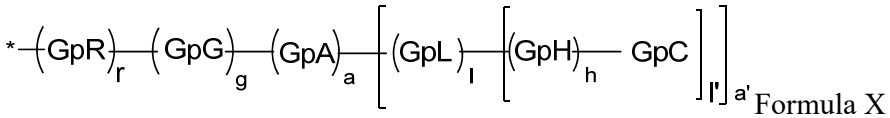
CLAIMS

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

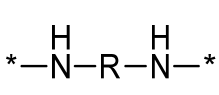
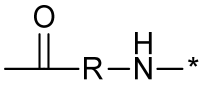
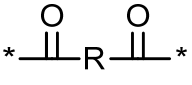
- a basal insulin whose isoelectric point pI is comprised from 5.8 to 8.5;

- a co-polyamino acid bearing carboxylate charges and hydrophobic radicals Hy, said co-polyamino acide consisting of glutamic or aspartic units, and said hydrophobic radicals Hy being according to formula X below:

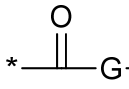
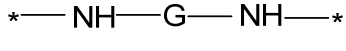

Formula X

in which

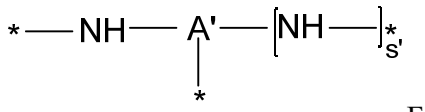
- GpR is chosen from the radicals according to formulas VII, VII' or VII'':


Formula VII or 
Formula VII' or 
Formula VII'';

- Identical or different GpG and GpH are chosen from the radicals according to formulas XI or XI';

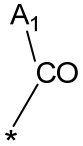

Formula XI 
Formula XI'

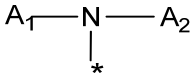
- - GpA is chosen from the radicals according to formula VIII

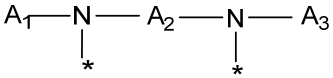


Formula VIII

In which A’ is chosen from the radicals according to formula VIII’, VIII’’ or VIII’’’

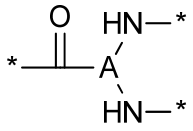






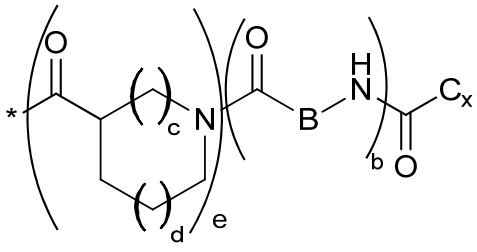
Formula VIII’ Formula VIII’’ Formula VIII’’’

- -GpL is chosen from the radicals according to formula XII



Formula XII,

- GpC is a radical according to formula IX:



Formula IX;

- The * indicates the attachment sites of the different groups bonded by the amide functions;

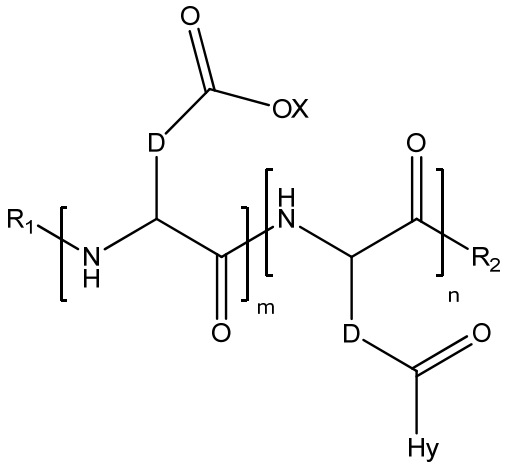
- a is an integer equal to 0 or to 1 and a’ = 1 if a = 0 and a’ = 1, 2 or 3 if a = 1;

- 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, and
- if e is different from 0, then at least one of g, h or l is different from 0; and
- if a = 0, then l = 0;
- A, A_1, A_2 and A_3, identical or different, are linear or branched alkyl radicals, and optionally substituted by a radical derived from a saturated, unsaturated or aromatic ring, comprising 1 to 8 carbon atoms.
- B is a linear or branched alkyl radical optionally comprising an aromatic nucleus, comprising 1 to 9 carbon atoms or an unsubstituted ether or polyether radical comprising from 4 to 14 carbon atoms and from 1 to 5 oxygen atoms;
- C_x is a linear or branched monovalent alkyl radical, optionally comprising a cyclic part, in which x indicates the number of carbon atoms and:
  - When the hydrophobic radical -Hy carries 1 -GpC, then $9 \leq x \leq 25$,
  - When the hydrophobic radical -Hy carries 2 -GpC, then $9 \leq x \leq 15$,
  - When the hydrophobic radical -Hy carries 3 -GpC, then $7 \leq x \leq 13$,
  - When the hydrophobic radical -Hy carries 4 -GpC, then $7 \leq x \leq 11$,
  - When the hydrophobic radical -Hy carries at least 5 -GpC, then $6 \leq x \leq 11$,

