



(51) International Patent Classification:

C08G 18/61 (2006.01) *A61F 2/14* (2006.01)
C08G 77/20 (2006.01) *B82Y 30/00* (2011.01)
A61L 27/52 (2006.01) *C08F 230/08* (2006.01)

(21) International Application Number:

PCT/US2016/025319

(22) International Filing Date:

31 March 2016 (31.03.2016)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/141,752 1 April 2015 (01.04.2015) US

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(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, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, 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, SA, 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, ST, 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, KM, ML, MR, NE, SN, TD, TG).

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(54) Title: NANOGELS FOR OPHTHALMIC APPLICATIONS

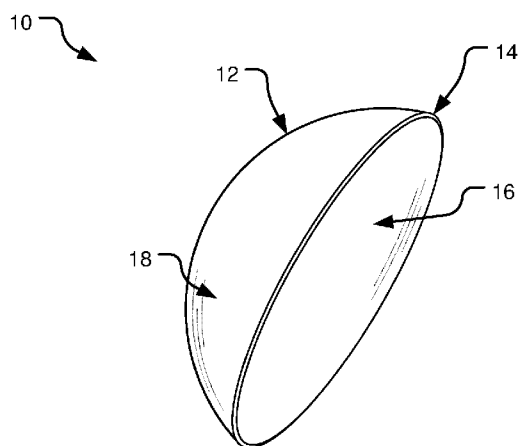


FIG. 1

(57) Abstract: Nanogels particularly suited for medical applications including lenses such as intraocular lenses, contact lenses and other corneal prosthetics. Two monomers that are very different in nature can be combined to form the nanogels without deleterious phase separation. The nanogels allow crosslinked nanoscale structures to be formed from vastly different monomers. The nanogels are particularly suited as a filler, e.g., within another polymer or a solvent, or as coating. The nanogels can be homogeneously dispersed in any matrix (e.g., solvent, polymer) and can be reacted within the matrix. If the matrix is optically clear, addition of the nanogels does not destroy the clarity of the matrix. The nanogels are also particularly suited as a therapeutic agent delivery conduit. In some implementations, the nanogels are siloxane nanogels, having been formed from a composition including a siloxane acrylate.



Published:

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

NANOGELES FOR OPHTHALMIC APPLICATIONS**CROSS-REFERENCE**

This PCT application claims priority to U.S. provisional application 62/141,752, filed April 1, 2015. For U.S. purposes, this application is a continuation application of U.S. provisional application 62/141,752, filed April 1, 2015.

TECHNICAL FIELD

This invention relates generally to polymeric compositions, particularly, to nanogels.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

None.

BACKGROUND

Medical devices have a diverse array of surface properties. In order to perform acceptably, and, e.g., to minimize the trauma to the patient, not be rejected, etc., the device and its surface are designed with the application in mind. For example, many medical devices require a combination of properties such as strength, thermal stability, structural stability, flexibility, opacity, radio-opacity, storage stability, lubricity, stability to sterilization treatment, etc., and of course, biocompatibility, in order to be effective for their intended purpose. Some devices need to be not just biocompatible but also either hydrophilic or hydrophobic. For example, some devices for ophthalmic purposes need to be clear and/or have a proper index of refraction.

Material selection is thus very important to the therapeutic efficacy of many medical devices since the properties of the materials used often dictate the properties of the overall device. However, the range of properties available from one, or even a combination of, material(s) is often not as broad as would be desired in medical device applications. As a result, many medical devices need to be manufactured from a combination of materials, processed in a specific manner, coated, and/or subjected to other treatments, in order to exhibit the desired and/or required characteristics.

The present disclosure provides nanogels that are particularly suited for medical devices and applications, including ophthalmic applications.

SUMMARY

The present disclosure is directed to nanogels for medical applications such as lenses (e.g., intraocular lenses and contact lenses), drug delivery devices and other corneal prosthetics. The nanogels are particularly suited as coatings on lenses, as fillers in lenses or as fillers in coatings on lenses, since in some implementations the nanogels are transparent. The nanogels are also particularly suited as a therapeutic agent delivery conduit. The nanogels enable a specific parameter of a device or material to be altered (such as the hydrophobicity, refractive index of a lens, equilibrium water content, tackiness, flexibility, durability, etc.) without impacting any other material properties. For example, the nanogels can be configured for storing and/or delivering therapeutic and/or active molecules, such as biological and non-biological active molecules (e.g., drugs, biologics (e.g., peptides, aptamers etc.)), with or without an associated coating that controls rate of delivery of the therapeutic or active molecule to the surrounding tissue. The nanogels can have a hydrophilic, hydrophobic, amphiphilic, and/or charged polymeric backbone with reactive pendent groups.

The nanogels are siloxane nanogels, having been formed from a composition including a siloxane acrylate.

The composition may include another acrylate, such as a urethane-based acrylate, in addition to the siloxane acrylate. Urethane-based acrylate(s) enable secondary interactions (reversible hydrogen bonding) within the composition. In some implementations, other monomer, polymer or copolymer material(s) may be used in place of the urethane-based acrylate(s), as long as they provide secondary interactions (reversible hydrogen bonding) in the composition and the resulting nanogel meets the criteria for an ophthalmic application such as an intraocular lens.

The composition may include include a hydrophilic monomer, such as a hydrophilic acrylate, in addition to the siloxane acrylate. By utilizing a hydrophilic monomer, and the siloxane monomer in a crosslinked nanogel format, phase separation of the monomers can be limited.

In one particular implementation, water-dispersible, crosslinked siloxane nanogels were synthesized via a free radical solution polymerization and then applied as optically

clear, functional coatings on the surface of ophthalmic biomaterials. The functionalized nanogels, which can contain hydrophilic and/or hydrophobic functional groups within a highly crosslinked, optically clear, dense network, can be used to modify and enhance highly targeted material properties on the surface of ophthalmic devices such as intraocular lenses and contact lenses while maintaining the underlying desirable bulk properties of the material.

These and various other features and advantages will be apparent from a reading of the following detailed description.

BRIEF DESCRIPTION OF THE DRAWING

FIG. 1 is a perspective view of a contact lens.

FIG. 2 is a perspective view of an intraocular lens.

FIG. 3 is an enlarged side view of a coated ophthalmic device.

FIG. 4 is a schematic diagram of a nanogel particle.

FIG. 5 is a stepwise schematic illustration of a method of providing a nanogel coating on an ophthalmic device.

FIG. 6 is a stepwise schematic illustration of a method of applying a therapeutic agent to a nanogel coating.

FIG. 7 is a graphical representation showing the uptake and cumulative release of an active agent from a nanogel coated lens substrate.

DETAILED DESCRIPTION

The present disclosure describes various nanogel compositions and the polymeric compositions used to make those nanogels. The nanogels are particularly conducive for use with medical devices, including intraocular lenses, such as implantable lenses and surface or removable lenses (e.g., contact lenses), other ophthalmic devices and/or corneal prosthetics. The nanogels are formed from a polymeric backbone and a reactive group, the backbone being hydrophilic, hydrophobic, amphiphilic, and/or charged and conductive. The nanogels can be formed from monomeric compositions that include at least one acrylate, such as a siloxane acrylate and, in some implementations, a siloxane acrylate with an acrylic copolymer, such as a urethane-based acrylic copolymer. In some implementations, the polymeric compositions include a siloxane acrylate and a hydrophilic monomer.

