hydroxyethyl acrylamide, bishydroxyethyl acrylamide, and 2,3-dihydroxypropyl (meth)acrylamide and the like and mixtures thereof.
84. The composition of claim 82 or 83 wherein G further comprises a residue of at least one charged monomers selected from the group consisting of methacrylic acid, acrylic acid, 3-acrylamidopropionic acid (ACA1), 4-acrylamidobutanoic acid, 5-acrylamidopentanoic acid (ACA2), 3-acrylamido-3-methylbutanoic acid (AMBA), *N*-vinylloxycarbonyl- α -alanine, *N*-vinylloxycarbonyl- β -alanine (VINAL), 2-vinyl-4,4-dimethyl-2-oxazolin-5-one (VDMO), reactive sulfonate salts, including, sodium-2-(acrylamido)-2-methylpropane sulphonate (AMPS), 3-sulphopropyl (meth)acrylate potassium salt, 3-sulphopropyl (meth)acrylate sodium salt, bis 3- sulphopropyl itaconate di sodium, bis 3- sulphopropyl itaconate di potassium, vinyl sulphonate sodium salt, vinyl sulphonate salt, styrene sulfonate, sulfoethyl methacrylate, and combinations thereof.
85. The composition of claim 81 where G, D and E are repeating units of the formulae



wherein U is selected from the group consisting of hydrogen, halogen, C₁-C₄ alkyl which may be optionally substituted with hydroxyl, alkoxy, aryloxy (OR''), carboxy, acyloxy, aroyloxy (O₂CR''), alkoxy-carbonyl, aryloxy-carbonyl (CO₂R'') and combinations thereof;

V is selected from the group consisting of hydrogen, R'', CO₂H, CO₂R'', COR'', CN, CONH₂, CONHR'', CONR''₂, O₂CR'', OR'' and halogen; cyclic and acyclic N-vinyl amides and combinations thereof;

R'' is independently selected from the group consisting of optionally substituted C₁-C₁₈ alkyl, C₂-C₁₈ alkenyl, aryl, heterocyclyl, alkaryl wherein the substituents are independently selected from the group that consists of epoxy, hydroxyl, alkoxy, acyl, acyloxy, carboxy and carboxylates, sulfonic acid and sulfonates, alkoxy- or aryloxy-carbonyl, isocyanato, cyano, silyl, halo, and dialkylamino; phosphoric acid;

R₁₅ is any carbon-containing structure that comprises a cross-link between two ζ-chains, and is derived from R'₁₅; and

R'₁₅ is any carbon-containing structure containing at least one group capable of forming a covalent, ionic or hydrogen bond with other ζ-chains.

86. The composition of claim 85, wherein

R₁ is selected from the group consisting of substituted and unsubstituted C₁₋₁₀ alkyl;

A is selected from the group consisting linear dialkyl or diaryl polysiloxanes of 6-200;

R₆ is selected from divalent groups selected from the group consisting of optionally substituted alkylene; optionally substituted saturated, unsaturated or aromatic carbocyclic or heterocyclic rings; optionally substituted alkylthio; optionally substituted alkoxy; or optionally substituted dialkylamino;

U is selected from the group consisting of H, methyl;

R'' is selected from the group consisting of methyl, pyrrolidonyl, -N-(CH₃)₂, -N(CH₃)-COCH₃ (N-vinyl acetamide), -CH₂CH₂-COOH, -CH₂CH₂CH₂-COOH, -CH₂CH₂CH₂CH₂-COOH, -(CH₃)₂-CH₂-SO₃H, -(CH₃)₂-CH₂-CO₂H, -CH₂CH₂CH₂-⁺N(CH₃)₂-CH₂CH₂CH₂-SO₃⁻, -CH₂CH₂CH₂-⁺N(CH₃)₂-CH₂CH₂-CO₂⁻, -CH₂CH₂CH₂-⁺N(CH₃)₂, and combinations thereof; and

R'₁₅ comprises one or more unsaturated bonds.

87. The composition of claim 85 wherein

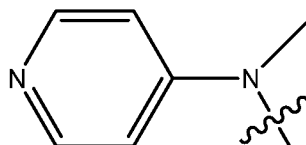
R₁ is selected from the group consisting of substituted or unsubstituted C₁₋₆ alkyl groups;

A is selected from the group consisting linear dialkyl or diaryl polysiloxanes of 6-20 repeating units;

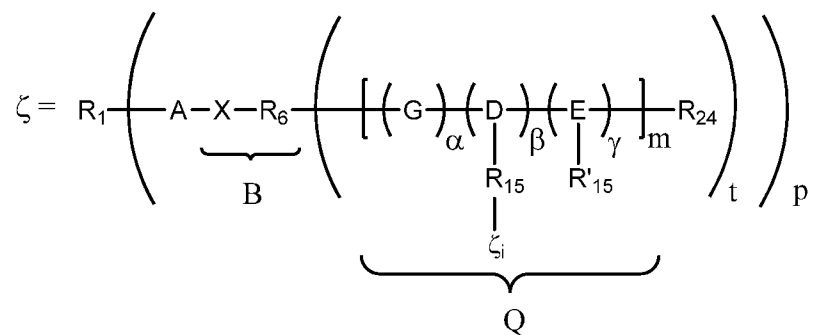
R₆ is selected from optionally substituted benzyl, optionally substituted phenyl, ethanoate, optionally substituted propionate, 4-cyanopentanoate, or isobutyroate functionalities;

V is selected from -N-(CH₃)₂.

88. The composition of claim 81 wherein Z comprises a switchable functional group,



89. The composition of claim 1 wherein block copolymer has primary chains, ζ , represented by the formula



wherein

R₁ is selected from the group consisting of substituted and unsubstituted C₁₋₂₄ alkyl;

A is selected from the group consisting of linear dialkyl or diaryl polysiloxanes having 6-1,000 repeating units, and alkenes having 2 to 25 carbon atoms which may be optionally substituted with atoms selected from S, O, N, P and combinations thereof;

R₆ is a free radical leaving group that initiates free radical polymerization;

X is selected from $-\text{O}-(\text{CO})-$, $-(\text{CO})\text{O}-$, $-\text{NR}_8-(\text{CO})-$, $-(\text{CO})\text{NR}_8-$, $-\text{O}-$, C_{1-12} alkylene, C_{1-4} alkylene or a direct bond;

G is a polymerization residue of at least one hydrophilic monomer;

D is a polymerization residue comprising at least one reactive group, R'_{15}

E is a polymerization residue comprising R_{15} a residue of a crosslinker which has polymerized with another polymer segment ζ_i

R_{24} is any agent capable of controlling polymerization.

α , β , γ are relative molar amounts (in mole fraction) of G, D, and E; and

t is 1 or an integer greater than 1; and p is 1 or an integer greater than 1.

90. The composition of claim 89 wherein R_{24} is selected from the group consisting of monovalent RAFT agents, ATRP agents, TERP agents and NMP agents.

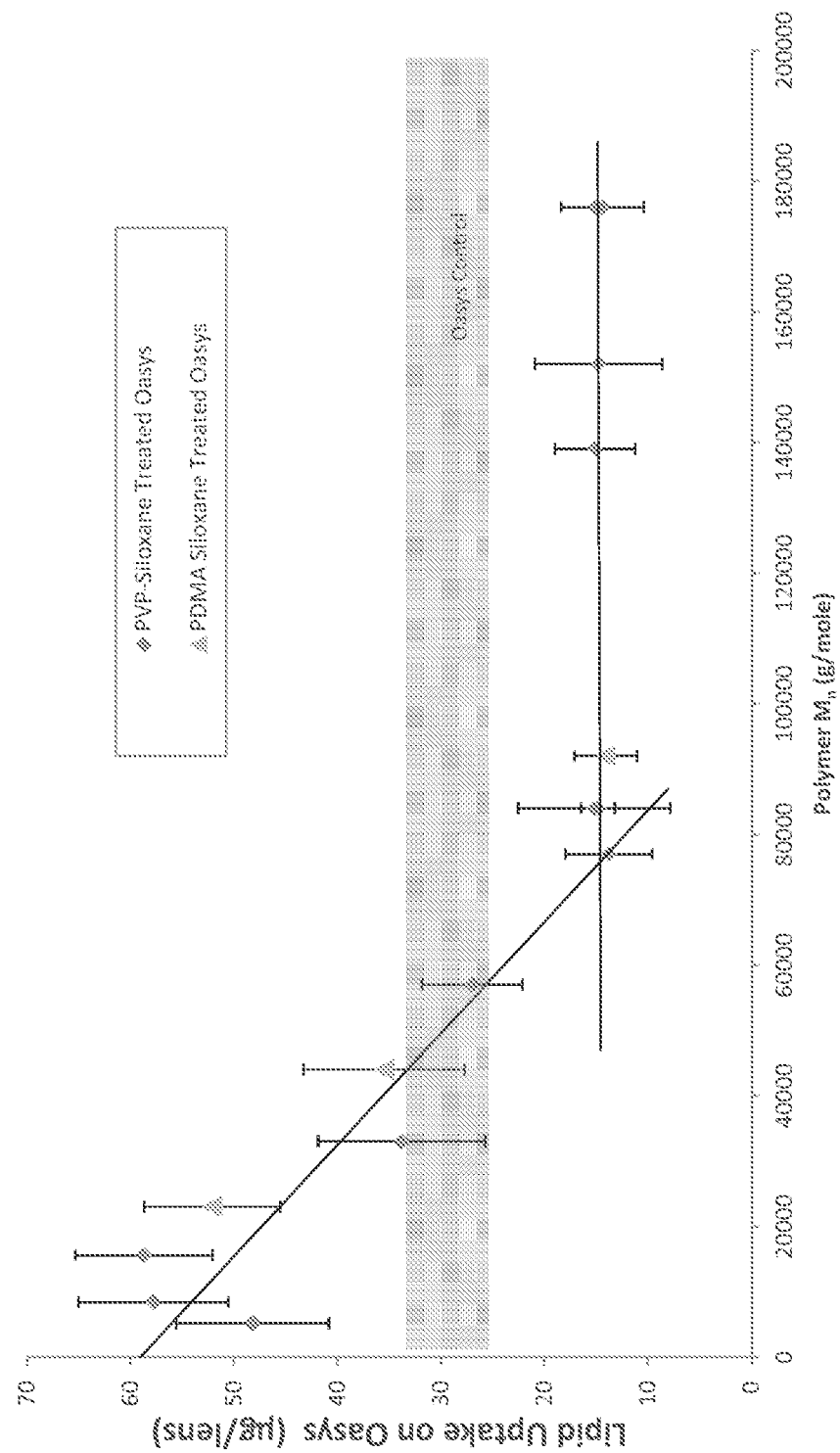


Figure 1
PRIOR ART

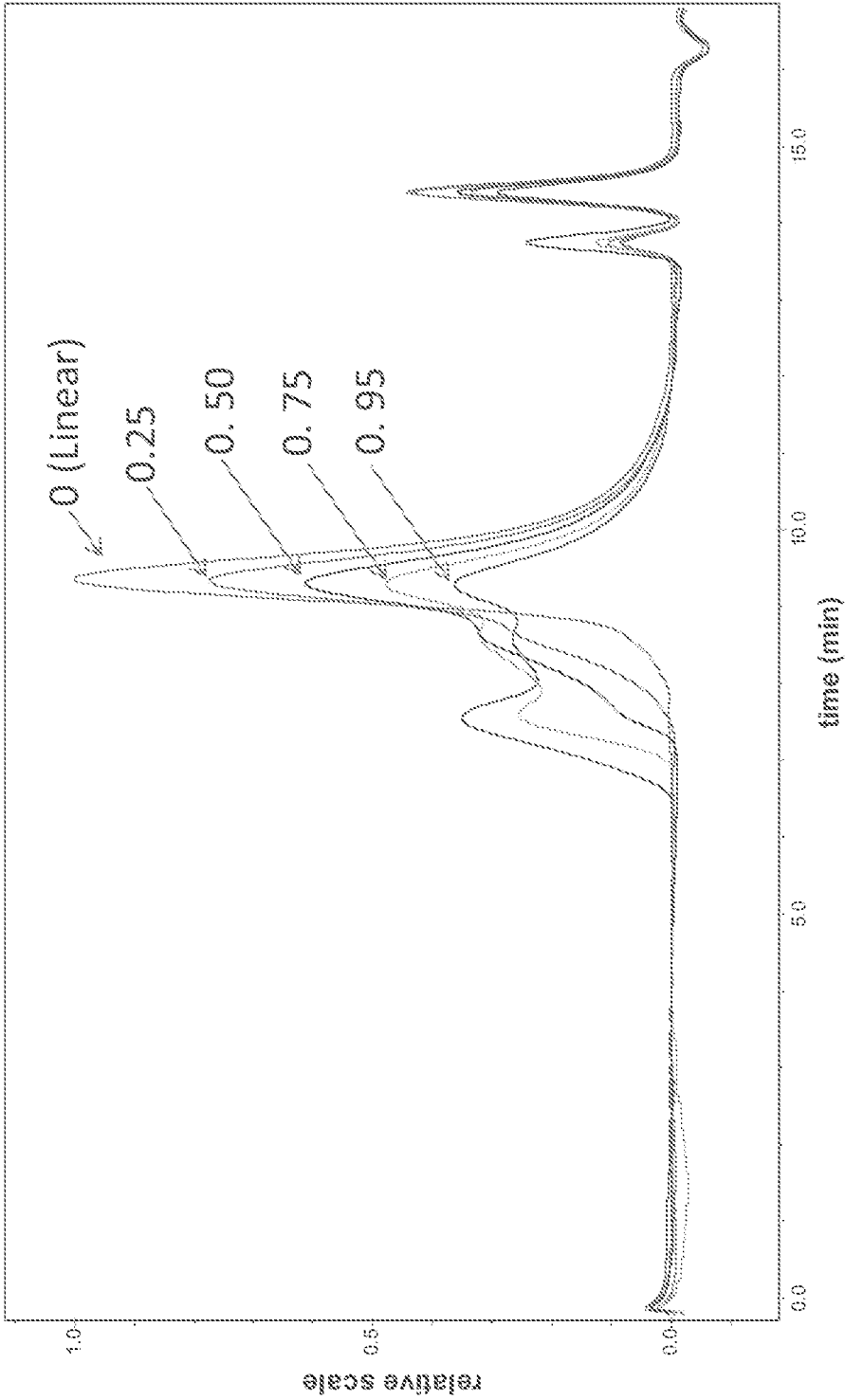


Figure 2

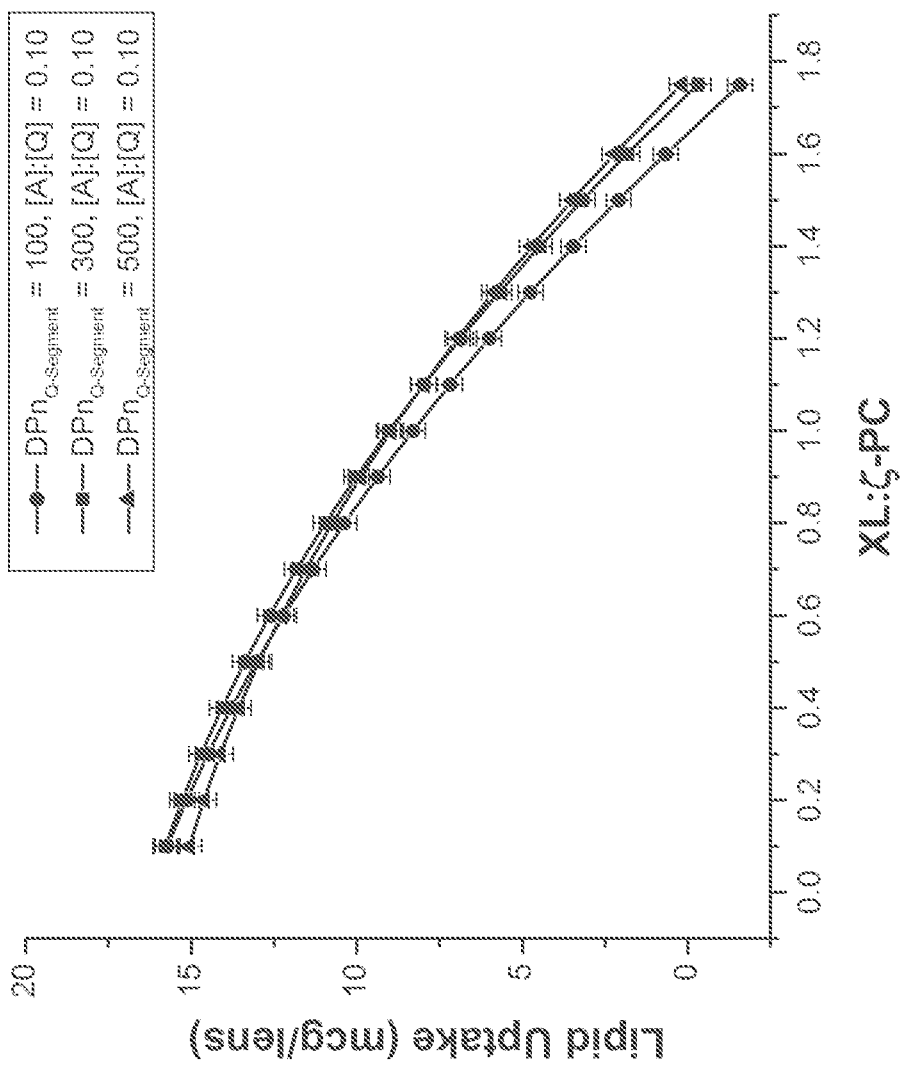


Figure 3

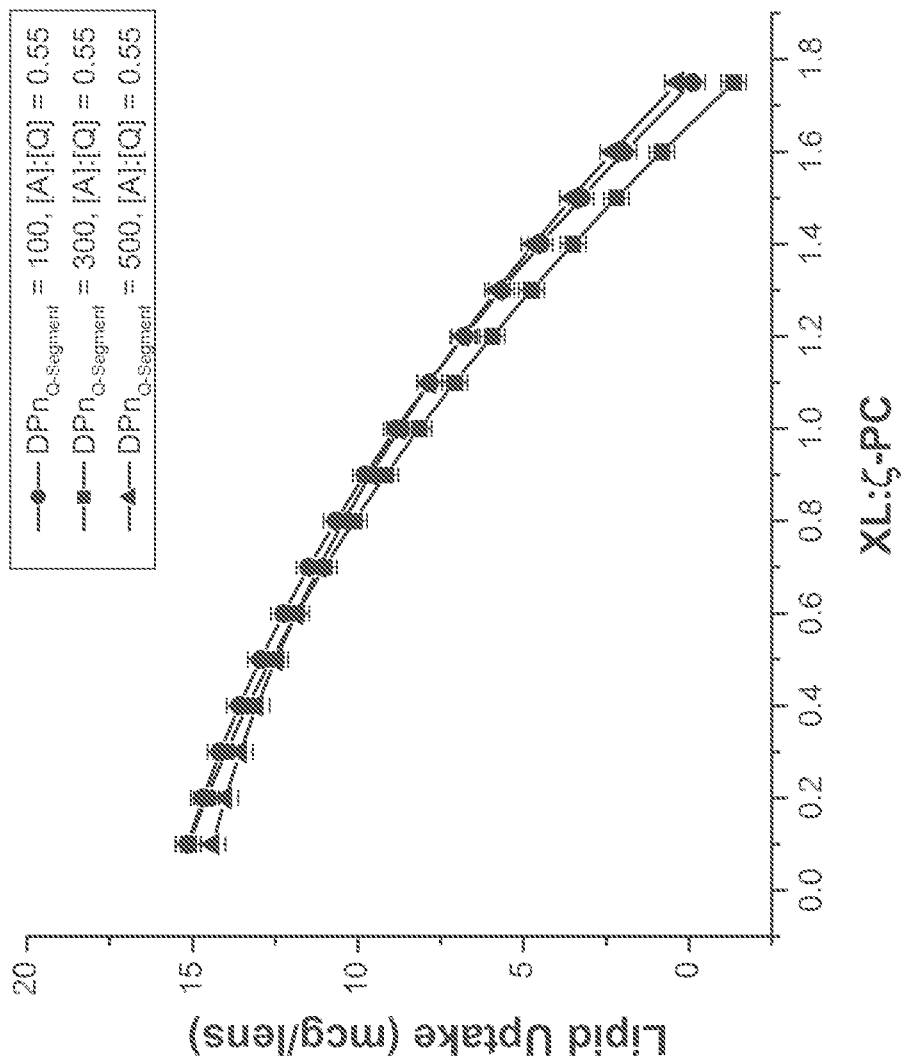


Figure 4

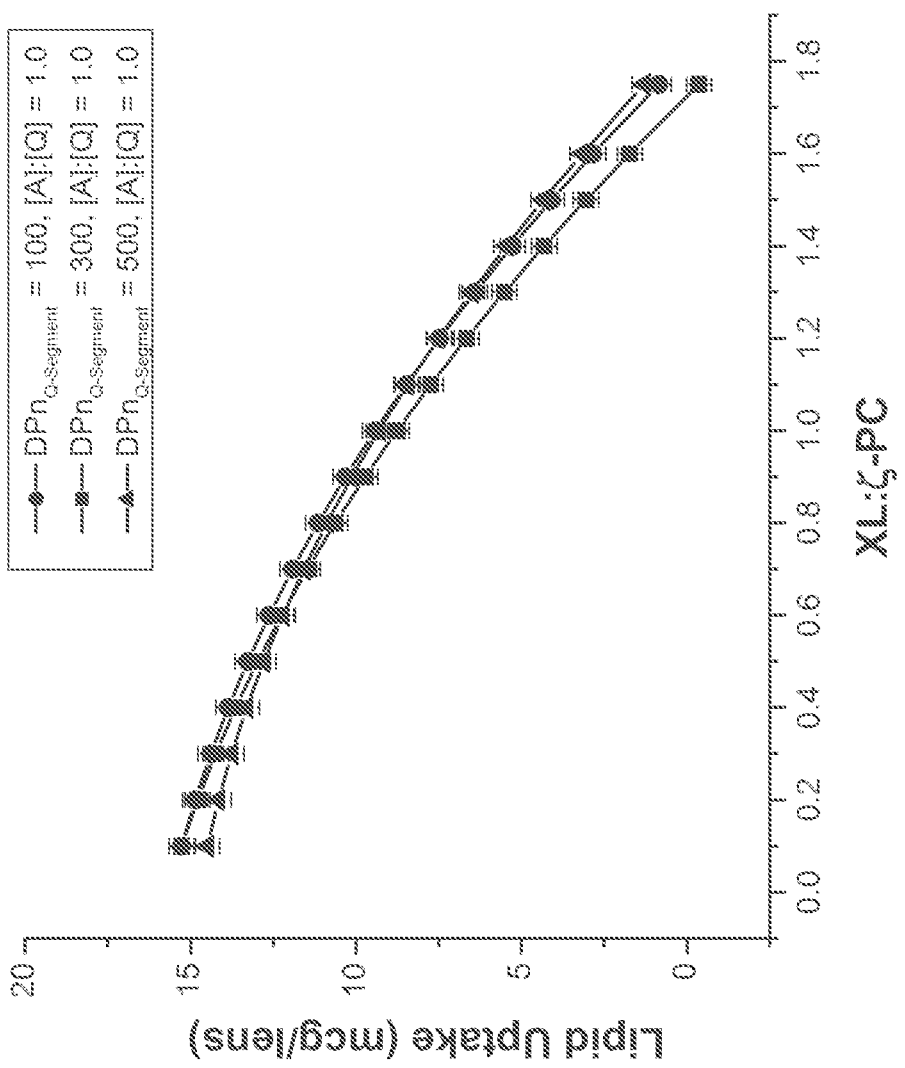


Figure 5

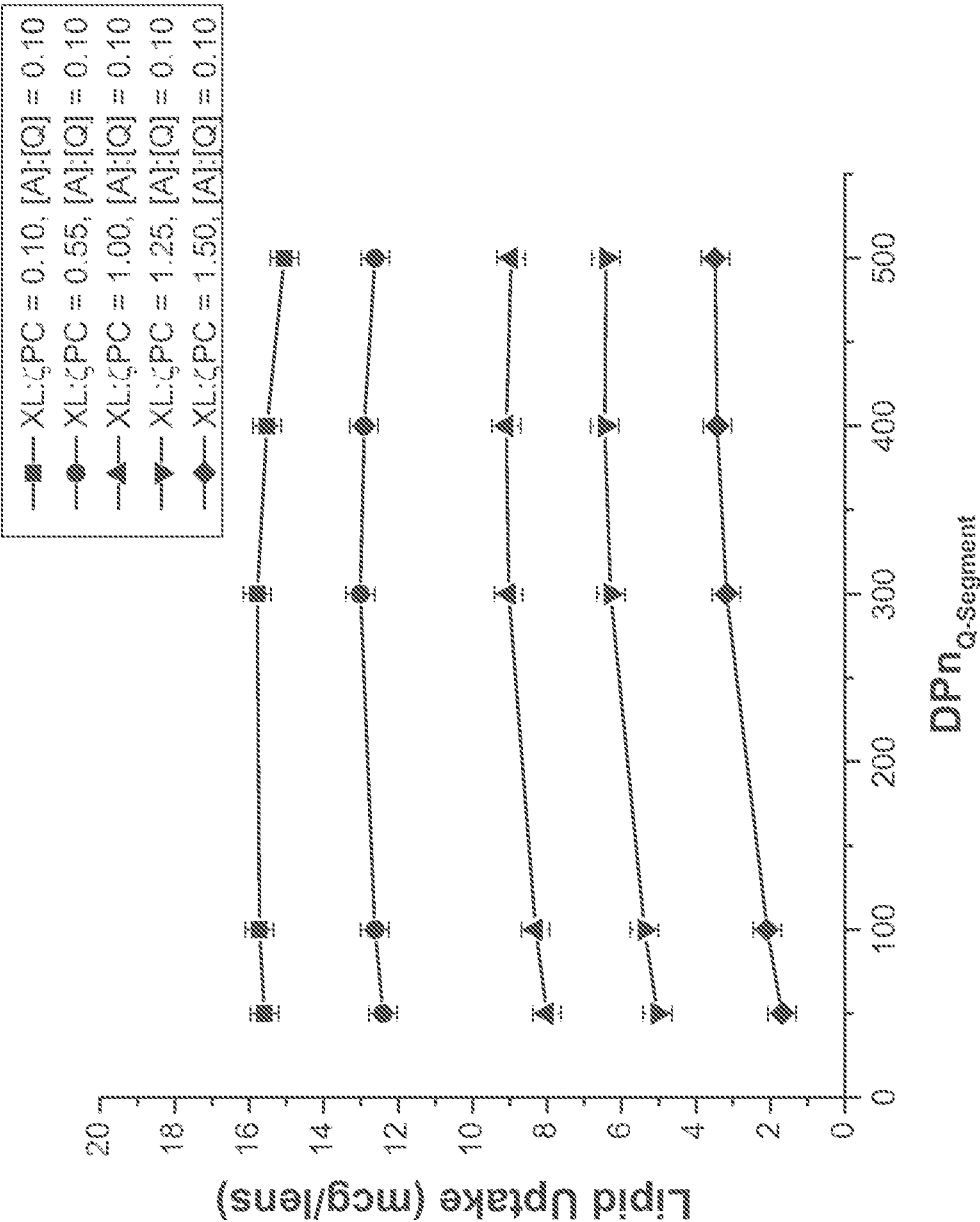


Figure 6

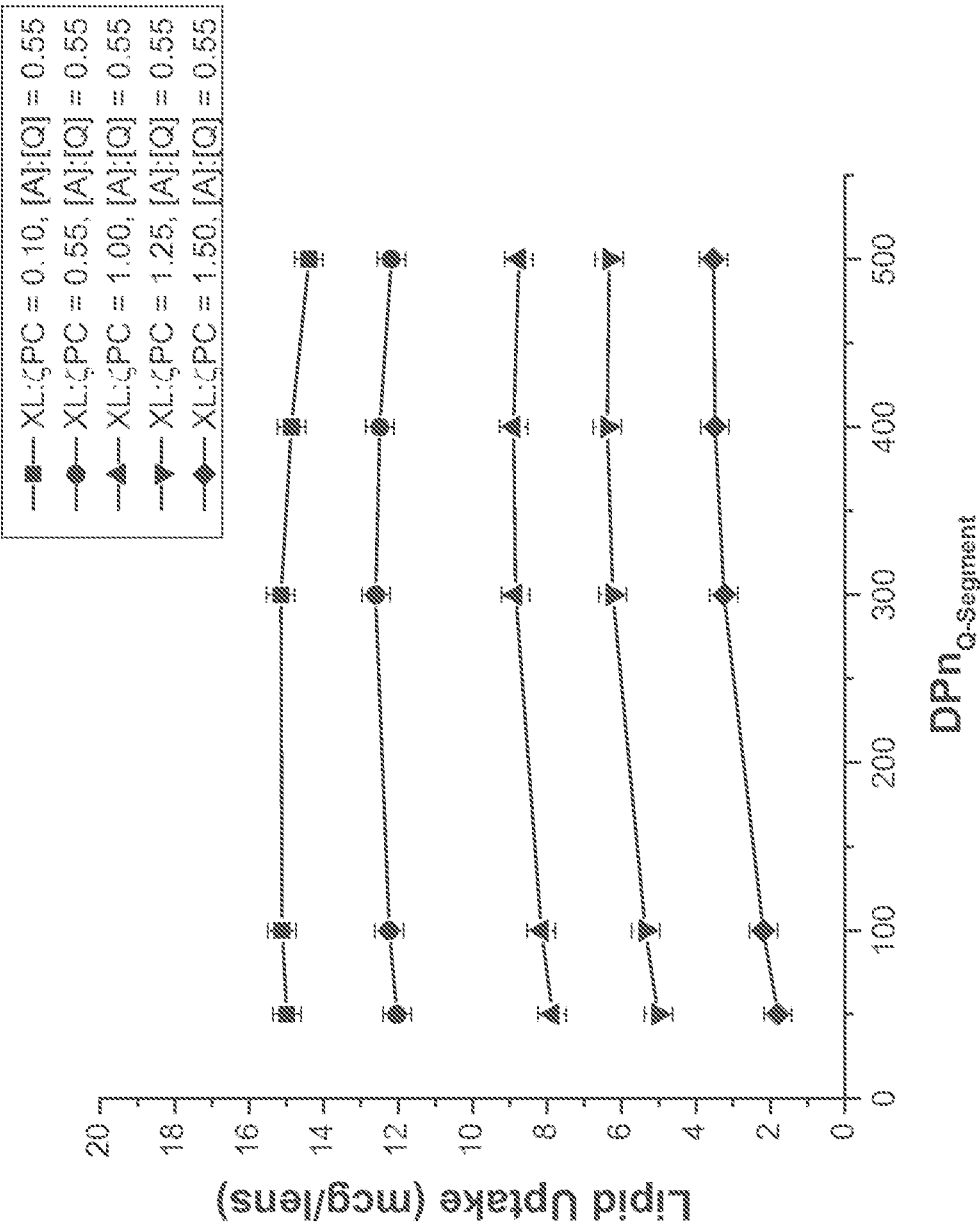


Figure 7

8/8

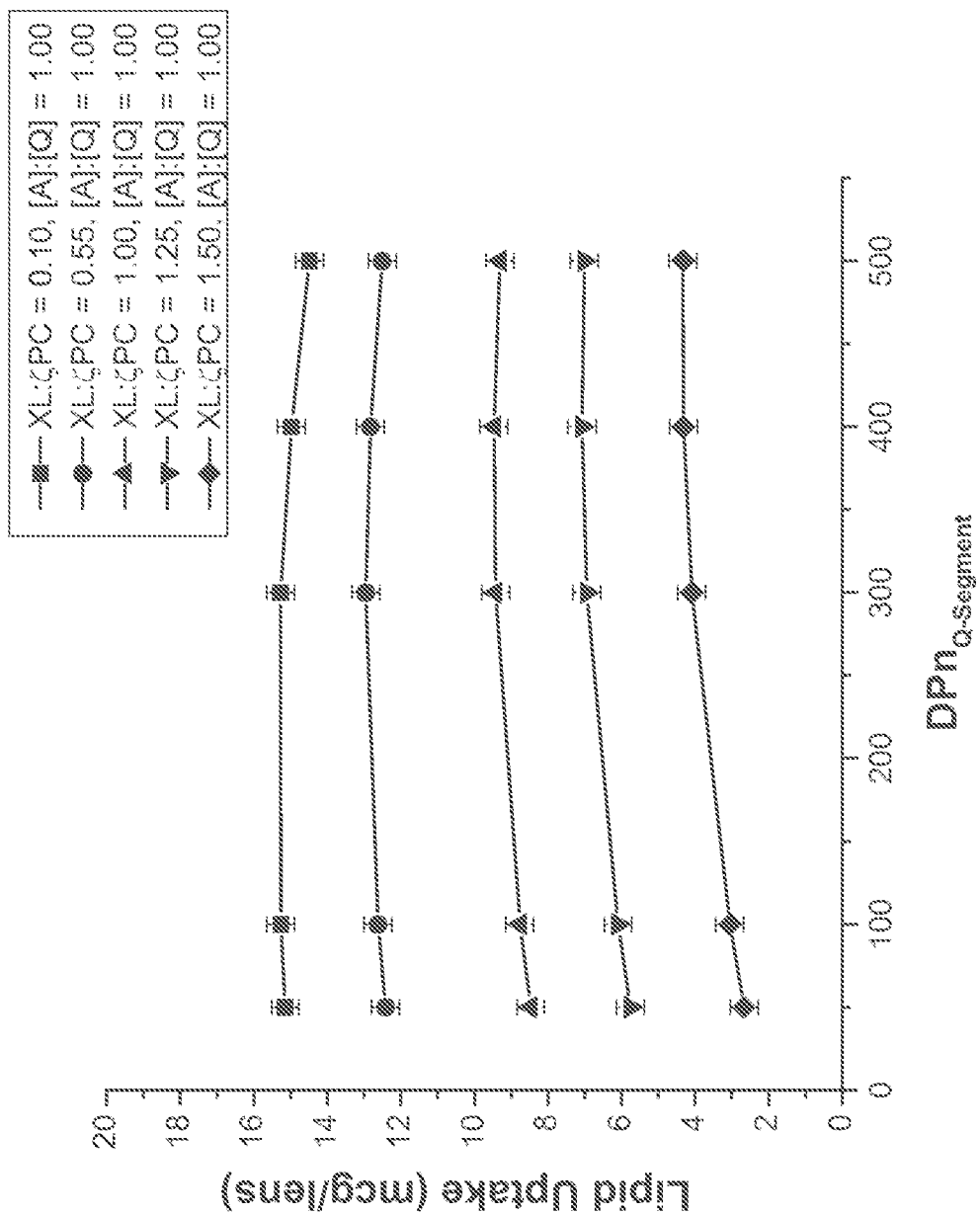


Figure 8



(12) 发明专利申请

(10) 申请公布号 CN 104334596 A

(43) 申请公布日 2015. 02. 04

(21) 申请号 201380027478. 7

(22) 申请日 2013. 05. 08

(30) 优先权数据

61/651, 767 2012. 05. 25 US

(85) PCT国际申请进入国家阶段日

2014. 11. 25

(86) PCT国际申请的申请数据

PCT/US2013/040066 2013. 05. 08

(87) PCT国际申请的公布数据

W02013/176886 EN 2013. 11. 28

(71) 申请人 庄臣及庄臣视力保护公司

地址 美国佛罗里达州

(72) 发明人 C. W. 斯卡勒斯 K. P. 麦卡贝

B. M. 希利

(74) 专利代理机构 中国专利代理(香港)有限公司 72001

代理人 罗文锋 梁谋

(51) Int. Cl.

