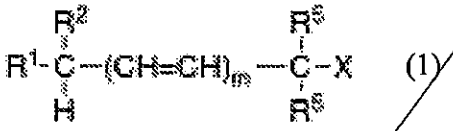
Claims

1. A method to prepare a biodegradable hydrogel said method comprising reacting at least a first reactive polymer with a cleavable crosslinker compound

wherein said cleavable crosslinker compound comprises a first functional group that reacts with the reactive polymer and a moiety that is cleaved by elimination under physiological conditions wherein said moiety comprises a second functional group that reacts with a reactive polymer.

2. The method of claim 1 wherein the cleavable crosslinker compound is of formula (1)



(1)

wherein

m is 0 or 1;

X comprises a functional group capable of connecting to a reactive polymer that is amenable to elimination under physiological conditions and said second functional group, Z^2;

wherein at least one of R^1, R^2, and R^5 comprises said first functional group Z^1 capable of connecting to a polymer;

wherein one and only one of R^1 and R^2 may be H or may be alkyl, arylalkyl or heteroarylalkyl, each optionally substituted;

at least one or both R^1 and R^2 is independently CN; NO_2;

optionally substituted aryl;

optionally substituted heteroaryl;

optionally substituted alkenyl;

optionally substituted alkynyl;

COR^3 or SOR^3 or SO_2R^3 wherein

R^3 is H or optionally substituted alkyl;

aryl or arylalkyl, each optionally substituted;

heteroaryl or heteroarylalkyl, each optionally substituted; or

OR^9 or NR^9_2 wherein each R is independently H or optionally substituted alkyl, or both R^9 groups taken together with the nitrogen to which they are attached form a heterocyclic ring;

SR^4 wherein

R^4 is optionally substituted alkyl;

aryl or arylalkyl, each optionally substituted; or

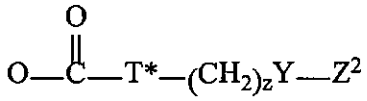
heteroaryl or heteroarylalkyl, each optionally substituted;

wherein R^1 and R^2 may be joined to form a 3-8 membered ring; and

each R^5 is independently H or is alkyl, alkenylalkyl, alkynylalkyl, $(OCH_2CH_2)_p$ O-alkyl wherein p=1-1000, aryl, arylalkyl, heteroaryl or heteroarylalkyl, each optionally substituted.

3. The method of claim 2 wherein

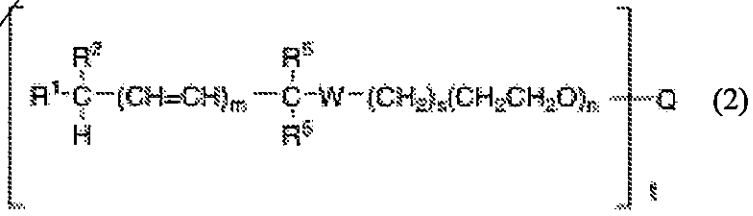
X is succinimidyl carbonate, sulfosuccinimidyl carbonate, nitrophenyl carbonate, chloroformate, fluoroformate, or



wherein T* is O, S or NR^6 wherein R^6 is H, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, or optionally substituted heteroarylalkyl; z is 1-6; and Y is absent or is OR^7 or SR^7, wherein R^7 is optionally substituted alkylene, optionally substituted phenylene or $(OCH_2CH_2)_p$, wherein p=1-1000, and Z^2 is a functional group capable of connecting with a reactive polymer.

4. The method of claim 3 wherein each of Z^1 and Z^2 independently comprises N_3, NH_2, NH-$CO_2{}^tBu$, SH, S^tBu, maleimide, CO_2H, $CO_2{}^tBu$, 1,3-diene, cyclopentadiene, furan, alkyne, cyclooctyne, acrylate, or acrylamide; and wherein when one Z comprises N_3 the other does not comprise alkyne or cyclooctyne; when one Z comprises SH the other does not comprise maleimide, acrylate, or acrylamide; when one Z comprises NH_2, the other does not comprise CO_2H; when one Z comprises 1,3-diene or cyclopentadiene the other does not comprise furan.

5. The method of Claim 1 wherein the cleavable linker compound has the formula



(2)

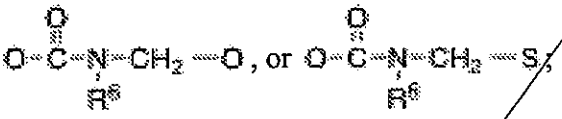
wherein

m is 0 or 1;

n is 1-1000;

s is 0-2;

t is 2,4, 8, 16 or 32;

W is O(C=O)O, O(C=O)NH, O(C=O)S, , or ;

Q is a core group having a valency=t;

wherein at least one of R^1, R^2, and R^5 comprises a functional group Z^1 capable of connecting to a polymer, and

at least one or both R^1 and R^2 is independently CN; NO_2;

optionally substituted aryl;

optionally substituted heteroaryl;

optionally substituted alkenyl;

optionally substituted alkynyl;

COR^3 or SOR^3 or SO_2R^3 wherein

R^3 is H or optionally substituted alkyl;

aryl or arylalkyl, each optionally substituted;

heteroaryl or heteroarylalkyl, each optionally substituted; or

OR^9 or NR^9_2 wherein each R is independently H or optionally substituted alkyl, or both R^9 groups taken together with the nitrogen to which they are attached form a heterocyclic ring;

SR^4 wherein

R^4 is optionally substituted alkyl;

aryl or arylalkyl, each optionally substituted; or

heteroaryl or heteroarylalkyl, each optionally substituted;

wherein R^1 and R^2 may be joined to form a 3-8 membered ring; and

wherein one and only one of R^1 and R^2 may be H or may be alkyl, arylalkyl or heteroarylalkyl, each optionally substituted; and

each R^5 is independently H or is alkyl, alkenylalkyl, alkynylalkyl, $(OCH_2CH_2)_p$ O-alkyl wherein p=1-1000, aryl, arylalkyl, heteroaryl or heteroarylalkyl, each optionally substituted.

