REVIEW ARTICLE

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A Short Review on Analysis of Itraconazole in Bulk Drug and in Pharmaceutical Dosage Form

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Abstract: Itraconazole (ITZ) is an antifungal triazole, used to treat systemic and superficial fungal infections. Its clinical effectiveness is limited due to its low water solubility which results in poor bioavailability. Therefore, there is a need to develop a trailblazer formulation capable to enhance solubility, dissolution and bioabsorption of ITZ for better topical and systemic use. In context to this, this review represents the summary of physicochemical characteristics, various nano dosage forms and analytical methods utilized for ITZ. The quantifications of ITZ have already been published in various kind of literature with a special focus on UV-Vis spectrophotometric, spectrofluorometric, HPLC and other hyphenated techniques. Numerous parameters like λmax, solvents, stationary phase, mobile phase, retention time, column have been demonstrated. This concise report reveals all the analytical methods already used with its important parameters for the estimation of ITZ that will benefit researchers and contribute to the existence in this area.

INTRODUCTION

Itraconazole (ITZ) is an antifungal drug that is orally potent. The powder is white or nearly white, chemically 4-[4-[4-[[cis-2-(2,4-dicholorophenyl)-2-(1H-1,2,4-triazole-1-ylmethyl)-1,3dioxolan-4-yl]methoxy]phenyl]piperazine-1yl] phenyl]-2- [(1RS)-1methylpropyl] -2,4-dihydro-3H-1,2,4-triazole-3-one] accompanied by molecular formula $C_{35}H_{38}Cl_2N_8O_4$ and molecular weight 706 gm/mol, it's chemical structure given below in Figure 1.

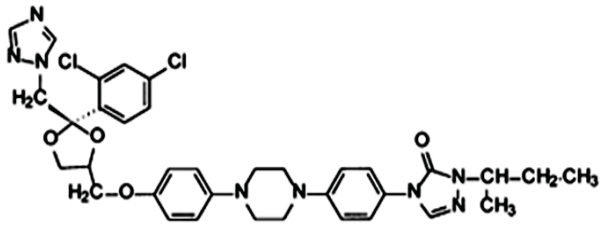

Figure 1: Chemical structure of itraconazole

It is water-insoluble, alcohol very slightly soluble and dichloromethane freely soluble. The log(s) (n-octanol/water) coefficient at pH 8.1 is 5.66. It contains a pKa of 3.7, which results in the extrapolation of values from the methanol solutions. The medicine may be administered orally or intravenously. It has been used for a wide spectrum of fungal species including dermatophytes, malassesic furfur, Aspergillus species, Candida species and Histoplasmos Capsulatum var. Capsulatum. ITZ mechanism of action concerns binding fungal cytochrome P-450 by inhibiting ergosterol synthesis, an essential component of the diagnosis in spreading fungal and yeast colonies and by disrupting membrane enzymes and membrane permeability. Through the enzyme CYP3A4, ITZ is metabolized primarily into three active metabolites, such as hydroxy-itraconazole, keto-itraconazole and N-desalkylitraconazole. It was used as a tool to confirm the potential of medicament-based interactions with several substrates, such as simvastatin, lidocaine, tacrolimus, sirolimus, etc. and is a potent inhibitor of CYP3A4 isozyme. [1-3]

OFFICIAL METHOD OF ITZ

As per the Official method in British Pharmacopoeia 2019 for ITZ Capsule the column used is Phenomenex Prodigy ODS (2) (150mm*4.6mm*5µm) having mobile phase Acetonitrile:0.01M potassium dihydrogen orthophosphate (Previously adjusted to pH 3.0 with orthophosphoric acid) 48:52. The flow rate is adjusted to 2.0 ml/min with column temperature 40°C and injection volume is 15 µl. The detector used for the method is UV Detector at wavelength 254nm. [4] ITZ is also official in the United State Pharmacopoeia 2019. [5]

NANO DRUG DELIVERY SYSTEM OF ITZ

Several techniques have been utilized for the solubility and permeability improvement of poorly water soluble drugs including crystal engineering approaches, particle size reduction, multi-component formation, polymorphism etc. among the various techniques, nano drug delivery has its potential value for the enhancement of various physical and chemical properties. [6-9]

Shadambikar *et al.*, [10] discussed that the hot-melt extrusion (HME) and the sonification of the probe were used for the preparation of pegylated ITZ nano lipid carrier (NLC). By optimizing HME parameters such as screw speed, screw design, barrel temperature, continuous production of NLCs can be achieved. The use of this method minimizes problems and differences associated with conventional nano-formulation batch methods. Our experiments have shown that process parameters affect formula quality, with pre-emulsion determining the final quality of the formulation in large part. A formula method for nanoscale particle preparation was developed with high trapping efficiency and NLCs with good aerosole properties. Without aggregation and agglomeration, the formulation was nebulized. The drug was found to be non-toxic to pulmonary epithelial cells. The spherical nature of the particles was shown by TEM. So, they conclude that ITZ formulations of PEGylated nanoparticles made with HME technology are considered to be a potential pulmonary drug delivery system with scalability in manufacturing.

