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Review

Chromatographic and electrophoretic techniques used in the analysis of triazole antifungal agents—a review

R.J. Ekiert, J. Krzek*, P. Talik

Jagiellonian University, Medical College, Pharmaceutical Faculty, Department of Inorganic and Analytical Chemistry, 9 Medyczna St., 30-688 Cracow, Poland

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ABSTRACT

Systematic review of literature coupled with integrative research of published data for triazole antifungal agents was done. The investigated literature covered chromatographic and electrophoretic methods developed in the last 10 years (2000–2009). The aim of this review was to compare different methodologies, assess preferences in the selection of analytical methods and to find still existing analytical problems. Last decade is characterized by dynamic development of instrumental methods, that results in advance and diversity of applied analytical procedures. The main focus was given to high-performance liquid chromatography (HPLC), the technique of choice in the analysis of most of pharmaceuticals. The review includes literature on 8 triazole antifungal drugs: fluconazole, itraconazole and terconazole from the first generation and posaconazole, voriconazole, ravuconazole, isavuconazole and albaconazole classified in second generation. Investigations of pharmaceutical formulations and biological samples were considered.

Contents

1. Introduction

1.1. Triazole antifungal agents

Fungicidal properties of azole agents were discovered in 1944 by D.W. Woolley. Chlormidazole is the first compound in this group which has been marketed and used in medical practice since 1958. It was recommended for topical application. Investigations led to registration of a variety of imidazolic drugs, namely ketoconazole, miconazole, econazole, clotrimazole, and bifonazole. Introduction of the first generation triazole derivatives brought real breakthrough in the prevention and treatment of invasive fungal infections. Fluconazole and itraconazole can be used by both parenteral and oral route, whereas terconazole was available in topical dosage form. Triazoles exhibit wider antifungal activity spectrum, better safety profile and higher efficacy, compared with hitherto used imidazole derivatives. In the 90s, the second generation triazoles were elaborated including voriconazole and posaconazole. Due to the strongest activity and lower toxicity they acquired permission for trade in recent years and are extensively used now. Their introduction to clinical practice hampered increasing the problem of microorganism resistance for the previous drugs [1–4]. Currently there are more triazole compounds in advanced investigation: ravuconazole, isavuconazole and albaconazole [5–9].

* Corresponding author. Tel.: +48 12 6205480; fax: +48 12 6205480.
E-mail address: jankrzek@cm-uj.krakow.pl (J. Krzek).

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As maintained by WHO Collaborating Centre for Drug Statistics Methodology anatomical-therapeutic-chemical classification (ATC) compounds under consideration are categorized as internally (J 02 AC) and externally (D 01 AC) used antifungal ones [10]. Azoles have common mode of action; they inhibit ergosterol synthesis, the main sterol constituent of fungal membranes, through blocking cytochrome P450-dependent enzyme: lanosterol 14-α-demethylase. Lack of ergosterol and accumulation of 14-α-methylated precursors result in dysfunction of membrane fluidity and activity of several enzymes located in membrane (e.g. chitin synthase). Consequently fungal growth and replication of its DNA are inhibited. Moreover azoles decrease adhesion potential of pathogen cells to host tissues and morphogenetic transformation of yeasts to mycelial form [1–9]. Triazoles have weak basic properties due to the presence of heterocyclic nitric atoms. They may form salts with acids. They are hardly soluble. Hopefully fluconazole is soluble in water what is utilized in preparing different kinds of pharmaceutical formulations. Almost all substances under consideration – excluding fluconazole – are chiral [11–13]. Triazole antifungals' chemical structure contain heterocyclic ring of 1,2,4-triazole as shown in Fig. 1.

1.2. Analytical methods

Triazoles can be analyzed by many different techniques, starting with classical ones (titrimetry), through optical and spectrophotometric, to electrochemical and separation methods. Reference pharmacopoeial elaborations [11–13] require for azoles, in most cases titrimetric method in waterless environment—acidimetric determination using perchloric acid as titrant. Endpoint should be established routinely in potentiometric way, or with indicator addition. Acidimetric determination is enabled by basic character of triazoles. It is important to note that this titrimetric procedure is suitable for analysing active substance *per se*, but is not proper to be determined in complex matrices such as medicinal preparations. The same case occurs for spectrophotometric techniques. There is necessity to analyze multi-ingredient samples by methods possessing separation potential.

Currently the most extensively used techniques in pharmaceutical analysis are chromatographical methods. They enable separation, identification and determination of huge amount of bilogically active compounds. Among chromatographical techniques the special focus should be given to liquid chromatography (LC), especially high-performance liquid chromatography (HPLC), the technique of choice in the analysis of drugs and emerging ultra performance liquid chromatography (UPLC). Gas chromatography (GC) enables determination of volatile compounds, whereas thin-layer chromatography (TLC) is exploited mainly in qualitative analysis. TLC was preceded by paper chromatography (PC), which is used even today in some kinds of examinations because of its simplicity. Supercritical fluid chromatography (SFC) is exploited especially in enantioselective analysis.

Another group of separation techniques with huge analytical potential is capillary electrophoresis (CE). According to separation mechanism, applied electrolytes and columns, we can distinguish capillary zone electrophoresis (CZE), capillary gel electrophoresis (CGE), capillary isoelectric focusing (CIEF), isotachophoresis (ITP), electrokinetic chromatography (EKC), micellar electrokinetic capillary chromatography (MEKC) and capillary electrochromatography (CEC). In all options of capillary electrophoresis partition is based on different rates of migration of analyzed compounds caused by external voltage. Obviously there is also possibility to determine drugs utilizing planar electrophoresis (PE).

Current analytical chemistry requires that all the methods should be validated. There is a necessity to prove that elaborated procedure is suitable for intended analytical purpose and

