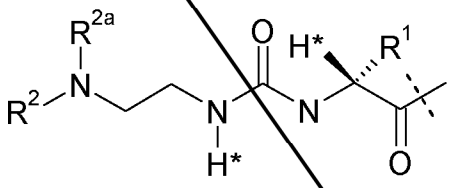
Claims

1. A prodrug or a pharmaceutically acceptable salt thereof comprising an exendin linker conjugate D-L, wherein

D represents an exendin moiety; and

-L is a non-biologically active linker moiety -L^1 represented by formula (I),



(I),

wherein the dashed line indicates attachment to one of the amino groups of the exendin by forming an amide bond;

R^1 is selected from C_{1-4} alkyl;

R^2 , R^{2a} are independently selected from the group consisting of H and C_{1-4} alkyl,

wherein L^1 is substituted with one L^2-Z and optionally further substituted, provided that the hydrogens marked with the asterisks in formula (I) are not replaced by a substituent and wherein

L^2 is a single chemical bond or a spacer; and

Z is a hydrogel.

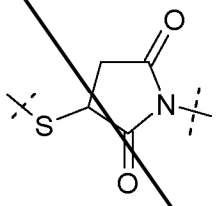
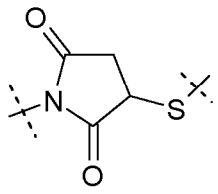
2. The prodrug of claim 1, wherein L^1 is not further substituted.

3. The prodrug of claim 1 or 2, wherein R^1 is -CH_3.

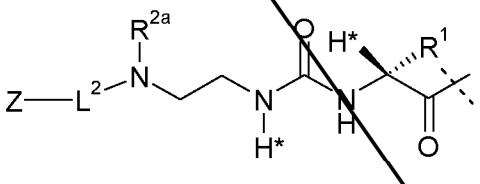
4. The prodrug of any of claims 1 to 3, wherein L^2 is a C_{1-20} alkyl chain, which is optionally interrupted by one or more groups independently selected from -O-; and C(O)N(R3aa); optionally substituted with one or more groups independently

selected from OH; and C(O)N(R3aaR3aaa); and wherein R3aa, R3aaa are independently selected from the group consisting of H; and C_{1-4} alkyl.

5. The prodrug of any of claims 1 to 4, wherein L^2 is attached to Z via a terminal group selected from


; and

.

6. The prodrug of any of claims 1 to 5, wherein L is represented by formula (Ia)

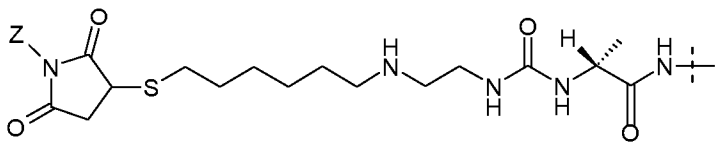

(Ia),

wherein the dashed line indicates attachment to the nitrogen of the exendin by forming an amide bond; and wherein

L_2 is a single chemical bond or a spacer,

Z is a hydrogel.

7. The prodrug of any of claims 1 to 6, wherein L is represented by formula (II)

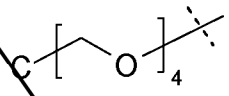

(II),

wherein the dashed line indicates attachment to the nitrogen of the exendin by forming an amide bond and

Z is a hydrogel.

8. The prodrug of any of claims 1 to 7, wherein the hydrogel is a PEG-based hydrogel comprised of backbone moieties.

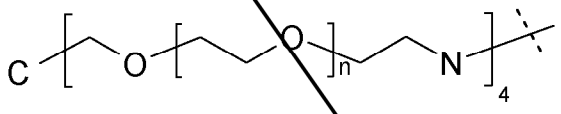
9. The prodrug of claim 8, wherein the backbone moieties comprise a branching core of the following formula:



,

wherein the dashed line indicates attachment to the remainder of the backbone moiety.

