(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 December 2022 (22.12.2022)

WIPO | PCT

(10) International Publication Number
WO 2022/264004 A1

(51) International Patent Classification:
*A61K 31/497* (2006.01) *A61K 9/10* (2006.01)
*A61K 9/26* (2006.01)

(21) International Application Number:
PCT/IB2022/055460

(22) International Filing Date:
13 June 2022 (13.06.2022)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
202121026278 13 June 2021 (13.06.2021) IN

(71) Applicant: **GLENMARK PHARMACEUTICAL LIMITED** [IN/IN]; B/2, Mahalaxmi Chambers, 22 Bhulabhai Desai Road, Mumbai 400 026 (IN).

(72) Inventors: **KULKARNI, Sushrut**; 1101, Balaji Residency, Sector -15, Plot no. 52/53, Kharghar, Maharashtra, Navi Mumbai 410 210 (IN). **DESHMUKH, Nitin**; Flat no.11, Gajanan Smruti, Kulkarni Colony, Sadhu Wasvani Road, Sharanpur Road, Maharashtra, Nashik 422002 (IN). **SATPUTE, Ravindra**; Flat no. 104, Dwarkesh Height, Near KBH Dental College, Kevadiban, Panchavati, Maharashtra, Nashik 422003 (IN). **BAGUL, Kunal**; House no. 415, MHB colony, Satpur Colony, Maharashtra, Nashik 422012 (IN).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

**Declarations under Rule 4.17:**
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *of inventorship (Rule 4.17(iv))*

**Published:**
— *with international search report (Art. 21(3))*
— *in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE*

(54) **Title:** PHARMACEUTICAL COMPOSITION COMPRISING ITRACONAZOLE

(57) **Abstract:** The invention relates to a stable solid oral pharmaceutical composition comprising itraconazole which provides reduction in pill burden in the treatment of fungal infections, including superficial infections, such as onychomycosis, as well as systemic fungal infections, for example, pulmonary or extrapulmonary blastomycosis, histoplasmosis, and aspergillosis. The application also relates to a process for preparing the pharmaceutical composition comprising itraconazole.

WO 2022/264004 A1

# PHARMACEUTICAL COMPOSITION COMPRISING ITRACONAZOLE

## PRIORITY DOCUMENT

This patent application claims priority to Indian Provisional Patent Application number 202121026278 (filed on June 13, 2021), the contents of which are incorporated by reference herein.

## FIELD OF THE INVENTION

The invention relates to a stable solid oral pharmaceutical composition comprising itraconazole which provides reduction in pill burden in the treatment of fungal infections, including superficial infections, such as onychomycosis, as well as systemic fungal infections, for example, pulmonary or extrapulmonary blastomycosis, histoplasmosis, and aspergillosis. The application also relates to a process for preparing the pharmaceutical composition comprising itraconazole.

## BACKGROUND OF THE INVENTION

Itraconazole is a broad spectrum triazole antifungal compound available for the treatment of fungal infections, including superficial infections, such as onychomycosis, as well as systemic fungal infections, for example, Blastomycosis, pulmonary and extrapulmonary, Histoplasmosis, including chronic cavitary pulmonary disease and disseminated, non-meningeal histoplasmosis, and Aspergillosis, pulmonary and extrapulmonary, in patients who are intolerant of or who are refractory to amphotericin B therapy.

Itraconazole is a highly variable drug with low bioavailability of 55%. The maximum daily dose of conventional itraconazole capsules in life threatening situations is 600 mg (six capsules of 100 mg strength in three divided doses of 200 mg).

The bioavailability of conventional itraconazole capsule dosage form varies greatly both between subjects (inter- subject) and from dose to dose in a single subject (intra-subject). In order to achieve maximum absorption, conventional itraconazole capsules needs to be taken with food and in the presence of an acidic gastric environment because bioavailability of the itraconazole is enhanced when ingested in the fasted state.

This inter and intra subject variability is matter of concern as itraconazole is known to have harmful side effects, especially upon overdosing. Itraconazole is well known for carrying a black-box warning for new or worsening congestive heart failure. The risk of cardiotoxicity increases with a dose greater than 400 mg/day. The other side effects being nausea, abdominal pain, dyspepsia, gastrointestinal discomfort, menstrual disorders, dizziness, constipation, vomiting, diarrhea, headache, increased hepatic enzyme levels, pruritus, rash, angioedema, and urticaria. On the other side, when insufficient itraconazole is administered, efficacy of the itraconazole is minimal and can contribute to drug resistance.

International Publication No. WO 2013/192566 discloses pharmaceutical compositions, such as solid oral dosage forms, comprising itraconazole, methods of making the compositions, and methods of using the same for treating disorders including, but not limited to, fungal infections. This patent application is silent on challenges of having high content of itraconazole and stability of the composition.

Some solid oral dosage forms containing magnesium stearate as lubricant are known for its hydrophobicity and possible negative effect on dissolution of active substances. The article from *Demuth et al* (Mol. Pharmaceutics, 2017, 14, 11, page 3927–3934) discloses deteriorated dissolution of itraconazole in presence of magnesium stearate.

Thus, there is need for a stable solid oral pharmaceutical composition comprising itraconazole which provides a therapeutically effective dose, has better bioavailability resulting in low dose, has high drug content, satisfactory dissolution and provides reduction in pill burden which ultimatly result in safe and better patient complaince in acute or chronic or life threatening conditions.

## SUMMARY OF THE INVENTION

The invention in one embodiment relates to a stable solid oral pharmaceutical composition comprising itraconazole in a solid dispersion with a matrix polymer and dissolution enhancing agent(s).

Another embodiment relates to a stable solid oral pharmaceutical composition comprising (a) itraconazole, (b) matrix polymer and (c) dissolution enhancing agent(s).

Another embodiment relates to a stable solid oral pharmaceutical composition comprising:

(a) itraconazole in a solid dispersion with a matrix polymer selected from hypromellose phthalate, copovidone, hypromellose acetate succinate, hypromellose, polymethacrylates, hydroxypropyl cellulose and cellulose acetate phthalate;

(b) dissolution enhancing agent(s) selected from combination of (i) dibasic calcium phosphate and (ii) silicified microcrystalline cellulose or combination of (i) dibasic calcium phosphate and (ii) microcrystalline cellulose.

Another embodiment relates to a stable solid oral pharmaceutical composition comprising itraconazole in a solid dispersion with a matrix polymer selected from hypromellose phthalate, copovidone, hypromellose acetate succinate, hypromellose, polymethacrylates, hydroxypropyl cellulose and cellulose acetate phthalate and dissolution enhancing agent(s) selected from combination of (i) dibasic calcium phosphate and (ii) silicified microcrystalline cellulose or combination of (i) dibasic calcium phosphate and (ii) microcrystalline cellulose.

