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PREPARATION AND EVALUCATION OF FAST DISINTEGRATION TABLETS OF POSACONAZOLE

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ABSTRACT

Posaconazole is a broad spectrum triazole antifungal agent with potent activity against various fungi, including yeast and moulds Clinical studies have demonstrated that the agent is efficacious as prophylaxis against inventive fungal infections inpatients at hedonist and may also useful in salvage therapy against invasive aspergillosis and mucomycosis However, the bioavailability Posaconazole following administration as oral suspension, which was the only formulation clinically available for many years variable negatively influenced several factors because many by the patients had sub therapeutic levels when the oral suspension was wed, overcome this limitation delayed release tablet was developed and is now available for clinical use. In addition, pharmacokinetic parameters following administration of the tablets were not Significantly affected by medication that increasing gastric motility, and the tablets could also be administrated without regard to food similar results have been found in patients at high risk for invasive fungal who have received.

KEYWORDS: Posaconazole, triazole, aspergillosis, mucomycosis.

INTRODUCTION

Posaconazole tablet formulation and appears to be well tolerated to date, although data regarding clinical efficacy are needed. Posaconazole is a triazole antifungal agent with a spectrum of activity that includes Candida and Cryptococcus specie and some endemic fungi. Posaconazole has received US Food and Drug Administration approval for the treatment of oropharyngeal, candidiasis including infections refractory to itraconazole and/or fluconazole. It is also approved as prophylaxis for invasive Aspergillus and Candida infections in patients aged >13 years who are at high risk of developing these infections, in adult and adolescent hematopoietic stem cell transplant recipients with graft-versus-host disease, and in persons with hematologic malignancies and prolonged neutropenia due to chemotherapy, who are at high risk of developing these infections. Approval for additional indications is being sought. Limited clinical experience suggests efficacy for the treatment of infections due to Zygomycetes and as salvage therapy for patients with invasive aspergillosis and coccidioido mycosis. Currently available only as an oral suspension, Posaconazole which has been well tolerated, requires administration with food or a nutritional supplement to assure adequate

bioavailability. Posaconazole predominantly eliminated in the feces where it appears as unchanged drug. Metabolism, mostly glucuronidation, plays only a minor role in its elimination, as does renal clearance; as a consequence, dose adjustment is not required in the presence of renal or hepatic insufficiency. Although not a substrate of hepatic CYP450 3A4 inhibits this enzyme and thus has the potential for significant pharmacokinetic interactions with drugs metabolized by this isoform. Its use in combination with CYP450 substrates that prolong the QTc interval is contraindicated, as is its use with ergot alkaloids; administration of Posaconazole with other substrates and/or inducers of this enzyme system requires caution. Posaconazole is both a substrate and inhibitor of P-glycoprotein. Currently, the major roles for Posaconazole in clinical practice are as prophylaxis for neutropenic patients with significant risk of infection with filamentous fungi. It may also have a role in the treatment of other filamentous fungal and some yeast infections, but assessment of its overall place in antifungal therapy awaits of further clinical experience.

MATERIALS AND METHODS

I. EQUIPMENT

The instruments include a tablet press (EKO made in India) and Tubul mixer made India. CAMAG developing tank single rectangular with internal dimension (21.611.2 6) cm all were made from CAMAG, Mumbai India was used. Analytical balance (new classic MS Mettler Asian ser India). The equipment includes: Monsanto type tablet hardness tester (IEC. Mumbai, India). Roche Friability electro lab, Bangalore. India, single pan balance (Hyderabad, AX200, India), Disintegration Apparatus USP (Electro lab, Bangalore, India). Graduated cylinder (Fisher Scientific, India), sieve 22(Asian scientific, India), glass bottles (Fisher Scientific, India).

II. REAGENTS AND CHEMICALS

Analytical grade reagents were used for the analytical part of this studyduring the pre-formulation and formulation steps. Methanol was made from chemo chemicals Mumbai India, and Techno Pharm hem Bahadurgarh, Haryana, India. Glacial acetic acid was made from India. Ethyl acetate was made from Techno Pharm chemical Bahadurgarh, Haryana, India, and Fisher Scientific, Delhi, India. Distilled water was in-house prepared at Hyderabad by reverse osmosis using RO- Purification System equipment made from Millipore India. Excipients included microcrystalline cellulose made from India, sodium carboxymethyl cellulose, and polyvinylpyrrolidone.

