EUROPEAN PATENT SPECIFICATION

(54) STABLE PROTEIN SOLUTION FILLED IN A CONTAINER MADE FROM A HYDROPHOBIC RESIN AND METHOD OF STABILIZING THE SAME

STABILE PROTEINLÖSUNG ABGEFÜLLT IN EINEM BEHÄLTNIS AUS HYDROPHOBEM HARZ UND EINE METHODE ZUR STABILISIERUNG DERSELBEN

SOLUTION DE PROTEINE STABLE CONTENUE DANS DES RÉCIPIENTS À BASE DE RÉSINE HYDROPHOBE ET PROCÉDÉ DE STABILISATION ASSOCIÉ

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EP-A- 0 524 802
EP-A- 0 879 611
EP-A1- 0 490 549
EP-A1- 0 559 146
WO-A1-89/01791
WO-A1-96/38503
GB-A- 2 193 631
JP-A- 11 146 910
US-A- 4 992 419

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The present invention relates to protein solution formulations wherein said protein is erythropoietin or granulocyte colony-stimulating factor which are easy to handle and stable over long periods. More specifically, the present invention relates to stable protein solution formulations prefilled in a resin container. The present invention also relates to methods for stabilizing protein solution formulations.

Prior Art

With the development of genetic recombination technology, various protein formulations are supplied in stable amounts. To ensure stability, these formulations are supplied in the dosage form of a lyophilized protein ingredient powder to be dissolved just before use in a water-soluble diluent, either separately packaged, or in the dosage form of a protein solution formulation containing additives which improve stability. When both dosage forms are compared, the solution dosage form is more advantageous in terms of convenience of use, but it is difficult to ensure its stability.

Usually, protein solution formulations are supplied to the market in a container such as a vial, ampoule or disposable syringe containing active proteins together with diluents, solubilizing agents, isotonizing agents, excipients, pH-modifiers, buffers, sulfur-containing reducing agents, antioxidants or the like. Such a container should satisfy the following requirements: (1) it should keep protein formulations stable under long-term storage conditions; (2) it should be sufficiently resistant to heat and pressure in order to tolerate conditions employed in sterilization; (3) it should have chemical resistance; (4) container fragments should not enter solution formulations during use; (5) if the container is a syringe, its plunger should have good slidability; (6) it should have transparency to enable turbidity of the solution or contaminants to be detected; (7) it should be able to be transported easily; and (8) it should be resist to leaching.

Glass containers are advantageous in terms of heat resistance, pressure resistance, chemical resistance and transparency, but involve complex and expensive processes such as coating of silicone or similar finishing agents and baking. Moreover, leaching from glass materials may cause drugs to become unstable or unsoluble matter to be produced. Glass containers are also inconvenient for transportation due to their weight and fragility.

Another problem with protein solution formulations is protein content loss caused by aggregation, denaturation or degradation, especially during long-term storage at room temperatures. Therefore, there is a demand for development of protein solution formulations for long-term storage at room temperatures, but no formulations which satisfy all of the requirements described above have been developed, and no stable protein formulations prefilled in a resin container have yet been supplied to the market.


EP-A-0 524 802 is directed to a container for a sanitary article consisting of a material containing a resin formed of a cyclic olefin compound or a bridged polycyclic hydrocarbon compound, as a polymeric component.

US-A-4,992,419 discloses a compatible storage-stable EPO preparation comprising EPO, a physiologically compatible buffer, 5 to 50 g/liter urea, 1 to 50 g/liter amino acid and 0.05 to 5 g/liter non-ionic wetting agent.

GB-A-2 193 631 is directed to a stable G-CSF containing pharmaceutical preparation containing in addition to the active agent at least one substance selected from a pharmaceutically acceptable surfactant, saccharide, protein and high-molecular weight compound.

EP-A1-0 556 034 is directed to a medical instrument capable of maintaining medicament liquids such as pharmaceuticals, nutriments in high quality and dosing correctly and sanitarily. The medical instrument comprises a material containing a resin formed of cyclic olefin compound or a bridged polycyclic hydrocarbon compound, as a polymeric component.

EP-A1-0 559 146 discloses medical implements such as syringes, ampoules, bottles made of a thermoplastic norbomere polymer.

Disclosure of the Invention

The inventors of the present invention examined reactivity between proteins and glass surfaces and reached the conclusion that polar residues originally present on glass material surfaces such as silanol or silylox might be primarily responsible for degradation and association of physiologically active proteins. Some means have been proposed and used to reduce the influence of these polar residues by, for example, coating polysilicone, alkylsilicone or the like on glass surfaces or by chemically masking silanol residues, but failed to essentially improve stability.

From the viewpoint of the affinity for container surfaces in contact with a protein solution particularly containing erythropoietin (EPO), the inventors hypothesized that when the normal phase of glass surfaces, i.e. stationary phase is
1) cycloolefin copolymer consisting of a copolymer of a cyclic olefin and an olefin,
2) ring-opened polymers of cycloolefins, and
3) hydrogenated ring-opened polymers of cycloolefins.

The present invention provides said protein solution formulation wherein the resin is a copolymer of a cyclic olefin and an olefin.

The present invention provides said protein solution formulation wherein the cycloolefin copolymer is a copolymer of norbornene or tetracyclododecene or a derivative thereof and ethylene or propylene.

The present invention provides said protein solution formulation wherein the cycloolefin copolymer is a copolymer of norbornene or tetracyclododecene and ethylene.

The present invention provides said protein solution formulation wherein the resin is a thermoplastic norbornene resin or a thermoplastic tetracyclododecene resin.

The present invention provides said protein solution formulation wherein the container is in the form selected from the group consisting of a vial, ampule, syringe and bottle.

The present invention provides said protein solution formulation wherein the protein is a gene recombinant protein.

The present invention provides said protein solution formulation wherein the protein is erythropoietin.

The present invention provides said protein solution formulation wherein the protein is granulocyte colony-stimulating factor.

The present invention provides said protein solution formulation wherein the protein is a protein having a sugar chain.

The present invention provides a method for stabilizing a protein solution formulation comprising storing said protein solution formulation in a container made from a hydrophobic resin at least in the part in contact with said formulation wherein said protein is erythropoietin or granulocyte colony-stimulating factor, and wherein said hydrophobic resin is selected from the group as described above.