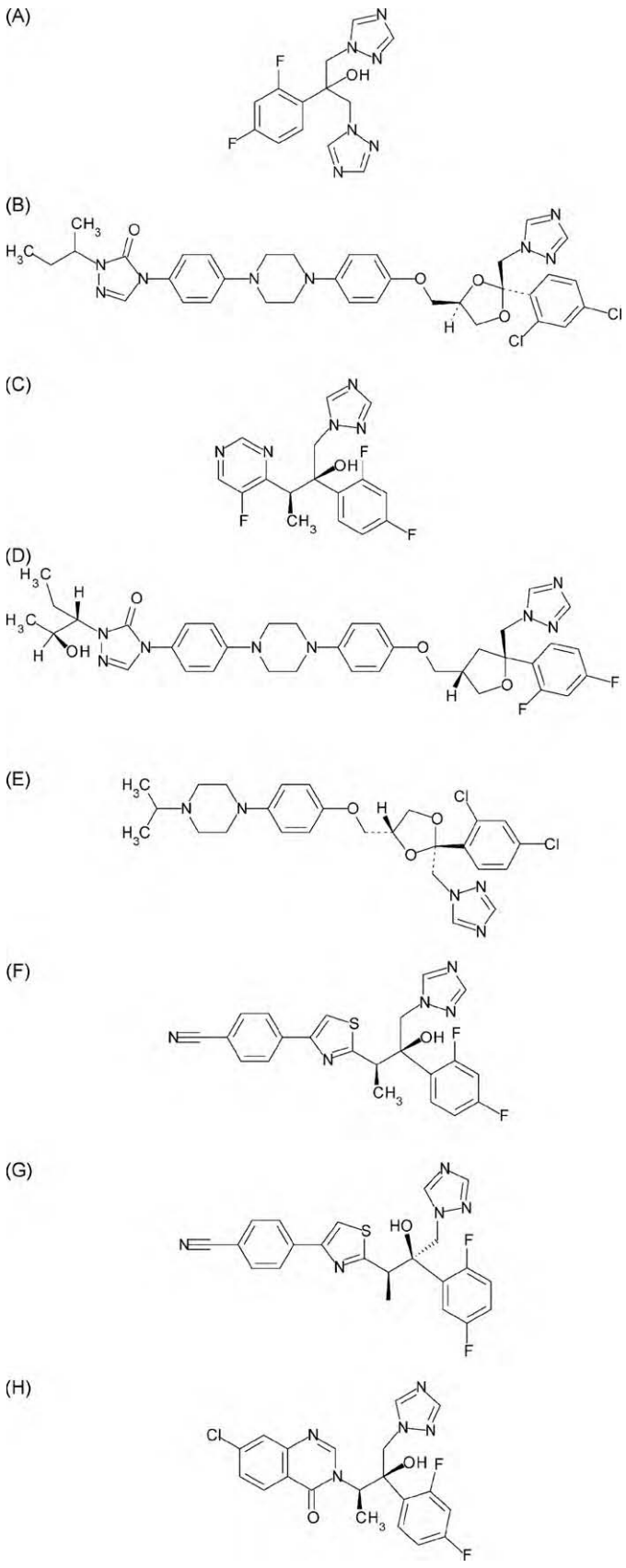

Fig. 1. Chemical structures of triazoles: fluconazole (A), itraconazole (B), voriconazole (C), posaconazole (D) terconazole (E), ravuconazole (F), isavuconazole (G) and albaconazole (H).

leads repetitively to the accurate results. There are many guidelines issued by medical authorities that advise how to perform validation. The most important ones are "Validation of analytical procedures. Text and methodology" which was released by International Conference on Harmonization (ICH) and "Guidance for industry; Bioanalytical Method Validation" issued by Food and Drug Administration. Criteria that need to be successfully fulfilled are selectivity/specifity, precision and linearity in defined range, accuracy. Usually there is also need to establish limit of method detection and quantification, robustness and ruggedness and perform system suitability testing. All analytical procedures mentioned in this paper were successfully validated. Investigated literature covered chromatographic and electrophoretic methods developed in the last 10 years (2000–2009) which become from all relevant biomedical databases.

2. Liquid chromatography

Current high-performance liquid chromatography is widely used in the analysis of triazole antifungal drugs. Amount of elaborations and diversity of applied parameters for substances under consideration can be clearly seen in Tables 1–7 . It is worth to focus on different detection possibilities, types of columns and variety of mobile phases. There are three types of detectors used: UV (ultra-violet) sometimes in form of DAD (diode array detector), MS (mass spectrometry) and fluorometric. In description of columns wherever RP is mentioned it means reversed phase, and ID is the abbreviation of internal diameter of column. Single particle size of column fillings is brought up in μm scale. Data are presented in the same form as in original papers.

We have found some other records for fluconazole [127–129], itraconazole [130–134], voriconazole [135–140] and posaconazole [141] connected with HPLC technique, which are not publicly available. There are only two papers describing HPLC-MS/MS procedures of analysis for isavuconazole [142,143] and two positions for ravuconazole: one with UV detection [144] and the other with fluorometry [145]. Literature contain no papers for terconazole and albaconazole. As presented in tables, LC analysis is usually carried out in the reversed-phase mode on C18 silica columns, ranging from 125 to 250 mm in length and internal diameter of 4.6 mm. Isocratic elution is applied commonly. Mobil phases typically contain mixtures based on acetonitrile, water, methanol and buffers (pH acidic or neutral). Such combination of parameters could be treated as "ideal configuration" for determinations both in pharmaceutical and biological matrices performed using HPLC technique. Differences in analytical procedures performed on pharmaceutical and biological matrices are seen only on the preparation stage. Biological matrix needs additional processes such as protein precipitation, dialysis, or extraction to solid phase using solid-phase extraction SPE, solid-phase microextraction SPME, accelerated solvent extrac-

Table 1
HPLC procedures used in the analysis of fluconazole in biological matrices.

