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(54) **LYOPHILIZED ANTI-FUNGAL COMPOSITION**

(76) Inventors: **Sachin Mittal**, Telford, PA (US); **Hossain Jahansouz**, Foster City, CA (US); **Suttilug Sotthivirat**, Lansdale, PA (US)

Correspondence Address:
MERCK
P O BOX 2000
RAHWAY, NJ 07065-0907 (US)

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(57) **ABSTRACT**

A lyophilized anti-fungal composition comprises (A) caspofungin, or a pharmaceutically acceptable salt thereof, in an effective amount; (B) one or more non-reducing sugars having a glass transition temperature T_g(s) of at least about 90° C.; and (C) an acetate buffer in an amount effective to provide a pH in a range of from about 5 to about 7; wherein the weight ratio of the one or more non-reducing sugars to caspofungin is in a range of from about 1.1:1 to about 10:1; the composition has a moisture content of about 0.8 wt. % or less; and the composition has a glass transition temperature T_g(c) of at least about 55° C. The lyophilized composition has good storage stability at temperatures up to and including room temperature. The composition can be reconstituted for use in preventing or treating fungal infections.

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LYOPHILIZED ANTI-FUNGAL COMPOSITION

FIELD OF THE INVENTION

[0001] The invention is directed to caspofungin-containing pharmaceutical compositions useful for treating and/or preventing fungal infections.

BACKGROUND OF THE INVENTION

[0002] Caspofungin is a macrocyclic lipopeptide echinocandin whose structural formula is disclosed in column 2, lines 32-52 of U.S. Pat. No. 5,952,300. Caspofungin is also described in U.S. Pat. No. 5,378,804, and methods for its preparation are described in U.S. Pat. No. 5,378,804, U.S. Pat. No. 5,552,521, U.S. Pat. No. 5,952,300 and U.S. Pat. No. 6,136,783. Caspofungin is an inhibitor of the synthesis of β-(1,3)-D-glucan, which is an integral part of the fungal cell wall. Caspofungin is useful as an antibiotic, especially as an antifungal agent or as an antiprotozoal agent. As an antifungal agent, it is useful for the control of both filamentous fungi and yeast. It is especially adaptable to be employed for the treatment of mycotic infections in mammals, especially those caused by *Candida* species such as *C. albicans, C. tropicalis, C. krusei, C. glabrata* and *C. pseudotropicalis*, and Aspergillus species such as *A. fumigatus, A. flavus* and *A. niger*. In particular, the compound has been found effective against putatively Amphotericin B- and Fluconazole-resistant *Candida* isolates. The compound is also useful for the treatment and/or prevention of *Pneumocystis carinii* pneumonia to which immune compromised patients, such as those suffering from AIDS, are especially susceptible.

[0003] Caspofungin is typically employed in a lyophilized composition that is reconstituted for intravenous infusion. Preferred lyophilized caspofungin compositions are acetate-buffered products such as those described in U.S. Pat. No. 5,952,300. Of particular interest is the lyophilized, acetate-buffered product containing caspofungin in the form of a diacetate salt, sucrose, mannitol, glacial acetic acid, and sodium hydroxide. Such a product is available from Merck & Co., Inc. under the trade name CANCIDAS in 35 mg, 50 mg, and 70 mg doses. CANCIDAS is indicated for empirical therapy for fungal infection in patients with fever and neutropenia, the treatment of Candidemia and certain other *Candida* infections, the treatment of esophageal Candidiasis, and the treatment of invasive Aspergillosis in patients who are resistant to or cannot tolerate other therapies.

[0004] Lyophilized, acetate-buffered, caspofungin products such as CANCIDAS are characterized by good storage stability at low temperature (e.g., 2° C. to 8° C.) under ambient storage conditions. More particularly, the compositions can be stored at low temperature (e.g., 5° C.) for many months with minimal formation of degradates. Nonetheless, lyophilized caspofungin-containing products with improved storage stability at low temperatures and/or satisfactory storage stability at higher temperatures is desirable. Improved storage stability at about 5° C. would provide for a longer shelf life thereby reducing the potential for product loss. Satisfactory storage stability at room temperature would eliminate the need for refrigeration and the special handling and extra costs associated therewith.

