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Analytical methods for the determination of some selected 4-quinolone antibacterials

DOI 10.1515/revac-2015-0020
Received December 15, 2015; accepted November 23, 2016; previously published online May 26, 2017

Abstract: A comprehensive review with 337 references for the analysis of some selected 4-quinolone drugs belonging to the first and second generations since 2006 up till now is presented. This group includes nalidixic acid, oxolinic acid, piromidic acid, pipemidic acid and rosoxacin from the first generation and enoxacin, fleroxacin, nadifloxacin, pefloxacin and rufloxacin from the second generation. The review covers most of the methods described for the analysis of these drugs, either *per se*, in dosage forms, biological fluids, environmental samples, cosmetics, animal tissues and feed-premix samples.

Keywords: chromatography; electrophoresis; flow injection analysis; quinolones; spectroscopy.

Introduction

4-Quinolones comprise a large and expanding group of synthetic antibacterial agents. The first drug of this class, nalidixic acid (NDA) was discovered in 1962 and was a modification of a compound isolated during the production of the antimalarial drug, chloroquine (Lesher et al. 1962), and was later approved for clinical use in 1965. However, its antibacterial spectrum of activity was restricted to the Enterobacteriaceae, and due to the limited absorption and distribution of the drug, it was effective solely for the treatment of urinary tract infections. A major advance occurred during the 1980s with the discovery that a fluorine atom at 6-position of the basic quinolone nucleus and a piperazine substitution at the 7-position were found to enhance the quinolone antibacterial activity and to increase the extent of oral absorption and distribution (Ball 2000).

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Drugs possessing this fluorine atom are known as the fluoroquinolones (FQs). The first FQ approved for use in clinical medicine was norfloxacin, followed shortly thereafter by ciprofloxacin in the mid-1980s. Poor oral bioavailability and tissue distribution with limited spectrum of activity were associated with the first generation drugs (Sweetman 2009).

Structural changes in the second generation FQs increased their oral bioavailability and systemic distribution, and broadened their spectrum of activity (Lesher et al. 1962). The favorable characteristics of the second generation drugs were maintained by the third generation FQs while exhibiting increased activity against Gram-positive bacteria, anaerobes and mycobacteria. Moreover, these compounds also exhibited excellent oral bioavailability and were associated with a prolonged terminal elimination half-life (Ball 2000). Lower central nervous system toxicities are another advantage of this group. Pharmacological actions and pharmacokinetics of FQs have been reviewed by many researchers (Schentag 2000, Martinez et al. 2006).

Physicochemical properties of FQs

The amphoteric property of FQs is a result of the modification in the quinolone core structure by inserting a fluorine atom at position C-6 and a piperazinyl or piperazine derivative group (R) at C-7.

Such chemical structure enhances their water solubility and provides them with a strong capability to form stable 1:1 complexes with several cations (e.g. magnesium, calcium, aluminum, iron and zinc) (Turiel et al. 2006, Sukul and Spiteller 2007). Although FQs show resistance to hydrolysis and heat, they seem to be highly photosensitive. Irradiation with UV radiation in water leads to defluorination and/or oxidative degradation of the amine side chain (Freccero et al. 2008, Sturini et al. 2010a).

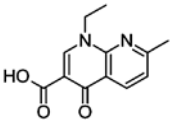
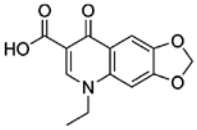
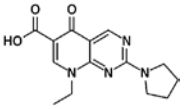
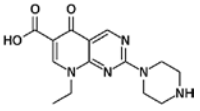
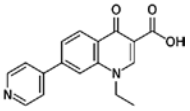
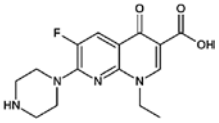
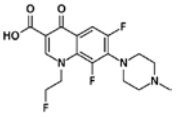
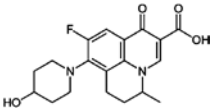
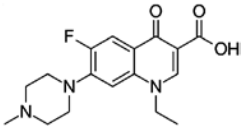
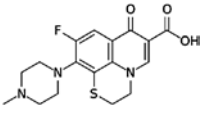
Literature survey of FQs

