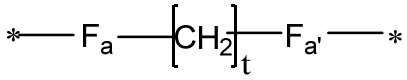
CLAIMS

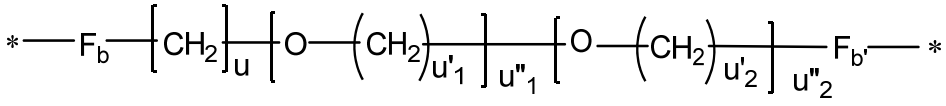
1. A composition in the form of an injectable aqueous solution, wherein the pH is comprised from 6.0 to 8.0, comprising at least:

- a basal insulin which isoelectric point pI is comprised from 5.8 to 8.5;
- a co-polyamino acid consisting of glutamic or aspartic units that is a co-polyamino acid according to formula I:

$$[Q(PLG)_k]\ [Hy]_j[Hy]_{j'} \qquad \text{Formula I}$$

- wherein:
- $j \geq 1$; $0 \leq j' \leq n'1$ and $j + j' \geq 1$ and $k = 2$,
- Q is a divalent linear or branched radical or spacer $([Q']_q[-*])_k$, where * represents a binding site of a group bound by an amide function, $1 \leq q \leq 5$ and $k = 2$,
- wherein Q' is selected from the group consisting of formula III and formula IV and forms $[Q']_q[-*]_k$:

-  Formula III

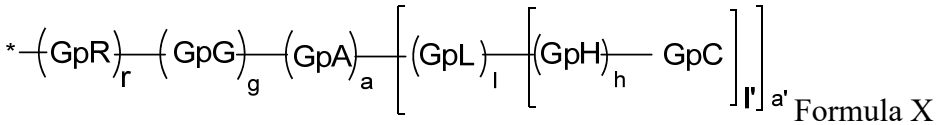
- 

Formula IV

- wherein:
- $1 \leq t \leq 8$,
- at least one of u_1'' or u_2'' is other than 0,

- if $u_1'' \neq 0$ then $u_1' \neq 0$ and if $u_2'' \neq 0$ then $u_2' \neq 0$,
- u_1' and u_2' are identical or different,
- $2 \leq u \leq 4$,
- $0 \leq u_1' \leq 4$,
- $0 \leq u_1'' \leq 4$,
- $0 \leq u_2' \leq 4$,
- $0 \leq u_2'' \leq 4$, and
- Fa, Fb, Fa', Fb' are identical or different and each represents function -NH- or -CO,
- the co-polyamino acid according to formula I bearing at least one hydrophobic radical -Hy, carboxylate charges and consisting of two chains of glutamic or aspartic units PLG bound together at least by the divalent linear or branched radical or spacer,
- the divalent linear or branched radical or spacer being bound to two glutamic or aspartic unit chains PLG by an amide function and,
- the amide function binding the divalent linear or branched radical or spacer to the two chains of glutamic or aspartic units results from a reaction between an amine function and an acid function respectively borne either by the Q' that is a precursor of the divalent linear or branched radical or spacer or by a glutamic or aspartic unit, and
- the hydrophobic radical -Hy being bound either to a terminal amino acid unit and then $j \geq 1$, or to a carboxyl function borne by one of the chains of the glutamic or aspartic units PLG and then $j' = n'1$ and $n'1$ is the mean number of monomeric units bearing a hydrophobic radical -Hy,

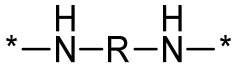
wherein the hydrophobic radical -Hy is a radical according to formula X:



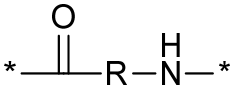
Formula X

wherein

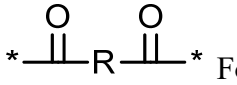
- GpR is selected from the group consisting of radicals according to formulas VII, VII' and VII'':



Formula VII

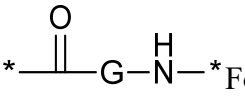


Formula VII'

