[0005] All references disclosed herein are hereby incorporated by reference in their entireties for all purposes.

OBJECTS AND SUMMARY

[0005a] In an aspect, there is provided the use of a sustained release drug-delivery system in the manufacture of a medicament for treatment of an ocular disease or condition in a patient, comprising a bio-orthogonal hydrogel and at least one active agent, the bio-orthogonal hydrogel comprising a covalently crosslinked polymer network and containing the at least one active agent, wherein the polymer network comprises

a) a plurality of polymer units,

b) chemical bonds that can be cleaved by hydrolysis, wherein at least one of the hydrolysable bonds is an ester bond, and

c) crosslinks formed by click chemistry reactions.

[0005b] In another aspect, there is provided the use of a sustained release drug-delivery system in the manufacture of a medicament for the treatment of an ocular disease or condition in a patient, the use comprising a bio-orthogonal hydrogel as defined above and an active agent, and further comprising a hydrogel that is the reaction product of at least two multi-arm precursors crosslinked via electrophile-nucleophile reactions, the hydrogel forming an interpenetrating network with the bio-orthogonal click chemistry crosslinked network as defined above.

[0005c] In another aspect, there is provided a sustained release drug-delivery as defined above, comprising a bio-orthogonal hydrogel and at least one active agent, the bio-orthogonal hydrogel comprising a covalently crosslinked polymer network and containing the at least one active agent, wherein the polymer network comprises

a) a plurality of polymer units,

b) chemical bonds that can be cleaved by hydrolysis, wherein at least one of the hydrolysable bonds is an ester bond, and

crosslinks formed by click chemistry reactions.

[0005d] In another aspect, there is provided a hydrogel for sustained drug-delivery, the hydrogel including an active agent,

the hydrogel comprising an interpenetrating covalently crosslinked dual polymer network and containing the at least one active agent, wherein the dual polymer network comprises

a) a plurality of polymer units,

b) chemical bonds that can be cleaved by hydrolysis, wherein at least one of the hydrolysable bonds is an ester bond, and

c) crosslinks formed by click chemistry reactions between first and second multi-arm precursors bearing functional groups reactive by click chemistry, and

d) crosslinks formed by electrophile-nucleophile reactions between third and fourth multi-arm precursors bearing functional groups reactive by electrophile-nucleophile reactions.

[0005e] In an aspect, there is provided a sustained release drug-delivery system for use as a medicament, or for use in treating a medical condition or disease in a patient, the system comprising a hydrogel as defined above.

[0005f] In an aspect, there is provided a a kit suitable for use for *in-situ* forming a sustained release drug-delivery system or hydrogel for sustained drug-delivery including an active agent as defined above, the kit comprising in separate containers:

a) a first container including a first precursor formulation including at least one first multi-arm precursor having first functional groups suitable for forming a connection by click chemistry with complementary second functional groups, and optionally at least one solvent;

b) a second container including a second precursor formulation including at least one second multi-arm precursor having second functional groups suitable for forming a connection by click chemistry with the first functional groups, and optionally at least one solvent; and

c) at least one active agent, included in a separate, third container and/or included in at least one, or both of the first and second containers, and optionally at least one solvent;

d) wherein at least one of the first multi-arm precursor and/or the at least one second multi-arm precursor is a polymer multi-arm precursor having polymer arms comprising polymer units, and wherein at least one of the first multi-arm precursors or the second multi-arm precursors includes a linker unit L comprising a hydrolysable ester bond.

[0006] It is an object of certain examples of the disclosure, and an example, to provide a pharmaceutically acceptable drug-delivery system such as an implant for sustained release of an active agent to the body of a patient.

[0007] It is a further object of certain examples of the disclosure, and an example, to provide a drug-delivery system such as an implant that is biodegradable, e.g., that is degraded *in-vivo*.

[0008] It is a further object of certain examples of the disclosure, and an example, to provide a biodegradable drug-delivery system such as an implant or insert, for sustained release of an active agent to a patient in need thereof.

[0009] It is a further object of certain examples of the disclosure, and an example, to provide a bio-orthogonal drug-delivery system for sustained release of an active agent for *in-situ* formation of an implant or insert at a treatment site within a living body.

[0010] In further objects and examples of certain examples of the disclosure, the active agent may be a small molecule active agent or a biomolecule active agent, e.g., a peptide, protein, virus and the like.

[0011] It is a further object of certain examples of the disclosure, and an example, to provide a method for manufacturing such drug-delivery systems.

[0012] It is a further object of certain examples of the disclosure, and an example, to provide methods for treating a disease/medical condition of a patient with a sustained release, bio-orthogonal drug-delivery system.

[0013] It is a further object of certain examples of the disclosure, and an example, to provide a kit comprising one or more sustained release biodegradable drug-delivery systems.

[0014] In certain examples, the present disclosure is directed to a sustained release drug-delivery system, comprising a bio-orthogonal hydrogel and at least one active agent, the bio-

orthogonal hydrogel comprising a biodegradable, covalently crosslinked polymer network and containing the at least one active agent, wherein the polymer network comprises a plurality of polymer units, chemical bonds that can be cleaved by hydrolysis, wherein at least one of the hydrolysable bonds is an ester bond, and crosslinks formed by click chemistry reactions.

[0015] In certain examples, the polymer network forming the hydrogel comprises at least one multi-arm unit having a core unit and three or more arms connected thereto, for example 3 to 10, or 4 to 8, or 4 to 6 arms, wherein a crosslink formed by click chemistry reaction is located on the arms, preferably at the polymer unit terminus of each arm. The polymer network can comprise first and second multi-arm units, wherein the crosslinks formed by click chemistry reactions are between the arms of the first multi-arm units and the second multi-arm units. The first multi-arm units and the second multi-arm units can have the same amount of arms or a different amount of arms, and the first multi-arm units and the second multi-arm units can have the same core unit or a different core unit. In other examples, the first multi-arm units and the second multi-arm units can have the same amount of arms or a different amount of arms, or the first multi-arm units and the second multi-arm units can have the same core unit or a different core unit.

[0016] In certain examples, at least one of the multi-arm units is a polymer multi-arm unit having polymer arms comprising the polymer units. The polymer units can be selected from at least one of polyethylene glycol (PEG), polyethylene oxide, polypropylene oxide, polypropylene glycol (PPG), polyvinyl alcohol (PVA), poly(vinylpyrrolidinone) (PVP), polylactic acid (PLA), polyglycolic acid (PGA), polylactic-co-glycolic acid (PLGA), p-dioxanone, trimethylene carbonate, caprolactone, random or block copolymers or combinations or mixtures of any of these, or one or more units of polyaminoacids, glycosaminoglycans, polysaccharides, or proteins. In certain examples, the polymer units in the hydrogel are polyethylene glycol units.

[0017] In certain examples, the hydrolysable ester bond can be part of a linker unit being located between the terminus of an arm of a multi-arm unit and the crosslinks formed by click chemistry reactions. The first multi-arm unit and/or the second multi-arm unit may include linker units comprising the hydrolysable ester bond, wherein the linker unit L can be the same or different in the first and second multi-arm unit. The linker unit L can be derived from or comprise a diacid, or an acid and amide group such as succinic, glutaric, adipic, azelaic diacids or acid-amides, or glutaramide.