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Yadav *et al*., [11] described that the purpose of the study is to enhance the dissolution rate and to develop the ITZ solid powder. The main ingredients for the formulated self-nanoemulsifying drug system were Cottonseed oil, Tween 80 and Transcutol. These formulations are characterized for thermodynamic stability, emulsifying rate, dilution and pH-effect ruggedness, size of the globules, zeta potential, in vitro studies, etc. Formulation obtain is with globule size 141.20±0.69 nm in size, PDI 0.29±0.04, zeta potentials 11.2±0.69 mV in size and fast dissolution, with more than 90% of drugs released within 30 minutes. Further optimized formulation cytotoxicity studies have revealed a safe formulation. It has been further identified, assessed and accepted for the results obtained. The solid self-nanoemulsifying formulation and the liquid self-nanoemulsifying formulation of the in vitro product are almost identical. Therefore, they concluded that implementing this strategy's approach might be seen as an alternative.

ITZ nanosuspension was produced by solvent-antisolvent nanoprecipitation method at various ratios combined with the drug alone (tween 80, SLS) was developed by researchers. [12] The results show that nano sizes were found for the particle sizes of all formulations made with ITZ. So, they concluded that a particle size of 42 nm and a Zeta of 21.86 mV have the most suitable formula. *In-vitro* cumulative release of nano-suspension (88%) was at (30) min when compared to pure (13%) and nanoparticles (98.5%) were at (30) min.

Kumar and his [13] team nicely explained that the aim was to develop nano-amorphous spray-dried ITZ powders to strengthen their oral bioavailability. A solvent-antisolvent precipitation, then spray drying approach was taken. The essential quality attribute was particle size. Spray drying with several auxiliary excipients of the nano-precipitated formulation to obtain amorphous nano-sized powder formulations. Lower drug concentration was obtained from the smallest precipitates. All auxiliary high molecular excipients and formulations containing mannitol during spray drying were unstable and crystallized. Disaccharide formulations were amorphous and non-aggregating. The superior performance of nano-amorphic formulations was demonstrated by *in-vitro* dissolution tests and *in-vivo* tests compared to amorphous melt-quench amorphous and crystalline ITZ formulations. Compared to macro-amorphous powders, this study shows superior oral bioavailability of nano-amorphous powders. They concluded that the nanocrystalline formulation was similar to the nanocrystalline formulation but showed a faster absorption profile.

Zheng *et al*., [14] studied the drug loading transferosomes have been prepared with the lipophilic ITZ as a model medicine to assess and evaluate the key element of transferosome quality. Transferosomes for drug loading were prepared using the method of film scattering. HPLC, transmission microscope electron, particulate size analyzer and *in-vitro* releases assessed the quality of transferosomes. ITZ transferosomes were a transparent ivory white solution with a mean capture efficiency of around 80%, with a diameter of approximately 100 nm and zeta potential of 45 mV, the form of hollow vesicles was spheroidal and had a good transdermal effect. It may be concluded by one-factor research those solvents, salt ion concentrations and homogenization pressure are significantly affected by the quality of transferosomes, etc. It is possible to use the preparation method obtained by screening and optimizing formulations and technology and to control quality.

Badawi and other co-workers [15] discussed that the crystalline nanoparticles of ITZ were prepared using a relatively simple, cheap sonoprecipitation technique in which organic in nature were both solvent and anti-solvent. The effects (oven and frosted drying) and formerly used matrix (Avicel PH101 and Aerosil® 200) on the dissolution performance were evaluated as key characteristics for nanocrystalline stabilizing type, such as hydroxypropyl-methylcellulose, hydroxypropyl cellulose, Inutec SP1® and F127. In 10 minutes, all of the prepared nanocrystals showed that the dissolved drug was 3.77–8.59 times better than that of pure ITZ. The following rank order can be given for the effect of the stabilizer type: pluronic F127 ≥ hydroxypropyl cellulose ≥ hydroxypropyl methylcellulose (HPMC) > inutec SP1. The freeze-dried Avicel PH-101 ITZ nanocrystals showed a better rate of dissolution than other nanocrystals. They conclude from Fourier transform infrared method that the chemical structure of the nanocrystals of ITZ has not been modified.