SUMMARY OF THE INVENTION

[0005] The present invention includes a lyophilized anti-fungal composition which comprises:

[0006] (A) caspofungin, or a pharmaceutically acceptable salt thereof, in an effective amount;

[0007] (B) one or more non-reducing sugars having a glass transition temperature T_g(s) of at least about 90° C.; and

[0008] (C) an acetate buffer in an amount effective to provide a pH in a range of from about 5 to about 7;

[0009] wherein:

[0010] the weight ratio of the one or more non-reducing sugars to caspofungin is in a range of from about 1.1:1 to about 10:1;

[0011] the composition has a moisture content of about 0.8 wt. % or less; and

[0012] the composition has a glass transition temperature T_g(c) of at least about 55° C.

[0013] The lyophilized anti-fungal composition of the present invention has good chemical and storage stability at and below room temperature (i.e., at or below about 30° C.). The composition typically has a stability exceeding that of known lyophilized caspofungin-containing compositions which employ sucrose and mannitol and have a T_g(c) in a range of from about 40° C. to about 45° C.

[0014] Embodiments, aspects and features of the present invention are either further described in or will be apparent from the ensuing description, examples, and appended claims.

DETAILED DESCRIPTION OF THE INVENTION

[0015] A first embodiment of the present invention (alternatively referred to herein as "Embodiment E1") is a lyophilized composition as originally described (i.e., as described in the Summary of the Invention) wherein the one or more non-reducing sugars is selected from the group consisting of trehalose, sucrose, raffinose, sorbitol and combinations thereof. Suitable combinations include any two of the sugars (e.g., trehalose and sucrose), any three of the sugars (e.g., trehalose, sucrose, and sorbitol), or all four of the sugars. In an aspect of this embodiment, the one or more non-reducing sugars is trehalose or a mixture of trehalose with any one of sucrose, raffinose and sorbitol. In a feature of this aspect, the non-reducing sugar is trehalose or a major amount of trehalose (i.e., trehalose is more than 50 wt. % of the mixture) with any one of sucrose, raffinose and sorbitol. In another feature of this aspect, the non-reducing sugar is trehalose or is a combination of at least about 80 wt. % trehalose with any one of sucrose, raffinose and sorbitol.

[0016] A second embodiment of the present invention (Embodiment E2) is a lyophilized composition as originally described wherein trehalose is the one or more non-reducing sugars; i.e., there is one non-reducing sugar present in the composition and that sugar is trehalose. This is alternatively and more simply expressed herein as "trehalose is the non-reducing sugar".

[0017] A third embodiment of the present invention (Embodiment E3) is a lyophilized composition as originally described or as set forth in either Embodiment E1 or E2 wherein the moisture content of the composition is about 0.5 wt. % or less.

[0018] A fourth embodiment of the present invention (Embodiment E4) is a lyophilized composition as originally described or as set forth in either Embodiment E1 or E2 wherein the moisture content of the composition is about 0.3 wt. % or less.

[0019] A fifth embodiment of the present invention (Embodiment E5) is a lyophilized composition as originally

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described or as set forth in any one of the foregoing embodiments wherein the glass transition temperature T_g(c) of the composition is at least about 90° C.

[0020] A sixth embodiment of the present invention (Embodiment E6) is a lyophilized composition as originally described or as set forth in any one of the foregoing embodiments wherein the glass transition temperature T_g(c) of the composition is in a range of from about 90° C. to about 125° C.

[0021] A seventh embodiment of the present invention (Embodiment E7) is a lyophilized composition as originally described or as set forth in any one of the foregoing embodiments wherein the non-reducing sugar-to-caspofungin weight ratio of the composition is in a range of from about 2:1 to about 8:1.

[0022] An eighth embodiment of the present invention (Embodiment E8) is a lyophilized composition as originally described or as set forth in any one of the foregoing embodiments wherein the non-reducing sugar-to-caspofungin weight ratio of the composition is in a range of from about 2:1 to about 6:1.

[0023] A ninth embodiment of the present invention (Embodiment E9) is a lyophilized composition as originally described wherein trehalose is the non-reducing sugar, the moisture content of the composition is about 0.5 wt. % or less, the glass transition temperature T_g(c) of the composition is at least about 90° C., and the trehalose-to-caspofungin weight ratio is in a range of from about 2:1 to about 8:1. In an aspect of this embodiment, the glass transition temperature T_g(c) is in a range of from about 90° C. to about 125° C.