In the following description, reference is made to the accompanying drawing that forms a part hereof and in which are shown by way of illustration at least one specific

implementation. The following description provides additional specific implementations. It is to be understood that other implementations are contemplated and may be made without departing from the scope or spirit of the present invention. The following detailed description, therefore, is not to be taken in a limiting sense. While the present description is not so limited, an appreciation of various aspects of the description will be gained through a discussion of the examples provided below.

As used herein, the singular forms “a”, “an”, and “the” encompass implementations having plural referents, unless the content clearly dictates otherwise. As used in this specification and the appended claims, the term “or” is generally employed in its sense including “and/or” unless the content clearly dictates otherwise.

Spatially related terms, including but not limited to, “lower”, “upper”, “beneath”, “below”, “above”, “on top”, etc., if used herein, are utilized for ease of description to describe spatial relationships of an element(s) to another. Such spatially related terms encompass different orientations of the device in addition to the particular orientations depicted in the figures and described herein. For example, if a structure depicted in the figures is turned over or flipped over, portions previously described as below or beneath other elements would then be above or over those other elements.

Turning to FIG. 1, a contact lens 10 is illustrated. Lens 10 has a flexible body 12 that has a domed shape in a quiescent state, a peripheral edge 14, and a first side 16 and a second side 18. In this illustrated implementation, first side 16 is the side that is closer to the eye when inserted in an eye and has a concave shape, and second side 18 is the outer surface and has a convex shape.

Lens 10 is non-tacky, biocompatible, has acceptable refractive index, and is free of visible imperfections and glistening. Lens 10 is sufficiently flexible and durable to survive multiple bending and unbending cycles while remaining undamaged. Lens 10 can be hydrophobic, hydrophilic, or neutral.

In FIG. 2, an intraocular lens (IOL) 20 is illustrated. Similar to contact lens 10 of FIG. 1, IOL 20 has a body 22 with a domed shape, a peripheral edge 24, and a first side 26 and an opposite second side (not shown). IOL 20 also has opposing arms 29, to facilitate handling of IOL 20. Unlike contact lens 10, however, IOL 20 is fairly rigid.

Lens 10 and IOL 20 are formed from a polymeric composition that may include any number of additives, fillers, etc. The nanogels of this disclosure are particularly conducive to being used as an additive (e.g., filler) in a polymeric composition used to form lens 10 or IOL

20. The nanogels can be used to modify or affect the physical structural properties of lens 10 or IOL 20 and/or the surface properties.

Present on lens 10 or IOL 20 may be a coating, for example, to modify the surface properties of lens 10 or IOL 20. FIG. 3 illustrates an ophthalmic device 30 (such as lens 10 or IOL 20) having a surface 32 with a coating 34 provided on surface 32. Coating 34 is composed of nanogel particles 36. In some implementations, two different nanogels are present in coating 34.

For example, a hydrophobic coating may be applied to a previously formed hydrophilic lens 10 or IOL 20. The nanogels of this disclosure are particularly conducive to being used in a coating composition on lens 10 and on IOL 20 independent of the polymeric composition forming lens 10 or IOL 20. In some implementations, the nanogels covalently react (e.g., via a redox reaction) with the polymeric material of lens 10 or IOL 20. In other implementations, the surface of lens 10 or IOL 20 may be treated (e.g., plasma treated) to form available reactive moieties on lens 10 or IOL 20 that readily react with the nanogels. The nanogels of this disclosure are also particularly conducive to being used in a coating composition on a medical device (e.g., implantable medical device).

As indicated above, the nanogels have a polymeric backbone with at least one reactive group. The backbone is, or is formed from a polymer that is, hydrophilic, hydrophobic, amphiphilic, or conductive. In most implementations the reactive group is an acrylate, but could alternately be an isocyanate or alcohol. FIG. 4 illustrates schematically a nanogel particle 40 having a core or backbone 42 with multiple reactive pendant groups 44 extending therefrom. In FIG. 4, not all reactive groups 44 are the same. In some implementations the reactive group 44 is an acrylate or an isocyanate or other reactive group.

The polymeric composition that will form the nanogel includes at least one siloxane acrylate. The polymeric composition may additionally include at least one acrylic copolymer or acrylate, such as a urethane-based acrylic copolymer. The siloxane acrylate may be a silicon-containing acrylate, diacrylate, triacrylate, tetracrylate, etc. The acrylate may be, for example, aliphatic or aromatic. Examples of suitable siloxane acrylates include silicone diacrylate (e.g., commercially available under the trade name "Ebecryl 350"), [tris(trimethylsiloxy)silyl]propyl methacrylate, and 3-(trimethoxysilyl)propyl methacrylate.

The siloxane acrylate(s) is at least 50 wt-% or 50 mol% of the total, uncured polymeric composition. In other implementations, the siloxane acrylate(s) is at least 60 wt-% or 60 mol% of the total, uncured polymeric composition, and in other implementations at least 65 wt-% or 65 mol%. Still further, the siloxane acrylate(s) can be at least 70 wt-% or 70

mol%, or at least 75 wt-% or 75 mol%, or at least 80 wt-% or 80 mol%, or at least 85 wt-% or 85 mol%, or at least 90 wt-% or 90 mol%, or at least 95 wt-% or 95 mol%, or at least 97 wt-% or 97 mol%, and in some implementations at least 98 or 99 wt-% or mol% of the total, uncured polymeric composition. In one particular implementation, the siloxane acrylate(s) is 50-100 wt-% of the total, uncured polymeric composition, e.g., 60-90 wt-%, or 70-80 wt-%, or 70 wt-%. In another particular implementation, the siloxane acrylate(s) is 50-100 mol% of the total, uncured polymeric composition, e.g., 60-90 mol%, or 70-80 mol%, or 70 mol%.

The polymer composition that will form the nanogel can include an acrylic copolymer (or, acrylate) such as an acrylate, a diacrylate, a triacrylate, a tetraacrylate, etc., and could be a, e.g., methacrylate, ethylacrylate, etc. It may be, for example, aliphatic or aromatic. The acrylate may be long-chain (e.g., having 13 to 25 carbon atoms) or may be short-chain.

If the acrylate is a urethane-based acrylic copolymer (or, urethane-based acrylate) it may be an acrylate, a diacrylate, a triacrylate, a tetracrylate, etc. It may be, for example, aliphatic or aromatic. The urethane-based acrylate may be long-chain (e.g., having 13 to 25 carbon atoms) or may be short-chain. Urethane-based acrylate(s) are preferred because they enable secondary interactions (reversible hydrogen bonding) within the composition.

For those implementations where an acrylate(s) (e.g., urethane-based acrylate and/or other acrylates) is present in addition to the siloxane acrylate, it is present as at least 10 wt-% or 10 mol% of the total, uncured polymeric composition that will form the nanogel. In other implementations, the acrylate(s) is at least 15 wt-% or 15 mol% of the total, uncured polymeric composition, and in other implementations at least 20 wt-% or 20 mol%. Still further, the acrylate(s) can be at least 25 wt-% or 25 mol%, or at least 30 wt-% or 30 mol%, or at least 35 wt-% or 35 mol%, or at least 40 wt-% or 40 mol%, or at least 45 wt-% or 45 mol%.

The polymeric composition that will form the nanogel can include other copolymer or monomer materials, including thermosetting materials (e.g., phenolic, epoxy, urea-formaldehyde, melamine formaldehyde, and the like) or thermoplastic materials (e.g., polyamide (nylon), polyethylene, polypropylene, polyester, polyurethane, polyetherimide, polysulfone, polystyrene, acrylonitrile-butadiene-styrene block copolymer, acetal polymer, polyvinyl chloride, and the like). The composition can include other materials such as, for example, photoinitiator(s), plasticizer(s), catalyst(s), accelerator(s), activator(s), coupling agent(s), lubricant(s), wetting agent(s), surfactant(s), UV blocker(s), UV stabilizer(s), and/or complexing agent(s). The polymeric composition can be 100% solids; that is, no solvent is

present. In some implementations, however, the polymeric composition that will form the nanogel is composed of only acrylate(s).

