or resist which prevent sterilant gas from being purged from an area, a patient could develop a superficial eye infection or a more serious condition such as endophthalmitis, such as patients that are already visually compromised before treatment. Therefore, it is desirable to maintain integrity of the medicament while reaching a suitable level of sterilization for all relevant portions and components of the syringe. Further, some sterilizing gases may be absorbed by many types of plastics and rubbers, which may negatively and/or undesirably impact the drug product inside and also subsequently negatively impact the efficacy, quality, and/or safety of the drug product. Other sterilizing gases may cause discoloration on the surface of the syringe, which may be undesirable for various reasons.

[0007] The present disclosure sets forth approaches embodying advantageous alternatives to existing external sterilization approaches, and that may address one or more of the challenges or needs mentioned herein, as well as provide other benefits and advantages.

SUMMARY

[0008] According to a first aspect of the present invention, there is provided a method of externally sterilizing a drug delivery device utilizing Nitrogen Dioxide (NO2) is provided, including placing the drug delivery device in a sterilization chamber, introducing into the chamber a dose of NO2 having a concentration of between 2 and 20 milligrams per Liter by applying a vacuum level of between 10 and 600 Torr (between 1333.22 Pa and 79993.4 Pa) and holding the vacuum level for a dwell time of between 2 and 20 minutes, repeating the step of introducing into the chamber a dose of NO2 for a number of pulses between 1 and 24, purging the sterilization chamber of at least substantially all of the NO2; and aerating the sterilization chamber.

[0009] The drug delivery device to be sterilized may be a pre-filled syringe comprising a barrel, a stopper, a plunger rod, and a backstop. The barrel of the pre-filled syringe may contain a medicament, such as a VEGF antagonist. The barrel may be a plastic barrel.

[0010] The vacuum level may be between about 100 and 500 Torr, between about 150 and 400 Torr, between about 150 and 300 Torr, or another suitable vacuum level.

[0011] The concentration of the dose of the NO2 may be between about 2 and 10 milligrams per Liter, between about 2 and 7 milligrams per Liter, or another suitable concentration of the dose.

[0012] The chamber may have a relative humidity of between about 70 and 90 percent or another suitable humidity.

[0013] The dwell time may be between about 2 and 12 minutes, between about 2 and 7 minutes, or another suitable dwell time.

[0014] The number of pulses may be between about 1 and 12, between about 1 and 8, between about 1 and 4, between about 1 and 2, or another suitable number of pulses.

[0015] The step of aerating the sterilization chamber may include aerating the sterilization chamber a number of cycles between about 12 and 70 or another suitable number of cycle to at least substantially prevent discoloration of the drug delivery device s.

[0016] The method of externally sterilizing the drug delivery device may achieve at least a 2 logs microbial reduction, may achieve at least a 3 logs microbial reduction, may achieve at least a 4 logs microbial reduction, may achieve at least a 5 logs microbial reduction, may achieve at least a 6 logs microbial reduction, or may achieve another suitable microbial reduction.

[0016a] According to a second aspect of the present invention, there is provided a method of externally sterilizing a drug delivery device utilizing Nitrogen Dioxide (NO2), comprising:

placing the drug delivery device in a sterilization chamber;

introducing into the chamber a dose of NO2 having a concentration of between 5 and 20 milligrams per Liter by applying a vacuum level of between 150 and 500 Torr (between 19998.4 Pa and 66661.2 Pa) and holding the vacuum level for a dwell time of between 5 and 10 minutes;

repeating the step of introducing into the chamber a dose of NO2 for a number of pulses between 1 and 8;

purging the sterilization chamber of at least substantially all of the NO2; and

aerating the sterilization chamber a number of cycles between 20 and 90.

[0016b] According to a third aspect of the present invention, there is provided a method of externally sterilizing a pre-filled syringe having a drug container and a medicament contained in the drug container, the method of externally sterilizing comprising the following steps:

placing the drug delivery device in a sterilization chamber;

introducing into the chamber a dose of Nitrogen Dioxide (NO2) having a predetermined concentration by applying a predetermined vacuum level and holding the vacuum level for a predetermined dwell time;

repeating the step of introducing into the chamber a dose of NO2 for a predetermined number of pulses;

purging the sterilization chamber of at least substantially all of the NO2;

aerating the sterilization chamber a predetermined number of cycles;

wherein the method of externally sterilizing the pre-filled syringe achieves at least a log 6 lethality target for the pre-filled syringe while realizing an ingress of NO2 gas into the drug container of less than 3.0 parts per million, as measured 30 days after externally sterilizing the pre-filled syringe.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] It is believed that the disclosure will be more fully understood from the following description taken in conjunction with the accompanying drawings. Some of the drawings may have been simplified by the omission of selected elements for the purpose of more clearly showing other elements. Such omissions of elements in some drawings are not necessarily indicative of the presence or absence of particular elements in any of the exemplary embodiments, except as may be explicitly delineated in the corresponding written description. Also, none of the drawings is necessarily to scale.