THE MOST PREFERRED EMBODIMENTS OF THE INTENTION

Suitable resins as container materials for use in the present invention include known resins represented by ring-opened polymers of cycloolefins such as norbornene or tetracyclododecene or derivatives thereof and hydrogenated products thereof; or copolymers having a cyclopentyl residue or substituted cyclopentyl residue inserted into the molecular chain by polymerization of a cycloolefin such as norbornene or tetracyclododecene or a derivative thereof and ethylene or propylene. Cycloolefins here include monocyclic and polycyclic compounds. Preferred are thermoplastic norbornene resins or thermoplastic tetracyclododecene resins. Thermoplastic norbornene resins include ring-opened polymers of norbornene monomers and hydrogenated products thereof, addition polymers of norbornene monomers, and addition polymers of norbornene monomers and olefins. Thermoplastic tetracyclododecene resins include ring-opened polymers of tetracyclododecene monomers and hydrogenated products thereof, addition polymers of tetracyclododecene monomers, and addition polymers of tetracyclododecene monomers and olefins. Thermoplastic norbornene resins are de-
scribed in, for example, JPA No. 14882/91, JPA No. 122137/91 and JPA No. 63807/92.

[0032] Especially preferred are cycloolefin copolymers (COCs) such as copolymers of norbornene and an olefin such as ethylene, and copolymers of tetracyclododecene and an olefin such as ethylene. Cycloolefin polymers (COPs) obtained by ring-opening polymerization and hydrogenation of norbornene are also preferred. Such COCs and COPs are described in, for example, JPA No. 300939/93 or JPA No. 317411/93. Preferred structures of such COCs and COPs are shown below.

(1) Examples of COC (copolymers of tetracyclododecene and ethylene)

(2) Examples of COC (copolymers of norbornene and an olefin such as ethylene)

(3) Examples of COP (hydrogenated ring-opened polymers of norbornenes)
Physiologically active proteins used as active ingredients in the present invention are selected from granulocyte colony-stimulating factor (G-CSF), colony-stimulating factor (CSF), and erythropoietin (EPO).

 Especially preferred physiologically active proteins used as active ingredients in the present invention are G-CSF, CSF, and EPO having a sugar chain. The sugar chain may be derived from any source, but preferably those added to mammalian cells. Mammalian cells include, for example, Chinese hamster ovary (CHO) cells, BHK cells, COS cells, human-derived cells, etc., among which CHO cells are most preferred.

When the physiologically active protein used as an active ingredient in the present invention is EPO, EPO may be prepared by any process, e.g., it may be extracted from human urine and isolated and purified by various techniques or may be produced by genetic engineering (see JPA No. 12288/86, for example) of Chinese hamster ovary (CHO) cells, BHK cells, COS cells, human-derived cells or the like and then extracted and isolated and purified by various techniques. EPO chemically modified with PEG is also included (see International Publication WO90/12874). EPO having no sugar chain and chemically modified with PEG or the like is also included. EPO analogs are also included, in which EPO has been modified to increase the number of one or more glycosylation sites at the N-linked carbohydrate chain binding site or O-linked carbohydrate binding site in the amino acid sequence of EPO (see JPA No. 151398/96 and JPA No. 606023/96, for example) or the amount of sugar chains have been increased by increasing the content of sialic acid without changing the number of sugar chain-binding sites.

When the physiologically active protein used as an active ingredient in the present invention is G-CSF, any high-purity human G-CSF can be used. G-CSF in the present invention may be prepared by any process, e.g., they may be extracted from cultured cells of a human tumor cell line and isolated and purified by various techniques or may be produced by genetic engineering in bacterial cells such as E. coli; yeast cells; animal culture cells such as Chinese hamster ovary (CHO), C127 or COS cells and then extracted and isolated and purified by various techniques. G-CSF is preferably produced by genetic recombination in E. coli, yeast or CHO cells, most preferably by genetic recombination in CHO cells. G-CSF chemically modified with PEG is also included (see International Publication WO90/12874).

Protein solution formulations of the present invention may contain diluents, solubilizing agents, isotonizing agents, excipients, pH-modifiers, soothing agents, buffers, sulfur-containing reducing agents, antioxidants or the like.
For example, isotonizing agents include polyethylene glycol; and sugars such as dextran, mannitol, sorbitol, inositol, glucose, fructose, lactose, xylose, mannose, maltose, sucrose, raffinose. Sulfur-containing reducing agents include N-acetylcysteine, N-acetylmethionine, thiocetic acid, thioglycolic acid, thioglycolic acid, thioglycolic acid and salts thereof, sodium thiosulfate, glutathione, and sulfhydryl-containing compounds such as thiokaloanionic acid having 1 to 7 carbon atoms. Antioxidants include erythorbic acid, dibutylhydroxytoluene, butylhydroxyanisole, β-toco-pherol, tocopherol acetate, L-ascorbic acid and salts thereof, L-ascorbyl palmitate, L-ascorbyl stearate, sodium bisulfite, sodium sulfite, triamyl gallate, propyl gallate or chelating agents such as disodium ethylenediamine tetraacetate (EDTA), sodium pyrophosphate, sodium metaphosphate. Other components commonly added to solution formulations may also be contained, e.g. inorganic salts such as sodium chloride, potassium chloride, calcium chloride, sodium phosphate, potassium phosphate, sodium bicarbonate; and organic salts such as sodium citrate, potassium citrate, sodium acetate.

[0043] Protein solution formulations of the present invention may further contain stabilizers suitable for various proteins including, but not limited to, surfactants (for example, nonionic surfactants such as sorbitan fatty acid esters, glycerin fatty acid esters, polyglycerin fatty acid esters, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene sorbitol fatty acid esters, polyoxyethylene glycerin fatty acid esters, polyethylene glycol fatty acid esters, polyoxyethylene alkyl ethers, polyoxyethylene polyoxypropylene alkyl ethers, polyoxyethylene alkyl phenyl ethers, polyoxyethylene hardened castor oils, polyoxyethylene beeswax derivatives, polyoxyethylene lanolin derivatives, polyoxyethylene fatty acid amides; cat-ionic surfactants such as alkyl sulfates, polyoxyethylene alkyl ether sulfates, alkyl sulfosuccinic acid ester salts; natural surfactants such as lecithin, glycerophospholipids, sphingophospholipids, sucrose fatty acid esters; especially preferred are polyoxyethylene sorbitan fatty acid esters, particularly polyoxyethylene sorbitan monooleate (Polysorbate 80) and polyoxyethylene sorbitol monolaurate (Polysorbate 20), and amino acids such as D-, L- and DL-leucine, tryptophan, serine, glutamic acid, arginine, histidine, lysine, methionine, phenylalanine and acetyltryptophan and salts thereof, preferably L-leucin, L-tryptophan, L-glutamic acid, L-arginine, L-histidine and L-lysine and salts thereof.