6. The method of claim 5 wherein Z^1 comprises N_3, NH_2, NH-$CO_2{}^tBu$, SH, S^tBu, maleimide, CO_2H, $CO_2{}^tBu$, 1,3-diene, cyclopentadiene, furan, alkyne, cyclooctyne, acrylate, or acrylamide.

7. The method of claim 2 wherein Z^1 comprises N_3, NH_2, NH-$CO_2{}^tBu$, SH, S^tBu, maleimide, CO_2H, $CO_2{}^tBu$, 1,3-diene, cyclopentadiene, furan, alkyne, cyclooctyne, acrylate, or acrylamide.

8. The method of claim 3 wherein each Z^1 and Z^2 independently comprises N_3, NH_2, NH-$CO_2{}^tBu$, SH, S^tBu, maleimide, CO_2H, $CO_2{}^tBu$, 1,3-diene, cyclopentadiene, furan, alkyne, cyclooctyne, acrylate, or acrylamide.

9. The method of claim 1 wherein the first and any second polymer is selected from the group consisting of homopolymeric or copolymeric polyethylene glycols, polypropylene glycols, poly(N-vinylpyrrolidone), polymethacrylates, polyphosphazenes, polylactides, polyacrylamides, polyglycolates, polyethylene imines, agaroses, dextrans, gelatins, collagens, polylysines, chitosans, alginates, hyaluronans, pectins, or carrageenans that either comprise suitable reactive functionalities in their native state or have been derivatized so as to comprise suitable reactive functionalities or is of the formula $[Z^3\text{-}(CH_2)_s(CH_2CH_2O)_n]_tQ$, wherein Z^3 is a reactive functional group, n is 10-1000 and s, Q, and t are as defined in claim 5.

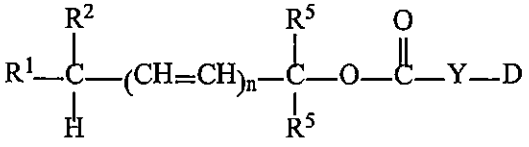
10. The method of claim 1 wherein a first and a second reactive polymer are reacted with said cleavable crosslinker compound, sequentially or simultaneously,

11. The method of claim 10 wherein the first and second functional groups are the same.

12. A hydrogel produced by the method of claims 1-11.

13. The hydrogel of claim 13 which further comprises a drug.

14. The hydrogel of claim 13 wherein the drug is contained in a residue of formula (3)



(3)

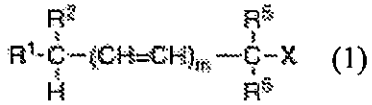
wherein at least one of R^1, R^2, R^5 comprises a first functional group for linking to a polymer and wherein R^1, R^2, R^5 and m are as defined in claim 2;

D is the residue of the drug; and

Y is NH or $NBCH_2$ wherein B is H, alkyl, arylalkyl, heteroaryl, or heteroarylalkyl, each optionally substituted.

15. A hydrogel that is biodegradable under physiological conditions which hydrogel comprises one or more polymers crosslinked by a linker that decomposes by an elimination reaction.

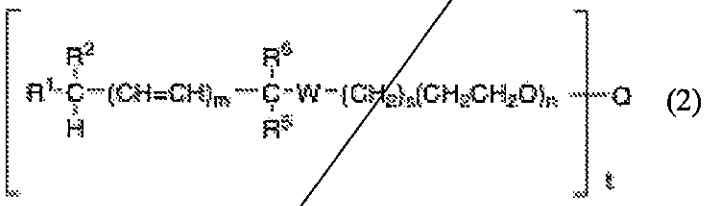
16. The hydrogel of claim 13 wherein the linker, when disposed in the polymer, is a residue of formula (1)



(1)

wherein at least one of R^1, R^2, R^5 is coupled to said one or more polymers as is X and wherein R^1, R^2, R^5 , m, and X are as defined in claim 2.

