bioavailability of active agents. For delivery of biomolecules such as peptides and proteins there is further a need to improve avidity and to extend half-life of receptor binding biomolecules by providing multivalent delivery possibilities.

[0007] Furthermore, dendrimers can have various applications in non-medical fields or industrial uses, such as antibody purification, applications in cosmetics, catalysis, electronics, agriculture, food, filtration, energy storage, construction materials, and further applications.

[0008] All references cited herein are incorporated by reference in their entireties for all purposes.

OBJECTS AND SUMMARY

[0008a] In an aspect, there is provided a hyperbranched macromolecule comprising building blocks which comprise:

a core unit having at least 3 connectivities *c*;

a plurality of polymeric arms connected to the core unit at the connectivities *c*,

at least one of the polymeric arms being connected by a hydrolyzable bond to a dendritic constitutional repeating unit,

the dendritic constitutional repeating unit comprising a branch unit connected to at least two polymeric arms each comprising an end group or being connected by a hydrolyzable bond to a next dendritic constitutional repeating unit that can again be connected by a chemical bond to further dendritic constitutional repeating units,

the polymeric arms of the outermost dendritic constitutional repeating unit of the hyperbranched macromolecule each comprising an end group;

wherein the polymeric arms consist of polyethylene glycol (PEG) units;

wherein at least one active agent is conjugated to at least one of the outermost polymeric arms, and

wherein the core unit and the branch unit are the same or different, and are derived from a polyol having at least 3 hydroxyl groups.

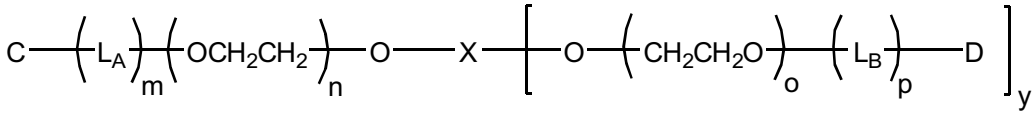
[0008b] In another aspect, there is provided a dendritic constitutional repeating unit precursor comprising:

- one polymeric arm comprising a functional group suitable for forming a connection by click chemistry (such as an azide, alkyne, alkene or tetrazine), and
- at least two polymeric arms comprising functional groups not reactive in click chemistry,

wherein the polymeric arms are connected to a branch unit having a connectivity *c*',

wherein the polymeric parts of the polymeric arms consist of polyethylene glycol (PEG) units; and

wherein the compound is represented by the Formula (iii):



(iii)

wherein C comprises a functional group suitable for click chemistry, (such as an alkyne, alkene, azide, or tetrazine),

D comprises functional groups not reactive in click chemistry (such as succinimidyl), and

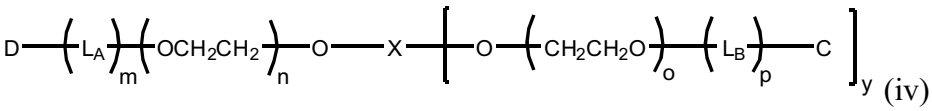
L_A, m, n, X, o, L_B, p and y are as defined herein.

[0008c] In another aspect, there is provided a reverse dendritic constitutional repeating unit precursor comprising:

- one polymeric arm comprising a functional group not reactive in click chemistry, and
- at least two polymeric arms comprising functional groups suitable for click chemistry (such as an azide, alkyne, alkene or tetrazine), and
- a branch unit having a connectivity *c*';

wherein the polymeric parts of the polymeric arms consist of polyethylene glycol (PEG) units, and

wherein the precursor is represented by the Formula (iv):



(iv)

wherein C comprises a functional group suitable for click chemistry, (such as an alkyne, alkene, azide, or tetrazine),

D comprises functional groups not reactive in click chemistry (such as succinimidyl), and L_A, m, n, X, o, L_B, p and y are as defined herein.

[0008d] In another aspect, there is provided a method for manufacturing a hyperbranched macromolecule as defined above by divergent synthesis, comprising the following steps:

(a) Providing a core unit having at least 3 connectivities *c*, a plurality of polymeric arms connected to the core unit having functional groups suitable for click chemistry at the termini of the polymeric arms;

(b) Providing dendritic constitutional repeating unit precursors comprising

- one polymeric arm comprising a functional group suitable for forming a connection by click chemistry with the corresponding functional groups of the polymeric arms connected to the core (such as an azide, alkyne, alkene or tetrazine), and
- at least two polymeric arms comprising functional groups not reactive in click chemistry,

(c) Forming a connection by click chemistry between the polymeric arms connected to the core and the polymeric arms of the dendritic constitutional repeating unit precursors,

(d) Optionally converting the functional groups of the at least two polymeric arms comprising functional groups not reactive in click chemistry into functional groups suitable for click chemistry, and

(e) Conjugating an active agent comprising a functional group to the outermost polymeric arms by reacting with the functional groups of the outermost polymeric arms, thereby forming a hyperbranched macromolecule-active agent conjugate,

wherein for higher generation *Gx* hyperbranched macromolecule, with x being an integer of 2 to 10, step (d) is compulsory, and further consecutive dendritic constitutional repeating unit precursors are connected to the functional groups suitable for click chemistry obtained in step (d) by click chemistry to the hyperbranched macromolecule before conjugating the active agent in step (e).