[0018] In certain examples, in the hydrogel of the sustained release drug-delivery system, crosslinks are formed by a click chemistry reaction such as a copper-free SPAAC or IEDDA reaction, involving reacting a first functional group of a first multi-arm precursor or unit with a complementary, second functional group of a second multi-arm precursor or unit, wherein the second, complementary functional group is capable of reacting with the first functional group in a click chemistry reaction, the first and second functional groups being selected from the pairs comprising an alkyne moiety such as a dibenzocyclooctyne (DBCO) or a bicyclo[6.1.0]-nonyne (BCN), and an azide; or a norbornene or trans-cyclooctene (TCO); and a tetrazine (Tz) moiety, or functionalized derivatives thereof. In certain examples, the crosslinks in the hydrogel formed by click chemistry reactions comprise a chemical group selected from triazole and dihydropyridazine.

[0019] In certain examples of the sustained release drug-delivery system of the present disclosure, the active agent is selected from the group consisting of therapeutically or diagnostically active agents. The active agent is dispersed in the hydrogel and can be selected from steroids; non-steroidal anti-inflammatory drugs (NSAIDS) such as Diclofenac, Ibuprofen, Meclofenamate, Mefanamic A, Salsalate, Sulindac, Tolmetin, Ketoprofen, Diflunisal, Piroxicam, Naproxen, Etodolac, Flurbiprofen, Fenoprofen C, Indomethacin, Celecoxib, Ketorolac, Nepafenac; intraocular pressure lowering drugs; antibiotics such as Ciprofloxacin; pain reliever such as Bupivacaine; calcium channel blockers such as Nifedipine; cell cycle inhibitors such as Simvastatin; proteins such as insulin; small molecule hydrophilic drugs, including carboxylic acid salts and amine salts; small molecule hydrophobic drugs, hydrophilic peptides and protein drugs, such as insulin, single chain antibody fragments, Fab fragments, IgG antibodies, fusion antibodies, etc.; aptamers; particularly Bupivacaine (BPV-HCl or base), Ropivacaine (RPV), Dexamethasone, Travoprost, Axitinib, non-steroidal anti-inflammatory drugs (NSAIDS), steroids, antibiotics, pain relievers, calcium-channel blockers, cell cycle inhibitors, chemotherapeutics, anti-viral drugs, anesthetics, hormones, anticancer drugs, antineoplastic agents, viruses, viruses for gene delivery such as AAV, protein binders such as nanobodies, affibodies, ankyrins, DARPins, etc., or any combinations thereof. In one example, the active agent is a small molecule active agent or a biomolecule active agent, preferably a small molecule active agent, a peptide, a protein or a virus; particularly preferred a small molecule active agent, a peptide, or a protein. In a preferred example, the active agent is Bevacizumab. The active

agent may not be a cell or a stem cell. In one example, the active agent may not be a biological sample, i.e. a tissue, a cell sample, a virus or a virion..

[0020] In certain examples, the sustained release drug-delivery system includes an active agent that is a peptide selected from the group consisting of Bevacizumab, Compstatin, APL-1, and Fc-III-4C, Beovu 15 (Brolucizumab), Zimura (Avacincaptad Pegol), Pegcetacoplan, Abicipar Pegol, Lampalizumab, Fovista, Risuteganib, AXT107, Elamipretide, THR149, ALM201, VGB3, and Largazole. In a particular preferred example, the sustained release drug-delivery system includes the active agent Bevacizumab. In some of these examples, the peptide active agent is included in one or more of precursor compositions that form a bio-orthogonal hydrogel *in-situ* at a treatment site.

[0021] In certain examples, the present disclosure is further directed to a method of manufacturing the sustained release drug delivery system comprising a bio-orthogonal hydrogel and at least one active agent, wherein the method comprises the steps of preparing a first mixture containing a first multi-arm precursor having first functional groups suitable for forming a connection by click chemistry with second functional groups, and at least one active agent, providing a second mixture containing a second multi-arm precursor having second functional groups suitable for forming a connection by click chemistry with the first functional groups, combining the first and second mixtures, and allowing the combined reaction mixture to gel by forming click chemistry connections between the first and second functional groups, thereby forming a hydrogel containing the at least one active agent; wherein at least one of the first multi-arm precursor or the second multi-arm precursor is a polymer multi-arm precursor having polymer arms comprising polymer units, and wherein at least one of the first multi-arm precursor or the second multi-arm precursor includes a linker unit L comprising a hydrolysable ester bond.

[0022] In certain examples of the method, at least one third multi-arm precursor having first or second functional groups suitable for forming click chemistry connections with either the first multi-arm precursor or the second multi-arm precursor can be added to one of the first or the second mixture. In some examples of the method, the first and/or second mixture comprises at least one solvent. The at least one solvent can be selected from water, aqueous buffered media such as PBS buffer or saline solutions; or organic solvents or any mixtures thereof. In certain examples, the method further comprises a step of removing the solvent or solvent mixture, for example by drying the formed gel.

[0023] In examples of the method, the multi-arm precursors can have a core unit and at least 3 arms, such as 3 to 10, or 4 to 8, or 4 to 6 arm, connected to the core unit, wherein the functional groups suitable for forming a connection by click chemistry are located at the terminus of the arms. The first multi-arm precursor and the second multi-arm precursor can have the same or a different amount of arms and/or have the same or a different core unit. In examples thereof, the polymer units are selected from at least one of polyethylene glycol (PEG), polyethylene oxide, polypropylene oxide, polypropylene glycol (PPG), polyvinyl alcohol (PVA), poly(vinylpyrrolidinone) (PVP), polylactic acid (PLA), polyglycolic acid (PGA), polylactic-co-glycolic acid (PLGA), p-dioxanone, trimethylene carbonate, caprolactone, random or block copolymers or combinations or mixtures of any of these, or one or more units of polyaminoacids, glycosaminoglycans, polysaccharides, or proteins. In certain examples, the polymer units are selected from at least one of polyethylene glycol (PEG) units, polypropylene glycol (PPG) units, polyglycolic acid (PGA), polylactic acid (PLA), or polylactic-co-glycolic acid (PLGA), random or block copolymers and/or combinations or mixtures of any of these, preferably polyethylene glycol units. In further examples, the covalently crosslinked polymer network comprises a plurality of hydrophobic polymer units and/or hydrophilic polymer units, wherein the hydrophobic polymer units are selected from at least one of polylactic acid (PLA), and polylactic-co-glycolic acid (PLGA) units; and/or wherein the hydrophilic polymer units are selected from at least one of polyethylene glycol units, polypropylene glycol units, or polyglycolic acid (PGA), preferably polyethylene glycol units.

[0024] In certain examples, the hydrolysable ester bond is part of a linker unit being located between the polymer unit terminus of an arm of a multi-arm precursor and the functional group suitable for forming a connection by click chemistry. The first multi-arm precursor or the second multi-arm precursor, or both, may include linker units L comprising the hydrolysable ester bond, wherein the linker units L can be the same or different in the first and second multi-arm precursor. The linker unit L can be derived from or can comprise a diacid, or an acid and amide group such as succinic, glutaric, adipic, azelaic diacids or acid-amides, or glutaramide.