What is claimed is:

1. A method of externally sterilizing a drug delivery device utilizing Nitrogen Dioxide (NO_2), comprising:

placing the drug delivery device in a sterilization chamber;

introducing into the chamber a dose of NO_2 having a concentration of between 2 and 20 milligrams per Liter by applying a vacuum level of between 10 and 600 Torr (between 1333.22 Pa and 79993.4 Pa) and holding the vacuum level for a dwell time of between 2 and 20 minutes;

repeating the step of introducing into the chamber a dose of NO_2 for a number of pulses between 1 and 24;

purging the sterilization chamber of at least substantially all of the NO_2; and

aerating the sterilization chamber.

2. A method as in claim 1, wherein the drug delivery device is a pre-filled syringe comprising a barrel, a stopper, a plunger rod, and a backstop and wherein the barrel contains a medicament.

3. A method as in claim 2, wherein the medicament is a VEGF antagonist.

4. A method as in any of claims 2-3, wherein the barrel is a plastic barrel.

5. A method as in any of claims 1-4, wherein the vacuum level is between 100 and 500 Torr (between 13332.2 Pa and 66661.2 Pa).

6. A method as in any of claims 1-5, wherein the vacuum level is between 150 and 400 Torr (between 19998.4 Pa and 53328.9 Pa).

7. A method as in any of claims 1-6, wherein the vacuum level is between 150 and 300 Torr (between 19998.4 Pa and 39996.7 Pa).

8. A method as in any of claims 1-7, wherein the concentration of the dose of NO_2 is between 2 and 10 milligrams per Liter.

9. A method as in any of claims 1-8, wherein the concentration of the dose of NO_2 is between 2 and 7 milligrams per Liter.

10. A method as in any of claims 1-9, wherein the chamber has a relative humidity is between 70 and 90 percent.

11. A method as in any of claims 1-10, wherein the dwell time is between 2 and 12 minutes.

12. A method as in any of claims 1-11, wherein the dwell time is between 2 and 7 minutes.

13. A method as in any of claims 1-12, wherein the number of pulses is between 1 and 12.

14. A method as in any of claims 1-13, wherein the number of pulses is between 1 and 8.

15. A method as in any of claims 1-14, wherein the number of pulses is between 1 and 4.

16. A method as in any of claims 1-15, wherein the number of pulses is between 1 and 2.

17. A method as in any of claims 1-16, wherein the step of aerating the sterilization chamber includes aerating the sterilization chamber a number of cycles between 12 and 70 cycles to at least substantially prevent discoloration of the drug delivery device.

18. A method as in any of claims 1-17, wherein the method of externally sterilizing the drug delivery device achieves at least a 2 logs microbial reduction.

19. A method as in any of claims 1-18, wherein the method of externally sterilizing the drug delivery device achieves at least a 3 logs microbial reduction.

20. A method as in any of claims 1-19, wherein the method of externally sterilizing the drug delivery device achieves at least a 4 logs microbial reduction.

21. A method as in any of claims 1-20, wherein the method of externally sterilizing the drug delivery device achieves at least a 5 logs microbial reduction.

22. A method as in any of claims 1-21, wherein the method of externally sterilizing the drug delivery device achieves at least a 6 logs microbial reduction.

23. A method of externally sterilizing a drug delivery device utilizing Nitrogen Dioxide (NO_2), comprising:

placing the drug delivery device in a sterilization chamber;

introducing into the chamber a dose of NO_2 having a concentration of between 5 and 20 milligrams per Liter by applying a vacuum level of between 150 and 500 Torr (between 19998.4 Pa and 66661.2 Pa) and holding the vacuum level for a dwell time of between 5 and 10 minutes;

repeating the step of introducing into the chamber a dose of NO_2 for a number of pulses between 1 and 8;

purging the sterilization chamber of at least substantially all of the NO_2; and

aerating the sterilization chamber a number of cycles between 20 and 90.

24. A method of externally sterilizing a pre-filled syringe having a drug container and a medicament contained in the drug container, the method of externally sterilizing comprising the following steps:

placing the drug delivery device in a sterilization chamber;

introducing into the chamber a dose of Nitrogen Dioxide (NO_2) having a predetermined concentration by applying a predetermined vacuum level and holding the vacuum level for a predetermined dwell time;

repeating the step of introducing into the chamber a dose of NO_2 for a predetermined number of pulses;

purging the sterilization chamber of at least substantially all of the NO_2;

aerating the sterilization chamber a predetermined number of cycles;

wherein the method of externally sterilizing the pre-filled syringe achieves at least a log 6 lethality target for the pre-filled syringe while realizing an ingress of NO_2 gas into the drug container of less than 3.0 parts per million, as measured 30 days after externally sterilizing the pre-filled syringe.