17. The hydrogel of claim 15 wherein said linker is a residue of formula (2)



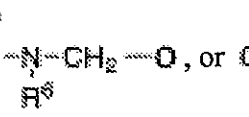
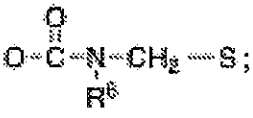
(2)

wherein at least two of said R^1, R^2, R^5 is coupled to said one or more polymers and wherein R^1, R^2, R^5 , m are as defined in claim 2, and

n is 1-1000;

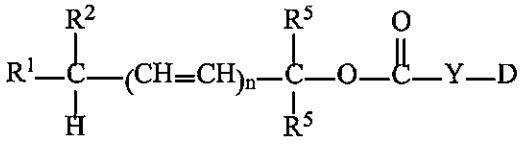
s is 0-2;

t is 2,4, 8, 16 or 32;

W is O(C=O)O, O(C=O)NH, O(C=O)S,  , or  ;

18. The hydrogel of any of claims 15-17 which further comprises a drug.

19. The hydrogel of claim 18 wherein said hydrogel includes a residue of formula (3)



(3)

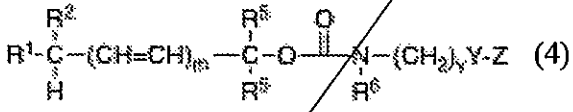
wherein at least one of R^1, R^2, R^5 comprises a first functional group for linking to a polymer and wherein R^1, R^2, R^5 and m are as defined in claim 2;

D is the residue of the drug; and

Y is NH or $NBCH_2$ wherein B is H, alkyl, arylalkyl, heteroaryl, or heteroarylalkyl, each optionally substituted.

20. The hydrogel of claim 16 or 17 wherein the polymer is of the formula $[Z^3\text{-}(CH_2)_s(CH_2CH_2O)_n]_tQ$, wherein Z^3 is a reactive functional group, n is 10-1000 and s, Q, and t are as defined in claim 5.

21. A crosslinking compound of formula (4)



(4)

wherein at least one of R^1, R^2, and R^5 further comprises a first functional group Z^1 capable of connecting to a polymer;

wherein

m is 0 or 1;

R^6 is H, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, or optionally substituted heteroarylalkyl;

v is 1-6;

Y is absent or is OR^7 or SR^7, wherein R^7 is optionally substituted alkylene, optionally substituted phenylene, or $(OCH_2CH_2)_p$, wherein p=1-1000;

Z^2 is a functional group capable of connecting with a reactive polymer;

at least one or both R^1 and R^2 is independently CN; NO_2;

optionally substituted aryl;

optionally substituted heteroaryl;

optionally substituted alkenyl;

optionally substituted alkynyl;

COR^3 or SOR^3 or SO_2R^3 wherein

R^3 is H or optionally substituted alkyl;

aryl or arylalkyl, each optionally substituted;

heteroaryl or heteroarylalkyl, each optionally substituted; or

OR^9 or NR^9_2 wherein each R is independently H or optionally substituted alkyl, or both R^9 groups taken together with the nitrogen to which they are attached form a heterocyclic ring;

SR^4 wherein

R^4 is optionally substituted alkyl;

aryl or arylalkyl, each optionally substituted; or

heteroaryl or heteroarylalkyl, each optionally substituted;

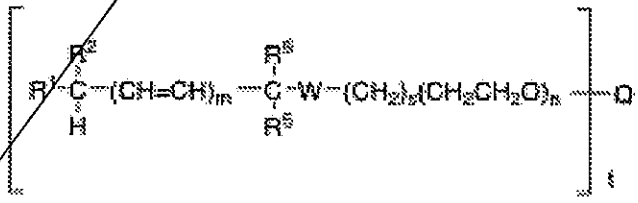
wherein R^1 and R^2 may be joined to form a 3-8 membered ring; and

wherein one and only one of R^1 and R^2 may be H or may be alkyl, arylalkyl or heteroarylalkyl, each optionally substituted; and

each R^5 is independently H or is alkyl, alkenylalkyl, alkynylalkyl, $(OCH_2CH_2)_p$ O-alkyl wherein p=1-1000, aryl, arylalkyl, heteroaryl or heteroarylalkyl, each optionally substituted.

22. The compound of claim 21 wherein each Z^1 and Z^2 comprises N_3, NH_2, NH-$CO_2{}^tBu$, SH, S^tBu, maleimide, CO_2H, $CO_2{}^tBu$, 1,3-diene, cyclopentadiene, furan, alkyne, cyclooctyne, acrylate, vinyl sulfone, vinyl sulfonamide, or acrylamide and wherein when one Z comprises N_3 the other Z does not comprise alkyne or cyclooctyne; when one Z comprises SH the other Z does not comprise maleimide, acrylate, or acrylamide; when one Z comprises NH_2 the other Z does not comprise CO_2H; when one Z comprises a 1,3-diene or cyclopentadiene the other Z does not comprise furan.

23. A crosslinking compound of formula (2)



(2)

wherein

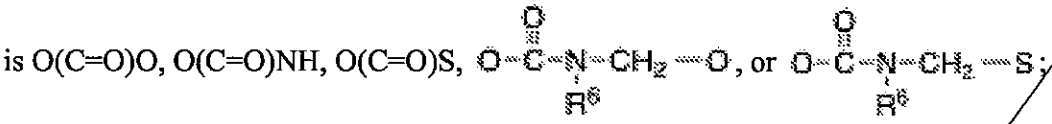
wherein in at least two instances R^1, R^2, and/or R^5 further comprises a functional group Z capable of connecting to a polymer;

m is 0 or 1;

n is 1-1000;

s is 0-2;

t is 2,4, 89, 16 or 32;

W is O(C=O)O, O(C=O)NH, O(C=O)S, , or ;

Q is a core group having a valency = t;

at least one or both R^1 and R^2 is independently CN; NO_2;

optionally substituted aryl;

optionally substituted heteroaryl;

optionally substituted alkenyl;

optionally substituted alkynyl;

