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(54) Benævnelse: **Farmaceutisk sammensætning med langsom frigivelse lavet af mikropartikler**

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DESCRIPTION

Description

Field of invention

[0001] The invention relates to pharmaceutical compositions made of microparticles which are used for the slow release of an active substance.

[0002] It more precisely relates to such compositions which comprise a copolymer of lactic and glycolic acid (PLGA) incorporating, as active substance, a water insoluble peptide salt.

State of the art

[0003] Compositions as defined above are disclosed in Swiss patent CH 679 207 A5.

[0004] US5540937 discloses a process for preparing microspheres for the prolonged release of the LHRH hormone and of its analogues, the hormone being dispersed in a water-insoluble polymer or copolymer matrix, the solvent evaporation process is characterized by the use of a pair of organic solvents of which one makes it possible more specifically to obtain a homogeneous suspension of the hormone in the pulverulent state by simply stirring and of which the other is slightly water-miscible so as to allow more specifically the microdispersion of the organic phase in the aqueous phase in which the hardening of the microspheres is performed. This process leads to the preparation of LHRH-containing microspheres which are noteworthy for their purity, especially to microspheres with complex matrices, as well as to formulations comprising at least two types of microspheres.

Definitions

[0005] In the present text, the term "microparticle" has to be understood as a solid object of any shape, e.g. microsphere or microgranule, having a median diameter of less than 250 micrometers.

[0006] The expression D (v,0.5), also mentioned as "median diameter", means that 50 % of the microparticles have a diameter which is less than the indicated value. Hence, if D (v,0.5) = 55 micrometers, 50 % of the microparticles have a diameter which is less than 55 micrometers.

[0007] In the same way, D (v,0.1) means that 10 % of the microparticles have a diameter which is less than the indicated value and D (v,0.9) means that 90% of the microparticles have a diameter which is less than the indicated value.
All above values are measured by laser diffraction.

[0008] The term "microgranule" refers to an object which is the result of a milling operation on an elongated product such as an extrudate.

[0009] The term PLGA XX/YY refers to a poly(D,L lactide-co-glycolide), where XX represents the lactide content, and YY represents the glycolide content. The ratio lactide/glycolide being expressed in mol percent.

[0010] The term "month" refers to 28 days.

General description of the invention

[0011] The objective of the invention is to offer several improvements with respect to the state of the art.

[0012] One of those improvements is to provide a continuous and efficient slow release of the active substance during at least a period covering the 6^{th} month after injection of the composition.

[0013] To this effect the invention concerns a pharmaceutical composition made of microparticles for the slow release of an LHRH agonist triptorelin, characterized in that said composition comprises a mixture of a first group of microparticles and a second group of microparticles, wherein

1. a) the microparticles of said first group are microgranules made of a copolymer of the PLGA type which incorporates triptorelin in the form of triptorelin pamoate; said copolymer comprising 85 % (molar) of lactic acid and having an inherent viscosity of 0.66 dl/g, as measured in chloroform at 25 °C and at a polymer concentration of 0.5 g/dL;
2. b) the microparticles of said second group are microgranules made of a copolymer of the PLGA type which incorporates triptorelin in the form of triptorelin pamoate and which comprises an amount of lactic acid of 75 % (molar) and having an inherent viscosity of 0.65 dl/g, as measured in chloroform at 25 °C and at a polymer concentration of 0.5 g/dL;

the microparticles of said first group furthermore having a size distribution defined as follows:

- D (v,0.1) is 20.5 micrometers,
- D (v,0.5) is 51.7 micrometers,

- D (v,0.9) is 96.9 micrometers

the microparticles of said second group furthermore having a size distribution defined as follows:

- D (v,0.1) is 23 micrometers,
- D (v,0.5) is 55 micrometers,
- D (v,0.9) is 99 micrometers

and wherein triptorelin is released in an important amount within hours following injection into a subject, and then shows a constant and significant release until 6 months after injection.

[0014] According to the present invention, said microparticles of said first group, and of said second group, are microgranules.

[0015] According to an embodiment of the present invention, both groups of microparticles are in a dose ratio, expressed in peptide content, of 50:50.

[0016] Yet a further aspect of the present invention concerns the above pharmaceutical composition for use in the treatment of prostate cancer, wherein said composition is administered once every 6 months.

[0017] The active substance is the LHRH agonist triptorelin (used as the pamoate salt thereof) which may be efficiently used in the treatment of prostate cancer.