[0044] Stable protein solution formulations of the present invention are normally administered via parenteral routes such as injection (subcutaneous or intravenous injection) or percutaneous, mucosal or nasal route, but may also be orally administered.

[0045] The amount of proteins contained in stable protein solution formulations of the present invention can be determined depending on the proteins used, the type of disease to be treated, the severity of the disease, the age of the patient and other factors.

[0046] Generally, proteins are contained in an amount of 0.01 μg - 100 mg/ml, preferably 0.5 μg - 50 mg/ml on the basis of the total amount of formulations of the present invention or injectable compositions after sugars have been added. For example, EPO is usually contained in solution formulations in an amount of 100 - 500,000 IU/ml (about 0.5 - 3000 μg/ml), preferably 200 - 100,000 IU/ml (about 1 - 600 μg/ml), more preferably 750 - 72,000 IU/ml (about 4 - 400 μg/ml). G-CSF is usually contained at a final dose concentration of 1 - 1000 μg/ml, preferably 10 - 800 μg/ml, more preferably 50 - 500 μg/ml. Antibodies are usually contained at a final dose concentration of 0.1 - 200 mg/ml, preferably 1 to 120 mg/ml.

[0047] Solution formulations of the present invention can be prepared by dissolving these components in an aqueous buffer known in the art of solution formulations such as phosphate and/or citrate buffers. Preferred phosphate buffers are sodium monohydrogen phosphate - sodium dihydrogen phosphate systems, and preferred citrate buffers are sodium citrate buffers.

[0048] When protein solution formulations of the present invention are erythropoietin solution formulations, they preferably contain EPO, a nonionic surfactant (such as Polysorbate 80, Polysorbate 20), an isotonizing agent (such as sodium chloride) and if desired, a stabilizer (such as an amino acid, preferably L-histidine) at pH 5.0 - 8.0, preferably 5.5 - 7.0.

[0049] When protein solution formulations of the present invention are G-CSF solution formulations, they preferably contain G-CSF, a nonionic surfactant (such as Polysorbate 80, Polysorbate 20), and if desired, a diluent, solubilizing agent, isotonizing agent, excipient, pH-modifier, soothing agents, buffer, sulfur-containing reducing agent, antioxidant at pH 5.0 - 8.0, preferably 6.0-7.0.

[0050] Stable protein solution formulations prefilled in a hydrophobic resin container of the present invention show very good EPO remaining levels as compared with glass containers even after an accelerated test at 40°C for 6 months as demonstrated by testing on EPO and G-CSF in the examples below.

[0051] The present invention also provides a method for stabilizing a protein solution formulation comprising storing said protein solution formulation filled in a resin container as defined above wherein said a protein is erythropoietin or granulocyte colony-stimulating factor. The term stabilization as used herein depends on the nature of the protein filled. In case of erythropoietin solution formulations, for example, it means that the remaining erythropoietin level is kept at 90% or more, preferably 95% or more, more preferably 98% or more after storage at 10°C for 2 years or more or at 25°C for 6 months or more, preferably one year or more, more preferably 2 years or more or at 40°C for 2 weeks or more.

[0052] The present invention permits protein solution formulations to be stably stored at room temperatures for a long period.
INDUSTRIAL APPLICABILITY

[0053] Protein solution formulations prefilled in a hydrophobic resin container of the present invention show no or little loss in physiologically active protein content and are thus more stable than conventional solution formulations prefilled in a glass container. The present invention permits even protein solution formulations conventionally stored at low temperatures to be stored at room temperatures for a long period. Resin containers of the present invention have the advantage that they can be prepared by a simpler thermoforming process. Moreover, resin containers are well-suited to transportation because they are lighter and less fragile than glass containers, and therefore, the present invention is extremely industrially useful.

EXAMPLES

[0054] The following examples show the results of long-term stability testing and accelerated testing on erythropoietin (EPO) or granulocyte colony-stimulating factor (G-CSF) used as representative examples. Various changes and modifications may be made by those skilled in the art.

[0055] In the following examples, evaluation of formulations was made by determining the content of EPO or G-CSF by RP-HPLC analysis.

Example 1: Long-term stability testing on EPO solution formulations stored at 10°C and 25°C

Preparation of an EPO solution formulation

[0056] A formulation containing the following components per 1 ml of the formulated solution was prepared and adjusted to pH 6.0 with 10 mM phosphate buffered saline.

<table>
<thead>
<tr>
<th>Component</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPO</td>
<td>1500 IU</td>
</tr>
<tr>
<td>Polyoxyethylene sorbitan monooleate (Polysorbate 80)</td>
<td>0.05 mg</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>8.5 mg</td>
</tr>
<tr>
<td>L-hystidine</td>
<td>1.35 mg</td>
</tr>
</tbody>
</table>

Test method

[0057] EPO solution formulations were prepared by filling 0.5 mL of the erythropoietin solution formulation prepared as described above into a glass container coated with silicone on the surface and a COP container (made from a COP, a hydrogenated ring-opened polymer of norbornene; Daikyo Resin CZ® manufactured by Daikyo Seiko), and subjected to stability testing at 10°C for 3 months and 9 months and at 25°C for 3 months, 6 months, 12 months and 24 months.

[0058] The EPO used in this example is a recombinant protein having a sugar chain produced in CHO cells.

[0059] The results (average of a triplicate test) are shown in Table 1 (storage at 10°C) and Table 2 (storage at 25°C) below. The values represent EPO contents determined by RP-HPLC analysis and the values in parentheses represent remaining levels expressed as percentages on the basis of the remaining levels at filling (initial) to 100%.

