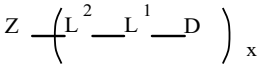
Claims

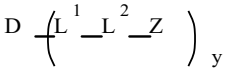
1. A dry pharmaceutical formulation, wherein the pharmaceutical formulation comprises a CNP conjugate, a buffering agent, a bulking agent and a pH-adjusting agent, wherein the CNP conjugate comprises a CNP moiety that is covalently and reversibly conjugated to a polymeric moiety, the buffering agent is succinic acid, the bulking agent is trehalose dihydrate and the pH-adjusting agent is Tris, and wherein the formulation comprises based on the total weight of the dry pharmaceutical formulation:

CNP conjugate	1.3 - 45.4 % (w/w)
succinic acid	0.2 - 3.2 % (w/w)
trehalose dihydrate	52.6 - 98.4 % (w/w)
Tris	0.1 - 5.6 % (w/w);

wherein the CNP conjugate is of formula (Ia) or (Ib):



(Ia),

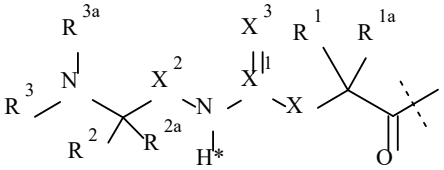


(Ib),

wherein

-D is the CNP moiety, wherein -D has the sequence of SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25 or SEQ ID NO:30;

-L^1- is a reversible linker moiety, wherein -L^1- is of formula (II):



(II)

,

wherein the dashed line indicates the attachment to a nitrogen of -D by forming an amide bond;

-X- is -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})-; or -C(R^7R^{7a})-;

X^1 is C; or S(O);

-X^2- is -C(R^8R^{8a})-; or -C(R^8R^{8a})-C(R^9R^{9a})-;

=X^3 is =O; =S; or =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, -R^{9a} are independently selected from the group consisting of -H; and C_{1-6} alkyl;

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

-R^7 is -N($R^{10}R^{10a}$); or -NR^{10}-(C=O)-R^{11};

-R^{7a}, -R^{10}, -R^{10a}, -R^{11} are independently of each other -H; or C_{1-6} alkyl;

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

optionally, 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}, -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;

optionally, 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, -R^2/-R^3 are joined together with the atoms to which they are attached to form a ring A;

optionally, -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

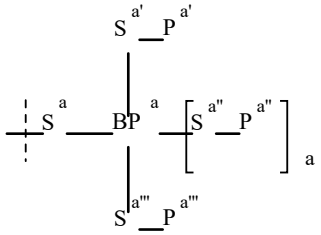
wherein -L^1- is substituted with -L^2-Z, provided that the hydrogen marked with the asterisk in formula (II) is not replaced by -L^2-Z;

-L^2- is a single chemical bond or a spacer moiety;

x is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 and 16;

y is an integer selected from the group consisting of 1, 2, 3, 4 and 5; and

-Z is the polymeric moiety, wherein -Z comprises a moiety of formula (a):



(a),

wherein

the dashed line indicates attachment to -L^2- or to the remainder of -Z;

BP^a is a branching point selected from the group consisting of -N<, -CR< and >C<;

-R is selected from the group consisting of -H and C_{1-6} alkyl;

a is 0 if BP^a is -N< or -CR< and a is 1 if BP^a is >C<;

-S^a-, -$S^{a'}$-, -$S^{a''}$- and -$S^{a'''}$- are independently of each other a chemical bond or are selected from the group consisting of C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl; wherein C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more -R^1, which are the same or different and wherein C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally interrupted by one or more groups selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-, -C(O)N(R^2)-, -S(O)$_2$N(R^2)-, -S(O)N(R^2)-, -S(O)$_2$-, -S(O)-, -N(R^2)S(O)$_2$N(R^{2a})-, -S-, -N(R^2)-, -OC(OR^2)(R^{2a})-, -N(R^2)C(O)N(R^{2a})-, and -OC(O)N(R^2)-;