- G is a branched alkyl radical of 1 to 8 carbon atoms, with said alkyl radical bearing one or more free carboxylic acid functions.
- R is a radical chosen from the group consisting of a divalent alkyl radical, linear or branched, comprising 1 to 12 carbon atoms, a divalent alkyl radical, linear or branched, comprising 1 to 12 carbon atoms bearing one or more -$CONH_2$ functions, or a unsubstituted ether or polyether radical comprising from 4 to 14 carbon atoms and 1 to 5 oxygen atoms:
- the hydrophobic radical(s) -Hy according to formula X being bonded 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 derived from the reaction of an amine function borne by the PLG and an acid function borne by the precursor -Hy' of the hydrophobic radica -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 derived from the reaction of an amine function of the precursor -Hy' of the hydrophobic -Hy radical and an acid function borne by the PLG,
- the ratio M between the number of hydrophobic radicals and the number of glutamic or aspartic units being from $0 < M \leq 0.5$;
- when several hydrophobic radicals are borne by a co-polyamino acid, then they are identical or different,
- the degree of polymerization DP in glutamic or aspartic units for PLG chains is comprised from 5 to 250;
- free carboxylic acid functions being in the form of an alkali metal salt chosen from the group consisting of Na^+ and K^+.

2. The composition according to claim 1, characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is chosen from the co-polyamino acids according to formula XXXa' below:



formula XXXa'

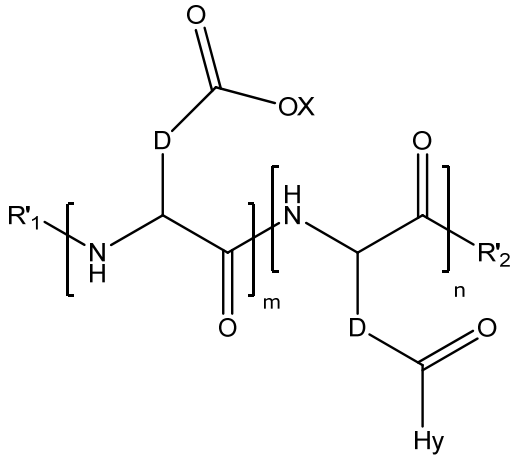
in which

- D represents, independently, either a -CH_2- group (aspartic unit) or a -CH_2-CH_2- group (glutamic unit),
- Hy is a hydrophobic radical chosen from the hydrophobic radicals according to formula X, in which r=1 and GpR is a radical according to formula VII,
- R_1 is a hydrophobic radical chosen from the hydrophobic radicals according to formula X in which r=0 or r=1 and GpR is a radical according to formula VII', or a radical chosen from the group consisting of an H, a linear acyl group in C2 to C10, a branched acyl group in C4 to C10, a benzyl, a terminal "amino acid" unit and a pyroglutamate,
- R_2 is a hydrophobic glutamate chosen from the hydrophobic radicals according to formula X in which r=1 and GpR is a radical

according to formula VII, or a -NR'R'' radical, R' and R", either identical or different, being chosen from the group comprised by H, the linear or branched or cyclic alkyls in C2 to C10, the benzyl, and said R' and R" alkyls which may form together one or more carbonated , saturated, unsaturated and/or aromatic cycle(s), and/or may comprise hetero-atoms, chosen from the group comprised of O, N and S;

- X represents a cationic entity chosen from the group comprising alkaline cations;
- n + m represents the degree of polymerization DP of the co-polyamino acid, namely, the average number of monomeric units per co-polyamino acid chain and $5 \leq n + m \leq 250$.