COR^3 or SOR^3 or SO_2R^3 wherein

R^3 is H or optionally substituted alkyl;

aryl or arylalkyl, each optionally substituted;

heteroaryl or heteroarylalkyl, each optionally substituted; or

OR^9 or NR^9_2 wherein each R is independently H or optionally substituted alkyl, or both R^9 groups taken together with the nitrogen to which they are attached form a heterocyclic ring;

SR^4 wherein

R^4 is optionally substituted alkyl;

aryl or arylalkyl, each optionally substituted; or

heteroaryl or heteroarylalkyl, each optionally substituted;

wherein R^1 and R^2 may be joined to form a 3-8 membered ring; and

wherein one and only one of R^1 and R^2 may be H or may be alkyl, arylalkyl or heteroarylalkyl, each optionally substituted; and

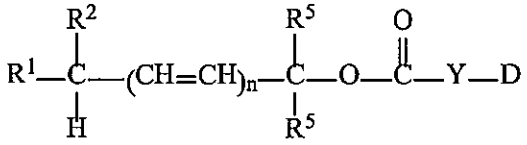
each R^5 is independently H or is alkyl, alkenylalkyl, alkynylalkyl, $(OCH_2CH_2)_p$ O-alkyl wherein p=1-1000, aryl, arylalkyl, heteroaryl or heteroarylalkyl, each optionally substituted.

24. The compound of claim 23 wherein Z^1 comprises an N_3, NH_2, NH-$CO_2{}^tBu$, SH, S^tBu, maleimide, CO_2H, $CO_2{}^tBu$, 1,3-diene, cyclopentadiene, furan, alkyne, cyclooctyne, acrylate, acrylamide, vinyl sulfone, or vinyl sulfonamide.

25. The compound of claim 23 wherein Q is pentaerythritol, tripentaerythritol, or hexaglycerin.

26. A method to prepare a drug-releasing degradable hydrogel comprising the steps of:

(a) reacting a first multivalent polymer comprising reactive functionalities with a substoichiometric amount of a linker-drug of formula (3)



(3)

wherein one of R^1, R^2, and R^5 is substituted with a group that is reactive with the reactive functionality present on the first polymer,

wherein

m is 0 or 1;

D is the residue of a drug;

Y is O, NH or $NBCH_2$, wherein B is H, alkyl, arylalkyl, heteroaryl, or heteroarylalkyl, each optionally substituted;

at least one or both R^1 and R^2 is independently CN; NO_2;

optionally substituted aryl;

optionally substituted heteroaryl;

optionally substituted alkenyl;

optionally substituted alkynyl;

COR^3 or SOR^3 or SO_2R^3 wherein

R^3 is H or optionally substituted alkyl;

aryl or arylalkyl, each optionally substituted;

heteroaryl or heteroarylalkyl, each optionally substituted; or

OR^9 or NR^9_2 wherein each R is independently H or optionally substituted alkyl, or both R^9 groups taken together with the nitrogen to which they are attached form a heterocyclic ring;

SR^4 wherein

R^4 is optionally substituted alkyl;

aryl or arylalkyl, each optionally substituted; or

heteroaryl or heteroarylalkyl, each optionally substituted;

wherein R^1 and R^2 may be joined to form a 3-8 membered ring; and

wherein one and only one of R^1 and R^2 may be H or may be alkyl, arylalkyl or heteroarylalkyl, each optionally substituted; and

each R^5 is independently H or is alkyl, alkenylalkyl, alkynylalkyl, $(OCH_2CH_2)_p$ O-alkyl wherein p=1-1000, aryl, arylalkyl, heteroaryl or heteroarylalkyl, each optionally substituted;

so as to form a drug-loaded first polymer;

(b) optionally isolating the drug-loaded first polymer; and

(c) crosslinking the remaining reactive functionalities on the drug-loaded first polymer with a cleavable crosslinking compound of formula (1) or formula (2) so as to form a hydrogel.

27. A drug-releasing degradable hydrogel prepared by the method of claim 26.

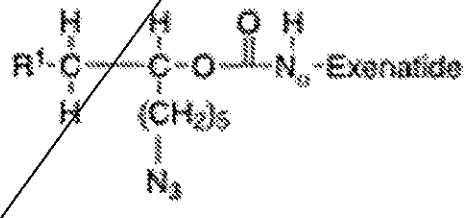
28. A drug-releasing degradable hydrogel of claim 27 wherein the reactive functionality on the first polymer is a cyclooctyne, and the reactive functionality on the compound of formulas (1), (2) and (3) is azide.

29. A drug-releasing degradable hydrogel of claim 27 wherein D is exenatide.

30. A drug-releasing degradable hydrogel of claim 27 wherein

the first polymer is an 8-arm polyethylene glycol comprising a cyclooctyne group at the terminus of each arm; and

the linker-drug of Formula (3) has the formula



wherein R^1=CN; NO_2;

optionally substituted aryl;

optionally substituted heteroaryl;

optionally substituted alkenyl;

optionally substituted alkynyl;

COR^3 or SOR^3 or SO_2R^3 wherein

R^3 is H or optionally substituted alkyl;

aryl or arylalkyl, each optionally substituted;

heteroaryl or heteroarylalkyl, each optionally substituted; or

OR^9 or NR^9_2 wherein each R^9 is independently H or optionally substituted alkyl, or both R^9 groups taken together with the nitrogen to which they are attached form a heterocyclic ring; or

SR^4 wherein

R^4 is optionally substituted alkyl;

aryl or arylalkyl, each optionally substituted; or

heteroaryl or heteroarylalkyl, each optionally substituted.

