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SUSTAINED RELEASE FORMULATION COMPRISING OCTREOTIDE AND THREE LINEAR POLYLACTIDE-CO-GLYCOLIDE POLYMERS

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ABSTRACT
The present invention relates to sustained release formulations comprising as active ingredient octreotide or a pharmaceutically-acceptable salt thereof and three different linear polylactide-co-glycolide polymers (PLGAs).
SUSTAINED RELEASE FORMULATION COMPRISING OCTREOTIDE AND THREE LINEAR POLYLACTIDE-CO-GLYCOLIDE POLYMERS

[0001] The present invention relates to sustained release formulations comprising as active ingredient octreotide or a pharmaceutically-acceptable salt thereof and three different linear poly(lactide-co-glycolide) polymers (PLGAs).

[0002] These pharmaceutical compositions according to the present invention are indicated for inter alia long-term maintenance therapy in acromegalic patients, and treatment of severe diarrhea and flushing associated with malignant carcinoid tumors and vasoactive intestinal peptide tumors (VIPomas).

[0003] Peptide drugs are usually administered systemically, e.g. parenterally. However, parenteral administration may be painful and cause discomfort, especially for repeated daily adrenalin injections. In order to minimize the number of injections to a patient, the drug substance should be administered as a depot formulation. A common drawback with injectable depot formulations is the fluctuation in plasma levels such as high peak levels together with plasma levels close to zero during the entire release period.

[0004] Sustained release formulations comprising as active ingredient octreotide or a pharmaceutically acceptable salt thereof and two or more different poly(lactide-co-glycolide) polymers (PLGAs) have, for instance, been also disclosed in WO2007/071395.

[0005] The present invention discloses a sustained release formulation comprising as active ingredient (drug substance) octreotide or a pharmaceutically acceptable salt thereof. Octreotide is a somatostatin analog having the following formula:

\[
\text{(D)Phe-Cys-Phe(D)Tyr-Lys-Thr-Cys-Thr}
\]

[0006] The active ingredient may be in the form of a pharmaceutically acceptable salt of octreotide, such as an acid addition salt with e.g. inorganic acid, polymeric acid or organic acid, for example with hydrochloric acid, acetic acid, lactic acid, citric acid, fumaric acid, malonic acid, maleic acid, tartaric acid, aspartic acid, benzoic acid, succinic acid or panopic (embonie) acid. Acid addition salts may exist as mono- or divalent salts, e.g. depending whether 1 or 2 acid equivalents are added. Preferred is the pamoate monosalt of octreotide.

[0007] The particle size distribution of the drug substance influences the release profile of the drug from the depot form. The drug substance which is used to prepare the depot formulation is crystalline or in the form of an amorphous powder. Preferred is an amorphous powder which has a particle size of about 0.1 microns to about 15 microns (99%<1 microns, 99%<15 microns), preferably from 1 to less than about 10 microns (90%<1 microns, 90%<10 microns). The drug substance preferentially undergoes a micronization process to present the required particle size distribution.

[0008] The present invention further provides a sustained release pharmaceutical composition (depot) comprising as active ingredient octreotide or a pharmaceutically-acceptable salt thereof incorporated in blends or mixtures of poly(lactide-co-glycolide)s (PLGAs), for instance in form of microparticles, implants or semisolids formulations.

[0009] Alternatively to blends of PLGAs, in another aspect of the present invention the pharmaceutical composition comprises a mixture of PLGA polymers containing the active ingredient; i.e. the active ingredient may be incorporated into one or more PLGAs in form of microparticles, implants or semisolids formulations and is then mixed with another microparticle or implant or semisolid formulation also comprising the active ingredient and one or more PLGAs.

[0010] The pharmaceutical composition according to the present invention allows a sustained release of the active ingredient over a period of more than three month, preferentially between three and six months. During the release of the active ingredient the plasma levels of octreotide are within the therapeutic range. It is understood that the exact dose of octreotide will depend on a number of factors, including the condition to be treated, the severity of the condition to be treated, the weight of the subject and the duration of therapy.

[0011] Surprisingly fluctuations in plasma levels can significantly be reduced by using a suitable combination of three different linear PLGAs in the pharmaceutical composition according to the present invention.

[0012] The drug substance is incorporated into a biodegradable polymer matrix consisting of three different linear poly(lactide-co-glycolide) polymers (PLGAs). The PLGAs have a lactide-glycolide monomer ratio of 100:0 to 40:60, preferably 90:10 to 40:60, more preferably 85:15 to 65:35.