C08F 293/00 (2006. 01)

G02B 1/00 (2006. 01)

C08J 7/00 (2006. 01)

B82Y 30/00 (2006. 01)

C08L 53/00 (2006. 01)

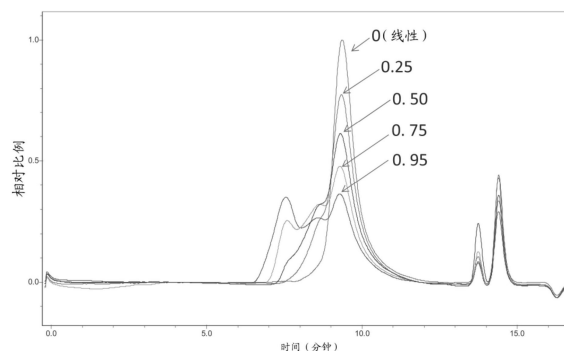
权利要求书9页 说明书49页 附图8页

(54) 发明名称

聚合物和纳米凝胶材料及其制备和使用方法

(57) 摘要

本文提供了组合物,其包含下式的嵌段共聚物:[A]-B-[Q],其中[A]为对基材具有亲和力的聚合物;B为连接基团,所述连接基团包含分子量不超过1000克/摩尔的任选地取代的多价连接基团;并且[Q]包含半交联的未胶凝聚合物,所述聚合物来源于烯键式不饱和单体与多官能烯键式不饱和单体的共聚。所述嵌段共聚物经由所述[Q]链段交联,但未宏观胶凝。所述[Q]链段为亲水性的并且具有在约10至约10,000范围内的聚合度。所述[A]链段位于所述嵌段共聚物的至少一个末端上,包含介于约1和约200个之间的重复单元。所述嵌段共聚物经由所述线性基材缔合型链段与包含至少一个疏水性位点的表面例如有机硅水凝胶缔合。所述聚合物可结合到用于制备所述有机硅水凝胶的制剂,或可在所述有机硅水凝胶形成后再与其接触。



1. 一种组合物,其包含下式的水溶性嵌段共聚物:

[A]-B-[Q],其中

[A] 为对医疗装置具有亲和力的链段;

B 为连接基团,其包含分子量不超过 1000 克 / 摩尔的任选地取代的多价连接基团;并且

[Q] 包含半交联的未胶凝链段,所述链段来源于至少一种烯键式不饱和单体与多官能烯键式不饱和单体的共聚。

2. 根据权利要求 1 所述的组合物,其中:

所述嵌段共聚物为稳定的、水溶性的并且交联但未宏观胶凝的;

[Q] 包含多个交联的一级聚合物链,每个一级聚合物链具有在约 10 至约 10,000 范围内的聚合度;并且

[A] 包含位于所述嵌段共聚物的至少一个末端上的线性基材缔合型链段,其中所述基材缔合型链段包含介于约 1 和约 1000 个之间的重复单元,并且所述嵌段共聚物经由所述线性基材缔合型链段与所述医疗装置的表面缔合。

3. 根据权利要求 2 所述的组合物,其中所述基材缔合型链段选自疏水性链段、亲水性基材缔合型链段、质子提供链段、质子接受链段、离子性链段、络合链段和刺激响应性链段。

4. 根据权利要求 3 所述的组合物,其中所述疏水性链段包含甲硅烷氧基基团。

5. 根据权利要求 3 所述的组合物,其中所述质子提供链段包含一种或多种醇。

6. 根据权利要求 3 所述的组合物,其中所述质子接受链段包含一种或多种酰胺。

7. 根据权利要求 3 所述的组合物,其中所述离子性链段包含以下中的一种或多种:羧酸盐、磺酸盐、铵盐和磷盐。

8. 根据权利要求 3 所述的组合物,其中所述络合链段包含一个或多个硼酸官能团和/或羟基官能团。

9. 根据权利要求 3 所述的组合物,其中所述刺激响应性链段包含选自以下的聚合物:温度响应性聚合物、pH 响应性聚合物、电解质响应性聚合物、光响应性聚合物,以及它们的混合物。

10. 根据权利要求 9 所述的组合物,其中所述温度响应性聚合物为聚(N-异丙基丙烯酰胺)(PNIPAM)。

11. 一种组合物,其包含两亲性纳米凝胶材料,所述两亲性纳米凝胶材料包含一种或多种交联的共聚物,其中所述共聚物包含具有在约 10 至约 10,000 范围内的聚合度的一个或多个亲水性链段,并且其中所述一个或多个亲水性链段在至少一个末端上包含线性有机硅链段,其中所述线性有机硅链段包含介于约 1 和约 200 个之间的甲硅烷氧基单元,并且所述两亲性纳米凝胶材料经由所述线性有机硅链段与包含至少一种部分疏水性基材的表面缔合。

12. 根据权利要求 11 所述的组合物,其中所述纳米凝胶的所述亲水性链段具有在约 50 至约 5,000 范围内的聚合度。

13. 根据权利要求 11 所述的组合物,其中所述纳米凝胶的所述亲水性链段具有在约 100 至约 1000 范围内的聚合度。

14. 根据权利要求 11 所述的组合物,其中所述纳米凝胶的所述亲水性链段具有在约

100 至约 500 范围内的聚合度。

15. 根据权利要求 11 所述的组合物,其中所述纳米凝胶的所述亲水性链段具有在约 100 至约 300 范围内的聚合度。

16. 根据权利要求 11 所述的组合物,其中所述亲水性链段和所述线性有机硅链段基于所述聚合度以约 1:1 至约 500:1 范围内的重量比存在于所述纳米凝胶中。

17. 根据权利要求 16 所述的组合物,其中所述亲水性链段与所述线性有机硅链段的重量比基于所述聚合度在约 1:1 至约 200:1 的范围内。

18. 根据权利要求 17 所述的组合物,其中所述亲水性链段与所述线性有机硅链段的重量比基于所述聚合度在约 1:1 至约 10:1 的范围内。

19. 根据权利要求 11 所述的组合物,其中所述亲水性链段的交联剂与一级链的摩尔比在约 0.01 至约 1.5 的范围内。

20. 根据权利要求 11 所述的组合物,其中所述亲水性链段与所述两亲性共聚物的具有小于约 1.5 的多分散性指数 (PDI) 的其它亲水性链段交联。

21. 根据权利要求 20 所述的组合物,其中所述亲水性链段通过共价键合、离子键合、氢键合或它们的组合进行交联。

22. 根据权利要求 11 所述的组合物,其中所述有机硅链段包含聚二烷基硅氧烷、聚二芳基硅氧烷,以及它们的混合物。

23. 根据权利要求 22 所述的组合物,其中所述烷基选自 C_1 - C_4 烷基。

24. 根据权利要求 22 所述的组合物,其中所述聚二烷基硅氧烷包含聚二甲基硅氧烷或聚二乙基硅氧烷。

25. 根据权利要求 11 所述的组合物,其中所述亲水性链段由选自以下的单体形成:乙烯基酰胺、乙烯基内酯、乙烯基酰亚胺、乙烯基内酰胺、亲水性(甲基)丙烯酸酯、(甲基)丙烯酰胺,以及它们的混合物。

26. 根据权利要求 20 所述的组合物,其中所述亲水性链段通过选自以下的交联剂进行交联: N,N' -亚烷基双(甲基)丙烯酰胺、聚亚烷基二醇二(甲基)丙烯酸酯、聚亚烷基二醇二(甲基)丙烯酰胺,以及它们的组合。

27. 根据权利要求 11 所述的组合物,其中所述包含至少一种部分疏水性基材的表面包含有机硅水凝胶,所述有机硅水凝胶在所述表面经所述两亲性纳米凝胶材料处理后具有不超过约 50° 的接触角。

28. 一种制备交联但未宏观胶凝的稳定嵌段共聚物的方法,所述方法包括:

(a) 使末端官能化的聚二烷基硅氧烷与能够控制不饱和单体的聚合的官能部分反应,以形成聚硅氧烷官能的受控自由基聚合 (CRP) 剂;

(b) 使所述聚硅氧烷官能的 CRP 剂与至少一种亲水性单体、自由基引发剂、交联剂和任选的溶剂接触;

(c) 在所述聚硅氧烷官能的 CRP 剂的存在下聚合所述至少一种亲水性单体,以在所述聚硅氧烷官能的 CRP 剂上形成亲水性链段,使得所述 CRP 化合物的活性部分位于所述亲水性链段的末端上,并且有机硅链段位于相对的末端上;以及

(d) 在聚合期间使所述亲水性链段交联。

29. 根据权利要求 28 所述的方法,其中所述 CRP 剂为可逆加成断裂转移 (RAFT) 剂。

30. 根据权利要求 28 所述的方法,其中所述 CRP 剂为原子转移自由基聚合 (ATRP) 剂。
31. 根据权利要求 28 所述的方法,其中所述 CRP 剂为碲化物介导的聚合 (TERP) 剂。
32. 根据权利要求 28 所述的方法,其中所述 CRP 剂为硝基氧介导的活性自由基聚合 (NMP) 剂。
33. 根据权利要求 11 所述的组合物,其中所述嵌段共聚物通过以下步骤形成:
- (a) 使羟基烷基封端的聚二烷基硅氧烷与 4-(溴甲基)苯甲酰基溴在至少一种受阻非亲核胺的存在下反应,并随后使硫代羰基硫代阴离子反应以形成聚硅氧烷官能的 RAFT 剂,其具有有机硅链段和位于所述有机硅链段的一个末端上的二硫化合物;
- (b) 使所述聚硅氧烷官能的 RAFT 剂与至少一种亲水性单体、自由基引发剂、交联剂和任选的溶剂接触;
- (c) 在所述聚硅氧烷官能的 RAFT 剂的存在下聚合所述至少一种亲水性单体,以在所述聚硅氧烷官能的 RAFT 剂上形成亲水性链段,使得所述二硫化合物位于所述亲水性链段的末端上,并且所述有机硅链段位于相对的末端上;以及
- (d) 在聚合期间使所述亲水性链段与交联剂交联。
34. 根据权利要求 11 所述的组合物,其中所述嵌段共聚物通过以下步骤形成:
- (a) 使硅烷封端的聚二烷基硅氧烷与 1-(氯甲基)-4-乙烯基苯在铂催化剂的存在下反应,并随后使硫代羰基硫代阴离子反应以形成聚硅氧烷官能的 RAFT 剂,所述聚硅氧烷官能化 RAFT 剂具有有机硅链段和位于所述有机硅链段的一个末端上的硫代羰基硫代化合物;
- (b) 使所述聚硅氧烷官能的 RAFT 剂与至少一种亲水性单体、自由基引发剂、交联剂和任选的溶剂接触;以及
- (c) 在所述聚硅氧烷官能的 RAFT 剂的存在下聚合至少一种亲水性单体,以在所述聚硅氧烷官能的 RAFT 剂上形成亲水性链段,使得所述二硫化合物位于所述亲水性链段的末端上,并且所述有机硅链段位于相对的末端上;以及
- (d) 在聚合期间使所述亲水性链段交联。
35. 一种方法,其包括在适于使嵌段共聚物与含有机硅的接触镜片缔合的接触条件下,使所述含有机硅的接触镜片与溶液接触,所述溶液以有效抑制所述镜片的类脂吸收率的量包含至少一种交联但未宏观胶凝的稳定嵌段共聚物,所述嵌段共聚物在所述聚合物的主链中包含具有在约 10 至约 10,000 范围内的聚合度的亲水性链段和位于所述嵌段共聚物的至少一个末端上的线性基材缔合型链段,其中所述基材缔合型链段包含介于约 1 和约 200 个之间的重复单元。
36. 根据权利要求 35 所述的方法,其中所述接触镜片包括有机硅水凝胶接触镜片。
37. 根据权利要求 35 所述的方法,其中所述亲水性链段的交联剂与一级链的摩尔比在约 0.01 至约 1.5 的范围内。
38. 根据权利要求 35 所述的方法,其中所述有效量为至少约 10ppm。
39. 根据权利要求 35 所述的方法,其中所述有效量为约 10ppm 至约 10,000ppm。
40. 根据权利要求 35 所述的方法,其中所述镜片的类脂吸收率不超过约 10 微克/镜片。
41. 一种方法,其包括:

(a) 形成反应混合物,所述反应混合物包含至少一种含有机硅组分、至少和至少一种交联但未宏观胶凝的稳定嵌段共聚物,所述嵌段共聚物在所述聚合物的主链中包含具有在约 10 至约 10,000 范围内的聚合度的亲水性链段和位于所述嵌段共聚物的至少一个末端上的线性有机硅链段,其中所述有机硅链段包含介于约 1 和约 200 个之间的甲硅烷氧基单元,以及

(b) 固化所述反应混合物以形成接触镜片。

42. 根据权利要求 41 所述的方法,其中所述反应混合物还包含至少一种亲水性组分。

43. 根据权利要求 41 所述的方法,其中所述反应混合物包含约 0.1 至约 50 重量 % 的所述嵌段共聚物。

44. 根据权利要求 43 所述的方法,其中所述反应混合物包含约 1 至约 20 重量 % 的所述嵌段共聚物。

45. 根据权利要求 44 所述的方法,其中所述反应混合物包含约 2 至约 15 重量 % 的所述嵌段共聚物。

46. 一种眼科装置,其包含含有机硅聚合物和至少一种交联但未宏观胶凝的稳定嵌段共聚物,所述嵌段共聚物在所述嵌段共聚物的主链中包含具有在约 10 至约 10,000 范围内的聚合度的亲水性链段和位于所述嵌段共聚物的至少一个末端上的线性基材缔合型链段,其中所述有机硅链段包含介于约 1 和约 200 个之间的甲硅烷氧基单元,其中所述嵌段共聚物经由所述线性基材缔合型链段与包含至少一个疏水性位点的表面缔合,并且向所述眼科装置提供与所述含有机硅聚合物相比降低至少约 20% 的类脂吸收率。

47. 根据权利要求 46 所述的眼科装置,其中所述类脂吸收率小于约 12 微克 / 镜片。

48. 根据权利要求 47 所述的眼科装置,其中所述类脂吸收率为约 10 微克 / 镜片或更少。

49. 根据权利要求 46 所述的眼科装置,其中所述亲水性链段的交联剂与一级链的摩尔比在约 0.01 至约 1.5 的范围内。

50. 根据权利要求 46 所述的眼科装置,其中所述至少一种稳定嵌段共聚物包含 6 至 60 个甲硅烷氧基重复单元。

51. 根据权利要求 46 所述的眼科装置,其中所述嵌段共聚物的所述亲水性链段具有在约 50 至约 5,000 范围内的聚合度。

52. 根据权利要求 51 所述的眼科装置,其中所述嵌段共聚物的所述亲水性链段具有在约 100 至约 1000 范围内的聚合度。

53. 根据权利要求 46 所述的眼科装置,其中亲水性链段和包含线性有机硅的所述线性基材缔合型链段基于所述聚合度以约 1:1 和约 500:1 范围内的重量比存在于所述嵌段共聚物中。

54. 根据权利要求 53 所述的眼科装置,其中所述亲水性链段与所述线性有机硅的重量比基于聚合度在约 1:1 和约 200:1 的范围内。

55. 根据权利要求 46 所述的眼科装置,其中所述至少一种稳定嵌段共聚物包含 6 至 60 个甲硅烷氧基重复单元。

56. 根据权利要求 55 所述的眼科装置,其中所述至少一种稳定嵌段共聚物包含 6 至 20 个甲硅烷氧基重复单元。

57. 一种眼科溶液,其包含至少一种交联但未宏观胶凝的稳定嵌段共聚物,所述嵌段共聚物在所述聚合物的主链中包含具有在约 10 至约 10,000 范围内的聚合度的亲水性链段和位于所述聚合物的至少一个末端上的线性基材缔合型链段,其中所述线性基材缔合型链段包含介于约 1 和约 200 个之间的甲硅烷氧基单元,其中所述嵌段共聚物以有效降低眼科装置与所述溶液接触时的类脂吸收率的量存在,并且所述眼科溶液为透明的。

58. 根据权利要求 57 所述的眼科溶液,其中所述亲水性链段的交联剂与一级链的摩尔比在约 0.01 至约 1.5 的范围内。

59. 根据权利要求 57 所述的眼科溶液,其中所述至少一种稳定嵌段共聚物包含 6 至 60 个甲硅烷氧基重复单元。

60. 根据权利要求 59 所述的眼科溶液,其中所述至少一种稳定嵌段共聚物包含 6 至 20 个甲硅烷氧基重复单元。

61. 根据权利要求 57 所述的眼科溶液,其中所述至少一种稳定嵌段共聚物以约 0.005 和约 2 重量 % 范围内的量存在。

62. 根据权利要求 61 所述的眼科溶液,其中所述至少一种稳定嵌段共聚物以约 0.01 和约 0.5 重量 % 范围内的量存在。

63. 根据权利要求 57 所述的眼科溶液,其中所述嵌段共聚物的所述亲水性链段具有在约 50 至约 1,000 范围内的聚合度。

64. 根据权利要求 63 所述的眼科溶液,其中所述嵌段共聚物的所述亲水性链段具有在约 100 至约 500 范围内的聚合度。

65. 根据权利要求 57 所述的眼科溶液,其中所述亲水性链段和包含线性有机硅链段的所述线性基材缔合型链段基于所述聚合度以约 1:1 至约 500:1 范围内的重量比存在于所述嵌段共聚物中。

66. 根据权利要求 65 所述的眼科溶液,其中所述亲水性链段与所述线性有机硅链段的重量比基于所述聚合度在约 1:1 至约 200:1 的范围内。

67. 根据权利要求 57 所述的眼科溶液,其中所述眼科装置为由包含至少一种疏水性组分的反应混合物形成的接触镜片。

68. 根据权利要求 58 所述的眼科溶液,其中所述接触镜片包含有机硅氢。

69. 根据权利要求 68 所述的眼科溶液,其中所述接触镜片为未涂布的。

70. 一种制备交联但未宏观胶凝的稳定嵌段共聚物的方法,所述方法包括:

(a) 使 (i) 大分子受控自由基聚合 (CRP) 剂与 (ii) 至少一种亲水性单体、自由基引发剂、交联剂和任选的溶剂接触,所述 CRP 剂具有下式

[A]-CRP

其中 [A] 为对医疗装置具有亲和力的聚合物链段,并且 CRP 为能够控制不饱和单体的聚合的官能末端部分;

(b) 在所述 [A]-CRP 剂的存在下聚合所述至少一种亲水性单体,以在所述 [A]-CRP 剂上形成亲水性链段,使得所述大分子 CRP 剂的活性部分位于所述亲水性链段的末端上,并且所述 [A] 链段位于相对的末端上;以及

(c) 在聚合期间或之后使所述亲水性链段交联。

71. 一种制备交联但未宏观胶凝的稳定嵌段共聚物的方法,所述方法包括:

(a) 使基材缔合型聚合物自由基引发剂与至少一种亲水性单体、能够传播和链转移的单体以及任选的溶剂接触；

(b) 引发至少一种亲水性单体与能够传播和链转移的单体的聚合，以在所述基材缔合型聚合物的至少一个末端上形成亲水性链段；以及

(c) 在聚合期间经由单体链转移使所述亲水性链段交联。

72. 根据权利要求 35 所述的方法，其中所述接触镜片在所述接触步骤之前未预处理。

73. 根据权利要求 35 所述的方法，其还包括在适于使第二聚合物与所述嵌段共聚物键合或缔合的条件下，使所述接触镜片与包含所述第二聚合物的第二溶液接触。

74. 根据权利要求 73 所述的方法，其中所述第二聚合物选自直链的、支化的或交联的聚合物，所述直链的、支化的或交联的聚合物包含能够与所述嵌段共聚物键合或缔合的基团。

75. 根据权利要求 74 所述的方法，其中所述嵌段共聚物在所述亲水性链段中包含质子提供基团，并且所述第二聚合物包含质子接受基团。

76. 根据权利要求 75 所述的方法，其中所述第二聚合物选自聚-N-乙烯基吡咯烷酮、聚-N-乙烯基-2-哌啶酮、聚-N-乙烯基-2-己内酰胺、聚-N-乙烯基-3-甲基-2-己内酰胺、聚-N-乙烯基-3-甲基-2-哌啶酮、聚-N-乙烯基-4-甲基-2-哌啶酮、聚-N-乙烯基-4-甲基-2-己内酰胺、聚-N-乙烯基-3-乙基-2-吡咯烷酮和聚-N-乙烯基-4,5-二甲基-2-吡咯烷酮、聚乙烯基咪唑、聚-N,N-二甲基丙烯酰胺、聚乙烯醇、聚氧化乙烯、聚-2-乙基-噁唑啉、肝素多醣、多糖，以及它们的混合物和共聚物。

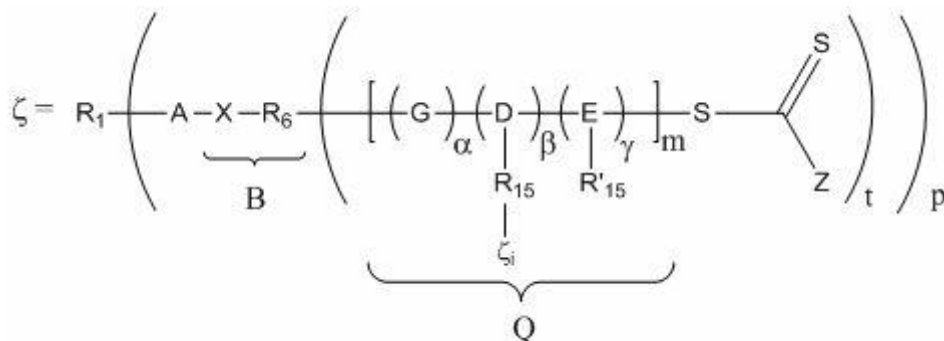
77. 根据权利要求 74 所述的方法，其中所述嵌段共聚物在所述亲水性链段中包含质子接受基团，并且所述第二聚合物包含质子提供基团。

78. 根据权利要求 74 所述的方法，其中所述至少一种第二聚合物以最多约 50,000ppm 的浓度存在于所述溶液中。

79. 根据权利要求 74 所述的方法，其中所述至少一种第二聚合物以介于约 10ppm 和 5000ppm 之间的浓度存在于所述溶液中。

80. 根据权利要求 74 所述的方法，其中所述第二接触步骤在介于约 6 和约 8 的 pH 下进行。

81. 根据权利要求 1 所述的组合物，其中嵌段共聚物具有由下式表示的一级链 ζ ：



其中

R_1 选自取代的和未取代的 C_{1-24} 烷基；

A 选自具有 6 至 1,000 个重复单元的线性二烷基或二芳基聚硅氧烷和具有 2 至 25 个碳

原子的亚烷基,所述碳原子可任选地被选自 S、O、N、P 以及它们的组合的原子取代;

R_6 为引发自由基聚合的自由基离去基团;

X 选自 $-O-(CO)-$ 、 $-(CO)O-$ 、 $-NR_8-(CO)-$ 、 $-(CO)NR_8-$ 、 $-O-$ 、 C_{1-12} 亚烷基、 C_{1-4} 亚烷基或直接键;

G 为至少一种亲水性单体的聚合残基;

D 为包含至少一个反应性基团 R'_{15} 的聚合残基;

E 为包含 R_{15} 的聚合残基, R_{15} 为与另一聚合物链段 ζ_i 聚合的交联剂的残基;

α 、 β 、 γ 为 G、D 和 E 的相对分子量(以摩尔分数为单位);

Z 选自氢、氯、氟、任选地取代的烷基、任选地取代的芳基、任选地取代的杂环基、任选地取代的烷硫基、任选地取代的烷氧基、任选地取代的烷氧基羰基、任选地取代的芳基氧基羰基($-COOR''$)、羧基($-COOH$)、任选地取代的酰氧基($-O_2CR''$)、任选地取代的氨基甲酰基($-CONR''_2$)、氰基($-CN$)、二烷基-或二芳基-膦酸酯基 $[-P(=O)(OR'')_2]$ 、二烷基-或二芳基-亚膦酸酯基 $[-P(=O)(OR'')_2]$ 以及由任何机制形成的聚合物链;

ζ_i 为与一级链 ζ 交联的另一个一级链;

t 为 1 或大于 1 的整数;并且 p 为 1 或大于 1 的整数。

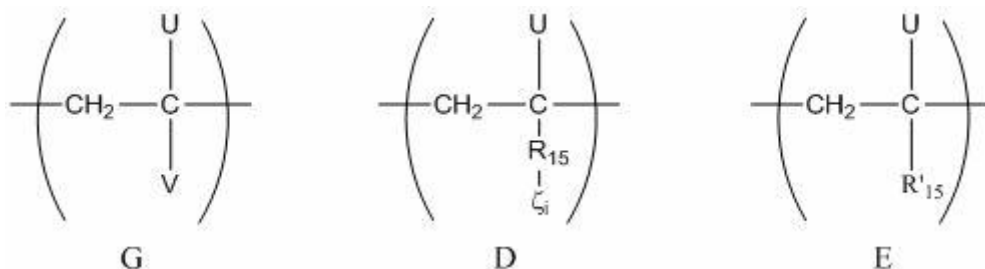
82. 根据权利要求 81 所述的组合物,其中 G 为选自以下的至少一种亲水性单体的残基:*N*-乙烯基吡咯烷酮、*N*-乙烯基-2-哌啶酮、*N*-乙烯基-2-己内酰胺、*N*-乙烯基-3-甲基-2-己内酰胺、*N*-乙烯基-3-甲基-2-哌啶酮、*N*-乙烯基-4-甲基-2-哌啶酮、*N*-乙烯基-4-甲基-2-己内酰胺、*N*-乙烯基-3-乙基-2-吡咯烷酮、*N*-乙烯基-4,5-二甲基-2-吡咯烷酮、乙烯基咪唑、*N,N*-二甲基丙烯酰胺、丙烯酰胺、*N,N*-双(2-羟乙基)丙烯酰胺、丙烯腈、*N*-异丙基丙烯酰胺、醋酸乙烯酯、(甲基)丙烯酸、(甲基)丙烯酸聚乙二醇酯、2-乙基噁唑啉、*N*-(2-羟丙基)(甲基)丙烯酰胺、*N*-(2-羟乙基)(甲基)丙烯酰胺、2-甲基丙烯酰氧基乙基磷酸胆碱、3-(二甲基(4-乙烯基苄基)铵基)丙烷-1-磺酸酯(DMVBAPS)、3-((3-丙烯酰胺基丙基)二甲基铵基)丙烷-1-磺酸酯(AMPDAPS)、3-((3-甲基丙烯酰胺基丙基)二甲基铵基)丙烷-1-磺酸酯(MAMPDAPS)、3-((3-(丙烯酰氧基)丙基)二甲基铵基)丙烷-1-磺酸酯(APDAPS)、甲基丙烯酰氧基(丙基)二甲基铵基)丙烷-1-磺酸酯(MAPDAPS)、*N,N*-二甲基氨基丙基(甲基)丙烯酰胺、*N*-乙烯基-*N*-甲基乙酰胺、*N*-乙烯基乙酰胺、*N*-乙烯基-*N*-甲基丙酰胺、*N*-乙烯基-*N*-甲基-2-甲基丙酰胺、*N*-乙烯基-2-甲基丙酰胺、*N*-乙烯基-*N,N'*-二甲基脲等,以及它们的混合物。

83. 根据权利要求 81 所述的组合物,其中 G 为选自以下的至少一种亲水性单体的残基:*N*-乙烯基吡咯烷酮、*N*-乙烯基-*N*-甲基乙酰胺、2-甲基丙烯酰氧基乙基磷酸胆碱、(甲基)丙烯酸、*N,N*-二甲基丙烯酰胺、*N*-羟丙基甲基丙烯酰胺、单甲基丙烯酸甘油酯、2-羟乙基丙烯酰胺、双羟乙基丙烯酰胺和 2,3-二羟丙基(甲基)丙烯酰胺等,以及它们的混合物。

84. 根据权利要求 82 或 83 所述的组合物,其中 G 还包含选自以下的至少一种带电单体的残基:甲基丙烯酸、丙烯酸、3-丙烯酰胺基丙酸(ACA1)、4-丙烯酰胺基丁酸、5-丙烯酰胺基戊酸(ACA2)、3-丙烯酰胺基-3-甲基丁酸(AMBA)、*N*-乙烯基氧基羰基- α -丙氨酸、*N*-乙烯基氧基羰基- β -丙氨酸(VINAL)、2-乙基-4,4-二甲基-2-噁唑啉-5-酮(VDMO)、反应性磺酸盐,包括 2-(丙烯酰胺基)-2-甲基丙磺酸钠(AMPS)、3-磺丙基(甲基)丙烯酸钾盐、3-磺丙基(甲基)丙烯酸钠盐、双 3-磺丙基衣康酸二钠、双 3-磺丙基衣康酸二钾、乙

烯基磺酸钠盐、乙烯基磺酸盐、苯乙烯磺酸盐、甲基丙烯酸磺乙酯,以及它们的组合。

85. 根据权利要求 81 所述的组合物,其中 G、D 和 E 为下式的重复单元:



其中 U 选自氢、卤素、可被羟基任选地取代的 C_1 - C_4 烷基、烷氧基、芳氧基 (OR'')、羧基、酰氧基、芳酰氧基 ($\text{O}_2\text{CR}''$)、烷氧基-羰基、芳氧基-羰基 ($\text{CO}_2\text{R}''$),以及它们的组合;

V 选自氢、 R'' 、 CO_2H 、 $\text{CO}_2\text{R}''$ 、 COR'' 、 CN 、 CONH_2 、 CONHR'' 、 CONR''_2 、 $\text{O}_2\text{CR}''$ 、 OR'' 和卤素;环状的 N- 乙烯基酰胺和无环的 N- 乙烯基酰胺以及它们的组合;

R'' 独立地选自任选地取代的 C_1 - C_{18} 烷基、 C_2 - C_{18} 烯基、芳基、杂环基、烷芳基,其中所述取代基独立地选自:环氧基、羟基、烷氧基、酰基、酰氧基、羧基和羧酸酯基、磺酸和磺酸酯基、烷氧基-或芳氧基-羰基、异氰酸酯基、氰基、甲硅烷基、卤素和二烷基氨基;磷酸;

R_{15} 为包含在两个 ζ -链之间的交联的任何含碳结构,并且来源于 R'_{15} ;并且

R'_{15} 为包含能够与其它 ζ -链形成共价键、离子键或氢键的至少一个基团任何含碳结构。

86. 根据权利要求 85 所述的组合物,其中

R_1 选自取代的和未取代的 C_{1-10} 烷基;

A 选自具有 6 至 200 个的线性二烷基或二芳基聚硅氧烷;

R_6 选自二价基团,所述二价基团选自任选地取代的亚烷基;任选地取代的饱和的、不饱和的或芳族碳环或杂环;任选地取代的烷硫基;任选地取代的烷氧基;或任选地取代的二烷基氨基;

U 选自 H、甲基;

R'' 选自甲基、吡咯烷酮基、 $-\text{N}-(\text{CH}_3)_2$ 、 $-\text{N}(\text{CH}_3)-\text{COCH}_3$ (N- 乙烯基乙酰胺)、 $-\text{CH}_2\text{CH}_2-\text{COOH}$ 、 $-\text{CH}_2\text{CH}_2\text{CH}_2-\text{COOH}$ 、 $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-\text{COOH}$ 、 $-(\text{CH}_3)_2-\text{CH}_2-\text{SO}_3\text{H}$ 、 $-(\text{CH}_3)_2-\text{CH}_2-\text{CO}_2\text{H}$ 、 $-\text{CH}_2\text{CH}_2\text{CH}_2-\text{N}(\text{CH}_3)_2-\text{CH}_2\text{CH}_2\text{CH}_2-\text{SO}_3^-$ 、 $-\text{CH}_2\text{CH}_2\text{CH}_2-\text{N}(\text{CH}_3)_2-\text{CH}_2\text{CH}_2-\text{CO}_2^-$ 、 $-\text{CH}_2\text{CH}_2\text{CH}_2-\text{N}(\text{CH}_3)_2$,以及它们的组合;并且

R'_{15} 包含一个或多个不饱和键。

87. 根据权利要求 85 所述的组合物,其中

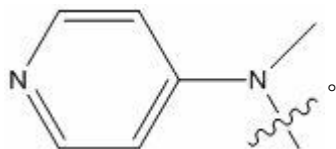
R_1 选自取代的或未取代的 C_{1-6} 烷基基团;

A 选自具有 6-20 个重复单元的线性二烷基或二芳基聚硅氧烷;

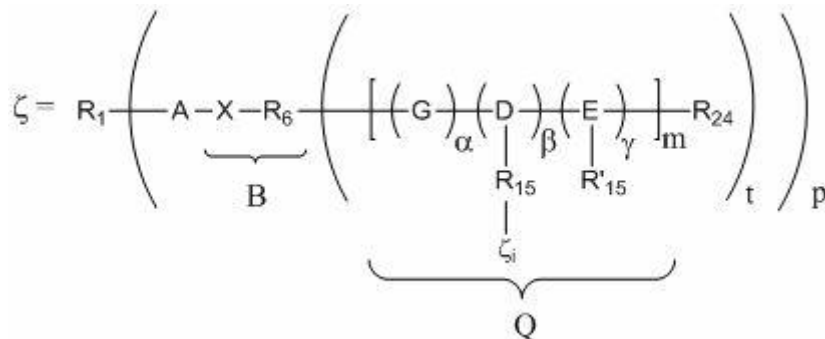
R_6 选自任选地取代的苄基、任选地取代的苯基、醋酸酯、任选地取代的丙酸酯、4- 氰戊酸酯或异丁酯官能团;

V 选自 $-\text{N}-(\text{CH}_3)_2$ 。

88. 根据权利要求 81 所述的组合物,其中 Z 包含可转换官能团



89. 根据权利要求 1 所述的组合物,其中嵌段共聚物具有由下式表示的一级链 ζ :



其中

R_1 选自取代的和未取代的 C_{1-24} 烷基;

A 选自具有 6-1,000 个重复单元的线性二烷基或二芳基聚硅氧烷和具有 2 至 25 个碳原子的亚烷基,所述碳原子可任选地被选自 S、O、N、P 以及它们的组合的原子取代;

R_6 为引发自由基聚合的自由基离去基团;

X 选自 $-O-(CO)-$ 、 $-(CO)O-$ 、 $-NR_8-(CO)-$ 、 $-(CO)NR_8-$ 、 $-O-$ 、 C_{1-12} 亚烷基、 C_{1-4} 亚烷基或直接键;

G 为至少一种亲水性单体的聚合残基;

D 为包含至少一个反应性基团 R'_{15} 的聚合残基;

E 为包含 R_{15} 的聚合残基, R_{15} 为与另一聚合物链段 ζ_i 聚合的交联剂的残基;

R_{24} 为能够控制聚合的任何剂;

α 、 β 、 γ 为 G、D 和 E 的相对摩尔量(以摩尔分数为单位);并且

t 为 1 或大于 1 的整数;并且 p 为 1 或大于 1 的整数。

90. 根据权利要求 89 所述的组合物,其中 R_{24} 选自单价 RAFT 剂、ATRP 剂、TERP 剂和 NMP 剂。

聚合物和纳米凝胶材料及其制备和使用方法

[0001] 相关专利申请

[0002] 本专利申请要求 2012 年 5 月 25 日提交的、名称为“Polymers and nanogel materials and Methods for Making and Using the Same”的美国临时专利申请 61/651767 的优先权,该专利申请的内容以引用方式并入。

技术领域

[0003] 本发明涉及交联但未宏观胶凝的嵌段共聚物,其具有至少一个可与聚合物基材缔合的末端链段。此类嵌段共聚物可为两亲性的或亲水性的。还提供了纳米凝胶材料。这些嵌段共聚物和纳米凝胶材料可结合到包括医疗装置的各种基材中,以改善其可润湿性和润滑性并且抑制其蛋白质和 / 或类脂吸收率。

背景技术

[0004] 自 20 世纪 50 年代起,接触镜片就已被商业化利用以改进视力。第一种接触镜片由硬质材料制得。尽管目前使用这些镜片,但由于其不佳的初始舒适度和相对较低的透氧度,这些镜片未被广泛使用。后来随着本领域的发展进步,出现了基于水凝胶的软性接触镜片。许多使用者发现软性镜片更舒适,并且增加的舒适水平允许软性接触镜片使用者比硬质接触镜片的使用者佩戴镜片长数小时。

[0005] 另一类可用的接触镜片为有机硅水凝胶接触镜片。将含有机硅组分与常规水凝胶组分混合以形成有机硅水凝胶,其与常规水凝胶相比表现出增加的透氧度。然而,一些有机硅水凝胶与常规水凝胶镜片相比表现出不利地高的接触角和蛋白质吸收率。

[0006] 已公开各种适用于处理预成型有机硅水凝胶接触镜片的化合物,其包括表面活性分段型嵌段共聚物、基本上水溶性的含有机硅表面活性剂、官能化混合 PDMS/ 极性两亲共聚物嵌段体系,包括聚二甲基硅氧烷 -PVP 嵌段共聚物和 (甲基) 丙烯酸酯化聚乙烯吡咯烷酮。美国专利申请序列 No. 2011/0275734 涉及 “non-reactive, hydrophilic polymers having terminal siloxanes”,其具有直链或支化的亲水性链段。仍然需要用于改善接触镜片,特别是有机硅水凝胶接触镜片的性质的方法。

发明内容

[0007] 本发明提供了赋予优异的可润湿性和润滑性以及降低的蛋白质和 / 或类脂吸收率的组合物,以及与其缔合的聚合物制品。还公开了制备和使用这些组合物的方法。组合物包含下式的嵌段共聚物:[A]-B-[Q],其中 [A] 为对医疗装置具有亲和力的聚合物链段;B 为连接基团,其包含分子量不超过 1000 克 / 摩尔的任选地取代的多价连接基团;并且 [Q] 包含半交联的未胶凝聚合物,所述聚合物来源于烯键式不饱和单体与多官能烯键式不饱和单体的共聚。此类嵌段共聚物可用作纳米凝胶组合物,所述纳米凝胶组合物包含至少一种交联但未宏观胶凝的稳定嵌段共聚物,所述稳定嵌段共聚物在所述聚合物的主链中包含聚合度在约 10 至约 10,000 范围内的亲水性链段和位于所述聚合物的至少一个末端上的线