each -T- is independently selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicyclyl, 8- to 30-membered carbopolycyclyl, and 8- to 30-membered heteropolycyclyl; wherein each -T- is independently optionally substituted with one or more -R^1, which are the same or different;

each -R^1 is independently selected from the group consisting of halogen, -CN, oxo (=O), -COOR^3, -OR^3, -C(O)R^3, -C(O)N(R^3R^{3a}), -S(O)$_2$N(R^3R^{3a}), -S(O)N(R^3R^{3a}), -S(O)$_2R^3$, -S(O)R^3, -N(R^3)S(O)$_2$N($R^{3a}R^{3b}$), -SR^3, -N(R^3R^{3a}), -NO$_2$, -OC(O)R^3, -N(R^3)C(O)R^{3a}, -N(R^3)S(O)$_2R^{3a}$, -N(R^3)S(O)R^{3a}, -N(R^3)C(O)OR^{3a},

$-N(R^3)C(O)N(R^{3a}R^{3b})$, $-OC(O)N(R^3R^{3a})$, and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;
each $-R^2$, $-R^{2a}$, $-R^3$, $-R^{3a}$ and $-R^{3b}$ is independently selected from the group consisting of -H, and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different; and
$-P^{a'}$, $-P^{a''}$ and $-P^{a'''}$ are independently a polymeric moiety.

2. The dry pharmaceutical formulation of claim 1, wherein the CNP moiety has the sequence of SEQ ID NO:24.

3. The dry pharmaceutical formulation of claim 1 or 2, wherein the formulation comprises based on the total weight of the dry pharmaceutical formulation:

CNP conjugate	1.3 - 38.7 % (w/w)
succinic acid	0.2 - 3.2 % (w/w)
trehalose dihydrate	52.6 - 98.4 % (w/w)
Tris	0.1 - 5.6 % (w/w).

4. The dry pharmaceutical formulation of any one of claims 1 to 3, wherein x of formula (Ia) is an integer selected from the group consisting of 1, 2, 3, 4, 6 and 8.

5. The dry pharmaceutical formulation of any one of claims 1 to 4, wherein y of formula (Ib) is an integer selected from the group consisting of 2, 3, 4 and 5.

6. The dry pharmaceutical formulation of any one of claims 1 to 5, wherein the CNP conjugate is of formula (Ia) and x is 1.

7. The dry pharmaceutical formulation of any one of claims 1 to 6, wherein -L^1- is connected to -D through an amide linkage.

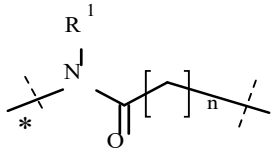
8. The dry pharmaceutical formulation of any one of claims 1 to 7, wherein the linkage between -Z and -L^2- is a stable linkage.

9. The dry pharmaceutical formulation of any one of claims 1 to 8, wherein -L^2- is a spacer moiety.

10. The dry pharmaceutical formulation of any one of claims 1 to 9, wherein -L^2- has a molecular weight in the range of from 14 g/mol to 750 g/mol.

11. The dry pharmaceutical formulation of any one of claims 1 to 10, wherein -L^2- has a chain length of 1 to 20 atoms.

12. The dry pharmaceutical formulation of any one of claims 1 to 11, wherein -L^2- is of formula (i):



(i),

wherein

the dashed line marked with the asterisk indicates attachment to -L^1-;

the unmarked dashed line indicates attachment to -Z;

-R^1 is selected from the group consisting of -H, C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl;

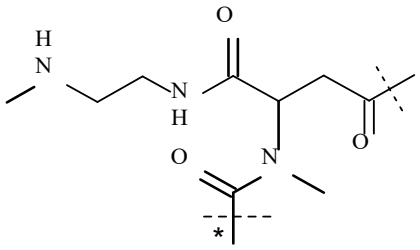
n is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 and 18; and

wherein the moiety of formula (i) is optionally further substituted.

