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Review Article

A Review on Analysis of Voriconazole.

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ABSTRACT
Voriconazole is a second generation triazole and is the result of a discovery programme aimed at improving the potency and spectrum of Fluconazole. The aim of this review is to focus on update of determination of Voriconazole in bulk and in pharmaceutical preparations using chromatographic and spectrophotometric methods. Voriconazole is estimated by RP-HPLC, UV, RP-UPLC, LC-MS methods. This review provides detailed information on separation conditions for Voriconazole alone, in the presence combination with other drugs and in presence of its degradation products.

KEYWORDS
Voriconazole, RP-HPLC, UV, RP-UPLC, LC-MS/MS, Spectrophotometry.

1. INTRODUCTION

Voriconazole is a broad spectrum, triazole antifungal agent and is indicated in adults and children aged 2 years and above as follows: Treatment of invasive aspergillosis. Treatment of candidemia in non-neutropenic patients.

Treatment of Fluconazole-resistant serious invasive Candida infections (including C. krusei). Treatment of serious fungal infections caused by Scedosporium spp. and Fusarium spp. Voriconazole Accord should be administered primarily to patients with progressive, possibly life-threatening infections. Prophylaxis of invasive fungal infections in high risk allergenic hematopoietic stem cell transplant (HSCT) recipients. [1]

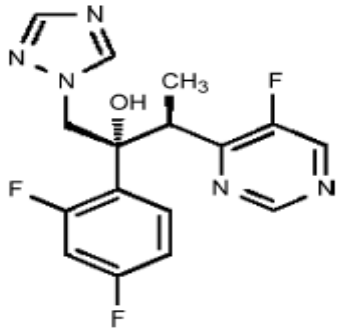

Fig. 1- Structure of Voriconazole

1.1. Mechanism of Action

Voriconazole is an Azole Antifungal. The mechanism of action of voriconazole is as a Cytochrome P450 3A4 Inhibitor, and Cytochrome P450 2C19 Inhibitor, and Cytochrome P450 2C9 Inhibitor. The chemical classification of voriconazole is Azoles. Voriconazole is a synthetic triazole with antifungal activity. Voriconazole selectively inhibits 14-alpha-lanosterol demethylation in fungi, preventing the production of ergosterol, an essential constituent of the fungal cell membrane, and resulting in fungal cell lysis. (NCI04). [1] HPLC Methods for Determination of Voriconazole Abdalla Shalaby et al.[2] Simple, sensitive and accurate stability indicating analytical method has been developed and validated for determination of voriconazole and its degradation products using RP-HPLC method with ultraviolet detection. The resulting method was applied for determination of voriconazole tablets. The procedure was developed and validated under acidic, basic, oxidative and photo irradiated conditions. The compounds were separated on C18 column using 0.05 mol L-1 disodium hydrogen phosphate buffer (pH 5.5): acetonitrile (1:1, v/v) as a mobile phase. at a flow rate of 1.0 mL per min and UV detection at 255 nm, the run time was less than 15 minutes The calibration curves were linear between 6.0 and 60 μg mL-1. The proposed method was simple, highly sensitive, precise, accurate and, is useful for routine quality control analysis and stability testing. It was found that voriconazole was more sensitive to the basic conditions, Photodegradation was observed only under severe conditions of light
exposure and oxidation may also appear, however, it was stable in acidic medium.

Sreeramamurthy Pyla et al. [3] A simple, accurate and precise reverse phase HPLC method was developed for the estimation of Voriconazole in bulk and pharmaceutical dosage form. The drug

was resolved on an enable C18G column (250 mm x 4.6 mm i.d, 5 µm particle size) used with photodiode array UV Visible detector using the mobile phase consisting of Acetonitrile and water in the ratio of 60:40V/V. The flow rate was 1 mL/min and the effluent was monitored at 256 nm. The retention time of the drug was 5.360 min. The linearity of the drug was found to be the concentration range 10-50 µg/mL. The method was found to be reproducible with relative standard deviation of <2%. The percentage recovery was 99.89-100.86%. The results of method have been validated according to ICH guidelines requirements. This method can be successfully employed for the quantitative analysis of Voriconazole in bulk and pharmaceutical dosage form.

D. Gowri Sankar et al.[4] A reverse phase high performance liquid chromatographic (RP-HPLC) method has been developed for the estimation of voriconazole in bulk and pharmaceutical formulations. The quantification was carried out using a RP-C-18 Hypersil BDS column (250 mm × 4.6 mm i.d., 5 µ particle size) in isocratic mode with mobile phase comprising water, acetonitrile and methanol in the ratio of 50:25:25 v/v. The mobile phase was pumped at a rate of 1.5 mL/min and detection was carried out at 256 nm. The linearity was found to be in the range of 20-400 µg/mL. The proposed method was statistically evaluated and can be applied for routine quality control analysis of voriconazole in tablets.