性基材缔合链段,其中所述基材缔合链段包含介于约 6 和约 10,000 个之间的重复单元。表面包含至少一个疏水性聚合物位点的眼科装置可与所述嵌段共聚物缔合。所述缔合经由线性基材缔合型链段与所述装置的表面进行,并且改善所述眼科装置的至少一种性质,例如相比于仅所述基材或含有机硅聚合物,其类脂吸收率降低至少约 20%。含有机硅聚合物的非限制性例子为有机硅水凝胶。所述嵌段共聚物可为两亲性的或亲水性的。所述缔合型链段可为亲水性的或疏水性的。

[0008] 还提供了抑制含有机硅的接触镜片的类脂吸收率的方法,这些方法包括将所述接触镜片与包含至少一种稳定嵌段共聚物的溶液接触,所述嵌段共聚物包含具有约 10 至约 10,000 的聚合度的亲水性链段和位于嵌段共聚物的至少一个末端上的基材缔合链段,其中所述基材缔合链段包含介于约 1 和约 200 个之间的甲硅烷氧基单元,并且所述嵌段共聚物经由所述基材缔合链段和包含聚合物或制品(例如有机硅水凝胶)的至少一个疏水性位点的表面缔合。

[0009] 本发明还提供了一种组合物,其包含下式的水溶性嵌段共聚物:

[0010] [A]-B-[Q],其中

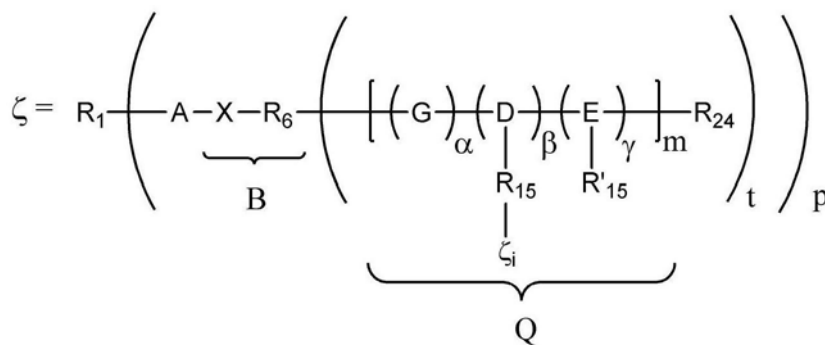
[0011] [A] 为对医疗装置具有亲和力的链段;

[0012] B 为连接基团,其包含分子量不超过 1000 克/摩尔的任选地取代的多价连接基团;并且

[0013] [Q] 包含半交联的未胶凝链段,所述链段来源于至少一种烯键式不饱和单体与多官能烯键式不饱和单体的共聚。

[0014] 本发明还涉及一种组合物,其包含具有由下式表示的一级链 ζ 的水溶性嵌段共聚物:

[0015]



[0016] 其中 R_1 、A、X、 R_6 、G、D、E、 R_{15} 、 R'_{15} 、t、p、m、 α 、 β 、 γ 如本文所定义,并且 R_{24} 为能够控制聚合的任何剂,以及在一些实施例中, R_{24} 选自单价 RAFT 剂、ATRP 剂、TERP 剂和 NMP 剂。

附图说明

[0017] 图 1 示出现有技术的类脂吸收率的性能相对于数均分子量的关系;

[0018] 图 2 示出根据制备例 3 使用渐增量的交联剂,即 (XL : ζ -PC 值从 0 至 0.95) 制备的一系列 PDMA-硅氧烷嵌段共聚物和根据制备例 4 的比较性直链 PDMA-硅氧烷的 GPC 重叠折射率迹线;

[0019] 图 3 示出类脂吸收率相对于 XL : ζ -PC 的关系,其中 $DP_{nQ-链段}$ 值不同, [A] : [Q]

的恒定摩尔比为 0.1；

[0020] 图 4 示出类脂吸收率相对于 XL： ζ -PC 的关系，其中 $DP_{nQ-链段}$ 值不同，[A]：[Q] 的恒定摩尔比为 0.55；

[0021] 图 5 示出类脂吸收率相对于 XL： ζ -PC 的关系，其中 $DP_{nQ-链段}$ 值不同，[A]：[Q] 的恒定摩尔比为 1.0；

[0022] 图 6 示出类脂吸收率相对于 $DP_{nQ-链段}$ 的关系，其中 XL： ζ -PC 不同，[A]：[Q] 的恒定摩尔比为 0.1；

[0023] 图 7 示出类脂吸收率相对于 $DP_{nQ-链段}$ 的关系，其中 XL： ζ -PC 不同，[A]：[Q] 的恒定摩尔比为 0.55；

[0024] 图 8 示出类脂吸收率相对于 $DP_{nQ-链段}$ 的关系，其中 XL： ζ -PC 不同，[A]：[Q] 的恒定摩尔比为 1.0；

具体实施方式

[0025] 在描述本发明的多个示例性实施例之前，应当理解本发明不限于在以下描述中所述的构造细节和方法步骤。本发明能够具有其它实施例，并能够以各种方式实践或实施。

[0026] 已经发现的是，虽然使用此前开发的具有末端硅氧烷的非反应性亲水性聚合物（其具有直链、支化或梳状亲水性链段），在降低接触镜片的类脂和 / 或蛋白质吸收率以及增强其润滑性和可润湿性方面有所进步，但随着分子量增加，达到了改善的性质的极限。图 1 示出相对于分子量的此极限。从图 1 中的图线可明显地看出，对于经分子量渐增的 PVP-硅氧烷共聚物处理的 senofilcon A 镜片，当亲水性 PVP 链段的分子量达到约 80kDa 时，其类脂吸收率降低至约 15 微克 / 镜片的最低水平。对于经分子量高于 80kDa 的 PVP-硅氧烷共聚物处理的镜片，并未观察到 senofilcon A 上的类脂吸收率有进一步的降低。意外地，已经发现的是，通过采用具有末端基材缔合链段和交联或“桥联”的亲水性链段的聚合物纳米凝胶，相比于同样包含末端基材缔合链段且具有类似分子量的类似非交联聚合物，可抑制更大程度的类脂吸收率。例如，图 1 示出用直链非交联 PDMA-硅氧烷共聚物（数均分子量 M_n 为约 23,000 克 / 摩尔）处理 senofilcon A 接触镜片使所述基材的类脂吸收率从约 30 微克 / 镜片增加至约 52 微克 / 镜片。另选地，用具有相等 M_n （约 23,050 克 / 摩尔）的交联 PDMA-硅氧烷材料（例如 PDMA-Sil 100-0.55-1.0）处理 senofilcon A 导致类脂吸收率从 30.0 显著下降至约 12.5 微克 / 镜片。

[0027] 半交联的未胶凝链段的存在可致使接触镜片具有改善的性质，例如降低的类脂和蛋白质吸收率以及较低的摩擦。另外，据认为交联剂的选择和交联度可根据所需应用和具体基材材料调整。

[0028] 如本文所用，“缔合”是指半交联嵌段共聚物在无需共价键合的情况下被保持在基材中或其上。缔合可包括物理保持（诸如缠结或锚固）或者氢键合、范得瓦尔（van der Waals）力、偶极-偶极相互作用、静电吸引，以及这些作用的组合。已意外地发现，半交联嵌段共聚物与基材之间的缔合是持续的，并且甚至使用手指摩擦来保持。当基材为接触镜片时，半交联嵌段共聚物在所需配戴周期内保持在所述接触镜片中和 / 或其上，包括在其中所述接触镜片为可重复配戴型镜片的实施例中，在经过手指摩擦清洗后仍保持在所述接触镜片中和 / 或其上。

[0029] 如本文所用,“缔合型链段”是指聚合物末端链段的一部分,其保持或缔合在基材的表面、区域或链段中或其上。所述缔合型链段可为亲水性的或疏水性的。

[0030] 如本文所用,“非反应性”是指半交联嵌段共聚物缺乏在反应、储存以及使用条件下形成共价键的官能团。例如,当亲水性聚合物与基材(例如接触镜片)在高压灭菌前接触时,只有很少(少于1重量%)的半交联嵌段共聚物含有残余反应性基团。即使有残余基团存在,接触条件也缺乏催化自由基反应所需的引发剂。因此,半交联嵌段共聚物不能与所述基材形成共价键。本领域技术人员将理解,虽然非常少量的半交联嵌段共聚物(少于5重量%及少于1重量%)可具有残余反应性基团,但残余反应性基团的量太少以致无法将所需量或功能量的半交联嵌段共聚物与基材缔合。使半交联嵌段共聚物保持与基材缔合的最主要作用是半交联嵌段共聚物的至少一部分的截留。

[0031] 术语“交联的”是指聚合物链通过一个桥基或多个桥基与一个或多个聚合物链连接,所述桥基由元素、基团或化合物构成,其通过主价键(包括共价键、离子键和氢键)来接合链上的某些碳原子。在本文所公开的本发明的各种实施例中,交联可经由共价键合、离子键合、氢键合等进行。共价交联的示例性实施例将包括单乙烯基单体与含有多个(即2或更多个)乙烯基取代基的单体在自由基共聚期间原位形成交联。此类聚合将导致多个聚合物链彼此共价交联以及(根据单体转化程度与交联剂的摩尔量)形成宏观胶凝。

[0032] 聚合物链的离子交联可在原位进行(即在聚合期间)或在聚合后进行。后者可能在将包含聚合物阳离子材料的水溶液添加至包含聚合物阴离子材料的水溶液中时进行。当混合二种离子聚合物时,发生聚合物-聚合物络合和小抗衡离子释放,导致形成离子性交联聚合物-聚合物络合物。此类络合物的溶解度主要由正电荷和负电荷的化学计量决定。在溶液中的多阴离子和多聚阳离子材料之间形成此类离子交联为本领域技术人员所熟知。前一种离子交联的情况可在单乙烯基单体与二乙烯基交联剂共聚时进行,所述二乙烯基交联剂由两个烯键式不饱和单体构成且所述两个烯键式不饱和单体经由离子键彼此连接。此类“离子交联剂”可通过如下来形成:简单的酸/碱化学作用将包含酸性(例如羧酸)部分的烯键式不饱和单体与包含碱性部分(例如叔胺)的烯键式不饱和单体混合,以形成单体-单体络合物或二乙烯基共价有机盐。

[0033] 在本发明的上下文中,经由氢键合的交联可在当具有多个质子提供部分的聚合物在溶液中与具有多个质子接受部分的聚合物组合时进行。在此类实施例中,所述二种聚合物能够形成可溶性或不可溶性络合物,具体取决于所述络合物中质子提供基团与质子接受基团的比率,以及存在于聚合物链上的额外可溶性或不可溶性部分的丰度。

[0034] 如本文所用,“纳米凝胶”是指在室温下可溶或无限期分散于水性溶液中的亚微米水凝胶颗粒。在一个或多个实施例中,溶液为澄清的。在一个实施例中,所述水溶液中至少约50重量%为水或镜片润湿溶液,在一些实施例中为至少约70重量%,在其它实施例中为至少约90重量%,在其它实施例中为至少约99重量%,以及在其它实施例中为至少约99.5重量%。

[0035] 所述聚合物纳米凝胶宏观上呈未胶凝状态,使得它们可溶于水溶液(包括眼科溶液和组合物)中。这些聚合物在其缔合或结合到眼科溶液或组合物中的温度下通常呈未胶凝状态。就眼科装置如接触镜片而言,一旦聚合物结合到接触镜片中或与接触镜片缔合后就可不需要保持凝胶。然而,对于眼科溶液,所述聚合物通常在储存过程中以及在一些实施

例中在使用过程中保持未胶凝。少量胶凝聚合物（少于约 5 重量%）可能是可接受的，并且在一些溶液中，如果胶凝聚合物的量过大，则可通过所述领域已知的方法（诸如过滤）来除去。

[0036] 本文提供的聚合物的实施例是在聚合物的亲水性链段之间以及沿着其无规交联。用于交联的剂称为交联剂。

[0037] 如本文所用，“至少部分疏水性的聚合物基体”是指那些包含来源于疏水性组分（诸如疏水性单体、大分子单体和预聚物）的重复单元。疏水性组分为不溶于水的组分，并且当其仅与他疏水性组分均聚或聚合时，其具有相对于例如眼科溶液如润湿液的大于约 90° 的接触角。至少部分疏水性的聚合物基体的例子包括由 PMMA 形成的接触镜片、有机硅、有机硅水凝胶（涂布的和未涂布的）、支架、导管等。疏水性单体、大分子单体和预聚物的例子是已知的并且包括包含有机硅基团、硅氧烷基团、未取代的烷基基团、芳基基团等的单体、大分子单体和预聚物。具体例子包括含有机硅组分，例如一甲基丙烯酰氧基丙基封端的单正丁基封端的聚二甲基硅氧烷（800-1000MW）（mPDMS）、一甲基丙烯酰氧基丙基封端的单正甲基封端的聚二甲基硅氧烷、TRIS、甲基丙烯酸甲酯、甲基丙烯酸月桂酯等。

[0038] 如本文所用，“稳定”是指化合物在经过 121°C 长达 30 分钟的单一高压灭菌周期期间不发生不利地影响润湿剂或润湿剂与聚合物基材组合的所需性质的变化。例如，硅氧烷链段与聚合物链段之间的酯键在一些实施例中是不可取的。所述高压灭菌可在干燥条件下或在眼科相容性盐水溶液（例如但不限于硼酸盐或磷酸盐缓冲盐水）存在下进行。

[0039] 如本文所用，“近单分散”是指多分散性指数（PDI）为 1.5 或更小并且是指是在交联的两亲性一级链的簇内个别一级链的聚合度和 / 或分子量。在一些实施例中，聚合物表现出小于约 1.3 的多分散性，并且在其它实施例中在约 1.05 至约 1.3 的范围内。本领域技术人员应理解，个别近单分散一级链在聚合期间在统计学上彼此交联，因此所得的两亲性交联嵌段共聚物簇将具有超过 1.5 的多分散性值。

[0040] 如本文所用，“聚合度”是指每个聚合物分子或聚合物链段的重复单元的数量。例如，在一个或多个实施例中，亲水性链段 [Q]（根据式 I）的聚合度范围为约 10 至约 10,000（或约 50 至约 5000、或约 300 至约 5000、或约 500 至约 2000、或约 100 至约 1000、或约 100 至约 500、或约 100 至约 300）

[0041] 如本文所用，“交联剂与一级链摩尔比”（XL : ζ -PC）是指在制备嵌段共聚物所使用的交联剂摩尔数与制备时所使用的一级链摩尔数的比率。一级链的数量由存在的受控自由基聚合（CRP）剂或控制剂的摩尔量决定。具体的实施例包括摩尔比范围为约 0.005 至约 10（或约 0.1 至约 5，或约 0.1 至约 1.5，或约 0.1 至约 1.25）的交联剂与一级链。示例性 CRP 剂包括但不限于：可逆加成断裂转移（RAFT）剂；原子转移自由基聚合（ATRP）剂；铈化物介导的聚合（TERP）剂；和 / 或硝基氧介导的活性自由基聚合（NMP）剂。

[0042] 如本文所用，“链段”或“嵌段”是指具有类似性质（诸如组成或亲水性）的重复单元的聚合物的一部分。

[0043] 如本文所用，“有机硅链段”是指 $-\text{[SiO]}-$ 。在每个 $-\text{[SiO]}-$ 重复单元中的 Si 原子可经烷基或芳基取代，优选地 C_{1-4} 烷基取代，并且在一个实施例中经甲基取代以形成二甲基硅氧烷重复单元。

[0044] 如本文所用，“线性有机硅链段”是指聚合物主链中具有硅和氧原子的硅氧烷重

复单元。例如：聚二甲基硅氧烷为线性有机硅链段的例子，因为 $-\text{SiO}-$ 基团包含于主链中。PolyTRIS 并非为线性有机硅链段，因为硅氧烷基团侧接于碳-碳主链。

[0045] 如本文所用，“亲水性缔合型链段”为亲水性的，但可经由氢键合或离子键合与基材缔合。例如，对于包含质子受体（诸如 DMA、NVP 或 PVP）的接触镜片，亲水性缔合型链段包含质子提供基团。合适的质子提供基团包括 4-丙烯酰胺基丁酸 (ACAAI) (3-丙烯酰胺基苯基) 硼酸 (APBA) 或乙烯基苯甲酸。

[0046] 如本文所用，“络合链段”或“络合基团”包括表现出强烈非共价相互作用的官能团对，例如与二醇官能团或生物素及抗生物素蛋白结合强烈相互作用的烷基或芳基硼酸。在一个实施例中，络合链段可包含单体例如 (4-乙烯基苯基) 硼酸、(3-丙烯酰胺基苯基) 硼酸，或 (4-丙烯酰胺基苯基) 硼酸或 N-(2-丙烯酰胺基乙基)-5-(-(3aS,4S,6aR)-2-氧代六氢-1H-噻吩[3,4-d]咪唑-4-基)戊酰胺。

[0047] 如本文所用，“刺激响应性组分”包括响应于环境条件的变化而发生物理或化学变化的组分。可引起变化的条件包括 pH、光、盐浓度、温度，它们的组合等。可用于制备刺激反应性组分的单体的例子包括但不限于 N-异丙基丙烯酰胺、乙烯基苯甲酸或丙烯酰胺基丁酸 (ACAAI) 等。

[0048] 如本文所用，“基材”是指制品，例如片材、膜、管或更复杂的形式，例如生物医学装置。

[0049] 如本文所用，“生物医学装置”为设计为在哺乳动物组织或流体中或在哺乳动物组织或流体上使用的任何制品。这些装置的例子包括但不限于导管、植入物、支架、缝合线、绷带和眼科装置，例如眼内镜片和接触镜片等。

[0050] 如本文所用，术语“镜片”指位于眼睛中或位于眼睛上的眼科装置。这些装置可提供光学矫正、美容增强作用、紫外线阻隔和可见光或眩光降低、治疗效果（包括伤口愈合、递送药物或营养物、诊断评估或监测），或它们的任何组合。术语镜片包括但不限于软性接触镜片、硬质接触镜片、眼内镜片、覆盖镜片、眼部插入物和光学插入物。

[0051] 如本文所用，“含有机硅的聚合物”为任何包含有机硅或硅氧烷重复单元的聚合物。含有机硅的聚合物可为均聚物，如有机硅弹性体，或共聚物例如氟-有机硅和有机硅水凝胶。如本文所用，“有机硅水凝胶”是包含含有机硅的重复单元以及在一些实施例中含水量为至少约 10%，并且在一些实施例中为至少约 20% 的聚合物。

[0052] 如本文所用，RAFT 聚合或 RAFT 是指可逆加成断裂链转移聚合。

[0053] 如本文所用，“反应性组分”为在聚合反应混合物中的在聚合反应时成为聚合物结构的一部分的组分因此，反应性组分包括与聚合物网络共价结合的单体和大分子单体。未成为聚合物结构的一部分的稀释剂和加工助剂不为反应性组分。

[0054] 如本文所用，“取代的”是指可包含卤素、酯基、芳基、烯烃基、炔烃基、酮基、醛基、醚基、羟基、酰胺基、胺基以及它们的组合的烷基基团。

[0055] 如本文所用，“自由基源”是指生成自由基的任何适合的方法，诸如合适的化合物（热引发剂，如过氧化物、过氧化酯或偶氮化合物）的热致均裂、来自单体（例如苯乙烯）的自发性生成、氧化还原引发体系、光化学引发体系或高能辐射，例如电子束、X-辐射或 γ -辐射。本领域技术人员通常将充当“自由基源”的化学物质称为引发剂，出于本发明的目的同样称为引发剂。

[0056] 如本文所用,“质子提供链段”或“质子提供基团”为在镜片形成、高压灭菌或储存条件下能够给质子接受链段或基团提供质子的官能团。质子提供官能团包括醇、酸、伯酰胺等。

[0057] 如本文所用,“质子接受链段”或“质子接受基团”为在镜片形成、高压灭菌或储存条件下能够接受质子的官能团。质子接受基团包括胺基、酰胺基、羰基等。

[0058] 在一个实施例中,本发明的嵌段共聚物为稳定的聚合物润湿剂并且包含亲水性链段和位于所述聚合物的至少一个末端上的基材缔合型链段。所述聚合物由至少一个 [A] 嵌段和至少一个 [Q] 嵌段构成,所述 [A] 嵌段包含 n 个重复单元和合适的含碳基团,所述 [Q] 嵌段包含 m 个重复单元和合适的含碳基团,然而 [A] 和 [Q] 经由连接基团 B 以任何顺序彼此连接(即 [A] 连接至 [Q] 或 [Q] 连接至 [A])。如果需要,可使用多个 [A] 和 / 或 [Q] 嵌段,只要 B 连接基团位于 [A] 和 [Q] 嵌段的任何组合之间。在此实施例中,A 被定义为对医疗装置的至少一部分具有亲和力的材料或聚合物;B 为连接基团,其包含分子量 (MW) 不超过 1000 克 / 摩尔的任选地取代的多价连接基团;并且 [Q] 包含半交联的未胶凝聚合物,所述聚合物来源于烯键式不饱和单体与多官能烯键式不饱和单体的共聚。以下结构为本发明的一个实施例的通用非限制性表示:

[0059] [A]-B-[Q]

[0060] 其中 [Q] 可包含或不包含能够控制自由基聚合的剂。[A] 选自对给定基材或医疗装置具有亲和力的材料。[A] 可选自包含直链或支化的硅氧烷、具有 4 至 24 个碳的疏水性烷基基团、质子提供官能团、质子接受官能团、离子性官能团、硼酸官能团、刺激响应性官能团、它们的组合等的聚合物和共聚物链段。对于具有多个间距相近的 A 链段的嵌段共聚物而言,具有 2 个或更多个碳的疏水性烷基基团可为合适的。在一个实施例中,[A] 包含含聚二甲基硅氧烷 (PDMS) 的结构、由其组成或基本上由其组成,并且对包含至少一种疏水性材料的医疗装置具有亲和力。例如,PDMS 可经由包含在 [A] 内的 PDMS 与包含在有机硅水凝胶接触镜片内的 PDMS 之间的疏水性-疏水性相互作用与所述接触镜片缔合。[A] 的其它实施例包括以下结构,所述结构包含质子提供官能团和质子接受官能团、由其组成或基本上由其组成。在一个此类实施例中,[A] 可包含多个质子提供官能团(例如醇)、由其组成或基本上由其组成,并由此对接受质子的医疗装置或其它表面具有亲和力。反之,[A] 可包含多个质子接受官能团(诸如酰胺)、由其组成或基本上由其组成,并由此对提供质子的医疗装置或其它表面具有亲和力。在其它实施例中,[A] 可包含多个离子性官能团(诸如羧酸盐、磺酸盐、铵盐或磷盐)、由其组成或基本上由其组成,并由此对带有与缔合链段 [A] 中的给定离子基团相反的电荷的医疗装置具有亲和力。[A] 的其它实施例可包括以下那些,其包含能够与医疗装置或表面上的其它互补官能团发生络合的官能团、由其组成或基本上由其组成;例如,[A] 可包含多个硼酸官能团、由其组成或基本上由其组成,并且可与包含多个羟基基团的医疗装置或表面缔合。在一个可供选择的实施例中,羟基基团可包含在 [A] 内并且可与包含多个硼酸官能团的表面缔合。在一些实施例中,[A] 为刺激响应性的,并且由在结合到聚合物形式时可导致所得聚合物在不同溶液条件下呈水溶性或水不溶性的官能团构成。例如,[A] 可包含在 32°C 的水中发生相变的温度响应性聚合物或共聚物(诸如聚(N-异丙基丙烯酰胺)(PNIPAM))、由其组成或基本上由其组成。因此,在低于 32°C 的溶液温度下,所述 PNIPAM[A] 嵌段为水溶性的和亲水性的,而在较高的溶液温度(即高于 32°C)

下,其为水不溶性的、疏水性的并且能够与包含至少一种疏水物的医疗装置或表面缔合。

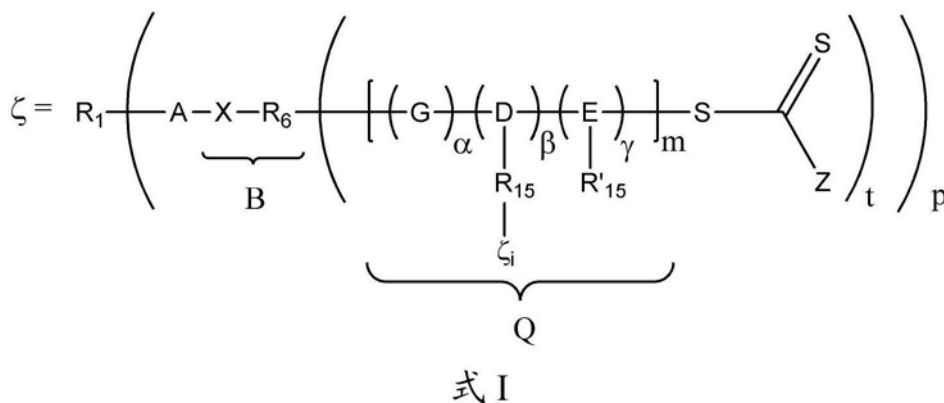
[0061] B被定义为连接基团,所述连接基团将[A]与[Q]以任何顺序彼此连接并且可作为MW小于约1000克/摩尔的任何任选地取代的多价结构存在。B的实施例包括任选地取代的多价脂族结构、任选地取代的多价芳基结构、任选地取代的多价亚烷基结构或直接键。

[0062] 结构[Q]由半交联的未胶凝聚合物构成,所述聚合物来源于烯键式不饱和单体与多官能烯键式不饱和单体的共聚。在一个实施例中,导致[Q]形成的聚合由包含在结构B内的碳原子引发。在此类实施例中,形成半交联的未胶凝聚合物,并且本领域的技术人员将理解所得的聚合物将在给定聚合物分子中包含多个[A]、B和[Q]结构,因为在多个传播[A]-B-[Q]链之间进行交联。

[0063] 聚合物润湿剂可有利地与基材以单一步骤缔合,而无需先前预处理。此外,因为[A]链段处于末端,可实现聚合物润湿剂的持续缔合,而无需与镜片共价键合、无需在基材本体中采用特殊单体如胺、羧酸盐或硫醇。

[0064] 在一个实施例中,聚合物润湿剂具有如式IA所示的通式结构和一级链指示符 ζ 。

[0065]

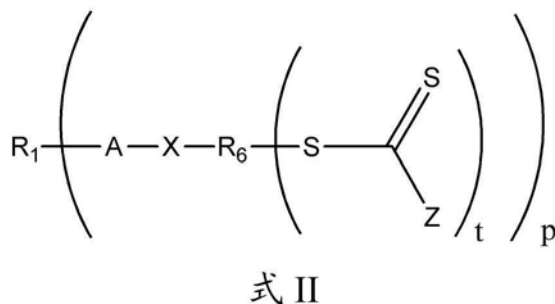


[0066] 其中 R_6 、 R_{15} 、 R'_{15} 、 X 、 G 、 D 、 E 、 Z 、 ζ 、 ζ_i 、 α 、 β 、 γ 、 n 、 m 、 t 和 p 定义如下,并且可通过使以下物质进行接触来形成:

[0067] 至少一种具有式 $H_2C = UV$ 的亲水性单体,

[0068] 链转移常数大于0.1的至少一种式II的RAFT剂;

[0069]



[0070] (iii) 由自由基源(即引发剂)产生的自由基;以及

[0071] (iv) 交联剂, $H_2C = UR'_{15}$

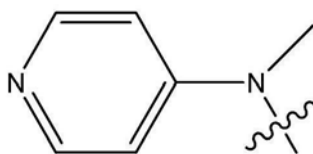
[0072] 在上式中, A选自具有6至1,000、6至200、6至60、6至50、6至20、6至15,并且在一些实施例中6至12个重复单元的线性二烷基或二芳基聚硅氧烷和具有2至25个碳原子的亚烷基,所述碳原子可任选地被选自S、O、N、P以及它们的组合的原子取代;

4- 氰戊酸酯或异丁酯官能团。在针对式 II 使用聚硅氧烷 RAFT 剂的实施例中,选择所使用的聚硅氧烷 RAFT 剂%以提供与基材的所需缔合水平,但可防止嵌段共聚物凝胶。

[0087] X 选自 $-O-(CO)-$ 、 $-(CO)O-$ 、 $-NR_8-(CO)-$ 、 $-(CO)NR_8-$ 、 $-O-$ 、 C_{1-12} 亚烷基、 C_{1-4} 亚烷基或直接键,并且在一些实施例中, R_8 选自 H、甲基、乙基或丙基;

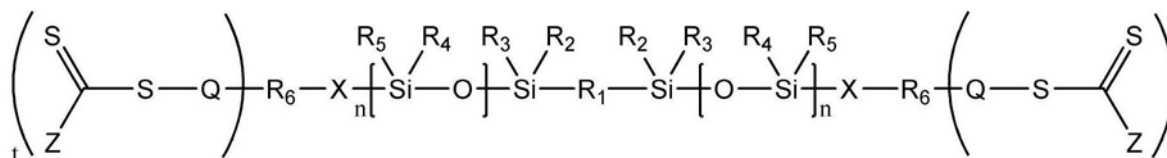
[0088] Z 选自氢、氯、氟、任选地取代的烷基、任选地取代的芳基、任选地取代的杂环基、任选地取代的烷硫基、任选地取代的烷氧基、任选地取代的烷氧基羰基、任选地取代的芳基氧基羰基 ($-COOR''$)、羧基 ($-COOH$)、任选地取代的酰氧基 ($-O_2CR''$)、任选地取代的氨基甲酰基 ($-CONR''_2$)、氰基 ($-CN$)、二烷基-或二芳基-磷酸酯基 [$-P(=O)(OR'')_2$]、二烷基-或二芳基-亚磷酸酯基 [$-P(=O)(OR'')_2$] 以及由任何机制形成的聚合物链;在其它实施例中,Z 可包含“可转换”官能团,其对溶液 pH 敏感而可调整 RAFT 剂的反应性。在其中采用“可转换”Z 基团的一个实施例中,Z 包含以下非限制性结构:

[0089]

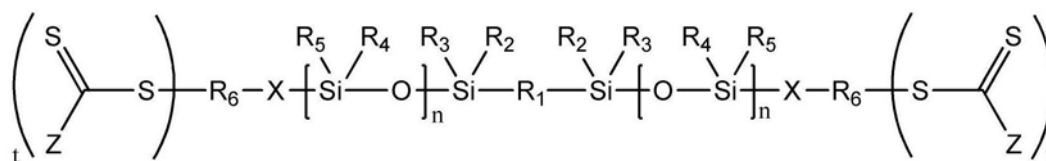


[0090] p 为 1 或大于 1 的整数、1 至 5、3 至 5,并且在一些实施例中为 1 或 2。当 $p \geq 2$ 时,则 R_1 选自来源于硅、硫、氧、氮、任选地取代的亚烷基、任选地取代的芳基、聚合物链或其组合中任一者的 p 价部分。此类实施例公开于以下式 I 和 II 的结构类似物 (即式 III 和 IV):

[0091]



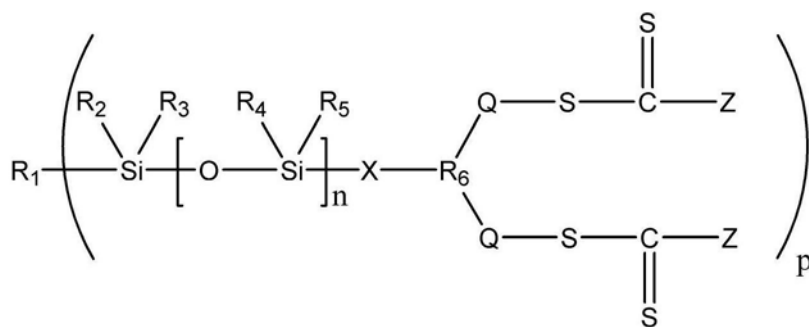
式 III



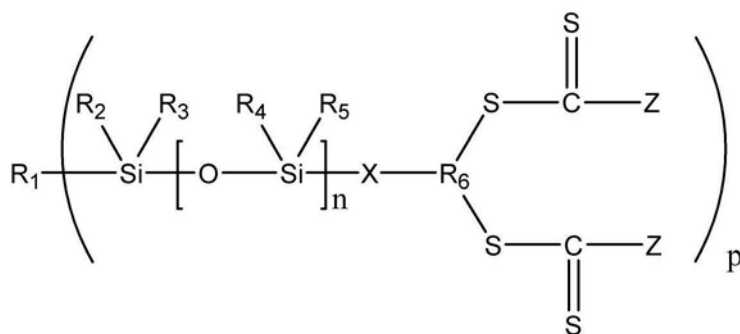
式 IV

[0092] 其中 R_1-R_6 、X、Z 和 n 如上所定义并且 t 为 1 或大于 1 的整数。当 $t \geq 2$ 时,则 R_6 为 p 价,并且可连接至不止一个硫代羰基硫代官能团。此类实施例公开于以下式 I 和 II 的结构类似物 (即式 V 和 VI):

[0093]



式 V



式 VI

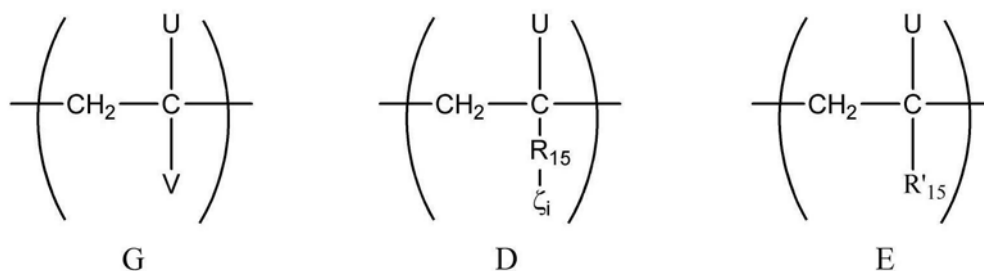
[0094] ζ_i 为与一级链 ζ 交联的另一个一级链,如上所公开。一个或多个 ζ_i 一级链可连接到 ζ 一级链,并且 ζ_i 一级链可进一步连接到或交联至附加 ζ_k 一级链等。本领域的技术人员应当理解, ζ 一级链与其它 ζ_i 一级链的交联以及 ζ_i 一级链与 ζ_k 一级链和 ζ_1 一级链与 ζ_1 一级链等的进一步交联为统计学上交联的([A]-B-[Q]形式的)嵌段共聚物的形成的广义描述,这些嵌段共聚物经其亲水性 Q-链段彼此无规交联。出于本发明的目的,在各种 ζ 、 ζ_i 和 $\zeta_k \dots$ 一级链的亲水性链段之间的所有交联情况有可能实现,如上所述的经由交联彼此连接的 ζ 、 ζ_i 和 $\zeta_k \dots$ 一级链嵌段共聚物的群组将被称为 ζ -簇。在不受理论的约束下,以下在 ζ -一级链之间交联的非限制性实例可在半交联的 ζ -簇的形成期间进行: ζ - ζ_i 、 ζ - ζ_k 、 ζ_k - ζ_i 、 ζ_i - ζ_i 、 ζ_k - $\zeta_k \dots$ 等。在单一簇中彼此连接的 ζ -一级链的数量随着若干变量变化,其中的一个变量包括交联剂与一级链的理论摩尔比(XL : ζ -PC)。在给定聚合中,例如 N, N'-二甲基丙烯酰胺与 N, N'-亚甲基双丙烯酰胺之间的共聚,如果单体与交联剂之间的反应性类似,则可假设交联剂将无规结合到 ζ -一级链中。这种沿着 ζ -一级链对潜在交联位点的无规结合以及这些侧交联位点与其它传播 ζ -一级链或 ζ -簇的碰撞频率被认为在很大程度上控制 ζ -簇的数量和每个簇中一级链的平均数量。

[0095] R'_{15} 为包含能够与其它 ζ -链形成共价键、离子键或氢键的至少一个基团的任何含碳结构,并且在一个实施例中选自与一级链 ζ 、 ζ_i 或 ζ_k 连接的烯键式不饱和部分。

[0096] R_{15} 为包含在两个 ζ -链之间的交联的任何含碳结构,并且来源于 R'_{15} 。 R'_{15} 任选地包含一个或多个不饱和键;

[0097] 亲水性链段 0 包含具有下式的 G、D 和 E 的统计学分布的重复单元:

[0098]