Another embodiment relates to a stable solid oral pharmaceutical composition comprising (a) itraconazole in an amount of 50 mg to 300 mg, (b) matrix polymer selected from hypromellose phthalate, copovidone, hypromellose acetate succinate, hypromellose, polymethacrylates, hydroxypropyl cellulose and cellulose acetate phthalate and (c) dissolution enhancing agent(s) selected from combination of (i) dibasic calcium phosphate and (ii) silicified microcrystalline cellulose or combination of (i) dibasic calcium phosphate and (ii) microcrystalline cellulose.

Another embodiment relates to a stable solid oral pharmaceutical composition comprising (a) itraconazole in an amount of 50 mg to 400 mg, (b) matrix polymer selected from hypromellose phthalate, copovidone, hypromellose acetate succinate, hypromellose, polymethacrylates, hydroxypropyl cellulose and cellulose acetate phthalate and (c) dissolution enhancing agent(s) selected from combination of (i) dibasic calcium phosphate and (ii) silicified microcrystalline cellulose or combination of (i) dibasic calcium phosphate and (ii) microcrystalline cellulose wherein

a. itraconazole is present in an amount from 20% w/w to 60% w/w, preferably from 30% w/w to 50% w/w and more preferably 40% w/w by total weight of the solid dispersion;
b. weight ratio of itraconazole to matrix polymer is in the range of about 1: 1 to about 1:3, or about 1: 1.5, based on the weight of itraconazole;
c. dissolution enhancing agent(s) is preferably present in an amount from 10% w/w to 80% w/w, more preferably in an amount from 20% w/w to 70% w/w, most preferably in an amount from 30% w/w to 60% w/w by total weight of the composition;

Another embodiment relates to a stable solid oral pharmaceutical composition comprising:

(a) itraconazole in a solid dispersion with a matrix polymer selected from hypromellose phthalate, copovidone, hypromellose acetate succinate, hypromellose, polymethacrylates, hydroxypropyl cellulose and cellulose acetate phthalate;
(b) dissolution enhancing agent(s) selected from combination of (i) dibasic calcium phosphate and (ii) silicified microcrystalline cellulose or combination of (i) dibasic calcium phosphate and (ii) microcrystalline cellulose wherein
i. itraconazole is present in an amount from 50 mg or 65 mg or 100 mg or 130 mg or 150 mg or 195 mg or 200 mg or 250 mg or 260 mg or 300 mg or 400 mg
ii. itraconazole is present in an amount from 20% w/w to 60% w/w, preferably from 30% w/w to 50% w/w and more preferably 40% w/w by total weight of the solid dispersion;
iii. weight ratio of itraconazole to matrix polymer is in the range of about 1: 1 to about 1:3, or about 1: 1.5, based on the weight of itraconazole;
iv. dissolution enhancing agent(s) is preferably present in an amount from 10% w/w to 80% w/w, more preferably in an amount from 20% w/w to 70% w/w, most preferably in an amount from 30% w/w to 60% w/w by total weight of the composition;

Another embodiment relates to a stable solid oral pharmaceutical composition comprising (a) itraconazole in an amount of 50 mg, (b) matrix polymer selected from hypromellose phthalate, copovidone, hypromellose acetate succinate, hypromellose, polymethacrylates, hydroxypropyl cellulose and cellulose acetate phthalate and (c)

dissolution enhancing agent(s) selected from combination of (i) dibasic calcium phosphate and (ii) silicified microcrystalline cellulose or combination of (i) dibasic calcium phosphate and (ii) microcrystalline cellulose.

Another embodiment relates to a stable solid oral pharmaceutical composition comprising (a) itraconazole in an amount of 65 mg, (b) matrix polymer selected from hypromellose phthalate, copovidone, hypromellose acetate succinate, hypromellose, polymethacrylates, hydroxypropyl cellulose and cellulose acetate phthalate and (c) dissolution enhancing agent(s) selected from combination of (i) dibasic calcium phosphate and (ii) silicified microcrystalline cellulose or combination of (i) dibasic calcium phosphate and (ii) microcrystalline cellulose.

Another embodiment relates to a stable solid oral pharmaceutical composition comprising (a) itraconazole in an amount of 100 mg, (b) matrix polymer selected from hypromellose phthalate, copovidone, hypromellose acetate succinate, hypromellose, polymethacrylates, hydroxypropyl cellulose and cellulose acetate phthalate and (c) dissolution enhancing agent(s) selected from combination of (i) dibasic calcium phosphate and (ii) silicified microcrystalline cellulose or combination of (i) dibasic calcium phosphate and (ii) microcrystalline cellulose.

Another embodiment relates to a stable solid oral pharmaceutical composition comprising (a) itraconazole in an amount of 130 mg, (b) matrix polymer selected from hypromellose phthalate, copovidone, hypromellose acetate succinate, hypromellose, polymethacrylates, hydroxypropyl cellulose and cellulose acetate phthalate and (c) dissolution enhancing agent(s) selected from combination of (i) dibasic calcium phosphate and (ii) silicified microcrystalline cellulose or combination of (i) dibasic calcium phosphate and (ii) microcrystalline cellulose.

Another embodiment relates to a stable solid oral pharmaceutical composition comprising (a) itraconazole in an amount of 130 mg, (b) matrix polymer, wherein itraconazole is dispersed in matrix polymer phase; wherein itraconazole is present in an amount from 20% w/w to 60% w/w, preferably from 30% w/w to 50% w/w and more preferably 40% w/w by total weight of the solid dispersion; wherein weight ratio of

itraconazole to matrix polymer is in the range of about 1: 1 to about 1:3, or about 1: 1.5, based on the weight of itraconazole.

Another embodiment relates to a stable solid oral pharmaceutical composition comprising (a) itraconazole in an amount of 130 mg, (b) matrix polymer selected from hypromellose phthalate, copovidone, hypromellose acetate succinate, hypromellose, polymethacrylates, hydroxypropyl cellulose and cellulose acetate phthalate wherein itraconazole is dispersed in matrix polymer phase; wherein itraconazole is present in an amount from 20% w/w to 60% w/w, preferably from 30% w/w to 50% w/w and more preferably 40% w/w by total weight of the solid dispersion; wherein weight ratio of itraconazole to matrix polymer is in the range of about 1: 1 to about 1:3, or about 1: 1.5, based on the weight of itraconazole.

Another embodiment relates to a stable solid oral pharmaceutical composition comprising (a) itraconazole in an amount of 200 mg, (b) matrix polymer selected from hypromellose phthalate, copovidone, hypromellose acetate succinate, hypromellose, polymethacrylates, hydroxypropyl cellulose and cellulose acetate phthalate and (c) dissolution enhancing agent(s) selected from combination of (i) dibasic calcium phosphate and (ii) silicified microcrystalline cellulose or combination of (i) dibasic calcium phosphate and (ii) microcrystalline cellulose.

Another embodiment relates to a stable solid oral pharmaceutical composition comprising (a) itraconazole in an amount of 300 mg, (b) matrix polymer selected from hypromellose phthalate, copovidone, hypromellose acetate succinate, hypromellose, polymethacrylates, hydroxypropyl cellulose and cellulose acetate phthalate and (c) dissolution enhancing agent(s) selected from combination of (i) dibasic calcium phosphate and (ii) silicified microcrystalline cellulose or combination of (i) dibasic calcium phosphate and (ii) microcrystalline cellulose.