Detection	Sample matrix	Chromatographic column	Analytic eluent	Reference
UV (210 nm)	Human blood	C18 Symmetry (250 mm × 4.6 mm ID; 5 μm)	Acetonitrile/water (36:64, v/v)	[14]
UV (210 nm)	Human plasma	CAPCELL PAK UG 120 C18 RP (250 mm × 4.6 mm ID; 5 μm)	Acetonitrile/sodium phosphate buffer (30:70, v/v, pH 5.7)	[17]
UV (260 nm)	Rat plasma and dialyzing fluid	CAPCELL PAK C18 (150 mm × 4.6 mm ID)	Acetate buffer (pH 5.0)/acetonitrile (80:20, v/v)	[18]
UV (260 nm)	Human serum	Lichrospher 60 RP select B (250 mm × 4.0 mm ID; 10 μm)	Methanol/water/glacial acetic acid (30:70:0.3, pH 5.6)	[19]
UV (210 nm)	Human plasma	Luna C18(2) (150 mm × 4.6 mm ID)	Acetate buffer (pH 5.0)/methanol (65:35)	[20]
UV (210 nm)	Rat plasma and microdialysate	Nucleosil® C18 HD (150 mm × 1.0 mm ID; 3 μm)	Diammonium phosphate buffer (pH 7.0)/acetonitrile (75:25, v/v)	[21]
UV (210 nm)	Human plasma	BDS Hypersil C18 (150 mm × 4.6 mm ID)	Sodium acetate buffer (pH 5.0)/methanol (78:22)	[22]
UV (210 nm)	Rat blood and dermis microdialysates	Nucleosil® C18 HD (150 mm × 1.0 mm ID; 3 μm)	Diammonium phosphate/acetonitrile (75:25, v/v, pH 7.0)	[23]
UV (210 nm)	Rat blood and bile	Zorbax extend phenyl RP C18 (150 mm × 4.6 mm ID; 5 μm)	Methanol/1-octanesulfonic acid (30:70, v/v, pH 3.0)	[24]
DAD-UV (210 nm)	Human and rat plasma	SuperPac Sephasil RP C18 (250 mm × 4.0 mm ID; 5 μm)	Sodium acetate (pH 5.0)/methanol (70:30)	[25]
UV (210 nm)	Human aqueous humor	Bondapak C-8 (150 mm × 6.0 mm ID; 5 μm)	Acetonitrile/water (15:85, v/v)	[26]
Fluorometric, DAD-UV, MS	Human plasma	No data	No data	[27]
DAD-UV (260 and 210 nm)	Human plasma	Gemini C6-Phenyl (150 mm × 4.6 mm ID; 5 μm)	Phosphate buffer (pH 7.0)/orthophosphoric acid/acetonitrile (gradient elution)	[29]
UV (261 nm)	Human saliva	Xterra RP18 (250 mm × 4.6 mm ID; 5 μm)	Acetate buffer (pH 5.0)/methanol (70:30, v/v)	[30]
UV (260 nm)	Human plasma	Symmetry C18 (150 mm × 3.9 mm ID; 5 μm)	Sodium acetate (pH 5.0)/methanol/acetonitrile (75:20:5, v/v/v)	[31]
DAD-UV (254 nm)	Human cerebrospinal fluid	Purospher STAR RP-18 (55 mm × 4.0 mm ID; 3 μm)	Sodium dihydrogen phosphate/methanol/acetonitrile (82.7:7.1:10.2)	[32]
No data	Rabbit eye	No data	No data	[33]
UV (210 nm)	Human serum	Nucleosil 100-5 C18 (250 mm × 4.6 mm ID; 5 μm)	Acetonitrile/sodium dihydrogen phosphate buffer (pH 5.0) (26.8:73.2, v/v)	[34]
UV [210 nm (1), 260 nm (2)]	Human plasma (1) and urine (2)	RP C8 Ultrasphere Octyl (250 mm × 4.6 mm ID; 5 μm)	Disodium phosphate buffer (pH 4.0)/acetonitrile (80:20)	[35]
DAD-UV (260 nm)	Rabbit vitreous, aqueous, retinachoroid and cornea	Lichrospher RP18	Methanol/potassium phosphate buffer (1:1)	[36]

Table 2
HPLC procedures used in the analysis of fluconazole in pharmaceutical matrices.

Detection	Sample matrix	Chromatographic column	Analytic eluent	Reference
UV (260 nm)	Pharmaceutical preparations (Diflucan capsules 50 mg or 150 mg; Diflucan i.v. infusion 2 mg/ml) and reference standard	RP Bondapak™ C18 (250 mm × 4.6 mm ID; 10 μm)	Acetonitrile/trishydroxymethyl aminomethane in phosphate buffer (pH 7.0) (55:45, v/v)	[15]
UV (254 nm)	Reference standard, 100.3% with respect to dry mass (Pliva SA)	Purosphere STAR RP-18 (55 mm × 4.0 mm ID; 3 μm)	Sodium dihydrogen phosphate·H_2O/methanol/acetonitrile (82.7:7.1:10.2, v/v/v)	[16]
UV (260 nm)	Pharmaceutical preparations in the form of capsules containing 200 mg (Diflucan, Biozole, Flucozole, Funa, Flunco 200, Stalene 200) and i.v. injections (Diflucan 2 mg/ml)	RP Hypersil ODS (120 mm × 46 mm ID; 5 μm)	Methanol/phosphate buffer (pH 7.0) (50:50)	[28]
UV (260 nm)	Pharmaceutical formulation in the form of capsules 250 mg prepared in laboratory	Purospher STAR RP-18 (150 mm × 4.6 mm ID; 5 μm)	Methanol/water (40:60, v/v)	[37]
UV (260 nm)	Pharmaceutical preparations in form of capsules (Flucan, Fluzide, Cancap, Antican-O), uncoated tablets (Zefun) and dispersible tablets (AF-150); all formulations claimed to contain 150 mg of fluconazole	Gemini C18 RP (150 mm × 4.6 mm ID; 5 μm)	Water/acetonitrile (65:35, v/v)	[38]
UV (260 nm)	Pharmaceutical injectable formulations	Synergi Fusion RP-80 C18 (150 mm × 4.6 mm ID; 4 μm)	Water/methanol (55:45, v/v)	[39]

Table 3
HPLC procedures used in the analysis of itraconazole in biological matrices.

Detection	Sample matrix	Chromatographic column	Analytic eluent	Reference
Fluorometric (emission 380 nm)	Human plasma	C18 Symmetry™ (150 mm × 3.9 mm ID)	Methanol/water (75:25, v/v)	[40]
MS/MS	Human plasma	YMC hydrosphere C18 (50 mm × 2.0 mm ID; 3 μm)	Acetonitrile/ammonium acetate (90:10, v/v)	[42]
UV (263 nm)	Human plasma	RP Symmetry C18	Water/acetonitrile (40:60, v/v, pH 7.8, diethylamine addition)	[45]
UV, fluorometric	Human plasma	No data	No data	[46]
No data	Human plasma	No data	No data	[47]
UV (263 nm)	Human plasma	Develosil C8-5 (150 mm × 4.6 mm ID; 5 μm)	Phosphate buffer/acetonitrile (35:65, v/v, pH 6.0)	[48]
UV (255 nm)	Human serum	Zorbax SB-C18 (250 mm × 4.6 mm ID; 5 μm)	Phosphate buffer (pH 6.0)/acetonitrile/methanol (35:45:20, v/v/v)	[49]
UV (263 nm)	Human plasma	Grand Pack C8 RP (150 mm × 4.6 mm ID; 5 μm)	Potassium dihydrogen phosphate (pH 4.5)/acetonitrile (47:53, v/v)	[50]
Fluorometric (emission 380 nm)	Human plasma	Kromasil RP C18 (250 mm × 4.6 mm ID; 5 μm)	Triethylamine (pH 2.8, orthophosphoric acid and acetonitrile addition)/isopropanol (90:10, v/v)	[51]
Fluorometric (emission 365 nm)	Human plasma	Genesis CN (250 mm × 4.6 mm ID; 4 μm)	Potassium dihydrogen phosphate/acetonitrile (1:1, v/v, pH 3.0, hydrochloric acid addition)	[52]
UV (263 nm)	Human plasma	Alltima C18 RP (250 mm × 4.6 mm ID; 5 μm)	Acetonitrile/water/methanol (570:350:80, v/v/v, pH 5.0, phosphoric acid addition)	[53]
Fluorometric (emission 363 nm)	Human plasma	Symmetry C18 RP (100 mm × 4.6 mm ID; 3.5 μm)	Acetonitrile/triethylamine water solution with phosphoric acid addition, (pH 3.0) (55:45, v/v)	[54]
Fluorometric (emission 365 nm)	Human plasma	NovaPak C18 (100 mm × 8.0 mm ID; 4 μm)	Water (phosphoric acid addition, pH 2.5)/acetonitrile/triethylamine (420:580:100, v/v/v)	[55]
MS	Rat plasma	BDS Hypersil C18 RP (50 mm × 2.0 mm ID; 3 μm)	Ammonium formate (pH 4.0)/acetonitrile (60:40, v/v)	[56]
MS	Dog plasma	Zorbax SB-C18 (30 mm × 4.6 mm ID, 3.5 μm)	Acetonitrile/ammonium acetate (pH 3.5) (60:40, v/v)	[57]
No data	Human blood and lung tissue	RP	No data	[58]
Fluorometric, DAD-UV, MS	Human plasma	No data	No data	[27]
DAD-UV (260 and 210 nm)	Human plasma	Gemini C6-Phenyl (150 mm × 4.6 mm ID; 5 μm)	Phosphate buffer (pH 7.0)/orthophosphoric acid/acetonitrile (gradient elution)	[29]

