LYOPHILIZED PHARMACEUTICAL COMPOSITIONS

CROSS REFERENCE

[0001] This Application claims the benefit of United States Provisional Application No. 62/188,025, filed July 2, 2015, which is incorporated herein by reference in its entirety.

BACKGROUND

[0002] DNA methylation is a post replicative chemical modification of DNA. Different cancers can be stratified by their abnormal DNA methylation profiles (degree of global or specific DNA methylation) and the hypermethylation of specific genes can be associated with the prognosis for gastric, lung, esophageal, pancreatic, and colon cancer. DNA methylation patterns can also be used to predict response or resistance to therapy in glioma and melanoma. Azacitidine and decitabine are two FDA approved hypomethylating agents (HMAs) that exert their therapeutic effect by inhibiting DNA methylation levels.

[0003] Dinucleotide compounds derived from decitabine for the development of therapies for similar indications have been described in U.S. Patent No. 7,700,567 and its equivalent WO2007041071. Drug formulations containing dinucleotide compounds of the type described in WO2007041071 are disclosed in WO2013033176. The disclosure in each of US 7,700,567, WO2007041071 and WO2013033176 is incorporated by reference in its entirety.

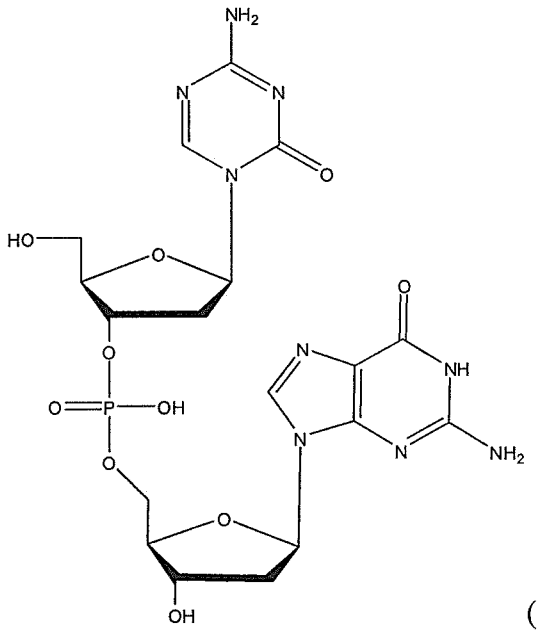
[0004] Lyophilization, often referred to as freeze drying, is a method of dehydration in which a solvent-containing substrate is frozen and then subjected to a vacuum so that the solvent is removed by sublimation, i.e. direct conversion from the the solid frozen state into the gaseous state.

INCORPORATION BY REFERENCE

[0005] Each patent, publication, and non-patent literature cited in the application is hereby incorporated by reference in its entirety as if each was incorporated by reference individually.

SUMMARY

[0006] In some examples, the disclosure provides a method of preparing a lyophilized pharmaceutical composition, the method comprising dissolving a compound of formula (1):

