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Itraconazole: A literature review on analytical and bio-analytical methods

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Abstract
This review is a collaborative overview of previously published approaches related to the analysis of Itraconazole either alone or in conjunction with other medications. Many spectroscopic approaches have been used, such as derivative techniques, chromogenic techniques. Newly developed and improved chromatographic methods are also available through the use of biological fluids and pharmaceutical formulations. Few LC-MS, GC, GC-MS and HPTLC approaches are also available in addition to these two techniques. World consistency by design or design by professional methodology is now used in this new analytical analysis to get better process validation methods. This succinct analysis work will direct an analyst to select the most suitable approach for designing and validating the best analytical method.

Keywords: chromogenic, LC-MS, GC-MS, Itraconazole

Introduction

A change in human health has occurred as pharmaceuticals advances every day. Impurities may develop in any stage, starting from manufacturing of bulk drug to packaging of finished product and further up to storage. Transportation and storage are the two phases in which impurities may occur frequently. In this condition, thus, impurities must be observed and quantified. Analytical instrumentation and techniques play an important part in identification and quantification [1].

Intermediate pharmaceutical research is an important method for the clinical phase control as it entails multiple stages such as examination of bulk medications, intermediate products, formulations of drugs, degradation products, structural stability of drugs and the toxic quality of drug materials. Itraconazole has a greater range of activity than fluconazole. In specific, it is potent against Aspergillus, which is not fluconazole. It is also approved for use in blastomycosis, sporotrichosis, histoplasmosis and onychomycosis [2].

Itraconazole is over 99% protein-bound and has virtually no penetration into cerebrospinal fluid. Therefore, it should not be used to treat meningitis or other central nervous system infections.

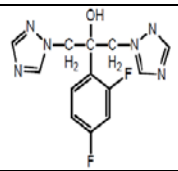
Candida virus is the most widespread source of opportunistic fungal infections worldwide that cause diseases ranging from superficial mucosal infections to spread systemic infections that are frequently life-threatening. Cutaneous Candidiasis or Skin Candidiasis is a fungal infection of the skin caused by candida fungi Epidemiological survey results from India shows that 67 to 90 per cent of cases of nosocomial candidemia were caused by Candida non-albicans of which C. tropicalis was the most dominant. In the last few decades, there have been numerous reports of Candida infections in India [3].

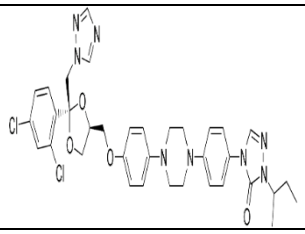
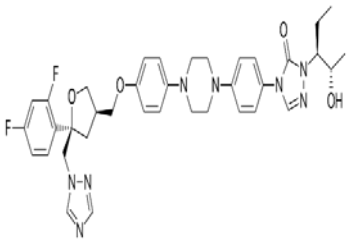
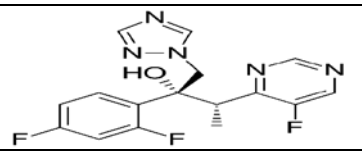
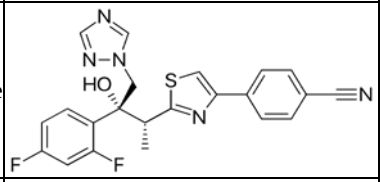
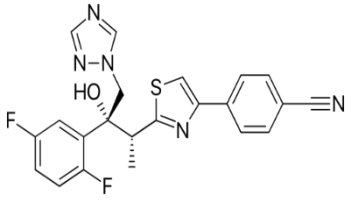
Itraconazole, invented in 1984, is a triazole fungistatic antifungal agent recommended for patients with fungal infections. The medication can be treated orally or intravenously. Itraconazole has a greater range of activity than fluconazole. In specific, it is potent against Aspergillus, which is not fluconazole. The mechanism of action of itraconazole is the same as the other azole antifungals [4].

Triazoles inhibit CYP P450 14 α- demethylase in fungi. This enzyme is involved in the Conversion of lanosterol to ergosterol biosynthesis may be affected. The basic nitrogen of the azole ring forms a tight bond. Ergosterol biosynthesis from squalene. Site of action of triazole antifungals (Fluconazole, Itraconazole, Voriconazole) [5].