The various components that form the polymeric composition of the nanogel are selected to provide stability under hydrolytic conditions. For example, the component(s) can be selected to resist undesired phase separation, which may be accomplished, e.g., by the use of aromatic rings on the side chains. Two or more monomers that are very different in nature (e.g., one hydrophobic and one hydrophilic) can be combined to form nanogels without having deleterious phase separation occur.

Using the compositions of this disclosure, crosslinked nanoscale structures can be formed from vastly different monomers, for example, from a hydrophilic monomer (e.g., HEA) and a hydrophobic monomer (e.g., any of the hydrophobic “Ebecryl” monomers). The different monomers create reactive nanogels having a backbone formed from the monomers. After the nanogels are synthesized, the nanogels can be used as a filler, e.g., within another polymer or a solvent, or as coating. The nanogels can be homogeneously dispersed in any matrix (e.g., solvent, polymer) and optionally reacted within the matrix. If the matrix is optically clear, addition of the nanogels does not destroy the clarity of the matrix.

FIG. 5 illustrates stepwise a suitable method 500 for applying a nanogel coating onto a substrate, such as an ophthalmic substrate. In FIG. 5, a functionalized nanogel 502 in solvent (e.g., water) is applied to a substrate 504, e.g., by spin coating. The nanogel 502 was synthesized and functionalized before participating in a two-part redox reaction with ammonium persulfate (APS) and N,N,N',N'-tetramethylethylenediamine (TEMED). Substrate 504 may be, e.g., poly(methyl methacrylate) (PMMA) lens substrate impregnated with APS. The interfacial polymerization reaction 506 between the aqueous dispersion of the nanogel and substrate 504 ensures a covalently crosslinked coating 508 on the surface of substrate 504.

Depending on the composition, the resulting nanogel and any coating therefrom can be charged, either anionic or cationic, or may be electrically conductive. As an example, nanogels formed from compositions including dimethyl aminoethyl methacrylate or poly(3,4-ethylenedioxythiophene)-tetramethacrylate are electrically conductive.

Electrically conductive and/or charged nanogels have potential applications in ophthalmology, such as for drug delivery (using ionically charged molecules to store and transport peptides and drugs), synthesizing electrochromically active nanogels that can be used to modify the refractive index of materials/coatings, for formulating a ‘smart lens’ by

electrochemically modifying the nanogels to change their absorption, refractive index and/or swelling behavior (multi-focal lenses), and as an anti-bacterial coating.

FIG. 6 illustrates stepwise a suitable method 600 for providing a controlled release active agent to a nanogel coating 602 via simple diffusion through its crosslinked meshwork.

5 In FIG. 6, a solution 604 of active (e.g., anti-inflammatory drug, e.g., dexamethasone) agent 606 (illustrated as stars) is applied to the nanogel coating 602 and retained thereon for an extended period of time (e.g., overnight). The result is the active agent 606 retained in and/or the nanogel coating 602. Over time, the active agent 606 is released from the coating 602.

The following abbreviations represent examples of particular acrylates that are
10 suitable for the polymeric compositions that can be used to form the nanogel:

DMAEMA : dimethyl aminoethyl methacrylate;

EB230 : aliphatic urethane-based diacrylate, commercially available under the trade name "Ebecryl 230;"

EB350 : silicone diacrylate, commercially available under the trade name "Ebecryl
15 350;"

HEA : 2-hydroxyl ethyl acrylate;

IBMA : isobornyl methacrylate;

IEM : 2-isocyanatoethyl methacrylate;

MMA : methyl methacrylate;

20 PEGDA : polyethylene glycol diacrylate;

PTMA: poly(3,4-ethylenedioxythiophene)-tetramethacrylate;

TRIS : [tris(trimethylsiloxy)silyl]propyl methacrylate;

3TSMA : 3-(trimethoxysilyl)propyl methacrylate; and

UDMA : urethane dimethacrylate.

25 Particular examples of polymeric compositions that can be used to form the nanogel(s) include: 3TSMA and UDMA; TRIS and UDMA; E350 and UDMA; MMA, E350 and E230; E350; PTMA, E350 and UDMA; and 3TSMA and PEGDA.

The polymeric composition that will form the nanogel can be cured by an energy source that can be a source of thermal energy or radiation energy, such as electron beam,
30 ultraviolet light, or visible light. Electron beam radiation is also known as ionizing radiation. Ultraviolet radiation refers to radiation having a wavelength within the range of about 200 to about 400 nanometers, preferably within the range of about 250 to 400 nanometers. It is preferred that 118 to 400 mWatt/cm² ultraviolet lights are used. Visible radiation refers to radiation having a wavelength within the range of about 400 to about 800 nanometers,

preferably in the range of about 400 to about 550 nanometers. The amount of energy required is dependent upon the chemical nature of the reactive groups in the polymeric composition, as well as upon the thickness of the polymeric composition. In other implementations, the polymeric composition can be cured by an initiating system that can be
5 a source of radicals, such as, e.g., thermal initiators, redox reactions, etc.

EXAMPLES: The following non-limiting examples were prepared. The objects, features and advantages of the present invention illustrated in the following examples, which incorporate particular materials and amounts, should not be construed to unduly limit this invention. All materials are commercially available unless otherwise stated or apparent. All
10 parts, percentages, ratios, etc., in the examples are by weight unless otherwise indicated.

The following abbreviations are used throughout the examples:

AIBN : azobisisobutyronitrile (from Aldrich Chemical Company (St. Louis, MO, USA));

DBTDL : dibutyltin dilaurate (from Aldrich Chemical Company (St. Louis, MO, USA));
15

DCM : dichloromethane (from BDH Chemicals (Radnor, NJ, USA));

EB350 : silicone diacrylate, commercially available under the trade name “Ebecryl 350” (from Allnex (Alpharetta, GA, USA));”

HEX : hexane (from Fisher Chemical (Fair Lawn, NJ, USA));

IBMA : isobornyl methacrylate (from TCI (Toshima, Kita-Ku, Tokyo, Japan));
20

IEM : 2-isocyanatoethyl methacrylate (from TCI (Toshima, Kita-Ku, Tokyo, Japan));

ME : 2-mercaptoethanol (from Acros Organics (New Jersey, USA));

MEK : methyl ethyl ketone (from Fisher Chemical (Fair Lawn, NJ, USA));

TOL : toluene (from Fisher Chemical (Fair Lawn, NJ, USA));

TRIS : [tris(trimethylsiloxy)silyl]propyl methacrylate (from Alfa Aesar (Ward Hill, MA, USA));
25

3TSMA : 3-(trimethoxysilyl)propyl methacrylate (Aldrich Chemical Company (St. Louis, MO, USA)); and

UDMA : urethane dimethacrylate (Aldrich Chemical Company (St. Louis, MO, USA)).
30

The following equipment/procedures were used to make or test the examples:

FTIR : A “Nicolet Nexus 670 FT-IR ESP” (400-4000 nm) was utilized during the nanogel synthesis to determine conversion of the polymeric composition.

IR Peaks (KBr, cm^{-1}): 2270 cm^{-1} (N=C=O), 1720 cm^{-1} (C=O), 1637 cm^{-1} (C=C), 1300 cm^{-1} (C=O), 1260 cm^{-1} (-OH, $\text{R}_3\text{-Si-O}$).