<table>
<thead>
<tr>
<th>Lot</th>
<th>Container material</th>
<th>Initial</th>
<th>3 months</th>
<th>9 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Glass</td>
<td>98.0% (100.0%)</td>
<td>98.6% (100.6%)</td>
<td>96.4% (98.4%)</td>
</tr>
<tr>
<td></td>
<td>COP</td>
<td>98.0% (100.0%)</td>
<td>98.7% (100.8%)</td>
<td>97.1% (99.0%)</td>
</tr>
<tr>
<td>2</td>
<td>Glass</td>
<td>93.4% (100.0%)</td>
<td>93.5% (100.2%)</td>
<td>91.1% (97.6%)</td>
</tr>
<tr>
<td></td>
<td>COP</td>
<td>92.7% (100.0%)</td>
<td>94.2% (101.6%)</td>
<td>92.0% (99.3%)</td>
</tr>
</tbody>
</table>
As shown from the tables above, remaining EPO levels in both glass and COP containers stored at 10°C for 3 months and 9 months were maintained at approximately 100% of the initial levels. Remaining EPO levels in COP containers stored at 25°C were maintained at 100% of the initial levels after 3 months, 6 months and 12 months and at about 96-98% even after 24 months, in contrast to the tendency toward a slight decrease in glass containers.

These results confirmed that protein solution formulations, especially protein solution formulations having a sugar chain such as EPO prefilled in a resin container of the present invention show very high stability even after storage at room temperatures for a long period.

Example 2: Accelerated testing on EPO solution formulations at 40°C

EPO solution formulations were prepared by filling a glass container and a COP container as described in Example 1 for storage under accelerated test conditions at 40°C for 2 months, 4 months and 6 months.

The results (average of a triplicate test) are shown in Table 3 below.

<table>
<thead>
<tr>
<th>Lot</th>
<th>Container material</th>
<th>Initial</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
<th>24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Glass</td>
<td>98.0%</td>
<td>97.1%</td>
<td>94.7%</td>
<td>89.4%</td>
<td>85.4%</td>
</tr>
<tr>
<td></td>
<td>(100.0%)</td>
<td>(99.0%)</td>
<td>(96.6%)</td>
<td>(91.4%)</td>
<td>(87.1%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>COP</td>
<td>98.0%</td>
<td>98.8%</td>
<td>98.1%</td>
<td>97.2%</td>
<td>96.2%</td>
</tr>
<tr>
<td></td>
<td>(100.0%)</td>
<td>(100.8%)</td>
<td>(100.1%)</td>
<td>(99.1%)</td>
<td>(98.2%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Glass</td>
<td>93.4%</td>
<td>92.1%</td>
<td>89.7%</td>
<td>85.3%</td>
<td>83.3%</td>
</tr>
<tr>
<td></td>
<td>(100.0%)</td>
<td>(98.6%)</td>
<td>(96.0%)</td>
<td>(91.4%)</td>
<td>(98.2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>COP</td>
<td>93.7%</td>
<td>93.7%</td>
<td>92.9%</td>
<td>91.7%</td>
<td>89.4%</td>
</tr>
<tr>
<td></td>
<td>(100.0%)</td>
<td>(101.1%)</td>
<td>(100.2%)</td>
<td>(99.0%)</td>
<td>(96.4%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Glass</td>
<td>97.0%</td>
<td>96.2%</td>
<td>93.8%</td>
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<td>88.6%</td>
</tr>
<tr>
<td></td>
<td>(100.0%)</td>
<td>(99.2%)</td>
<td>(96.7%)</td>
<td>(99.0%)</td>
<td>(98.2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>COP</td>
<td>96.7%</td>
<td>98.1%</td>
<td>97.5%</td>
<td>96.3%</td>
<td>94.9%</td>
</tr>
<tr>
<td></td>
<td>(100.0%)</td>
<td>(101.5%)</td>
<td>(100.8%)</td>
<td>(99.6%)</td>
<td>(98.1%)</td>
<td></td>
</tr>
</tbody>
</table>

As shown from the tables above, remaining EPO levels in both glass and COP containers stored at 10°C for 3 months and 9 months were maintained at approximately 100% of the initial levels. Remaining EPO levels in COP containers stored at 25°C were maintained at 100% of the initial levels after 3 months, 6 months and 12 months and at about 96-98% even after 24 months, in contrast to the tendency toward a slight decrease in glass containers.

These results confirmed that protein solution formulations, especially protein solution formulations having a sugar chain such as EPO prefilled in a resin container of the present invention show very high stability even after storage at room temperatures for a long period. Example 2: Accelerated testing on EPO solution formulations at 40°C

EPO solution formulations were prepared by filling a glass container and a COP container as described in Example 1 for storage under accelerated test conditions at 40°C for 2 months, 4 months and 6 months.

The results (average of a triplicate test) are shown in Table 3 below.

<table>
<thead>
<tr>
<th>Lot</th>
<th>Container material</th>
<th>Initial</th>
<th>2 month</th>
<th>4 months</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Glass</td>
<td>98.0%</td>
<td>84.2%</td>
<td>79.8%</td>
<td>72.3%</td>
</tr>
<tr>
<td></td>
<td>(100.0%)</td>
<td>(85.9%)</td>
<td>(81.4%)</td>
<td>(73.7%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>COP</td>
<td>98.0%</td>
<td>94.9%</td>
<td>92.8%</td>
<td>87.5%</td>
</tr>
<tr>
<td></td>
<td>(100.0%)</td>
<td>(96.9%)</td>
<td>(94.7%)</td>
<td>(89.3%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Glass</td>
<td>93.4%</td>
<td>83.6%</td>
<td>79.4%</td>
<td>67.1%</td>
</tr>
<tr>
<td></td>
<td>(100.0%)</td>
<td>(89.6%)</td>
<td>(85.1%)</td>
<td>(71.8%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>COP</td>
<td>92.7%</td>
<td>89.6%</td>
<td>86.1%</td>
<td>81.2%</td>
</tr>
<tr>
<td></td>
<td>(100.0%)</td>
<td>(96.6%)</td>
<td>(92.9%)</td>
<td>(87.6%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Glass</td>
<td>97.0%</td>
<td>88.8%</td>
<td>82.8%</td>
<td>73.1%</td>
</tr>
<tr>
<td></td>
<td>(100.0%)</td>
<td>(91.5%)</td>
<td>(85.3%)</td>
<td>(75.4%)</td>
<td></td>
</tr>
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<td></td>
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<td>92.8%</td>
<td>88.7%</td>
<td>85.7%</td>
</tr>
<tr>
<td></td>
<td>(100.0%)</td>
<td>(96.0%)</td>
<td>(91.8%)</td>
<td>(88.6%)</td>
<td></td>
</tr>
</tbody>
</table>
These results show that EPO solution formulations filled in a COP container were more stable than those filled in a glass container at 40°C for up to 6 months.