Table 4
HPLC procedures used in the analysis of itraconazole in pharmaceutical matrices.

Detection	Sample matrix	Chromatographic column	Analytic eluent	Reference
UV (210 nm)	Pharmaceutical formulation (nanoparticles dispersion, 145 nm) and reference standard	Zorbax SB-Aq	Phosphoric acid/acetonitrile (90:10, v/v)	[41]
UV (260 nm)	Pharmaceutical formulation in the form of mixture of itraconazole and ordered mesoporous silica (triblock copolymer Pluronic P123, sodium silicate, water)	Hypersil RP-18 (150 mm × 4.6 mm ID; 5 μm)	Acetonitrile/tetrabutyl ammonium hydrogen sulfate (55:45, v/v)	[43]
UV (260 nm)	Pharmaceutical formulation; solid dispersions in polyethyleneglycol PEG 6000 and hydroxypropylmethylcellulose HPMC 2910 E5	LiChrospher 100 RP-18 (12.5 mm × 4.0 mm ID; 5 μm)	Acetonitrile/tetrabutyl ammonium hydrogen sulfate (55:45, v/v)	[44]
UV (260 nm)	Pharmaceutical formulation; solid dispersions in D-α-tocopheryl polyethylene glycol TPGS 1000 and polyvidone-vinylacetate PVPVA 64	LiChrospher 100 RP-18 (12.5 mm × 4.0 mm ID, 5 μm)	Acetonitrile/tetrabutyl ammonium hydrogen sulfate (55:45, v/v)	[59]
DAD-UV (220 nm)	Cosmetic preparation (antidandruff shampoo and lotion)	Discovery RP-Amide C16 (150 mm × 4.6 mm ID; 5 μm)	Acetonitrile/sodium perchlorate aqueous solution (pH 3.0) (gradient elution)	[60]

tion ASE, etc.). In case of pharmaceutical matrices, especially when tablets are analysed, milling, crushing, grinding with further sonication or shaking is needed. In both conditions dilution, enrichment or derivatization should be considered. Miscellaneous procedures can be ideal for various analytical purposes so diversity in applied conditions should be treated as an advantage. All analyses performed on pharmaceutical formulations or preparations were drug assays, their purpose was to determine triazole active substance.

One interesting paper describing ultra-pressure liquid chromatographic (UPLC) elaboration for, among others, several azoles: flubendazole, propiconazole, ketoconazole, miconazole and itraconazole, focuses on matrix effects [146]. This research was carried out on 100 mm × 2.1 mm ID; 1.8 μm column. Electrospray ionization MS/MS was used for detection purposes.

3. Gas chromatography

GC is seldom employed in researches of azole antifungal drugs despite, that these compounds can be determined directly without the need of derivatization. There were only two publications in this subject. Ekiert et al. [147] presented holistic method for identification, separation and determination of six commonly used azoles; bifonazole, clotrimazole, econazole, fluconazole, ketoconazole and miconazole. Flame-ionization detector (FID) was used and cholesterol acted as internal standard. Lima and colleagues [148] showed how GC–MS can be used for determination of fluconazole in serum and amniotic fluid of rats. Tioconazole was of internal standard. In both procedures injection has been made with split and derivatization was unnecessary. In the first paper HP-1 column (15 m × 0.25 mm ID) with polydimethylsiloxane enabled analysis, whereas in the second CBP-5 (30 m × 0.25 mm ID) phenylmethylpolysiloxane.

4. Thin-layer chromatography

TLC is the next technique not used too extensively in the analysis of TAA. There is a pity that researchers do not exploit it enough because it gives large analytical possibilities in conjunction with densitomery, even comparable with those obtained with HPLC. We found only three papers. Ekiert et al. [149] discovered new procedure for the separation and identification of four azoles; bifonazole, fluconazole, itraconazole and ketoconazole. Because of exploitation of densitometric detection qualitative analysis was performed too. Estimation of the hydrophobicity of bifonazole, clotrimazole, fenticonazole, fluconazole, ketoconazole, miconazole, metronidazole and itraconazole was performed by Aleksic et al. [150]. Marciniec et al. [16] investigated the influence of ionizing radiation on fluconazole stability. Results show negligible destruction.

As in all TLC elaborations, composition of mobile phase plays a pivotal role in successful separation. Ekiert et al. [149] used two phases: hexane-ethyl acetate-methanol-water-glacial acetic acid and chloroform-ethyl acetate-glacial acetic acid-water. Aleksic et al. [150] carried analysis with: acetone-n-hexane, methanol-toluene, and methyl ethyl ketone-toluene containing different amounts of organic modifier. Marciniec et al. [16] employed five different compositions: toluene-isopropanol-25% ammonia, chloroform-methanol-water, cyclopean-ethylene chloride-methanol-100% acetic acid, 1-butanol-water-100% acetic acid, and chloroform-aceton-methanol-25% ammonia. In all three described procedures chromatographic process was performed on silica gel 60 plates.

5. Supercritical fluid chromatography

There are only two papers describing analytical procedures using SFC. Results published by Toribio et al. [151] and Garzotti and Hamdan [152] present enantioselective separation of 4 compounds in azole group: miconazole, econazole, sulconazole and itraconazole. In the first paper DAD detector was used, whereas in the second, hybrid quadrupole time of flight (Q-Tof2) MS and UV detection were employed. Toribio used amylose-based chiral stationary phase Chiralpak AD, Garzotti Chiralpak AD and cellulose-based Chiralcel OD and Chiralcel OJ. All these columns have dimensions of 250 mm × 4.6 mm. Times of analysis performed by Toribio was below 10 min for miconazole, econazole and sulconazole. Itraconazole was highly retained. Garzotti and Hamdan reached time below 25 min for all analytes.