GPC : Prepared nanogels were characterized by triple-detection gel permeation chromatography (Viscotek, Houston, TX, USA) in tetrahydrofuran using a series of four columns spanning 10^4 - 10^7 molecular weights. The molecular weight, hydrodynamic radius, and polydispersity were determined through right/low angle light scattering detection calibrated with a 65 kDa poly(methyl methacrylate) standard.

The following general synthesis process used to make the examples.

The nanogels of the Comparative Example and Examples 1 through 3 were synthesized in a 100 mL single-neck round bottom flask in 10 gram batches using a 70:30 molar ratio of a monomethacrylate monomer (e.g., IBMA, TRIS, 3TSMA, or E350) to dimethacrylate monomer (UDMA), respectively. Free-radical polymerization was carried out in solution using a four-fold (4x) excess of MEK (relative to total monomer mass), unless otherwise specified. 20 mol% ME (relative to total monomer content) was added as a chain transfer agent to reduce the chances for macrogelation and provide sites for post-polymerization re-functionalization with methacrylate groups. AIBN at 1 wt% (relative to total monomer content) was used as a thermal initiator for the reaction.

The solution (which was clear) was stirred at 200 revolutions per minute in a 80°C oil bath with a circulate water condenser in place until the methacrylate conversion was greater than 85% (FTIR: C=C peak areas 1300 cm^{-1} , 1637 cm^{-1} ; reference peaks 1260 cm^{-1} , 1720 cm^{-1}) as determined by initial and final FTIR readings. The product was precipitated dropwise into 10-fold excess hexanes (relative to volume of MEK), unless otherwise specified.

The isolated product was further functionalized with methacrylate groups by re-dissolving the nanogel in 20 mL DCM and adding IEM (1:1 molar equivalent IEM:ME) and a trace of DBTDL catalyst. A second precipitation was repeated, unless otherwise specified. Residual solvent after the precipitation was removed under vacuum to isolate the methacrylate-functionalized reactive nanogels. The final product was characterized using GPC and NMR.

Nanogel Comparative Example - 7:3 molar ratio IBMA:UDMA

A 7:3 molar ratio of IBMA and UDMA were weighed in a 100 mL one-neck round bottom flask. 20 mol% of chain-transfer agent ME (relative to total monomer content), a four-fold (4x) excess of MEK (relative to total monomer content) and a magnetic stirrer were added to the flask. Once the solution was homogeneously mixed, 1 wt% thermal initiator AIBN (relative to total monomer content) was added to kick-start the free-radical

polymerization. After an initial FTIR spectra was taken, the solution was stirred at 200 revolutions per minute in an 80°C oil bath with a circulated water condenser in place.

After 85% of the vinyl groups had converted (as determined by FTIR peak analysis), the clear nanogel mixture was removed from heat and precipitated dropwise into 10-fold excess hexanes (relative to volume of MEK). The hexane layer was poured off, isolating the solid nanogel product. The isolated nanogels were further functionalized with methacrylate groups by re-dissolving them in 20mL DCM, adding IEM (1:1 molar equivalent IEM:ME) and a trace of DBTDL catalyst. Methacrylate-functionalization was determined by initial and final FTIR readings (FTIR: C=N peak areas 2270 cm⁻¹, reference peak C=O 1720). The methacrylate-functionalized nanogel was isolated through a second precipitation. Any residual solvent was removed by reduced pressure and the final product was a white powder. The nanogels were further characterized using GPC and NMR.

Nanogel Example 1 - 7:3 molar ratio 3TSMA:UDMA

Example 1 was prepared as described above using a 7:3 molar ratio of 3TSMA:UDMA, 20 mol% ME, 1 wt% AIBN, 8x MEK, 1:1 IEM:ME, with 2 precipitations.

8x MEK was used in Example 1 instead of 4x MEK because when 4x was used, the composition macrogeled at 80°C during rotovap (NG 7d B1P35); for the failed macrogeled example, no second precipitation was done.

FTIR reference peaks for Example 1 were C=C 1300, 1637; Ref 1720, 1260, 1550. The FTIR 815 peak was washed out by siloxane groups.

Similar formulations (i.e., 7:3 molar ratio of 3TSMA:UDMA, 20 mol% ME, 1 wt% AIBN, 1:1 IEM:ME, with 2 precipitations) were also prepared but with 4x MEK and 6x MEK.

Nanogel Example 2 - 7:3 molar ratio TRIS:UDMA

Example 2 was prepared as described above using a 7:3 molar ratio of TRIS:UDMA, 20 mol% ME, 1 wt% AIBN, 2x MEK, with no precipitations.

2x MEK was used in Example 2 instead of 4x MEK because when 4x was used, the resulting nanogel was too small for GPC. To increase the size, solvent excess was decreased.

FTIR reference peaks for Example 2 were C=C 1300, 1637; Ref 1260. The FTIR 815 peak was washed out by siloxane groups.

No precipitation was achieved for this Example. Solvents that were tried were water, ethyl acetate, HEX, methanol, 1-propanol, ethanol, and acetonitrile. Precipitating in acetonitrile gave a very low yield: MW=58,682; PDI=2.639; Rh= 5.31. A 60:40 ratio of

acetonitrile:hexane was able to produce a precipitate, but it was a hazy, white gel rather than a powder.

Additionally, the synthesis procedure differed from that above in that after 85% of the vinyl groups had converted and the clear nanogel mixture was removed from heat, the residual MEK solvent was removed under reduced pressure (Rotovap Settings: 40°C, 100RPM). It further differed that after the FTIR readings, residual solvent was removed by reduced pressure and the final product was a hazy white gel rather than a powder.

Similar formulations (i.e., 7:3 molar ratio of TRIS:UDMA, 20 mol% ME, 1 wt% AIBN, with no precipitations) were also prepared by with 8x MEK, and 4x MEK. Also, a 6:4 molar ratio of TRIS:UDMA, 20 mol% ME, 1 wt% AIBN, 4x MEK, with no precipitations, was prepared.

Nanogel Example 3 - 7:3 molar ratio E350:UDMA

Example 3 was prepared as described above using a 7:3 molar ratio of E350:UDMA, 20 mol% ME, 1 wt% AIBN, 4x toluene, with 1 precipitation.

4x toluene was used in Example 3 instead of 4x MEK because E350 washes out the 1260 peak and thus had to use 1720 peak for conversion determination.

FTIR reference peaks for Example 3 were C=C 1300; Ref 1720.

Only one precipitation was done because there was 100% IEM conversion.

Additionally, a trace of BHT inhibitor was added instead of doing a second precipitation.

When a second precipitation was tried, the overall yield decreases.

The resulting product was a clear, amber gel rather than a powder.

Nanogel Example 4 - 7:3 molar ratio E350:UDMA

Example 4 was prepared as described in Example 3 using a 7:3 molar ratio of E350:UDMA, 20 mol% ME, 1 wt% AIBN, 6x MEK, with 1 precipitation.

The nanogels of Examples 5 and 6 were synthesized in a 500 mL single-neck round bottom flask with a magnetic stirrer. The monomers T3TSMA and PEGDA were added to the flask, as was thermal initiator AIBN at 1 wt% (relative to total monomer content) and 20 mol% ME (relative to total monomer content) as a chain transfer agent to reduce the chances for macrogelation and provide sites for post-polymerization re-functionalization with methacrylate groups. A four-fold (4x) excess of toluene relative to the total weight of the monomers was added. Free radical polymerization was facilitated by continuously stirring the mixture at 90 °C for 4 hours.