Example 3: Accelerated testing on EPO solution formulations at 50°C

EPO solution formulations were prepared by filling a glass container and a COP container as described in Example 1 for storage under accelerated test conditions at 50°C for one month, 2 months and 3 months, respectively.

The results (average of a triplicate test) are shown in Table 4 below.

Table 4: Results of accelerated testing at 50°C

<table>
<thead>
<tr>
<th>Lot</th>
<th>Container material</th>
<th>Initial</th>
<th>1 month</th>
<th>2 months</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Glass</td>
<td>98.0% (100.0%)</td>
<td>68.5% (69.9%)</td>
<td>48.4% (49.4%)</td>
<td>34.5% (35.2%)</td>
</tr>
<tr>
<td></td>
<td>COP</td>
<td>98.0% (100.0%)</td>
<td>81.6% (83.2%)</td>
<td>65.9% (67.3%)</td>
<td>55.5% (56.7%)</td>
</tr>
<tr>
<td>2</td>
<td>Glass</td>
<td>93.4% (100.0%)</td>
<td>60.2% (64.5%)</td>
<td>45.2% (48.4%)</td>
<td>33.4% (35.8%)</td>
</tr>
<tr>
<td></td>
<td>COP</td>
<td>92.7% (100.0%)</td>
<td>77.3% (83.4%)</td>
<td>62.6% (67.5%)</td>
<td>52.3% (56.4%)</td>
</tr>
<tr>
<td>3</td>
<td>Glass</td>
<td>97.0% (100.0%)</td>
<td>65.6% (67.6%)</td>
<td>46.8% (48.3%)</td>
<td>28.6% (29.4%)</td>
</tr>
<tr>
<td></td>
<td>COP</td>
<td>96.7% (100.0%)</td>
<td>79.4% (82.2%)</td>
<td>65.0% (67.3%)</td>
<td>55.2% (57.1%)</td>
</tr>
</tbody>
</table>

Each of the three lots filled in both glass and COP containers showed an equal tendency towards a decrease in remaining levels under acceleration at 50°C, without any variation from lot to lot. In accelerated testing at 50°C for up to 3 months, EPO solution formulations filled in a COP container were more stable than those filled in a glass container.

Example 4: Accelerated testing on EPO solution formulations at 60°C

EPO solution formulations were prepared by filling a glass container and a COP container as described in Example 1 and for storage under accelerated test conditions at 60°C for one week, 2 weeks and 3 weeks, respectively.

The results (average of a triplicate test) are shown in Table 5 below.

Table 5: Results of accelerated testing at 60°C

<table>
<thead>
<tr>
<th>Lot</th>
<th>Container material</th>
<th>Initial</th>
<th>1 week</th>
<th>2 weeks</th>
<th>3 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Glass</td>
<td>98.0% (100.0%)</td>
<td>80.1% (81.7%)</td>
<td>70.2% (71.6%)</td>
<td>55.9% (57.0%)</td>
</tr>
<tr>
<td></td>
<td>COP</td>
<td>98.0% (100.0%)</td>
<td>87.9% (89.7%)</td>
<td>80.4% (82.0%)</td>
<td>73.2% (74.7%)</td>
</tr>
<tr>
<td>2</td>
<td>Glass</td>
<td>93.4% (100.0%)</td>
<td>74.5% (79.8%)</td>
<td>65.6% (70.3%)</td>
<td>51.7% (55.4%)</td>
</tr>
<tr>
<td></td>
<td>COP</td>
<td>92.7% (100.0%)</td>
<td>83.0% (89.5%)</td>
<td>75.6% (81.5%)</td>
<td>68.5% (73.9%)</td>
</tr>
<tr>
<td>3</td>
<td>Glass</td>
<td>97.0% (100.0%)</td>
<td>79.5% (81.9%)</td>
<td>65.1% (67.1%)</td>
<td>54.4% (56.1%)</td>
</tr>
<tr>
<td></td>
<td>COP</td>
<td>96.7% (100.0%)</td>
<td>86.1% (89.0%)</td>
<td>78.4% (81.1%)</td>
<td>68.6% (70.9%)</td>
</tr>
</tbody>
</table>
Each of the three lots filled in both glass and COP containers showed an equal tendency towards a decrease in remaining levels under acceleration at 60°C, without any variation from lot to lot. In accelerated testing at 60°C for up to 3 months, EPO solution formulations filled in a COP container were more stable than those filled in a glass container.

Example 5: Accelerated testing on G-CSF solution formulations at 40°C

Preparation of a G-CSF solution formulation

A formulation containing the following components per 1 ml of the formulated solution was prepared and adjusted to pH 6.5 with 1 mol/L hydrochloric acid.

<table>
<thead>
<tr>
<th>Component</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>G-CSF</td>
<td>125 µg</td>
</tr>
<tr>
<td>Polyoxyethylene sorbitan monooleate (Polysorbate 20)</td>
<td>0.1 mg</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>7.5 mg</td>
</tr>
</tbody>
</table>

Test method

G-CSF solution formulations were prepared by filling 0.5 mL of the G-CSF solution formulation prepared as described above in a glass container uncoated with silicone on the surface, a glass container coated with silicone on the surface and a COP container (made from a COP, a hydrogenated ring-opened polymer of norbornene; Daikyo Resin CZ® manufactured by Daikyo Seiko), and stored under accelerated test conditions at 40°C for 2 weeks.

The G-CSF used in this example is a recombinant protein having a sugar chain produced in CHO cells.

The results (average of a triplicate test) are shown in Table 6 below. The values represent G-CSF contents determined by RP-HPLC analysis and the values in parentheses represent remaining levels expressed as percentages on the basis of the remaining levels at filling (initial) to 100%.

