COMPOSITIONS IN THE FORM OF AN INJECTABLE AQUEOUS SOLUTION, COMPRISING HUMAN GLUCAGON AND AN END-GRAFTED COPOLYAMINO ACID

[0001] Human glucagon is a short-acting hyperglycemic hormone that allows the increase of glycemia, thus correcting a hypoglycemic level that can result from an insulin excess. It enables the release of glucose by stimulation of hepatic glycogenolysis and it has insulin antagonistic properties (hypoglycemic). Human glucagon is normally secreted by the alpha cells of the islets of Langerhans in the pancreas when hypoglycemia is detected.

[0002] Human glucagon is used for therapeutic purposes, such as the emergency treatment of severe hypoglycemia, also referred to as "rescue," but also in a diagnostic context in the performance of medical examinations, for example, in order to inhibit gastrointestinal motility. Other applications are also considered for human glucagon, in particular its use in a bi-hormonal glycemia regulation system, also referred to as artificial pancreas, and in congenital hyperinsulinism, which is a rare disease characterized by very high insulin levels.

[0003] The clinical use of human glucagon has been limited because of some of its disadvantageous properties in terms of development of a stable pharmaceutical product with therapeutic intent. Indeed, human glucagon has a very low solubility at physiological pH and a high physical instability, due to its propensity to form fibrils in a large pH range. This is the reason why the only commercial products based on human glucagon (Glucagen®, NOVO NORDISK and Glucagon for injection, ELI LILLY) are lyophilized forms to be reconstituted extemporaneously.

[0004] The studies of Onoue et al. (Pharm. Res. 2004, 21(7), 1274-83) have shown the potentially dangerous characters of these fibrils: fibrillated human glucagon being cytotoxic in mammalian cells in culture.

[0005] In addition to its physical instability, human glucagon undergoes various types of chemical degradation. In an aqueous solution, it degrades rapidly to form several degradation products. At least 16 degradation products of human glucagon have been identified by Kirsh et al. (International Journal of Pharmaceutics, 2000, 203, 115-125). The chemical degradation of this human glucagon is thus rapid and complex.

[0006] The poor chemical and physical stability of human glucagon in solution has led pharmaceutical companies such as NOVO NORDISK, ELI LILLY and more recently FRESENIUS KABI to market this human glucagon in the form of a lyophilizate to be reconstituted at acidic pH (pH < 3) immediately before injection. Human glucagon in lyophilizate form is more stable, and the preparation of the formulation at acidic pH immediately before use makes it possible to obtain a clear solution. However, once the product is reconstituted, it has to be used rapidly, because it undergoes an extremely rapid chemical and physical degradation in the acidic reconstitution buffer, with appearance of human glucagon fibrils within 24 hours after the reconstitution and/or gelling of the composition. However, this presentation of the product is unsatisfactory because it requires a very rapid use of the formulation. This instability not only makes it impossible to use it in a pump, but it also presents the disadvantage of leading to large product losses in diagnostic use. In fact, since a composition of this type is no longer usable a few hours after its preparation, this leads to wastage.

[0007] Finally, even in the application of an emergency treatment for severe hypoglycemic reactions that can occur during insulin therapy in diabetic patients, the formulation to be reconstituted is also not ideal because it involves a long and complicated preparation, for example, the package insert of GlucaGen® describes a 5-step procedure for injecting the recommended dose. Moreover, a study of the company LOCEMIA demonstrates that very few

persons (approximately 10% of the participants) who were supposed to perform the reconstitution in emergency were capable of delivering the appropriate dose. Finally, the acidic pH of the solutions of human glucagon can generate pain upon injection in the patient.

[0008] Thus, there is a need for a ready-to-use human glucagon solution. Today, the solutions that are most advanced clinically speaking in order to enable the delivery of human glucagon circumvent the problem of stability of human glucagon in aqueous solution in different ways.

[0009] The company LOCEMIA has developed a lyophilized human glucagon spray which is currently being tested in phase 3 clinical study, and which is intended to be administered by the intranasal route. This spray is suitable for a so-called "rescue" use, that is to say in the case of a severe hypoglycemia, since it is ready to use and thus easy to use, in contrast to the solutions that need to be reconstituted. However, this product is not suitable for use in a pump or for a use that requires a precise control of the delivered quantity of human glucagon.

[00010] As for XERIS, it has developed a liquid formulation of human glucagon based on a polar aprotic solvent, such as DMSO, which is currently being tested in clinical studies. However, ever though the injection of a solution of organic solvents for "rescue" use can be considered, it is largely preferable to have an aqueous human glucagon solution for chronic use. Compositions comprising a combination with other peptides have been considered, notably amylin or a GLP-1 RA (glucagon-like peptide-1 receptor agonist).

[00011] Finally, in the face of the difficulties of formulation of human glucagon, analogs of human glucagon are in the process of being developed by large pharmaceutical companies such as NOVO NORDISK, SANOFI or ELI LILLY, in order to obtain formulations that have a stability compatible with pharmaceutical use. However, these peptides of which the primary

sequence has been modified in comparison to the peptide of human origin can present a safety risk for the patients.

[00012] Thus, there is a major advantage in a solution that makes it possible to improve the solubilization and the stability, both chemical and physical, of human glucagon in an aqueous solution at a pH close to physiological pH, that is to say from 6.0 to 8.0. This may lead to a pharmaceutical product that is easier to use by the patient in emergency, but it could also open the field to new therapeutic applications of human glucagon, such as its use in a bi-hormonal artificial pancreas, for example.

[00013] The prior art proposes solutions in order to attempt to solve this problem.

[00014] Some documents propose using an alkaline pH. For example, US2015291680 teaches the solubilization of human glucagon at 1 mg/mL by using a pH from 8.8 to 9.4 and by using ferulic acid or tetrahydrocurcumin. However, apart from the fact that an alkaline pH is used, this solution presents the disadvantage of leading to a rather limited stability of the human glucagon over time. The article by Jackson et al. (Curr. Diab. Rep., 2012, 12, 705-710) proposes formulating human glucagon at an alkaline pH (approximately 10), in order to limit the formation of fibrils. However, this solution does not prevent a rapid chemical degradation of human glucagon.

[00015] The application WO2014096440 (NOVOZYME), on the other hand, considers using a slightly acidic pH (approximately 5.5) in the presence of albumin and polysorbate, in order to improve the stability by reducing the rate of fibril formation. However, this solution presents a limited improvement of the stability. Most of the solutions described in the prior art making it possible to obtain a clear solution of human glucagon and to prevent aggregation,

gelling or precipitation of the human glucagon involve the use of surfactants, detergents or other known solubilizing agents.

[00016] For example, Matilainen et al. (J. Pharm. Sci., 2008, 97, 2720-2729 and Eur. J. Pharm. Sci., 2009, 36, 412-420) described the use of cyclodextrin in order to limit the rate of formation of fibrils of human glucagon. However, the improvement provided does not appear to be sufficient for considering use in a pump.

[00017] The solutions proposed comprise hydrophilic surfactants:

- GB1202607 (NOVO NORDISK) describes the use of anionic or cationic detergents.

- US6384016 (NOVO NORDISK) and US2011097386 (BIODEL) use lysophospholipids (or lysolecithins).

- WO2015095389 (AEGIS) describes non-ionic surfactants such as dodecyl maltoside for improving the bioavailability of therapeutic agents, in the case of delivery by application on the mucous membranes or the epidermis, and, in particular, in the case of ocular, nasal, oral or nasolacrimal delivery. This document describes that the presence of alkyl glycosides leads to an improvement of the absorption of human glucagon at the ocular site,

- the application WO2012059764 (ARECOR) describes cationic surfactants and, more precisely, aromatic ammonium chlorides.

[00018] The surfactants indicated in the above documents can be too toxic or irritating for chronic use by the subcutaneous route. For example, the lysophospholipids (or lysolecithins) are known to lyse the red blood cells due to their hemolytic properties. In a subcutaneous injection, this can cause local damage to the tissues and pains at the injection site. In the case of continuous injection by means of a pump, this can lead to pains and/or irritation at the site of insertion of the

needle. The international application WO2011138802 (Sun Pharma) describes a ready-to-use solution of human glucagon in a micellar aqueous solution at a pH from 5 to 7.5 in the presence of a pegylated lipid (pegylated distearoylphosphatidylethanolamine). However, Garay et al. (Expert Opin Drug Deliv (2012) 9, 1319-1323) teach that polyethylene glycol is both immunogenic and antigenic. This may be prejudicial to patients with anti-PEG antibodies. Moreover, Ganson et al. (J. Allergy Clin. Immunol. (2015) doi: 10.1016/j.jaci.2015.10.034) describe that a clinical study pertaining to pegnivacogin coupled to 40 kDa methoxypolyethylene glycol (mPEG) led to inflammatory responses starting with the first dose of pegnivacogin in 3 of the 640 patients. Among these three patients, two met the anaphylaxis criteria, and one had an isolated dermal reaction; each event was considered serious, and one was even considered life threatening to the patient. These adverse events resulted in the stopping of the clinical trial and raise the problem of the adverse effects of pegylated compounds.

[00019] The document WO2013101749 (LATITUDE) describes nanoemulsions of human glucagon. However, relatively moderate performances are claimed in terms of chemical stability, that is to say that the composition comprises at least 75% of the initial concentration after 3-7 days at 37 °C.

[00020] In addition, it should be noted that, to this date, to the knowledge of the applicant, no pharmaceutical formulation comprising human glucagon in the form of an aqueous solution is being tested in a clinical study.

[00021] Thus, a need remains for a liquid aqueous formulation at a pH close to physiological pH, from 6.0 to 8.0, which enables the solubilization and the obtention of a satisfactory stability of human glucagon, both in terms of physical stability and chemical

stability. More particularly, there is a need for such a formulation that can be used in a bi-hormonal pump (insulin/human glucagon).

[00022] This need is particularly clear with Tan et al. (Diabetes, 2013, 62, 1131-138) that shows that combining human glucagon with a GLP-1 RA is an attractive proposition for treating obesity and diabetes. Yet, being able to formulate human glucagon in a stable manner in an aqueous solution at a pH close to physiological pH from 6.0 to 8.0 allow for more favorable conditions to be able to improve the stability of the GLP-1 RA which are sensitive to acidic or alkaline conditions.

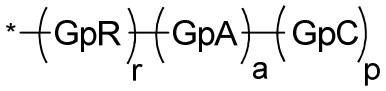
[00023] The co-polyamino acids bearing carboxylate charges and hydrophobic radicals Hy according to the invention present an excellent resistance to hydrolysis. This can be observed particularly under accelerated conditions, for example, in hydrolysis tests at alkaline pH (pH 12).

[00024] In addition, forced oxidation tests, for example, of the Fenton oxidation type, show that the co-polyamino acids bearing carboxylate charges and hydrophobic radicals Hy present a good resistance to oxidation.

[00025] The invention thus relates to physically stable compositions in the form of an injectable aqueous solution, the pH of which is from 6.0 to 8.0, comprising at least:

a) human glucagon, and

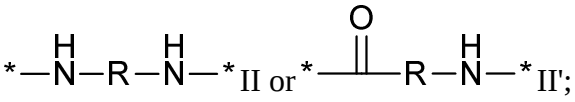
b) a co-polyamino acid bearing carboxylate charges and hydrophobic radicals Hy, said co-polyamino acid consisting of glutamic or aspartic units, and said hydrophobic radicals Hy being radicals of the following formula I:



Formula I

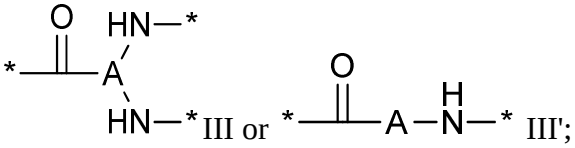
in which

– GpR is a radical of formula II or II':



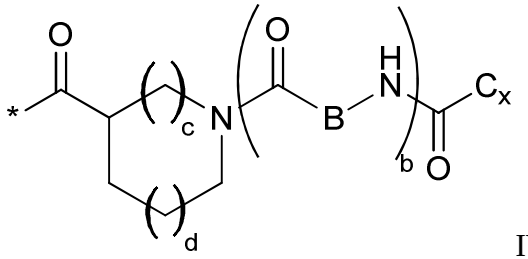
II or II';

– GpA is a radical of formula III or III':



III or III';

– GpC is a radical of formula IV:



IV;

– the * indicate the sites of attachment of the different groups;

– a is a whole number equal to 0 or 1;

– b is a whole number equal to 0 or 1;

– p is a whole number equal to 1 or 2, and

- if p is equal to 1, then a is equal to 0 or 1 and GpA is a radical of formula III', and
- if p is equal to 2, then a is equal to 1 and GpA is a radical of formula III;

– c is a whole number equal to 0 or 1, and, if c is equal to 0, then d is equal to 1 or 2;
– d is a whole number equal to 0, to 1 or 2;
– r is a whole number equal to 0 or 1, and
  - if r is equal to 0, then the hydrophobic radical of formula I is bound to the co-polyamino acid via a covalent bond between a carbonyl of the hydrophobic radical and a nitrogen atom in N-terminal position of the co-polyamino acid therefore forming an amide function originating from the reaction of an amine function in N-terminal position of the precursor of the co-polyamino acid and an acid function borne by the precursor of the hydrophobic radical, and
  - if r is equal to 1, then the hydrophobic radical of formula I is bound to the co-polyamino acid:
    - via a covalent bond between a nitrogen atom of the hydrophobic radical and a carbonyl of the co-polyamino acid therefore forming an amide function originating from the reaction between an amine function of the precursor of the hydrophobic radical and an acid function borne by the precursor of the co-polyamino acid, or
    - via a covalent bond between a carbonyl of the hydrophobic radical and a nitrogen atom in N-terminal position of the co-polyamino acid therefore forming an amide function originating from the reaction of an acid function

of the precursor of the hydrophobic radical and an amine function in N terminal position borne by the precursor of the co-polyamino acid;

– R is a radical selected from the group consisting of:

- a linear or branched divalent alkyl radical comprising, if GpR is a radical of formula II, from 2 to 12 carbon atoms, or, if GpR is a radical of formula II', from 1 to 11 carbon atoms;
- a linear or branched divalent alkyl radical comprising, if GpR is a radical of formula II, from 2 to 11 carbon atoms, or, if GpR is a radical of formula II', from 1 to 11 carbon atoms, said alkyl radical bearing one or more $-CONH_2$ functions, and
- an unsubstituted ether or polyether radical comprising from 4 to 14 carbon atoms and from 1 to 5 oxygen atoms;

– A is a linear or branched alkyl radical comprising from 1 to 6 carbon atoms;

– B is a linear or branched alkyl radical, optionally comprising an aromatic ring, comprising from 1 to 9 carbon atoms;

– C_x is a linear or branched monovalent alkyl radical, in which x indicates the number of carbon atoms, and:

- if p is equal to 1, x is from 11 to 25 ($11 \leq x \leq 25$);
- if p is equal to 2, x is from 9 to 15 ($9 \leq x \leq 15$),

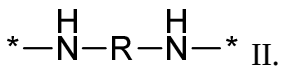
– the ratio i between the number of hydrophobic radicals and the number of glutamic or aspartic units being between $0 < i \leq 0.5$;

– 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 is from 5 to 250;

– the free acid functions being in the form of a salt of an alkaline cation selected from the group consisting of Na^+ and K^+.

[00026] In an embodiment, GpR is a radical of formula II:

 II.

[00027] In an embodiment, the composition is characterized in that the pH is from 6.6 to 7.8.

[00028] In an embodiment, the composition is characterized in that the pH is from 7.0 to 7.8.

[00029] In an embodiment, the composition is characterized in that the pH is from 6.8 to 7.4.

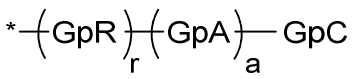
[00030] In an embodiment, the composition is characterized in that said hydrophobic radicals are selected from the hydrophobic radicals of formula I in which p is equal to 1, and, if x is less than or equal to 14 ($x \leq 14$), then r = 0 or r = 1.

[00031] In an embodiment, the composition is characterized in that said hydrophobic radicals are selected from the hydrophobic radicals of formula I in which p is equal to 1, and, if x is from 15 to 16 ($15 \leq x \leq 16$), then r = 1.

[00032] In an embodiment, the composition is characterized in that said hydrophobic radicals are selected from the hydrophobic radicals of formula I in which p is equal to 1, and, if x is greater than 17 ($17 \leq x$), then r = 1 and R is an ether or polyether radical.

[00033] In an embodiment, the composition is characterized in that said hydrophobic radicals are selected from the hydrophobic radicals of formula I in which, if p is equal to 1, then x is from 17 to 25 ($17 \leq x \leq 25$).

[00034] In an embodiment, the composition is characterized in that said hydrophobic radicals are selected from the hydrophobic radicals of formula I in which p = 1, represented by the following formula V:



formula V

GpR, GpA, GpC, r and a have the definitions given above.

[00035] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V, in which r is equal to 1 (r = 1), and a is equal to 0 (a = 0).

[00036] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which r is equal to 1 (r = 1) and a is equal to 1 (a = 1).

[00037] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which GpR is a radical of formula II.

[00038] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which GpR is a radical of formula II, in which R is a divalent linear alkyl radical comprising from 2 to 12 carbon atoms.

[00039] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula Vin which GpR is a radical of formula II in which R is a divalent alkyl radical comprising from 2 to 6 carbon atoms.

[00040] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which GpR is a radical of formula II in which R is a divalent linear alkyl radical comprising from 2 to 6 carbon atoms.

[00041] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which GpR is a radical of formula II in which R is a divalent alkyl radical comprising from 2 to 4 carbon atoms.

[00042] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which GpR is a radical of formula II in which R is a divalent linear alkyl radical comprising from 2 to 4 carbon atoms.

[00043] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which GpR is a radical of formula II in which R is a divalent alkyl radical comprising 2 carbon atoms.

[00044] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which GpR is a radical of formula II'.

[00045] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which GpR is a radical of formula II' in which R is a divalent linear alkyl radical comprising from 1 to 11 carbon atoms.

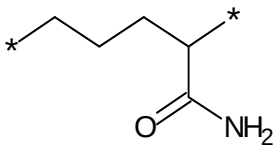
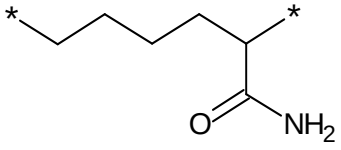
[00046] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which GpR is a radical of formula II' in which R is a divalent alkyl radical comprising from 1 to 6 carbon atoms.

[00047] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which GpR is a radical of formula II or II', in which R is a

divalent alkyl radical comprising from 2 to 5 carbon atoms and bearing one or more amide functions (-$CONH_2$).

[00048] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which GpR is a radical of formula II' or II, in which R is a divalent linear alkyl radical comprising from 2 to 5 carbon atoms and bearing one or more amide functions (-$CONH_2$).

[00049] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which GpR is a radical of formula II or II' in which R is a radical selected from the group consisting of the radicals represented by the formulas below:

	Formula X1
	Formula X2

[00050] In an embodiment, the composition is characterized in that the hydrophobic radical of formula V in which GpR is a radical of formula II or II', in which R is a radical of formula X1.

[00051] In an embodiment, the composition is characterized in that the hydrophobic radical of formula V in which GpR is a radical of formula II or II', in which R is a radical of formula X2.

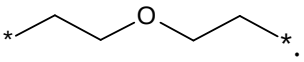
[00052] In an embodiment, the composition is characterized in that the radical R is bound to the co-polyamino acid via an amide function borne by the carbon in delta or epsilon position (or in position 4 or 5) with respect to the amide function (-$CONH_2$).

[00053] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which GpR is a radical of formula II or II', in which R is an unsubstituted linear ether or polyether radical comprising from 4 to 14 carbon atoms and from 1 to 5 oxygen atoms.

[00054] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which GpR is a radical of formula II or II', in which R is an ether radical.

[00055] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which GpR is a radical of formula II or II', in which R is an ether radical comprising from 4 to 6 carbon atoms.

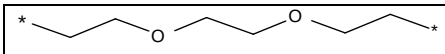
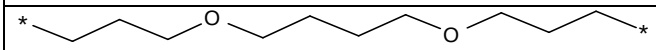
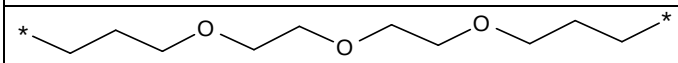
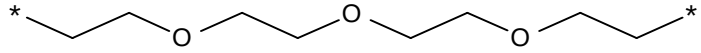
[00056] In an embodiment, the composition according to the invention is characterized in that the hydrophobic radical is a radical of formula V in which GpR is a radical of formula II, in which R is a divalent alkyl radical comprising 6 carbon atoms.

[00057] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which GpR is a radical of formula II or II', in which R is an ether radical represented by the formula .

[00058] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which GpR is a radical of formula II or II', in which R is a polyether radical.

[00059] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which GpR is a radical of formula II or II', in which R is a linear polyether radical comprising from 6 to 10 carbon atoms and from 2 to 3 oxygen atoms.

[00060] In an embodiment, the composition is characterized in that the hydrophobic radical of formula V in which GpR is a radical of formula II or II', in which R is a polyether radical selected from the group consisting of the radicals represented by the formulas below:

	Formula X3
	Formula X4
	Formula X5
	Formula X6

[00061] In an embodiment, the composition is characterized in that the hydrophobic radical of formula V in which GpR is a radical of formula II or II', in which R is a radical of formula X3.

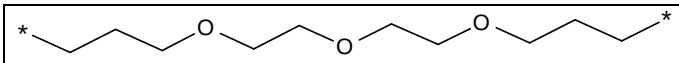
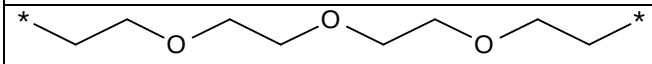
[00062] In an embodiment, the composition is characterized in that the hydrophobic radical of formula V in which GpR is a radical of formula II or II', in which R is a radical of formula X4.

[00063] In an embodiment, the composition is characterized in that the hydrophobic radical of formula V in which GpR is a radical of formula II or II', in which R is a radical of formula X5.

[00064] In an embodiment, the composition is characterized in that the hydrophobic radical of formula V in which GpR is a radical of formula II or II', in which R is a radical of formula X6.

[00065]

[00066] In an embodiment, the composition is characterized in that the hydrophobic radical of formula V in which GpR is a radical of formula II in which R is a polyether radical selected from the group consisting of the radicals represented by the formulas X5 and X6 below:

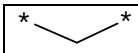
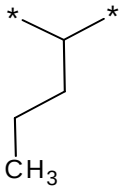
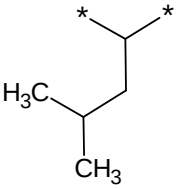
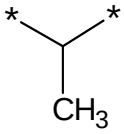
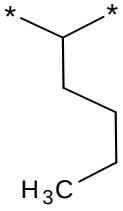
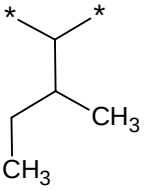
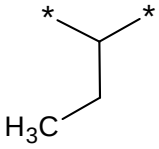
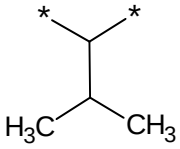
	Formula X5
	Formula X6

[00067] In an embodiment, the composition is characterized in that the hydrophobic radical of formula V in which GpR is a radical of formula II in which R is a polyether radical of formula X5.

[00068] In an embodiment, the composition is characterized in that the hydrophobic radical of formula V in which GpR is a radical of formula II in which R is a polyether radical of formula X6.

[00069] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which a is equal to 0 (a = 0) and r is equal to 0 (r = 0).

[00070] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which a is equal to 1 (a = 1), and the radical GpA of formula III' is selected from the group consisting of the radicals represented by the formulas below:

 Formula Y1	 Formula Y2	 Formula Y3
 Formula Y4	 Formula Y5	 Formula Y6
 Formula Y7	 Formula Y8	

[00071] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which a is equal to 1 (a = 1), and the radical GpA of formula III' is a radical of formula Y1.

[00072] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which a is equal to 1 (a = 1), and the radical GpA of formula III' is a radical of formula Y2.

[00073] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which a is equal to 1 (a = 1) and the radical GpA of formula III' is a radical of formula Y3.

[00074] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which a is equal to 1 (a = 1) and the radical GpA of formula III' is a radical of formula Y4.

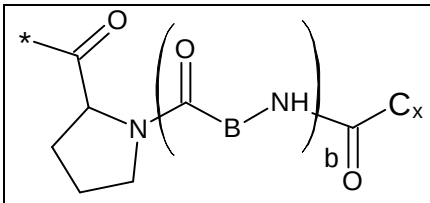
[00075] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which a is equal to 1 (a = 1) and the radical GpA of formula III' is a radical of formula Y5.

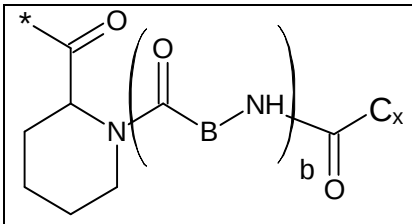
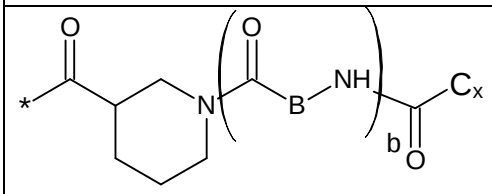
[00076] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which a is equal to 1 (a = 1) and the radical GpA of formula III' is a radical of formula Y6.

[00077] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which a is equal to 1 (a = 1) and the radical GpA of formula III' is a radical of formula Y7.

[00078] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which a is equal to 1 (a = 1) and the radical GpA of formula III' is a radical of formula Y8.

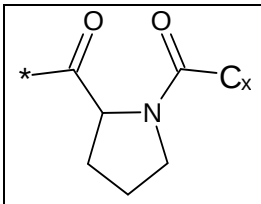
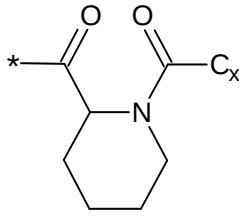
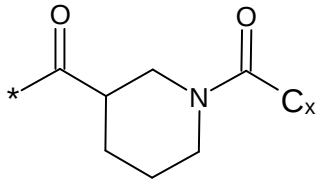
[00079] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which the radical GpC of formula IV is selected from the group consisting of the radicals of formula IVa, IVb or IVc represented hereafter:

	Formula IVa

	Formula IVb
	Formula IVc

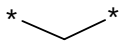
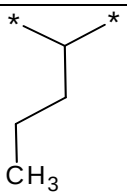
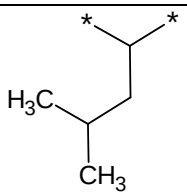
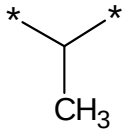
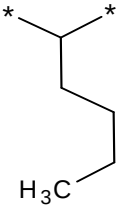
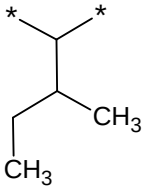
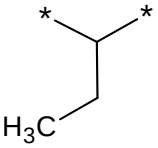
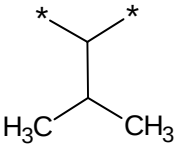
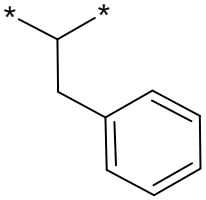
[00080] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which the radical GpC is of formula IVa.

[00081] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which the radical GpC of formula IV is selected from the group consisting of the radicals of formula IVa, IVb or IVc in which b is equal to 0, having formulas IVd, IVe and IVf, respectively, represented hereafter:

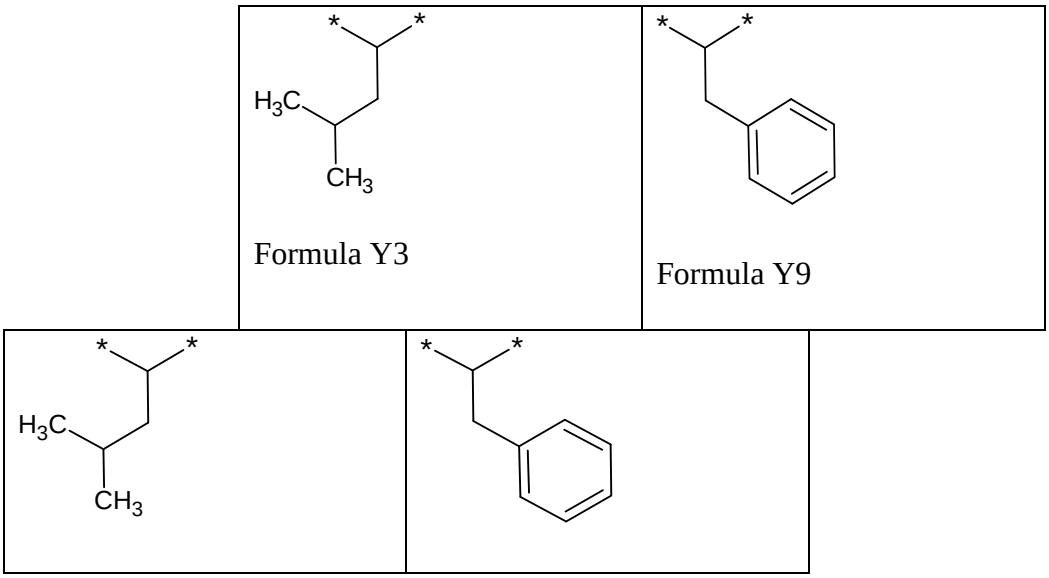
	Formula IVd
	Formula IVe
	Formula IVf

[00082] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which the radical GpC corresponds to formula IV or IVa in which b = 0, and corresponds to formula IVd.

[00083] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which the radical GpC of formula IV in which b = 1 is selected from the group consisting of the radicals in which B is an amino acid residue selected from the group consisting of the radicals represented by the formulas below:

 Formula Y1	 Formula Y2	 Formula Y3
 Formula Y4	 Formula Y5	 Formula Y6
 Formula Y7	 Formula Y8	 Formula Y9

[00084] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which the radical GpC of formula corresponds to formula IV or IVa in which b = 1, is selected from the group consisting of the radicals in which B is an amino acid residue selected from the group consisting of the radicals represented by the formulas below:

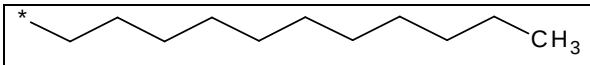
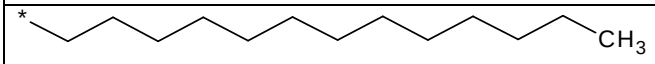


[00085] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which the radical GpC of formula IV is selected from the group consisting of the radicals in which Cx is selected from the group consisting of the linear alkyl radicals.

[00086] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which the radical GpC of formula IV is selected from the group consisting of radicals in which Cx is selected from the group consisting of the branched alkyl radicals.

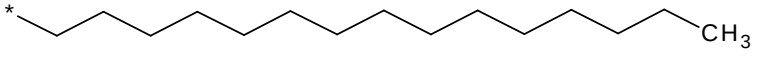
[00087] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which the radical GpC of formula IV is selected from the group consisting of alkyl radicals in which Cx is selected from the group consisting of the alkyl radicals comprising from 11 to 14 carbon atoms.

[00088] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which the radical GpC of formula IV is selected from the group consisting of radicals in which Cx is selected from the group consisting of the radicals represented by the formulas below:

	x=11
	x=13

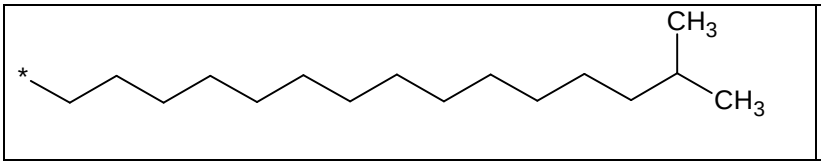
[00089] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which the radical GpC of formula IV is selected from the group consisting of the radicals in which Cx is selected from the group consisting of the alkyl radicals comprising from 15 to 16 carbon atoms.

[00090] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which the radical GpC of formula IV is selected from the group consisting of the radicals in which Cx is selected from the group consisting of the radicals represented by the formulas below:

	x=15

[00091] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which the radical GpC of formula IV is selected from the

group consisting of the radicals in which Cx is selected from the group consisting of the radicals represented by the formulas below:

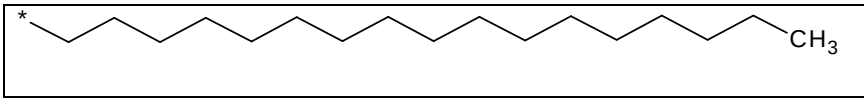


x=16

[00092] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which the radical GpC of formula IV is selected from the group consisting of the radicals in which Cx is selected from the group consisting of the alkyl radicals comprising from 17 to 25 carbon atoms.

[00093] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which the radical GpC of formula IV is selected from the group consisting of the radicals in which Cx is selected from the group consisting of the alkyl radicals comprising from 17 to 18 carbon atoms.

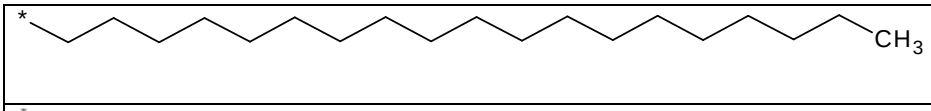
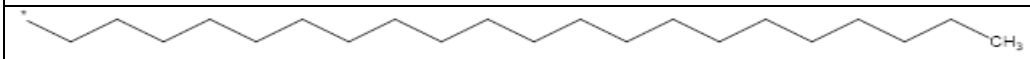
[00094] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which the radical GpC of formula IV is selected from the group consisting of the radicals in which Cx is selected from the group consisting of the alkyl radicals represented by the formulas below:



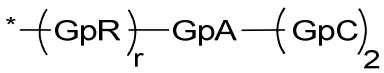
x=17

[00095] In an embodiment, the composition characterized in that the hydrophobic radical is a radical of formula V in which the radical GpC of formula IV is selected from the group consisting of the radicals in which Cx is selected from the group consisting of the alkyl radicals comprising from 18 to 25 carbon atoms.

[00096] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula V in which the radical GpC of formula IV is selected from the group consisting of the radicals in which Cx is selected from the group consisting of the alkyl radicals represented by the formulas below:

	x=19
	x = 21

[00097] In an embodiment, the composition is characterized in that said hydrophobic radicals of formula I are selected from the hydrophobic radicals of formula I in which a = 1 and p = 2, represented by the following formula VI:



Formula VI

in which

GpR, GpA, GpC, r and a have the definitions given above.

[00098] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula VI in which GpR is a radical of formula II.

[00099] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula VI in which GpR is a radical of formula II in which R is a divalent linear alkyl radical comprising from 2 to 12 carbon atoms.

[000100] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula VI in which GpR is a radical of formula II in which R is a divalent alkyl radical comprising from 2 to 6 carbon atoms.

[000101] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula VI in which GpR is a radical of formula II in which R is a divalent linear alkyl radical comprising from 2 to 6 carbon atoms.

[000102] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula VI in which GpR is a radical of formula II in which R is an alkyl radical comprising from 2 to 4 carbon atoms.

[000103] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula VI in which GpR is a radical of formula II in which R is a divalent linear alkyl radical comprising from 2 to 4 carbon atoms.

[000104] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula VI in which GpR is a radical of formula II in which R is a divalent linear alkyl radical comprising 2 carbon atoms.

[000105] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula VI in which GpR is a radical of formula II'.

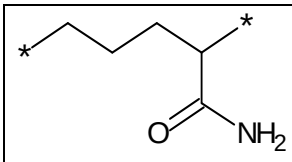
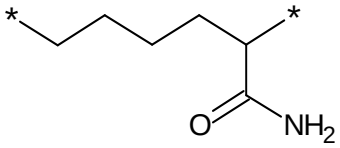
[000106] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula VI in which GpR is a radical of formula II' in which R is a divalent linear alkyl radical comprising from 1 to 11 carbon atoms.

[000107] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula VI in which GpR is a radical of formula II' in which R is a divalent alkyl radical comprising from 1 to 6 carbon atoms.

[000108] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula VI in which GpR is a radical of formula II or II', in which R is a divalent alkyl radical comprising from 2 to 5 carbon atoms and bearing one or more amide functions (-CONH2).

[000109] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula VI in which GpR is a radical of formula II or II', in which R is a divalent linear alkyl radical comprising from 2 to 5 carbon atoms and bearing one or more amide functions (-CONH2).

[000110] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula VI in which GpR is a radical of formula II or II' in which R is a radical selected from the group consisting of the radicals represented by the formulas below:

	Formula X1
	Formula X2

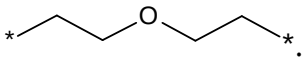
[000111] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula VI in which the amine function of the GpR radical involved in the formation of the amide function which binds said GpR radical to the co-polyamino acid is borne by a carbon in delta or epsilon position (or in position 4 or 5) with respect to the amide function (-CONH2).

[000112] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula VI in which GpR is a radical of formula II or II', in which R is an unsubstituted linear ether or polyether radical comprising from 4 to 14 carbon atoms and from 1 to 5 oxygen atoms.

[000113] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula VI in which GpR is a radical of formula II or II' in which R is an ether radical.

[000114] In an embodiment, the composition is characterized in that the ether radical R is a radical comprising from 4 to 6 carbon atoms.

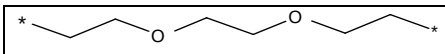
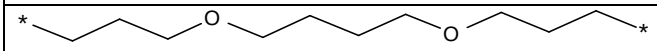
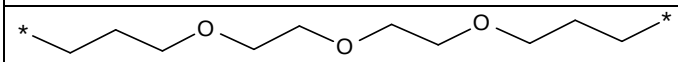
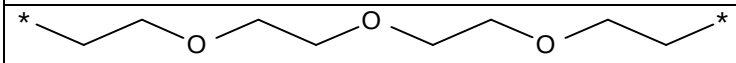
[000115] In an embodiment, the composition is characterized in that the ether radical is



[000116] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula VI in which GpR is a radical of formula II or II', in which R is a polyether radical.

[000117] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula VI in which GpR is a radical of formula II or II', in which R is a linear polyether radical comprising from 6 to 10 carbon atoms and from 2 to 3 oxygen atoms.

[000118] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula VI in which GpR is a radical of formula II or II' in which R is a linear polyether radical selected from the group consisting of the radicals represented by the formulas below:

	Formula X3
	Formula X4
	Formula X5
	Formula X6

[000119] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula VI in which GpR is a radical of formula II or II' in which R is a linear polyether radical of formula X3.

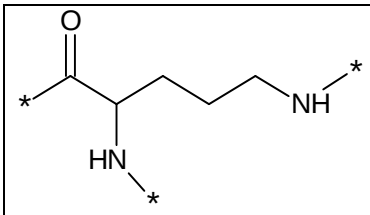
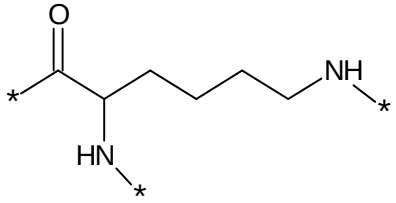
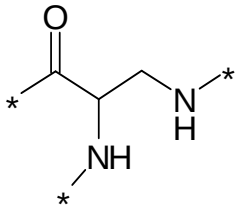
[000120] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula VI in which GpR is a radical of formula II or II' in which R is a linear polyether radical of formula X4.

[000121] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula VI in which GpR is a radical of formula II or II' in which R is a linear polyether radical of formula X5.

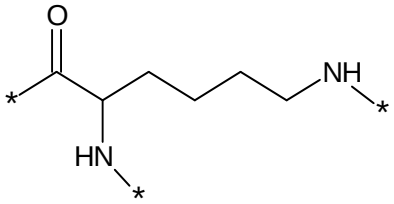
[000122] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula VI in which GpR is a radical of formula II or II' in which R is a linear polyether radical of formula X6.

[000123]

[000124] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula VI in which the radical GpA of formula III is selected from the group consisting of the radicals of formulas IIIa, IIIb and IIIc represented hereafter:

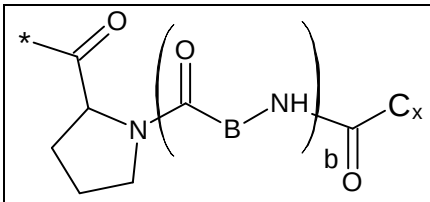
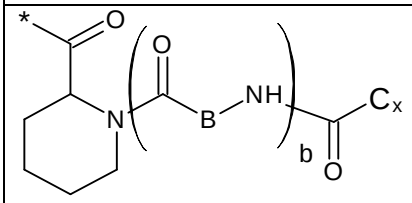
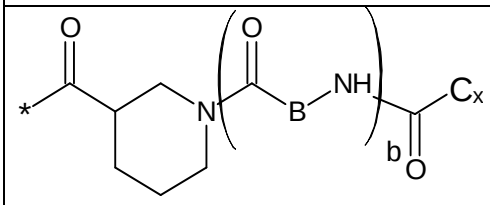
	Formula IIIa
	Formula IIIb
	Formula IIIc

[000125] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula VI in which the radical GpA of formula III is a radical of formula IIIb represented hereafter:

	Formula IIIb

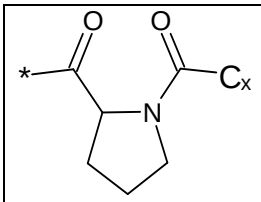
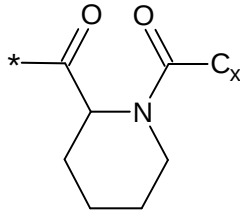
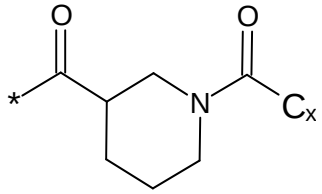
[000126] In an embodiment, the composition according to the invention is characterized in that the hydrophobic radical is a radical of formula VI in which the radical GpA of formula III is a radical of formula IIIc.