[0025] In certain examples of the method, the first and second functional groups suitable for forming a connection by click chemistry comprise moieties selected from the group consisting of alkyne such as a dibenzocyclooctyne (DBCO), or a bicyclo[6.1.0]-nonyne (BCN), cycloalkyne, strained or terminal alkene such as norbornene, or a trans-cyclooctene (TCO), azide or tetrazine

(Tz), or functionalized derivatives thereof. The first and second functional groups suitable for forming a connection by click chemistry may comprise moieties selected from dibenzocyclooctyne and azide.

[0026] According to a further example, the disclosure is directed to the sustained release drug-delivery system described herein for use as a medicament, or to a method of treatment comprising treating a disease or medical condition in a patient with a sustained release drug-delivery system as described herein. The treatment may be an ocular treatment, for example the treatment of an ocular disease such as back-of-the-eye diseases such as any ocular disease of the posterior segment that affects the vasculature and integrity of the retina, macula or choroid leading to visual acuity disturbances, loss of sight or blindness, particularly disease states of the posterior segment resulting from age, trauma, surgical interventions, such as age-related macular degeneration (AMD) cystoid macular edema (CME), diabetic macular edema (DME), posterior uveitis, and diabetic retinopathy, or other medical conditions described herein further below.

[0027] In certain examples of the treatment method, the drug delivery system or hydrogel can be formulated for direct injection at a treatment site of a patient, for example by parenteral administration, intratumoral injection, injection into the eye such as intravitreal, intracameral, subconjunctival, retrobulbar, sub-tenon, subretinal, or suprachoroidal injections. The hydrogel can be formulated for and administered by direct injection, by oral application, incorporated in gels, or incorporated in implants. In certain examples, the drug delivery system comprises two or more different active agents, for example for use in a combination therapy involving the administration of more than one active agent.

[0028] In certain examples, the method of treatment involves an *in-situ* formation of the hydrogel of the drug-delivery system at a treatment site of a patient. The hydrogel can be formed *in-situ* at a treatment site of a patient by combining a first formulation comprising the first mixture of the manufacturing method described above and a second formulation comprising a second mixture and allowing the combined formulation mixture to gel *in-situ* at the treatment site. The first formulation and the second formulation can be combined shortly before administering the formulation mixture at the treatment site.

[0029] In certain examples involving an *in-situ* formation of the hydrogel of the drug-delivery system at a treatment site of a patient, the hydrogel can be formed *in-situ* by

administering a suspension comprising a first mixture of the manufacturing method described above, a second mixture of the manufacturing method described above, and a hydrophobic organic liquid at the treatment site of the patient and allowing the combined formulation to gel *in-situ* at the treatment site. The hydrophobic organic liquid can be included in at least one of the first or second mixture and may be a biocompatible oil. In certain examples thereof, the active agent is dissolved or dispersed in the hydrophobic organic liquid, or the active agent is the hydrophobic organic liquid or forms at least a part thereof.

[0030] In certain examples, the drug delivery system may be provided as a kit for forming a hydrogel including an active agent, the kit comprising a first precursor mixture and a second precursor mixture in separate containers for mixing and gel formation when needed. In an example thereof, the first formulation can be provided in a first syringe, and the second formulation in a second syringe, and the two formulations can be combined in a Y-type mixer before direct injection at the treatment site.

[0031] In an alternative example of the treatment method, the first formulation and the second formulation are each administered at the treatment site, thereby combining the formulations at the treatment site, and allowing the combined formulations to gel *in-situ* at the treatment site. The first formulation can be in a first syringe, the second formulation in a second syringe, and the two formulations are injected simultaneously or successively at the treatment site.

[0032] Further examples of the disclosure are described herein below.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: HPLC analysis showing 1:1 (black) and 1:2 (blue) reaction of 4armPEG SAP with DBCO-Amine

Figure 2: The use of magnetic beads to remove the excess of DBCO-Amine in the system.

Figure 3: Graphical summary of the effect of the number of arms on gel time and swelling.

Figure 4: Sustained release profiles of gold nanoparticles from DBCO/Azide gels

CLAIMS

1. Use of a sustained release drug-delivery system in the manufacture of a medicament for treatment of an ocular disease or condition in a patient, comprising a bio-orthogonal hydrogel and at least one active agent, the bio-orthogonal hydrogel comprising a covalently crosslinked polymer network and containing the at least one active agent, wherein the polymer network comprises

a) a plurality of polymer units,

b) chemical bonds that can be cleaved by hydrolysis, wherein at least one of the hydrolysable bonds is an ester bond, and

c) crosslinks formed by click chemistry reactions.

2. The use of claim 1, wherein the drug-delivery system is for the treatment of an ocular disease such as back-of-the-eye diseases such as any ocular disease of the posterior segment that affects the vasculature and integrity of the retina, macula or choroid leading to visual acuity disturbances, loss of sight or blindness, particularly disease states of the posterior segment resulting from age, trauma, surgical interventions, such as age-related macular degeneration (AMD) cystoid macular edema (CME), diabetic macular edema (DME), posterior uveitis, and diabetic retinopathy.

3. The use of claim 1 or 2, wherein the drug-delivery system is for the treatment of an ocular disease selected from the group consisting of retinal neovascularisation, choroidal neovascularisation, Wet AMD, Dry AMD, retinal vein occlusion, diabetic macular edema, retinal degeneration, hyphema, presbyopia, corneal graft rejection, retinoblastoma, melanoma, myosis, mydriasis, glaucoma, conjunctivitis, intraocular infections, choroidal neovascularization (CNV), intraocular tumors, retinal neuroinflammation, inflammation, autoimmune uveitis, uveitis, proliferative vitreoretinopathy, and corneal degeneration, acute and chronic macular neuroretinopathy, central serous chorioretinopathy, macular edema, acute multifocal placoid pigment epitheliopathy, Behcet's disease, birdshot retinochoroidopathy, posterior uveitis, posterior scleritis, serpiginous choroiditis, subretinal fibrosis, uveitis syndrome, Vogt-Koyanagi Harada syndrome, retinal arterial occlusive disease, central retinal vein occlusion, disseminated intravascular coagulopathy, branch retinal vein occlusion, hypertensive fundus changes, ocular ischemic syndrome, retinal arterial microaneurysms, Coat's disease, parafoveal telangiectasis, hemi-retinal vein occlusion, papillophlebitis, carotid artery disease (CAD), frosted branch

angiitis, sickle cell retinopathy, angioid streaks, familial exudative vitreoretinopathy, Eales disease, proliferative vitreal retinopathy, diabetic retinopathy, retinal disease associated with tumors, congenital hypertrophy of the retinal pigment epithelium (RPE), posterior uveal melanoma, choroidal hemangioma, choroidal osteoma, choroidal metastasis, combined hamartoma of the retina and retinal pigmented epithelium, retinoblastoma, vasoproliferative tumors of the ocular fundus, retinal astrocytoma, intraocular lymphoid tumors, myopic retinal degeneration, acute retinal pigment epithelitis, glaucoma, endophthalmitis, cytomegalovirus retinitis, retinal cancers, retinitis pigmentosa, Leber's Congenital Amaurosis, Choroideremia, X-linked 106 retinitis pigmentosa, best vitelliform macular dystrophy, x-linked retinoschisis, achromatopsia CNGA3, achromotopsia CNGB3, LHON, Stargardt disease, Usher syndrome, Norrie disease, Bardet-Biedl syndrome, and red-green color blindness.