6. Capillary electrophoresis

Some interesting researches were done using CE technique. We have found seven adequate publications. Breadmore and Thormann [153] performed stereoselective separation and determination of itraconazole and its active metabolite hydroxyitraconazole in

Table 5
HPLC procedures used in the analysis of voriconazole in biological matrices.

Detection	Sample matrix	Chromatographic column	Analytic eluent	Reference
UV (260 nm)	Human plasma	ReproSil-Pur Basic C18 (150 mm × 2.0 mm ID; 5 μm)	Aqueous ammonium phosphate monobasic/acetonitrile (50:50, v/v)	[63]
UV (255 nm)	Human plasma	C8 plus Satisfaction (250 mm × 3.0 mm ID; 5 μm)	Sodium potassium phosphate buffer (pH 6.0)/acetonitrile/water (45:52.5:2.5, v/v/v)	[64]
UV (255 nm)	Human serum	Zorbax SB-C18 (250 mm × 4.6 mm ID; 5 μm)	Phosphate buffer (pH 6.0)/acetonitrile/methanol (35:45:20, v/v/v)	[49]
UV (256 nm)	Rat and dog plasma	Diamonsil C(18) (250 mm × 4.6 mm ID; 5 μm)	Acetonitrile/water/acetic acid (55:45:0.25, v/v/v)	[65]
Fluorometric (emmision 372 nm)	Human plasma and saliva	Luna C18 100A (250 mm × 3.0 mm ID; 5 μm)	Potassium dihydrogen phosphate buffer (pH 6.8, addition of tetramethylethylenodiamine)/acetonitrile (55:45, v/v)	[66]
UV (255 nm)	Human plasma	C18 (250 mm × 4.6 mm ID; 5 μm)	Acetonitrile/ammonium dihydrogen phosphate buffer (pH 6.0) (50:50, v/v)	[67]
UV (255 nm)	Human plasma	Pinkerton ISRP GFF II® (150 mm × 4.6 mm ID; 5 μm)	Acetonitrile/potassium dihydrogen phosphate buffer (pH 6.0) (17:83, v/v)	[68]
MS/MS	Rat plasma	Shim-pack C18 (150 mm × 4.6 mm ID; 5 μm)	Acetonitrile/water/formic acid (60:40:0.05, v/v/v)	[69]
UV (255 nm)	Human plasma	Chromolith® RP 18e (100 mm × 4.6 mm ID)	Ammoniumdihydrogencarbonate buffer (pH 5.8)/acetonitrile/tetrahydrofuran (72:25:3, v/v/v)	[70]
UV (254 nm)	Human plasma	C18 (250×4.6 mm ID; 5 μm)	Phosphate buffer (pH 7.4, addition of tetramethylethylenodiamine)/acetonitrile/ammonium acetate (gradient elution) and phosphate buffer (pH 7.4, addition of tetramethylethylenodiamine)/acetonitrile (65:35, v/v)	[71]
No data	Human vitreous humor	No data	No data	[72]
UV (254 nm)	Alpaca plasma	BetaBasic-18 (150 mm × 4.6 mm ID; 5 μm)	Tetramethylethylenodiamine (pH 7.4)/methanol (35:65, v/v)	[73]
UV (255 nm)	Human plasma	C18	No data	[74]
MS/MS	Human plasma	Atlantis C18 (50 mm × 2.1 mm ID; 5 μm)	No data	[76]
UV (254 nm)	Human plasma and microdialysate	LiChrospher-100 RP18 (125 mm × 4.0 mm ID; 5 μm)	Acetonitrile/ammonium phosphate buffer (pH 6.0) (40:60, v/v)	[77]
DAD-UV (256 nm)	Rabbit aqueous humor	Atlantis C18	No data	[78]
UV (254 nm)	Rat microdialysate	Schimadzu C18 RP (150 mm × 4.0 mm ID)	Acetonitrile/ammonium monobasic phosphate buffer (60:40, v/v, pH 6.0)	[79]
MS/MS	Human plasma	No data	No data	[80]
UV (255 nm)	Human plasma	Ultrasphere ODS Beckman (250 mm × 4.6 mm ID)	Acetonitrile/ammonium phosphate buffer (1:1, v/v, pH 6.0)	[81]
UV (255 nm)	Human aqueous and vitreous fluid	C18 (250 mm × 4.6 mm ID; 5 μm)	Acetonitrile/ammonium phosphate buffer (pH 6.0) (50:50, v/v)	[82]
DAD-UV (255 nm)	Human plasma	Nucleosil 300-5, RP C18 (150 mm × 4.6 mm ID)	Methanol/sodium acetate buffer (pH 5.0) (1:1, v/v)	[83]
UV (254 nm)	Human serum and plasma	Supelcosil LC-18-DB (250 mm × 4.6 mm ID; 5 μm)	Acetonitrile/potassium phosphate (pH 3.0) (gradient elution)	[84]
UV (254 nm)	Guinea pig blood, skin tissue and interstitial fluid	LiChrospher-100 RP-18 (125 mm × 4.0 mm ID; 5 μm)	Acetonitrile/ammonium phosphate buffer (46:54, v/v, pH 6.0)	[85]
UV (255 nm)	Human serum	Kromasil (250 mm × 4.6 mm ID; 5 μm)	Acetonitrile/ammonium phosphate buffer (1:1, v/v, pH 6.0)	[86]
UV (257 nm)	Rabbit vitreous and aqueous humor	Lichrospher 100RP-18e (250 mm × 4.0 mm ID; 5 μm)	Acetonitrile/water, both with trifluoroacetic acid addition (gradient elution)	[87]
DAD-UV	Human synovial fluid and bone tissue	No data	No data	[88]
DAD-UV (255 nm)	Human plasma	Nucleosil 300-5, RP C18 (150 mm × 4.6 mm ID)	Methanol/sodium acetate buffer (pH 5.0) (1:1, v/v)	[90]
UV (1) and MS (2)	Human plasma (1) and human aqueous humor (2)	Luna C18 (500 mm × 2.0 mm ID; 3 μm)	Ammonium acetate (including acetic acid)/acetonitrile (65:35, v/v)	[91]
UV (1) and MS (2)	Human plasma (1) and human brain tissue (2)	Luna C18 (500 mm × 2.0 mm ID; 3 μm)	Ammonium acetate (including acetic acid)/acetonitrile (65:35, v/v)	[92]
MS	Human plasma and urine	Luna C18 (250 mm × 4.6 mm ID; 5 μm)	Phosphate buffer (pH 7.4, tetramethylethylenediamine addition)/acetonitrile (55:45, v/v)	[93]
MS	Human plasma and bronchoalveolar lavage	No data	No data	[94]
MS/MS	Human plasma	LiCrospher® 100 RP-18 (125 mm × 4.0 mm ID; 5 μm)	Water/methanol (95:5, v/v)	[95]
UV (255 nm), MS	Human serum	Sphereclone ODS2 (150 mm × 4.6 mm ID; 3 μm)	Acetontrile/ammonium dihydrogen phosphate buffer (40:60, v/v, pH 6.0)	[96]
UV (255 nm)	Guinea pig plasma	BDS-C18 Hypersil (100 mm × 4.6 mm ID; 3 μm)	Acetonitrile/sodium phosphate (pH 3.0) (45:55, v/v)	[97]

Table 5 (*Continued*).