A. B. Khetre et al.[5] This study describes the development and validation of stability indicating HPLC method for voriconazole, an antifungal drug. Voriconazole was subjected to stress degradation under different conditions recommended by International Conference on Harmonization. The sample so generated was used to develop a stability-indicating high performance liquid chromatographic method for voriconazole. The peak for voriconazole was well resolved from peaks of degradation products, using a Hypersil C18 (250×4.6 mm) column and a mobile phase comprising of acetonitrile: water (40:60, v/v), at flow rate of 1 ml/min. Detection was carried out using photodiode array detector. A linear response ($r > 0.99$) was observed in the range of 5-25 µg/ml. The method showed good recoveries (average 100.06%) and relative standard deviation for intra and inter-day were ≤ 1.5 %. The method was validated for specificity and robustness also.

G. Naveen Kumar Reddy et al.[6] Simple, rapid, sensitive, accurate, robust & rugged stability indicating analytical method for determination of voriconazole in pharmaceutical formulations is developed and validated by using UPLC & applied the developed and validated method for determining the assay of voriconazole in tablets (Vfend®), as there is no official monograph & no analytical method by UPLC. Chromatography was performed with mobile phase containing sodium dihydrogen ortho phosphate & acetonitrile in the ratio of 50:50,adjusted to pH 5.50±0.05 with dilute NaOH, with a flow rate of 0.5mL/min, C-18 column & UV detection at 254nm.The method was validated for linearity, accuracy, ruggedness, robustness, precision & bench top stability of sample & standard solution. Voriconazole tablets were subjected to different stress conditions like acid, alkali, peroxide, thermal, water & UV studies and checked for its specificity, degradation &stability. The developed method was very rapid with a run time of 1 min, accurate, robust, rugged and stable.

Shan Cheng et al.[7] A simple and rapid high-performance liquid chromatographic method with UV detection is developed and validated to determine the concentration of voriconazole in rat and beagle dog plasma. After protein precipitation using acetonitrile, the supernatant solution is

chromatographed on a Diamonsil C18 column (250 × 4.6-mm i.d., 5 μm). The mobile phase used is a combination of acetonitrile–water–acetic acid (55:45:0.25, v/v/v) with a pH of 4.0. Detection is achieved by a UV detector monitored at a wavelength of 256 nm. The matrix calibration curves are obtained both in the concentration range of 0.10–50.0 μg/mL in rat and beagle dog plasma, with the lower limit of quantitation of 0. 10 μg/mL. The intra- and inter-assay precisions in terms of % relative standard deviation are lower than 8.6% and 6.0% in rat and beagle dog plasma, respectively. The accuracy in terms of % relative error ranged from –0.5% to 8.0% and –0.5% to 6.0% in rat and beagle dog plasma, respectively. This validated method is successfully applied to determine the concentration of voriconazole in plasma after intravenous administration of 36 mg/kg voriconazole to rats and 10 mg/kg voriconazole to beagle dogs, respectively.

Üstündağ Okur et al. [8] The aim of the present study was to develop and validate a High-Performance Liquid Chromatography (HPLC) method for the determination of voriconazole in drug substances and in situ gel. A mixture of acetonitrile and ultrapure water (50:50) (v/v) was used as mobile phase. The column was a C18 column (150x4.6mm with 5μm particles). The eluent was monitored with UV detection at 256 nm and flow rate was set to 1 mL/min. The method was validated partially with respect to system suitability, linearity, limits of detection (LOD) and quantitation (LOQ), precision, accuracy, specificity, selectivity and stability. Obtained results showed that the analytical method had good linearity, accuracy, precision, selectivity and stability. Analytical method development results indicated that the LOD was 0.022 μg/mL; LOQ was 0.065 μg/mL and assay exhibited a linear range of 1- 30 μg/mL.

Saidulu Goli et al. [9] A new simple, precise, accurate and selective RP-HPLC method has been developed and validated for voriconazole in parental dosage form. The method was carried out on an Intersil ODS-C18 (150X4.6X5μ) column with a mobile phase consisting of mixed phosphate buffer, ACN and Methanol (65:30:5) and flow rate of 2.0 mL min-1. Detection was carried out at 257 nm. The retention time for VCZ was found to be 6.413 min. The VCZ % recovery was within the range between 99.55- 99.63%. The percentage RSD for precision and accuracy of the method was found to be less than 2%. The method was validated as per ICH guidelines. The developed method was validated for precision, accuracy, sensitivity and robustness. The developed method can be used for routine analysis of titled drug in formulation.