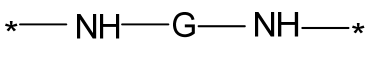


Formula VII'';

- GpG and GpH are identical or different and selected from the group consisting of radicals according to formulas XI and XI':

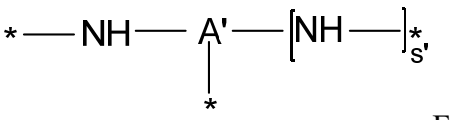


Formula XI



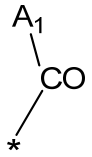
Formula XI'

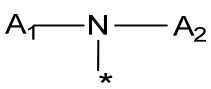
- GpA is a radical according to formula VIII:

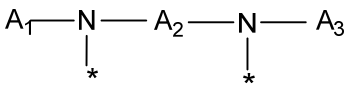


Formula VIII

wherein A' is selected from the group consisting of radicals according to VIII', VIII'' and VIII''':

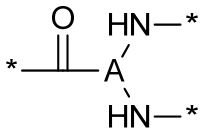






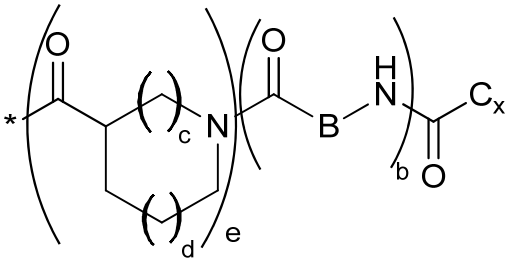
Formula VIII' Formula VIII'' Formula VIII'''

- GpL is a radical according to formula XII:



Formula XII,

- GpC is a radical according to formula IX:



Formula IX;

- the * indicates the binding sites of the different groups bound by amide functions;

- a is an integer equal to 0 or to 1 and a' = 1 if a = 0 and a' = 1, 2 or 3 if a = 1;

- a' is an integer equal to 1, to 2 or to 3;

- b is an integer equal to 0 or to 1;

- c is an integer equal to 0 or to 1, and if c is equal to 0 then d is equal to 1 or to 2;

- d is an integer equal to 0, to 1 or to 2;
- e is an integer equal to 0 or to 1;
- g is an integer equal to 0, to 1, to 2, to 3 to 4 to 5 or to 6;
- h is an integer equal to 0, to 1, to 2, to 3 to 4 to 5 or to 6;
- l is an integer equal to 0 or 1 and l' = 1 if l = 0 and l' = 2 if l = 1;
- r is an integer equal to 0, to 1 or to 2, and
- s' is an integer equal to 0 or 1;
- A, A_1, A_2 and A_3 identical or different are linear or branched alkyl radicals comprising from 1 to 8 carbon atoms and/or substituted by a radical from a saturated, unsaturated or aromatic ring;
- B is a radical selected from the group consisting of a non-substituted ether comprising from 4 to 14 carbon atoms and from 1 to 5 oxygen atoms, non-substituted polyether radical comprising from 4 to 14 carbon atoms and from 1 to 5 oxygen atoms, a linear alkyl radical comprising from 1 to 9 carbon atoms, a branched alkyl radical comprising from 1 to 9 carbon atoms, a linear alkyl radical comprising an aromatic nucleus and comprising from 1 to 9 carbon atoms, and a branched alkyl radical comprising an aromatic nucleus and comprising from 1 to 9 carbon atoms;
- C_x is a linear or branched monovalent alkyl radical, and/or comprising a cyclic part, wherein x indicates the number of carbon atoms and:
  - when the hydrophobic radical -Hy bears 1 -GpC, then $9 \leq x \leq 25$,
  - when the hydrophobic radical -Hy bears 2 -GpC, then $9 \leq x \leq 15$,
  - when the hydrophobic radical -Hy bears 3 -GpC, then $7 \leq x \leq 13$,