[0018] The LHRH agonist triptorelin is released in an important immediate amount within hours following injection and then shows a constant and significant release over a long period of at least 168 days, i.e. 6 months

Detailed description of the invention

[0019] The invention is discussed below in a more detailed way with examples, the first being illustrated by the following figure :

Figure 1 shows triptorelin, LHRH agonist, serum levels obtained with the pharmaceutical biodegradable composition of example 1,

Figure 2 shows triptorelin, LHRH agonist, serum levels obtained with the pharmaceutical biodegradable composition of example 3,

Figure 3 shows triptorelin, LHRH agonist, serum levels obtained with the pharmaceutical biodegradable composition of example 4,

[0020] In the following examples the viscosity is expressed in dl/g and is measured at a polymer concentration of 0.5 g/dl.

Example 1

[0021] A formulation of microgranules of triptorelin pamoate is prepared with the following process.

[0022] Approximately 12 % (w/w) of triptorelin pamoate is mixed with approximately 88 % (w/w) PLGA 75/25 having a viscosity of 0,65 dl/g, at room temperature. The given mixture is duly homogenized, subjected to progressive compression and simultaneously to a progressive heating, before extrusion. The extrudate is cut into pellets and ground at a temperature of about -100°C. The microgranules obtained after grinding are sieved below 180 micrometers. Their size distribution is defined as follows :

D (v,0.1) = 23 micrometers

D (v,0.5) = 55 micrometers

D (v,0.9) = 99 micrometers

[0023] An unclaimed formulation of microspheres of triptorelin pamoate and PLGA 85/15 having an inherent viscosity of 0.68 dl/g is prepared as follows :
Aqueous phase is prepared by mixing, under magnetic stirring, at a temperature of 40°C, 240 g of polyvinyl alcohol and 11760 g of purified water. In parallel, the organic phase is prepared by total dissolution of 12 g of polymer 85/15 poly(D,L lactide-co-glycolide) (PLGA) in 45 g of ethyl acetate under magnetic stirring.

[0024] 3000 mg of triptorelin pamoate are suspended in 30 g of ethyl acetate and placed under magnetic stirring. This solution is incorporated to the organic phase previously prepared. The organic phase is then introduced in a homogenisation chamber simultaneously with the said aqueous phase. Both phases are mixed in order to obtain an emulsion and the extraction of the solvent from the organic phase and to isolate a suspension of microspheres.

[0025] Finally the formulation of microspheres is recovered by filtration and dried by lyophilization.

[0026] The microspheres have a size distribution defined as follows :

D (v,0.1) = 15.6 micrometers

D (v,0.5) = 33.4 micrometers

D (v,0.9) = 60.8 micrometers

[0027] The formulation of microspheres and the formulation of microgranules are mixed in a vial in order to have a 50:50 dose ratio of each formulation. The mixture is suspended in an appropriate aqueous medium, lyophilised and sterilized by gamma irradiation.

[0028] The purity measured on the obtained pharmaceutical biodegradable composition is 98.3% and the burst evaluated in vitro (in a phosphate buffer pH 7.4) over a 6-hour period is 22.1%.

[0029] In this example, the obtained pharmaceutical formulation is tested in vivo and the animal model is the rat. The formulation as described above is suspended in water for injection and is administered at a concentration dose of 18 mg/kg to 6 rats.

[0030] The LHRH agonist triptorelin of said pharmaceutical biodegradable composition is released in an important immediate amount within hours following injection and then shows a constant and significant release over a long period of at least 168 days, i.e. 6 months.

Example 2

[0031] A formulation of microgranules of triptorelin pamoate is prepared as described in example 1.

[0032] An unclaimed formulation of microspheres of triptorelin pamoate is prepared as described in example 1 with PLGA 90/10 having an inherent viscosity of 0.7 dl/g. The microspheres have a size distribution defined as follows :

D (v,0.1) = 17.6 micrometers

D (v,0.5) = 39.9 micrometers

D (v,0.9) = 84.2 micrometers

[0033] The formulation of microspheres and the formulation of microgranules are mixed in a vial in order to have a 50:50 dose ratio of each formulation. The mixture is suspended in an appropriate aqueous medium, lyophilised and sterilized by gamma irradiation.

[0034] The purity measured on the obtained pharmaceutical biodegradable composition is 98.3% and the burst evaluated in vitro (in a phosphate buffer pH 7.4) over a 6-hour period is 19.4%.

[0035] The LHRH agonist triptorelin of said pharmaceutical biodegradable composition is released in an important immediate amount within hours following injection and then shows a constant and significant release over a long period of at least 168 days, i.e. 6 months.

Example 3

[0036] A formulation of microgranules of triptorelin pamoate is prepared as described in example 1.

[0037] Another formulation of microgranules is prepared as described in example 1 with PLGA 85/15 having an inherent viscosity of 0.66 dl/g.

