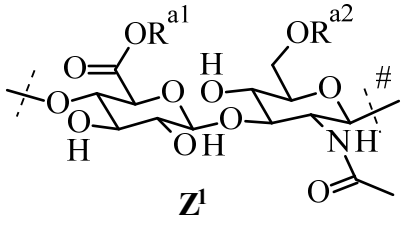
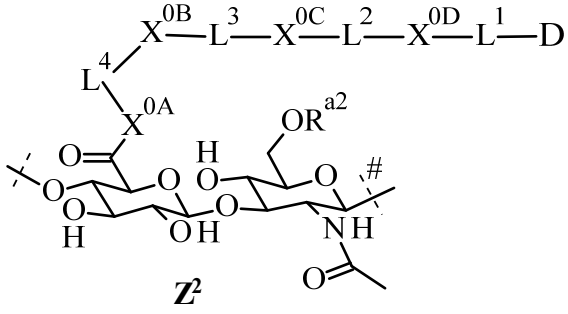
Claims

1. A conjugate comprising crosslinked hyaluronic acid strands to which a plurality of drug moieties are covalently and reversibly conjugated, wherein the conjugate comprises a plurality of connected units selected from the group consisting of



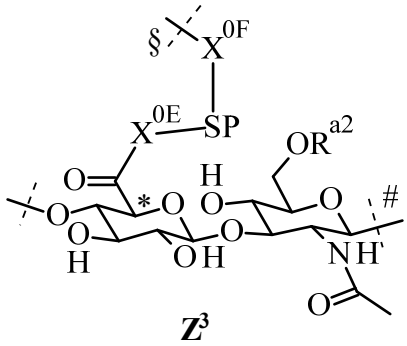
Z¹

,



Z²

,



Z³

and ,

wherein

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

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

a dashed line marked with § indicates a point of connection between at least two units Z^3 via a moiety -CL-;

each -D is independently a drug moiety;

each -L^1- is independently a linker moiety to which -D is covalently and reversibly conjugated;

each -L^2-, -L^3- and -L^4- is independently either absent or a spacer moiety;

each -CL- is independently a moiety connecting at least two units Z^3 and wherein there is at least one degradable bond in the direct connection between any two carbon atoms marked with the * connected by a moiety -CL-;

each -SP- is independently absent or a spacer moiety;

each -R^{a1} is independently selected from the group consisting of -H, C_{1-4} alkyl, an ammonium ion, a tetrabutylammonium ion, a cetyl methylammonium ion, an alkali metal ion and an alkaline earth metal ion;

each -R^{a2} is independently selected from the group consisting of -H and C_{1-10} alkyl;

each -X^{0A}-, -X^{0B}-, -X^{0C}-, -X^{0D}-, -X^{0E}- and -X^{0F}- is independently either absent or a linkage;

optionally -X^{0A}- and/or -X^{0B}- form together with -L^4- or parts of -L^4- one or more ring structure selected from the group consisting of 4- to 7-membered heterocyclyl, 8- to 11-membered heterobicyclyl and adamantyl;

optionally -X^{0B}- and/or -X^{0C}- form together with -L^3- or parts of -L^3- one or more ring structure selected from the group consisting of 4- to 7-membered heterocyclyl, 8- to 11-membered heterobicyclyl and adamantyl;

optionally, -X^{0C}- and/or -X^{0D}- form together with -L^2- or parts of -L^2- one or more ring structure selected from the group consisting of 4- to 7-membered heterocyclyl, 8- to 11-membered heterobicyclyl and adamantyl;

optionally -X^{0E}- and/or -X^{0F}- form together with -SP- or parts of -SP- one or more ring structure selected from the group consisting of 4- to 7-membered heterocyclyl, 8- to 11-membered heterobicyclyl and adamantyl;

wherein

all units Z^1 present in the conjugate may be the same or different;

