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A Review on analytical techniques for the estimation of Posaconazole in pharmaceutical dosage form

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ABSTRACT

Pharmaceutical drugs play a vital function in human existence by aiding in the treatment of various disorders. As a consequence, developing analytical methods has become the primary activity of analysis. People have been searching for safe and effective ways to cure viral infections since ancient times. Due to the emergence of new fungal infections, the discovery of medications for their treatment is becoming equally important in the contemporary context. These medications should be validated before they are released to the market. High-performance liquid chromatography (HPLC) in conjunction with ultraviolet (UV), photodiode array detectors (PDA), mass spectrophotometer (MS) detectors, and other technologies is one of the quickest, safest, and most precise methods for determining and separating pharmaceutical drugs, impurities, and biological samples. When compared to older liquid chromatography techniques, HPLC is more flexible and takes less time to quantify pharmaceuticals. Posaconazole is a triazole antifungal drug that is used to treat invasive infections by Candida species and Aspergillus species in severely immunocompromised patients. The current research demonstrated that the HPLC technique, as well as the spectroscopic approach, has been the most commonly examined for analysis. The investigatory review may give thorough facts to researchers functioning in the Posaconazole analytical study.

Keywords: Posaconazole, HPLC, Spectroscopy, LC-MS, Pharmaceutical analysis.

INTRODUCTION

Pharmaceutical analysis is a branch of practical chemistry that involves a series of process for identification, determination, quantification and purification of a substance, separation of the components of a solution or mixture, or determination of structure of chemical compounds. The substance may be a single compound or a mixture of compounds and it may be in any of the dosage form. The substance used as pharmaceuticals are animals, plants, microorganisms, minerals and various synthetic

products[1,2]. The main goal of the pharmaceutical industry is to provide drug products with sufficient quality, efficacy and safety.The development of a new drug product and its production consist of many pharmaceutical processes, including analytical testing. The analytical data generated support further decisions on how development should be pursued or provide information on whether a drug product should be released[3].Analytical methods are among the most critical processes in drug product development and production. They play a key role in supporting other development and production processes throughout all stages of a drug product's life cycle. It is essential that an analytical method be precise, accurate and reliable, making it suitable for its intended purpose[4,5].

In most situations, the separation of analytes present in a sample is the main operating principle of an analytical procedure. Liquid chromatography methods, such as HPLC or UPLC, are most typically used, generally in reversed-phase mode with UV absorbance detection. The goals of analysis vary based on the quantity, significance, and relationship of analytes that must be identified. The most often used analytical procedures are those for assaying an active pharmaceutical ingredient (API) or determining its associated compounds and degradationproducts[3,4]. An analytical technique for determining stressed condition maintained products must be capable of detecting their rise during the product's shelf life, and the assay method must be capable of detecting any reduction in the drug substance's content during the product's shelf life. Such approaches are used to indicate stability[7-9].

Since 2000, the most of medications available to treat fungal infections has grown by 30%. However, variations in the antifungal spectrum of activity, absorption, formulation, drug interactions, and adverse effects necessitate a thorough understanding of each medication class[11,12,13]. Posaconazole is a potent triazole antifungal agent used in the prevention of invasive fungal infections due to aspergillosis and candida in high risk patients. Posaconazole therapy is associated with transient, asymptomatic serum aminotransferase elevations and is a suspected but rare cause of clinically apparent acute drug induced liver injury[10]. It is approved for the prevention of invasive Candida and Aspergillus infections in immune-compromised individuals, patients with hematologic malignancies with extended neutropenia following chemotherapy or hematopoietic stem cell transplant-tation recipients with graft versus host disease. Posaconazole is thought to block lanosterol 14-demethylase, an enzyme that converts lanosterol to ergosterol, an important component of the fungal cell membrane[14].

Chemically Posaconazole is known as 4-{4-[4-(4-{[(3R,5R)-5-(2,4-difluorophenyl)-5-(1H-1,2,4-triazol-1-ylmethyl)-tetrahydrofuran-3l]methoxy}phenyl)piperazin-1-yl]phenyl}-2-[(1S,2S)-1-ethyl-2-hydroxy-propyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Figure. 1), is a triazole antifungal drug, approved by the FDA in 2006 and characterized for the broader spectra of action between triazoles, besides the less potential of interactions.It is the first azole agent to demonstrate activity against the zygomycetes, a difficult-to-treat family that includes Mucor and Rhizopus species[12,15].