31. The hydrogel of claim 30 wherein the cleavable crosslinking compound is of Formula (2).

32. The hydrogel of claim 31 wherein in said Formula (2), m is 0, n is 90-110, s is 0, t is 4, W is O(C=O)NH, Q is $C(CH_2)_4$, R^1 is CN, R^2 and one of R^5 is H, and the other R^5 is $(CH_2)_5N_3$.

33. The hydrogel of claim 32 wherein R^1 in Formula (3) is SO_2R^3 wherein

R^3 is H or optionally substituted alkyl;

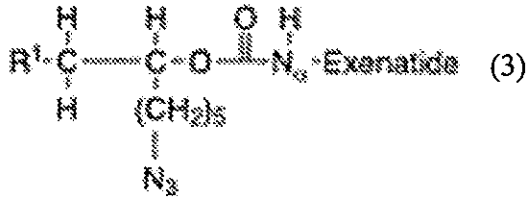
aryl or arylalkyl, each optionally substituted;

heteroaryl or heteroarylalkyl, each optionally substituted; or

OR^9 or NR^9_2 wherein each R^9 is independently H or optionally substituted alkyl, or both R^9 groups taken together with the nitrogen to which they are attached form a heterocyclic ring.

34. The hydrogel of claim 33 wherein R^1 in Formula (3) is $MeSO_2$.

35. A drug releasing degradable hydrogel wherein a multi-armed polymer of formula $[Z^3\text{-}(CH_2)_s(CH_2CH_2O)_n]_tQ$, wherein Z^3 is a reactive functional group, n is 10-1000 and s, Q, and t are as defined in claim 5 is cross linked by a cleavable cross linking compound of Formula (1) or Formula (2) to which hydrogel is coupled a linker-drug of Formula (3)



(3)

wherein R^1=CN; NO_2;

optionally substituted aryl;

optionally substituted heteroaryl;

optionally substituted alkenyl;

optionally substituted alkynyl;

COR^3 or SOR^3 or SO_2R^3 wherein

R^3 is H or optionally substituted alkyl;

aryl or arylalkyl, each optionally substituted;

heteroaryl or heteroarylalkyl, each optionally substituted; or

OR^9 or NR^9_2 wherein each R^9 is independently H or optionally substituted alkyl, or both R^9 groups taken together with the nitrogen to which they are attached form a heterocyclic ring; or

SR^4 wherein

R^4 is optionally substituted alkyl;

aryl or arylalkyl, each optionally substituted; or

heteroaryl or heteroarylalkyl, each optionally substituted.

36. The hydrogel of claim 35 wherein the cleavable crosslinking compound is of Formula (2).

37. The hydrogel of claim 36 wherein in said Formula (2), m is 0, n is 90-110, s is 0, t is 4, W is O(C=O)NH, Q is $C(CH_2)_4$, R^1 is CN, R^2 and one of R^5 is H, and the other R^5 is $(CH_2)_5N_3$.

38. The hydrogel of any of claims 35-37 wherein R^1 in Formula (3) is SO_2R^3 wherein

R^3 is H or optionally substituted alkyl;

aryl or arylalkyl, each optionally substituted;

heteroaryl or heteroarylalkyl, each optionally substituted; or

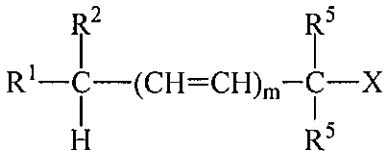
OR^9 or NR^9_2 wherein each R^9 is independently H or optionally substituted alkyl, or both R^9 groups taken together with the nitrogen to which they are attached form a heterocyclic ring.

39. The hydrogel of claim 38 wherein R^1 in Formula (3) is $MeSO_2$.

CLAIMS:

1. A hydrogel that is biodegradable under physiological conditions which hydrogel comprises one or more polymers crosslinked by a linker that decomposes by a beta elimination reaction,

wherein the linker, when disposed in the polymer, is a residue of formula (1)



(1)

wherein at least one of R^1, R^2, R^5 is coupled to through a first functional group to said one or more polymers and wherein X is coupled to a polymer through a second functional group,

wherein one and only one of R^1 and R^2 may be H or may be alkyl, arylalkyl or heteroarylalkyl, each optionally substituted;

at least one or both R^1 and R^2 is independently CN; NO_2;

optionally substituted aryl;

optionally substituted heteroaryl;

optionally substituted alkenyl;

optionally substituted alkynyl;

COR^3 or SOR^3 or SO_2R^3 wherein

R^3 is H or optionally substituted alkyl;

aryl or arylalkyl, each optionally substituted;

heteroaryl or heteroarylalkyl, each optionally substituted; or

OR^9 or NR^9_2 wherein each R^9 is independently H or optionally substituted alkyl, or both R^9 groups taken together with the nitrogen to which they are attached form a heterocyclic ring;