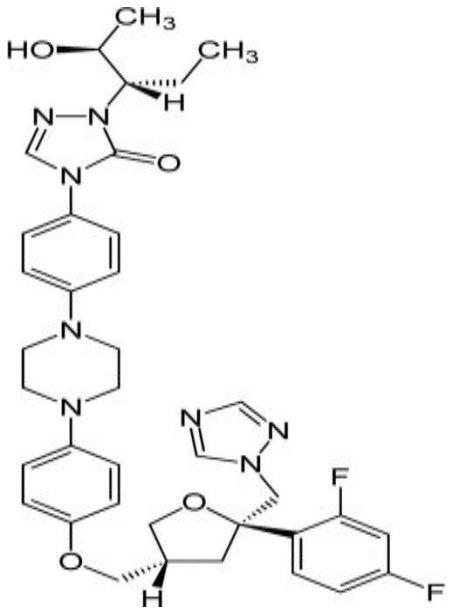
III. MATERIALS AND SELECTION OF EXCIPIENTS

Selections of excipients were based on excipients commonly found in medicines available on the market. Excipients that were used in the compatibility studies include Microcrystalline Cellulose (MCC) Microcrystalline Cellulose (Avicel PH101). Anhydrous Lactose, magnesium stearate, Sodium lauryl Sulphate (SLS), Croscarmellose Sodium (CCM), Sodium starch glycolate (SSG), Sodium saccharin, Cross povidone (CP) and polyvinyl pyrrolidone k-30 (PVP K-30). These are some of the common excipients.

Excipient Compatibility studies were conducted as follows, 200mg of excipient was mixed with 200mg of Posaconazole (1:1 binary mixture) in order to prepare samples for detection of any incompatibility. The samples were stored in a stability chamber (402 "C. RH 75%), oven (50°c), and room temperature (30.2°c). Then the samples were physically observed for caking. Liquefaction, Discoloration. Odor, and Gel formation at 0, 7, 14, 21. 30, 60, and 90 days of storage.

ACTIVE PHARMACEUTICAL INGREDIENT

Posaconazole



Structural formula: C37H42F2N8O4

Molecular weight:700.8 g/mol

Posaconazole is an approved lipophilic triazole antifungal agent that exhibits potent and broad-spectrum antifungal activity in vitro and in vivo against most Candida Cryptococcus neoformans, Aspergillus spp., many Zygomycetes, endemic fungi and dermatophytes. It has been documented that Posaconazole has potency and spectrum of activity similar to those of itraconazole and superior to those of fluconazole against clinically important isolates of Candida neoformans and Aspergillus. This new triazole has been developed for the treatment of fungal infections, which most often occur in severely immuno compromised patients, such as organ transplant patients or cancer patients undergoing chemotherapy. Since Posaconazole has low solubility in aqueous and acidic media, its absorption is dose limited and significantly dependent upon food intake .The time to reach the maximum plasma concentration has been reported to be 5–8 hours following oral administration of a single dose. The aim of the method is to development and validation for the determination of Posaconazole in pharmaceutical formulation.

1. METHODS

PREPARATION OF FAST DISSOLVING TABLETS

Three different concentrations of croscarmellose, sodium starch glycolate and cross povidone were mixed separately with other excipients & little quantity of water with the process of wet granulation. In Petridis and kept in hot air oven at 70°C for 40 min then removed. There are different concentrations of magnesium stearate and talc were incorporated separately with powder blend. Talc and Magnesium stearate, were added as lubricants.

PREPARATION OF POWDER BLEND/MIX

The active ingredient and the excipients were passed through sieve and then weighed according to each formulation requirement. The active ingredient and excipients were mixed blended for 10 min after which evaluation of blend characteristics were performed.

Compression of powder blend mix

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9
Posaconazole	300	300	300	300	300	300	300	300	300
croscarmellose	5	15	25	-	-	-	-	-	-
Crossprovidone	-	-	-	5	15	25	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	5	15	25
Aspartame	6	6	6	6	6	6	6	6	6
lactose	193	188	183	187	188	183	178	188	183
talc	5	5	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5	5	5
Microcrystalline cellulose (mcc)	144	131	126	136	131	139	131	131	126
Total weight (mg)	650	650	650	650	650	650	650	650	650