Many reviews were published in the literature dealing with the pharmacology of FQs (Schentag 2000,

Martinez et al. 2006). The determination of FQs in solid environmental matrices (Speltini et al. 2011) was also reported. Recent analytical techniques (Samanidou et al. 2005a,b) used for the determination of FQs in pharmaceuticals and samples of biological origin were also reviewed. A review concerned with analytical methods for the determination of the third and fourth generation FQs in biological matrices and pharmaceutical formulations by liquid chromatography was recently reported (Sousa et al. 2012); therefore, the authors in this work were concerned with earlier generations. Another review on the separation methods for the determination of some FQs was published (Saleh et al. 2013). Moreover, the spectrophotometric methods for the determination of FQs were also reviewed (Kaura et al. 2008).

Although many recent reviews covered the analytical methods for the determination of FQs, many drugs of the first and second generations were not reviewed since 2005, namely, NDA, oxolinic acid (OXA), piromidic acid, pipemidic acid (PIA) and rosoxacin (ROX) from the first generation and enoxacin (ENX), fleroxacin (FRX), nadifloxacin (NFX), pefloxacin (PFX) and rufloxacin (RFX) from the second generation, since 2006 up till now. The structural formulae of the selected drugs are listed in Table 1.

Table 1: Chemical structure of the selected 4-quinolones.

Name	Structural formula	Abbreviation
Nalidixic acid		NDA
Oxolinic acid		OXA
Piromidic acid		PMA
Pipemidic acid		PIA
Rosoxacin		ROX
Enoxacin		ENX
Fleroxacin		FRX
Nadifloxacin		NFX
Pefloxacin		PFX
Rufloxacin		RFX

Official and compendial methods of analysis

NDA is the subject of monographs in both the British Pharmacopoeia (2009) and the United States Pharmacopoeia (2007). Spectrophotometric measurement of its alkaline solution at 334 nm is described in BP, while the USP used non-aqueous titration with lithium methoxide as a titrant for its assay in pure form, and high performance liquid chromatography (HPLC) with UV detection at 254 nm for its quantitation in tablets and oral suspensions.

OXA, PIA and PFX are official drugs in the BP (The British Pharmacopoeia 2009), which recommends a non-aqueous potentiometric titration method using tetrabutyl ammonium hydroxide or perchloric acid as titrant for PIA and PFX for their determination.

Reported methods of analysis

Spectroscopic methods

UV-VIS spectrophotometry

Estimation of NDA in pharmaceutical formulations by UV spectrometry (Maheshwari et al. 2006), and the study of its complexation equilibria with proton and metal ions in aqueous organic mixtures, was carried out (Gandhi and Sekhon 2007). A eutectic liquid obtained by triturating phenol crystals and metformin hydrochloride in a 4:1 ratio on weight basis was employed to extract NDA from fine powder of tablets. Distilled water was used for dilution purpose to carry out spectrophotometric estimation at 330 nm without utilizing any organic solvent (Maheshwari et al. 2015).

The interaction of cobalt (II) with OXA in the absence or presence of the Lewis bases 2,2′-bipyridine,

2,2′-bipyridylamine, 1,10-phenanthroline, pyridine or 4-benzylpyridine resulted in the formation of a series of mononuclear complexes which were characterized with physicochemical and spectroscopic techniques (Irgi et al. 2015). The hydrophilic ionic liquids and potassium hydrogen phosphate formation of an aqueous two-phase system for the determination of OXA was investigated (Yan et al. 2009).

