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Research Article

Formulation and evaluation of Itraconazole granules

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ABSTRACT

The aim of present study is preparation and evaluation of itraconazole granules. Poorly water soluble drugs like itraconazole are chosen for the present study. According to the BCS classification, Itraconazole belongs to class-II category (highly permeable and low soluble drug). Itraconazole is a weak basic drug (pK_a=3. 7) having partition coefficient value of 8.1. Itraconazole is used for the treatment of fungal infections. In this study, The Parameters such as Sieve analysis, Rheological parameters, In vitro dissolution studies, Accelerated stability studies and the Test formulation was compared with marketed formulation are evaluated.

Keywords: Itraconazole; Granules; In vitro dissolution; Accelerated stability studies.

INTRODUCTION

Granulation refers to the process in which primary powder particles are made to adhere to form larger, multiparticle entities called granules. The bonds are formed by compression or by using a binding agent. Granulation is extensively used for the manufacturing of tablets, pellets (M. E. Aulton). Itraconazole is a broad spectrum triazole derivative and chemically it is 4-[4-[4-[4-[[cis-2- (2,4-dichlorophenyl)-2- (1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-methoxy] phenyl] piperazin-1-yl] phenyl]-2-[(1RS)-1-methylpropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (British Pharmacopoeia, 2009). The mechanism of itraconazole acts by inhibiting fungal cytochrome. P- 450 and sterol C- 14 α- demethylation that results in inhibition of cell membrane ergosterol synthesis (William KN et al., 1995). Itraconazole used for the treatment of systemic and superficial mycosis (Gupta AK, 1994). According to Biopharmaceutical Classification Systems, Itraconazole belongs to Class II drug (low aqueous solubility and high permeability) (Martinello VC, 2009). Itraconazole is weakly basic (pK_a=3. 7) and highly hydrophobic (octanol/water partition coefficient at pH=8. 1, log *P*=5. 66) (Fromtling RA, 1987). Itraconazole elimination half life is 20 hrs (Sweetman SC, 2007).

MATERIALS AND METHODS

Itraconazole procured from Metrochem API Pvt. Ltd, Hyderabad, India. Hydroxy propyl methyl cellulose E5 supplied by Ruitai Pharmaceutical Co, China. Crospovidone, Calcium carbonate, Sodium lauryl sulphate were supplied by Loba Chemie Pvt. Ltd. , Mumbai. Tween – 80, Diethyl Phthalate, Isopropyl alcohol are procured from S. D. Fine –Chem. Ltd, Mumbai, India. All other reagents used in this study were of analytical grade.

Formulation of Itraconazole granules

The blended mixtures of compounds formulation of granules were given in table 1.

Method of preparation of Itraconazole granules

Weigh all the Raw materials accurately as given in the formula. The drug solution was prepared by dissolving Itraconazole, HPMC E5 and Crospovidone in a mixture of Methylene dichloride and Isopropyl alcohol. Load the sugar granules into the Fluid bed processor. Spray the drug solution over the sugar granules with the aid of Peristaltic pump. Dry the drug loaded granules and sieved.

Table 1: Formulation of Itraconazole Granules

S. No.	Name of the ingredient	Quantity in gms for 500 grams granules
1	Itraconazole	110. 000
2	Sucrose	175. 000
3	Mannitol	157. 500
4	HPMC E 5	30. 000
5	Calcium carbonate	10. 000
6	Crospovidone	10. 000
7	Tween – 80	2. 000
8	Titanium dioxide	2. 000
9	Sodium lauryl sulphate	3. 500
10	Diethyl Phthalate	Q. S.
11	Isopropyl alcohol	Q. S
12	Dichloromethane	Q. S

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Table 2: Rheological Parameters of Itraconazole Granules

S. NO	PARAMETER	RESULT
1	Bulk density	0.552±0.03
2	Tapped density	0.645±0.32
3	Carr's Index	13.86±2.3
4	Hausner's ratio	1.16±0.0

Evaluation of Itraconazole granules

Incompatibility Studies

The prepared formulation containing itraconazole with HPMC and other excipients blend shows the characteristic peaks of the drug and the excipients blend. This suggests that the absence of any interaction between the drug and the excipients.

Description

The prepared formulations are appeared as white to off white colored granules.

Identification and preparation of calibration curve

Scan the standard solution and test solution, as prepared for Assay estimation, between 220 and 350nm. Both should have same maxima 254 nm.

