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SUMMARY BASED ON DIFFERENT ANALYTICAL METHOD DEVELOPMENT AND VALIDATION OF POSACONAZOLE IN PHARMACEUTICAL DOSAGE FORM

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ABSTRACT

Posaconazole is pharmaceutical drug used for the treatment of fungal infection. This review is based on analytical method development and validation Posaconazole and its combination with many drugs. Several analytical methods have been carried out its estimation like UV, HPLC, LC/MS, HPLC – DAD and UHPLC – UV, Stability indicating HPLC, UPLC – MS/MS, Stability indicating UPLC, LC-MS/MS, Mass Spectrometry. An most reliable and reproducible HPLC method have been developed for estimation of Posaconazole. This review paper will be useful for future research and study purpose. It gives wide range of information about various analytical methods development and validation of posaconazole.

KEYWORDS: Posaconazole, Antifungal, Posanol, UV Spectrophotometry, HPLC, UHPLC.

INTRODUCTION

Posaconazole is the newest triazole anti-fungal agent. Posaconazoleis “Fig. 1” designated chemically as 4-{4-[4-(4-{(3R,5R)-5-(2,4-dichlorophenyl)-5-(1H-1,2,4-triazole-1-ylmethyl)-tetrahydrofuran-3-yl]methoxy}phenyl)piperazine-1-yl]phenyl}-2-[(1S,2S)-1-ethyl-2-hydroxy -propyl]-2,4dihydro-3H-1,2,4-triiazole-3-0ne. It is structurally related to Itraconazole and has activity against Candida species, Aspergillus species, Cryptococcus neoformans, the zycomycetes and other filamentanous fungi. The evaluation of oral triazole anti-fungal agents began in the 1980s. Posaconazole has enhanced activity against many almost all kind of fungal pathogens compared with activities of the other azoles.[1]. Posaconazole is a highly lipophilic drug. It disturbs fungi growth by inhibiting cytochrome P450 lanosterol 14α-

demethylase (CYP51A1) that leads to blockage of ergosterol synthesis in the fungal cell membrane. It is orally bioavailable and reaches plasma Maximum concentration by 10 hours post dose, meaning that its elimination is rather slow and the mean of its half - life is 20 hours. Similar to previous triazoles, posaconazole inhibits CYP3A4; however, the risk of drug-drug interaction is still considered to be lower compared to earlier drugs, partially because posaconazole elimination by CYP-pathways is very limited. Posaconazole is excreted in the feces (76.9%), mainly as uncharged drug, or excreted in urine (14%) as conjugated drug or unchanged. In vitro studies have shown that posaconazole is conjugated with UDP-glucuronosyltransferase 1A4 (UGT1a4) to form Posaconazole glucuronide.[2]

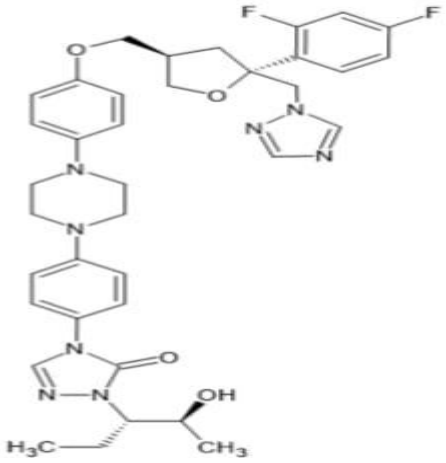

Fig. 1: Structure of posaconazole.

UV Spectrophotometric method

Andressa da S. Bitencourt *et al.*, Prostated UV spectrophotometry for determination of Posaconazole. This method was developing a simple, fast and reproducible Spectrophotometric method for the analysis of posaconazole in raw material. The established conditions were: methanol as extracting solvent, detections wavelength of 260 nm, Shimadzu double beam spectrophotometer 1800 model with 1 cm quartz cells.[3]

HPLC Methods

Various numbers of analytical methods has been developed and validated for HPLC, which are listed below. Table 1 indicates HPLC in different methods.

Carsten Muller *et al.*, Prostated HPLC analysis of the antifungal agent posaconazole in patient with haematological diseases. After precipitation of the proteins with acetonitrile, the

clear supernatant was evaporated in a centrifugal evaporator, and the residue was dissolved in the HPLC elution. Separation was done on a chromatography performed by injecting a 50 mul aliquot of the resuspended sample onto a Multohyp C_{18} BDS column (250 x 4 mm). Column temperature was maintained at 50 º C. The flow rate was 1 ml min^{-1}. Retention time of posaconazole was about 9 min and itraconazole was 17 min.

Peter H. Tang *et al.,* Prostated for the determination of Posaconazole in plasma/serum by HPLC. Posaconazole and internal standard ketoconazole in the methanol extract are subsequently analyzed by using a fluorescence (FL) detector at optimized wavelengths (excitation 245 nm and emission 380 nm). The method achieves a linear detector response for peak height measurements over the concentration range of 0.1–10 µg/mL which adequately covers the therapeutic range for appropriate patient monitoring. The chromatographic time is less than 8 min per injection, an improvement over most published HPLC/FL or HPLC/UV methods.