式 VII

[0099] 术语 α 、 β 和 γ 表示构成亲水性链段 Q 的 G、D 和 E 的相对摩尔量（以摩尔分数表示）。在一些实施例中， α 等于约 0.85 至约 0.999、约 0.92 至约 0.999、约 0.95 至约 0.999 和约 0.97 至约 0.999，而对于 α 的各相应范围而言， β 和 γ 的总和将等于约 0.15 至约 0.001、约 0.08 至约 0.001、约 0.05 至约 0.001 和约 0.025 至约 0.001。出于所公开的发明的目的，在 ζ -一级链的亲水性链段 Q 中，D 的摩尔分数（即 β ）相比于 E 的摩尔分数（即 γ ）旨在最大化，从而最大化 Q 与其它 ζ -一级链的 Q-链段的交联数量，即剩余非常少的未反应的 R'_{15} 部分。 α 、 β 和 γ 的所有摩尔分数范围基于一个给定实施例的单体进料中所采用的单体和交联剂的相对量，并且假设所述单体和交联剂上的乙烯基取代基的反应性差异最小，即发生接近统计学的结合。在一个实施例中，本发明的纳米凝胶基本上不含未反应的 R'_{15} 基团。当 R'_{15} 包含双键时，这可经由 FTIR 或其它能够检测双键存在的方法来证实。

[0100] U 选自氢、卤素、可被羟基任选地取代的 C_1 - C_4 烷基、烷氧基、芳氧基 (OR'')、羧基、酰氧基、芳酰氧基 (O_2CR'')、烷氧基-羰基、芳氧基-羰基 (CO_2R'')，以及它们的组合；并且在一些实施例中选自 H 和甲基。

[0101] V 独立地选自氢、 R'' 、 CO_2H 、 CO_2R'' 、 COR'' 、CN、 $CONH_2$ 、 $CONHR''$ 、 $CONR''_2$ 、 O_2CR'' 、 OR'' 和卤素；以及环状的和无环的 N-乙烯基酰胺以及它们的组合；

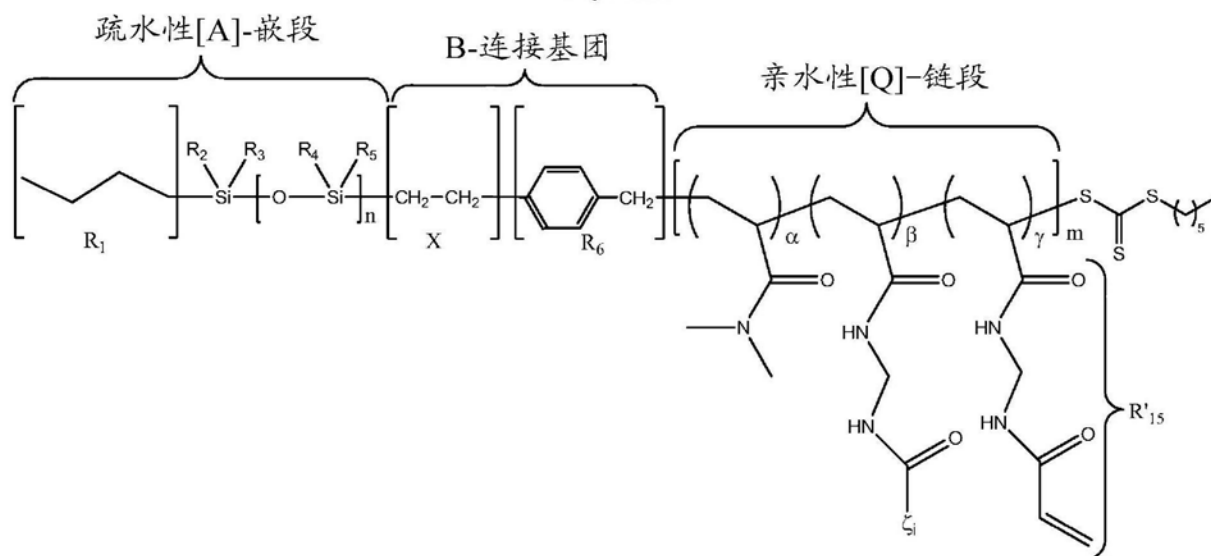
[0102] R'' 独立地选自任选地取代的 C_1 - C_{18} 烷基、 C_2 - C_{18} 烯基、芳基、杂环基、烷芳基，其中所述取代基独立地选自环氧基、羟基、烷氧基、酰基、酰氧基、羧基和羧酸酯基、磺酸和磺酸酯基、烷氧基-或芳氧基-羰基、异氰酸酯基、氰基、甲硅烷基、卤素和二烷基氨基；磷酸。在一个实施例中， R'' 选自甲基、吡咯烷酮基、 $-N-(CH_3)_2$ 、 $-N(CH_3)-COCH_3$ (N-乙烯基乙酰胺)、 $-CH_2CH_2-COOH$ 、 $-CH_2CH_2CH_2-COOH$ 、 $-CH_2CH_2CH_2CH_2-COOH$ 、 $-(CH_3)_2-CH_2-SO_3H$ 、 $-(CH_3)_2-CH_2-CO_2H$ 、 $-CH_2CH_2CH_2-N(CH_3)_2-CH_2CH_2CH_2-SO_3^-$ 、 $-CH_2CH_2CH_2-N(CH_3)_2-CH_2CH_2-CO_2^-$ 、 $-CH_2CH_2CH_2-N(CH_3)_2$ ，以及它们的组合。在另一个实施例中，V 选自 $-N-(CH_3)_2$ 。

[0103] 在一个实施例中，取代基 R_2 至 R_5 是相同的。在另一个实施例中， R_2 至 R_5 是相同的且选自甲基、乙基或苯基。在另一个实施例中， R_2 至 R_5 是相同的且选自甲基或乙基。在另一个实施例中， R_2 至 R_5 中的每一者为甲基。

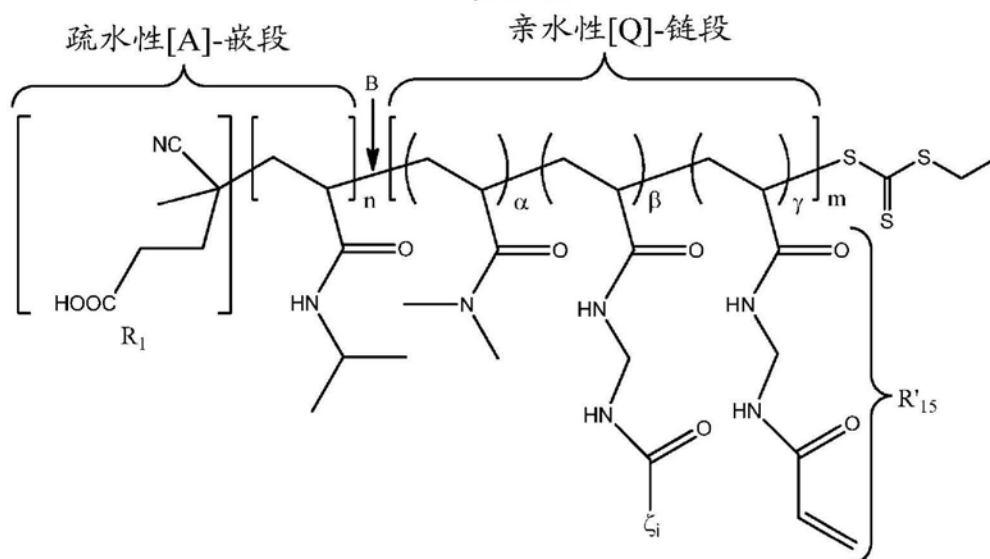
[0104] 稳定嵌段共聚物的实例在下面的式 VIII 中示出，其中取代基 R_1 、X 和 R_6 以括号标示。

[0105]

式 XIII



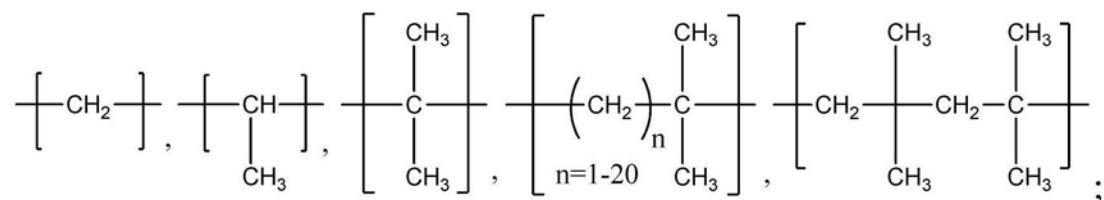
式 XIIIa



[0106] 在另一个实施例中, X 选自乙烯基或 $-O(C=O)-$, 其中乙烯基由于其水解稳定性而为优选的。

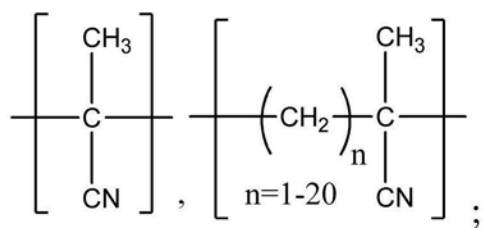
[0107] 在另一个实施例中, R_6 为亚烷基, 选自:

[0108]



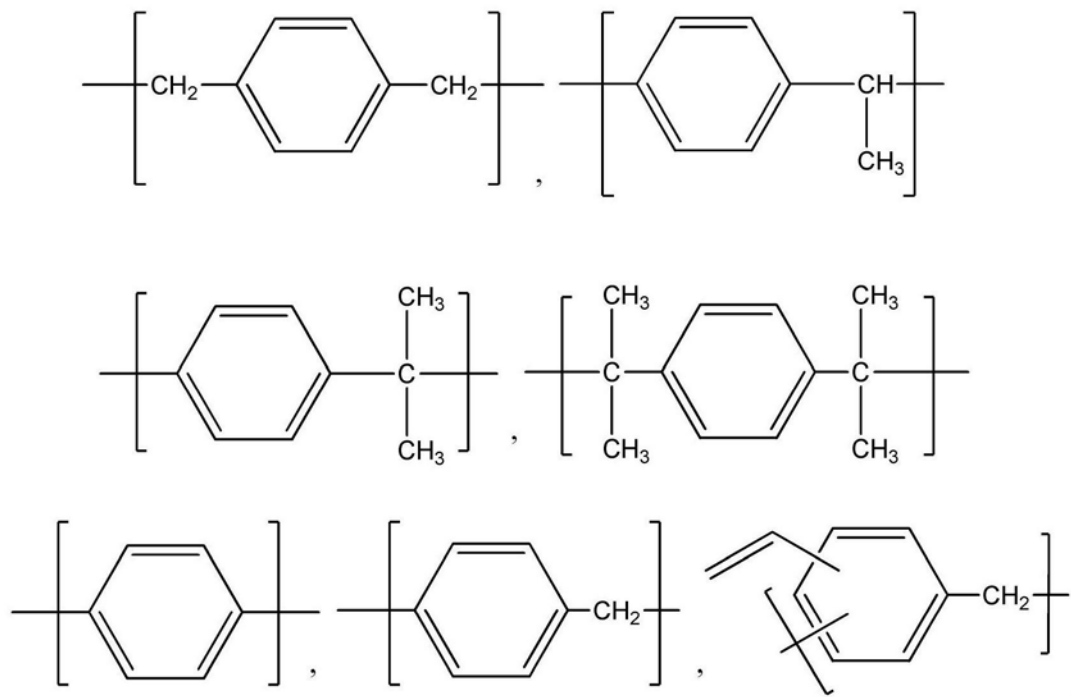
[0109] 腈烷基, 选自:

[0110]



[0111] 或芳族基团,选自:

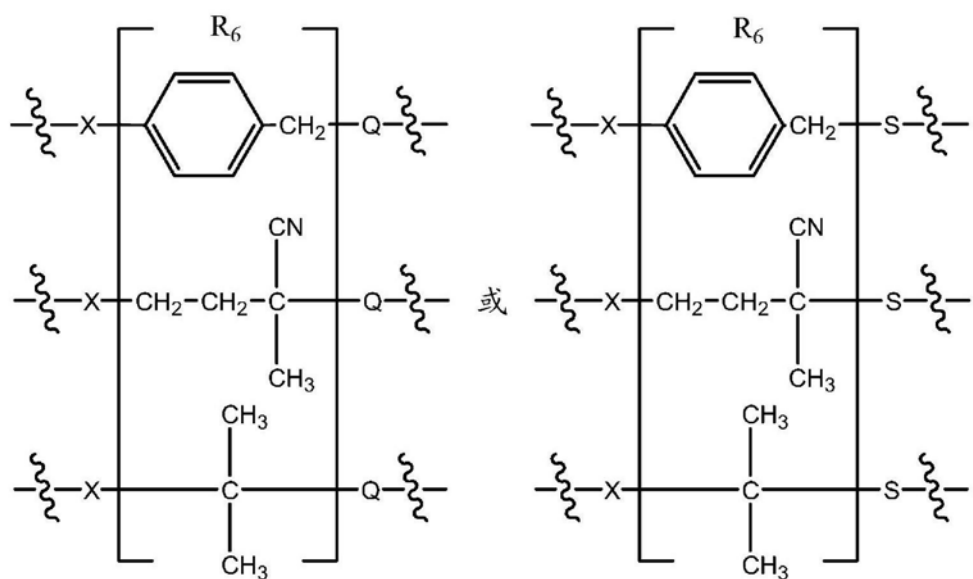
[0112]



[0113] R_6 的选择将取决于所选择的硫代羰基化合物和用于下一个步骤中聚合的单体。

[0114] 在一个实施例中, R_6 选自以下结构,其中 Q 和 X 如上所定义:

[0115]

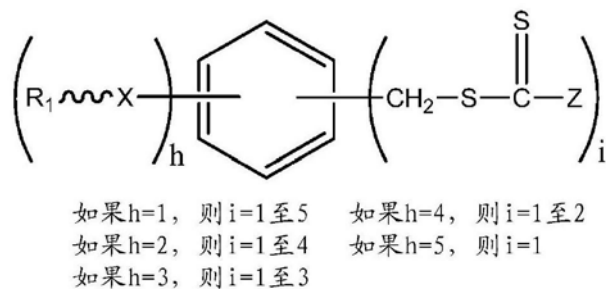


式 IX

[0116] R_6 聚硅氧烷官能的 RAFT 剂 (右) 最终共聚物 (左) 的结构

[0117] 在其中 R_6 为 p 价的一个实施例中, 其可由以下结构构成:

[0118]



[0119] 其中 R_1 和 X 如上所定义, 并且 Z 选自任选地取代的烷氧基、任选地取代的烷硫基、任选地取代的芳基或任选地取代的苄基。在一个实施例中, Z 为任选地取代的烷硫基, 并且在另一个实施例中, Z 为任选地取代的烷氧基。

[0120] 应当理解, 上述的取代可以任意组合方式进行组合。例如, 上述说明包括具有三个单独定义的 Z 取代基家族的化合物家族。这些取代基家族的任一者可与所公开的其它取代基的取代基家族组合。

[0121] 嵌段共聚物的亲水性链段的聚合度通常在约 10 至约 10,000 的范围内。在一些实施例中, 聚合度为至少约 100, 或至少约 300, 或甚至在其它实施例中至少约 500。在另外的实施例中, 嵌段共聚物的亲水性链段具有在以下范围内的聚合度: 约 300 至约 10,000、约 300 至约 5,000、约 500 至约 10,000、约 500 至约 5,000、约 500 至约 2000 和约 700 至约 2000。聚合度可获自 MALDI-TOF、SEC-MALLS、NMR 或它们的组合。

[0122] 每个 ζ -一级链的亲水性链段 Q 为交联的或半交联的。即, 不像此前公开的仅具有直链、支化或梳状结构的技术, 所述亲水性链段沿着形成亲水性链段的嵌段共聚物经由共价键、离子键或氢键无规交联。交联剂具有一个或多个反应性或缔合型官能团以使得本发明的两亲性共聚物经其亲水性链段彼此反应和 / 或缔合。示例性共价交联剂包括: N, N' - 亚甲基双 (甲基) 丙烯酰胺; N, N' - 亚乙基双 (甲基) 丙烯酰胺; N, N' - 亚丙基双 (甲基) 丙烯酰胺; N, N' - 亚丁基双 (甲基) 丙烯酰胺; N, N' - 五亚甲基双 (甲基) 丙烯酰胺; N, N' - 六亚甲基双 (甲基) 丙烯酰胺; 所有其它 N, N' - 亚烷基双 (甲基) 丙烯酰胺; 所有聚亚烷基二醇二 (甲基) 丙烯酸酯, 包括但不限于乙二醇二 (甲基) 丙烯酸酯、三乙二醇二 (甲基) 丙烯酸酯、四乙二醇二 (甲基) 丙烯酸酯; 和所有聚亚烷基二醇二 (甲基) 丙烯酰胺, 包括但不限于 N, N' - ((氧基双 (乙烷 -2,1-二基)) 二丙烯酰胺、N, N' - (((氧基双 (乙烷 -2,1-二基)) 双 (氧基)) 双 (乙烷 -2,1-二基)) 二丙烯酰胺、氰尿酸三烯丙酯 (TAC)、1,3-二乙烯基咪唑烷 -2-酮和 3,3'' 亚烷基双 (1-乙烯基吡咯烷 -2-酮), 其中亚烷基具有 1 至 12 个碳原子。

[0123] 也可使用在主链上具有官能团且可被可逆断裂或裂解的交联剂。例如, 可使用 N, N' - 胱胺二 (甲基) 丙烯酰胺作为交联剂。在半交联嵌段共聚物与基材缔合后, 胱胺中的二硫键可被裂解并且再成形以产生与基材基体更紧密缠结的互穿网络。

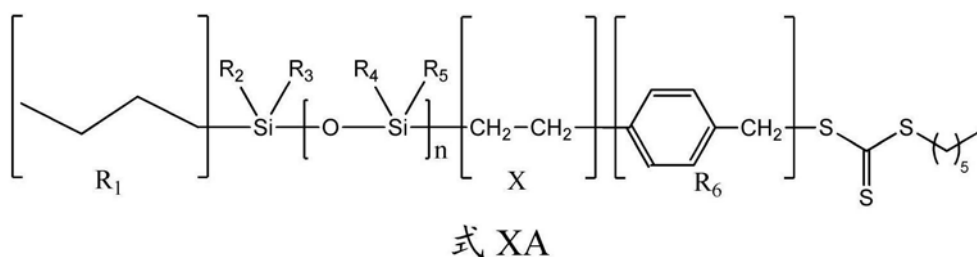
[0124] 在交联反应混合物中 RAFT 剂与交联剂的摩尔比大于约 0.1、大于约 0.2、大于约 0.3、大于约 0.5、大于约 0.75、大于约 1、大于约 2、大于约 5 并且在一些情况下大于约 10。在一个实施例中, 交联剂不含有机硅并且交联反应混合物中 RAFT 剂与交联剂的摩尔比大

于约 0.1。在其中交联剂包含硅氧烷的实施例中,所述交联反应混合物中 RAFT 剂与交联剂的摩尔比大于约 0.3。在交联反应混合物中,交联剂与理论性一级链的摩尔量的摩尔比 (“XL : ζ -PC”) 可介于 0.01 : 1.0 和 6.0 : 1.0 之间,其中优选的是 XL : ζ -PC 的以下非限制性值: 0.1 : 1.0、0.2 : 1.0、0.25 : 1.0、0.3 : 1.0、0.4 : 1.0、0.5 : 1.0、0.55 : 1.0、0.6 : 1.0、0.7 : 1.0、0.75 : 1.0、0.8 : 1.0、0.9 : 1.0、1.0 : 1.0、1.2 : 1.0、1.25 : 1.0、1.5 : 1.0、3.0 : 1.0、5.0 : 1.0、7.0 : 1.0,或甚至 10.0 : 1.0。在一些实施例中,可能有利的是选择能在广泛的温度和溶液条件下提供可溶性嵌段共聚物的 XL : ζ -PC,以允许容易地结合到不同的制品和溶液中。例如,包含作为亲水性链段的 PDMA (聚(N, N-二甲基丙烯酰胺)) 和有机硅链段的嵌段共聚物可有利地具有小于约 1.25 : 1 的 XL : ζ -PC,以防止聚合物的宏观胶凝。在其它实施例中,可能有利的是选择向经处理的基材的类脂吸收率提供所需降低的 XL : ζ -PC 值,其中 XL : ζ -PC 可降低类脂吸收量。

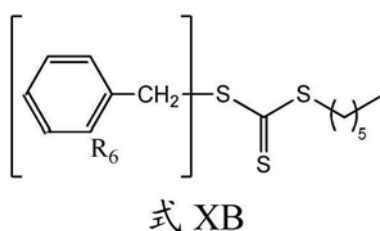
[0125] 本领域技术人员将理解,在可控自由基聚合 (CRP) 体系中形成的一级链的数量由受控自由基聚合 (CRP) 剂或控制剂的浓度来决定。就 RAFT 聚合而言,控制剂将为硫代羰基硫代官能团控制剂。就 ATRP 而言,所述控制剂将为铜配体络合物。就本文公开的本发明的目的而言,可采用任何 CRP 剂。在其它实施例中,可能不需要 CRP 剂,只要可形成纳米凝胶并且不造成宏观胶凝即可。

[0126] 在本发明的一些实施例中,可能有利的是改变每个 ζ -簇的缔合链数量,或每个亲水性链段 [Q] 的缔合型链段 [A] 平均数目 (即 [A] : [Q] 的比率) 以改善所得交联、未胶凝、两亲性共聚物的溶解度。这可通过在相同的聚合反应中使用两种 CRP 剂 (即包含至少一种 CRP 剂的 [A] 链段 ([A]-CRP) 和不包含缔合 [A] 链段的 CRP 剂) 以形成交联的未胶凝缔合型嵌段共聚物来实现。在其中采用 RAFT 聚合的实施例中,在相同的聚合反应中一起使用理想比率的式 II 和不含有机硅的结构类似物 (即不含缔合型链段的 CRP 剂),以产生交联但未经凝胶的两亲性共聚物,其中每个 ζ -簇或每个亲水性 [Q] 链段具有减少量的有机硅 [A] 链段。下式 X 详示基于 RAFT 的 CRP 剂的结构,其可用于控制每个 ζ -簇中的缔合型有机硅 [A] 链段的数量的此类实施例中。

[0127]



[0128]



[0129] 为了减少给定实施例中每个亲水性 [Q] 链段的有机硅 [A] 链段的数量并从而将每个 ζ -簇的有机硅的数量减少至所需水平,式 XA 和 XB 可一起用于形成最终交联、未胶凝的嵌段共聚物。对本领域技术人员将显而易见的是,如此形成的 ζ -簇包含具有基材缔合型链段的一级链和不具基材缔合型链段的一级链。考虑式 XA 和 XB 的摩尔量允许发展理论条件以定量每个亲水性 [Q] 链段的基材缔合型链段的数量,即缔合型 [A] 链段与亲水性 [Q] 链段 ([A] : [Q]) 的比率。在希望改变 [A] : [Q] 比率的实施例中,可采用在 0.001 : 1 至 10 : 1 范围内的目标值,其中 0.01 : 1、0.2 : 1、0.25 : 1、0.3 : 1、0.4 : 1、0.5 : 1、0.55 : 1、0.6 : 1、0.7 : 1、0.75 : 1、0.8 : 1、0.9 : 1 和甚至 0.99 : 1 的范围用于希望将每个亲水性 [Q] 链段的基材缔合型 [A] 链段的量减少至低于一致性的实施例。例如,在其中所述基材缔合型 [A] 链段为有机硅的实施例中,每个亲水性 [Q] 链段的基材缔合型有机硅 [A] 链段的量将增加至 1 以上,可使用 1.1 : 1、1.5 : 1、2.0 : 1.0、3.0 : 1.0 或甚至 10.0 : 1.0 的范围;然而,这需要使用与式 XA 所示不同的有机硅官能 RAFT 剂,即需要具有多种有机硅的 RAFT 剂以超过 1.0 的 [A] : [Q] 比率。对本领域技术人员应显而易见的是 1.0 : 1.0 的 [A] : [Q] 比率可在不存在式 XB 的情况下使用式 XA 来实现。

[0130] 在一个实施例中,亲水性 [Q] 链段可由已知亲水性单体形成。亲水性单体是在 25°C 以 10 重量%的浓度与水混合时产生澄清的单相的那些。合适的亲水性单体家族的例子包括:乙烯基酰胺、乙烯基酰亚胺、乙烯基内酰胺、亲水性(甲基)丙烯酸酯、(甲基)丙烯酸酰胺、苯乙烯、乙烯基醚、乙烯基碳酸酯、乙烯基氨基甲酸酯、乙烯基脲,以及它们的混合物。

[0131] 合适的亲水性单体的例子包括 N- 乙烯基吡咯烷酮、N- 乙烯基-2- 哌啶酮、N- 乙烯基-2- 己内酰胺、N- 乙烯基-3- 甲基-2- 己内酰胺、N- 乙烯基-3- 甲基-2- 哌啶酮、N- 乙烯基-4- 甲基-2- 哌啶酮、N- 乙烯基-4- 甲基-2- 己内酰胺、N- 乙烯基-3- 乙基-2- 吡咯烷酮、N- 乙烯基-4,5- 二甲基-2- 吡咯烷酮、乙烯基咪唑、N,N- 二甲基丙烯酰胺、丙烯酰胺、N,N- 双(2- 羟乙基) 丙烯酰胺、丙烯腈、N- 异丙基丙烯酰胺、醋酸乙烯酯、(甲基) 丙烯酸、(甲基) 丙烯酸聚乙二醇酯、2- 乙基噁唑啉、N-(2- 羟丙基)(甲基) 丙烯酰胺、N-(2- 羟乙基)(甲基) 丙烯酰胺、2- 甲基丙烯酰氧基乙基磷酰胆碱、3-(二甲基(4- 乙烯基苄基) 铵基) 丙烷-1- 磺酸酯(DMBAPS)、3-((3- 丙烯酰胺基丙基) 二甲基铵基) 丙烷-1- 磺酸酯(AMPDAPS)、3-((3- 甲基丙烯酰胺基丙基) 二甲基铵基) 丙烷-1- 磺酸酯(MAMPDAPS)、3-((3- 丙烯酰氧基) 丙基) 二甲基铵基) 丙烷-1- 磺酸酯(APDAPS)、甲基丙烯酰氧基(丙基) 二甲基铵基) 丙烷-1- 磺酸酯(MAPDAPS)、N,N- 二甲基氨基丙基(甲基) 丙烯酰胺、N- 乙烯基-N- 甲基乙酰胺、N- 乙烯基乙酰胺、N- 乙烯基-N- 甲基丙酰胺、N- 乙烯基-N- 甲基-2- 甲基丙酰胺、N- 乙烯基-2- 甲基丙酰胺、N- 乙烯基-N,N'- 二甲基脲等,以及它们的混合物。在一个实施例中,亲水性单体包含:N- 乙烯基吡咯烷酮、N- 乙烯基-N- 甲基乙酰胺、2- 甲基丙烯酰氧基乙基磷酰胆碱、(甲基) 丙烯酸、N,N- 二甲基丙烯酰胺、N- 羟丙基甲基丙烯酰胺、单甲基丙烯酸甘油酯、2- 羟乙基丙烯酰胺、双羟乙基丙烯酰胺和 2,3- 二羟丙基(甲基) 丙烯酰胺等,以及它们的混合物。在一些实施例中,所述亲水性链段也可包含带电单体,包括但不限于:甲基丙烯酸、丙烯酸、3- 丙烯酰胺基丙酸(ACA1)、4- 丙烯酰胺基丁酸、5- 丙烯酰胺基戊酸(ACA2)、3- 丙烯酰胺基-3- 甲基丁酸(AMBA)、N- 乙烯基氧基羰基- α - 丙氨酸、N- 乙烯基氧基羰基- β - 丙氨酸(VINAL)、2- 乙基-4,4- 二甲基-2- 噁

唑啉-5-酮 (VDMO)、反应性磺酸盐, 包括 2-(丙烯酰胺基)-2-甲基丙磺酸钠 (AMPS)、3-磺丙基(甲基)丙烯酸钾盐、3-磺丙基(甲基)丙烯酸钠盐、双 3-磺丙基衣康酸二钠、双 3-磺丙基衣康酸二钾、乙烯基磺酸钠盐、乙烯基磺酸盐、苯乙烯磺酸盐、甲基丙烯酸磺乙酯, 其组合等。在其中亲水性链段包含至少一带电亲水性单体的实施例中, 可能有利的是包含非带电亲水性单体以作为在所述亲水性链段中的共聚单体。在另一个实施例中, 所述带电亲水性单体无规地分布在整个 [Q] 链段中。

[0132] 亲水性链段与线性基材缔合型链段的聚合度 (DP) 比率介于约 1 : 1 和约 1000 : 1 之间, 在其它实施例中, 其介于约 3 : 1 和约 200 : 1 之间、介于约 10 : 1 和约 100 : 1 之间, 并且在其它实施例中, 介于约 10 : 1 和 50 : 1 之间。

[0133] 嵌段共聚物可经由多个聚合过程来形成。在一个实施例中, 嵌段共聚物利用 RAFT 聚合形成。在其它实施例中, 嵌段共聚物利用 ATRP 形成。然而在另一个实施例中, 嵌段共聚物利用 TERP 形成。在其它实施例中, 嵌段共聚物利用任何已知的受控自由基聚合机制形成。在另一个实施例中, 嵌段共聚物通过常规自由基聚合反应形成。

[0134] 在一个实施例中, 其可被称为亲水性-亲水性嵌段共聚物或甚至仿生亲水性-亲水性嵌段共聚物, 亲水性-亲水性嵌段共聚物包含对镜片不具亲和力的一个亲水性嵌段 (即“非缔合型”[Q] 链段) 和对存在于镜面表面上和 / 或本体内的化学部分具高度亲和力的另一种亲水性嵌段 (即“缔合型”[A] 链段)。在本发明的实施例中, 所述嵌段共聚物彼此间的交联是在非缔合型亲水性嵌段的主链上进行的, 因此使缔合型亲水性链段可用于与制品或装置的表面连接。此类缔合型亲水性-亲水性嵌段共聚物的示例性实施例可包括聚(4-丙烯酰胺基丁酸-嵌段-N,N-二甲基丙烯酰胺)(聚(ACAII-b-DMA))、聚((3-丙烯酰胺基苯基)硼酸-嵌段-N,N-二甲基丙烯酰胺)(聚(APBA-b-DMA)) 和聚(3-((3-甲基丙烯酰胺基丙基)二甲基铵基)丙烷-1-磺酸酯-嵌段-N-(2-羟丙基)甲基丙烯酰胺)(聚(MAMPDAPS-b-HPMA)) 和聚(3-((3-丙烯酰胺基丙基)二甲基铵基)丙烷-1-磺酸酯-嵌段-N,N-二甲基丙烯酰胺)(聚(AMPDAPS-b-DMA))。实施例可用于处理常规或有机硅水凝胶材料, 前提条件是缔合型嵌段的亲和力受到调控, 以适应要处理的镜面或装置表面。具有合适功能性和建构的非缔合型亲水性嵌段共聚物可高度模拟在角膜上皮表面上的结合粘蛋白的行为, 可非常适合用于对接触镜片医疗装置的表面进行改性以改善其润滑性、沉积物吸收率以及可能改善舒适度。不受理论的约束, 据推测非缔合型亲水性链段的交联特性可高度模拟经由二硫键交联、氢键合和分子缠结所发生的粘蛋白-粘蛋白相互作用。

[0135] 聚硅氧烷 RAFT 剂

[0136] 式 II 的聚硅氧烷 RAFT 剂可通过将至少一种反应性有机硅与正交反应性化合物上的至少一个反应性基团反应而形成。在相继或同步反应中, 反应性硫代羰基硫代亲核物质与正交反应性化合物上的至少一个其它反应性基团反应。正交反应性化合物包含至少两个反应性基团, 其具有不同的反应性或反应机制, 使得一个基团处的反应不需其它反应性基团中的至少一者的反应即可完成或接近完成。正交反应性化合物具有如下结构:

[0137] $RG^1-R_6-RG^2$

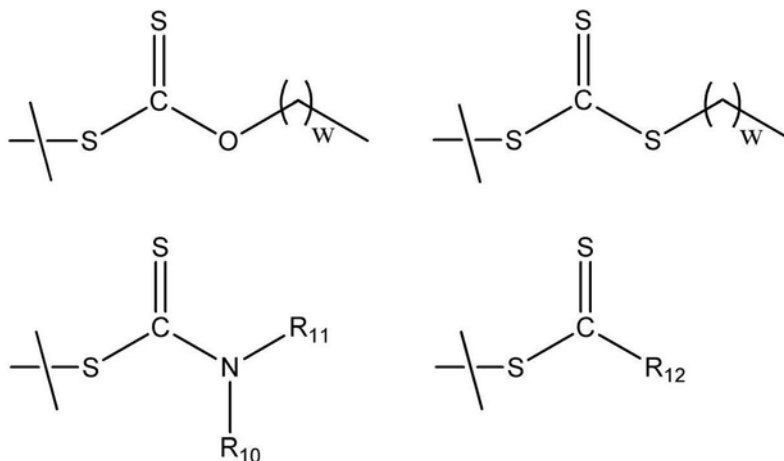
[0138] 其中 R_6 为如上定义的自由基离去基团, 并且 RG^1 和 RG^2 独立地选自正交反应性基团, 例如但不限于酰基卤和烷基卤、活性酯和烷基卤、烷基卤和不饱和双键, 以及它们的混合物等。烷基卤的例子包括 C_{1-20} 溴化物、 C_{1-20} 氯化物和 C_{1-20} 碘化物, 并且更具体地为甲基

溴、乙基溴、甲基氯、乙基氯、甲基碘、乙基碘、苄基溴、苄基氯或苄基碘。

[0139] 酰基卤的例子包括乙酰氯、乙酰溴、乙酰碘、苄基氯、苄基溴、苄基碘、丙酰氯、丙酰溴和丙酰碘。不饱和双键的例子包括乙烯基双键和丙烯基双键。活性酯的例子包括 N- 羧基琥珀亚胺基-、对硝基苯酚- 和全氟化酚羰基酯。正交反应性化合物的具体例子包括但不限于：对氯甲基苯乙烯、4- (溴甲基) 苯甲酰基溴化物 (4-BBB)、2- 溴丙酰基溴化物、2- 溴乙酰基溴化物, 以及它们的组合等。其它组合对于本领域技术人员将是显而易见的。

[0140] 合适的硫代羰基硫代部分可包括黄原酸酯、二硫酯、二硫代氨基甲酸酯、三硫代碳酸酯等。具体的和优选的硫代羰基硫代官能团在以下结构中示出：

[0141]



[0142] 其中 w 为 1 至 12 的整数, R_{10} 、 R_{11} 和 R_{12} 可为任选地取代的烷基或芳基基团, 并且在一些实施例中为被氨基基团任选地取代的烷基或芳基。在一个实施例中, R_{10} 为 C_1 - C_6 烷基 (最优选的是 C_1) 并且 R_{11} 为苯基基团或杂环基团。在其它实施例中, R_{10} 为 C_{1-6} 烷基并且 R_{11} 为碳连接的芳族杂环 (例如 4- 吡啶基)。在其它实施例中, R_{12} 为苯基或苄基, 并且优选苯基。

[0143] 在一个实施例中, 聚合剂为至少一种含硫代羰基硫代的化合物, 并且在实施例中, 为至少一种黄原酸酯。在另一个实施例中, 含硫代羰基硫代的化合物为二硫代氨基甲酸酯。在另一个实施例中, 使用至少一种三硫代碳酸酯。在另一个实施例中, 使用二硫代酯。

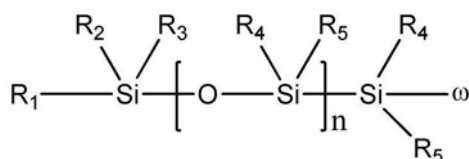
[0144] 合适的反应性硫代羰基硫代亲核物质的例子包括但不限于 O- 烷基 - 黄原酸盐、N- 烷基 - 氨基二硫代甲酸盐、S- 烷基 - 三硫代碳酸盐、N- 烷基 - 氨基二硫代甲酸盐以及苯基、苄基或烷基二硫酸盐。优选的硫代羰基硫代亲核物质包括 O- 烷基 - 黄原酸盐和 S- 烷基 - 三硫代碳酸盐。具体例子包括以下的第 I 和 II 族碱金属盐：二钾三硫代碳酸酯、O- 乙基二硫代碳酸酯、O- 丙基二硫代碳酸酯、O- 丁基二硫代碳酸酯、O- 戊基二硫代碳酸酯、O- 己基二硫代碳酸酯、O- 癸基二硫代碳酸酯、O- 十二烷基二硫代碳酸酯、O- (2,3- 二羟丙基) 二硫代碳酸酯、乙基三硫代碳酸酯、丙基三硫代碳酸酯、丁基三硫代碳酸酯、戊基三硫代碳酸酯、己基三硫代碳酸酯、癸基三硫代碳酸酯、十二烷基三硫代碳酸酯、2,3- 二羟丙基三硫代碳酸酯、甲基 (苯基) 氨基二硫代甲酸盐、甲基 (吡啶 -4- 基) 氨基二硫代甲酸盐、苯并二硫代酸酯和 2- 苯基二硫代乙烷酯。

