initially the drug release is insufficient because of the time needed for the body fluids to penetrate the implant. It now has been found that the addition of specific agents overcomes this initial drop in the release of TMC278 from the implant.

Summary

In a first aspect, there is provided an implantable one piece device comprising a biocompatible, biodegradable polymer mixed with rilpivirine in base-form or as pharmaceutically acceptable salt form and with one or more release-enhancing agents selected from the group consisting of poloxamers, polysorbates, and a combination of dimethyl sulfoxide (DMSO) and poly(vinyl pyrrolidone)(PVP), wherein the device contains from 25% by weight to 70 % by weight of rilpivirine in base-form or as pharmaceutically acceptable salt form.

In a second aspect, there is provided the device as defined herein, for use in the treatment of HIV infection when administered intermittently at a time interval from 2 weeks to 3 months.

In a third aspect, there is provided the device as defined herein, for use in the prevention against transmission of HIV when administered intermittently at a time interval from 2 weeks to 3 months.

Brief Description of Figures

Figure 1: Scanning electron micrographs (SEMs) of PLGA 50/50 rods containing 60% TMC278 (left) without DMSO and (right) with 10% (w/w) DMSO after 4 weeks incubation in PBS at 37°C.

Figure 2: (left) Differential scanning calorimetry thermogram (first heat) of recrystallized TMC278 dispersed in PLGA, with (right) a thermogram (first heat) of TMC278 dispersed in DMSO/ PLGA.

Figure 3: SEM micrographs of (left) TMC278 crystals after re-crystallization and (right) before recrystallization.

Description of the Invention

This invention concerns an implantable device comprising a biocompatible, biodegradable polymer mixed with TMC278 and with one or more release-enhancing agents selected from the group consisting of poloxamers, polysorbates, and a combination of dimethyl sulfoxide (DMSO) and poly(vinyl pyrrolidone)(PVP).

The implantable device in particular is a one-piece device. In one embodiment the weight of the device is equal or greater than 100 mg, or is equal or greater than 200 mg, or is equal or greater than 400 mg, or is equal or greater than 500 mg, or is equal or greater than 800 mg, or is equal or greater than 1000 mg, or is equal or greater than 1200 mg, or is equal or greater than 1200 mg. Too large devices are not practicable, an upper limit may be about 2 g; or about 1.5 g.

The percent by weight of TMC278 in the implantable device of the invention may be from about 10% to about 80%, from about 10% to about 70%, or from about 20% to about 65%, or from about 25% to about 60% or from about 40% to about 60%, or from about 50% to about 80%, or from about 50% to about 60%. In one embodiment the device contains from about 50% to about 70%, or from about 55% to about 65%, for example about 60% of TMC278. The higher loadings of TMC278, such as in the above ranges starting at about 50%, are preferred where less frequent administrations are desired, this to keep the devices sufficiently compact for convenience of administration and for the comfort of the patient.

Claims

1. An implantable device comprising a biocompatible, biodegradable polymer mixed with rilpivirine in base-form or as pharmaceutically acceptable salt form and with one or more release-enhancing agents selected from the group consisting of poloxamers, polysorbates, and a combination of dimethyl sulfoxide (DMSO) and poly(vinyl pyrrolidone)(PVP).

2. The device of claim 1, wherein the device is an implantable one piece device.

3. The device of claim 1 or 2, wherein the device weighs more than 100 mg.

4. The device of any of claims 1 - 3, wherein the device weighs more than 300 mg.

5. The implantable device of any of claims 1 - 4, shaped as a cylinder.

6. The implantable device of claim 5, having a diameter that is in the range of 0.5 mm to 4 mm, and a length that is in the range of 1.0 cm to 4 cm.

7. The implantable device of claim 5, having a diameter that is in the range of 1.0 mm to 3.0 mm, and a length that is in the range of 1.5 cm to 3.5 cm.

8. The device of any of claims 1 - 7, wherein the device contains from 10% to 70%, or from 40% to 60%, or from 50% to 60%, of rilpivirine in base-form or as pharmaceutically acceptable salt form.

9. The device of any of claims 1 - 8, wherein the biocompatible, biodegradable polymer is selected from copolymers of lactide (which includes lactic acid, d-, 1- and meso lactide) and glycolide (including glycolic acid).

10. The device of claim 9, wherein the biocompatible, biodegradable polymer is a copolymer of lactide and glycolide in a molar ratio of 50% to 65% lactide to 35% to 50% glycolide.