[0038] Approximately 20% (w/w) of triptorelin pamoate is mixed with approximately 80% (w/w) PLGA 85/15 at room temperature. The given mixture is duly homogenized, subjected to progressive compression and simultaneously to a progressive heating, before extrusion. The extrudate is cut into pellets and ground at a temperature of about -100°C. The microgranules obtained after grinding are sieved below 180 micrometers. Their size distribution is defined as follows :

D (v,0.1) = 20.5 micrometers

D (v,0.5) = 51.7 micrometers

D (v,0.9) = 96.9 micrometers

[0039] The 2 formulations of microgranules are mixed in a vial in order to have a 50:50 dose ratio of each formulation. The mixture is suspended in an appropriate aqueous medium, lyophilised and sterilized by gamma irradiation.

[0040] The purity measured on the obtained pharmaceutical biodegradable composition is 98.8% and the burst evaluated in vitro (in a phosphate buffer pH 7.4) over a 6-hour period is 45.0%.

[0041] In this example, the obtained pharmaceutical formulation is tested in vivo and the animal model is the rat. The formulation as described above is suspended in water for injection and is administered at a concentration dose of 18 mg/kg to 6 rats.

[0042] The LHRH agonist triptorelin of said pharmaceutical biodegradable composition is released in an important immediate amount within hours following injection and then shows a constant and significant release over a long period of at least 168 days, i.e. 6 months (see Fig. 2).

Example 4

[0043] An unclaimed formulation of microspheres of triptorelin pamoate and PLGA 95/5 having an inherent viscosity of 0.18 dl/g is prepared as follows :
Aqueous phase is prepared by mixing, under magnetic stirring, at a temperature of 40°C, 800 g of polyvinyl alcohol and 40 L of purified water. In parallel, the organic phase is prepared by total dissolution of 80 g of PLGA 95/5 in 334 g of isopropyl acetate under magnetic stirring.

[0044] 20 g of triptorelin pamoate are suspended in 100 g of isopropyl acetate and placed under magnetic stirring. This solution is incorporated to the organic phase previously prepared. The organic phase is then introduced in a homogenisation chamber simultaneously with the said aqueous phase. Both phases are mixed in order to obtain an emulsion and the extraction of the solvent from the organic phase and to isolate a suspension of microspheres.

[0045] Finally the formulation of microspheres is recovered by filtration and dried by lyophilization.

[0046] The microspheres have a size distribution defined as follows :

D (v,0.1) = 17.8 micrometers

D (v,0.5) = 37.1 micrometers

D (v,0.9) = 74.8 micrometers

[0047] This formulation of microspheres is suspended in an appropriate aqueous medium, lyophilised and sterilized by gamma irradiation.

[0048] The purity measured on the obtained pharmaceutical biodegradable composition is 99.2% and the burst evaluated in vitro (in a phosphate buffer pH 7.4) over a 6 hours period is 10.9%.

[0049] In this example, the obtained pharmaceutical formulation is tested in vivo and the animal model is the rat. The formulation as described above is suspended in water for injection and is administered at a concentration dose of 18 mg/kg to 6 rats.

[0050] The LHRH agonist triptorelin of said pharmaceutical biodegradable composition is released in an important immediate amount within hours following injection and then shows a constant and significant release over a long period of at least 168 days, i.e. 6 months (see Fig. 3).

Example 5

[0051] In order to increase patients' compliance and convenience the inventors also developed a formulation as defined in previous example 3 which allows one injection every 6 Months (24 Weeks). The study discussed in this example investigated the efficacy and safety of this formulation after 2 consecutive intramuscular injections of triptorelin pamoate 22.5 mg in 120 patients with advanced prostate cancer. Four-weekly testosterone assessments were performed over 48 weeks.

[0052] Serum testosterone concentrations fell to castrate levels (≤1.735 nmol/L) in 97.5% of the patients on D29, and 93% of the patients maintained castration from Week 8 to 48. Five out of 8 patients who escaped castration had only an isolated testosterone breakthrough without rising PSA (Prostate Specific Antigen), indicating maintained efficacy. Only one of these isolated breakthroughs was a true "acute-on-chronic" phenomenon after the second injection.

[0053] The median relative decreases in PSA from baseline were 96.9% at Week 24, and 96.4% at Week 48, when 80.9% of patients had a normal PSA.

[0054] The type and incidence of AEs (Adverse Events) were comparable with those observed with the registered triptorelin formulations. As with other GnRH agonists, the most frequent drug related AEs were hot flushes (71.7% of patients). The study drug was very well tolerated locally.