[0145] 正交反应性化合物与硫代羰基硫代亲核物质的反应形成与基材缔合型 [A] 链段结合的链转移剂。为了进行示意性的说明, 将针对基材缔合型 [A] 链段使用反应性线性聚

硅氧烷来对本发明进行描述。这些反应的顺序并非绝对关键,并且组分可以上述顺序反应,同在一个反应釜中,或硫代羰基硫代亲核物质与正交反应性组分可预反应以形成链转移剂,所述链转移剂然后与反应性线性聚硅氧烷反应。

[0146] 当 R_1 为单价时,反应线性聚硅氧烷一端以 R_1 (如上所定义) 封端,另一端以能够与正交反应性基团 RG^1 和 RG^2 中的至少一种者反应的基团封端。例如,当 RG^1 或 RG^2 中的至少一种者为乙烯基时,聚硅氧烷反应性基团可为硅烷在 RG^1 或 RG^2 中的至少一者为活性酯的另一个实例中,聚硅氧烷反应性基团可为亲核部分,如伯醇或伯胺,其可选自氨基丙基或羟基丙基。聚硅氧烷可选自 C_1 - C_4 聚烷基和聚芳基硅氧烷。合适的聚硅氧烷的例子包括聚二甲基硅氧烷、聚二乙基硅氧烷、聚二苯基硅氧烷,以及它们的共聚物。反应线性聚硅氧烷可选自下式的化合物:

[0147]



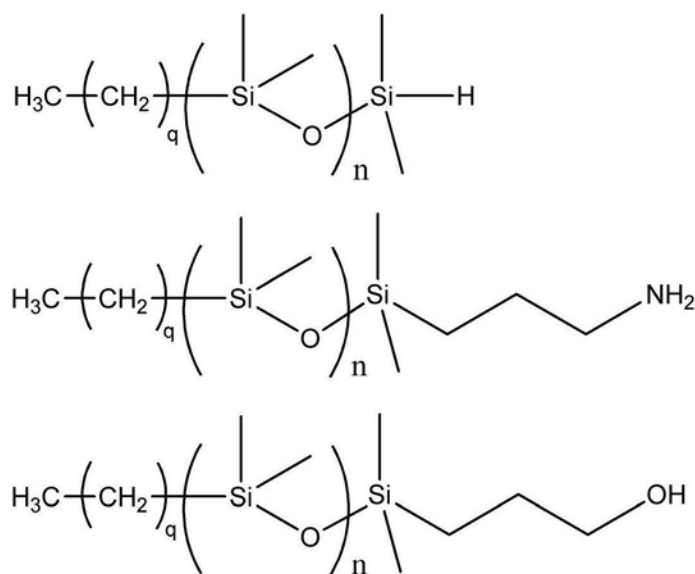
式 XI

[0148] 其中 R_1 至 R_5 为如上所定义,并且 n 为约 6 至约 200、约 6 至约 60、约 6 至约 50、约 6 至约 20、约 6 至约 15、约 6 至约 12,并且在一些实施例中,为约 10 至约 12 个硅氧烷重复单元。例如,应当理解,在一些实施例中, n 表示范围。例如,其中 n 为 10 的反应性线性聚硅氧烷可包含具有 8 至 12 个重复单元 (10 个左右) 的聚硅氧烷,并且在一些实施例中为聚二烷基硅氧烷,并且在另一个实施例中为聚二甲基硅氧烷。在一些实施例中, R_1 为 C_{1-4} 烷基基团并且 R_2 至 R_5 为甲基。在另一个实施例中, R_1 选自甲基、乙基、丙基或丁基。

[0149] ω 独立地选自 H、未取代的 C_{1-12} 烷基、被羟基、氨基等取代的 C_{1-12} 基,并且在一些实施例中, ω 选自未取代的 C_{1-4} 烷基、被羟基、氨基等取代的 C_{1-4} 烷基以及它们的组合。

[0150] 反应性直链聚硅氧烷的具体例子包括

[0151]

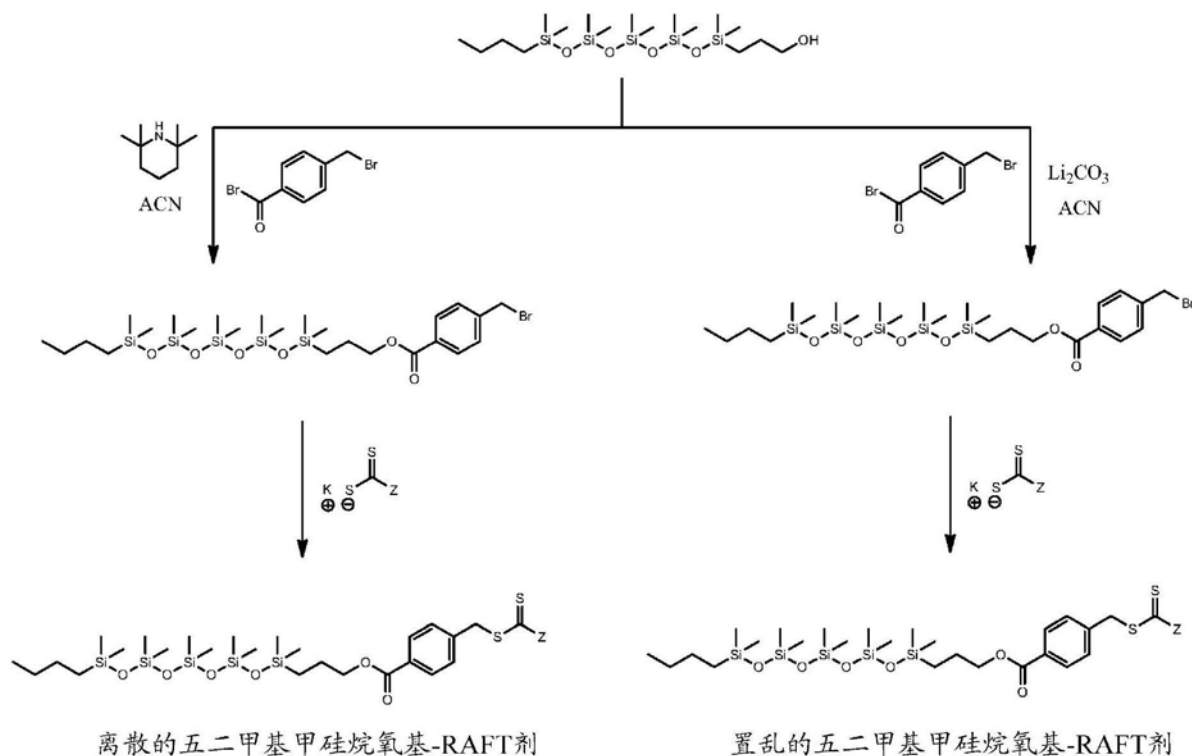


[0152] 在一个实施例中, q 为 0 至 9、0 至 5,并且在一些实施例中为 0 至 3,并且在一些实

施例中为 0 或 3。

[0153] 当聚硅氧烷官能的 RAFT 剂经由与包含酰基卤和烷基卤两者的正交反应性化合物（例如 4-BBB）进行酯化或酰胺化而形成时，所述反应可在至少一种酸清除剂的存在下进行。这描述于以下的反应方案 I 中。酸清除剂包括碳酸盐，例如 Na_2CO_3 或 Li_2CO_3 、叔胺例如三乙胺（TEA），或非亲核受阻仲胺例如 2,2,6,6-四甲基哌啶（TMP）。为防止聚硅氧烷在反应过程中的非受控置乱（scrambling），TMP 与碳酸盐相比是优选的。另外，在一些实施例中，TMP 比 TEA 是优选的，由于其与烷基卤和酰基卤的低反应性。可使用空间位阻叔胺，例如乙基-二（2-甲基丙基）胺，只要其与烷基卤和酰基卤的反应性非常低即可。

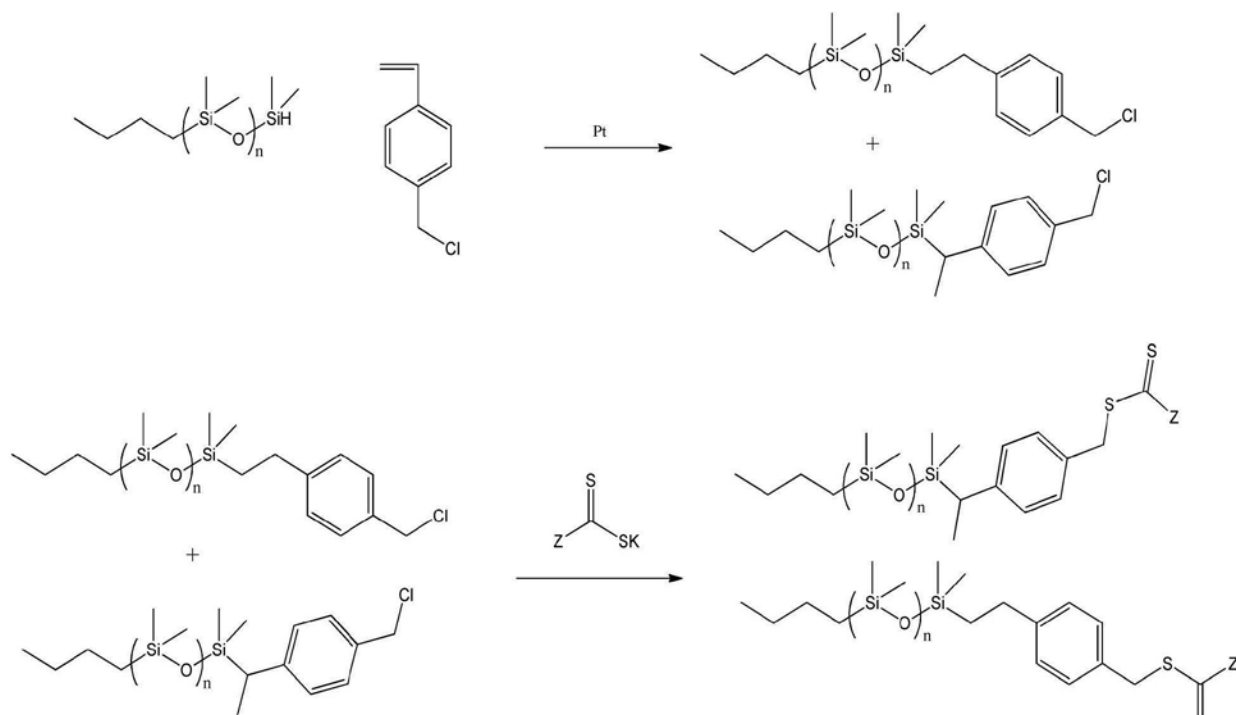
[0154]



反应方案 I

[0155] 当聚硅氧烷官能的 RAFT 剂采用与包含反应性双键和烷基卤的正交反应性化合物经由氢化硅烷化化学作用而制备时（例如 1-(氯甲基)-4-乙烯基苯），反应在 Pt 催化剂（例如 Karstedt 催化剂）的存在下进行。反应方案 II 所示的反应路径优选的是酯化或酰胺化，因为所需的反应步骤较少并且聚硅氧烷的置乱较轻。此外，此反应路径的最终产物在 R_6 与聚二烷基硅氧烷链之间产生更加水解稳定的键合（即 X）。在最终的 RAFT 聚合物中，这在聚二烷基硅氧烷链段与聚合物之间产生纯含碳二价连接部分。

[0156]



反应方案 II

[0157] 与正交反应性化合物反应的聚二烷基硅氧烷基团和硫代羰基硫代部分的数量取决于反应性硅的性质、正交反应性组分上特定官能团的性质和数量,和用于形成感兴趣的最终化合物的硫代羰基硫代亲核物质的反应性质,即聚二烷基硅氧烷官能的 RAFT 剂。例如,如果羟基丙基末端正丁基聚二甲基硅氧烷与 4-(溴甲基)苯甲酰基溴化物(4-BBB)在 TMP(参见反应方案 I)的存在下反应,则本领域技术人员应可预期在羟基丙基末端正丁基聚二甲基硅氧烷与 4-BBB 的酰基溴之间观察到酯形成。预期硫代羰基硫代亲核物质盐不与 4-BBB 上的氯化酸反应;相反,预期 4-BBB 上的酰基溴将被所述硫代羰基硫代亲核物质盐置换。如果使用包含一种酰基卤和两种烷基卤的正交反应性化合物而非 4-BBB,例如 3,5-双(溴甲基)苯甲酰基溴化物,则应可期待获得包含两种分离但共价连接的硫代羰基硫代部分的聚二烷基硅氧烷官能的 RAFT 剂。当在亲水性单体的存在下进行聚合时,此特定聚硅氧烷官能的 RAFT 剂将产生聚合物结构,其在链的一端包含单一聚硅氧烷链段,而在另一端包含两个亲水性链段。本领域技术人员将理解,利用上述氢化硅烷化化学作用并产生具有两个或更多个亲水性链段和一个直链有机硅链段的结构或具有两个或更多个线性有机硅链段和一个亲水性链段的结构类似合成路径是适用的。

[0158] 反应可在 0℃ 至约 100℃ 下进行。在一个实施例中,反应在约环境温度下进行。反应可进行约 1 分钟至约 24 小时的时间,并且在一些实施例中为约 1 小时至约 3 小时。反应产物为聚硅氧烷 RAFT 剂或有机硅官能的 [A]-CRP 剂。

[0159] 反应可在无添加情况下进行或在至少一种极性非质子溶剂中进行,所述溶剂能够溶解官能的聚硅氧烷、硫代羰基化合物和正交反应性化合物及其反应所形成的中间体。合适的溶剂包括乙腈、丙酮、DMF、NMP,以及它们的组合等。

[0160] 在一个实施例中,使聚二甲基硅氧烷 RAFT 剂与适当选择的单体、自由基引发物质(即自由基引发剂,如 CGI-819 或 AIBN),和任选的能够使反应中所使用或产生的所有反应物和产物溶剂化的溶剂接触。此步骤的反应时间为约 1 分钟至约 12 小时,并且在一些实施

例中为约 1 小时至约 6 小时。反应温度包括介于约 0℃ 和约 150℃ 之间的温度。

[0161] 聚合条件

[0162] 在通过使聚硅氧烷官能的 RAFT 剂或缔合型 [A]-CRP 剂和非有机硅官能的 RAFT 剂（需要时）与至少一种亲水性单体、自由基引发剂和交联剂接触所产生的给定聚合中，每个 ζ -一级链的数均分子量 M_{nZ-PC} 可利用以下公式计算：

$$[0163] \quad M_{n_{\zeta-PC}} = M_{n_M} + M_{n_{XL}} + \varepsilon + \phi$$

[0164] 其中

[0165]

$$M_{n_M} = \frac{[M]}{([CTA_{\text{有机硅}}] + [CTA_{\text{标准}}])} \cdot X \cdot MW_{\text{单体}} \quad M_{n_{XL}} = \frac{[XL]}{([CTA_{\text{有机硅}}] + [CTA_{\text{标准}}])} \cdot \frac{X}{\psi} \cdot MW_{XL}$$

[0166]

$$\varepsilon = \frac{[CTA_{\text{有机硅}}]}{([CTA_{\text{有机硅}}] + [CTA_{\text{标准}}])} \cdot MW_{CTA_{\text{有机硅}}} \quad \phi = \frac{[CTA_{\text{标准}}]}{([CTA_{\text{有机硅}}] + [CTA_{\text{标准}}])} \cdot MW_{CTA_{\text{标准}}}$$

[0167] M_{nM} 、 M_{nXL} 、 ε 和 ϕ 表示（当总和时）等于 ζ -一级链的数均分子量（即 M_{nZ-PC} ）的单体、交联剂、有机硅官能的 RAFT 剂和非有机硅官能的 RAFT 剂的各个分子量贡献。 ψ 为交联剂上的反应性官能团数量， $[M]$ 为反应性单体浓度， $[XL]$ 为交联剂浓度， X 为以分数形式表示的转化程度， $[CTA_{\text{有机硅}}]$ 为有机硅官能的 RAFT 剂的浓度， $[CTA_{\text{Std}}]$ 为非有机硅 RAFT 剂的浓度（如果有使用），和 $MW_{\text{单体}}$ 、 MW_{XL} 、 $MW_{CTA_{\text{有机硅}}}$ 和 $MW_{CTA_{\text{Std}}}$ 分别为反应性单体、交联剂、有机硅官能的 RAFT 剂和非有机硅 RAFT 剂的分子量。

[0168] 通过重排此公式可得亲水性聚合物链段 $DP_{nQ-\text{链段}}$ 在给定转换率下的预计聚合度（DP）。如果 X 为 1（即聚合达 100% 转化率）并且 $MW_{CTA_{\text{有机硅}}}$ 和 $MW_{CTA_{\text{Std}}}$ 可在计算中忽略，因为它们不是 Q -链段的部分，则公式被缩减至这样的表达式，其预计在达到 100% 转换率的给定聚合所得到的单一 ζ -一级链中的亲水性 Q 链段的目标数均 DP， $DP_{nQ-\text{链段}}$ ：

[0169]

$$M_{n_{Q-\text{链段}}} = M_{n_M} + M_{n_{XL}}$$

[0170] 求解 $DP_{nQ-\text{链段}}$ 得到：

[0171]

$$DP_{n_{Q-\text{链段}}} = \frac{M_{n_M}}{MW_M} + \frac{M_{n_{XL}}}{\frac{MW_{XL}}{\psi}} = DP_{n_M} + \frac{DP_{n_{XL}}}{\psi}$$

[0172]

$$DP_{n_{Q-\text{链段}}} = \frac{[M]}{([CTA_{\text{有机硅}}] + [CTA_{\text{标准}}])} + \frac{[XL]}{([CTA_{\text{有机硅}}] + [CTA_{\text{标准}}])} \cdot \frac{1}{\psi}$$

[0173] 公式 2

[0174] 对本领域技术人员应显而易见的是，虽然这些公式预计 ζ -一级链的数均分子量 M_{nZ-PC} 和亲水性 $[Q]$ 链段的数均聚合度，即 $DP_{nQ-\text{链段}}$ ，但其无法预计由交联剂参与 RAFT 聚合所形成的 ζ -簇的总 DP 或整体平均分子量，因为 ζ -一级链彼此之间无规交联而并且与其它

生长的 ζ -簇交联。给定 ζ -簇的分子量远高于在 ζ -簇内的个别 ζ -一级链的分子量，并且可能是也可能不是给定聚合的平均 M_{nz-pc} 的整倍数。

[0175] 一种目标 $DP_{nQ-链段}$ 在 10 至 10,000，优选 50 至 1500，更优选 50 至 1000，最优选 50 至 500 的范围内。

[0176] 使亲水性单体在适当的聚二烷基硅氧烷 RAFT 剂和交联剂存在下聚合以形成嵌段共聚物的聚合条件基于使用的引发剂体系进行选择，以提供链生长与终止之间所需的平衡。其它聚合组分如溶剂、引发剂和添加剂也可加以选择，使得它们对链传播自由基具有低转移常数并且可与所有其它聚合组分完全可混溶。

[0177] 交联剂可在反应开始时就加入聚合溶液或等到反应后期添加以调控所形成的纳米凝胶材料的建构，使其具有所需的结构或特性。另选地，交联剂上的反应性基团可经选择，使其不太无规地结合到传播的聚合物主链中，因此形成交联剂密度分布较不均匀的聚合物纳米凝胶。如果希望聚合物纳米凝胶“非均质 (blocky)”结合，则可使用对于传播的单乙烯基单体具有不同反应性的交联剂例如，二甲基丙烯酰化交联剂可用于以丙烯酰胺基、单乙烯基单体形成的纳米凝胶。对于采用 CRP 的一些实施例，这导致交联剂“递变 (tapered)”结合到 Q-链段主链中，即，各 Q 链段的一端比另一端富含二乙烯基单体。另选地，对于希望交联剂无规分布于整个 Q 链段中的实施例，可选择使得两个反应位点均与传播的单乙烯基单体具有类似反应性（或相同官能团）的交联剂。在一些实施例中，可采用包含不同反应性的官能团的交联剂，例如 2-(丙烯酰氧基)乙基甲基丙烯酸酯或 N-(2-丙烯酰胺基乙基)甲基丙烯酰胺。本领域技术人员可预期，相比于包含所有反应性官能团具有相符反应性的类似体系，此类结构也可以不太无规的方式结合到整个 Q-链段中。

[0178] 在嵌段共聚物经由 RAFT 制备的实施例中，引发体系的选择应使得在反应条件下，引发剂或引发自由基与转移剂无实质的不利相互作用。引发剂也应具有在反应介质或单体混合物中的必要溶解度。基于所选的亲水性单体选择引发剂。例如，使用自由基反应性亲水性单体时，引发剂可为任何能够提供自由基源的引发剂，例如光引发剂、热引发剂、氧化还原引发剂和 γ 引发剂。合适的光引发剂包括下述的 UV 和可见光引发剂。热引发剂选择为在聚合温度下具有适当的半衰期。这些引发剂可包括以下化合物中的一种或多种：2,2'-偶氮双(异丁腈)、2,2'-偶氮双(2-氰基-2-丁烷)、二甲基 2,2'-偶氮双二甲基异丁酸酯 4,4'-偶氮双(4-氰基戊酸)、1,1'-偶氮双(环己烷甲腈)、2-(叔丁基偶氮)-2-氰基丙烷、2,2'-偶氮双[2-甲基-N-(1,1-双(羟甲基)-2-羟乙基)丙酰胺]、2,2'-偶氮双[2-甲基-N-羟乙基]-丙酰胺、2,2'-偶氮双(N,N'-二甲基烯异丁基脒基)二盐酸盐、2,2'-偶氮双(2-脒基丙烷)二盐酸盐、2,2'-偶氮双(N,N'-二甲基烯异丁基胺)、2,2'-偶氮双(2-甲基-N-[1,1-双(羟甲基)-2-羟乙基]丙酰胺)、2,2'-偶氮双(2-甲基-N-[1,1-双(羟甲基)乙基]丙酰胺)、2,2'-偶氮双[2-甲基-N-(2-羟乙基)丙酰胺]、2,2'-偶氮双(异丁基酰胺)二水合物、2,2'-偶氮双(2,2,4-三甲基戊烷)、2,2'-偶氮双(2-甲基丙烷)、过氧乙酸叔丁酯、过氧苯甲酸叔丁酯、过氧辛酸叔丁酯、过氧新癸酸叔丁酯、过氧异丁酸叔丁酯、过氧新戊酸叔戊基酯、过氧新戊酸叔丁酯、过氧二碳酸二异丙基酯、过氧二碳酸二环己基酯、二枯基过氧化物、二苯酰过氧化物、二月桂酰过氧化物、过氧二硫酸钾、过氧二硫酸铵、次硝酸二叔丁酯、次硝酸二异丙苯酯。在一个实施例中，热引发剂选自在适度升高的温度下产生自由基的引发剂，例如月桂基过氧化物、苯甲酰过氧化物、过碳

酸异丙酯、偶氮双异丁腈,它们的组合等。

[0179] 氧化还原引发剂的例子包括以下氧化剂与还原剂的组合:

[0180] 氧化剂:过氧二硫酸钾、过氧化氢、叔丁基过氧化氢。

[0181] 还原剂:铁(II)、钛(III)、硫代硫酸钾、硫酸氢钾。

[0182] 在一个实施例中,引发剂选自光引发剂,所述光引发剂在反应介质或单体混合物中具有必要溶解度,并且在聚合条件下具有适当的自由基产生量子产率。例子包括安息香衍生物、二苯甲酮、酰基氧化膦和光氧化还原体系。在另一个实施例中,引发剂选自可见光引发剂,所述可见光引发剂选自1-羟基环己基苯基酮、2-羟基-2-甲基-1-苯基-丙-1-酮、双(2,6-二甲氧基苯甲酰基)-2,4,4-三甲基戊基氧化膦(DMBAPO)、双(2,4,6-三甲基苯甲酰基)-苯基氧化膦(Irgacure 819)、2,4,6-三甲基苄基二苯基氧化膦和2,4,6-三甲基苯甲酰基二苯基氧化膦、安息香甲酯,和樟脑醌与4-(N,N-二甲基氨基)苯甲酸乙酯的组合,它们的组合等。在另一个实施例中,引发剂包含至少一种含氧化膦的光引发剂,并且在另一个实施例中,为双(2,4,6-三甲基苯甲酰基)-苯基氧化膦。当使用光引发剂时,使用选定光引发剂的激发波长内的辐射来照射反应混合物。

[0183] 聚合可在溶液、悬浮液或乳液中以间歇模式、连续模式或进料模式进行。在一个实施例中,通过将聚合剂加入到包含聚硅氧烷末端链转移剂的反应混合物中进行所述工艺。其它条件也可使用并且是本领域所已知的。

[0184] 嵌段共聚物

[0185] 本文提供的嵌段共聚物可经由已知方法纯化,例如溶剂沉淀和/或后续溶剂萃取,或通过渗析或相关纯化技术(例如但不限于切向流过滤(TFF))。

[0186] 本文提供的嵌段共聚物具有至少一个末端基材缔合型链,并且在一些利用RAFT聚合并且使用前未移除RAFT剂的实施例中,RAFT聚合剂位于嵌段共聚物的末端。

[0187] 通常,RAFT聚合剂不是热稳定或水解稳定的,因此本发明实施例的有益效果在于RAFT聚合剂位于末端,因此结合到聚合物基材之前可被容易地裂解或取代。在其最终使用前,嵌段共聚物可经分离并用于与另一合适的单体的后续“链延伸”聚合中。另选地,RAFT聚合剂可留存于嵌段共聚物上,并且在结合到聚合物基材中或使用期间(如果RAFT和/或其降解剂为无毒的、非刺激性的)发生裂解。在一个实施例中,在嵌段共聚物结合到基材之前或溶液与基材接触之前移除RAFT聚合剂。移除末端基团的合适方法包括但不限于与胺反应,诸如US7109276、US6794486、US7807755、US2007232783、US2010137548、US5385996和US5874511中所公开。其它端基移除技术如热解或自由基还原也可在一些实施例中使用。

[0188] 在一个实施例中,嵌段共聚物具有如上式I的结构。

[0189] 在另一个实施例中,嵌段共聚物可通过常规自由基反应形成。在此实施例中,可经由US2010/0099829和共同提交的专利申请USSN 61/482,260中所述的方法通过至少一种亲水性单体与偶氮型大分子引发剂的自由基反应来形成嵌段共聚物,所述偶氮型大分子引发剂的疏水性链段的分子量介于约300和约1800之间。

[0190] 疏水性或部分疏水性基材

[0191] 本文所公开的嵌段共聚物可与各种疏水性、部分疏水性、亲水性或两亲性基材,诸如由聚硅氧烷、有机硅水凝胶、常规水凝胶、聚甲基丙烯酸甲酯、聚乙烯、聚丙烯、聚碳酸酯、

聚对苯二甲酸乙二酯、聚四氟乙烯、玻璃、金属,它们的混合物和共聚物等形成的聚合物制品非共价地缔合。发生缔合的前提条件是嵌段共聚物的 [A] 嵌段内所包含的官能团与给定基材之上或之中存在的官能团之间具有有足够的亲和力。可经处理以与本发明的嵌段共聚物的基材缔合的实例包括用于植入式装置、缝合线、移植基材、泪点塞、导管、支架、伤口敷料、外科器械、眼科装置等的聚合物和金属。

[0192] 至少部分疏水性聚合物基材的另外的例子包括用于可植入装置(诸如进行关节置换)的高度交联的超高分子量聚乙烯(UHMWPE),其分子量通常为至少约 400,000,并且在一些实施例中为约 1,000,000 至约 10,000,000,这由大致为 0 的熔融指数(ASTM D-1238)和大于 8 并且在一些实施例中介于约 25 和 30 之间的降低比重所界定。

[0193] 适用作制备缝合线中的纱线以及伤口敷料的可吸收聚合物包括但不限于:脂族聚酯,其包括但不限于以下各项的均聚物和共聚物及其聚合物共混物:丙交酯(其包括乳酸、d-丙交酯、l-丙交酯和内消旋丙交酯)、乙交酯(包括乙醇酸)、 ϵ -己内酯、对二氧杂环己酮(1,4-二氧杂环己烷-2-酮)、三亚甲基碳酸酯(1,3-二氧杂环己烷-2-酮)、三亚甲基碳酸酯的烷基衍生物、 δ -戊内酯、 β -丁内酯、 γ -丁内酯、 ϵ -癸内酯、羟基丁酸酯、羟基戊酸酯、1,4-二氧杂环庚烷-2-酮(包括其二聚体 1,5,8,12-四氧杂环十四烷-7,14-二酮)、1,5-二氧杂环庚烷-2-酮、6,6-二甲基-1,4-二氧杂环己烷-2-酮,以及它们的聚合物共混物。

[0194] 非可吸收的聚合物材料诸如但不限于聚酰胺(聚己二酰己二胺(尼龙 66)、聚癸二酰己二胺(尼龙 610)、聚己酰胺(尼龙 6)、聚十二酰胺(尼龙 12)和聚六亚甲基间苯二甲酰胺(尼龙 61)、它们的共聚物和共混物)、聚酯(如聚对苯二甲酸乙二醇酯、聚对苯二甲酸丁酯、它们的共聚物和共混物)、含氟聚合物(如聚四氟乙烯和聚偏二氟乙烯)、聚烯烃(如聚丙烯,包括全同立构和间同立构聚丙烯及其共混物,以及主要由与杂同立构聚丙烯共混的全同立构或间同立构聚丙烯构成的共混物(例如于 1985 年 12 月 10 日公布的转让给爱惜康公司(Ethicon, Inc.)的美国专利 4,557,264 中所描述,所述专利据此以引用方式并入),以及聚乙烯,例如于 1985 年 12 月 10 日公布的转让给爱惜康公司的美国专利 4,557,264 中所描述),以及它们的组合。

[0195] 泪点塞的主体可由任何合适的生物相容性聚合物制成,包括但不限于有机硅、有机硅共混物、有机硅共聚物(例如 PHEMA(聚羟乙基甲基丙烯酸酯)、聚乙二醇、聚乙烯吡咯烷酮和甘油的亲水性单体)。其它合适的生物相容性材料包括例如氟化聚合物,诸如例如聚四氟乙烯(“PTFE”)、聚偏二氟乙烯(“PVDF”)和特氟隆;聚丙烯;聚乙烯;尼龙;乙烯-乙烯醇(“EVA”)。

[0196] 超声外科器械的聚合物部件可以由聚酰亚胺、氟化乙烯丙烯(FEP 特氟隆)、PTFE 特氟隆、有机硅橡胶、EPDM 橡胶制成,其中的任何一种可填充诸如特氟隆或石墨等材料,也可不填充。实例在 US20050192610 和 US6458142 中有所公开。对于这些实施例而言,可将嵌段共聚物与使至少部分疏水性聚合物基体溶胀的溶剂混合,然后与聚合物基体接触。

[0197] 在一个实施例中,使嵌段共聚物与预成型制品结合,这些制品包括有机硅眼科装置,例如镜片或泪点塞、有机硅水凝胶制品,例如有机硅水凝胶镜片。在此实施例中,据信末端聚硅氧烷与包含疏水性聚合物组分的基材缔合。在此实施例中,将嵌段共聚物溶解在也使基材溶胀的溶剂中。将聚合物基材与包含嵌段共聚物的溶液接触。当基材为有机硅水凝

胶制品（例如接触镜片）时，合适的溶剂包括润湿溶液、储存液和清洁溶液。以此实施例为例，将有机硅水凝胶镜片置于包含嵌段共聚物的润湿溶液中。基于溶液中的所有组分计，存在于溶液中的嵌段共聚物的量介于约 0.001 和约 10% 之间，在一些实施例中，介于约 0.005 和约 2% 之间，并且在其它实施例中，介于约 0.01 和约 0.5 重量% 之间。

[0198] 润湿溶液可为任何用于储存接触镜片的水性溶液。典型溶液包括但不限于盐水溶液、其它缓冲溶液和去离子水。优选的含水溶液为包含盐（包括但不限于氯化钠、硼酸钠、磷酸钠、磷酸氢钠、磷酸二氢钠或它们的相应钾盐）的盐水溶液。这些成分一般组合以形成包含酸及其共轭碱的缓冲溶液，使得添加酸和碱仅引起 pH 相对小的变化。缓冲溶液可附加地包括 2-(N-吗啉)乙磺酸(MES)、氢氧化钠、2,2'-双(羟甲基)-22'-次氨基三乙醇、n-三(羟甲基)甲基-2-氨基乙磺酸、柠檬酸、柠檬酸钠、碳酸钠、碳酸氢钠、乙酸、乙酸钠、乙二胺四乙酸等，以及它们的组合。优选地，溶液为硼酸盐缓冲盐水溶液或磷酸盐缓冲盐水溶液。溶液还可包含已知的附加组分，例如粘度调节剂、抗微生物剂、润湿剂、抗粘剂、防腐剂、高分子电解质、稳定剂、螯合剂、抗氧化剂，它们的组合等。

[0199] 嵌段共聚物也可用有机溶剂（使用或不用水作为共溶剂）来与镜片缔合。在一个实施例中，有机溶剂用于使医疗装置（例如接触镜片医疗装置）溶胀和溶解嵌段共聚物，使得嵌段共聚物可被吸收。可选择合适的溶剂以使医疗装置溶胀和溶解嵌段共聚物或实现两者。在另一个实施例中，溶剂也可作为生物相容性的，以简化制备。在足以结合润滑和表面润湿有效量的嵌段共聚物的条件下使基材与嵌段共聚物接触。如本文所用，润滑有效量是赋予一定程度的润滑性所必需的量，这种润滑性在使用装置时用手可以感觉到（例如在手指间摩擦装置）。另外，如本文所用，表面润湿有效量是赋予镜片一定程度的增大的可润湿性所必需的量，这种可润湿性通过已知的接触角测量技术（即静滴法、俘泡法或动态接触角测量）测得。已经发现的是，在一个实施例中，当装置为软性接触镜片时，只需 50ppm 的嵌段共聚物就可以提供改善的镜片“触感”和用静滴法测得的减小的表面接触角。在加工润湿溶液、储存溶液或清洁溶液中，大于约 50ppm，并且更优选大于约 100ppm 的嵌段共聚物的量将更明显地改善触感。因此，在此实施例中，嵌段共聚物在溶液中的浓度可以为最多约 50,000ppm，在一些实施例中，介于约 10 和 5000ppm 之间，并且在一些实施例中，介于约 10 和约 2000ppm 之间。在一个实施例中，包含嵌段共聚物的溶液没有可见雾度（澄清）。可以对润湿镜片进行热处理，以增加渗透并缠结在镜片中的嵌段共聚物的量。合适的热处理包括但不限于常规的热灭菌循环，其包括约 120℃ 的温度和约 20 分钟的时间，并可以在高压釜中进行。如果不使用热灭菌，则可以单独对润湿镜片进行热处理。单独热处理的合适温度包括至少约 40℃，并优选地介于约 50℃ 和溶液的沸点之间。合适的热处理时间包括至少约 10 分钟。应当理解，更高的温度将需要更短的处理时间。

[0200] 本发明的有益效果是，使半交联嵌段共聚物与所需基材缔合的步骤可以单一步骤进行而无需预处理、共价反应或粘结层。然而，在一些实施例中，可能有利的是将基材 / 半交联嵌段共聚物结构体与附加的聚合物或纳米凝胶接触以形成层状涂层。附加的聚合物可为线性的、支化的或交联的，并且可具有位于聚合物的一个末端或位于整个聚合物上的缔合基团每种附加的聚合物包含能够与前层聚合物中所包含的基团缔合或反应的基团。因此，对于初始用 [Q] 链段中包含质子提供基团的半交联嵌段共聚物处理的基材而言，附加聚合物将包含质子接受基团、由其组成或基本上由其组成。可施加若干个 WSC 和额外聚合

物的交替的层。包含质子接受基团的聚合物的例子包括但不限于聚-N-乙烯基吡咯烷酮、聚-N-乙烯基-2-哌啶酮、聚-N-乙烯基-2-己内酰胺、聚-N-乙烯基-3-甲基-2-己内酰胺、聚-N-乙烯基-3-甲基-2-哌啶酮、聚-N-乙烯基-4-甲基-2-哌啶酮、聚-N-乙烯基-4-甲基-2-己内酰胺、聚-N-乙烯基-3-乙基-2-吡咯烷酮和聚-N-乙烯基-4,5-二甲基-2-吡咯烷酮、聚乙烯基咪唑、聚-N-N-二甲基丙烯酰胺、聚乙烯醇、聚氧化乙烯、聚-2-乙基-噁唑啉、肝素多醣、多糖,它们的混合物和共聚物(包括嵌段的或无规的、支化的、多链的、梳状的或星状)。可使用聚-N-乙烯基吡咯烷酮(PVP)和聚-N-N-二甲基丙烯酰胺的聚合物和共聚物。