[0024] A tenth embodiment of the present invention (Embodiment E10) is a lyophilized composition as originally described wherein trehalose is the non-reducing sugar, the moisture content is about 0.3 wt. % or less, the glass transition temperature T_g(c) is at least about 90° C., and the trehalose-to-caspofungin weight ratio is in a range of from about 2:1 to about 6:1. In an aspect of this embodiment, the glass transition temperature T_g(c) is in a range of from about 90° C. to about 125° C.

[0025] An eleventh embodiment of the present invention (Embodiment E11) is a lyophilized composition as originally described which is prepared by lyophilizing an aqueous solution comprising the caspofungin or its salt, the acetate buffer, and the one or more non-reducing sugars, wherein in the solution:

[0026] (A) the caspofungin or its salt has a concentration in a range of from about 5 mg/mL to about 200 mg/mL;

[0027] (B) the one or more non-reducing sugars has a concentration ratio on a mg/mL basis with respect to caspofungin in a range of from about 2:1 to about 10:1; and

[0028] (C) the acetate buffer has a concentration in a range of from about 12.5 mM to about 200 mM.

[0029] Aspects of Embodiment E11 include the lyophilized composition as just described in Embodiment E11, wherein:

[0030] (A1) the one or more non-reducing sugars is a sugar selected from the group consisting of trehalose, sucrose, raffinose, sorbitol and combinations thereof.

[0031] (A2) trehalose is the non-reducing sugar.

[0032] (A3) the moisture content of the composition is about 0.5 wt. % or less.

[0033] (A4) the moisture content of the composition is about 0.3 wt. % or less.

[0034] (A5) the glass transition temperature T_g(c) of the composition is at least about 90° C.

[0035] (A6) the glass transition temperature T_g(c) of the composition is in a range of from about 90° C. to about 125° C.

[0036] (A7) the non-reducing sugar(s)-to-caspofungin weight ratio of the composition is in a range of from about 2:1 to about 8:1.

[0037] (A8) the non-reducing sugar(s)-to-caspofungin weight ratio of the composition is in a range of from about 2:1 to about 6:1.

[0038] (A9) trehalose is the non-reducing sugar, the moisture content of the composition is about 0.5 wt. % or less, and the glass transition temperature T_g(c) is at least about 90° C.

[0039] (A 10) the composition is the same as set forth in A9, except that the moisture content is about 0.3 wt. % or less.

[0040] (A11) trehalose is the non-reducing sugar, the moisture content is of about 0.5 wt. % or less, the glass transition temperature T_g(c) is at least about 90° C., and the trehalose-to-caspofungin weight ratio is in a range of from about 2:1 to about 8:1.

[0041] (A12) trehalose is the non-reducing sugar, the moisture content is about 0.3 wt. % or less, the glass transition temperature T_g(c) is at least about 90° C., and the trehalose-to-caspofungin weight ratio is in a range of from about 2:1 to about 6:1.

[0042] (A13) the composition is the same as set forth in A11 except that the glass transition temperature T_g(c) is in a range of from about 90° C. to about 125° C.

[0043] (A14) the composition is the same as set forth in A12 except that the glass transition temperature T_g(c) is in a range of from about 90° C. to about 125° C.

[0044] A twelfth embodiment of the present invention (Embodiment E12) is a lyophilized composition as set forth in Embodiment E11, wherein in the aqueous solution from which the lyophilized composition is prepared:

[0045] (A) the concentration of caspofungin or its salt is in a range of from about 30 mg/mL to about 50 mg/mL;

[0046] (B) the concentration ratio of the non-reducing sugar(s) to caspofungin is in a range of from about 4:1 to about 8:1; and

[0047] (C) the concentration of the acetate buffer is in a range of from about 20 mM to about 60 mM.

[0048] A thirteenth embodiment of the present invention (Embodiment E13) is a lyophilized composition as set forth in Embodiment E12, wherein trehalose is the non-reducing sugar, the moisture content of the composition is about 0.5 wt. % or less (e.g., about 0.3 wt. % or less), and the glass transition temperature T_g(c) of the composition is at least about 90° C. (e.g., in a range of from about 90° C. to about 125° C.).

