CLAIMS

1. A method to sterilize a crosslinked hydrogel, wherein the crosslinked hydrogel comprises a cross-linker that is degradable by beta elimination, which method comprises:

(1) adjusting the pH of a medium containing said crosslinked hydrogel to pH 2-5, and

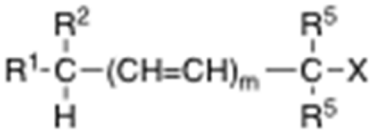
(2) heating said crosslinked hydrogel at a temperature of up to about 121 °C for up to 1 hour.

2. The method of claim 1, wherein the medium comprises a non-reactive buffer.

3. The method of claim 2, wherein said buffer is phosphate or acetate buffer.

4. The method of claim 1, wherein the rate of cross-linker degradation by beta elimination is controlled by one or more substituents contained in the cross-linker.

5. The method of claim 4, wherein the cross-linker is of the formula:



wherein

m is 0 or 1;

X comprises a functional group connecting the crosslinker to a first polymer;

at least one of R^1, R^2, and R^5 comprises a functional group Z connecting the crosslinker to a second 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; SOR^3; SO_2R^3; or SR^4,

wherein:

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

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

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;

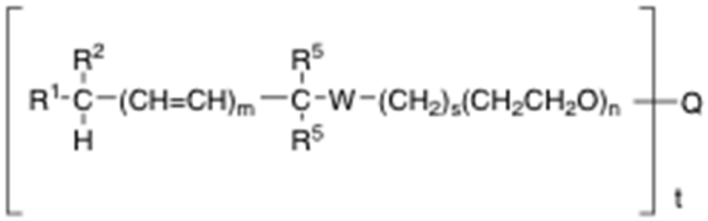
R^4 is optionally substituted alkyl;

aryl or arylalkyl, each optionally substituted; or

heteroaryl 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 the cross-linker is of the formula:



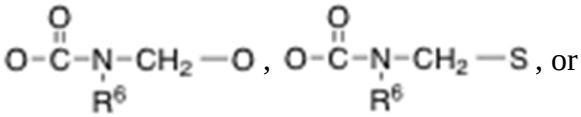
wherein

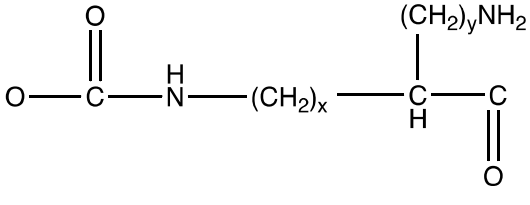
m is 0 or 1;

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

 , wherein x and y = 0-4;

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 connecting the crosslinker to a second 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; SOR^3; SO_2R^3; or SR^4; wherein

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

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

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;

R^4 is optionally substituted alkyl;

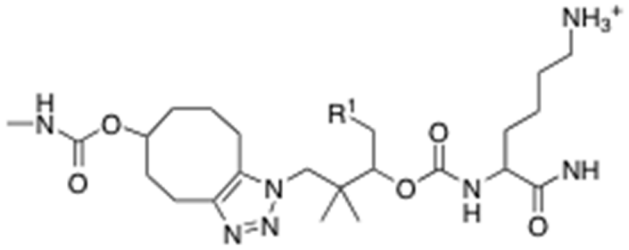
aryl or arylalkyl, each optionally substituted; or

heteroaryl or heteroarylalkyl, each optionally substituted; and

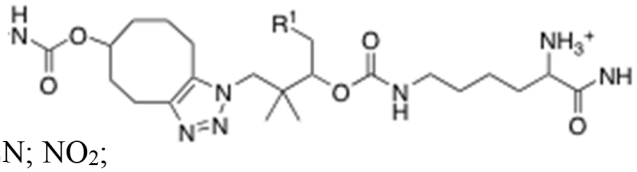
each R^5 is independently H or is alkyl, alkenylalkyl, alkynylalkyl, $(OCH_2CH_2)_p$ O-alkyl wherein p=1-1000, aryl, arylalkyl, heteroaryl or heteroarylalkyl, each optionally substituted.

6. The method of Claim 5, wherein X is a carbamate and Z is a triazole, carboxamide, or carbamate.

7. The method of Claim 1, wherein the cross-linker is of the formula:



or



, wherein

R^1 is CN; NO_2;

optionally substituted aryl;

optionally substituted heteroaryl;

optionally substituted alkenyl;

optionally substituted alkynyl;

COR^3; SOR^3; SO_2R^3; or SR^4,

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; and

R^4 is optionally substituted alkyl;

aryl or arylalkyl, each optionally substituted; or

heteroaryl or heteroarylalkyl, each optionally substituted.

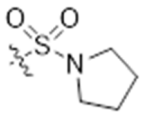
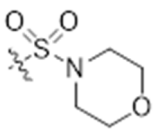
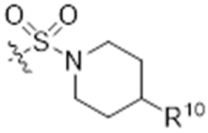
8. The method of Claim 7, wherein R^1 is CN or SO_2R^3 wherein

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.