[0008e] In another aspect, there is provided a method for manufacturing a hyperbranched macromolecule as defined above by convergent synthesis, comprising the following steps:

I) Providing dendritic constitutional repeating unit precursors comprising
- one polymeric arm comprising a functional group suitable for forming a connection by click chemistry (such as an azide, alkyne, alkene or tetrazine), and
- at least two polymeric arms comprising functional groups not reactive in click chemistry,

II) Conjugating active agents comprising a functional group to at least one of the at least two polymeric arms comprising functional groups not reactive in click chemistry of the dendritic constitutional repeating unit precursors,

III) Providing a core unit having at least 3 connectivities *c*, a plurality of polymeric arms connected to the core unit having functional groups suitable for click chemistry (such as an azide, alkyne, alkene or tetrazine) at the termini of the polymeric arms, and

IV) Forming a connection by click chemistry between the polymeric arms connected to the core provided in step III) and the polymeric arm comprising a functional group suitable for forming a connection by click chemistry of the active agent conjugated dendritic constitutional repeating unit precursors obtained in step II), thereby forming a hyperbranched macromolecule-active agent conjugate.

[0008f] In another aspect, there is provided a hyperbranched macromolecule as defined above, for use as a medicament.

[0008g] In another aspect, there is provided the use of a hyperbranched macromolecule as defined above, in the manufacture of a medicament for treating a disease or medical condition in a patient

[0009] It is thus an object of certain examples of the present disclosure to provide a dendrimer platform based on polyethylene glycol building blocks that are highly variable and flexible for being adapted to several uses and applications, and easy to synthesize.

[0010] A further object of certain examples of the present disclosure is to provide systems with optimized drug delivery and site-specific targeting, specifically for treating a condition at the eye.

[0011] It is another object of certain examples of the present disclosure to provide delivery systems for sustained release drug delivery that allow increasing half-life of the active agent, an enhancement of efficacy, avidity and bioavailability of active agents.

[0012] It is another object of certain examples of the present disclosure to provide biodegradable drug delivery systems that can be tuned for their degradation rate and active agent release rate using a wide range of different biodegradable molecular groups, including hydrolyzable groups and linkages that are built into the molecular structure of the drug delivery system. The biodegradable drug delivery systems of certain examples should be fully resorbable and degradable to the initial building blocks that can be easily cleared from the local tissues and ultimately the body.

[0013] It is another object of certain examples of the present disclosure to provide biodegradable drug delivery systems leading to enhanced binding affinity and/or avidity of the active agent, e.g., biomolecules such as peptides or proteins to biological targets.

[0014] 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.

[0015] A further object of certain examples of the present disclosure to provide dendrimers for applications also in non-medical fields or industrial uses, such as antibody purification, cosmetic applications, catalytic applications, applications in electronics, agriculture, food, filtration, energy storage, construction materials, coatings, adhesives, water purification, oil recovery, fragrance release, paper making, environmental sensing and release Systems, membranes, textiles, printing inks, surface chemistry applications, thickeners, detergents, rheology modifiers, scaffolding, or 3D-printing.

[0016] The above objects are solved by the disclosures as described in the independent claims. Advantageous modifications are disclosed in the dependent claims.

[0017] Some examples of the present disclosure are directed to a hyperbranched macromolecule comprising a core unit having at least 3 connectivities *c*, a plurality of polymeric arms connected to the core unit at the connectivities *c*, at least on of the polymeric arms being connected by a hydrolyzable bond to a dendritic constitutional repeating unit (DCRU), the dendritic constitutional repeating unit /DCRU) comprising a branch unit connected to at least two polymeric arms each comprising an end group or being connected to a next dendritic constitutional repeating unit that may again be connected to a further dendritic constitutional repeating unit, the polymeric arms of the outermost dendritic constitutional repeating unit each comprising an end group; wherein the polymeric arms consist of polyethylene glycol (PEG) units; wherein optionally at least one active agent is conjugated to at least one of the outermost polymeric arms. In some examples, at least 10%, preferably about 20 to 100 % of the chemical bonds of the connections can be cleaved by hydrolysis. The bonds cleavable by hydrolysis are preferably ester bonds. In certain examples, the ester bonds are introduced by using linkers derived from organic diacids.

[0018] In some examples, the building blocks or fragments of the hyperbranched macromolecule obtained/obtainable after cleaving all hydrolyzable bonds of the connections have an average molecular weight (Mn) of less than 50,000 Daltons. The active agent may be covalently or non-covalently bound to the hyperbranched macromolecule. In certain examples, the active agent is covalently conjugated to the hyperbranched macromolecule.

[0019] In certain examples, the hyperbranched macromolecule is a generation *G*0 dendrimer-like branched macromolecule wherein the surface end groups of the branched macromolecule are the end groups at the polymeric arms connected to the core unit without further connections to DCRU´s. In other examples, the hyperbranched macromolecule is a higher generation *G*x dendrimer-like hyperbranched macromolecule, with x being an integer of 1 to 10 defining the number of consecutively connected dendritic constitutional repeating units in the hyperbranched macromolecule, the polymeric arms of the outermost dendritic constitutional repeating unit each comprising an end group, wherein the at least one active agent is conjugated to at least one of the outermost polymeric arms.

