Claims

1. A method for preparing hydrogel microspheres or pharmaceutically acceptable salts thereof comprising a crosslinked hyaluronic acid (HA), wherein the method comprises the steps of:
    (a) mixing a solution A with a solution B to form an emulsion, wherein solution A comprises a first functionalized HA that is modified with one or more -FG_1 and optionally further functional groups and a second functionalized HA that is modified with one or more -FG_2 and optionally further functional groups, wherein each -FG_1 and -FG_2 are functional group moieties that are different from each other, wherein -FG_1 on the first functionalized HA reacts with -FG_2 on the second functionalized HA to form a plurality of crosslinks which results in the formation of hydrogel HA microspheres;
    (b) optionally, adding a pH-adjusting agent to the emulsion of step (a); and
    (c) collecting the obtained hydrogel HA microspheres of step (a) or (b).

2. The method of claim 1, wherein solution A of step (a) further comprises a buffering agent.

3. The method of claim 1 or 2, wherein solution B of step (a) comprises an emulsifying agent and a solvent.

4. The method of any one of claims 1 to 3, wherein the method comprises the steps of:
    (a) mixing a solution A with a solution B to form an emulsion, wherein solution A comprises a first functionalized HA that is modified with one or more -FG_1 and a second functionalized HA that is modified with one or more -FG_2, wherein -FG_1 and -FG_2 are functional group moieties that are different from each other and wherein -FG_1 on the first functionalized HA reacts with -FG_2 on the second functionalized HA to form a plurality of crosslinks which results in the formation of hydrogel HA microspheres;
    (b) optionally, adding a pH-adjusting agent to the emulsion of step (a);
    (c) collecting the obtained hydrogel HA microspheres of step (b);

(d) optionally, size fractionating the obtained hydrogel HA microspheres of step (c) to obtain microspheres with a particular particle size distribution;

(e) optionally, washing the microspheres obtained in step (c) or (d);

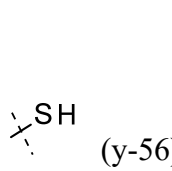
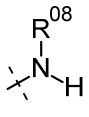
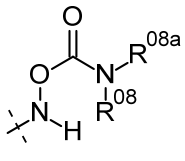
(f) optionally, incubating the hydrogel HA microspheres of step (c), (d) or (e) in a buffering agent of a pH ranging from about 8 to about 12;

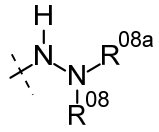
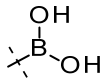
(g) optionally, incubating the hydrogel HA microspheres of step (c), (d), (e) or (f) with a reducing agent;

(h) optionally, washing the microspheres obtained in step (f) or (g); and

(i) optionally, collecting the hydrogel HA microspheres of step (d), (e), (f), (g) or (h).

5. The method of any one of claims 1 to 4, wherein -FG_1 is independently selected from the group consisting of:

 (y-56),  (y-1),  (y-6),  (y-39),

 (y-44) and  (y-49);

wherein the dashed line indicates the attachment to the first functionalized HA;

-Y^{01} is independently selected from the group consisting of -F, -Cl, -Br and -I;

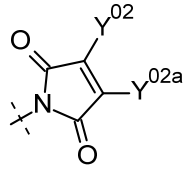
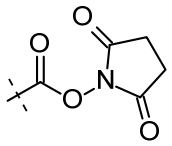
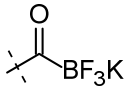
each -R^{08} and -R^{08a} is independently selected from the group consisting of halogen, -H, -CN, -T^0, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl; wherein -T^0, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more -R^{09}, which are the same or different, and wherein C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally interrupted by one or more groups selected from the group consisting of -T^0-, -C(O)O-, -O-, -C(O)-, -C(O)N(R^{010})-, -S(O)$_2$N(R^{010})-, -S(O)N(R^{010})-, -S(O)$_2$-, -S(O)-, -N(R^{010})S(O)$_2$N(R^{010a})-, -S-, -N(R^{010})-, -OC(OR^{010})(R^{010a})-, -N(R^{010})C(O)N(R^{010a})-, and -OC(O)N(R^{010})-;

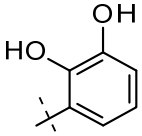
each T^0 is independently selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl, and 8- to 11-membered

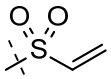
heterobicyclyl; wherein each T^0 is independently optionally substituted with one or more $-R^{09}$, which are the same or different; and

each $-R^{09}$, $-R^{010}$ and $-R^{010a}$ is independently selected from the group consisting of -H and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different; and

$-FG_2$ is independently selected from the group consisting of:


(y-57),

(y-16),

(y-9),

(y-47),

(y-85),

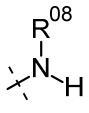
(y-56) and

(y-86);

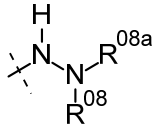
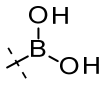
wherein the dashed line indicates the attachment to the second functionalized HA;

each $-Y^{02}$ and $-Y^{02a}$ is independently selected from the group consisting of -H and -Br;

provided that $-FG_1$ is of formula (y-56) then $-FG_2$ is of formula (y-57) or (y-86); if $-FG_1$ is of formula (y-1) then $-FG_2$ is of formula (y-16) or (y-47); if $-FG_1$ is of formula (y-44) then $-FG_2$ is of formula (y-16) or (y-47); if $-FG_1$ is of formula (y-6) then $-FG_2$ is of formula (y-9); if $-FG_1$ is of formula (y-49) then $-FG_2$ is of formula (y-85); if $-FG_1$ is of formula (y-44) then $-FG_2$ is of formula (y-47); or if $-FG_1$ is of formula (y-39) then $-FG_2$ is of formula (y-56).