3. The composition according to the preceding claim, characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is chosen from the co-polyamino acids according to formula XXXa', in which $R_1 = R'_1$ and $R_2 = R'_2$, according to formula XXXa below:

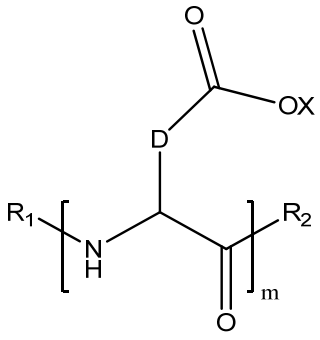


formula XXXa'

in which

- m, n, X, D and Hy have the definitions given above,
- R'_1 is a radical chosen from the group consisting of an H, a linear acyl group in C2 to C10, a branched acyl group in C4 to C10, a benzyl, a terminal “amino acid” unit and a pyroglutamate,
    - R_2 is a radical -NR’R’’, R’ and R” l, either identical or different, being chosen from the group comprised by H, the linear or branched or cyclic alkyls in C2 to C10, the benzyl, and said R’ and R” alkyls which may form together one or more carbonated, saturated, unsaturated and/or aromatic cycle(s), and may comprise hetero-atoms, chosen from the group comprised of O, N and S;

4. The composition according to claim 2, characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is chosen from the co-polyamino acids according to formula XXXa’ in which n = 0 according to formula XXXb below:



formula XXXb

in which m, X, D, R_1 and R_2 have the definitions given above and at least R_1 or R_2 is a radical hydrophobic according to formula X.

5. The composition according to claim 4, characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is chosen from the co-polyamino acids of XXXa' in which n = 0 according to formula XXXb and R_1 or R_2 is a hydrophobic radical according to formula X.

6. The composition according to any one of claims 4 and 5, characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is chosen from the co-polyamino acids according to formulas XXXb in which R_2 is a hydrophobic radical according to formula X in which r = 1 and GpR is according to formula VII.

7. The composition according to any one of claims 2 to 6, characterized in that R_1 is a radical chosen from the group consisting of a linear acyl group in C_2 to C_{10}, a branched acyl group in C_4 to C_{10}, a benzyl, a terminal "amino acid" unit and a pyroglutamate.

8. The composition according to the preceding claim, characterized in that R_1 is a radical chosen from the group consisting of a linear acyl group in C_2 to C_{10} or a branched acyl group in C_4 to C_{10}.

9. The composition according to any one of claims 2 to 8, characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is chosen from the co-polyamino acids according to formulas XXXa', XXXa or XXXb in which the co-polyamino acid is chosen from the co-polyamino acids in which group D is a $-CH_2-$ group (aspartic unit).

10. The composition according to any one of claims 2 to 8, characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is chosen from the co-copyamino acids according to formulas XXXa', XXXa or XXXb in which the co-polyamino acid is chosen from the co-polyamino acids in which group D is a CH_2-CH_2-group (glutamic unit).

11. The composition according to any one of the preceding claims, characterized in that the basal insulin whose isoelectric point is comprised from 5.8 to 8.5 is insulin glargine.

12. The composition according to any one of the preceding claims, characterized in that it comprises from 40 to 500 U/mL of basal insulin whose isoelectric point is comprised from 5.8 to 8.5.

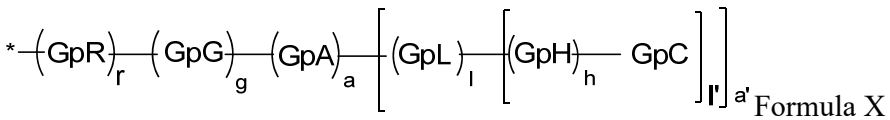
13. The composition according to any one of the preceding claims, characterized in that the concentration of co-polyamino acid bearing carboxylate chargres and hydrophobic radicals is at most 60 mg/mL.

14. The composition according to any one of the preceding claims, characterized in that the concentration of co-polyamino acid bearing carboxylate charges and hydrophobic radicals is at most 40 mg/mL.

15. The composition according to any one of the preceding claims, characterized in that the concentration of co-polyamino acid bearing carboxylate charges and hydrophobic radicals is at most 20 mg/mL.

16. The composition according to any one of the preceding claims, characterized in that the concentration of co-polyamino acid bearing carboxylate charges and hydrophobic radicals is at most 10 mg/mL.