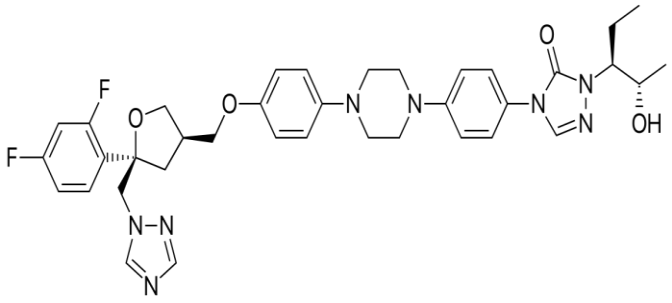

Fig 1: Structure of Posaconazole

Quantitative & Qualitative Analytical Techniques for Posaconazole

Quantitative & Qualitative analysis techniques help to determine precisely the concentration of each variable and type of medication present in the sample.

High performance liquid chromatography

HPLC gives a constant quantitative accuracy and precision for the determination of active pharmaceutical compounds and associated substances employing a range of colonnade, solvents, and detectors in the same phase and may be accomplished on fully automated equipment using HPLC System. HPLC has good replicability and may be applied to a wide range of various chemical forms by carefully selecting the HPLC column chemistry. Chiral molecules are also possible to be isolated by HPLC into their respective enantiomers. HPLC is the most effective method for meeting the majority of the quantitative analytical needs for a variety of drugs. Today, HPLC, particularly reversed HPLC, is widely used. It is primarily a fluid chromatographic method for isolating and quantifying complicated mixtures of resolved elements(16). Various HPLC methods and its characteristics available in literature has shown in table 1.

Table 1: Performance attributes of HPLC method[17-25]

Author	Drug	Stationary phase	Mobile phase	Application	Wave length
Gurumurthy.Telugu, Dr.P.Venkata Suresh	Posaconazole	C18 Inertsil ODS-2V column (250×4.6, 5µm)	Acetonitrile: Water in the ratio of (90:10v/v)	In API and Tablet Formulation	262nm
Peter H. Tang	Posaconazole InPlasma/Serum	ODS HYPERSIL, 5-_m, 250 _ 4.6 mm	Ammonium acetate (0.1 M): water:acetonitrile:TFA (409/590/1, v/v/v)	In Plasma /Serum	245 nm (Ex) and 380 nm (Em)
Cássia V. Garcia et al..,	Posaconazole	Shim-pack C8 (250 × 4.6 mm; 5 µm)	methanol-water (75:25, v/v),	Bulk Assay	260nm
E.Cendejas-BuenoaA et al..,	posaconazole	Sunfire C18 (5 µm 4.6 ×150 mm)	(60:40 acetonitrile:water)	HPLC/UV or bioassay	260nm
Hadeel A. Khalil	Posaconazole and Vincristine	HC-C18(4.6×250mm, 5 µm)column attached to HC-C18 (4.6 × 12.5 mm, 5 µm)	acetonitrile and 0.015 M potassium dihydrogen orthophosphate (30 : 70 to 80 : 20, linear over 7 minutes)	In Rat Plasma	220 and 262nm
D.N.Madhusudana et al..,	Flucytosine and Posaconazole	C18 LiChrospher RP-HPLC (250 mm×4.6 mm, 5 µm)	Acetonitrile:15 mM of Kh2po4 anhydrous buffer (pH 6.0 adjusted with 0.1N NaOH) in the ratio of (75:25%, V/V)	Simultaneous estimation	246nm
S. Kathirvel et al..,	Posaconazole	Inertsil ODS-3V C18 (150 x 4.6mm with 5µ)	Water:Methanol	Stability indicating Studies	225 & 260nm
SonaliP. Mahaparale et al..,	Posacanazole	C18 (250x4.6mm) column	Acetonitrile:Water (55:45v/v).	Bioanalytical studies	262nm
L. Ravi Teja, et al..,	Posaconazole &its impurites	Inersil ODS-2, 250 x 4.6 mm, 5.0 µm	Phosphate Buffer (pH 62.5):Acetonitrile(20:80).	Impurity determination	260nm
Cherukuru Nagaraju et al..,	Posaconazole	chiral pack, IC, 250 x 4.6 mm, 5 µm	Isopropylalcohol, dichloro methane and diethyl amine (50:50:0.1 v/v/v).	Identification &Quantification	262nm

Table 2: Performance attributes of HPLC-DAD method[27-28]

Author	Drug	Stationary phase	Mobile phase	Application	Wave length
Santana ACSGV et al..,	Benznidazole and Posaconazole	Discovery C8 column (250 mm × 4.6 mm;5 µm),	methanol/acetate buffer (pH 3.5) (71:29)	Simultaneous Quantification by QBD	260nm
Dalia A. Hamdy and Tarek S. Belal.	Posaconazole	Zorbax SB-C18 (4.6 × 250 mm, 5 μm)	acetonitrile: 15 mM potassium dihydrogen orthophosphate (30 : 70 to 80 : 20, linear over 7 minutes)	In bulk powder and Suspension Dosage Form	262 nm