4. The use of any one of claims 1 to 3, wherein the drug delivery system is formulated for direct injection at a treatment site of a patient, preferably the drug delivery system is formulated for parenteral administration, intratumoral injection, injection into the eye such as intravitreal, intracameral, subconjunctival, retrobulbar, sub-tenon, subretinal, or suprachoroidal injections.

5. The use of any one of claims 1 to 4, wherein the drug delivery system is to be administered by direct injection, by oral application, or is incorporated in implants.

6. The use of any one of claims 1 to 5, wherein the drug-delivery system is to be administered to a body space of a patient by any one of subcutaneously, intramuscularly, intrathecally, epidurally, intraperitoneally, intradermally, subcutaneously, intercostally, intra-articularly, intrasynovially, intraspinally, orally, nasally, rectally, intratumoral, or intravaginal administration.

7. The use of claim 6, wherein intra-articular administration is to a joint selected from knee, elbow, hip, sternoclavicular, temporomandibular, carpal, tarsal, wrist, ankle, intervertebral disk, or ligamentum flavum.

8. The use of any one of claims 1 to 7, wherein the hydrogel of the drug-delivery system is formed *in-situ* at a treatment site of a patient.

9. The use of any one of claims 1 to 8, wherein the polymer network comprises or is composed of multi-arm units each having a core unit X and ≥ 3 arms, preferably in the range of 3 to 10, or 4 to 8, or 4 to 6 arms, attached to the core unit, wherein a crosslink formed by click chemistry reaction is located at the terminus of each arm linking it with another arm attached to another core of a multi-arm unit.

10. The use of any one of claims 1 to 9, wherein the polymer network comprises first, second, and optionally more multi-arm units, wherein the crosslinks formed by click chemistry reactions are between the arms of the first multi-arm units and the second or more multi-arm units, wherein multi-arm units have the same or a different amount of arms and/or have the same or a different core unit X.

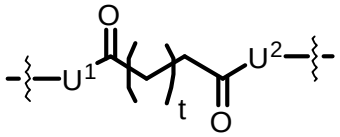
11. The use of claims 9 to 10, wherein at least one of the multi-arm units is a polymer multi-arm unit having polymer arms comprising polymer units, wherein the polymer multi-arm units have an average molecular weight of 1,000 to 100,000 Daltons.

12. The use according to any of the preceding claims, wherein the polymer units are selected from at least one of polyethylene glycol (PEG) units, polypropylene glycol (PPG) units, polyglycolic acid (PGA), polylactic acid (PLA), or polylactic-co-glycolic acid (PLGA), random or block copolymers and/or combinations or mixtures of any of these, preferably polyethylene glycol units.

13. The use of any one of the preceding claims, wherein each of the polymer units have an average molecular weight (Mn) in the range from about 1,000 to about 100,000 Daltons, or from about 2,000 to about 50,000 Daltons, or from about 3,000 to about 30,000 Daltons, wherein the average molecular weight (Mn) of the arms of the first multi-arm unit and the arms of the second multi-arm unit are the same or different.

14. The use of any one of claims 9 to 13, wherein the hydrolysable ester bond is part of a linker unit L being located between the polymer unit terminus of an arm of a multi-arm unit and the crosslinks formed by click chemistry reactions.

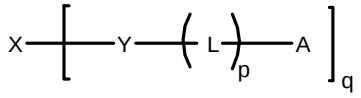
15. The use of claim 14, wherein the linker unit L comprises a structure represented by Formula (i):



(i)

wherein U^1 and U^2 are independently NH or O and can be the same or different, wherein at least one, preferably both, of U^1 and U^2 is O, and wherein t is an integer from 0 to 10, such as a diacid, such as succinic, glutaric, adipic, or azelaic diacids.

16. The use of any one of claims 1 to 15, wherein the polymer network comprises multi-arm units represented by formula (ii):



(ii)

wherein X is the core unit of a multi-arm unit, Y is a polymeric unit, L is a linker unit comprising the hydrolysable ester bond, A is a crosslink formed by a click chemistry reaction, p is either 0 or 1, and q is an integer from 3 to 10.

17. The use of any one of the preceding claims, wherein the crosslinks are formed by a click chemistry reaction such as a copper-free SPAAC or IEDDA reaction, wherein a first functional group of a first multi-arm precursor or unit is reacted with at least one complementary, second functional group of a second multi-arm precursor or unit, wherein the second, complementary functional group is capable of reacting with the first functional group in a click chemistry reaction, the first and second functional groups being selected from the pairs comprising an alkyne moiety such as a dibenzocyclooctyne (DBCO) or a bicyclo[6.1.0]nonyne (BCN), and an azide; or a norbornene or trans-cyclooctene (TCO); and a tetrazine (Tz) moiety.

18. The use of any one of the preceding claims, wherein the active agent is selected from the group consisting of therapeutically or diagnostically active agents.

19. The use of any one of the preceding claims, wherein the active agent is a small molecule active agent or a biomolecule active agent, preferably a small molecule active agent, a peptide, a protein, an aptamer, or a virus.

20. The use of any one of the preceding claims, wherein the active agent is selected from steroids; non-steroidal anti-inflammatory drugs (NSAIDS) such as Diclofenac, Ibuprofen, Meclofenamate, Mefanamic A, Salsalate, Sulindac, Tolmetin, Ketoprofen, Diflunisal, Piroxicam, Naproxen, Etodolac, Flurbiprofen, Fenoprofen C, Indomethacin, Celecoxib, Ketorolac, Nepafenac; intraocular pressure lowering drugs; antibiotics such as Ciprofloxacin; pain reliever such as Bupivacaine; calcium channel blockers such as Nifedipine; cell cycle inhibitors such as Simvastatin; proteins such as insulin; small molecule hydrophilic drugs, including carboxylic acid salts and amine salts; small molecule hydrophobic drugs, hydrophilic peptides and protein drugs, such as insulin, single chain antibody fragments, Fab fragments, IgG antibodies, fusion antibodies, etc.; aptamers; particularly Bupivacaine (BPV-HCl or base), Ropivacaine (RPV), Dexamethasone, Travoprost, Axitinib, non-steroidal anti-inflammatory drugs (NSAIDS), steroids, antibiotics, pain relievers, calcium-channel blockers, cell cycle inhibitors, chemotherapeutics, anti-viral drugs, anesthetics, hormones, anticancer drugs, antineoplastic agents, viruses, viruses for gene delivery such as AAV, protein binders such as nanobodies, affibodies, ankyrins, DARPins, etc., or any combinations thereof.