13. The dry pharmaceutical formulation of claim 12, wherein n of formula (i) is selected from the group consisting of 3, 4, 5, 6, 7, 8 and 9.

14. The dry pharmaceutical formulation of any one of claims 1 to 13, wherein -Z has a molecular weight ranging from 5 to 200 kDa.

15. The dry pharmaceutical formulation of any one of claims 1 to 14, wherein the CNP conjugate is of formula (IIf):

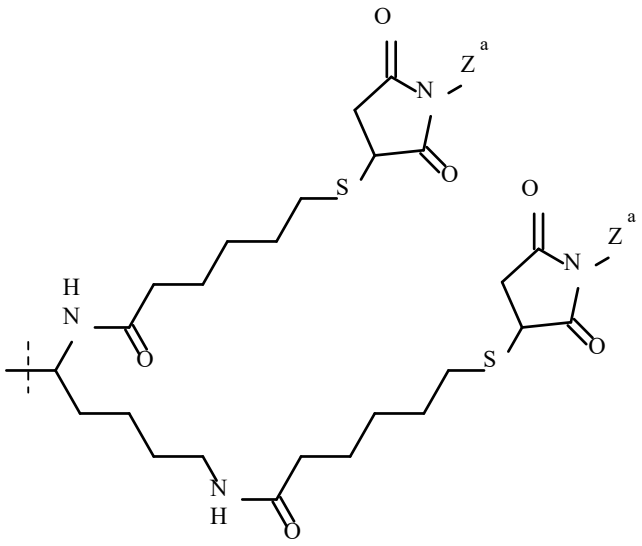


(IIf),

wherein

the unmarked dashed line indicates the attachment to a nitrogen of -D by forming an amide bond; and

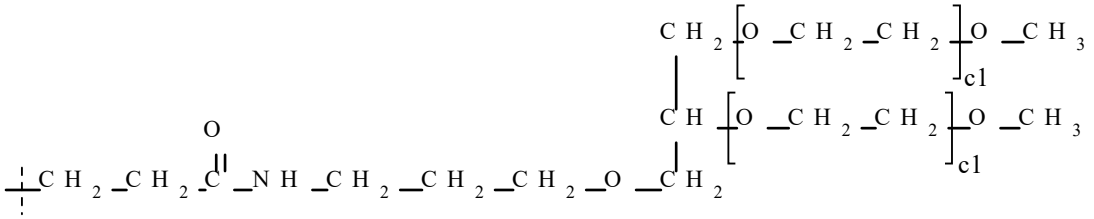
the dashed line marked with the asterisk indicates attachment to -Z having the structure



,

wherein

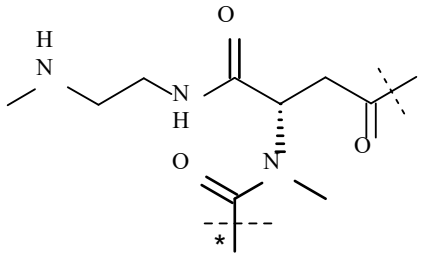
each -Z^a is



wherein

each c1 is an integer independently ranging from 200 to 250.