[000127] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula VI in which the radical GpC of formula IV is selected from the group consisting of the radicals of formulas IVa, IVb and IVc represented hereafter:

	Formula IVa
	Formula IVb
	Formula IVc

[000128] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula VI in which the radical GpC is of formula IVa.

[000129] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula VI in which the radical GpC of formula IV is selected from the group consisting of the radicals of formula IVa, IVb or IVc in which b is equal to 0, corresponding to the formulas IVd, IVe and IVf, respectively, represented hereafter:

	Formula IVd
	Formula IVe
	Formula IVf

[000130] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula VI in which the radical GpC corresponds to formula IV or IVa in which b=0, and it corresponds to formula IVd.

[000131] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula VI in which the radical GpC of formula IV is selected from the group consisting of the radicals in which Cx is selected from the group consisting of the linear alkyl radicals comprising from 9 to 15 carbon atoms.

[000132] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula VI in which the radical GpC of formula IV is selected from the group consisting of the radicals in which Cx is selected from the group consisting of the branched alkyl radicals comprising from 9 to 15 carbon atoms.

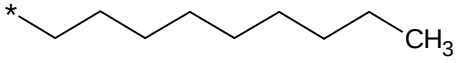
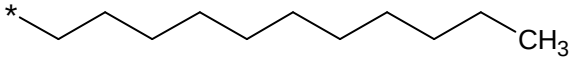
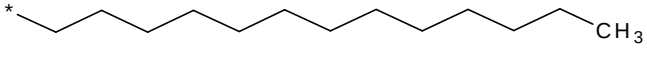
[000133] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula VI in which the radical GpC of formula IV is selected from the

group consisting of the radicals in which Cx is selected from the group consisting of the alkyl radicals comprising 9 or 10 carbon atoms.

[000134] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula VI in which the radical GpC of formula IV is selected from the group consisting of the radicals in which Cx is selected from the group consisting of the alkyl radicals comprising from 11 to 15 carbon atoms.

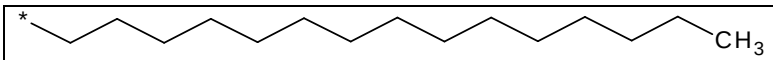
[000135] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula VI in which the radical GpC of formula IV is selected from the group consisting of the radicals in which Cx is selected from the group consisting of the alkyl radicals comprising from 11 to 13 carbon atoms.

[000136] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula VI in which the radical GpC of formula IV is selected from the group consisting of the radicals in which Cx is selected from the group consisting of the radicals represented by the formulas below:

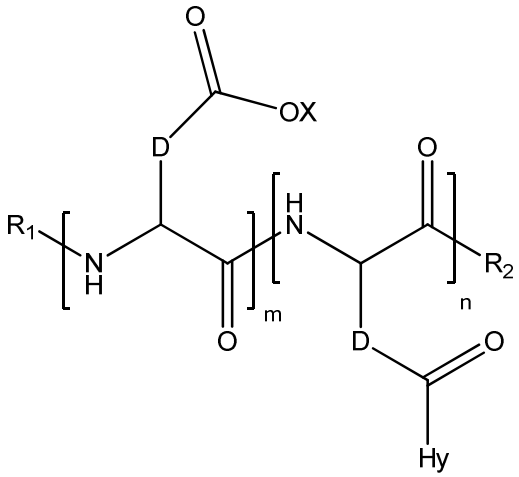
	x = 9
	x = 11
	x = 13

[000137] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula VI in which the radical GpC of formula IV is selected from the group consisting of the radicals in which Cx is selected from the group consisting of the alkyl radicals comprising 14 or 15 carbon atoms.

[000138] In an embodiment, the composition is characterized in that the hydrophobic radical is a radical of formula VI in which the radical GpC of formula IV is selected from the group consisting of the radicals in which Cx is selected from the group consisting of the radicals represented by the formulas below:

	x=15

[000139] In an embodiment, the composition is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of the following formula VII:



Formula VII

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 selected from the hydrophobic radicals of formula I, V or VI, in which r = 1 and GpR is a radical of Formula II,

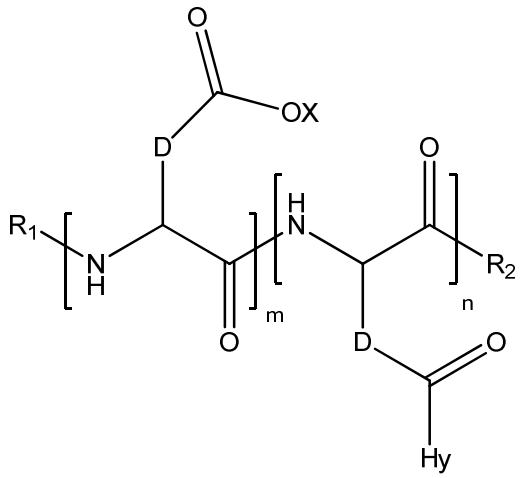
- R_1 is a hydrophobic radical selected from the hydrophobic radicals of formula I, V or VI in which r = 0 or r = 1 and GpR is a radical of Formula II', or a radical selected from the group consisting of H, a C2 to C10 linear acyl group, a C3 to C10 branched acyl group, benzyl, a terminal "amino acid" unit and a pyroglutamate,

- R_2 is a hydrophobic radical selected from the hydrophobic radicals of formula I, V or VI in which r = 1 and GpR is a radical of Formula II, or a -NR'R" radical, R' and R" which are identical or different being selected from the group consisting of H, the C2 to C10 linear or branched or cyclic alkyls, benzyl, and said alkyl R' and R" together optionally forming one or more saturated, unsaturated and/or aromatic carbon rings and/or optionally comprising heteroatoms selected from the group consisting of O, N and S;

- X represents H or a cationic entity selected from the group comprising the metal cations;

- n + m represents the degree of polymerization DP of the co-polyamino acid, that is to say the average number of monomer units per co-polyamino acid chain, and $5 \leq n + m \leq 250$.

[000140] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of the following formula VII:



Formula VII

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 selected from the hydrophobic radicals of formula I, V or VI, in which r = 1 and GpR is a radical of Formula II,
- R_1 is a hydrophobic radical selected from the hydrophobic radicals of formula I, V or VI in which r = 0 or r = 1 and GpR is a radical of Formula II', or a radical selected from the group consisting of H, a C2 to C10 linear acyl group, a C3 to C10 branched acyl group, benzyl, a terminal "amino acid" unit and a pyroglutamate,
- R_2 is a hydrophobic radical selected from the hydrophobic radicals of formula I, V or VI in which r = 1 and GpR is a radical of Formula II, or a -NR'R" radical, R' and R" which are identical or different being selected from the group consisting of H, the C2 to C10 linear or branched or cyclic alkyls, benzyl, and said alkyl R' and R" together optionally forming one or

more saturated, unsaturated and/or aromatic carbon rings and/or optionally comprising heteroatoms selected from the group consisting of O, N and S;

- at least one of R_1 or R_2 is a hydrophobic radical as defined above,
- X represents H or a cationic entity selected from the group comprising the metal cations;
- n + m represents the degree of polymerization DP of the co-polyamino acid, that is to say the average number of monomer units per co-polyamino acid chain, and $5 \leq n + m \leq 250$.

[000141] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VII in which at least one of R_1 or R_2 is a hydrophobic radical of formula I, V or VI.

[000142] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VII in which at least one of R_1 or R_2 is a hydrophobic radical of formula VI.

[000143] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VII in which at least one of R_1 or R_2 is a hydrophobic radical of formula VI, and Hy is a radical of formula VI, in which r = 1.

[000144] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VII in which at least one of R_1 or R_2 is a hydrophobic radical of formula VI, in which r = 1, and for GpC, b = 0.

[000145] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VII in which R_1 is a hydrophobic radical of formula VI.

[000146] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VII in which R_1 is a hydrophobic radical of formula VI and R_2 is a -NR'R" radical, R' and R" being as defined above.

[000147] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VII in which R_1 is a hydrophobic radical of formula VI and R_2 is a -NR'R" radical, R' and R" being as defined above, and Hy is a radical of formula VI, in which r = 1.

[000148] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VII. In an embodiment, the composition according to the invention is characterized in that co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VII in which R_1 is a hydrophobic radical of formula VI and R_2 is a -NR'R" radical, R' and R" being as defined above, and Hy is a radical of formula VI, in which r = 1, and for GpC, b = 0.

[000149] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VII in which R_2 is a hydrophobic radical of formula I, V or VI.

[000150] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VII in which R_2 is a hydrophobic radical of formula VI.

[000151] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VII in which R_2 is a hydrophobic radical of formula VI and R_1 is a -NR'R" radical, R' and R" being as defined above.

[000152] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VII in which R_2 is a hydrophobic radical of formula VI and R_1 is a -NR'R" radical, R' and R" being as defined above, and Hy is a radical of formula VI, in which r = 1.

[000153]

[000154] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VII in which R_2 is a hydrophobic radical of formula VI and R_1 is a -NR'R" radical, R' and R" being as defined above, and Hy is a radical of formula VI, in which r = 1, and for GpC, b = 0.

[000155] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VII in which R_1 and R_2 are a hydrophobic radical of formula I, V or VI.

[000156] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VII in which R_1 and R_2 are a hydrophobic radical of formula VI.

[000157] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VII in which R_1 and R_2 are a hydrophobic radical of formula VI, and Hy is a radical of formula VI, in which r = 1.

[000158] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VII in which R_1 and R_2 are a hydrophobic radical of formula VI, and Hy is a radical of formula VI, in which r = 1, and for GpC, b= 0.

[000142] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VII in which R_2 is a hydrophobic radical of formula I, V or VI in which r = 1 GpR is of formula II.

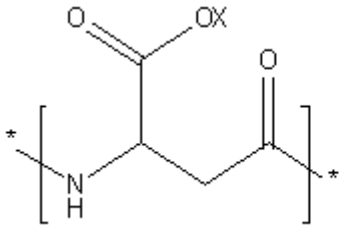
[000159] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VII in which R_2 is a hydrophobic radical of formula VI in which r = 1 and GpR is of formula II.

[000160] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected

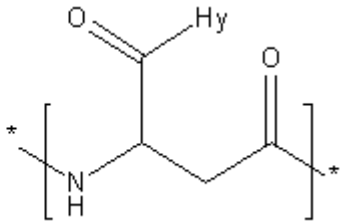
from the co-polyamino acids of formula VII in which R_2 is a hydrophobic radical of formula VI in which r = 1, GpR is of formula II and GpC is of formula IV in which b = 0, c = 0 and d = 1.

[000161] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VII in which R_2 is a hydrophobic radical of formula VI in which r = 1, GpR is of formula II and GpC is of formula IV in which b = 0, c = 0, d = 1 and x = 13.

[000162] In an embodiment, the composition according to the invention is characterized in that, when the co-polyamino acid comprises aspartate units, then the co-polyamino acid can, in addition, comprise monomer units of formula VIII and/or VIII':

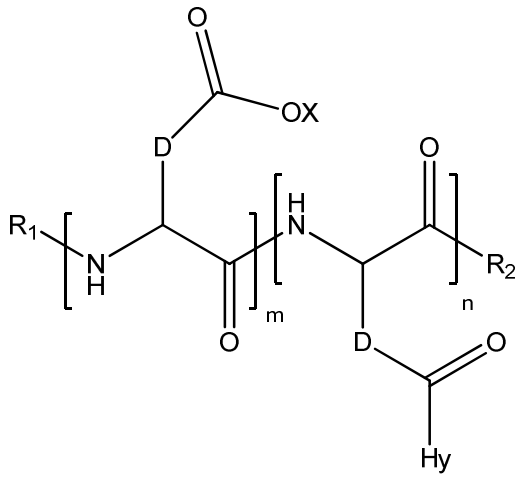


Formula VIII



Formula VIII'

[0001] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of the following formula VII:



Formula VII

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 selected from the hydrophobic radicals of formula I, V or VI, in which r = 1 and GpR is a radical of Formula II,
- R_1 is a hydrophobic radical selected from the hydrophobic radicals of formula I, V or VI in which r = 0 or r = 1 and GpR is a radical of Formula II', or a radical selected from the group consisting of H, a C2 to C10 linear acyl group, a C3 to C10 branched acyl group, benzyl, a terminal "amino acid" unit and a pyroglutamate,
- R_2 is a hydrophobic radical selected from the hydrophobic radicals of formula I, V or VI in which r = 1 and GpR is a radical of Formula II, or a -NR'R" radical, R' and R" which are identical or different being selected from the group consisting of H, the C2 to C10 linear or branched or cyclic alkyls, benzyl, and said alkyl R' and R" together optionally forming one or

more saturated, unsaturated and/or aromatic carbon rings and/or optionally comprising heteroatoms selected from the group consisting of O, N and S;

- at least one of R_1 or R_2 is a hydrophobic radical as defined above,
- X represents a cationic entity selected from the group comprising the alkaline cations;
- $n \geq 1$ and n + m represents the degree of polymerization DP of the co-polyamino acid, that is to say the average number of monomer units per co-polyamino acid chain, and $5 \leq n + m \leq 250$;

[000163] The co-polyamino acid bearing carboxylate charges and at least one hydrophobic radical of formula I can also be referred to as "co-polyamino acid" in the present description.

[000164] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VII in which $n \geq 1$ and at least one of R1 or R2 is a hydrophobic radical of formula I, V or VI.

[000165] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VII in which $n \geq 1$ and R1 is a hydrophobic radical of formula I, V or VI.

[000166] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VII in which $n \geq 1$ and R2 is a hydrophobic radical of formula I, V or VI.

[000167] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected

from the co-polyamino acids of formula VII in which n ≥ 1, R1 is a hydrophobic radical of formula I, V or VI in which r = 0.

[000142] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VII in which n ≥ 1, R2 is a hydrophobic radical of formula I, V or VI in which r = 1 and GpR is of formula II.

[000168] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VII in which n ≥ 1, R2 is a hydrophobic radical of formula VI in which r = 1 and GpR is of formula II.

[000169] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VII in which n ≥ 1, R2 is a hydrophobic radical of formula VI in which r = 1, GpR is of formula II and GpC is of formula IV.

[000170] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VII in which n ≥ 1, R2 is a hydrophobic radical of formula VI in which r = 1, GpR is of formula II and GpC is of formula IV in which b = 0, c = 0 and d = 1.

[000171] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VII in which n ≥ 1, R2 is a hydrophobic radical of

formula VI in which r = 1, GpR is of formula II and GpA is of formula IV in which b = 0, c = 0, d = 1 and x = 13.

[000172] In an embodiment, the composition is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VIIb in which R1 is a hydrophobic radical of formula VI in which r = 0.

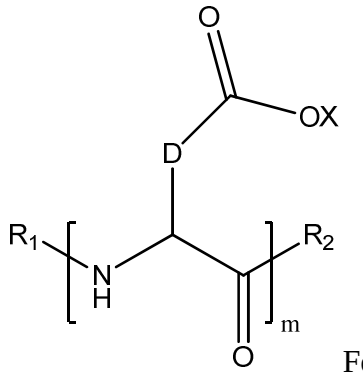
[000173] In an embodiment, the composition is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VIIb in which R1 is a hydrophobic radical of formula VI in which r = 0, and GpC is of formula IV.

[000174] In an embodiment, the composition is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VIIb in which R1 is a hydrophobic radical of formula VI in which r = 0, and GpC is of formula IV with b = 0, c = 0 and d = 1.

[000175] In an embodiment, the composition is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VIIb in which R1 is a hydrophobic radical of formula VI in which r = 0, and GpC is of formula IV with b = 0, c = 0, d = 1 and x = 13.

[000176] "Defined co-polyamino acid" is understood to mean a co-polyamino acid bearing carboxylate charges and at least one hydrophobic radical, a co-polyamino acid of formula VIIb.

[000177] In an embodiment, the composition is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VII in which n = 0 of the following formula VIIb:



Formula VIIb

in which m, X, D, R_1 and R_2 have the definitions defined above and at least one R_1 or R_2 is a hydrophobic radical of formula I, V or VI.

[000178] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VII in which n = 0 of formula VIIb and R1 or R2 is a hydrophobic radical of formula I, V or VI.

[000179] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VIIb in which at least one of R1 or R2 is a hydrophobic radical of formula VI.

[000180] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VIIb in which R1 is a hydrophobic radical of formula VI.

[000181] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VIIb in which R_1 is a hydrophobic radical of formula VI and R2 is a -NR'R" radical, R' and R" being as defined above.

[000182] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VIIb in which R_1 is a hydrophobic radical of formula VI and R_2 is a -NR'R" radical, R' and R" being as defined above.

[000183] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VII in which R_1 is a hydrophobic radical of formula VI in which r = 1, and for GpC, b = 0 and R_2 is a -NR'R" radical, R' and R" are as defined above.

[000184] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VIIb in which R_2 is a hydrophobic radical of formula I, V or VI.

[000185] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VIIb in which R_2 is a hydrophobic radical of formula VI.

[000186] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected

from the co-polyamino acids of formula VII in which R_2 is a hydrophobic radical of formula VI and R_1 is a radical selected from the group consisting of H, a C2 to C10 linear acyl group, a C3 to C10 branched acyl group, benzyl, a terminal "amino acid" unit and a pyroglutamate.

[000187] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VIIb in which R_2 is a hydrophobic radical of formula VI in which r = 0 and R_1 is a radical selected from the group consisting of H, a C2 to C10 linear acyl group, a C3 to C10 branched acyl group, benzyl, a terminal "amino acid" unit and a pyroglutamate.

[000188] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VIIb in which R_2 and Hy are hydrophobic radicals of formula VI in which r = 0, and for GpC, b = 0 and R_1 is a radical selected from the group consisting of H, a C2 to C10 linear acyl group, a C3 to C10 branched acyl group, benzyl, a terminal "amino acid" group and a pyroglutamate.

[000189] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VII in which R_1 and R_2 are hydrophobic radicals of formula I, V or VI.

[000190] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VII in which R_1 and R_2 are hydrophobic radicals of formula VI.

[000191] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VII in which R_1 and R_2 are hydrophobic radicals of formula VI, in which r = 1 and GpR of formula II for R_2 and r = 0 for R_1.

[000192] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VII in which R_1 and R_2 are hydrophobic radicals of formula VI, GpA = 0 and b = 0, in which r = 1 and GpR of formula II for R_2 and r = 0 for R_1.

[000193] In an embodiment, the composition is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VIIb in which R_1 is a hydrophobic radical of formula I, V or VI in which r = 0 or r = 1 and GpR is of formula II'.

[000194] In an embodiment, the composition is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VIIb in which R_2 is a hydrophobic radical of formula I, V or VI in which r = 1 and GpR is of formula II.

[000195] In an embodiment, the composition is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VII in which R_2 is a hydrophobic radical, in particular with $n \geq 1$, or VIIb in which R1 is a radical selected from the group consisting of a C2 to C10 linear acyl group, a C3 to C10 branched acyl group, benzyl, a terminal "amino acid" unit and a pyroglutamate.

[000196] In an embodiment, the composition is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VII in which R_2 is a hydrophobic radical, in particular with $n \geq 1$, or VIIb in which R_1 is a radical selected from the group consisting of a C2 to C10 linear acyl group or a C3 to C10 branched acyl group.

[000197] In an embodiment, the composition is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VII in which at least one of R_1 or R_2 is a hydrophobic radical, in particular with $n \geq 1$, and at the or VIIb in which the group D is a group –CH2- (aspartic unit).

[000198] In an embodiment, the composition is characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VII in which at least one of R_1 or R_2 is a hydrophobic radical, in particular with $n \geq 1$, or VIIb in which the group D is a $–CH_2-CH_2-$ group (glutamic acid).

[000199] In an embodiment, the composition is characterized in that the ratio i between the number of hydrophobic radicals and the number of glutamic or aspartic units is from 0.007 to 0.3.

[000200] In an embodiment, the composition is characterized in that the ratio i between the number of hydrophobic radicals and the number of glutamic of glutamic or aspartic units is from 0.01 to 0.3.

[000201] In an embodiment, the composition is characterized in that the ratio i between the number of hydrophobic radicals and the number of glutamic or aspartic units is from 0.03 to 0.3.

[000202] In an embodiment, the composition is characterized in that the ratio i between the number of hydrophobic radicals and the number of glutamic or aspartic units is from 0.02 to 0.2.

[000203] In an embodiment, the composition is characterized in that the hydrophobic radical corresponds to formula VI and the ratio i between the number of hydrophobic radicals and the number of glutamic or aspartic units is from 0.007 to 0.3.

[000204] In an embodiment, the composition is characterized in that the hydrophobic radical corresponds to formula VI, and the ratio i between the number of hydrophobic radicals and the number of glutamic or aspartic units is from 0.03 to 0.3. In an embodiment, the composition is characterized in that the hydrophobic radical corresponds to formula VI, and the ratio i between the number of hydrophobic radicals and the number of glutamic or aspartic units is from 0.05 to 0.2.

[000205] In an embodiment, the composition is characterized in that the hydrophobic radical corresponds to formula VI and the ratio i between the number of hydrophobic radicals and the number of glutamic or aspartic units is from 0.007 to 0.15.

[000206] In an embodiment, the composition is characterized in that the hydrophobic radical corresponds to formula VI and the ratio i between the number of hydrophobic radicals and the number of glutamic or aspartic units is from 0.01 to 0.1.

[000207] In an embodiment, the composition is characterized in that the hydrophobic radical corresponds to formula VI and the ratio i between the number of hydrophobic radicals and the number of glutamic or aspartic units is from 0.02 to 0.08.

[000208] In an embodiment, the composition is characterized in that the hydrophobic radical corresponds to formula VI in which the radical Cx comprises from 9 to 10 carbon atoms

and the ratio i between the number of hydrophobic radicals and the number of glutamic or aspartic units is from 0.05 to 0.3.

[000209] In an embodiment, the composition is characterized in that the hydrophobic radical corresponds to formula VI in which the radical Cx comprises from 9 to 10 carbon atoms and the ratio i between the number of hydrophobic radicals and the number of glutamic or aspartic units is from 0.03 to 0.15.

[000210] In an embodiment, the composition is characterized in that the hydrophobic radical corresponds to formula VI in which the radical Cx comprises from 11 to 12 carbon atoms and the ratio i between the number of hydrophobic radicals and the number of glutamic or aspartic units is from 0.05 to 0.2.

[000211] In an embodiment, the composition is characterized in that the hydrophobic radical corresponds to formula VI in which the radical Cx comprises from 11 to 12 carbon atoms and the ratio i between the number of hydrophobic radicals and the number of glutamic or aspartic units is from 0.03 to 0.2.

[000212] In an embodiment, the composition is characterized in that the hydrophobic radical corresponds to formula VI in which the radical Cx comprises from 11 to 12 carbon atoms and the ratio i between the number of hydrophobic radicals and the number of glutamic or aspartic units is from 0.015 to 0.1.

[000213] In an embodiment, the composition is characterized in that the hydrophobic radical corresponds to formula VI in which the radical Cx comprises from 11 to 12 carbon atoms and the ratio i between the number of hydrophobic radicals and the number of glutamic or aspartic units is from 0.02 to 0.08.

[000214] In an embodiment, the composition is characterized in that the hydrophobic radical corresponds to formula VI in which the radical Cx comprises from 13 to 15 carbon atoms and the ratio i between the number of hydrophobic radicals and the number of glutamic or aspartic units is from 0.03 to 0.15.

[000215] In an embodiment, the composition is characterized in that the hydrophobic radical corresponds to formula VI in which the radical Cx comprises from 13 to 15 carbon atoms and the ratio i between the number of hydrophobic radicals and the number of glutamic or aspartic units is from 0.01 to 0.1.

[000216] In an embodiment, the composition is characterized in that the hydrophobic radical corresponds to formula VI in which the radical Cx comprises from 13 to 15 carbon atoms, and the ratio i between the number of hydrophobic radicals and the number of glutamic or aspartic units is from 0.01 to 0.06.

[000217] In an embodiment, the composition is characterized in that the hydrophobic radical corresponds to formula V, and the ratio i between the number of hydrophobic radicals and the number of glutamic or aspartic units is from 0.007 to 0.3.

[000218] In an embodiment, the composition is characterized in that the hydrophobic radical corresponds to formula V, and the ratio i between the number of hydrophobic radicals and the number of glutamic or aspartic units is from 0.01 to 0.3.

[000219] In an embodiment, the composition is characterized in that the hydrophobic radical corresponds to formula V, and the ratio i between the number of hydrophobic radicals and the number of glutamic or aspartic units is from 0.05 to 0.3.

[000220] In an embodiment, the composition is characterized in that the hydrophobic radical corresponds to formula V, and the ratio i between the number of hydrophobic radicals and the number of glutamic or aspartic units is from 0. 1 to 0.3.

[000221] In an embodiment, the composition is characterized in that the hydrophobic radical corresponds to formula V, and the ratio i between the number of hydrophobic radicals and the number of glutamic or aspartic units is from 0.015 to 0.2.

[000222] In an embodiment, the composition is characterized in that the hydrophobic radical corresponds to formula V in which the radical Cx comprises from 11 to 14 carbon atoms, and the ratio i between the number of hydrophobic radicals and the number of glutamic or aspartic units is from 0.1 to 0.3.

[000223] In an embodiment, the composition is characterized in that the hydrophobic radical corresponds to formula V in which the radical Cx comprises from 11 to 14 carbon atoms, and the ratio i between the number of hydrophobic radicals and the number of glutamic or aspartic units is from 0.1 to 0.2.

[000224] In an embodiment, the composition is characterized in that the hydrophobic radical corresponds to formula V in which the radical Cx comprises from 15 to 16 carbon atoms, and the ratio i between the number of hydrophobic radicals and the number of glutamic or aspartic units is from 0.04 to 0.2.

[000225] In an embodiment, the composition is characterized in that the hydrophobic radical corresponds to formula V in which the radical Cx comprises from 15 to 16 carbon atoms, and the ratio i between the number of hydrophobic radicals and the number of glutamic or aspartic units is from 0.06 to 0.2.

[000226] In an embodiment, the composition is characterized in that the hydrophobic radical corresponds to formula V in which the radical Cx comprises from 15 to 16 carbon atoms, and the ratio i between the number of hydrophobic radicals and the number of glutamic or aspartic units is from 0.04 to 0.15.

[000227] In an embodiment, the composition is characterized in that the hydrophobic radical corresponds to formula V in which the radical Cx comprises from 17 to 18 carbon atoms, and the ratio i between the number of hydrophobic radicals and the number of glutamic or aspartic units is from 0.02 to 0.2.

[000228] In an embodiment, the composition is characterized in that the hydrophobic radical corresponds to formula V in which the radical Cx comprises from 17 to 18 carbon atoms, and the ratio i between the number of hydrophobic radicals and the number of glutamic or aspartic units is from 0.02 to 0.15.

[000229] In an embodiment, the composition is characterized in that the hydrophobic radical corresponds to formula V in which the radical Cx comprises from 17 to 18 carbon atoms, and the ratio i between the number of hydrophobic radicals and the number of glutamic or aspartic units is from 0.02 to 0.06.

[000230] In an embodiment, the composition is characterized in that the hydrophobic radical corresponds to formula V in which the radical Cx comprises from 19 to 25 carbon atoms, and the ratio i between the number of hydrophobic radicals and the number of glutamic or aspartic units is from 0.01 to 0.1.

[000231] In an embodiment, the composition is characterized in that the hydrophobic radical corresponds to formula V in which the radical Cx comprises from 19 to 25 carbon atoms,

and the ratio i between the number of hydrophobic radicals and the number of glutamic or aspartic units is from 0.01 to 0.06.

[000232] In an embodiment, the composition is characterized in that the hydrophobic radical corresponds to formula V in which the radical Cx comprises from 19 to 25 carbon atoms, and the ratio i between the number of hydrophobic radicals and the number of glutamic or aspartic units is from 0.01 to 0.05.

[000233] In an embodiment, the composition according to the invention is characterized in that n + m is from 10 to 250.

[000234] In an embodiment, the composition according to the invention is characterized in that n + m is from 10 to 200.

[000235] In an embodiment, the composition according to the invention is characterized in that n + m is from 10 to 100.

[000236] In an embodiment, the composition according to the invention is characterized in that n + m is from 10 to 50.

[000237] In an embodiment, the composition according to the invention is characterized in that n + m is from 15 to 150.

[000238] In an embodiment, the composition according to the invention is characterized in that n + m is from 15 to 100.

[000239] In an embodiment, the composition according to the invention is characterized in that n + m is from 15 to 80.

[000240] In an embodiment, the composition according to the invention is characterized in that n + m is from 15 to 65.

[000241] In an embodiment, the composition according to the invention is characterized in that n + m is from 20 to 60.

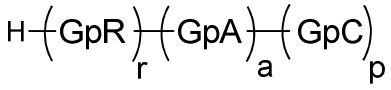
[000242] In an embodiment, the composition according to the invention is characterized in that n + m is from 20 to 50.

[000243] In an embodiment, the composition according to the invention is characterized in that n + m is from 20 to 40.

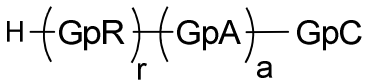
[000244] The invention also relates to said co-polyamino acid bearing carboxylate charges and hydrophobic radicals of formula I and the precursors of said hydrophobic radicals.

[000245] The co-polyamino acid bearing carboxylate charges and hydrophobic radicals of formula I are soluble in distilled water at a pH from 6 to 8, at a temperature of 25 °C, and at a concentration of less than 100 mg/mL.

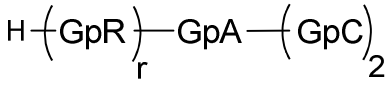
[000246] In an embodiment, the invention also relates to the precursors of said hydrophobic radicals of formula I', V' and VI':



formula I'



formula V'



formula VI'

GpR, GpA, GpC, r, a, p have the definitions given above.

[000247]

[000248] The invention moreover relates to a method for preparing stable injectable compositions.

[000249] "Soluble" is understood to mean capable of enabling the preparation of a clear, particle-free solution at a concentration of less than 100 mg/mL in distilled water at 25 °C.

[000250] "Solution" is understood to mean a liquid composition free of visible particles, using the procedure according to the pharmacopoeias EP 8.0, under point 2.9.20, and US <790>.

[000251] "Physically stable composition" is understood to mean compositions which, after a certain storage time at a certain temperature meet the criteria of visual inspection described in the European, American and international pharmacopoeias, that is to say compositions which are clear and contain no visible particles, and are also colorless.

[000252] "Chemically stable composition" is understood to mean compositions which after a certain storage time at a certain temperature, present a minimum recovery of the active ingredients and are in compliance with the specifications applicable to the pharmaceutical products.

[000253] A conventional method for measuring the stabilities of the proteins or peptides consists in measuring the formation of fibrils with the aid of Thioflavin T, also referred to as ThT. This method makes it possible, under temperature and stirring conditions that enable an acceleration of the phenomenon, to measure the lag time before the formation of fibrils by measuring the increase in fluorescence. The compositions according to the invention have a lag time before the formation of fibrils which is clearly greater than the lag time of the glucagon at the pH of interest.

[000254] "Injectable aqueous solution" is understood to mean water-based solutions which meet the conditions of the EP and US pharmacopoeias, and which are sufficiently liquid to be injected.

[000255] "Co-polyamino acid consisting of glutamic or aspartic units" is understood to mean noncyclic linear chains of glutamic acid or aspartic acid units bound together by peptide bonds, said chains having a C-terminal part corresponding to the carboxylic acid of one end and an N-terminal part corresponding to the amine of the other end of the chain.

[000256] "Alkyl radical" is understood to mean a linear or branched carbon chain which comprises no heteroatom.

[000257] The co-polyamino acid is a statistical or block co-polyamino acid.

[000258] The co-polyamino acid is a statistical co-polyamino acid in the chain of the glutamic and/or aspartic units.

[000259] In the formulas, the * indicate the sites of attachment of the different elements represented.

[000260] In formulas I, V and VI, the * indicate the sites of attachment of the hydrophobic radicals to the co-polyamino acid. The radicals Hy are attached to the polyamino acid via amide functions.

[000261] In formulas II and II', the * indicate, from left to right, respectively, the sites of attachment of GpR:

- to the co-polyamino acid and
- to the GpA if a = 1, or to GPC if a = 0.

[000262] In formulas III and III', the * indicate, from left to right, respectively, the sites of attachment of GpA:

- to GpR if r = 1, or to the co-polyamino acid if r = 0, and

- to GpC.

[000263] In formula IV, the * indicates the site of attachment of GpC:

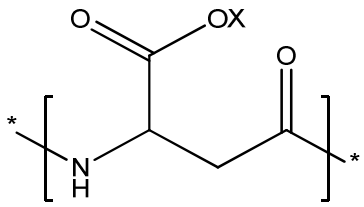
- to GpA if a = 1, GpR if r = 1 and a = 0, or to the co-polyamino acid if r = 0 and a = 0.

[000264] All the attachments between the different groups GpR, GpA and GpC are amide functions.

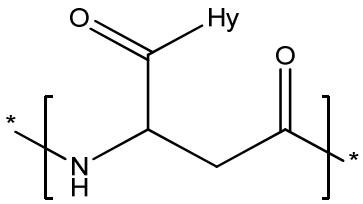
[000265] The radicals Hy, GpR, GpA, GpC, and D are each independently identical or different from one monomer unit to the next.

[000266] When the co-polyamino acid comprises one or more aspartic unit(s), it (they) can undergo structural rearrangements.

[000267] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acids obtained moreover comprise monomer units of formula VIII and/or VIII':

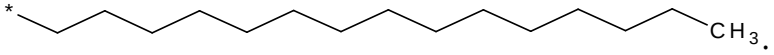


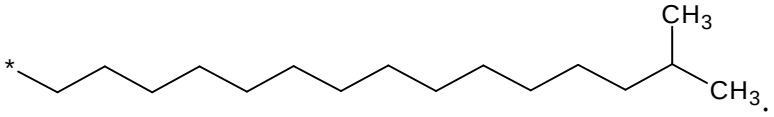
Formula VIII

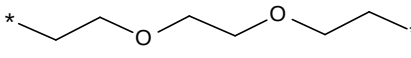
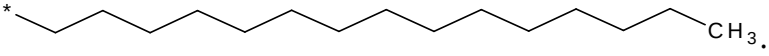


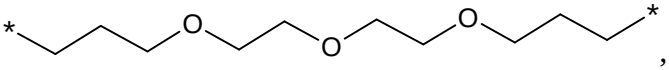
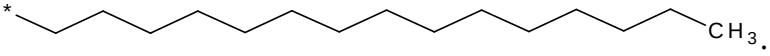
Formula VIII'

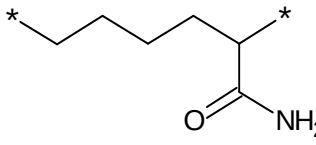
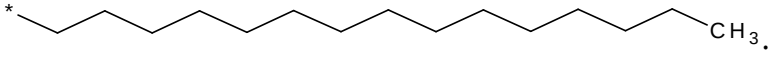
[000268] In an embodiment, the at least one hydrophobic radical of formula I is selected from the radicals of formula I in which, r = 1, a = 0, p = 1, GpR corresponds to formula II in

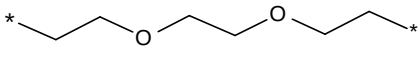
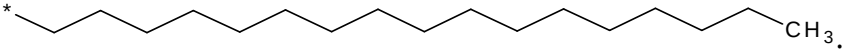
which R is -CH2-CH2-, GpC corresponds to formula IVd in which x = 15 and Cx is .

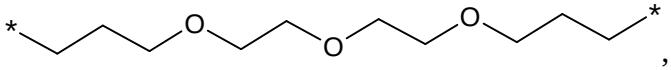
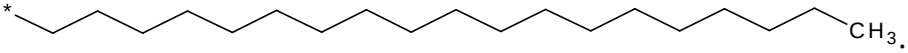
[000269] In an embodiment, the at least one hydrophobic radical of formula I is selected from the radicals of formula I in which, r = 1, a = 0, p = 1, GpR corresponds to formula II in which R is -CH2-CH2-, GpC corresponds to formula IVd in which x = 16 and Cx is .

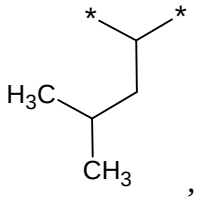
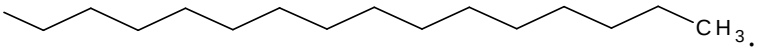
[000270] In an embodiment, the at least one hydrophobic radical of formula I is selected from the radicals of formula I in which r = 1, a = 0, p = 1, GpR corresponds to formula II in which R is , GpC corresponds to formula IVd in which x = 15 and Cx is .

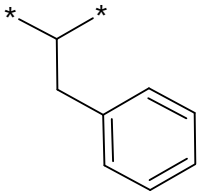
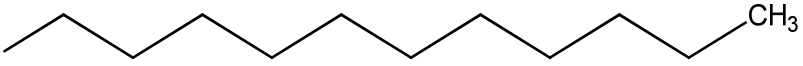
[000271] In an embodiment, the at least one hydrophobic radical of formula I is selected from the radicals of formula I in which r = 1, a = 0, p = 1, GpR corresponds to formula II in which R is , GpC corresponds to formula IVd in which x = 15 and Cx is .

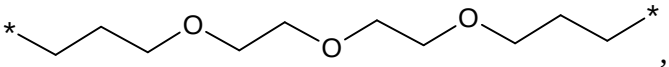
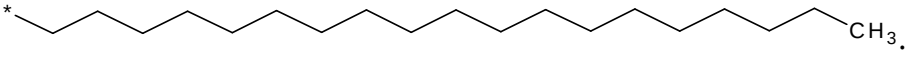
[000272] In an embodiment, the at least one hydrophobic radical of formula I is selected from the radicals of formula I in which r = 1, a = 0, p = 1, GpR corresponds to formula II in which R is , GpC corresponds to formula IVd in which x = 15 and Cx is .

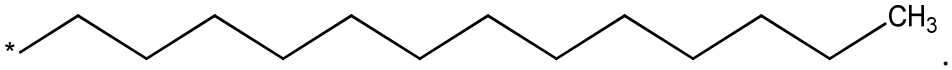
[000273] In an embodiment, the at least one hydrophobic radical of formula I is selected from the radicals of formula I in which r = 1, a = 0, p = 1, GpR corresponds to formula II in which R is , GpC corresponds to formula IVd in which x = 17 and Cx is .

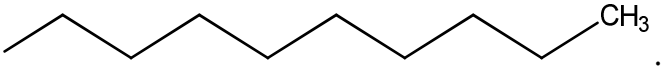
[000274] In an embodiment, the at least one hydrophobic radical of formula I is selected from the radicals of formula I in which r = 1, a = 0, p = 1, GpR corresponds to formula II in which R is , GpC corresponds to formula IVd in which x = 19 and Cx is .

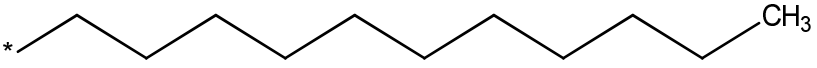
[000275] In an embodiment, the at least one hydrophobic radical of formula I is selected from the radicals of formula I in which r = 1, a = 0, p = 1, GpR corresponds to formula II in which R is -CH2-CH2-, GpC corresponds to formula IVa in which b = 1, B is , x = 15 and Cx is .

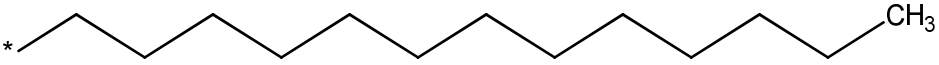
[000276] In an embodiment, the at least one hydrophobic radical of formula I is selected from the radicals of formula I in which r = 1, a = 0, p = 1, GpR corresponds to formula II in which R is -CH2-CH2-, GpC corresponds to formula IVa in which b = 1, B is , x = 11 and Cx is .

[000277] In an embodiment, the at least one hydrophobic radical of formula I is selected from the radicals of formula I in which r = 1, a = 0, p = 1, GpR corresponds to formula II in which R is , GpC corresponds to formula IVf in which x = 19 and Cx is .

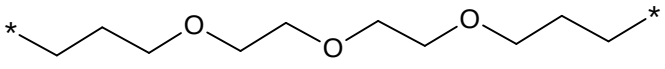
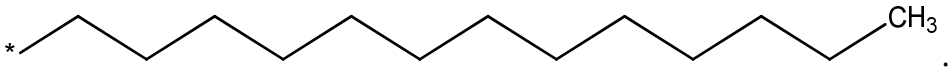
[000278] In an embodiment, the at least one hydrophobic radical of formula I is selected from the radicals of formula I in which r = 1, a = 0, p = 1, GpR corresponds to formula II in which R is -CH2-CH2-, GpC corresponds to formula IVd in which x = 13 and Cx is .

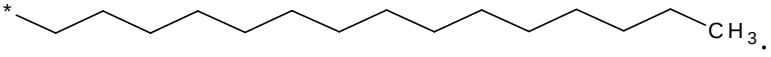
[000279] In an embodiment, the at least one hydrophobic radical of formula I is selected from the radicals of formula I in which r = 1, a = 1, p = 2, GpR corresponds to formula II in which R is -CH2-CH2-, GpA corresponds to formula IIIb, GpC corresponds to formula IVd in which x = 9 and Cx is .