[0201] 第二溶液可为上述用于使基材与半交联嵌段共聚物接触的任何溶液。至少一种第二聚合物在溶液中的浓度为最多约 50,000ppm、介于约 10 和 5000ppm 之间,或介于约 10 和 2000ppm 之间。因为两种聚合物均为非离子聚合物,所以可在介于约 6 和 8 之间的 pH(并且在一些实施例中为约 7 的 pH)下进行附加处理步骤

[0202] 许多有机硅水凝胶材料都是已知的并可以使用,包括但不限于 senofilcon、galyfilcon、lotrafilcon A 和 lotrafilcon B、delefilcon、balafilcon、comfilcon、osmofilcon、enfilcon、filcon II、filcon IV 等等。几乎任何有机硅水凝胶聚合物都可用本发明的嵌段共聚物处理,包括但不限于 US6,637,929、W003/022321、W003/022322、US5,260,000、US5,034,461、US6,867,245、W02008/061992、US 5,760,100、US7,553,880、US20100048847、US2006/0063852 中所公开的那些。

[0203] 可将类似的方法用于由有机硅水凝胶之外的聚合物制成的基材主要的变化是溶剂的选择,溶剂应溶解嵌段共聚物并使基材溶胀。可以使用溶剂的混合物,如果需要,也可以包括附加组分,例如表面活性剂。例如,在制品为有机硅制品的情况下,例如有机硅接触镜片或有机硅泪点塞,则可将嵌段共聚物溶解在诸如脂族醇、水以及它们的混合物的溶剂中。具体实例包括异丙醇、正丙醇等,浓度如上文所述。

[0204] 在另一个实施例中,可以将嵌段共聚物包含在制备聚合物制品的反应混合物中。在此类实施例中,嵌段共聚物的有效量可占有所有镜片组分总重量的约 0.1%至 50%,优选地为约 1%至 20%,最优选地为约 2%至 15%。例如,在制品为有机硅水凝胶接触镜片的情况下,在具有一种或多种含有机硅组分和一种或多种亲水性组分的接触镜片反应混合物中可包含最多约 20 重量%的嵌段共聚物。用于制备本文所公开的聚合物的含有机硅组分和亲水性组分可为现有技术中用于制备有机硅水凝胶的任何已知组分。这些术语,具体而言,含有机硅组分和亲水性组分不是互斥的,这在于含有机硅组分可在一定程度上亲水性的,而亲水性组分可包含一些有机硅,因为含有机硅组分可以具有亲水性基团,而亲水性组分可具有有机硅基团。

[0205] 本文所公开的嵌段共聚物的一个优点是,在非反应性嵌段共聚物由 RAFT 形成的实施例中,易于根据所选制品的制造要求来控制分子量(MW)和分子量分布(MWD)。例如,在嵌段共聚物结合到低粘度反应性单体混合物(例如用于形成浇注模塑的接触镜片的那些)中的一个实施例中,嵌段共聚物的 MW 可保持低于约 100,000g/mol。在采用可控聚合的一个实施例中, α -一级链的多分散性小于约 1.3。 ζ -簇将具有大于 1.3 的多分散性值。与市售的聚合物例如 PVP 相比,具有较低 MW 的嵌段共聚物允许添加更高浓度的根据本发明实施例的嵌段共聚物。常规的聚合物例如 PVP 具有较高的多分散性,这会形成极粘稠的单体混

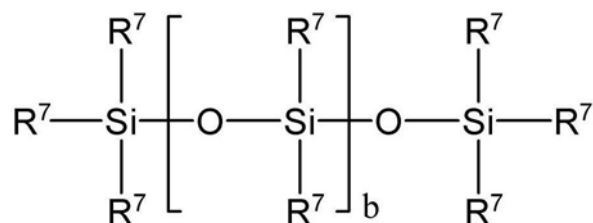
合物,从而由于粘性而往往会产生加工方面的问题。

[0206] 使用 RAFT 制备本发明的纳米凝胶允许形成纳米尺寸的凝胶,而不形成宏观上胶凝的共聚物。除此之外,相比于具有相等分子量的相同线性聚合物,此类纳米凝胶表现出显著较低的粘度。如上所提及的,具有较低粘度的高分子量聚合物对许多加工应用而言较为理想,包括使给定反应性单体混合物制剂的粘度和“粘性”最小化。

[0207] 含有机硅组分是在单体、大分子单体或预聚合物中含有至少一个 $[-Si-O-]$ 基团的组分。在一个实施例中, Si 和所连接的 O 以大于 20 重量%, 并且在另一个实施例中大于含有机硅组分总分子量的 30 重量% 的量存在于含有机硅组分中。可用的含有机硅组分包含可聚合的官能团,例如 (甲基) 丙烯酸酯、(甲基) 丙烯酰胺、N- 乙烯基内酰胺、N- 乙烯基酰胺和苯乙烯基官能团。可用的含有机硅组分的例子可见于美国专利 3, 808, 178 ; 4, 120, 570 ; 4, 136, 250 ; 4, 153, 641 ; 4, 740, 533 ; 5, 034, 461 ; 5, 760, 100 ; 4, 139, 513 ; 5, 998, 498、US2006/0063852 和 5, 070, 215 以及 EP080539 中。本文列举的所有专利的全部内容据此全文以引用方式并入。这些参考文献公开了烯属含有机硅组分的多个例子。

[0208] 合适的含有机硅组分包括下式的化合物：

[0209]



式 XII

[0210] 其中 R^7 独立地选自一价反应性基团、一价烷基基团或一价芳基基团, 上述任何基团还可以包含选自羟基、氨基、氧杂、羧基、烷基羧基、烷氧基、酰胺基、氨基甲酸酯基、碳酸酯基、卤素或它们的组合的官能团 ; 并且一价硅氧烷链包含 1 至 100 个 SiO 重复单元, 所述重复单元还可以包含选自烷基、羟基、氨基、氧杂基、羧基、烷基羧基、烷氧基、酰氨基、氨基甲酸酯基、卤素或它们的组合的官能团 ;

[0211] 其中 $b = 0$ 至 500, 其中应当理解, 当 b 不为 0 时, b 为众数等于指定值的分布 ;

[0212] 其中至少一个 R^7 包含一价反应性基团, 并且在一些实施例中, 1 至 3 个 R^7 包含一价反应性基团。

[0213] 如本文所用, “一价反应性基团” 为可经历自由基和 / 或阳离子聚合的基团。自由基反应性基团的非限制性例子包括 (甲基) 丙烯酸酯、苯乙烯基、乙烯基、乙烯基醚、取代或未取代的 C_{1-6} 烷基 (甲基) 丙烯酸酯、(甲基) 丙烯酰胺、 C_{1-6} 烷基 (甲基) 丙烯酰胺、N- 乙烯基内酰胺、N- 乙烯基酰胺、 C_{2-12} 烯基、 C_{2-12} 烯基苯基、 C_{2-12} 烯基萘基、 C_{2-6} 烯基苯基、 C_{1-6} 烷基、O- 乙烯基氨基甲酸酯以及 O- 乙烯基碳酸酯。所述 C_{1-6} 烷基的合适取代基包括醚基、羟基、羧基、卤素以及它们的组合。阳离子反应性基团的非限制性例子包括乙烯基醚或环氧基团, 以及它们的混合物。在一个实施例中, 自由基反应性基团包括 (甲基) 丙烯酸酯、丙烯酰氧基、(甲基) 丙烯酰胺, 以及它们的混合物。

[0214] 合适的一价烷基基团和芳基基团包含未取代的一价 C_1-C_{16} 烷基基团、 C_6-C_{14} 芳基基团, 诸如取代的和未取代的甲基、乙基、丙基、丁基、2- 羟丙基、丙氧基丙基、聚乙烯氧基丙

基,它们的组合等。

[0215] 在一个实施例中, R^7 选自 C_{1-6} 烷基(甲基)丙烯酸酯和 C_{1-6} 烷基(甲基)丙烯酰胺,其可被羟基、亚烷基醚或它们的组合未取代或取代。在另一个实施例中, R^7 选自丙基(甲基)丙烯酸酯和丙基(甲基)丙烯酰胺,其中所述丙基可任选地被羟基、亚烷基醚或它们的组合取代。

[0216] 在一个实施例中, b 为 0, 一个 R^7 为一价反应性基团, 并且至少 3 个 R^7 选自具有 1 至 16 个碳原子的一价烷基基团, 并且在另一个实施例中, 选自具有 1 至 6 个碳原子的一价烷基基团。本实施例的有机硅组分的非限制性例子包括 2-甲基, 2-羟基-3-[3-[1,3,3,3-四甲基-1-[(三甲基硅烷基)氧基]二硅氧烷基]丙氧基]丙酯(“SiGMA”)、

[0217] 2-羟基-3-甲基丙烯酰氧基丙基-三(三甲基甲硅烷氧基)硅烷、

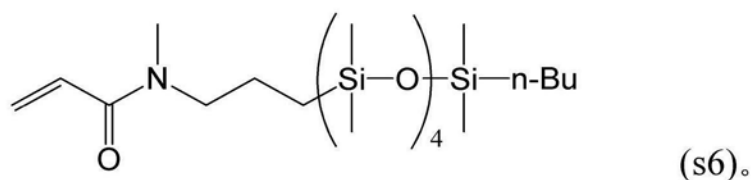
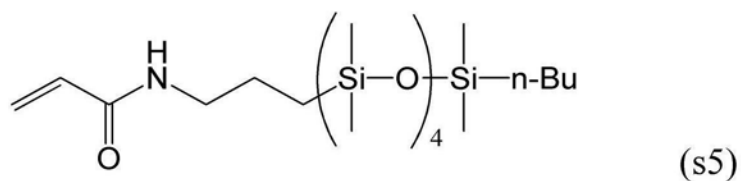
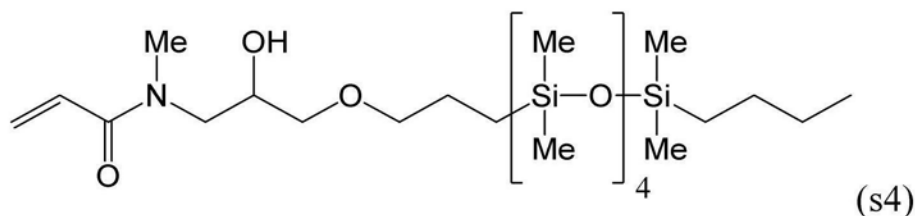
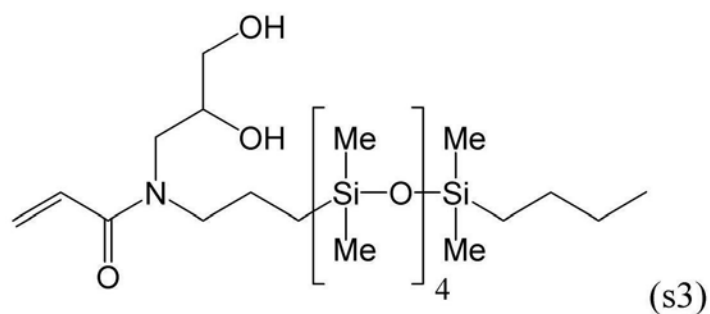
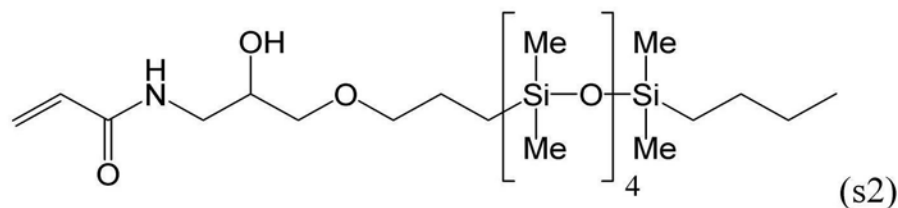
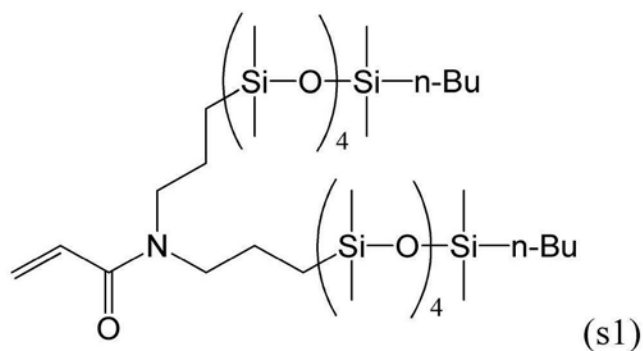
[0218] 3-甲基丙烯酰氧基丙基三(三甲基甲硅烷氧基)硅烷(“TRIS”)、

[0219] 3-甲基丙烯酰氧基丙基双(三甲基甲硅烷氧基)甲基硅烷和

[0220] 3-甲基丙烯酰氧基丙基五甲基二硅氧烷。

[0221] 在另一个实施例中, b 为 2 至 20、3 至 15, 或者在一些实施例中为 3 至 10; 至少一个末端 R^7 包含一价反应性基团, 并且剩余的 R^7 选自具有 1 至 16 个碳原子的一价烷基基团, 并且在另一个实施例中, 选自具有 1 至 6 个碳原子的一价烷基基团。在另一个实施例中, b 为 3 至 15, 一个末端 R^7 包含选自取代或未取代的 C_{1-6} 烷基(甲基)丙烯酸酯、取代或未取代的 C_{1-6} 烷基(甲基)丙烯酰胺的一价反应性基团, 另一个末端 R^7 包含具有 1 至 6 个碳原子的一价烷基基团, 并且剩余的 R^7 包含具有 1 至 3 个碳原子的一价烷基基团。本实施例的有机硅组分的非限制性例子包括(单-(2-羟基-3-甲基丙烯酰氧基丙基)-丙基醚封端的聚二甲基硅氧烷(400-1000MW))(“OH-mPDMS”)、一甲基丙烯酰氧基丙基封端的单正丁基封端的聚二甲基硅氧烷(800-1000MW)、(“mPDMS”)、N-(2,3-二羟基丙烷)-N'-(丙基四(二甲基甲硅烷氧基)二甲基丁基硅烷)丙烯酰胺和式(s1)至(s6)的甲基丙烯酰胺有机硅;

[0222]

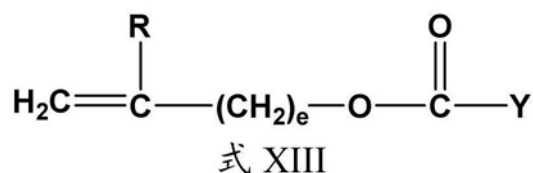


[0223] 在另一个实施例中, b 为 5 至 400 或 10 至 300, 两个末端 R^7 包含一价反应性基团, 并且剩余的 R^7 独立地选自具有 1 至 18 个碳原子的一价烷基基团, 所述一价烷基基团在碳原子之间可具有醚键并且还可包含卤素。

[0224] 在另一个实施例中, 1 至 4 个 R^7 包含乙烯基碳酸酯或如下式所示的乙烯基氨基甲

酸酯：

[0225]

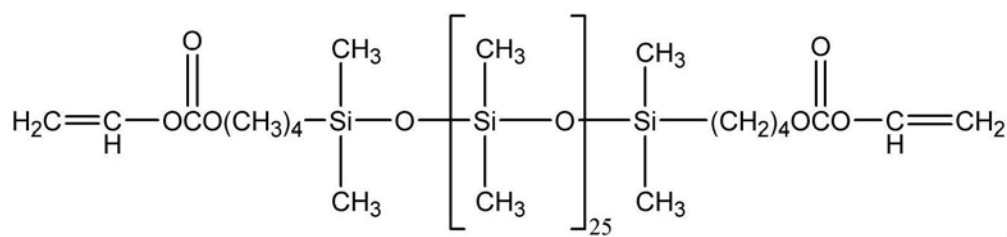


[0226] 其中：Y 表示 O、S 或 NH；

[0227] R 代表氢或甲基；并且 q 为 0 或 1。

[0228] 含有机硅的乙烯基碳酸酯或乙烯基氨基甲酸酯单体具体地包含：1,3-双[4(乙烯氧基羰基氧基)丁-1-基]四甲基二硅氧烷；3-(乙烯氧基羰基硫基)丙基[三(三甲基甲硅烷氧基)硅烷]；3-[三(三甲基甲硅烷氧基)甲硅烷基]丙基烯丙基氨基甲酸酯；3-[三(三甲基甲硅烷氧基)甲硅烷基]丙基乙烯基氨基甲酸酯；碳酸三甲基甲硅烷基乙基乙烯酯；碳酸三甲基甲硅烷基甲基乙烯酯，并且

[0229]



[0230] 在期望生物医学装置的模量在约 200 以下的情况下，只有一个 R^7 应包含一价反应性基团，并且剩余的 R^7 基团中不超过两个将包含一价硅氧烷基团。

[0231] 在一个需要有机硅水凝胶镜片的实施例中，所述镜片将由反应性混合物制成，其中基于制备聚合物的反应性单体组分的总重量计，所述反应性混合物包含至少约 20 重量%，在一些实施例中介于约 20 重量%和 70 重量%之间的含有机硅组分。

[0232] 另一类含有机硅组分包括以下式的聚氨酯大分子单体：

[0233] $(\text{*D*A*D*G})_a\text{*D*D*E}^1$ ；

[0234] $\text{E}(\text{*D*G*D*A})_a\text{*D*G*D*E}^1$ 或；

[0235] $\text{E}(\text{*D*A*D*G})_a\text{*D*A*D*E}^1$

[0236] 式 XIV-XVI

[0237] 其中：

[0238] D 代表具有 6 至 30 个碳原子的烷二基、烷基环烷二基、环烷二基、芳二基或烷基芳二基，

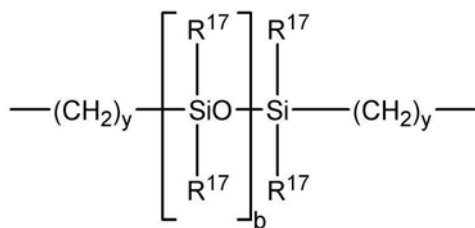
[0239] G 代表具有 1 至 40 个碳原子并且主链中可包含醚、硫代键或胺键的烷二基、环烷二基、烷基环烷二基、芳二基或烷基芳二基；

[0240] * 代表氨基甲酸酯或脲基键；

[0241] a 为至少 1；

[0242] A 代表下式的二价聚合基团：

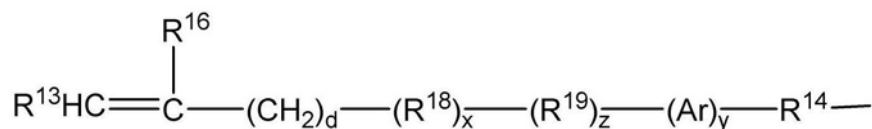
[0243]



式 XVII

[0244] R^{17} 独立地代表具有 1 至 10 个碳原子并且碳原子之间可包含醚键的烷基基团或氟代烷基基团； y 为至少 1；并且 b 提供 400 至 10,000 的部分重量； E 和 E^1 的每一个独立地代表可聚合的不饱和有机基，其由下式表示：

[0245]

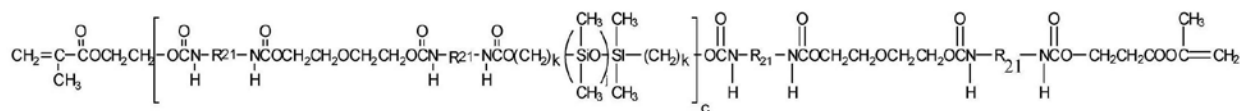


式 XVIII

[0246] 其中： R^{16} 为氢或甲基； R^{13} 为氢、具有 1 至 6 个碳原子的烷基基团或 $\text{---CO---Y---R}^{20}$ 基团，其中 Y 为 ---O--- 、 ---S--- 或 ---NH--- ； R^{20} 为 C_{1-6} 一价烷基，并且在一些实施例中为未取代的 C_{1-3} 烷基； R^{14} 为具有 1 至 12 个碳原子的二价基团； R^{14} 为具有 1 至 12 个碳原子的二价基团； R^{18} 代表 ---CO--- 或 ---OCO--- ； R^{19} 代表 ---O--- 或 ---NH--- ； Ar 代表具有 6 至 30 个碳原子的芳基； d 为 0 至 6； x 为 0 或 1； y 为 0 或 1；并且 z 为 0 或 1。

[0247] 在一个实施例中，含有机硅组分包含由下式表示的聚氨酯大分子单体：

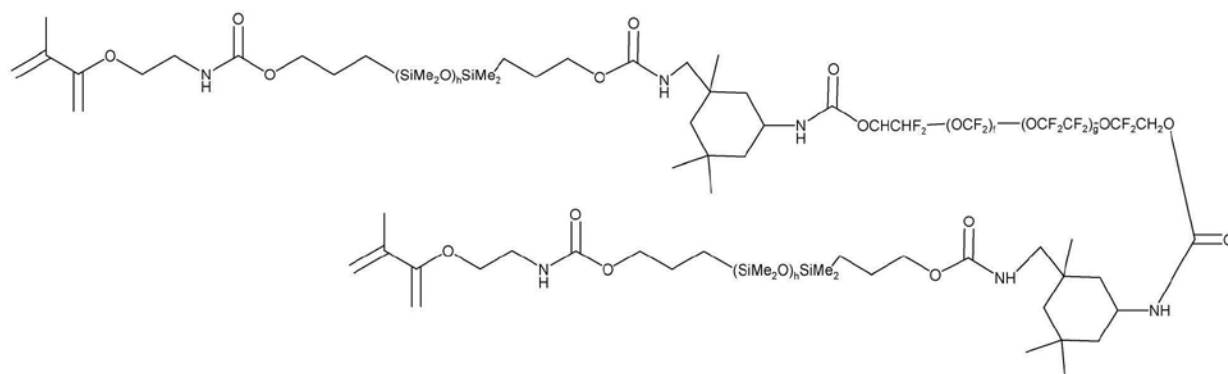
[0248]



式 XIX

[0249] 其中 R^{21} 为移除异氰酸酯基团后的二异氰酸酯的双自由基，例如异佛乐酮二异氰酸酯的双自由基， c 为 1 至 5， k 为 3 至 4 并且 i 为 10 至 200 或 10 至 100。其它合适的含有机硅的大分子单体为由氟醚、羟基封端的聚二甲基硅氧烷、异佛乐酮二异氰酸酯和甲基丙烯酸异氰基乙酯反应形成的式 XIX 的化合物（其中 $f+g$ 为在 10 至 30 范围内的数值， h 为在 20 至 30、22 至 26 或 25 范围内的数值）。

[0250]



式 XX

[0251] 其它适用的含有机硅组分包括描述于 W0 96/31792 中的那些,例如含有聚硅氧烷、聚亚烷基醚、二异氰酸酯、聚氟代烃、聚氟醚和多糖基团的大分子单体。另一类合适的含有机硅组分包括通过 GTP 制备的含有机硅的大分子单体,诸如美国专利 5,314,960、5,331,067、5,244,981、5,371,147 和 6,367,929 中所公开的那些。美国专利 5,321,108、5,387,662 和 5,539,016 描述了具有极性氟化接枝或侧基的聚硅氧烷,所述极性氟化接枝或侧基具有连接至末端二氟取代的碳原子的氢原子。US 2002/0016383 描述了含有醚键和硅氧烷键的亲水性硅氧烷基甲基丙烯酸酯以及含有聚醚基团和聚硅氧烷基基团的可交联单体。上述任何聚硅氧烷也可用作含有机硅组分。

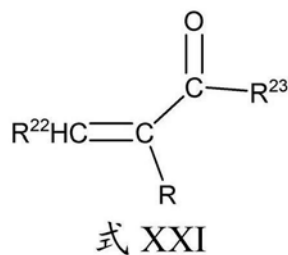
[0252] 在其中需要小于约 120psi 的模量的本发明的一个实施例中,镜片制剂中所用的含有机硅组分的质量分数的大部分应该仅含有一个可聚合的官能团(“单官能的含有机硅组分”)。在该实施例中,为了确保氧气传递率和模量的所需平衡,优选的是所有具有超过一个可聚合的官能团的组分(“多官能组分”)构成反应性组分的不超过 10mmol/100g,并且优选构成反应性组分的不超过 7mmol/100g。

[0253] 在另一个实施例中,反应混合物基本上不含包含三甲基甲硅烷氧基基团的含有机硅组分。

[0254] 含有机硅组分可以基于所有反应性组分计最多约 85 重量%,在一些实施例中介于约 10 和约 80 重量%之间,并且在其它实施例中介于约 20 和约 70 重量%之间的量存在。

[0255] 亲水性组分包括与剩余反应性组分结合时能够为所得镜片提供至少约 20%,并且在一些实施例中为至少约 25%的水含量的那些。合适的亲水性组分包括亲水性单体、预聚物和聚合物,所述亲水性组分可以基于所有反应性组分的重量计介于约 10 至约 60 重量%之间,在一些实施例中介于约 15 至约 50 重量%之间,并且在其它实施例中介于约 20 至约 40 重量%之间的量存在。可用于制备所述聚合物的亲水性单体具有至少一个可聚合双键和至少一个亲水性官能团。可聚合双键的例子包括丙烯酸、异甲基丙烯酸、丙烯酰胺基、甲基丙烯酰胺基、富马酸、马来酸、苯乙烯基、异丙烯基苯基、0-乙基酯、0-乙基氨基甲酸酯、烯丙基、0-乙基乙酰基和 N-乙基内酰胺以及 N-乙基酰胺基双键。此类亲水性单体本身可用作交联剂。“丙烯酸型”或“含丙烯酸的”单体为包含以下丙烯酸基团的那些单体

[0256]



[0257] 其中 R 为 H 或 CH₃、R²² 为 H、烷基或羰基, 并且 R²³ 为 O 或 N, 还已知其易于聚合, 例如 N, N-二甲基丙烯酰胺 (DMA)、(甲基)丙烯酸 2-羟乙酯、甲基丙烯酸甘油酯、2-羟乙基甲基丙烯酰胺、聚乙二醇单甲基丙烯酸酯、甲基丙烯酸、丙烯酸、它们的混合物等。

[0258] 可结合到水凝胶中的亲水性含乙烯基单体包括诸如以下的单体: N-乙烯基内酰胺 (例如 N-乙烯基吡咯烷酮 (NVP)、N-乙烯基-2-哌啶酮、N-乙烯基-2-己内酰胺、N-乙烯基-3-甲基-2-己内酰胺、N-乙烯基-3-甲基-2-哌啶酮、N-乙烯基-4-甲基-2-哌啶酮、N-乙烯基-4-甲基-2-己内酰胺、N-乙烯基-3-乙基-2-吡咯烷酮、N-乙烯基-4, 5-二甲基-2-吡咯烷酮); N-乙烯基-N-甲基乙酰胺、N-乙烯基-N-乙基乙酰胺、N-乙烯基-N-乙基甲酰胺、N-乙烯基甲酰胺、N-2-羟乙基乙烯基氨基甲酸酯、N-羧基-β-丙氨酸 N-乙烯基酯、乙烯基咪唑, 其中在一个实施例中 NVP 是优选的。

[0259] 可使用的附加亲水性单体包括丙烯酰胺、N, N-双(2-羟乙基)丙烯酰胺、丙烯腈、N-异丙基丙烯酰胺、醋酸乙烯酯、(甲基)丙烯酸、(甲基)丙烯酸聚乙二醇酯、2-乙基噁唑啉、N-(2-羟丙基)(甲基)丙烯酰胺、N-(2-羟乙基)(甲基)丙烯酰胺、2-甲基丙烯酰氧基乙基磷酸胆碱、3-(二甲基(4-乙烯基苄基)铵基)丙烷-1-磺酸酯 (DMVBAPS)、3-((3-丙烯酰胺基丙基)二甲基铵基)丙烷-1-磺酸酯 (AMPDAPS)、3-((3-甲基丙烯酰胺基丙基)二甲基铵基)丙烷-1-磺酸酯 (MAMPDAPS)、3-((3-(丙烯酰氧基)丙基)二甲基铵基)丙烷-1-磺酸酯 (APDAPS)、甲基丙烯酰氧基(丙基)二甲基铵基)丙烷-1-磺酸酯 (MAPDAPS)、N-乙烯基-N-甲基乙酰胺、N-乙烯基乙酰胺、N-乙烯基-N-甲基丙酰胺、N-乙基-N-甲基-2-甲基丙酰胺、N-乙基-2-甲基丙酰胺、N-乙基-N, N'-二甲基脲等, 以及它们的混合物。在一个实施例中, 合适的亲水性单体包括 N-乙烯基吡咯烷酮、N-乙基-N-甲基乙酰胺、2-甲基丙烯酰氧基乙基磷酸胆碱、(甲基)丙烯酸、N, N-二甲基丙烯酰胺、N-羟丙基甲基丙烯酰胺、单甲基丙烯酸甘油酯、2-羟乙基丙烯酰胺、双羟乙基丙烯酰胺和 2, 3-二羟丙基(甲基)丙烯酰胺等, 以及它们的混合物。

[0260] 在一些实施例中, 亲水性单体也可包含带电单体, 包括但不限于: 甲基丙烯酸、丙烯酸、3-丙烯酰胺基丙酸 (ACA1)、4-丙烯酰胺基丁酸、5-丙烯酰胺基戊酸 (ACA2)、3-丙烯酰胺基-3-甲基丁酸 (AMBA)、N-乙烯基氧基羰基-α-丙氨酸、N-乙烯基氧基羰基-β-丙氨酸 (VINAL)、2-乙基-4, 4-二甲基-2-噁唑啉-5-酮 (VDMO)、反应性磺酸盐, 包括 2-(丙烯酰胺基)-2-甲基丙磺酸钠 (AMPS)、3-磺丙基(甲基)丙烯酸钾盐、3-磺丙基(甲基)丙烯酸钠盐、双 3-磺丙基衣康酸二钠、双 3-磺丙基衣康酸二钾、乙烯基磺酸钠盐、乙烯基磺酸盐、苯乙烯磺酸盐、甲基丙烯酸磺乙酯, 它们的组合等。

[0261] 可被使用的其它亲水性单体包括末端羟基基团中的一个或多个由含有可聚合双键的官能团取代的聚氧乙烯多元醇。例子包括末端羟基中的一个或多个由含有可聚合双键的官能团取代的聚乙二醇。例子包括聚乙二醇, 其与一种或多种等当量的封端基团 (如甲

基丙烯酸异氰酸根合乙酯 (“IEM”)、甲基丙烯酸酐、甲基丙烯酰氯、乙烯基苯甲酰氯等)反应,以产生聚乙烯多元醇,所述聚乙烯多元醇具有通过连接部分(如氨基甲酸酯或酯基)键合至聚乙烯多元醇的一个或多个末端可聚合的烯属基团。

[0262] 另外的例子为公开于美国专利 5,070,215 中的亲水性乙烯基碳酸酯或乙烯基氨基甲酸酯单体,以及公开于美国专利 4,190,277 中的亲水性噁唑酮单体。其它合适的亲水性单体对于本领域技术人员而言是显而易见的。

[0263] 在一个实施例中,可结合到本文所公开的聚合物中的亲水性单体包括诸如以下的亲水性单体:N,N-二甲基丙烯酰胺(DMA)、2-羟乙基丙烯酸酯、甲基丙烯酸甘油酯、2-羟乙基甲基丙烯酰胺、N-乙烯基吡咯烷酮(NVP)、N-乙烯基甲基丙烯酰胺、HEMA 和聚乙二醇单甲基丙烯酸酯。

[0264] 在另一个实施例中,亲水性单体包括 DMA、NVP、HEMA 以及它们的混合物。

[0265] 用于形成基材例如接触镜片的反应性混合物还可包含一种或多种聚合物型润湿剂作为亲水性组分。如本文所用,用于反应混合物中的此类聚合物型润湿剂是指重均分子量不小于约 5,000 道尔顿的物质,其中所述物质与有机硅水凝胶制剂结合后增加固化的有机硅水凝胶的可润湿性。在一个实施例中,这些聚合物型润湿剂的重均分子量大于约 30,000;在另一个实施例中介于约 150,000 至约 2,000,000 道尔顿之间,在一个实施例中介于约 300,000 至约 1,800,000 道尔顿之间,并且在另一个实施例中介于约 500,000 至约 1,500,000 道尔顿之间。

[0266] 另选地,聚合物型润湿剂的分子量也可以用基于运动粘度测量的 K 值表示,如 Encyclopedia of Polymer Science and Engineering, N-Vinyl Amide Polymers, &, 第二版,第 17 卷,第 198-257 页, John Wiley Sons Inc.) 中所述。以此方式表示时,亲水性单体的 K 值大于约 46,在一个实施例中, K 值介于约 46 和约 150 之间。反应混合物中的聚合物型润湿剂的合适的量基于所有反应性组分的总量计包括约 1 至约 20 重量%,在一些实施例中为约 5 至约 20%,并且在其它实施例中为约 6 至约 17%。

[0267] 聚合物型润湿剂的例子包括但不限于聚酰胺、聚内酯、聚酰亚胺、聚内酰胺以及官能化的聚酰胺、聚内酯、聚酰亚胺、聚内酰胺,例如通过使 DMA 与较低摩尔量的羟基官能化单体(如 HEMA)共聚,然后使所得共聚物的羟基与包含可自由基聚合基团的材料(如异氰酸乙酯基甲基丙烯酸酯或甲基丙烯酰氯)反应而官能化的 DMA。也可以使用由 DMA 或 n-乙烯基吡咯烷酮与甲基丙烯酸缩水甘油酯制成的聚合物型润湿剂。可将甲基丙烯酸缩水甘油酯的环打开而得到可与其它亲水性预聚物结合用于混合体系中的二醇,以提高反应性混合物中的组分的相容性。在一个实施例中,聚合物型润湿剂在其主链中包含至少一个环状部分,例如但不限于环状酰胺或环状酰亚胺。聚合物型润湿剂包括但不限于聚-N-乙烯基吡咯烷酮、聚-N-乙烯基-2-哌啶酮、聚-N-乙烯基-2-己内酰胺、聚-N-乙烯基-3-甲基-2-己内酰胺、聚-N-乙烯基-3-甲基-2-哌啶酮、聚-N-乙烯基-4-甲基-2-哌啶酮、聚-N-乙烯基-4-甲基-2-己内酰胺、聚-N-乙烯基-3-乙基-2-吡咯烷酮和聚-N-乙烯基-4,5-二甲基-2-吡咯烷酮、聚乙烯基咪唑、聚-N,N-二甲基丙烯酰胺、聚乙烯醇、聚丙烯酸、聚氧化乙烯、聚-2-乙基-噁唑啉、肝素多醣、多糖,它们的混合物和共聚物(包括嵌段的或无规的、支化的、多链的、梳状的或星状),其中聚-N-乙烯基吡咯烷酮(PVP)在一个实

施例中是特别优选的。也可使用共聚物,例如 PVP 的接枝共聚物。

[0268] 用于反应混合物中的聚合物型润湿剂改善了医疗装置的可润湿性,特别是体内可润湿性。不受任何理论的约束,据信聚合物型润湿剂为氢键受体,其在水性环境中与水形成氢键合,从而有效地变得更具亲水性。不存在水有利于反应混合物中聚合物型润湿剂的结合。除了具体指定的聚合物型润湿剂外,预期任何聚合物都可用,前提条件是当将所述聚合物加入制剂中时,所述聚合物 (a) 基本上不与反应混合物发生相分离,和 (b) 赋予所得固化聚合物网络以可润湿性。在一些实施例中,优选的是在反应温度下将聚合物型润湿剂溶于稀释剂中。

[0269] 还可使用相容剂。在一些实施例中,相容组分可为任何官能化的含有机硅单体、大分子单体或预聚物,其在聚合和 / 或形成最终制品时与所选亲水性组分相容。可使用 W003/022321 中公开的相容性测试选择合适的相容剂。在一些实施例中,反应性混合物中包含还含有羟基的有机硅单体、预聚物或大分子单体。例子包括 3- 甲基丙烯酰氧基 -2- 羟基丙氧基) 丙基双 (三甲基甲硅烷氧基) 甲基硅烷、单 - (3- 甲基丙烯酰氧基 -2- 羟基丙氧基) 丙基封端的单 - 丁基封端的聚二甲基硅氧烷 (MW 1100)、含羟基官能化的有机硅的 GTP 大分子单体、含聚二甲基硅氧烷的羟基官能化的大分子单体,它们的组合等。在另一个实施例中,聚合物型润湿可用作相容组分。