SR^4 wherein

R^4 is optionally substituted alkyl;

aryl or arylalkyl, each optionally substituted; or

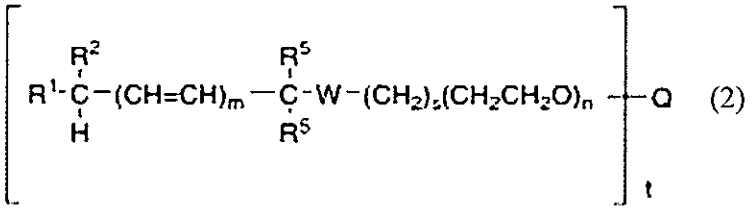
heteroaryl or heteroarylalkyl, each optionally substituted;

wherein R^1 and R^2 may be joined to form a 3-8 membered ring; and

each R^5 is independently H or is alkyl, alkenylalkyl, alkynylalkyl, $(OCH_2CH_2)_p$ O-alkyl wherein p=1-1000, aryl, arylalkyl, heteroaryl or heteroarylalkyl, each optionally substituted,

wherein X is a carbonate, a carbamate, thioether, an ester or optionally substituted phenol wherein X is coupled to the polymer through said second functional group; or

wherein said linker is a residue of formula (2)



(2)

wherein at least two of said R^1, R^2, R^5 are coupled through functional groups to said one or more polymers;

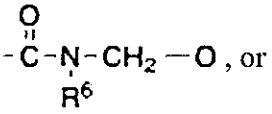
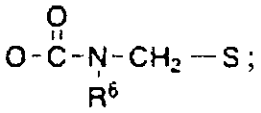
m is 0 or 1;

n is 1-1000;

s is 0-2;

t is 2,4, 8, 16 or 32;

Q is a core group having the valency t;

W is O(C=O)O, O(C=O)NH, O(C=O)S, , or ;

wherein R^6 is H, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, or optionally substituted heteroarylalkyl;

wherein one and only one of R^1 and R^2 may be H or may be alkyl, arylalkyl or heteroarylalkyl, each optionally substituted;

at least one or both R^1 and R^2 is independently CN; NO_2;

optionally substituted aryl;

optionally substituted heteroaryl;

optionally substituted alkenyl;

optionally substituted alkynyl;

COR^3 or SOR^3 or SO_2R^3 wherein

R^3 is H or optionally substituted alkyl;

aryl or arylalkyl, each optionally substituted;

heteroaryl or heteroarylalkyl, each optionally substituted; or

OR^9 or NR^9_2 wherein each R^9 is independently H or optionally substituted alkyl, or both R^9 groups taken together with the nitrogen to which they are attached form a heterocyclic ring;

SR^4 wherein

R^4 is optionally substituted alkyl;

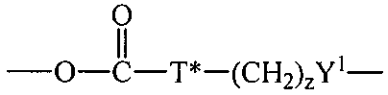
aryl or arylalkyl, each optionally substituted; or

heteroaryl or heteroarylalkyl, each optionally substituted;

wherein R^1 and R^2 may be joined to form a 3-8 membered ring; and

each R^5 is independently H or is alkyl, alkenylalkyl, alkynylalkyl, $(OCH_2CH_2)_p$ O-alkyl wherein p=1-1000, aryl, arylalkyl, heteroaryl or heteroarylalkyl, each optionally substituted.

2. The hydrogel of claim 1, wherein in formula (1), X is



wherein T* is O, S or NR^6 wherein R^6 is H, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, or optionally substituted heteroarylalkyl;

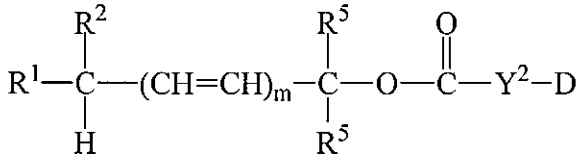
z is 1-6; and

Y^1 is absent or is OR^7 or SR^7, wherein R^7 is optionally substituted alkylene, optionally substituted phenylene or $(OCH_2CH_2)_p$, wherein p=1-1000, wherein Y^1 is coupled to a polymer through said second functional group.

3. The hydrogel of claim 1 or 2 wherein each said functional group independently comprises N_3, NH_2, NH-$CO_2{}^tBu$, SH, S^tBu, maleimide, CO_2H, $CO_2{}^tBu$, 1,3-diene, cyclopentadiene, furan, alkyne, cyclooctyne, acrylate, or acrylamide; and wherein when one functional group comprises N_3 the other does not comprise alkyne or cyclooctyne; when one functional group comprises SH the other does not comprise maleimide, acrylate, or acrylamide; when one functional group comprises NH_2, the other does not comprise CO_2H; when one functional group comprises 1,3-diene or cyclopentadiene the other does not comprise furan.