Another embodiment relates to a stable solid oral pharmaceutical composition comprising (a) itraconazole in an amount of 400 mg, (b) matrix polymer selected from hypromellose phthalate, copovidone, hypromellose acetate succinate, hypromellose, polymethacrylates, hydroxypropyl cellulose and cellulose acetate phthalate and (c) dissolution enhancing agent(s) selected from combination of (i) dibasic calcium phosphate

and (ii) silicified microcrystalline cellulose or combination of (i) dibasic calcium phosphate and (ii) microcrystalline cellulose.

Another embodiment relates to a stable solid oral pharmaceutical composition comprising (a) itraconazole is present in an amount from 130 mg or 150 mg or 195 mg or 200 mg or 250 mg or 260 mg or 300 mg or 400 mg, (b) matrix polymer selected from hypromellose phthalate, copovidone, hypromellose acetate succinate, hypromellose, polymethacrylates, hydroxypropyl cellulose and cellulose acetate phthalate wherein itraconazole is dispersed in matrix polymer phase; wherein itraconazole is present in an amount from 20% w/w to 60% w/w, preferably from 30% w/w to 50% w/w and more preferably 40% w/w by total weight of the solid dispersion; wherein weight ratio of itraconazole to matrix polymer is in the range of about 1: 1 to about 1:3, or about 1: 1.5, based on the weight of itraconazole.

In another embodiment, the weight ratio of itraconazole to matrix polymer is in the range of about 1: 0.5 to about 1:5 based on the weight of itraconazole.

Another embodiment relates to a stable solid oral pharmaceutical composition comprising itraconazole that minimises the number of capsules required for the therapeutically effective dose, ideally to fewer than 4 units, preferably two or three units.

Another embodiment relates to a stable solid oral pharmaceutical composition comprising itraconazole in a solid dispersion with a matrix polymer and dissolution enhancing agent(s) wherein the said composition is devoid of magnesium stearate.

Another embodiment relates to a stable solid oral pharmaceutical composition comprising itraconazole in a solid dispersion with a matrix polymer and dissolution enhancing agent(s) wherein the said composition is devoid of surfactant.

Another embodiment relates to a stable solid oral pharmaceutical composition comprising itraconazole in a solid dispersion with a matrix polymer and dissolution enhancing agent(s), wherein itraconazole is present in an amount of 50 mg or 65 mg or 100 mg or 130 mg or 150 mg or 195 mg or 200 mg or 250 mg or 260 mg or 300 mg or 400 mg of itraconazole.

Another embodiment relates to a stable solid oral pharmaceutical composition comprising itraconazole in a solid dispersion with a matrix polymer and dissolution enhancing agent(s), wherein itraconazole is present in an amount from 20% w/w to 60%

w/w, preferably from 30% w/w to 50% w/w and more preferably 40% w/w by total weight of the solid dispersion.

Another embodiment relates to a stable solid oral pharmaceutical composition comprising itraconazole in a solid dispersion with a matrix polymer and dissolution enhancing agent(s), wherein dissolution enhancing agent(s) is preferably present in an amount from 10% w/w to 80% w/w, more preferably in an amount from 20% w/w to 70% w/w, most preferably in an amount from 30% w/w to 60% w/w by total weight of the composition.

Another embodiment relates to a stable solid oral pharmaceutical composition comprising itraconazole in a solid dispersion with a matrix polymer and dissolution enhancing agent(s), wherein itraconazole is present in an amount of 20% to 60%, and preferably from 30% to 50% and more preferably 40% by weight of the solid dispersion.

Another embodiment relates to a stable solid oral pharmaceutical composition comprising itraconazole in a solid dispersion with a matrix polymer and dissolution enhancing agent(s), wherein weight ratio of itraconazole to matrix polymer is in the range of about 1: 1 to about 1:3, or about 1: 1.5, based on the weight of itraconazole.

In another embodiment, the matrix polymer is hypromellose phthalate.

Another embodiment relates to a stable solid oral pharmaceutical composition comprising

a) itraconazole in an amount of 130 mg in a solid dispersion with a matrix polymer wherein itraconazole is present in an amount from 20% w/w to 60% w/w by total weight of the solid dispersion; and
b) dissolution enhancing agent(s).

Another embodiment relates to a stable solid oral pharmaceutical composition, wherein itraconazole is present in an amount from 30 % w/w to 50% w/w by total weight of the solid dispersion.

Another embodiment relates to a stable solid oral pharmaceutical composition, wherein itraconazole is present in an amount of about 40% w/w by total weight of the solid dispersion.

Another embodiment relates to a stable solid oral pharmaceutical composition, wherein matrix polymer selected from hypromellose phthalate, copovidone, hypromellose

acetate succinate, hypromellose, polymethacrylates, hydroxypropyl cellulose and cellulose acetate phthalate.

Another embodiment relates to a stable solid oral pharmaceutical composition, wherein dissolution enhancing agent(s) is selected from combination of (i) dibasic calcium phosphate and (ii) silicified microcrystalline cellulose or combination of (i) dibasic calcium phosphate and (ii) microcrystalline cellulose.

Another embodiment relates to a stable solid oral pharmaceutical composition, wherein dissolution enhancing agent(s) is present in an amount from 10% w/w to 80% w/w by total weight of the composition.

Another embodiment relates to a stable solid oral pharmaceutical composition, wherein dissolution enhancing agent(s) is present in an amount from 20% w/w to 70% w/w by total weight of the composition.

Another embodiment relates to a stable solid oral pharmaceutical composition, wherein dissolution enhancing agent(s) is present in an amount from 30% w/w to 60% w/w by total weight of the composition.

In another embodiment, the dissolution enhancing agent(s), is combination of (i) dibasic calcium phosphate and (ii) silicified microcrystalline cellulose in the ratio of 1:1 to 1:4.

In another embodiment, the dissolution enhancing agent(s), is combination of (i) dibasic calcium phosphate and (ii) microcrystalline cellulose in the ratio of 1:1 to 1:4.

Another embodiment relates to a stable solid oral pharmaceutical composition comprising itraconazole in capsule dosage form.

Another embodiment relates to a method of producing a stable solid oral pharmaceutical composition of itraconazole comprising:

(i) a suitable amount itraconazole with a desired amount of at least one matrix polymer was dissolved in methylene chloride and ethanol with continuous stirring;

(ii) the solution from step (i) was spray-dried to form solid dispersion as a spray dried powder. The spray dried solid dispersion was further dried in suitable dryer.

(iii) the solid dispersion of itraconazole and matrix polymer was mixed properly with dissolution enhancing agent(s) and one or more pharmaceutically acceptable excipient like disintegrant, lubricant or glidant;

(iv) the blend from step (iii) was filled in suitable capsules.

Another embodiment relates to method of producing a stable solid oral pharmaceutical composition of itraconazole by blending process.