[0270] 含羟基组分也可在形成基材 (例如接触镜片) 期间用作交联剂。

[0271] 相对于制备诸如接触镜片的基材而言,通常需向反应混合物中添加一种或多种交联剂 (也称为交联单体),例如乙二醇二甲基丙烯酸酯 (“EGDMA”)、三羟甲基丙烷三甲基丙烯酸酯 (“TMPTMA”)、三甲基丙烯酸甘油酯、聚乙二醇二甲基丙烯酸酯 (其中聚乙二醇优选地具有最多例如约 5000 的分子量) 以及其它聚 (甲基) 丙烯酸酯 (例如上述包含两个或更多个末端甲基丙烯酸酯部分的封端的聚氧乙烯多元醇)。交联剂可以常用量使用,如在反应混合物中约 0.000415 至约 0.0156 摩尔每 100 克反应性组分。另选地,如果在亲水性单体和 / 或含有机硅的单体用作交联剂时,向反应混合物中添加交联剂是任选的。亲水性单体可用作交联剂并且当存在时不需要向反应混合物中添加另外的交联剂的例子包括上文所述的包含两个或更多个末端甲基丙烯酸酯部分的聚氧乙烯多元醇。

[0272] 可用作交联剂,并且当存在时,不需要向反应混合物中添加交联性单体的含有机硅单体的例子包括 α , ω - 双甲基丙烯酰丙基聚二甲基硅氧烷。

[0273] 反应混合物可包含附加组分,例如但不限于紫外线吸收剂、光致变色化合物、药物和营养化合物、抗微生物化合物、活性调色剂、颜料、可共聚和非聚合染料、脱模剂,以及它们的组合。

[0274] 通常将反应性组分混合在稀释剂中,以形成反应混合物。合适的稀释剂是本领域已知的。适于有机硅水凝胶的稀释剂在 W003/022321、US6,020,445 中有所公开,其公开内容以引用方式并入本文。

[0275] 适于有机硅水凝胶反应混合物的稀释剂类别包括具有 2 至 20 个碳的醇、具有 10 至 20 个碳原子的衍生自伯胺的酰胺和具有 8 至 20 个碳原子的羧酸。在一些实施例中,优选伯醇和叔醇。优选的类别包括具有 5 至 20 个碳原子的醇和具有 10 至 20 个碳原子的羧酸。

[0276] 可使用的具体稀释剂包括 1- 乙氧基 -2- 丙醇、二异丙基氨基乙醇、异丙醇、3,7- 二

甲基-3-辛醇、1-癸醇、1-十二烷醇、1-辛醇、1-戊醇、2-戊醇、1-己醇、2-己醇、2-辛醇、3-甲基-3-戊醇、叔戊醇、叔丁醇、2-丁醇、1-丁醇、2-甲基-2-戊醇、2-丙醇、1-丙醇、乙醇、2-乙基-1-丁醇、(3-乙酰氧基-2-羟丙基氧基)丙基双(三甲基甲硅烷氧基)甲基硅烷、1-叔丁氧基-2-丙醇、3,3-二甲基-2-丁醇、叔丁氧基乙醇、2-辛基-1-十二烷醇、癸酸、辛酸、十二烷酸、2-(二异丙基氨基)乙醇,它们的混合物等。

[0277] 优选的稀释剂包括 3,7-二甲基-3-辛醇、1-十二烷醇、1-癸醇、1-辛醇、1-戊醇、1-己醇、2-己醇、2-辛醇、3-甲基-3-戊醇、2-戊醇、叔戊醇、叔丁醇、2-丁醇、1-丁醇、2-甲基-2-戊醇、2-乙基-1-丁醇、乙醇、3,3-二甲基-2-丁醇、2-辛基-1-十二烷醇、癸酸、辛酸、十二烷酸,它们的混合物等。

[0278] 更优选的稀释剂包括 3,7-二甲基-3-辛醇、1-十二烷醇、1-癸醇、1-辛醇、1-戊醇、1-己醇、2-己醇、2-辛醇、1-十二烷醇、3-甲基-3-戊醇、1-戊醇、2-戊醇、叔戊醇、叔丁醇、2-丁醇、1-丁醇、2-甲基-2-戊醇、2-乙基-1-丁醇、3,3-二甲基-2-丁醇、2-辛基-1-十二烷醇,它们的混合物等。

[0279] 适于不含有机硅的反应混合物的稀释剂包括甘油、乙二醇、乙醇、甲醇、乙酸乙酯、二氯甲烷、聚乙二醇、聚丙二醇、低分子量 PVP(例如 US4,018,853、US 4,680,336 和 US 5,039,459 中所公开,包括但不限于二元醇的硼酸酯),它们的组合等。

[0280] 可使用稀释剂的混合物。基于反应性混合物中全部组分的总重量计,稀释剂可以最多约 55 重量%的量使用。更优选地,基于反应性混合物中全部组分的总重量计,稀释剂可以小于约 45 重量%,更优选介于约 15 和约 40 重量%之间的量使用。

[0281] 在用于形成诸如与接触镜片的基材的反应混合物中优选地包含聚合引发剂。聚合引发剂包括在适当地升高的温度下产生自由基的化合物(例如月桂基过氧化物、过氧化苯甲酰、过碳酸异丙酯、偶氮二异丁腈等),以及光引发剂体系(例如芳族 α -羟基酮、烷氧基氧基安息香、苯乙酮、酰基氧化膦、双酰基氧化膦,和叔胺加上二酮,它们的混合物等)。光引发剂的示例性例子为 1-羟基环己基苯基酮、2-羟基-2-甲基-1-苯基-丙-1-酮、双(2,6-二甲氧基苯甲酰基)-2,4,4-三甲基戊基氧化膦(DMBAPO)、双(2,4,6-三甲基苯甲酰基)-苯基氧化膦(Irgacure 819)、2,4,6-三甲基苄基二苯基氧化膦和 2,4,6-三甲基苯甲酰基二苯基氧化膦、安息香甲酯,和苝醌与 4-(N,N-二甲基氨基)苯甲酸乙基酯的组合。可商购获得的可见光引发剂体系包括 Irgacure 819、Irgacure 1700、Irgacure 1800、Irgacure 819、Irgacure 1850(所有均得自汽巴特殊化学品公司(Ciba Specialty Chemicals)) 和 Lucirin TPO 引发剂(购自巴斯夫公司(BASF))。市售的 UV 光引发剂包括 Darocur 1173 和 Darocur 2959(汽巴特殊化学品公司)。可被使用的这些和其它光引发剂在 Volume III, Photoinitiators for Free Radical Cationic & Anionic Photopolymerization, 2nd Edition by J.V. Crivello & K. Dietliker; edited by G. Bradley; John Wiley and Sons; New York; 1998 年(第 III 卷,用于自由基阳离子和阴离子光聚合的光引发剂),第二版, J.V. Crivello 与 K. Dietliker 著; G. Bradley 编辑; 纽约约翰威立国际出版公司; 1998 年)中有所公开,其以引用方式并入本文。在反应混合物中使用有效量(例如,按重量计每 100 份反应单体约 0.1 份至约 2 份)的引发剂以引发反应混合物的光聚合。可取决于所用的聚合引发剂,使用热或可见光或紫外光或其它方式的适当选择来引发反应混合物的聚合。作为另外一种选择,引发可在没有使用光引发剂下进行,

例如, e⁻ 照射。然而, 当使用光引发剂时, 优选的引发剂为双酰基氧化膦, 如双 (2,4,6-三甲基苯甲酰基)-苯基氧化膦 (Irgacure 819[®]) 或 1-羟基环己基苯基酮与双 (2,6-二甲氧基苯甲酰基)-2,4,4-三甲基戊基氧化膦 (DMBAPO) 的组合, 聚合引发的优选方法是经由可见光。最优选的是双 (2,4,6-三甲基苯甲酰基)-苯基氧化膦 (Irgacure 819[®])。

[0282] 反应混合物中存在的含有机硅单体的优选范围为反应混合物中反应性组分的约 5 至 95 重量%, 更优选约 30 至 85 重量%, 最优选约 45 至 75 重量%。存在的亲水性单体的优选范围为反应混合物中反应性组分的约 5 至 80 重量%, 更优选约 10 至 60 重量%, 最优选约 20 至 50 重量%。存在的稀释剂的优选范围为总反应混合物 (包括反应性和非反应性组分) 的约 2 至 70 重量%, 更优选约 5 至 50 重量%, 最优选约 15 至 40 重量%。

[0283] 反应混合物可通过本领域技术人员已知的任何方法来形成, 诸如摇振或搅动, 并且通过已知的方法用于形成聚合物制品或装置。

[0284] 例如, 生物医学装置可通过将反应性组分和稀释剂与聚合引发剂混合, 并通过适当的条件固化以形成可随后通过车床加工、切割等成型为适当形状的产品而制备。作为另外一种选择, 反应混合物可被放置在模具中, 并随后固化成适当的制品。

[0285] 已知多种方法用于在接触镜片制造中加工反应混合物, 包括旋模成型和静模铸造。旋模成型法在美国专利 3,408,429 和 3,660,545 中有所公开, 而静模铸造法在美国专利 4,113,224 和 4,197,266 中有所公开。制备接触镜片的优选方法是通过模塑有机硅水凝胶而实施, 该方法是经济的, 并且能够精确地控制含水镜片的最终形状。对于该方法, 将反应混合物放入具有最终所需有机硅水凝胶, 即水-溶胀聚合物的形状的模具中, 并且使反应混合物经受使单体聚合的条件, 从而产生最终所需的产品形状中的聚合物/稀释剂混合物。然后, 用溶剂处理所述聚合物/稀释剂混合物, 以移除稀释剂, 并最终用水替代它, 从而形成最终尺寸和形状与原始模塑聚合物/稀释剂制品的尺寸和形状非常相似的有机硅水凝胶。此方法可用于形成接触镜片, 并在美国专利 4,495,313; 4,680,336; 4,889,664; 和 5,039,459 中有进一步的描述, 这些专利以引用方式并入本文。

[0286] 本发明的生物医学装置 (特别是眼科镜片) 的各种性质均衡, 这使得它们特别有用。此类性质包括透明度、水含量、透氧度和接触角。根据本发明实施例的至少一种的嵌段共聚物的结合提供了具有非常理想的与溶液的可润湿性/接触角的制品, 和改善的生物性能, 如通过降低的脂质运载蛋白、类脂和粘蛋白吸收量所表明。结合嵌段共聚物的有机硅水凝胶接触镜片将表现出小于约 60°, 并且在一些实施例中小于约 40° 的接触角, 以及使接触角减小 40%, 并且在一些实施例中减小 50% 或更多。可使类脂吸收率降低 50% 或更多, 并且可制备具有约 12 μg、10 μg 或甚至 5 μg 或更少的有机硅水凝胶镜片。在一个实施例中, 生物医学装置为水含量大于约 17%, 优选地大于约 20% 并且更优选地大于约 25% 的接触镜片。

[0287] 适于含有机硅镜片的透氧度优选地大于约 40 巴勒, 并且更优选地大于约 60 巴勒。

[0288] 在一些实施例中, 本发明的制品具有上述透氧度、水含量和接触角的组合。上文范围的所有组合被认为是在本发明的范围内。

[0289] 以下非限制性实例对本发明进行进一步的描述。

[0290] 在室温下使用 KRUSS DSA-100 TM 器械, 用去离子水作为探测剂溶液, 通过静滴技术确定镜片的可润湿性。在去离子水中冲洗待测试的镜片 (3-5/样品), 以移除残留的润湿

溶液。将每个测试镜片置于用润湿溶液浸湿的不含棉绒的吸收擦拭物上。使镜片的两侧与擦拭物接触以移除表面水分,而不干燥镜片为了确保适当整平,将镜片“碗面向下”置于接触镜片塑料模具上的凸形表面上。将塑料模具和镜片置于静滴器械夹持器上,确保注射器正确的居中对齐并且注射器对应指定的液体。用 DSA 100 滴形分析软件在注射器顶端上形成 3 至 4 微升的去离子水液滴,确保液滴远离镜片悬挂。通过将针头向下移动使液滴平滑地释放到镜片表面上。释放液滴后立即将针头撤走。使液滴在镜片上平衡 5 至 10 秒,根据在液滴图像与镜片表面之间测得的接触角计算接触角。

[0291] 可如下方法测量水含量:使待测试的镜片在润湿溶液中放置 24 小时。用棉签从润湿溶液中取出三个测试镜片中的每一个,并将其置于用润湿溶液浸湿的擦拭物上。使镜片的两侧均与擦拭物接触。用镊子将测试镜片放入称重盘中称重。如上所述制备另外两组样品并称重。将盘称量三次,其平均值即为湿重。

[0292] 通过将样品盘置于预热至 60℃ 的真空烘箱中达 30 分钟,从而测量干重。施加真空,直至达到至少 0.4 英寸的汞柱。关闭真空阀和泵,并且将镜片干燥 4 小时。打开放气阀,使烘箱达到大气压。移出盘并称重。如下计算水含量:

[0293] 湿重=盘和镜片的组合湿重-称重盘的重量

[0294] 干重=盘和镜片的组合干重-称重盘的重量

[0295]

$$\% \text{水含量} = \frac{(\text{湿重} - \text{干重})}{\text{干重}} \times 100$$

湿重

[0296] 计算样品的水含量的平均值和标准偏差并记录。

[0297] 可用 ISO 18369-4:2006(E) 中大致描述的极谱法测定透氧度 (Dk),但进行以下变型。在含 2.1% 氧气的环境下进行测量。通过为测试室配备以合适比率设置的氮气和空气输入创建此环境,例如 1800ml/min 的氮气和 200ml/min 的空气。用所调整的 pO₂ 计算 t/Dk。使用硼酸盐缓冲盐水。通过使用加湿的纯氮气环境而不施加 MMA 镜片来测量暗电流。在测量之前不吸干镜片。在测量区域中堆叠四个具有均匀厚度的镜片,而非使用不同厚度的镜片。测量具有明显不同的厚度值的 4 个样品的 L/Dk,并将 L/Dk 相对于厚度作图。回归斜率的倒数为样品的初测 Dk。如果样品的初测 Dk 小于 90 巴勒,则对初测 L/Dk 值施加 (1+(5.88(以 cm 表示的 CT))) 的边缘校正。如果样品的初测 Dk 大于 90 巴勒,则对初测 L/Dk 值施加 (1+(3.56(以 cm 表示的 CT))) 的边缘校正。将 4 个样品的经边缘校正的 L/Dk 值对厚度作图。回归斜率的倒数为样品的 Dk。使用弧形传感器而非平传感器。所得的 Dk 值以巴勒为单位记录。

[0298] 脂质运载蛋白吸收率可使用以下溶液和方法测量。得自牛乳,包含 B 乳球蛋白(脂质运载蛋白)的脂质运载蛋白溶液 (Sigma, L3908) 以 2mg/mL 的浓度溶解于磷酸盐缓冲盐水溶液中 (Sigma, D8662),用 1.37g/L 的碳酸氢钠和 0.1g/L 的 D-葡萄糖来补充。

[0299] 对于每个实例的三个镜片使用脂质运载蛋白溶液测试,并且使用 PBS 作为对照溶液测试三个。测试镜片在无菌纱布上吸干以移除润湿溶液并使用无菌镊子无菌地转移至无菌的每个孔包含 2mL 的脂质运载蛋白溶液的 24 孔细胞培养板上(每个孔一个镜片)。将每个镜片完全浸入溶液中。对照镜片使用 PBS 作为浸泡溶液代替脂质运载蛋白来制备。包含镜片浸入在脂质运载蛋白溶液的板以及包含对照镜片浸入在 PBS 中的板被保鲜膜蒙上以

防止蒸发和脱水,放置在具有以 100rpm 搅拌的轨道式震荡器上并在 35℃ 下温育 72 小时。在 72 小时温育期后,镜片通过浸渍镜片至三个 (3) 单独的包含约 200mL 体积 PBS 的小瓶中被冲洗 3 至 5 次。镜片在纸巾上吸干以移除过量的 PBS 溶液并转移至每个孔包含 1mL 的 PBS 溶液的无菌 24 孔板中。

[0300] 脂质运载蛋白吸收率可使用镜片上的二喹啉甲酸法测定,所述方法使用 QP-BCA 试剂盒 (Sigma, QP-BCA),遵循由制造商所述的步骤 (标准物制备在试剂盒中有所描述),并且通过从在脂质运载蛋白溶液中浸湿的镜片所测定的光密度减去在 PBS 中浸湿的镜片 (背景) 所测量的光密度进行计算。光密度使用能够在 562nm 处读取光密度的 SynergyII 微板读数器测量。

[0301] 粘蛋白吸收率可使用以下溶液和方法测量。得自牛颌下腺,包含粘蛋白的粘蛋白溶液 (Sigma, M3895- 型 1-S) 以 2mg/mL 的浓度溶解于磷酸盐缓冲盐水溶液中 (Sigma, D8662),用 1.37g/l 的碳酸氢钠和 0.1g/l 的 D- 葡萄糖来补充。

[0302] 对于每个实例的三个镜片使用粘蛋白溶液测试,并且使用 PBS 作为对照溶液测试三个。测试镜片在无菌纱布上吸干以移除润湿溶液并使用无菌镊子无菌地转移至无菌的每个孔包含 2mL 的粘蛋白溶液的 24 孔细胞培养板上 (每个孔一个镜片)。将每个镜片完全浸入溶液中。对照镜片使用 PBS 作为浸泡溶液代替脂质运载蛋白来制备。

[0303] 包含镜片浸入在粘蛋白的板以及包含对照镜片浸入在 PBS 中的板被保鲜膜蒙上以防止蒸发和脱水,放置在具有以 100rpm 搅拌的轨道式震荡器上并在 35℃ 下温育 72 小时。在 72 小时温育期后,镜片通过浸渍镜片至三个 (3) 单独的包含约 200mL 体积 PBS 的小瓶中被冲洗 3 至 5 次。镜片在纸巾上吸干以移除过量的 PBS 溶液并转移至每个孔包含 1mL 的 PBS 溶液的无菌 24 孔板中。

[0304] 粘蛋白吸收率可使用镜片上的二喹啉甲酸法测定,所述方法使用 QP-BCA 试剂盒 (Sigma, QP-BCA),遵循由制造商所述的步骤 (标准物制备在试剂盒中有所描述),并且通过从在粘蛋白溶液中浸湿的镜片所测定的光密度减去在 PBS 中浸湿的镜片 (背景) 所测量的光密度进行计算。光密度使用能够在 562nm 读取光密度的 SynergyII 微板读数器测量。

[0305] 用重组角膜上皮组织构建体在体外评估细胞活力。组织构建体为全层角膜上皮 (得自 Skinethics 的角膜上皮组织),其在聚碳酸酯插件上在空气-液体界面处体外重组和生长,形成完全分层的上皮构建体。

[0306] 为了评估镜片,将镜片钻孔活组织检查 (0.5cm²) 局部施加到组织上,然后在 37℃ 和 5% 的 CO₂ 条件下进行 24 小时温育。移除镜片活组织检查,并用 PBS 洗涤组织。然后使用 MTT 比色测定 (Mosman, T. Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays. J. Immunol. Methods, 65 ;55-63 (1983) (Mosman, T., 对细胞生长和生存的快速比色测定:用于增殖和细胞毒性测定,《免疫学方法杂志》,第 65 卷第 55-63 页,1983 年)) 测量细胞活力:在 MTT 的存在下,在 37℃ 和 5% 的 CO₂ 条件下对组织进行 3 小时的温育,然后在异丙醇中提取组织。然后使用微板读数器测量异丙醇提取物在 550nm 处的吸光度。结果用 PBS 对照的百分比表示 (将用 PBS 处理过的组织与用镜片处理过的组织进行对比)。

[0307] 为了对溶液进行评估,将 30 μg 溶液局部施加到组织上。细胞活力的测试如针对镜片所述。各评估均一式三份进行。

[0308] 用如下方法测量类脂吸收率：

[0309] 为进行研究的每个镜片类型创建标准曲线。将带标记的胆固醇（用 NBD 标记的胆固醇（[7-硝基苯并- ζ -2-氧杂-1,3-二唑-4-基]，CH-NBD ;Avanti, Alabaster, AL）在 35℃ 下溶于 1mg/mL 的类脂的甲醇储备溶液中。从所述储备溶液中获取等分试样，在 pH 7.4 的磷酸盐缓冲盐水（PBS）中以 0 至 100micg/mL 范围内的浓度制作标准曲线。

[0310] 将每种浓度的一毫升的标准品放入 24 孔细胞培养板的孔中。将每种类型的 10 个镜片放入另一个 24 孔板中，与标准曲线样品一起在浓度为 20micg/ml 的 1mL 的 CH-NBD 中浸泡。将另一组镜片（5 个镜片）浸泡在不含类脂的 PBS 中，以校正镜片本身产生的任何自体荧光。所有浓度均在 pH 7.4 的磷酸盐缓冲盐水（PBS）中形成。将标准曲线板、测试板（包括浸泡在 CH-NBD 中的镜片）和对照板（包括浸泡在 PBS 中的镜片）均包裹在铝箔中保持黑暗，并在 35℃ 下在搅拌下温育 24 小时。24 小时后，从培养箱中取出标准曲线板、测试板和对照板。立即在微板荧光读数器（Synergy HT）上读取标准曲线板。

[0311] 通过将每个单独的镜片在容纳有大约 100ml 的 PBS 的 3 个连续小瓶中浸渍 3 至 5 次以冲洗测试板和对照板上的镜片，从而确保只测定结合的类脂，而无携带的类脂。然后将镜片放入新的 24 孔板中，其中每个孔包含 1mL 的 PBS，然后在荧光读数器上读取。读取试验样品之后，移除 PBS，并如前所述将相同浓度的 1mL 的 CH-NBD 新鲜溶液放到镜片上，然后放回 35℃ 的培养箱中，摇动，直至下一个周期。将此工序重复 15 天，直至镜片上的类脂完全饱和。仅记录饱和时所获得的类脂量。

[0312] 如下所述测量溶菌酶吸收率：用于溶菌酶吸收率测试的溶菌酶溶液包含得自鸡肉蛋白的溶菌酶（Sigma, L7651），以 2mg/mL 的浓度溶于补充有 1.37g/l 的碳酸氢钠和 0.1g/l 的 D-葡萄糖的磷酸盐缓冲盐水中。

[0313] 脂质运载蛋白溶液包含来自牛乳（Sigma, L3908）的 B 乳球蛋白（脂质运载蛋白），其中 B 乳球蛋白以 2mg/ml 的浓度溶于补充有 1.37g/l 的碳酸氢钠和 0.1g/l 的 D-葡萄糖的磷酸盐缓冲盐水中。

[0314] 对于每个实例，使用每种蛋白溶液测试 3 个镜片，并使用 PBS 作为对照溶液测试 3 个镜片。测试镜片在无菌纱布上吸干以移除润湿溶液并使用无菌镊子无菌地转移至无菌的每个孔包含 2mL 的溶菌酶溶液的 24 孔细胞培养板上（每个孔一个镜片）。将每个镜片完全浸入溶液中。将 2mL 的溶菌酶溶液放置在孔中而不接触镜片作为对照。

[0315] 包含镜片的板和仅包含蛋白质溶液并且镜片在 PBS 中的对照板被保鲜膜蒙上以防止蒸发和脱水，放置在具有以 100rpm 搅拌的轨道式震荡器上并在 35℃ 下温育 72 小时。在 72 小时温育期后，镜片通过浸渍镜片至三个 (3) 单独的包含约 200mL 体积 PBS 的小瓶中被冲洗 3 至 5 次。镜片在纸巾上吸干以移除过量的 PBS 溶液，并转移至无菌锥形管中（每根管 1 个镜片），包含一定体积的 PBS 的每根管基于期望的基于每个镜片组合物估计的溶菌酶吸收率测定。在每个管中欲被测量的溶菌酶浓度需要在如制造商所述的白蛋白标准物范围内（0.05 微克至 30 微克）。已知吸收溶菌酶程度低于 100 μ g 每个镜片的样品被稀释 5 倍。已知溶菌酶吸收程度高于 500 μ g 每个镜片的样品（诸如依他菲康 A 镜片）被稀释 20 倍。

[0316] PBS 的 1mL 等分试样被用于所有样品之外的依他菲康。20mL 用于依他菲康 A 镜片。用相同的方式处理每个对照镜片，不同的是孔板包含 PBS，而非溶菌酶或脂质运载蛋白

溶液。

[0317] 按照制造商所描述的程序（在试剂盒中描述了标准制备方法），使用 QP-BCA 试剂盒（Sigma, QP-BCA），使用镜片上双辛丁酸法测定溶菌酶和脂质运载蛋白吸收率，并通过从在溶菌酶溶液中浸泡的镜片上测得的光密度减去在 PBS 中浸泡过的镜片（背景）上测得的光密度算出。

[0318] 光密度可使用能够在 562nm 处读取光密度的 SynergyII 微板读数器测量。

[0319] 以下缩写将用于整个制备例和实例中并且具有以下含义。

[0320] ACA1 3- 丙烯酰胺基丙酸；

[0321] ACA2 5- 丙烯酰胺基戊酸；

[0322] 4-BBB 4-(溴甲基) 苯甲酰基溴 (Sigma-Aldrich)；

[0323] DMA N, N- 二甲基丙烯酰胺

[0324] Irgacure-819 双 (2,4,6- 三甲基苯甲酰基)- 苯基氧化膦 (汽巴特殊化学品公司)；

[0325] KX 0- 乙基乙基黄原酸钾；

[0326] mPDMS 一甲基丙烯酰氧基丙基封端的单正丁基封端的聚二甲基硅氧烷 (800-1000MW)；

[0327] NaHTTC 己基三硫代碳酸钠；

[0328] HBTTC S- 己基 -S' - 苄基 - 三硫代碳酸酯

[0329] XG1996TTC S- 己基 -S' -4-(2-(正丁基聚二甲基甲硅烷氧基二甲基甲硅烷基) 乙基) 苄基三硫代碳酸酯；

[0330] nBPDMS-H 3-(正丁基四甲基甲硅烷氧基二甲基甲硅烷基) 丙醇

[0331] MBA N, N' - 亚甲基双丙烯酰胺

[0332] NVP N- 乙 烯 基 吡 咯 烷 酮 (Acros 化 学 公 司 (Acros Chemical)), 其通过真空蒸馏进一步纯化；

[0333] NRPTHF 制备例 3 中制备的聚硅氧烷封端的嵌段共聚物对比物；

[0334] PTHPWCL 制备例 3 中制备的具有交联的聚硅氧烷封端的嵌段共聚物；

[0335] HO-mPDMS 单 -(2- 羟基 -3- 甲基丙烯酰氧基丙基)- 丙基醚封端的聚二甲基硅氧烷 (400-1000MW)；

[0336] SBX 3-(正丁基四甲基甲硅烷氧基二甲基甲硅烷基) 丙基 4-((乙氧基硫代甲酰硫) 甲基) 苯甲酸酯；

[0337] SiGMA 2- 甲基 -,2- 羟基 -3-[3-[1,3,3,3- 四甲基 -1-[(三甲基甲硅烷基) 氧化] 二硅氧烷基] 丙氧基] 丙基酯；

[0338] TRIS-VC 三 (三甲基甲硅烷氧基) 甲硅烷基丙基乙烯基氨基甲酸酯；

[0339] V₂D₂₅ 含有机硅的乙烯基碳酸酯，在 US5,260,000 的第 4 栏第 33-42 行中有所描述

[0340] XG-1996 4-(2-(正丁基聚二甲基甲硅烷氧基二甲基甲硅烷基) 乙

基) 苄基氯, MW ~ 1000 ;

[0341] XG1996HTTC S- 己基 -S' -4-(2-(正丁基聚二甲基甲硅烷氧基甲硅烷基) 乙基) 苄基三硫代碳酸酯 (制备例 1); 以及

[0342] D30 3,7- 二甲基 -3- 辛醇

[0343] 硼酸盐缓冲液为包含以下组分的眼科溶液

[0344]

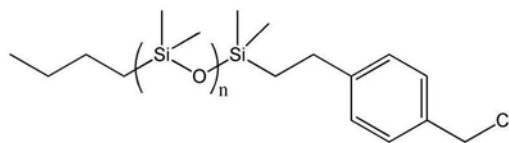
组分	重量%
去离子水	98.48
氯化钠	0.44
硼酸	0.89
十水合硼酸钠	0.17
乙二胺四乙酸盐 (EDTA)	0.01

[0345] 制备例 1 : 有机硅 - 官能团大分子 RAFT 剂的合成 : S- 己基 -S' -4-(2-(正丁基聚二甲基甲硅烷氧基二甲基甲硅烷基) 乙基) 苄基三硫代碳酸酯 (XG1996TTC)。

[0346] XG-1996 (示出于下式 XX 中, Mw 分布以约 1000 克 / 摩尔为中心, 对应于平均重复, m 为 10 至 12) (10g, 10 摩尔), 溶解于 1L 的圆底烧瓶约 250mL 的丙酮中。将己基三硫代碳酸钠 (NaHTTC) 溶解于 100mL 的丙酮中并且加入到反应混合物中。将反应混合物搅拌过夜。亮黄色溶液中沉淀出白色固体。经由旋转蒸发移除丙酮, 将粗产物在 250mL 的去离子水与 250mL 的己烷之间分配。分离出己烷层并且用己烷 (3×200mL) 萃取水层。合并所有的有机层, 用盐水 (250mL) 清洗, 并经 Na₂SO₄ 干燥。使己烷中的粗产物通过硅胶塞以除去浊度。经由旋转蒸发去除己烷, 留下澄清黄色油状产物 S- 己基 -S' -4-(2-(正丁基聚二甲基甲硅烷氧基甲硅烷基) 乙基) 苄基三硫代碳酸酯 (XG1996HTTC)。¹H NMR (300MHz, CDCl₃) : δ (ppm) 0.00-0.05 (m, 60H), 0.52 (t, 2H), 0.83-0.91 (m, 8H), 1.22-1.44 (m, 10H), 1.63-1.73 (m, 2H), 2.61 (t, 2H), 3.34 (t, 2H), 4.56 (s, 2H), 7.14 (d, 2H), 7.21 (d, 2H)。

[0347] XG-1996 :-(2-(正丁基聚二甲基甲硅烷氧基二甲基甲硅烷基) 乙基) 苄基氯, MW ~ 1000 克 / 摩尔

[0348]



式 XX

[0349] 制备例 2 : 标准非有机硅 RAFT 剂的合成 : S- 己基 -S' 苄基 - 三硫代碳酸酯 (HBTTC)

[0350] 将煤油中的钠块 (Sigma Aldrich 批号 13322HH) 在氮气下缓慢加入 20mL 的甲醇以形成甲醇钠。将所得溶液以若干等分试样加入到包含 1- 己硫醇 (Sigma Aldrich 批号 #09818LE) 的烧瓶中。经由注射器滴加二硫化碳 (Sigma Aldrich 批号 04897JJ)。溶液立刻变成黄色。使溶液反应 15 分钟。然后经由注射器滴加苄基溴 (Sigma Aldrich 批号 #14714PD)。随即形成沉淀。使反应继续进行 2 小时。最终在烧瓶底部形成黄色油状物。利用旋转蒸发移除甲醇, 并用去离子水和己烷使产物与钠盐分离。水层为大约 50mL 并且用

50mL 的己烷萃取三次。合并己烷, 经 Na_2SO_4 干燥, 并经由旋转蒸发减压干燥。 ^1H NMR (300MHz, CDCl_3) : δ (ppm) 0.875–1.125 (t, 3H), 1.25–1.63 (m, 6H), 1.63–1.95 (m, 2H), 3.25–3.63 (t, 2H), 4.63–4.8 (s, 2H), 7.25–7.5 (m, 5H)

[0351] 制备例 3: 在 XG1996TTC 和 HBTTC 的存在下具有交联 PTHPWCL 的聚 DMA 基聚硅氧烷封端的嵌段共聚物的合成

[0352] 一系列的 PDMA 基 PTHPWCL 经由 RAFT 聚合制备, 其中目标 $\text{DP}_{\text{nQ-链段}}$ 、交联剂与 ζ -一级链比率 (XL : ζ -PC) 以及有机硅链段与亲水性 Q 链段的比率 ($[\text{A}]$: $[\text{Q}]$) 存在变化。

[0353] DMA 得自嘉化学公司 (Jarchem), 并经由真空蒸馏进一步纯化。XG1996TTC 根据上述制备例 1 合成, HBTTC 根据制备例 2 合成。Irgacure 819 以 10mg/mL 的浓度溶于正丙醇中。

[0354] 对于实例 A 的合成而言, 通过将 30g 的 DMA、0.101g 的 XG1996TTC、0.260g 的 HBTTC 和 0.017g 的 CGI-819 溶解到 20mL 的琥珀色玻璃瓶内的 30g 的正丙醇中来制备聚合溶液。然后, 向聚合溶液中加入 0.157g 的 N, N'-亚甲基双丙烯酰胺。在室温条件下搅拌所得的溶液直至均匀。将容纳有最终聚合溶液的琥珀色小瓶用橡胶隔片封口, 并用 N_2 吹扫 20 分钟以移除溶液中的 O_2 。最后将密封的广口瓶置于 N_2 手套箱中储存。

[0355] 将聚合溶液在 N_2 气氛下用 4 颗标准 Phillips TL20W/03 RS 灯泡以 $2.0\text{mW}/\text{cm}^2$ 的强度照射 45 分钟来将聚合溶液固化至转化率 ρ 为 0.96 或 96%。在固化前, 将聚合溶液倒入直径 80mm 的结晶盘, 然后置于反射玻璃表面上。

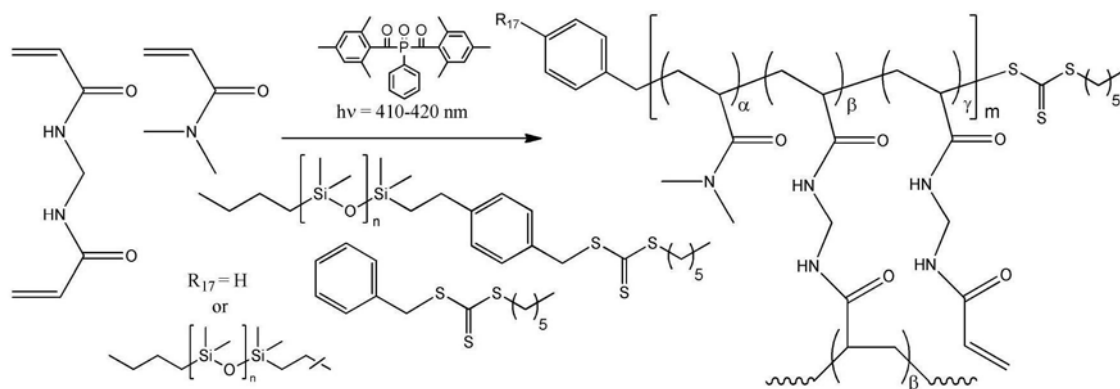
[0356] 固化后, 将所得高度粘稠的聚合材料以 5mL 的乙醇稀释。搅拌聚合的溶液, 然后将其滴加至 500mL 剧烈搅拌的冷二乙醚中以沉淀产物。将沉淀的聚合物真空干燥若干小时。

[0357] 实例 B 至 P 根据实例 A 制备, 其中成分量经调节以满足表 1 所列出的所需目标 $\text{DP}_{\text{nQ-链段}}$ 、XL : ζ -PC 比率和 $[\text{A}]$: $[\text{Q}]$ 比率。制备各实例所使用的具体的量可见下表 2 中。具体实例的单体转化率 r 在表 1 中示出。

[0358] 经由 SEC-RI 分析所得聚合物的 MW 和 MWD。图 2 示出交联 PDMA-硅氧烷的 A-P 实例的尺寸排阻色谱法-折射率 (SEC-RI) 结果, 并与根据制备例 3 制备的比较性直链 PDMA-硅氧烷比较。亲水性链段的聚合度连同多分散性指数一起测量。

[0359] 下面示出经由 RAFT 聚合的 PTHPWCL 的通用合成:

[0360]



[0361] 所得的分子量、多分散性指数 (PDI) 和转化率 (ρ) 提供于表 1 中。

[0362] 表 1

[0363]

实例	DP _{nQ} -链段	XL:ζ-PC	[A]:[Q]	M _n (克/摩尔)	M _w (克/摩尔)	PDI	ρ
A	300	1.00	0.10	53,030	195,400	3.7	0.96

[0364]