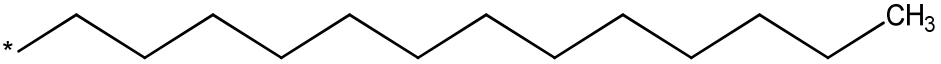
[000280] In an embodiment, the at least one hydrophobic radical of formula I is selected from the radicals of formula I in which r = 1, a = 1, p = 2, GpR corresponds to formula II in which R is -CH2-CH2-, GpA corresponds to formula IIIb, GpC corresponds to formula IVd in which x = 11 and Cx is .

[000281] In an embodiment, the at least one hydrophobic radical of formula I is selected from the radicals of formula I in which r = 1, a = 1, p = 2, GpR corresponds to formula II in which R is -CH2-CH2-, GpA corresponds to formula IIIb, GpC corresponds to formula IVd in which x = 13 and Cx is 

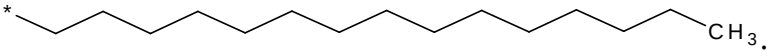
.

[000282] In an embodiment, the at least one hydrophobic radical of formula I is selected from the radicals of formula I in which r = 1, a = 1, p = 2, GpR corresponds to formula II in which R is , GpA corresponds to formula IIIb, GpC corresponds to formula IVd in which x = 13 and Cx is .

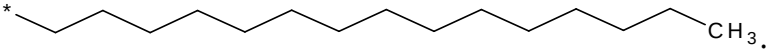
[000283] In an embodiment, the at least one hydrophobic radical of formula I is selected from the radicals of formula I in which r = 1, a = 1, p = 2, GpR corresponds to formula II in which R is -CH2-CH2, GpA corresponds to formula IIIb, GpC corresponds to formula IVd in which x = 15 and Cx is .

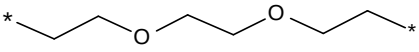
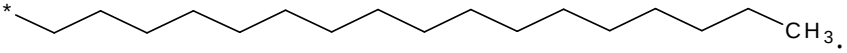
[000284] In an embodiment, the at least one hydrophobic radical of formula I is selected from the radicals of formula I in which r = 1, a = 1, p = 2, GpR corresponds to formula II in which R is -CH2-CH2, GpA corresponds to formula IIIa, GpC corresponds to formula IVd in which x = 13 and Cx is 

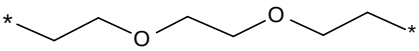
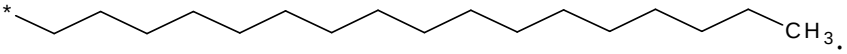
.

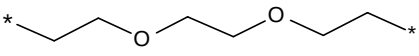
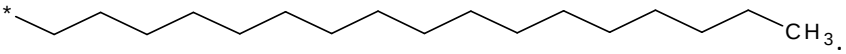
[000285] In an embodiment, the at least one hydrophobic radical of formula I is selected from the radicals of formula I in which r = 1, a = 1, p = 2, GpR corresponds to formula II in which R is –(CH2)6, GpA corresponds to formula IIIb, GpC corresponds to formula IVd in which x = 15 and Cx is .

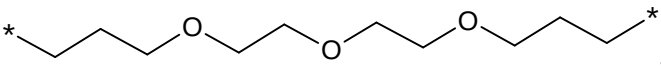
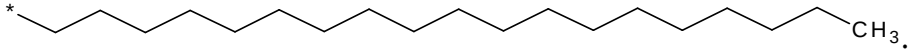
[000286] The values of the degree of polymerization DP and of ratio i are estimated by ^1H NMR in D_2O by comparing the integration of the signals originating from the hydrophobic groups with the integration of the signals originating from the main chain of the co-polyamino acid.

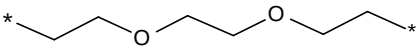
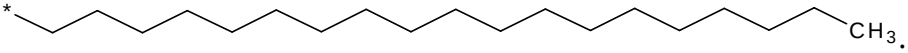
[000287] In an embodiment, the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is a co-polyamino acid of formula VII or VIIb, in which DP = 25 +/- 5, $0.033 \leq i \leq 0.05$, and the hydrophobic radical of formula I is selected from the radicals of formula I in which r = 1, a = 0, p = 1, GpR corresponds to formula II in which R is $-CH_2-CH_2-$, GpC corresponds to formula IVd in which x = 15 and Cx is .

[000288] In an embodiment, the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is a co-polyamino acid of formula VII or VIIb, in which DP = 30 +/- 5, $0.028 \leq i \leq 0.04$, and the at least one hydrophobic radical of formula I is selected from the radicals of formula I in which r = 1, a = 0, p = 1, GpR corresponds to formula II in which R is , GpC corresponds to formula IVd in which x = 17 and Cx is .

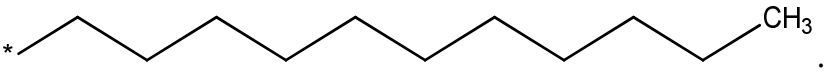
[000289] In an embodiment, the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is a co-polyamino acid of formula VII or VIIb, in which DP = 45 +/- 10, $0.018 \leq i \leq 0.028$, and the at least one hydrophobic radical of formula I is selected from the radicals of formula I in which r = 1, a = 0, p = 1, GpR corresponds to formula II in which R is , GpC corresponds to formula IVd in which x = 17 and Cx is .

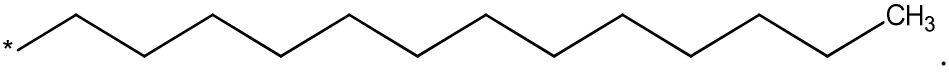
[000290] In an embodiment, the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is a co-polyamino acid of formula VII or VIIb, in which DP = 60 +/- 10, $0.014 \leq i \leq 0.02$, and the at least one hydrophobic radical of formula I is selected from the radicals of formula I in which r = 1, a = 0, p = 1, GpR corresponds to formula II in which R is , GpC corresponds to formula IVd in which x = 17 and Cx is .

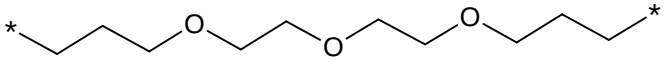
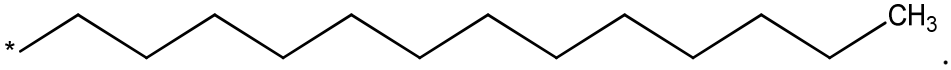
In an embodiment, the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is a co-polyamino acid of formula VII or VIIb, in which DP = 25 +/- 5, $0.033 \leq i \leq 0.05$, and the hydrophobic radical of formula I is selected from the radicals of formula I in which r = 1, a = 0, p = 1, GpR corresponds to formula II in which R is , GpC corresponds to formula IVd in which x = 19 and Cx is .

[000291] In an embodiment, the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is a co-polyamino acid of formula VII or VIIb, in which DP = 25 +/- 5, $0.025 \leq i \leq 0.07$, and the at least one hydrophobic radical of formula I is selected from the radicals of formula I in which r = 1, a = 0, p = 1, GpR corresponds to formula II in which R is , GpC corresponds to formula IVd in which x = 19 and Cx is .

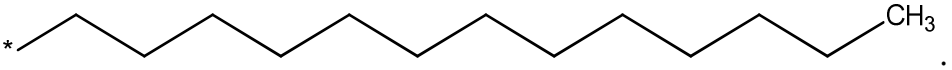
[000292] In an embodiment, the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is a co-polyamino acid of formula VII or VIIb, in which DP = 27 +/- 5,

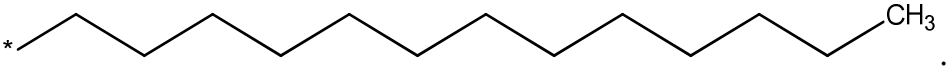
$0.031 \leq i \leq 0.045$, and the at least one hydrophobic radical of formula I is selected from the radicals of formula I in which r = 1, a = 1, p = 2, GpR corresponds to formula II in which R is -CH2-CH2-, GpA corresponds to formula IIIb, GpC corresponds to formula IVd in which x = 11 and Cx is .

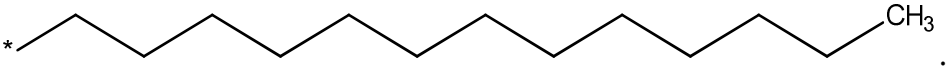
[000293] In an embodiment, the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is a co-polyamino acid of formula VII or VIIb, in which DP = 22 +/- 5, $0.037 \leq i \leq 0.055$, and the at least one hydrophobic radical of formula I is selected from the radicals of formula I in which r = 1, a = 1, p = 2, GpR corresponds to formula II in which R is -CH2-CH2-, GpA corresponds to formula IIIb, GpC corresponds to formula IVd in which x = 13 and Cx is .

[000294] In an embodiment, the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is a co-polyamino acid of formula VII or VIIb, in which DP = 22 +/- 5, $0.037 \leq i \leq 0.055$, and the at least one hydrophobic radical of formula I is selected from the radicals of formula I in which r = 1, a = 1, p = 2, GpR corresponds to formula II in which R is , GpA corresponds to formula IIIb, GpC corresponds to formula IVd in which x = 13 and Cx is .

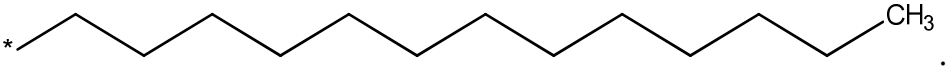
[000295] In an embodiment, the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is a co-polyamino acid of formula VII or VIIb, in which DP = 60 +/- 10, $0.014 \leq i \leq 0.02$, and the at least one hydrophobic radical of formula I is selected from the

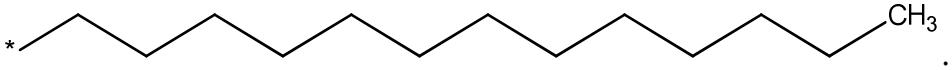
radicals of formula I in which r = 1, a = 1, p = 2, GpR corresponds to formula II in which R is -CH2-CH2-, GpA corresponds to formula IIIb, GpC corresponds to formula IVd in which x = 13 and Cx is .

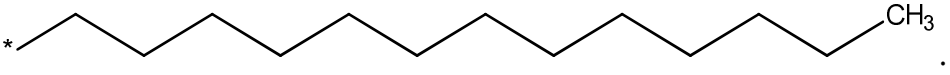
[000296] In an embodiment, the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is a co-polyamino acid of formula VII or VIIb, in which DP = 40 +/- 5, $0.022 \leq i \leq 0.029$, and the at least one hydrophobic radical of formula I is selected from the radicals of formula I in which r = 1, a = 1, p = 2, GpR corresponds to formula II in which R is -CH2-CH2-, GpA corresponds to formula IIIb, GpC corresponds to formula IVd in which x = 13 and Cx is .

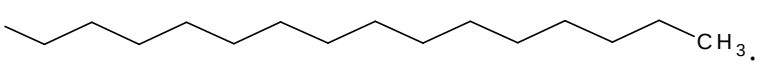
[000297] In an embodiment, the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is a co-polyamino acid of formula VII or VIIb, in which DP = 25 +/- 5, $0.02 \leq i \leq 0.06$, and the at least one hydrophobic radical of formula I is selected from the radicals of formula I in which r = 1, a = 1, p = 2, GpR corresponds to formula II in which R is -CH2-CH2-, GpA corresponds to formula IIIb, GpC corresponds to formula IVd in which x = 13 and Cx is .

[000298] In an embodiment, the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is a co-polyamino acid of formula VII or VIIb, in which DP = 17 +/- 4, $0.04 \leq i \leq 0.1$, and the at least one hydrophobic radical of formula I is selected from the radicals of formula I in which r = 1, a = 1, p = 2, GpR corresponds to formula II in which R is -CH2-

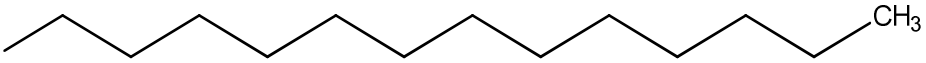
CH2-, GpA corresponds to formula IIIb, GpC corresponds to formula IVd in which x = 13 and Cx is .

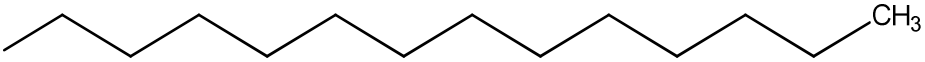
[000299] In an embodiment, the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is a co-polyamino acid of formula VII or VIIb, in which DP = 9 +/- 2, $0.09 \leq i \leq 0.2$, and the at least one hydrophobic radical of formula I is selected from the radicals of formula I in which r = 1, a = 1, p = 2, GpR corresponds to formula II in which R is -CH2-CH2-, GpA corresponds to formula IIIb, GpC corresponds to formula IVd in which x = 13 and Cx is .

[000300] In an embodiment, the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is a co-polyamino acid of formula VII or VIIb, in which DP = 20 +/- 5, $0.04 \leq i \leq 0.08$, and the at least one hydrophobic radical of formula I is selected from the radicals of formula I in which r = 1, a = 1, p = 2, GpR corresponds to formula II in which R is -CH2-CH2-, GpA corresponds to formula IIIb, GpC corresponds to formula IVd in which x = 13 and Cx is .

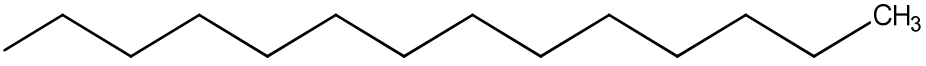
[000301] In an embodiment, the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is a co-polyamino acid of formula VII or VIIb, in which DP = 23 +/- 5, $0.035 \leq i \leq 0.08$, and the at least one hydrophobic radical of formula I is selected from the radicals of formula I in which r = 1, a = 1, p = 2, GpR corresponds to formula II in which R is -CH2-CH2-, GpA corresponds to formula IIIb, GpC corresponds to formula IVd in which x = 15 and Cx is .

[000302] In an embodiment, the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is a co-polyamino acid of formula VII or VIIb, in which DP = 20 +/- 5,

$0.04 \leq i \leq 0.08$, and the at least one hydrophobic radical of formula I is selected from the radicals of formula I in which r = 1, a = 1, p = 2, GpR corresponds to formula II in which R is -CH2-CH2-, GpA corresponds to formula IIIc, GpC corresponds to formula IVd in which x = 13 and Cx is 

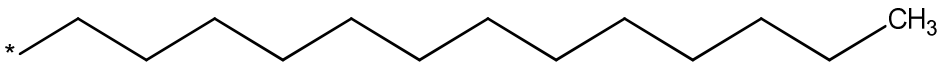
[000303] In an embodiment, the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is a co-polyamino acid of formula VII or VIIb, in which DP = 20 +/- 5, $0.04 \leq i \leq 0.08$, and Hy, as well as R1 and/or R2, is a hydrophobic radical of formula I selected from the radicals of formula I in which r = 1, a = 1, p = 2, GpR corresponds to formula II in which R is -CH2-CH2-, GpA corresponds to formula IIIb, GpC corresponds to formula IVd in which x = 13 and Cx is 

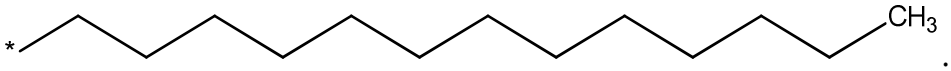
.

[000304] In an embodiment, the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is a co-polyamino acid of formula VII or VIIb, in which DP = 20 +/- 5, $0.04 \leq i \leq 0.08$, and the at least one hydrophobic radical of formula I is selected from the radicals of formula I in which r = 0, a = 1, p = 2, GpR corresponds to formula II in which R is -CH2-CH2-, GpA corresponds to formula IIIb, GpC corresponds to formula IVd in which x = 13 and Cx is 

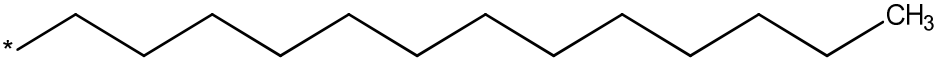
.

[000305] In an embodiment, the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is a co-polyamino acid of formula VII or VIIb, in which DP = 20 +/- 5, $0.08 \leq i \leq 0.20$, and R1 is a hydrophobic radical of formula I selected from the radicals of formula I in which r = 0, a = 1, p = 2, GpR corresponds to formula II in which R is -CH2-CH2-, GpA corresponds to formula IIIb, GpC corresponds to formula IVd in which x = 13 and Cx is



and R2 a hydrophobic radical of formula I is selected from the radicals of formula I in which r = 1, a = 1, p = 2, GpR corresponds to formula II in which R is -CH2-CH2-, GpA corresponds to formula IIIb, GpC corresponds to formula IVd in which x = 13 and Cx is 

.

[000306] In an embodiment, the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is a co-polyamino acid of formula VII or VIIb, in which DP = 25 +/- 5, $0.035 \leq i \leq 0.08$, and the at least one hydrophobic radical of formula I is selected from the radicals of formula I in which r = 1, a = 1, p = 2, GpR corresponds to formula II in which R is –(CH2)6, GpA corresponds to formula IIIb, GpC corresponds to formula IVd in which x = 14 and Cx is 

.

[000307] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid originates from a polyamino acid obtained by polymerization.

[000308] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid originates from a polyamino acid obtained by ring-opening polymerization of a glutamic acid N-carboxyanhydride derivative or an aspartic acid N-carboxyanhydride derivative.

[000309] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid originates from a polyamino acid obtained by polymerization of a glutamic acid N-carboxyanhydride derivative or of an aspartic acid N-carboxyanhydride derivative described in the review article Adv. Polym. Sci. 2006, 202, 1-18 (Deming, T.J.).

[000310] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid originates from a polyamino acid obtained by polymerization of a glutamic acid N-carboxyanhydride derivative.

[000311] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid originates from a polyamino acid obtained by polymerization of a glutamic acid N-carboxyanhydride derivative selected from the group consisting of methyl glutamate N-carboxyanhydride (GluOMe-NCA), benzyl glutamate N-carboxyanhydride (GluOBzl-NCA), and t-butyl glutamate N-carboxyanhydride (GluOtBu-NCA).

[000312] In an embodiment, the glutamic acid N-carboxyanhydride derivative is methyl L-glutamate N-carboxyanhydride (L-GluOMe-NCA).

[000313] In an embodiment, the glutamic acid N-carboxyanhydride derivative is benzyl L-glutamate N-carboxyanhydride (L-GluOBzl-NCA).

[000314] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid originates from a polyamino acid obtained by polymerization of a glutamic acid N-carboxyanhydride derivative or of an aspartic acid N-carboxyanhydride derivative , using as initiator an organometallic complex of a transition metal, as described in the publication Nature 1997, 390, 386-389 (Deming, T.J.).

[000315] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid originates from a polyamino acid obtained by polymerization of a glutamic acid N-carboxyanhydride derivative or of an aspartic acid N-carboxyanhydride derivative, using, as initiator, ammonia or a primary amine as described in the patent FR 2,801,226 (Touraud, F. et al.) and the references cited in this patent.

[000316] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid originates from a polyamino acid obtained by polymerization of a glutamic acid N-carboxyanhydride derivative or of an aspartic acid N-carboxyanhydride derivative, using as initiator hexamethyldisilazane, as described in the publication J. Am. Chem. Soc. 2007, 129, 14114-14115 (Lu H. et al.) or a silylated amine as described in the publication J. Am. Chem. Soc. 2008, 130, 12562-12563 (Lu H. et al.).

[000317] In an embodiment, the composition according to the invention is characterized in that the method for synthetizing the polyamino acid obtained by polymerization of a glutamic acid N-carboxyanhydride derivative or an aspartic acid N-carboxyanhydride derivative from which the co-polyamino acid originates comprises a step of hydrolysis of ester functions.

[000318] In an embodiment, this step of hydrolysis of ester functions can consist of a hydrolysis in an acidic medium or a hydrolysis in an alkaline medium or it can be carried out by hydrogenation.

[000319] In an embodiment, this step of hydrolysis of ester groups is a hydrolysis in an acidic medium.

[000320] In an embodiment, this step of hydrolysis of ester groups is carried out by hydrogenation.

[000321] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid originates from a polyamino acid obtained by depolymerization of a polyamino acid of higher molecular weight.

[000322] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid originates from a polyamino acid obtained by enzymatic depolymerization of a polyamino acid of higher molecular weight.

[000323] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid originates from a polyamino acid obtained by chemical depolymerization of a polyamino acid of higher molecular weight.

[000324] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid originates from a polyamino acid obtained by enzymatic and chemical depolymerization of a polyamino acid of higher molecular weight.

[000325] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid originates from a polyamino acid obtained by depolymerization of a polyamino acid of higher molecular weight selected from the group consisting of sodium polyglutamate and sodium polyaspartate.

[000326] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid originates from a polyamino acid obtained by depolymerization of a sodium polyglutamate of higher molecular weight.

[000327] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid originates from a polyamino acid obtained by depolymerization of a sodium polyaspartate of higher molecular weight.

[000328] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid is obtained by grafting a hydrophobic group onto a poly-L-glutamic acid or poly-L-aspartic acid using the methods for forming amide bonds, which are well known to the person skilled in the art.

[000329] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid is obtained by grafting of a hydrophobic group onto a poly-L-

glutamic acid or poly-L-aspartic acid using the methods for forming amide bonds, used for peptide synthesis.

[000330] In an embodiment, the composition according to the invention is characterized in that the co-polyamino acid is obtained by grafting of a hydrophobic group onto a poly-L-glutamic acid or poly-L-aspartic acid as described in the patent FR 2,840,614 (Chan, Y.P.; et al.).

[000331] In an embodiment, the concentration of co-polyamino acid bearing carboxylate charges and hydrophobic radicals is at most 40 mg/mL.

[000332] In an embodiment, the concentration of co-polyamino acid bearing carboxylate charges and hydrophobic radicals is at most 30 mg/mL.

[000333] In an embodiment, the concentration of co-polyamino acid bearing carboxylate charges and hydrophobic radicals is at most 20 mg/mL.

[000334] In an embodiment, the concentration of co-polyamino acid bearing carboxylate charges and hydrophobic radicals is at most 10 mg/mL.

[000335] In an embodiment, the concentration of co-polyamino acid bearing carboxylate charges and hydrophobic radicals is at most 5 mg/mL.

[000336] In an embodiment, the concentration of co-polyamino acid bearing carboxylate charges and hydrophobic radicals is at most 2.5 mg/mL.

[000337] In an embodiment, the concentration of co-polyamino acid bearing carboxylate charges and hydrophobic radicals is at most 1 mg/mL.

[000338] In an embodiment, the concentration of co-polyamino acid bearing carboxylate charges and hydrophobic radicals is at most 0.5 mg/mL.

[000339] In an embodiment, the weight ratio of co-polyamino acid bearing carboxylate charges and hydrophobic radicals over glucagon is from 1.5 to 25.

[000340] In an embodiment, the weight ratio of co-polyamino acid bearing carboxylate charges and hydrophobic radicals over glucagon is from 2 to 20.

[000341] In an embodiment, the weight ratio of co-polyamino acid bearing carboxylate charges and hydrophobic radicals over glucagon is from 2.5 to 15.

[000342] In an embodiment, the weight ratio of co-polyamino acid bearing carboxylate charges and hydrophobic radicals over glucagon is from 2 to 10.

[000343] In an embodiment, the weight ratio of co-polyamino acid bearing carboxylate charges and hydrophobic radicals over glucagon is from 2 to 7.

[000344] Human glucagon is used at doses that vary depending on the applications.

[000345] In the emergency treatment of hypoglycemia, the recommended dosage is 1 mg by the intramuscular or intravenous route (0.5 mg if the body weight is less than 25 kg). This administration is carried out with a solution of human glucagon at the concentration of 1 mg/mL.

[000346] In pumps, the daily dose considered is approximately 0.5 mg; thus the solutions can comprise from 0.25 mg/mL to 5 mg/mL of human glucagon.

[000347] In an embodiment, the solutions can comprise from 0.5 mg/mL to 3 mg/mL of human glucagon.

[000348] In the treatment of obesity, the daily dose considered is approximately 0.5 mg, the solutions thus can comprise from 0.25 mg/mL to 5 mg/mL of human glucagon.

[000349] In an embodiment, the concentration of human glucagon is from 0.25 to 5 mg/mL.

[000350] In an embodiment, the concentration of human glucagon is from 0. 5 to 4 mg/mL.

[000351] In an embodiment, the concentration of human glucagon is from 0.75 to 3 mg/mL.

[000352] In an embodiment, the concentration of human glucagon is from 0.75 to 2.5 mg/mL.

[000353] In an embodiment, the concentration of human glucagon is from 0.75 to 2 mg/mL.

[000354] In an embodiment, the concentration of human glucagon is from 1 to 2 mg/mL.

[000355] In an embodiment, the molar ratio [hydrophobic radical]/[human glucagon] is less than 20.

[000356] In an embodiment, the molar ratio [hydrophobic radical]/[human glucagon] is less than 15.

[000357] In an embodiment, the molar ratio [hydrophobic radical]/[human glucagon] is less than 10.

[000358] In an embodiment, the molar ratio [hydrophobic radical]/[human glucagon] is less than 5.

[000359] In an embodiment, the molar ratio [hydrophobic radical]/[human glucagon] is less than 2.5.

[000360] In an embodiment, the molar ratio [hydrophobic radical]/[human glucagon] is less than 1.5.

[000361] In an embodiment, the molar ratio [co-polyamino acid bearing carboxylate charges and hydrophobic radicals Hy]/[human glucagon] is less than 20.

[000362] In an embodiment, the molar ratio [co-polyamino acid bearing carboxylate charges and hydrophobic radicals Hy]/[human glucagon] is less than 15.

[000363] In an embodiment, the molar ratio [co-polyamino acid bearing carboxylate charges and hydrophobic radicals Hy]/[human glucagon] is less than 10.

[000364] In an embodiment, the molar ratio [co-polyamino acid bearing carboxylate charges and hydrophobic radicals Hy]/[human glucagon] is less than 5.

[000365] In an embodiment, the molar ratio [co-polyamino acid bearing carboxylate charges and hydrophobic radicals Hy]/[human glucagon] is less than 2.5.

[000366] In an embodiment, the molar ratio [co-polyamino acid bearing carboxylate charges and hydrophobic radicals Hy]/[human glucagon] is less than 1.5.

[000367] Human glucagon is a highly preserved polypeptide comprising a simple chain of 29 amino acid residues having the following sequence H-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Met-Asn-Thr-OH.

[000368] It can be obtained in different manners, by recombinant peptide synthesis.

[000369] Human glucagon is available from numerous sources. For example, the human glucagon produced by Bachem via peptide synthesis is available, in particular under reference 407473.

[000370] In an embodiment, the composition comprises, in addition, a nicotinic compound or one of the derivatives thereof.

[000371] In an embodiment, the composition comprises nicotinamide.

[000372] In an embodiment, the concentration of nicotinamide ranges from 10 to 160 mM.

[000373] In an embodiment, the concentration of nicotinamide ranges from 20 to 150 mM.

[000374] In an embodiment, the concentration of nicotinamide ranges from 40 to 120 mM.

[000375] In an embodiment, the concentration of nicotinamide ranges from 60 to 100 mM.

[000376] In an embodiment, the composition comprises, in addition, a polyanionic compound.

[000377] In an embodiment, the polyanionic compound is selected from the group consisting of the carboxylic polyacids and the Na^+, K^+, Ca^{2+} or Mg^{2+} salts thereof.

[000378] In an embodiment, the carboxylic acid is selected from the group consisting of citric acid, tartaric acid and the Na^+, K^+, Ca^{2+} or Mg^{2+} salts thereof.

[000379] In an embodiment, the polyanionic compound is selected from the group consisting of the phosphoric polyacids and the Na^+, K^+, Ca^{2+} or Mg^{2+} salts thereof.

[000380] In an embodiment, the phosphoric polyacid is triphosphate and the Na^+, K^+, Ca^{2+} or Mg^{2+} salts thereof.

[000381] In an embodiment, the polyanionic compound is citric acid and the Na^+, K^+, Ca^{2+} or Mg^{2+} salts thereof.

[000382] In an embodiment, the polyanionic compound is tartaric acid and the Na^+, K^+, Ca^{2+} or Mg^{2+} salts thereof.

[000383] In an embodiment, the polyanionic compound is triphosphoric acid and the Na^+, K^+, Ca^{2+} or Mg^{2+} salts thereof.

[000384] In an embodiment, the concentration of polyanionic compound is from 1 to 20 mM.

[000385] In an embodiment, the concentration of polyanionic compound is from 2 to 15 mM.

[000386] In an embodiment, the concentration of polyanionic compound is from 3 to 12 mM.

[000387] In an embodiment, the concentration of polyanionic compound is 10 mM.

[000388] In an embodiment, the concentration of polyanionic compound is 5 mM.

[000389] In an embodiment, the concentration of polyanionic compound is 10 mM for concentrations of glucagon from 0.5 mg/mL to 3 mg/mL.

[000390] In an embodiment, the concentration of polyanionic compound is 10 mM for concentrations of glucagon from 0.5 mg/mL to 2 mg/mL.

[000391] In an embodiment, the concentration of polyanionic compound is 10 mM for concentrations of glucagon from 1 mg/mL to 2 mg/mL.

[000392] In an embodiment, the concentration of polyanionic compound is 5 mM for concentrations of glucagon from 0.5 mg/mL to 3 mg/mL.

[000393] In an embodiment, the concentration of polyanionic compound is 5 mM for concentrations of glucagon from 0.5 mg/mL to 2 mg/mL.

[000394] In an embodiment, the concentration of polyanionic compound is 5 mM for concentrations of glucagon from 1 mg/mL to 2 mg/mL.

[000395] In an embodiment, the concentration of citric acid and the Na^+, K^+, Ca^{2+} or Mg^{2+} salts thereof is from 1 to 20 mM.

[000396] In an embodiment, the concentration of citric acid and the Na^+, K^+, Ca^{2+} or Mg^{2+} salts thereof is from 2 to 15 mM.

[000397] In an embodiment, the concentration of citric acid and the Na^+, K^+, Ca^{2+} or Mg^{2+} salts thereof is from 3 to 12 mM.

[000398] In an embodiment, the concentration of citric acid and the Na^+, K^+, Ca^{2+} or Mg^{2+} salts thereof is 10 mM.

[000399] In an embodiment, the concentration of citric acid and the Na^+, K^+, Ca^{2+} or Mg^{2+} salts thereof is 5 mM.

[000400] In an embodiment, the concentration of citric acid and the Na^+, K^+, Ca^{2+} or Mg^{2+} salts thereof is 10 mM for concentrations of glucagon from 0.5 mg/mL to 3 mg/mL.

[000401] In an embodiment, the concentration of citric acid and the Na^+, K^+, Ca^{2+} or Mg^{2+} salts thereof is 10 mM for concentrations of glucagon from 0.5 mg/mL to 2 mg/mL.

[000402] In an embodiment, the concentration of citric acid and the Na^+, K^+, Ca^{2+} or Mg^{2+} salts thereof is 10 mM for concentrations of glucagon from 1 mg/mL to 2 mg/mL.

[000403] In an embodiment, the concentration of citric acid and the Na^+, K^+, Ca^{2+} or Mg^{2+} salts thereof is 5 mM for concentrations of glucagon from 0.5 mg/mL to 3 mg/mL.

[000404] In an embodiment, the concentration of citric acid and the Na^+, K^+, Ca^{2+} or Mg^{2+} salts thereof is 5 mM for concentrations of glucagon from 0.5 mg/mL to 2 mg/mL.

[000405] In an embodiment, the concentration of citric acid and the Na^+, K^+, Ca^{2+} or Mg^{2+} salts thereof is 5 mM for concentrations of glucagon from 1 mg/mL to 2 mg/mL.

[000406] In an embodiment, the compositions according to the invention comprise, in addition, a gastrointestinal hormone.

[000407] "Gastrointestinal hormones" is understood to mean the hormones selected from the group consisting of the GLP-1 RA for agonists of the human glucagon-like peptide-1 receptor (glucagon like peptide-1 receptor agonist)Glucagon like) and GIP (glucose-dependent insulinotropic peptide), oxyntomodulin (a derivative of human proglucagon), peptide YY, amylin, cholecystokinin, pancreatic polypeptide (PP), ghrelin and enterostatin, the analogs or derivatives thereof and/or the pharmaceutically acceptable salts thereof.

[000408] In an embodiment, the gastrointestinal hormones are analogs or derivatives of GLP-1 RA (Glucagon like peptide-1 receptor agonist) selected from the group consisting of exenatide or Byetta® (ASTRA-ZENECA), liraglutide or Victoza® (NOVO NORDISK), lixisenatide or Lyxumia® (SANOFI), albiglutide or Tanzeum® (GSK) or dulaglutide or

Trulicity® (ELI LILLY & CO), the analogs or derivatives thereof and the pharmaceutically acceptable salts thereof.

[000409] In an embodiment, the gastrointestinal hormone is pramlintide or Symlin® (ASTRA-ZENECA).

[000410] In an embodiment, the gastrointestinal hormone is exenatide or Byetta®, the analogs or derivatives thereof and the pharmaceutically acceptable salts thereof.

[000411] In an embodiment, the gastrointestinal hormone is liraglutide or Victoza®, the analogs or derivatives thereof and the pharmaceutically acceptable salts thereof.

[000412] In an embodiment, the gastrointestinal hormone is lixisenatide or Lyxumia®, the analogs or derivatives thereof and the pharmaceutically acceptable salts thereof.

[000413] In an embodiment, the gastrointestinal hormone is albiglutide or Tanzeum®, the analogs or derivatives thereof and the pharmaceutically acceptable salts thereof.

[000414] In an embodiment, the gastrointestinal hormone is dulaglutide or Trulicity®, the analogs or derivatives thereof and the pharmaceutically acceptable salts thereof.

[000415] In an embodiment, the gastrointestinal hormone is pramlintide or Symlin®, the analogs or derivatives thereof and the pharmaceutically acceptable salts thereof.

[000416] "Analog," when used in reference to a peptide or a protein, is understood to mean a peptide or a protein in which one or more constitutive residues of amino acids have been substituted by other residues of amino acids and/or in which one or more constitutive residues of amino acids have been eliminated and/or in which one or more constitutive residues of amino acids have been added. The admissible percentage of homology for the present definition of an analog is 50%.

[000417] "Derivative," when used in reference to a peptide or a protein, is understood to mean a peptide or a protein or an analog which has been chemically modified by a substituent which is not present in the peptide or the protein or the analog of reference, that is to say a peptide or a protein which has been modified by creation of covalent bonds, in order to introduce substituents.

[000418] In an embodiment, the substituent is selected from the group consisting of the fatty chains.

[000419] In an embodiment, the concentration of gastrointestinal hormone is within a range from 0.01 to 10 mg/mL.

[000420] In an embodiment, the concentration of exenatide, the analogs or derivatives thereof and the pharmaceutically acceptable salts thereof is within a range from 0.04 to 0.5 mg/mL.

[000421] In an embodiment, the concentration of liraglutide, the analogs or derivatives thereof and the pharmaceutically acceptable salts thereof is within a range from 1 to 10 mg/mL.

[000422] In an embodiment, the concentration of lixisenatide, the analogs or derivatives thereof and the pharmaceutically acceptable salts thereof is within a range from 0.01 to 1 mg/mL.

[000423] In an embodiment, the concentration of pramlintide, the analogs or derivatives thereof and the pharmaceutically acceptable salts thereof is within a range from 0.1 to 5 mg/mL.

[000424] In an embodiment, the compositions according to the invention are produced by mixing of human glucagon solutions obtained by reconstitution of lyophilizate and of solutions

of GLP-1 RA (Glucagon like peptide-1 receptor agonist) GLP-1 RA, of analog or of derivative of GLP-1 RA, said solutions of GLP-1 RA being commercial or reconstituted from lyophilizate.

[000425] In an embodiment, the compositions according to the invention comprise, in addition, buffers.

[000426] In an embodiment, the compositions according to the invention comprise buffers at concentrations from 0 to 100 mM.

[000427] In an embodiment, the compositions according to the invention comprise buffers at concentrations from 15 to 50 mM.

[000428] In an embodiment, the compositions according to the invention comprise a buffer selected from the group consisting of a phosphate buffer, Tris (trishydroxymethylaminomethane) or sodium citrate.

[000429] In an embodiment, the buffer is sodium phosphate.

[000430] In an embodiment, the buffer is Tris (trishydroxymethylaminomethane).

[000431] In an embodiment, the buffer is sodium citrate.

[000432] In an embodiment, the composition comprises, in addition, a zinc salt, in particular zinc chloride.

[000433] In an embodiment, the concentration of zinc salt is from 50 to 5000 µM.

[000434] In an embodiment, the concentration of zinc salt is from 100 to 2000 µM.

[000435] In an embodiment, the concentration of zinc salt is from 200 to 1500 µM.

[000436] In an embodiment, the concentration of zinc salt is from 200 to 1000 µM.

[000437] In an embodiment, the zinc concentration is such that the molar ratio [zinc]/[glucagon] is from 0.1 to 2.5.

[000438] In an embodiment, the zinc concentration is such that the molar ratio [zinc]/[glucagon] is from 0.2 to 2.

[000439] In an embodiment, the zinc concentration is such that the molar ratio [zinc]/[glucagon] is from 0.5 to 1.5.

[000440] In an embodiment, the zinc concentration is such that the molar ratio [zinc]/[glucagon] is 1.

[000441] In an embodiment, the compositions according to the invention comprise, in addition, preservatives.

[000442] In an embodiment, the preservatives are selected from the group consisting of m-cresol and phenol, alone or in a mixture.

[000443] In an embodiment, the compositions according to the invention comprise, in addition, antioxidants.

[000444] In an embodiment, the antioxidants are selected from methionine.

[000445] In an embodiment, the concentration of preservatives is from 10 to 50 mM.

[000446] In an embodiment, the concentration of preservatives is from 10 to 40 mM.

[000447] In an embodiment, the compositions according to the invention comprise, in addition, a surfactant.

[000448] In an embodiment, the surfactant is selected from the group consisting of propylene glycol or polysorbate.

[000449] The compositions according to the invention can, in addition, comprise additives such as tonicity agents.

[000450] In an embodiment, the tonicity agents are selected from the group consisting of sodium chloride, mannitol, saccharose, sorbitol and glycerol.

[000451] The compositions according to the invention can comprise, in addition, all the excipients in accordance with the pharmacopoeias and compatible with human glucagon and the gastrointestinal hormones, in particular the GLP-1 RA, used at the conventional concentrations.

[000452] The invention also relates to a pharmaceutical composition according to the invention, characterized in that it is obtained by drying and/or lyophilization.

[000453] In the case of local and systemic releases, the modes of administration considered are by intravenous, subcutaneous, intradermal or intramuscular route.

[000454] The transdermal, oral, nasal, vaginal, ocular, buccal, pulmonary routes of administration are also considered.

[000455] The invention also relates to single-dose formulations at pH from 6.6 to 7.8 comprising human glucagon.

[000456] The invention also relates to single-dose formulations at a pH from 6.6 to 7.8 comprising human glucagon and a gastrointestinal hormone, as defined above.

[000457] In an embodiment, the single-dose formulations comprise, in addition, a substituted co-polyamino acid as defined above.

[000458] In an embodiment, the formulations are in the form of an injectable solution. In an embodiment, the GLP-1 RA, analog or derivative of GLP-1 RA is selected from the group comprising exenatide (Byetta®), liraglutide (Victoza®), lixisenatide (Lyxumia®), albiglutide (Tanzeum®), dulaglutide (Trulicity®) or one of the derivatives thereof.

[000459] In an embodiment, the gastrointestinal hormone is exenatide.

[000460] In an embodiment, the gastrointestinal hormone is liraglutide.

[000461] In an embodiment, the gastrointestinal hormone is lixisenatide.

[000462] In an embodiment, the gastrointestinal hormone is albiglutide.

[000463] In an embodiment, the gastrointestinal hormone is dulaglutide.

[000464] Moreover and no less importantly, the applicant was able to verify that human glucagon in the presence of a co-polyamino acid bearing carboxylate charges and at least one hydrophobic radical according to the invention preserves its action, whether alone or in combination with a gastrointestinal hormone.

[000465] The preparation of a composition according to the invention has the advantage that it can be carried out by simple mixing of a solution of human glucagon, of a solution of GLP-1 RA, of an analog or a derivative of GLP-1 RA, and of a co-polyamino acid bearing carboxylate charges and at least one hydrophobic radical according to the invention, in aqueous solution or in lyophilized form. If necessary, the pH of the preparation is adjusted to pH 7.

[000466] In an embodiment, the mixture of human glucagon and of substituted co-polyamino acid is concentrated by ultrafiltration before the mixing with GLP-1 RA, an analog or a derivative of GLP-1 RA in aqueous solution and in lyophilized form.

[000467] If necessary, the composition of the mixture is adjusted in terms of excipients such as glycerol, m-cresol and polysorbate (Tween®) by addition of concentrated solutions of these excipients within the mixture. If necessary, the pH is adjusted to 7.