<table>
<thead>
<tr>
<th>Container material</th>
<th>Initial</th>
<th>2 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glass (uncoated with silicone oil)</td>
<td>100.1% (100.0%)</td>
<td>85.4% (85.3%)</td>
</tr>
<tr>
<td>Glass (coated with silicone oil)</td>
<td>100.1% (100.0%)</td>
<td>84.8% (84.7%)</td>
</tr>
<tr>
<td>COP</td>
<td>100.1% (100.0%)</td>
<td>94.6% (94.5%)</td>
</tr>
</tbody>
</table>

Remaining levels as compared with the initial levels were 85.4% (uncoated with silicone oil) and 84.8% (coated with silicone oil) in glass containers in contrast to 94.6% in COP containers. These results show that G-CSF solution formulations filled in a COP container were more stable than those filled in a glass container at 40°C for up to 2 weeks.

Example 6: Impurities-leaching test and adsorption test to containers

An erythropoietin solution formulation containing 1500 IU or 48000 IU of EPO per 1 ml of the formulated solution was prepared. The formulation containing 1500 IU was prepared as described in Example 1. The formulation containing 48000 IU was prepared as follows.

A formulation containing the following components per 1 ml of the formulated solution was prepared and adjusted to pH 6.0 with 25 mM phosphate buffered saline.

<table>
<thead>
<tr>
<th>Component</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPO</td>
<td>48000 IU</td>
</tr>
<tr>
<td>Polyoxyethylene sorbitan monooleate (Polysorbate 80)</td>
<td>0.05 mg</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>7.0 mg</td>
</tr>
<tr>
<td>L-hystidine</td>
<td>1.35 mg</td>
</tr>
</tbody>
</table>

EPO solution formulations were prepared by filling 0.5 mL of the formulation prepared as described above into a glass syringe coated with silicone on the surface, a COP syringe, a COP vial (both made from a COP, a hydrogenated...
ring-opened polymer of norbornene; Daikyo Resin CZ® manufactured by Daikyo Seiko), a glass ampule uncoated with silicone on the surface and a glass vial uncoated with silicone on the surface.

Impurities-leaching test

[0079] Evaluation was made to determine whether or not any peak of impurities leached from each container other than the peak of EPO is observed when remaining levels in EPO solution formulations prepared in various containers were assayed. No peak of impurities was observed in any of the samples, which confirmed that no impurities were leached from containers.

Adsorption test to containers

[0080] EPO in each container was recovered and the recovery (%) based on the formulated EPO solution was determined. The results (average of a triplicate test) are shown in Table 7.

Table 7: Recovery based on the formulated solution

<table>
<thead>
<tr>
<th></th>
<th>1500 IU</th>
<th>48,000 IU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glass syringe (coated with silicone oil)</td>
<td>98.7%</td>
<td>99.7%</td>
</tr>
<tr>
<td>COP syringe</td>
<td>99.3%</td>
<td>99.6%</td>
</tr>
<tr>
<td>COP vial</td>
<td>99.6%</td>
<td>100.0%</td>
</tr>
<tr>
<td>Glass ampule (uncoated with silicone oil)</td>
<td>93.6%</td>
<td>99.7%</td>
</tr>
<tr>
<td>Glass vial (uncoated with silicone oil)</td>
<td>94.1%</td>
<td>-</td>
</tr>
</tbody>
</table>

[0081] EPO prepared in COP containers showed a recovery comparable to or higher than that of EPO prepared in a glass container coated with silicone oil and much higher than that obtained in glass containers uncoated with silicone oil. Thus, COP containers exhibited superior characteristics as containers with less adsorption to container walls being observed.

Example 7: Long-term stability testing and accelerated testing on EPO solution formulations in various resin containers

[0082] EPO solution formulations were prepared by filling 0.5 mL of an erythropoietin solution formulation containing 1500 IU EPO per 1 ml of the formulated solution (prepared as described in Example 1) into a glass container, a COP container (made from a COP, a hydrogenated ring-opened polymer of norbornene; Daikyo Resin CZ® manufactured by Daikyo Seiko), and a COC container (a copolymer of tetracyclododecene and an olefin such as ethylene: Apel® manufactured by Mitsui Chemicals).

[0083] Thus prepared EPO solution formulations were subjected to (1) stability testing at 25°C for 2 months, 3 months and 6 months, and EPO solution formulations filled in glass and COC containers were further subjected to (2) accelerated testing at 40°C for 2 months, 4 months and 6 months, (3) accelerated testing at 50°C for 1 month, 2 months and 3 months, and (4) accelerated testing at 60°C for 1 week, 2 weeks and 3 weeks. The results (average of a triplicate test) are shown in Tables 8, 9, 10 and 11 below, respectively. The values represent remaining levels expressed as percentages on the basis of the remaining levels at filling (initial) to 100%.

Table 8: Results of log-term stability testing at 25°C

<table>
<thead>
<tr>
<th>Container</th>
<th>2 months</th>
<th>3 months</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glass vial</td>
<td>97.4%</td>
<td>97.8%</td>
<td>95.1%</td>
</tr>
<tr>
<td>COP vial</td>
<td>100.2%</td>
<td>99.9%</td>
<td>99.9%</td>
</tr>
<tr>
<td>COC vial</td>
<td>100.1%</td>
<td>100.2%</td>
<td>100.1%</td>
</tr>
</tbody>
</table>
Table 9: Results of accelerated testing at 40°C

<table>
<thead>
<tr>
<th>Container</th>
<th>2 months</th>
<th>4 months</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glass vial</td>
<td>86.7%</td>
<td>68.2%</td>
<td>43.5%</td>
</tr>
<tr>
<td>COC vial</td>
<td>96.8%</td>
<td>87.6%</td>
<td>83.1%</td>
</tr>
</tbody>
</table>

Table 10: Results of accelerated testing at 50°C

<table>
<thead>
<tr>
<th>Container</th>
<th>1 month</th>
<th>2 months</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glass vial</td>
<td>62.5%</td>
<td>41.4%</td>
<td>24.0%</td>
</tr>
<tr>
<td>COC vial</td>
<td>84.9%</td>
<td>71.8%</td>
<td>57.9%</td>
</tr>
</tbody>
</table>

Table 11: Results of accelerated testing at 60°C

<table>
<thead>
<tr>
<th>Container</th>
<th>1 week</th>
<th>2 weeks</th>
<th>3 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glass vial</td>
<td>69.7%</td>
<td>50.3%</td>
<td>32.9%</td>
</tr>
<tr>
<td>COC vial</td>
<td>82.2%</td>
<td>69.5%</td>
<td>57.8%</td>
</tr>
</tbody>
</table>

In all the tests, EPO solution formulations prepared in resin containers showed higher remaining levels than those prepared in glass containers.