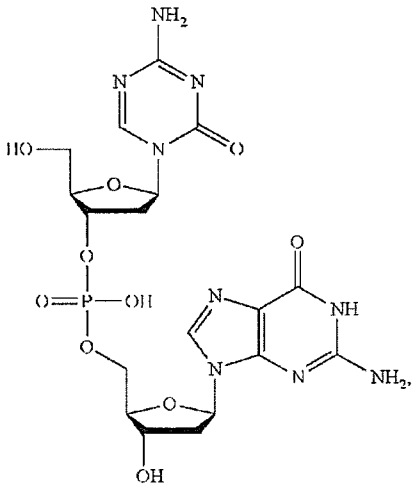


(1),

or a pharmaceutically-acceptable salt thereof, in a solvent comprising dimethylsulfoxide (DMSO) to form a solution, wherein the solvent is then removed by a freeze-drying process to give a lyophilized product, wherein the freeze-drying process comprises: (i) a first freezing stage in which the solution is frozen by reducing the temperature thereof to a temperature of no greater than about -20 °C; (ii) a first warming stage in which the temperature of the frozen solution is raised to a temperature in the range from about -15 °C to about 5 °C, wherein the temperature in the range from about -15 °C to about 5 °C keeps the solution frozen; (iii) a second freezing stage in which the temperature of the solution is lowered to a temperature of no greater than about -20 °C; (iv) a primary drying stage, wherein the primary drying stage comprises a sublimation step in which the DMSO is removed by sublimation from the solution in its frozen state under reduced pressure to give a partially dried product; and (v) a secondary drying stage in which the DMSO is removed by evaporation from the partially dried product in a non-frozen state under reduced pressure to give the lyophilized product.

[0006a] In one aspect, the present disclosure provides a method of preparing a lyophilized pharmaceutical product, the method comprising dissolving a compound of formula (1):

(1)



or a pharmaceutically-acceptable salt thereof, in a solvent comprising dimethylsulfoxide (DMSO) to form a solution, wherein the solvent is then removed by a freeze-drying process to give the lyophilized pharmaceutical product, wherein the freeze-drying process comprises:

(i) a first freezing stage in which the solution is frozen by reducing the temperature thereof to a temperature of no greater than about −20° C;

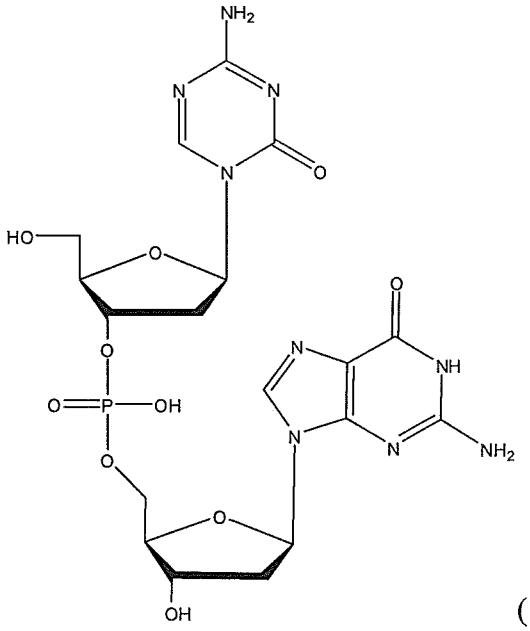
(ii) a first warming stage in which the temperature of the frozen solution is raised to a temperature in the range from about −15° C to about 5° C, wherein the temperature in the range from about −15° C to about 5° C keeps the solution frozen;

(iii) a second freezing stage in which the temperature of the solution is lowered to a temperature of no greater than about −20° C;

(iv) a primary drying stage, wherein the primary drying stage comprises a sublimation step in which the DMSO is removed by sublimation from the solution in its frozen state under reduced pressure to give a partially dried product, wherein the reduced pressure in the primary drying stage is from about 5 μBar to about 40 μBar; and

(v) a secondary drying stage in which the DMSO is removed by evaporation from the partially dried product in a non-frozen state under reduced pressure to give the lyophilized pharmaceutical product.

[0007] In some examples, the disclosure provides a pharmaceutical composition prepared by a process comprising the steps of: dissolving a compound of formula (1):