Another embodiment relates to method of producing a stable solid oral pharmaceutical composition of itraconazole by roll compaction process.

## DETAILED DESCRIPTION OF THE INVENTION

It is also to be understood that the terminology used herein is for describing particular embodiments only, and is not intended to be limiting. The term singular forms "a," "an" and "the" include plural references unless the context clearly dictates otherwise.

The term "stable solid oral pharmaceutical composition" means a solid oral pharmaceutical composition which exhibits substantial chemical stability (assay / total impurity) of itraconazole and NLT 70% (Q) of labelled amount of itraconazole is dissolved in 60 minutes under specified dissolution conditions over a period of 3 months or 6 months or 9 months or 12 months or 24 months at ambient conditions (e.g., about 30°C and a relative humidity (RH) of about 75%) or at accelerated conditions (e.g., at about 40°C and about 75% RH).

The dissolution conditions used are 0.5% SLS in Water / 75 RPM / 900ml /paddle and the limit is NLT 70% (Q) of labelled amount of itraconazole dissolved in 60 minutes.

The term “Itraconazole” as used herein includes the base form and pharmaceutically acceptable salts, solvates, hydrates, prodrugs, enantiomers, esters, polymorphs, complex, co-crystals thereof.

The term “active ingredient” (used interchangeably with “active” or “active agent” or “drug” or “medicament”) as used herein include itraconazole.

As used herein, the term “matrix polymer” means a material that exhibits low hygroscopicity and high softening temperature comprising a polymer or a blend of two or more polymers.

As used herein, by "low hygroscopicity" we mean having an equilibrium water content<10% at 50% relative humidity, as determined by Dynamic Vapour Sorption (DVS), disclosed in Bergren, M. S. Int. J. Pharm 103:103-114 (1994).

As used herein, by "high softening temperature" we mean that the material, in "as received" form (that is to say, without having been exposed to high humidity) exhibits a glass transition temperature (Tg) or melting point (Tm)>100°C., as determined by Differential Scanning Calorimetry (DSC). The person of ordinary skill in the art will appreciate that Tg is a measurement appropriate for polymers that are in an amorphous state or form and Tm is a measurement that is appropriate for polymers that are in a crystalline state or form.

Suitable matrix polymers for use in the invention include: hypromellose phthalate (hydroxypropylmethylcellulose phthalate, HPMCP), copovidone, hypromellose acetate succinate (hydroxypropylmethylcellulose acetate succinate, HPMCAS), , hypromellose (hydroxypropylmethylcellulose, HPMC), polymethacrylates (poly(methacrylic acid, methyl methacrylate 1:1; poly(methacrylic acid, ethyl acrylate) 1:1), hydroxypropyl cellulose (HPC), and cellulose acetate phthalate (CAP).

As used herein, the term “dissolution enhancing agent(s)” means combination of specific pharmaceutically acceptable excipients which aid in the increase of dissolution of solid oral pharmaceutical composition comprising itraconazole. It was found that use of these combination of specific excipents selected from combination of (i) dibasic calcium phosphate and (ii) silicified microcrystalline cellulose or combination of (i) dibasic calcium phosphate and (ii) microcrystalline cellulose significantly increased the dissolution of solid oral pharmaceutical composition comprising itraconazole. The components of “dissolution enhancing agent(s)” are dibasic calcium phosphate or dicalcium phosphate or dibasic calcium phosphate (anhydrous), microcrystalline cellulose, silicified microcrystalline cellulose (PROSOLV® SMCC 50), AVICEL® DG (Microcrystalline Cellulose + Dicalcium Phosphate, Anhydrous; 75:25). AVICEL® DG is a synergistic combination of 75 percent microcrystalline cellulose and 25 percent anhydrous dibasic calcium phosphate, produced using a spray-dried, co-processing technology. The “dissolution enhancing agent(s)” according to present invention is combination of two different excipients, where dibasic calcium phosphate is common and the other excipient can be microcrystalline cellulose or other suitable excipient.

The various pharmaceutically acceptable excipients selected from the group of diluents, disintegrants, binders, lubricants, glidants. Additional excipients may be included in the formulation.

Suitable diluents include, for example, lactose, sugar, starches, modified starches, mannitol, sorbitol, calcium sulphate, xylitol, lactitol and the like.

Suitable binders include, for example, gum acacia, gum tragacanth, guar gum, pectin, wax binders, methylcellulose, carboxymethylcellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, gelatine, polyvinylpyrollidone (PVP), sodium alginate and the like.

Suitable disintegrants include, for example, crosscarmellose sodium, crospovidone, sodium starch glycollate and the like.

Suitable lubricants include, for example, sodium stearyl fumarate, polyethylene glycol, talc and the like.

Suitable glidant include, for example, colloidal silicon dioxide and the like.

Additional conventional excipients, which may be added, include preservatives, stabilisers, anti-oxidants, antiadherents or glidants.

Other suitable diluents, binders, disintegrants, lubricants and additional excipients which may be used are described in the Handbook of Pharmaceutical Excipients, 9th Edition; The Theory and Practice of Industrial Pharmacy, 3rd Edition; Remington's Pharmaceutical Sciences 23rd Edition.

In certain embodiments, one or more diluents will be present in an amount of 1%w/w to 70 %w/w by total weight of the composition. In certain embodiments, one or more disintegrants will be present in an amount of 1%w/w to 20%w/w and especially 4% w/w to 10% %w/w by total weight of the composition.

The term "solid dispersion" as used herein means systems in which itraconazole is dispersed in matrix polymer. In the present invention, the definition of a solid dispersion does not encompass physical mixtures from dry or wet mixing or dry blending operations.

The method for preparing solid dispersions are known in the art and typically comprise the steps of dissolving the drug and the matrix polymer in a common solvent and evaporating the solvent. The solvent can be routinely selected according to the polymer used. Examples of solvents are: acetone, acetone/dichloromethane,

methanol/dichloromethane, dichloromethane / ethanol, acetone/water, acetone/methanol, acetone/ethanol, dichloromethane/ethanol or ethanol/water. Methods for evaporating solvent include rotary evaporation, spray drying, lyophilisation and thin film evaporation. Alternatively, solvent removal may be accomplished by cryogenic freezing followed by lyophilisation. Other techniques may be used such as melt extrusion, solvent controlled precipitation, pH controlled precipitation, supercritical fluid technology and cryogenic co milling.

The solid dispersion composition of itraconazole with particular types of matrix polymer increased the bioavailability of itraconazole compared to the conventional capsule product. The increased bioavailability could be useful in enabling a reduction in the daily dose of itraconazole required to achieve comparable biological exposure seen with a conventional formulation, e.g. a conventional capsule of itraconazole. By increasing the unit dose of higher bioavailablity composition, the dosing frequency can be reduced alongwith reduction of side effects. The solid dispersion formulations of the invention exhibit increased bioavailability and by increasing drug loading it is likely to require fewer dose units compared to conventional itraconazole formulations. However there were challenges in terms of development of solid oral pharmaceutical composition comprising itraconazole in a solid dispersion with a matrix polymer, which are discussed and resolved in present invention.