[0013] The PLGAs according to the present invention have a molecular weight (MW) ranging from 1,000 to 500,000 Da, preferably from 5,000 to 100,000 Da. The architecture of the polymers is linear.

[0014] The inherent viscosity (IV) of the PLGAs according to the present invention is below 0.9 dl/g in CHCl₃, preferentially below 0.8 dl/g in CHCl₃. The inherent viscosities can be measured by the conventional methods of flow time measurement, as described for example in “Pharmacopoeia Européenne”, 1997, pages 17-18 (capillary tube method). Unless stated otherwise, these viscosities have been measured in chloroform at a concentration of 0.5% at 25°C, or in hexafluoroisopropanol at a concentration of 0.5% at 30°C.

[0015] End groups of the PLGAs according to the present invention can be but are not limited to hydroxy, carboxy, ester or the like.

[0016] The drug substance content of the depot formulation (the loading) is in a range of 1% to 30%, preferably 15% to 25%, more preferably 15% to 20%. The loading is defined as the weight ratio of drug substance as free base to the total mass of the PLGA formulation.

[0017] Suitable polymers are commonly known but not limited to those commercially available as RESOMER® by Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany, LACTEL® by Absorbable Polymers International (API), Pelham, Ala., USA; MEDISORB® by Alkermes, Inc., Cambridge, Mass., USA; PURASORB® by PURAC biochem By, Gorinchem, The Netherlands. Examples of suitable polymers are listed in Table 1.
<table>
<thead>
<tr>
<th>No</th>
<th>Product name</th>
<th>Polymer</th>
<th>Inherent viscosity (dL/g)</th>
<th>Producer</th>
<th>Supplier</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Resomer® R 202 H</td>
<td>Linear Poly(DL-lactide) free carboxylic acid end group</td>
<td>0.16-0.24&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Boehringer</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Resomer® R 202 S</td>
<td>Linear Poly(DL-lactide) free carboxylic acid end group</td>
<td>0.16-0.24&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Boehringer</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Resomer® R 203 S</td>
<td>Linear Poly(DL-lactide) free carboxylic acid end group</td>
<td>0.25-0.35&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Boehringer</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Resomer® RG 752 H</td>
<td>Linear Poly(DL-lactide-co-glycolide) 75:25</td>
<td>0.14-0.22&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Boehringer</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Resomer® RG 752 S</td>
<td>Linear Poly(DL-lactide-co-glycolide) 75:25</td>
<td>0.16-0.24&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Boehringer</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Resomer® CG RG 75:25 or Resomer® RG Type 75:25 S</td>
<td>Linear Poly(DL-lactide-co-glycolide) 75:25</td>
<td>0.32-0.44&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Boehringer</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Lactel® 100D020 A</td>
<td>Linear Poly(DL-lactide) free carboxylic acid end group</td>
<td>0.15-0.25&lt;sup&gt;22&lt;/sup&gt;</td>
<td>APIDirect</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Lactel® 100D040 A</td>
<td>Linear Poly(DL-lactide) free carboxylic acid end group</td>
<td>0.25-0.54&lt;sup&gt;22&lt;/sup&gt;</td>
<td>APIDirect</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Lactel® 100D040</td>
<td>Linear Poly(DL-lactide) free carboxylic acid end group</td>
<td>0.25-0.54&lt;sup&gt;22&lt;/sup&gt;</td>
<td>APIDirect</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Lactel® 100D065</td>
<td>Linear Poly(DL-lactide-co-glycolide) 85:15</td>
<td>0.55-0.75&lt;sup&gt;22&lt;/sup&gt;</td>
<td>APIDirect</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Lactel® 85D065</td>
<td>Linear Poly(DL-lactide-co-glycolide) 65:35</td>
<td>0.55-0.75&lt;sup&gt;22&lt;/sup&gt;</td>
<td>APIDirect</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Lactel® 75D065</td>
<td>Linear Poly(DL-lactide-co-glycolide) 50:50</td>
<td>0.55-0.75&lt;sup&gt;22&lt;/sup&gt;</td>
<td>APIDirect</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Lactel® 65D065</td>
<td>Linear Poly(DL-lactide-co-glycolide) 50:50</td>
<td>0.66-0.80</td>
<td>Alkemnes</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Medisorb® 100 DL HIGH IV</td>
<td>Linear Poly(DL-lactide)</td>
<td>0.50-0.65</td>
<td>Alkemnes</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Medisorb® 100 DL LOW IV</td>
<td>Linear Poly(DL-lactide)</td>
<td>0.50-0.65</td>
<td>Alkemnes</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Medisorb® 8515 DL HIGH IV</td>
<td>Linear Poly(DL-lactide-co-glycolide) 85:15</td>
<td>0.66-0.80</td>
<td>Alkemnes</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Medisorb® 8515 DL LOW IV</td>
<td>Linear Poly(DL-lactide-co-glycolide) 85:15</td>
<td>0.50-0.65</td>
<td>Alkemnes</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Medisorb® 7525 DL HIGH IV</td>
<td>Linear Poly(DL-lactide-co-glycolide) 75:25</td>
<td>0.66-0.80</td>
<td>Alkemnes</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Medisorb® 7525 DL LOW IV</td>
<td>Linear Poly(DL-lactide-co-glycolide) 75:25</td>
<td>0.50-0.65</td>
<td>Alkemnes</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Medisorb® 6535 DL HIGH IV</td>
<td>Linear Poly(DL-lactide-co-glycolide) 65:35</td>
<td>0.66-0.80</td>
<td>Alkemnes</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>Medisorb® 6535 DL LOW IV</td>
<td>Linear Poly(DL-lactide-co-glycolide) 65:35</td>
<td>0.50-0.65</td>
<td>Alkemnes</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Medisorb® 5050 DL HIGH IV</td>
<td>Linear Poly(DL-lactide-co-glycolide) 50:50</td>
<td>0.66-0.80</td>
<td>Alkemnes</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>Medisorb® 5050 DL LOW IV</td>
<td>Linear Poly(DL-lactide-co-glycolide) 50:50</td>
<td>0.50-0.65</td>
<td>Alkemnes</td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup>IV has been determined in chloroform at a concentration of 0.1% at 25°C.
<sup>2</sup>IV has been determined in chloroform at a concentration of 0.5 g/dL at 30°C.
<sup>3</sup>IV has been determined in Hexadecane/propionate at a concentration of 0.5 g/dL at 30°C.

