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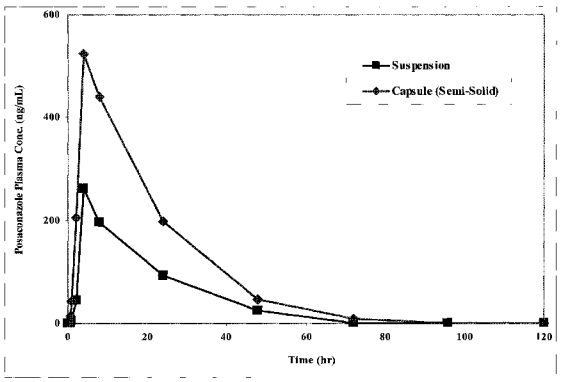
(54) **Title**: SEMI-SOLID ORAL PHARMACEUTICAL COMPOSITIONS

Figure 1



(57) **Abstract**: The present invention provides semi-solid pharmaceutical compositions comprising a weakly basic and poorly-aqueous soluble azole, a monohydric organic alcohol and at least one nonionic surfactant. In the most preferred embodiment, the weakly basic and poorly-aqueous soluble azole is posaconazole. The present invention also provides methods for treating and/or preventing fungal infections in a mammal using the oral pharmaceutical compositions disclosed herein.

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SEMI-SOLID ORAL PHARMACEUTICAL COMPOSITIONS

FIELD OF THE INVENTION

The present invention relates to novel oral pharmaceutical compositions comprising a semi-solid composition of a weakly basic and poorly-aqueous soluble azole, a monohydric organic alcohol and at least one nonionic surfactant. Such pharmaceutical compositions of posaconazole provide enhanced bioavailability of posaconazole in a solid dosage form as compared to an oral suspension. The invention also relates to methods for treating and/or preventing fungal infections using said pharmaceutical compositions.

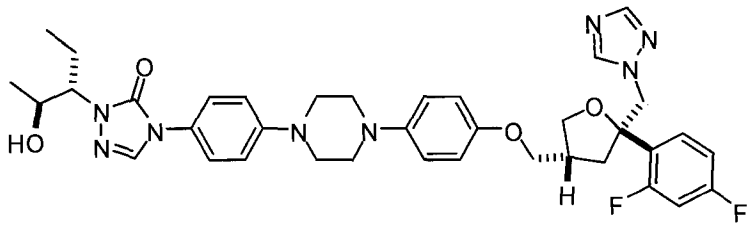
BACKGROUND OF THE INVENTION

Identification of any publication in this section or any section of this application is not an admission that such publication is prior art to the present invention.

Weakly basic and poorly-aqueous soluble (at intestinal pH) drugs comprising an azole functional group often show poor bioavailability or irregular absorption. Although these drugs are often soluble in a low pH environment, such as the stomach (pH 1-2), these drugs are largely insoluble at a higher pH environment, as found in the small intestine (pH 5-7). Consequently, such drugs can precipitate out of solution as they pass from the low pH environment of the stomach into the higher pH environment of the small intestine. Examples of such weakly basic and poorly-aqueous soluble azole drugs are difenamizole, epirizole, fluconazole, itraconazole, ketoconazole, letrozole, posaconazole, ravuconazole, saperconazole, terconazole, and voriconazole.

Certain of these weakly basic and poorly-aqueous soluble azole drugs, including, but not limited to, itraconazole, posaconazole and terconazole have been developed for treatment and/or prevention of fungal infections, including invasive fungal infections. Thus far, the development of these drugs has been problematic as their solubility in aqueous solution is highly pH-dependent which results in difficulties in providing sufficient and easily controlled bioavailability.

United States Patent Nos. 5,703,079 and 5,661,151 disclose posaconazole, a broad spectrum anti-fungal agent, the structure of which is illustrated below:



POSACONAZOLE
pKa1 = 3.6 (piperazine)
pKa2 = 4.6 (triazole)

Posaconazole is partially solubilized in an aqueous acidic solvent having a pH of about pH 1 or more acidic. In a pH 1 aqueous solvent, for example, posaconazole has a solubility of about 790 μg/mL. In contrast, in a solvent less acidic than about pH > 4, posaconazole has a solubility of less than 1 μg/mL.

U.S. Patent No. 5,834,472 ('472 Patent) describes a pharmaceutical composition of posaconazole, a non-ionic surfactant and a diluent. U.S. Patent No. 5,972,381 ('381 Patent) describes pharmaceutical compositions of posaconazole and a soluble or insoluble polymer, such as, povidone or crospovidone, the components being present in particularly recited ratios. U.S. Patent No. 5,846,971 ('971 Patent) describes pharmaceutical capsule compositions of posaconazole coated onto inert beads and a binder. None of the '472, '381, or the '971 Patents describe pharmaceutical compositions comprising posaconazole which provide consistent bioavailability.

U.S. Patent Application Publication No. US2003/0055067 describes pharmaceutical compositions of micronized particles of posaconazole together with a surfactant and thickening agent in the form of liquid suspensions, including an oral suspension commercially available under the tradename NOXAFIL™. To maximize bioavailability from adminiatration of a NOXAFIL™ suspension it is recommended to administer NOXAFIL™ several times a day with food or a nutritional supplement. It is always desirable to provide a solid dosage form, which provides, for example, ease of portability, storage, and administration. Solid oral dosage forms also promote patient compliance by avoiding the need for any additional equipment to administer the dose, for example, a dosing instrument. In addition, there remains a need for a solid dosage form of posaconazole which provides low variability in bioavailability and which reduces the "food effect", thus avoiding the need for administration in combination with food. Likewise, a

solid dosage form with sufficient bioavailability would provide a treatment regimen wherein the number of doses administered per day to achieve the desired therapeutic plasma concentration could be reduced.

Consequently, there is a need for pharmaceutical compositions with enhanced bioavailability of a weakly basic and poorly-aqueous soluble azole, including posaconazole. Such compositions would reduce the dose and/or absorption variability required for the same or better therapeutic effect, reduce the cost of goods for the product, and/or reduce the dosing regimen. Solid dosage forms of such drugs would provide greater convenience for patients and hence promote patient compliance. These and other objectives are provided by the novel pharmaceutical compositions of the present invention.

SUMMARY OF THE INVENTION

In one aspect the present invention provides a pharmaceutical composition which can be incorporated into a solid dosage form suitable for oral administration. In some embodiments, pharmaceutical compositions of the present invention meet the aforementioned need for reduced variability in the bioavailability of posaconazole, for example, a reduction of variability in bioavailability amongst a population of patients. In some embodiments, pharmaceutical compositions of the present invention show a reduction in the food effect associated heretofore with oral administration of pharmaceutical formulations comprising posaconazole. In some embodiments, pharmaceutical compositions of the invention are suitable for the preparation of dosage forms having ahigh drug loading, for example, a drug loading of $\geq$ 100 mg drug per unit dosage form. Such pharmaceutical compositions may provide sufficient bioavailability to eliminate the need for administration with food and/or reduce the number of doses administered per day to achieve the desired therapeutic plasma concentration(s) of posaconazole.