Regarding ROX, a selective spectrophotometric method for its determination was carried out based on the reaction with alkaline sodium nitroprusside forming a red chromogen measured at 455 nm (Askal et al. 2008). Another report described the formation of yellow-colored water-soluble ion-pair complexes with 2% (w/v) β-naphthol in sulfuric acid at room temperature (Darwish et al. 2006).

A spectrophotometric titration method in a wide range of pH was utilized for the estimation of complex-formation equilibrium between ENX and Al(III), Fe(III), Cu(II) and Zn(II) ions (Urbaniak and Kokot 2013). Another method has been established for the assay of ENX using sodium 1,2-naphthoquinone-4-sulfonate as a derivatizing chromogenic reagent (Wu et al. 2010). ENX was also assayed based on an association complex formation with Al (III) and erythrosine (Yamaguchi et al. 2009). Moreover, ENX and ciprofloxacin were determined simultaneously using a simulated system based on a partial least-squares method (Ajuan 2008). On the other hand, the determination of ENX and PFX based on charge transfer reaction with alizarin red in ethanol-water medium or phosphate buffer was also postulated (Li and Zhang 2008, Zhang and Lin 2009).

Regarding the analysis of FRX, one report concerned with the determination of its content in powder for injection with chrome azurol was described (Quan et al. 2009).

A multi-wavelength method for simultaneous estimation of NFX and ibuprofen in formulated hydro-gel preparations was presented (Kalantre and Pishwikar 2012). Another report suggested three UV methods for the estimation of NFX in pharmaceutical dosage forms by measuring its absorbance at 296.5 nm (method A), or measure its first-order derivative spectra at 278 nm (method B), or measuring the area under curve in the wavelength range (method C) (Kulkarni et al. 2010).

A simple zero-order UV spectrophotometric method for the estimation of PFX in bulk and tablet formulation was developed. Single point standardization was used for quantitative estimation of the drug and absorbance was determined at 288 nm using methanol as a solvent system (Raghunath et al. 2015). Based on the charge transfer reaction between PFX and chloranilic acid in methanol, a spectrophotometric method was established for the determination of PFX in pharmaceuticals (Pang et al. 2013). PFX was also quantified based on oxidation with cerium (IV) in the presence of perchloric acid and subsequent measurement of the excess Ce (IV) by its reaction with p-dimethylaminobenzaldehyde to give a colored product measured at 470 nm (Adegoke et al. 2010). PFX was estimated in pharmaceutical bulk and tablet dosage forms using UV detection at 277.5 nm in a 100 mM HCl medium (Misra et al. 2008). It was also determined in pharmaceutical formulations using three different salts of iron. These methods are based on the formation of complexes with ferric nitrate, ferric chloride or iron ammonium citrate in which the carboxylic group of PFX undergoes complexion with iron (Siddiqui et al. 2010).

The simultaneous determination of PFX and its structurally similar metabolite, norfloxacin, was described based on the monitoring of a kinetic spectrophotometric reaction of the two analytes with potassium permanganate as an oxidant, and measurement of the reaction process following the absorbance decrease of potassium permanganate at 526 nm (Ni et al. 2008).

Analytical studies were carried out to evaluate the use of N-bromosuccinimide (NBS) as an analytical reagent for the spectrophotometric assay of PFX. The procedures involved the reaction of the studied drug with NBS and subsequent measurement of the excess NBS by its reaction with phenylenediamine to give a violet-colored product that was measured spectrophotometrically at 530 nm (Askal et al. 2007). Another spectrophotometric method was described for the assay of PFX in bulk drug and in tablets. The described method was based on ion-pair formation with bromophenol blue dye at pH 5.2 followed by extraction and measurement of the dye absorbance at 590 nm (Basavaiah et al. 2007). Finally, the influence of Al^{3+} on the absorption characteristics of PFX had been studied where the absorbance of the Al^{3+}-PFX complex was measured at 275 nm (Zhang et al. 2006b).