4. The hydrogel of any of claims 1-3 which further comprises a drug.

5. The hydrogel of claim 4 wherein said hydrogel includes a residue of formula (3)



(3)

wherein at least one of R^1, R^2, R^5 is coupled to a polymer;

m is 0 or 1;

D is a drug or prodrug;

Y^2 is NH or $NBCH_2$ wherein B is H, alkyl, arylalkyl, heteroaryl, or heteroarylalkyl, each optionally substituted; and

wherein one and only one of R^1 and R^2 may be H or may be alkyl, arylalkyl or heteroarylalkyl, each optionally substituted;

at least one or both R^1 and R^2 is independently CN; NO_2;

optionally substituted aryl;

optionally substituted heteroaryl;

optionally substituted alkenyl;

optionally substituted alkynyl;

COR^3 or SOR^3 or SO_2R^3 wherein

R^3 is H or optionally substituted alkyl;

aryl or arylalkyl, each optionally substituted;

heteroaryl or heteroarylalkyl, each optionally substituted; or

OR^9 or NR^9_2 wherein each R^9 is independently H or optionally substituted alkyl, or both R^9 groups taken together with the nitrogen to which they are attached form a heterocyclic ring;

SR^4 wherein

R^4 is optionally substituted alkyl;

aryl or arylalkyl, each optionally substituted; or

heteroaryl or heteroarylalkyl, each optionally substituted;

wherein R^1 and R^2 may be joined to form a 3-8 membered ring; and

each R^5 is independently H or is alkyl, alkenylalkyl, alkynylalkyl, $(OCH_2CH_2)_p$ O-alkyl wherein p=1-1000, aryl, arylalkyl, heteroaryl or heteroarylalkyl, each optionally substituted.

6. The hydrogel of any of claims 1-5 wherein

one of R^1 and R^2 is H and the other is CN or SO_2R^3 wherein R^3 is optionally substituted alkyl;

aryl or arylalkyl, each optionally substituted; or

heteroaryl or heteroarylalkyl, each optionally substituted; or

OR^9 or NR^9_2 wherein each R^9 is independently H or optionally substituted alkyl, or both R^9 groups taken together with the nitrogen to which they are attached form a heterocyclic ring; and/or

one of R^5 is H and the other is $(CH_2)_n$ Z wherein n is 1-6 and Z is a functional group to connect to said polymer.

7. The hydrogel of any of claims 1-6, wherein the polymer is of the formula $[-(CH_2)_s(CH_2CH_2O)_n]_tQ$, wherein

n is 10-1000;

s is 0-2;

t is 2,4, 8, 16 or 32 and represents the number of arms of said polymer; and

Q is a core group having a valency=t,

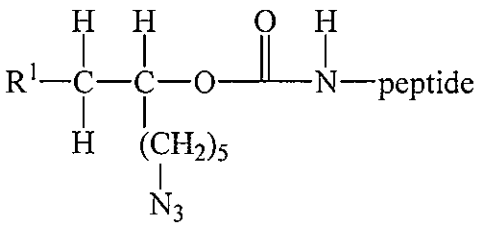
and said polymer is coupled to said linkers through functional groups at the terminus of each of said arms.

8. The hydrogel of claim 8 wherein t is 4 and each arm of said polymer is terminated by two orthogonal functional groups.

9. The hydrogel of claim 7 or 8 wherein Q is pentaerythritol, tripentaerythritol, or hexaglycerin.

10. The hydrogel of claim 6 wherein

the polymer is the residue of an 8-arm polyethylene glycol comprising a cyclooctyne group at the terminus of each arm wherein at least some of said arms have been coupled to



wherein R^1=CN; NO_2;

optionally substituted aryl;

optionally substituted heteroaryl;

optionally substituted alkenyl;

optionally substituted alkynyl;

COR^3 or SOR^3 or SO_2R^3 wherein

R^3 is H or optionally substituted alkyl;

aryl or arylalkyl, each optionally substituted;

heteroaryl or heteroarylalkyl, each optionally substituted; or

OR^9 or $NR^9{}_2$ wherein each R^9 is independently H or optionally substituted alkyl, or both R^9 groups taken together with the nitrogen to which they are attached form a heterocyclic ring; or

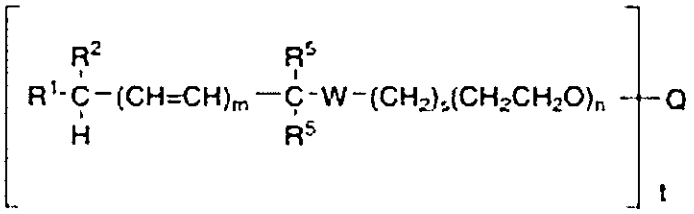
SR^4 wherein

R^4 is optionally substituted alkyl;

aryl or arylalkyl, each optionally substituted; or

heteroaryl or heteroarylalkyl, each optionally substituted.

11. The hydrogel of any of claims 6 – 10, wherein the cleavable crosslinking compound is the formula



wherein m is 0,

n is 90-110,

s is 0,

t is 4,

W is O(C=O)NH,

Q is $C(CH_2)_4$,

R^1 is CN or SO_2NR^3, wherein R^3 is optionally substituted alkyl;

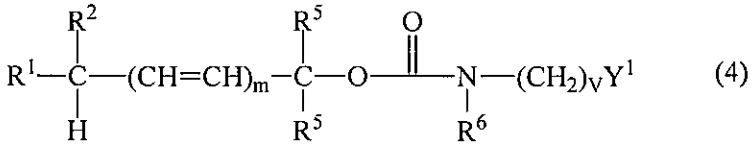
aryl or arylalkyl, each optionally substituted; or

heteroaryl or heteroarylalkyl, each optionally substituted;

R^2 and one of R^5 is H, and

the other R^5 is $(CH_2)_5N_3$.