In some embodiments, the present invention provides an oral pharmaceutical composition comprising: a) posaconazole; b) a monohydric organic alcohol; and c) at least one nonionic surfactant; wherein the oral pharmaceutical composition is a semi-solid composition.

In some embodiments, the present invention provides an oral pharmaceutical composition comprising: a) a weakly basic and poorly-aqueous soluble azole which is difenamizole, epirizole, fluconazole, itraconazole, ketoconazole, letrozole, ravuconazole, saperconazole, terconazole, or voriconazole; b) a monohydric organic alcohol; and c) at

least one nonionic surfactant; wherein the oral pharmaceutical composition is a semi-solid composition.

In some embodiments of the present invention, preferably the monohydric organic alcohol is isopropanol, t-butanol, phenol, cresol, or benzyl alcohol, or a mixture of two or more thereof. In some embodiments, the monohydric organic alcohol is benzyl alcohol.

In some embodiments, preferably at least one nonionic surfactant is a polyoxyethylene fatty alcohol ether, a polyoxyethylene sorbitan fatty acid ester, a polyoxyethylene fatty acid ester, a sorbitan ester, glycerol monostearate, a polyethylene glycol, a polypropylene glycol, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, an aryl alkyl polyether alcohol, a polyoxyethylene-polyoxypropylene copolymer, a poloxamine, polyvinyl alcohol, polyvinylpyrrolidone, or a macrogol. In some embodiments, preferably at least one nonionic surfactant is a polyethylene glycol 660 hydroxystearate, a polyethoxylated castor oil, or a block copolymer of ethylene oxide and propylene oxide. In some embodiments preferably at least one nonionic surfactant is a block copolymer of ethylene oxide and propylene oxide, more preferably it is a block copolymer of the formula $HO(C_2H_4O)a(C_3H_6O)b(C_2H_4O)aH$ wherein a = 80 and b= 27. In some embodiments preferably at least one nonionic surfactant is: Pluronic® F68, also known as Poloxamer 188 (a block copolymer of ethylene oxide and propylene oxide, represented by the formula $HO(C_2H_4O)a(C_3H_6O)b(C_2H_4O)aH$ wherein a = 80 and b= 27); Cremophor EL® (polyethoxylated castor oil); or Solutol® HS15 (polyethylene glycol 660 hydroxystearate). In some embodiments, preferably two or more non-ionic surfactants are used to prepare the semi-solid pharmaceutical compositions of the present invention, more preferably two or more non-ionic surfactants selected from the above-recited non-ionic surfactants.

In some embodiments optionally it is preferred for a pharmaceutical composition of the invention to be combined with one or more pharmaceutically acceptable excipients.

Another aspect of the invention provides methods for preparing the pharmaceutical compositions of the present invention. In some embodiments preferably the preparatory method comprises the steps of: (a) dissolving posaconazole in a monohydric organic alcohol; and (b) adding at least one nonionic surfactant while applying vigorous agitation at a temperature from about 35 °C to about 70 °C.

In aother aspect the present invention provides methods for preparing a a semi-solid composition pharmaceutical composition comprising a weakly basic and poorly-aqueous soluble azole comprising the steps of: (a) dissolving a weakly basic and poorly-aqueous

soluble azole in a monohydric organic alcohol; and (b) adding at least one nonionic surfactant while applying vigorous agitation at a temperature from about 35 °C to about 70 °C. In some embodiments of the method of the invention it is preferred for the azole employed to be difenamizole, epirizole, fluconazole, itraconazole, ketoconazole, letrozole, ravuconazole, saperconazole, terconazole, or voriconazole.

Another aspect of the invention provides methods for the treatment and/or prevention of a fungal infection comprising administering a pharmaceutical composition of the present invention, preferably a composition comprising posaconazole, to a patient in need thereof. In some embodiments it is preferred to treat patients suffering from a otomycosis or chromomycosis condition. In some embodiments it is preferred to treat patients having an *Asperillus* or *Candida* fungal infection. In some embodiments it is preferred to treat patients having a fungal infection is caused by a zygomycetes such as Mucor, Rhizopus, Rhizomucor etc. In some embodiments it is preferred to treat patients having a fungal infection is caused by a dermatophyte such as Tinea corporis, Tinea cruris, Tinea pedis, Tinea barbae, Tinea capitis, Tinea nigra, Tinea favosa, or Tinea Imbricata or any other organism associated with onychomycosis.

In some embodiments it is preferred to administer orally a pharmaceutical composition of the invention daily in a single or divided dose. In some embodiments administering a pharmaceutical composition of the invention in a daily divided dose, it is preferred to administer the composition of the invention twice-a-day.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a linear:linear graph of the mean plasma concentration of posaconazole over a time period of 120 hrs post-dose following a single oral administration of 60 mg posaconazole to male cynomolgus monkeys in a semi-solid composition, or, as a comparative example, an oral suspension of posaconazole.

Figure 2 is a graph of the mean Cmax concentration of posaconazole following a single oral administration of 60 mg posaconazole to male cynomolgus monkeys in a semi-solid composition, or, as a comparative example, an oral suspension of posaconazole.

Figure 3 is a graph of the mean exposure (AUC(tf)) of posaconazole following a single oral administration of 60 mg posaconazole to male cynomolgus monkeys in a semi-solid composition, or, as a comparative example, an oral suspension of posaconazole.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as those commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. The materials, methods and examples are illustrative only, and are not intended to be limiting. All publications, patents and other documents mentioned herein are incorporated by reference in their entirety.

As used herein, the term "AUC" is the area under the plasma concentration-time curve from time zero to a certain time period of the sample. For example, AUC (4h) means the area under the plasma concentration-time curve from time zero to 4 hours.

As used herein, the term "AUC(tf)" is the area under the plasma concentration-time curve from time zero to the time of the final quantifiable sample.

As used herein, the term "CL/F" is the apparent total clearance of the drug from plasma after oral administration. CL/F is calculated by dividing the dose administered by the AUC.

The term "patient" refers to an animal including a mammal (e.g., a human).

The term "pharmaceutically acceptable excipient" refers to a non-toxic excipient that may be administered to a patient, together with the weakly basic and poorly-aqueous soluble azoles as described herein, which does not destroy the pharmacological activity thereof.

The term "treating" or "treatment" is intended to mean mitigating or alleviating the symptoms of the recited condition, disease or disorder in a mammal such as a human.

The term "pharmacokinetics" refers to the process by which a drug is absorbed, distributed, metabolized, and eliminated by the body. Pharmacokinetic parameters include, but are not limited to "maximum plasma concentration" or "Cmax," "area under the plasma concentration time curve" or "AUC," and "time to Cmax" or "Tmax."

As used herein, the term "t1/2" refers to the half-life of the drug.

As used herein, the term "weakly basic and poorly-aqueous soluble azole" refers to a compound comprising an azole functional group which is difenamizole, epirizole, fluconazole, itraconazole, ketoconazole, letrozole, posaconazole, ravuconazole, saperconazole, terconazole, or voriconazole. Especially preferred is posaconazole.