- when the hydrophobic radical -Hy bears 4 -GpC, then $7 \leq x \leq 11$,
- when the hydrophobic radical -Hy bears 5 or more -GpC, then $6 \leq x \leq 11$,

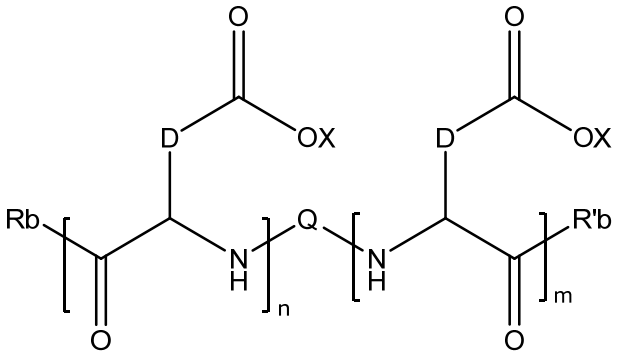
- G is a branched alkyl radical of 1 to 8 carbon atoms, the alkyl radical bearing one or a plurality of free carboxylic acid function(s);
- R is a radical selected from the group consisting of a linear or branched, divalent alkyl radical comprising from 1 to 12 carbon atoms, a linear or branched, divalent alkyl radical comprising from 1 to 12 carbon atoms bearing one or a plurality of functions $-CONH_2$ and a non-substituted ether or polyether radical comprising from 4 to 14 carbon atoms and from 1 to 5 oxygen atoms;
- the hydrophobic radical(s) -Hy according to formula X being bound to the PLG:
  - via a covalent bond between a carbonyl of the hydrophobic radical -Hy and a nitrogen atom borne by the PLG thus forming an amide function obtained from the reaction of an amine function borne by the PLG and an acid function borne by ta precursor -Hy' of the hydrophobic radical -Hy, and
  - via a covalent bond between a nitrogen atom of the hydrophobic radical -Hy and a carbonyl borne by the PLG thus forming an amide function obtained from the reaction of an amine function of the precursor -Hy' of the hydrophobic radical -Hy and an acid function borne by the PLG,
- a ratio M between the number of hydrophobic radicals and the number of glutamic or aspartic units being between $0 < M \leq 0.5$;

- when a plurality of hydrophobic radicals are borne by a co-polyamino acid then they are identical or different;

- a degree of polymerization DP in glutamic or aspartic units for the PLG chains is comprised from 5 to 250; and

- free carboxylic acid functions are in a form of alkali cation salt selected from the group consisting of Na^+ and K^+.

2. The composition according to claim 1, wherein the co-polyamino acid bearing carboxylate charges and at least one hydrophobic radical -Hy is a co-polyamino acid according to formula XXXb:



formula XXXb

wherein,

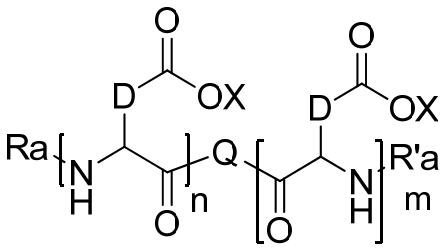
- D represents, independently, either a group -CH_2- (aspartic acid) or a group -CH_2-CH_2- (glutamic acid),

- X represents a cationic entity selected from the group consisting of alkali cations,

- Rb and R'b, which are identical or different, are either a hydrophobic radical -Hy, or a radical selected from the group consisting of an OH, an amino group, a terminal amino acid unit and a pyroglutamate,

- at least one of Rb and R'b being a hydrophobic radical -Hy,
- Q and Hy are as defined above,
- n + m represents the degree of polymerization DP of the co-polyamino acid, namely the mean number of monomeric units per co-polyamino acid chain and $5 \leq n + m \leq 250$.