[0049] A fourteenth embodiment of the present invention (Embodiment E14) is a lyophilized composition as set forth in Embodiment E13, wherein in the aqueous solution from which the lyophilized composition is prepared:

[0050] (A) the concentration of caspofungin or its salt is in a range of from about 30 mg/mL to about 50 mg/mL;

[0051] (B) the concentration of trehalose is in a range of from about 180 mg/mL to about 300 mg/mL (i.e., a trehalose to caspofungin concentration ratio of about 6:1); and

[0052] (C) the acetate buffer has a concentration in a range of from about 20 mM to about 60 mM.

[0053] A fifteenth embodiment of the present invention (Embodiment E15) is a lyophilized composition as originally described or as set forth in any of the foregoing embodiments

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or aspects or features thereof, wherein the composition is substantially free of reducing sugars. Reducing sugars can have a detrimental effect on the stability of the lyophilized compositions of the present invention (see below), and thus the compositions preferably contain little or no reducing sugar. The term "substantially free" in this context means that no reducing sugar is included as a component in the preparation of the lyophilized composition and/or that essentially no reducing sugar is present in the lyophilized composition.

[0054] An "effective amount" of caspofungin in the lyophilized composition is an amount of caspofungin (on a free base basis) that upon reconstitution of the lyophilized composition can be employed (e.g., via parenteral administration) in a therapeutically or prophylactically effective amount to treat or prevent a fungal infection or the like.

[0055] The term "pharmaceutically acceptable salt" refers to a salt which is not biologically or otherwise undesirable (e.g., is neither toxic nor otherwise deleterious to the recipient thereof). The caspofungin salt can suitably be a mono-, di-, or tri-acid salt. The salts are suitably prepared by treating the free base with a suitable organic or inorganic acid. Suitable salts include acid addition salts such as the salts formed by treating the free base with hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, maleic acid, critic acid, or acetic acid.

[0056] The term "non-reducing sugar" refers to a carbohydrate that does not reduce alkaline solutions of copper. Non-reducing sugars do not participate in the Maillard reaction with compounds containing primary amines (e.g., amino acids). The reducing or non-reducing nature of a sugar can be determined by the Fehling's test, which monitors the reduction of Cu ++ to Cu+, with concomitant oxidation of the sugar. Non-reducing sugars do not react in the Fehling's test (i.e., they do not lead to the formation of cuprous oxide). Exemplary non-reducing sugars suitable for use in the present invention include trehalose, sucrose, raffinose, and sorbitol.

[0057] A "reducing sugar" refers to a carbohydrate that does reduce alkaline solutions of copper (e.g., does react in the Fehling's test) and does participate in the Maillard reaction with compounds containing primary amines.

[0058] The glass transition temperatures referred to herein (e.g., T_g(s) and T_g(c)) are the transition temperatures determined using differential scanning calorimetry (DSC). DSC measures the change in heat capacity between the glassy and rubbery states and is typically indicated by a change in baseline in a DSC thermogram.

[0059] The glass transition temperature T_g(c) of the lyophilized composition of the present invention will typically decrease as the amount of moisture in the composition increases. Furthermore, even in cases where the lyophilized composition can tolerate a relatively large amount of moisture and still have a suitable T_g(c), the presence of a relatively large amount of moisture is often deleterious for other reasons. For example, the moisture can be a source of chemical degradation of the active ingredient by, for example, hydrolysis. Accordingly, the lyophilized composition of the present invention is characterized by having a low moisture content. More particularly, for the purposes of this invention, if (i) the amount of moisture in the composition is about 0.8 wt. % or less and (ii) the T_g(c) of the lyophilized composition is at least about 55° C., then the composition is deemed to have a low moisture content and to be a composition of the present invention. Both (i) and (ii) must be satisfied for the composition to be a composition of the present invention. Thus, if a lyophilized composition has a moisture content of less than about 0.8 wt. % but its T_g(c) is below about 55° C., the composition is not a composition of the present invention. Furthermore, if a lyophilized composition has a T_g(c) above about 55° C. but its moisture content is more than 0.8 wt. %, the composition is not considered as having a low moisture content and is not a composition of the present invention. The lyophilized composition of the invention typically has a moisture content of less than about 0.5 wt. % and a T_g(c) above about 55° C., and preferably has a moisture content of less than about 0.5 wt. % and a T_g(c) above about 90° C.