SEMI-SOLID PHARMACEUTICAL COMPOSITIONS

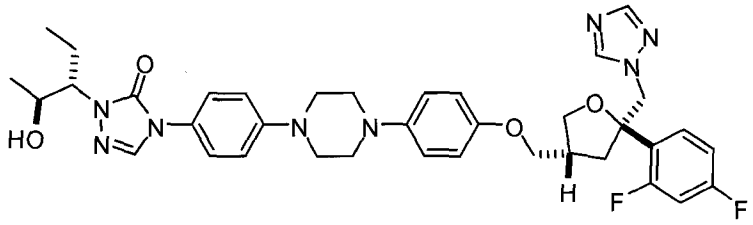
In most preferred embodiments, the present invention provides oral semi-solid pharmaceutical compositions comprising posaconazole, a monohydric organic alcohol and at least one nonionic surfactant which meet the aforementioned need for sufficient and/or reduced variability in the bioavailability of posaconazole. Such pharmaceutical compositions include, but are not limited to, soft-gel capsules, hard shell gelatin capsules, and liquigel capsules. In fact, the pharmaceutical compositions provided herein are suitable for high drug loading dosage forms with $\geq$ 100 mg drug per unit dosage form. The pharmaceutical compositions of the present invention provide sufficient bioavailability to eliminate the need for administration with food and/or reduce the number of doses administered per day to achieve the desired therapeutic plasma concentration(s) of posaconazole.

In one preferred embodiment, the ranges (% w/w) of components for the semi-solid compositions provided herein are 5-30 % posaconazole, 5-45 % benzyl alcohol, 20-60% polyethylene glycol 660 hydroxystearate (e.g., Solutol® HS 15), 1-20 % a block copolymer of ethylene oxide and propylene oxide, represented by the formula $HO(C_2H_4O)a(C_3H_6O)b(C_2H_4O)aH$ wherein a = 80 and b= 27 (e.g., Pluronic® F68, also known as Poloxamer 188). In an alternative preferred embodiment, the ranges (% w/w) of components for the semi-solid compositions provided herein are 5-30 % posaconazole, 5-45 % benzyl alcohol, 20-60% polyethoxylated castor oil (e.g., Cremophor EL®), 1-20 % a block copolymer of ethylene oxide and propylene oxide, represented by the formula $HO(C_2H_4O)a(C_3H_6O)b(C_2H_4O)aH$ wherein a = 80 and b= 27 (e.g., Pluronic® F68, also known as Poloxamer 188)

In other embodiments, the present invention also provides oral pharmaceutical compositions comprising a weakly basic and poorly-aqueous soluble azole which is difenamizole, epirizole, fluconazole, itraconazole, ketoconazole, letrozole, ravuconazole, saperconazole, terconazole, or voriconazole in a semi-solid composition. In certain such embodiments, the weakly basic and poorly-aqueous soluble azole is the antifungal agent

fluconazole, itraconazole, ketoconazole, ravuconazole, saperconazole, terconazole, or voriconazole. In certain such embodiments, the weakly basic and poorly-aqueous soluble azole is the antifungal agent itraconazole or terconazole.

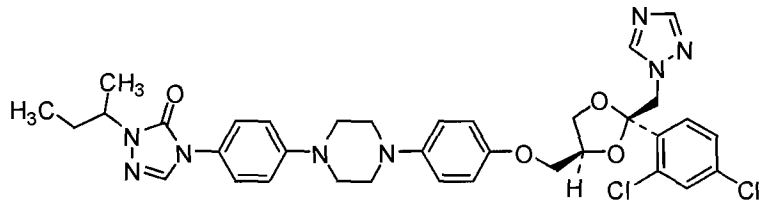
Posaconazole has the following structure:



POSACONAZOLE
pKa1 = 3.6 (piperazine)
pKa2 = 4.6 (triazole)

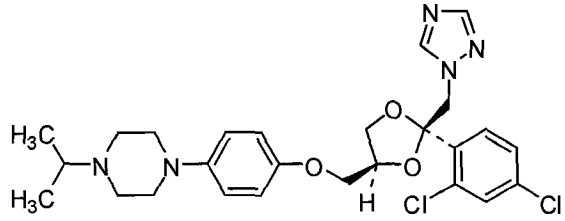
Posaconazole, available from Schering Corporation, Kenilworth, N.J., can be prepared according to Examples 24 and 32 of U.S. Pat. No. 5,661,151 and WO 95/17407. Posaconazole is partially solubilized in a strong acidic aqueous solution with a pH 1 or lower, where it has a solubility of about 790 μg/mL. In contrast, at pH > 4, posaconazole has a solubility of less than 1 μg/mL in aqueous solution.

Itraconazole, available from Janssen Pharmaceutica, N.V., Beerse, Belgium and described in U.S. Patent No. 4,267,179, has a pKa = 3.7 and is practically insoluble in water and diluted acidic solutions. Itraconazole has the following structure:



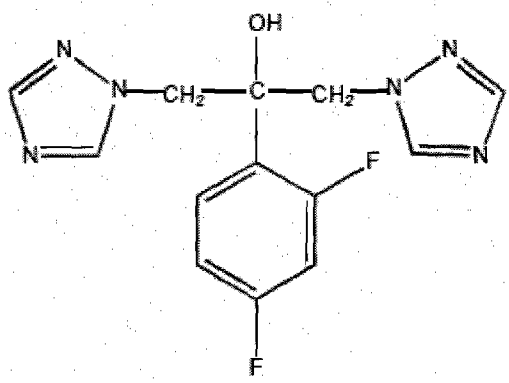
ITRACONAZOLE

Terconazole, available from Janssen Pharmaceutica, N.V., Beerse, Belgium and described in U.S. Patent No. 4,223,036, is practically insoluble (< 0.1 mg/ml) in water has the following structure:

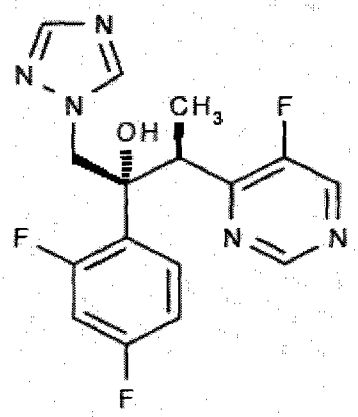


TERCONAZOLE

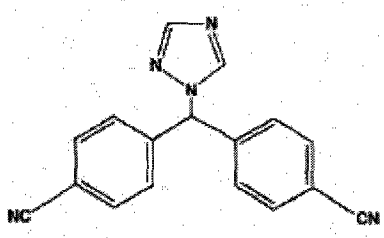
Fluconazole, available from Pfizer, New York, N.Y. and described in U.S. Patent No. 6,790,957, is practically insoluble in water (about 1 ug/ml) and has the following structure:



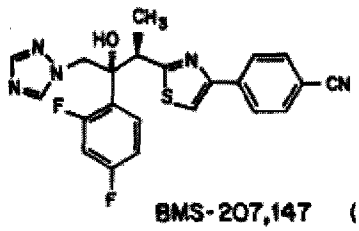
Voriconazole (formerly UK 109496), available from Pfizer, New York, N.Y. and described in U.S. Patent No. 5,278,175, has the following structure:



Letrozole, described in U.S. Patent No. 4,978,672, is practically insoluble in water and has the following structure:

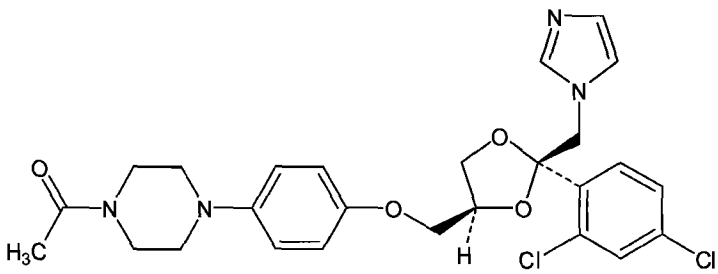


Ravuconazole (BMS-207147; formerly ER-30346), available from Bristol-Myers Squibb, Princeton, N.J. and described in U.S. Patent No. 5,648,372, has the following structure:

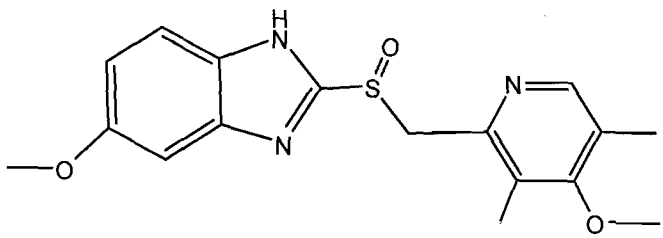


BMS-207,147 (RAVUCONAZOLE)

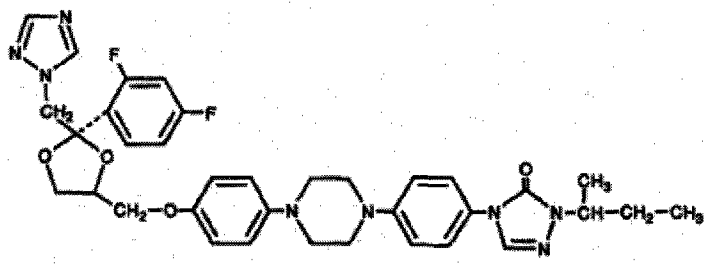
Ketoconazole, described in U.S. Patent No. 4,144,346, has the following structure:



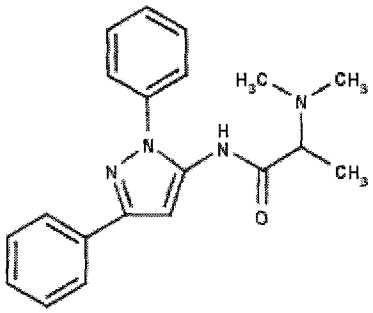
Epirazole (Omeprazole), described in U.S. Patent No. 4,255,431, has the following structure:



Saperconazole, available from Janssen Pharmaceutica, N.V., Beerse, Belgium and described in U.S. Patent No. 4,916,134, which is poorly soluble in water has the following structure:



Difenamizole, described in JP 68 6621, which is practically insoluble in water has the following structure:



In certain embodiments, the monohydric alcohol includes, but is not limited to, isopropanol, t-butanol, phenol, cresol, benzyl alcohol or a cycloalkyl alcohol, preferably benzyl alcohol.

In certain embodiments, at least one nonionic surfactant is a polyoxyethylene fatty alcohol ether, a polyoxyethylene sorbitan fatty acid ester, a polyoxyethylene fatty acid ester, a sorbitan ester, glycerol monostearate, a polyethylene glycol, a polypropylene glycol, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, an aryl alkyl polyether alcohol, a polyoxyethylene-polyoxypropylene copolymer, a poloxamine, polyvinyl alcohol, polyvinylpyrrolidone, or a macrogol. In certain preferred embodiments, at least one nonionic surfactant is a polyethylene glycol 660 hydroxystearate, a polyethoxylated castor oil, or a block copolymer of ethylene oxide and propylene oxide. In one preferred embodiment, at least one nonionic surfactant is a block copolymer of ethylene oxide and propylene oxide, represented by the formula $HO(C_2H_4O)a(C_3H_6O)b(C_2H_4O)aH$ wherein a = 80 and b= 27. In certain embodiment, at least one nonionic surfactant is Pluronic® F68 (also known as specifically Poloxamer 188, a block copolymer of ethylene oxide and propylene oxide, represented by the formula $HO(C_2H_4O)a(C_3H_6O)b(C_2H_4O)aH$ wherein a = 80 and b= 27), Cremophor EL® (polyethoxylated castor oil), or Solutol® HS15 (polyethylene glycol 660 hydroxystearate).

In preferred embodiments, the semi-solid compositions of the present invention disclosed herein are formulated into pharmaceutical compositions for oral administration, herein termed "oral" pharmaceutical compositions. Suitable oral dosage forms include, but are not limited to, soft-gel capsules, hard shell gelatin capsules, and liquigel capsules. In certain embodiments, such oral compositions may optionally further comprise one or more pharmaceutically acceptable excipients. In certain embodiments, oral dosage forms as described herein have a drug loading capacity of at least 50 mg, 75 mg, 100 mg, or 125 mg per oral dosage form.

Suitable excipients are well known in the art. Generally, excipients include, but are not limited to, surface active agents (e.g., sodium lauryl sulfate and polysorbate 80), drug complexing agents or solubilizers (e.g., polyethylene glycols, caffeine, xanthene, gentisic acid and cylodextrins), diluents (e.g., lactose, mannitol, xylitol, microcrystalline cellulose, calcium diphosphate, and starch), disintegrants (e.g., sodium starch glycolate, sodium alginate, carboxymethyl cellulose sodium, methyl cellulose, low-substituted hydroxypropylcellulose (L-HPC (such as LH-21, and LH-B1) and croscarmellose sodium), glidants (e.g., silicon dioxide and Talc), binders (e.g., methyl cellulose, microcrystalline cellulose, starch, HPMCAS, and gums such as guar gum, and tragacanth), lubricants(e.g., magnesium stearate and calcium stearate), pH modifiers (e.g., citric acid, acetic acid, ascorbic acid, lactic acid, aspartic acid, succinic acid, and phosphoric acid), anti-oxidants (e.g., ascorbic acid, butylated hydroxytoluene, and butylated hydroxyanisole), pigments, and flavorants which may be used for customary purposes and in typical amounts without affecting the properties of the compositions. These excipients may be mixed or granulated with weakly basic and poorly-aqueous soluble azole before or after the semi-solid composition is made, in order to formulate the composition into a suitable oral composition.