The reaction was monitored by following the diminishing (meth)acrylate peak at 814 cm⁻¹ on the FTIR and once approximately 80 % double bond conversion was achieved, the

resulting nanogel reaction mixture was precipitated via the drop-wise addition to an eight-fold (8x) excess of hexane. The precipitate was filtered and the residual solvent removed under reduced pressure to isolate the nanogel, which was then further functionalized via a base-catalyzed Michael addition reaction in which mercaptosuccinic acid was added to the residual acrylate groups in the nanogel to provide pendant dicarboxylate end groups. For the carboxylation step, 1 g nanogel was dispersed in 30 mL methanol in a sealed 50 mL round bottom flask. The reaction was monitored periodically via mid-FT-IR spectra until the residual acrylate peak at 816 cm^{-1} indicated a conversion of 90%, thereby ensuring that a portion of the pendent acrylate reactive functionality was still maintained within the nanogel network. The reaction mixture was then dialyzed against deionized water for 48 hours by frequently changing the water. Following this, the dialysate was freeze-dried to obtain the reactive, carboxylic-acid functionalized, water dispersible siloxane nanogel.

Nanogel Example 5 - 7:3 molar ratio 3TSMA:PEGDA

Example 5 was prepared as described above using a 7:3 molar ratio of 3TSMA: PEGDA.

Nanogel Example 6 - 5:5 molar ratio 3TSMA:PEGDA

Example 6 was prepared as described above using a 5:5 molar ratio of 3TSMA:PEGDA.

To demonstrate the ability of the nanogel to form coatings on biomaterials, a PMMA substrate was photopolymerized along with a long chain urethane acrylate to mimic the properties of a flexible hydrophobic IOL ("lens substrate"). A two-part redox reaction was implemented to generate a crosslinked coating on the surface of the material, similar to the process shown in FIG. 5.

For Part 1 of the two-part redox reaction (see FIG. 5), a solution of $50\text{ }\mu\text{L}$ nanogel/(5mM) TEMED (1mg/mL) was prepared. For Part 2 of the redox reaction (see FIG. 5), a 1 cm^2 lens substrate, which was immersed in 5mM APS solution for 30 seconds, was generated. Subsequently, 1 mg/mL of the nanogel/TEMED solution was dropped on the lens substrate, placed within a spin-coater (available from Laurell Technologies, model WS-650Mz-23NPP) and a coating was generated (at 1000 rpm for 5 min) on the substrate. The lens substrate was removed, dried for 30 minutes at room temperature and washed copiously with distilled water to remove any unbounded nanogel, APS and/or TEMED from the surface. This process ensured that only the covalently tethered nanogels remained as a coating on the surface of the substrate.

The nanogel coated lens substrate was then immersed in dexamethasone solution (1mg/mL) overnight and subsequently washed thrice with deionized water to remove free

surface dexamethasone. The samples were then dried at 60 °C for 48 hours and stored at room temperature.

The total drug content on the lens substrate and *in vitro* release kinetics of the dexamethasone with and without nanogel was observed in the following manner. A dex-
5 loaded lens substrate (without nanogel coating) and a dex-loaded nanogel coated lens substrate were extracted by immersing the samples in 5 mL of ethanol at elevated temperature (45 °C) for two days and the total drug content was estimated by measuring the optical density (OD) at 239 nm using a UV–Visible Spectrophotometer. The extraction cycle was repeated three times to ensure that the entire adsorbed drug was extracted. The dex-
10 loaded substrate and nanogel coated substrate were then immersed in 10 mL of PBS (pH 7.4) and kept in an oven at 37 °C. The dexamethasone release at regular time intervals (1h, 2h, 4h, 24h, 48h, 72h, 120h, 168h) was recorded at 239 nm and compared with the concentrations of standard solutions of dexamethasone. A calibration plot was constructed between the OD and concentration of standard solutions of dexamethasone. The
15 dexamethasone released was quantified from the calibration plot. The results are illustrated in FIG. 7.

FIG. 7 shows the dexamethasone uptake and cumulative release of dexamethasone from the lens substrate (dashed line) and the dexamethasone with nanogel-coated lens substrate (solid line) over a period of one week (168 hours). The nanogel enabled 10x uptake
20 of dexamethasone within the lens and approximately 94 % of the dexamethasone was released within the period of 168 hours. The nanogel coated lens substrate cumulative release profiles were comparable to the lens substrate without the nanogel (82%).

The above specification, examples, and data provide a complete description of the structure, features and use of exemplary implementations of the invention. Since many
25 implementations of the invention can be made without departing from the spirit and scope of the invention, the invention resides in the claims hereinafter appended. Furthermore, structural features of the different implementations may be combined in yet another implementation without departing from the recited claims.

WHAT IS CLAIMED IS:

1. An ophthalmic device comprising a nanogel having a siloxane-containing polymeric backbone and at least one reactive pendant group being an acrylate or isocyanate, the polymeric backbone being hydrophilic, hydrophobic, amphiphilic, or electrically conductive.
2. The ophthalmic device of claim 1, wherein the nanogel is either anionic or cationic.
3. The ophthalmic device of claim 1, wherein the nanogel is a filler in the ophthalmic device.
4. The ophthalmic device of claim 1, wherein the nanogel is in a coating on the ophthalmic device.
5. The ophthalmic device of claim 4, wherein the nanogel is bonded to functional groups present within the ophthalmic device.
6. The ophthalmic device of claim 5, wherein the nanogel is covalently bonded to functional groups present within the ophthalmic device.
7. The ophthalmic device of claim 1, wherein the nanogel affects at least one of the refractive index, equilibrium water content, tackiness, flexibility, and durability of the ophthalmic device.
8. The ophthalmic device of claim 1, wherein the nanogel is a carrier for a therapeutic molecule.
9. The ophthalmic device of claim 1, wherein the device is a contact lens.
10. The ophthalmic device of claim 1, wherein the device is an intraocular lens.

11. A polymeric composition for forming a nanogel, the composition comprising a hydrophobic siloxane acrylate and a hydrophilic urethane-based acrylate.
12. The polymeric composition of claim 11, comprising at least 50 wt-% or at least 50 mol% siloxane acrylate(s).
13. The polymeric composition of claim 11, composition comprising about 70 mol% siloxane acrylate(s) and about 30 mol% urethane-based acrylate(s).
14. An ophthalmic device comprising a siloxane nanogel having at least one acrylate or isocyanate pendant group, the polymeric backbone being hydrophilic, hydrophobic, amphiphilic, or electrically conductive.
15. The ophthalmic device of claim 14, wherein the device is a contact lens.
16. The ophthalmic device of claim 14, wherein the device is an intraocular lens.
17. The ophthalmic device of claim 14, wherein the siloxane nanogel is present as a coating on the ophthalmic device.
18. The ophthalmic device of claim 15, the coating further comprising a therapeutic molecule.