Description of Figure 1:

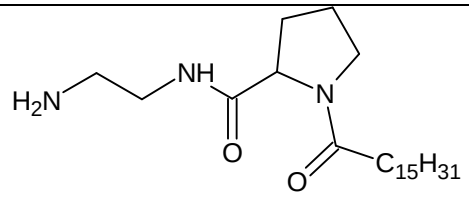
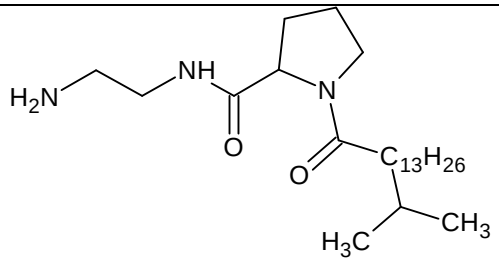
[000468] The median pharmacodynamic curves of glycemia expressed by the glucose difference with respect to the basal level are represented in Figure 1. This figure represents the post-injection time on the abscissa and the glucose level as percentage on the ordinate.

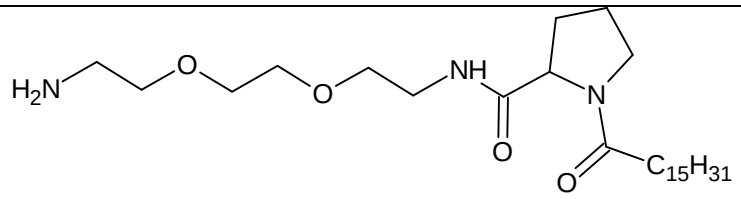
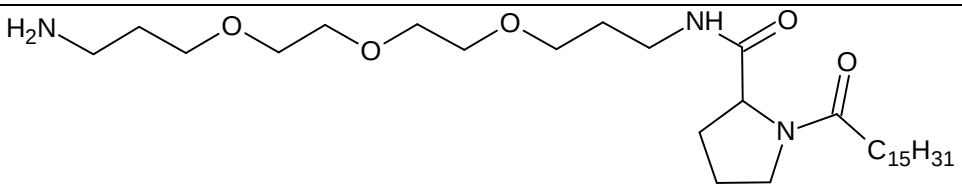
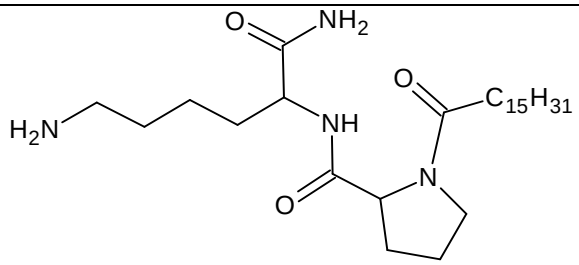
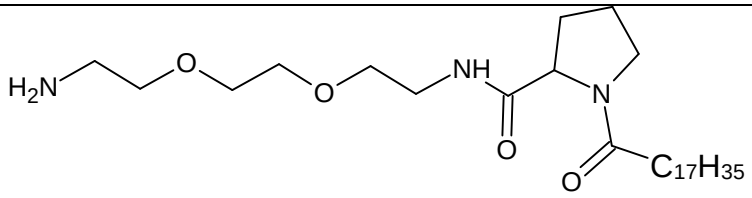
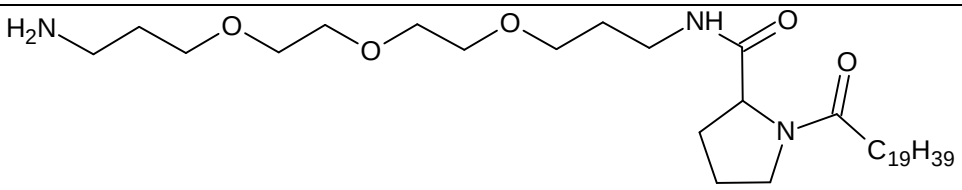
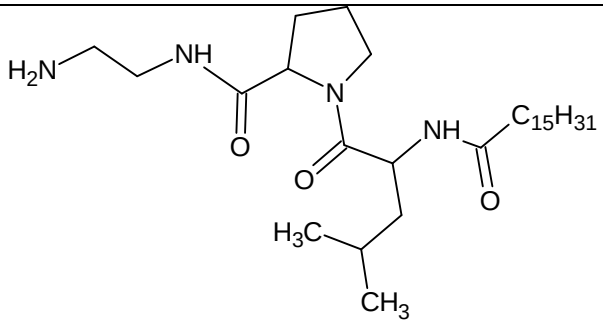
[000469] The curve representing the results obtained with the composition of Example CB1e is represented by empty squares, and the curve representing the results of the composition of glucagen® is represented by filled circles.

Part A

AA: Synthesis of the hydrophobic molecules in which p = 1

[000470] The hydrophobic radicals are represented in the following table by the corresponding hydrophobic molecule before grafting onto the co-polyamino acid.

No.	Structure of the hydrophobic molecule before grafting onto the co-polyamino acid
AA1	
AA2	

AA3	
AA4	
AA5	
AA6	
AA7	
AA8	

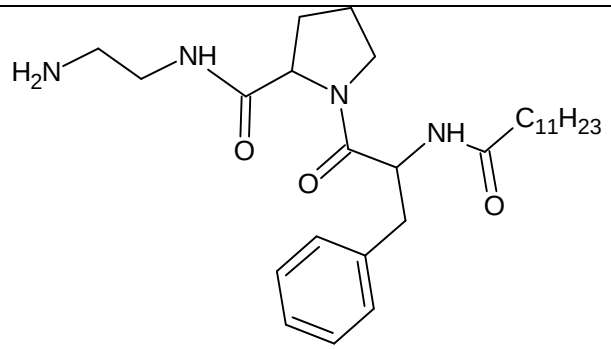
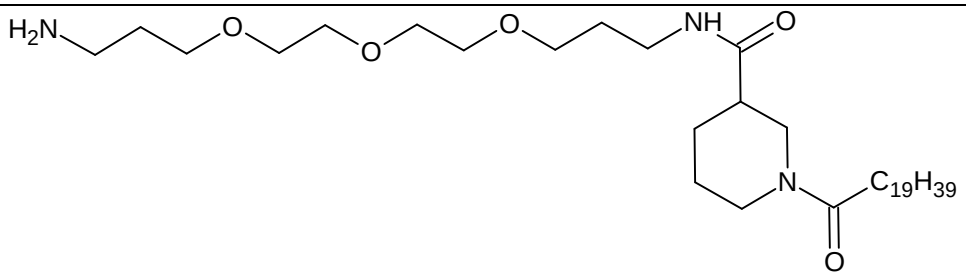
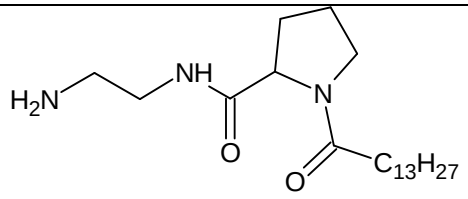
AA9	
AA10	
AA12	

Table 1A: list and structures of the hydrophobic molecules synthesized according to the invention.

Example AA1: molecule AA1

Molecule A1: product obtained by the reaction between palmitoyl chloride and L-proline.

[000471] A solution of palmitoyl chloride (23.0 g, 83.7 mmol) in acetone (167 mL) is added dropwise within 90 minutes to a solution of L-proline (10.6 g, 92.1 mmol) in 1 N aqueous sodium hydroxide (230 mL; 230 mmol). After 14 h of stirring at room temperature, the heterogeneous mixture is cooled to 0 °C, then filtered through a sintered filter to yield a white solid which is washed with water (2 x 100 mL), then diisopropyl ether (100 mL). The solid is dried at reduced pressure. The solid is then dissolved at reflux in 200 mL of water, then 8 mL of 37% hydrochloric acid solution are added until obtaining pH = 1. The opalescent reaction

mixture is then cooled to 0 °C. The precipitate obtained is filtered through a sintered filter, then washed with water (5 x 50mL) until filtrates of physiological pH from 6.0 to 8.0 are obtained, to be dried subsequently in an oven at 50 °C under vacuum overnight. The product is purified by recrystallization in diisopropyl ether. A white solid is obtained.

Yield: 22.7 g (77%).

^{1}H NMR ($CDCl_3$, ppm): 0.88 (3H); 1.19-1.45 (24H); 1.58-1.74 (2H); 1.88-2.14 (3H); 2.15-2.54 (3H); 3.47 (1H); 3.58 (1H); 4.41 (0.1H); 4.61 (0.9H) 6.60-8.60 (1H).

Molecule A2: product obtained by reaction between molecule A1 and Boc-ethylenediamine.

[000472] *N*,*N*-diisopropylethylamine (DIPEA) (68.8 g, 532.3 mmol), 1-hydroxybenzotriaolze (HOBt) (37.1 g, 274.6 mmol), then N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (EDC) (53.1 g, 277.0 mmol) are added successively and at room temperature to a solution of molecule A1 (75.1 g, 212.4 mmol) in 1500 mL of chloroform. After 15 minutes of stirring at room temperature, a solution of Boc-ethylenediamine (Boc-ethylenediamine) (37.6 g, 234.7 mmol) in 35 mL of chloroform is added. After 18 h of stirring at room temperature, a 0.1 N HCl solution (2.1 L), then a saturated NaCl solution (1 L) are added. The phases are separated, then the organic phase is washed successively with a 0.1 N HCl/saturated NaCl solution (2.1 L/1 L), a saturated NaCl solution (2 L), a saturated NaHCO3 solution (2 L), then a saturated NaCl solution (2 L). The organic phase is dried over anhydrous sodium sulfate, filtered, then concentrated at reduced pressure. The solid obtained is purified by triturations in diisopropyl ether (3 x 400 mL), to yield a solid after drying under vacuum at 40 °C.

Yield: 90.4 g (86%).

^{1}H NMR ($CDCl_3$, ppm): 0.88 (3H); 1.20-1.37 (24H); 1.44 (9H); 1.54-1.70 (2H); 1.79-1.92 (1H); 1.92-2.04 (1H); 2.03-2.17 (1H); 2.17-2.44 (3H); 3.14-3.36 (4H); 3.43 (1H); 3.56 (1H); 4.29 (0.1 H); 4.51 (0.9 H); 4.82 (0.1H); 5.02 (0.9H); 6.84 (0.1H); 7.22 (0.9H).

Molecule AA1

[000473] A 4 M hydrochloric acid solution in dioxane (100 mL, 400 mmol) is added dropwise at 0 °C to a solution of molecule A2 (20.1 g, 40.5 mmol) in 330 mL of dichloromethane. After 3 h 30 of stirring at room temperature, the solution is concentrated at reduced pressure. The residue is purified by flash chromatography (methanol, dichloromethane) to yield a white solid of molecule AA1 as a hydrochloride salt.

Yield: 16.3 g (93%).

^{1}H NMR ($CDCl_3$, ppm): 0.88 (3H); 1.07-1.40 (24H); 1.49-1.63 (2H); 1.77-2.18 (4H); 2.18-2.45 (2H); 3.14-3.32 (2H); 3.42-3.63 (2H); 3.63-3.84 (2H); 4.37 (0.1H); 4.48 (0.9H); 6.81-8.81 (4H).

LC/MS (ESI): 396.5; (calculated ($[M+H]^+$): 396.4).

Example AA2: molecule AA2

Molecule A3: 15-methylhexadecan-1-ol.

[000474] Magnesium (9.46 g, 389 mmol) in the form of chips is introduced into a three-neck flask under argon. The magnesium is covered with anhydrous THF (40 mL), and a few drops of 1-bromo-3-methylbutane are added at room temperature to initiate the reaction. After the observation of an exothermic reaction and slight turbidity of the medium, the rest of the 1-bromo-3-methylbutane (53.87 g, 357 mmol) is added dropwise within 90 min, while the temperature of the medium remains stable from 50 to 60 °C. The reaction medium is then heated at 70 °C for 2 h.

[000475] A solution of 12-bromo-1-dodecanol (43 g, 162.1 mmol) in THF (60 mL) is added dropwise to a solution of CuCl (482 mg, 4.86 mmol) dissolved in NMP (62 mL) at 0 °C in a three-neck flask are argon. The solution of extemporaneously prepared hot organic magnesium solution is then added dropwise to this solution in a manner so as to maintain the temperature of the medium below 20 °C. The mixture is then stirred at room temperature for 16 h. The medium is cooled to 0 °C and the reaction is stopped by addition of a 1N aqueous HCl solution until the pH is 1, and the medium is extracted with ethyl acetate. After washing of the organic phase with a saturated NaCl solution and drying over Na_2SO_4, the solution is filtered and concentrated under vacuum to yield an oil. After purification by DCVC on a silica gel (cyclohexane, ethyl acetate), an oil which crystallizes at room temperature is obtained.

Yield: 32.8 g (74%)

^{1}H NMR ($CDCl_3$, ppm): 0.87 (6H); 1.14 (2H); 1.20-1.35 (22H); 1.50-1.55 (3H); 3.64 (2H).

Molecule A4: 15-methylhexadecanoic acid.

[000476] Potassium permanganate (38.2 g, 241.5 mmol) is added in small portions to a solution of molecule A3 (20.65 g, 80.5 mmol) and tetrabutylammonium bromide (14.02 g, 42.5 mmol) in a mixture of acetic acid/dichloroethane/water (124/400/320 mL) at room temperature. After stirring at reflux for 5 h and return to room temperature, the medium is acidified at pH 1 by gradual addition of 5N HCl. Na_2SO_3 (44.6 g, 354.3 mmol) is then added gradually until discoloration of the medium. The aqueous phase is extracted with dichloromethane, and the combined organic phases are dried over Na_2SO_4, filtered and concentrated under vacuum. After purification by chromatography on silica gel (cyclohexane, ethyl acetate, acetic acid), a white solid is obtained.

Yield: 19.1 g (quantitative)

^{1}H NMR ($CDCl_3$, ppm): 0.87 (6H); 1.14 (2H); 1.22-1.38 (20H); 1.51 (1H); 1.63 (2H); 2.35 (2H).

Molecule A5: product obtained by reaction between molecule A4 and L-proline.

[000477] Dicyclohexyl carbodiimide (DCC) (8.01 g, 38.8 mmol) and N-hydroxysuccinimide (NHS) (4.47 g, 38.8 mmol) are added successively to a solution of molecule A4 (10 g, 37 mmol) in THF (360 mL) at 0 °C. After 17 h of stirring at room temperature, the medium is cooled to 0 °C for 20 min, filtered through a sintered filter. L-Proline (4 g, 37.7 mmol), trimethylamine (34 mL) and water (30 mL) are added to the filtrate. After stirring at room temperature for 20 h, the medium is treated with a 1N aqueous HCl solution until the pH is 1. The aqueous phase is extracted with dichloromethane (2 x 125 ml). The combined organic phases are washed with a 1N aqueous HCl solution (2 x 100 ml), water (100 mL), then a saturated aqueous NaCl solution (100 mL). After drying over Na_2SO_4, the organic phase is filtered, concentrated under vacuum, and the residue is purified by chromatography on silica gel (cyclohexane, ethyl acetate, acetic acid).

Yield: 9.2 g (72%)

^{1}H NMR ($CDCl_3$, ppm): 0.86 (6H); 1.14 (2H); 1.22-1.38 (20H); 1.50 (1H); 1.67 (2H); 1.95-2.10 (3H); 2.34 (2H); 2.49 (1H); 3.47 (1H); 3.56 (1H); 4.61 (1H).

LC/MS (ESI): 368.3; (calculated ($[M+H]^+$): 368.6).

Molecule A6: product obtained by reaction between molecule A5 and Boc-ethylenediamine.

[000478] Triethylamine (TEA) (5.23 mL) and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) at room temperature are added to a solution of molecule A5 (9.22 g, 25.08 mmol) in a mixture of THF/DMF (200/50 mL). After 10 min of stirring, Boc-ethylenediamine (4.42 g, 27.6 mmol) is added. After stirring at room temperature

for 17 h, the mixture is diluted with water (300 mL) at 0 °C and cold stirred for 20 min. The precipitate formed is filtered through a sintered filter, and the filtrate is extracted with ethyl acetate. The combined organic phases are washed with a saturated solution of $NaHCO_3$, washed over Na_2SO_4, filtered, concentrated under vacuum, and the residue is purified by flash chromatography (ethyl acetate, methanol).

Yield: 6.9 g (54%)

^1H NMR ($CDCl_3$, ppm): 0.86 (6H); 1.15 (2H); 1.22-1.38 (20H); 1.43 (9H); 1.50 (1H); 1.64 (4H); 1.85 (1H); 1.95 (1H); 2.10 (1H); 2.31 (2H); 3.20-3.35 (3H); 3.45 (1H); 3.56 (1H); 4.51 (1H); 5.05 (1H); 7.24 (1H).

LC/MS (ESI): 510.6; (calculated ($[M+H]^+$): 510.8).

Molecule AA2

[000479] A 4N HCl solution in dioxane (13 mL) is added to a solution of molecule A6 (5.3 g, 10.40 mmol) in dichloromethane (50 mL) at 0 °C. After 5 h of stirring at 0 °C, the medium is concentrated under vacuum, taken up in water and lyophilized to yield a white solid of molecule AA2 as a hydrochloride salt.

Yield: 4.6 g (99%)

^1H NMR (D_2O, ppm): 0.91 (6H); 1.22 (2H); 1.22-1.50 (20H); 1.63 (3H); 1.98 (1H); 2.10 (2H); 2.26 (1H); 2.39 (1H); 2.43 (1H); 3.22 (2H); 3.45-3.60 (3H); 3.78 (1H); 4.42 (1H).

LC/MS (ESI): 410.4; (calculated ($[M+H]^+$): 410.7).

Example AA3: molecule AA3

Molecule A7: product obtained by the reaction between molecule A1 and Boc-tri(ethylene glycol)diamine.

[000480] By a method similar to the one used for the preparation of molecule A2, applied to molecule A1 (4.0 g, 11.3 mmol) and to Boc-tri(ethylene glycol)diamine (3.1 g, 12.4 mmol), a colorless oil is obtained after purification by flash chromatography (methanol, toluene).

Yield: 5.5 g (84%).

^{1}H NMR ($CDCl_3$, ppm): 0.88 (3H); 1.09-1.39 (24H); 1.44 (9H); 1.64 (2H); 1.79-2.01 (2H); 2.06-2.43 (4H); 3.23-3.68 (14H); 4.33 (0.2H); 4.56 (0.8H); 5.25 (1H); 6.49 (0.2H); 7.13-7.50 (0.8H)

Molecule AA3

[000481] By a method similar to the one used for the preparation of molecule AA1, applied to molecule A7 (5.5 g, 9.4 mmol), a white solid of molecule AA3 as a hydrochloride salt is obtained after purification by flash chromatography (methanol, dichloromethane).

Yield: 4.3 g (92%).

^{1}H NMR (DMSO-d6, ppm): 0.85 (3H); 1.08-1.40 (24H); 1.40-1.52 (2H); 1.71-2.02 (4H); 2.02-2.31 (2H); 2.90-2.98 (2H); 3.15-3.47 (5H); 3.50-3.66 (7H); 4.24 (0.6H); 4.32 (0.4H); 7.83 (0.6H); 7.95 (3H); 8.17 (0.4H).

LC/MS (ESI): 484.6; (calculated ($[M+H]^+$): 484.4).

Example AA4: molecule AA4

Molecule A8: product obtained by the reaction between molecule A1 and Boc-1-amino-4,7,10-trioxa-13-tridecaneamine.

[000482] By a method similar to the one used for the preparation of molecule A2, applied to molecule A1 (4.5 g, 12.7 mmol) and to Boc-1-amino-4,7,10-trioxa-13-tridecaneamine (4.5 g, 14.0 mmol), a yellow oil is obtained after purification by flash chromatography (methanol, dichloromethane).

Yield: 7.7 g (92%).

^{1}H NMR ($CDCl_3$, ppm): 0.88 (3H); 1.22-1.37 (24H); 1.44 (9H); 1.59-1.67 (2H); 1.67-2.00 (6H); 2.06-2.45 (4H); 3.18-3.76 (18H); 4.28 (0.2H); 4.52 (0.8H); 4.69-5.04 (1H); 6.77 (0.2H); 7.20 (0.8H).

Molecule AA4

[000483] By a method similar to the one used for the preparation of molecule AA1, applied to molecule A8 (7.7 g, 11.8 mmol), a yellow oil is obtained after purification by flash chromatography (methanol, dichloromethane). Coevaporation with diisopropyl ether makes it possible to obtain the molecule AA4 as a hydrochloride salt in the form of a white solid which is dried under vacuum at 50 °C.

Yield: 5.4 g (76%).

^{1}H NMR ($CDCl_3$, ppm): 0.88 (3H); 1.08-1.40 (24H); 1.49-1.65 (2H); 1.76-2.39 (10H); 3.07-3.28 (3H); 3.34-3.80 (15H); 4.34 (0.05H); 4.64 (0.95H); 7.35 (0.05H); 7.66-8.58 (3.95H).

LC/MS (ESI): 556.7; (calculated ($[M+H]^+$): 556.5).

Example AA5: molecule AA5

[000484] Molecule A9: product obtained by reaction between molecule A1 and N-Boc-L-lysine methyl ester.

[000485] By a method similar to the one used for the preparation of molecule A2, applied to molecule A1 (4 g, 11.3 mmol) and to N-Boc-L-lysine methyl ester (3.2 g, 12.4 mmol), a colorless oil is obtained after purification by flash chromatography (methanol, dichloromethane).

Yield: 4.9 g (73%).

^{1}H NMR ($CDCl_3$, ppm): 0.88 (3H); 0.99-1.54 (37H); 1.54-1.75 (3H); 1.75-2.04 (3H); 2.04-2.41 (4H); 2.94-3.19 (2H); 3.19-3.81 (5H); 4.28-4.64 (2H); 4.94 (1H); 6.45 (0.1H); 7.36 (0.9H).

LC/MS (ESI): 596.7; (calculated ($[M+H]^+$): 596.5).

Molecule A10: product obtained by treatment of molecule A9 with ammonia.

[000486] 320 mL of a 7N ammonia solution in methanol are added to a suspension of molecule A9 (4.9 g, 8.2 mmol) in 10 mL of methanol. After 19 h of stirring at room temperature in closed atmosphere, an additional 100 mL of ammonia solution are added. After 24 h of stirring at room temperature in closed atmosphere, the reaction medium is concentrated at reduced pressure. The residue is purified by trituration in diisopropyl ether at reflux (100 mL) to yield a white solid which is dried under vacuum at 50 °C.

Yield: 4.1 g (85%).

^{1}H NMR ($CDCl_3$, ppm): 0.88 (3H); 1.06-1.57 (37H); 1.57-1.79 (3H); 1.88-2.41 (7H); 3.09 (2H); 3.49 (1H); 3.62 (1H); 4.34 (1H); 4.51 (1H); 4.69-4.81 (1H); 5.43 (0.95H); 5.57 (0.05H); 6.25 (0.05H); 6.52 (0.95H); 6.83 (0.05H); 7.11 (0.95H).

Molecule AA5

[000487] By a method similar to the one used for the preparation of molecule AA1, applied to molecule A10 (388 mg, 0.67 mmol), a white solid of molecule AA5 as a hydrochloride salt is obtained after purification by trituration in diisopropyl ether.

Yield: 292 mg (85%).

^{1}H NMR (DMSO-d6, ppm): 0.85 (3H); 1.06-2.34 (38H); 2.61-2.81 (2H); 3.29-3.68 (2H); 4.05-4.17 (1.7H); 4.42 (0.3H); 7.00 (1H); 7.16 (0.7H); 7.43 (0.3H); 7.73-8.04 (3.7H); 8.16 (0.3H).

LC/MS (ESI): 481.6; (calculated ($[M+H]^+$): 481.4).

Example AA6: molecule AA6

Molecule A11: product obtained by the reaction between stearoyl chloride and L-proline.

[000488] By a method similar to the one used for the preparation of molecule A1, applied to L-proline (5.0 g, 43.4 mmol) and to stearoyl chloride (12.0 g, 39.6 mmol), a white solid is obtained after purification by flash chromatography (methanol, dichloromethane).

Yield: 5.37 g (36%)

^{1}H NMR ($CDCl_3$, ppm): 0.88 (3H); 1.26-1.37 (28H); 1.64-1.70 (2H); 1.88-2.10 (3H); 2.36 (2H); 2.54-2.58 (1H).; 3.46 (1H); 3.56 (1H); 4.62 (1H).

LC/MS (ESI): 382.6; (calculated ($[M+H]^+$): 382.3).

Molecule A12: product obtained by reaction between molecule A11 and Boc-tri(ethyleneglycol)diamine.

[000489] By a method similar to the one used for the preparation of molecule A6, applied to molecule A11 (33.81 g, 88.6 mmol) and to Boc-tri(ethylene glycol)diamine (26.4 g, 106.3 mmol) in THF using DIPEA instead of TEA, a white solid is obtained after purification by flash chromatography (ethyl acetate, methanol).

Yield: 43.3 g (80%)

^{1}H NMR ($CDCl_3$, ppm): 0.87 (3H); 1.24 (30H); 1.43 (9H); 1.61 (2H); 1.82 (1H); 1.96 (1H); 2.25-2.45 (2H); 3.25-3.65 (14H); 4.30 (0.15H); 4.53 (0.85H); 5.25 (1H); 6.43 (0.15H); 7.25 (0.85H).

LC/MS (ESI): 612.6; (calculated ($[M+H]^+$): 612.9).

Molecule AA6

[000490] By a method similar to the one used for the preparation of molecule AA2, applied to molecule A12 (43 g, 70.3 mmol), the residue obtained after concentration under vacuum is triturated in acetonitrile. The suspension is filtered, and the solid is washed with acetonitrile, then

acetone. After drying under vacuum, a white solid of molecule AA6 as a hydrochloride salt is obtained.

Yield: 31.2 g (81%)

^{1}H NMR (DMSO-d_6, ppm): 0.85 (3H); 1.23 (28H); 1.45 (2H); 1.70-2.05 (4H); 2.13 (1H); 2.24 (1H); 2.95 (2H); 3.10-3.25 (2H); 3.30-3.65 (10H); 4.20-4.45 (1H); 7.85-8.25 (4H).

LC/MS (ESI): 512.4; (calculated ($[M+H]^+$): 512.8).

Example AA7: molecule AA7

Molecule A13: product obtained by reaction between arachidonic acid and L-proline.

[000491] By a method similar to the one used for the preparation of molecule A5, applied to arachidonic acid (15.51 g, 49.63 mmol) and to L-proline (6 g, 52.11 mmol) using DIPEA instead of TEA, a white solid is obtained after purification by column chromatography on silica gel (cyclohexane, ethyl acetate, acetic acid).

Yield: 12.9 g (63%)

^{1}H NMR ($CDCl_3$, ppm): 0.88 (3H); 1.28 (34H); 1.66 (2H); 1.95-2.15 (2H); 2.34 (2H); 2.45 (1H); 3.47 (1H); 3.56 (1H); 4.60 (1H).

LC/MS (ESI): 410.4; (calculated ($[M+H]^+$): 410.6).

Molecule A14: product obtained by the reaction between molecule A13 and Boc-1-amino-4,7,10-trioxa-13-tridecane.

[000492] By a method similar to the one used for the preparation of molecule A12, applied to molecule A13 (10.96 g, 26.75 mmol) and to Boc-1-amino-4,7,10-trioxa-13-tridecane (10.29 g, 32.11 mmol), a solid is obtained after purification by column chromatography on silica gel (cyclohexane, ethyl acetate, methanol).

Yield: 14.2 g (75%)

^{1}H NMR ($CDCl_3$, ppm): 0.88 (3H); 1.24 (32H); 1.43 (9H); 1.57-2.00 (8H); 2.10-2.45 (4H); 3.20-3.75 (18H); 4.30 (0.20H); 4.55 (0.80H); 5.03 (1H); 6.75 (0.20H); 7.20 (0.80H).

LC/MS (ESI): 712.8; (calculated ($[M+H]^+$): 713.1).

Molecule AA7

[000493] After a method similar to the one used for the preparation of molecule AA2, applied to molecule A14 (14.25 g, 20.01 mmol), the residue obtained after concentration under vacuum of the reaction medium is dissolved in methanol and evaporated at reduced pressure, the operation being repeated 4 times to yield a white solid of molecule AA7 as a hydrochloride salt.

Yield: 12.7 g (98%)

^{1}H NMR (DMSO-d_6, ppm): 0.85 (3H); 1.23 (32H); 1.45 (2H); 1.64 (2H); 1.70-2.05 (6H); 2.10-2.30 (2H); 2.82 (2H); 3.08 (2H); 3.30-3.60 (14H); 4.15-4.30 (1H); 7.73-8.13 (4H).

LC/MS (ESI): 612.7; (calculated ($[M+H]^+$): 612.9).

Example AA8: molecule AA8

Molecule A15: product obtained by the reaction between L-leucine and palmitoyl chloride.

[000494] By a method similar to the one used for the preparation of molecule A1, applied to L-leucine (15.0 g, 114.4 mmol) and to palmitoyl chloride (34.5 g, 125 mmol), a white solid is obtained by trituration in diisopropyl ether.

Yield: 13.0 g (31%)

^{1}H NMR ($CDCl_3$, ppm): 0.88 (3H); 0.96 (6H); 1.16-1.35 (24H); 1.55-1.77 (5H); 2.23 (2H); 4.55-4.60 (1H); 5.88 (1H).

Molecule A16: product obtained by the reaction between molecule A15 and L-proline methyl ester

[000495] By a method similar to the one used for the preparation of molecule A2, applied to molecule A15 (6.00 g, 16.2 mmol) and to L-proline methyl ester (3.23 g, 19.5 mmol), a slightly yellow oil is obtained after purification by flash chromatography (methanol, dichloromethane).

Yield: 5.8 g (74%)

^{1}H NMR ($CDCl_3$, ppm): 0.83-1.00 (9H); 1.18-1.32 (24H); 1.40-1.73 (5H); 1.84-2.33 (6H); 3.47-3.89 (2H); 3.70 (1.14H); 3.71 (1.21H); 3.74 (0.53H); 3.76 (0.12H); 4.40-4.56 (1H); 4.63-4.67 (0.04H); 4.84 (0.38); 4.90 (0.40); 5.06 (0.18); 5.99 (0.18H); 6.08-6.21 (0.82).

LC/MS (ESI): 481.6; (calculated ($[M+H]^+$): 481.4).

Molecule A17: product obtained by saponification of the methyl ester of molecule A16.

[000496] 1N sodium hydroxide (13.5 mL, 13.5 mmol) is added to a solution of molecule A16 (5.8 g, 12.06 mmol) in 30 mL of methanol. After 20 h of stirring at room temperature, the solution is diluted with water, then acidified with 20 mL of 1 N hydrochloric acid at 0 °C. The precipitate is filtered, then rinsed with water (50 mL), before it being solubilized in 50 mL of dichloromethane. The organic phase is dried over Na2SO4, filtered, then concentrated at reduced pressure to yield a colorless oil.

[000497] Yield: 4.5 g (80%)

^{1}H NMR ($CDCl_3$, ppm): 0.85-0.99 (9H); 1.14-1.41 (24H); 1.43-1.72 (5H); 1.87-2.47 (7H); 3.48-3.55 (0.6H); 3.56-3.62 (0.4H); 3.83-3.90 (0.4H); 3.90-3.96 (0.6H); 4.52-4.56 (0.6H); 4.56-4.59 (0.4H); 4.80-4.86 (0.4H); 4.86-4.91 (0.6H); 6.05 (0.4H); 6.11 (0.6H).

LC/MS (ESI): 467.6; (calculated ($[M+H]^+$): 467.4).

Molecule A18: product obtained by the reaction between Boc-ethylenediamine and molecule A17.

[000498] By a method similar to the one used for the preparation of molecule A2, applied to molecule A17 (4.5 g, 9.64 mmol) and to Boc-ethylenediamine (1.70 g, 10.61 mmol), a colorless oil is obtained after purification by flash chromatography (methanol, dichloromethane).

Yield: 2.0 g (34%)

^{1}H NMR ($CDCl_3$, ppm): 0.83-0.99 (9H); 1.19-1.32 (24H); 1.44 (9H); 1.48-2.37 (14H); 3.09-3.99 (4H); 4.28-5.01 (2H); 5.64-6.04 (1H); 6.87-7.06 (1H).

LC/MS (ESI): 609.7; (calculated ($[M+H]^+$): 609.5).

Molecule AA8

[000499] By a method similar to the one used for the preparation of molecule AA1, applied to molecule A18 (2 g, 3.28 mmol), a solid of molecule AA8 as a hydrochloride salt is obtained after purification by flash chromatography (methanol, dichloromethane).

Yield: 1.5 g (90%)

^{1}H NMR ($CDCl_3$, ppm): 0.83-1.00 (9H); 1.18-1.32 (24H); 1.37-1.77 (5H); 1.93-2.41 (6H); 3.07-3.97 (6H); 4.44-4.77 (2H); 7.66-8.21 (2H).

LC/MS (ESI): 509.6; (calculated ($[M+H]^+$): 509.4).

Example AA9: molecule AA9

Molecule A19: product obtained by the reaction between lauric acid and L-phenylalanine.

[000500] By a method similar to the one used for the preparation of molecule A5, applied to lauric acid (8.10 g, 40.45 mmol) and to L-phenylalanine (7 g, 42.38 mmol), a white solid is obtained.

Yield: 12.7 g (98%)

^{1}H NMR (DMSO-d_6, ppm): 0.86 (3H); 1.10-1.30 (16H); 1.36 (2H); 2.02 (2H); 2.82 (1H); 3.05 (1H); 4.42 (1H); 7.15-7.30 (5H); 8.05 (1H); 12.61 (1H).

LC/MS (ESI): 348.2; (calculated ($[M+H]^+$): 348.5).

Molecule A20: product obtained by the reaction between molecule A19 and the hydrochloride salt of the methyl ester of L-proline.

[000501] By a method similar to the one used for the preparation of molecule A6, applied to molecule A19 (9.98 g, 28.72 mmol) and to the hydrochloride salt of the methyl ester of L-proline (5.23 g, 31.59 mmol), a colorless oil is obtained after purification by column chromatography on silica gel (cyclohexane, ethyl acetate).

Yield: 5.75 g (44%)

^{1}H NMR ($CDCl_3$, ppm): 0.88 (3H); 1.10-1.30 (16H); 1.50-1.75 (3H); 1.80-2.02 (3H); 2.17 (2H); 2.65 (0.5H); 2.95 (1H); 3.05-3.20 (1.5H); 3.50-3.65 (1H); 3.75 (3H); 4.29 (0.5H); 4.46 (0.5H); 4.70 (0.1H); 4.95 (0.9H); 6.20-6.30 (1H); 7.15-7.30 (5H).

LC/MS (ESI): 459.2; (calculated ($[M+H]^+$): 459.6).

Molecule A21: product obtained by saponification of molecule A20.

[000502] Lithium hydroxide (LiOH) (600.49 mg, 25.07 mmol) is added to a solution of molecule A20 (5.75 g, 12.54 mmol) in a mixture of THF/methanol/water (40/40/40 mL) at 0 °C, then the mixture is stirred at room temperature for 20 h. After evaporation of the organic solvents in a vacuum, the aqueous phase is diluted in water, acidified with a 1 N aqueous HCl solution until the pH is 1. The product is then extracted with ethyl acetate. The combined organic phases

are washed with a saturated aqueous NaCl solution, dried over Na_2SO_4, filtered and concentrated at reduced pressure to yield a colorless oil.

Yield: 5.7 g (quantitative)

^{1}H NMR ($CDCl_3$, ppm): 0.88 (3H); 1.10-1.30 (16H); 1.50-1.80 (3H); 1.67-2.02 (2H); 2.20 (2H); 2.25 (0.4H); 2.60 (0.6H); 2.85-3.10 (2.6H); 3.55-3.65 (1.4H); 4.35 (0.6H); 4.55 (0.4H); 4.94 (1H); 6.28 (0.4H); 6.38 (0.6H); 7.20-7.30 (5H).

LC/MS (ESI): 445.2; (calculated ($[M+H]^+$): 445.6).

Molecule A22: product obtained by reaction between Boc-ethylenediamine and molecule A21.

[000503] By a method similar to the one used for the preparation of molecule A6, applied to molecule A21 (5.67 g, 12.75 mmol) and to Boc-ethylenediamine (2.25 g, 14.03 mmol), a colorless oil is obtained after purification by column chromatography on silica gel (dichloromethane, methanol).

Yield: 5.7 g (76%)

^{1}H NMR ($CDCl_3$, ppm): 0.88 (3H); 1.25 (16H); 1.43 (9H); 1.58 (2.6H); 1.75-1.95 (1.4H); 2.15-2.30 (3H); 2.64 (0.5H); 2.95-3.10 (2.5H); 3.20-3.40 (4H); 3.45 (0.5H); 3.55 (0.2H); 3.66 (1H); 4.44 (1H); 4.50 (0.2H); 4.60 (0.6H); 4.99 (0.7H); 5.54 (0.5H); 5.95 (0.2H); 6.17 (1H); 6.60 (0.5H); 7.07 (0.5H); 7.20-7.40 (5H).

LC/MS (ESI): 587.4; (calculated ($[M+H]^+$): 587.8).

Molecule AA9

[000504] After a method similar to the one used for the preparation of molecule AA2, applied to molecule A22 (5.66 g, 9.65 mmol), the residue obtained after concentration under

vacuum of the reaction medium is dissolved in methanol and evaporated at reduced pressure, the operation being repeated 4 times to yield a white foam of molecule AA9 as a hydrochloride salt.

Yield: 4.9 g (97%)

^{1}H NMR (DMSO-d_6, 120 °C, ppm): 0.89 (3H); 1.26 (16H); 1.43 (2H); 1.68 (0.6H); 1.75-2.00 (3H); 2.05-2.25 (2.4H); 2.82-3.05 (5H); 3.38 (2H); 3.50-3.70 (1.4H); 4.25 (0.6H); 4.63 (0.4H); 4.77 (0.6H); 7.25-7.50 (5H); 7.55-8.20 (4H).

LC/MS (ESI): 487.4; (calculated ($[M+H]^+$): 487.7).

Example AA10: molecule AA10

Molecule A23: product obtained by the reaction between nipecotic acid and arachidonic acid

By a method similar to the one used for the preparation of molecule A5, applied to arachidonic acid (2.30 g, 7.37 mmol) and to nipecotic acid (1.00 g, 7.74 mmol), a white solid is obtained after filtration of the aqueous phase acidified until the pH is 1, and washing of the solid with water, then dichloromethane.

Yield: 1.65 g (53%)

1H NMR ($CDCl_3$, ppm): 0.88 (3H); 1.07-1.88 (37H); 2.10 (1H); 2.28-2.45 (2H); 2.52 (1H); 2.91-3.17 (1.5H); 3.42 (0.5H); 3.72 (0.5H); 3.84 (0.5H); 4.08 (0.5H); 4.56 (0.5H).

LC/MS (ESI): 424.4; 848.0; (calculated ($[M+H]^+$): 424.4; ($[2M+H]^+$): 847.8).

Molecule A24: product obtained by the reaction between molecule A23 and Boc-1-amino-4,7,10-trioxa-13-tridecaneamine.

DIPEA (1.01 g, 7.79 mmol) and TBTU (1.31 g, 4.09 mmol) are added successively and at room temperature to a suspension of molecule A23 (1.65 g, 3.89 mmol) in 20 mL of THF. After 30

minutes of stirring, Boc-1-amino-4,7,10-trioxa-13-tridecaneamine (1.37 g, 4.28 mmol) is added, and the reaction medium is stirred at room temperature for 18 h. After evaporation of the solvent at reduced pressure, the residue is diluted with ethyl acetate (100 mL), the organic phase is washed successively with a saturated aqueous $NaHCO_3$ solution, a 1 N aqueous HCl solution, a saturated aqueous NaCl solution, dried over Na_2SO_4, filtered and concentrated at reduced pressure. A white solid is obtained after purification by flash chromatography (cyclohexane, ethyl acetate, methanol).

Yield: 1.97 g (70%)

^{1}H NMR ($CDCl_3$, ppm): 0.88 (3H); 1.15-2.70 (54H); 3.10-3.46 (6H); 3.46-3.71 (12.6H); 3.92 (0.4H); 4.17 (0.6H); 4.49 (0.4H); 4.80-5.16 (1H); 6.35-6.76 (1H).

LC/MS (ESI): 726.8; (calculated ($[M+H]^+$): 726.6).

Molecule AA10

By a method similar to the one used for the preparation of molecule AA1, applied to molecule A24 (1.97 g, 2.71 mmol), a white solid of molecule AA10 is obtained after evaporation of the solvent, trituration in acetone, filtration and washing with acetone, then drying at reduced pressure at 50 °C.

Yield: 1.66 g (92%)

^{1}H NMR (DMSO-d_6, ppm): 0.86 (3H); 1.09-1.90 (42H); 2.05-2.68 (5H); 2.45-2.68 (1H); 2.78-3.19 (6H); 3.36-3.44 (2H); 3.44-3.60 (10H); 3.69-3.87 (1H); 4.20 (0.4H); 4.35 (0.6H).

LC/MS (ESI): 626.7; (calculated ($[M+H]^+$): 626.5).

Example AA12: molecule AA12

Molecule A26: product obtained by the reaction between myristoyl chloride and L-proline (1646-22-CNI)

Myristoyl chloride (322 g, 1.30 mol) in solution in dichloromethane (1.63 L) is added slowly within 1 h to a solution of L-proline (300.40 g, 2.61 mol) in 2 N aqueous sodium hydroxide (1.63 L) at 0 °C. At the end of the addition, the temperature of the reaction medium is brought back to 20 °C within 2 h, then stirred for an additional 2 h. The mixture is cooled to 0 °C, then a 37% HCl solution (215 mL) is added within 15 minutes. The reaction medium is stirred for 10 min at 0 °C, then for 1 h from 0 °C to 20 °C. The organic phase is separated, washed with a 10% HCl solution (3 x 430 mL), a saturated aqueous NaCl solution (430 mL), dried over Na_2SO_4, filtered through cotton, then concentrated at reduced pressure. The residue is solubilized in heptane (315 mL), then pentane (1.6 L) is added under mechanical stirring. A white solid is obtained after filtration through a sintered filter and drying at reduced pressure.