Claims

1. A stable protein solution formulation filled in a container made from a hydrophobic resin at least for the part in direct contact with said formulation, wherein said protein is erythropoietin or granulocyte colony-stimulating factor, and wherein said hydrophobic resin is selected from the group consisting of
   1) cycloolefin copolymer consisting of a copolymer of a cyclic olefin and an olefin,
   2) ring-opened polymers of cycloolefins, and
   3) hydrogenated ring-opened polymers of cycloolefins.

2. The protein solution formulation of Claim 1 wherein the container is made from a resin.

3. The protein solution formulation of Claim 1 or 2 wherein the ring-opened polymers of cycloolefins are ring-opened polymers of norbornene or tetracyclododecene.

4. The protein solution formulation of Claim 1 or 2 wherein the hydrogenated ring-opened polymers of cycloolefins are hydrogenated ring-opened polymers of norbornene or tetracyclododecene.

5. The protein solution formulation of Claim 1 or 2 wherein the cycloolefin copolymer is a copolymer of norbornene or tetracyclododecene or a derivative thereof and ethylene or propylene.

6. The protein solution formulation of Claim 5 wherein the cycloolefin copolymer is a copolymer of norbornene or tetracyclododecene and ethylene.

7. The protein solution formulation of Claim 1 or 2 wherein the resin is a thermoplastic norbornene resin or a thermoplastic tetracyclododecene resin.

8. The protein solution formulation of any one of Claims 1 to 7 wherein the container is in the form selected from the group consisting of a vial, ampule, syringe and bottle.

9. The protein solution formulation of Claim 12, which is a prefilled syringe solution formulation.
10. The protein solution formulation of any one of Claims 1 to 9 wherein the protein is a gene recombinant protein.

11. The protein solution formulation of Claim 10 wherein the protein is erythropoietin.

12. The protein solution formulation of Claim 10 wherein the protein is granulocyte colony-stimulating factor.

13. The protein solution formulation of any one of Claims 1 to 12 wherein the protein is a protein having a sugar chain.

14. The protein solution formulation of any one of Claims 1 to 13 capable of being stored at room temperatures for a long period.

15. A method for stabilizing a protein solution formulation comprising storing said protein solution formulation filled in a container made from a hydrophobic resin at least for the part in direct contact with said formulation, wherein said protein is erythropoietin or granulocyte colony-stimulating factor, and wherein said hydrophobic resin is selected from the group consisting of

   1) cycloolefin copolymer consisting of a copolymer of a cyclic olefin and an olefin,
   2) ring-opened polymers of cycloolefins, and
   3) hydrogenated ring-opened polymers of cycloolefins.

16. A method for stabilizing a protein solution formulation at room temperatures for a long period comprising storing said protein solution formulation filled in a container made from a hydrophobic resin at least for the part in direct contact with said formulation, wherein said protein is erythropoietin or granulocyte colony-stimulating factor, and wherein said hydrophobic resin is selected from the group consisting of

   1) cycloolefin copolymer consisting of a copolymer of a cyclic olefin and an olefin,
   2) ring-opened polymers of cycloolefins, and
   3) hydrogenated ring-opened polymers of cycloolefins.

Patentansprüche

1. Formulierung einer stabilen Proteinlösung, die in einem Behälter abgefüllt ist, welcher zumindest für den Teil, der in direktem Kontakt mit der Formulierung steht, aus einem hydrophoben Harz gemacht ist, wobei das Protein Erythropoietin oder Granulocyten-koloniestimulierender Faktor ist, und wobei das hydrophobe Harz ausgewählt ist aus der Gruppe bestehend aus
   
   1) Cycloolefin-Copolymer bestehend aus einem Copolymer aus einem cyclischen Olefin und einem Olefin,
   2) Cycloolefin-Polymeren mit geöffnetem Ring, und
   3) hydrierten Cycloolefin-Polymeren mit geöffnetem Ring.

2. Formulierung der Proteinlösung nach Anspruch 1, wobei der Behälter aus einem Harz hergestellt ist.

3. Formulierung der Proteinlösung nach Anspruch 1 oder 2, wobei die Cycloolefin-Polymeren mit geöffnetem Ring Norbomen- oder Tetracyclododecen-Polymeren mit geöffnetem Ring sind.

4. Formulierung der Proteinlösung nach Anspruch 1 oder 2, wobei die hydrierten Cycloolefin-Polymeren mit geöffnetem Ring hydrierte Norbomen- oder Tetracyclododecen-Polymeren mit geöffnetem Ring sind.

5. Formulierung der Proteinlösung nach Anspruch 1 oder 2, wobei das Cycloolefin-Copolymer ein Copolymer aus Norbomen oder Tetracyclododecen oder einem Derivat davon und Ethylen oder Propylen ist.

6. Formulierung der Proteinlösung nach Anspruch 5, wobei das Cycloolefin-Copolymer ein Copolymer aus Norbomen oder Tetracyclododecen und Ethylen ist.

7. Formulierung der Proteinlösung nach Anspruch 1 oder 2, wobei das Harz ein thermoplastisches Norbomenharz oder ein thermoplastisches Tetracyclododecenharz ist.
8. Formulierung der Proteinlösung nach einem der Ansprüche 1 bis 7, wobei der Behälter in der Form vorliegt, ausgewählt aus der Gruppe bestehend aus einem Fläschchen, einer Ampulle, einer Spritze und einer Flasche.

9. Formulierung der Proteinlösung nach Anspruch 8, die eine Formulierung einer zuvor abgefüllten Spritzenlösung ist.

10. Formulierung der Proteinlösung nach einem der Ansprüche 1 bis 9, wobei das Protein ein Protein eines rekombinanten Gens ist.

11. Formulierung der Proteinlösung nach Anspruch 10, wobei das Protein Erythropoietin ist.

12. Formulierung der Proteinlösung nach Anspruch 10, wobei das Protein Granulocyten-koloniestimulierender Faktor ist.

13. Formulierung der Proteinlösung nach einem der Ansprüche 1 bis 12, wobei das Protein ein Protein ist, das eine Zuckerkette hat.