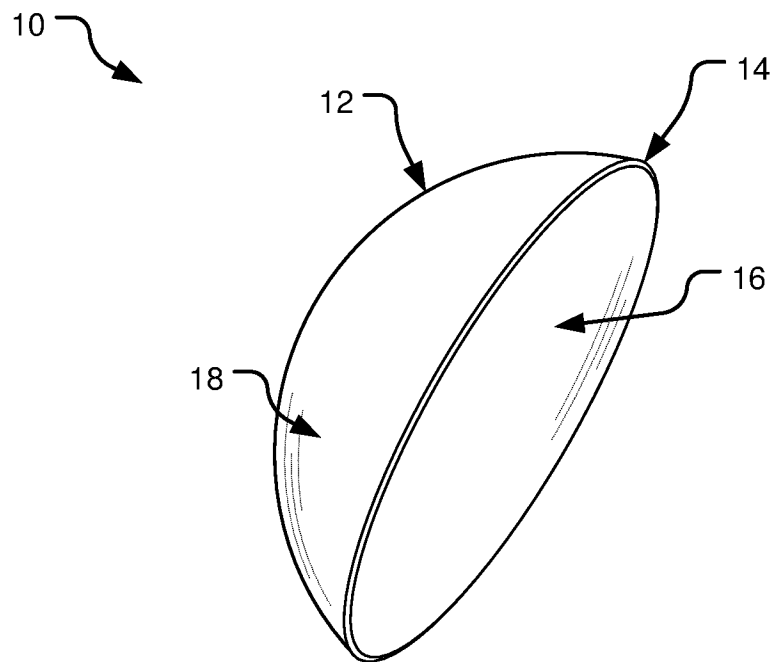


FIG. 1

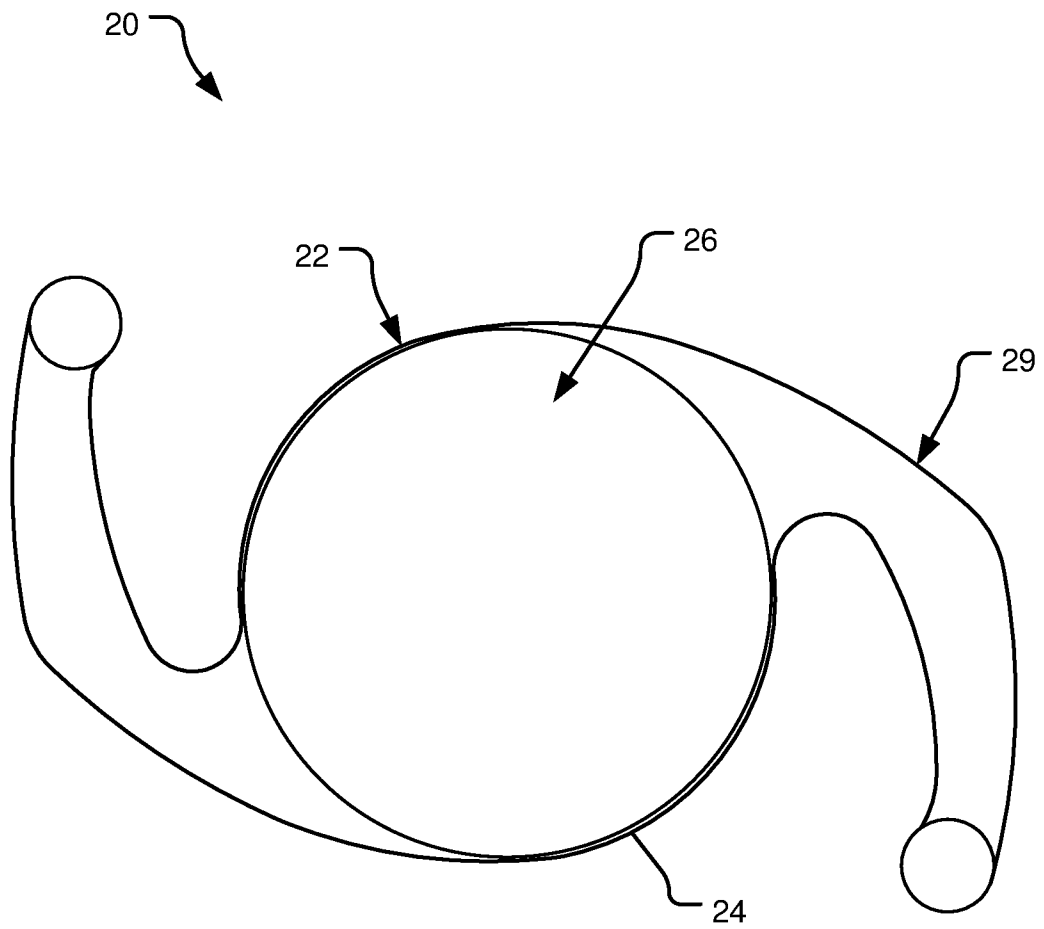


FIG. 2

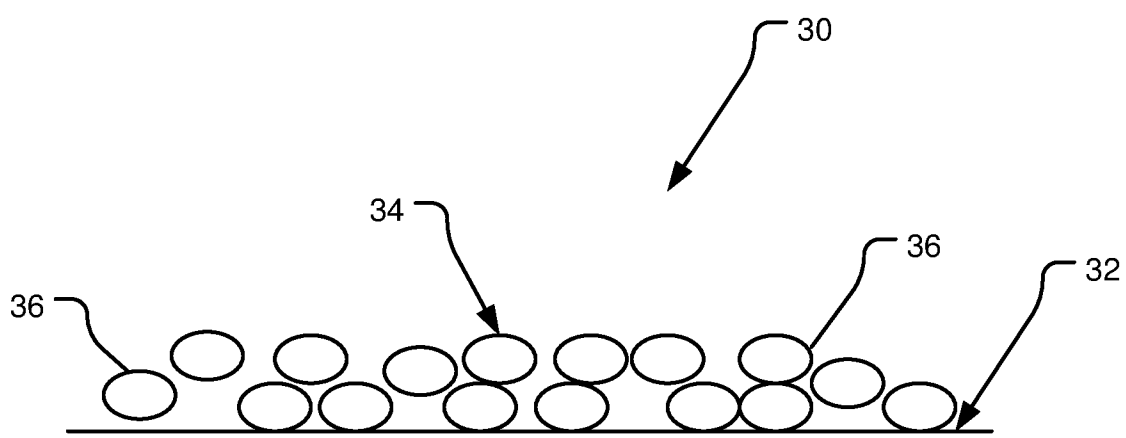


FIG. 3