They have a lower affinity for mammalian P450's. The effect is fungistatic, but may be fungicidal at higher concentrations. Detail about the Triazole derivatives given in table no.1

Table 1: Details of Triazole Derivatives

Drug	Structure	IUPAC Name	Molecular weight	Solubility
Fluconazole		2-(2,4-difluorophenyl)-1,3-bis(1,2,4-triazol-1-yl) propan-2-ol	306.27 g/mol	Fluconazole is soluble in organic solvents such as ethanol, DMSO, and dimethyl formamide, which should be exclude with an inert gas.
Itraconazole		2-butan-2-yl-4-[4-[4-[4-[[(2*R*,4*S*)-2-(2,4-dichlorophenyl)-2-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl] methoxy] phenyl] piperazin-1-yl] phenyl]-1,2,4-triazol-3-one	705.64 g/mol	The solubility in 0.1N HCl is approximately 4-6 µg/mL and in water is 1-4 ng/mL.

				
Posaconazole		4-[4-[4-[4-[[(3*R*,5*R*)-5-(2,4-difluorophenyl)-5-(1,2,4-triazol-1-ylmethyl) oxolan-3-yl] methoxy] phenyl] piperazin-1-yl] phenyl]-2-[(2*S*,3*S*)-2-hydroxypentan-3-yl]-1,2,4-triazol-3-one	700.8 g/mol	Posaconazole is soluble in Organic solvents such as DMSO and dimethyl formamide. The solubility of Posaconazole in these solvents is approximately 0.5 mg/ml.
Voriconazole		4-[2-[(2*R*,3*R*)-3-(2,4-difluorophenyl)-3-hydroxy-4-(1,2,4-triazol-1-yl) butan-2-yl]-1,3-thiazol-4-yl] benzonitrile	349.3 g/mol	Voriconazole has a low aqueous solubility, its maximum solubility being in acidic conditions
Ravuconazole		4-{2-[(2R,3R)-3-(2,4-Difluorophenyl)-3-hydroxy-4-(1H-1,2,4-triazol-1-yl)-2-butanyl]-1,3-thiazol-4-yl} benzonitrile	437.5 g/mol	Revuconazole is soluble in Organic solvents such as DMSO: 20mg/ml, clear.
Isavuconazole		4-[2-[(2*R*,3*R*)-3-(2,5-difluorophenyl)-3-hydroxy-4-(1,2,4-triazol-1-yl) butan-2-yl]-1,3-thiazol-4-yl] benzonitrile	437.5g/mol	Isavuconazole is soluble in Organic solvents such as DMSO: 2mg/ml, clear.

Itraconzole

From all these Triazole derivatives in this present journal about Itraconazole is discussed briefly.

Itraconazole (ITZ) chemically, 2-butan-2-yl-4-[4-[4-[4-[[(2*R*,4*S*)-2-(2,4-dichlorophenyl)-2-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl] methoxy] phenyl] piperazin-1-yl] phenyl]-1,2,4-triazol-3-one[6]. (Fig.1)

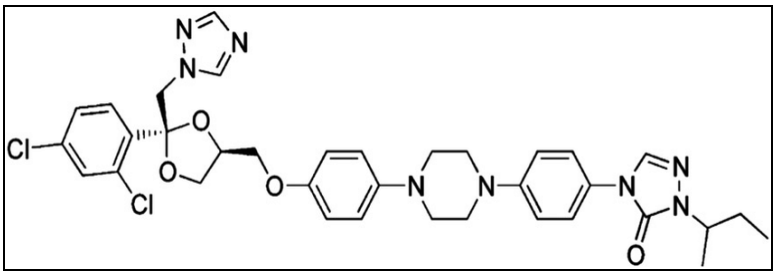


Fig 1: Chemical structure and IUPAC name of Itraconazole.

Its bioavailability 55%, protein binding 99.8%, metabolism via hepatic, biological half-life 21 h and root of excretion through renal. Several analytical methods based on UV, RP-HPLC, LC-MS, GC and GCMS was reported for the pharmacokinetic determination of Itrconazole in plasma and urine of humans, rats and dogs [7].

This review paper focuses the analytical procedure available for the estimation of itraconazole i.e., electrochemical methods, UV/VIS- spectrophotometric methods, HPLC/LC-MS, GC-MS, The details about the previous studies are discussed in Table no. 2, 3, 4, 5 and 6.