[0055] The study discussed above shows that Triptorelin 6-Month formulation is efficacious and safe in inducing chemical castration in patients with advanced prostate cancer. This new convenient formulation requires only 1 injection every 24 weeks, and shows comparable efficacy and safety with the marketed 1- and 3-Month formulations.

REFERENCES CITED IN THE DESCRIPTION

Cited references

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Patent documents cited in the description

- CH679207A5 [0003]
- US5540937A [0004]

Patentkrav

1. Farmaceutisk sammensætning lavet af mikropartikler til den langsomme frigivelse af et LHRH-agonist-triptorelin, **kendetegnet ved, at** nævnte sammensætning omfatter en blanding af en første gruppe af mikropartikler og en anden gruppe af mikropartikler, hvor

a) mikropartiklerne af nævnte første gruppe er mikrogranulater lavet af en copolymer af PLGA-typen, der inkorporerer triptorelin i formen af triptorelin-pamoat; hvor nævnte copolymer omfatter 85 (molprocent) af mælkesyre og har en iboende viskositet på 0,66 dl/g, som målt i kloroform ved 25°C og ved en polymerkoncentration på 0,5 g/dL;

b) mikropartiklerne af nævnte anden gruppe er mikrogranulater lavet af en copolymer af PLGA-typen, der inkorporerer triptorelin i formen af triptorelin-pamoat, og som omfatter en mængde af mælkesyre på 75 (molprocent) og har en iboende viskositet på 0,65 dl/g, som målt i kloroform ved 25°C og ved en polymerkoncentration på 0,5 g/dL;

hvor mikropartiklerne af nævnte første gruppe yderligere har en størrelsesfordeling defineret som følger:

- D (v,0,1) er 20,5 mikrometer,
- D (v,0,5) er 51,7 mikrometer,
- D (v,0,9) er 96,9 mikrometer

hvor mikropartiklerne af nævnte anden gruppe yderligere har en størrelsesfordeling defineret som følger:

- D (v,0,1) er 23 mikrometer,
- D (v,0,5) er 55 mikrometer,
- D (v,0,9) er 99 mikrometer

og hvor triptorelin frigives i en vigtig mængde inden for timer efterfølgende injektion i et individ, og derefter viser en konstant og signifikant frigivelse indtil 6 måneder efter injektion.

2. Farmaceutisk sammensætning ifølge krav 1, hvor begge grupper af mikropartikler er i et dosisforhold, udtrykt i peptidindhold, på 50:50.

3. Farmaceutisk sammensætning ifølge et hvilket som helst af kravene 1 til 2 til anvendelse i behandlingen af prostatakræft, hvor nævnte sammensætning administreres en gang hver 6. måned.