6. The method of any one of claims 1 to 5, wherein the pH-adjusting agent increases the pH of the emulsion of step (a) and $-FG_1$ is independently selected from the group consisting of:


(y-56),

(y-1),

(y-39),

(y-44) and

(y-49);

wherein the dashed line indicates the attachment to the first functionalized HA;

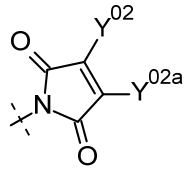
$-Y^{01}$ is independently selected from the group consisting of -F, -Cl, -Br and -I;

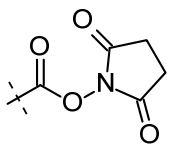
each -R^{08} and -R^{08a} is independently selected from the group consisting of halogen, -H, -CN, -T^0, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl; wherein -T^0, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more -R^{09}, which are the same or different, and wherein C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally interrupted by one or more groups selected from the group consisting of -T^0-, -C(O)O-, -O-, -C(O)-, -C(O)N(R^{010})-, -S(O)$_2$N(R^{010})-, -S(O)N(R^{010})-, -S(O)$_2$-, -S(O)-, -N(R^{010})S(O)$_2$N(R^{010a})-, -S-, -N(R^{010})-, -OC(OR^{010})(R^{010a})-, -N(R^{010})C(O)N(R^{010a})-, and -OC(O)N(R^{010})-;

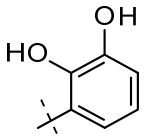
each T^0 is independently selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl, and 8- to 11-membered heterobicyclyl; wherein each T^0 is independently optionally substituted with one or more -R^{09}, which are the same or different; and

each -R^{09}, -R^{010} and -R^{010a} is independently selected from the group consisting of -H and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different; and

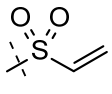
-FG_2 is independently selected from the group consisting of:



(y-57),


(y-16),


(y-85),

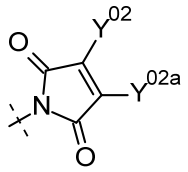

(y-56) and


(y-86);

wherein the dashed line indicates the attachment to the second functionalized HA;

each -Y^{02} and -Y^{02a} is independently selected from the group consisting of -H and -Br;

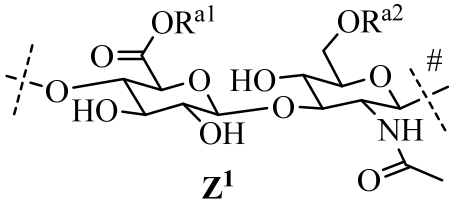
provided that -FG_1 is of formula (y-56) then -FG_2 is of formula (y-57) or (y-86); if -FG_1 is of formula (y-1) then -FG_2 is of formula (y-16); if -FG_1 is of formula (y-44) then -FG_2 is of formula (y-16); or if -FG_1 is of formula (y-39) then -FG_2 is of formula (y-56).

7. The method of any one of claims 1 to 6, wherein -FG_1 is  (y-56), wherein the dashed line indicates the attachment to the first functionalized HA, -FG_2 is  (y-57), wherein the dashed line indicates the attachment to the second functionalized HA, the pH-adjusting agent increases the pH of the emulsion of step (a) from about 1 to about 9, preferably from about 1 to about 5.5, more preferably from about 2 to about 4 and wherein each -Y^{02} and -Y^{02a} is independently selected from the group consisting of -H and -Br.

8. The method of any one of claims 1 to 7, wherein the method comprises the following steps:

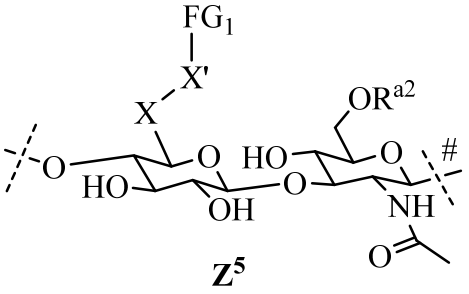
(a) mixing a solution A with a solution B to form an emulsion, wherein solution A comprises a first functionalized HA that is modified with one or more -FG_1 and a second functionalized HA that is modified with one or more -FG_2, wherein -FG_1 and -FG_2 are functional group moieties that are different from each other and wherein -FG_1 on the first functionalized HA reacts with -FG_2 on the second functionalized HA to form a plurality of crosslinks which results in the formation of hydrogel HA microspheres, wherein

the first functionalized HA comprises a plurality of each of the following linearly connected Z^1 and Z^5 units:



Z^1

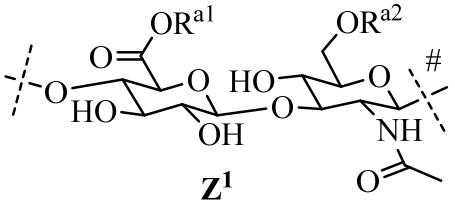
and



Z^5

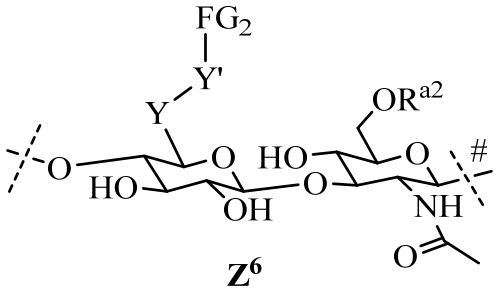
,

the second functionalized HA comprises a plurality of each of the following linearly connected Z^1 and Z^6 units:



Z¹

and



Z⁶

,

wherein

an unmarked dashed line indicates a point of attachment to an adjacent unit at a dashed line marked with # or to a hydrogen atom;

a dashed line marked with # indicates a point of attachment to an adjacent unit at an unmarked dashed line or to a hydroxyl group;

each R^{a1} is independently selected from the group consisting of -H, C_{1-10} alkyl, an ammonium ion, a tetrabutylammonium ion, a cetyl trimethylammonium ion, an alkali metal ion and an alkaline earth metal ion;

each $-R^{a2}$ is independently -H or C_{1-10} alkyl;

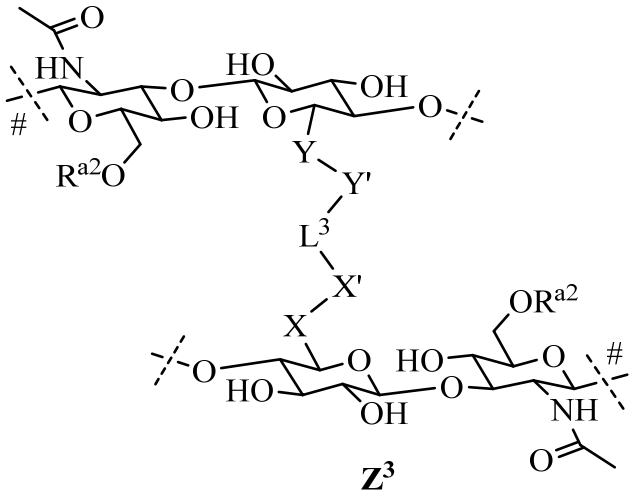
each $-FG_1$, $-FG_2$ is independently the functional group moiety;

each -X-, -Y- is independently a carbonyl group or absent;

each -X'-, -Y'- is independently a spacer moiety or absent;

(b) adding a pH-adjusting agent to the emulsion of step (a);

(c) collecting the obtained hydrogel HA microspheres of step (a) or (b), wherein said hydrogel comprises a plurality of Z^3 units:



Z³

,

wherein

an unmarked dashed line indicates a point of attachment to an adjacent unit at a dashed line marked with # or to a hydrogen atom;

a dashed line marked with # indicates a point of attachment to an adjacent unit at an unmarked dashed line or to a hydroxyl group;

each -R^{a2}, -X-, -Y-, -X'- and -Y'- are defined as in step (a);

each -L^3- is independently a linkage moiety or absent;

(d) optionally, size fractionating the obtained hydrogel HA microparticles of step (a), (b) or (c) to obtain microspheres with a particular particle size distribution;

(e) optionally, washing the hydrogel HA microspheres obtained in step (a), (b), (c) or (d);

(f) optionally, incubating the hydrogel HA microspheres of step (a), (b), (c), (d) or (e) in a buffering agent of a pH ranging from about 8 to about 12;

(g) optionally, incubating the hydrogel HA microspheres of step (a), (b), (c), (d), (e) or (f) with a reducing agent;

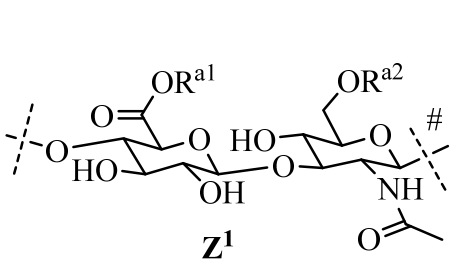
(h) optionally, washing the microspheres obtained in step (f) or (g); and

(i) optionally, collecting the hydrogel HA microspheres of step (d), (e), (f), (g) or (h).

9. The method of any one of claims 1 to 8, wherein the method comprises the following steps:

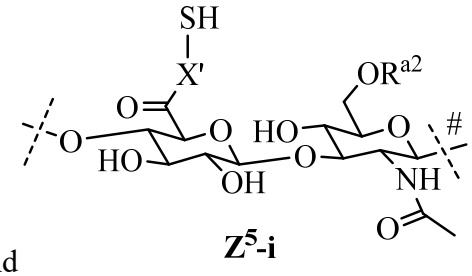
(a) mixing a solution A with a solution B to form an emulsion, wherein solution A comprises a first functionalized HA that is modified with one or more thiol functional groups and a second functionalized HA that is modified with one or more maleimide functional groups, wherein the thiol functional groups on the first functionalized HA react with the maleimide functional groups on the second functionalized HA to form a plurality of crosslinks which results in the formation of hydrogel HA microspheres, wherein

the first functionalized HA comprises a plurality of each of the following linearly connected Z^1 and Z^5-i units:



Z^1

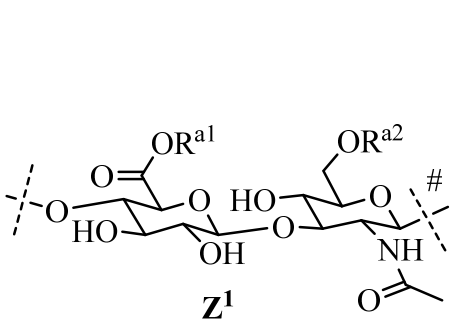
and



Z^5-i

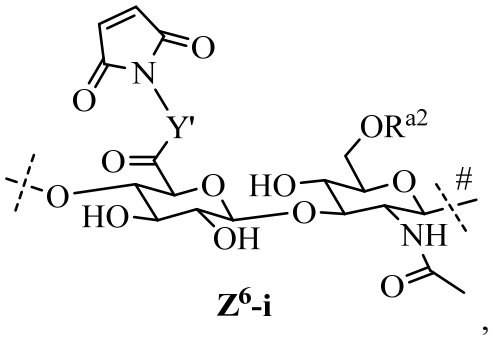
,

the second functionalized HA comprises a plurality of each of the following linearly connected Z^1 and Z^6-i units:



Z^1

and



Z^6-i

,

wherein

an unmarked dashed line indicates a point of attachment to an adjacent unit at a dashed line marked with # or to a hydrogen atom;

a dashed line marked with # indicates a point of attachment to an adjacent unit at an unmarked dashed line or to a hydroxyl group;

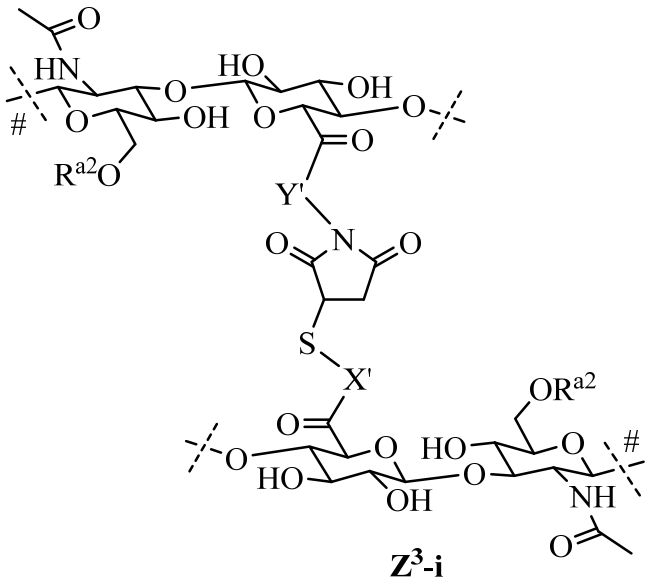
each R^{a1} is independently selected from the group consisting of -H, C_{1-10} alkyl, an ammonium ion, a tetrabutylammonium ion, a cetyl trimethylammonium ion, an alkali metal ion and an alkaline earth metal ion;

each $-R^{a2}$ is independently -H or C_{1-10} alkyl;

each -X'-, -Y'- is independently a spacer moiety or absent;

(b) adding a pH-adjusting agent to the emulsion of step (a);

(c) collecting the obtained hydrogel HA microspheres of step (a) or (b), wherein said hydrogel comprises a plurality of Z^3-i units:



Z^3-i

wherein

an unmarked dashed line indicates a point of attachment to an adjacent unit at a dashed line marked with # or to a hydrogen atom;

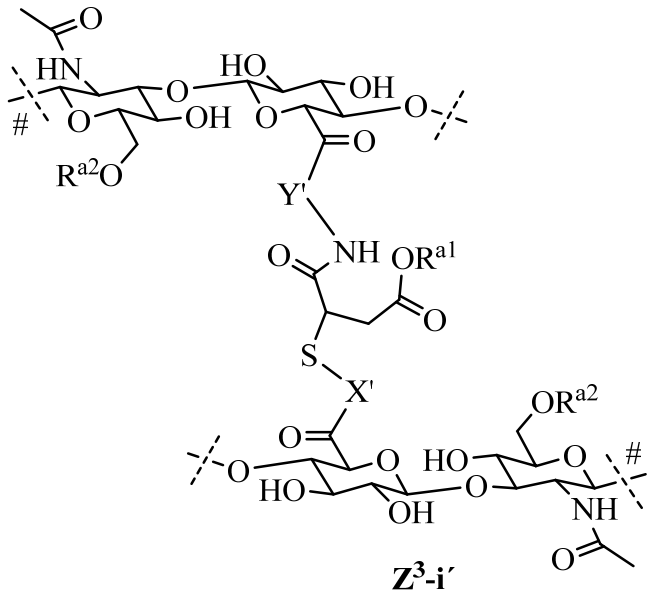
a dashed line marked with # indicates a point of attachment to an adjacent unit at an unmarked dashed line or to a hydroxyl group;

each -R^{a2}, -X'- and -Y'- are defined as in step (a);

(d) optionally, size fractionating the obtained hydrogel HA microparticles of step (a), (b) or (c) to obtain microspheres with a particular particle size distribution;

(e) optionally, washing the hydrogel HA microspheres obtained in step (a), (b), (c) or (d);

(f) optionally, incubating the hydrogel HA microspheres of step (a), (b), (c), (d) or (e) in a buffering agent of a pH ranging from about 8 to about 12, to provide hydrogel HA microspheres comprising a plurality of Z^3-i′ units:



Z^3-i′

wherein

an unmarked dashed line indicates a point of attachment to an adjacent unit at a dashed line marked with # or to a hydrogen atom;

a dashed line marked with # indicates a point of attachment to an adjacent unit at an unmarked dashed line or to a hydroxyl group;

each R^{a1}, -R^{a2}, -X'- and -Y'- are defined as in step (a);

(g) optionally, incubating the hydrogel HA microspheres of step (a), (b), (c), (d), (e) or (f) with a reducing agent;

(h) optionally, washing the microspheres obtained in step (f) or (g); and

(i) optionally, collecting the hydrogel HA microspheres of step (d), (e), (f), (g) or (h).