Table 1: Represent reported HPLC methods.

Compounds	Methods	Wave Length (nm)	Flow Rate (ml/ min)	Retention Time (min)	Author Name
Posaconazole	HPLC	250	1.00	9.00	Carsten Muller[4]
Posaconazole	HPLC	245	1.00	<8.00	Peter.H[5]
Posaconazole	Stability Indicating HPLC	-	1.00	8.5	Cassia V. Garcia[6]
Posaconazole	Stability Indicating RP-HPLC	225	1.00	7.00	Kathirvel[7]
Posaconazole	HPLC-DAD AND UHPLC-UV	262	1.5	5.00	Dalia A. Hamdy[8]
Posaconazole + Voriconazole	HPLC with UV detection	255	1.00 and 0.95	-	Stephanie Chhun[9]

Cassia V. Garcia *et al.,* Prostated for the stability indicating HPLC method was developed for the determination of Posaconazole in bulk. Chromatographic separation was achieved using an isocratic elution in a reversed-phase system, with a mobile phase composed of methanol-water (75:25, v/v), at 1.0 mL min^{-1} flow. Samples were exposed to degradation under thermal, oxidative and acid/basic conditions, and no interference in the analysis was

observed. System suitability was evaluated and results were satisfactory (N = 4,900.00 tailing factor 1.04; RSD between injections = 0.65). The retention time of posaconazole was about 8.5 min and the method was validated within the concentration range 5–60 μg mL^{-1} (r = 0.9996).

Kathirvel S *et al.,* Reported stability indicating RP-HPLC method for the determination of Process Related Impurities in Posaconazole API. The determination was done for active pharmaceutical ingredient in the presence of degradation products, and its process-related impurities. The chromatographic separation was achieved on a waters HPLC system with PDA detector and column employed for the present investigation was inertsil ODS-3V C_{18} (150 x 4.6mm with 5μ particle size) and empower 2 software provided by waters was used throughout the experiment. The method employed a linear gradient elution and the detection wavelength was set at 225 nm (for intermediate A impurity) and 260 nm (for intermediate B, diastereomer, formyl and benzyl posaconazole impurity). The drug was subjected to stress conditions of hydrolysis (acid and base), oxidation, photolysis and thermal degradation as per International Conference on Harmonization (ICH) prescribed stress conditions to show the stability-indicating power of the method.

Dalia A. Hamdy *et al.,* Prostated for the newly developed HPLC-DAD and UHPLC-UV assays for the determination of Posaconazole in bulk powder and suspension dosage form. For HPLC-DAD assay, samples were injected through Zorbax SB-C_{18} (4.6 × 250 mm, 5 μm) column. The gradient elution composed of the mobile phase acetonitrile: 15 mM potassium dihydrogen orthophosphate (30: 70 to 80: 20, linear over 7 minutes) pumped at 1.5 mL /min. For UHPLC-UV assay, samples were injected through Kinetex-C_{18} (2.1 × 50 mm, 1.3 μm) column. The mobile phase composed of acetonitrile: potassium dihydrogen orthophosphate (45: 55) pumped isocratically at 0.4 mL /min. Detection wavelength was 262 nm in both methods. Both assays were proven sensitive and selective according to ICH guidelines. UHPLC-UV assay exhibited some economic and chromatographic separation superiority.

Stephanie Chhun *et al.,* Prostated simultaneous quantification of Voriconazole and Posaconzole in human plasma by HPLC with UV detection. An internal standard diazepam was added to 100 mL of human plasma followed by 3 mL of hexane-methylene chloride (70:30, v/v). The organic layer was evaporated to dryness and the residue was reconstituted with 100 mL of mobile phase before being injected in the chromatographic system. The compounds were separated on a C_8 column using sodium potassium phosphate buffer (0.04

M, p^H 6.0): acetonitrile: ultrapure water (45:52.5:2.5, v/v/v) as mobile phase. All compounds were detected at a wavelength of 255 nm. The assay was linear and validated over the range 0.2-10.0 mg/L for voriconazole and 0.05-10.0 mg/L for posaconazole**.**

UPLC

Vadlamanu Durga Prasad *et al.*, reported stability-indicating UPLC method has been developed and validated for the determination of related substances of Posaconazole in bulk drug. Forth- with simple UPLC chromatographic separations were achieved on a Waters Acquity BEH shield C_{18} (100 mm length, 2.1 mm internal diameter and 1.7 µm particle size) with a mobile phase containing 0.1% Orthophosphoric acid (i.e. 1 mL in 1000 mL water) in gradient combination with acetonitrile (ACN) at a flow rate of 0.5 mL/min and the eluent were monitored at 210 nm.[10]