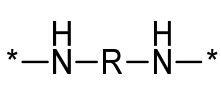
17. Co-polyamino acid bearing carboxylate charges and hydrophobic radicals Hy, said co-polyamino acid consisting of glutamic or aspartic units and said hydrophobic radicals Hy chosen from the hydrophobic radicals according to formula X as defined below:



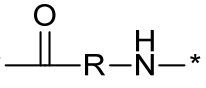
Formula X

in which

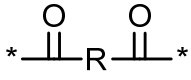
GpR is chosen from the radicals according to formulas VII, VII' or VII':



Formula VII or

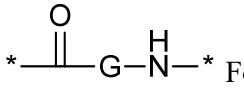


Formula VII' or

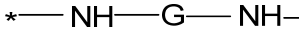


Formula VII'';

- Identical or different GpG and GpH are chosen from the radicals according to formulas XI or XI';

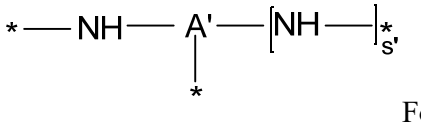


Formula XI



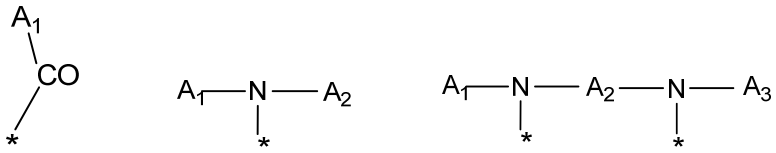
Formula XI'

- GpA is chosen from the radicals according to formula VIII



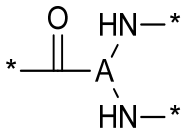
Formula VIII

In which A' is chosen from the radicals according to formula VIII',VIII'' or VIII'''



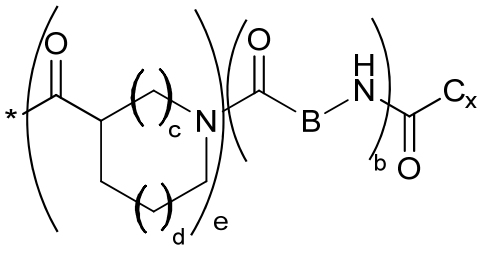
Formula VIII' Formula VIII'' Formula VIII'''

- -GpL is chosen from the radicals according to formula XII



Formula XII,

- GpC is a radical according to formula IX:



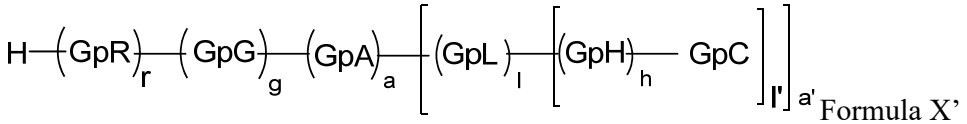
Formula IX;

- The * indicates the attachment site of the different groups bonded by the amide functions;
- a is an integer equal to 0 or to 1 and a' = 1 if a = 0, 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, and at least one of g, h or l is different from 0;
- l is an integer equal to 0 or 1 and l' = 1 if l = 0, and l' = 2 if l = 1;
- r is integer equal to 0, to 1, or to 2, and
- s' is an integer equal to 0 or 1;
- and if e is different from 0, then at least one of g, h or l is different from 0;
- and if a = 0, then l = 0;
- 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 optionally substituted by a radical derived from a saturated, unsaturated or aromatic cycle;
- B is an unsubstituted ether or polyether radical comprising 4 to 14 carbon atoms and from 1 to 5 oxygen atoms or a linear or branched alkyl radical, optionally including an aromatic nucleus, comprising from 1 to 9 carbon atoms.
- C_x is a linear or branched monovalent alkyl radical, optionally comprising a cyclic part, in which 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 -GpC, then $6 \leq x \leq 11$,

- G is a linear or branched alkyl radical of 1 to 8 carbon atoms, said alkyl radical bearing one or more free carboxylic acid function(s),
- R is a radical chosen from the group consisting of a divalent, linear or branched alkyl radical, comprising from 1 to 12 carbon atoms, a divalent, linear or branched alkyl radical, comprising from 1 to 12 carbon atoms bearing one or more -$CONH_2$ functions, or an unsubstituted 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 bonded 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 derived from the reaction of an amine function borne by the PLG and and acid function borne by the 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 resulting from the reaction of an amine function of the precursor -Hy' of the hydrophobic radical -Hy and an acid function borne by the PLG,
- the ratio M between the number of hydrophobic radicals and the number of glutamic or aspartic units being from $0 < M \leq 0.5$;
- when several hydrophobic radicals are borne by a co-polyamino acid, then they are identical or different,
- the degree of polymerization DP in glutamic or aspartic units for PLG chains is comprised from 5 to 250;
- free carboxylic acid functions being in the form of an alkali metal salt chosen from the group consisting of Na^+ and K^+.