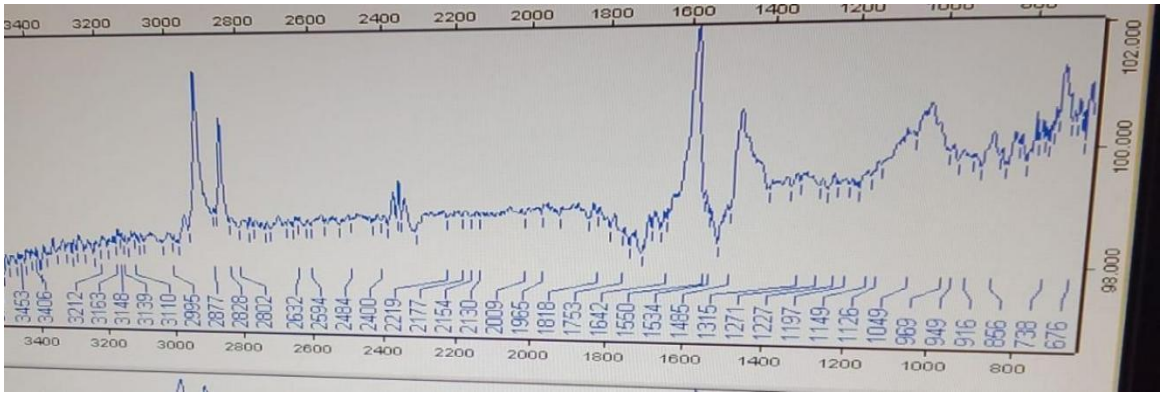
The mixed was granulated by using a wet granulation method and then compressed at a constant compression force following which evaluation were performed let of 650mg.

FT-IR Spectroscopy

Fourier transmitted Infrared (FT-IR) spectroscopy was conducted usingthermo Nicolet.

Nexus 670 Spectrophotometer and the spectrum was recorded in the wavelength region of 4000 to 500 cm'. The procedure consisted of dispersing a sample (drug alone or mixture of drug and excipients) in KBr and compressing into discs by applying a pressure. The pellet was placed in the light path and the spectrum was obtained.

Cross povidone



FT-IR Spectra of sodium starch glycolate

Absorbance peak value	Type of vibration	Functional group	Range of region
1509	NO2 stretch	Nitro	1500-1550
1455	CH2 Bend	Alkene	1400-1500
1117	C-F stretch	Halogen	1100-1200
800	C-CL stretch	Halogen	1000-800
740	C-Br Bend	Halogen	650-750

FT-IR Spectra of crossprovidone

Absorbance peak value	Type of vibration	Functional group	Range of region
2995	OH stretch	Alcohol	2900-3000
2877	N-H stretch	Amine	2800-2900
2219	CH3-CH3 stretch	Alkyne	2050-2300
1550	NO2 stretch	Nitro	1500-1550
1485	CH2 Bend	Alkaline	1400-1500

FT-IR Spectra of croscarmellose

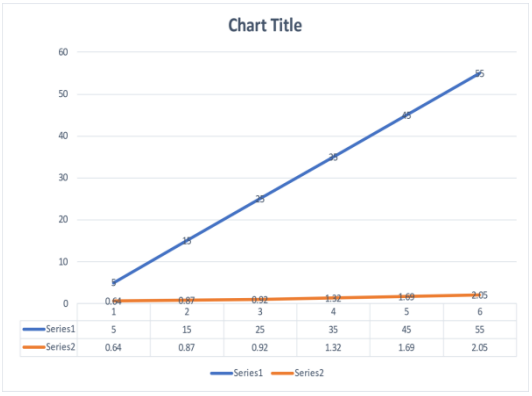
Absorbance peak value	Type of vibration	Functional group	Range of region
2995	OH stretch	Alcohol	2900-3000
2877	N-H stretch	Amine	2800-2900
2219	CH3-CH3 stretch	Alkyne	2050-2300
1550	NO2 stretch	Nitro	1500-1550
1485	CH2 Bend	Alkaline	1400-1500

In-vitro drug release studies

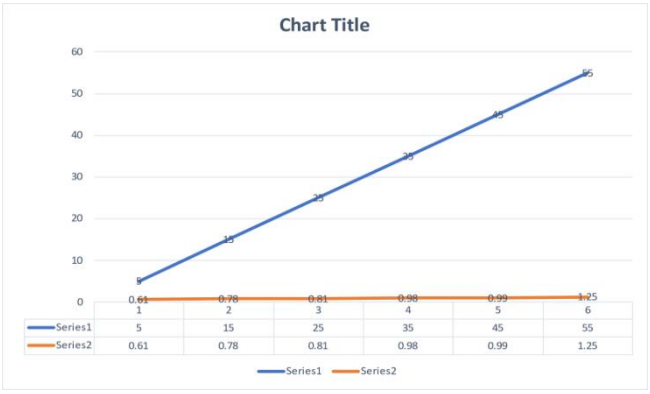
The dissolution conditions used for studying the drug release from the fast Disintegration tablets of Posaconazole were dissolution test apparatus USP type two, speed 100rpm, stirrer paddletype, volume of medium 900ml. Volume withdrawn 5ml, medium used phosphate buffer solution PH 6.8 temperature 37 ± 0.5°C. The vitro dissolution studies of all formulations [F1 to F9] were conducted and the result were presented in the below table.