[0020] In certain examples of the present disclosure, the core unit and the branch units of the hyperbranched macromolecule are the same or different and independently of each other have a connectivity *c* of 3 to 10, or 4 to 8, or 4 to 6, or 4. In certain examples, the core unit and the branch unit are the same or different and are each derived from a polyol having at least 3 hydroxyl groups. In certain examples, the polyol is selected from the group consisting of glycerol, pentaerythritol, xylitol, dipentaerythritol, tripentaerythritol, hexaglycerol, isomalt, lactitol, maltitol, mannitol, or sorbitol.

[0021] In certain examples of the present disclosure, the polymeric arms in the hyperbranched macromolecule comprise PEG units having an average molecular weight (Mw) in the range from about 1,000 to about 80,000 Daltons, or from about 10,000 to about 60,000 Daltons, or from about 15,000 to about 50,000 Daltons. In certain examples, the average molecular weight of the polymeric arm PEG units attached to the core is the same or different than that of the polymeric arms in the dendritic constitutional repeating units. The average molecular weight of the polymeric arm PEG units attached to the core can be higher or lower than that of the polymeric arms in the dendritic constitutional repeating units. For higher generation *G*x hyperbranched macromolecules, with x being an integer of 2 to 10, the average molecular weight of the

polymeric arm PEG units can decrease or increase from the innermost polymeric arms to the outermost polymeric arms.

[0022] In certain examples of the present disclosure, the end groups attached to the outermost polymeric arms are grafted to the termini of the polymeric arms directly or via a difunctional linker comprising hydrolyzable bonds such as a carboxyl group, a dicarboxyl group, carboxamide group, dicarboxamide group, a functionalized aliphatic, heteroaliphatic, or aromatic or heteroaromatic group. In further examples, the end groups attached to the outermost polymeric arms are functional groups selected from electrophiles such as activated ester groups such as succinimidyl esters, succinimidyl carbonates; nitrophenyl carbonates, aldehydes, ketones, acrylates, acrylamides, maleimides, vinylsulfones, iodoacetamides, alkenes, alkynes, azides, norbornenes, epoxides, mesylates, tosylates, tresyls, cyanurates, orthopyridyl disulfides, or halogen; nucleophiles such as an amine, such as a primary amine, a hydroxyl, an alcohol, a thiol, an azide anion, and a carboxyl group; functional groups for click chemistry; functional groups for cycloadditions, such as 1,3-dipolar cycloadditions, [3+2] cycloadditions such as alkene-nitrone cycloadditions or alkyne-nitrone cycloadditions, [4+2] cycloadditions; functional groups for thiol-ene reactions; hetero-Diels-Alder cycloadditions; functional groups for nucleophilic ring openings, functional groups for non-aldol type carbonyl reactions; functional groups for addition reactions to carbon-carbon multiple bonds, polymerizable vinyl groups, or combinations thereof.

[0023] In certain examples of the present disclosure, the end groups attached to the outermost polymeric arms are linker-spaced functional groups selected from succinimidyl succinate (SS), succinimidyl glutarate (SG), succinimidyl adipate (SAP), succinimidyl azelate (SAZ), and succinimidyl glutaramide (SGA).

[0024] In certain examples of the present disclosure, the end groups attached to the outermost polymeric arms are functional groups selected from an alkyne compound such as a dibenzocyclooctyne (DBCO), or a bicyclo[6.1.0]-nonyne (BCN); or a norbornene, or a trans-cyclooctene (TCO); an azide , a 3,4 dihydroxyphenylacetic acid (DHPA),or a tetrazine (Tz).

[0025] In certain examples of the present disclosure, the connection between the polymeric arms connected to the core unit and the first dendritic constitutional repeating unit and/or the

connections between consecutive dendritic constitutional repeating units are formed by click chemistry.

[0026] In certain examples of the present disclosure, the connection is formed by click chemistry, wherein the connection is formed by reacting a polymeric arm functionalized with an alkyne, cycloalkyne, or strained or terminal alkene moiety with a polymeric arm functionalized with an azide or a tetrazine moiety in a SPAAC or an IEDDA type click chemistry coupling reaction. In certain examples, the alkyne moiety is a dibenzocyclooctyne moiety.

[0027] In certain examples of the present disclosure, the connection between the polymeric arms connected to the core unit and the first dendritic constitutional repeating unit and/or the connections between consecutive dendritic constitutional repeating units are formed between the polymeric arms connected to the core unit and polymeric arms connected to the branch unit of the dendritic constitutional repeating units and/or between the polymeric arms of a dendritic constitutional repeating unit and polymeric arms of consecutive dendritic constitutional repeating units.

[0028] In certain examples of the present disclosure, the active agent conjugated to at least one of the end groups located at the surface of the hyperbranched macromolecule is selected from the group consisting of therapeutically or diagnostically active agents.

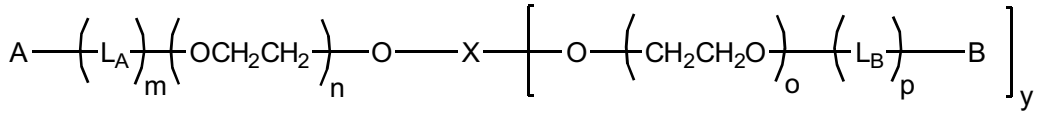
[0029] In certain examples of the present disclosure, the active agent conjugated to at least one of the end groups located at the surface of the dendrimer is selected from steroids; non-steroidal anti-inflammatory drugs (NSAIDS) such as Diclofenac, Ibuprofen, Meclofenamate, Mefanamic A, Salsalate, Sulindac, 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.