Yield: 410.6 g (97%)

^{1}H NMR ($CDCl_3$, ppm): 0.88 (3H); 1.28 (20H); 1.70 (2H); 1.90-2.10 (3H); 2.36 (2H); 2.51 (1H); 3.47 (1H); 3.56 (1H); 4.61 (1H).

LC/MS (ESI): 326.4; 651.7; (calculated ($[M+H]^+$): 326.3; ($[2M+H]^+$): 651.6).

Molecule A27: product obtained by the reaction between molecule A26 and Boc-ethylenediamine.

HOBt (1.83 g, 11.98 mmol), then Boc-ethylenediamine (1.62 g, 10.14 mmol) are added successively to a solution of molecule A26 (3.00 g, 9.21 mmol) at room temperature in methyl-THF (50 mL), and the medium is cooled to 0 °C. EDC (2.29 g, 11.98 mmol) is added, then the mixture is stirred for 17 h between 0 °C and room temperature. The reaction medium is then

washed with a saturated aqueous NH_4Cl solution (50 mL), a saturated aqueous $NaHCO_3$ solution (50 mL), then a saturated aqueous NaCl solution (50 mL), dried over Na_2SO_4, filtered and concentrated at reduced pressure. A white solid is obtained after recrystallization in methanol.

Yield: 2.34 g (49%).

^{1}H NMR ($CDCl_3$, ppm): 0.88 (3H); 1.16-1.38 (20H); 1.44 (9H); 1.56-1.71 (2H); 1.78-2.45 (6H); 3.11-3.72 (6H); 4.30 (0.1H); 4.51 (0.9H); 4.87 (0.1H); 5.04 (0.9H); 6.87 (0.1H); 7.23 (0.9H).

LC/MS (ESI): 468.0; (calculated ($[M+H]^+$): 468.4).

Molecule AA12

By a method similar to the one used for the preparation of molecule AA1, applied to molecule A27 (2.34 g, 5.00 mmol), a white solid of molecule AA12 is obtained after evaporation of the solvent and triturations in diisopropyl ether.

Yield: 1.5 g (74%)

^{1}H NMR (MeOD-d4, ppm): 0.90 (3H); 1.21-1.43 (20H); 1.54-1.66 (2H); 1.85-2.28 (4H); 2.39 (2H); 3.00-3.17 (2H); 3.30-3.40 (1H); 3.43-3.71 (3H); 4.29 (0.94H); 4.48 (0.06H).

LC/MS (ESI): 368.2; (calculated ($[M+H]^+$): 368.3).

Example AA14: molecule AA14

Resin AA14-1: product obtained by the reaction between 4,7,10-trioxa-1,13-tridecanediamine and the resin 2-Cl-trityl chloride

[000505] DIPEA (8.64 mL, 49.60 mmol) is added to a solution of 4,7,10-trioxa-1,13-tridecanediamine (10.87 mL, 49.60 mmol) in dichloromethane (50 mL) at room temperature. This solution is poured onto the resin 2-Cl-trityl chloride which was washed beforehand with

dichloromethane (100-200 mesh, 1% DVB, 1.24 mmol/g) (4.00 g, 4.96 mmol) in a reactor adapted for peptide synthesis on a solid support. After 2 h of stirring at room temperature, HPLC grade methanol (0.8 mL/g resin, 3.2 mL) is added, and the mixture is stirred at room temperature for 15 min. The resin is filtered, washed successively with dichloromethane (3 x 50 mL), DMF (2 x 50 mL), dichloromethane (2 x 50 mL), isopropanol (1 x 50 mL) and dichloromethane (3 x 50 mL).

Resin AA14-2: product obtained by reaction between the resin AA14-1 and Fmoc-glycine.

[000506] DIPEA (5.18 mL, 29.76 mmol) is added to a suspension of Fmoc-glycine (4.42 g, 14.88 mmol) and 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide-hexafluorophosphate (HATU, 5.66 g, 14.88 mmol) in a mixture of DMF/dichloromethane 1:1 (60 mL) . After complete solubilization, the solution obtained is poured onto resin AA14-1. After 2 h of stirring at room temperature, resin is filtered, washed successively with DMF (3 x 60 mL), isopropanol (1 x 60 ml) and dichloromethane (3 x 60 mL).

[000507] Resin AA14-3: product obtained by reaction between resin AA14-2 and a mixture of DMF/piperidine 80:20. The resin AA14-2 is treated with a mixture of DMF/piperidine 80:20 (50 mL). After 30 minutes of stirring at room temperature, the resin is filtered, washed successively with DMF (3 x 50 mL), isopropanol (1 x 50 mL) and dichloromethane (3 x 50 mL).

Resin AA14-4: product obtained by the reaction between resin AA14-3 and Fmoc-proline.

[000508] By a method similar to the one used for resin AA14-2, applied to resin AA14-3 and Fmoc-proline (5.02 g, 14.88 mmol) in DMF (50 mL), resin AA14-4 is obtained.

Resin AA14-5: product obtained by reaction between resin AA14-4 and a mixture of DMF/piperidine 80:20.

[000509] By a method similar to the one used for resin AA14-3, applied to resin AA14-4 and a mixture of DMF/piperidine 80:20 (50 mL), resin AA14-5 is obtained.

Resin AA14-6: product obtained by reaction between resin AA14-5 and palmitic acid.

[000510] By a method similar to the one used for the preparation of resin AA14-4, applied to resin AA14-5 and to palmitic acid (3.82 g, 14.88 mmol), resin AA14-6 is obtained.

[000511] **Molecule AA14 (1843-04-CBU)** The resin AA14-6 is treated with a mixture of TFA/dichloromethane 1:1 (50 mL). After 30 minutes of stirring at room temperature, the resin is filtered and washed with dichloromethane (3 x 50 mL). The solvents are evaporated under vacuum. Two coevaporations are then carried out on the residue with dichloromethane (50 mL), then diisopropyl ether (50 mL). The residue is solubilized in dichloromethane (50 mL), and the organic phase is washed with a 1 N aqueous NaOH solution (1 x 50 mL), then a saturated NaCl solution (2 x 50 mL). After drying over Na2SO4, the organic phase is filtered, concentrated under vacuum, and the residue is filtered by chromatography on silica gel (dichloromethane, methanol, NH4OH).

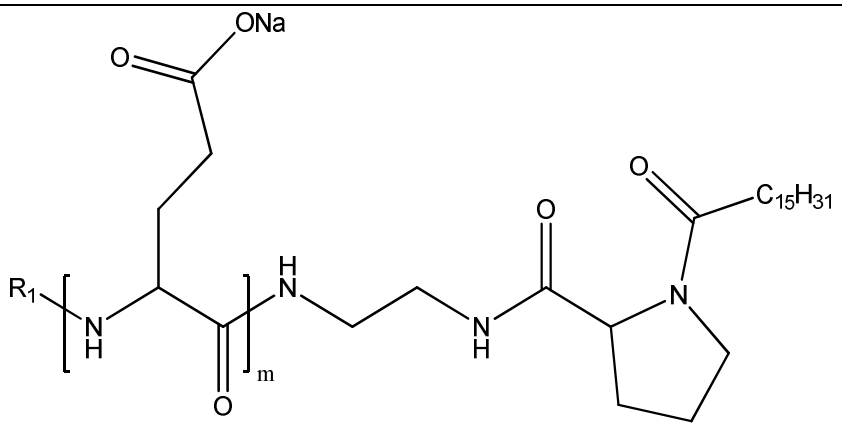
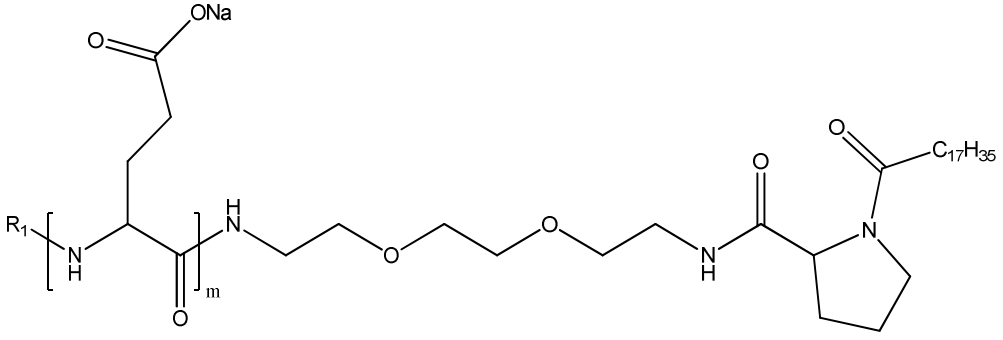
Yield: 1.65 g (54% global over 7 steps)

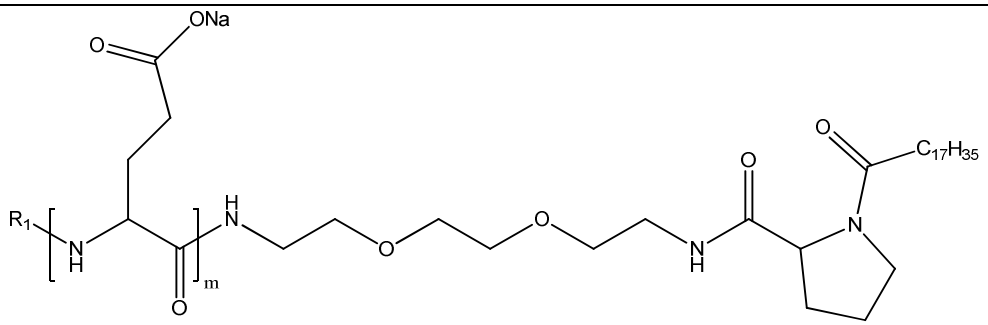
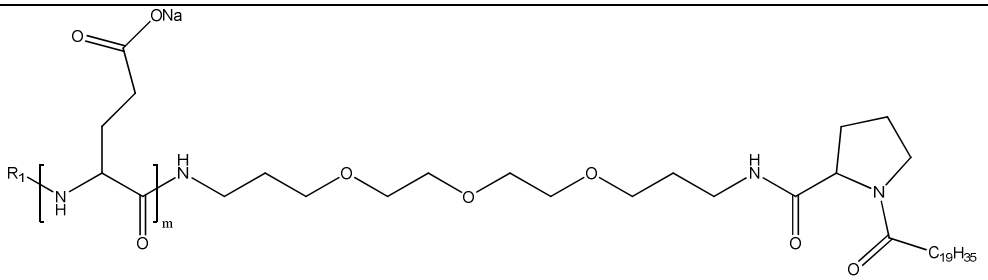
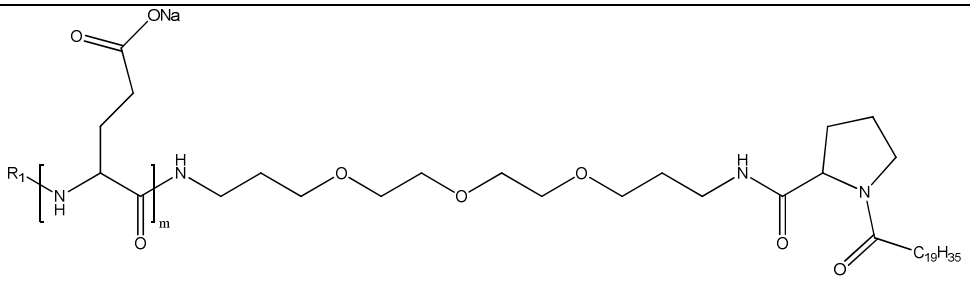
^{1}H NMR ($CDCl_3$, ppm): 0.88 (3H); 1.18-2.39 (38H); 2.79 (2H); 3.23-3.44 (2H); 3.47-3.69 (14H); 3.76 (0.92H); 3.82 (0.08H); 3.98 (0.08H); 4.03 (0.92H); 4.34 (0.08H); 4.39 (0.92H); 7.00-7.40 (2H).

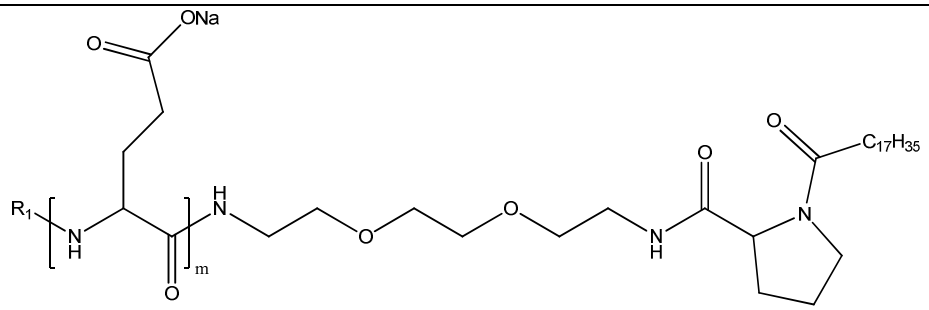
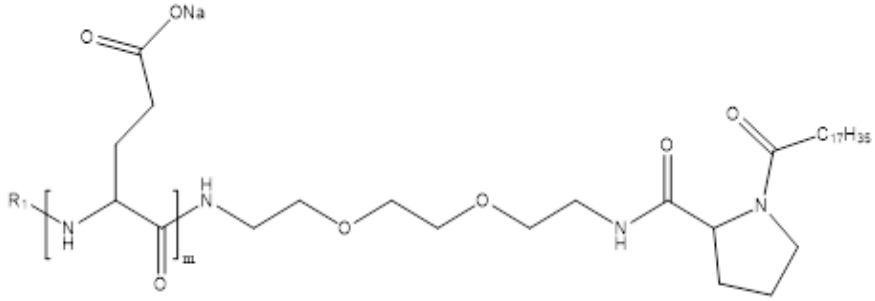
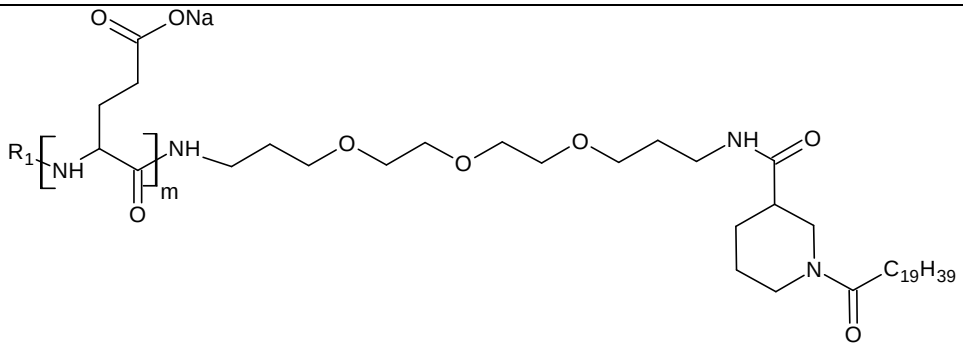
LC/MS (ESI): 613.7; (calculated ($[M+H]^+$): 613.5).

Table 1b

Defined co-polyamino acids of formula VII or VIIb:

Example No.	co-polyamino acids bearing carboxylates charges and hydrophobic radicals
AB14	 i = 0.04, DP (m) = 25 R_1 = H or pyroglutamate
AB15	

	i = 0.033, DP (m) = 30 R_1 = H or pyroglutamate
AB16	 i = 0.021, DP (m) = 48 R_1 = H or pyroglutamate
AB17	 i = 0.038, DP (m) = 26 R_1 = H or pyroglutamate
AB18	 i = 0.045, DP (m) = 22 R_1 = H or pyroglutamate

AB19	 i = 0.015, DP (m) = 65 R_1 = H or pyroglutamate
AB20	 i = 0.017, DP (m) = 60 R1=CH_3-CO-, H or pyroglutamate
AB21’	 i = 0.04, DP (m) = 25 R_1 = H or pyroglutamate

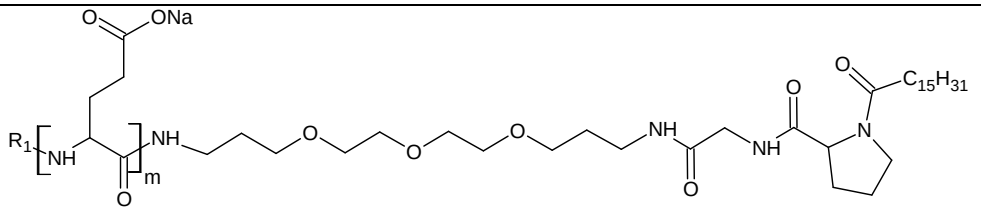
AB23	 i = 0.045, DP (m) = 22 R_1 = H or pyroglutamate

Table 1c: list of the co-polyamino acids synthesized according to the invention.

Part AB: synthesis of the co-polyamino acids

Example AB14: Co-polyamino acid AB14 - sodium poly-L-glutamate modified at one of its ends by molecule AA1 and having a number average molecular weight (Mn) of 3400 g/mol

[000512] The hydrochloride salt of molecule AA1 (2.03 g, 4.70 mmol), chloroform (5 mL), molecular sieve 4 Å (1.3 g) as well as Amberlite IRN 150 ion exchange resin (1.3 g) are introduced successively into an appropriate container. After 1 h of stirring on rollers, the medium is filtered and the resin is rinsed with chloroform. The mixture is evaporated, then co-evaporated with toluene. The residue is solubilized in anhydrous DMF (30 mL) to be used directly in the polymerization reaction.

[000513] γ-Benzyl-L-glutamate N-carboxyanhydride (25.59 g, 97.2 mmol) is placed under vacuum for 30 min in a round-bottom flask dried in the oven, then anhydrous DMF (140 mL) is introduced. The mixture is stirred under argon until the solubilization is complete, cooled to 4 °C, then the solution of molecule AA1 prepared as described above is introduced rapidly. The mixture is stirred between 4 °C and room temperature for 2 days, then heated at 65 °C for 2 h. The reaction mixture is then cooled to room temperature, then poured dropwise into diisopropyl

ether (1.7 L) under stirring. The white precipitate is recovered by filtration, washed two times with diisopropyl ether (140 mL), then dried under vacuum at 30 °C to obtain a white solid. The solid is diluted in TFA (160 mL), and then a 33% hydrobromic acid solution (HBr) in acetic acid (62 mL, 354 mmol) is added dropwise and at 0 °C. The solution is stirred for 2 h at room temperature, then poured dropwise onto a 1:1 (v/v) mixture of diisopropyl ether/water and under stirring (1.9 L). After 2 h of stirring, the heterogeneous mixture is allowed to rest overnight. The white precipitate is recovered by filtration, washed successively with a 1:1 (v/v) mixture of diisopropyl ether and water (280 mL), then with water (140 mL). The solid obtained is solubilized in water (530 mL) by adjusting the pH to 7 by addition of a 10 N aqueous sodium hydroxide solution. After solubilization, the theoretical concentration is adjusted to 20 g/L theoretical by addition of water until obtaining a final volume of 800 mL. The mixture is filtered through a 0.45µm filter, then purified by ultrafiltration against a 0.9% NaCl solution, then water until the conductimetry of the permeate is less than 50 µS/cm. The solution of co-polyamino acid is then concentrated to approximately 30 g/L theoretical and the pH is adjusted to 7.0. The aqueous solution is filtered through a 0.2-µm filter and stored at 4 °C.

Dry extract: 24.1 mg/g

DP (estimated by ^{1}H NMR) = 25 therefore i = 0.04

The calculated average molecular weight of the co-polyamino acid AB14 is 3378 g/mol.

HPLC-aqueous SEC (calibrant PEG): Mn = 3400 g/mol.

Example AB15: Co-polyamino acid AB15 - sodium poly-L-glutamate modified at one of its ends by molecule AA6 and having a number average molecular weight (Mn) of 4100 g/mol

[000514] By a method similar to the one used for the preparation of the co-polyamino acid AB14, applied to the hydrochloride salt of molecule AA6 (2.16 g, 3.94 mmol) and to 25.58 g

(97.2 mmol) of γ-benzyl-L-glutamate N-carboxyanhydride, a sodium poly-L-glutamate modified at one of its ends by molecule AA6 is obtained.

Dry extract: 45.5 mg/g

DP (estimated by ^{1}H NMR) = 30 therefore i = 0.033

The calculated average molecular weight of the co-polyamino acid AB15 is 5005 g/mol.

HPLC-aqueous SEC (calibrant PEG): Mn = 4100 g/mol.

Example AB16: Co-polyamino acid AB16 - sodium poly-L-glutamate modified at one of its ends by molecule AA6 and having a number average molecular weight (Mn) of 6500 g/mol

[000515] By a method similar to the one used for the preparation of the co-polyamino acid AB14, applied to the hydrochloride salt of molecule AA6 (2.39 g, 4.36 mmol) and to 50.0 g (189.9 mmol) of γ-benzyl-L-glutamate N-carboxyanhydride, a sodium poly-L-glutamate modified at one of its ends by molecule AA6 is obtained.

Dry extract: 28.5 mg/g

DP (estimated by ^{1}H NMR) = 48 therefore i = 0.021

The calculated average molecular weight of the co-polyamino acid AB16 is 7725 g/mol.

HPLC-aqueous SEC (calibrant PEG): Mn = 6500 g/mol.

Example AB17: Co-polyamino acid AB17 - sodium poly-L-glutamate modified at one of its ends by molecule AA7 and having a number average molecular weight (Mn) of 3500 g/mol

[000516] By a method similar to the one used for the preparation of the co-polyamino acid AB14, applied to the hydrochloride salt of molecule AA7 (2.80 g, 4.32 mmol) and to 25.0 g

(94.9 mmol) of γ-benzyl-L-glutamate N-carboxyanhydride, a sodium poly-L-glutamate modified at one of its ends by molecule AA7 is obtained.

Dry extract: 25.2 mg/g

DP (estimated by ^{1}H NMR) = 26 therefore i = 0.038

The calculated average molecular weight of the co-polyamino acid AB17 is 4500 g/mol.

HPLC-aqueous SEC (calibrant PEG): Mn = 3500 g/mol.

Example AB18: Co-polyamino acid AB18 - sodium poly-L-glutamate modified at one of its ends by molecule AA7 and having a number average molecular weight (Mn) of 3700 g/mol

[000517] A sodium poly-L-glutamate modified at one of its ends by molecule AA7 is obtained by polymerization of glutamic acid γ-methyl N-carboxyanhydride (25.0 g, 133.6 mmol) by using the hydrochloride salt of molecule AA7 (2.80 g, 4.32 mmol) as initiator and by carrying out a deprotection of the methyl esters using a 37% hydrochloric acid solution according to the method described in the patent application FR-A-2 801 226.

Dry extract: 44.3 mg/g

DP (estimated by ^{1}H NMR) = 22 therefore i = 0.045

The calculated average molecular weight of the co-polyamino acid AB18 is 3896 g/mol.

HPLC-aqueous SEC (calibrant PEG): Mn = 3700 g/mol.

Example AB19: Co-polyamino acid AB19 - sodium poly-L-glutamate modified at one of its ends by molecule AA6 and having a number average molecular weight (Mn) of 10500 g/mol

[000518] By a method similar to the one used for the preparation of the co-polyamino acid AB14, applied to the hydrochloride salt of molecule AA6 (1.64 g, 2.99 mmol) and to γ-benzyl-L-

glutamate N-carboxyanhydride (49.3 g, 187 mmol), a sodium poly-L-glutamate modified at one of its ends by molecule AA6 is obtained.

Dry extract: 23.4 mg/g

DP (estimated by ^{1}H NMR) = 65 therefore i = 0.015

The calculated average molecular weight of the co-polyamino acid AB19 is 10293 g/mol.

HPLC-aqueous SEC (calibrant PEG): Mn = 10500 g/mol.

Example AB20: Co-polyamino acid AB20 - sodium poly-L-glutamate capped at one of its ends by an acetyl group and modified at one of its ends by molecule AA6 and having a number average molecular weight (Mn) of 10400 g/mol

[000519] The hydrochloride salt of molecule AA6 (0.545 g, 1.00 mmol), chloroform (10 mL), molecular mesh 4 Å (3 g), as well as Amberlite IRN 150 ion exchange resin (3 g) are introduced successively into an appropriate container. After 1 h of stirring on rollers, the medium is filtered, and the resin is rinsed with chloroform. The mixture is evaporated, then coevaporated with toluene. The residue is solubilized in anhydrous DMF (10 mL) to be used directly in the polymerization reaction.

[000520] γ-Benzyl-L-glutamate N-carboxyanhydride (17.0 g, 64.6 mmol) is placed under vacuum for 30 min in a round-bottom flask dried beforehand in the oven, then anhydrous DMF (30 mL) is added. The mixture is stirred under argon until the solubilization is complete, cooled to 4 °C, then the solution of molecule AA6 prepared as described above is introduced rapidly. The mixture is stirred between 4 °C and room temperature for 2 days, then precipitated in diisopropyl ether (0.6 L). The precipitate is recovered by filtration, washed two times with diisopropyl ether (40 mL), then dried to yield a white solid which is dissolved in 80 mL of THF.

DIPEA (1.7 mL, 9.8 mmol), then acetic anhydride (0.9 mL, 9.5 mmol) are added successively to this solution. After one night of stirring at room temperature, the solution is poured slowly into diisopropyl ether (480 mL) for a duration of 30 min and under stirring. After 1 h of stirring, the precipitate is filtered, washed two times with diisopropyl ether (80 mL), then dried under vacuum at 30 °C to yield a poly(gamma-benzyl-L-glutamic) acid capped at one of its ends by an acetyl group and modified at the other one of its ends by molecule AA6 in the form of a white solid.

[000521] The solid is diluted in TFA (65 mL), and a solution of 33% hydrobromic acid solution (HBr) in acetic acid (45 mL, 257.0 mmol) is then added dropwise and at 4 °C. The solution is stirred for 2 h at room temperature, then poured dropwise onto a 1:1 (v/v) mixture of diisopropyl ether/water and under stirring (780 mL). After 2 h of stirring, the heterogeneous mixture is allowed to rest for one night. The white precipitate is recovered by filtration, washed successively with a 1:1 (v/v) mixture of diisopropyl ether and water (70 mL), then with water (70 mL). The solid obtained is solubilized in water (300 mL) by adjusting the pH to 7 by addition of a 10 N aqueous sodium hydroxide solution, then a 1 N aqueous sodium hydroxide solution. After solubilization, the theoretical concentration is adjusted to 20 g/L theoretical by addition of water until obtaining a final volume of 440 mL. The mixture is filtered through a 0.45-µm filter, then purified by ultrafiltration against a 0.9% NaCl solution, then water, until the conductimetry of the permeate is less than 50 µS/cm. The solution of co-polyamino acid is then concentrated to approximately 30 g/L theoretical and the pH is adjusted to 7. The aqueous solution is filtered through a 0.2-µm filter and stored at 4 °C.

Dry extract: 21.5 mg/g

DP (estimated by ^{1}H NMR) = 60 therefore i = 0.017

The calculated average molecular weight of the co-polyamino acid AB20 is 9619 g/mol.

HPLC-aqueous SEC (calibrant PEG): Mn = 10,400 g/mol.

Example AB21':

Co-polyamino acid AB21' - sodium poly-L-glutamate modified at one of its ends by molecule AA10 and having a number average molecular weight (Mn) of 3478 g/mol

[000522] By a method similar to the one used for the preparation of the co-polyamino acid AB14, applied to the hydrochloride salt of molecule AA10 (0.916 g, 1.38 mmol) and to γ-benzyl-L-glutamate N-carboxyanhydride (7.19 g, 27.3 mmol), a sodium poly-L-glutamate modified at one of its ends by molecule AA10 is obtained.

Dry extract: 14.8 mg/g

DP (estimated by ^{1}H NMR) = 25 therefore i = 0.04

The calculated average molecular weight of the co-polyamino acid AB21' is 4364 g/mol.

HPLC-aqueous SEC (calibrant PEG): Mn = 3478 g/mol.

Example AB23:

Co-polyamino acid AB23 - sodium poly-L-glutamate modified at one of its ends by molecule AA14 and having a number average molecular weight (Mn) of 3600 g/mol

[000523] By a method similar to the one used for the preparation of the co-polyamino acid AB14, applied to molecule AA14 in free amine form (0.820 g, 1.34 mmol) and to γ-benzyl-L-glutamate N-carboxyanhydride (7.75 g, 29.4 mmol), a sodium poly-L-glutamate modified at one of its ends by molecule AA14 is obtained.

Dry extract: 16.8 mg/g

DP (estimated by ^{1}H NMR) = 22 therefore i = 0.045

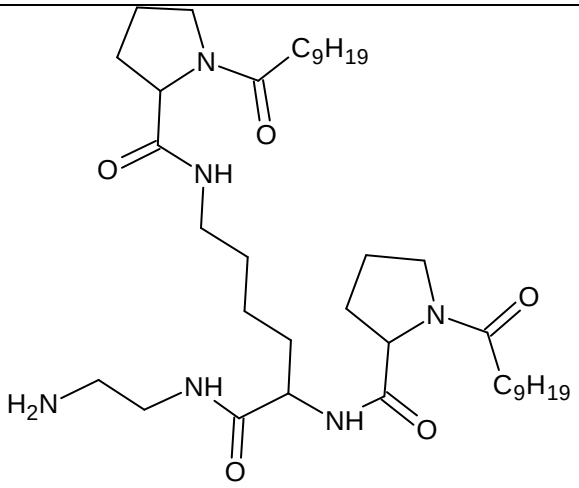
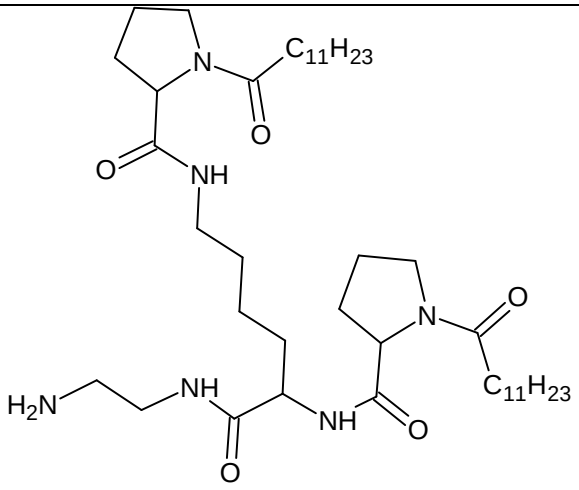
The calculated average molecular weight of the co-polyamino acid AB23 is 3897 g/mol.

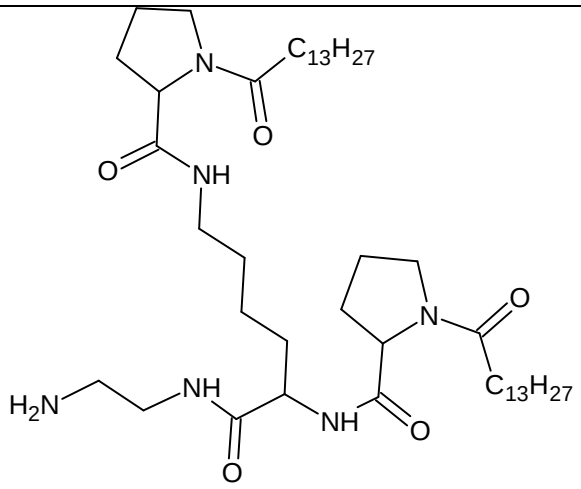
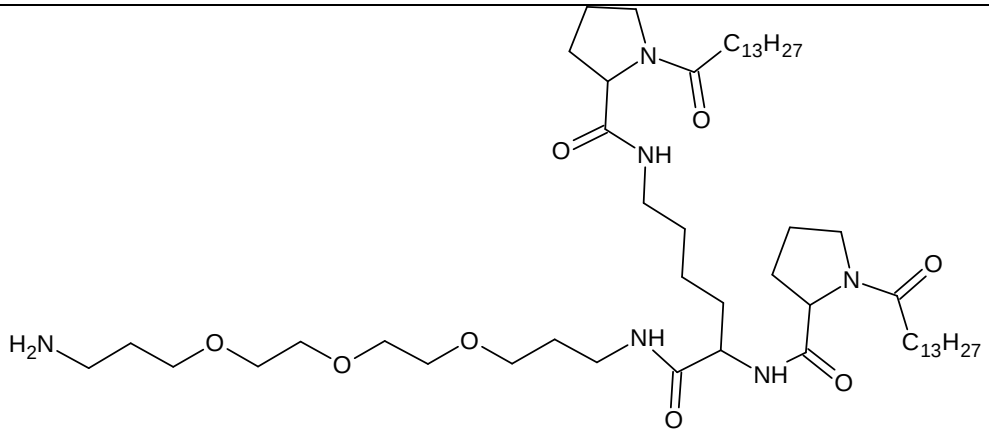
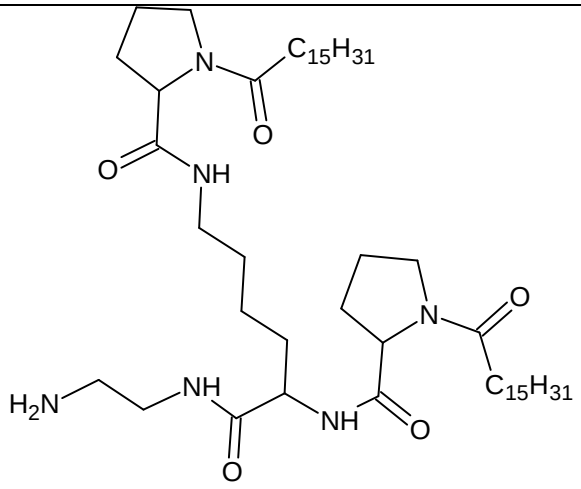
HPLC-aqueous SEC (calibrant PEG): Mn = 3600 g/mol.

Part B:

BB: synthesis of the hydrophobic molecules in which p = 2

[000524] The radicals are presented in the following table by the corresponding hydrophobic molecule before grafting onto the co-polyamino acid.

No.	Structure of the hydrophobic molecule before grafting onto the co-polyamino acid
BA1	
BA2	

BA3	
BA4	
BA5	

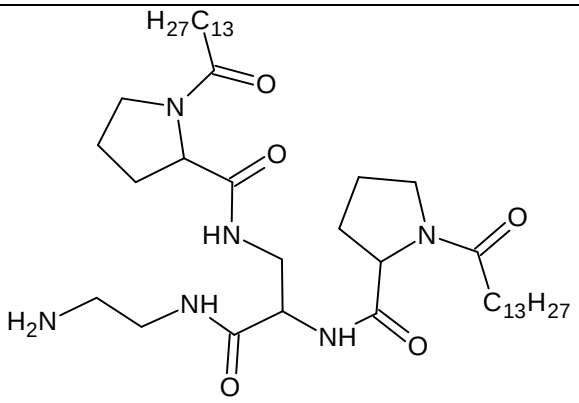
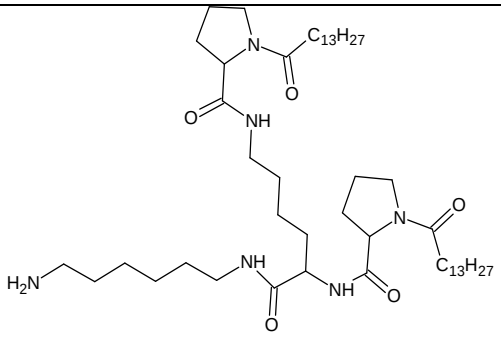
BA6	
BA7	

Table 1d: list of the hydrophobic molecules synthesized according to the invention.

Part BA: Synthesis of the hydrophobic molecules in which p = 2

Example BA1: molecule BA1

Molecule B1: product obtained by the reaction between decanoic acid and L-proline.

[000525] Dicyclohexyl carbodiimide (DCC) (16.29 g, 78.96 mmol) and N-hydroxysuccinimide (NHS) (9.09 g, 78.96 mmol) are successively added to a solution of decanoic acid (14.28 g, 82.91 mmol) in THF (520 mL) at 0 °C. After 60 h of stirring at room temperature, the mixture is cooled to 0 °C for 20 min, filtered through a sintered filter. L-Proline (10 g, 86.86 mmol), diisopropylethylamine (DIPEA) (68.8 mL) and water (60 mL) are added to the filtrate. After 24 h of stirring at room temperature, the medium is diluted with water (300 mL). The aqueous phase is washed with ethyl acetate (2 x 250 mL), acidified to pH ~1 with a 1 N aqueous HCl solution, then extracted with dichloromethane (3 x 150 mL). The combined organic phases are dried over Na_2SO_4, filtered, concentrated under vacuum, and the residue is purified by chromatography on silica gel (cyclohexane, ethyl acetate).

Yield: 14.6 g (69%)

^{1}H NMR ($CDCl_3$, ppm): 0.87 (3H); 1.26 (12H); 1.65 (2H); 2.02 (3H); 2.34 (2H); 2.41 (1H); 3.48 (1H); 3.56 (1H); 4.58 (1H).

LC/MS (ESI): 270.2; (calculated ($[M+H]^+$): 270.4)

Molecule B2: product obtained by the reaction between molecule B1 and L-lysine.

[000526] By a method similar to the one used for the preparation of molecule B1, applied to molecule B1 (14.57 g, 54.07 mmol) and to L-lysine (4.15 g, 28.39 mmol), a yellow oil is obtained.

Yield: 16.4 g (93%)

^{1}H NMR ($CDCl_3$, ppm): 0.88 (6H); 1.26 (24H); 1.35-1.65 (8H); 1.85-2.35 (12H); 2.53 (0.2H); 2.90 (0.8H); 3.45-3.75 (5H); 4.50-4.70 (3H); 7.82 (1H).

LC/MS (ESI): 649.6; (calculated ($[M+H]^+$): 649.9).

Molecule B3: product obtained by reaction between molecule B2 and Boc-ethylenediamine.

[000527] DIPEA (8.80 mL) and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU, 8.52 g, 26.54 mmol) at room temperature are added to a solution of molecule B2 (16.4 g, 25.27 mmol) in THF (170 mL). After 30 min of stirring, Boc-ethylenediamine (4.45 g, 27.8 mmol) is added. After stirring at room temperature for 2 h, the solvent is evaporated at reduced pressure and the residue is diluted with ethyl acetate (400 mL). The organic phase is washed with water (250 mL), a saturated aqueous NaHCO3 solution (250 mL), a 1 N aqueous HCl solution (250 mL), a saturated aqueous NaCl solution (250 mL) and dried over Na_2SO_4. After filtration and concentration under vacuum, the residue obtained is purified by chromatography on silica gel (ethyl acetate, methanol) to yield a colorless oil.

Yield: 12.8 g (64%)

^{1}H NMR ($CDCl_3$, ppm): 0.87 (6H); 1.25-1.60 (42H); 1.80-2.05 (4H); 2.15-2.45 (9H); 3.10-3.75 (10H); 4.30 (1H); 4.50 (2H); 5.50 (0.6H); 5.89 (0.2H); 6.15 (0.2H); 7.03 (1H); 7.47 (1H).

LC/MS (ESI): 791.8; (calculated ($[M+H]^+$): 792.1).

Molecule BA1

[000528] 4 N HCl solution in dioxane (20.2 mL) is added to a solution of molecule B3 (12.78 g, 16.15 mmol) in dichloromethane (110 ml) at 5 °C. After 20 h of stirring at 5 °C, the medium is concentrated under vacuum. The residue obtained is dissolved in methanol and

evaporated under vacuum, this operation being repeated 4 times to yield a white solid of molecule BA1 as a hydrochloride salt.

Yield: 11.4 g (97%)

^{1}H NMR (DMSO-d_6, ppm): 0.85 (6H); 1.25-1.50 (33H); 1.57 (1H); 1.70-2.40 (12H); 2.82 (2H); 3.00 (2H); 3.25-3.70 (6H); 4.05-4.50 (3H); 7.75-8.45 (6H).

LC/MS (ESI): 691.6; (calculated ($[M+H]^+$): 692.0).

Example BA2: molecule BA2

Molecule B4: product obtained by the reaction between lauric acid and L-proline.

[000529] By a method similar to the one used for the preparation of molecule B1, applied to lauric acid (31.83 g, 157.9 mmol) and to L-proline (20 g, 173.7 mmol), a yellow oil is obtained.

Yield: 34.3 g (73%)

^{1}H NMR ($CDCl_3$, ppm): 0.87 (3H); 1.26 (16H); 1.70 (2H); 1.90-2.10 (3H); 2.35 (2H); 2.49 (1H); 3.48 (1H); 3.56 (1H); 4.60 (1H).

LC/MS (ESI): 298.2; (calculated ($[M+H]^+$): 298.4).

Molecule B5: product obtained by the reaction between molecule B4 and L-lysine.

[000530] By a method similar to the one used for the preparation of molecule B1, applied to molecule B4 (33.72 g, 113.36 mmol) and to L-lysine (8.70 g, 59.51 mmol), a white solid is obtained.

Yield: 26.2 g (66%)

^{1}H NMR ($CDCl_3$, ppm): 0.88 (6H); 1.26 (32H); 1.35-1.65 (8H); 1.85-2.35 (15H); 2.87 (1H); 3.40-3.75 (5H); 4.50-4.75 (3H); 7.87 (1H).