Sieve analysis

Arrange the sample collector, 20 ASTM sieve and 120 ASTM sieve. Weigh and transfer 100 grams of the sample into 20 ASTM sieve and shake for 5 minutes. Collect the 20 ASTM retains (W_{20}) from 20 mesh and 120 ASTM passes (W_{120}) from the sample collector.

$$\%\ Retains\ on\ 20\ ASTM\ = \frac{W_{20}\ in\ gram}{Weight\ of\ sample\ in\ grams} \times 100$$

$$\%\ Passings\ through\ 120\ ASTM\ = \frac{W_{120}\ in\ gram}{Weight\ of\ sample\ in\ grams} \times 100$$

Moisture content

Standardization of Karl Fischer Reagent

Transfer about 25 ml Methanol into Karl Fischer titration vessel, titrate with Karl Fischer reagent and determine the end point potentiometrically. Weigh accurately about 0. 15g of disodium tartrate and transfer quantitatively into the Karl Fischer titration vessel. Titrate with Karl Fischer-reagent and determine the end point potentiometrically. Note down the volume of Karl Fischer reagent consumed. The strength of Karl Fischer reagent is expressed as water equivalence (mg/ml).

$$Water\ equivalence\ = \frac{Wt.of\ di-sodium\ tartrate\ \times\ 15.66\ \times 1000}{100\ \times\ volume\ of\ KF\ reagent\ consumed}$$

Standardization should be done at least in duplicate. If the values differ by more than 0.5% then third standardization has to be done.

Determination of water

Weigh accurately about 1.5g of sample such that a minimum of 5ml Karl Fischer reagent should be consumed and transfer into the titration vessel containing previously titrated methanol with Karl Fischer reagent. Titrate with Karl Fischer reagent and determine the end point potentiometrically.

$$Water\ (\%)\ = \frac{Total\ Volume\ \times\ Water\ equivalence\ \times\ 100}{1000 \times Wt.\ of\ the\ sample}$$

Rheological parameters

Bulk density

Weigh accurately about 15.0 grams of granules then pour into 20 ml measuring (Nessler's) cylinder and measure the total volume occupied by granules (Sakarkar DM, Kshirsagar RV), (Lachmann H, 1987).

$$Bulk\ density\ (BD)\ = \frac{Weight\ of\ Granules}{Volume\ occupied\ by\ Granules}$$

Tapped density

Weigh 15 grams of granules then pour into 20 ml measuring (Nessler's) cylinder then tap the measuring cylinder for 100 times then measure the total volume occupied by granules.

$$Tapped\ density\ (TD)\ = \frac{Weight\ of\ Granules}{Volume\ occupied\ by\ Granules\ after\ tapping}$$

Hausner's ratio

The ratio between the bulk density and tapped density is called as Hausner's ratio.

$$Hausner's\ ratio\ = \frac{Bulk\ density}{Tapped\ density}$$

Carr's index

$$Carr's\ index\ = \frac{Bulk\ density - Tapped\ density}{Tapped\ density}$$

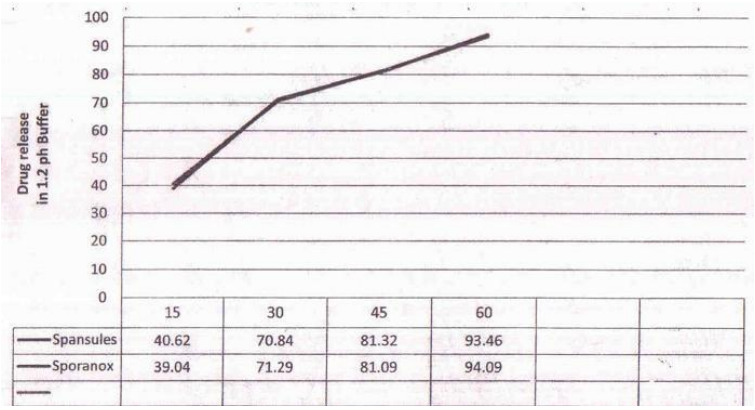
The above evaluated parameters were given in table:2.

***In vitro* dissolution studies**

Weigh accurately the itraconazole granules equivalent to 100mg (466mg of pellets) transfer into each of the six vessels and stirred at 37ºC±2ºC with 100rpm for 60

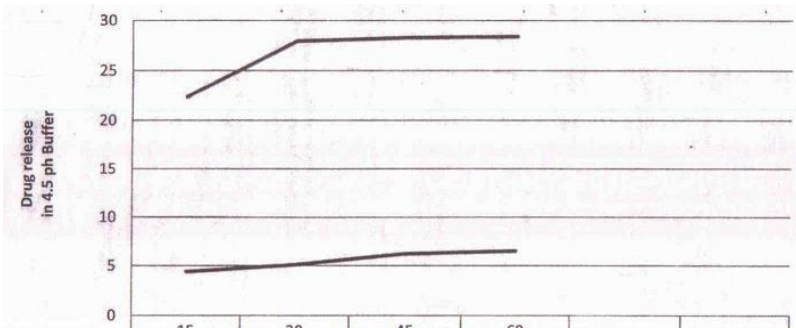
Table 3: Accelerated Stability Studies of Itraconazole Granules

S. No	Description	Moisture Content	Assay	Dissolution	Duration
1	White to off white colored Granules	1.72 %	22.70%	95.45%	0 days
2	White to off white colored Granules	1.70 %	22.58%	95.23%	90 days
3	White to off white colored Granules	1.68 %	22.42%	94.67%	180 days



	15	30	45	60		
Spansules	40.62	70.84	81.32	93.46		
Sporanox	39.04	71.29	81.09	94.09		

Figure 1: Comparative dissolution pattern of Itraconazole 22% w/w Granules in 1. 2 pH buffer



	15	30	45	60		
Spansules	22.37	27.95	28.3	28.41		
Sporanox	4.39	5.1	6.23	6.51		

Figure 2: Comparative dissolution pattern of Itraconazole 22% w/w Granules in 4. 5 pH buffer

minutes using USP XXIII type II apparatus. Collect 25ml sample at 15,30,45,60 minutes from each vessel and filter through Whatman filter paper no. 15 into 6 different test tubes. Discard the first 10ml and transfer 5ml into a 50ml volumetric flask. Add 5ml of methanol and make up to volume with gastric fluid (0.1N HCl, 900ml) without pepsin.