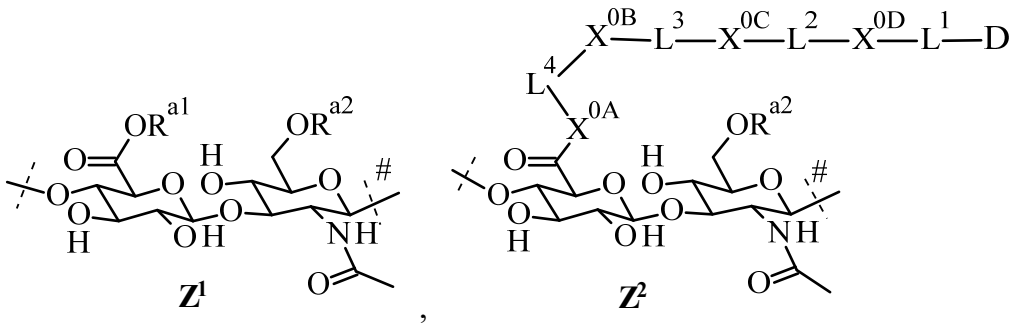
all units Z^2 present in the conjugate may be the same or different;

all units Z^3 present in the conjugate may be the same or different;

at least one unit Z^3 is present per hyaluronic acid strand which is connected to at least one unit Z^3 on a different hyaluronic acid strand; and

the conjugate comprises at least one moiety -L^1-D.

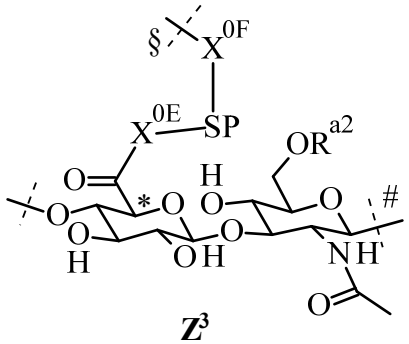
2. The conjugate of claim 1, wherein the conjugate comprises crosslinked hyaluronic acid strands to which a plurality of drug moieties are covalently and reversibly conjugated, wherein the conjugate comprises a plurality of connected units selected from the group consisting of



Z¹

Z²

,



Z³

and ,

wherein

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

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

a dashed line marked with § indicates a point of connection between at least two units Z^3 via a moiety -CL-;

-D, -L^1-, -L^2-, -L^3-, -L^4-, -SP-, -CL-, -X^{0A}-, -X^{0B}-, -X^{0C}-, -X^{0D}-, -X^{0E}-, -X^{0F}-, -R^{a1} and -R^{a2} are used as in claim 1;

wherein

all units Z^1 present in the conjugate may be the same or different;

all units Z^2 present in the conjugate may be the same or different;

all units Z^3 present in the conjugate may be the same or different;

the number of Z^1 units ranges from 1% to 98% of the total number of units present in the conjugate;

the number of Z^2 units ranges from 1% to 98% of the total number of units present in the conjugate, provided at least one unit Z^2 is present in the conjugate;

the number of Z^3 units ranges from 1% to 97% of the total number of units present in the conjugate, provided that at least one unit Z^3 is present per strand; and

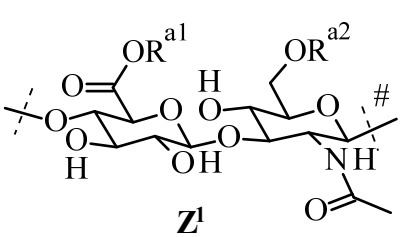
wherein at least 70% of all hyaluronic acid strands comprise at least one moiety Z^2 and at least one moiety Z^3.

3. The conjugate of claim 2, wherein the number of units Z^2 ranges from 1% to 70% of all units present in the conjugate.

4. The conjugate of claim 2 or 3, wherein the number of units Z^3 ranges from 1% to 30%.

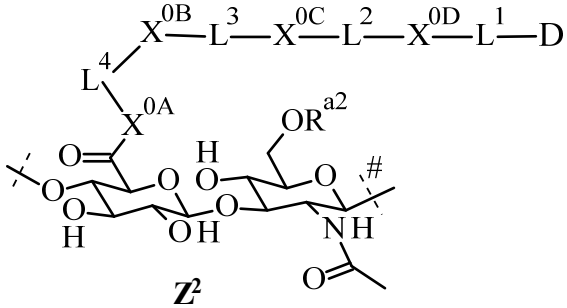
5. The conjugate of any one of claims 2 to 4, wherein the number of units Z^1 ranges from 10% to 97%.