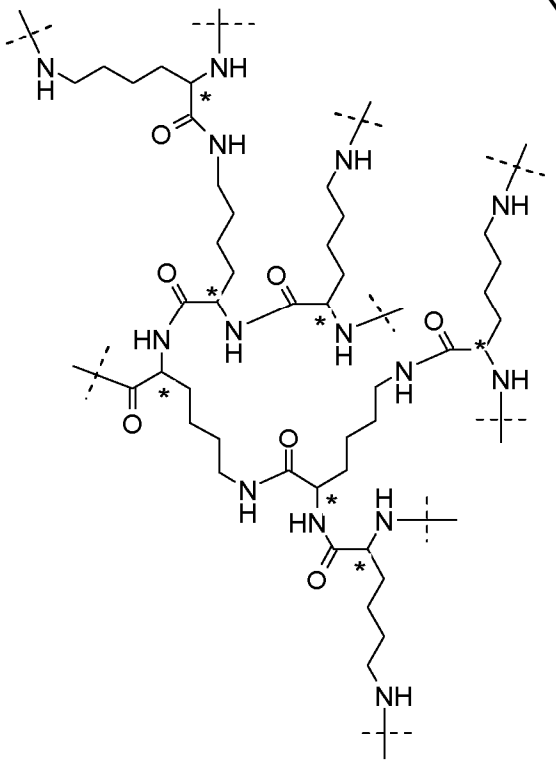
10. The prodrug of claim 8, wherein the backbone moieties comprise a structure of the following formula:



,

wherein n is an integer of from 5 to 50 and the dashed line indicates attachment to the rest of the molecule.

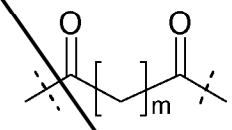
11. The prodrug of any of claims 8 to 10, wherein the backbone moiety comprises a hyperbranched moiety Hyp of the following formula:



,

wherein the dashed lines indicate attachment to the rest of the molecule; and carbon atoms marked with asterisks indicate S-configuration.

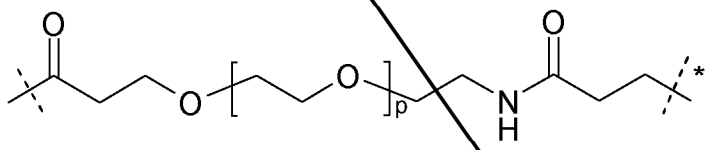
12. The prodrug of any of claims 8 to 11, wherein the backbone moieties comprise at least one spacer of the following formula:



,

wherein one of the dashed lines indicates attachment to the hyperbranched moiety Hyp and the second dashed line indicates attachment to the rest of the molecule; and
wherein m is an integer of from 2 to 4.

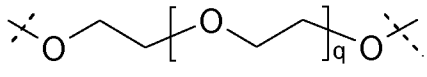
13. The prodrug of any of claims 8 to 12, wherein the backbone moieties comprise at least one spacer of the following formula:



,

wherein the dashed line marked with the asterisk indicates the bond between the hydrogel and the N of the thiosuccinimide group of claim 5;
wherein the other dashed line indicates attachment to Hyp; and wherein p is an integer of from 0 to 10.

14. The prodrug of any of claims 8 to 13, wherein the backbone moieties are linked together through crosslinker moieties comprising the following structure



,

wherein q is an integer from 3 to 100.

15. A pharmaceutical composition comprising a prodrug of any of claims 1 to 14 or a pharmaceutical salt thereof together with at least one pharmaceutically acceptable excipient.

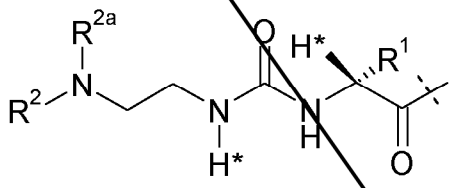
16. The prodrug of any of claims 1 to 14 or the pharmaceutical composition of claim 15 for use as a medicament.

17. The prodrug of any of claims 1 to 14 or the pharmaceutical composition of claim 15 for use in a method of treating or preventing diseases or disorders which can be treated by exendin.