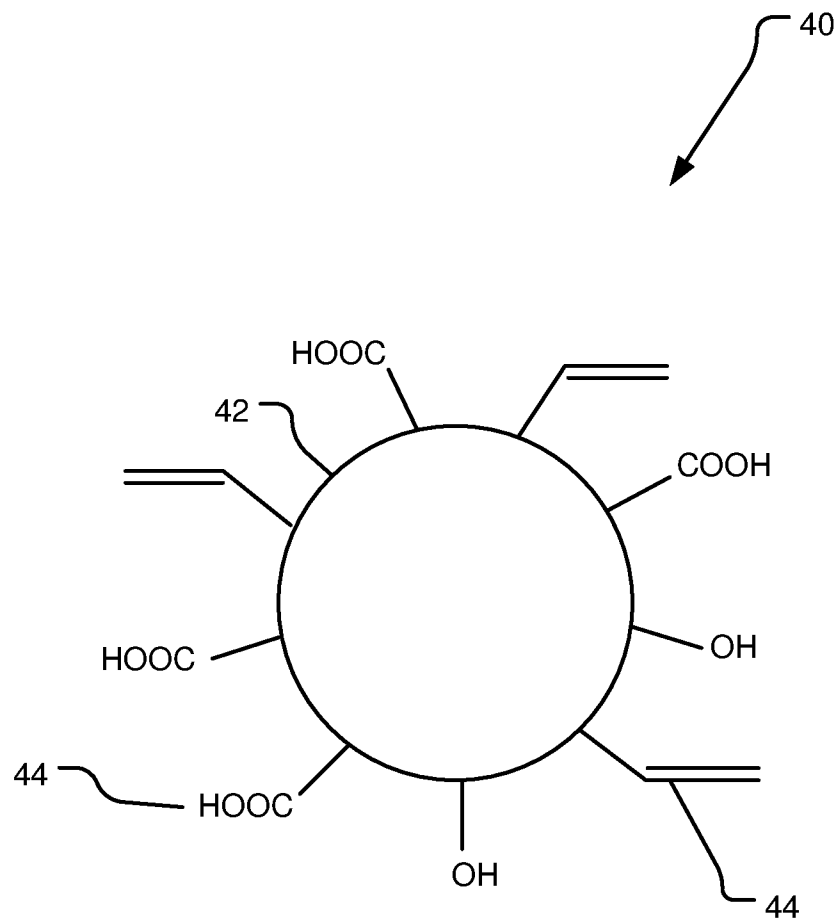


FIG. 4

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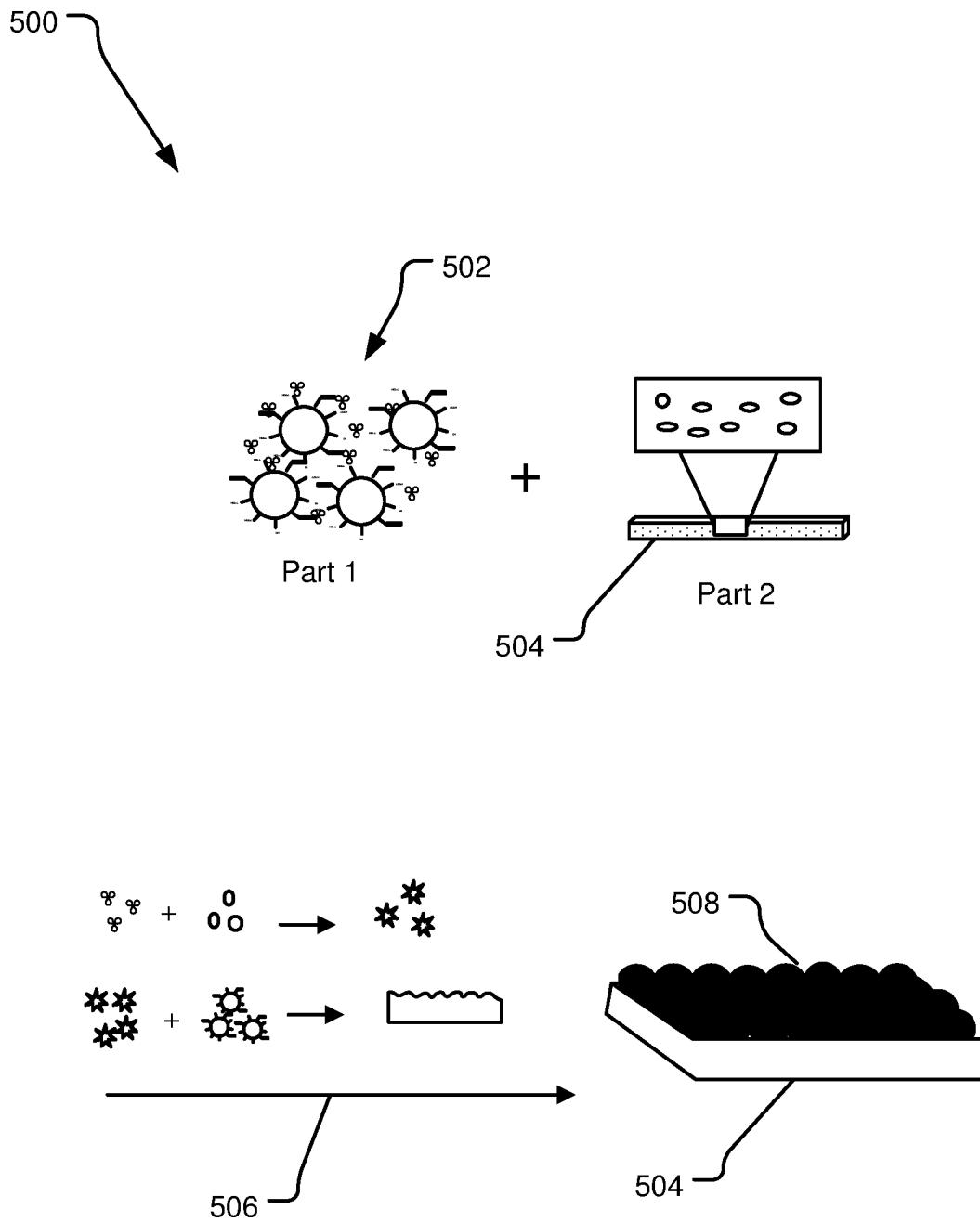