UV Visible spectroscopy

Spectrophotometric approaches based on UV absorption and chemical reactions are useful in pharmacopoeia. Spectrophotometry is the quantitative examination of a material's reflection or transmission qualities as a function of wavelength. These techniques have the benefit of requiring less time and work. These approaches are likewise incredibly precise and precise. In recent years, there has been a tremendous increase in the use of UV-vis spectrophotometry, particularly in the approach of generating pharmacological doses. We can learn a lot about atomic and molecular structure by examining how atoms and molecules interact with light (EMR). EMR spectrum areas supply numerous forms of information as a result of such interactions[26]. Different UV methods and its characteristics available in literature has shown in table 3.

Table 3: Performance attributes of UV spectroscopy method[29]

Author	Drug	Buffer & Diluent	Linearity range (µg/ml)	Application	Wave length
Andressa da S. Bitencourt et al	Posaconazole	C18 Inertsil ODS-2V column (250×4.6, 5µm)	5.0 a 25.0 µg/mL	In raw material	260nm

High Performance Thin-Layer chromatography

As technology advanced, high performance chromatography with a thin layer (HPTLC) emerged as an essential pharmaceutical analysis method. HPTLC is a quick and versatile separation method for analysing a large number of samples. This approach is advantageous in many ways since it is simple to handle and needs less time for analysis of the raw sample clean-up difficult. HPTLC evaluates all chromatograms without regard to time restrictions using a variety of criteria. Furthermore, several samples and standards are created concurrently yet individually on each plate, resulting in higher performance dependability. HPTLC is used to quantify the administration of drugs such as ethinyl estradiol, cyposterone, alfuzosin, and pentazocin. Available HPTLC methods and its characteristics in literature has shown in table 4.

Table 4: Performance attributes of HPTLC method[30-31]

Author	Drug	Stationary phase	Mobile phase	Application	Wave length
H.A.Khalila et al..,	Posaconazole	Merck HPTLC plates (20×10 cm aluminium plates with 250 µm layer thickness precoated with silicagel 60 F254)	Acetone and chloroform (1:2, by volume),	In suspension dosage form	262nm
Mohit G. Dewani.	Voriconazole	protein-free supernata nt was spotted on plates precoated with silica gel 60 F254.	toluene : methanol : triethylamine in the ratio of 6:4:0.1 v/v/v.	in Human Plasma	254 nm

Ultra-Performance Liquid Chromatography

UPLC for particles with diameters less than 2m achieves higher resolution, velocity, and sensitivity than high-performance liquid chromatography (HPLC). In the pharmaceutical markets of the twenty-first century, new methodologies are being investigated, and medication production times are being reduced. Meanwhile, UPLC analysis provides enhanced product consistency, and this expansion is not limited to analytical laboratories. Under extremely high pressure, the UPLC is isolated and measured (up to 100M Pa)[32]. Table 5 shows UPLC methods Characteristics available in literature.

Table 5: Performance attributes of UPLC method[33-34]

Author	Drug	Stationary phase	Mobile phase	Application	Wave length
Vadlamanu Durga Prasad et al..,	Posaconazole	Waters Acquity BEH shield C18 (100 mm length, 2.1 mm internal diameter and 1.7 µm particle size)	0.1% Orthophosphoric acid (i.e. 1 mL in 1000 mL water) in gradient combination with acetonitrile (ACN)	Determination in bulk drug form	210nm
Dalia A. Hamdy et al..,	Posaconazole	Kinetex-C18 (2.1 × 50 mm, 1.3 μm) column	acetonitrile: 15 mM potassium dihydrogen orthophosphate (45 : 55)	In bulk drug form and suspension dosage form	262 nm

LC -MS Techniques

LC/MS is a popular approach for liquid chromatographs that is constantly changing. The recommended chromatographic tool is LC/MS. Liquid spectrometrychromatographic mass (LC-MS/MS) is a mass spectrometry fluid chromatography technology (HPLC). Analytical chemistry combines the capacity to physically isolate liquid chromatography (or HPLC) with mass spectrometry for mass analysis. LC-MS/MS is widely utilised in quality and quantity analysis in laboratory research for medicinal components, medical goods, and biological samples. It has been utilised repeatedly in drug development at several levels, including metabolic stability screening, metabolite detection, live drug screening, impurity discovery, peptide mapping, and glycoprotein mapping. LC-MS has been effectively used in a variety of applications, including therapeutic medicinal monitoring (TDM), clinical and forensic toxicology, and doping control.This advancement in LC-MS was initially and continues to be inspired by the demand for more powerful analytical and bio-analytical methods that are sensitive and selective in correctly and precisely distinguishing target analytes from high complexity mixtures. With the advancement of two-dimensional hyphenated (2D) apparatus, the use of liquid (LC) and mass spectrometric (MS) chromatography has become a powerful approach[35].Table 6 shows LC-MS & UPLC-MS Characteristics methods available in literature.