6. The conjugate of claim 1, wherein the conjugate comprises crosslinked hyaluronic acid strands to which a plurality of drug moieties are covalently and reversibly conjugated, wherein the conjugate comprises a plurality of connected units selected from the group consisting of



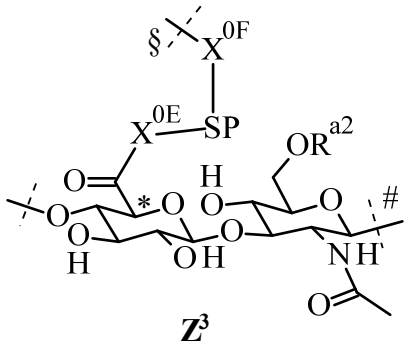
Z¹

,



Z²

,



Z³

and ,

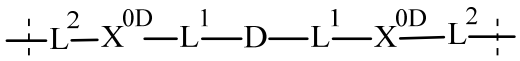
wherein

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

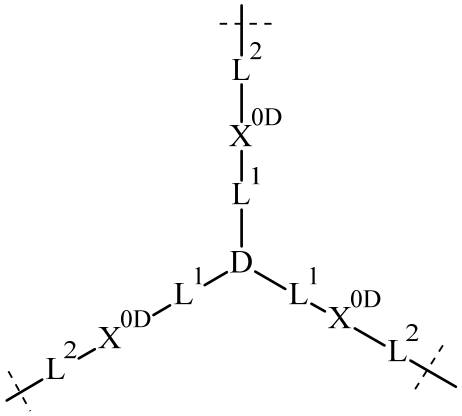
a dashed line marked with # indicates a point of attachment to an adjacent unit at an unmarked dashed line or to a hydroxyl;

a dashed line marked with § indicates a point of connection between at least two units Z^3 via a moiety -CL-;

each -CL- comprises at least one degradable bond between the two carbon atoms marked with the * connected by a moiety -CL- and each -CL- is independently selected from the group consisting of formula (C-i) and (C-ii)



(C-i),



(C-ii),

wherein

dashed lines indicate attachment to a moiety -X^{0F}- of a unit Z^3;

-D, -L^1-, -L^2-, -L^3-, -L^4-, -SP-, -X^{0A}-, -X^{0B}-, -X^{0C}-, -X^{0D}-, -X^{0E}-, -X^{0F}-, -R^{a1} and -R^{a2} are used as in claim 1;

wherein

all units Z^1 present in the conjugate may be the same or different;

all units Z^2 present in the conjugate may be the same or different;

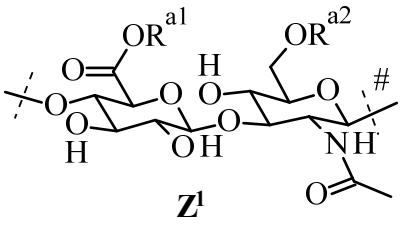
all units Z^3 present in the conjugate may be the same or different;

the number of Z^1 units ranges from 1% to 98% of the total number of units present in the conjugate;

the number of Z^2 units ranges from 0% to 98% of the total number of units present in the conjugate;

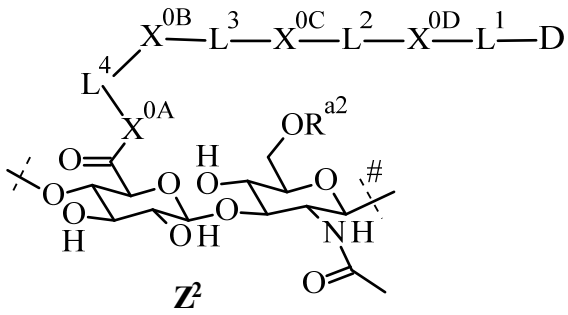
the number of Z^3 units ranges from 1% to 97% of the total number of units present in the conjugate, provided that at least one unit Z^3 is present per strand which is connected to at least one unit Z^3 on a different hyaluronic acid strand.