Detection	Sample matrix	Chromatographic column	Analytic eluent	Reference
MS	Human plasma and urine	Luna C18 (50 mm × 2.0 mm ID; 3 μm)	Ammonia acetate (acetic acid addition)/acetonitrile (65:35, v/v)	[98]
DAD-UV (254 nm)	Human plasma	Luna C18 (250 mm × 4.6 mm ID; 5 μm)	Phosphate buffer (pH 7.4, tetramethylethylenediamine addition)/acetonitrile (55:45, v/v)	[99]
No data	Human aqueous and vitreous	No data	No data	[100]
MS/MS	Human serum	Nucleodur 100-5 C18ec (125 mm × 4.6 mm ID; 5 μm)	Formic acid in water/acetonitrile (50:50, v/v)	[101]
UV (254 nm)	Human plasma, dialysate, urine and pharmaceutical preparation	Luna RP C18 (250 mm × 4.5 mm ID; 5 μm)	Phosphate buffer (pH 7.4, tetramethylethylenediamine addition)/acetonitrile (55:45, v/v)	[102]
UV (255 nm)	Human vitreous, aqueous and plasma	C18 (250 mm × 4.6 mm ID; 5 μm)	Acetonitrile/ammonium phosphate buffer (pH 6.0) (1:1, v/v)	[103]
DAD-UV (254 nm)	Human plasma	Luna C18 (250 mm × 4.6 mm ID; 5 μm)	Phosphate buffer (pH 7.4, tetramethylethylenediamine addition)/acetonitrile (55:45, v/v)	[104]
UV (254 nm)	Mouse, rat, rabbit, guinea pig, dog and human plasma	Spherisorb ODS2 (250 mm × 4.6 mm ID; 5 μm)	Tetramethylethylenediamine buffer (pH 7.4)/methanol (30:70, v/v)	[105]
MS/MS	Microsomes	No data	No data	[106]
DAD-UV (255 nm), MS	Rabbit aqueous humor	Delta PAK RP C18 (300 mm × 3.9 mm ID; 15 μm)	Acetonitrile/water/trifluoroacetic acid (70:29.99:0.01, v/v/v)	[107]
UV	Human plasma and saliva	No data	No data	[108]
Fluorometric, DAD-UV, MS	Human plasma	No data	No data	[27]
DAD-UV (260 nm and 210 nm)	Human plasma	Gemini C6-Phenyl (150 mm × 4.6 mm ID; 5 μm)	Phosphate buffer (pH 7.0)/orthophosphoric acid/acetonitrile (gradient elution)	[29]
UV (254 nm)	Human and guinea pig cerebrospinal fluid and brain tissue	No data	No data	[112]
DAD-UV	Human cerebrospinal fluid	No data	No data	[113]

human blood. Breadmore et al. [154] also determined itraconazole, hydroxyitraconazole and ketoconazole in human serum and plasma by MEKC. Another enantiomeric separation of itraconazole which was fully successful, was performed by Castro-Puyana et al. [155]. It was the first separation of all four stereoisomers of itraconazole done by EKC. Moreover, Castro-Puyana et al. [156] separated EKC isomers of ketoconazole and terconazole and performed enantioselective separation of six azoles: miconazole, econazole, sulconazole, ketoconazole, terconazole and bifonazole by EKC [157]. Crego et al. [158,159] analyzed ketoconazole, clotrimazole, itraconazole, fluconazole and voriconazole employing CZE.

Enantiomeric separations are a great advantage of capillary electrophoretic methods. In Breadmore and Thormann work [153] sulfated β-cyclodextrin (β-CD) acted as the chiral selector.

Table 6
HPLC procedures used in the analysis of voriconazole in pharmaceutical matrices.

Detection	Sample matrix	Chromatographic column	Analytic eluent	Reference
UV (250 nm)	Pharmaceutical formulations; regular production samples	Agilent Zorbax SB-C18 (250 mm × 4.6 mm ID; 5 μm)	Ammonium phosphate dibasic buffer (pH 6.0)/acetonitrile (52:48, v/v)	[61]
DAD-UV (255 nm)	Pharmaceutical formulation; solution (2%, 1%) prepared by reconstitution lyophilized powder (Vfend i.v. preparation) with water containing 0.01% benzalkonium chloride	C18 PhenoSphere-NEXT (250 mm × 4.6 mm ID; 5.0 μm)	Acetonitrile/water (60:40, v/v)	[62]
DAD-UV (255 nm)	Pharmaceutical formulation; 0.9% sodium chloride and 5% dextrose solutions prepared with lyophilized powder (Vfend 200 mg)	LiChrospher® 100 RP-8 (125 mm × 4.6 mm ID; 5 μm)	Methanol/triethylamine (pH 6.0) (50:50, v/v)	[75]
UV (256 nm)	Pharmaceutical formulation; 1 mg/ml solution prepared by dissolving Vfend preparation in water	RP C18 (250 mm × 4.6 mm ID; 5 μm)	Acetonitrile/water (50:50, v/v)	[89]
DAD-UV (255 nm)	Pharmaceutical formulation; oral suspension powder prepared by dilution of voriconazole in methanol to form 1 μg/ml solution	Phenomenex C18 RP (250 mm × 4.6 mm ID; 5 μm)	Water/acetonitrile (40:60, v/v, pH 4.5, acetic acid addition)	[109]
UV (255 nm)	Pharmaceutical preparation; Vfend tablets 50 mg, working solution 50 μg/ml	LiChrospher 100 RP-8 (125 mm × 4.6 mm ID; 5 μm)	Methanol/triethylamine solution (pH 6.0) (50:50, v/v)	[110]
DAD-UV (255 nm)	Pharmaceutical formulation; voriconazole 4 mg/ml solution in 5% dextrose	RP C18 Symmetry (250 mm × 4.6 mm ID; 5 μm)	Acetonitrile/phosphoric dihydrogen buffer (pH 6.0) (50:50, v/v)	[111]

Table 7
HPLC procedures used in the analysis of posaconazole in biological matrices.