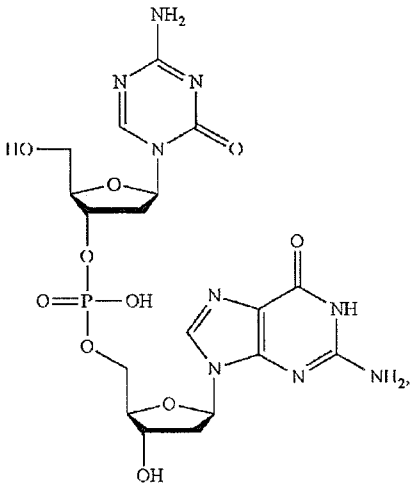


(1), or a pharmaceutically-acceptable salt thereof, in a solvent comprising dimethylsulfoxide (DMSO) to form a solution, wherein the solvent is then removed by a freeze-drying process to give a lyophilized product, wherein the freeze-drying process comprises: (i) a first freezing stage in which the solution is frozen by reducing the temperature thereof to a temperature of no greater than about -20 °C; (ii) a first warming stage in which the temperature of the frozen solution is raised to a temperature in the range from about -15 °C to about 5 °C, wherein the temperature in the range from about -15 °C to about 5 °C keeps the solution frozen; (iii) a second freezing stage in which the temperature of the solution is lowered to a temperature of no greater than about -20 °C; (iv) a primary drying stage, wherein the primary drying stage comprises a sublimation step in which the DMSO is removed by sublimation from the solution in its frozen state under reduced pressure to give a partially dried product; and (v) a secondary drying stage in which the DMSO is removed by evaporation from the partially dried product in a non-frozen state under reduced pressure to give the lyophilized product.

[0007a] In one aspect, the present disclosure provides pharmaceutical product prepared by a process comprising the steps of:

dissolving a compound of formula (1):

(1)



or a pharmaceutically-acceptable salt thereof, in a solvent comprising dimethylsulfoxide (DMSO) to form a solution, wherein the solvent is then removed by a freeze-drying process to give a lyophilized product, wherein the freeze-drying process comprises:

(i) a first freezing stage in which the solution is frozen by reducing the temperature thereof to a temperature of no greater than about −20° C;

(ii) a first warming stage in which the temperature of the frozen solution is raised to a temperature in the range from about −15° C to about 5° C, wherein the temperature in the range from about −15° C to about 5° C keeps the solution frozen;

(iii) a second freezing stage in which the temperature of the solution is lowered to a temperature of no greater than about −20° C;

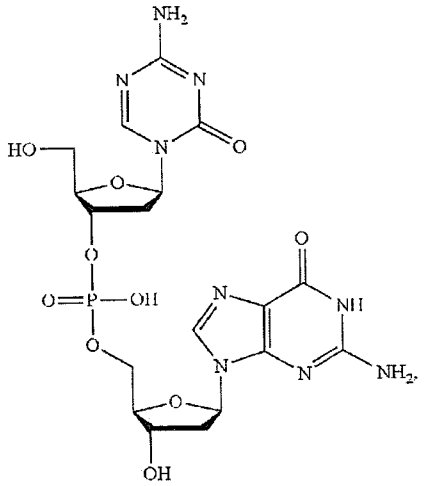
(iv) a primary drying stage, wherein the primary drying stage comprises a sublimation step in which the DMSO is removed by sublimation from the solution in its frozen state under reduced pressure to give a partially dried product; and

(v) a secondary drying stage in which the DMSO is removed by evaporation from the partially dried product in a non-frozen state under reduced pressure to give the lyophilized product,

wherein any residual DMSO present in the lyophilized product is in an amount corresponding to no more than 35 mg per 100 mg equivalent of a free base of the compound of formula (1).

[0007b] In one aspect, the present disclosure provides a method of preparing a lyophilized pharmaceutical product, the method comprising dissolving a compound of formula (1):

(1)



or a pharmaceutically-acceptable salt thereof, in a solvent comprising dimethylsulfoxide (DMSO) to form a solution, wherein the solvent is then removed by a freeze-drying process to give the lyophilized pharmaceutical product, wherein the freeze-drying process comprises:

(i) a first freezing stage in which the solution is frozen by reducing the temperature thereof to a temperature of no greater than about −20° C;

(ii) a first warming stage in which the temperature of the frozen solution is raised to a temperature in the range from about −15° C to about 5° C, wherein the temperature in the range from about −15° C to about 5° C keeps the solution frozen;