LC/MS (ESI): 705.6; (calculated ($[M+H]^+$): 706.0).

Molecule B6: product obtained by reaction between Boc-ethylenediamine and molecule B5.

[000531] By a method similar to the one used for the preparation of molecule B3, applied to molecule B5 (25.74 g, 36.51 mmol) and to Boc-ethylenediamine (6.43 g, 40.16 mmol), a colorless oil is obtained.

Yield: 30.9 g (quantitative)

^1H NMR ($CDCl_3$, ppm): 0.88 (6H); 1.35-1.65 (50H); 1.85-2.35 (13H); 3.05-3.75 (10H); 4.25-4.65 (3H); 5.50 (0.4H); 5.88 (0.2H); 6.16 (0.2H); 7.08 (1H); 7.26 (1H); 7.49 (0.2H)

LC/MS (ESI): 847.8; (calculated ($[M+H]^+$): 848.2).

Molecule BA2

[000532] After a method similar to the one used for the preparation of molecule BA1, applied to molecule B6 (30.9 g, 36.47 mmol), the residue obtained after concentration under vacuum is dissolved in methanol and evaporated under vacuum, this operation being repeated 4 times to yield a white solid of molecule BA2 as a hydrochloride salt after drying at reduced pressure.

Yield: 27.65 g (97%)

^1H NMR (DMSO-d_6, ppm): 0.85 (6H); 1.10-2.40 (54H); 2.75-3.15 (4H); 3.25-3.60 (6H); 4.05-4.50 (3H); 7.50-8.50 (6H).

LC/MS (ESI): 747.6; (calculated ($[M+H]^+$): 748.1).

Example BA3: molecule BA3

Molecule B7: product obtained by the reaction between myristic acid and L-proline.

[000533] By a method similar to the one used for the preparation of molecule B1, applied to myristic acid (18.93 g, 82.91 mmol) and to L-proline (10 g, 86.86 mmol), a yellowish oil is obtained.

Yield: 20 g (78%)

^{1}H NMR ($CDCl_3$, ppm): 0.88 (3H); 1.28 (20H); 1.70 (2H); 1.90-2.10 (3H); 2.36 (2H); 2.51 (1H); 3.47 (1H); 3.56 (1H); 4.61 (1H).

LC/MS (ESI): 326.2; (calculated ($[M+H]^+$): 326.6).

Molecule B8: product obtained by the reaction between molecule B7 and L-lysine

[000534] By a method similar to the one used for the preparation of molecule B1, applied to molecule B7 (20.02 g, 61.5 mmol) and to L-lysine (4.72 g, 32.29 mmol), a white solid is obtained.

Yield: 12.3 g (53%)

^{1}H NMR (DMSO-d_6, ppm): 0.85 (6H); 1.26 (40H); 1.35-1.50 (6H); 1.50-2.10 (10H); 2.10-2.25 (4H); 3.01 (2H); 3.31-3.55 (4H); 4.10-4.40 (3H); 7.68 (0.6H); 7.97 (1H); 8.27 (0.4H); 12.50 (1H).

LC/MS (ESI): 761.8; (calculated ($[M+H]^+$): 762.1).

Molecule B9: product obtained by the reaction between Boc-ethylenediamine and molecule B8.

[000535] By a method similar to the one used for the preparation of molecule B3, applied to molecule B8 (12 g, 15.77 mmol) and to Boc-ethylenediamine (3.03 g, 18.92 mmol), a colorless

oil is obtained after purification by column chromatography on silica gel (ethyl acetate, methanol).

Yield: 12.5 g (88%)

^{1}H NMR (DMSO-d_6, ppm): 0.85 (6H); 1.20-1.55 (55H); 1.50-2.25 (14H); 2.95-3.10 (6H); 3.31-3.55 (4H); 4.10-4.40 (3H); 6.74 (1H); 7.60-8.25 (3H).

LC/MS (ESI): 904.1; (calculated ($[M+H]^+$): 904.3).

Molecule BA3

[000536] By a method similar to the one used for the preparation of molecule BA1, applied to molecule B9 (12.5 g, 13.84 mmol), the residue obtained after concentration under vacuum is dissolved in methanol and evaporated under vacuum, this operation being repeated 4 times to yield a white solid of molecule BA3 as a hydrochloride salt after drying at reduced pressure.

Yield: 9.2 g (79%)

^{1}H NMR (DMSO-d_6, ppm): 0.85 (6H); 1.10-1.65 (48H); 1.70-2.35 (12H); 2.85 (2H); 3.01 (2H); 3.25-3.65 (6H); 4.10-4.50 (3H); 7.70-8.40 (6H).

LC/MS (ESI): 803.9; (calculated ($[M+H]^+$): 804.2).

Example BA4: molecule BA4

Molecule B10: product obtained by the reaction between molecule B8 and Boc-1-amino-4,7,10-trioxa-13-tridecane.

[000537] By a method similar to the one used for the preparation of molecule B3, applied to molecule B8 (29.80 g, 39.15 mmol) and to Boc-1-amino-4,7,10-trioxa-13-tridecane (15.05 g, 46.96 mmol), a thick colorless oil is obtained.

Yield: 25.3 g (61%)

^{1}H NMR (DMSO-d_6, ppm): 0.85 (6H); 1.25-2.35 (75H); 2.85-3.20 (6H); 3.25-3.65 (16H); 4.10-4.45 (3H); 6.38 (0.1H); 6.72 (0.9H); 7.50-8.25 (3H).

LC/MS (ESI): 1064.2; (calculated ($[M+H]^+$): 1064.5).

Molecule BA4

[000538] After a method similar to the one used for the preparation of molecule BA1, applied to molecule B10 (25.3 g, 23.8 mmol), the residue obtained after concentration under vacuum is dissolved in methanol and evaporated under vacuum, this operation being repeated 4 times to yield a white solid of molecule BA4 as a hydrochloride salt after drying at reduced pressure.

Yield: 20.02 g (84%)

^{1}H NMR (DMSO-d_6, ppm): 0.85 (6H); 1.15-2.35 (66H); 2.80-3.20 (6H); 3.30-3.65 (16H); 4.10-4.45 (3H); 7.55-8.60 (6H).

LC/MS (ESI): 964.9; (calculated ($[M+H]^+$): 964.6).

Example BA5: molecule BA5

Molecule B11: product obtained by reaction between palmitoyl chloride and L-proline.

[000539] By a method similar to the one used for the preparation of molecule A26, applied to palmitoyl chloride (15.39 g, 55.99 mmol) and to L-proline (12.89 g, 111.98 mmol), a white solid of molecule B11 is obtained.

Yield: 19.10 g (96%)

^{1}H NMR ($CDCl_3$, ppm): 0.88 (3H); 1.19-1.45 (24H); 1.58-1.74 (2H); 1.88-2.14 (3H); 2.15-2.54 (3H); 3.47 (1H); 3.58 (1H); 4.41 (0.1H); 4.61 (0.9H) 6.60-8.60 (1H).

LC/MS (ESI): 354.4; 707.8; (calculated ($[M+H]^+$): 354.3; ($[2M+H]^+$): 707.6).

Molecule B12: product obtained by reaction between molecule B11 and L-Lysine.

[000540] By a method similar to the one used for the preparation of molecule B1, applied to molecule B11 (19.10 g, 54.02 mmol) and to L-lysine (4.15 g, 28.36 mmol), an oily residue is obtained after concentration of the reaction medium at reduced pressure. This residue is diluted in water (150 mL), washed with ethyl acetate (2 x 75 mL), then the aqueous phase is acidified until the pH is 1 by slow addition of 6 N HCl. The product is extracted 3 times with dichloromethane, the organic phase is dried over Na_2SO_4, then filtered and concentrated at reduced pressure to yield 11.2 g of yellow oily residue. In parallel, the previous organic phase of ethyl acetate is washed with a 2 N aqueous HCl solution (2 x 75 mL), a saturated aqueous NaCl solution (75 mL), dried over Na_2SO_4, filtered and concentrated to yield 10.2 g of yellow oily residue. A white solid is obtained after recrystallization of each one of these residues in acetone.

Yield: 11.83 g (54%)

^{1}H NMR ($CDCl_3$, ppm): 0.87 (6H); 1.06-2.44 (70H); 2.78-2.96 (1H); 3.35-3.75 (5H); 4.28-4.43 (0.1H); 4.43-4.52 (0.2H); 4.52-4.61 (1.8H); 4.61-4.75 (0.9H); 7.74-8.02 (2H).

LC/MS (ESI): 818.0; (calculated ($[M+H]^+$): 818.7).

Molecule B13: product obtained by coupling between molecule B12 and Boc-ethylenediamine

[000541] By a method similar to the one used for the preparation of molecule A27, applied to molecule B12 (18.00 g, 22.02 mmol) in solution in THF and to Boc-ethylenediamine (4.23 g, 26.43 mmol), a white solid is obtained after recrystallization two times in acetonitrile.

Yield: 17.5 g (83%)

^{1}H NMR (DMSO-d6, ppm): 0.85 (6H); 1.15-2.29 (79H); 2.92-3.12 (6H); 3.30-3.59 (4H); 4.06-4.13 (0.65H); 4.16-4.29 (2H); 4.38-4.42 (0.35H); 6.71-6.76 (1H); 7.60-7.69 (1.3H); 7.76-7.81 (0.65H); 7.93-7.97 (0.35H); 8.00-8.04 (0.35H); 8.10-8.17 (0.35H).

LC/MS (ESI): 960.4; (calculated ($[M+H]^+$): 960.8).

Molecule BA5

[000542] By a method similar to the one used for the preparation of molecule BA1, applied to molecule B13 (24.4 g, 25.43 mmol), the residue obtained after concentration under vacuum is solubilized in dichloromethane (150 mL), the organic phase is washed 2 times with a 2 M aqueous sodium hydroxide solution (90 mL). Acetonitrile (120 mL) is added, and the dichloromethane is eliminated by concentration at reduced pressure. The medium is then allowed to rest for 72 h, and a white solid is obtained after filtration and rinsing with acetonitrile, then drying at reduced pressure. This operation is repeated 4 times.

Yield: 14.28 g (65%)

^{1}H NMR (DMSO-d6, ppm): 0.85 (6H); 1.06-2.32 (70H); 2.53-2.63 (2H); 2.89-3.61 (10H); 4.04-4.43 (3H); 7.55-7.62 (0.65H); 7.65-7.72 (0.65H); 7.80 (0.65H); 7.91 (0.35H); 8.03 (0.35H); 8.14-8.23 (0.35H).

LC/MS (ESI): 860.0; (calculated ($[M+H]^+$): 860.8).

Example BA6: molecule BA6

Molecule B14: product obtained by coupling between molecule A26 and 2,3-diaminopropionic acid

[000543] By a method similar to the one used for the preparation of molecule B1, applied to molecule A26 (80.00 g, 245.78 mmol) and to 2,3-diaminopropionic dihydrochloride (22.84 g, 129.04 mmol), a white solid is obtained after recrystallization in acetonitrile.

Yield: 69 g (78%)

^{1}H NMR (DMSO-d6, ppm): 0.86 (6H); 1.08-1.38 (40H); 1.40-1.55 (4H); 1.68-2.30 (12H); 3.16-3.66 (6H); 4.20-4.39 (3H); 7.67-8.31 (2H); 12.70 (1H).

LC/MS (ESI): 719.4; 741.5; (calculated ($[M+H]^+$): 719.6; ($[M+Na]^+$): 741.6).

Molecule B15: product obtained by coupling between molecule B14 and Boc-ethylenediamine

[000544] By a method similar to the one used for the preparation of molecule A27, applied to molecule B14 (32.00 g, 44.50 mmol) in solution in dichloromethane and to Boc-ethylenediamine (8.56 g, 53.40 mmol), a colorless oil is obtained after purification by chromatography on silica gel (ethyl acetate, methanol).

Yield: 24.5 g (64%)

^{1}H NMR (DMSO-d6, ppm): 0.85 (6H); 1.16-2.42 (65H); 2.89-3.14 (4H); 3.17-3.66 (6H); 4.11-4.43 (3H); 6.77 (1H); 7.38-8.23 (3H).

LC/MS (ESI): 861.7; (calculated ($[M+H]^+$): 861.7).

Molecule BA6

[000545] By a method similar to the one used for the preparation of molecule BA5, applied to molecule B15 (24.50 g, 28.45 mmol), a white solid is obtained after recrystallization in acetonitrile.

Yield: 19.7 g (91%)

^{1}H NMR (DMSO-d6, ppm): 0.85 (6H); 1.10-2.40 (58H); 2.51-2.62 (2H); 2.90-3.16 (2H); 3.16-3.67 (6H); 4.04-4.47 (3H); 7.33-8.27 (3H).

LC/MS (ESI): 761.5; (calculated ($[M+H]^+$): 761.6).

Example BA7: molecule BA7

Molecule B16: product obtained by the reaction between *N*-(*tert*-butoxycarbonyl)-1.6-diaminohexane and molecule B8

[000546] By a method similar to the one used for the preparation of molecule A27, applied to molecule B8 (10 g, 13.14 mmol) and to N-(tert-butoxycarbonyl)-1,6-diaminohexane (3.41 g, 15.77 mmol) in dichloromethane, a white solid is obtained after recrystallization in acetonitrile.

Yield: 10.7 g (85%)

^{1}H NMR ($CDCl_3$, ppm): 0.88 (6H); 1.17-2.40 (79H); 3.00-3.71 (10H); 4.26-4.58 (3H); 4.67 (1H); 6.74 (1H); 7.34-7.49 (2H).

LC/MS (ESI): 959.9; (calculated ($[M+H]^+$): 959.8).

Molecule BA7

[000547] After a method similar to the one used for the preparation of molecule BA1, applied to molecule B16 (10.5 g, 10.94 mmol), a 2 N aqueous NaOH solution is added dropwise to the reaction medium cooled to 0 °C. The aqueous phase is extracted with dichloromethane, then the organic phase is washed 3 times with a 5% aqueous NaCl solution. After drying over Na2SO4, the organic phase is filtered, concentrated under vacuum and the residue is recrystallized in acetonitrile.

Yield: 5.4 g (58%)

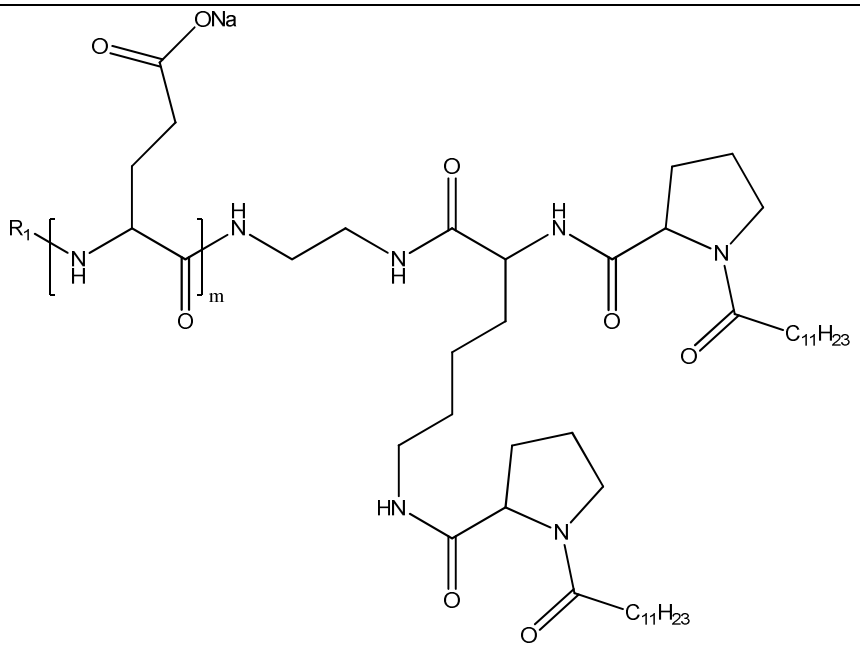
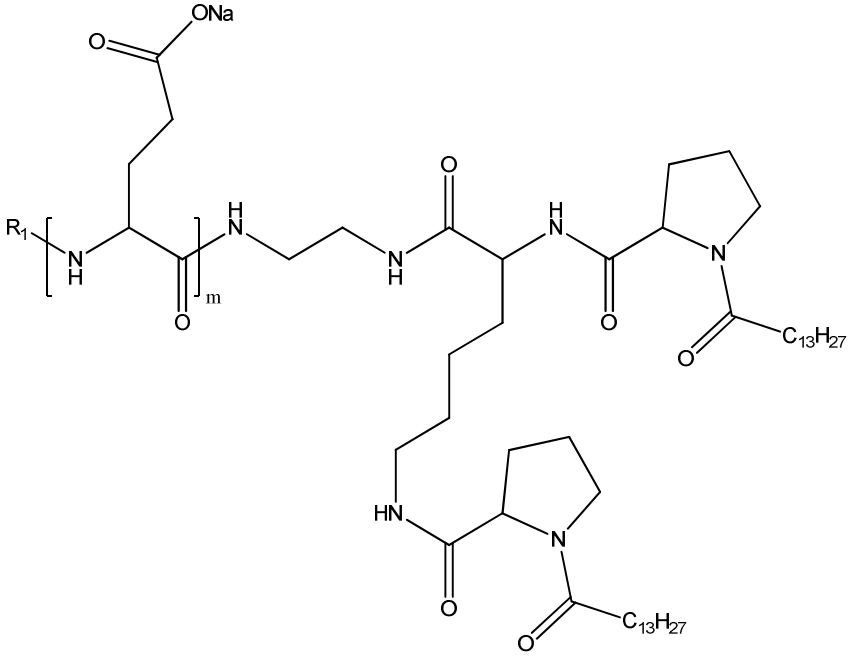
^{1}H NMR ($CDCl_3$, ppm): 0.88 (6H); 1.19-2.40 (72H); 2.67 (2H); 3.03-3.70 (8H); 4.26-4.57 (3H); 6.71 (1H); 7.39-7.49 (2H).

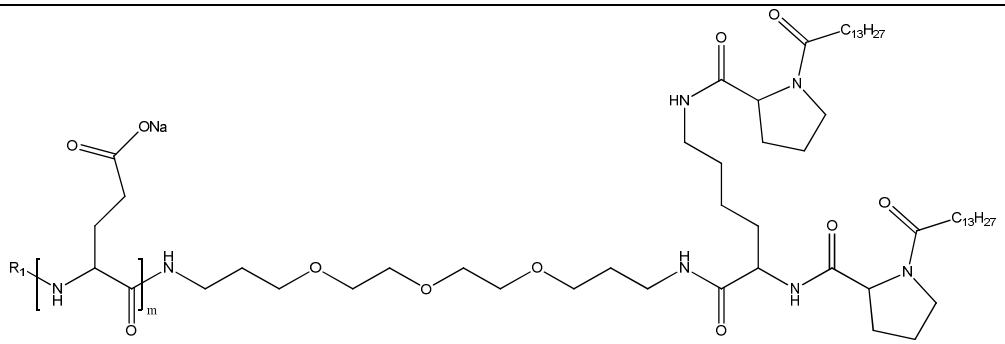
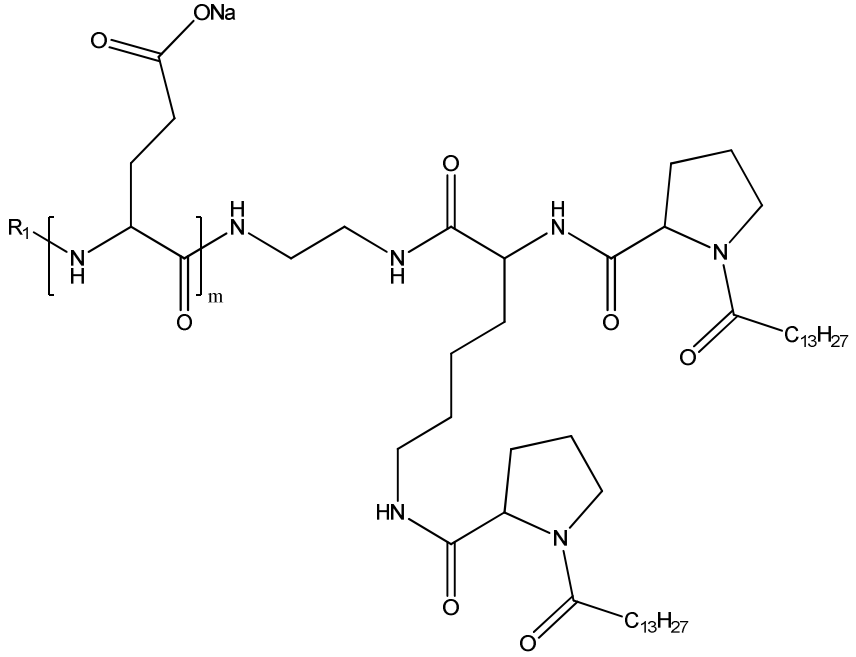
LC/MS (ESI): 859.8; (calculated ($[M+H]^+$): 859.7).

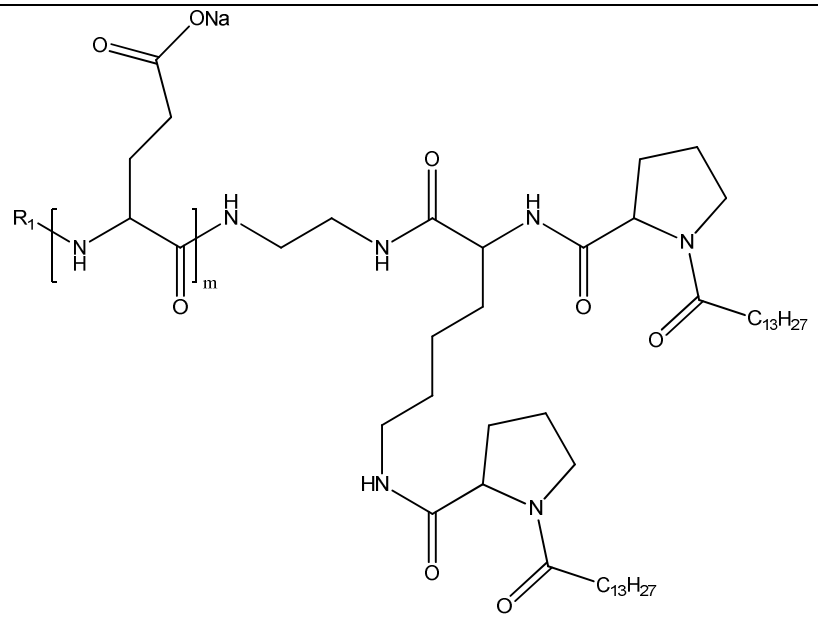
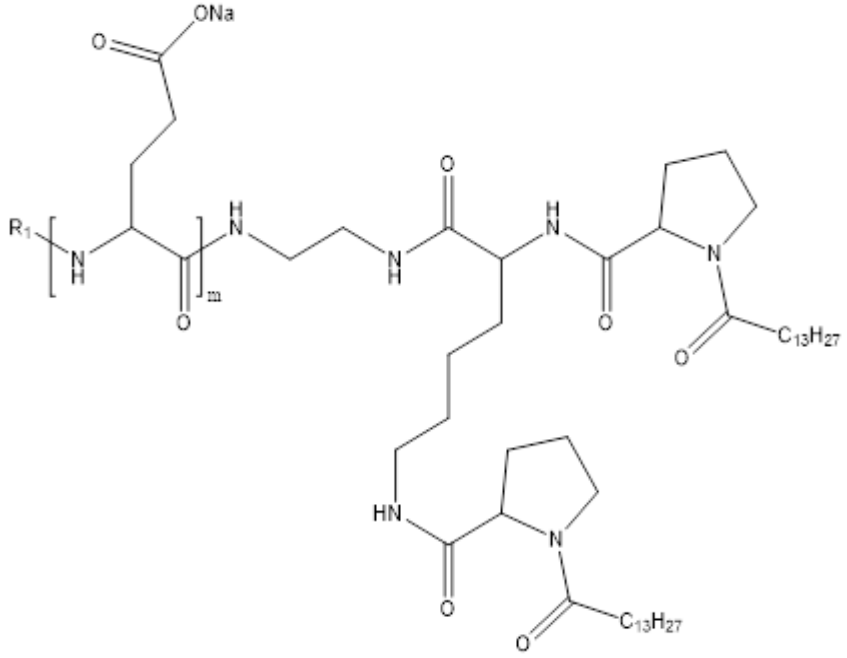
BB: Synthesis of the co-polyamino acids

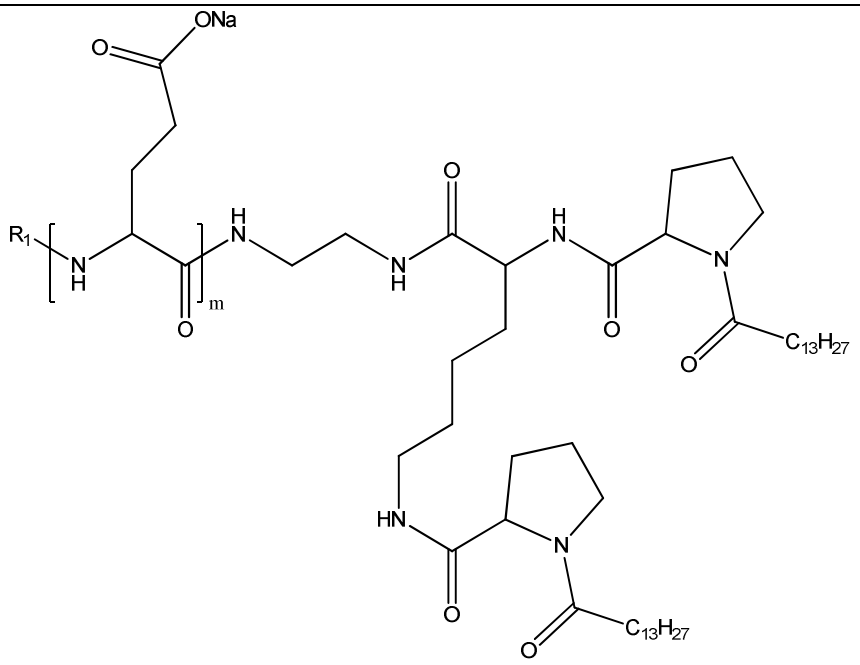
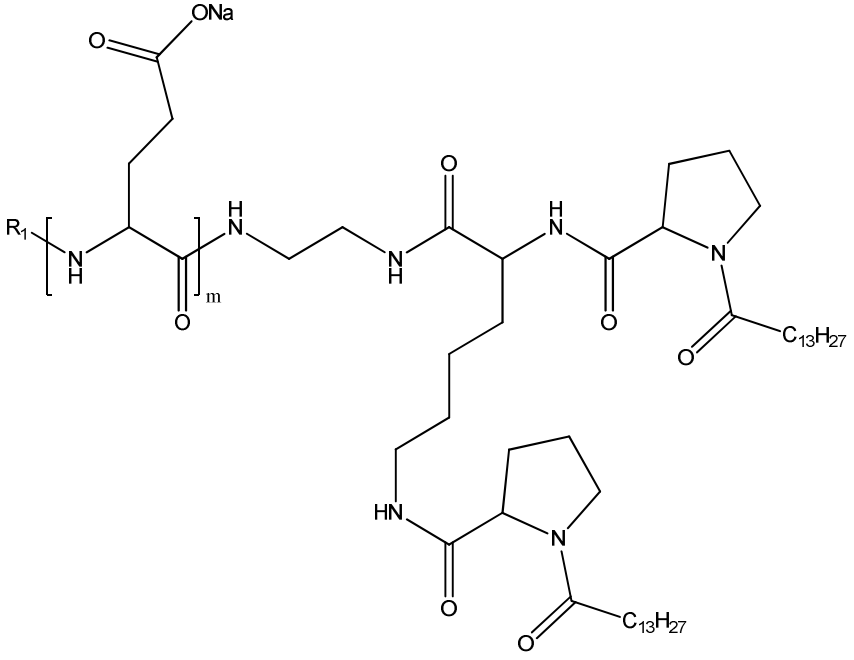
Defined co-polyamino acids defined of formulas VII or VIIb

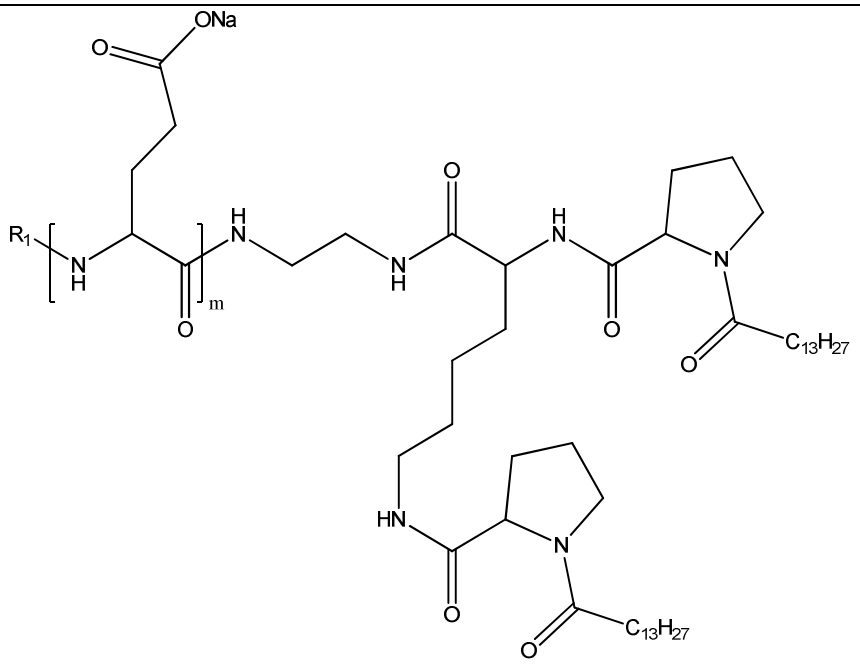
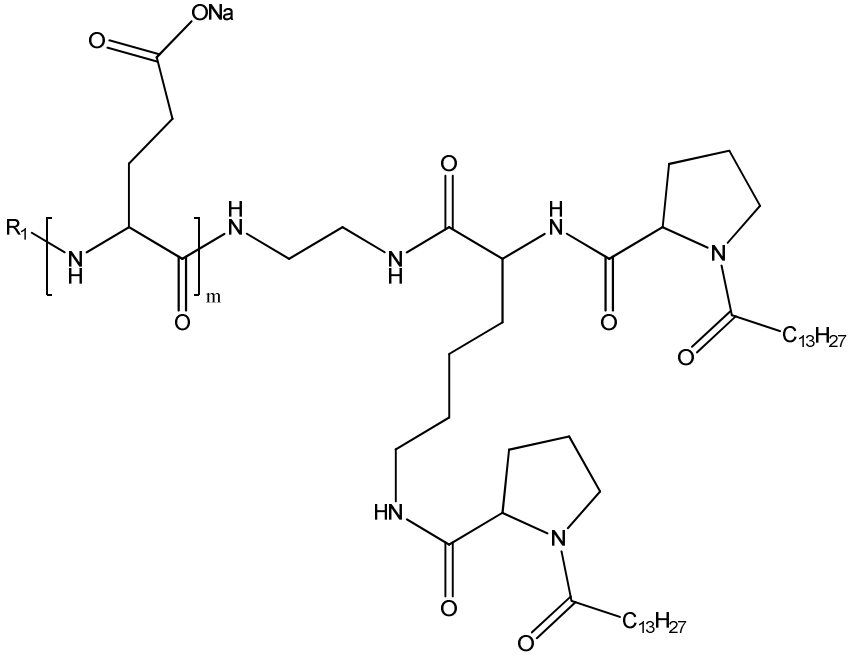
No.	co-polyamino acids bearing carboxylate charges and hydrophobic radicals

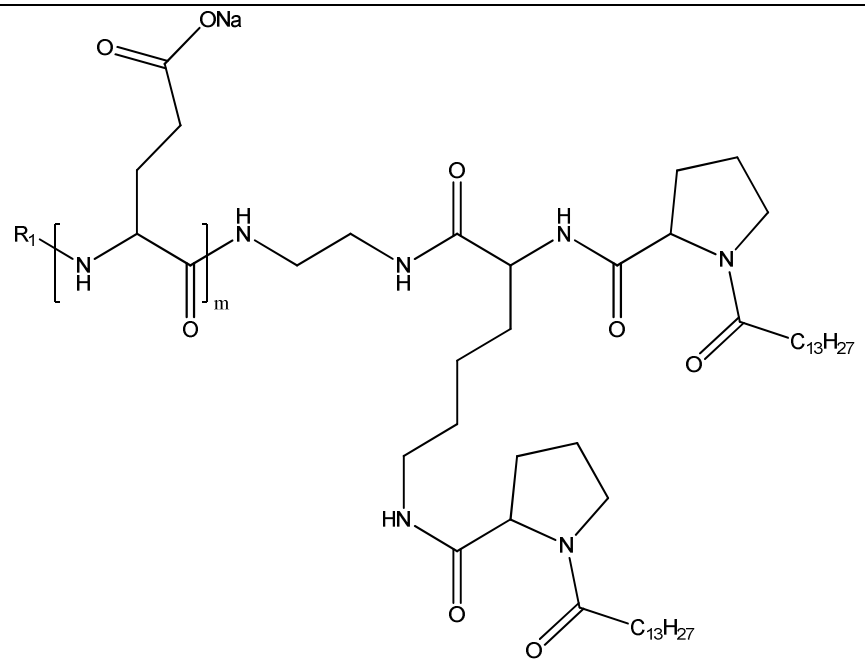
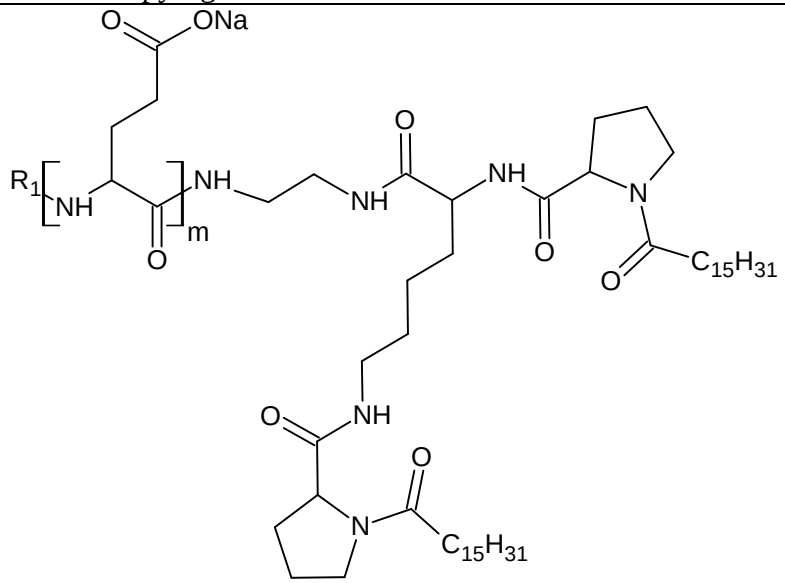
BB14	 i = 0.034, DP (m) = 29 R_1 = H or pyroglutamate
BB15	 i = 0.042, DP (m) = 24 R_1 = H or pyroglutamate

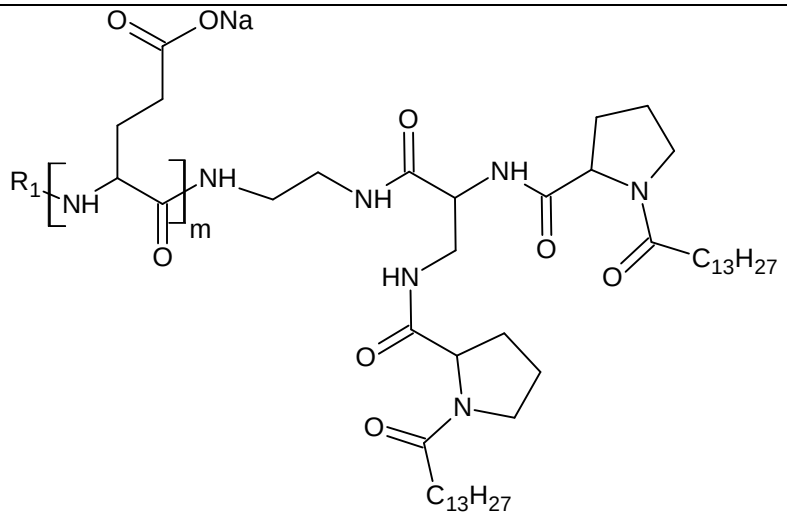
BB16	 i = 0.043, DP (m) = 23 R_1 = H or pyroglutamate
BB17	 i = 0.015, DP (m) = 65 R_1 = H or pyroglutamate

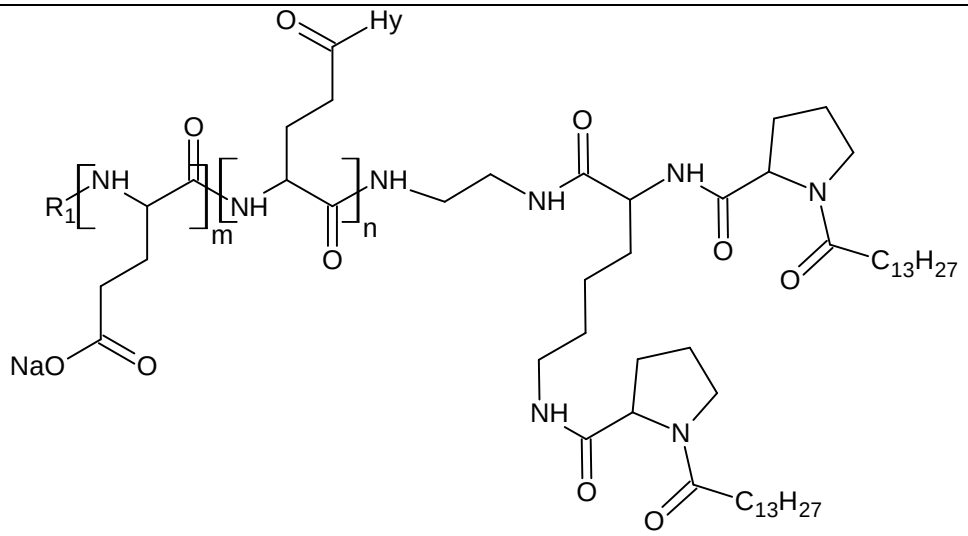
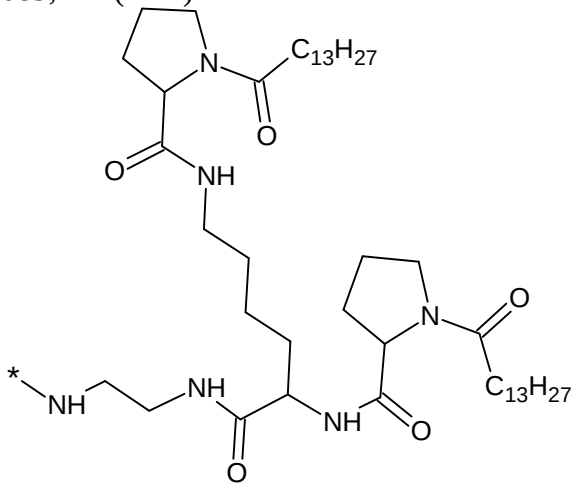
BB18	 i = 0.025, DP (m) = 40 R_1 = H or pyroglutamate
BB19	 i = 0.04, DP (m) = 25 R_1 = H or pyroglutamate

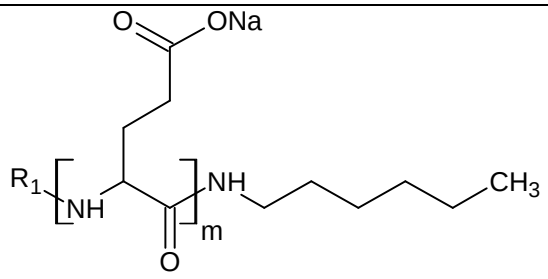
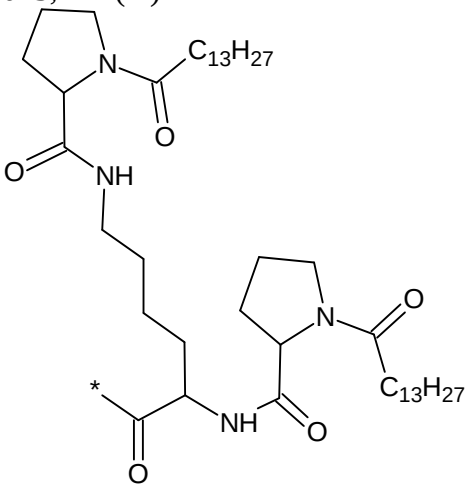
BB20	 i = 0.059, DP (m) = 17 R_1 = H or pyroglutamate
BB21	 i = 0.11, DP (m) = 9 R_1 = H or pyroglutamate

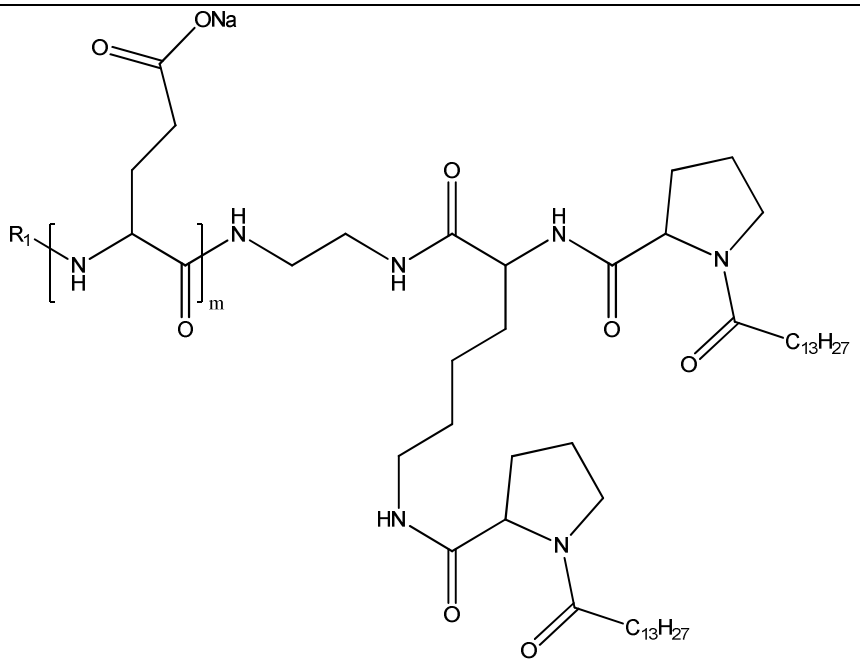
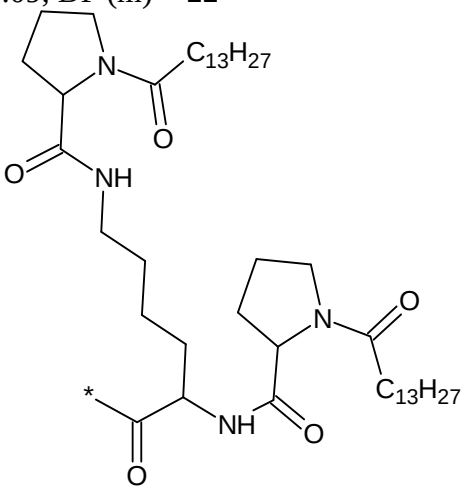
BB22	 i = 0.048, DP (m) = 21 R_1 = H or pyroglutamate
BB23	 i = 0.048, DP (m) = 21 R_1 = H or pyroglutamate

BB24	 i = 0.040, DP (m) = 25 R_1 = H or pyroglutamate
BB25	 i = 0.043, DP (m) = 23 R_1 = H or pyroglutamate

BB26	 i = 0.048, DP (m) = 21 R_1 = H or pyroglutamate

BB27	 i = 0.089, DP (m+n) = 22  Hy = R_1 = H or pyroglutamate

BB42	 i = 0.045, DP (m) = 22  R_1 =

BB43	 i = 0.09, DP (m) = 22  R_1 =

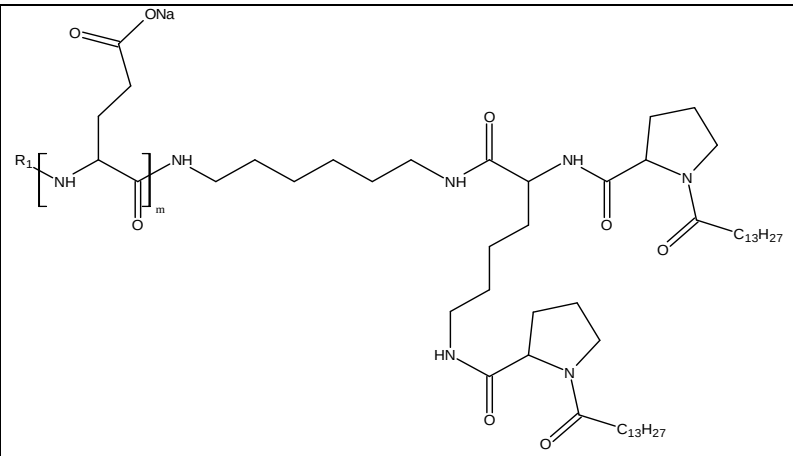
BB44	 i = 0.04, DP (m) = 25 R_1 = H or pyroglutamate

Table 1f: list of the co-polyamino acids synthesized according to the invention.