Another embodiment relates to a stable solid oral pharmaceutical composition comprising itraconazole in a solid dispersion with a matrix polymer and dissolution enhancing agent(s).

Another embodiment relates to a stable solid oral pharmaceutical composition comprising (a) itraconazole, (b) matrix polymer and (c) dissolution enhancing agent(s).

Another embodiment relates to a stable solid oral pharmaceutical composition comprising:

(a) itraconazole in a solid dispersion with a matrix polymer selected from hypromellose phthalate, copovidone, hypromellose acetate succinate, hypromellose, polymethacrylates, hydroxypropyl cellulose and cellulose acetate phthalate;

(b) dissolution enhancing agent(s) selected from combination of (i) dibasic calcium phosphate and (ii) silicified microcrystalline cellulose or combination of (i) dibasic calcium phosphate and (ii) microcrystalline cellulose.

Another embodiment relates to a stable solid oral pharmaceutical composition comprising itraconazole in a solid dispersion with a matrix polymer selected from hypromellose phthalate, copovidone, hypromellose acetate succinate, hypromellose, polymethacrylates, hydroxypropyl cellulose and cellulose acetate phthalate and dissolution enhancing agent(s) selected from combination of (i) dibasic calcium phosphate and (ii) silicified microcrystalline cellulose or combination of (i) dibasic calcium phosphate and (ii) microcrystalline cellulose.

Another embodiment relates to a stable solid oral pharmaceutical composition comprising (a) itraconazole in an amount of 50 mg to 300 mg, (b) matrix polymer selected from hypromellose phthalate, copovidone, hypromellose acetate succinate, hypromellose, polymethacrylates, hydroxypropyl cellulose and cellulose acetate phthalate and (c) dissolution enhancing agent(s) selected from combination of (i) dibasic calcium phosphate and (ii) silicified microcrystalline cellulose or combination of (i) dibasic calcium phosphate and (ii) microcrystalline cellulose.

Another embodiment relates to a stable solid oral pharmaceutical composition comprising (a) itraconazole in an amount of 65 mg, (b) matrix polymer selected from hypromellose phthalate, copovidone, hypromellose acetate succinate, hypromellose, polymethacrylates, hydroxypropyl cellulose and cellulose acetate phthalate and (c) dissolution enhancing agent(s) selected from combination of (i) dibasic calcium phosphate and (ii) silicified microcrystalline cellulose or combination of (i) dibasic calcium phosphate and (ii) microcrystalline cellulose.

Another embodiment relates to a stable solid oral pharmaceutical composition comprising (a) itraconazole in an amount of 130 mg, (b) matrix polymer selected from hypromellose phthalate, copovidone, hypromellose acetate succinate, hypromellose, polymethacrylates, hydroxypropyl cellulose and cellulose acetate phthalate and (c) dissolution enhancing agent(s) selected from combination of (i) dibasic calcium phosphate and (ii) silicified microcrystalline cellulose or combination of (i) dibasic calcium phosphate and (ii) microcrystalline cellulose.

Another embodiment relates to a stable solid oral pharmaceutical composition comprising (a) itraconazole in an amount of 130 mg, (b) matrix polymer, wherein itraconazole is dispersed in matrix polymer phase; wherein itraconazole is present in an amount from 20% w/w to 60% w/w, preferably from 30% w/w to 50% w/w and more preferably 40% w/w by total weight of the solid dispersion; wherein weight ratio of itraconazole to matrix polymer is in the range of about 1: 1 to about 1:3, or about 1: 1.5, based on the weight of itraconazole.

Another embodiment relates to a stable solid oral pharmaceutical composition comprising (a) itraconazole in an amount of 130 mg, (b) matrix polymer selected from hypromellose phthalate, copovidone, hypromellose acetate succinate, hypromellose, polymethacrylates, hydroxypropyl cellulose and cellulose acetate phthalate wherein itraconazole is dispersed in matrix polymer phase; wherein itraconazole is present in an amount from 20% w/w to 60% w/w, preferably from 30% w/w to 50% w/w and more preferably 40% w/w by total weight of the solid dispersion; wherein weight ratio of itraconazole to matrix polymer is in the range of about 1: 1 to about 1:3, or about 1: 1.5, based on the weight of itraconazole.

Another embodiment relates to a stable solid oral pharmaceutical composition comprising itraconazole that minimises the number of capsules required for the therapeutically effective dose, ideally to fewer than 4 units, preferably two or three units.

Another embodiment relates to a stable solid oral pharmaceutical composition comprising itraconazole in a solid dispersion with a matrix polymer and dissolution enhancing agent(s) wherein the said composition is devoid of magnesium stearate.

Another embodiment relates to a stable solid oral pharmaceutical composition comprising itraconazole in a solid dispersion with a matrix polymer and dissolution enhancing agent(s) wherein the said composition is devoid of surfactant.

Another embodiment relates to a stable solid oral pharmaceutical composition comprising itraconazole in a solid dispersion with a matrix polymer and dissolution enhancing agent(s), wherein itraconazole is present in an amount of 50 mg or 65 mg or 100 mg or 130 mg or 150 mg or 195 mg or 200 mg or 250 mg or 260 mg or 300 mg or 400 mg of itraconazole.

Another embodiment relates to a stable solid oral pharmaceutical composition comprising itraconazole in a solid dispersion with a matrix polymer and dissolution enhancing agent(s), wherein itraconazole is present in an amount from 20% w/w to 60% w/w, preferably from 30% w/w to 50% w/w and more preferably 40% w/w by total weight of the solid dispersion.

Another embodiment relates to a stable solid oral pharmaceutical composition comprising itraconazole in a solid dispersion with a matrix polymer and dissolution enhancing agent(s), wherein dissolution enhancing agent(s) is preferably present in an amount from 10% w/w to 80% w/w, more preferably in an amount from 20% w/w to 70% w/w, most preferably in an amount from 30% w/w to 60% w/w by total weight of the composition.

Another embodiment relates to a stable solid oral pharmaceutical composition comprising itraconazole in a solid dispersion with a matrix polymer and dissolution enhancing agent(s), wherein itraconazole is present in an amount of 20% to 60%, and preferably from 30% to 50% and more preferably 40% by weight of the solid dispersion.

Another embodiment relates to a stable solid oral pharmaceutical composition comprising itraconazole in a solid dispersion with a matrix polymer and dissolution enhancing agent(s), wherein weight ratio of itraconazole to matrix polymer is in the range of about 1: 1 to about 1:3, or about 1 : 1.5, based on the weight of itraconazole.

In another embodiment, the matrix polymer is hypromellose phthalate.

In another embodiment, the dissolution enhancing agent(s), is combination of (i) dibasic calcium phosphate and (ii) silicified microcrystalline cellulose in the ratio of 1:1 to 1:4.

In another embodiment, the dissolution enhancing agent(s), is combination of (i) dibasic calcium phosphate and (ii) microcrystalline cellulose in the ratio of 1:1 to 1:4.