Burapapadh *et al*., [16] studied nanoemulsions with ITZ, a poorly water-solvent drug-using pectin as a polymer emulsifying agent. Nanoemulsions have been prepared to prevent high pressure through simple homogenization. The effects on the droplet size, morphology and zeta potential of pectin-based emulsions were also examined by type of internal phase and pectin concentration. Nanoemulsions were achieved in the internal phase of chloroform while caprylic/capric triglycerides can only produce micron-sized emulsions. Because of the high number of hydrophobic molecules, pectin with high esterification offered good emulsion properties. With increasing pectin concentration, the droplet size of the emulsions decreased. To achieve the nano-size emulsions arising from the molecular association between pectin and ITZ, the addition of ITZ to the emulsion formulation was essential. 3% (w/w) pectin appears to have the highest percent creaming of the most stable emulsion. The nanoemulsions obtained may subsequently be developed as a drug system self-emulsifying.

Chivate and his team [17] described in his study that Kollicoat® Smartseal (1st water-based polymer dispersion) for taste masking and moisture barrier and also having ability to form solid dispersion. In this study, the purpose of this work was to verify their feasibility to improve pharmacokinetic action *in-vivo* comparison with the ITZ model like high melting point. *In-vivo* performance in rat's solid dispersions of ITZ were prepared, identified and tested. The findings revealed that a good thermoplastic behaviour of 120°C–220°C was present. The plasticizing effect of ITZ was on the carrier. The *in-vitro* results showed

Table 1: Analytical Data for Reported Spectrophotometric Methods

S. No.	Drug	Matrix	Solvent/ Reagent	Detection (nm)	Linearity (µg/ ml)	LOD (µg/ml)	LOQ (µg/ml)	Ref
1	ITZ	Bulk Drug	Methanol	262	4-14	2.6	7.8	[2]
2	ITZ	Amorphous Solid Dispersion	0.1N HCl: 0.2N Na3PO4 (3:4 V/V)	263	0.04-40	10	25	[18]
3	ITZ	Bulk and Capsule	Potassium Buffer/ Methanol **Method A** Zero Order	255	5-60	0.39	1.19	[19]
			Method B First Order	270	5-60	0.66	2.01	
4	ITZ	Bulk and capsule	Acidic Ethanol	262	2-12	0.785	2.38	[20]
5	ITZ	Bulk and capsule	Methanol	262	2-14	0.175	0.531	[21]
6	ITZ	Drug	**Method A** Ferric Chloride (0.033M) 1,10 Phenanthroline (0.1M)	520	12.5-75	1.4	4.33	
			Method B Ferric Chloride (0.033M) 3-methyl- 2-benzothiazoline hydrazine	630	25-200	6.4	19.6	[22]
7	ITZ	Drug	Acetonitrile	259	0-20	0.55	1.6	[23]

that the solubility was 20 times higher than ITZ. The results of thermal analysis promote an amorphous forming possibility of a solid solution. As a carrier to be used in HME for solutions to enhance highly insoluble drugs like ITZ, Kollicoat® Smartseal has shown a high potential. It did not present any processing difficulties and the results were well supported by *in-vitro* studies.

ANALYTICAL METHODS

UV/VIS Spectrophotometric Methods

In the laboratories where modern and high-priced devices such as those required for GC or HPLC do not exist spectrophotometric methods may be used to determine drugs. These methods, particularly for developing countries, are versatile and economically. The advantages are severe such as simple, easy and cost-effective, as well as less time-consuming than other methods. The spectrometric methods are available to quantify ITZ as one entity are described in Table 1.

Spectroflourometric Methods

In addition to the UV visible spectrophotometric method, the spectrofluorimetric method of ITZ has also been estimated. [24, 25]

For the determination of ITZ in Pharmaceuticals and biological fluids, a highly sensitive fluorometric method was developed. The proposed method was based on the measurement of the indigenous fluorescence intensity of ITZ accurate in methanol at 380 nm following a 260 nm excitation. The lower detection limit is found to be 0.05µg/ml and the fluorescence intensity vs. concentration plot was equilateral over 0.2 to 2.0 µg/ml. [26]

Elimansi and his [27] team quantified of ITZ in combination with terbinafine in the biological matrix. The assessment was based on the increase in the spectrofluorometric selectivity, allowing for the successful estimation of terbinafine at 257nm and ITZ at 319 nm. For both drugs over a range of 0.1–0.7 µg/ml for terbinafine and 0.5- 4.0 µg/ml for ITZ, ICH validation guidelines have been observed for the fully validate the method and linearity have been obtained. Detection limits for both terbinafine and ITZ were down to 0.013 and 0.1 µg/ml and quantify limits were 0.04 and 0.032 µg/ml respectively.

