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मैं, अधोहस्ताक्षरी जो पेटेंट अधिनियम, 1970 की धारा 73(3) के तहत महानियंत्रक एकस्व, अभिकल्प एवं व्यापार चिह्न की ओर से प्रमाणपत्र हस्ताक्षर व जारी करने के लिए प्राधिकृत अधिकारी हूँ, एतदद्वारा यह प्रमाणित करता(ती) हूँ कि निम्नलिखित पेटेंट आवेदन के संबंध मे फाइल दस्तावेज़(जों) की सही प्रतिलिपि इसके साथ संलग्न है:

I, the undersigned, being an officer duly authorized to sign and issue the certificate on behalf of the Controller General of Patents, Designs and Trademarks in accordance with the provisions of Section 73(3) of the Patents Act, 1970, hereby certify that annexed hereto is a True Copy of the document(s) as filed in connection with the following Patent Application:

क) आवेदन संख्या / a) Application Number: ***202121026278***
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1) ***Application for Grant of Patent (Form-1)***
2) ***Provisional Specification filed on 13/06/2021***

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दिनांक/Dated this 11th day of JULY, 2022.

(SAPNA NARVARIYA)
सहायक नियंत्रक पेटेंट व डिजाइन/ ***Assistant Controller of Patents and Designs***
(प्राधिकृत हस्ताक्षरी/ ***Authorized Signatory)***

FORM 1 THE PATENTS ACT 1970 (39 of 1970) and THE PATENTS RULES, 2003 **APPLICATION FOR GRANT OF PATENT** (See section 7, 54 and 135 and sub-rule (1) of rule 20)			(FOR OFFICE USE ONLY)		
			Application No.		
			Filing date:		
			Amount of Fee paid:		
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			Signature:		
1. APPLICANT'S REFERENCE / IDENTIFICATION NO. (AS ALLOTTED BY OFFICE)					
2. TYPE OF APPLICATION [Please tick (√) at the appropriate category]					
Ordinary (√)		Convention ( )		PCT-NP ( )	
Divisional ( )	Patent of Addition ( )	Divisional ( )	Patent of Addition ( )	Divisional ( )	Patent of Addition ( )

3A. APPLICANT(S)				
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3B. CATEGORY OF APPLICANT [Please tick (√) at the appropriate category]			
Natural Person ( )	Other than Natural Person		
	Small Entity ( )	Startup ( )	Others (√)

4. INVENTOR(S) [Please tick (√) at the appropriate category]				
Are all the inventor(s) same as the applicant(s) named above?	Yes ( )		No (√)	
If "No", furnish the details of the inventor(s)				
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			City	Nashik
			State	Maharashtra

			Country	India
			Pin Code	422012
5. TITLE OF THE INVENTION				
PHARMACEUTICAL COMPOSITION COMPRISING ITRACONAZOLE				
~~**6. AUTHORISED REGISTERED PATENT AGENT(S)**~~			~~IN/PA No.~~	
			~~Name~~	
			~~Mobile No.~~	
7. ADDRESS FOR SERVICE OF APPLICANT IN INDIA			Name	Dr. Pramod Sagar Deputy General Manager, IPM
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~~**8. IN CASE OF APPLICATION CLAIMING PRIORITY OF APPLICATION FILED IN CONVENTION COUNTRY, PARTICULARS OF CONVENTION APPLICATION**~~

~~Country~~	~~Application Number~~	~~Filing date~~	~~Name of the applicant~~	~~Title of the invention~~	~~IPC (as classified in the convention country)~~

~~**9. IN CASE OF PCT NATIONAL PHASE APPLICATION, PARTICULARS OF INTERNATIONAL APPLICATION FILED UNDER PATENT CO-OPERATION TREATY (PCT)**~~

~~International application number~~	~~International filing date~~

~~**10. IN CASE OF DIVISIONAL APPLICATION FILED UNDER SECTION 16, PARTICULARS**~~

~~OF ORIGINAL (FIRST) APPLICATION~~	
~~Original (first) application No.~~	~~Date of filing of original (first) application~~
~~11. IN CASE OF PATENT OF ADDITION FILED UNDER SECTION 54, PARTICULARS OF MAIN APPLICATION OR PATENT~~	
~~Main application/patent No.~~	~~Date of filing of main application~~
12. DECLARATIONS	
(i) Declaration by the inventor(s) **(In case the applicant is an assignee:** the inventor(s) may sign herein below or the applicant may upload the assignment or enclose the assignment with this application for patent or send the assignment by post/electronic transmission duly authenticated within the prescribed period). I/We, the above named inventor(s) is/are the true & first inventor(s) for this Invention and declare that the applicant(s) herein is/are my/our assignee or legal representative. (a) Date (b) Signature(s) (c) Name(s): KULKARNI Sushrut (a) Date (b) Signature(s) (c) Name(s): DESHMUKH Nitin (a) Date (b) Signature(s) (c) Name(s): SATPUTE Ravindra (a) Date (b) Signature(s) (c) Name(s): BAGUL Kunal	
(iii) Declaration by the applicant(s) I/We the applicant(s) hereby declare(s) that: - □ I am/ We are in possession of the above-mentioned invention.	