[0018] Plasma levels with low variability can be achieved over a time period of more than three months, preferentially between three and six month, only with pharmaceutical compositions according to the present invention, not with formulations containing only one single polymer from the table above.

[0019] In addition, the pharmaceutical composition according to the present invention can be manufactured aseptically or non-aseptically and sterilized terminally by gamma irradiation. Preferred is terminal sterilization by gamma irradiation, resulting in a product with the highest sterility assurance possible.

[0020] The pharmaceutical composition according to the present invention may also contain one or more pharmaceutical excipients modulating the release behavior in an amount of 0.1% to 50%. Examples of such agents are: Poly(vinylpyrrolidone), carboxymethyl cellulose sodium (CMC-Na), dextrin, poly(ethylene glycol), suitable surfactants such as poloxamers, also known as poly(ethylene oxide-block-oxypropylene), Poly(ethylene oxide)-sorbitan-fatty acid esters known and commercially available under the trade name TWEEN® (e.g. Tween 20, Tween 40, Tween 60, Tween 80, Tween 65 Tween 85, Tween 21, Tween 61, Tween 81), Sorbitan fatty acid esters e.g. of the type known and commercially available under the trade name SPAN, Lecithins, inorganic salts such as zinc carbonate, magnesium hydroxide, magnesium carbonate, or protamine, e.g. human protamine or salmon protamine, or natural or synthetic polymers bearing amine-residues such as polylsine.

[0021] The pharmaceutical composition according to the present invention can be a depot mixture or a polymer blend of different polymers in terms of compositions, molecular
weight and/or polymer architectures. A polymer blend is defined herein as a solid solution or suspension of three different linear polymers in one implant or microparticle. A mixture of depositions or blends is defined herein as a mixture of two or more depositions or blends or microparticles or semisolid formulations of different composition with one or more PEGs in each deposit. Preferred is a pharmaceutical composition wherein the three PEGs are present as polymer blend.

[0022] The pharmaceutical composition according to the present invention can be in the form of implants, semisolids (gel), or microspheres which solidify in situ once they are injected or microparticles. Preferred are microparticles. Preparation of microparticles comprising octenode or a pharmaceutically acceptable salt thereof is known; and for instance disclosed in U.S. Pat. No. 5,445,832 or U.S. Pat. No. 5,538,739.

[0023] The following part of the invention is focused on polymer microparticles although the descriptions are applicable for implants, semisolids and liquids as well.