7. The conjugate of claim 1, wherein the conjugate comprises crosslinked hyaluronic acid strands to which a plurality of drug moieties are covalently and reversibly conjugated, wherein the conjugate comprises a plurality of connected units selected from the group consisting of



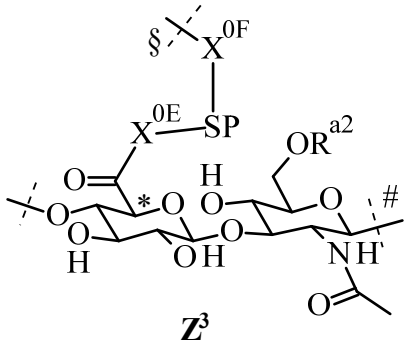
Z¹

,



Z²

,



Z³

and ,

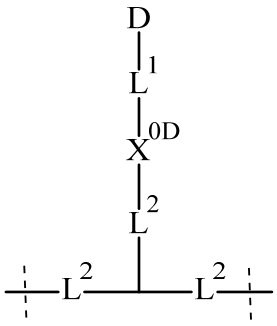
wherein

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

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

a dashed line marked with § indicates a point of connection between two units Z^3 via a moiety -CL-;

each -CL- comprises at least one degradable bond between the two carbon atoms marked with the * connected by a moiety -CL- and each -CL- is independently of formula (D-i)



(D-i),

wherein

dashed lines indicate attachment to a moiety -X^{OF}- of a unit Z^3;

-D, -L^1-, -L^2-, -L^3-, -L^4-, -SP-, -X^{0A}-, -X^{0B}-, -X^{0C}-, -X^{0D}-, -X^{0E}-, -X^{0F}-, -R^{a1} and -R^{a2} are used as defined in claim 1;

wherein

all units Z^1 present in the conjugate may be the same or different;

all units Z^2 present in the conjugate may be the same or different;

all units Z^3 present in the conjugate may be the same or different;

the number of units Z^1 ranges from 1% to 99% of the total number of units present in the conjugate;

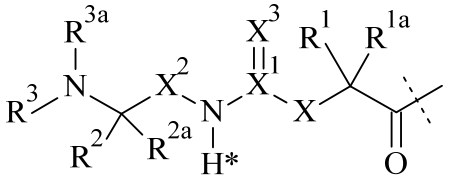
the number of units Z^2 ranges from 0% to 98% of the total number of units present in the conjugate; and

the number of units Z^3 ranges from 1% to 97% of the total number of units present in the conjugate, provided that at least one unit Z^3 is present per strand.

8. The conjugate of any one of claims 1 to 7, wherein -D is an antibiotic moiety.

9. The conjugate of any one of claims 1 to 7, wherein -D is an anti VEGF antibody moiety or fragment thereof.

10. The conjugate of any one of claims 1 to 9, wherein $-L^1-$ is of formula (I):



,

wherein the dashed line indicates the attachment to a nitrogen, hydroxyl or thiol of -D;

-X- is selected from the group consisting of $-C(R^4R^{4a})-$, $-N(R^4)-$, -O-, $-C(R^4R^{4a})-C(R^5R^{5a})-$, $-C(R^5R^{5a})-C(R^4R^{4a})-$, $-C(R^4R^{4a})-N(R^6)-$, $-N(R^6)-C(R^4R^{4a})-$, $-C(R^4R^{4a})-O-$, $-O-C(R^4R^{4a})-$, and $-C(R^7R^{7a})-$,

X^1 is selected from the group consisting of C and S(O);

$-X^2-$ is selected from the group consisting of $-C(R^8R^{8a})-$ and $-C(R^8R^{8a})-C(R^9R^{9a})-$;

$=X^3$ is selected from the group consisting of =O, =S, and =N-CN;