Detection	Sample matrix	Chromatographic column	Analytic eluent	Reference
UV (260 nm)	Human plasma	ReproSil-Pur Basic C18 (150 mm × 2.0 mm ID; 5 μm)	Aqueous ammonium phosphate monobasic/acetonitrile (50:50, v/v)	[63]
UV (255 nm)	Human plasma	C8 plus Satisfaction (250 mm × 3.0 mm ID; 5 μm)	Sodium potassium phosphate buffer (pH 6.0)/acetonitrile/water (45:52.5:2.5, v/v/v)	[64]
MS/MS	Mouse, rat, dog and monkey serum	Beckman (150 mm × 4.6 mm ID; 5 μm)	Acetonitrile/water/ammonium acetate (45:54.95:0.05, v/v/v) and acetonitrile/ammonium acetate (99.95:0.05, v/v)	[114]
Fluorometric (emission 357 nm)	Human serum	Nucleodur® 100-5 C18ec (125 mm × 4.0 mm ID; 5 μm)	Formic acid (water solution)/acetonitrile (55:45, v/v)	[115]
MS/MS	Human plasma	Halo C18 (50 mm × 2.1 mm ID; 2.7 μm)	Acetic acid (water solution)/acetonitrile (gradient elution)	[116]
MS/MS	Human pulmonary epithelial lining fluid, alveolar cells and blood	No data	No data	[117]
UV (260 nm)	Human plasma	Luna RP C8 (150 mm × 4.6 mm ID; 5 μm)	Phosphate buffer (pH 6.7)/acetonitrile/methanol (43:49:8, v/v/v)	[118]
Fluorometric (emission 365 nm)	Human serum	Multohyp C18 BDS (250 mm × 4.6 mm)	Acetonitrile/methanol/phosphate buffer (8:1:1, v/v/v)	[119]
MS/MS	Human plasma	Polaris C-18A (50 mm × 2.0 mm ID; 5 μm)	Water/methanol/formic acid/acetonitrile (gradient elution)	[120]
UV, MS/MS	Human urine, feces and blood	Zorbax Rx-C8 (250 mm × 4.6 mm ID; 5 μm) and C18	Water/methanol/formic acid (gradient elution) and methanol/ammonium acetate (85:15, v/v)	[121]
DAD-UV	Human liver microsomes	Zorbax Rx-C8 (250 mm × 4.6 mm ID; 5 μm)	Water/methanol (gradient elution)	[122]
UV (262 nm)	Human plasma	C18 Intersil ODS-2 (150 mm × 4.6 mm ID; 5 μm)	Ammonium phosphate buffer (pH 4.5)/acetonitrile/methylene chloride/triethylamine (1060:940:10:1, v/v/v/v)	[123]
UV (262 nm)	Dog serum	C18 Ultrasphere ODS (150 mm × 4.6 mm ID; 5 μm)	Ammonium phosphate monobasic/acetonitrile/triethylamine (530:470:0.5, v/v/v)	[124]
Fluorometric (emission 390 nm)	Plasma or serum from rat, dog, monkey and human	Chiracel OD and Chiralpak AD	Hexane/ethanol/diethylamine (30:70:0.2, v/v/v and 35:65:0.3, v/v/v)	[125]
UV (262 nm)	Mouse, rat, rabbit, dog and monkey serum	C18 Ultrasphere (150 mm × 4.6 mm ID; 5 μm)	Acetonitrile/ammonium phosphate monobasic/methylene chloride/triethylamine (500:500:5:0.5, v/v/v/v)	[126]
Fluorometric, DAD-UV, MS	Human plasma	No data	No data	[27]
DAD-UV (260 nm and 210 nm)	Human plasma	Gemini C6-Phenyl (150 mm × 4.6 mm ID; 5 μm)	Phosphate buffer (pH 7.0)/orthophosphonic acid/acetonitrile (gradient elution)	[29]

Castro-Puyana [155–157] used neutral CD selector: heptakis-2,3,6-tri-*O*-methyl-β-CD and in one research [157] another neutral selector: (2-hydroxy)propyl-β-CD. In all elaborations fused-silica capillaries (50–75 μm ID) and UV detection enabled analysis. Time of single run was in most cases below 10 min.

7. Simultaneous determinations of TAA

Some authors find the simultaneous analysis of two or more azole antifungal agents to be justified. Certain biological or environmental samples could contain several of azoles. That's why any efforts leading to contemporary identification and determination are interesting and valuable from research and application point of view. Separation methods, such as chromatographical or electrophoretical ones are very helpful in this kind of analysis. There are 17 such elaborations published in 2000–2009. We specify papers describing parallel determination of triazoles or triazole with imidazole antifungal agents. 7 separations were performed by HPLC and include itraconazole with voriconazole [49], posaconazole and voriconazole [63,64], fluconazole, itraconazole, voriconazole, posaconazole [27], fluconazole, itraconazole, voriconazole, posaconazole with ketoconazole [29], clotrimazole, ketoconazole and fluconazole [15], ketoconazole, tioconazole, econazole, miconazole and itraconazole [60].

Four analyses were carried out using CE: two for ketoconazole, clotrimazole, itraconazole, fluconazole and voriconazole [158,159]. Castro-Puyana et al. [156] separated ketoconazole and terconazole in pharmaceutical formulations and performed enantioselective separation of miconazole, econazole, sulconazole, ketoconazole, terconazole and bifonazole [157]. Both SFC elaborations refer to parallel miconazole, econazole, sulconazole and itraconazole determination [151,152]. UPLC is the only paper that describes simultaneous analysis of flubendazole, propiconazole, ketoconazole, miconazole and itraconazole [146]. Ekiert and coworkers have separated bifonazole, clotrimazole, econazole, fluconazole, ketoconazole and miconazole by GC [147] and bifonazole, fluconazole, itraconazole and ketoconazole using TLC-densitometry [149]. Many azole agents (bifonazole, clotrimazole, fenticonazole, fluconazole, ketoconazole, miconazole, metronidazole and itraconazole) were analyzed by Aleksic et al. [150] in one run.

All described separation techniques are potent to perform partition of several azoles. Researcher need only to adjust parameters

such as mobile phase composition (polarity, pH), flow speed, applied or injected amount of sample. One can try different types of columns, i.e. stationary phases or detection modes, to find suitable type for assumed purpose. For example Ekiert et al. [147] in order to optimize capillary GC separation conditions had to set up temperature programme, inlet and detector temperature, choose type of column, detector, injection mode (split, splitless or on-column), find suitable internal standard and consider derivatization. Even details could be important but lead to successful result.

8. Data analysis and discussion

In this paper we have considered all chromatographic and electrophoretic techniques used in order to analyse triazole antifungal agents. There are no publications utilizing paper chromatography or planar electrophoresis. Isavuconazole and ravuconazole were analyzed only by HPLC, terconazole only by CE. There are no relevant publications for albaconazole. For the second generation triazoles there are no analytical elaborations performed by UPLC, GC, TLC or SFC. Generally the number of publications describing UPLC, GC, TLC, SFC or CE methods is not too big. We conclude that it is caused by their limitations. Investigators pay an attention mainly to HPLC. The use of different techniques elaborated in order to determine TAA is presented in Fig. 2. Diagram vividly shows primacy of high-performance liquid chromatography.

