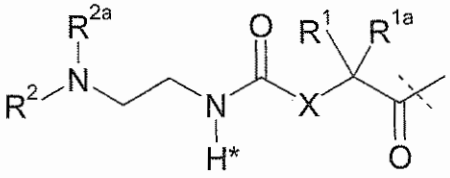
Thus an object of the present invention is to provide an insulin containing prodrug that meets at least partially the above requirements.

The object is achieved by a prodrug or a pharmaceutically acceptable salt thereof comprising an insulin linker conjugate D-L, wherein

D represents the insulin moiety; and

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



(I)

,

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

X is $C(R^3R^{3a})$; or $N(R^3)$;

R^{1a}, R^{3a} are independently selected from the group consisting H, $NH(R^{2b})$, $N(R^{2b})C(O)R^4$ and C_{1-4} alkyl;

R^1, R^2 R^{2a}, R^{2b}, R^3, R^4 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 hydrogen marked with the asterisk in formula (I) is not replaced by a substituent and wherein

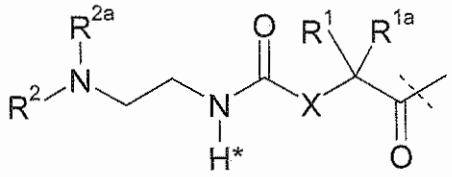
L^2 is a single chemical bond or a spacer; and

Z is a hydrogel.

In one embodiment, there is provided a prodrug or a pharmaceutically acceptable salt thereof comprising an insulin linker conjugate D-L, wherein

D represents the insulin moiety; and

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



(I)

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

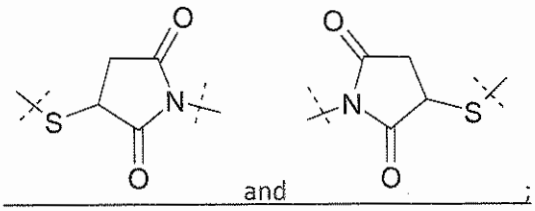
X is $C(R^3R^{3a})$; or $N(R^3)$;

R^{1a}, R^{3a} are independently selected from the group consisting H, $NH(R^{2b})$, $N(R^{2b})C(O)R^4$ and C_{1-4} alkyl;

R^1, R^2 R^{2a}, R^{2b}, R^3, R^4 are independently selected from the group consisting of H and C_{1-4} alkyl,

wherein L^1 is substituted with one L^2-Z, provided that the hydrogen marked with the asterisk in formula (I) is not replaced by a substituent and 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 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

;

Z is a hydrogel, wherein the hydrogel Z is a biodegradable poly(ethylene glycol) (PEG) based water-insoluble hydrogel;
with a backbone moiety of formula C-(A-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.

It was now surprisingly discovered, that a prodrug of the present invention may provide insulin release from a subcutaneous depot in structurally intact form over time periods of at least 2 days between administrations. As a further advantage structural integrity of the released insulin may be provided by a well-hydrated polymer matrix minimizing intermolecular contact of insulin molecules

R^1, R^2 R^{2a}, R^{2b}, R^3, R^4 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 hydrogen marked with the asterisk in formula (IV) is 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 reactive biodegradable hydrogel;

Preferably, R^2 in formula (IV) is replaced by L^{2}*.

Preferably, R^1 in formula (IV) is replaced by L^{2}*.

Preferably, X in formula (IV) is $N(R^3)$.

More preferably, X in formula (IV) is $C(R^3R^{3a})$ and R^{3a} is $N(R^{2b})C(O)R^4$.

More preferably, X in formula (IV) is $C(R^3R^{3a})$ and R^{3a} is replaced by L^{2}*.

Even more preferably, X in formula (IV) is $C(R^3R^{3a})$, R^{3a} is $N(R^{2b})$-L^{2}*.

Preferably, L* in formula (IV) is not further substituted.

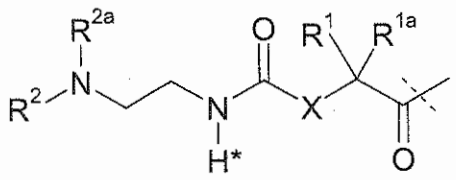
Preferably, L^{2}* in formula (IV) comprises a thiol group.

Preferably, L^{2}* in formula (IV) comprises a maleimide group.

In one embodiment, there is provided a insulin-linker reagent D-L*, wherein

D represents an insulin 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 insulin by forming an amide bond;

X is $C(R^3R^{3a})$; or $N(R^3)$;

R^{1a}, R^{3a} are independently selected from the group consisting H, $NH(R^{2b})$, $N(R^{2b})C(O)R^4$ and C_{1-4} alkyl;

R^1, R^2 R^{2a}, R^{2b}, R^3, R^4 are independently selected from the group consisting of H and C_{1-4} alkyl,

wherein L* is substituted with one L^{2*}, provided that the hydrogen marked with the asterisk in formula (IV) is not replaced by a substituent and wherein

L^{2*} is a C_{1-20} alkyl chain, which is optionally interrupted by one or more groups independently selected from -O- and $C(O)N(R^{3aa})$ and is optionally substituted with one or more groups 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 connected to L* and comprising a chemical functional group intended for conjugation to a reactive biodegradable hydrogel.

The hydrogel for the prodrug of the present invention can be obtained from the preparation methods in form of microparticles. In a preferred embodiment of the invention, the reactive hydrogel is a shaped article such as a mesh or a stent. Most preferably, the hydrogel is formed into microparticulate beads which can be administered as subcutaneous or intramuscular injection by means of a standard syringe. Such soft beads may have a diameter of between 1 and 500 micrometer.