B	100	0.10	0.55	12,570	13,830	1.1	0.95
C	300	0.55	0.55	44,040	74,960	1.7	0.97
D	500	0.55	1.00	52,640	112,700	2.1	0.98
E	300	0.55	0.55	45,180	77,390	1.7	0.97
F	100	0.55	0.10	16,890	25,120	1.5	0.94
G	500	0.10	0.55	45,260	55,790	1.2	0.96
H	300	0.55	0.55	46,640	75,740	1.6	0.96
I	300	1.00	1.00	238,600	841,500	3.5	1.00
J	500	1.00	0.55	104,400	303,300	2.9	1.00
K	100	1.00	0.55	157,300	756,800	4.8	1.00
L	300	0.10	0.10	29,210	32,690	1.1	0.97
M	500	0.55	0.10	49,870	78,140	1.6	0.94
N	100	0.55	1.00	23,050	54,610	2.4	0.97
O	300	0.10	1.00	31,720	38,510	1.2	0.98
P	100	1.25	0.1	43,270	450,100	10.4	0.94

[0365] 表 2

[0366]

样品名称	DP _{nQ} -链段	XL:ζ-PC	[A]:[Q]	MBA (g)	DMA (g)	CGI (mg)	n-Prop (g)	CTA _{有机硅} (mg)	CTA _{标准} (mg)
A	300	1.00	0.10	0.157	30	17.0	30	101	260
B	100	0.10	0.55	0.049	30	50.8	30	1668	388
C	300	0.55	0.55	0.086	30	17.0	30	557	130
D	500	0.55	1.00	0.051	30	10.2	30	607	0
E	300	0.55	0.55	0.086	30	17.0	30	557	130
F	100	0.55	0.10	0.260	30	51.0	30	305	780
G	500	0.10	0.55	0.010	30	10.2	30	333	78
H	300	0.55	0.55	0.086	30	17.0	30	557	130
I	300	1.00	1.00	0.156	30	17.0	30	1013	0
J	500	1.00	0.55	0.094	30	10.2	30	334	78
K	100	1.00	0.55	0.470	30	51.2	30	1683	392
L	300	0.10	0.10	0.015	30	17.0	30	101	259
M	500	0.55	0.10	0.051	30	10.2	30	61	155
N	100	0.55	1.00	0.260	30	51.0	30	3047	0
O	300	0.10	1.00	0.015	30	17.0	30	1010	0
P	100	1.25	0.1	0.59	30	51.5	30	308	788

[0367] 制备例 4a-c

[0368] 对比物:聚 DMA 基聚硅氧烷封端的聚合物 NRPTHF 的合成。

[0369] 制备例 19-21 :在 XG1996TTC 的存在下经由 RAFT 聚合合成多种分子量的 PDMA 基非反应性聚硅氧烷封端的亲水性聚合物

[0370] 通过使用如下表 3 所列出的组分和量根据以下工序来制备一系列具有不同分子量的含 DMA 的 NRPTHF。对于所有制备例,有机硅链段的长度保持恒定在 10 至 12 个重复单元,即所有的聚合物均由相同的制备例 5 的 XG1996HTTC 制备。标定三种 DMA : XG1996HTTC 比率以改变亲水性聚合物的分子量,包括 300、600 和 1000。

[0371] 将蒸馏的 DMA 加入 120mL 的琥珀色玻璃广口瓶中。然后,将稀释剂 (D30 或戊醇)、XG1996HTTC 和 Irgacure-819 加入到单体中,加温并搅拌以确保均质性。将容纳有最终聚合溶液的琥珀色广口瓶置于 N₂ 气氛中,用 N₂ 吹扫 20 分钟以移除溶液中的 O₂。将广口瓶密封,置于 N₂ 手套箱中直至使用。

[0372] 经由 SEC-MALLS 分析聚合物的 MW 和 MWD,如下所述。结果示在下表 14 中示出。

[0373] 表 3

[0374]

制备例编号	4a	4b	4c
DP	300	600	1000
材料	(g)	(g)	(g)
XG1996HTTC	9.67	0.58	0.290
DMA	250.0	30.0	25.0
CGI-819	0.176	0.0021	0.0053
D30	0.0	30.0	25.0
戊醇	250.0	0	0.0

[0375] 表 4

[0376]

制备例编号	样品类型	Mn (克 / 摩尔)	Mw (克 / 摩尔)	PDI
4a	PDMA-Sil	23,720	27,790	1.17
4b	PDMA-Sil	44,830	49,480	1.10
4c	PDMA-Sil	92,180	102,700	1.11

[0377] 比较例 1-3

[0378] 将三个 senofilcon 镜片从其包装中取出并移至容纳有润湿溶液的玻璃小瓶中,所述润湿溶液包含 500ppm 的制备例 4a-c 中制备的非反应性聚硅氧烷封端的亲水性聚合物 (NRPTHF)。将镜片在 NRPTHF 润湿溶液中重新润湿,以 121℃ 高压灭菌 28 分钟,消毒后使其浸泡于环境温度下的 NRPTHF 润湿溶液中至少 24 小时。测量镜片的静滴接触角,并记录于

表 5 中。

[0379] 表 5

[0380]

实例编号	制备例		DP	类脂吸收率 (微克 / 镜片)	接触角 (°)
比较例 1	4a	PDMA-Sil-23K	222	52.1 (6.6)	55.7 (5.0)
比较例 2	4b	PDMA-Sil-44K	434	35.5 (7.8)	50.5 (1.7)
比较例 3	4c	PDMA-Sil-92K	918	14.1 (3.0)	43.7 (3.4)

[0381] 实例 A-P

[0382] 对于各实例,将生产质量的 senofilcon A 镜片从其包装中取出并移至容纳有润湿溶液的玻璃小瓶中,所述润湿溶液包含制备例 2 中制备的具有交联的聚硅氧烷封端的嵌段共聚物 (“PTHPWCL”),浓度在 30/70 体积 / 体积 IPA/ 硼酸盐缓冲液混合物中为 5000ppm。将镜片在 PTHPWCL 润湿溶液中重新润湿,使其浸泡于环境温度下的 PTHPWCL 润湿溶液中至少 24 小时。然后将处理过的镜片在新鲜润湿溶液中重新润湿,随后在 124℃ 灭菌 30 分钟。

[0383]

实例	DP _{nQ-链段}	XL:ζ-PC	[A]:[Q]	M _n (克/摩尔)	M _w (克/摩尔)	PDI	类脂吸收率 (微克/镜片) *
A	300	1.00	0.10	53,030	195,400	3.7	9.5
B	100	0.10	0.55	12,570	13,830	1.1	15.4
C	300	0.55	0.55	44,040	74,960	1.7	12.8
D	500	0.55	1.00	52,640	112,700	2.1	12.8
E	300	0.55	0.55	45,180	77,390	1.7	12.2
F	100	0.55	0.10	16,890	25,120	1.5	12.4
G	500	0.10	0.55	45,260	55,790	1.2	14.4
H	300	0.55	0.55	46,640	75,740	1.6	12.6
I	300	1.00	1.00	238,600	841,500	3.5	9.5
J	500	1.00	0.55	104,400	303,300	2.9	8.4
K	100	1.00	0.55	157,300	756,800	4.8	8.4
L	300	0.10	0.10	29,210	32,690	1.1	15.7

[0384]

M	500	0.55	0.10	49,870	78,140	1.6	12.7
N	100	0.55	1.00	23,050	54,610	2.4	12.5
O	300	0.10	1.00	31,720	38,510	1.2	15.1
P	100	1.25	0.1	43,270	450,100	10.4	5.2

[0385] * 类脂吸收率 = CH-NBD 吸收率。可使用 +/-0.4 微克 / 镜片的合并标准差来评估统计学显著性。

[0386] 图 3、4 和 5 示出对于所有 [A] : [Q] 比率和目标 DP_{nQ-链段} 值,类脂吸收率随着 XL : ζ-PC 增加而显著降低。

[0387] 图 6、7 和 8 也示出对于所有的 [A] : [Q] 比率,类脂吸收率随着 XL : ζ -PC 增加而显著降低。图 6 至 8 也示出 $DPn_{Q-链段}$ 对于经嵌段共聚物处理的镜片的类脂吸收率的影响不如交联剂与一级链的比率 XL : ζ -PC 的影响那么大。这表明紧密网目是理想的。

[0388] 图 9、10 和 11 示出不同聚合度和 [A] : [Q] 比率下的类脂吸收率表面反应,其中交联剂与一级链的比率 XL : ζ -PC 恒定。

[0389] 从这些图可看出,使用较高量的交联剂来形成本发明的纳米凝胶材料可导致形成这样的结构,所述结构在用于处理接触镜片医疗装置时可显著降低装置的类脂和蛋白质吸收特征。

[0390] 在整个本说明书中关于“一个实施例”、“某些实施例”、“一个或多个实施例”或“实施例”意指与实施例相关描述的具体特征、结构、材料或特性包括于本发明的至少一个实施例中。因此,诸如“在一个或多个实施例中”、“在某些实施例中”、“在一个实施例中”或“在实施例中”的短语在整个说明书中各个位置的出现不必指本发明的同一实施例。此外,在一个或多个实施例中,具体特征、结构、材料或特性可以任何合适的方式组合。

[0391] 尽管本文已结合具体实施例进行了描述,但应当理解,这些实施例仅为本发明的原理和应用的示例性描述。对于本领域的技术人员将显而易见的是,可在不脱离本发明的实质和范围的情况下对本发明的方法和装置进行多种修改和变型。因而,本发明旨在包括落入随附的权利要求书及其等同物的范围内的修改和变型。

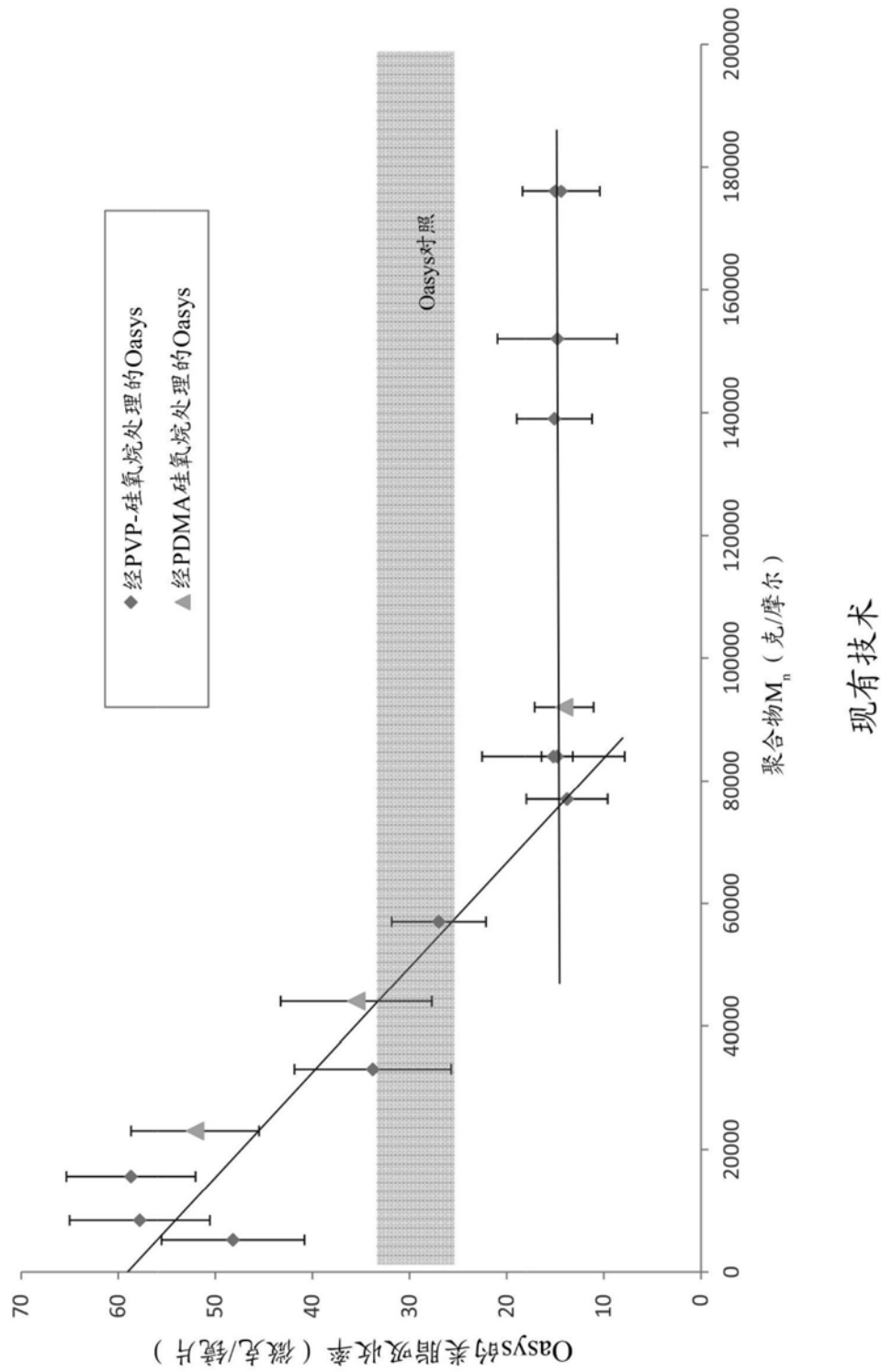


图 1

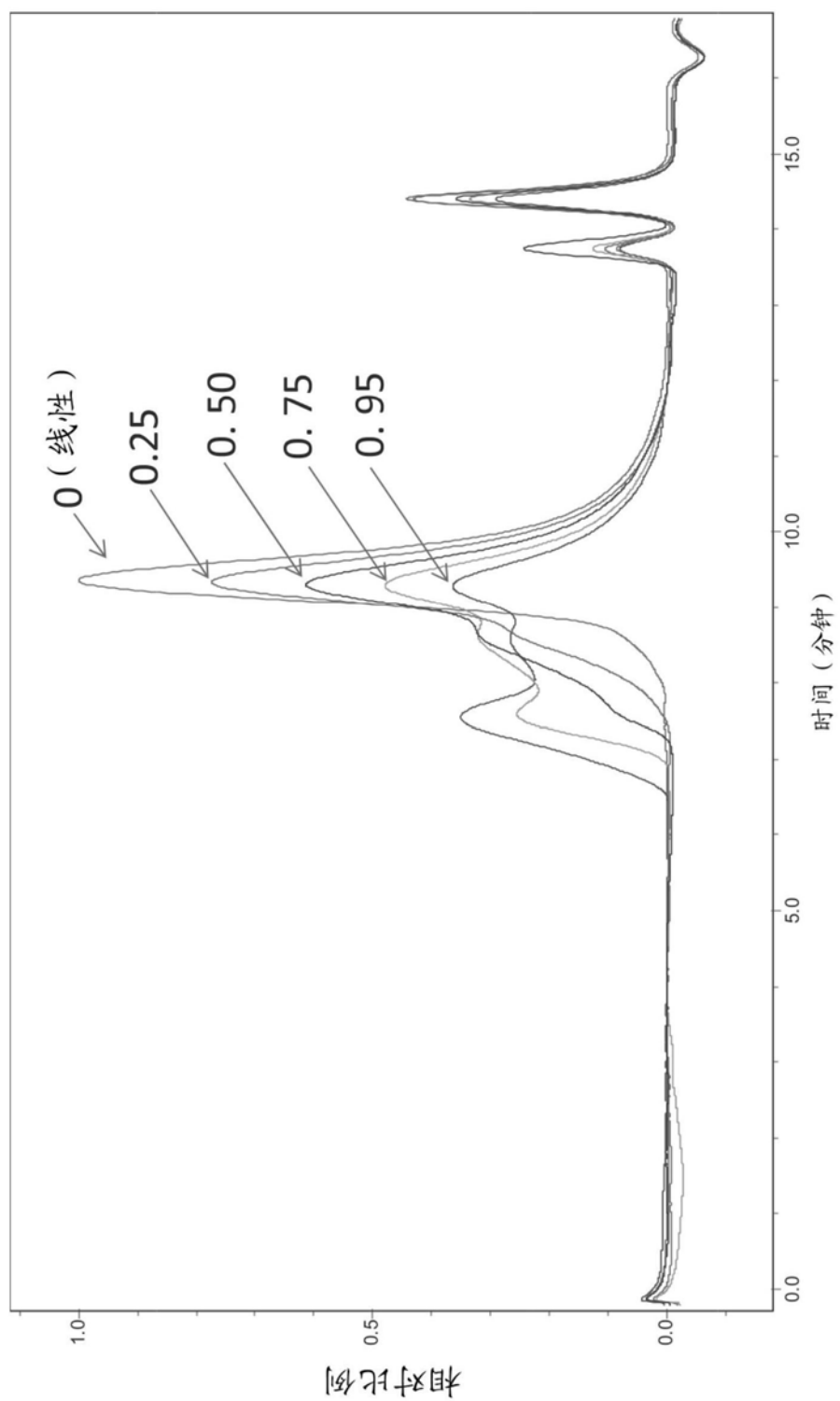


图 2

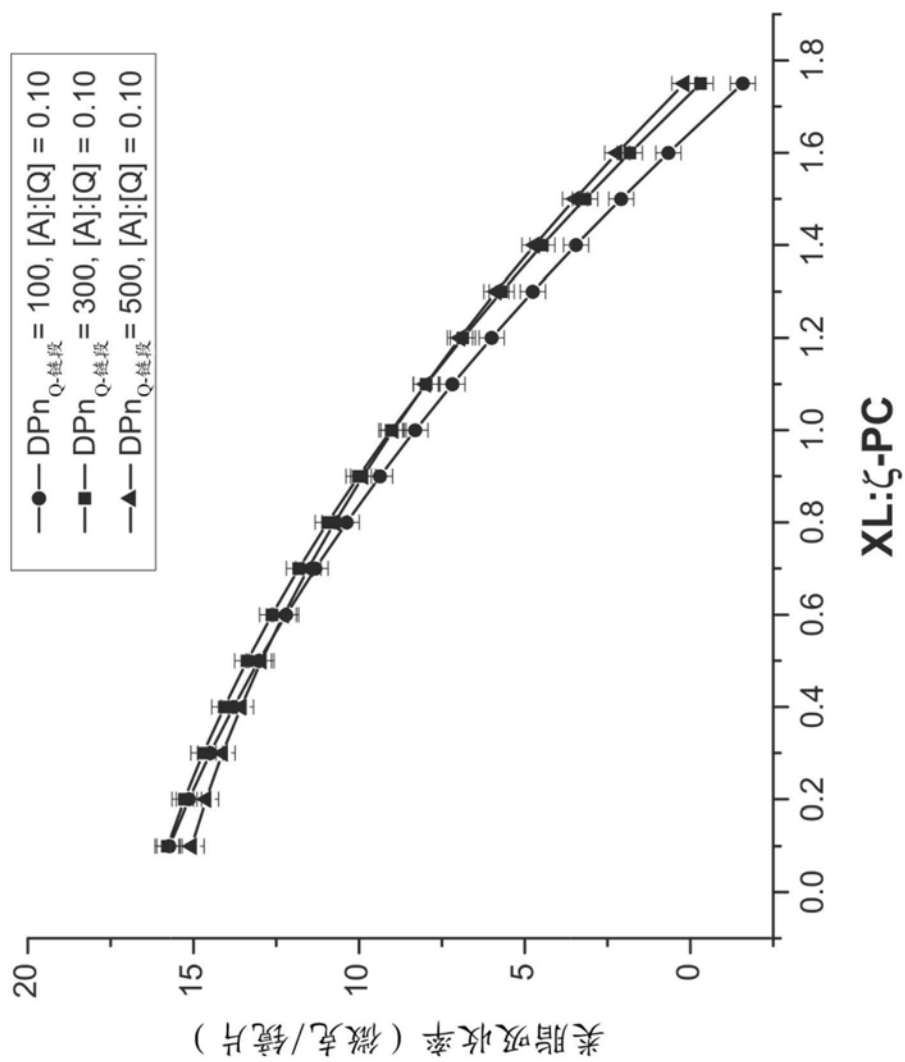


图 3

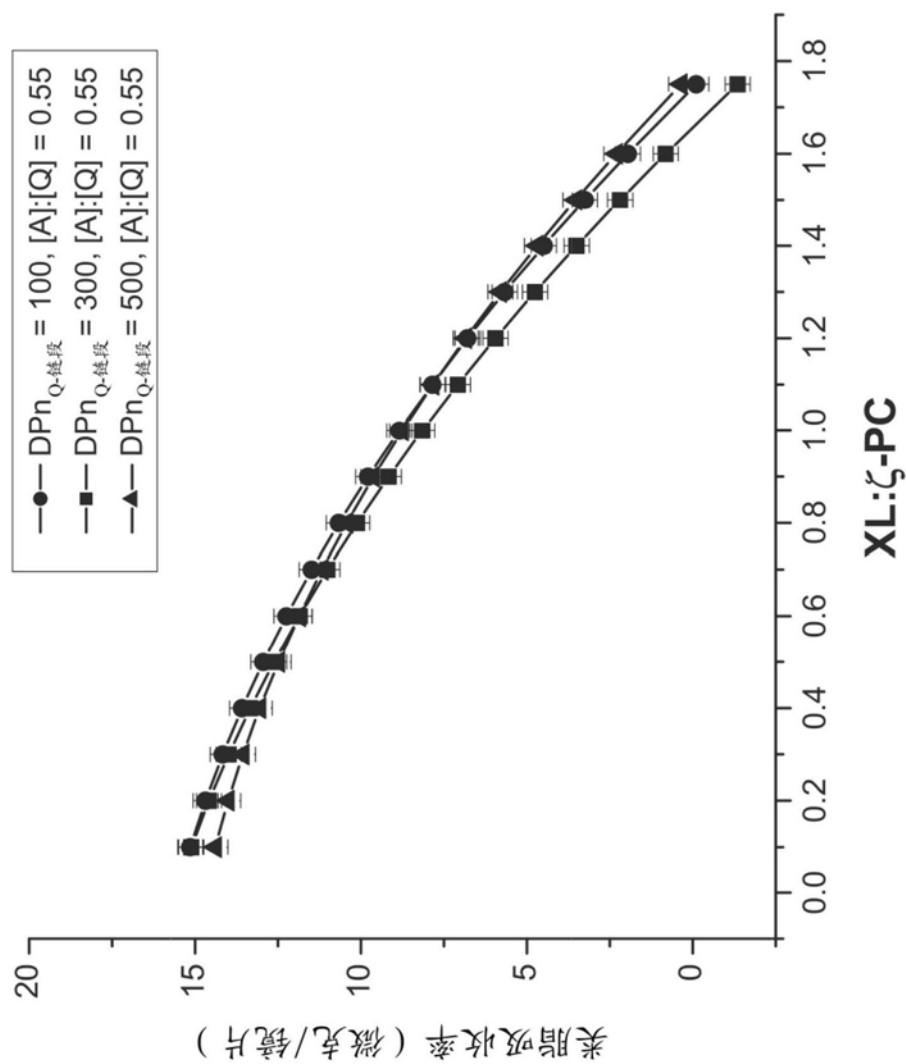


图 4

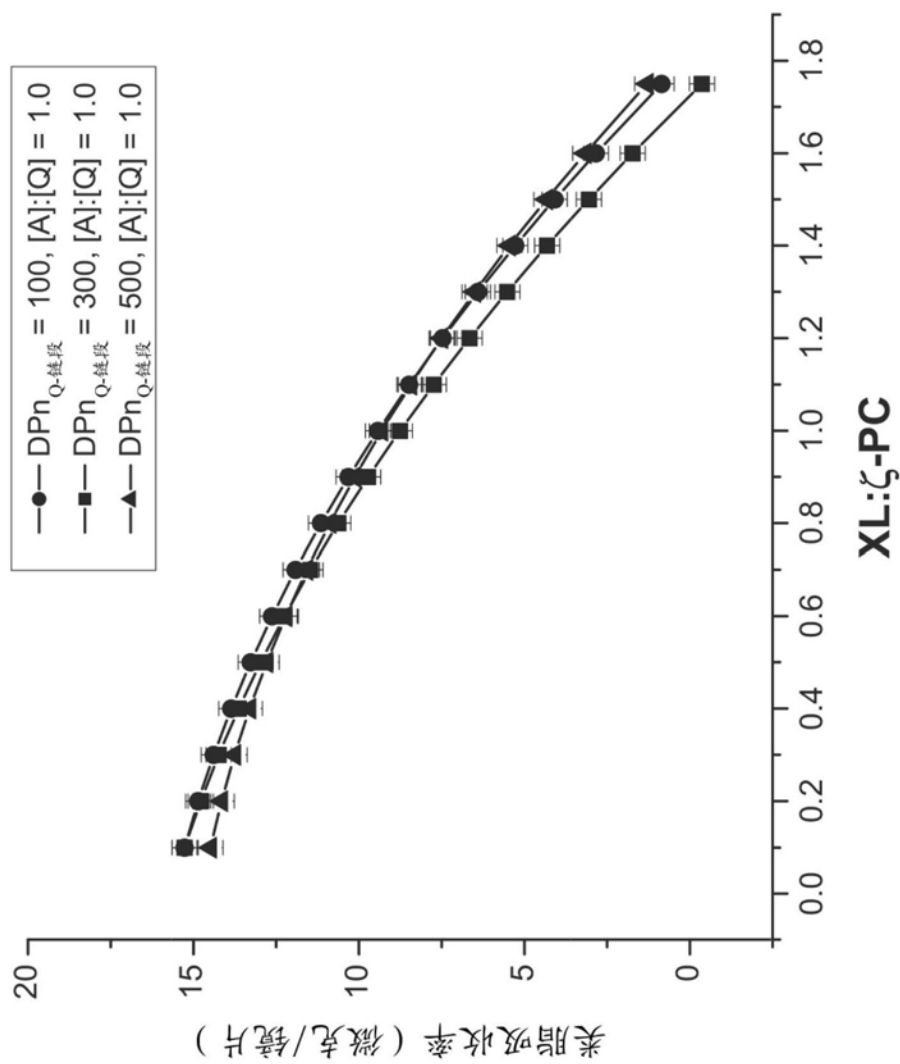


图 5

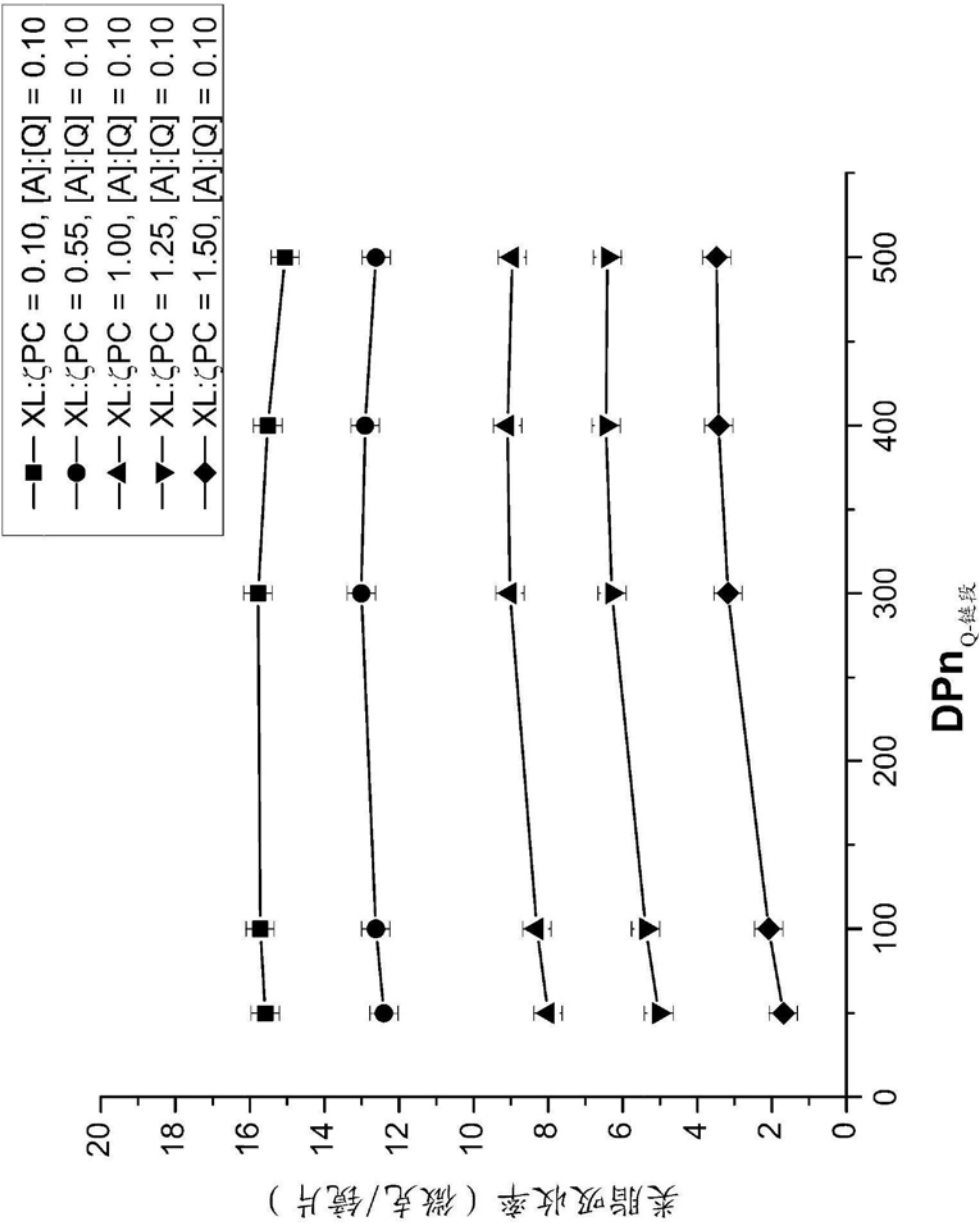


图 6

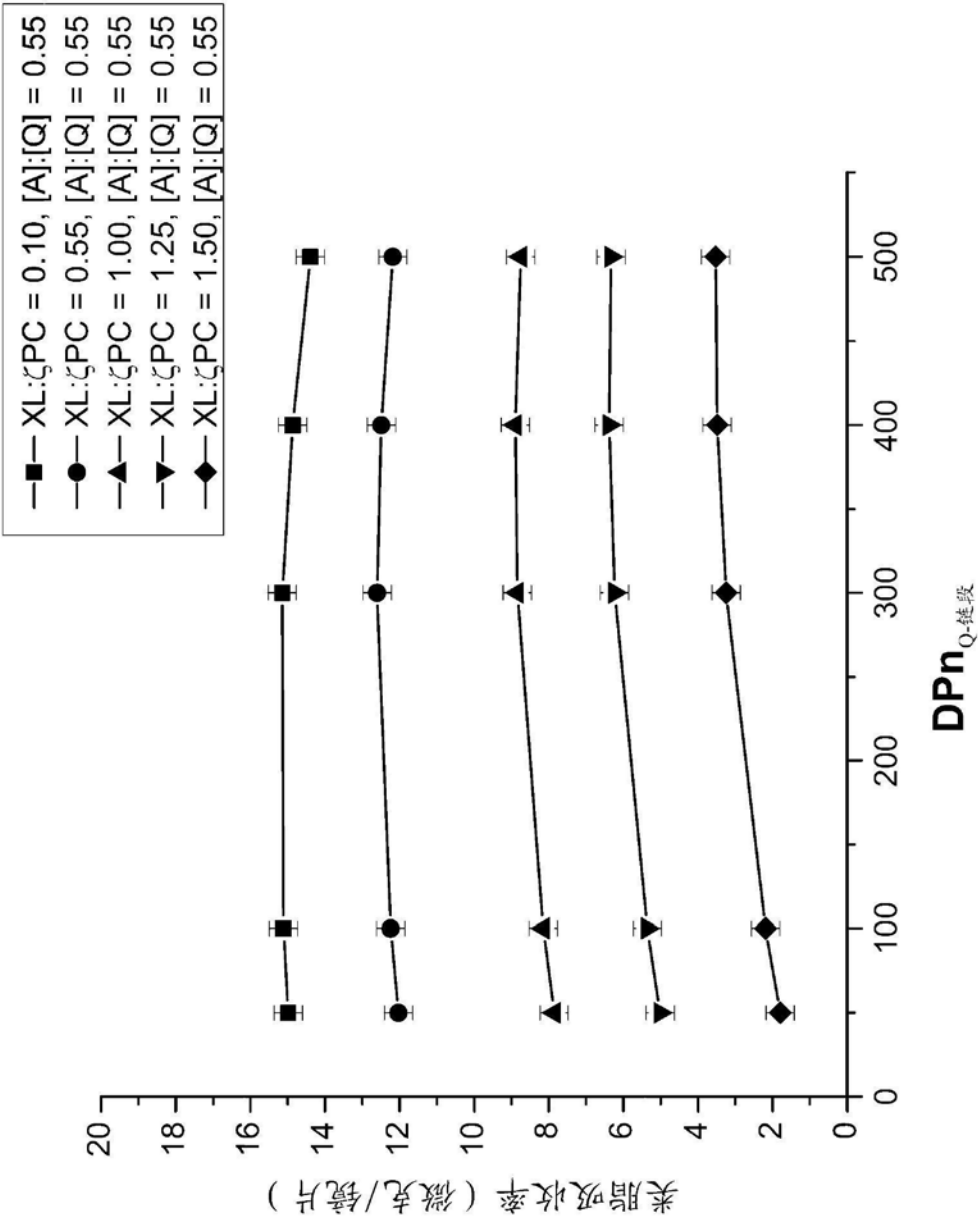


图 7

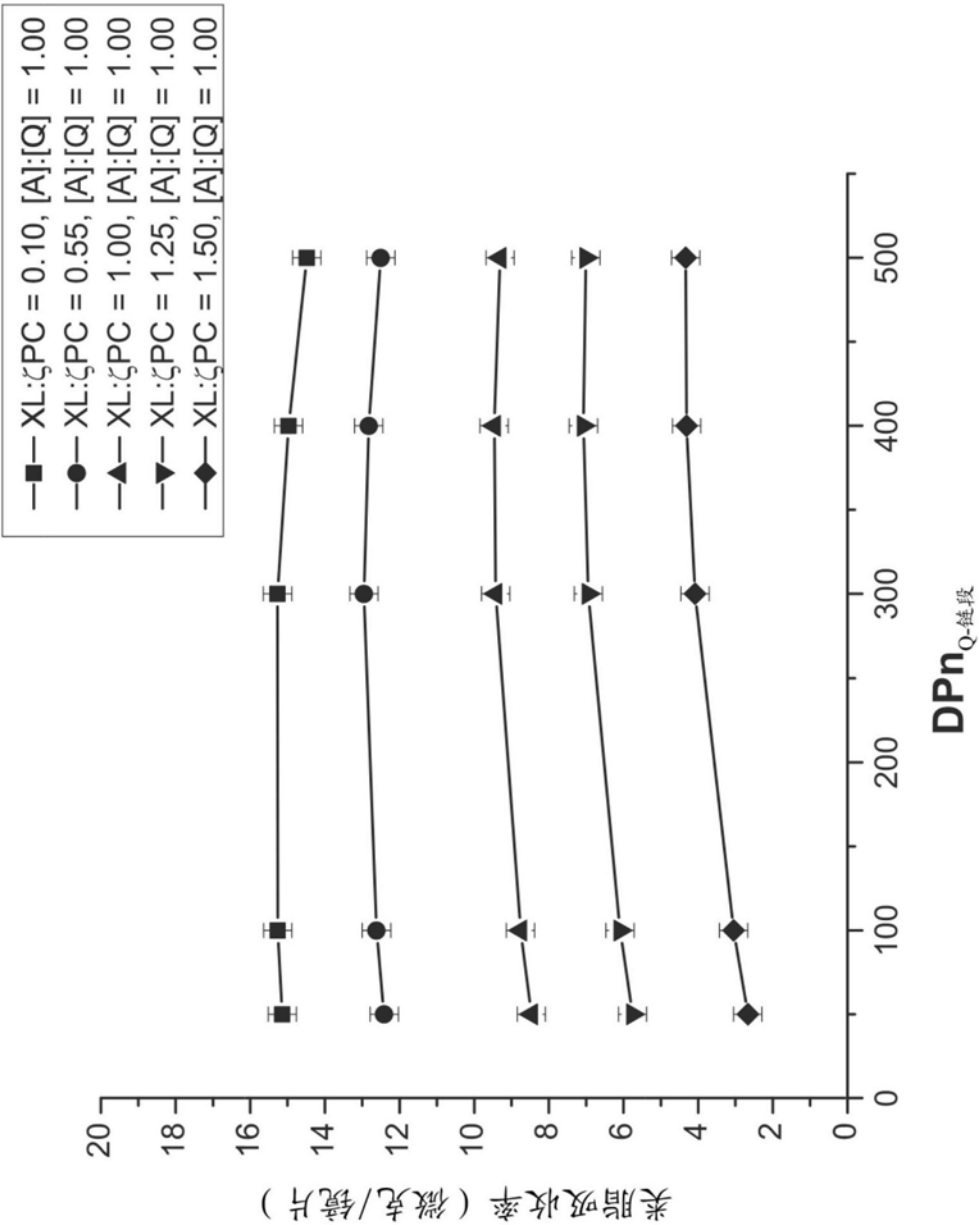


图 8