High-Performance Liquid Chromatography

HPLC is represented by different analytical methods. These are the most popular quantitative chromatographic method drug(s). HPLC is also one of the most confident methods characterized by its precision for quantification, sensitivity and roughness. [28] Table 2 mentions the available HPLC methods for Individual drug ITZ quantification.

High Performance Thin Layer Chromatography

Instrumental planar chromatographic methods for qualitative as well as quantitative drug tests are seen as reliable, fast and precise; this proves to be an alternative method for drug testing. [46] Few HPTLC methods for determining the ITZ alone are available.

Parikh *et al*., [47] have developed an HPTLC method for the analysis of ITZ in bulk drugs and pharmaceutical formulations. The stationary phase consisted of Silica Gel 60 F_{254}.TLC plates with a mobile phase of Toluene: Chloroform: Methanol in the ratio 5: 5: 1.5 v/v. The densitometric detection was done at 260 nm and the Rf value was found to be 0.52±0.02. Linearity was between 1,000 and 6,000 ng/band. The limit of detection and the limit of quantification were 180.29 and 546.34 ng/band, respectively.

Mirza *et al*., have developed an HPTLC method for the analysis of ITZ in bulk drug and pharmaceutical formulations. The stationary phase consisted of Silica Gel 60 F_{254}. TLC plates with a mobile phase of Toluene: Ethyl

Table 2: Analytical Data for Reported High Performance Liquid Chromatography Methods of ITZ

Matrix	Column	Mobile Phase	Wavelength (nm)	Flow Rate (ml/min)	LOD (µg/ml)	LOQ (µg/ml)	Ref
Human Pediatric Serum	Summetry C-18 (150mm×3.9mm, 5µm)	Methanol:water (75: 25V/V)	250	1	0.75	0.4	[29]
Capsule	Inrtsil C-18 (250mm×4.6mm, 5µm)	Terrtabutyl ammonium hydrogen sulphet buffer: CAN (40:60V/V)	225	1.5	0.85	2.60	[30]
Capsule	C-18G Column (250mm×4.6mm, 5µm)	ACN:AcOH 0.1% (50:50V/V)	264	1	0.4389	1.342	[31]
Dosage form	Thermohypersil BDSC-18 (150mm×4.6mm, 5µm)	Buffer:ACN (65:35V/V)	225	1.5	0.85	2.60	[32]
Capsule	SurfireC-18 (150mm×4.6mm, 5µm)	ACN: ultrapure water (70:30V/V)	262	0.8	0.06	0.125	[33]
Capsule	HiQSil C18-HS (250mm×4.6mm, 5µm)	ACH:water (90: 10V/V)	263	1	0.335	1.165	[34]
Impurities	ZorbaxEclipseX DB-C18, (150mm×4.6mm, 5µm)	ACN:o-phosphoric acid (50:50V/V)	256	1	0.1	0.05	[35]
Capsule	Kromasil C- 18 (250mm×4.6mm, 5µm)	[ACN-buffer (54:46)] -2-propanol (50:50V/V)	264	1	-	-	[36]
Dosage form	Dionex C-18 (250mm×4.6mm, 5µm)	Methanol: pH 7.5 potassium dihydrogen phosphate (40.60V/V)	306	1.5	1.859	6.167	[37]
Capsule	RSiL C-18 (150mm×2.1mm, 5µm)	Water:CAN (40:60V/V)	254	0.5	1	-	[38]
Emulsion	C18 analytical column	ACN: phosphate buffer saline 0.05M (60: 40 V/V)	190	1	0.86	2.60	[39]
Human Serum	C18 analytical column	Cold ACN	-	-	0.25	0.50	[40]
Human Serum	Zorbax SB-C18, 5µm	50mM Phosphate buffer (pH 6): ACN: Methanol (35: 45: 20 V/V)	255	1.7	0.03	0.1	[41]
Human Serum	A Genesis CN Column (250mm×4.6mm, 4µm)	0.02M Potassium dihydrogen phosphate: ACN (1: 1 V/V) (Adjust pH 3)	260	0.9	-	0.003	[42]
Human Plasma	Develosil C-18 (150mm×4.6mm, 4.6µm)	Phosphate buffer:ACN (35:65V/V)	263	0.9	-	0.003	[43]
Human Plasma	Bondapak RadialpakC-18 (100mm×8mm, 4µm)	Methanol: water (80:20V/V)	261	2	0.25	-	[44]
Capsule	Thermohypersil BDS C-18 (150mm×4.6mm, 5µm)	ACN: buffer (35:65V/V)	260	1.5	-	-	[45]