Another embodiment relates to a stable solid oral pharmaceutical composition comprising itraconazole in capsule dosage form.

Another embodiment relates to a stable solid oral pharmaceutical composition comprising:

a) itraconazole in a solid dispersion with a matrix polymer selected from hypromellose phthalate, copovidone, hypromellose acetate succinate, hypromellose, polymethacrylates, hydroxypropyl cellulose and cellulose acetate phthalate;

b) dissolution enhancing agent(s) selected from combination of (i) dibasic calcium phosphate and (ii) silicified microcrystalline cellulose or combination of (i) dibasic calcium phosphate and (ii) microcrystalline cellulose wherein

i. itraconazole is present in an amount from 50 mg or 65 mg or 100 mg or 130 mg or 150 mg or 195 mg or 200 mg or 250 mg or 260 mg or 300 mg or 400 mg

ii. itraconazole is present in an amount from 20% w/w to 60% w/w, preferably from 30% w/w to 50% w/w and more preferably 40% w/w by total weight of the solid dispersion;

iii. weight ratio of itraconazole to matrix polymer is in the range of about 1: 1 to about 1:3, or about 1: 1.5, based on the weight of itraconazole;

iv. dissolution enhancing agent(s) is preferably present in an amount from 10% w/w to 80% w/w, more preferably in an amount from 20% w/w to 70% w/w, most preferably in an amount from 30% w/w to 60% w/w by total weight of the composition;

Another embodiment relates to a stable solid oral pharmaceutical composition comprising:

a) itraconazole in a solid dispersion with a matrix polymer selected from hypromellose phthalate, copovidone, hypromellose acetate succinate, hypromellose, polymethacrylates, hydroxypropyl cellulose and cellulose acetate phthalate;

b) dissolution enhancing agent(s) selected from combination of (i) dibasic calcium phosphate and (ii) silicified microcrystalline cellulose or combination of (i) dibasic calcium phosphate and (ii) microcrystalline cellulose wherein

i. itraconazole is present in an amount from 50 mg or 65 mg or 100 mg or 130 mg or 150 mg or 195 mg or 200 mg or 250 mg or 260 mg or 300 mg or 400 mg

ii. itraconazole is present in an amount from 20% w/w to 60% w/w by total weight of the solid dispersion;

iii. weight ratio of itraconazole to matrix polymer is in the range of about 1: 1 to about 1:3 based on the weight of itraconazole;

iv. dissolution enhancing agent(s) is preferably present in an amount from 20% w/w to 70% w/w by total weight of the composition.

Another embodiment relates to a method of producing a stable solid oral pharmaceutical composition of itraconazole comprising:

(i) a suitable amount itraconazole with a desired amount of at least one matrix polymer was dissolved in methylene chloride and ethanol with continuous stirring;

(ii) the solution from step (i) was spray-dried to form solid dispersion as a spray dried powder. The spray dried solid dispersion was further dried in suitable dryer.

(iii) the solid dispersion of itraconazole and matrix polymer was mixed properly with dissolution enhancing agent(s) and one or more pharmaceutically acceptable excipient like disintegrant, lubricant or glidant;

(iv) the blend from step (iii) was filled in suitable capsules.

Another embodiment relates to method of producing a stable solid oral pharmaceutical composition of itraconazole by blending process.

Another embodiment relates to method of producing a stable solid oral pharmaceutical composition of itraconazole by roll compaction process.

The solid oral pharmaceutical composition can be in provided form of capsule, tablet, powder, sachet and the like, and particularly a capsule. The composition can also comprise one or more additional antifungal agents.

**Comparative Examples**

Table 1: Composition and dissolution details of Comparative Example 1 - 3

| Composition Details | Comparative Example 1 (Mg / Capsule) | Comparative Example 2 (Mg / Capsule) | Comparative Example 3 (Mg / Capsule) |
|---|---|---|---|
| **Stage A** | | | |
| Itraconazole | 130.00 | 130.00 | 130.00 |
| Hypromellose Phthalate | 200.00 | 200.00 | 200.00 |
| Methylene Chloride | q.s | q.s | q.s |
| Ethanol | q.s | q.s | q.s |
| **Stage B** | | | |
| Microcrystalline Cellulose | 116.78 | - | - |
| Dicalcium Phosphate, Anhydrous | - | 179.50 | - |

| | | | |
|---|---|---|---|
| Silicified Microcrystalline Cellulose (PROSOLV® SMCC) | - | - | 172.70 |
| Sodium Starch Glycollate | 58.85 | 42.00 | 42.00 |
| Colloidal Silicon Dioxide | 3.12 | 3.20 | - |
| Sodium Stearyl Fumarate | 6.25 | 5.30 | 5.30 |
| **Total Fill Weight** | **515.00** | **560.00** | **550.00** |
| **Capsule Size** | "00" | "00" | "00" |
| Dissolution Parameters as per BP medium: (0.5% SLS in Water/ 75 RPM/900ml/paddle) Limit: NLT 70%(Q) in 60 min | 64.5% in 60 minutes | 54.2 % in 60 minutes | 47.5 % in 60 minutes |

**Manufacturing Steps:**

1. Itraconazole and Hypromellose Phthalate were dissolved in methylene chloride and Ethanol with continuous stirring;
2. The solution from step (1) was spray-dried to form solid dispersion as a spray dried powder. The spray dried solid dispersion was further dried in suitable dryer;
3. The dried drug-polymer solid dispersion fron step (2) was blended properly with excipients of Stage B and filled in suitable capsules.

In comparative examples 1-3, it was found that the dissolution was low (Less than 70% in 60 minutes). It was observed that use of Microcrystalline Cellulose or Silicified Microcrystalline Cellulose (PROSOLV® SMCC) or Dicalcium Phosphate, Anhydrous are not sufficient to achieve the desired dissolution of itraconazole in 60 minutes.

**Examples**

Table 2: Composition and dissolution details of Example 1 – 2

| Composition Details | Example 1 (Mg / Capsule) | Example 2 (Mg / Capsule) |
|---|---|---|
| **Stage A** | | |
| Itraconazole | 130.00 | 130.00 |
| Hypromellose Phthalate | 200.00 | 200.00 |
| Methylene Chloride | q.s | q.s |
| Ethanol | q.s | q.s |
| **Stage B** | | |
| Microcrystalline Cellulose + Dicalcium Phosphate, Anhydrous (AVICEL® DG; 75:25) | 169.50 | - |

| | | |
|---|---|---|
| Silicified Microcrystalline Cellulose (PROSOLV® SMCC 50) | - | 119.50 |
| Dicalcium Phosphate | - | 50.00 |
| Sodium Starch Glycollate | 42.00 | 42.00 |
| Colloidal Silicon Dioxide | 3.20 | 3.20 |
| Sodium Stearyl Fumarate | 5.30 | 5.30 |
| **Total Fill Weight** | **550.00** | **550.00** |
| **Capsule Size** | "00" | "00" |
| Dissolution Parameters as per BP medium: (0.5% SLS in Water/ 75 RPM/900ml/paddle) Limit: NLT 70%(Q) dissolved in 60 min | 100.6 % in 60 minutes | 91.8 % in 60 minutes |

Manufacturing Steps:

1. Itraconazole and Hypromellose Phthalate were dissolved in methylene chloride and Ethanol with continuous stirring;
2. The solution from step (1) was spray-dried to form solid dispersion as a spray dried powder. The spray dried solid dispersion was further dried in suitable dryer;
3. The dried drug-polymer solid dispersion fron step (2) was blended properly with excipients of Stage B and filled in suitable capsules.