3. The composition according to claim 1, wherein the co-polyamino acid bearing carboxylate charges and at least one hydrophobic radical -Hy is a co-polyamino acid according to formula XXXa hereinafter:



Formula XXXa

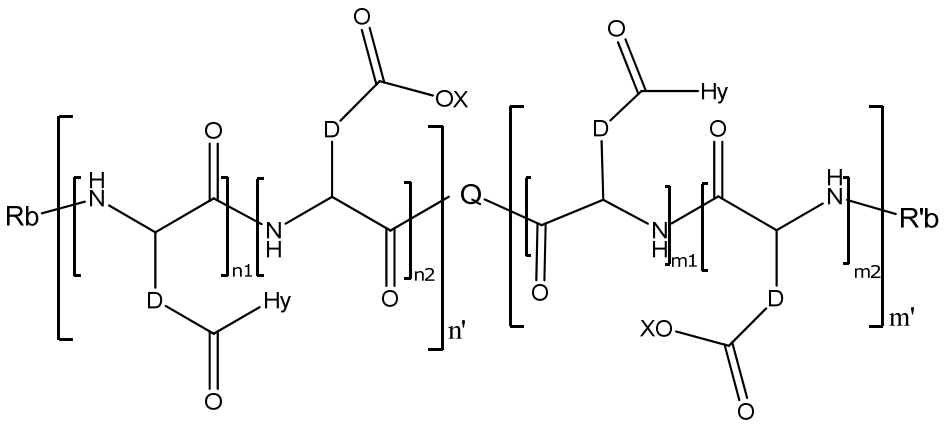
wherein,

- D represents, independently, either a group $-CH_2-$ (aspartic acid) or a group $-CH_2-CH_2-$ (glutamic acid),
- X represents a cationic entity selected from the group consisting of alkali cations,
- Ra and R'a, which are identical or different, are either a hydrophobic radical -Hy, or a radical selected from the group consisting of an H, a C2 to C10 linear acyl group, a C3 to C10 branched acyl group, a benzyl, a terminal amino acid unit and a pyroglutamate,

at least one of Ra and R’a being a hydrophobic radical -Hy,

- Q and -Hy are as defined in Formula I,
- n + m represents the degree of polymerization DP of the co-polyamino acid, namely the mean number of monomeric units per co-polyamino acid chain and $5 \leq n + m \leq 250$.

4. The composition according to claim 1, wherein the co-polyamino acid bearing carboxylate charges and at least one hydrophobic radical -Hy is a co-polyamino acid according to formula XXXb':



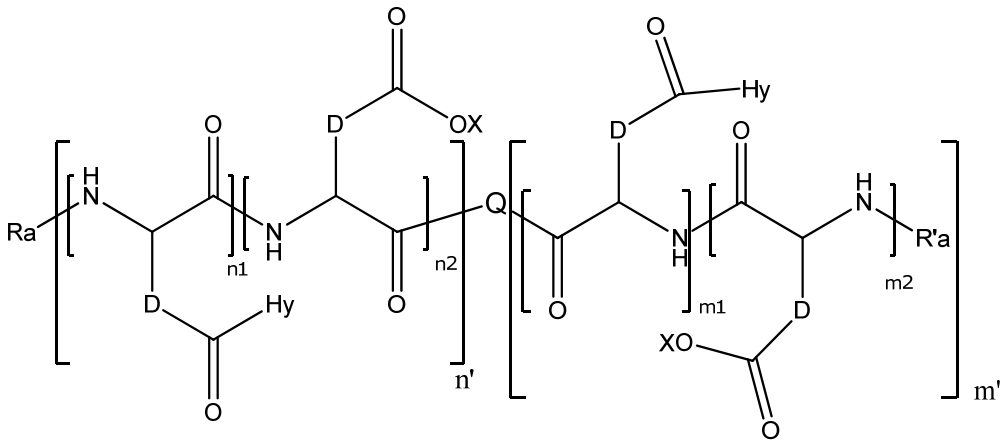
Formula XXXb'

wherein:

- D represents, independently, either a group $-CH_2-$ (aspartic acid) or a group $-CH_2-CH_2-$ (glutamic acid),
- X represents a cationic entity selected from the group consisting of alkali cations,
- Q and Hy are as defined in Formula I,