Time/Min	F1	F2	F3	F4	F5	F6	F7	F8	F9
0Min	0	0	0	0	0	0	0	0	0
5Min	0.58	0.64	0.61	0.68	0.61	0.58	0.72	0.70	0.73
15Min	0.74	0.87	0.78	0.72	0.77	0.69	0.79	0.77	0.89
25Min	0.82	0.92	0.81	0.78	0.84	0.71	0.89	0.88	0.92
30Min	0.89	1.32	0.98	0.88	0.89	0.77	0.94	0.95	0.98
45Min	0.95	1.69	0.99	0.91	0.98	0.89	1.2	0.98	1.5
55Min	1.24	2.05	1.25	1.2	1.8	0.99	1.8	1.1	1.9

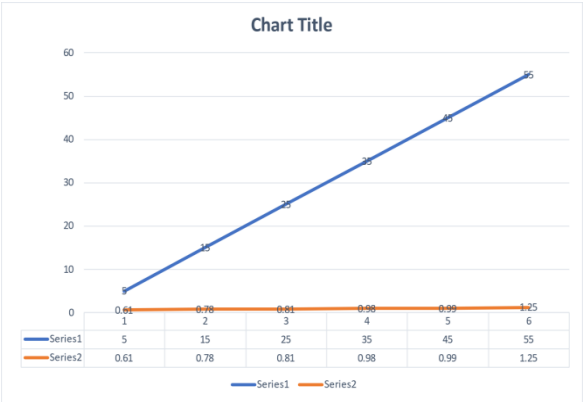
DISSOLUTION GRAPHS



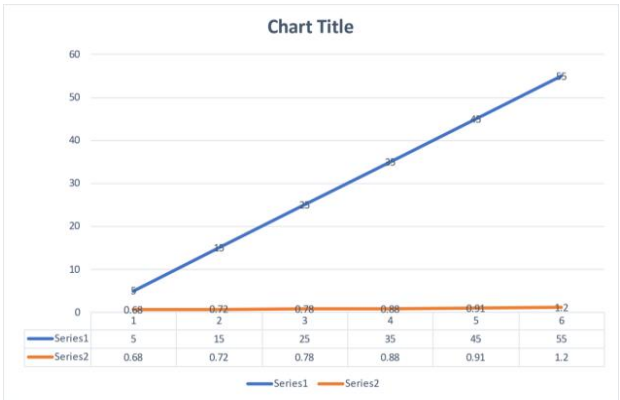
F1 Dissolution graph



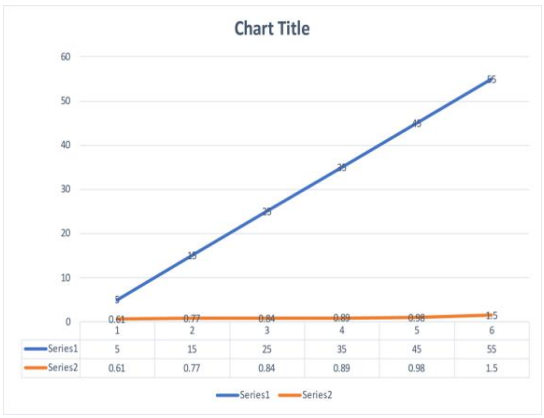
F2 Dissolution graph



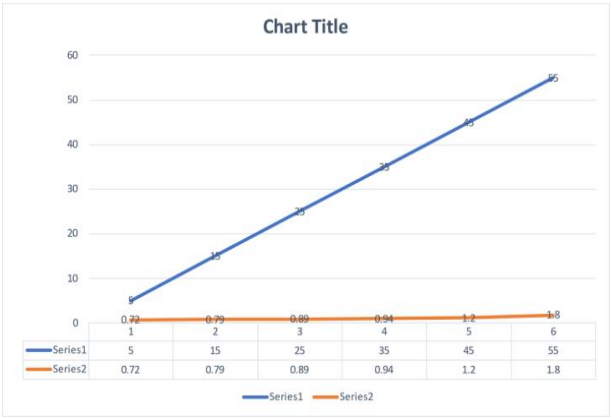
F3 Dissolution graph



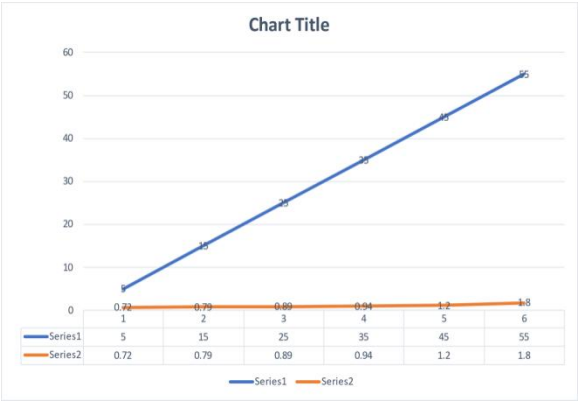
F4 Dissolution graph



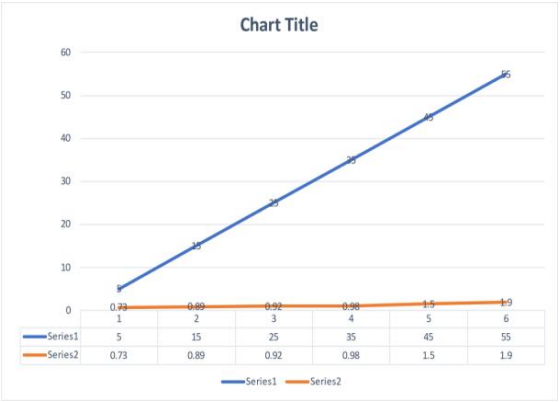
F5 Dissolution graph



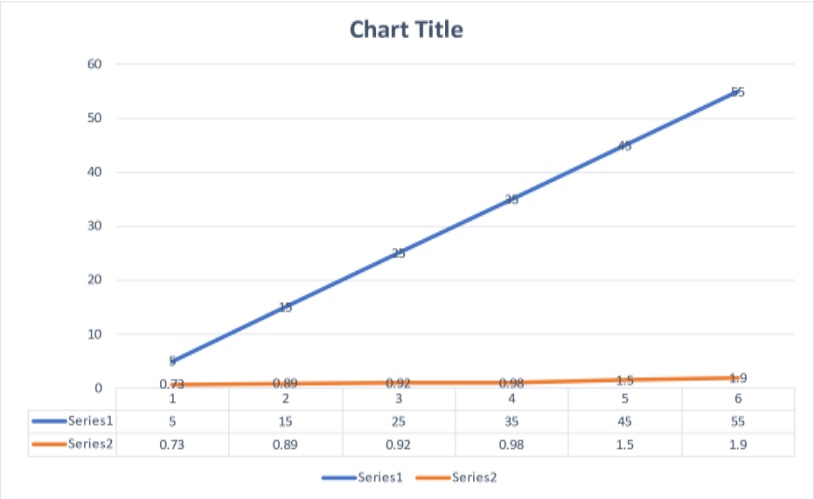
F6 Dissolution graph



F7 Dissolution graph



F8 Dissolution graph



F9 Dissolution graph

Summary

Posaconazole Fast Dissolving Tablets were Prepared with Wet granulation method. Super giant's croscarmellose, crosspovidone & Sodium Starch Glycolate were used along with Excipients. Standard graph shows linearity. Friability (0.25 ± 0.08), Hardness (6.2 ± 0.2) & Thickness (2.6 ± 0.03) are shown within the limits as per Indian Pharmacopoeia. Disintegration shown with Posaconazole Tablets with sodium starch Glycolate was < 15min. Dissolution graphs were found to be satisfactory. FTIR peaks stretching and Bending were found satisfactory no drug polymer interaction.

Posaconazole is soluble in 6.8 phosphate buffer. Posaconazole is a class two drug [High permeability and low solubility]. Evaluation parameters like friability 0.25 ± 0.08 shows within the limits. SSG polymer batch [F8] shown good dissolution and disintegration.

CONCLUSION

Fast dissolving tablets of Posaconazole were prepared by using different super disintegrants croscarmellose, cross povidone, sodium starch gluconate. A total of three formulations were prepared for each super disintegrant. All the physical characteristics of the formulations were found to be well within the limits of official standards. All the time period, when tested for in vitro disintegration time amongst all the formulations, formulation containing sodium starch gluconate is fulfilling all the parameters satisfactorily and has shown fastest disintegration. Over all, the results suggest that suitably formulated fast dissolving tablet disintegration, there by enhance absorption leading to increased bioavailability. FTIR shows no interaction between drug and polymers. Thus, the present study demonstrated potential for rapid absorption, improved bioavailability, effective therapy and increased patient compliance.

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