10. The method of claim 8 or 9, wherein steps (d) and (e) are not optional and steps (f) to (h) are not present.

11. The method of any one of claims 1 to 10, wherein the pH-adjusting agent is selected from the group consisting of N,N,N',N'-tetramethylethylene diamine (TMEDA), 1,4-dimethylpiperazine, 4-methylmorpholine, 4-ethylmorpholine, 1,4-diazabicyclo[2.2.2]octane, 1,1,4,7,10,10-hexamethyltriethylenetetramine, 1,4,7-trimethyl-1,4,7-triazacyclononane, tris[2-(dimethylamino)ethyl]amine, triethylamine, diisopropylethylamine (DIPEA), trimethylamine, N,N-dimethylethylamine,

N,N,N′,N′-tetramethyl-1,6-hexanediamine, N,N,N′,N″,N″-pentamethyldiethylenetriamine, 1,8-diazabicyclo[5.4.0]undec-7-ene, 1,5-diazabicyclo[4.3.0]non-5-ene and hexamethylenetetramine.

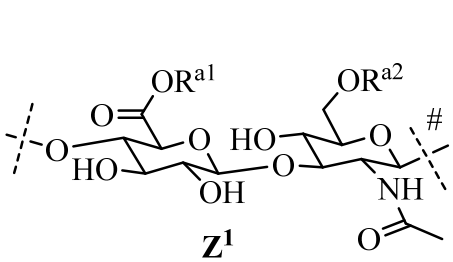
12. The method of any one of claims 1 to 11, wherein each -X'- and -Y'- are independently a spacer moiety selected from the group consisting of -T′-, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl; wherein C_{1-50} alkyl, C_{2-50} alkenyl and C_{2-50} alkynyl are optionally substituted with one or more $-R^{y1}$, which are the same or different and wherein C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally interrupted by one or more groups selected from the group consisting of -T′-, -C(O)O-, -O-, -C(O)-, $-C(O)N(R^{y2})-$, $-S(O)_2N(R^{y2})-$, $-S(O)N(R^{y2})-$, $-S(O)_2-$, -S(O)-, $-N(R^{y2})S(O)_2N(R^{y2a})-$, -S-, $-N(R^{y2})-$, $-OC(OR^{y2})(R^{y2a})-$, $-N(R^{y2})C(O)N(R^{y2a})-$ and $-OC(O)N(R^{y2})-$;
each T′ is independently selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicyclyl, 8- to 30-membered carbopolycyclyl and 8- to 30-membered heteropolycyclyl; wherein each T′ is independently optionally substituted with one or more $-R^{y1}$, which are the same or different;

each $-R^{y1}$ is independently selected from the group consisting of halogen, -CN, oxo (=O), $-COOR^{y3}$, $-OR^{y3}$, $-C(O)R^{y3}$, $-C(O)N(R^{y3}R^{y3a})$, $-S(O)_2N(R^{y3}R^{y3a})$, $-S(O)N(R^{y3}R^{y3a})$, $-S(O)_2R^{y3}$, $-S(O)R^{y3}$, $-N(R^{y3})S(O)_2N(R^{y3a}R^{y3b})$, $-SR^{y3}$, $-N(R^{y3}R^{y3a})$, $-NO_2$, $-OC(O)R^{y3}$, $-N(R^{y3})C(O)R^{y3a}$, $-N(R^{y3})S(O)_2R^{y3a}$, $-N(R^{y3})S(O)R^{y3a}$, $-N(R^{y3})C(O)OR^{y3a}$, $-N(R^{y3})C(O)N(R^{y3a}R^{y3b})$, $-OC(O)N(R^{y3}R^{y3a})$, and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different; and each $-R^{y2}$, $-R^{y2a}$, $-R^{y3}$, $-R^{y3a}$, $-R^{y3b}$ is independently selected from the group consisting of -H and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different.

13. The method of any one of claims 1 to 12, wherein the method comprises the following steps:
(a) mixing a solution A with a solution B to form an emulsion, wherein solution A comprises a first functionalized HA that is modified with one or more thiol functional

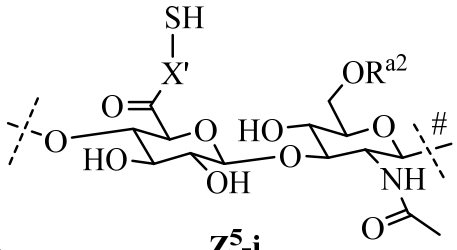
groups and a second functionalized HA that is modified with one or more maleimide functional groups, wherein the thiol functional groups on the first functionalized HA react with the maleimide functional groups on the second functionalized HA to form a plurality of crosslinks which results in the formation of hydrogel HA microspheres, wherein,

the first functionalized HA comprises a plurality of each of the following linearly connected Z^1 and Z^5-i units:



Z^1

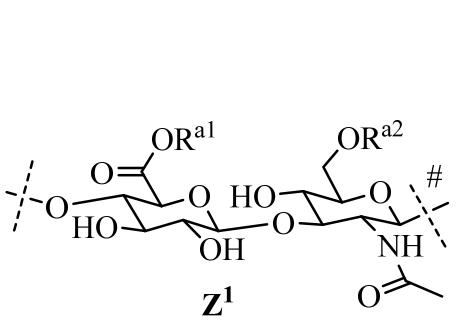
and



Z^5-i

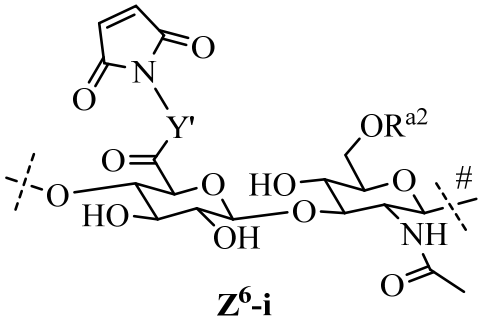
,

the second functionalized HA comprises a plurality of each of the following linearly connected Z^1 and Z^6-i units:



Z^1

and



Z^6-i

,

wherein

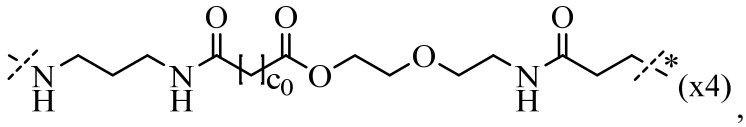
an unmarked dashed line indicates a point of attachment to an adjacent unit at a dashed line marked with # or to a hydrogen atom;

a dashed line marked with # indicates a point of attachment to an adjacent unit at an unmarked dashed line or to a hydroxyl group;

each R^{a1} is H or an alkali metal ion;

each $-R^{a2}$ is -H;

each -X'- is of formula (x4):

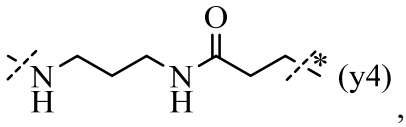


(x4)

,

wherein the unmarked dashed line indicates the attachment to the carbonyl group, the dashed line marked with an asterisk indicates the attachment to the sulfur atom and c_0 is 7;

each -Y'- is of formula (y4):

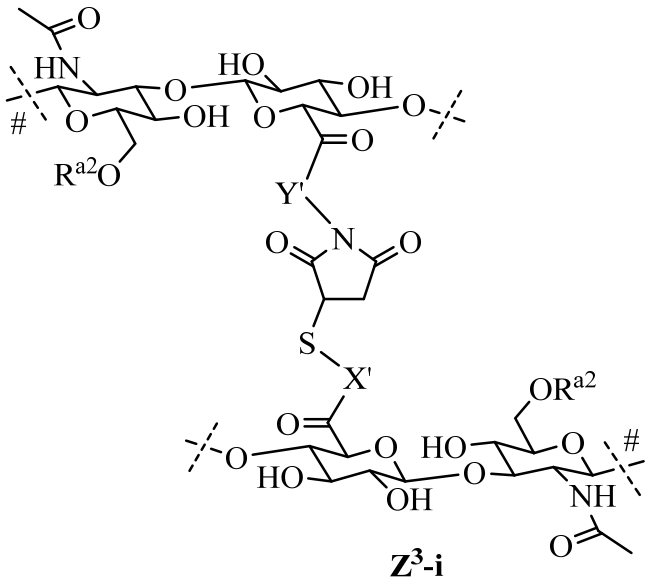


,

wherein the unmarked dashed line indicates the attachment to the carbonyl group and the dashed line marked with an asterisk indicates the attachment to the nitrogen atom of the maleimide ring;

(b) adding TMEDA to the emulsion of step (a);

(c) collecting the obtained hydrogel HA microspheres of step (a) or (b), wherein said hydrogel comprises a plurality of Z^3-i units:



Z^3-i

wherein

an unmarked dashed line indicates a point of attachment to an adjacent unit at a dashed line marked with # or to a hydrogen atom;

a dashed line marked with # indicates a point of attachment to an adjacent unit at an unmarked dashed line or to a hydroxyl group;

each -R^{a2}, -X'- and -Y'- are defined as in step (a);

(d) size fractionating the obtained hydrogel HA microparticles of step (c) to obtain microspheres with a particular particle size distribution;
(e) washing the hydrogel HA microspheres obtained in step (d); and
(f) collecting the hydrogel HA microspheres of step (e).

14. The method of any one of claims 1 to 13, wherein the molecular weight of the first and second functionalized HA independently ranges from about 80 kDa to about 250 kDa, such as from about 90 kDa to about 200 kDa or such as from about 100 kDa to about 150 kDa.

15. The method of any one of claims 9 to 14, wherein the degree of thiol functionalization in Z^5-i is about 5% and the degree of maleimide functionalization in Z^6-i is about 10%.

16. The method of any one of claims 1 to 15, wherein in step (a) solution A further comprises citrate and/or histidine, preferably at a pH of about 2.

17. The method of any one of claims 1 to 16, wherein in step (a) solution B comprises heptane and sorbitan monooleate or tetradecane and sorbitan monooleate.

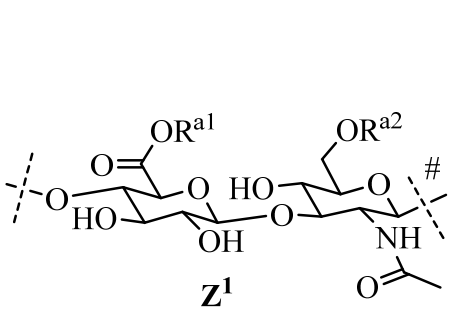
18. The method of any one of claims 1 to 17, wherein in step (b) the pH-adjusting agent is TMEDA and increases the pH of the emulsion of step (a), preferably to a pH of about 4.