16. The dry pharmaceutical formulation of any one of claims 1 to 15, wherein the CNP conjugate is of formula (IIf '):

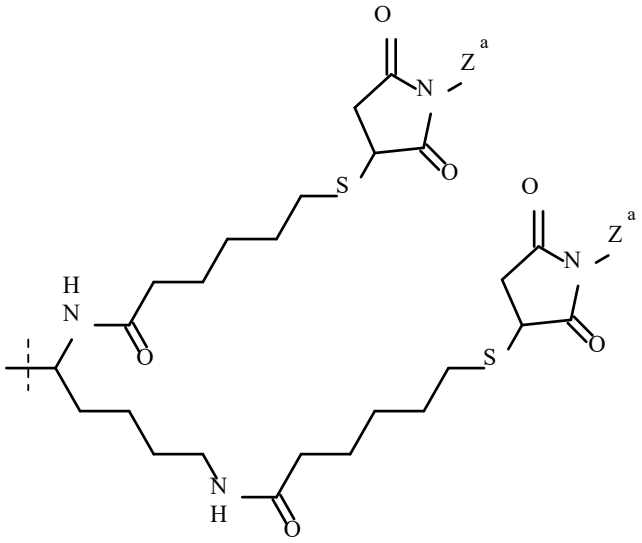


(IIf '),

wherein

the unmarked dashed line indicates the attachment to a nitrogen provided by the side chain of the lysine at position 26 of the CNP moiety of SEQ ID NO:24 by forming an amide bond; and

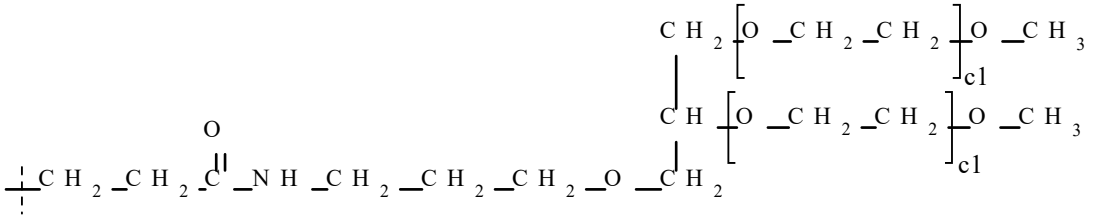
the dashed line marked with the asterisk indicates attachment to -Z having the structure



,

wherein

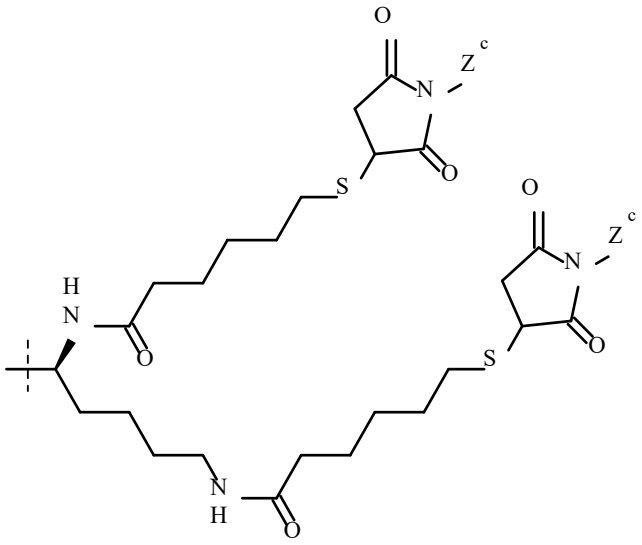
each -Z^a is



wherein

each c1 is an integer independently ranging from 200 to 250.

17. The dry pharmaceutical formulation of any one of claims 1 to 16, wherein -Z is of formula (h-i):

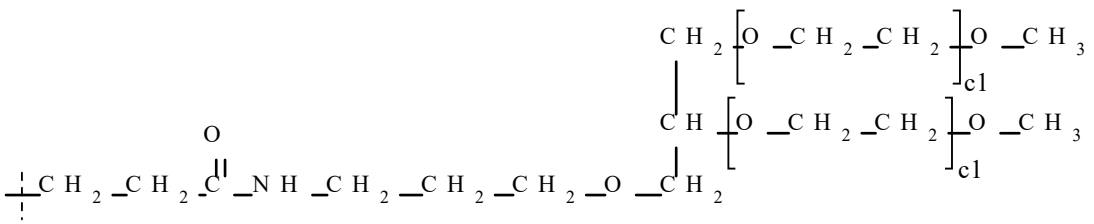


(h-i),

wherein

the dashed line indicates attachment to -L^2-; and

each -Z^c is a moiety



,

each c1 is an integer independently ranging from 200 to 250.