(iii) a second freezing stage in which the temperature of the solution is lowered to a temperature of no greater than about −20° C;

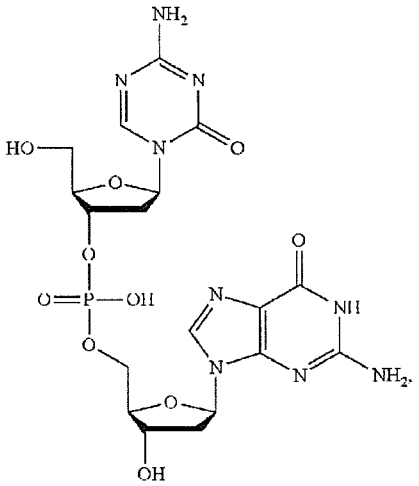
(iv) a primary drying stage, wherein the primary drying stage comprises a sublimation step in which the DMSO is removed by sublimation from the solution in its frozen state under reduced pressure to give a partially dried product; and

(v) a secondary drying stage in which the DMSO is removed by evaporation from the partially dried product in a non-frozen state under reduced pressure to give the lyophilized pharmaceutical product,

wherein in an amount of the lyophilized pharmaceutical product obtained from 1 gram of the solution, there is a residual DMSO content of no greater than about 20 mg.

[0007c] In one aspect, the present disclosure provides method of preparing a lyophilized pharmaceutical product, the method comprising dissolving a compound of formula (1):

(1)



or a pharmaceutically-acceptable salt thereof, in a solvent comprising dimethylsulfoxide (DMSO) to form a solution, wherein the solvent is then removed by a freeze-drying process to give the lyophilized pharmaceutical product, wherein the freeze-drying process comprises:

(i) a first freezing stage in which the solution is frozen by reducing the temperature thereof to a temperature of no greater than about −20° C;

(ii) a first warming stage in which the temperature of the frozen solution is raised to a temperature in the range from about −15° C to about 5° C, wherein the temperature in the range from about −15° C to about 5° C keeps the solution frozen;

(iii) a second freezing stage in which the temperature of the solution is lowered to a temperature of no greater than about −20° C;

(iv) a primary drying stage, wherein the primary drying stage comprises a sublimation step in which the DMSO is removed by sublimation from the solution in its frozen state under reduced pressure to give a partially dried product; and

(v) a secondary drying stage in which the DMSO is removed by evaporation from the partially dried product in a non-frozen state under reduced pressure to give the lyophilized pharmaceutical product,

wherein any residual DMSO present in the lyophilized pharmaceutical product is in an amount corresponding to no more than 35 mg per 100 mg equivalent of a free base of the compound of formula (1).

BRIEF DESCRIPTION OF THE FIGURES

[0008] FIGURE 1 is a plot of DMSO removal with time as the lyophilization process of the invention progresses. DMSO removal profiles for four formulations A, B, C and D of

different concentrations are shown in **FIGURE 1**.

DETAILED DESCRIPTION

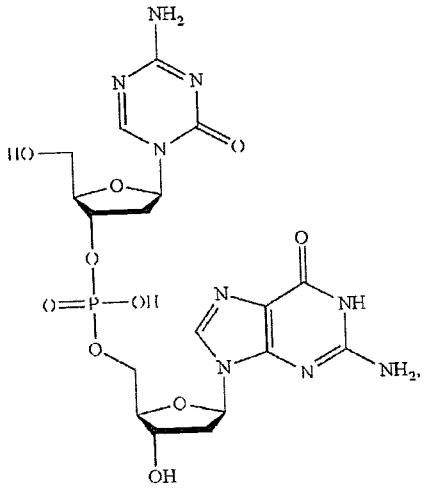
[0009] This application relates to lyophilized pharmaceutical compositions containing a dinucleotide derived from decitabine and to methods for the preparation and use of decitabine-derived dinucleotide compositions.