19. Hydrogel HA microspheres or pharmaceutically acceptable salts thereof obtainable by any of the methods of any one of claims 1 to 18.

20. A drug conjugate or pharmaceutically acceptable salt thereof comprising the hydrogel HA microspheres of claim 19.

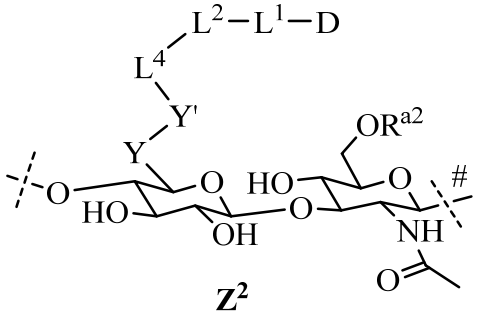
21. A drug conjugate or pharmaceutically acceptable salt thereof comprising a hyaluronic acid (HA) hydrogel microsphere comprising crosslinked HA chains or pharmaceutically acceptable salt thereof comprising crosslinked HA chains to which a plurality of drug

moieties is covalently and reversibly conjugated, said drug conjugate comprising a plurality of each of the following units:



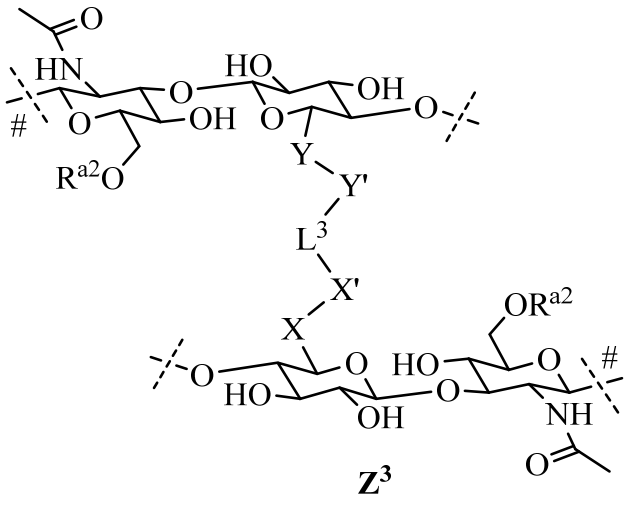
Z¹

,



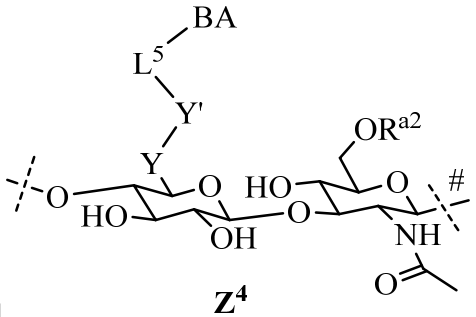
Z²

,



Z³

and



Z⁴

,

wherein

an unmarked dashed line indicates a point of attachment to an adjacent unit at a dashed line marked with # or to a hydrogen atom;

a dashed line marked with # indicates a point of attachment to an adjacent unit at an unmarked dashed line or to a hydroxyl group;

each R^{a1} is independently selected from the group consisting of -H, C_{1-10} alkyl, an ammonium ion, a tetrabutylammonium ion, a cetyl trimethylammonium ion, an alkali metal ion and an alkaline earth metal ion;

each $-R^{a2}$ is independently -H or C_{1-10} alkyl;

each -X-, -Y- is independently a carbonyl group or absent;

each -X'-, -Y'- is independently a spacer moiety or absent;

wherein each -D is independently a drug moiety that is covalently and reversibly conjugated to -L^1-;

each -L^1- is independently a reversible linker moiety;

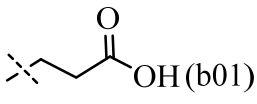
each -L^2- is independently a spacer moiety or absent;

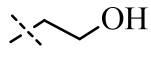
each -L^3-, -L^4-, -L^5- is independently a linkage moiety or absent; and

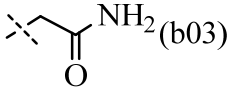
each -BA is independently a blocking agent.

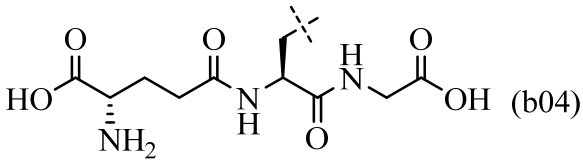
22. The drug conjugate or pharmaceutically acceptable salt thereof of claim 21, wherein said drug conjugate comprises Z^1 in a range of about 50% to about 98%, Z^2 in a range of about 0.1% to about 20%, Z^3 in a range of about 0.1% to about 20% and Z^4 in a range of about 0.1% to about 10%.