LC-MS

Moustapha Hassan *et al.*, Reported for the quantification method for the determination of Posaconazole in Mouse Tissues using Liquid Chromatography-Mass Spectrometry. Fast and selective liquid chromatography spectrometry (LC-MS) method was developed for the quantification of posaconazole in different mouse organs. Organs were homogenized and diluted in isotonic NaCl solution. Protein was precipitated using acetonitrile containing internal standard and analyzed. The analysis was carried out using gradient condition with mobile phases consisting of aqueous formic acid and pure acetonitrile. Analysis was run at a flow-rate of 0.51 mL/min.[2]

Sheng-Yu Lin *et al.*, Prostated of the detection of Posaconazole by Surface-Assisted Laser Desorption/Ionization mass spectrometry with dispersive Liquid-Liquid micro extraction. A simple, rapid, and sensitive method for the detection of Posaconazole using dispersive liquid-liquid micro extraction (DLLM) coupled to surface-assisted laser desorption/ionization mass spectrometric detection (SALDI/MS) was developed. After the DLLM, Posaconazole was detected using SALDI/MS with colloidal gold and α-cyano-4-hydroxycinnamic acid (CHCA) as the co-matrix. Under optimal extra and detection conditions, the calibration curve, which ranged from 1.0 to 100.0 nm for Posaconazole, was observed to be linear.[11]

LC-MS/MS

Jennifer M. Cunliffe *et al.*, Reported LC-MS/MS method Posaconazole for the determination of Posaconazole concentrations in human plasma was validated. Posaconazole was extracted

from human plasma using mixed-mode cation exchange solid phase extraction in a 96-well plate format followed by gradient separation on a fused-core Halo C_{18} column. The analyte and its corresponding internal standard were detected using a Sciex API 4000 triple quadrupole LC–MS/MS system equipped with a TurboIonSpray™ ionization source operated in the positive ion mode. The calibration range of the method was 5.00–5000 ng/mL using a 50 µL aliquot of plasma. The assay inter-run accuracy and precision were—4.6–2.8% and 2.3–8.7%, respectively (n = 18).[12]

Hyojin Chae *et al.,* Reported LC-MS/MS method Posaconazole for the determination of posaconazole concentration is adult patient with hematologic malignancy. Posaconazole has an important role in the prophylaxis of invasive fungal infections (IFIs), however oral suspension formulation is associated with variable bioavailability. One hundred twenty-two adult patients with AML/MDS undergoing remission induction chemotherapy were enrolled. They received posaconazole as prophylaxis and 557 posaconazole measurements were performed with a validated LC-MS/MS method. Posaconazole value of ≥ 338 ng/ml on day 3 predicted the achievement of ≥ 500 ng/ml at day 7 (sensitivity: 78.5%, specificity: 66.7%, AUC: 0.747). Food intake (P=0.0014) and proton pump inhibitor (P=0.0063) were significantly associated with higher and lower posaconazole concentrations, respectively. TDM of posaconazole oral suspension formulation is recommended based on the exposure-response relationship of the present study.[13]

UPLC-MS/MS

Suili Yang *et al.,* Prostated for the determination of UPLC-MS/MS method for studying the pharmacokinetic interaction between Dasatinib and Posaconazole in rats. An ultrahigh-performance liquid chromatography-tandem mass spectrometry method was established to measure the plasma concentrations of dasatinib and posaconazole in rats simultaneously. Simple protein precipitation with acetonitrile was applied to extract dasatinib and posaconazole in samples. The chromatographic separation of analytes was conducted on an UPLC BEH C_{18} column using a mobile phase consisting of 0.1% aqueous formic acid and acetonitrile. Dasatinib alters the pharmacokinetics of posaconazole. Attention should be paid to the unexpected risk of adverse clinical outcomes when posaconazole is co-administered with dasatinib.[14]

CONCLUSION

This review article contains numerous numbers of analytical method development and validation for posaconcole and its combination with few other drugs. The various analytical methods listed above are UV Spectrophotometric, HPLC, Stability indicating HPLC, UPLC – MS/MS, UPLC, LC-MS, LC–MS/MS, HPLC-DAD with UHPLC – UV. This analytical review will be useful for future research purposes based on Information regarding Posaconacole and its combination with few drugs. HPLC was found to be most deliberate for detection of Posaconazole. This review will be helpful for further analytical method development and validation for Posaconazole in combination bulk and in pharmaceutical dosage forms.

ABBREVIATIONS

UV- Ultraviolet visible Spectrophotometer, HPLC – High Performance Liquid chromatography, RP-HPLC – Reverse phase High Performance Liquid Chromatography, UPLC – Ultra performance liquid Chromatography, UHPLC – Ultra High performance liquid Chromatography, DAD – Diode array Detector, LC – Liquid Chromatography, MS – Mass Spectrophotometer, NaCl-Sodium Chloride.

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