[0030] In certain examples of the present disclosure, the active agent covalently or non-covalently conjugated to at least one of the end groups located at the surface of the hyperbranched macromolecule is a peptide selected from the group consisting of compstatin, APL-1, and Fc-III-4C, Beovu (Brolucizumab), Zimura (Avacincaptad Pegol), Pegcetacoplan, Abicipar Pegol, Lampalizumab, Fovista, Risuteganib, AXT107, Elamipretide, THR149, ALM201, VGB3, and Largazole.

[0031] In certain examples of the present disclosure, the active agent is covalently bound to at least 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or up to 100% of the end groups located at the surface of the hyperbranched macromolecule.

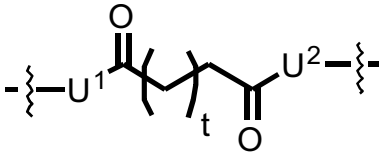
[0032] In certain examples of the disclosure, the dendritic constitutional repeating unit is represented by the formula (i):

(i) 

wherein A is a connection to a polymeric arm that is connected to the core unit, or A is a connection to B of a preceding dendritic constitutional repeating unit represented by Formula (i), L_A is a linker, m is either 0 or 1, n is an integer from 20 to 2000, o is an integer from 20 to 2000, n and o can be different or the same, X is the branch unit such as a polyol derived unit, L_B is a linker, p is either 0 or 1, B comprises an end group located at the surface of the hyperbranched macromolecule or is a connection to A of a consecutive dendritic constitutional repeating unit or a connection to an active agent, L_A and L_B can be different or the same, m and p can be different or the same, and y is an integer from 2 to 9, wherein $y = c - 1$ with c being the connectivity c of the branch unit X; and wherein the dendritic constitutional units in the hyperbranched macromolecules may be the same or different.

[0033] In certain further examples, A comprises a functional group formed by click chemistry such as a triazole or dihydropyrazine and/or the linker L_A and/or L_B comprise a diacid and/or an acid diamido group, a carboxyl and/or a carboxamide group such as succinate, glutarate, adipate,

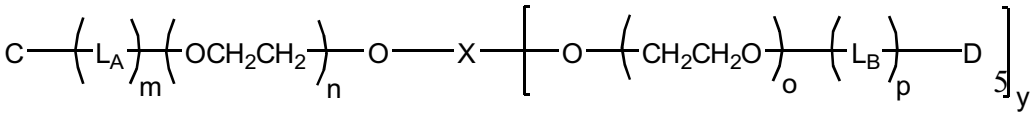
azelate, or glutaramide. In certain examples, the linker L_A and/or L_B comprises a structure represented by Formula (ii):

(ii) 

wherein U^1 and U^2 are independently NH or O and can be the same or different, and wherein t is an integer from 0 to 10. The linker L_A and/or L_B may further comprise a polyethylene glycol unit between the bond to B and the carboxyl group, carboxamide group or structure of Formula (ii).

[0034] In certain examples of the disclosure, the present disclosure provides a method for manufacturing a hyperbranched macromolecule as described herein by divergent synthesis, comprising the steps of (a) providing a core unit having at least 3 connectivities *c*, a plurality of polymeric arms connected to the core unit having functional groups suitable for click chemistry at the termini of the polymeric arms; (b) providing dendritic constitutional repeating unit precursors comprising one polymeric arm comprising a functional group suitable for forming a connection by click chemistry with the corresponding functional groups of the polymeric arms connected to the core, (such as an azide, alkyne, alkene or tetrazine), and at least two polymeric arms comprising functional groups not reactive in click chemistry; (c) forming a connection by click chemistry between the polymeric arms connected to the core and the polymeric arms of the dendritic constitutional repeating unit precursors, (d) optionally converting the functional groups of the at least two polymeric arms comprising functional groups not reactive in click chemistry into functional groups suitable for click chemistry, and (e) conjugating an active agent comprising a functional group to the outermost polymeric arms by reacting with the functional groups of the outermost polymeric arms, thereby forming a hyperbranched macromolecule-active agent conjugate. For a higher generation *G*x hyperbranched macromolecule, with x being an integer of 2 to 10, step (d) can be compulsory and further consecutive dendritic constitutional repeating unit precursors are connected to the functional groups suitable for click chemistry obtained in step (d) by click chemistry to the hyperbranched macromolecule before conjugating the active agent in step (f).

[0035] In certain examples of the method, the dendritic constitutional repeating unit precursor in step (c) is represented by the Formula (iii):



(iii)

wherein C comprises a functional group suitable for click chemistry (such as an alkyne, alkene, azide, or tetrazine), D comprises functional groups not suitable for click chemistry such as succinimidyl, and L_A, m, n, X, o, L_B, p and y are as defined above, and wherein the dendritic constitutional repeating units may be the same or different.

[0036] In a further example of the method, the disclosure relates to a method for manufacturing a hyperbranched macromolecule as described herein by convergent synthesis, comprising the steps of (I) providing dendritic constitutional repeating unit precursors comprising one polymeric arm comprising a functional group suitable for forming a connection by click chemistry (such as an azide, alkyne, alkene or tetrazine), and at least two polymeric arms comprising functional groups not reactive in click chemistry; (II) conjugating active agents comprising a functional group to at least one of the at least two polymeric arms comprising functional groups not reactive in click chemistry of the dendritic constitutional repeating unit precursors; (III) providing a core unit having at least 3 connectivities *c*, a plurality of polymeric arms connected to the core unit having functional groups suitable for click chemistry (such as an azide, alkyne, alkene or tetrazine) at the termini of the polymeric arms; and (IV) forming a connection by click chemistry between the polymeric arms connected to the core provided in step III) and the polymeric arm comprising a functional group suitable for forming a connection by click chemistry of the active agent conjugated dendritic constitutional repeating unit precursors obtained in step II), thereby forming a hyperbranched macromolecule-active agent conjugate. In examples of this method, the dendritic constitutional repeating unit precursor in step I) is represented by the Formula (iii) as described above.