FIG. 5

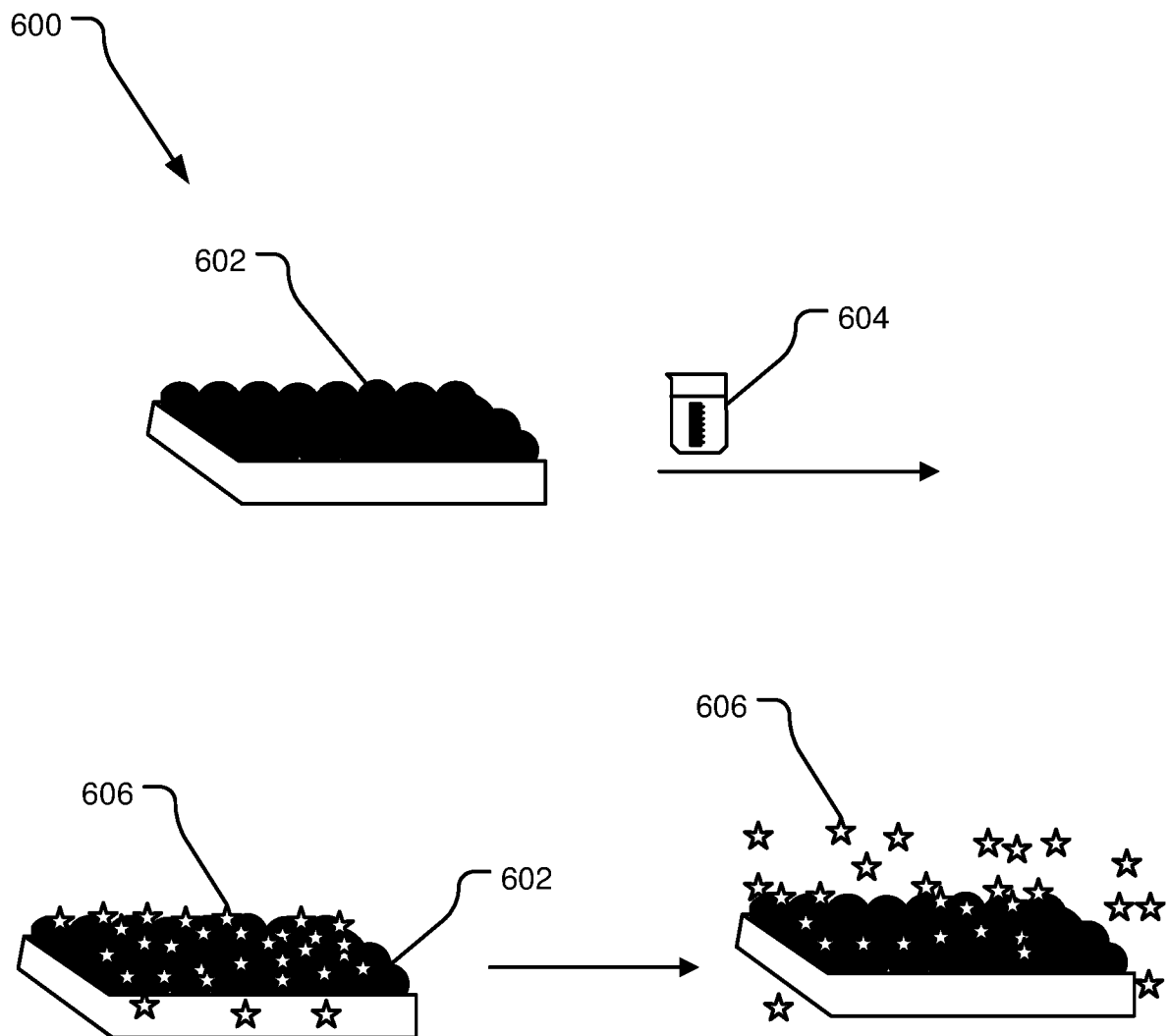


FIG. 6

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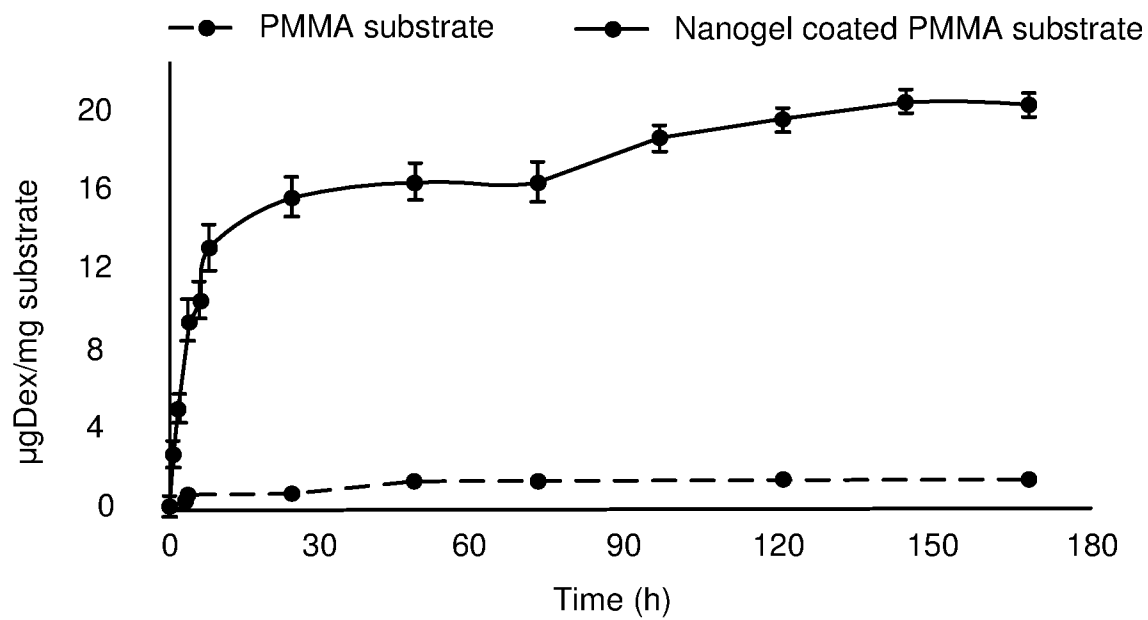
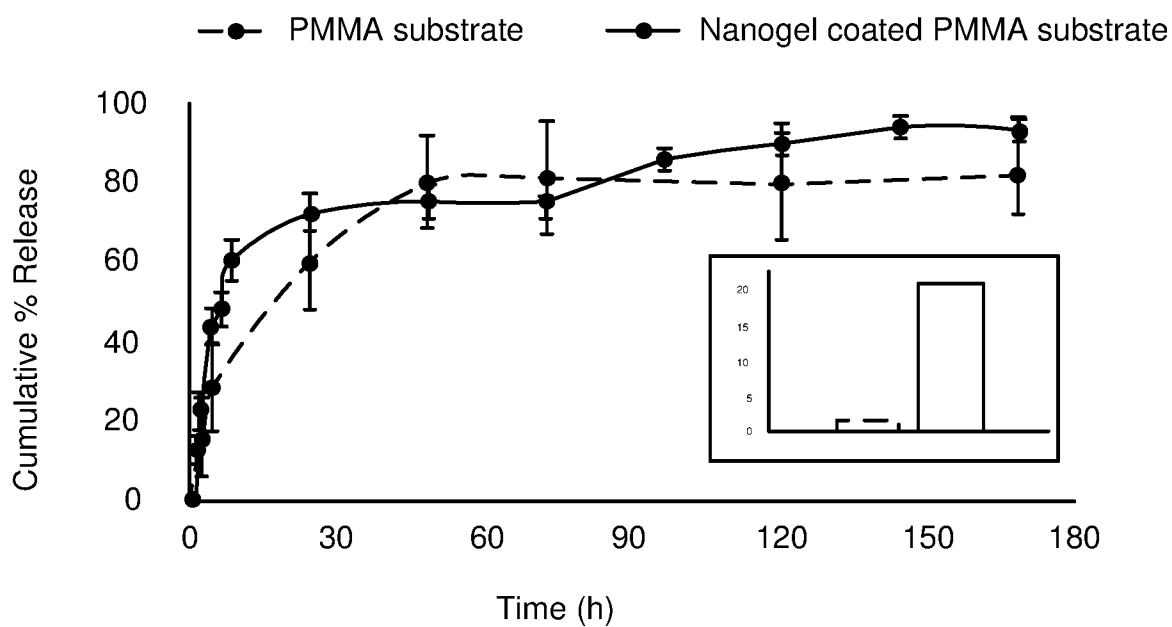


FIG. 7

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US16/25319

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C08G 18/61, 77/20; A61L 27/52; A61F 2/14; B82Y 30/00; C08F 230/08 (2016.01)

CPC - C08G 77/20; A61L 27/52; A61F 2/14; G02B 1/043; B82Y 30/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8) Classifications: C08G 18/61, 77/20; A61L 27/52; A61F 2/14; B82Y 30/00; C08F 230/08 (2016.01)

CPC Classifications: C08G 77/20; A61L 27/52; A61F 2/14; G02B 1/043; Y10S 977/773; B82Y 30/00

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

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

PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data); Google Scholar; Google; EBSCO
ophthalmic device, contact lens, intraocular lens, siloxane acrylate, urethane acrylate, hydrogel, nanogel

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---	WO 2013/176886 A2 (JOHNSON & JOHNSON VISION CARE, INC.) 28 November 2013; paragraphs [0001], [0005], [0025], [0037], [0040]-[0041] [0049], [0061], [00132], [00152], [00224], [00226], [00230]; claims 11, 24	1, 4-5, 7-10, 14-18 ----
Y		2-3, 6
X ---	US 2005/0018130 A1 (DAHI, A et al.) 27 January 2005; paragraph [0080]; claims 26, 29-30, 32	11 ---
Y		12-13
Y	US 2007/0269488 A1 (RAVI, N) 22 November 2007; claims 12-13	2
Y	US 5,628,794 A (LINDSTROM, RL) 13 May 1997; figure 4; column 5, lines 20-21	3
Y	WO 2014/177871 A1 (COOPERVISION INTERNATIONAL HOLDING COMPANY, LP) 6 November 2014; paragraphs [0008], [0010]	6
Y	US 5,710,302 A (KUNZLER, JF et al.) 20 January 1998; column 3, lines 24-25; column 6, lines 28-29; claim 11	12-13



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

18 May 2016 (18.05.2016)

Date of mailing of the international search report

23 JUN 2016

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