23. The drug conjugate or pharmaceutically acceptable salt thereof of claim 21 or 22, wherein -BA is selected from the group consisting of

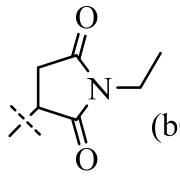

(b01),


(b02),


(b03),

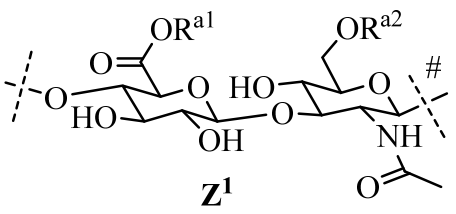

(b04)

and


(b05),

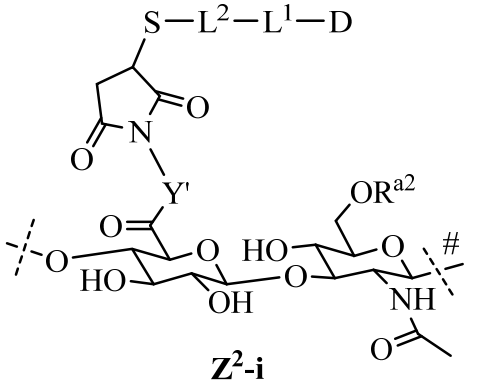
wherein the dashed line indicates the attachment to -L^5-.

24. The drug conjugate or pharmaceutically acceptable salt thereof of any one of claims 21 to 23, wherein said drug conjugate comprises a plurality of each of the following units:



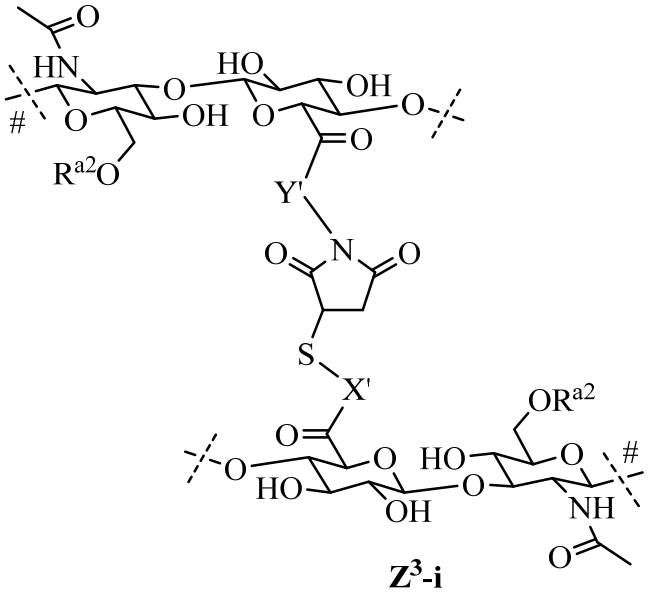
Z^1

,



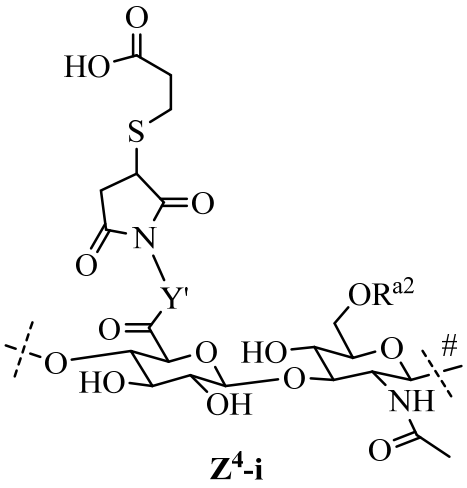
Z^2-i

,



Z^3-i

and



Z^4-i

,

each R^{a1} is independently selected from the group consisting of -H, C_{1-10} alkyl, an ammonium ion, a tetrabutylammonium ion, a cetyl trimethylammonium ion, an alkali metal ion and an alkaline earth metal ion;

each -R^{a2} is independently -H or C_{1-10} alkyl;

each -X'-, -Y'- is independently a spacer moiety or absent;

wherein each -D is independently a drug moiety that is covalently and reversibly conjugated to -L^1-;

each -L^1- is independently a reversible linker moiety;

each -L^2- is independently a spacer moiety or absent; and

wherein said drug conjugate comprises Z^1 in a range of about 50% to about 98%, Z^2-i in a range of about 0.1% to about 20%, Z^3-i in a range of about 0.1% to about 20% and Z^4-i in a range of about 0.1% to about 10%.

25. The drug conjugate or pharmaceutically acceptable salt thereof of any one of claims 21 to 24, wherein -D is selected from the group consisting of small molecule, medium size, peptide and protein drug moieties.

26. The drug conjugate or pharmaceutically acceptable salt thereof of any one of claims 21 to 25, wherein -D is a protein drug moiety.

27. The drug conjugate or pharmaceutically acceptable salt thereof of any one of claims 21 to 26, wherein -D is a monoclonal or polyclonal antibody or fragment or fusion thereof.

28. The drug conjugate or pharmaceutically acceptable salt thereof of any one of claims 21 to 27, wherein each R^{a1} is H or an alkali metal ion and -R^{a2} is -H.

29. A pharmaceutical composition comprising the drug conjugate or pharmaceutically acceptable salt thereof of any one of claims 21 to 28 and at least one pharmaceutically acceptable excipient.

30. The drug conjugate or pharmaceutically acceptable salt thereof of any one of claims 21 to 28 or the pharmaceutical composition of claim 29 for use as a medicament.

31. The use of the drug conjugate or pharmaceutically acceptable salt thereof of any one of claims 21 to 28 or the pharmaceutical composition of claim 29 in the manufacture of a medicament for treating an ocular disease.