acetate: Ammonia in the ratio 1: 5: 0.1 v/v. The densitometric detection was done at 266 nm and the Rf value was found to be 0.77 ± 0.02. Linearity was between 50 and 2000 ng/band. The limit of detection and the limit of quantification were 14.29 and 43.31 ng/band, respectively. [48]

Liquid Chromatography–Mass Spectroscopy (LC-MS)

A quick and highly sensitive method for the determination of ITZ in human plasma and rat plasma has been validated and applied for pharmacokinetic and bioequivalence studies in humans and rats and their data are estimated as per Table 3.

Table 3: Analytical Data for Reported LC/MS Methods

Drug	Matrix	Stationary Phase	Mobile Phase	Flow Rate (ml/min)	Retention Time (min)	Ref
ITZ	Human Plasma	HyPurity C-18 (50mm×4.6mm ×5mm) column	Ammonia Solution: ACN (20:80 v/v)	0.50	2.08	[49]
ITZ	Human Plasma	YMC hydrosphere C-18 (50mm×2mm × 3mm) column	ACN:1mM Ammonium Acetate (90:10v/v)	0.25	0.9	[50]
ITZ	Rat Heparinized plasma	BDS Hypersil C-18 (50mm×2mm × 3mm) column	10mM Ammonium formate (pH 4): ACN (60:40v/v)	0.3	2.48	[51]
ITZ	Human Plasma	TSKgel ODS-100V (75mm×2mm, 3µm)	ACN: Ammonium Acetate 5mM (pH6) (57:43 V/V)	0.2	7	[52]
ITZ	Human Plasma	Hypersil Gold C18 column (50mm×2.1mm,1.9µm)	0.1% Formic acid: ACN (45:55V/V)	0.34	3	[53]

Table 4: Analytical Data for Reported GC/MS Methods

Drug	Matrix	Stationary Phase	Mobile Phase	Flow Rate (ml/min)	Ref.
ITZ	API	ZB-5 MS, (30m*25mm*0.25µm)	Helium	1	[54]
ITZ	API	ZB-5 MS, (30m*25mm*0.25µm)	Helium	1	[55]
ITZ	API	ZB-324 (30m*0.53mm*3µm)	Nitrogen	3	[56]

Gas Chromatography–Mass Spectroscopy (GC-MS)

Gas chromatography is a technique that vaporizes the mixture of the sample into gaseous agents and separates them on a porous solid or liquid support based on the boiling point of the agents and their differential adsorption. It is widely applied in many industries such as forensics, food, environmental testing, pharmaceuticals, petrochemical products, pesticides and fragrances, molecular weight and volatile compounds. Table 4 mentions the available GC-MS methods for individual drug ITZ quantification.

DISCUSSION

ITZ has made a remarkable contribution since its approval as a member of the triazole drug group. The dosage form in pharmaceuticals, namely capsules, injections and oral solutions are available in market. Due to limited solubility and dissolution, there is a need to develop a trailblazer formulation capable to enhance solubility, dissolution and bioabsorption of ITZ for better topical and systemic use. Regarding to this, the review summarized the physicochemical characteristics and various nano dosage forms namely nanoparticles, nano lipid carrier, self-nanoemulsifying and nanosuspension. This manuscript also demonstrated various analytical techniques for the quantification of ITZ in different pharmaceutical formulations and in biological samples. For the determination of the ITZ as a bulk drug and in drug formulations, UV-Vis spectrophotometric techniques are most commonly used. In combination with spectrophotometric methods, it was observed that the variable number of solvents were utilized for estimating ITZ. Notable methods have been reported for estimation in combination with other drugs by HPLC in pharmaceuticals and a few numbers of LC/MS methods are available for estimation of the drug in biological fluid.

CONCLUSION

In the current review, the available analytical methods forthe ITZ estimation from various kind of literature include a wide range such as UV-Vis spectrophotometry, spectrofluorometric, HPLC and various hyphenated chromatography technique over the last decade. Several parameters like λmax, solvents, stationary phase, mobile phase, retention time, column have been demonstrated. Finally, the analyst and experienced formulators will soon strive to develop more environmentally friendly methods for estimating the ITZ using fewer toxic solvents.

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