[0037] For a higher generation *Gx* hyperbranched macromolecule, with x being an integer of 2 to 10, the active agent conjugated dendritic constitutional repeating unit precursors obtained in step II) can be connected by click chemistry to reverse dendritic constitutional repeating unit precursors comprising one polymeric arm comprising a functional group not reactive in click chemistry, and at least two polymeric arms comprising functional groups suitable for click chemistry (such as an

azide, alkyne, alkene or tetrazine), wherein the functional group not reactive in click chemistry of the one polymeric arm is subsequently converted to a functional group suitable for click chemistry before connecting to further reverse dendritic constitutional repeating unit precursors or before forming a connection by click chemistry with the polymeric arms connected to the core in step IV), thereby forming higher generation hyperbranched macromolecules. In an example, dendritic constitutional repeating unit precursors having different active agents conjugated to the polymeric arms can be obtained by performing steps I) and II) for each active agent conjugated dendritic constitutional repeating unit precursor, and a mixture of the obtained active agent conjugated dendritic constitutional repeating unit precursors is then used for step IV), thereby forming a hyperbranched macromolecule-active agent conjugate having different active agents at different regions of the surface of the hyperbranched macromolecule.

[0038] In a further example, the disclosure relates to a hyperbranched macromolecule as described herein, for use as a medicament. In a further example, the disclosure relates to a method of treatment, wherein the method comprises treating a disease or medical condition in a patient with a hyperbranched macromolecule of examples of the disclosure. In an example thereof, the hyperbranched macromolecule is used for an ocular treatment, such as 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.

[0039] In further examples, the hyperbranched macromolecule is used in the treatment of an ocular disease selected from the group consisting of retinal neovascularization, choroidal neovascularization, 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 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.

[0040] In certain examples, the hyperbranched macromolecule is formulated for direct injection at a treatment site of a patient, for example by parenteral administration, intra-tumoral injection, injection into the eye such as intravitreal, intracameral, subconjunctival, retrobulbar, sub-tenon, subretinal, or suprachoroidal injections. The hyperbranched macromolecule can be administered by direct injection, by oral application, incorporated in gels, or incorporated in implants.

DEFINITIONS

[0041] The terms “hyperbranched macromolecule” or “hyperbranched polymer”, or simply “branched polymer” or “branched macromolecule” are all interchangeably used herein to designate dendrimer-like branched macromolecules or polymers that have a tree-like structure like dendrimers, and the term “dendrimer” is used herein as a synonym thereof. However, while dendrimers are monodispersed, highly symmetric molecules of exactly defined composition, the hyperbranched macromolecules of the present invention are polydisperse molecules because they include polyethylene glycol arms or units that have a certain polydispersity like most synthetic

CLAIMS

1. A hyperbranched macromolecule comprising building blocks which comprise:

a core unit having at least 3 connectivities *c*;

a plurality of polymeric arms connected to the core unit at the connectivities *c*,

at least one of the polymeric arms being connected by a hydrolyzable bond to a dendritic constitutional repeating unit,

the dendritic constitutional repeating unit comprising a branch unit connected to at least two polymeric arms each comprising an end group or being connected by a hydrolyzable bond to a next dendritic constitutional repeating unit that can again be connected by a chemical bond to further dendritic constitutional repeating units,

the polymeric arms of the outermost dendritic constitutional repeating unit of the hyperbranched macromolecule each comprising an end group;

wherein the polymeric arms consist of polyethylene glycol (PEG) units;

wherein at least one active agent is conjugated to at least one of the outermost polymeric arms, and

wherein the core unit and the branch unit are the same or different, and are derived from a polyol having at least 3 hydroxyl groups.

2. The hyperbranched macromolecule according to claim 1, wherein at least 10%, preferably about 20 to 100 % of the connections in the macromolecule can be cleaved by hydrolysis.

3. The hyperbranched macromolecule according to any one of the preceding claims, wherein each of the building blocks (fragments) of the hyperbranched macromolecule obtained after cleaving all hydrolyzable bonds of the connections in the macromolecule has an average molecular weight (Mn) of less than 50,000 Daltons, such as less than 45,000 Daltons, or less than 40,000 Daltons, or less than 35,000 Daltons, or less than 30,000 Daltons.

4. The hyperbranched macromolecule according to any one of the previous claims, being a higher generation *G*x hyperbranched macromolecule, with x being an integer of 1 to 10

defining the number of consecutively connected dendritic constitutional repeating units in the hyperbranched macromolecule.

5. The hyperbranched macromolecule according to claim 1, wherein the polyol is selected from the group consisting of glycerol, pentaerythritol, xylitol, dipentaerythritol, tripentaerythritol, hexaglycerol, isomalt, lactitol, maltitol, mannitol, or sorbitol.