$-R^1$, $-R^{1a}$, $-R^2$, $-R^{2a}$, $-R^4$, $-R^{4a}$, $-R^5$, $-R^{5a}$, $-R^6$, $-R^8$, $-R^{8a}$, $-R^9$ and $-R^{9a}$ are independently selected from the group consisting of -H and C_{1-6} alkyl;

$-R^3$ and $-R^{3a}$ are independently selected from the group consisting of -H and C_{1-6} alkyl, provided that in case one of $-R^3$ and $-R^{3a}$ or both are other than -H they are connected to N to which they are attached through an sp^3-hybridized carbon atom;

-R^7 is selected from the group consisting of -$N(R^{10}R^{10a})$ and -NR^{10}-(C=O)-R^{11};

-R^{7a}, -R^{10}, -R^{10a} and -R^{11} are independently selected from the group consisting of -H and C_{1-6} alkyl;

alternatively, one or more of the pairs -R^{1a}/-R^{4a}, -R^{1a}/-R^{5a}, -R^{1a}/-R^{7a}, -R^{4a}/-R^{5a} and -R^{8a}/-R^{9a} form a chemical bond;

alternatively, one or more of the pairs -R^1/-R^{1a}, -R^2/-R^{2a}, -R^4/-R^{4a}, -R^5/-R^{5a}, -R^8/-R^{8a} and -R^9/-R^{9a} are joined together with the atom to which they are attached to form a C_{3-10} cycloalkyl or 3- to 10-membered heterocyclyl;

alternatively, one or more of the pairs -R^1/-R^4, -R^1/-R^5, -R^1/-R^6, -R^1/-R^{7a}, -R^4/-R^5, -R^4/-R^6, -R^8/-R^9 and -R^2/-R^3 are joined together with the atoms to which they are attached to form a ring A;

alternatively, -R^3/-R^{3a} are joined together with the nitrogen atom to which they are attached to form a 3- to 10-membered heterocycle;

A is 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; and

wherein -L^1- is substituted with -X^{0D}-L^2- and wherein -L^1- is optionally further substituted, provided that the hydrogen marked with the asterisk in formula (I) is not replaced by -X^{0D}-L^2- or a substituent.

11. The conjugate of any one of claims 1 to 10, wherein -CL- is C_{1-50} alkyl, which is optionally interrupted by one or more atoms or groups selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-, -C(O)N(R^{c1})-, -$S(O)_2$-, -S(O)-, -S-, -N(R^{c1})-, -OC(OR^{c1})(R^{c1a})- and -OC(O)N(R^{c1})-;

wherein -T- is 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; and

-R^{c1} and -R^{c1a} are selected from the group consisting of -H and C_{1-6} alkyl.

12. A pharmaceutical composition comprising at least one conjugate of any one of claims 1 to 11 and at least one excipient.

13. The conjugate of any one of claims 1 to 11 or the pharmaceutical composition of claim 12 for use in therapy.

14. Use of the conjugate of any one of claims 1 to 11 or the pharmaceutical composition of claim 12 in the preparation of a medicament for treating a disease that can be treated with D-H or D-OH.

15. A method of preparing a pharmaceutical formulation comprising a conjugate of any one of claims 1 to 11, wherein the method comprises the steps of

(a) providing said conjugate;

(b) subjecting the conjugate of step (a) to a solution comprising a buffering agent, a surfactant and a salt comprising multivalent ions to which a swelling agent is added after addition of said solution;

(c) homogenizing the admixture of step (b);

(d) deswelling the conjugate of step (c) in a deswelling solution comprising at least a deswelling agent;

(e) isolating the conjugate from the admixture of step (d);

(f) subjecting the conjugate of step (e) to a solution comprising a buffering agent, a surfactant, a salt comprising bivalent ions, a hydrophilic polymer of a molecular weight higher than 10 kDa, a density-modifying agent and a polarity-modifying agent, to which a swelling agent is added after addition of said solution;

(g) homogenizing the admixture of step (f);

(h) deswelling the conjugate of step (g) in a deswelling solution comprising at least a deswelling agent;

(i) isolating the conjugate from the admixture of step (h); and

wherein, there may be optional washing steps between steps (c) and (d), (f) and (g), and (g) and (h).