18. An exendin-linker reagent D-L*, wherein

D represents an exendin moiety; and

-L* is a non-biologically active linker reagent represented by formula (IV),



(IV),

wherein the dashed line indicates the attachment to one of the amino groups of the exendin by forming an amide bond;

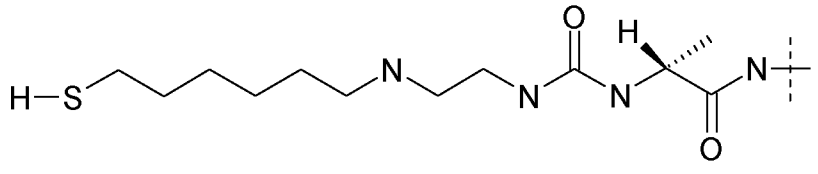
R^1 is selected from C_{1-4} alkyl;

R^2, R^{2a}, are independently selected from the group consisting of H and C_{1-4} alkyl,

wherein L* is substituted with one L^{2*} and optionally further substituted, provided that the hydrogens marked with the asterisks in formula (IV) are not replaced by a substituent and wherein

L^{2*} is a spacer connected to L* and comprising a chemical functional group intended for conjugation to a hydrogel.

19. An exendin-linker conjugate intermediate D-L', wherein L' is of formula (III)



(III),

wherein the dashed line indicates the attachment to one of the amino groups of the exendin moiety by forming an amide bond;

D represents an exendin moiety.

20. A process for the preparation of a prodrug of any of claims 1 to 14, comprising the steps of

(a) contacting at temperatures between room temperature and 4°C in a buffered aqueous solution of pH 5.5-8 an aqueous suspension comprising maleimide-functionalized hydrogel microparticles with a solution comprising the exendin-linker reagent of claim 17, wherein the chemical functional group of L^{2*} comprises a thiol group, resulting in an exendin-linker-hydrogel conjugate;

(b) optionally, treating the exendin-linker-hydrogel conjugate from step (a) with a thiol-containing compound of 34 Da to 500 Da at temperatures between room temperature and 4°C in a buffered aqueous solution of pH 5.5-8.

21. A process for the preparation of a prodrug of any of claims 1 to 14, comprising the steps of

(a) contacting at temperatures between room temperature and 4°C in a buffered aqueous solution of pH 5.5-8 an aqueous suspension comprising thiol-functionalized hydrogel microparticles with a solution comprising the exendin-linker reagent of claim 18, wherein the chemical functional group of L^{2*} comprises a maleimide group resulting in an exendin-linker-hydrogel conjugate;

(b) optionally, treating the exendin-linker-hydrogel conjugate from step (a) with a maleimide-containing compound of 100 to 300 Da at temperatures between room temperature and 4°C in a buffered aqueous solution of pH 5.5-8.

22. A process for preparing a needle injectable prodrug comprising the step of

(a) preparing a prodrug of any of claims 1 to 14 in the form of microparticles;

(b) sieving the microparticles

(c) selecting a fraction with a prodrug bead diameter of between 25 and 80 µm.

(d) suspending the bead fraction of step (c) in an aqueous buffer solution suitable for injection.

CLAIMS

1. A prodrug or a pharmaceutically acceptable salt thereof comprising an exendin linker conjugate D-L and a hydrogel Z with a backbone moiety of the formula $C(A\text{-}Hyp)_4$, wherein

each A is independently selected from the formula $-(CH_2)_{n1}(OCH_2CH_2)_nX-$,

wherein:

- n1 is 1 or 2;
- n is an integer ranging from 5 to 50; and
- X is an amide linkage linking A and Hyp;

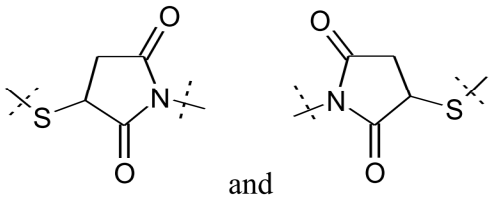
- each Hyp is independently selected from hyperbranched polypeptides comprising lysine;

- the backbone is crosslinked by poly(ethylene glycol)-based crosslinker moieties, comprising m ethylene glycol units, wherein m is an integer ranging from 10-70, and terminated by at least two hydrolytically degradable bonds;

- a linker L^2 connected to the backbone moiety, wherein:

- L^2 is a single chemical bond or is a C_{1-20} alkyl chain, which is optionally interrupted by one or more groups independently selected from -O- and $C(O)N(R^{3aa})$ and is optionally substituted with one or more groups and independently selected from OH and $C(O)N(R^{3aa}R^{3aaa})$, wherein R^{3aa} and R^{3aaa} are independently selected from the group consisting of H and C_{1-4} alkyl; and