CLAIMS

WHAT IS CLAIMED IS:

1. A method of preparing a lyophilized pharmaceutical product, the method comprising dissolving a compound of formula (1):

(1)



or a pharmaceutically-acceptable salt thereof, in a solvent comprising dimethylsulfoxide (DMSO) to form a solution, wherein the solvent is then removed by a freeze-drying process to give the lyophilized pharmaceutical product, wherein the freeze-drying process comprises:

(i) a first freezing stage in which the solution is frozen by reducing the temperature thereof to a temperature of no greater than about −20° C;

(ii) a first warming stage in which the temperature of the frozen solution is raised to a temperature in the range from about −15° C to about 5° C, wherein the temperature in the range from about −15° C to about 5° C keeps the solution frozen;

(iii) a second freezing stage in which the temperature of the solution is lowered to a temperature of no greater than about −20° C;

(iv) a primary drying stage, wherein the primary drying stage comprises a sublimation step in which the DMSO is removed by sublimation from the solution in its frozen state under reduced pressure to give a partially dried product, wherein the reduced pressure in the primary drying stage is from about 5 μBar to about 40 μBar; and

(v) a secondary drying stage in which the DMSO is removed by evaporation from the partially dried product in a non-frozen state under reduced pressure to give the lyophilized pharmaceutical product.

2. The method of claim 1, wherein the compound of formula (1) is in the form of a sodium salt.

3. The method of claim 1, wherein the solvent is non-aqueous.

4. The method of claim 1, wherein the lyophilized pharmaceutical product has a dissolution time, at ambient temperature, and without the aid of mechanised stirring, in a non-aqueous solvent containing 65% (v/v) propylene glycol; 25% (v/v) glycerine; and 10% (v/v) ethanol, of no greater than about 20 minutes.

5. The method of claim 1, wherein in an amount of the lyophilized pharmaceutical product obtained from 1 gram of the solution, there is a residual DMSO content of no greater than about 20 mg.

6. The method of claim 1, wherein any residual DMSO present in the lyophilized pharmaceutical product is in an amount corresponding to no more than 35 mg per 100 mg equivalent of a free base of the compound of formula (1).

7. The method of claim 1, further comprising packing the lyophilized pharmaceutical product in a sealed pharmaceutical container.

8. The method of claim 1, further comprising dissolving the lyophilized pharmaceutical product in another solvent to form an injectable liquid composition.

9. The method of claim 8, wherein the another solvent is a non-aqueous solvent.

10. The method of claim 1, wherein the solution further comprises a co-solvent.

11. The method of claim 1, further comprising reconstituting the lyophilized pharmaceutical product in a pharmaceutically acceptable solvent to give a liquid formulation containing a compound of formula (1) or the pharmaceutically acceptable salt thereof.

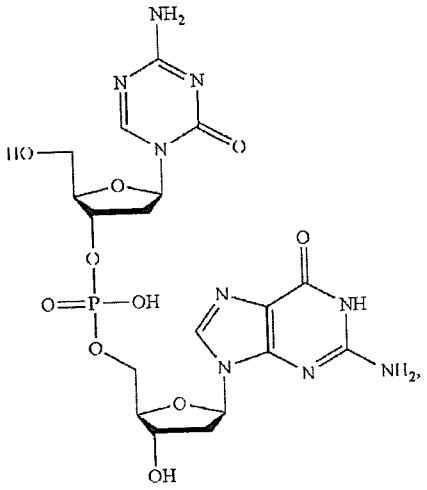
12. The method of claim 1, wherein the temperature in the primary drying stage is from about −3° C to about −9° C.