METHODS OF PREPARING SEMI-SOLID PHARMACEUTICAL COMPOSITIONS

Another aspect of the invention provides methods for preparing the semi-solid pharmaceutical compositions of the present invention. In most preferred embodiments, the invention provides methods for preparing a semi-solid composition of posaconazole, comprising: dissolving posaconazole in a monohydric organic alcohol and adding at least one nonionic surfactant while applying vigorous agitation at an elevated temperature. Such elevated temperatures may be from about 35 °C to about 70 °C. Suitable monohydric organic alcohols include isopropanol, t-butanol, phenol, cresol, and benzyl alcohol. In one

preferred embodiment, the monohydric organic alcohol is benzyl alcohol. In certain embodiments, at least one nonionic surfactant is a polyoxyethylene fatty alcohol ether, a polyoxyethylene sorbitan fatty acid ester, a polyoxyethylene fatty acid ester, a sorbitan ester, glycerol monostearate, a polyethylene glycol, a polypropylene glycol, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, an aryl alkyl polyether alcohol, a polyoxyethylene-polyoxypropylene copolymer, a poloxamine, polyvinyl alcohol, polyvinylpyrrolidone, or a macrogol. In certain preferred embodiments, at least one nonionic surfactant is a polyethylene glycol 660 hydroxystearate, a polyethoxylated castor oil, or a block copolymer of ethylene oxide and propylene oxide. In one preferred embodiment, at least one nonionic surfactant is a block copolymer of ethylene oxide and propylene oxide, specifically $HO(C_2H_4O)a(C_3H_6O)b(C_2H_4O)aH$ wherein a = 80 and b= 27. In a preferred embodiment, at least one nonionic surfactant is Pluronic® F68, also known as Poloxamer 188 (a block copolymer of ethylene oxide and propylene oxide, represented by the formula $HO(C_2H_4O)a(C_3H_6O)b(C_2H_4O)aH$ wherein a = 80 and b= 27), Cremophor EL® (polyethoxylated castor oil), or Solutol® HS15 (polyethylene glycol 660 hydroxystearate).

At an ambient temperature (i.e., 15-25 °C), the composition is a semi-solid matrix. In one embodiment, the resulting mixture is encapsulated in eiterh soft-gel capsules or in hard shell gelatin capsules.

Two exemplary semi-solid compositions of posaconazole referred to therein as "Exemplary Composition A" and "Exemplary Composition B," are presented in Table 1.

In one preferred embodiment, the ranges (% w/w) of components for the semi-solid compositions provided herein are 5-30 % posaconazole, 5-45 % benzyl alcohol, 20-60% polyethylene glycol 660 hydroxystearate (e.g., Solutol® HS 15), 1-20 % a block copolymer of ethylene oxide and propylene oxide, represented by the formula $HO(C_2H_4O)a(C_3H_6O)b(C_2H_4O)aH$ wherein a = 80 and b= 27) (e.g., Pluronic® F68, also known as Poloxamer 188). In an alternative preferred embodiment, the ranges (% w/w) of components for the semi-solid compositions provided herein are 5-30 % posaconazole, 5-45 % benzyl alcohol, 20-60% polyethoxylated castor oil (e.g., Cremophor EL®), 1-20 % Poloxamer 188 (e.g., Pluronic® F68).

Table 1: Semi-solid compositions of posaconazole.

Components	Exemplary Composition A (%w/w)	Exemplary Composition B (%w/w)
Posaconazole	10.3	10.3
Benzyl Alcohol	25.3	25.9
polyethylene glycol 660 hydroxystearate (e.g., Solutol® HS 15)	57.7	-----
polyethoxylated castor oil (e.g., Cremophor EL®)	-----	56.9
a block copolymer of ethylene oxide and propylene oxide, represented by the formula $HO(C_2H_4O)a(C_3H_6O)b(C_2H_4O)aH$ wherein a = 80 and b= 27 (e.g., Pluronic® F68, also known as Poloxamer 188)	6.7	6.9

In certain alternative embodiments, the invention provides methods for preparing a semi-solid composition, comprising: a weakly basic and poorly-aqueous soluble azole which is difenamizole, epirizole, fluconazole, itraconazole, ketoconazole, letrozole, ravuconazole, saperconazole, terconazole, or voriconazole, a monohydric organic alcohol and at least one nonionic surfactant which comprises: dissolving the weakly basic and poorly-aqueous soluble azole in the monohydric organic alcohol followed by addition of a surfactant while applying vigorous agitation at an elevated temperature. Such elevated temperatures may be from about 35 °C to about 70 °C. At an ambient temperature (i.e., 15-20 °C), the composition is a semi-solid matrix. In one embodiment, the resulting mixture is encapsulated in either soft-gel capsules or in hard shell gelatin capsules.

METHODS OF TREATMENT

Another aspect of the invention provides methods for the treatment and/or prevention of a fungal infection in a patient comprising administering to the patient a composition according to the invention. In some embodiments, preferably the oral pharmaceutical compositions comprise posaconazole. In some embodiments it is preferred to treat patients suffering from an otomycosis or chromomycosis condition. In some embodiments it is preferred to treat fungal infections due to *Asperillus sp.* or *Candida sp.* (including *Candida albicans*), or those caused by zygomycetes, for example Mucor, Rhizopus or Rhizomucor, or those caused by dermatophytes, for example, but not limited to *Tinea sp.*, (e.g. but not limited to, *Tinea corporis*, *Tinea cruris*, *Tinea pedis*, *Tinea barbae*,

Tinea capitis, *Tinea nigra*, *Tinea favosa*,,*or Tinea Imbricata*), or *Trichophyton sp.*, (e.g., but not limited to, *Trichophyton rubrum*, *Trichophyton interdigitale*, *Trichophyton tonsurans*, *Trichophyton soudanense*, or *Trichophyton violaceum*), or *Epidermophyton sp.* (e.g., but not limited to, *Epidermophyton floccosum*), or *Microsporum sp.* (e.g., but not limited to *Microsporum gypseum*) or any other agent associated with onychomycosis. Notably, NOXAFIL™ (posaconazole) is currently indicated for prophylaxis of invasive *Aspergillus* and *Candida* infections in patients, 13 years of age and older, who are at high risk of developing these infections due to being severely immunocomprised, such as hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host disease (GVHD) or those with hematologic malignancies with prolonged neutropenia from chemotherapy. NOXAFIL™ (posaconazole) is also indicated for the treatment of oropharmygeal candidiasis, including oropharyngeal candidiasis refractory to itraconazole and/or fluconazole.

In certain embodiments, the pharmaceutical compositions described herein may be administered to a patient in need thereof every 8 hours, every 12 hours, or every 24 hours. In certain such embodiments a dose is administered to a patient in need thereof every 12 hours, or every 24 hours. In certain such embodiments, a dose comprises at least one oral dosage form. In certain such embodiments, a dose may comprise at least one additional oral dosage form administered simultaneously with the first dosage form, or within about 5 minutes, or even ten minutes of the first oral dosage form.

The pharmaceutical compositions of the present invention are administered to a patient according to a dosing regimen. It should be understood that the specific dosing regimen for any particular patient will depend on a variety of factors, including species, age, body weight, body surface area, height, general health, sex, diet, time of administration, rate of excretion, drug combination, specific disease being treated, the severity of the condition, the renal and hepatic function of the patient, the particular active ingredient employed, and the judgment of the treating physician.