- Rb and R'b, which are identical or different, are either a hydrophobic radical -Hy, or a radical selected from the group consisting of an -OH, an amine group, a terminal amino acid unit and a pyroglutamate,
- at least one of Rb and R’b is a hydrophobic radical -Hy,
- n1+m1 represents the number of glutamic units or aspartic units of the PLG chains of the co-polyamino acid bearing a radical -Hy,
- n2+m2 represents the number of glutamic units or aspartic units of the PLG chains of the co-polyamino acid not bearing a radical -Hy,
- n1+n2 = n’ and m1+m2 = m’,
- n’ + m’ represents the degree of polymerization DP of the co-polyamino acid, namely the mean number of monomeric units per co-polyamino acid chain and $5 \leq n' + m' \leq 250$.

5. The composition according to claim 1, wherein the co-polyamino acid bearing carboxylate charges and at least one hydrophobic radical -Hy is a co-polyamino acid according to formula XXXa’ hereinafter:

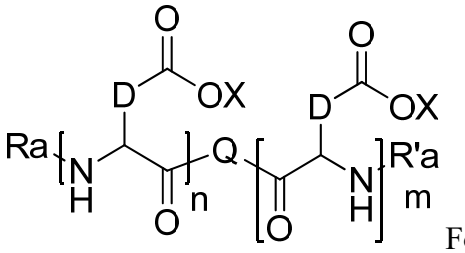


Formula XXXa’

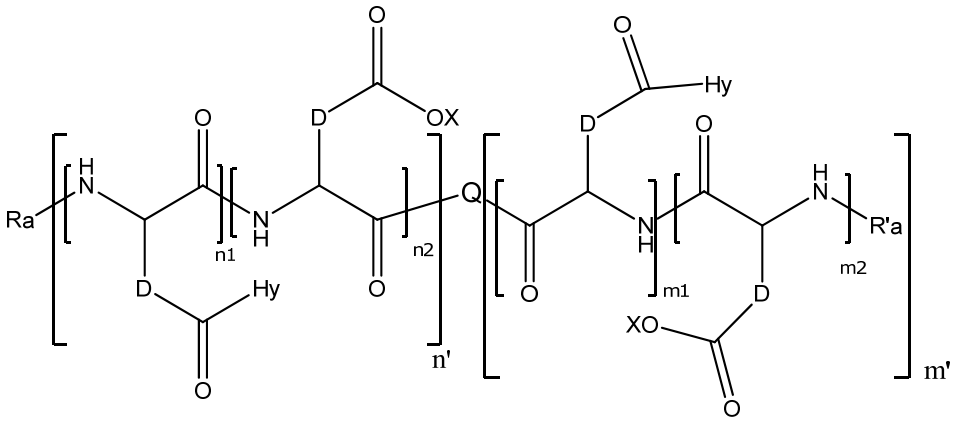
wherein:

- D represents, independently, either a group -CH_2- (aspartic acid) or a group -CH_2-CH_2- (glutamic acid),
- X represents a cationic entity selected from the group consisting of alkali cations,
- Ra and R’a, which are identical or different, are either a hydrophobic radical -Hy, or a radical selected from the group consisting of an H, a C2 to C10 linear acyl group, a C3 to C10 branched acyl group, a benzyl, a terminal amino acid unit and a pyroglutamate,
- Q and Hy are as defined in Formula I,
- n_1+m_1 represents the number of glutamic units or aspartic units of the PLG chains of the co-polyamino acid bearing a radical -Hy,
- n_2+m_2 represents the number of glutamic units or aspartic units of the PLG chains of the co-polyamino acid not bearing a radical -Hy,
- $n_1+n_2 = n’$ and $m_1+m_2 = m’$.