Verma Vikrant et al.[10] The present research article describes the method development and validation of two drugs voriconazole and itraconazole by an innovative HPLC method in the dosage form that is solid in nature i.e. tablets. Inertsil ODS-C18 column (150mm, 4.6mm, 5μm) was used for the study and mobile phase consists of buffer (pH-5) and Methanol in the mixture of 20:80 for itraconazole and water and methanol in the mixture of 80:20 for voriconazole. The wavelength for the chromatographic separation used was 306nm for itraconazole and 256nm for voriconazole. Injection volume was maintained at 20μl. A wide variety of mobile phase combinations used for the study and system contains integrated degasser. Flow rates were maintained at 1ml/min throughout the process for mobile phase combinations. In this method, ICH guidelines were used for validation studies. After analysis of different research and review articles, it came to light that HPLC method development of voriconazole and itraconazole has been done in different dosage forms but less work is done on solid dosage forms and hence still

there is huge potential for new methods to be developed in solid dosage form with different mobile phase combinations.

Peter H. Tang et al. [11] This paper describes a simple and rapid high performance liquid chromatographic (HPLC) method with fluorescence detection (FL) for the determination of voriconazole concentration in human plasma and serum. Ketoconazole is selected as the internal standard. Acetonitrile alone is used to precipitate protein and extract voriconazole and ketoconazole in human plasma and serum using a single dilution step procedure. Following protein precipitation and extraction, voriconazole and ketoconazole in the extract are quantitated by injecting directly onto the HPLC system. Limit of quantitation and linearity (0.1-10 μg/mL) of the method adequately cover the therapeutic range for appropriate drug monitoring. This method has shown some essential improvements such as allowing a small portion of the extract to be analyzed (10 μL) and completing an isocratic chromatography in <7 min per injection when compared to most published HPLC/FL and HPLC/UV methods. This method would be of interest to analytical and clinical laboratories equipped with the HPLC/FL systems because it employs simple, rapid, and cost-effective procedures without time-consuming solvent evaporation and residual reconstitution.

1.2. HPTLC Methods for Determination of Voriconazole

Mohit G. Dewani1 et al.[12] Voriconazole is a new antifungal agent that is a derivative of Fluconazole, having wide-spectrum activity and a fungicidal action against Candida and Aspergillus species. Voriconazole displays non-linear pharmacokinetics in adults but has linear pharmacokinetics in children. Inter individual variability is generally high; both in children and adults, and diverse manifestations of toxicity are possibly attributed to high drug concentrations. This indicates the need to monitor voriconazole concentration in plasma after oral dose. A simple, selective and sensitive high performance thin layer chromatographic method for the determination of voriconazole in human plasma is developed and validated. After precipitation of plasma proteins with acetonitrile, the protein-free supernatant was spotted on plates precoated with silica gel 60 F254. Cephalexin was used as an internal standard. The mobile phase consisted of a mixture of toluene: methanol: triethylamine in the ratio of 6:4:0.1 v/v/v. The drug showed considerable absorbance at 254 nm. The method was found to be linear over the concentration range of 50–400 ng/band. Mean drug recovery was found to be 98.82%. Voriconazole in plasma samples was stable when stored for different stability conditions. The method was found to be precise and accurate and can further be extended for pharmacokinetic studies for therapeutic drug monitoring of voriconazole in routine clinical practice.

Mrinalini C. Damle et al. [13] A simple, accurate, precise and rapid high-performance thin-layer chromatographic method for determination of voriconazole as a bulk drug and in pharmaceutical formulations was developed and validated. The method employed TLC aluminum plates precoated with silica gel 60 F254 as the stationary phase. The solvent system consisted of methanol: toluene (3: 7 v/v) as mobile phase. Densitometric analysis of voriconazole was carried out at 255 nm. The system was found to give compact spots for voriconazole at Rf of 0.58 ± 0.02. The linear regression analysis data showed good linear relationship in the concentration range 200–1000 ng per spot. The limits of detection and quantitation were 12.05 and 36.55

ng/spot. The method was validated for precision, accuracy, specificity and robustness. The method has been successfully applied in the analysis of marketed formulation.