Other features and embodiments of the invention will become apparent by the following examples which are given for illustration of the invention rather than limiting its intended scope.

EXAMPLES

BIOAVAILABILITY COMPARISON OF POSACONAZOLE COMPOSITIONS

Adult male monkeys (6 monkeys/group) were dosed after an overnight fast with one of two different oral compositions as illustrated in Table 2. Food was returned at 4 hrs post-dose and body weight was recorded on the day of dosing. Blood was collected from each monkey pre-dose, as well as 0.25, 0.5, 1, 2, 4, 8, 24, 48, 72, 96, and 120 hr post-dose for determining the concentration of posaconazole in the plasma and to calculate the pharmacokinetic (PK) parameters for each composition.

The two different posaconazole compositions examined were an oral suspension (described in U.S. Publication No. 2003/0055067) as well as a capsule dosage form of the semi-solid composition referred to herein as Exemplary Composition B.

Table 2: Dosing of Posaconazole Compositions in Monkeys

Group No.	Composition	Dosing Composition Concentration	Actual Mean Dose Administered (mg)	Actual Mean Dose Administered (mg/kg) (*CV)
1	Oral Suspension	40 mg/mL	60	13.2 (4)
2	Capsule (Exemplary Composition B)	60 mg/capsule	60	15.6 (11)
*CV = the coefficient of variation defined as the ratio of the standard deviation to the mean				

The resulting mean plasma concentration for each composition over time is displayed graphically in Figure 1. In addition, the mean Cmax and AUC for each composition is shown in Figures 2 and 3, respectively. Likewise, the mean (CV, %) AUC (tf), AUC/dose, and CL/F for each posaconazole composition examined is summarized in Table 3 below.

Table 3: Mean (CV, %) pharmacokinetic parameters for posaconazole compositions.

Mean (CV,%) Pharmacokinetic Parameters		
Posaconazole		
	Oral Administration	
Parameter	Oral Suspension	Capsule Exemplary Composition B
AUC(tf)[a]	4950 (30)	11400 (47)
AUC/Dose[b]	373 (29)	725 (46)
CL/F[c]	11.8 (29)	6.14 (46)
CV = the coefficient of variation defined as the ratio of the standard deviation to the mean a: AUC(tf) = ng-hr/mL b: Normalized to 1 mg dose (mg/kg); expressed as (ng-hr/mL)/(mg/kg) c: CL/F = L/hr		

In addition, the individual and mean (CV, %) plasma concentrations and pharmacokinetic parameters for each posaconazole composition examined is detailed in Tables 4 and 5 below.

Table 4: Individual and mean (CV, %) plasma concentration and pharmacokinetic parameters for posaconazole following a single oral administration of 60 mg posaconazole to male cynomolgus monkeys in oral suspension.

	ng Posaconazole/mL						
	Cynomolgus Monkey No.						
Time Point (hr)	1001	1002	1003	1004	1005	1006	Mean[3] (n = 6) CV (%)
Pre-dose	0	0	0	0	0	0	0 (NC)
0.25	0	0	0	0	0	0	0 (NC)
0.5	0	0	0	0	0	0	0 (NC)
0.75	0	0	0	0	0	0	0 (NC)
1	10.9	0	0	0	0	20.2	5.18 (165)
2	91.4	50.6	70.8	37.7	0	15.6	44.4 (77)
4	300	321	190	200	332	221	261 (25)
8	207	209	128	148	296	181	195 (30)
24	164	63.3	47.8	77.9	119	82.2	92.4 (46)
48	41.4	12.5	18.7	24.6	26.1	26.9	25.0 (39)
72	0	0	0	0	0	0	0 (NC)
96	0	0	0	0	0	0	0 (NC)
120	0	0	0	0	0	0	0 (NC)

Cmax (ng/mL)	300	321	190	200	332	221	261 (25)
Tmax (hr)	4	4	4	4	4	4	4.00 (4 – 4)
AUC(tf)							
(ng-hr/mL)	6890	4550	3140	3990	6650	4480	4950 (30)
tf(hr)	48	48	48	48	48	48	48.0 (0)
t1/2(hr)	16.7	9.88	14.6	15.4	11.4	14.6	13.7 (19)
CL/F (L/hr)	7.61	12.7	17.0	13.2	8.48	11.9	11.8 (29)
Dose (mg/kg)	12.9	13.0	13.2	12.8	14.2	13.2	13.2 (4)
AUC/Dose[b]	534	350	238	312	468	339	373 (29)

CV = the coefficient of variation defined as the ratio of the standard deviation to the mean
NC = Not calculated
a: Tmax expressed as median (min – max)
b: Normalized to 1 mg dose (mg/kg); expressed as (ng-hr/mL)/(mg/kg)

Table 5: Individual and mean (CV, %) plasma concentration and pharmacokinetic parameters for posaconazole following a single oral administration of 60 mg posaconazole to male cynomolgus monkeys in Capsule (semi-solid posaconazole composition referred to herein as Exemplary Composition B).

	ng Posaconazole/mL						
	Cynomolgus Monkey No.						
Time Point (hr)	4001	4002	4003	4004	4005	4006	Mean[3] (n = 6) CV (%)
Pre-dose	0	0	0	0	0	0	0 (NC)
0.25	0	0	0	18.2	0	0	3.03 (245)
0.5	13.6	0	0	0	0	0	2.27 (245)
0.75	41.9	0	0	15.1	31.9	0	14.8 (124)
1	65.9	0	30.5	29.5	135	0	43.5 (117)
2	238	106	151	148	511	67.8	204 (79)
4	287	335	435	634	1060	393	524 (55)
8	250	286	337	675	724	359	439 (47)
24	72.7	175	135	319	275	214	198 (46)
48	11.2	61.2	28.1	88.2	58.3	34.1	46.9 (59)
72	0	14.8	0	22.0	16.7	0	8.92 (113)
96	0	0	0	0	0	0	0 (NC)
120	0	0	0	0	0	0	0 (NC)
Cmax (ng/mL)	287	335	435	675	1060	393	531 (55)
Tmax (hr)	4	4	4	8	4	4	4.00 (4 – 8)
AUC(tf) (ng-hr/mL)	5360	9170	7960	17700	18400	9560	11400 (47)
tf(hr)	48	72	48	72	72	48	60.0 (22)
t1/2(hr)	8.93	13.5	11.1	12.4	11.9	11.5	11.6 (13)
CL/F (L/hr)	10.9	6.34	7.14	3.32	3.21	5.93	6.14 (46)
Dose (mg/kg)	15.4	16.7	13.6	14.3	18.2	15.4	15.6 (11)
AUC/Dose[a]	348	549	585	1240	1010	621	725 (46)

CV = the coefficient of variation defined as the ratio of the standard deviation to the mean
NC = Not calculated
a: Tmax expressed as median (min – max)
b: Normalized to 1 mg dose (mg/kg); expressed as (ng-hr/mL)/(mg/kg)

Notably, the semi-solid composition increased posaconazole exposure when compared to the oral suspension indicating an increase in enhanced bioavailability. In fact,

the difference in mean AUC(tf) and mean Cmax was about 2 times for the semi-solid composition compared to the oral suspension.