[0060] T_g(s), the glass transition temperature of the one or more non-reducing sugars employed in the lyophilized anti-fungal composition of the invention is the glass transition temperature of the sugar(s) after lyophilization of the non-reducing sugar(s) in the same manner as the anti-fungal composition is lyophilized, wherein the lyophilization generates an amorphous form of the non-reducing sugar(s). The T_g(s) value of the one or more non-reducing sugars used in the present invention is at least about 90° C. and is typically in a range of from about 90° C. to about 125° C.

[0061] When more than one non-reducing sugar is employed, it is the T_g(s) value of the sugars together in a mixture (after lyophilization) that must be at least about 90° C. A non-reducing sugar whose glass transition temperature is below 90° C. can be included in the composition, provided that the T_g(s) of all of the non-reducing sugars together (after lyophilization) is about 90° C. or higher. Typically, however, each of the non-reducing sugars employed in the lyophilized composition has an individual glass transition temperature of at least about 90° C.

[0062] The moisture content of the lyophilized composition is determined by the Karl Fisher coulometry method, wherein the residual water is extracted from the composition using methanol or some other suitable extraction agent. The water present in the methanol or other reagent is then titrated with a Karl Fischer solution that reacts with the water to form colorless hydrogen iodide. When all of the water has been consumed, free iodine, which has color, appears, thereby indicating an end point before which the conductivity of the solution will have changed. The moisture content can then be determined from a measurement of the amount of HI formed during the titration.

[0063] The term "about", when modifying the quantity of a substance or composition, or the value of a physical property (e.g., moisture content, T_g(c), T_g(s), or the like) of a substance or composition, or the value of a parameter characterizing a process, or the like refers to variation in the numerical quantity that can occur, for example, through typical measuring and handling procedures employed in the preparation, characterization, and use of the lyophilized compositions of the invention; for making concentrates or use solutions in the real world; through inadvertent error in these procedures; through differences in the manufacture, source, or purity of the ingredients employed to make or use the compositions or carry out the procedures; and the like. In one embodiment, the term "about" means the reported numerical value ±10% thereof. In an aspect of this embodiment, the term "about" means the reported numerical value ±5% thereof.

[0064] An "effective amount" of an acetate buffer is an amount of the buffer that can provide, with suitable adjustment as needed by addition of base (e.g., a hydroxide such as NaOH), a pH in the indicated range in the aqueous solution

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from which the lyophilized composition of the invention is prepared (i.e., in the pre-lyophilization solution).

[0065] Unless expressly stated to the contrary, a reference to pH herein means the pH at ambient temperature; i.e., at a temperature in a range of from about 20° C. to about 25° C.

[0066] The lyophilized compositions of the present invention are not limited to the active ingredient (i.e., caspofungin) or its salt, the acetate buffer and the non-reducing sugar(s). The composition can include other components such as (i) a minor amount of a bulking agent (e.g., a polyol) in addition to the non-reducing sugar(s) or (ii) an anti-oxidant such as BHT, BHA, alpha-tocopherol, or ascorbic acid. If employed, the bulking agent is typically present in an amount of less than about 10 wt. %, preferably less than about 5 wt. %, with respect to the non-reducing sugar(s).

[0067] The present invention also includes a process for preparing a lyophilized anti-fungal composition with a moisture content of less than about 0.8 wt. % (alternatively referred to herein as "Process P1"), which comprises

[0068] (A) preparing an aqueous solution with a pH in a range of from about 5 to about 7 and comprising an effective amount of caspofungin or a pharmaceutically acceptable salt thereof, one or more non-reducing sugars having a glass transition temperature T_g(s) of at least about 90° C., and an acetate buffer, wherein the concentration ratio, on a weight per unit volume basis, of the one or more non-reducing sugars to caspofungin is in a range of from about 1.1:1 to about 10:1; and

[0069] (B) freeze-drying the aqueous solution to provide the lyophilized anti-fungal composition.

[0070] A first embodiment of Process P1 (alternatively referred to herein as "Embodiment P1-E1") is the process as originally described, wherein Step A further comprises:

[0071] (a1) dissolving the one or more non-reducing sugars in water;

[0072] (a2) adding acetic acid and then adjusting the pH to be in a range of from about 4.5 to about 5.5 by addition of base;

[0073] (a3) adding caspofungin or its salt and adjusting the pH to a value in a range of from about 5 to about 7 (e.g., about 6) by addition of more base; and

[0074] (a4) optionally filtering the resulting aqueous solution.