Atul A. Shirkhedkar et al. [14] Voriconazole is used as an antifungal agent. A new rapid, simple, economical and environmental friendly Reversed -Phase High-Performance Thin-Layer Chromatography (RP-HPTLC) has been developed and validated for quantitative determination of voriconazole in bulk and in cream formulation. RP-HPTLC separation was performed on aluminum plates precoated with silica gel 60RP-18F-254S as the stationary phase using Acetonitrile: Water (60:40% v/v) as mobile phase. Quantification was achieved by densitometric analysis at 257 nm over the concentration range of 200–1200 ng/band. The method was found to give compact and well resolved band for Voriconazole at Retention factor (Rf) 0.48 ± 0.02. The linear regression analysis data for calibration graph showed good linear relationship with r^2= 0.999. The method was validated for precision, recovery, robustness, ruggedness and sensitivity as per International conference on Harmonization (ICH) guidelines. The Limit of Detection (LOD) and Limit of Quantification (LOQ) were found to be 19.99 ng and 60.60 ng, respectively. The proposed developed RP-HPTLC method can be applied for identification and quantitative determination of Voriconazole in bulk and in cream formulation.

1.3. LC-MS/MS Methods or Determination of Voriconazole

X.Li et al.[15] A rapid and sensitive method for the determination of voriconazole in human plasma was developed. Voriconazole and the internal standard were extracted from plasma samples by liquid–liquid extraction with 2 ml of diethyl ether: dichloromethane (60: 40, v/v). The chromatographic separation was accomplished isocratically on a 150×4.6 mm, 5 mm Zorbax extend C18 column at a flow rate of 0.7 mL/min. Detection by electro spray positive ionization mass spectrometry in the multiple-reaction monitoring mode was completed within 3.2 min. Linearity was over the concentration range 20-2000ng/ml with a limit of detection of5ng/ml. Intra- and inter-day precision measured as relative standard deviation was <4.40% and <5.44%, respectively. The method was applied in a bioequivalence study of two tablet formulations of voriconazole.

Michael Vogeser et al. [16] A convenient liquid chromatography-tandem mass spectrometry method for the quantification of the triazole antifungal agent voriconazole in plasma samples is described. Fenbuconazole is used as an internal standard. After protein precipitation, automated solid-phase extraction is applied. Electro spray ionization in the positive mode is used and the following mass transitions are recorded: voriconazole, 350™127; and fenbuconazol, 337™125. The analytical run time is 4 min. The response was linear from 78 to 5000 mg/L. The total coefficient of variation (ns16) was 12.6% for a low-concentration pool (143 mg/L), 4.7% for a medium-concentration pool (419 mg/L), and 5.0% for a high-concentration pool (4304 mg/L). The method is proposed for future investigations that should be performed to test the hypothesis that therapeutic drug monitoring of voriconazole is clinically useful.

Lei Zhou et al. [17] A novel method based on liquid chromatography–mass spectrometry with electro spray ionization (LC–MS) has been developed for analysis of voriconazole in aqueous humor. The separation was achieved on a reversed-phase C18 column eluted by 70% acetonitrile–30% water–0.01% TFA. The correlation between the concentration of voriconazole to peak area was linear (r2=0.9990) between 0.04 and 60 ng, with a coefficient of variance of

less than 3%. Limit of quantitation (LOQ) was estimated to be 5 ng/ml voriconazole with an injection volume of 2 µl of aqueous humor. Both intra-day and inter-day imprecision were less than 3% over the whole analytical range. Parallel analyses of voriconazole samples by LC–MS and by high-performance liquid chromatography (HPLC)–UV showed that the two methods were highly correlated (r2=0.9985). LC–MS was used to the determine voriconazole levels achieved in the aqueous humor of the rabbit eye, following topical application of 5 or 10 µg voriconazole in the form of eye drops for 11 days b.i.d. The lower dosage produced an aqueous humor concentration of 7.29±5.84 µg/ml, while the higher dosage produced a concentration of 14.56±12.90 µg/ml.