Table 2: Stability data of Example 1 at 30°C / 75%RH

| Itraconazole Capsules 130 mg | Initial | 1 Month 30°C / 75%RH | 2 Month 30°C / 75%RH | 3 Month 30°C / 75%RH | 6 Month 30°C / 75%RH |
|---|---|---|---|---|---|
| Total Impurity (NMT 1%) | 0.51 | 0.53 | 0.54 | 0.63 | 0.60 |
| Assay (95% - 105%) | 99.1 | 101.3 | 102.2 | 102.1 | 101.5 |
| Dissolution (NLT 70%(Q) in 60 min) | 100.6 | 101.2 | 100.9 | 101.4 | 94.9 |

Table 3: Stability data of Example 1 at 40°C / 75%RH

| Itraconazole Capsules 130 mg | Initial | 1 Month 40°C / 75%RH | 2 Month 40°C / 75%RH | 3 Month 40°C / 75%RH | 6 Month 40°C / 75%RH |
|---|---|---|---|---|---|
| Total Impurity (NMT 1%) | 0.51 | 0.53 | 0.57 | 0.63 | 0.58 |
| Assay (95% - 105%) | 99.1 | 100.7 | 102.7 | 101.8 | 103.5 |
| Dissolution (NLT 70%(Q) in 60 min) | 100.6 | 95.3 | 96.0 | 93.0 | 89.7 |

Table 4: Composition and dissolution details of Example 3

| Composition Details | Example 3 (Mg / Capsule) |
|---|---|
| **Stage A** | |
| Itraconazole | 65.00 |
| Hypromellose Phthalate | 100.00 |
| Methylene Chloride | q.s |
| Ethanol | q.s |
| **Stage B** | |
| Microcrystalline Cellulose + Dicalcium Phosphate, Anhydrous (AVICEL® DG; 75:25) | 84.75 |
| Silicified Microcrystalline Cellulose (PROSOLV® SMCC 50) | - |
| Dicalcium Phosphate | - |
| Sodium Starch Glycollate | 21.00 |
| Colloidal Silicon Dioxide | 1.60 |
| Sodium Stearyl Fumarate | 2.65 |
| **Total Fill Weight** | **275.00** |
| **Capsule Size** | "0" |
| Dissolution Parameters as per BP medium: (0.5% SLS in Water/ 75 RPM/900ml/paddle) Limit: NLT 70%(Q) dissolved in 60 min | 97.2% in 60 minutes |

Manufacturing Steps:

1. Itraconazole and Hypromellose Phthalate were dissolved in methylene chloride and Ethanol with continuous stirring;
2. The solution from step (1) was spray-dried to form solid dispersion as a spray dried powder. The spray dried solid dispersion was further dried in suitable dryer;
3. The dried drug-polymer solid dispersion fron step (2) was blended properly with excipients of Stage B and filled in suitable capsules.

Table 5: Composition and dissolution details of Example 4

| Composition Details | Example 4 (Mg / Capsule) |
|---|---|
| **Stage A – Solid Dispersion** | |
| Itraconazole | 130.00 |
| Hypromellose Phthalate | 200.00 |
| Methylene Chloride | q.s |
| Ethanol | q.s |
| **Stage B – Roll Compaction** | |

| | |
|---|---|
| Dicalcium Phosphate, Anhydrous | 80.00 |
| Silicified Microcrystalline Cellulose (PROSOLV® SMCC 50) | 188.10 |
| Sodium Starch Glycollate | 42.00 |
| Sodium Stearyl Fumarate | 1.40 |
| **Stage C – Extragranular** | |
| Colloidal Silicon Dioxide | 3.20 |
| Sodium Stearyl Fumarate | 5.30 |
| **Total Fill Weight in Capsule** | **650.00** |
| Dissolution Parameters as per BP medium: (0.5% SLS in Water/ 75 RPM/900ml/paddle) Limit: NLT 70%(Q) dissolved in 60 min | 83.5 % in 60 minutes |

Manufacturing Steps:

1. Itraconazole and Hypromellose Phthalate were dissolved in methylene chloride and Ethanol with continuous stirring;
2. The solution from step (1) was spray-dried to form solid dispersion as a spray dried powder. The spray dried solid dispersion was further dried in suitable dryer;
3. The dried drug-polymer solid dispersion from step (2) was roll compacted with excipients from Stage B in roll compactor. The compacted mass was milled and screened.
4. The blend from step (3) was mixed properly with excipients of Stage C and filled in suitable capsules.

It is observed that use of dissolution enhancing agent(s) in Examples 1-4 has resulted in achievemnt of desired dissolution profile of itraconazole.

Table 6: Composition of Example 5 – 7

| Composition Details | Example 5 (Mg / Capsule) | Example 6 (Mg / Capsule) | Example 7 (Mg / Capsule) |
|---|---|---|---|
| **Stage A** | | | |
| Itraconazole | 130.00 | 130.00 | 130.00 |
| Hypromellose Phthalate | 200.00 | 200.00 | 195.00 |
| Methylene Chloride | q.s | q.s | q.s |
| Ethanol | q.s | q.s | q.s |
| **Stage B** | | | |
| Microcrystalline Cellulose + Dicalcium Phosphate, Anhydrous (AVICEL® DG; 75:25) | - | - | 174.50 |
| Silicified Microcrystalline Cellulose | 42.38 | 84.75 | - |

| | | | |
|---|---|---|---|
| (PROSOLV® SMCC 50) | | | |
| Dicalcium Phosphate | 127.12 | 84.75 | - |
| Sodium Starch Glycollate | 42.00 | 42.00 | 42.00 |
| Colloidal Silicon Dioxide | 3.20 | 3.20 | 3.20 |
| Sodium Stearyl Fumarate | 5.30 | 5.30 | 5.30 |
| **Total Fill Weight** | **550.00** | **550.00** | **550.00** |
| **Capsule Size** | "00" | "00" | "00" |

Manufacturing Steps:

1. Itraconazole and Hypromellose Phthalate were dissolved in methylene chloride and Ethanol with continuous stirring;
2. The solution from step (1) was spray-dried to form solid dispersion as a spray dried powder. The spray dried solid dispersion was further dried in suitable dryer;
3. The dried drug-polymer solid dispersion fron step (2) was blended properly with excipients of Stage B and filled in suitable capsules.