Table 6: Performance attributes of LC-MS/UPLC-MS methods[35-40]

Author	Drug	Column	Mobile phase	Application
Ibrahim El-Serafi et al..,	Posaconazole	LC-MS Phenomenex Kinetex C18 (2.6 µm particle size, 50 mm	gradient condition with aqueous formic acid and pure acetonitrile.	For Quantitative determination In mouse
Lorena Baietto et al..,	Itraconazole, Voriconazole, and Posaconazole	LC-MS, C18 Atlantis T-3 5-µm (150 mm by 4.6 mm, inside diameter [i.d.])	The mobile phase composed initially of 50:50 water with formic acid (0.05%)/acetonitrile with formic acid (0.05%) was then ramped to 20:80 within 6.5 min	Quantification In Human plasma
Lorena Baietto et al..,	Dasatinib and Posaconazole	Simple protein precipitation with	0.1% aqueous formic acid and acetonitrile	Pharmacokinetic interaction b/w Dasatinib

		acetonitrile, UPLC BEH C18 column		and Posaconazole
Laurent Arthur Decosterd et al..,	Fluconazole, Itraconazole, Hydroxyitraconazole, Posaconazole, Voriconazole	2.1-mm by 30-mm Acquity UPLC C18 1.7-µm analytical colum	10mM ammonium formate in ultrapure water plus 0.1% FA (solvent A) and acetonitrile plus 0.1% FA (solvent B)	Quantification In Human plasma
Sankha S Basu et al..,	fluconazole, voriconazole, posaconazole, itraconazole, and hydroxyitraconazole	positive-mode electrospray ionization and collision-induced dissociation MS	-	Simultaneous measurement in serum
Chen-Jian Zhou et al..,	Posaconazole	Xevo TQ-S triple quadrupole tandem mass spectrometer and multiple reaction monitoring (MRM) Acquity UPLC BEH C18 column with gradient elution	Acetonitrile and 0.1% formic acid	Drug-Drug Interactions of Selinexor with Posaconazole in Rats

Electrophoresis

In advancement of the life sciences, capillary electrophoresis (CE) played a major role. This method is now used to analyze large and small molecules in applications in which it works better than fluid chromatography or is complementary to them. Routine CE analyzesand latest advances in metabolomic methods are explored for profiling small molecules in biological samples[41].Table 7 shows Capillary electropheresis Characteristic method.

Table 7: Performance attributes of Capillary electropheresis method[35-40]

Author	Drug	Detection	Buffer	Application
Hsiao-Wei Liao et al..,	Posaconazole	field-amplified sample stacking (FASS)	1.25 M formic acid as the background electrolyte and 0.2 M formic acid in 95% (v/v) methanol	Determination in patient plasma

Nuclear Magnetic Resonance technique

NMR Spectroscopy, also known as Magnetic Resonance Spectroscopy, is a spectroscopic method that monitors local magnet fields surrounding atomic nuclei (MRS). The sample is placed in a magnetic field, and the NMR signal is produced by a nuclear-resonant stimulation of the sample's nuclei with radio waves that sensitive radio receivers detect. The intramolecular magnetic field surrounding an atom in a molecule alters the frequency of the resonance, revealing information on the electronic structure and functional groups of themolecule[42]. Table 8 shows NMR Characteristic method.

Table 8: Performance attributes of NMR method[43]

Author	Drug	Detection	Application
Xingyu Lu et al..,	Posaconazole	field-amplified sample stacking (FASS)	Molecular Interactions

CONCLUSION

The current review covered several analytical approaches used to evaluate TDF, FTC, and EFV. Numerous tests have been performed, including bio-analytical, HPLC, UPLC, HPTLC, UV/Vis-Spectroscopy, LC-MS, LC-ESI-MS, and others.for evaluation of posaconazole in bulk and in its

combination with other drugs from pharmaceutical formulations and also biological fluids.Posaconazole in bulk and in combination with other medications from pharmaceutical formulations and biological fluids was evaluated using LC-MS, LC-ESI-MS, and other techniques. The most researched approach for estimating posaconazole in pharmaceutical dosage forms was liquid chromatography with UV detection, whereas hyphenated LS-MS and LSMS/MS methods were described for determining posaconazole and its metabolite in plasma and other biological fluids. A few chromatography techniques,such as HPTLC and Stability-indicating HPLC, UPLC, and HPTLC, are also included. A few basic UV-Spectrophometric techniques can be utilised for regular posaconazole analysis.

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