[0024] The microparticles according to the present invention may have a diameter from a few micrometers to a few millimeters, e.g. from about 0.01 microns to about 2 mm, e.g. from about 0.1 microns to about 500 microns. For pharmaceutical microparticles, diameters of at most about 250 microns, e.g. 10 to 200 microns, preferably 10 to 130 microns, more preferably 10 to 90 microns.

[0025] The microparticles according to the present invention may be mixed or coated with an anti-agglomerating agent or covered by a layer of an anti-agglomerating agent, e.g. in a filled syringe or vial. Suitable anti-agglomerating agents include, e.g. mannitol, glucose, dextrose, sucrose, sodium chloride, or water soluble polymers such as polyvinylpyrrolidone or polyethylene glycol, e.g. with the properties described above. For microparticles according to the present invention in dry state preferably an anti-agglomerating agent is present in an amount of about 0.1 to about 10%, preferably about 3% to 5%, e.g. about 4% by weight of the microparticles. A preferred anti-agglomerating agent in this respect is mannitol.

[0026] Alternatively, an anti-agglomerating agent can be applied to the microparticles during their manufacturing process. For example, at the step of filtering/washing the microparticles they can be additionally rinsed with an aqueous solution of an anti-agglomerating agent. Thus, a layer of the anti-agglomerating agent is formed on the surface of the microparticles. Preferably, the anti-agglomerating agent is present in the microparticles at an amount of less than 10%, preferably less than 2%, most preferably less than 0.5% by weight of the microparticles. A preferred anti-agglomerating agent is mannitol.

[0027] The manufacturing process for the depot formulation of the current invention is described in detail for microparticles:

[0028] The microparticles may be manufactured by several processes known in the art, e.g., coacervation or phase separation, spray drying, water-in-oil (W/O) or water-in-oil-in-water (W/O/W) or solids-in-oil-in-water (S/O/W) emulsion/suspension methods followed by solvent extraction or solvent evaporation. The emulsion/suspension method is a preferred process which comprises the following steps:

[0029] (i) preparation of an internal organic phase comprising

[0030] (ii) preparation of an external aqueous phase containing stabilizers and optionally but preferably buffer salts;

[0031] (iii) mixing the internal organic phase with the external aqueous phase e.g. with a device creating high shear forces, e.g. with a turbine or static mixer, to form an emulsion; and

[0032] (iv) hardening the microparticles by solvent evaporation or solvent extraction, washing the microparticles, e.g. with water, collecting and drying the microparticles, e.g. freeze-drying or drying under vacuum, and sieving the microparticles through 140 μm.

[0033] Suitable organic solvents for the polymers include e.g. ethyl acetate, acetone, THF, acetoniitrile, or halogenated hydrocarbons, e.g. methylene chloride, chloroform or hexafluoroisopropanol.

[0034] Suitable examples of a stabilizer for step (ii) include Poly(vinylalcohol) (PVA), in an amount of 0.1 to 5%, Hydroxyethyl cellulose (HEC) and/or hydroxypropyl cellulose (HPC), in a total amount of 0.01 to 5%, Polyvinyl pyrrolidone, Gelatin, preferably porcine or fish gelatin.

[0035] The dry microparticles composition can be terminally sterilized by gamma irradiation (overkill sterilization), optionally in bulk or after filling in the final container resulting in the highest sterility assurance possible. Alternatively the bulk sterilized microparticles can be resuspended in a suitable vehicle and filled as a suspension into a suitable device such as double chamber syringe with subsequent freeze drying.

[0036] The pharmaceutical composition according to the present invention containing microparticles may also contain a vehicle to facilitate reconstitution.

[0037] Prior to administration, the microparticles are suspended in a suitable vehicle for injection. Preferably, said vehicle is water based containing pharmaceutical excipients such as mannitol, sodium chloride, glucose, dextrose, sucrose, or glycine, non-ionicsurfactants (e.g. polysorbates, poly(oxyethylene)-sorbitan-fatty acid esters, carboxymethyl cellulose sodium (CMC-Na), sorbitol, poly(vinylpyrrolidone), or aluminum monostearate in order to ensure isotonicity and to improve the wettability and sedimentation properties of the microparticles. The wetting and viscosity enhancing agents may be present in an amount of 0.01 to 1%, the isotonicity agents are added in a suitable amount to ensure an isotonic injectable suspension.

[0038] The invention further provides the use of a pharmaceutical composition according to the present invention for inter alia long-term maintenance therapy in acromegalic patients, and treatment of severe diarrhea and flushing associated with malignant carcinoid tumors and vasodepressor intestinal peptide tumors (VIPoma tumors).