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the appended claims.

Claims:

1. An oral pharmaceutical composition comprising:

a) a weakly basic and poorly-aqueous soluble azole which is difenamizole, epirizole, fluconazole, itraconazole, ketoconazole, letrozole, ravuconazole, saperconazole, terconazole, or voriconazole;

b) a monohydric organic alcohol; and

c) at least one nonionic surfactant;

wherein the oral pharmaceutical composition is a semi-solid composition.

2. An oral pharmaceutical composition comprising:

a) posaconazole;

b) a monohydric organic alcohol; and

c) at least one nonionic surfactant;

wherein the oral pharmaceutical composition is a semi-solid composition.

3. The oral pharmaceutical composition of claim 2, wherein the monohydric organic alcohol is isopropanol, t-butanol, phenol, cresol, or benzyl alcohol.

4. The oral pharmaceutical composition of claim 3, wherein the monohydric organic alcohol is benzyl alcohol.

5. The oral pharmaceutical composition of claim 2, wherein at least one nonionic surfactant is a polyoxyethylene fatty alcohol ether, a polyoxyethylene sorbitan fatty acid ester, a polyoxyethylene fatty acid ester, a sorbitan ester, glycerol monostearate, a polyethylene glycol, a polypropylene glycol, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, an aryl alkyl polyether alcohol, a polyoxyethylene-polyoxypropylene copolymer, a poloxamine, polyvinyl alcohol, polyvinylpyrrolidone, or a macrogol.

6. The oral pharmaceutical composition of claim 2, wherein at least one nonionic surfactant is a polyethylene glycol 660 hydroxystearate.

7. The oral pharmaceutical composition of claim 2, wherein at least one nonionic surfactant is a polyethoxylated castor oil.

8. The oral pharmaceutical composition of claim 2, wherein at least one nonionic surfactant is a block copolymer of ethylene oxide and propylene oxide.

9. The oral pharmaceutical composition of claim 2, wherein at least one nonionic surfactant is a block copolymer of ethylene oxide and propylene oxide, represented by the formula $HO(C_2H_4O)a(C_3H_6O)b(C_2H_4O)aH$ wherein a = 80 and b= 27.

10. The pharmaceutical composition of claim 2, further comprising one or more pharmaceutically acceptable excipients.

11. A method for treating and/or preventing a fungal infection, comprising the step of administering to a patient in need thereof an oral pharmaceutical composition comprising:

a) posaconazole;

b) a monohydric organic alcohol; and

c) at least one nonionic surfactant;

wherein the oral pharmaceutical composition is a semi-solid composition.

12. The method of claim 11, wherein the fungal infection is an *Aspergillus* or a *Candida* infection.

13. The method of claim 11, wherein the fungal infection is caused by a zygomycetes.

14. The method of claim 11, wherein the fungal infection is caused by a dermatophyte.

15. The method of claim 11, wherein the oral pharmaceutical composition is administered twice-a-day.

16. The method of claim 11, wherein the oral pharmaceutical composition is administered once-a-day.

17. A method for preparing a pharmaceutical composition of posaconazole in a semi-solid composition comprising the steps of:

(a) dissolving posaconazole in a monohydric organic alcohol; and

(b) adding at least one nonionic surfactant while applying vigorous agitation at a temperature from about 35 °C to about 70 °C.

Figure 1

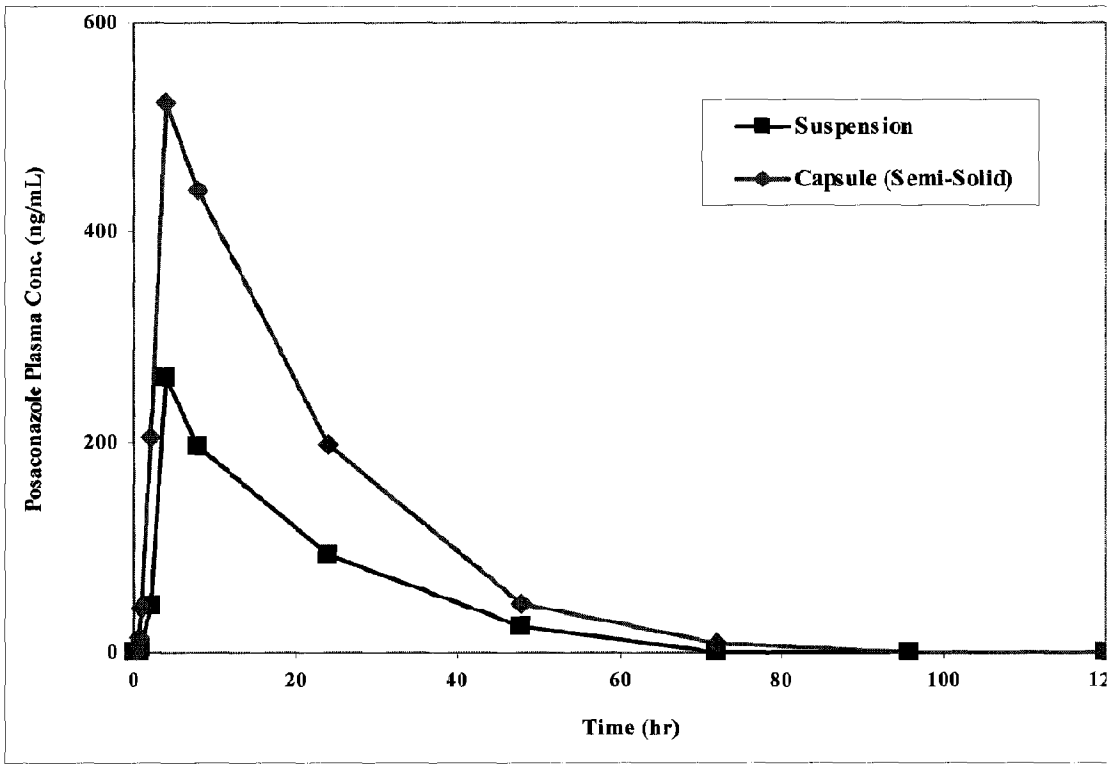

600
400
200
0
Posaconazole Plasma Conc. (ng/mL)
0
20
40
60
80
100
12
Time (hr)
Suspension
Capsule (Semi-Solid)