12. A crosslinking compound of formula (4)



(4)

wherein at least two of R^1, R^2, and R^5 and Y further comprise a functional group capable of connecting to a polymer;

wherein

m is 0 or 1;

R^6 is H, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, or optionally substituted heteroarylalkyl;

v is 1-6;

Y^1 is H or is a bond if Y^1 comprises a functional group or is OR^7 or SR^7, wherein R^7 is optionally substituted alkylene, optionally substituted phenylene, or $(OCH_2CH_2)_p$, wherein p=1-1000;

at least one or both R^1 and R^2 is independently CN; NO_2;

optionally substituted aryl;

optionally substituted heteroaryl;

optionally substituted alkenyl;

optionally substituted alkynyl;

COR^3 or SOR^3 or SO_2R^3 wherein

R^3 is H or optionally substituted alkyl;

aryl or arylalkyl, each optionally substituted;

heteroaryl or heteroarylalkyl, each optionally substituted; or

OR^9 or NR^9_2 wherein each R^9 is independently H or optionally substituted alkyl, or both R^9 groups taken together with the nitrogen to which they are attached form a heterocyclic ring;

SR^4 wherein

R^4 is optionally substituted alkyl;

aryl or arylalkyl, each optionally substituted; or

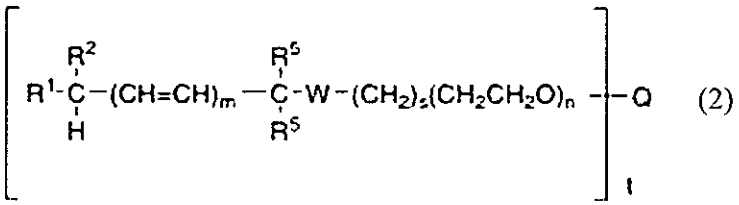
heteroaryl or heteroarylalkyl, each optionally substituted;

wherein R^1 and R^2 may be joined to form a 3-8 membered ring; and

wherein one and only one of R^1 and R^2 may be H or may be alkyl, arylalkyl or heteroarylalkyl, each optionally substituted; and

each R^5 is independently H or is alkyl, alkenylalkyl, alkynylalkyl, $(OCH_2CH_2)_p$ O-alkyl wherein p=1-1000, aryl, arylalkyl, heteroaryl or heteroarylalkyl, each optionally substituted;

or of formula (2)



(2)

wherein in at least two instances R^1, R^2, and/or R^5 further comprises a functional group capable of connecting to a polymer;

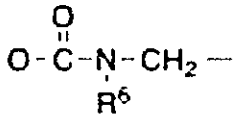
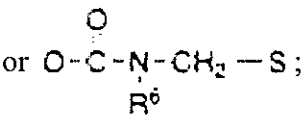
m is 0 or 1;

n is 1-1000;

s is 0-2;

t is 2, 4, 8, 16 or 32;

Q is a core group having a valency = t;

W is O(C=O)O, O(C=O)NH, O(C=O)S, , or ;

wherein R^6 is H, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, or optionally substituted heteroarylalkyl;

at least one or both R^1 and R^2 is independently CN; NO_2;

optionally substituted aryl;

optionally substituted heteroaryl;

optionally substituted alkenyl;

optionally substituted alkynyl;

COR^3 or SOR^3 or SO_2R^3 wherein

R^3 is H or optionally substituted alkyl;

aryl or arylalkyl, each optionally substituted;

heteroaryl or heteroarylalkyl, each optionally substituted; or

OR^9 or NR^9_2 wherein each R^9 is independently H or optionally substituted alkyl, or both R^9 groups taken together with the nitrogen to which they are attached form a heterocyclic ring;

SR^4 wherein

R^4 is optionally substituted alkyl;

aryl or arylalkyl, each optionally substituted; or

heteroaryl or heteroarylalkyl, each optionally substituted;

wherein R^1 and R^2 may be joined to form a 3-8 membered ring; and

wherein one and only one of R^1 and R^2 may be H or may be alkyl, arylalkyl or heteroarylalkyl, each optionally substituted; and

each R^5 is independently H or is alkyl, alkenylalkyl, alkynylalkyl, $(OCH_2CH_2)_p$ O-alkyl wherein p=1-1000, aryl, arylalkyl, heteroaryl or heteroarylalkyl, each optionally substituted.

13. The crosslinking compound of claim 12 wherein each functional group capable of connection to a polymer comprises N_3, NH_2, NH-$CO_2{}^tBu$, SH, S^tBu, maleimide, CO_2H, $CO_2{}^tBu$, 1,3-diene, cyclopentadiene, furan, alkyne, cyclooctyne, acrylate, vinyl sulfone, vinyl sulfonamide, or acrylamide and wherein when one group comprises N_3 the other does not comprise alkyne or cyclooctyne; when one group comprises SH the other does not comprise maleimide, acrylate, or acrylamide; when one group comprises NH_2 the other does not comprise CO_2H; and when one group comprises a 1,3-diene or cyclopentadiene the other does not comprise furan.

14. The crosslinking compound of claim 12 or 13 wherein Q is pentaerythritol, tripentaerythritol, or hexaglycerin.

15. A method to prepare a biodegradable hydrogel of any of claims 1-11 said method comprising reacting polymer(s) with a cleavable crosslinker which crosslinker

comprises at least two functional groups separated by a moiety that is cleaved by β- elimination under physiological conditions,

wherein said functional groups react with said polymer(s) to form said biodegradable hydrogel.