[0039] The utility of the pharmaceutical compositions according to the present invention can be shown in standard clinical or animal studies.

[0040] The invention further provides a kit comprising the depot formulation in a vial, optionally equipped with a transfer set, together with a water-based vehicle in an ampoule, vial or prefilled syringe or as microparticles and vehicle separated in a double chamber syringe.

EXPERIMENTAL PART

[0041] The following examples are illustrative, but do not serve to limit the scope of the invention described herein. The examples are meant only to suggest a method of practicing the present invention.

Example 1

Microparticle Preparation

[0042] An appropriate amount of the PEG polymers is dissolved in an appropriate amount of dichloromethane to
give an appropriate polymer concentration as stated in column “PLGA conc.” in Table 2. An appropriate amount of drug substance is weight into a glass beaker and the polymer solution is poured over the drug substance so that the resulting microparticles have a drug load as stated in column “drug load”.

E.g. for microparticles with a drug load of 20% and a polymer concentration of 20% the numbers are as the following: 3.547 g of the PLGA polymers are dissolved into 17.7 ml dichromoromethane to give a 20% (w/v) polymer solution. 1.453 g of octreotide pamoate (corresponding to 1.00 g ~20% octreotide free base) is weight into a glass beaker and the polymer solution is poured over the drug substance.

The suspension is homogenized with an Ultra-Turrax rotor-stator mixer with 20000 rpm for 1 min under cooling with an ice/water mixture. This suspension is referred to as S/O suspension.

The S/O suspension is mixed with the 0.5% PVA18-88 solution by pumping the S/O suspension with the help of a flexible tube pump (Perpex, Viton tube) at a rate of 10 ml/min into a turbine and by pumping the aqueous solution with a gear pump (Ismatec MV-Z/B with pumping head PV140) at a rate of 200 ml/min into the same turbine. The two solutions are mixed in the turbine at 4500 rpm. The homogenized S/O/W emulsion is collected into a 2 L glass beaker which is prefilled with 200 ml of the buffered PVA solution.

The S/O/W emulsion is then heated up to 52° C in 5 h. The temperature of 52° C is hold for further 30 min, before the batch is cooled to room temperature again. During this process escaping dichromoromethane is removed by vacuum and the batch is stirred by a 4 blade-propeller-stirrer at 250 rpm.

As a result, microparticles are formed out of the S/O/W emulsion. The microparticles are collected by filtration (5 µm). They are washed 7 times with 200 ml water and dried for 36 h at 20° C. and 0.030 mbar. The dried microparticles are sieved through 140 µm and filled under nitrogen into glass vials. Prepared in that way, the microparticles are sterilized by gamma-irradiation with a dose of 30 kGy.

The particle size of the microparticles is measured by laser light diffraction. The microparticles are resuspended in white spirit using ultrasonic. Table 2 gives the diameter x[10] (90% of all particles are smaller than this value) after 120 seconds of ultrasonic treatment.

The assay of the microparticles is determined by HPLC after dissolving the microparticles with ultra sound in a 3:2 mixture of acetone and methanol and further 1:1 dilution with a sodium acetate buffer (pH 4). The solution is cleared from residual particulate matter by centrifugation.

### Table 2

<table>
<thead>
<tr>
<th>Ex.</th>
<th>Batch</th>
<th>Drug Load (%)</th>
<th>PLGA conc. (%)</th>
<th>Process info</th>
<th>Assay size X[10] (µm)</th>
<th>Particle size (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-1</td>
<td>20</td>
<td>20</td>
<td>33</td>
<td>34</td>
<td>7/38</td>
<td>68.4</td>
</tr>
</tbody>
</table>

A: PLGA 65:35, ester 0.6 dl/g (%)  
B: PLGA 75:25, ester 0.4 dl/g (%)  
C: PLGA 85:15, ester 0.6 dl/g (%)

### Table 3

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMC-Na</td>
<td>0</td>
<td>0</td>
<td>0.05</td>
<td>0.14</td>
<td>0.28</td>
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<td>0.99</td>
<td>0.90</td>
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<td>Pluronic F68</td>
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<td>0.04</td>
<td>0.04</td>
<td>0.04</td>
</tr>
</tbody>
</table>

### Example 3

**Microparticle Suspension**

180 mg of microparticles of example 1-1 are suspended in 1.0 ml of a vehicle of composition D (Table 5) in a 6 R vials. The suspensions are homogenized by shaking for about 30 seconds by hand. The reconstituted suspension may be injected without any issues using a 20 Gauge needle.

