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Development and validation of a liquid chromatographic method for the stability study of a pharmaceutical formulation containing voriconazole using cellulose tris(4-chloro-3-methylphenylcarbamate) as chiral selector and polar organic mobile phases

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SUMMARY

The ophthalmic solution of voriconazole, i.e. (2*R*,3*S*)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol, made from an injection formulation which also contains sulfobutylether-β-cyclodextrin sodium salt as an excipient (Vfend®), is used for the treatment of fungal keratitis. A liquid chromatographic (LC) method using polar organic mobile phase and cellulose tris(4-chloro-3-methylphenylcarbamate) coated on silica as chiral stationary phase was successfully developed to evaluate the chiral stability of the ophthalmic solution. The percentage of methanol (MeOH) in the mobile phase containing acetonitrile (ACN) as the main solvent significantly influenced the retention and resolution of voriconazole and its enantiomer ((2*S*,3*R*)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol). The optimized mobile phase consisted of ACN/MeOH/diethylamine/trifluoroacetic acid (80/20/0.1/0.1; v/v/v/v). The method was found to be selective not only regarding the enantiomer of voriconazole but also regarding the specified impurities described in the monograph from the European Pharmacopoeia. The LC method was then fully validated applying the strategy based on total measurement error and accuracy profiles. Under the selected conditions, the determination of 0.1% of voriconazole enantiomer could be performed. Finally, a stability study of the ophthalmic solution was conducted using the validated LC method.

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1. Introduction

Voriconazole, i.e. (2*R*,3*S*)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (cf. Fig. 1), marketed as a single stereoisomer, is an antifungal agent which has a potent activity against a broad spectrum of pathogens, including *Aspergillus*, *Candida*, *Cryptococcus*, *Fusarium*, and *Scedosporium* [1]. It is used in eye drops for the treatment of fungal keratitis [2–5]. The ophthalmic solution of (2*R*,3*S*)-voriconazole is prepared from the injection formulation (Vfend®) which also contains sulfobutylether-β-cyclodextrin (SBE-β-CD) sodium salt as an excipient in order to enhance the solubility of the drug.

Owens et al. developed a capillary electrophoretic method for the complete separation of the four voriconazole stereoisomers using SBE-β-CD as chiral selector [6]. They also described the separation of (2*R*,3*S*)-voriconazole and its enantiomer in liquid chromatography (LC) using neutral and anionic CDs as additives in the mobile phase. Al-Badriyeh et al. carried out a stability study of (2*R*,3*S*)-voriconazole 1% ophthalmic solution in LC using a C18 analytical column and a mobile phase consisting in a mixture of ACN and water (60:40; v/v) [7]. The samples, stored at 2–8 °C, were found to be stable during the study duration, i.e. 14 weeks. As a achiral LC method was used, the possible conversion of (2*R*,3*S*)-voriconazole to its enantiomer could not be evaluated.

In the monograph of voriconazole from the European Pharmacopoeia, five specified impurities are described: impurity D (voriconazole enantiomer), impurities A and C (obtained after in situ degradation of voriconazole in alkaline conditions),

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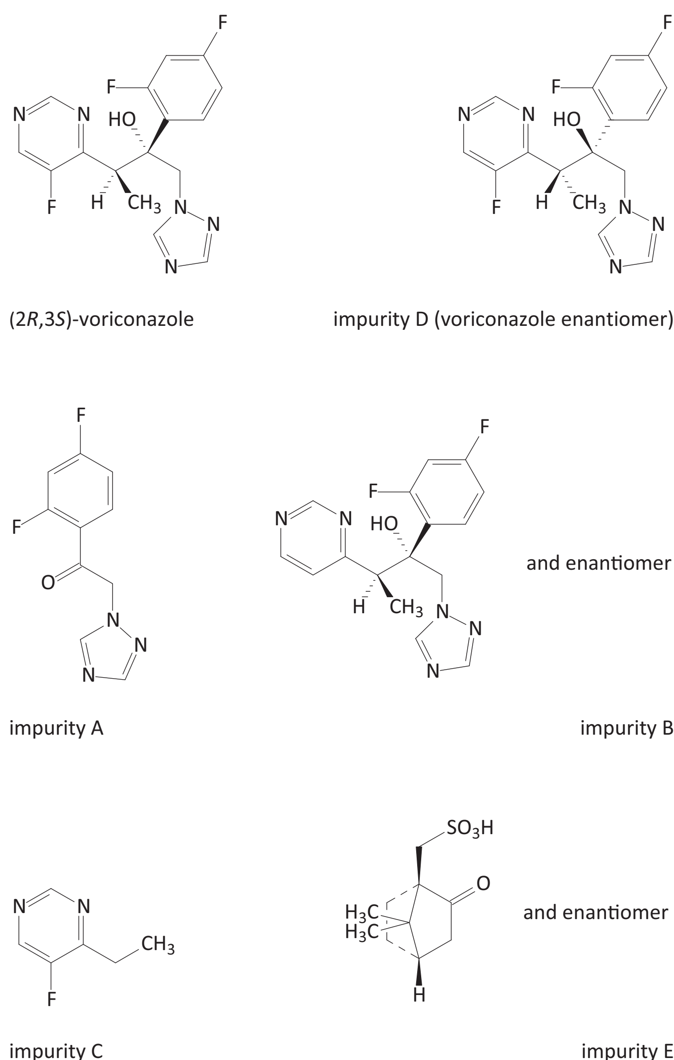