Part BB: synthesis of the co-polyamino acids

Example BB14: co-polyamino acid BB14 - sodium poly-L-glutamate modified at one of its ends by molecule BA2 and having a number average molecular weight (Mn) of 4020 g/mol

[000548] The hydrochloride salt of molecule BA2 (2.12 g, 2.70 mmol), chloroform (40 mL), molecular sieve 4 Å (1.5 g) as well as Amberlite IRN 150 ion exchange resin (1.5 g) are introduced successively into an appropriate container. After 1 h of stirring on rollers, the medium is filtered and the resin is rinsed with chloroform. The mixture is evaporated, then co-evaporated with toluene. The residue is solubilized in anhydrous DMF (20 mL) to be used directly in the polymerization reaction.

[000549] γ-Benzyl-L-glutamate *N*-carboxyanhydride (18 g, 68.42 mmol) is placed under vacuum for 30 min in a round-bottom flask dried beforehand in the oven, then anhydrous DMF (100 mL) is introduced. The mixture is stirred under argon until the solubilization is complete, cooled to 4 °C, then the solution of molecule BA2 prepared as described above is introduced rapidly. The mixture is stirred between 4 °C and room temperature for 2 days, then heated at 65

°C for 2 h. The reaction mixture is then cooled to room temperature, then poured dropwise into diisopropyl ether (1.2 L) under stirring. The white precipitate is recovered by filtration, washed two times with diisopropyl ether (100 mL), then dried under vacuum at 30 °C to obtain a white solid. The solid is diluted in TFA (105 mL), and a 33% hydrobromic acid solution (HBr) in acetic acid (38 mL, 220 mmol) is then added dropwise and at 0 °C. The solution is stirred for 2 h at room temperature, then poured dropwise onto a 1:1 (v/v) mixture of diisopropyl ether/water and under stirring (600 mL). After 2 h of stirring, the heterogeneous mixture is allowed to rest overnight. The white precipitate is recovered by filtration, washed successively with a 1:1 (v/v) mixture of diisopropyl ether and water (200 mL), then with water (100 mL). The solid obtained is solubilized in water (450 mL) by adjusting the pH to 7 by addition of a 10 N aqueous sodium hydroxide solution, then a 1 N aqueous sodium hydroxide solution. The mixture is filtered through a 0.45-µm filter, then purified by ultrafiltration against a 0.9% NaCl solution, then water until the conductimetry of the permeate is less than 50 µS/cm. The solution of co-polyamino acid is then concentrated to approximately 30 g/L theoretical and the pH is adjusted to 7. The aqueous solution is filtered through a 0.2-µm filter and stored at 4 °C.

Dry extract: 22.3 mg/g.

DP (estimated by ^{1}H NMR) = 29 therefore i = 0.034.

The calculated average molecular weight of the co-polyamino acid BB14 is 5089 g/mol.

HPLC-aqueous SEC (calibrant PEG): Mn = 4020 g/mol.

Example BB15: co-polyamino acid BB15 - sodium poly-L-glutamate modified at one of its ends by molecule BA3 and having a number average molecular weight (Mn) of 3610 g/mol

[000550] By a method similar to the one used for the preparation of the co-polyamino acid BB14, applied to the hydrochloride salt of the molecule BA3 (3.62 g, 4.32 mmol) and to 25.0 g (94.97 mmol) of γ-benzyl-L-glutamate *N*-carboxyanhydride, a sodium poly-L-glutamate modified at one of its ends by the molecule BA3 is obtained.

Dry extract: 26.5 mg/g

DP (estimated by ^{1}H NMR) = 24 therefore i = 0.042.

The calculated average molecular weight of the co-polyamino acid BB15 is 4390 g/mol.

HPLC-aqueous SEC (calibrant PEG): Mn = 3610 g/mol.

Example BB16: co-polyamino acid BB16 - sodium poly-L-glutamate modified at one of its ends by molecule BA4 and having a number average molecular weight (Mn) of 3300 g/mol

[000551] By a method similar to the one used for the preparation of the co-polyamino acid BB14, applied to the hydrochloride salt of the molecule BA4 (5.70 g, 5.70 mmol) and to 29.99 g (113.9 mmol) of γ-benzyl-L-glutamate *N*-carboxyanhydride, a sodium poly-L-glutamate modified at one of its ends by the molecule BA4 is obtained.

Dry extract: 32.3 mg/g

DP (estimated by ^{1}H NMR) = 23 therefore i = 0.043.

The calculated average molecular weight of the co-polyamino acid BB16 is 4399 g/mol.

HPLC-aqueous SEC (calibrant PEG): Mn = 3300 g/mol.

Example BB17: co-polyamino acid BB17 - sodium poly-L-glutamate modified at one of its ends by molecule BA3 and having a number average molecular weight (Mn) of 10700 g/mol

[000552] By a method similar to the one used for the preparation of the co-polyamino acid BB14, applied to the hydrochloride salt of the molecule BA3 (2.51 g, 3 mmol) and at 52.7 g (200 mmol) of γ-benzyl-L-glutamate *N*-carboxyanhydride, a sodium poly-L-glutamate modified at one of its ends by the molecule BA3 is obtained.

Dry extract: 24.5 mg/g

DP (estimated by ^{1}H NMR) = 65 therefore i = 0.015.

The calculated average molecular weight of the co-polyamino acid BB17 is 10585 g/mol.

HPLC-aqueous SEC (calibrant PEG): Mn = 10700 g/mol.

Example BB18: co-polyamino acid BB18 - sodium poly-L-glutamate modified at one of its ends by molecule BA3 and having a number average molecular weight of 6600 g/mol

[000553] By a method similar to the one used for the preparation of the co-polyamino acid BB14, applied to the hydrochloride salt of the molecule BA3 (2.51 g, 3 mmol) and at 31.6 g (120 mmol) of γ-benzyl-L-glutamate *N*-carboxyanhydride, a sodium poly-L-glutamate modified at one of its ends by the molecule BA3 is obtained.

Dry extract: 27.3 mg/g

DP (estimated by ^{1}H NMR) = 40 therefore i = 0.025.

The calculated average molecular weight of the co-polyamino acid BB18 is 6889 g/mol.

HPLC-aqueous SEC (calibrant PEG): Mn = 6600 g/mol.

Example BB19: co-polyamino acid BB19 - sodium poly-L-glutamate modified at one of its ends by the molecule BA3 and having a number average molecular weight (Mn) of 3400 g/mol

[000554] By a method similar to the one used for the preparation of the co-polyamino acid BB14, applied to the hydrochloride salt of the molecule BA3 (36.26 g, 43.2 mmol) and of γ-benzyl-L-glutamate *N*-carboxyanhydride (250.0 g, 949.7 mmol), a sodium poly-L-glutamate modified at one of its ends by molecule BA3 is obtained.

Dry extract: 22.4 mg/g

DP (estimated by ^{1}H NMR) = 25 therefore i = 0.04.

The calculated average molecular weight of the co-polyamino acid BB19 is 4540 g/mol.

HPLC-aqueous SEC (calibrant PEG): Mn = 3400 g/mol.

Example BB20:

co-polyamino acid BB20 - sodium poly-L-glutamate modified at one of its ends by the molecule BA3 and having a number average molecular weight (Mn) of 2500 g/mol

[000555] By a method similar to the one used for the preparation of the co-polyamino acid BB14, applied to the molecule BA3 in free amine form (1.017 g, 12.7 mmol) and of γ-benzyl-L-glutamate *N*-carboxyanhydride (5.0 g, 19.0 mmol), a sodium-L-glutamate modified at one of its ends by the molecule BA3 is obtained.

Dry extract: 11.2 mg/g

DP (estimated by ^{1}H NMR) = 17 therefore i = 0.059.

The calculated average molecular weight of the co-polyamino acid BB20 is 3332 g/mol.

HPLC-aqueous SEC (calibrant PEG): Mn = 2500 g/mol.

Example BB21:

co-polyamino acid BB21 - sodium poly-L-glutamate modified at one of its ends by the molecule BA3 and having a number average molecular weight (Mn) of 1100 g/mol

[000556] By a method similar to the one used for the preparation of the co-polyamino acid BB14, applied to the molecule BA3 in free amine form (3.814 g, 4.75 mmol) and of γ-benzyl-L-glutamate *N*-carboxyanhydride (10.0 g, 38.0 mmol), a sodium-poly-L-glutamate modified at one of its ends by the molecule BA3 is obtained.

Dry extract: 16.1 mg/g

DP (estimated by ^{1}H NMR) = 9 therefore i = 0.11.

The calculated average molecular weight of the co-polyamino acid BB21 is 2123 g/mol.

HPLC-aqueous SEC (calibrant PEG): Mn = 1100 g/mol.

Example BB22:

co-polyamino acid BB22 - sodium poly-D-glutamate modified at one of its ends by the molecule BA3 and having a number average molecular weight (Mn) of 2900 g/mol

[000557] By a method similar to the one used for the preparation of the co-polyamino acid BB14, applied to the molecule BA3 in free amine form (2.77 g, 3.45 mmol) and of γ-benzyl-D-glutamate *N*-carboxyanhydride (20.0 g, 76.0 mmol), a sodium-poly-D-glutamate modified at one of its ends by the molecule BA3 is obtained.

Dry extract: 15.2 mg/g

DP (estimated by ^{1}H NMR) = 21 therefore i = 0.048.

The calculated average molecular weight of the co-polyamino acid BB22 is 3936 g/mol.

HPLC-aqueous SEC (calibrant PEG): Mn = 2900 g/mol.

Example BB23:

co-polyamino acid BB23 - a random copolymer of unit sodium D- or L-glutamate, modified at one of its ends by the molecule BA3 and having a number average molecular weight (Mn) of 2800 g/mol

[000558] γ-Benzyl-L-glutamate N-carboxyanhydride (20.0 g, 76.00 mmol) and γ-benzyl-D-glutamate N-carboxyanhydride (20.0 g, 76.00 mmol) are placed under vacuum for 30 min in a round-bottom flask dried beforehand in the oven, then anhydrous DMF (75 mL) is introduced. The mixture is stirred under argon until the solubilization is complete, cooled to 4 °C, then a solution of molecule BA3 in free amine form (5.55 g, 6.91 mmol) in chloroform (14.5 mL) is introduced rapidly. The mixture is stirred between 4 °C and room temperature for 18 h, then heated at 65 °C for 2 h. The reaction mixture is then cooled to room temperature, then poured dropwise into diisopropyl ether (1.2 L) under stirring. The white precipitate is recovered by filtration, washed three times with diisopropyl ether (80 mL), then dried under vacuum at 30 °C until obtaining a white solid. The solid is diluted in TFA (152 mL), and a 33% hydrobromic acid (HBr) solution in acetic acid (106 mL, 220 mmol) is then added dropwise and at 0 °C. The solution is stirred for 3 h at room temperature then poured dropwise onto a 1:1 (v/v) mixture of diisopropyl ether/water and under stirring (1.84 L). The aqueous phase is separated in a dropping funnel, and the pH is adjusted to 7.2 by addition of a 10 N aqueous NaOH solution. After addition of water (250 mL), the mixture is filtered through a 0.45-µm filter then purified by ultrafiltration against a 0.9% NaCl solution, then water until the conductimetry of the permeate is

less than 50 µS/cm. The solution of co-polyamino acid is then concentrated to approximately 25 g/L, filtered through a 0.2-µm filter and stored at 4 °C.

Dry extract: 28.2 mg/g.

DP (estimated by ^{1}H NMR) = 21 therefore i = 0.048.

The calculated average molecular weight of the co-polyamino acid BB23 is 3936 g/mol.

HPLC-aqueous SEC (calibrant PEG): Mn = 2800 g/mol.

Example BB24: co-polyamino acid BB24 - a block copolymer of sodium poly-D-glutamate and sodium poly-L-glutamate, modified at one of its ends by the molecule BA3 and having a number average molecular weight (Mn) of 2800 g/mol

γ-Benzyl-D-glutamate N-carboxyanhydride (13.5 g, 51.3 mmol) is placed under vacuum for 30 min in a round-bottom flask dried beforehand in the oven, then anhydrous DMF (52 mL) is introduced. The mixture is stirred under argon until the solubilization is complete, cooled to 0 °C, then a solution of molecule BA3 in free amine form (3.43 g, 4.27 mmol) in chloroform (8.6 mL) is introduced rapidly. The mixture is stirred at 0 °C for 24 h, then a solution of γ-tert-butyl-L-glutamate N-carboxyanhydride (13.5 g, 58.9 mmol) in DMF (15 mL) is added. The mixture is then stirred between 0 °C and room temperature for 21 h, then heated at 65 °C for 2 h. The reaction mixture is then cooled to room temperature, then poured dropwise into diisopropyl ether (0.8 L) under stirring. The white precipitate is recovered by filtration, washed three times with diisopropyl ether (52 mL), then dried under vacuum at 30 °C until obtaining a white solid. The solid is diluted in TFA (96 mL), and a 33% hydrobromic acid (HBr) solution in acetic acid (68 mL, 388 mmol) is then added dropwise and at 0 °C. The solution is stirred for 2 h at room temperature, then poured dropwise onto a 1:1 (v/v) mixture of diisopropyl ether/water and under

stirring (1.2 L). After 2 h of stirring, the heterogeneous mixture is allowed to rest overnight. The white precipitate is recovered by filtration, washed successively with a 1:1 (v/v) mixture of diisopropyl ether and water (100 mL), then with water (100 mL). The solid obtained is solubilized in water (900 ml) by adjusting the pH to 7 by addition of a 10 N aqueous sodium hydroxide solution, then a 1N aqueous sodium hydroxide solution. The mixture is filtered through a 0.45-µm filter, then purified by ultrafiltration against a 0.9% NaCl solution, then water until the conductimetry of the permeate is less than 50 µS/cm. The solution of co-polyamino acid is then concentrated to approximately 20 g/L theoretical and the pH is adjusted to 7. The aqueous solution is filtered through a 0.2-µm filter and stored at 4 °C.

Dry extract: 23.9 mg/g

DP (estimated by ^{1}H NMR) = 25 therefore i = 0.04

The calculated average molecular weight of the co-polyamino acid BB24 is 4541 g/mol.

HPLC-aqueous SEC (calibrant PEG): Mn = 2800 g/mol.

Example BB25:

co-polyamino acid BB25 - sodium poly-L-glutamate modified at one of its ends by the molecule BA5 and having a number average molecular weight (Mn) of 2800 g/mol

[000559] By a method similar to the one used for the preparation of the co-polyamino acid BB14, applied to the molecule BA5 in free amine form (1.70 g, 1.98 mmol) and of γ-benzyl-L-glutamate N-carboxyanhydride (11.46 g, 43.5 mmol), a sodium-L-glutamate modified at one of its ends by the molecule BA5 is obtained.

Dry extract: 19.8 mg/g

DP (estimated by ^{1}H NMR) = 23 therefore i = 0.043

The calculated average molecular weight of the co-polyamino acid BB25 is 4295 g/mol.

HPLC-aqueous SEC (calibrant PEG): Mn = 2800 g/mol.

Example BB26:

co-polyamino acid BB26 - sodium poly-L-glutamate modified at one of its ends by the molecule BA6 and having a number average molecular weight (Mn) of 2900 g/mol

[000560] By a method similar to the one used for the preparation of the co-polyamino acid BB14, applied to the molecule BA6 in free amine form (3.05 g, 4.01 mmol) and of γ-benzyl-L-glutamate N-carboxyanhydride (22.78 g, 86.5 mmol), a sodium-L-glutamate modified at one of its ends by the molecule BA6 is obtained.

Dry extract: 16.9 mg/g

DP (estimated by ^{1}H NMR) = 21 therefore i = 0.048

The calculated average molecular weight of the co-polyamino acid BB26 is 3894 g/mol.

HPLC-aqueous SEC (calibrant PEG): Mn = 2900 g/mol.

Example BB27:

co-polyamino acid BB27 - sodium poly-L-glutamate modified at one of its ends by molecule BA3 and modified by molecule BA3 and having a number average molecular weight (Mn) of 2300 g/mol.

[000561] Co-polyamino acid BB27-1: poly-L-glutamic acid having a number average molecular weight (Mn) of 3600 g/mol, modified at one of its ends by molecule BA3 and capped at the other end by pidolic acid.

[000562] γ-Benzyl-L-glutamate N-carboxyanhydride (122.58 g, 466 mmol) is placed under vacuum for 30 min in a round-bottom flask dried beforehand in the oven, then anhydrous DMF (220 mL) is introduced. The mixture is stirred under argon until the solubilization is complete, cooled to -10 °C, then a solution of molecule BA3 in free amine form (17.08 g, 21.3 mmol) in chloroform (40 mL) is introduced rapidly. The mixture is stirred at a temperature between 0 °C and room temperature for 2 days, then heated at 65 °C for 4 h. The reaction medium is then cooled to 25 °C, then pidolic acid is added (13.66 g, 105.8 mmol), HOBt (2.35 g, 15.3 mmol) and EDC (20.28 g, 105.8 mmol). After 24 h of stirring at 25 °C, the solution is concentrated under vacuum to eliminate the chloroform and 50% of the DMF. The reaction mixture is then heated at 55 °C and 1150 mL of methanol are introduced in 1 h. The reaction mixture is then cooled to 0 °C. After 18 h, the white precipitate is recovered by filtration, washed three times with 270 mL of diisopropyl ether, then dried under vacuum at 30 °C in order to obtain a white solid. The solid is diluted in TFA (390 mL), and a 33% hydrobromic acid solution (HBr) in acetic acid (271 mL, 1547 mmol) is then added dropwise and at 0 °C. The solution is stirred for 2 h at room temperature, then poured dropwise onto a 1:1 (v/v) mixture of diisopropyl ether/water and under stirring (970 mL). After 2 h of stirring, the heterogeneous mixture is allowed to stand overnight. The white precipitate is recovered by filtration, washed successively with diisopropyl ether (380 mL), then two times with water (380 mL). The solid obtained is solubilized in water (3.6L) by adjusting the pH to 7 by adding a 10 N aqueous sodium hydroxide solution, then 1 N aqueous sodium hydroxide solution. The mixture is filtered through a 0.45-µm filter, then purified by ultrafiltration against a 0.9% NaCl solution, a 0.1 N NaOH solution, a 0.9% NaCl solution, a phosphate buffer solution (150 mM), a 0.9% NaCl solution, then water until the conductimetry of the permeate is less than 50 µS/cm. The solution of co-polyamino acid is then

concentrated to approximately 30 g/L theoretical, filtered through a 0.2-µm filter, then acidified to pH 2 under stirring addition of a 37% HCl solution. The precipitate is then recovered by filtration, washed two times with water, then dried under vacuum at 30 °C to obtain a white solid.

Co-polyamino acid BB27

[000563] By a method similar to the one used for the preparation of the co-polyamino acid BB2, applied to molecule BA3 in free amine form (1.206 g, 1.50 mmol) and to co-polyamino acid BB27-1 (5.5 g, 33.4 mmol), a sodium poly-L-glutamate modified at one of its ends by molecule BA3 and modified by molecule BA3 is obtained.

Dry extract: 19.0 mg/g

DP (estimated based on ^{1}H NMR): 22

Based on ^{1}H NMR: i = 0.089

The calculated average molecular weight of co-polyamino acid BB27 is 4826 g/mol.

HPLC-aqueous SEC (calibrant PEG): Mn = 2300 g/mol.

Example BB42:

co-polyamino acid BB42 - sodium poly-L-glutamate modified at one of its ends by the molecule B8 and having a number average molecular weight (Mn) of 3200 g/mol

[000564] DCC (0.659 g, 3.19 mmol) and NHS (0.365 g, 3.17 mmol) are added to a solution of molecule B8 (2.366 g, 3.11 mmol) in DMF (19.5 mL). After 16 h of stirring at room temperature, the solution is filtered to be used directly in the following reaction.

[000565] γ-Benzyl-L-glutamate N-carboxyanhydride (18.0 g, 68.4 mmol) is placed under vacuum for 30 min in a round-bottom flask dried beforehand in the oven, then anhydrous DMF (40 mL) is introduced. The mixture is then stirred under argon until the dissolution is complete, cooled to 0 °C, then hexylamine (0.411 mL, 3.11 mmol) is introduced rapidly. After 30 h of stirring at 0 °C, the solution of molecule B8 prepared above is added. The solution is stirred between 0 °C and room temperature for 72 h, then poured dropwise into diisopropyl ether (0.9 L) under stirring. The precipitate is recovered by filtration, washed with diisopropyl ether (5 times 100 mL), then dried under vacuum at 30 °C to yield a white solid. The solid is diluted in TFA (69 mL), then the solution is cooled to 4 °C. A 33% HBr solution in acetic acid (48 mL, 0.274 mol) is then added dropwise. The mixture is stirred at room temperature for 2 h, then poured dropwise onto a 1:1 (v/v) mixture of diisopropyl ether and water under stirring (0.8 L). After 2 h of stirring, the heterogeneous mixture is left to rest overnight. The white precipitate is recovered by filtration, washed with a 1:1 (v/v) mixture of diisopropyl ether and water (70 mL), then with water (70 mL). The solid obtained is then solubilized in water (0.42 L) by adjusting the pH to 7 by addition of a 10 N aqueous sodium hydroxide solution, then a 1 N aqueous sodium hydroxide solution. After solubilization, the theoretical concentration is adjusted to 20 g/L theoretical by addition of water until obtaining a final volume of 0.63 L. The solution is filtered through a 0.45-µm filter, then purified by ultrafiltration against a 0.9% NaCl solution, then water until the conductimetry of the permeate is less than 50 µS/cm. The solution obtained is filtered through a 0.2-µm filter and stored at 2-8 °C.

Dry extract: 22.2 mg/g

DP (estimated based on ^{1}H NMR): 22

Based on ^{1}H NMR: i = 0.045

The calculated average molecular weight of the co-polyamino acid BB42 is 4160 g/mol.

HPLC-aqueous SEC (calibrant PEG): Mn = 3200 g/mol.

Example BB43:

co-polyamino acid BB43 - sodium poly-L-glutamate modified at one of its ends by molecule BA3 and at the other end by molecule B8 and having a number average molecular weight (Mn) of 2000 g/mol

[000566] DCC (0.257 g, 1.24 mmol) and NHS (0.143 g, 1.24 mmol) are added to a solution of B8 (0.946 g, 1.24 mmol) in DMF (8 mL). After 16 h of stirring at room temperature, the solution is filtered to be used directly in the following reaction.

[000567] γ-Benzyl-L-glutamate N-carboxyanhydride (6.0 g, 22.8 mmol) is placed under vacuum for 30 min in a round-bottom flask dried in the oven beforehand, then anhydrous DMF (14 mL) is introduced. The mixture is then stirred under argon until the dissolution is complete, cooled to 0 °C, then a solution of molecule BA3 in free amine form (0.832 g, 1.04 mmol) in chloroform (2.0 mL) is introduced rapidly. After 18 h of stirring at 0 °C, the solution of molecule B8 prepared beforehand is added. The solution is stirred between 0 °C and room temperature for 22 h, then poured dropwise into diisopropyl ether (0.34 L) under stirring. The precipitate is recovered by filtration, washed with diisopropyl ether (7 times 15 mL), then dried under vacuum at 30 °C to yield a white solid. The solid is diluted in TFA (23 mL), then the solution is cooled to 4 °C. A 33% HBr solution in acetic acid (15 mL, 85.7 mmol) is then added dropwise. The mixture is stirred at room temperature for 2 h, then poured dropwise onto a 1:1 (v/v) mixture of diisopropyl ether and water under stirring (0.28 L). After 2 h of stirring, the heterogeneous mixture is allowed to rest overnight. The white precipitate is recovered by filtration, washed two

times with a 1:1 (v/v) mixture of diisopropyl ether and water (24 mL), then two times with water (24 mL). The solid obtained is then solubilized in water (0.16 L) by adjusting the pH to 12 by addition of a 10 N aqueous sodium hydroxide solution, then a 1 N aqueous sodium hydroxide solution. After 30 minutes, the pH is adjusted to 7 by slow addition of a 1N aqueous HCl solution. The solution is filtered through a 0.45-µm filter, then purified by ultrafiltration against a 0.9% NaCl solution, then water until the conductimetry of the permeate is less than 50 µS/cm. The solution obtained is filtered through a 0.2-µm filter and stored at 2-8 °C.

Dry extract: 18.9 mg/g

DP (estimated based on ^{1}H NMR): 22

Based on ^{1}H NMR: $i_1 = 0.09$

The calculated average molecular weight of the co-polyamino acid BB43 is 4871 g/mol.

HPLC-aqueous SEC (calibrant PEG): Mn = 2000 g/mol.

Example BB44:

co-polyamino acid BB44 - sodium poly-L-glutamate modified at one of its ends by the molecule BA7 and having a number average molecular weight (Mn) of 3300 g/mol

[000568] By a method similar to the one used for the preparation of the co-polyamino acid BB14, applied to molecule BA7 in free amine form (4.45 g, 5.18 mmol) and to 30.0 g (113.96 mmol) of γ-benzyl-L-glutamate N-carboxyanhydride, a sodium poly-L-glutamate modified at one of its ends by molecule BA7 is obtained.

Dry extract: 29.0 mg/g

DP (estimated by ^{1}H NMR) = 25 thus i = 0.04

The calculated average molecular weight of the co-polyamino acid BB44 is 4597 g/mol.

HPLC-aqueous SEC (calibrant PEG): Mn = 3300 g/mol.

Part CE: counter-examples co-polyamino acids

Part C:

The glucagon used is human glucagon originating from a peptide synthesis process. It originates from the company Bachem (reference 407473).

Example C1: Solution of Glucagon at 2 mg/mL

[000569] Powdered glucagon (80 mg) is introduced into a 45-mL flask. A 0.003 N aqueous hydrochloric acid solution (40 mL) is added. The glucagon powder is mixed by repeated inversions of the tube until the dissolution of the glucagon is complete. The solution of glucagon at 2 mg/mL is then filtered through a membrane (0.22 µm).

Example C2: Solution of Glucagon at 4 mg/mL

[000570] Powdered glucagon (160 mg) is introduced into a 45-mL flask. A 0.006 N aqueous hydrochloric acid solution (40 mL) is added. The glucagon powder is mixed by repeated inversions of the tube until the dissolution of the glucagon is complete. The solution of glucagon at 4 mg/mL is then filtered through a membrane (0.22 µm).

Example C3: Solution of Glucagon at 6 mg/mL

[000571] Powdered glucagon (240 mg) is introduced into a 45-mL flask. A 0.01 N aqueous hydrochloric acid solution (40 mL) is added. The glucagon powder is mixed by repeated

inversions of the tube until the dissolution of the glucagon is complete. The solution of glucagon at 6 mg/mL is then filtered through a membrane (0.22 µm).

Example C4: Solution of Glucagon at 10 mg/mL

[000572] Powdered glucagon (400 mg) is introduced into a 45-mL flask. A 0.01 N aqueous hydrochloric acid solution (40 mL) is added. The glucagon powder is mixed by repeated inversions of the tube until the dissolution of the glucagon is complete. The solution of glucagon at 10 mg/mL is then filtered through a membrane (0.22 µm).

[000573] At first, tests were carried out to verify whether the polyamino acids make it possible to solubilize the glucagon, and the minimum concentration of co-polyamino acid necessary to solubilize the glucagon was determined.

Example CA1: Compositions of co-polyamino acid AB16 at variable concentrations and glucagon concentration of 1 mg/mL.

[000574] 2X mg of co-polyamino acid AB16 were weighed on a precision scale, and 2 mL of a 10 mM phosphate buffer solution comprising m-cresol (46 mM), glycerol (548 mM) were added. The composition is stirred until dissolution of the co-polyamino acid, then the solution is filtered through a membrane (0.22 µm).

[000575] 2 mL of a glucagon solution as prepared in Example C1 are mixed at 2 mL of the solution of co-polyamino acid as prepared above, leading to a composition comprising X mg/mL of co-polyamino acid and 1 mg/mL of glucagon.

[000576] A visual inspection was carried out to determine whether or not a clear solution was obtained. The result of the minimum concentration is presented in Table 5.

Example CA3: Composition of co-polyamino acid BB14 at variable concentrations and a glucagon concentration of 1 mg/mL.

[000577] In the same manner as described in Example CA1, compositions comprising X mg/mL of co-polyamino acid BB14 and 1 mg/mL of glucagon are prepared.

[000578] A visual inspection was carried out to determine whether or not a clear solution was obtained. The result of the minimum concentration is presented in Table 5.

Example CA5: Composition of co-polyamino acid BB15 at variable concentrations and a glucagon concentration of 1 mg/mL.

[000579] In the same manner as described in Example CA1, compositions comprising X mg/mL of co-polyamino acid BB15 and 1 mg/mL of glucagon are prepared.

[000580] A visual inspection was carried out to determine whether or not a clear solution was obtained. The result of the minimum concentration is presented in Table 5.

Example	Co-polyamino acid	Minimum concentration of co-polyamino acid (in mg/mL) for the solubilization of human glucagon (1 mg/mL)
CA1	AB16	≤ 0.82
CA3	BB14	≤ 0.82
CA5	BB15	≤ 1.25

Table 5: Minimum concentration of co-polyamino acid (in mg/mL) for the solubilization of human glucagon (1 mg/mL).

Example CA7: Solution of co-polyamino acid BB15 at 4.4 mg/mL and of glucagon at 2 mg/mL

[000581] 17.2 mg of co-polyamino acid BB15 are weighed on a precision scale, and 2 mL of a 10 mM phosphate buffer solution comprising m-cresol (46 mM), glycerol (548 mM) are

added. The composition is stirred until dissolution of the co-polyamino acid, then the solution is filtered through a membrane (0.22 µm).

[000582] 2 mL of glucagon solution as prepared in Example C2 are mixed with 2 mL of the solution of co-polyamino acid BB15 as prepared above.

[000583] A clear solution is obtained.

Example CA8: Solution of co-polyamino acid BB15 at 4.4 mg/mL and of glucagon at 3 mg/mL

[000584] 2 mL of a glucagon solution as prepared in Example C3 are mixed with 2 mL of the solution of co-polyamino acid BB15 as prepared in Example CA7.

[000585] A clear solution is obtained.

Example CA9: Solution of co-polyamino acid BB15 at 4.4 mg/mL and of glucagon at 5 mg/mL

[000586] 2 mL of a glucagon solution as prepared in Example C4 are mixed with 2 mL of the solution of co-polyamino acid BB15 as prepared in Example CA7.

[000587] A clear solution is obtained.

[000588] Tests were carried out in order to verify whether the co-polyamino acids make it possible to stabilize the glucagon, then determine a minimum concentration of co-polyamino acid necessary in order to stabilize the glucagon.

Example CB1: Solution of co-polyamino acid BB15 at variable concentrations and a glucagon concentration of 1 mg/mL

[000589] 2X mg of co-polyamino acid BB15 are weighed on a precision scale, and 2 mL of a 10 mM phosphate buffer solution comprising m-cresol (46 mM), glycerol (548 mM) are added. The composition is stirred until dissolution of the co-polyamino acid, then the solution is filtered through a membrane (0.22 µm).

[000590] 2 mL of a glucagon solution as prepared in Example C1 are mixed with 2 mL of the solution of co-polyamino acid as prepared above, leading to a composition comprising X mg/mL of co-polyamino acid and 1 mg/mL of glucagon.

[000591] Then three samples of 1 mL each of these solutions are prepared and placed under static conditions at 37 °C.

[000592] A visual inspection is carried out at 7 days, 14 days and 21 days, see Table 6.

[000593] The study of the physical stabilities of the compositions of Examples CB1a to CB1g described in the table below was carried out on volumes of 1 mL of composition in flasks having a capacity of 3 mL (Adelphi - ref: VCDIN2RDLS1).

Example	Concentration of co-polyamino acid BB15 (mg/mL)	Stable at 7 days	Stable at 14 days	Stable at 21 days
CB1a	0.4	no	no	no
CB1b	0.8	no	no	no
CB1c	1.2	no	no	no
CB1d	2.5	no	no	no
CB1e	3.8	yes	yes	yes
CB1f	5.1	yes	yes	yes
CB1g	6.4	yes	yes	yes

Table 6: Series of concentrations for determining the minimum molar ratio hydrophobic radical/glucagon

Concentration series were prepared with other co-polyamino acids, leading to the obtention of the following stable solutions.

Example CB5: Solution of co-polyamino acid AB15 at 14 mg/mL and of glucagon at 1 mg/mL

[000594] 56 mg of co-polyamino acid AB15 are weighed on a precision scale, and 2 mL of a 10 mM phosphate buffer solution comprising m-cresol (46 mM), glycerol (548 mM) are added. The composition is stirred until dissolution of the co-polyamino acid, then the solution is filtered through a membrane (0.22 µm).

[000595] 2 mL of a glucagon solution as prepared in Example C1 are mixed with 2 mL of the solution of co-polyamino acid as prepared above. Then three samples of 1 mL each of this solution are prepared and placed under static conditions at 37 °C.

Example CB6: Solution of co-polyamino acid AB16 at 16.2 mg/mL and of glucagon at 1 mg/mL

[000596] 64.8 mg of co-polyamino acid AB16 are weighed on a precision scale, and 2 mL of a 10 mM phosphate buffer solution comprising m-cresol (46 mM), glycerol (548 mM) are added. The composition is stirred until dissolution of the co-polyamino acid, then the solution is filtered through a membrane (0.22 µm).

[000597] 2 mL of a glucagon solution as prepared in Example C1 are mixed with 2 mL of the solution of co-polyamino acid as prepared above. Then three samples of 1 mL each of this solution are prepared and placed under static conditions at 37 °C.

Example CB7: Solution of co-polyamino acid AB17 at 6.4 mg/mL and of glucagon at 1 mg/mL

[000598] 25.6 mg of co-polyamino acid AB17 are weighed on a precision scale, and 2 mL of a 10 mM phosphate buffer solution comprising m-cresol (46 mM), glycerol (548 mM) are added. The composition is stirred until dissolution of the co-polyamino acid, then the solution is filtered through a membrane (0.22 µm).

[000599] 2 mL of a glucagon solution as prepared in Example C1 are mixed with 2 mL of the solution of co-polyamino acid as prepared above. Then three samples of 1 mL each of this solution are prepared and placed under static conditions at 37 °C.

Example CB15: Solution of co-polyamino acid BB14 at 9.1 mg/mL and of glucagon at 1 mg/mL

[000600] 36.4 mg of co-polyamino acid BB14 are weighed on a precision scale, and 2 mL of a 10 mM phosphate buffer solution comprising m-cresol (46 mM), glycerol (548 mM) are added. The composition is stirred until dissolution of the co-polyamino acid, then the solution is filtered through a membrane (0.22 µm).

[000601] 2 mL of a glucagon solution as prepared in Example C1 are mixed with 2 mL of the solution of co-polyamino acid as prepared above. Then three samples of 1 mL each of this solution are prepared and placed under static conditions at 37 °C.

Example CB16: Solution of co-polyamino acid BB16 at 3.8 mg/mL and of glucagon at 1 mg/mL

[000602] 15.2 mg of co-polyamino acid BB16 are weighed on a precision scale, and 2 mL of a 10 mM phosphate buffer solution comprising m-cresol (46 mM), glycerol (548 mM) are added. The composition is stirred until dissolution of the co-polyamino acid, then the solution is filtered through a membrane (0.22 µm).

[000603] 2 mL of a glucagon solution as prepared in Example C1 are mixed with 2 mL of the solution of co-polyamino acid as prepared above. Then three samples of 1 mL each of this solution are prepared and placed under static conditions at 37 °C.

Example CB17: Solution of co-polyamino acid BB16 at 6.3 mg/mL and of glucagon at 1 mg/mL

[000604] 25.2 mg of co-polyamino acid BB16 are weighed on a precision scale, and 2 mL of a 10 mM phosphate buffer solution comprising m-cresol (46 mM), glycerol (548 mM) are added. The composition is stirred until dissolution of the co-polyamino acid, then the solution is filtered through a membrane (0.22 µm).

[000605] 2 mL of a glucagon solution as prepared in Example C1 are mixed with 2 mL of the solution of co-polyamino acid as prepared above. Then three samples of 1 mL each of this solution are prepared and placed under static conditions at 37 °C.

Example CB18: Solution of co-polyamino acid BB15 at 4.4 mg/mL and of glucagon at 2 mg/mL

[000606] 17.6 mg of co-polyamino acid BB15 are weighed on a precision scale, and 2 mL of a 10 mM phosphate buffer solution comprising m-cresol (46 mM), glycerol (548 mM) are added. The composition is stirred until dissolution of the co-polyamino acid, then the solution is filtered through a membrane (0.22 µm).

[000607] 2 mL of a glucagon solution as prepared in Example C2 are mixed with 2 mL of the solution of co-polyamino acid as prepared above. Then three samples of 1 mL each of this solution are prepared and placed under static conditions at 37 °C.

Example CB19: Solution of co-polyamino acid BB15 at 8.8 mg/mL and of glucagon at 2 mg/mL

[000608] 35.4 mg of co-polyamino acid BB15 are weighed on a precision scale, and 2 mL of a 10 mM phosphate buffer solution comprising m-cresol (46 mM), glycerol (548 mM) are added. The composition is stirred until dissolution of the co-polyamino acid, then the solution is filtered through a membrane (0.22 µm).

[000609] 2 mL of a glucagon solution as prepared in Example C2 are mixed with 2 mL of the solution of co-polyamino acid as prepared above. Then three samples of 1 mL each of this solution are prepared and placed under static conditions at 37 °C.