11. The device of any of claims 1 – 10, wherein the device contains from 15 % to 25 % of biocompatible, biodegradable polymer.

12. The device of any of claims 1 – 11, wherein the release-enhancing agent is a poloxamer.

13. The device of claim 12, wherein the release-enhancing agent is poloxamer 338.

14. The device of any of claims 1 – 13, wherein the device contains from 1% to 40% , or from 10% to 30%, or of 15% to 25%, of said release-enhancing agent.

15. The device of any of claims 1 – 14, wherein the device contains from 10% to 80%, or from 10% to 30%, or from 15 to 25%, e.g. 20%, of said biocompatible, biodegradable polymer.

16. The device of any of claims 1 – 15, wherein when present, the amount of DMSO is in the range of 3% to 10%.

17. The device of any of claims 1 – 15, administered intermittently at a time interval from 2 weeks to 3 months, for treating HIV infection.

18. The device of any of claims 1 –17 wherein rilpivirine is used in base-form.

Claims

1. An implantable one piece device comprising a biocompatible, biodegradable polymer mixed with rilpivirine in base-form or as pharmaceutically acceptable salt form and with one or more release-enhancing agents selected from the group consisting of poloxamers, polysorbates, and a combination of dimethyl sulfoxide (DMSO) and poly(vinyl pyrrolidone)(PVP), wherein the device contains from 25% by weight to 70 % by weight of rilpivirine in base-form or as pharmaceutically acceptable salt form.

2. The device of claim 1, wherein the device weighs more than 100 mg.

3. The device of claim 1, wherein the device weighs more than 500 mg.

4. The device of any of claims 1 - 3, shaped as a cylinder.

5. The device of claim 4, having a diameter that is in the range of 0.5 mm to 4 mm, and a length that is in the range of 1.0 cm to 4 cm.

6. The device of claim 4, having a diameter that is in the range of 1.0 mm to 3.0 mm, and a length that is in the range of 1.5 cm to 3.5 cm.

7. The device of any of claims 1 - 6, wherein the device contains from 25% by weight to 60% by weight of rilpivirine in base-form or as pharmaceutically acceptable salt form.

8. The device of claim 7, wherein the device contains from 40% by weight to 60% by weight of rilpivirine in base-form or as pharmaceutically acceptable salt form.

9. The device of claim 8, wherein the device contains from 50% by weight to 60% by weight of rilpivirine in base-form or as pharmaceutically acceptable salt form.

10. The device of any of claims 1 - 9, wherein the biocompatible, biodegradable polymer is selected from copolymers of lactide (which includes lactic acid, d-, 1- and meso lactide) and glycolide (including glycolic acid).

11. The device of claim 10, wherein the biocompatible, biodegradable polymer is a copolymer of lactide and glycolide in a molar ratio of 50% to 65% lactide to 35% to 50% glycolide.

12. The device of any of claims 1 – 11, wherein the release-enhancing agent is a poloxamer.

13. The device of claim 12, wherein the release-enhancing agent is poloxamer 338.

14. The device of any of claims 1 – 13, wherein the device contains from 1% to 40% w/w relative to the total weight of the implantable device of said release-enhancing agent.

15. The device of claim 14, wherein the device contains from 10% to 30% w/w relative to the total weight of the implantable device of said release-enhancing agent.

16. The device of claim 15, wherein the device contains from 15% to 25% w/w relative to the total weight of the implantable device of said release-enhancing agent.

17. The device of any of claims 1 – 16, wherein the device contains from 10% to 80% w/w relative to the total weight of the implantable device of said biocompatible, biodegradable polymer.

18. The device of claim 17, wherein the device contains from 10% to 30% w/w relative to the total weight of the implantable device of said biocompatible, biodegradable polymer.

19. The device of claim 18, wherein the device contains from 15 to 25% w/w relative to the total weight of the implantable device of said biocompatible, biodegradable polymer.

20. The device of claim 19, wherein the device contains 20% w/w relative to the total weight of the implantable device of said biocompatible, biodegradable polymer.

21. The device of any of claims 1 – 20, wherein when present, the amount of DMSO is in the range of 3% to 10% w/w relative to the total weight of the implantable device.

22. The device of any of claims 1 – 21, for use in the treatment of HIV infection when administered intermittently at a time interval from 2 weeks to 3 months.

23. The device of any of claims 1 – 21, for use in the prevention against transmission of HIV when administered intermittently at a time interval from 2 weeks to 3 months.

24. The device of any of claims 1 – 23 wherein rilpivirine is used in base-form.