- L^2 is attached to Z via a terminal group selected from the group consisting of



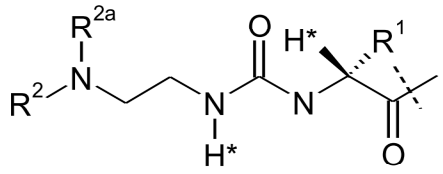
and

;

and D is an exendin and

-L is a non-biologically active linker $-L^{1;}$;

L^1 is of formula (I),



(I),

wherein the dashed line indicates attachment to one of the amino groups of the exendin by forming an amide bond;

R^1 is selected from C_{1-4} alkyl;

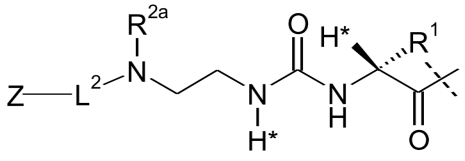
R^2 and R^{2a} are independently selected from the group consisting of H and C_{1-4} alkyl;

L^1 is substituted with one L^2-Z, wherein L^2-Z replaces one of the hydrogen atoms in R^1, R^2 or R^{2a}, provided that the hydrogens marked with the asterisks in formula (I) are not replaced.

2. The prodrug of claim 1, wherein L^1 is not further substituted.

3. The prodrug of claim 1, wherein R^1 is $-CH_3$.

4. The prodrug of claim 1, wherein L is represented by formula (Ia)



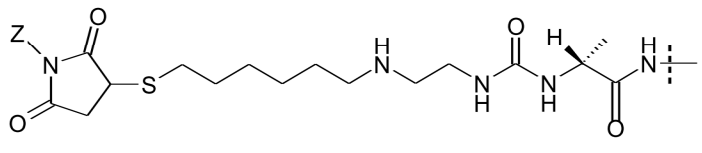
(Ia),

wherein the dashed line indicates attachment to the nitrogen of the exendin by forming an amide bond; and wherein

L_2 is a single chemical bond or a spacer,

Z is a hydrogel.

5. The prodrug of claim 1, wherein L is represented by formula (II)

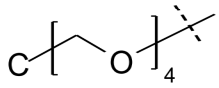


(II),

wherein the dashed line indicates attachment to the nitrogen of the exendin by forming an amide bond and

Z is a hydrogel.

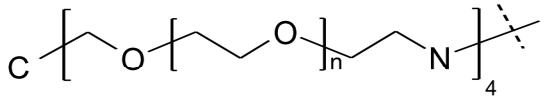
6. The prodrug of claim 1, wherein the backbone moiety comprises a branching core of the following formula



,

wherein the dashed line indicates attachment to the remainder of the backbone moiety.

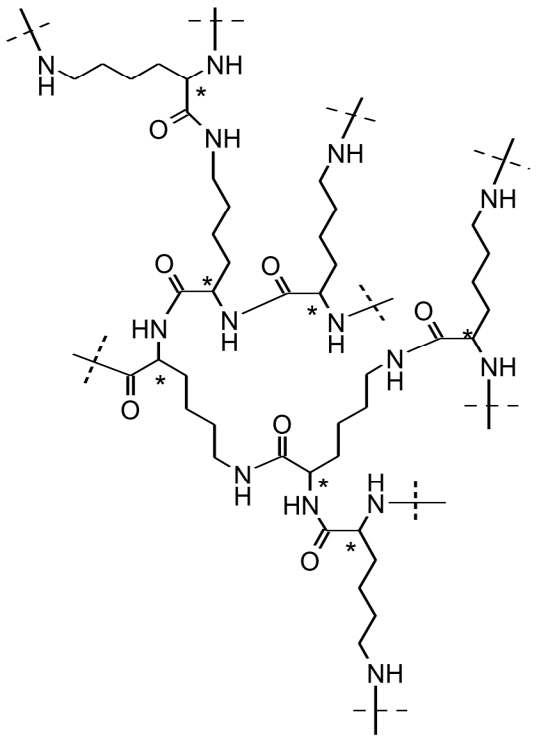
7. The prodrug of claim 1, wherein the backbone moiety comprises a structure of the following formula:



,

wherein n is an integer of from 5 to 50 and the dashed line indicates attachment to the rest of the molecule.