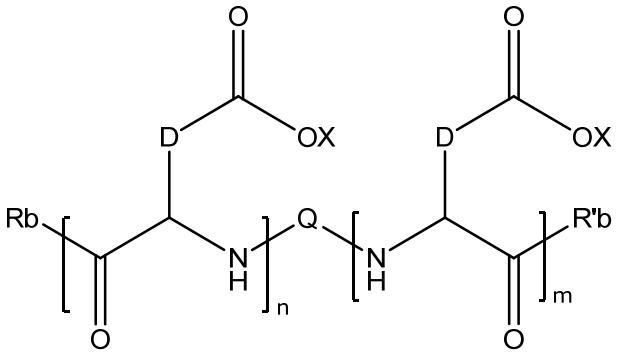
6. The composition according to claim 1, wherein the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is a co-polyamino acid selected from the group according to formulas XXXa, XXXa', XXXb and XXXb':



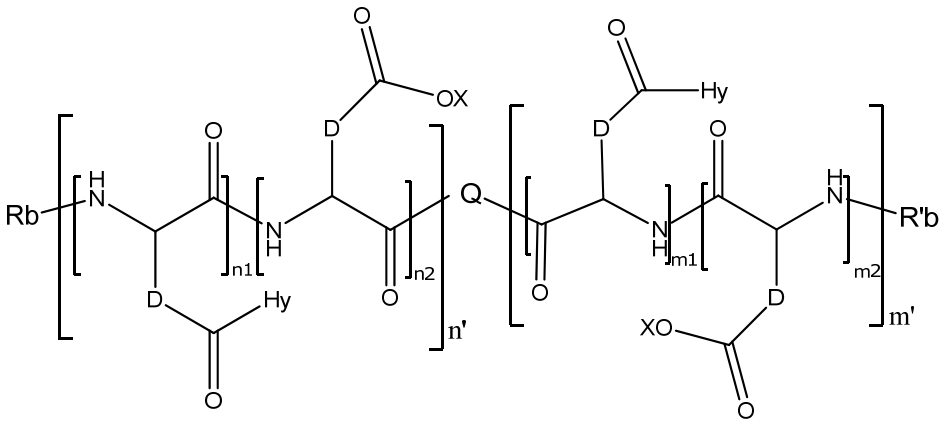
Formula XXXa



Formula XXXa'



Formula XXXb



Formula XXXb’

wherein

the group D is a group -CH_2- (aspartic unit),

X represents a cationic entity selected from the group consisting of alkali cations,

Ra and R'a, which are identical or different, are either a hydrophobic radical -Hy, or a radical selected from the group consisting of an H, a C2 to C10 linear acyl group, a C3 to C10 branched acyl group, a benzyl, a terminal amino acid unit and a pyroglutamate,

Rb and R'b, which are identical or different, are either a hydrophobic radical -Hy, or a radical selected from the group consisting of an -OH, an amine group, a terminal amino acid unit and a pyroglutamate, at least one of Rb and R'b is a hydrophobic radical -Hy,

Q and Hy are as defined in Formula I,

n1+m1 represents the number of glutamic units or aspartic units of the PLG chains of the co-polyamino acid bearing a radical -Hy,

n2+m2 represents the number of glutamic units or aspartic units of the PLG chains of the co-polyamino acid not bearing a radical -Hy,

n1+n2 = n’ and m1+m2 = m’, and

n’ + m’ represents the degree of polymerization DP of the co-polyamino acid, namely the mean number of monomeric units per co-polyamino acid chain and $5 \leq n' + m' \leq 250$.

7. The composition according to claim 1, wherein the basal insulin which isoelectric point is comprised from 5.8 to 8.5 is insulin glargine.

8. The composition according to claim 1, wherein it comprises from 40 to 500 U/mL of basal insulin which isoelectric point is comprised from 5.8 to 8.5.

9. The composition according to claim 1, wherein the concentration of co-polyamino acid bearing carboxylate charges and hydrophobic radicals is not more than 60 mg/mL.

10. The composition according to claim 1, wherein the concentration of co-polyamino acid bearing carboxylate charges and hydrophobic radicals is not more than 40 mg/mL.