Fig. 1. Structures of (2*R*,3*S*)-voriconazole and its specified impurities D, A, B, C and E.

impurity B ((2*RS*,3*SR*)-2-(2,4-difluorophenyl)-3-pyrimidin-4-yl-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol) and impurity E ((±)-10-camphorsulfonic acid) (cf. Fig. 1) [8]. According to this monograph, the enantiomeric purity of (2*R*,3*S*)-voriconazole is controlled by a LC method. The separation has to be achieved on a chiral stationary phase (CSP), namely silica gel (5 μm) coated with β-CD, using a mobile phase made up of a mixture of ACN and a pH 5.0 ammonium acetate solution (18:82; v/v). Under these conditions, the analysis time is about 11 min and an enantioresolution of at least 4.0 between the peaks due to (2*R*,3*S*)-voriconazole and impurity D (eluting after the active enantiomer) is obtained. The limit in impurity D is settled to 0.2%. Specified impurities A, B and C are determined using another achiral LC method.

To the best of our knowledge, the chiral stability of (2*R*,3*S*)-voriconazole solution has never been investigated. The main goal of this study is to develop a reliable LC method for the determination of (2*R*,3*S*)-voriconazole and its enantiomer in 1% solution prepared from Vfend®, selectively from its related substances. To achieve this goal, a CSP with cellulose tris(4-chloro-3-methylphenylcarbamate) and a polar organic mobile phase were used. Moreover, the method was fully validated according to the strategy proposed by a Commission of the Société Française des Sciences et Techniques Pharmaceutiques (SFSTP) for the validation of quantitative analytical procedures [9–11]. From a statistical point of view, this strategy is based on the use of accuracy profiles which take into account the total error, i.e. estimation of systematic and random errors of measurement. Finally, a stability study of the 1% ophthalmic solution was conducted using the validated LC method.

2. Materials and methods

2.1. Instrumentation

The chromatographic system from Agilent Technologies (Waldbronn, Germany) consisted in a quaternary pump, an automatic injector, a thermostated column compartment and a diode array detector, all of 1100 series. The Chemstation software was used for system control and data acquisition. The chiral column Sepapak-4 (250 mm × 4.6 mm I.D.; 5 μm), equivalent to Lux® Cellulose 4 from Phenomenex, was provided by Sepaserve (Münster, Germany). The chiral selector adsorbed on aminopropylsilanized silica was cellulose tris(4-chloro-3-methylphenylcarbamate).

The statistical calculations for validation were performed by means of e.noval version 3.0 software (Arlenda, Liège, Belgium).

2.2. Chemicals and reagents

Voriconazole and its impurities B and D were supplied by EDQM (Strasbourg, France). Vfend® powder for solution for perfusion was supplied by Pfizer (Kent, UK). Acetonitrile (ACN) and methanol (MeOH) of HPLC grade were provided by J.T.Baker (Deventer, The Netherlands). Diethylamine (DEA) and (±)-10-camphorsulfonic acid were supplied by Sigma-Aldrich (Steinheim, Germany). Trifluoroacetic acid (TFA) pro analysis was obtained from VWR Chemicals (Leuven, Belgium).

2.3. Chromatographic conditions

The mobile phases consisted of a mixture of ACN, MeOH, acidic additive (TFA) and basic additive (DEA). In all experiments, the basic and acidic additives percentages were settled at 0.1% (v/v). The optimal mobile phase consisted of ACN/MeOH/DEA/TFA (80/20/0.1/0.1; v/v/v/v), pumped at a constant flow-rate of 1.0 ml/min. The temperature was set at 40 °C, unless otherwise stated, and the injection volume was 40 μl. The analytes were detected photometrically at 256 nm.

Resolution (R_s) was calculated according to the standard expression based on peak width at half height [8].

2.4. Standard solutions

2.4.1. Solutions used for method development

The sample solutions were prepared by dissolving the analytes at concentrations ranging from 75 to 100 μg/ml for (2*R*,3*S*)-voriconazole and from 2 to 50 μg/ml for the impurities A, B, C and D in the tested mobile phase.

2.4.2. Sample solutions used for validation

2.4.2.1. Solutions used for calibration. Three calibration curves (k = 3) ranging from 50 to 150% relative to the nominal concentration of (2*R*,3*S*)-voriconazole, i.e. 100 μg/ml (m = 3), were carried out. Two independent samples (n = 2) were prepared per concentration level.

Three calibration curves (k = 3) ranging from 0.1 to 10 μg/ml of impurity D (m = 5) were carried out in a mixture of water and mobile phase (20:80; v/v). Two replicates (n = 2) were prepared per concentration level.

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