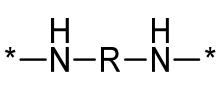
18. Precusor Hy' of the hydrophobic radical -Hy according to formula X' as defined below:

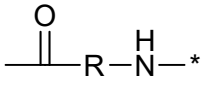


Formula X'

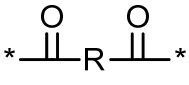
in which

GpR is chosen from the radicals according to formulas VII, VII' or VII'':



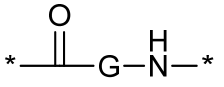
Formula VII or 

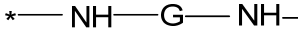
Formula VII' or



Formula VII'';

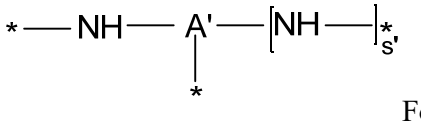
- Identical or different GpG and GpH are chosen from the radicals according to formulas XI or XI';



Formula XI 

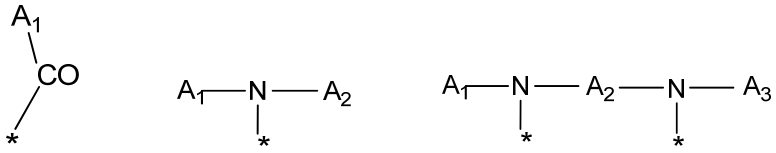
Formula XI'

- GpA is chosen from the radicals according to formula VIII



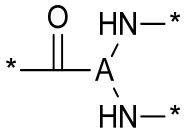
Formula VIII

In which A' is chosen from the radicals according to formula VIII',VIII'' or VIII'''



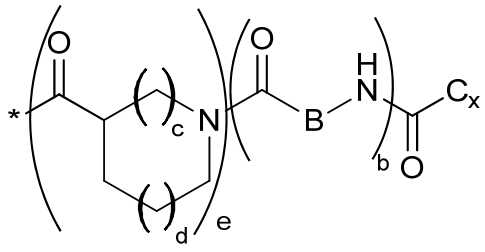
Formula VIII’ Formula VIII’’ Formula VIII’’’

- -GpL is chosen from the radicals according to formula XII



Formula XII,

- GpC is a radical according to formula IX:



Formula IX;

- The * indicate the attachment sites of the different groups bonded by the amide functions;
- a is an integer equal to 0 or to 1 and a’ = 1 if a = 0, 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, and at least one of g or h is different from 0;
- l is an integer equal to 0 or 1 and l' = 1 if l = 0, and l' = 2 if l = 1;
- r is integer equal to 0, to 1, or to 2, and
- s' is an integer equal to 0 or 1;
- and if e is different from 0, then at least one of g, h or l is different from 0;
- and if a = 0, then l = 0;
- 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 optionally substituted by a radical from a saturated, unsaturated or aromatic cycle;

- B is an unsubstituted ether or polyether radical comprising from 4 to 14 carbon atoms and from 1 to 5 oxygen atoms or a linear or branched alkyl radical, optionally including an aromatic nucleus, comprising from 1 to 9 carbon atoms.

- C_x is a linear or branched monovalent alkyl radical, optionally comprising a cyclic part, in which 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 -GpC, then $6 \leq x \leq 11$,

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

- R is a radical chosen from the group consisting of a divalent, linear or branched alkyl radical, comprising from 1 to 12 carbon atoms, a divalent, linear or branched alkyl

radical, comprising from 1 to 12 carbon atoms bearing one or more -$CONH_2$ function(s), or an unsubstituted 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 bonded 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 derived from the reaction of an amine function borne by the PLG and an acid function borne by the precursor -Hy' of the hydrophobic radica -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 derived from the reaction of an amine function of the precursor -Hy' of the hydrophobic radical -Hy and an acid function borne by the PLG,
- the ratio M between the number of hydrophobic radicals and the number of glutamic or aspartic units being from $0 < M \leq 0.5$;
- when several hydrophobic radicals are borne by a co-polyamino acid, then they are identical or different,
- free carboxylic acid functions being in the form of an alkali metal salt chosen from the group consisting of Na^+ and K^+.