11. The composition according to claim 1, wherein the concentration of co-polyamino acid bearing carboxylate charges and hydrophobic radicals is not more than 20 mg/mL.

12. The composition according to claim 1, wherein the concentration of co-polyamino acid bearing carboxylate charges and hydrophobic radicals is not more than 10 mg/mL.

13. A co-polyamino acid bearing carboxylate charges and at least one hydrophobic radical according to formula X, according to formula I:

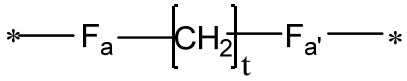
$$[Q(PLG)_k]\,[Hy]_j[Hy]_{j'} \qquad \text{Formula I}$$

wherein:

- $j \geq 1$; $0 \leq j' \leq n'1$ and $j + j' \geq 1$ and $k = 2$,

- Q is a divalent linear or branched radical or spacer $([Q']_q[-*])_k$, where * represents a binding site of a group bound by an amide function, $1 \leq q \leq 5$ and $k = 2$,

- wherein Q' is of formula III and forms $[Q']_q[-*]_k$:

-  Formula III

- wherein $1 \leq t \leq 8$, and

- Fa and Fa' are identical or different and each represents function -NH-,

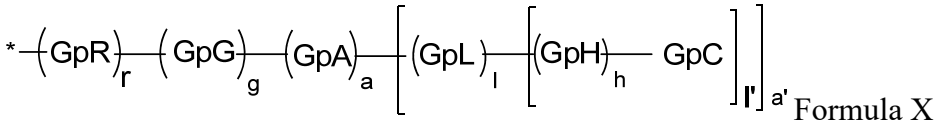
- said co-polyamino acid according to formula I bearing at least one hydrophobic radical -Hy, carboxylate charges and consisting of at least two chains of glutamic or aspartic units PLG bound together at least by the divalent linear or branched radical or spacer,

- the divalent linear or branched radical or spacer being bound to two glutamic or aspartic unit chains PLG by an amide function and,

- the amide function binding the divalent linear or branched radical or spacer to the two chains of glutamic or aspartic units results result from a reaction between an amine function and an acid function respectively borne either by the precursor Q' of the divalent linear or branched radical or spacer or by a glutamic or aspartic unit,

- the hydrophobic radical -Hy being bound either to a terminal amino acid unit and then $j \geq 1$, or to a carboxyl function borne by one of the chains of the glutamic or aspartic units PLG and then $j' = n'1$ and n'1 is the mean number of monomeric units bearing a hydrophobic radical -Hy,

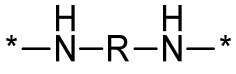
and wherein the at least one hydrophobic radical -Hy according to formula X is as defined hereinafter:



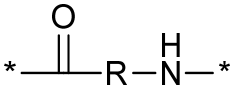
Formula X

wherein

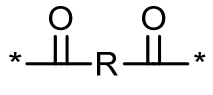
- GpR is selected from the group consisting of radicals according to formulas VII, VII' and VII'':



Formula VII

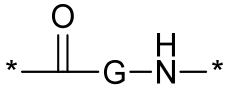


Formula VII'

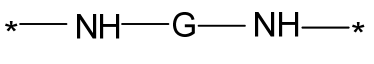


Formula VII'';

- GpG and GpH are identical or different and are selected from the group consisting of radicals according to formulas XI and XI':

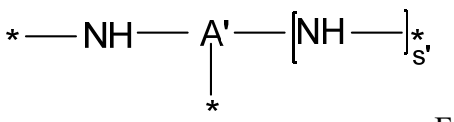


Formula XI



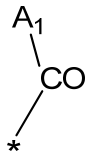
Formula XI'

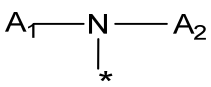
- - GpA is a radical according to formula VIII