☐ The provisional/~~complete~~ specification relating to the invention is filed with this application.

~~☐ The invention as disclosed in the specification uses the biological material from India and the necessary permission from the competent authority shall be submitted by me/us before the grant of patent to me/us.~~

☐ There is no lawful ground of objection(s) to the grant of the Patent to me/us.

☐ I am/we are the true & first inventor(s).

☐ I am/we are the assignee or legal representative of true & first inventor(s).

~~☐ The application or each of the applications, particulars of which are given in Paragraph 8, was the first application in convention country/countries in respect of my/our invention(s).~~

~~☐ I/We claim the priority from the above mentioned application(s) filed in convention country/countries and state that no application for protection in respect of the invention had been made in a convention country before that date by me/us or by any person from which I/We derive the title.~~

~~☐ My/our application in India is based on international application under Patent Cooperation Treaty (PCT) as mentioned in Paragraph 9.~~

~~☐ The application is divided out of my /our application particulars of which is given in Paragraph 10 and pray that this application may be treated as deemed to have been filed on DD/MM/YYYY under section 16 of the Act.~~

~~☐ The said invention is an improvement in or modification of the invention particulars of which are given in Paragraph 11.~~

13. FOLLOWING ARE THE ATTACHMENTS WITH THE APPLICATION

(a) Form 2

Item	Details	Fee	Remarks
~~Complete~~ / provisional specification)#	No. of pages 19	₹ 8000=00	
~~No. of Claim(s)~~	~~No. of claims and No. of pages~~		
~~Abstract~~	~~No. of pages~~		
No. of Drawing(s)	No. of drawings and No. of pages		

In case of a complete specification, if the applicant desires to adopt the drawings filed with his provisional specification as the drawings or part of the drawings for the complete specification under rule 13(4), the number of such pages filed with the provisional specification are required to be mentioned here.

~~(b) Complete specification (in conformation with the international application)/as amended before the International Preliminary Examination Authority (IPEA), as applicable (2 copies).~~

~~(c) Sequence listing in electronic form~~

~~(d) Drawings (in conformation with the international application)/as amended before the International Preliminary Examination Authority (IPEA), as applicable (2 copies).~~

~~(e) Priority document(s) or a request to retrieve the priority document(s) from DAS (Digital Access Service) if the applicant had already requested the office of first filing to make the priority document(s) available to DAS.~~

~~(f) Translation of priority document/Specification/International Search Report/International Preliminary Report on Patentability.~~

(g) Statement and Undertaking on Form 3

~~(h) Declaration of Inventorship on Form 5~~

~~(i) Power of Authority~~

~~(j).....~~

Total fee ₹ 8000 - paid online

I/We hereby declare that to the best of my/our knowledge, information and belief the fact and matters slated herein are correct and I/We request that a patent may be granted to me/us for the said invention.

Dated this 12th day of June, 2021.

Signature:

Name: Dr. Pramod Sagar, Deputy General Manager, IPM

To

The Controller of Patents

The Patent Office, at Mumbai.

FORM 2

THE PATENTS ACT, 1970

(39 of 1970)

&

THE PATENTS RULES, 2003

PROVISIONAL SPECIFICATION

(*See* Section 10 and rule 13)

Title: PHARMACEUTICAL COMPOSITION COMPRISING ITRACONAZOLE

Applicant:

GLENMARK PHARMACEUTICALS LIMITED,

an Indian Company,

registered under the Company's Act 1957 and

having its office at

B/2, Mahalaxmi Chambers,

22 Bhulabhai Desai Road,

Mumbai – 400026, India

The following specification describes the invention.

PHARMACEUTICAL COMPOSITION COMPRISING ITRACONAZOLE

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 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 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 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 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.

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 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 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 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 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 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 excipents 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 - 6

Composition Details	Example 5 (Mg / Capsule)	Example 6 (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		
Silicified Microcrystalline Cellulose (PROSOLV® SMCC 50)	42.38	84.75
Dicalcium Phosphate	127.12	84.75
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"

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.

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.

Dated this 12th day of June 2021

Signature _____

Dr. Pramod Sagar

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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.