6. The hyperbranched macromolecule according to any one of the preceding claims, wherein the average molecular weight of the polymeric arm PEG units attached to the core is higher than that of the polymeric arms in the dendritic constitutional units, or

the average molecular weight of the polymeric arm PEG units attached to the core is lower than that of the polymeric arms in the dendritic constitutional units.

7. The hyperbranched macromolecule according to any one of the preceding claims, wherein for a higher generation *Gx* hyperbranched macromolecule, with x being an integer of 2 to 10, the average molecular weight of the polymeric arm PEG units decreases from the innermost polymeric arms to the outermost polymeric arms; or wherein the average molecular weight of the polymeric arm PEG units increases from the innermost polymeric arms to the outermost polymeric arms.

8. The hyperbranched macromolecule according to any one of the preceding claims, wherein the at least one arm connected to the core unit or branch unit is connected to the dendritic constitutional unit via a difunctional linker forming hydrolyzable bonds comprising a carboxyl group, a dicarboxyl group, carboxamide group, dicarboxamide group, a functionalized aliphatic, heteroaliphatic, or aromatic or heteroaromatic group.

9. The hyperbranched macromolecule according to any one of the preceding claims, wherein the (linker) end groups attached to the outermost polymeric arms are functional groups selected from succinimidyl succinate (SS), succinimidyl glutarate (SG), succinimidyl adipate (SAP), succinimidyl azelate (SAZ), and succinimidyl glutaramide (SGA), or

wherein the end groups attached to the outermost polymeric arms are functional groups selected from an alkyne compound such as a dibenzocyclooctyne (DBCO), or a bicyclo[6.1.0]-nonyne (BCN); or a norbornene, or a trans-cyclooctene (TCO); an azide, a 3,4 dihydroxyphenylacetic acid (DHPA), or a tetrazine (Tz).

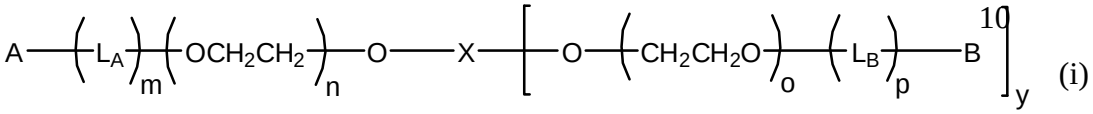
10. The hyperbranched macromolecule according to any one of the preceding claims, wherein the connection between the polymeric arms connected to the core unit and the first dendritic constitutional repeating unit and/or the connections between consecutive dendritic constitutional repeating units are formed by click chemistry, optionally with click chemistry functionalized linkers that include a hydrolyzable bond.

11. The hyperbranched macromolecule according to any of the preceding claims, wherein the active agent conjugated to at least one of the outermost polymeric arms 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, and/or wherein the active agent conjugated to at least one of the outermost polymeric arms is a peptide or aptamer selected from the group consisting of Compstatin, APL-1, and Fc-III-4C, Beovu (Brolucizumab), Zimura (Avacincaptad Pegol), Pegcetacoplan, Abicipar Pegol,

Lampalizumab, Fovista, Risuteganib, AXT107, Elamipretide, THR149, ALM201, VGB3, and Largazole.

12. The hyperbranched macromolecule according to any of the preceding claims, wherein the active agent is bound to at least 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or up to 100% of the outermost polymeric arms.

13. The hyperbranched macromolecule according to any of the preceding claims, wherein a dendritic constitutional repeating unit is represented by Formula (i):



(i)

wherein A is a connection to a polymeric arm that is connected to the core unit, or A is a connection to B of a preceding dendritic constitutional repeating unit represented by Formula (i),

L_A is a linker,

m is either 0 or 1,

n is an integer from 20 to 2000, o is an integer from 20 to 2000,

n and o can be different or the same,

X is a branch unit having a connectivity *c*',

L_B is a linker, p is either 0 or 1,

B comprises an end group located at the surface of the hyperbranched macromolecule or is a connection to A of a consecutive dendritic constitutional repeating unit or an active agent,

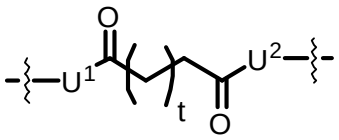
L_A and L_B can be different or the same,

m and p can be different or the same, and

y is an integer from 2 to 9, wherein y = *c'* – 1 with *c'* being the connectivity *c'* of the branch unit X; and wherein the dendritic constitutional units in the hyperbranched macromolecules may be the same or different.

14. The hyperbranched macromolecule according to claim 13, wherein the connection between A and B comprises a functional group formed by click chemistry, such as a triazole or dihydropyrazine; and/or
wherein the linker L_A and/or L_B comprise a diacid and/or an acid diamido group such as succinate, glutarate, adipate, azelate, or glutaramide.

15. The hyperbranched macromolecule according to any of claims 13 to 14, wherein the linker L_A and/or L_B comprises a structure represented by Formula (ii):

(ii) 

wherein U^1 and U^2 are independently NH or O and can be the same or different, and wherein t is an integer from 0 to 10.

16. The hyperbranched macromolecule according to any of the preceding claims, wherein the hyperbranched macromolecule further comprises at least one extender unit comprising polyethylene glycol (PEG) units, wherein the extender unit is linear, difunctional and connected to the polymeric arm of a dendritic constitutional repeating unit or the polymeric arm connected to the core unit and to either an end group or a polymeric arm of a next dendritic constitutional repeating unit.