13. The method of claim 1, wherein the temperature in the secondary drying stage is from about 30° C to about 65° C.

14. A pharmaceutical product prepared by a process comprising the steps of:

dissolving a compound of formula (1):

(1)



or a pharmaceutically-acceptable salt thereof, in a solvent comprising dimethylsulfoxide (DMSO) to form a solution, wherein the solvent is then removed by a freeze-drying process to give a lyophilized product, wherein the freeze-drying process comprises:

(i) a first freezing stage in which the solution is frozen by reducing the temperature thereof to a temperature of no greater than about −20° C;

(ii) a first warming stage in which the temperature of the frozen solution is raised to a temperature in the range from about −15° C to about 5° C, wherein the temperature in the range from about −15° C to about 5° C keeps the solution frozen;

(iii) a second freezing stage in which the temperature of the solution is lowered to a temperature of no greater than about −20° C;

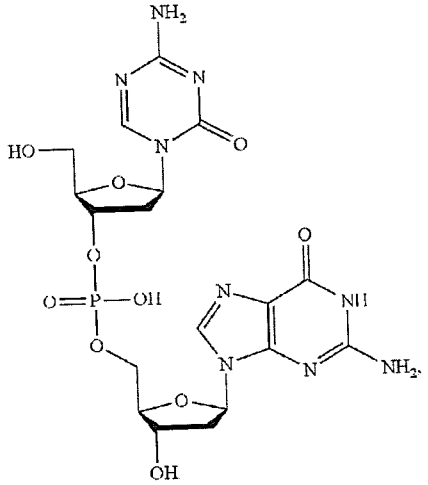
(iv) a primary drying stage, wherein the primary drying stage comprises a sublimation step in which the DMSO is removed by sublimation from the solution in its frozen state under reduced pressure to give a partially dried product; and

(v) a secondary drying stage in which the DMSO is removed by evaporation from the partially dried product in a non-frozen state under reduced pressure to give the lyophilized product,

wherein any residual DMSO present in the lyophilized product is in an amount corresponding to no more than 35 mg per 100 mg equivalent of a free base of the compound of formula (1).

15. A method of preparing a lyophilized pharmaceutical product, the method comprising dissolving a compound of formula (1):

(1)



or a pharmaceutically-acceptable salt thereof, in a solvent comprising dimethylsulfoxide (DMSO) to form a solution, wherein the solvent is then removed by a freeze-drying process to give the lyophilized pharmaceutical product, wherein the freeze-drying process comprises:

(i) a first freezing stage in which the solution is frozen by reducing the temperature thereof to a temperature of no greater than about −20° C;

(ii) a first warming stage in which the temperature of the frozen solution is raised to a temperature in the range from about −15° C to about 5° C, wherein the temperature in the range from about −15° C to about 5° C keeps the solution frozen;

(iii) a second freezing stage in which the temperature of the solution is lowered to a temperature of no greater than about −20° C;

(iv) a primary drying stage, wherein the primary drying stage comprises a sublimation step in which the DMSO is removed by sublimation from the solution in its frozen state under reduced pressure to give a partially dried product; and

(v) a secondary drying stage in which the DMSO is removed by evaporation from the partially dried product in a non-frozen state under reduced pressure to give the lyophilized pharmaceutical product,

wherein in an amount of the lyophilized pharmaceutical product obtained from 1 gram of the solution, there is a residual DMSO content of no greater than about 20 mg.

16. The method of claim 15, wherein the compound of formula (1) is in the form of a sodium salt.

17. The method of claim 15, wherein the solvent is non-aqueous.

18. The method of claim 15, wherein the lyophilized pharmaceutical product has a dissolution time, at ambient temperature, and without the aid of mechanised stirring, in a non-aqueous solvent containing 65% (v/v) propylene glycol; 25% (v/v) glycerine; and 10% (v/v) ethanol, of no greater than about 20 minutes.

19. The method of claim 15, further comprising packing the lyophilized pharmaceutical product in a sealed pharmaceutical container.

20. The method of claim 15, further comprising dissolving the lyophilized pharmaceutical product in another solvent to form an injectable liquid composition.