Table 2: Summery of methods related to HPLC technique

S. No	Stationary phase	Mobile phase	PH	Wavelength	Flow rate	Reference
Itraconazole with Terbinafine						
1	C18(250mmx50mm,5um)	Mixture of Acetonitrile& Triethalamine (90:10)	--	225nm	1.2ml/min	8
Itraconazole with Hydroxy Itaconazole						
2	C18(250mmx4.6mm)	% triethylamine solution adjusted to pH 2.8 with orthophosphoric	2.8	264nm	1.0ml/min	9

		acid–acetonitrile (46:54)]–isopropanol (90:10, v/v)				
Itraconazole						
3	C18,5um column(250x4.6mm)	Tetrabutyl ammonium hydrogen sulphate buffer solution and acetonitrile (40:60v/v)		225nm	1.5ml/min	10
4	C18 column,150mmx4.6mm,5um	0.08M Tetra butyl ammonium hydrogen sulphate &Acetonitrile (65:35)	--		1.5ml/min	11
5	C18 column,1.8um(4.6x50mm)	0.08M Tetra butyl ammonium hydrogen sulphate buffer and Acetonitrile (80:20 v/v)		235nm		12
6	C18column 150x4.6mm,5um	Buffer: Acetonitrile (65:35)		225nm	1.5mi/min	13
7	C18 column (250mm,4.6mm,5um)	Acetonitrile and glacial acetic acid (50:50v/v)	5	264nm	1ml/min	14
8	C18-HS (250x4.6mm)	Acetonitrile and double distilled water (90:10)	--	263nm	1.0mi/min	15
9	C18 column (100x2.1mm,1.7um)	Triethalamine buffer&Tetrahydro furan (50:50)	2.5	260nm	0.4ml/min	16

Table 3: Summery of Analysis of Itraconazole by UV-Spectroscopy methods

S. No	Drug	Method	Description	Reference
1	Method Development and Validation of Itraconazole	Uv-Spectrophotometer	Detection wavelength: 267 nm in Methanol Linearity range: 0.2-1.0µg/ml Co-relation Co-efficient: 0.991% Recovery range: 99.5-100% RSD: ≤0.2%	17
2	Estimation of Itraconazole Bulk Drug and Pharmaceutical Formulation	Uv-Spectrophotometer	Detection wavelength: 262 nm in Methanol Linearity range: 4-14µg/ml Co-relation Co-efficient: 0.991% Recovery range: 99.11-101.18% RSD: ≤0.1%	18

Table 4: Summery of Analysis of Itraconazole by LCMS methods

S. No	Stationary phase	Mobile phase	Flow rate	Reference
Itraconazole with Hydroxy Itraconazole				
1	Rod RP-18e column (50 mm × 4.6 mm)	10 mM ammonium formate buffer (pH 4.0): methanol (20:80, v/v)	0.6 ml/min.	19
2	HyPurity C18 (50 mm × 4.6 mm, 5 m) column	ammonia solution: acetonitrile (20:80, v/v)	0.50 mL/min	20
Itraconazole				
3	Hypersil Gold (50x4.6) mm, 3µ column	methanol: buffer solution (90:10, v/v)	0.500 mL/minute	21

Table 5: Summery of Analysis of Itraconazole by GC methods

S.no	Stationary phase	Mobile phase	Flow rate	Reference
1	ZB-624, 30m length, 0.53 mm internal diameter, and 3.0 um	Nitrogen	3.0ml/min	22

Table 6: Summery of Analysis of Itraconazole by GCMC methods

S.no	Stationary phase	Mobile phase	Flow rate	Reference
1	ZB-5MS, 30 m × 0.25 mm × 0.25 µm	Helium	1.0 mL/min	23
2	ZB-5 ms 30 m × 0.25 mm × 0.25 µm column,	Helium	1.0 ml/min.	24

Quality by Design

For improving the analytical method presently Quality by Design technique is used widely. Quality by design (QBD) which is discussed in ICH Q8, Q9 and Q2 is well established for the development and manufacture of pharmaceuticals [25].

Benefits of Quality by Design Method

It helps in the development of a robust method. As per design setup sources of variability can be better controlled. Method Transfer success is greater when a method is transferred from research level to quality control department [26]. This methodology gives room for the invention of new methods by continual improvement over the life cycle [27].

Conclusion

This review did illustrate the various Spectrophotometric as well as the Chromatographic methods. Thus, the development and due validation for estimation of Itraconazole was done. According to this review it was concluded that for Itraconazole different Spectroscopic & Chromatographic methods are available for single component as well as for combination and also it was found that the mobile phase containing phosphate buffer, methanol and acetonitrile were common for higher of the chromatographic method to provide more resolution. It was observed that most common combination of Itraconazole was with Voriconazole (ex. SPORANOX). For chromatographic method flow rate is observed in the range of 0.4-1.5 ml/min to get good retention time. For higher of the Spectroscopic methods common solvent is Methanol. Hence this all methods found to be simple, precise, accurate, economic, and reproducible in nature. But from this review it was clear that available methods can be improved by using Design of Expert (DOE) technique, which will give more accurate and precise result.

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Conflict of interest

The authors declare that they have no conflict of interest.

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