Example CB20: Solution of co-polyamino acid BB15 at 6.3 mg/mL, of glucagon at 1 mg/mL and of L-methionine at 0.1 mg/mL

[000610] A solution of co-polyamino acid BB15 at 12.6 mg/mL is prepared by dissolving 46.5 mg of lyophilizate of co-polyamino acid BB15 with 1.6 mL of water, 1.3 mL of m-cresol at 126.7 mM, 358 µL of glycerol at 4.9 M, 360 µL of a 100 mM phosphate buffer solution and 75 µL of L-methionine at 9.8 mg/mL. The solution is filtered through a membrane (0.22 µm).

[000611] 2 mL of a glucagon solution as prepared in Example C2 are mixed with 2 mL of the solution of co-polyamino acid as prepared above. Then three samples of 1 mL each of this solution are prepared and placed under static conditions at 37 °C.

Example CB21: Solution of co-polyamino acid BB15 at 6.3 mg/mL, of glucagon at 1 mg/mL and of L-methionine at 1 mg/mL

[000612] A solution of co-polyamino acid BB15 at 12.6 mg/mL is prepared by dissolving 46.5 mg of lyophilizate of co-polyamino acid BB15 with 937 µL of water, 1.3 mL of m-cresol at

126.7 mM, 358 µL of glycerol at 4.9 M, 360 µL of a 100 mM phosphate buffer solution and 733 µL of L-methionine at 9.8 mg/mL. The solution is filtered through a membrane (0.22 µm).

[000613] 2 mL of a glucagon solution as prepared in Example C2 are mixed with 2 mL of the solution of co-polyamino acid as prepared above. Then three samples of 1 mL each of this solution are prepared and placed under static conditions at 37 °C.

Example CB22: Solution of co-polyamino acid BB15 at 6.3 mg/mL, of glucagon at 1 mg/mL and of exenatide at 0.1 mg/mL

[000614] 14 mg of exenatide (Bachem; Product No. -4044219) are introduced into Eppendorf tubes, then 1.4 mL of water is added. The powder is mixed by means of repeated inversions, and the solution of exenatide at 10 mg/mL is filtered through a membrane (0.22 µm).

[000615] A solution of co-polyamino acid BB15 at 12.6 mg/mL is prepared by dissolving 28.3 mg of lyophilizate of co-polyamino acid BB15 with 937 µL of water, 817 µL of m-cresol at 126.7 mM, 224 µL of glycerol at 4.9 M, 225 µL of a buffer solution at 100 mM and 45 µL of exenatide at 10 mg/mL. The solution is filtered through a membrane (0.22 µm).

[000616] The final solution is prepared by mixing 2 mL of a glucagon solution as prepared in Example C1 and 2 mL of the solution of BB15 at 12.6 mg/mL as prepared above. The mixture is homogenized manually and contains 1 mg/mL of glucagon, 0.1 mg/mL of exenatide, 6.3 mg/mL of BB15, 5 mM of phosphate buffer, 23 mM of m-cresol and 249 mM of glycerol.

[000617] Three samples of 1 mL each of this solution are prepared and placed under static conditions at 37 °C.

Example CB23: Solution of co-polyamino acid BB15 at 6.3 mg/mL, of glucagon at 1 mg/mL and of exenatide at 0.25 mg/mL

[000618] A solution of exenatide at 10 mg/mL is obtained in the same manner as described in Example CB22.

[000619] A solution of co-polyamino acid BB15 at 12.6 mg/mL is prepared by dissolving 28.4 mg of lyophilizate of co-polyamino acid BB15 with 872 µL of water, 817 µL of m-cresol at 126.7 mM, 224 µL of glycerol at 4.9 M, 225 µL of a phosphate buffer solution at 100 mM and 113 µL of exenatide at 10 mg/mL. The solution is filtered through a membrane (0.22 µm).

[000620] The final solution is prepared by mixing 2 mL of a glucagon solution as prepared in Example C1 and 2 mL of the solution of co-polyamino acid BB15 at 12.6 mg/mL as prepared above. The mixture is homogenized manually and contains 1 mg/mL of glucagon, 0.25 mg/mL of exenatide, 6.3 mg/mL of BB15, 5 mM of phosphate buffer, 23 mM of m-cresol and 249 mM of glycerol.

[000621] Three samples of 1 mL each of this solution are prepared and placed under static conditions at 37 °C.

[000622] Example CB24: Solution of co-polyamino acid BB15 at 6.3 mg/mL, of glucagon at 1 mg/mL and of exenatide at 0.5 mg/mL

[000623] A solution of co-polyamino acid BB15 at 12.6 mg/mL is prepared by dissolving 28.2 mg of lyophilizate of co-polyamino acid BB15 with 750 µL of water, 817 µL of m-cresol at 126.7 mM, 224 µL of glycerol at 4.9 M, 225 µL of a phosphate buffer solution at 100 mM and 226 µL of exenatide at 10 mg/mL, as prepared in the example above. The solution is filtered through a membrane (0.22 µm).

[000624] The final solution is prepared by mixing 2 mL of a solution of glucagon as prepared in Example C1 and 2 mL of the solution of BB15 at 12.6 mg/mL as prepared above. The mixture is homogenized manually and contains 1 mg/mL of glucagon, 0.5 mg/mL of exenatide, 6.3 mg/mL of co-polyamino acid BB15, 5 mM of phosphate buffer, 23 mM of m-cresol and 249 mM of glycerol.

[000625] Three samples of 1 mL each of this solution are prepared and placed under static conditions at 37 °C.

Example CB26: composition of co-polyamino acid BB15 at 3.8 mg/mL, glucagon at 1 mg/mL and citrate at pH 7.1

[000626] 7.6 mg of co-polyamino acid BB15 are weighed on a precision scale and diluted in water, and, by successive additions of concentrated glycerol solutions, phosphate buffer and citrate, an aqueous solution is obtained with a final concentration of BB15 (7.6 mg/mL), of glycerol (550 mM), of phosphate originating from a mixture of NaH_2PO_4 and Na_2HPO_4, (4 mM) and of sodium citrate (10 mM). The solution is filtered through a membrane (0.22 µm).

[000627] 2 mL of a glucagon solution as prepared in Example C1 are mixed with 2 mL of the co-polyamino acid solution as prepared above, in such a manner as to obtain a composition comprising 3.8 mg/mL of co-polyamino acid BB15, 1 mg/mL of glucagon and 5 mM of citrate. The pH of the solution is adjusted to pH 7.1 ± 0.1. This solution is filtered through a membrane (0.22 µm).

[000628] In a manner similar to the composition described in Example CB26, compositions CB27, CB30 and CB30' are also prepared (Table 6a). L-Methionine is present at 1 mg/mL in the compositions CB30 and CB30'.

[000629] In a manner similar to the composition described in Example CB26, and by adding a zinc chloride solution at the time of the mixing of the solutions of glucagon and of co-polyamino acid, the compositions CB28 and CB29 have also been prepared in a manner so as to obtain the desired concentrations (Table 6a).

[000630] The compositions prepared above were transferred into cartridges (easy-to-fill from OMPI of 3 mL - Ref P40B4100.3250) in the amount of 1 mL per cartridge and placed under static conditions at 37 °C.

Compositions	Glucagon (mg/mL)	Glycerol (mM)	Co-polyamino acid (mg/mL)	Citrate (mM)	Zinc (mM)	pH
CB26	1	250	BB15 (3.8)	5	0	7.1
CB27	1	250	BB15 (3.8)	10	0	7.1
CB28	1	250	BB15 (3.8)	5	0.3	7.1
CB29	1	250	BB15 (3.8)	10	0.3	7.1
CB30	1	250	BB19 (3.3)	10	0	7.1
CB30'	1	250	BB19 (3.9)	10	0	7.1

Table 6a: composition of co-polyamino acid, glucagon at 1 mg/mL and citrate at pH 7.1.

Example CB31: composition of co-polyamino acid BB15 at 11.3 mg/mL, glucagon at 3 mg/mL and citrate

[000631] 22.7 mg of co-polyamino acid BB15 are weighed on a precision scale and diluted in water, and, by successive additions of concentrated solutions of glycerol, phosphate buffer, citrate and m-cresol, an aqueous solution with a final concentration of BB15 (22.7 mg/mL), of

glycerol (530 mM), of phosphate (4 mM), of sodium citrate (20 mM) and of m-cresol (54 mM) is obtained. The solution is filtered through a membrane (0.22 µm).

[000632] 2 mL of a glucagon solution as prepared in Example C3 are mixed with 2 mL of the solution of co-polyamino acid as prepared above in a manner so as to obtain a composition at 11.3 mg/mL of co-polyamino acid BB15, 3 mg/mL of glucagon and 10 mM of citrate. The pH of the solution is adjusted to pH 7.1 ± 0.1. The solution is filtered through a membrane (0.22 µm).

[000633] In a manner similar to the composition described in Example CB31, and by adding a zinc chloride solution at the time of the mixing of the solutions of glucagon and of co-polyamino acid, the compositions CB32 to CB34 were also prepared in a manner so as to obtain the desired concentrations (Table 6b).

[000634] The compositions prepared above are transferred into 3 cartridges (easy-to-fill from OMPI of 3 mL - Ref P40B4100.3250) in the amount of 1 mL per cartridge and placed under static conditions at 37 °C.

Compositions	Glucagon (mg/mL)	Glycerol (mM)	BB15 (mg/mL)	Citrate (mM)	Zinc (mM)	m-cresol (mM)	pH
CB31	3	250	11.3	10	0	27	7.1
CB32	3	250	11.3	10	0.3	27	7.1
CB33	3	250	11.3	10	0.9	27	7.1
CB34	3	250	11.3	10	1.8	27	7.1

Table 6b: compositions of co-polyamino acid BB15 at 11.3 mg/mL, glucagon at 3 mg/mL and citrate at pH 7.1.

Examples CB35 to CB83: compositions of co-polyamino acid

[0001] In a manner similar to the composition described in Example CB31, the compositions CB35 to CB84 were also prepared in a manner so as to obtain the desired concentrations (Table 6c).

[0002] In all the compositions, the glucagon concentration is 1 mg/mL and the phosphate buffer concentration is 2 mM.

Compositions	Co-polyamino acid	co-polyamino acid (mg/mL)	Glycerol (mM)	m-cresol (mM)	Methionine (mg/mL)
CB35	BB15	3.8	292	0	1
CB36		3.8	277	15	1
CB37		3.8	265	27	1
CB38		3.8	0	0	1
CB39	AB21’	3.8	256	27	0
CB40		6.3	247		0
CB41		8.8	239	27	0
CB42	BB20	2.9	264	27	0
CB43		4.8	261	27	0
CB44		6.7	258	27	0
CB45	BB21	1.8	266	27	0
CB46		3.0	264	27	0
CB47		4.3	262	27	0
CB48	BB23	3.4	263	27	0
CB49		5.6	260	27	0
CB50		7.9	256	27	0
CB51	BB17	8.6	246	27	0
CB52		14.3	231	27	0
CB53		20.0	216	27	0
CB54	BB25	3.7	264	27	0
CB55		6.2	263	27	0
CB56		8.7	259	27	0
CB57	BB27	1.7	263	27	0
CB58		6.9	260	27	0
CB59		9.7	257	27	0
CB60	BB42	3.6	261	27	0
CB61		6.0	256	27	0
CB62		8.4	251	27	0
CB69	BB14	3.5	261	27	0
CB70		5.8	256	27	0
CB71	BB43	4.3	263	27	0
CB72		7.1	259	27	0
CB73		9.9	255	27	0
CB74	BB15	3.8	263	27	0
CB75		6.3	260	27	0

CB76		8.8	257	27	0
CB77		7.6	258	27	0
CB78		11.3	253	27	0
CB79	BB15	2.9	265	27	0
CB80	BB15	3.3	264	27	0
CB81	BB27	2.8	265	27	0
CB82	BB27	3.0	265	27	0
CB83	BB27	3.5	264	27	0

Table 6c: compositions of glucagon at pH 7.2 +/- 0.1 in the presence of co-polyamino acid

Examples CB84 to CB89: compositions of co-polyamino acid

[0003] In a manner similar to the composition described in Example CB31, the compositions CB84 to CB89 were also prepared in a manner so as to obtain the desired concentrations (Table 6d).

[0004] In all the compositions, the phosphate buffer concentration is 2 mM.

Compositions	Glucagon (mg/mL)	Co-polyamino acid	co-polyamino acid (mg/mL)	Glycerol (mM)	m-cresol (mM)	Methionine (mg/mL)	Excipients
CB84	1	BB15	3.9	262	0	1	Citrate 10 mM
CB85	3	BB15	9.8	265	27	1	Zn 300µM
CB86	2	BB15	8.8	219	27	1	Citrate 10 mM
CB87	2	BB15	9.1	134	27	1	Citrate 10 mM Nicotinamide 80 mM
CB88	2	BB15	6.3	188	27	1	Nicotinamide 80 mM
CB89	1	BB42	3.6	261	27	0	

Table 6d: compositions of glucagon at pH 7.2 +/- 0.1 in the presence of co-polyamino acid

Part C' - counter-example formulations

[0005] The cetyltrimethylammonium bromide (CTAB) originates from the company Sigma-Aldrich (ref A6909).

[0006] The dodecyl maltoside (DDM) originates from the company Sigma-Aldrich (ref: D4641).

[0007] The name (mPEG-DSPE 2000) originates from the company Interchim (ref: KV5081).

[0008] The myristoyl lysophosphatidyl choline (LMPC) originates from the company Combi-Block (ref: QE-2488).

[0009] In a manner similar to the composition described in Example CB1, compositions CEC1 to CEC10 are also prepared in a manner so as to obtain the desired concentrations (Table 6e).

[00010] In all the compositions, the glucagon concentration is 1 mg/mL. The concentration of phosphate buffer is 2 mM and the concentration of m-cresol is 27 mM.

Compositions	compounds of the prior art	compounds of the prior art (mg/mL)	Glycerol (mM)	m-cresol (mM)
CEC1	CTAB	0.3	267	27
CEC2	CTAB	15.7	182	27
CEC3	CTAB	39.3	53	27
CEC4	DDM	0.4	268	27
CEC5	DDM	3.2	262	27
CEC6	DDM	10.7	247	27
CEC7	PEG-DSPE	2.4	267	27
CEC8	PEG-DSPE	10.9	229	27
CEC9	LMPC	0.4	268	27
CEC10	LMPC	2.1	264	27

Table 6e: compositions of glucagon at 1 mg/mL at pH 7.2 +/- 0.1 in the presence of compounds of the prior art at different concentrations.

Part D: STABILITY

Example D1: Physical stability of compositions of co-polyamino acid/glucagon

[00011] The visual inspection of the samples placed under static conditions at 37 °C is carried out at 0, 7, 14 and 21 days at 37 °C in order to detect the appearance of visible particles or turbidity. This inspection is carried out according to the recommendations of the European Pharmacopoeia (EP 2.9.20): the samples are subjected to illumination of at least 2000 lux and are observed on a white background and a black background. When particles are visible in at least 2 of the 3 samples, the composition is considered unstable. Thus, stable means that on the day of inspection at least 2 samples were free of particles.

[00012] The results of the visual inspections are reported in the following Table 7.

[00013] The study of the physical stabilities of the compositions of Examples CB1e, CB2 to CB25 described in the table below was carried out on volumes of 1 mL of composition in flasks having a capacity of 3 mL (Adelphi - ref: VCDIN2RDLS1).

Example	Co-Polyamino acid (mg/mL)	Glucagon (mg/mL)	Exenatide (mg/mL)	L-methionine (mg/mL)	Stable at 7 days	Stable at 14 days	Stable at 21 days
CB1e	BB15 (3.8)	1	0	0	yes	yes	yes
CB5	AB15 (14)	1	0	0	yes	yes	yes
CB6	AB16 (16.2)	1	0	0	yes	yes	yes
CB7	AB17 (6.4)	1	0	0	yes	yes	yes
CB15	BB14 (9.1)	1	0	0	yes	yes	no
CB16	BB16 (3.8)	1	0	0	yes	yes	no
CB17	BB16 (6.3)	1	0	0	yes	yes	yes
CB18	BB15 (4.4)	2	0	0	yes	yes	no
CB19	BB15 (8.6)	2	0	0	yes	yes	yes
CB20	BB15 (6.3)	1	0	0.1	yes	yes	yes-
CB21	BB15 (6.3)	1	0	1	yes	yes	yes
CB22	BB15 (6.3)	1	0.1	0	yes	yes	yes

CB23	BB15 (6.3)	1	0.25	0	yes	yes	yes
CB24	BB15 (6.3)	1	0.5	0	yes	yes	yes
CB25	AB21 (8.6)	1	0	0	yes	yes	yes

" - " means not observed

Table 7: Results of the visual inspections of compositions comprising a co-polyamino acid and glucagon

Example D1a: Physical stability of compositions of co-polyamino acid/glucagon/citrate.

[00014] The visual inspection of the samples is carried out as described above in Example D1.

[00015] The results of the visual inspections of the compositions at 1 mg/mL and 3 mg/mL of glucagon are reported in Table 7a.

[00016] The study of the physical stabilities of the compositions of Examples CB26 to CB34 described in the table below was carried out on volumes of 1 mL of composition in cartridges having a capacity of 3 mL (easy-to-fill from OMPI of 3 mL - Ref P40B4100.3250). Due to the specificities of this container, the stabilities observed are often greater than those observed in flasks.

Compositions	Co-polyamino acid (mg /mL)	Glucagon (mg/mL)	Citrate (mM)	Zinc (mM)	Stable at 14 days	Stable at 21 days	Stable at 28 days	Stable at 35 days	Stable at 42 days
CB26	BB15 (3.8)	1	5	0	Yes	Yes	Yes	Yes	Yes

CB27	BB15 (3.8)	1	10	0	Yes	Yes	Yes	Yes	Yes
CB28	BB15 (3.8)	1	5	0.3	Yes	Yes	Yes	Yes	Yes
CB29	BB15 (3.8)	1	10	0.3	Yes	Yes	Yes	Yes	Yes
CB30	BB19 (3.3)	1	10	0	Yes	Yes	-	-	-
CB30’	BB19 (3.9)	1	10	0	Yes	Yes	-	-	-
CB31	BB15 (11.3)	3	10	0	yes	no	No	No	No
CB32	BB15 (11.3)	3	10	0.3	yes	Yes	no	No	No
CB33	BB15 (11.3)	3	10	0.9	yes	Yes	Yes	no	No
CB34	BB15 (11.3)	3	10	1.8	yes	Yes	no	No	No

" - " means not measured

Table 7a: Results of the visual inspections of compositions at 37 °C comprising a co-polyamino acid, glucagon, citrate, with or without zinc.

The compositions comprising co-polyamino acid BB19 at 3.8 mg/mL, glucagon at 1 mg/mL and citrate at 5 or 10 mM, with zinc at 0.3 mM or without zinc have a physical stability at 37 °C under static conditions in a cartridge of at least 42 days.

The compositions comprising co-polyamino acid BB15 at 3.3 and 3.9 mg/mL, glucagon at 1 mg/mL, citrate at 10 mM, and L-methionine (1 mg/mL) having a physical stability at 37 °C under static conditions in a cartridge of at least 21 days.

The compositions of co-polyamino acid BB15 at 11.3 mg/mL, of glucagon at 3 mg/mL, and of citrate at 10 mM, with or without zinc have a physical stability at 37 °C under static conditions in a cartridge of at least 14 days.

[00017] The study of the physical stabilities of the compositions of Examples CB35 to CB78 described in the table below was carried out on compositions at 1, 2 or 3 mg/mL of glucagon, in parallel with a study of the stability of products described in the prior art as excipient of glucagon.

Compositions	Glucagon (mg/mL)		co-polyamino acid (mg/mL)	container	Stable at					
					7 days	14 days	21 days	28 days	35 days	42 days
CB35	1	BB15	3.8	cartridge	yes	yes	yes	yes	yes	no
CB35	1		3.8	flask	yes	yes	no	-	-	-
CB36	1		3.8	flask	yes	yes	yes	no	-	-
CB37	1		3.8	flask	yes	yes	yes	yes	yes	no
CB38	1		3.8	flask	yes	yes	no	-	-	-
CB39	1	AB21’	3.8	flask	yes	no	-	-	-	-
CB40	1		6.3	flask	yes	yes	yes	yes	yes	yes
CB41	1		8.8	flask	yes	yes	yes	yes	yes	yes
CB42	1	BB20	2.9	flask	yes	yes	yes	no	-	-
CB43	1		4.8	flask	yes	yes	Yes	yes	yes	yes
CB44	1		6.7	flask	yes	yes	Yes	yes	yes	yes
CB45	1	BB21	1.8	flask	yes	yes	Yes	no	-	-
CB46	1		3.0	flask	yes	yes	Yes	Yes	Yes	yes
CB47	1		4.3	Flask	yes	yes	Yes	Yes	Yes	Yes
CB48	1	BB23	3.4	Flask	yes	yes	yes	yes	no	-
CB49	1		5.6	flask	yes	yes	yes	yes	yes	yes
CB50	1		7.9	flask	yes	yes	yes	yes	yes	yes
CB51	1	BB17	8.6	flask	yes	yes	yes	yes	yes	yes
CB52	1		14.3	flask	yes	yes	yes	yes	yes	yes
CB53	1		20	flask	yes	yes	yes	yes	yes	yes
CB54	1	BB25	3.7	flask	yes	yes	yes	yes	no	-

CB55	1		6.2	flask	yes	yes	yes	yes	yes	yes
CB56	1		8.7	flask	yes	yes	yes	yes	yes	yes
CB57	1	BB27	4.2	flask	yes	yes	yes	yes	yes	yes
CB58	1		6.9	flask	yes	yes	yes	yes	yes	yes
CB59	1		9.7	flask	yes	yes	yes	yes	yes	yes
CB60	1	BB42	3.6	flask	yes	yes	yes	yes	yes	yes
CB61	1		6.0	flask	yes	yes	yes	yes	yes	yes
CB62	1		8.4	flask	yes	yes	yes	yes	yes	yes
CB71	1	BB43	4.3	flask	yes	yes	yes	yes	-	-
CB72	1		7.1	flask	yes	yes	yes	yes	-	-
CB73	1		9.9	flask	yes	yes	yes	yes	-	-
CB74	1	BB15	3.8	flask	yes	yes	yes	yes	-	-
CB75	1		6.3	flask	yes	yes	yes	yes	-	-
CB76	1		8.8	flask	yes	yes	yes	yes	-	-
CB77	2		7.6	flask	yes	yes	yes	yes	-	-
CB78	3		11.3	flask	yes	yes	yes	yes	-	-
CEC1	1	CTAB	0.3	flask	no	-	-	-	-	-
CEC2	1	CTAB	15.7	flask	yes	yes	yes	yes	yes	yes
CEC3	1	CTAB	39.3	flask	yes	yes	yes	yes	yes	yes
CEC4	1	DDM	0.4	flask	no	-	-	-	-	-
CEC5	1	DDM	3.2	flask	no	-	-	-	-	-
CEC6	1	DDM	10.7	flask	no	-	-	-	-	-
CEC7	1	mPEG -DSPE	2.4	flask	no	-	-	-	-	-
CEC8	1	mPEG -DSPE	10.9	flask	no	-	-	-	-	-
CEC9	1	LMPC	0.4	flask	no	-	-	-	-	-
CEC10	1	LMPC	2.1	flask	no	-	-	-	-	-

Table 7b: Results of the physical stabilities at 37 °C under static conditions of the compositions with co-polyamino acids or commercial products in the presence of glucagon.

Conclusions:

At the concentrations tested, the compositions of co-polyamino acids in the presence of glucagon are more stable than the formulations of the commercial products in the presence of glucagon.

Example D2: Chemical stability of compositions of co-polyamino acid/glucagon

[00018] An RP-HPLC method adapted based on the USP instructions was used to determine the concentration of glucagon and of its degradation products. This method was used in order to evaluate the chemical stability of the glucagon of the compositions. The HPLC conditions are as follows:

- Column: 4.6 x 150 mm, C-18

- Mobile phase A: Solution S/acetonitrile 80/20 (v/v), solution S being a 150 mM potassium dihydrogenophosphate solution in water, adjusted to pH 2.7 with an 85% phosphoric acid solution

- Mobile phase B: water/acetonitrile 60/40 (v/v)

- Mobile phase C: water/acetonitrile 10/90 (v/v)

- Column temperature: 45 °C

- Detection: UV 210 nm

- Temperature of the autosampler: 4 °C

[00019] The recovery was measured on samples at 7, 14 and 21 days at 37 °C under static conditions. The chemical stability data, that is to say the glucagon recovery obtained by RP-HPLC, is presented in the following Table 8.

[00020] The study of the chemical stabilities of the compositions described in the table below was carried out on compositions in flasks (1 mL of composition in flask having a capacity of 3 mL (Adelphi - ref: VCDIN2RDLS1)).

Example	Co-Polyamino acid (mg/mL)	Glucagon (mg/mL)	Exenatide (mg/mL)	L-methionine (mg/mL	Recovery at 7 days	Recovery at 14 days	Recovery at 21 days
CB1e	BB15 (3.8)	1	0	0	≥ 95	-	≥ 85
CB15	BB14 (9.1)	1	0	0	-	≥ 90	-
CB17	BB16 (6.3)	1	0	0	≥ 95	≥ 90	≥ 90
CB18	BB15 (4.4)	2	0	0	≥ 95	≥ 90	≥ 85
CB19	BB15 (8.6)	2	0	0	≥ 95	≥ 90	≥ 90
CB20	BB15 (6.3)	1	0	0.1	≥ 95	≥ 90	-
CB21	BB15 (6.3)	1	0	1	≥ 95	≥ 90	-
CB23	BB15 (6.3)	1	0.25	0	≥ 95	≥ 90	-
CB24	BB15 (6.3)	1	0.5	0	≥ 95	≥ 90	-

" - " means not measured

Table 8: Measurements of recovery of compositions comprising a co-polyamino acid and glucagon

Example D2a: Chemical stability of compositions of co-polyamino acid/glucagon/citrate

[00021] In a manner similar to Example D2, the recovery was measured on samples at 2, 4 and 6 weeks at 37 °C under static conditions. The chemical stability data, that is to say glucagon recovery data obtained by RP-HPLC, is presented in the following table.

[00022] The study of the chemical stabilities of the compositions of Examples CB26 to CB29 and CB31 to CB34 described in the table below was carried out on samples of compositions collected in cartridges (1 mL of composition in cartridge having a capacity of 3 mL (easy-to-fill from OMPI of 3 mL - Ref P40B4100.3250)).

Compositions	Co-Polyamino acid (mg/mL)	Glucagon (mg/mL)	Citrate (mM)	Zinc (mM)	Recovery at 14 days	Recovery at 28 days	Recovery at 42 days
CB26	BB15 (3.8)	1	5	0	≥ 85	≥ 85	≥ 85
CB27	BB15 (3.8)	1	10	0	≥ 90	≥ 90	≥ 80
CB28	BB15 (3.8)	1	5	0.3	≥ 90	≥ 90	≥ 85
CB29	BB15 (3.8)	1	10	0.3	≥ 95	≥ 90	≥ 80
CB31	BB15 (11.3)	3	10	0	≥ 90	-	≥ 75
CB32	BB15 (11.3)	3	10	0.3	≥ 95	-	≥ 85
CB33	BB15 (11.3)	3	10	0.9	≥ 95	-	≥ 85
CB34	BB15 (11.3)	3	10	1.8	≥ 95	-	≥ 85

" - " means not measured

Table 8a: Measurements of recovery of compositions comprising a co-polyamino acid, glucagon and citrate

Physicochemistry

Results of the visual observations conducted on the mixture and of the measurements of fibril formation by ThT

Principle

[00023] The poor stability of a peptide can lead to the formation of amyloid fibrils defined as ordered macromolecular structures. These structures can possibly result from the formation of gel within the sample.

[00024] The test of monitoring the fluorescence of Thioflavin T (ThT) is used in order to analyze the physical stability of the solutions. Thioflavin is a small molecule probe that has a characteristic fluorescence signature when it binds to fibrils of the amyloid type (Naiki et al. (1989) Anal. BioChem. 177, 244-249, LeVine (1999) Methods. Enzymol. 309, 274-284).

[00025] This method makes it possible to monitor the formation of fibrils for low ThT concentrations within undiluted solutions. This monitoring is carried out under accelerated stability conditions: under stirring and at 37 °C.

Experimental conditions

[00026] The samples are prepared just before the start of the measurement. The preparation of each composition is described in the associated example. Thioflavin T was added to the composition from a concentrated stock solution so as to induce a negligible dilution of the composition. The concentration of Thioflavin T in the composition is 40 µM.

[00027] A volume of 150 µL of the composition was introduced into a well of a 96-well plate, then 2.7 µL of concentrated ThT solution was introduced. Each composition was analyzed

in three tests (triplicate) conducted on one plate. The plate was sealed with transparent film in order to prevent the evaporation of the composition.

[00028] This plate was then placed into the enclosure of a plate reader (EnVision 2104 Multilabel, Perkin Elmer). The temperature was regulated at 37 °C, and a lateral stirring at 960 rpm with amplitude 1 mm was carried out.

[00029] A reading of the fluorescence intensity in each well was carried out with an excitation wavelength of 442 nm and an emission wavelength of 482 nm over time.

[00030] The fibril formation process manifests itself in a strong increase in fluorescence after a delay referred to as lag time.

[00031] The lag time is determined visually, taking into consideration the time when the fluorescence signal starts to increase significantly above the baseline.

The lag time value reported corresponds to the average of the lag time measurements conducted on three wells.

The lag time results obtained are presented in the table below.

Compositions	Glucagon (mg/mL)	co-polyamino acid	co-polyamino acid (mg/mL)	Lag time
CB37	1	B15	3.8	>68
CB42	1	BB20	2.9	>68
CB45	1	BB21	1.8	57.7
CB48	1	BB23	3.4	>68
CB51	1	BB17	8.6	>68
CB54	1	BB25	3.7	>68
CB57	1	BB27	4.2	>70
CB60	1	BB42	3.6	>70
CB71	1	BB43	4.3	>88.1
CB79	1	BB15	2.9	73

CB80	1	BB15	3.3	>109
CB81	1	BB27	2.8	58.6
CB82	1	BB27	3.0	>109
CB83	1	BB27	3.5	>109
CEC1	1	CTAB	0.3	NS
CEC7	1	mPEG-DSPE	2.4	2.6
CEC9	1	LMPC	0.4	3.7

NS = Not significant (one hypothesis is that the CTAB quenches the fluorescence signal of ThT)

Part F: Pharmacodynamic studies in pigs

[00032] Studies were conducted for the purpose of evaluating the pharmacodynamics of a composition of co-polyamino acid BB15 and of glucagon (Example CB1e) at a dose of 2 µg/kg in pigs.

[00033] The hypoglycemic effects of this composition of Example CB1e were compared in relation to an injection of a glucagon solution (Glucagon®, NOVO NORDISK) at 2 µg/kg.

[00034] Twelve animals which had fasted for approximately 5.5 hours beforehand received injections in the flank at the dose of 2 µg/kg using a Junior Star® pen. To account for the regulatory effects of glycemia by the secretion of insulin in response to the hyperglycemic effect induced by the injection of glucagon, 30 minutes before the injection, 44 µg/kg of octeotide is administered to the pigs by the subcutaneous route. Three blood samples were drawn in the hour preceding the injection (T-40min, T-20min and T-10min), in order to determine the base level of glucose and of glucagon. Blood samples were then drawn during the 3 hours after the administration. The glycemia is determined by means of a glucometer.

[00035] The median pharmacodynamic curves of glycemia expressed by the difference in glucose relative to the basal level are represented in Figure 1.

[00036] The curve representing the results obtained with the composition of Example CB1e is represented by empty squares, and the curve representing the results of the glucagen® composition is represented by filled circles.

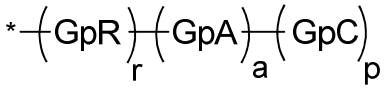
[00037] The pharmacodynamic results obtained based on the administration of the formulation of Example CB1e and of Glucagen® show a hyperglycemic activity rapidly after injection with a maximum glycemia being reached 30 minutes after injection. These pharmacodynamic profiles show that the formulation of Example CB1e and of commercial human glucagon (Glucagen®) have similar pharmacodynamics properties.

CLAIMS

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

a) human glucagon;

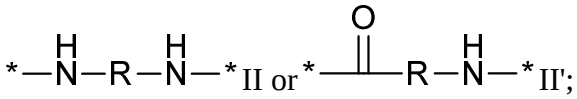
b) a co-polyamino acid bearing carboxylate charges and hydrophobic radicals Hy, said co-polyamino acid consisting of glutamic or aspartic units, and said hydrophobic radicals Hy being radicals of the following formula I:



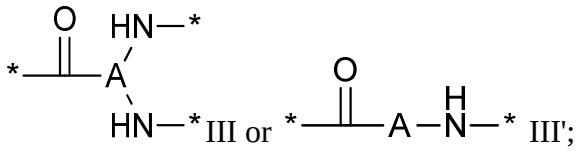
Formula I

in which

– GpR is a radical of formula II or II':

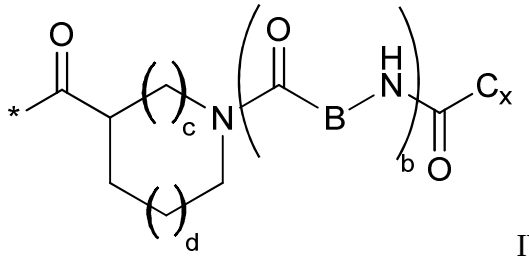


– GpA is a radical of formula III or III':


III or

III';

– GpC is a radical of formula IV:


IV;

– the * indicate the sites of attachment of the different groups bound by amide functions;

– a is a whole number equal to 0 or 1;

– b is a whole number equal to 0 or 1;

– p is a whole number equal to 1 or 2, and

- if p is equal to 1, then a is equal to 0 or 1 and GpA is a radical of formula III', and
- if p is equal to 2, then a is equal to 1 and GpA is a radical of formula III;

– c is a whole number equal to 0 or 1, and, if c is equal to 0, then d is equal to 1 or 2;

– d is a whole number equal to 0, to 1 or 2;

– r is a whole number equal to 0 or 1, and

- if r is equal to 0, then the hydrophobic radical of formula I is bound to the co-polyamino acid via a covalent bond between a carbonyl of the hydrophobic radical and a nitrogen atom in the N-terminal position of the co-polyamino acid, thus forming an amide function , and

- if r is equal to 1, then the hydrophobic radical of formula I is bound to the co-polyamino acid:
  - via a covalent bond between a nitrogen atom of the hydrophobic radical and a carbonyl of the co-polyamino acid therefore forming an amide function originating from the reaction between an amine function of the precursor of the hydrophobic radical and an acid function borne by the precursor of the co-polyamino acid, or
  - via a covalent bond between a carbonyl of the hydrophobic radical and a nitrogen atom in N-terminal position of the co-polyamino acid therefore forming an amide function originating from the reaction of an acid function of the precursor of the hydrophobic radical and an amine function in N terminal position borne by the precursor of the co-polyamino acid;

– R is a radical selected from the group consisting of:

- a linear or branched divalent alkyl radical comprising, if GpR is a radical of formula II, from 2 to 12 carbon atoms, or, if GpR is a radical of formula II', from 1 to 11 carbon atoms;
- a linear or branched divalent alkyl radical comprising, if GpR is a radical of formula II, from 2 to 11 carbon atoms, or, if GpR is a radical of formula II', from 1 to 11 carbon atoms, said alkyl radical bearing one or more -CONH2 functions, and
- an unsubstituted ether or polyether radical comprising from 4 to 14 carbon atoms and from 1 to 5 oxygen atoms;

– A is a linear or branched alkyl radical comprising from 1 to 6 carbon atoms;

– B is a linear or branched alkyl radical, optionally comprising an aromatic ring, comprising from 1 to 9 carbon atoms;

– C_x is a linear or branched monovalent alkyl radical, in which x indicates the number of carbon atoms, and:

- if p is equal to 1, x is from 11 to 25 ($11 \leq x \leq 25$);
- if p is equal to 2, x is from 9 to 15 ($9 \leq x \leq 15$),

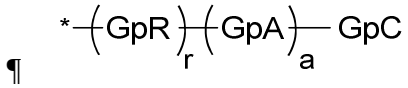
– the ratio i between the number of hydrophobic radicals and the number of glutamic or aspartic units being between $0 < i \leq 0.5$;

– 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 is from 10 to 250;

– the free acid functions being in the form of a salt of an alkaline cation selected from the group consisting of Na^+ and K^+.

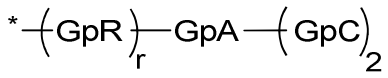
2. The composition according to Claim 1, characterized in that said hydrophobic radicals are selected from the hydrophobic radicals of formula I in which p = 1, represented by the following formula V:

¶ 

formula V

GpR, GpA, GpC, r and a have the definitions given above.

3. The composition according to Claim 1, characterized in that said hydrophobic radicals are selected from the hydrophobic radicals of formula I in which a = 1 and p = 2, represented by the following formula VI:

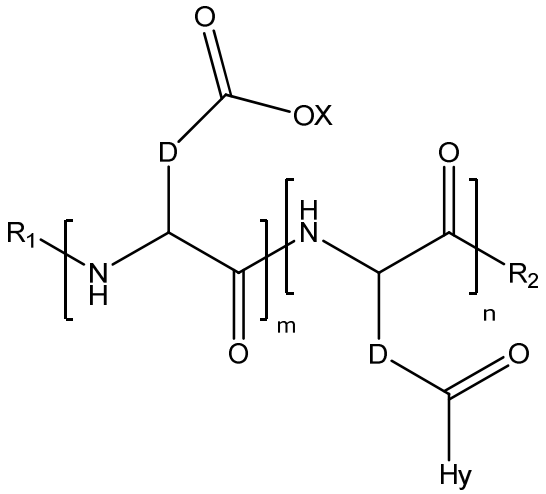


Formula VI

in which

GpR, GpA, GpC, r and a have the definitions given above.

4. The composition according to any one of the preceding claims, characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of the following formula VII:

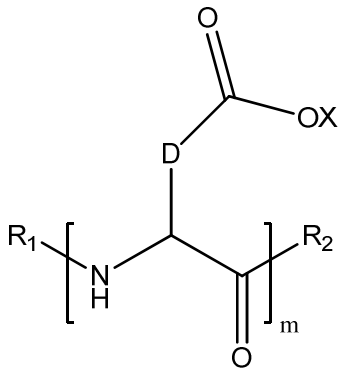


formula VII

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 selected from the hydrophobic radicals of formula I, V or VI, in which r = 1 and GpR is a radical of Formula II,
- R_1 is a hydrophobic radical selected from the hydrophobic radicals of formula I, V or VI in which r = 0 or r = 1 and GpR is a radical of Formula II', or a radical selected from the group consisting of H, a C2 to C10 linear acyl group, a C3 to C10 branched acyl group, benzyl, a terminal "amino acid" unit and a pyroglutamate,
- R_2 is a hydrophobic radical selected from the hydrophobic radicals of formula I, V or VI in which r = 1 and GpR is a radical of Formula II, or a -NR'R" radical, R' and R" which are identical or different being selected from the group consisting of H, the C2 to C10 linear or branched or cyclic alkyls, benzyl, and said alkyl R' and R" together optionally forming one or more saturated, unsaturated and/or aromatic carbon rings and/or optionally comprising heteroatoms selected from the group consisting of O, N and S;
- at least of R_1 or R_2 is a hydrophobic radical as defined above,
- X represents an H or a cationic entity selected from the group comprising the metal cations;
- n + m represents the degree of polymerization DP of the co-polyamino acid, that is to say the average number of monomer units per chain and $5 \leq n + m \leq 250$.

5. The composition according to Claim 4, characterized in that co-polyamino acid bearing carboxylate charges and hydrophobic charges is selected from the co-polyamino acids of formula VII in which n = 0 of the following formula VIIb:



Formula VIIb

in which m, X, D, R_1 and R_2 have the definitions given above and at least one R_1 or R_2 is a hydrophobic radical of formula I, V or VI.

6. The composition according to Claim 5, characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formula VIIb in which R_2 is a hydrophobic radical of formula I, V or VI in which r = 1 and GpR is of formula II'.

7. The composition according to any one of Claims 4 to 7, characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-

polyamino acids of formula VII, VIIb in which the at least one co-polyamino acid is selected from the co-polyamino acids in which group D is a $–CH_2-$ group (aspartic unit).

8. The composition according to any one of Claims 4 to 7, characterized in that the co-polyamino acid bearing carboxylate charges and hydrophobic radicals is selected from the co-polyamino acids of formulas VII, VIIb in which the at least one co-polyamino acid is selected from the co-polyamino acids in which group D is a group $–CH_2-CH_2-$ (glutamic unit).

9. 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.

10. The composition according to any one of the preceding claims, characterized in that the concentration of human glucagon is from 0.25 to 5 mg/mL.

11. The composition according to any one of the preceding claims, characterized in that the molar ratio [hydrophobic radical]/[human glucagon] is less than 15.

12. The composition according to any one of the preceding claims, characterized in that it comprises, in addition, a polyanionic compound.

13. The composition according to any one of the preceding claims, characterized in that it comprises, in addition, a zinc salt.

14. The composition according to any one of the preceding claims, characterized in that it comprises, in addition, a gastrointestinal hormone.

15. The composition according to Claim 13, characterized in that the gastrointestinal hormone is selected from the group consisting of exenatide, liraglutide, lixisenatide, albiglutide and dulaglutide, their analogs or derivatives and their pharmaceutically acceptable salts thereof.

16. The composition according to any one of Claims 13 and 14, characterized in that the concentration of gastrointestinal hormone is within an interval from 0.01 to 10 mg/mL.