DRAWINGS

Drawing

Fig. 1

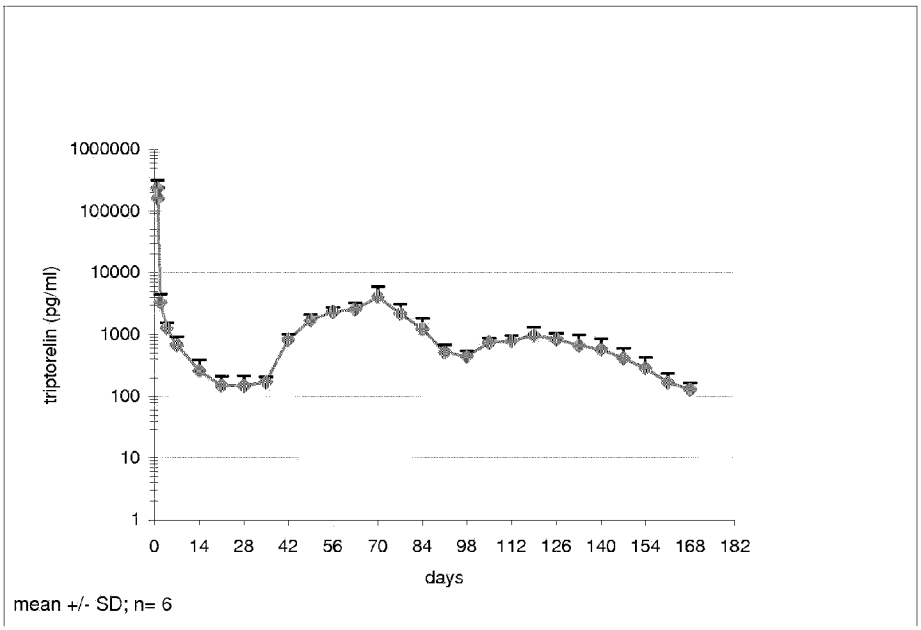
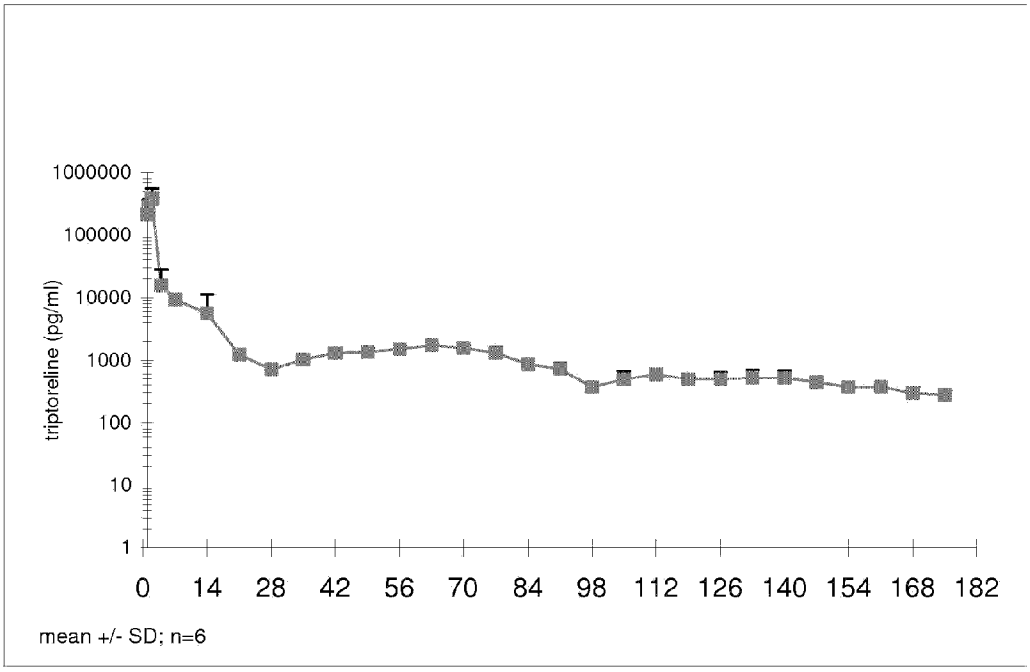


Fig. 2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1000
100
10
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84
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112
126
140
154
168
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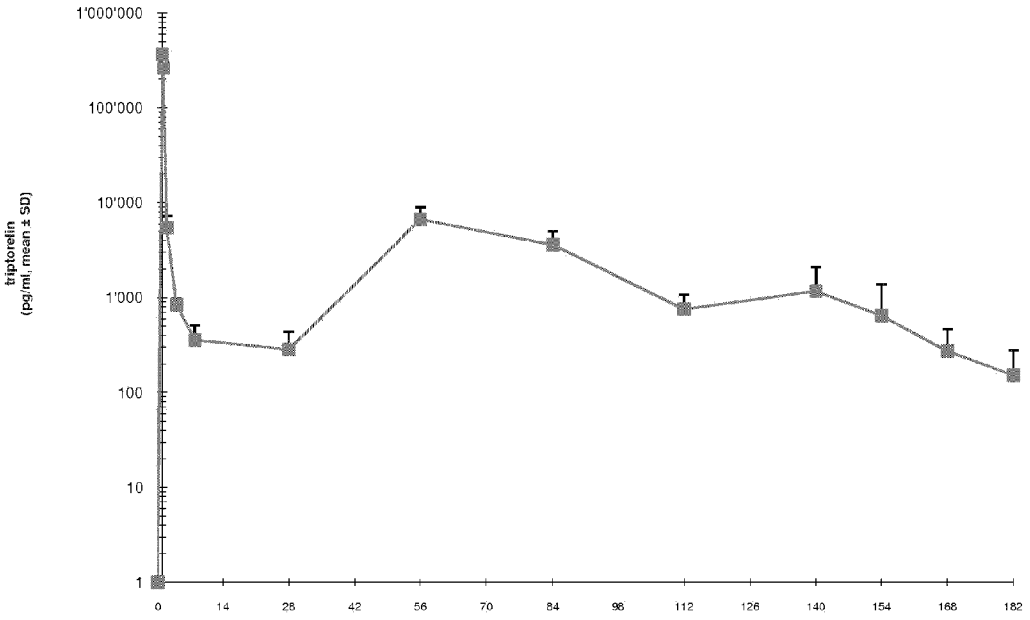
mean +/- SD; n=6

Fig. 3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(pg/ml, mean ± SD)
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100'000
10'000
1'000
100
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1
0
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56
70
84
98
112
126
140
154
168
182