21. The method of claim 20, wherein the another solvent is a non-aqueous solvent.

22. The method of claim 15, wherein the solution further comprises a co-solvent.

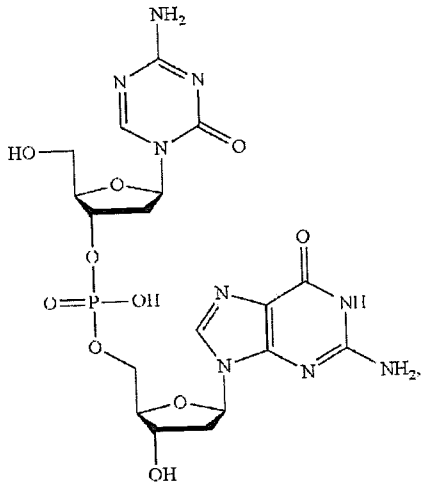
23. The method of claim 15, further comprising reconstituting the lyophilized pharmaceutical product in a pharmaceutically acceptable solvent to give a liquid formulation containing a compound of formula (1) or the pharmaceutically acceptable salt thereof.

24. The method of claim 15, wherein the temperature in the primary drying stage is from about −3° C to about −9° C.

25. The method of claim 15, wherein the temperature in the secondary drying stage is from about 30° C to about 65° C.

26. A method of preparing a lyophilized pharmaceutical product, the method comprising dissolving a compound of formula (1):

(1)



or a pharmaceutically-acceptable salt thereof, in a solvent comprising dimethylsulfoxide (DMSO) to form a solution, wherein the solvent is then removed by a freeze-drying process to give the lyophilized pharmaceutical product, wherein the freeze-drying process comprises:

(i) a first freezing stage in which the solution is frozen by reducing the temperature thereof to a temperature of no greater than about −20° C;

(ii) a first warming stage in which the temperature of the frozen solution is raised to a temperature in the range from about −15° C to about 5° C, wherein the temperature in the range from about −15° C to about 5° C keeps the solution frozen;

(iii) a second freezing stage in which the temperature of the solution is lowered to a temperature of no greater than about −20° C;

(iv) a primary drying stage, wherein the primary drying stage comprises a sublimation step in which the DMSO is removed by sublimation from the solution in its frozen state under reduced pressure to give a partially dried product; and

(v) a secondary drying stage in which the DMSO is removed by evaporation from the partially dried product in a non-frozen state under reduced pressure to give the lyophilized pharmaceutical product,

wherein any residual DMSO present in the lyophilized pharmaceutical product is in an amount corresponding to no more than 35 mg per 100 mg equivalent of a free base of the compound of formula (1).

27. The method of claim 26, wherein the compound of formula (1) is in the form of a sodium salt.

28. The method of claim 26, wherein the solvent is non-aqueous.

29. The method of claim 26, wherein the lyophilized pharmaceutical product has a dissolution time, at ambient temperature, and without the aid of mechanised stirring, in a non-aqueous solvent containing 65% (v/v) propylene glycol; 25% (v/v) glycerine; and 10% (v/v) ethanol, of no greater than about 20 minutes.

30. The method of claim 26, further comprising packing the lyophilized pharmaceutical product in a sealed pharmaceutical container.

31. The method of claim 26, further comprising dissolving the lyophilized pharmaceutical product in another solvent to form an injectable liquid composition.

32. The method of claim 31, wherein the another solvent is a non-aqueous solvent.

33. The method of claim 26, wherein the solution further comprises a co-solvent.

34. The method of claim 26, further comprising reconstituting the lyophilized pharmaceutical product in a pharmaceutically acceptable solvent to give a liquid formulation containing a compound of formula (1) or the pharmaceutically acceptable salt thereof.

35. The method of claim 26, wherein the temperature in the primary drying stage is from about −3° C to about −9° C.

36. The method of claim 26, wherein the temperature in the secondary drying stage is from about 30° C to about 65° C.