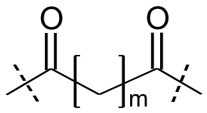
8. The prodrug of claim 1, wherein the backbone moiety comprises a hyperbranched moiety Hyp of the following formula:



,

wherein the dashed lines indicate attachment to the rest of the molecule; and carbon atoms marked with asterisks indicate S-configuration.

9. The prodrug of claim 1, wherein the backbone moiety comprises at least one spacer of the following formula:

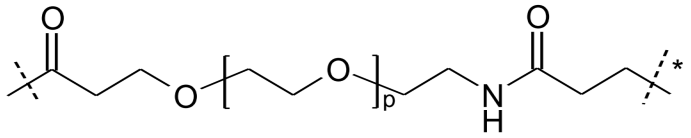


,

wherein one of the dashed lines indicates attachment to the hyperbranched moiety Hyp and the second dashed line indicates attachment to the rest of the molecule; and

wherein m is an integer of from 2 to 4.

10. The prodrug of claim 1, wherein the backbone moiety comprises at least one spacer of the following formula:

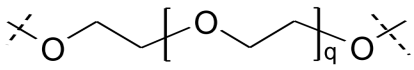


,

wherein the dashed line marked with the asterisk indicates the bond between the hydrogel and the N of the thiosuccinimide group of claim 1;

wherein the other dashed line indicates attachment to Hyp; and wherein p is an integer of from 0 to 10.

11. The prodrug of claim 1, wherein the backbone moiety is linked through crosslinker moieties comprising the following structure



,

wherein q is an integer from 3 to 100.

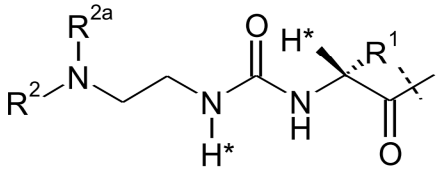
12. A pharmaceutical composition comprising the prodrug of claim 1 or a pharmaceutical salt thereof together with at least one pharmaceutically acceptable excipient.

13. Use of an effective amount of the pharmaceutical composition of claim 12 for the manufacture of a medicament for treating or preventing diseases or disorders which can be treated by exendin in a patient in need thereof.

14. An exendin-linker reagent D-L*, wherein

D is an exendin moiety; and

-L* is a non-biologically active linker reagent represented by formula (IV),



(IV),

wherein the dashed line indicates the attachment to one of the amino groups of the exendin by forming an amide bond;

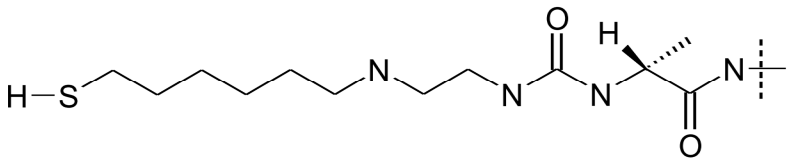
R^1 is selected from C_{1-4} alkyl;

R^2, R^{2a}, are independently selected from the group consisting of H and C_{1-4} alkyl,

wherein L* is substituted with one L^2* and optionally further substituted, provided that the hydrogens marked with the asterisks in formula (IV) are not replaced by a substituent and wherein

L^2* is a spacer connected to L* and comprising a chemical functional group intended for conjugation to a hydrogel.

15. An exendin-linker conjugate intermediate D-L', wherein L' is of formula (III)



(III),

wherein the dashed line indicates the attachment to one of the amino groups of the exendin moiety by forming an amide bond;

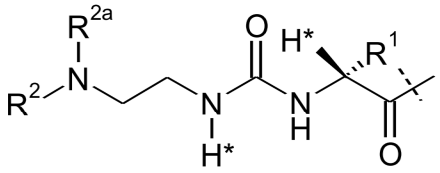
D is an exendin moiety.