17. The hyperbranched molecule according to any one of the preceding claims, wherein at least one, or all, preferably all, building blocks selected from core unit, core unit including polymeric arms at the connectivities *c*, dendritic constitutional repeating unit, linkers and extenders, between hydrolyzable bonds, have a molecular weight less than 50,000 Daltons, such as less than 45,000 Daltons, or less than 40,000 Daltons, or less than 35,000 Daltons, or less than 30,000 Daltons.

18. A dendritic constitutional repeating unit precursor comprising:

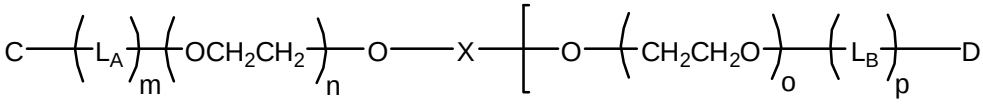
- one polymeric arm comprising a functional group suitable for forming a connection by click chemistry (such as an azide, alkyne, alkene or tetrazine), and

- at least two polymeric arms comprising functional groups not reactive in click chemistry,

wherein the polymeric arms are connected to a branch unit having a connectivity *c*',

wherein the polymeric parts of the polymeric arms consist of polyethylene glycol (PEG) units; and

wherein the compound is represented by the Formula (iii):



(iii)

wherein C comprises a functional group suitable for click chemistry, (such as an alkyne, alkene, azide, or tetrazine),

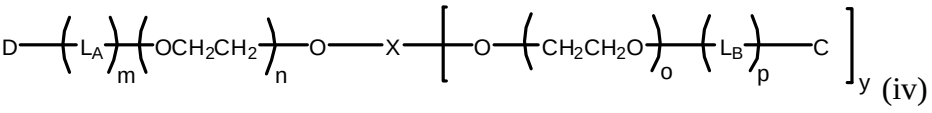
D comprises functional groups not reactive in click chemistry (such as succinimidyl), and L_A, m, n, X, o, L_B, p and y are as defined in claims 13 to 15.

19. A reverse dendritic constitutional repeating unit precursor comprising:

- one polymeric arm comprising a functional group not reactive in click chemistry, and
- at least two polymeric arms comprising functional groups suitable for click chemistry (such as an azide, alkyne, alkene or tetrazine), and
- a branch unit having a connectivity *c*';

wherein the polymeric parts of the polymeric arms consist of polyethylene glycol (PEG) units, and

wherein the precursor is represented by the Formula (iv):



(iv)

wherein C comprises a functional group suitable for click chemistry, (such as an alkyne, alkene, azide, or tetrazine),

D comprises functional groups not reactive in click chemistry (such as succinimidyl), and L_A, m, n, X, o, L_B, p and y are as defined in the previous claims.

20. A method for manufacturing a hyperbranched macromolecule according to any one of claims 1 to 19 by divergent synthesis, comprising the following steps:

(a) Providing a core unit having at least 3 connectivities *c*, a plurality of polymeric arms connected to the core unit having functional groups suitable for click chemistry at the termini of the polymeric arms;

(b) Providing dendritic constitutional repeating unit precursors comprising

- one polymeric arm comprising a functional group suitable for forming a connection by click chemistry with the corresponding functional groups of the polymeric arms connected to the core (such as an azide, alkyne, alkene or tetrazine), and
- at least two polymeric arms comprising functional groups not reactive in click chemistry,

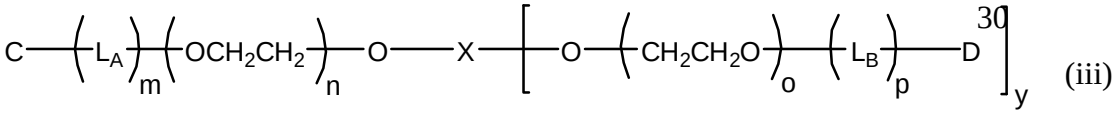
(c) Forming a connection by click chemistry between the polymeric arms connected to the core and the polymeric arms of the dendritic constitutional repeating unit precursors,

(d) Optionally converting the functional groups of the at least two polymeric arms comprising functional groups not reactive in click chemistry into functional groups suitable for click chemistry, and

(e) Conjugating an active agent comprising a functional group to the outermost polymeric arms by reacting with the functional groups of the outermost polymeric arms, thereby forming a hyperbranched macromolecule-active agent conjugate,

wherein for higher generation *Gx* hyperbranched macromolecule, with x being an integer of 2 to 10, step (d) is compulsory, and further consecutive dendritic constitutional repeating unit precursors are connected to the functional groups suitable for click chemistry obtained in step (d) by click chemistry to the hyperbranched macromolecule before conjugating the active agent in step (e.

21. The method according to claim 20, wherein the dendritic constitutional repeating unit precursor in step (c) is represented by the Formula (iii):



(iii)

wherein C comprises a functional group suitable for click chemistry, (such as an alkyne, alkene, azide, or tetrazine),
D comprises functional groups not reactive in click chemistry (such as succinimidyl), and L_A, m, n, X, o, L_B, p and y are as defined in the previous claims; and wherein the dendritic constitutional units may be the same or different.