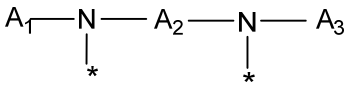


Formula VIII

wherein A’ is selected from the group consisting of radicals according to VIII’, VIII’’ or VIII’’’

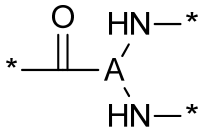






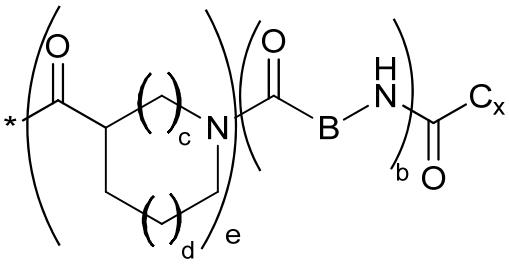
Formula VIII’ Formula VIII’’ Formula VIII’’’

- GpL is a radical according to formula XII



Formula XII,

- GpC is a radical according to formula IX:



Formula IX;

- the * indicates the binding sites of the different groups bound by the amide function;
- a is an integer equal to 0 or to 1 and a’ = 1 if a = 0 and a’ = 1, 2 or 3 if a = 1;
- a’ is an integer equal to 1, to 2 or to 3;
- b is an integer equal to 0 or to 1;

- c is an integer equal to 0 or to 1, and if c is equal to 0 then d is equal to 1 or to 2;
- d is an integer equal to 0, to 1 or to 2;
- e is an integer equal to 0 or to 1;
- g is an integer equal to 0, to 1, to 2, to 3 to 4 to 5 or to 6;
- h is an integer equal to 0, to 1, to 2, to 3 to 4 to 5 or to 6;
- l is an integer equal to 0 or 1 and l' = 1 if l = 0 and l' = 2 if l = 1;
- r is an integer equal to 0, to 1 or to 2, and
- s' is an integer equal to 0 or 1;
- A, A_1, A_2 and A_3 identical or different are linear or branched alkyl radicals comprising from 1 to 8 carbon atoms and/or substituted by a radical from a saturated, unsaturated or aromatic ring;
- B is a radical selected from the group consisting of a non-substituted ether comprising from 4 to 14 carbon atoms and from 1 to 5 oxygen atoms, a non-substituted polyether radical comprising from 4 to 14 carbon atoms and from 1 to 5 oxygen atoms, a linear alkyl radical comprising from 1 to 9 carbon atoms, a branched alkyl radical comprising from 1 to 9 carbon atoms, a linear alkyl radical comprising an aromatic nucleus and comprising from 1 to 9 carbon atoms, and a branched alkyl radical comprising an aromatic nucleus and comprising from 1 to 9 carbon atoms;
- C_x is a linear or branched monovalent alkyl radical, optionally comprising a cyclic part, wherein x indicates the number of carbon atoms and:
  - when the hydrophobic radical -Hy bears 1 -GpC, then $9 \leq x \leq 25$,

- when the hydrophobic radical -Hy bears 2 -GpC, then $9 \leq x \leq 15$,
- when the hydrophobic radical -Hy bears 3 -GpC, then $7 \leq x \leq 13$,
- when the hydrophobic radical -Hy bears 4 -GpC, then $7 \leq x \leq 11$,
- when the hydrophobic radical -Hy bears 5 or more -GpC, then $6 \leq x \leq 11$,

- G is a branched alkyl radical of 1 to 8 carbon atoms, said alkyl radical bearing one or a plurality of free carboxylic acid function(s); and

- R is a radical selected from the group consisting of a linear or branched, divalent alkyl radical comprising from 1 to 12 carbon atoms, a linear or branched, divalent alkyl radical comprising from 1 to 12 carbon atoms bearing one or a plurality of functions $-CONH_2$, and a non-substituted ether or polyether radical comprising from 4 to 14 carbon atoms and from 1 to 5 oxygen atoms.

14. A method for improving the physicochemical stability of the composition according to claim 1, by adding one or more ionic species selected from the group of anions, cations and zwitterions.