STABILIZED EFINACONAZOLE FORMULATIONS

CROSS REFERENCES TO RELATED APPLICATIONS

[0001] The present application claims priority to U.S. Provisional Patent Application No. 61/886,569, filed on October 3, 2013, and U.S. Provisional Patent Application No. 61/922,867, filed on January 1, 2014, which applications are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

[0002] Triazole anti-fungal compounds, such as ketoconazole, itraconazole, and fluconazole are known and have been the subject of scientific study, pharmaceutical development, and medical use. Although compounds in this class often exhibit antifungal activity, they differ in terms of efficacy and usefulness in different types of pharmaceutical formulations and treatments. Efinaconazole (CAS registry number 164650-44-6) is a triazole that has demonstrated activity in the treatment of onychomycosis. Formulations useful for the topical delivery of efinaconazole in the treatment of onychomycosis and other triazole antifungal drugs have been described in, *e.g.*, U.S. Patent No. 8,486,978. Some formulations containing triazole active ingredients exhibit varying degrees of instability during storage. Certain formulations are known to discolor within storage periods as short as one or two days, resulting in composition colors ranging from yellow to deep red or brown. Such discoloration can discourage the prescribed use of the compositions by patients who are reluctant to self-administer the discolored compositions. Stabilized formulations of triazoles such as efinaconazole are therefore needed. The present invention addresses this need.

SUMMARY

[0003] The present disclosure provides a liquid or semisolid composition containing about 0.5% to about 15% efinaconazole by weight, butylated hydroxytoluene (BHT), and a salt of ethylenediaminetetraacetic acid (EDTA). The amounts of BHT and the salt of EDTA are sufficient to ensure the composition is: (i) colorless upon initial formulation, and (ii) colorless or pale yellow after storage for at least three weeks at a temperature of at least about 40 °C. In some embodiments, the composition is colorless or pale yellow after storage for one month at a temperature of about 65 °C.

[0003a] In a first aspect of the present disclosure, there is provided a composition comprising about 8% to about 12% efinaconazole by weight, water, C12-15 alkyl lactate, diisopropyl adipate, cyclomethicone, ethanol, butylated hydroxytoluene (BHT), a salt of ethylenediaminetetraacetic acid (EDTA), and citric acid,

wherein the amount of BHT is in the range of about 0.01% (w/w) to about 2% (w/w),

wherein the amount of the salt of EDTA is in the range of about 0.0001% (w/w) to about 1.5% (w/w),

wherein the amount of citric acid is in the range of about 0.05% (w/w) to about 0.25% (w/w),

wherein the composition is formulated as a solution, and

wherein the amounts of BHT and the salt of EDTA are sufficient to ensure the composition is (i) colorless upon initial formulation and (ii) colorless or pale yellow after storage for three weeks at a temperature of about 40° C.

[0004] In some embodiments, the amount of efinaconazole is in the range of about 8% (w/w) to about 12% (w/w). In some embodiments, the amount of efinaconazole is about 10% (w/w). In some embodiments, the amount of efinaconazole is in the range of about 0.5% (w/w) to about 5% (w/w). In some embodiments, the amount of efinaconazole is about 2% (w/w).

[0005] In some embodiments, the amount of BHT is in the range of about 0.01% (w/w) to about 2% (w/w).

[0006] In some embodiments, the amount of EDTA or EDTA salt is in the range of about 0.0001% (w/w) to about 1.5% (w/w). In some embodiments, the amount of EDTA or EDTA salt is in the range of about 0.0001% (w/w) to about 0.0005% (w/w). In some embodiments, the composition is formulated as a solution. In some embodiments, the amount of EDTA or EDTA salt is about 0.00025% (w/w) and the amount of BHT is about 0.1% (w/w).

[0007] In some embodiments, the amount of EDTA or EDTA salt is in the range of about 0.01% (w/w) to about 1% (w/w). In some embodiments, the composition is formulated as a gel. In some embodiments, the amount of EDTA or EDTA salt is about 0.1 % (w/w) and the amount of BHT is about 0.1% (w/w).

[0008] In some embodiments, the composition further comprises from about 0.01% citric acid (w/w) to about 1% citric acid (w/w). In some embodiments, the composition comprises from about 0.05% citric acid (w/w) to about 0.25% citric acid (w/w). In some embodiments, the composition comprises from about 0.075% citric acid (w/w) to about 0.15% citric acid (w/w).

[0009] In some embodiments, the color of the composition is determined by visual inspection. In some embodiments, the color is determined by assessing UV-vis absorbance values.

[0010] In some embodiments, after storage for at least one month at 65 °C the composition exhibits UV-vis absorbance values of 0.4 absorbance units (AU) or less at 400 nm; 0.1 AU or less at 500 nm; and/or 0.1 AU or less at 600 nm. In some embodiments, after storage for at least one month at 65 °C the composition exhibits UV-vis absorbance values of: 0.4 AU or less at 400 nm; 0.1 AU or less at 500 nm; and 0.1 AU or less at 600 nm.

[0011] In some embodiments, after storage for at least one month at 65 °C the composition exhibits UV-vis absorbance values of 0.2 AU or less at 400 nm; 0.03 AU or less at 500 nm;

and/or (iii) 0.03 AU or less at 600 nm. In some embodiments, after storage for at least one month at 65 °C the composition exhibits UV-vis absorbance values of: 0.2 AU or less at 400 nm; 0.03 AU or less at 500 nm; and 0.03 AU or less at 600 nm.