22. A method for manufacturing a hyperbranched macromolecule according to any one of claims 1 to 19 by convergent synthesis, comprising the following steps:

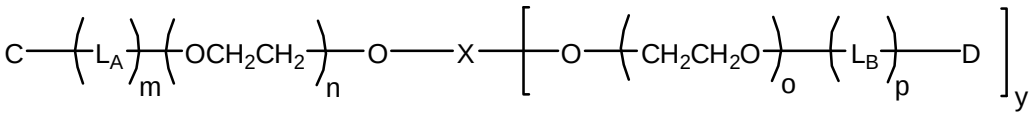
I) Providing dendritic constitutional repeating unit precursors comprising
- one polymeric arm comprising a functional group suitable for forming a connection by click chemistry (such as an azide, alkyne, alkene or tetrazine), and
- at least two polymeric arms comprising functional groups not reactive in click chemistry,

II) Conjugating active agents comprising a functional group to at least one of the at least two polymeric arms comprising functional groups not reactive in click chemistry of the dendritic constitutional repeating unit precursors,

III) Providing a core unit having at least 3 connectivities *c*, a plurality of polymeric arms connected to the core unit having functional groups suitable for click chemistry (such as an azide, alkyne, alkene or tetrazine) at the termini of the polymeric arms, and

IV) Forming a connection by click chemistry between the polymeric arms connected to the core provided in step III) and the polymeric arm comprising a functional group suitable for forming a connection by click chemistry of the active agent conjugated dendritic constitutional repeating unit precursors obtained in step II), thereby forming a hyperbranched macromolecule-active agent conjugate.

23. The method according to claim 22, wherein a dendritic constitutional repeating unit precursor in step I) is represented by the Formula (iii):



(iii)

wherein C comprises a functional group suitable for click chemistry (such as an alkyne, alkene, azide, or tetrazine),

D comprises functional groups not reactive in click chemistry (such as succinimidyl), and L_A, L_B, m, n, X, o, p, and y are as defined in the previous claims, and wherein the dendritic constitutional units may be the same or different, and/or

wherein for higher generation *Gx* hyperbranched macromolecule, with x being an integer of 2 to 10, the active agent conjugated dendritic constitutional repeating unit precursors obtained in step II) are connected by click chemistry to reverse dendritic constitutional repeating unit precursors comprising:

- one polymeric arm comprising a functional group not reactive in click chemistry, and
- at least two polymeric arms comprising functional groups suitable for click chemistry (such as an azide, alkyne, alkene or tetrazine),

wherein the functional group not reactive in click chemistry of the one polymeric arm is subsequently converted to a functional group suitable for click chemistry before connecting to further reverse dendritic constitutional repeating unit precursors or before forming a connection by click chemistry with the polymeric arms connected to the core in step IV), thereby forming higher generation hyperbranched macromolecules.

24. The method according to claims 22 to 23, wherein dendritic constitutional repeating unit precursors having different active agents conjugated to the polymeric arms are obtained by performing steps I) and II) for each active agent conjugated dendritic constitutional repeating unit precursor, and a mixture of the obtained active agent conjugated dendritic constitutional repeating unit precursors is used for step IV), thereby forming a hyperbranched macromolecule-active agent conjugate having different active agents at different regions of the surface of the hyperbranched macromolecule.

25. The method according to any one of claims 20 to 24, wherein the outermost polymeric arms of the hyperbranched macromolecule have terminal maleimide functional groups, and peptides or active agents are conjugated thereto via maleimide-thiol reaction, and
wherein the terminal maleimide functional groups are provided by reacting DBCO or azide functionalized terminal functional group of the hyperbranched macromolecule with click chemistry linkers having an azide or DBCO functionality connected to a maleimide group, such as DBCO-maleimide, DBCO-PEG3-maleimide, DBCO-PEG4-maleimide, or azido-PEG3-maleimide.

26. A hyperbranched macromolecule according to any of claims 1 to 19, for use as a medicament.

27. Use of a hyperbranched macromolecule according to any of claims 1 to 19, in the manufacture of a medicament for treating a disease or medical condition in a patient.

28. The hyperbranched macromolecule for use, or the use according to claims 26 or 27, wherein the hyperbranched macromolecule is used for an ocular treatment.

29. The hyperbranched macromolecule for use, or the use according to claims 26 to 28,
wherein the hyperbranched macromolecule is used in 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, and/or
wherein the hyperbranched macromolecule is used in 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 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.

30. The hyperbranched macromolecule for use, or the use according to any of claims 26 to 29, wherein the hyperbranched macromolecule is formulated for direct injection at a treatment site of a patient, for example by parenteral administration, intra-tumoral injection, injection into the eye such as intravitreal, intracameral, subconjunctival, retrobulbar, sub-tenon, subretinal, or suprachoroidal injections, and/or
wherein the hyperbranched macromolecule is administered by direct injection, by oral application, incorporated in gels, or incorporated in implants.

31. The hyperbranched macromolecule for use, or the use according to any of claims 26 to 30, wherein the hyperbranched macromolecule comprises two or more different active

agents at different dendrons or regions on the surface of the hyperbranched macromolecule.

32. The hyperbranched macromolecule of any one of claims 1 to 19, the hyperbranched molecule for use, or the use according to any of 26 to 31, wherein the hyperbranched macromolecule comprises one active agent at different positions or regions on the surface of the hyperbranched macromolecule with different hydrolyzable groups for varying the release of the active agent at different rates, or

wherein the hyperbranched macromolecule comprises two or more different active agents at different positions or regions on the surface of the hyperbranched macromolecule with different hydrolyzable groups for varying the release of the same or different active agents at different rates.