HPLC is the most versatile technique. It can be used for separation, identification and determination of active substances, excipients and impurities in one run. HPLC is proper for stability and pharmacokinetic studies. Time of analysis is short what enable significant throughput. HPLC is characterized by high resolution, selectivity, sensitivity, precision and accuracy. Derivatization of analytes is necessary very rarely, typically it enables direct quantitation. Technique is can be automated, and is widely available and flexible: there are many kinds of column fillings and detection modes. UV detector is used most often but if analyte has fluorescence properties fluorometric detector will fit. High-performance liquid chromatography can be joined with other detectors too: electrochemical, mass spectrometric, light-scattering, refractometric or utilizing circular dichroism phenomenon. Technique is commonly employed for enantioselective examinations. There are also some drawbacks of HPLC. Compared with e.g. biological assays or TLC procedures, high-performance liquid chromatography should be treat as an expensive method in terms of use and cost of instrumentation.

Preferences in employing detectors within high-performance liquid chromatography procedures are shown in Fig. 3. UV detector is most common due to its simplicity and convenience. Quite often DAD-UV mode is employed which gives much more information about the full spectra. As excitation and emission fluorescence spectra falls in the UV range this provides high sensitivity and minimizes background interferences. MS detectors are characterized by great sensitivity. Tandem mass spectrometry was employed rarely; it is a good solution for the identification of unknown agents. No LC-NMR or LC-IR investigations were made. It is justified by the fact that structure elucidation is not the purpose of investigations in pharmaceutical or clinical practice, where health-care professionals know or predict occurrence of concrete medication. To date, there were no electrochemical detectors employed. It is a surprise because they are extensively used in current analytical chemistry.

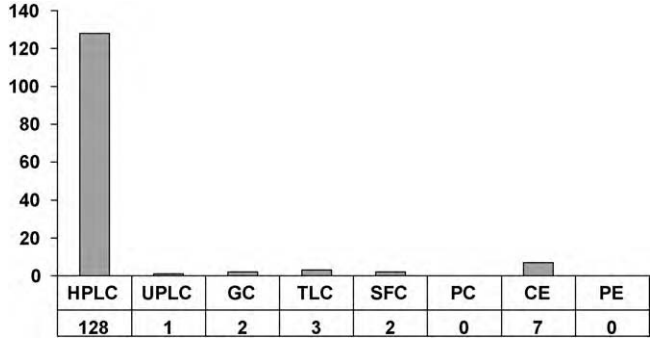

Fig. 2. Number of publications in 2000–2009 describing chromatographic or electrophoretic analysis of triazole antifungal agents. HPLC, high-performance liquid chromatography; UPLC, ultra-performance liquid chromatography; GC, gas chromatography; TLC, thin-layer chromatography; SFC, supercritical fluid chromatography; PC, paper chromatography; CE, capillary electrophoresis; PE, planar electrophoresis.

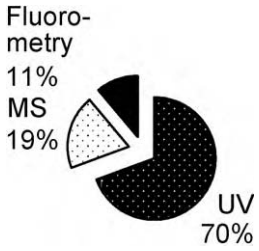

Fig. 3. Types of detection utilized in high-performance liquid chromatographic (HPLC) analytical procedures of triazole antifungal agents in 2000–2009. UV, ultraviolet detection; MS, mass spectrometric detection.

UPLC provides better performance than HPLC. UPLC is faster technique, provide better resolution, higher sensitivity, uses decreased amount of valuable solvents and is less vulnerable to matrix effects [146,160,161]. This technique operates at a pressure of 1000 bar, compared with approximately 400 bar in HPLC. GC remains the best solution when volatile (often after additional derivatization process), thermally stable and unpolar substance is analyzed. GC advantage is high sensitivity. TLC is a great tool in identification procedures but for qualitative purposes need to be hyphen with densitometry. The number of publications on SFC in TAA group is less. Despite its advantages, SFC technique does not supersede HPLC or GC. Nevertheless it plays a key role in the separation of chiral and high weight compounds [151,162–164].

CE has an excellent separation efficiency and uncommon speed (more rapid than HPLC). Consumption of reagents and sample is minimal. Sample does not need complicated, labour-consuming preparation. Disadvantages of this technique are: quite high limit of detection, poor precision and sometimes problems with accuracy. Capillary electrophoresis should be treated as alternative or complementary technique to HPLC. It promises a lot, but needs further development [165–168].

There are some interesting papers concerning therapeutic drug monitoring (TDM) of triazoles [169–171] which state that itaconazole, voriconazole and posaconazole concentrations should be monitored in clinical practice in order to reduce drug toxicity and optimize efficacy. Fluconazole has stable enough pharmacokinetic profile and is recommended for monitoring only in special cases. There are no relevant data available for ravuconazole. There is need to remember performing itraconazole determination that this compound has an active methabolite–hydroxyitraconazole, which also has to be determined. Therapeutic drug monitoring is also very important in terms of increasing resistance of fungi. It is a matter of international concern [27]. Authors engaged in TDM, indicate that techniques appropriate and useful in TDM are chromatographic ones, especially HPLC, capillary electrophoresis or bioassay.

9. Conclusions

Presented systematic review combined with integrative research covers chromatographic and electrophoretic techniques

elaborated in 2000–2009 which are used for analysis of 8 TAA: fluconazole, itraconazole, terconazole, posaconazole, voriconazole, ravuconazole, isavuconazole and albaconazole. Data analysis revealed that HPLC with UV detection is the technique of choice in the determination of azole antifungal drugs in pharmaceutical and medical researches.

Because of undeniable advantages HPLC remains the gold standard in analytical chemistry. It is the most versatile and flexible tool. Other techniques are employed rarely but have also great analytical potential. In specific aspects UPLC, SFC or CE excel high-performance liquid chromatography (e.g. resolution in chiral analysis). We predict that these three techniques will be developed and more popular in future. Recent preferences in the analysis of azoles prove today's primacy of HPLC and confirm general trends moving towards more sensitive methods, with higher resolution potential, consuming less amounts of samples and reagents and require less time.

Discussed state-of-the-art procedures show many advances in analytical practices and achievements. TAA can be separated, identified and determined in many different matrices. Triazoles can be analyzed concomitantly in one sample or besides other substances. Enantioselective separation is possible with sufficient resolution. Elaborated procedures enable fast and specific quantification of even very small quantities of azoles. There is a great need and opportunity for the development of new analytical procedures using emerging techniques, especially for latest entities in the TAA group; albaconazole, ravuconazole and isavuconazole. There are few data connected with stability, particularly photostability of TAA and parallel determination with degradation products. This omitted area will be a subject of author's planned investigations.

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