16. A process for the preparation of the prodrug of claim 1, comprising the steps of

(a) contacting at temperatures between room temperature and 4°C in a buffered aqueous solution of pH 5.5-8 an aqueous suspension comprising maleimide-functionalized hydrogel microparticles with a solution comprising an exendin-linker reagent D-L*, wherein an exendin-linker reagent D-L*, wherein

D is an exendin moiety; and

-L* is a non-biologically active linker reagent represented by formula (IV),



(IV),

wherein the dashed line indicates the attachment to one of the amino groups of the exendin by forming an amide bond;

R^1 is selected from C_{1-4} alkyl;

R^2, R^{2a}, are independently selected from the group consisting of H and C_{1-4} alkyl,

wherein L* is substituted with one L^2* and optionally further substituted, provided that the hydrogens marked with the asterisks in formula (IV) are not replaced by a substituent and wherein

L^2* is a spacer connected to L* and comprising a chemical functional group intended for conjugation to a hydrogel wherein the chemical functional group of L^2* comprises a thiol group, resulting in an exendin-linker-hydrogel conjugate;

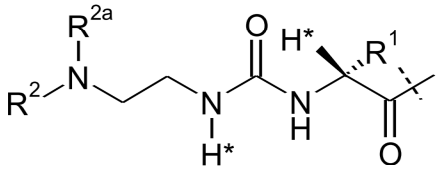
(b) optionally, treating the exendin-linker-hydrogel conjugate from step (a) with a thiol-containing compound of 34 Da to 500 Da at temperatures between room temperature and 4°C in a buffered aqueous solution of pH 5.5-8.

17. A process for the preparation of the prodrug of claim 1, comprising the steps of

(a) contacting at temperatures between room temperature and 4°C in a buffered aqueous solution of pH 5.5-8 an aqueous suspension comprising thiol-functionalized hydrogel microparticles with a solution comprising an exendin-linker D-L*, wherein

D is an exendin moiety; and

-L* is a non-biologically active linker reagent represented by formula (IV),



(IV),

wherein the dashed line indicates the attachment to one of the amino groups of the exendin by forming an amide bond;

R^1 is selected from C_{1-4} alkyl;

R^2, R^{2a}, are independently selected from the group consisting of H and C_{1-4} alkyl, wherein L* is substituted with one L^2* and optionally further substituted, provided that the hydrogens marked with the asterisks in formula (IV) are not replaced by a substituent and wherein

L^2* is a spacer connected to L* and comprising a chemical functional group intended for conjugation to a hydrogel wherein the chemical functional group of L2* comprises a maleimide group resulting in an exendin-linker-hydrogel conjugate;

(b) optionally, treating the exendin-linker-hydrogel conjugate from step (a) with a maleimide-containing compound of 100 to 300 Da at temperatures between room temperature and 4°C in a buffered aqueous solution of pH 5.5-8.

18. A process for preparing a needle injectable prodrug comprising the step of

(a) preparing the prodrug of claim 1 in the form of microparticles;

(b) sieving the microparticles;

(c) selecting a fraction with a prodrug bead diameter of between 25 and 80 μm; and

(d) suspending the bead fraction of step (c) in an aqueous buffer solution suitable for injection.

19. The prodrug of claim 1 wherein the crosslinker has a molecular weight in the range of from 0.5 KDa to 5KDa.

20. The prodrug of claim 1 wherein in formula I, R^2 is replaced by $L^2 – Z$.

21. The prodrug of claim 1 wherein in formula I, R^1 is CH_2-L^2-Z.

22. The prodrug of claim 1 in the form of microparticulate beads.

23. The prodrug of claim 22 wherein the microparticulate beads have a diameter ranging from 1 to 500 micrometers.

24. The prodrug of claim 1 wherein exendin is a compound of sequence ID 1, ID 2, ID 3, ID 4, ID 5, ID 6, ID 7, ID 8, ID 9, ID 10, ID 11, ID 12, ID 13, ID, 14, ID 15, ID 16, ID 17, ID 18, ID 19, ID 20, ID 21, or ID 22.

25. The prodrug of claim 24 wherein exendin is a compound of sequence ID 1, ID 13, ID 15, ID 21 or ID 22.

26. The prodrug of claim 25 wherein exendin is a compound of sequence ID 1, ID 13 or ID 21.

27. The prodrug of claim 1 wherein exendin is lixisenatide.

28. The prodrug of claim 1 wherein the exendin is attached to L^1 through an N-terminal nitrogen of the exendin.