14. Formulierung der Proteinlösung nach einem der Ansprüche 1 bis 13, die dazu geeignet ist, bei Raumtemperaturen für einen langen Zeitraum aufbewahrt zu werden.

15. Verfahren zum Stabilisieren einer Formulierung einer Proteinlösung, umfassend das Aufbewahren der Formulierung der Proteinlösung abgefüllt in einem Behälter, der zumindest für den Teil, der in direktem Kontakt mit der Formulierung steht, aus einem hydrophoben Harz hergestellt ist, wobei das Protein Erythropoietin oder Granulocyten-koloniestimulierender Faktor ist, und wobei das hydrophobe Harz ausgewählt ist aus der Gruppe bestehend aus

   1) Cycloolefin-Copolymer bestehend aus einem Copolymer aus einem cyclischen Olefin und einem Olefin,
   2) Cycloolefin-Polymeren mit geöffnetem Ring, und
   3) hydrierten Cycloolefin-Polymeren mit geöffnetem Ring.

16. Verfahren zum Stabilisieren einer Formulierung einer Proteinlösung bei Raumtemperaturen für einen langen Zeitraum, umfassend das Aufbewahren der Formulierung der Proteinlösung abgefüllt in einem Behälter, der zumindest für den Teil, der in direktem Kontakt mit der Formulierung steht, aus einem hydrophoben Harz hergestellt ist, wobei das Protein Erythropoietin oder Granulocyten-koloniestimulierender Faktor ist, und wobei das hydrophobe Harz ausgewählt ist aus der Gruppe bestehend aus

   1) Cycloolefin-Copolymer bestehend aus einem Copolymer aus einem cyclischen Olefin und einem Olefin,
   2) Cycloolefin-Polymeren mit geöffnetem Ring, und
   3) hydrierten Cycloolefin-Polymeren mit geöffnetem Ring.

Revendications

1. Formulation d’une solution de protéine stable contenue dans un récipient constitué d’une résine hydrophobe au moins pour la partie en contact direct avec ladite formulation, ladite protéine étant l’érythropoïétine ou le facteur de croissance hématoïétique G-CSF et ladite résine hydrophobe étant choisie dans le groupe consistant en :

   a) un copolymère de cyclo-oléfine consistant en un copolymère d’une oléfine cyclique et d’une oléfine,
   b) des polymères obtenus par ouverture de cycle de cyclo-oléfines, et
   c) des polymères hydrogénés obtenus par ouverture de cycle de cyclo-oléfines.

2. Formulation d’une solution de protéine selon la revendication 1, dans laquelle le récipient est constitué d’une résine.

3. Formulation d’une solution de protéine selon la revendication 1 ou 2, dans laquelle les polymères obtenus par ouverture de cycle de cyclo-oléfines sont des polymères obtenus par ouverture de cycle de norbornène ou de tétracyclododécène.

4. Formulation d’une solution de protéine selon la revendication 1 ou 2, dans laquelle les polymères hydrogénés obtenus par ouverture de cycle de cyclo-oléfines sont des polymères hydrogénés obtenus par ouverture de cycle de norbornène ou de tétracyclododécène.
5. Formulation d’une solution de protéine selon la revendication 1 ou 2, dans laquelle le copolymère de cyclo-oléfine est un copolymère de norbornène ou de tétracyclododécène ou d’un dérivé de ceux-ci et d’éthylène ou de propylène.

6. Formulation d’une solution de protéine selon la revendication 5, dans laquelle le copolymère de cyclo-oléfine est un copolymère de norbornène ou de tétracyclododécène et d’éthylène.

7. Formulation d’une solution de protéine selon la revendication 1 ou 2, dans laquelle la résine est une résine de norbornène thermoplastique ou une résine de tétracyclododécène thermoplastique.

8. Formulation d’une solution de protéine selon l’une quelconque des revendications 1 à 7, dans laquelle le récipient présente une forme choisie dans le groupe consistant en un fiole, une ampoule, une seringue ou une bouteille.

9. Formulation d’une solution de protéine selon la revendication 8, qui est une seringue préremplie de la formulation de solution.

10. Formulation d’une solution de protéine selon l’une quelconque des revendications 1 à 9, dans laquelle la protéine est une protéine recombinante de gène.

11. Formulation d’une solution de protéine selon la revendication 10, dans laquelle la protéine est l’érythropoïétine.

12. Formulation d’une solution de protéine selon la revendication 10, dans laquelle la protéine est le facteur de croissance hématopoiétique G-CSF.

13. Formulation d’une solution de protéine selon l’une quelconque des revendications 1 à 12, dans laquelle la protéine est une protéine possédant une chaîne de type sucre.

14. Formulation d’une solution de protéine selon l’une quelconque des revendications 1 à 13 pouvant être stockée à température ambiante pendant une longue période de temps.

15. Procédé de stabilisation d’une formulation d’une solution de protéine comprenant le stockage de ladite formulation d’une solution de protéine contenue dans un récipient constitué d’une résine hydrophobe au moins par la partie en contact direct avec ladite formulation, ladite protéine étant l’érythropoïétine ou le facteur de croissance hématopoiétique G-CSF, et ladite résine hydrophobe étant choisie dans le groupe consistant en :

   a) un copolymère de cyclo-oléfine consistant en un copolymère d’une oléfine cyclique et d’une oléfine,
   b) des polymères obtenus par ouverture de cycle de cyclo-oléfines, et
   c) des polymères hydrogénés obtenus par ouverture de cycle de cyclo-oléfines.

16. Procédé de stabilisation d’une formulation d’une solution de protéine à température ambiante pendant une longue période de temps comprenant le stockage de ladite formulation d’une solution de protéine contenue dans un récipient constitué d’une résine hydrophobe au moins pour la partie en contact direct avec ladite formulation, ladite protéine étant l’érythropoïétine ou le facteur de croissance hématopoiétique G-CSF, et ladite résine hydrophobe étant choisie dans le groupe consistant en :

   a) un copolymère de cyclo-oléfine consistant en un copolymère d’une oléfine cyclique et d’une oléfine,
   b) des polymères obtenus par ouverture de cycle de cyclo-oléfines, et
   c) des polymères hydrogénés obtenus par ouverture de cycle de cyclo-oléfines.
REFERENCES CITED IN THE DESCRIPTION

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