[0012] In some embodiments, after storage for at least one month at 65 °C the composition exhibits UV-vis absorbance of 0.1 AU or less at 400 nm; 0.01 AU or less at 500 nm; and/or (iii) 0.01 AU or less at 600 nm. In some embodiments, after storage for at least one month at 65 °C the composition exhibits UV-vis absorbance values of: 0.1 AU or less at 400 nm; 0.01 AU or less at 500 nm; and (iii) 0.01 AU or less at 600 nm.

[0013] In some embodiments, the composition is a pharmaceutically acceptable formulation that is effectively absorbed in the treatment of the nail.

[0014] The present disclosure also provides methods of treating or preventing a fungal infection. The methods include administering a therapeutically effective amount of a formulation of the present disclosure to a patient in need of such treatment.

[0014a] In a second aspect of the present disclosure, there is provided a composition disclosed herein for use in treating a fungal infection.

[0014b] In a third aspect of the present disclosure, there is provided a use of a composition disclosed herein in the manufacture of a medicament for treating a fungal infection.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] Figure 1 shows efinaconazole solutions exhibiting varying levels of discoloration due to instability during storage.

[0016] Figure 2 shows UV-vis absorbance values for efinaconazole solutions exhibiting varying levels of discoloration, measured at (A) 400 nm, (B) 500 nm, and (C) 600 nm.

DETAILED DESCRIPTION OF THE INVENTION

I. Definitions

[0017] As used herein, the term "pharmaceutical composition" refers to a mixture containing a pharmaceutically active ingredient, such as efinaconazole, and one or more pharmaceutically acceptable excipients (antioxidants, preservatives, carriers, *etc.*). Compositions for topical administration are formulated as solutions, sprays, ointments, lotions, gels, shampoos, and the like. "Pharmaceutically acceptable" compositions are those in which substituent components such as carriers, diluents, and excipients are compatible with each other and with the active ingredient. Pharmaceutically acceptable compositions are frequently made with pharmaceutical-grade active agents and excipients. It will be

WHAT IS CLAIMED IS:

1. A composition comprising about 8% to about 12% efinaconazole by weight, water, C12-15 alkyl lactate, diisopropyl adipate, cyclomethicone, ethanol, butylated hydroxytoluene (BHT), a salt of ethylenediaminetetraacetic acid (EDTA), and citric acid,

wherein the amount of BHT is in the range of about 0.01% (w/w) to about 2% (w/w),

wherein the amount of the salt of EDTA is in the range of about 0.0001% (w/w) to about 1.5% (w/w),

wherein the amount of citric acid is in the range of about 0.05% (w/w) to about 0.25% (w/w),

wherein the composition is formulated as a solution, and

wherein the amounts of BHT and the salt of EDTA are sufficient to ensure the composition is (i) colorless upon initial formulation and (ii) colorless or pale yellow after storage for three weeks at a temperature of about 40° C.

2. The composition of claim 1, wherein the amount of efinaconazole is about 10% (w/w).

3. The composition of claim 1, wherein the amount of the salt of EDTA is in the range of about 0.0001% (w/w) to about 0.0005% (w/w).

4. The composition of claim 3, wherein the amount of the salt of EDTA is about 0.00025% (w/w) and the amount of BHT is about 0.1% (w/w).

5. The composition of claim 1, wherein the amount of the salt of EDTA is in the range of about 0.01% (w/w) to about 1% (w/w).

6. The composition of claim 5, wherein the amount of the salt of EDTA is about 0.1% (w/w) and the amount of BHT is about 0.1% (w/w).

7. The composition of claim 1, wherein the composition comprises from about 0.075% citric acid (w/w) to about 0.15% citric acid (w/w).

8. The composition of claim 1, wherein the color of the composition is determined by visual inspection.

9. The composition of claim 1, wherein the color is determined by assessing UV-vis absorbance values.

10. The composition of claim 9, wherein after storage for one month at 65° C. the composition exhibits UV-vis absorbance values of 0.4 absorbance units (AU) or less at 400 nm; 0.1 AU or less at 500 nm; and/or 0.1 AU or less at 600 nm.

11. The composition of claim 1, wherein the composition is a pharmaceutically acceptable formulation that is effectively absorbed in the treatment of the nail.

12. The composition of claim 1, comprising:

ethanol in an amount ranging from 50% to 70% by weight,
cyclomethicone in an amount ranging from 10% to 15% by weight,
diisopropyl adipate in an amount ranging from 8% to 15% by weight, and
C12-15 alkyl lactate in an amount ranging from 8% to 15% by weight.

13. The composition of claim 12, wherein the amount of the salt of EDTA is about 0.00025% (w/w) and the amount of BHT is about 0.1% (w/w).

14. The composition of claim 12, wherein the amount of citric acid is in the range of about 0.075% (w/w) to about 0.15% (w/w).

15. The composition of claim 13, wherein the amount of citric acid is in the range of about 0.075% (w/w) to about 0.15% (w/w).

16. A composition according to claim 11 for use in treating a fungal infection.

17. Use of a composition according to claim 11 in the manufacture of a medicament for treating a fungal infection.