Standard preparation

Weigh accurately about 11.0 mg of itraconazole working standard into a 100ml volumetric flask. Dissolve in methanol and make up to the mark with methanol. Transfer 5ml of the above solution into a 50ml volumetric flask and make up to the mark with gastric fluid without pepsin.

Blank Preparation

Transfer 5ml of methanol into 50ml volumetric flask and make up to mark with gastric fluid without pepsin. Determine the Light Absorption maxima of the standard and test samples using the blank at 254 nm using Schimadzu U. V. spectrophotometer.

$$Dissolution\ \% = \frac{Amt}{Ast} \times \frac{Pst}{100} \times \frac{1}{10} \times \frac{900}{Pmt} \times \frac{50}{5} \times \frac{Pot.Std}{100}$$

Amt = absorbance of sample

Ast = absorbance of standard

Pst = Wt. of standard in milligrams,

Pmt = wt. of sample in grams.

Pot. Std = purity of working standard

Assay

Standard solution preparation

Weigh accurately about100mg of Itraconazole working standard and transfer into a 100 ml volumetric flask. Dissolve and dilute to volume with diluent mixture (Methanol: HCl (99: 1) then transfer 1 ml into a 50 ml volumetric flask and dilute to the volume with diluents mixture.

Test sample preparation

Accurately weigh Itraconazole granules equivalent to 100mg of Itraconazole (450mg of Granules) transfer into a 100ml volumetric flask. Add 50ml of the diluent mixture heat it on water bath for 15 min. Cool and makeup the volume with diluent mixture and filter it. Transfer 1 ml of the filtrate into a 50ml volumetric flask and makeup the volume with diluent mixture and measure the absorbance at 258 nm of the test and standard solutions.

Blank preparation

Take 1ml of the diluents mixture into 50ml volumetric flask and dilute it to the volume with methyl alcohol.

$$Assay = \frac{AT}{AS} \times \frac{WS}{100} \times \frac{1}{50} \times \frac{100}{WT} \times \frac{50}{1} \times P$$

AT	=	Absorbance of test solution
AS	=	Absorbance of standard solution
WS	=	Weight of working standard
WT	=	Weight of test sample
P	=	Potency of working standard
Assay	=	Assay obtained for Granules

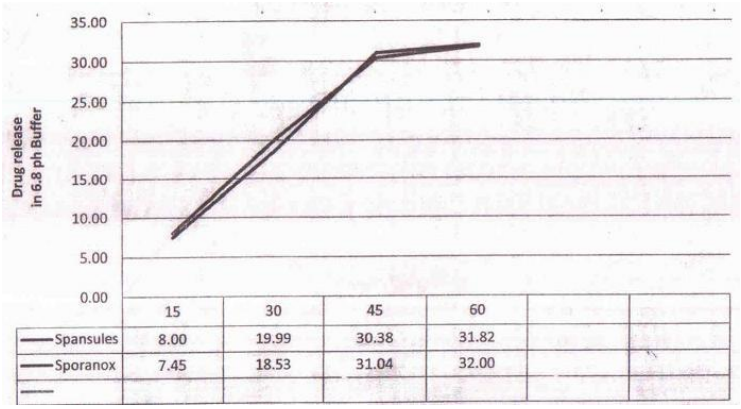


Figure 3: Comparative dissolution pattern of Itraconazole 22% w/w Granules in 6. 8 pH buffer

Accelerated stability studies

The selected formulation was kept at 40°± 2°C with 75 ± 5% RH. Samples of aliquots are collected at 0,90,180 days for evaluation of description, moisture content, assay and in vitro drug release studies (table:3)

The prepared itraconazole formulation was compared with marketed formulation (sporanox). The prepared formulation showing good drug release in 1. 2 ph, 4. 5 ph, 6. 8 ph phosphate buffers.

Following are the comparative dissolution studies graphs of itraconazole (fig:1, fig:2, fig:3.)

RESULTS AND DISCUSSIONS

The standard graph was plotted by taking percentage on x- axis and area on y – axis. This graph providing straight line indicates that the drug solution is showing linearity. From the rheological parameters it was observed that the granules having good flow properties. From the In vitro dissolution studies plots, we observed that as the time increases the % of drug release is increased in the 1.2 pH buffer (0.1 N HCl) and 6.8 pH phosphate buffer. The dissolution profile of selected formulation was compared with marketed formulation. The drug release rate was good when stored under accelerated conditions.

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