B.V. Araujo et al [18] A rapid, simple and sensitive LC–MS/MS analytical method was developed and validated for the determination of voriconazole (VRC) in rat plasma, using ketoconazole as internal standard (IS). Analysis was performed on a Shimadzu® HPLC system using a Shimadzu® C18 column and isocratic elution with acetonitrile–water–formic acid (60:40:0.05, v/v/v), at a flow of 1.0 mL/min (split ratio 1:5), and a mass spectrometer Micromass®, equipped with a double quadruple and an electro spray ionization interface, operated in a positive mode. Plasma samples were deproteinized with methanol (1:2) and 30 µL of the supernatant was injected into the system. The retention times of VRC and IS were approximately 3.3 and 2.7 min, respectively. Calibration curves in spiked plasma were linear over the concentration range of 50–2500 ng/mL with determination coefficient >0.98. The lower limit of quantification was 50 ng/mL. The accuracy of the method was within 5%. Intra- and inter-day relative standard deviations were less or equal to 12.5 and 7.7%, respectively. The applicability of the LC–MS–MS method for pharmacokinetic studies was tested using plasma samples obtained after intravenous administration of VRC to male Wistar rats. The reported method provided the necessary sensitivity, linearity, precision, accuracy, and specificity to allow the determination of VRC in pre-clinical pharmacokinetic studies.

1.4. Derivative Spectrophotometric Method for Determination of Voriconazole

Mrinalini C. Damle et al. [19] A derivative spectrophotometric method for the simultaneous determination of Voriconazole and its hydrolytic degradation product has been developed. The objective of this study was to evaluate the utility of derivative Spectrophotometry for the determination of Voriconazole Working standard (VORIWS) in presence of its degradation product without prior separation. First derivative Spectrophotometry allowed specific determination of VORIWS at 269.8nm and 234.2nmwith no contribution by the products formed after alkali and acid treatment respectively. Similarly, both acid and alkali catalyzed hydrolytic products were determined at 325nm with no interference by VORIWS. The Beer's law is obeyed in the concentration range of 50-150mgmL-1 for both VORIWS and its hydrolytic product. The percentage recovery for VORIWS was found to be 99.16-101.23%.LOD and LOQ values were also determined. Intra and interday precision values were within range. The results indicate that proposed method is simple, rapid and specific.

Deepan T. et al. [20] A simple, accurate, precise and economic spectrophotometric method has been developed for the determination of voriconazole in their bulk powder and pharmaceutical dosage form. Voricanazole showed maximum absorbance at 256 nm with 0.1 N Hydrochloric acid as solvent. Beer's law was obeyed in the concentration range 10-60 µg/mL with regression

coefficient of 0.999. The concentration of active component were then determined from the calibration curve obtained by measuring the amplitude at 256 nm for Voricanazole. Accuracy and precision of the developed methods have been tested in addition recovery studies have been carried out in order to confirm their accuracy. The slope, intercept and correlation coefficient was found to be 0.0372, 0.0279 and0.9995. This method is simple, precise, accurate, sensitive and reproducible and can be used for the routine quality control testing of the marketed formulations.

Mohamed A. Zayed et al. [21] The reactions of rose bengal reagent (Rbeng) with three antifungal drugs Fluconazole (FLZ), Voriconazole (VRZ) and Butoconazole nitrate (BTZ) had been studied for the development of simple, rapid, sensitive spectrophotometric methods for micro-determining of these drugs in pure and in their dosage forms. This method is based on the formation of ion-pairs between the drugs and Rbeng reagent. The spectra of the formed ion pairs were measured at pH = 6.5 for FLZ and pH = 6 for VRZ at 575 nm. The spectra of the formed ion pair for BTZ was measured at pH = 4 and at 580 nm. All solutions spectra are measured at selected optimum temperature 20-30^{o}C. Beer's law was valid in the concentration ranges 30.63 – 76.57, 34.93– 97.81 and 14.2 – 45.1 µg ml-1 with recovery of (98.00 - 101.9, 97.92 - 102.2, and 98.20 - 101.3 % for FLZ, VRZ and BTZ, respectively. The values SD = 0.1210 – 0.4148, 0.4365– 1.018 and 0.0748 - 0.4362, RSD =0.1790 – 1.152, 0.5248 - 1.648 and 0.3314 - 1.011%, the Sandell sensitivity (S) = 0.063, 0.076, 0.017 µg cm-2, LOQ = 8 , 12.96, 13.27 µg ml-1 and LOD =2.6, 4.4, 4.3 µg ml-1 were calculated for FLZ, VRZ and BTZ, respectively. The results obtained revealed accuracy, precision and sensitivity of the suggested procedures. These methods were applied for analysis of these drugs in their pharmaceutical formulations. The results obtained were found to be in good agreement with those given by official methods, as evaluated by F- and t- tests.

2. CONCLUSION

Various methods for determination of Voriconazole have been reported. Some RP- HPLC assay methods were used to estimate Voriconazole. UV methods are also reported. Research papers on UPLC, Spectrophotometry, LC-MS, and LC-MS/MS are also reported. Bioanalytical methods are also reported in which Voriconazole is determined in human and rat plasma.

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