21. The use of any one of the preceding claims, wherein the active agent is a peptide selected from the group consisting of Compstatin, APL-1, and Fc-III-4C, Beovu 15 (Brolucizumab), Bevacizumab (Avastin), Zimura (Avacincaptad Pegol), Pegcetacoplan, Abicipar Pegol, Lampalizumab, Fovista, Risuteganib, AXT107, Elamipretide, THR149, ALM201, VGB3, and Largazole, or an aptamer.

22. The use of any one of the preceding claims, wherein the active agent is contained in the hydrogel without being covalently conjugated to the hydrogel, or wherein the active agent is contained in the hydrogel and covalently conjugated to the hydrogel.

23. The use of any one of the preceding claims, wherein the polymer network of the bio-orthogonal hydrogel is the reaction product of a first multi-arm precursor having functional groups comprising an azide (N_3) moiety and a second multi-arm precursor having functional groups comprising a dibenzocyclooctyne (DBCO) moiety .

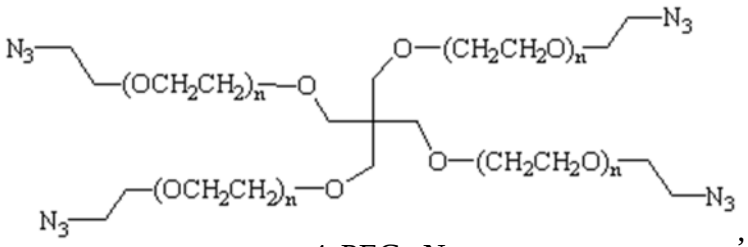
24. The use of any one of the preceding claims, wherein the polymer network of the bio-orthogonal hydrogel is the reaction product of a first multi-arm precursor having functional groups comprising an azide (N_3) moiety and a second multi-arm precursor having functional groups comprising a dibenzocyclooctyne (DBCO), and the active agent is a small molecule active agent, a peptide, a protein, an aptamer, or a virus.

25. The use of any one of the preceding claims, wherein polymer network of the bio-orthogonal hydrogel is the reaction product of a first precursor formulation comprising a mixture of two or more first precursors that have each different first functional groups suitable for forming a connection by click chemistry with complementary second functional groups, but not reacting with each other; or wherein the polymer network of the bio-orthogonal hydrogel is the reaction product of a second precursor formulation comprising a mixture of two or more second precursors that have each different second functional groups suitable for forming a connection by click chemistry with complementary first functional groups, but not reacting with each other; and wherein the different first or second functional groups are selected to have different kinetic rate constants or reaction rates in their click reactions with the corresponding second or first functional group counterparts.

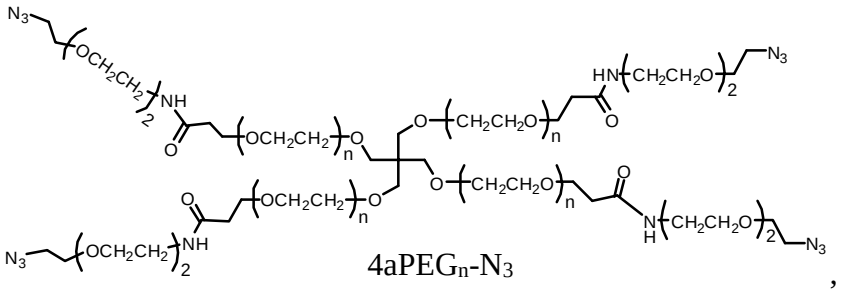
26. The use of any one of claims 24 or 25, wherein the first and second functional groups are selected from pairs comprising a strained alkyne moiety such as a dibenzocyclooctyne (DBCO) or a bicyclo[6.1.0]nonyne (BCN), and an azide; or a norbornene or trans-cyclooctene (TCO), and a tetrazine (Tz) moiety; or a strained alkyne moiety such as a dibenzocyclooctyne

(DBCO) or a bicyclo[6.1.0]nonyne (BCN), and a tetrazine (Tz) moiety; or any combinations thereof.

27. The use of any one of claims 24 to 26, wherein the first multi-arm precursor having functional groups comprising an azide (N_3) moiety is selected from the group consisting of:,

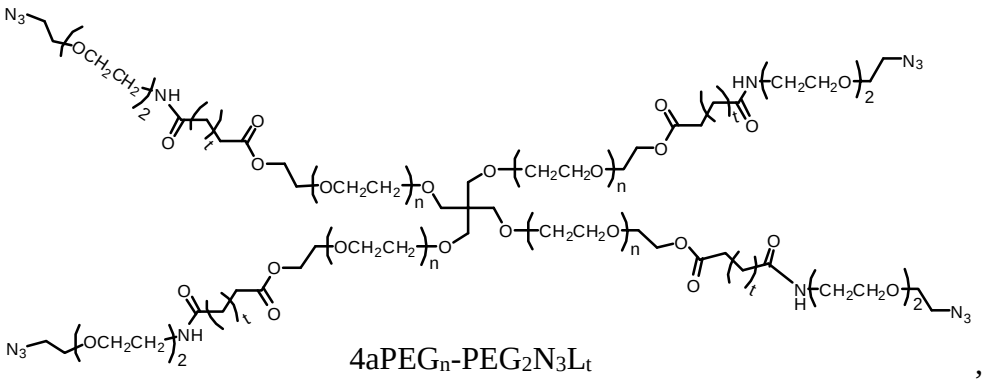


4aPEG$_n$-N$_3$,



4aPEG$_n$-N$_3$,

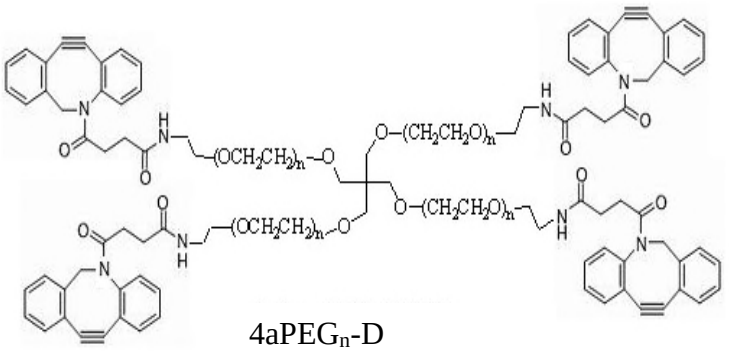
and



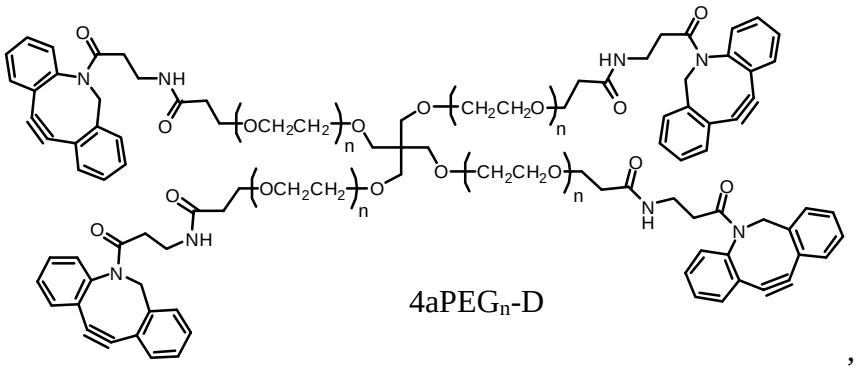
4aPEG$_n$-PEG$_2$N$_3$L$_t$,

wherein n is 1 to 2300, and t is an integer from 0 to 10, or the corresponding 8 arm versions thereof.