Figure 2

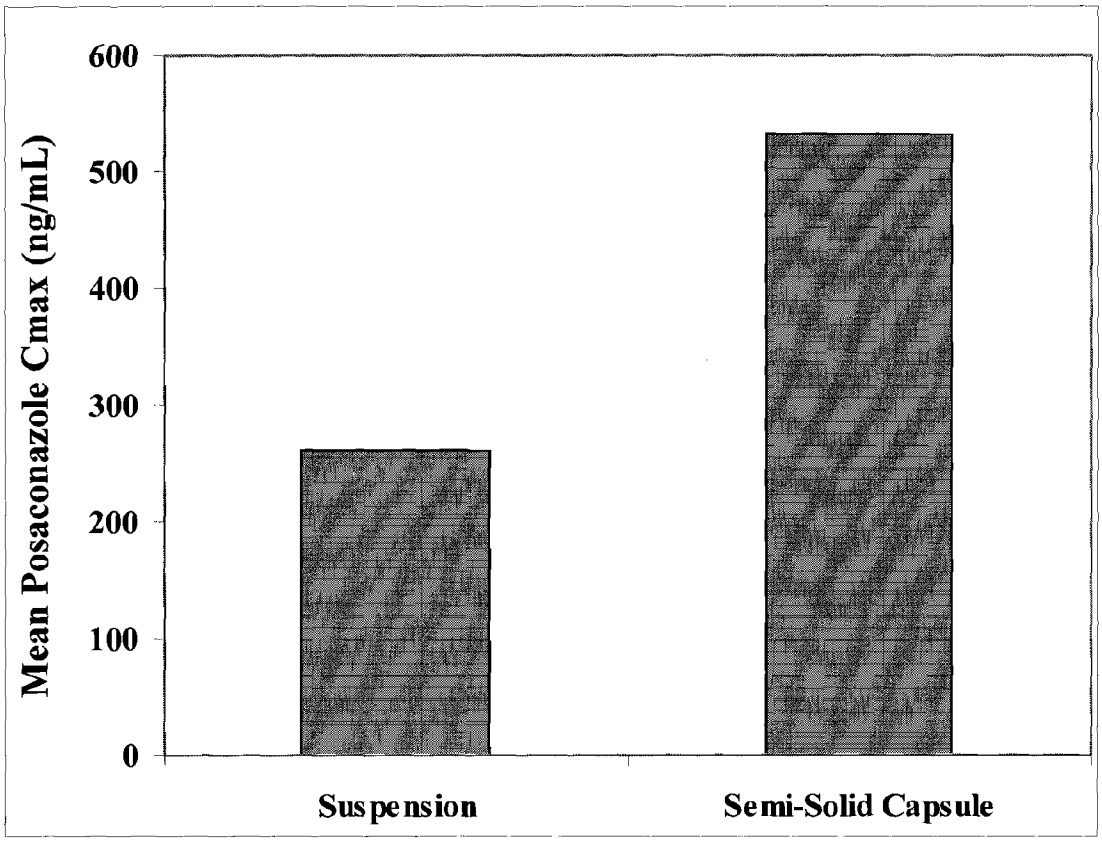
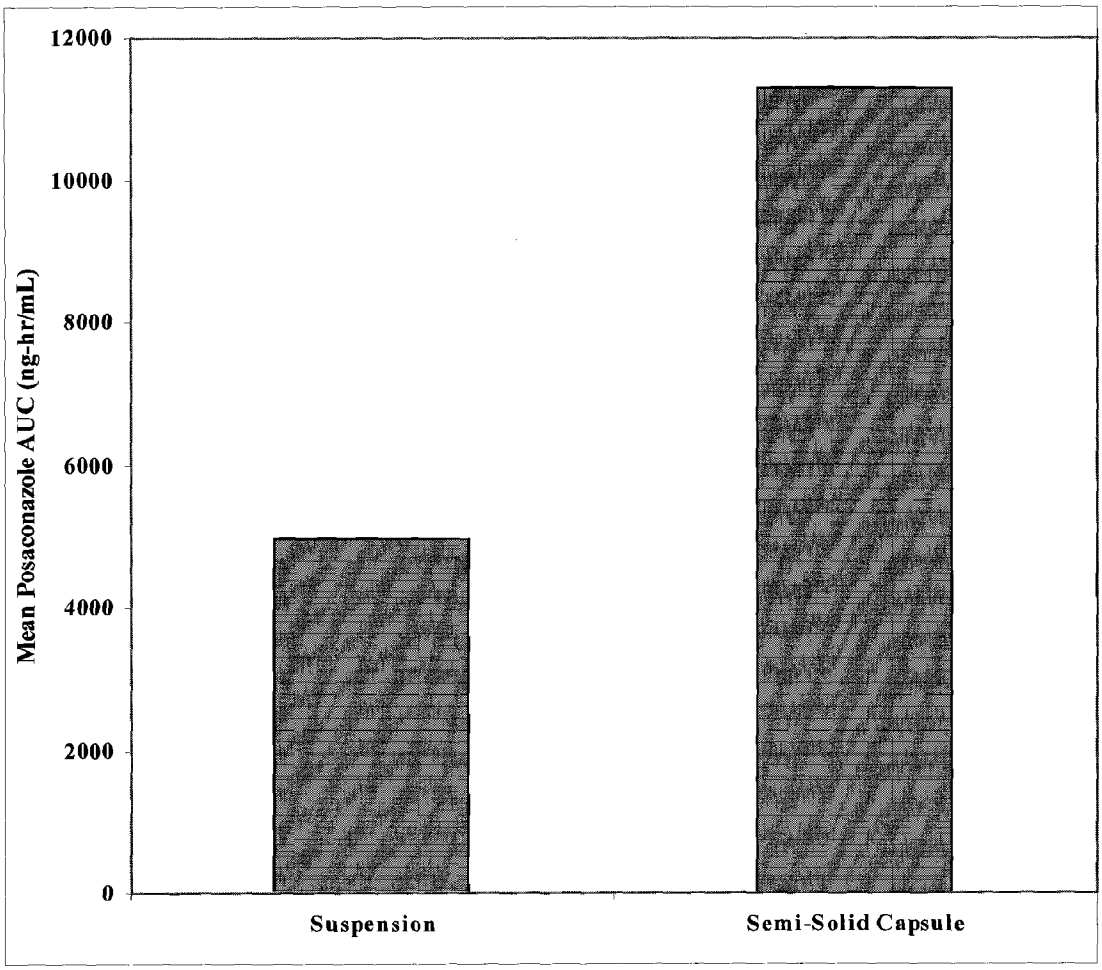

Mean Posaconazole Cmax (ng/mL)
600
500
400
300
200
100
0
Suspension
Semi-Solid Capsule

Figure 3


12000
10000
8000
6000
4000
2000
0
Mean Posaconazole AUC (ng-hr/mL)
Suspension
Semi-Solid Capsule

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/040644

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/48 A61K31/496

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO 03/017986 A (WON JIN BIOPHARMA CO LTD [KR]; LEE BEOM JIN [KR]; LEE DONG WON [KR]; C) 6 March 2003 (2003-03-06) page 17, line 21 - page 18, line 5 examples 17,18 claims 1-11	1 2-17
X	WO 2005/023262 A (HANMI PHARM IND CO LTD [KR]) 17 March 2005 (2005-03-17) example 1	1
Y	US 5 834 472 A (SANGEKAR SURENDRA A [US] ET AL) 10 November 1998 (1998-11-10) cited in the application column 2, line 23 - line 28 column 4, line 28 - line 30 column 4, line 53 - line 54 claims 1,2	2-17
	-/--	

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 June 2009	01/07/2009

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/040644

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2009/040644

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