[0075] When more than one non-reducing sugar is employed in sub-step a1 of Step A in the Process P1, the sugars can be dissolved in any convenient way. For example, the sugars can be mixed together and the dry mixture dissolved in water to provide the solution employed in sub-step a2, or alternatively the sugars can be dissolved individually in separate portions of water to provide separate aqueous sub-solutions and the separate sub-solutions added together and optionally diluted if necessary to give the solution employed in sub-step a2, or alternatively the sugars can be added separately to the same portion of water and dissolved therein and optionally diluted if necessary to provide the solution employed in sub-step a2. When added separately, the individual non-reducing sugars can be added concurrently or at different times in any order.

[0076] A second embodiment of Process P1 (Embodiment P1-E2) is the process as originally described or as set forth in Embodiment P1-E1, wherein in the aqueous solution resulting from Step A the caspofungin or its salt has a concentration in a range of from about 5 mg/mL to about 200 mg/mL, and the concentration ratio of the non-reducing sugar(s) to caspofungin is in a range of from about 2:1 to about 10:1.

[0077] A third embodiment of Process P1 (Embodiment P1-E3) is the process as originally described or as set forth in Embodiment P1-E1, wherein in the aqueous solution resulting from Step A the caspofungin or its salt has a concentration in a range of from about 30 mg/mL to about 50 mg/mL, and the concentration ratio of the non-reducing sugar(s) to caspofungin is in a range of from about 4:1 to about 8:1.

[0078] A fourth embodiment of Process P1 (Embodiment P1-E4) is the process as originally described or as set forth in any one of Embodiments P1-E1 to P1-E3, wherein the one or more non-reducing sugars is selected from the group consisting of trehalose, sucrose, raffinose, sorbitol and mixtures thereof.

[0079] A fifth embodiment of Process P1 (Embodiment P1-E5) is the process as originally described or as set forth in any one of Embodiments P1-E1 to P1-E3, wherein trehalose is the non-reducing sugar.

[0080] A sixth embodiment of Process P1 (Embodiment P1-E6) is the process as originally described or as set forth in any one of the foregoing embodiments of P1, wherein the moisture content of the lyophilized composition is about 0.5 wt. % or less.

[0081] A seventh embodiment of Process P1 (Embodiment P1-E7) is the process as originally described or as set forth in any one of the foregoing embodiments of P1, wherein the moisture content of the lyophilized composition is about 0.3 wt. % or less.

[0082] An eighth embodiment of Process P1 (Embodiment P1-E8) is the process as originally described or as set forth in any one of the foregoing embodiments of P1, wherein the lyophilized composition has a glass transition temperature T_g(c) of at least about 90° C. (e.g., in a range of from about 90° C. to about 125° C.).

[0083] The present invention also includes a lyophilized anti-fungal composition prepared by the process P1 as originally described or as set forth in any one of the foregoing embodiments of P1.

[0084] The freeze-drying (i.e, lyophilizing) of the aqueous solution resulting from Step A of Process P1 involves first cooling the solution to a temperature at or below the freezing point of the solution (i.e., below its glass transition temperature if the solution forms a glass upon cooling and below its eutectic point if the frozen solution is crystalline). The frozen solution is then typically subjected to a primary drying step in which the temperature is gradually raised under vacuum in a drying chamber to remove most of the water, and then to a secondary drying step typically at a higher temperature than employed in the primary drying step to remove the residual moisture in the lyophilized composition. The freeze drying step typically requires 48 hours or more to complete. The lyophilized composition is then appropriately sealed and stored (e.g., in stoppered vials) for later use. Tang et al., *Pharmaceutical Research* 2004, vol. 21, pp. 191-200 describes the scientific principles pertaining to freeze drying and guidelines for designing suitable freeze drying processes. Further description of freeze drying is found in *Remington—The Science and Practice of Pharmacy,* 2006, 21st edition, Lippincott Williams & Wilkins, pp. 828-831.

[0085] The lyophilized compositions of the present invention are characterized by having good chemical and storage stability at temperatures up to and including room temperature. Caspofungin has two main degradation products. The

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