28. The use of any one of claims 24 to 27, wherein the second multi-arm precursor having functional groups comprising a dibenzocyclooctyne (DBCO) moiety is selected from the group consisting of:

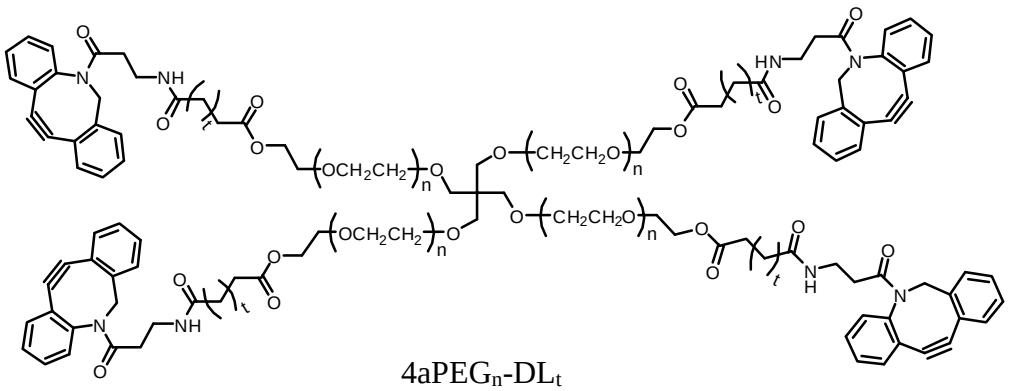


4aPEG$_n$-D ,



4aPEG$_n$-D ,

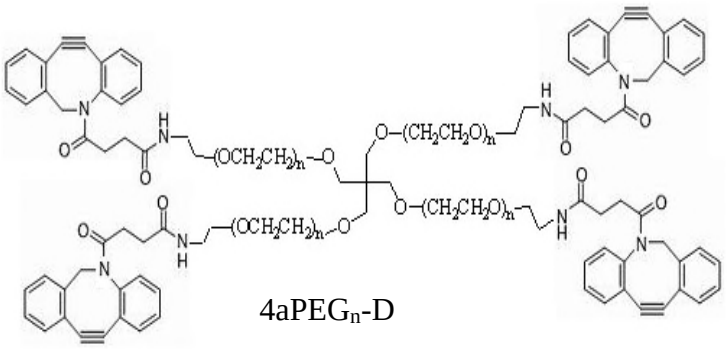
and



4aPEG$_n$-DL$_t$,

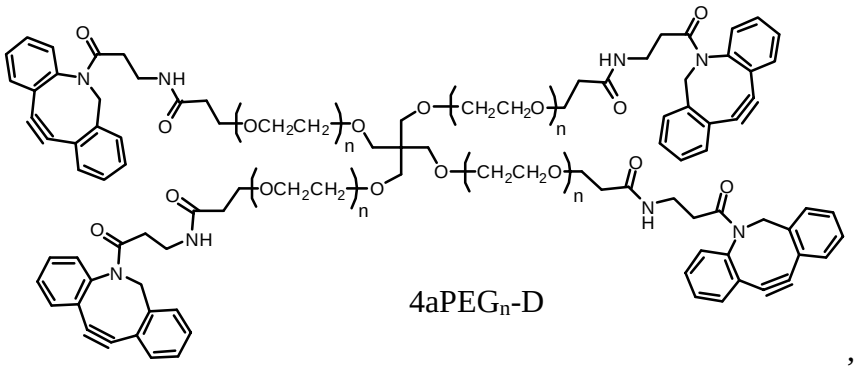
wherein n is 1 to 2300, and t is an integer from 0 to 10, or the corresponding 8 arm versions thereof.

29. The use of any one of the previous claims, wherein the polymer network of the bio-orthogonal hydrogel is the reaction product of reacting at least one, preferably one, of the following first multi-arm precursors having functional groups comprising an azide (N_3) moiety with at least one, preferably with one of the following second multi-arm precursor having functional groups comprising a dibenzocyclooctyne (DBCO) moiety:



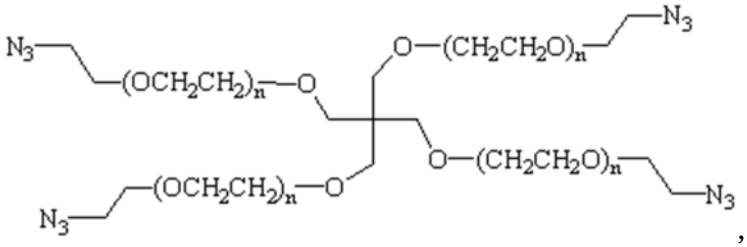
4aPEG$_n$-D

,



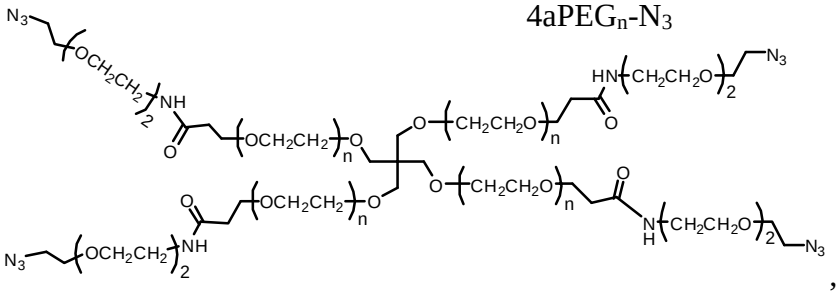
4aPEG$_n$-D

,



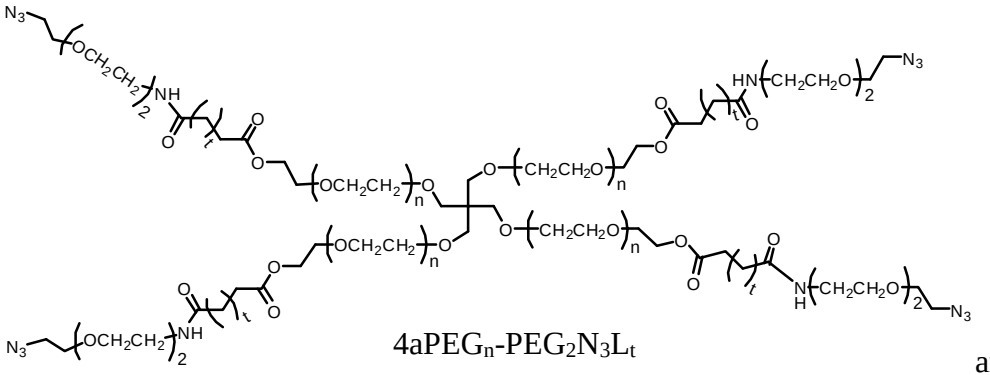
4aPEG$_n$-N$_3$

,



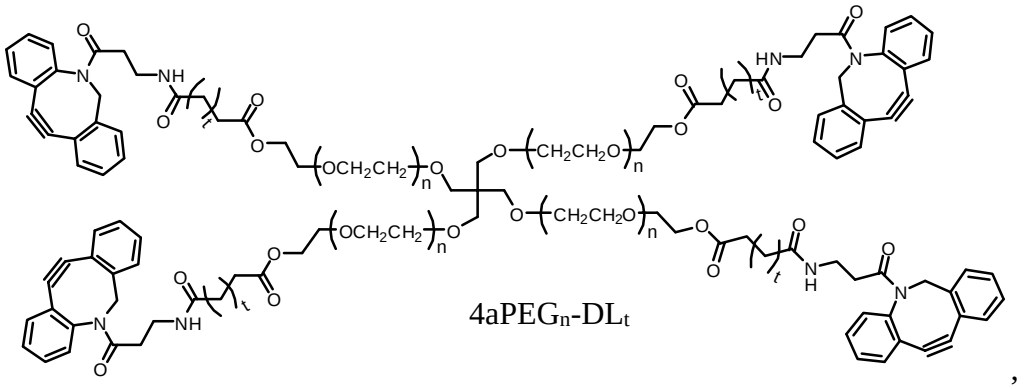
4aPEG$_n$-PEG$_2$N$_3$

,



4aPEG$_n$-PEG$_2$N$_3$L$_t$

and

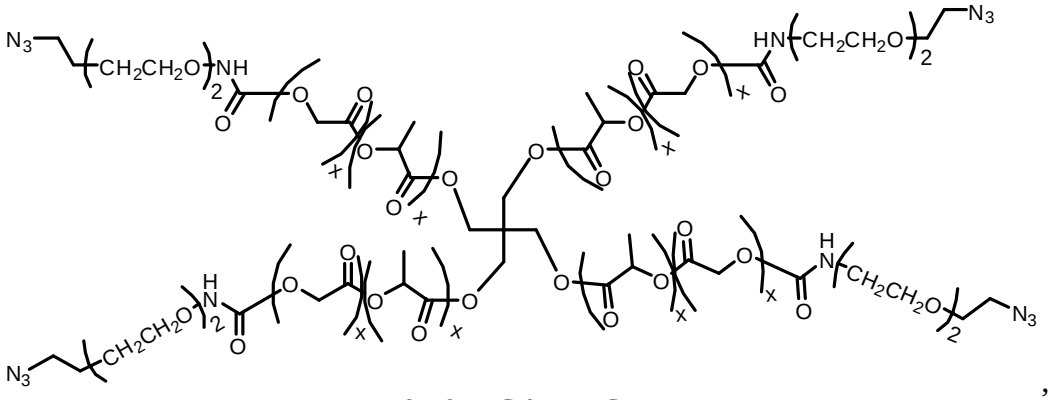


4aPEG$_n$-DL$_t$

,

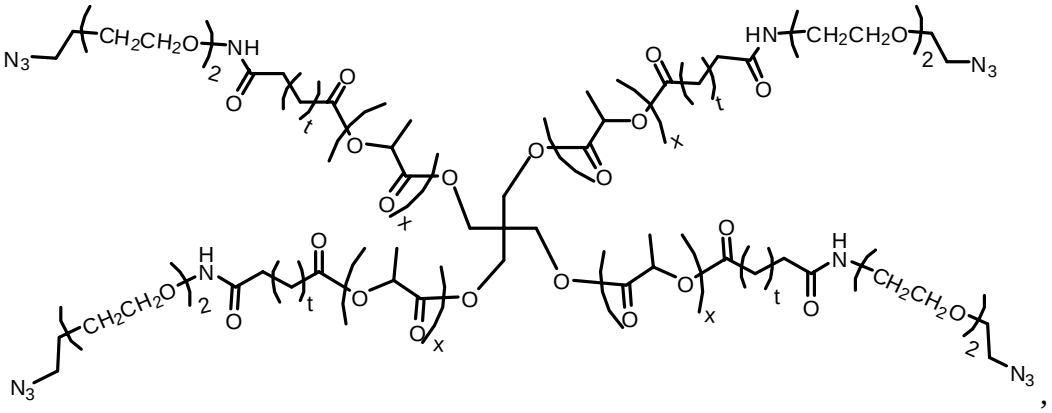
wherein n is 1 to 2300, and t is an integer from 0 to 10, or corresponding 8 arm versions of the above.

30. The use of any one of the previous claims, wherein the polymer network of the bio-orthogonal hydrogel is the reaction product of reacting at least one, such as one, of the following first multi-arm precursors having functional groups comprising an azide (N_3) moiety with at least one, such as one of the following second multi-arm precursor having functional groups comprising a dibenzocyclooctyne (DBCO) moiety:

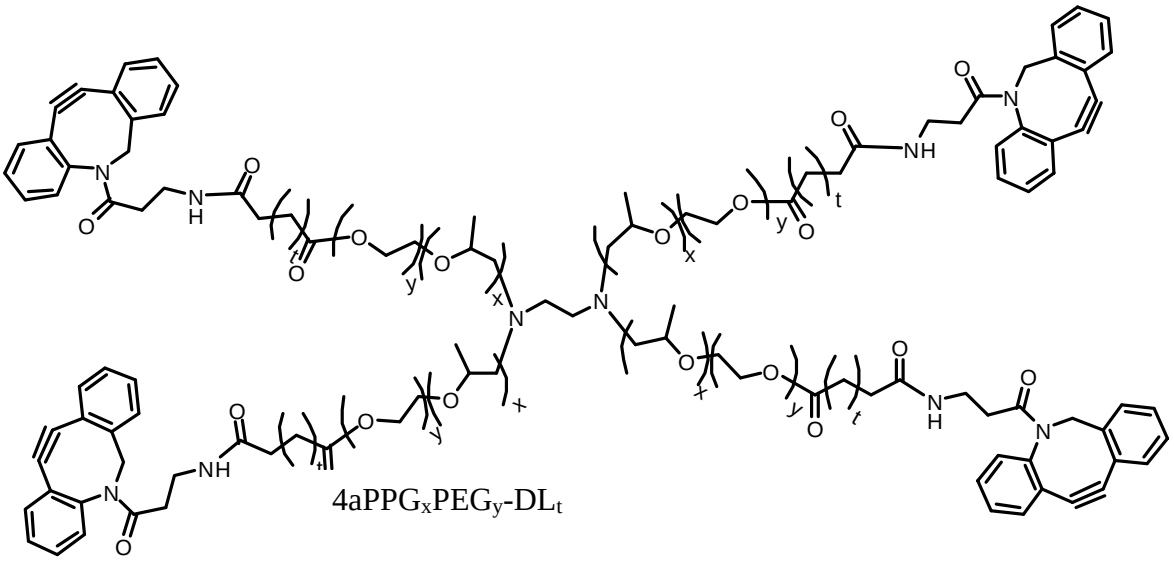


4a50:50PLGA$_x$-PEG$_2$N$_3$

,

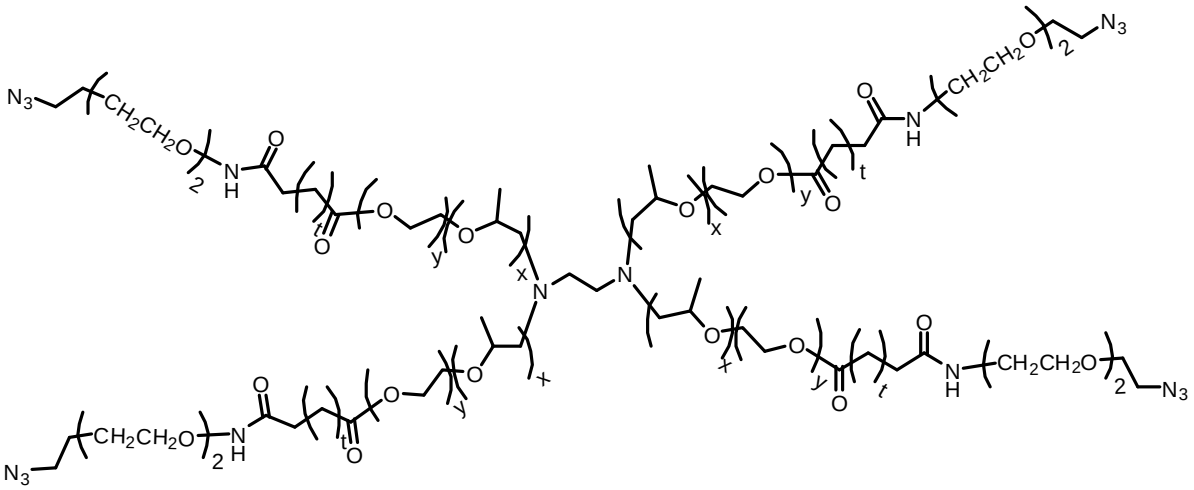


4aPLA$_x$-PEG$_2$N$_3$L$_t$,



4aPPG$_x$PEG$_y$-DL$_t$,

and



4aPPG$_x$PEG$_y$-PEG$_2$N$_3$L$_t$,

wherein x, y defining the number of PPG, PEG, PLA or PGA units and t is an integer from 0 to 10, or the corresponding 8-arm versions thereof.

31. Use of a sustained release drug-delivery system in the manufacture of a medicament for the treatment of an ocular disease or condition in a patient, the use comprising a bio-orthogonal hydrogel as described in any one of claims 1 to 30 and an active agent, and further comprising a hydrogel that is the reaction product of at least two multi-arm precursors crosslinked via electrophile-nucleophile reactions, the hydrogel forming an interpenetrating network with the bio-orthogonal click chemistry crosslinked network described in any one of claims 1 to 30.

32. A sustained release drug-delivery system as described in any of the previous claims, comprising a bio-orthogonal hydrogel and at least one active agent, the bio-orthogonal hydrogel comprising a covalently crosslinked polymer network and containing the at least one active agent, wherein the polymer network comprises

a) a plurality of polymer units,

b) chemical bonds that can be cleaved by hydrolysis, wherein at least one of the hydrolysable bonds is an ester bond, and

c) crosslinks formed by click chemistry reactions.

33. A hydrogel for sustained drug-delivery, the hydrogel including an active agent, the hydrogel comprising an interpenetrating covalently crosslinked dual polymer network and containing the at least one active agent, wherein the dual polymer network comprises

a) a plurality of polymer units,

b) chemical bonds that can be cleaved by hydrolysis, wherein at least one of the hydrolysable bonds is an ester bond, and

c) crosslinks formed by click chemistry reactions between first and second multi-arm precursors bearing functional groups reactive by click chemistry, and

d) crosslinks formed by electrophile-nucleophile reactions between third and fourth multi-arm precursors bearing functional groups reactive by electrophile-nucleophile reactions.

34. The hydrogel of claim 33, wherein the functional groups reactive by click chemistry are selected from the from pairs comprising a strained alkyne moiety such as a dibenzocyclooctyne (DBCO) or a bicyclo[6.1.0]nonyne (BCN), and an azide; or a norbornene or trans-cyclooctene (TCO), and a tetrazine (Tz) moiety; or a strained alkyne moiety such as a

dibenzocyclooctyne (DBCO) or a bicyclo[6.1.0]nonyne (BCN), and a tetrazine (Tz) moiety; or any combinations thereof.

35. The hydrogel of claim 33 or 34, wherein the functional groups reactive by electrophile-nucleophile reactions are selected from electrophiles such as activated ester groups, such as succinimidyl esters, succinimidyl carbonates; nitrophenyl carbonates, aldehydes, ketones, acrylates, acrylamides, maleimides, vinylsulfones, iodoacetamides, alkenes, epoxides, mesylates, tosylates, tresyls, cyanurates, orthopyridyl disulfides, or halogen; and nucleophiles such as an amine, such as a primary amine, a hydroxyl, an alcohol, a thiol, an azide anion, and a carboxyl group; preferably from amine and N-hydroxy succinimide groups.

36. The hydrogel of any one of claims 33 to 35, wherein the dual polymer network is formed by reacting a first multi-arm precursor having functional groups comprising an azide (N_3) and/or tetrazine (Tz) moiety with a second multi-arm precursor having functional groups comprising a dibenzocyclooctyne (DBCO) or Norbornene (Nor) moiety, in the presence of a third precursor having terminal amine (NH_2) groups with a fourth multi-arm precursor having terminal N-hydroxy succinimide (NHS) groups.

37. The hydrogel of any one of claims 33 to 36, wherein the first to fourth precursors are independently of each other selected from multi-arm polyethylene glycol (PEG) precursors having from 3 to 10 PEG arms, such as or 4 to 8 PEG arms.

38. A sustained release drug-delivery system for use as a medicament, or for use in treating a medical condition or disease in a patient, the system comprising a hydrogel of any one of claims 33 to 37.

39. A kit suitable for use for *in-situ* forming a sustained release drug-delivery system or hydrogel for sustained drug-delivery including an active agent as defined in any one of the previous claims, the kit comprising in separate containers:

a) a first container including a first precursor formulation including at least one first multi-arm precursor having first functional groups suitable for forming a connection by click chemistry with complementary second functional groups, and optionally at least one solvent;

b) a second container including a second precursor formulation including at least one second multi-arm precursor having second functional groups suitable for forming a connection by click chemistry with the first functional groups, and optionally at least one solvent; and

c) at least one active agent, included in a separate, third container and/or included in at least one, or both of the first and second containers, and optionally at least one solvent;

d) wherein at least one of the first multi-arm precursor and/or the at least one second multi-arm precursor is a polymer multi-arm precursor having polymer arms comprising polymer units, and wherein at least one of the first multi-arm precursors or the second multi-arm precursors includes a linker unit L comprising a hydrolysable ester bond.