Table 7: Composition of Example 8 – 10

| Composition Details | Example 8 (Mg / Capsule) | Example 9 (Mg / Capsule) | Example 10 (Mg / Capsule) |
|---|---|---|---|
| **Stage A** | | | |
| Itraconazole | 130.00 | 130.00 | 130.00 |
| Hypromellose Phthalate | 390.00 | 520.00 | 87.00 |
| Methylene Chloride | q.s | q.s | q.s |
| Ethanol | q.s | q.s | q.s |
| **Stage B** | | | |
| Microcrystalline Cellulose + Dicalcium Phosphate, Anhydrous (AVICEL® DG; 75:25) | 97.77 | 92.77 | 470.77 |
| Sodium Starch Glycollate | 68.73 | 68.73 | 68.73 |
| Colloidal Silicon Dioxide | 4.50 | 4.50 | 4.50 |
| Sodium Stearyl Fumarate | 9.00 | 9.00 | 9.00 |
| **Total Fill Weight** | **700.00** | **825.00** | **770.00** |

Manufacturing Steps:

1. Itraconazole and Hypromellose Phthalate are dissolved in methylene chloride and Ethanol with continuous stirring;
2. The solution from step (1) is spray-dried to form solid dispersion as a spray dried powder. The spray dried solid dispersion was further dried in suitable dryer;

3. The dried drug-polymer solid dispersion from step (2) is blended properly with excipients of Stage B and filled in suitable capsules.

Although the invention herein has been described with reference to particular embodiments, it is to be understood that these embodiments are merely illustrative of the principles and application of the present invention. It is therefore to be understood that numerous modifications may be made to the illustrative embodiments and that other arrangements may be devised without departing from the spirit and scope of the present invention as described above.

All publications, patents, and patent applications cited in this application are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated herein by reference.

## Claims

**We Claim**:

1. A stable solid oral pharmaceutical composition comprising
   a. itraconazole in an amount of 130 mg in a solid dispersion with a matrix polymer wherein itraconazole is present in an amount from 20% w/w to 60% w/w by total weight of the solid dispersion; and
   b. dissolution enhancing agent(s).

2. The stable solid oral pharmaceutical composition according to claim 1, wherein itraconazole is present in an amount from 30 % w/w to 50% w/w by total weight of the solid dispersion.

3. The stable solid oral pharmaceutical composition according to claim 1, wherein itraconazole is present in an amount of about 40% w/w by total weight of the solid dispersion.

4. The stable solid oral pharmaceutical composition according to claim 1, wherein matrix polymer selected from hypromellose phthalate, copovidone, hypromellose acetate succinate, hypromellose, polymethacrylates, hydroxypropyl cellulose and cellulose acetate phthalate.

5. The stable solid oral pharmaceutical composition according to claim 1, wherein the matrix polymer is hypromellose phthalate.

6. The stable solid oral pharmaceutical composition according to claim 1, wherein weight ratio of itraconazole to matrix polymer is in the range of about 1: 1 to about 1:3, or about 1: 1.5, based on the weight of itraconazole.

7. The stable solid oral pharmaceutical composition according to claim 1, wherein dissolution enhancing agent(s) is selected from combination of (i) dibasic calcium

phosphate and (ii) silicified microcrystalline cellulose or combination of (i) dibasic calcium phosphate and (ii) microcrystalline cellulose.

8. The stable solid oral pharmaceutical composition according to claim 1, wherein dissolution enhancing agent(s) is present in an amount from 10% w/w to 80% w/w by total weight of the composition.

9. The stable solid oral pharmaceutical composition according to claim 1, wherein dissolution enhancing agent(s) is present in an amount from 20% w/w to 70% w/w by total weight of the composition.

10. The stable solid oral pharmaceutical composition according to claim 1, wherein dissolution enhancing agent(s) is present in an amount from 30% w/w to 60% w/w by total weight of the composition.

11. The stable solid oral pharmaceutical composition according to claim 1, wherein said composition comprising itraconazole is in capsule dosage form.

12. A method of producing a stable solid oral pharmaceutical composition of itraconazole in an amount of 130 mg comprising:
(i) a suitable amount itraconazole with a desired amount of at least one matrix polymer was dissolved in solvent with continuous stirring;
(ii) the solution from step (i) was spray-dried to form solid dispersion as a spray dried powder. The spray dried solid dispersion was further dried in suitable dryer.
(iii) the solid dispersion of itraconazole and matrix polymer was mixed properly with dissolution enhancing agent(s) and one or more pharmaceutically acceptable excipient like disintegrant, lubricant, or glidant;
(iv) the blend from step (iii) was filled in suitable capsules.

13. A stable solid oral pharmaceutical composition comprising

a. itraconazole in a solid dispersion with a matrix polymer selected from hypromellose phthalate, copovidone, hypromellose acetate succinate, hypromellose, polymethacrylates, hydroxypropyl cellulose and cellulose acetate phthalate;
b. dissolution enhancing agent(s) selected from combination of (i) dibasic calcium phosphate and (ii) silicified microcrystalline cellulose or combination of (i) dibasic calcium phosphate and (ii) microcrystalline cellulose.

14. The stable solid oral pharmaceutical composition according to claim 13, wherein itraconazole is present in an amount of 50 mg or 65 mg or 100 mg or 130 mg or 150 mg or 195 mg or 200 mg or 250 mg or 260 mg or 300 mg or 400 mg.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2022/055460

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/497,A61K9/26,A61K9/10 Version=2022.01

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 practicable, search terms used)

PatSeer, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 2002/100407 A1 (SMARTRIX TECHNOLOGIES INC. [CA]) 19 December 2002 (19.12.2002) (Family None) Abstract, Examples 1-2, Claims 1, 11,22-32; | 1-4,6-14 |
| Y | Abstract, Examples 1-2, Claims 1, 11,22-32; | 5 |
| Y | CN 105126110 A (NATIONAL SUN YAT SEN UNIVERSITY, [CN]) 09 December 2015 (09.12.2015)(Family None) Abstract, Claims 1-3; | 5 |
| A | 2005/0226924 A1 (KYU-HYUN LEE [KR] et al) 13 October 2005 (13.10.2005) Abstract, Examples 4-6; | 1-14 |

☐ Further documents are listed in the continuation of Box C.

☒ 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

"D" document cited by the applicant in the international application

"E" earlier application or patent 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 |
|---|---|
| 30-08-2022 | 30-08-2022 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| Indian Patent Office<br>Plot No.32, Sector 14,Dwarka,New Delhi-110075<br>Facsimile No. | Veera R Kattula<br>Telephone No. +91-1125300200 |

**INTERNATIONAL SEARCH REPORT**
Information on patent family members

International application No.
PCT/IB2022/055460

| Citation | Pub.Date | Family | Pub.Date |
|---|---|---|---|
| US 20050226924 A1 | 13-10-2005 | KR 100479367 B1 | 29-03-2005 |
| | | JP 2005298472 A | 27-10-2005 |
| | | CN 1798562 A | 05-07-2006 |
| | | WO 2005099708 A1 | 27-10-2005 |