9. The method of Claim 7, wherein R^1 is CN; SO_2Me; SO_2NMe_2;  ;  ;  ; or $SO_2(Ph\text{-}R^{10})$, wherein R^{10} is H, alkyl, alkoxy, NO_2, or halogen.

10. The method of Claim 1, wherein sterilization is achieved by heating to 121 ^oC with a hold time of 20 minutes.

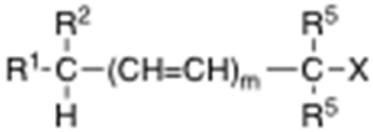
11. The method of any one of claims 1-10, wherein step (1) comprises adjusting the pH of the medium containing said crosslinked hydrogel to between 3 and 4.

12. The method of any one of claims 1-11, wherein the hydrogel comprises [Gln^{28}]exenatide.

13. A hydrogel comprising a cross-linker degradable by a beta-elimination mechanism that has been sterilized by adjusting to pH 2-5, and heating at a temperature of up to about 121 °C.

14. The hydrogel of Claim 13, wherein the hydrogel is in the form of a suspension of microparticles.

15. The hydrogel of Claim 13, wherein the cross-linker degradable by a beta-elimination mechanism has the formula



wherein

m is 0 or 1;

X comprises a functional group connecting the crosslinker to a first polymer;

at least one of R^1, R^2, and R^5 comprises a functional group Z connecting the crosslinker to a second 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; SOR^3; SO_2R^3; or SR^4,

wherein:

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

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

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;

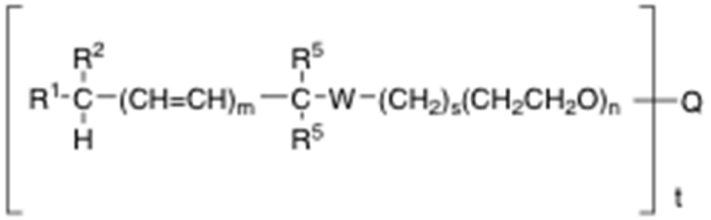
R^4 is optionally substituted alkyl;

aryl or arylalkyl, each optionally substituted; or

heteroaryl 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 the cross-linker degradable by a beta-elimination mechanism has the formula



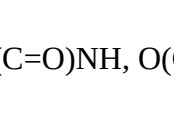
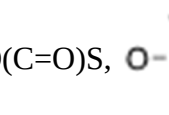
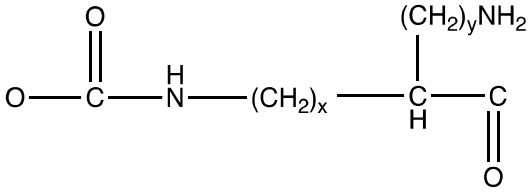
wherein

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  , wherein x and y = 0-4;

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 connecting the crosslinker to a second 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; SOR^3; SO_2R^3; or SR^4; wherein

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

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

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;

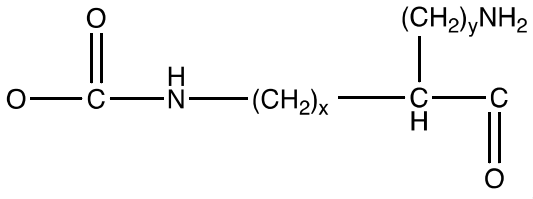
R^4 is optionally substituted alkyl;

aryl or arylalkyl, each optionally substituted; or

heteroaryl or heteroarylalkyl, each optionally substituted; and

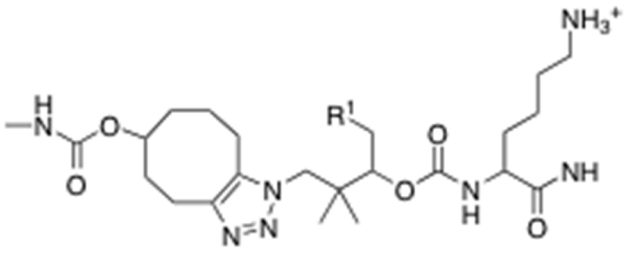
each R^5 is independently H or is alkyl, alkenylalkyl, alkynylalkyl, $(OCH_2CH_2)_p$ O-alkyl wherein p=1-1000, aryl, arylalkyl, heteroaryl or heteroarylalkyl, each optionally substituted.

16. The hydrogel of Claim 15, wherein m = 0, R^2 is H, one R^5 is H and the other is $C(Me)_2(CH_2)_nZ$ wherein n = 0-6, and W is

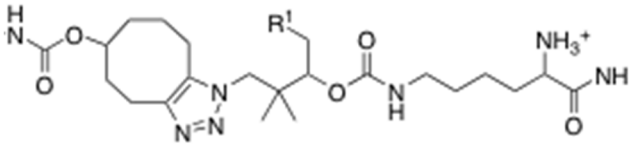


, wherein x and y = 0-4.

17. The hydrogel of Claim 15, wherein the hydrogel comprises a cross-linker of the formula:



or



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18. The hydrogel of Claim 13, wherein the hydrogel has been sterilized by heating a suspension of the hydrogel in buffer at pH 2-5 to a temperature of 121 ^{o}C for a hold time of 20 minutes.