### Example 4

**Lyoophilisation of the Microparticles**

180 mg of microparticles of example 1-1 are reconstituted in 1 ml of the vehicle composition F (Table 3), homogenized by stirring for 1 to 12 hours and then freeze-dried in a lyophilizer. Reconstitution of the lyophilized microparticles with 1 ml pure water (aqua ad injectabilia) resulted in fast and good wetting of the microparticles that may be injected without any issues using a 20 Gauge needle.

### Example 5

**Release Profile In Vivo (Rabbits)**

Microparticles containing octreotide are suspended in 1 ml of a suitable aqueous vehicle and the resulting suspension is injected intramuscularly (i.m.) into male New Zealand White bastard rabbits in a dose of 12 mg/kg. For each dosage form (test group) 4 animals are used. After defined time periods (indicated in the table 4) plasma samples are taken and analyzed for octreotide concentration.
TABLE 4

<table>
<thead>
<tr>
<th>Ex.</th>
<th>Time after Administration (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch</td>
<td>0.021</td>
</tr>
<tr>
<td>1-1</td>
<td>20.250</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Ex.</th>
<th>Time after Administration (days)</th>
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<tr>
<td>1-1</td>
<td>1.557</td>
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</table>

1. A sustained release pharmaceutical composition comprising as active ingredient octreotide or a pharmaceutically-acceptable salt thereof and three different linear polylactide-co-glycolide polymers (PLGAs).

2. The pharmaceutical composition according to claim 1 wherein the PLGAs are present as polymer blend.

3. The pharmaceutical composition according to claim 1 wherein the PLGAs have a lactide-glycolide monomer ratio of 90:10 to 40:60.

4. The pharmaceutical composition according to claim 3 wherein the PLGAs have a lactide-glycolide monomer ratio of 85:15 to 65:35.

5. The pharmaceutical composition according to claim 1 wherein the inherent viscosity of the PLGAs is below 0.9 dl/g in CHCl₃.

6. The pharmaceutical composition according to claim 5 wherein the inherent viscosity of the PLGAs is below 0.8 dl/g in CHCl₃.

7. The pharmaceutical composition according to claim 1 comprising the pamonoate salt of octreotide.

8. The pharmaceutical composition according to claim 1 wherein the release of the active ingredient is three or more months.

9. The pharmaceutical composition according to claim 8 wherein the release of the active ingredient is between three and six months.

10. The pharmaceutical composition according to claim 1 in form of microparticles, a semisolid or an implant.

11. The pharmaceutical composition according to claim 10 in form of microparticles.

12. The pharmaceutical composition according to claim 11 wherein the microparticles have a diameter between 10 μm and 90 μm.

13. The pharmaceutical composition according to claim 11 wherein the microparticles are additionally covered or coated with an anti-agglomerating agent.

14. The pharmaceutical composition according to claim 13 wherein the microparticles are coated with an anti-agglomerating agent and the anti-agglomerating agent is present in an amount of less than 2% by weight of the microparticles.

15. The pharmaceutical composition according to claim 13 wherein the anti-agglomerating agent is mannitol.

16. The pharmaceutical composition according to claim 1 sterilized by gamma irradiation.

17. (canceled)

18. A method of administering octreotide or a pharmaceutically-acceptable salt thereof for long-term maintenance therapy in acromegalic patients, and treatment of severe diarrhea and flushing associated with malignant carcinoid tumors and vasoreactive intestinal peptide tumors (VIPomas tumors), said method comprising administering to a patient in need of octreotide or a pharmaceutically-acceptable salt thereof a pharmaceutical composition according to claim 1.

19. A process of manufacturing microparticles according to claim 11 comprising
(i) preparation of an internal organic phase comprising
   (ia) dissolving the polymer or polymers in a suitable organic solvent or solvent mixture;
   (ib) dissolving/suspending/emulsification of the drug substance in the polymer solution obtained in step (ia);
(ii) preparation of an external aqueous phase containing stabilizers;
   (iii) mixing the internal organic phase with the external aqueous phase to form an emulsion; and
   (iv) hardening the microparticles by solvent evaporation or solvent extraction, washing the microparticles, drying the microparticles and sieving the microparticles through 140 μm.

20. An administration kit comprising the pharmaceutical composition according to claim 1 in a vial, together with a water-based vehicle in an ampoule, vial or prefilled syringe or as microparticles and vehicle separated in a double chamber syringe.

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