Spectrofluorimetric methods

Several spectrofluorimetric methods for the determination of FQs were recorded. The use of lanthanide ions in some of such methods was mentioned in the literature for the assay of OXA, NDA, PIA, ENX and PFX; this could be summarized as follows.

The influence of the nature of micellar surfactant solutions on the sensitized fluorescence of mixed ligand chelates Tb^{3+}-1,10-phenanthroline-OXA and Tb^{3+}-1,10-phenanthroline-NDA was studied (Smirnova and Nevryueva 2010). On the other hand, a time-resolved

fluorescence analytical method was developed using a Eu^{3+} ion as a fluorescent probe for the quantitation of PIA (Liu et al. 2008b), where intra-molecular energy transfer occurs in the europium complex with PIA and the characteristics fluorescence of the Eu^{3+} ion with the maximum λ_{em} of 616 nm after excitation at λ 274 nm. Another study of the influence of silver nanoparticles on the second-order scattering and the fluorescence of the complexes of Tb^{3+} with PIA was reported in the literature (Ding et al. 2006).

The fluorescence system of ENX-Tb^{3+}-sodium dodecyl benzene sulfonate (SDBS) was investigated (Tong and Xiang 2007). The results indicated that the fluorescence intensity of Tb^{3+}-SDBS was greatly enhanced by ENX. Studies of the complex between PFX and Tb^{3+} (Li and Song 2014), and the fluorescent characteristics and content determination of PFX in yttrium-PFX, were performed (Ping et al. 2010). On the other hand, Tb^{3+} was found to react with PFX to form a 1:2 coordination complex with the characteristics fluorescence of Tb^{3+} in a neutral medium (Liao et al. 2008a). In another study, a ternary coordination complex was formed among Eu^{3+}, PFX and EDTA due to the intra-molecular energy transfer of the coordination complex (Bian and Xu 2007).

Metal complexation was also utilized for the spectrofluorimetric determination of FQs. The interactions between ENX and heavy metal ions were studied using fluorescence spectroscopy at different temperatures (Han et al. 2012). It was shown that the fluorescence intensity of ENX could be apparently quenched by Cu^{2+}, Pb^{2+} and Mn^{2+} due to static quenching. On the other hand, in a hexamine-HCl buffer of pH 5.8, the synergistic sensitization effect of sodium dodecyl sulfate and Al^{3+} on the fluorescence of ENX was observed (Ma et al. 2011). In another report based on the evident increase in the relative fluorescence intensity of FRX by complexing with Al^{3+}, a new method of synchronous fluorescence spectrometry to rapidly determine FRX was developed (Cai et al. 2012). It was also shown that FRX and Zn^{2+} have a powerful ability to quench the bovine serum albumin fluorescence via a non-radiative energy transfer mechanism (Wu et al. 2007).

Derivatization was also applied to assay some FQs. ENX, for instance, was determined based on derivatization with 4-chloro-7-nitrobenzofurazan in borate buffer of pH 9 to yield a yellow product (Ulu 2009). Meanwhile, ENX and PFX were assayed in their pharmaceutical dosage forms or in biological fluids through charge transfer complex formation with bromanil (Salem et al. 2007) and fluoranil (Geffken and Salem 2006). Another fluorescence spectrometric method for the determination of PFX was established based on the charge transfer reaction with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (Xu et al. 2007).

Micellar-enhanced fluorimetry was also applied to determine FRX (Aodeng and Liu 2006) and PFX (Bian et al. 2006), because it was found that sodium dodecyl sulfate could greatly enhance the fluorescence signal of the latter using Britten-Robinson buffer solution of pH 5.3.

Fluorescence quenching could also be used to analyze FRX, PFX and ENX. The interaction between FRX and pepsin was investigated (Lian et al. 2013). Static quenching was suggested and it was proved that the fluorescence quenching of pepsin by FRX was related to the formation of a new complex and a non-radiation energy transfer. Meanwhile, the quantitative determination of traces PFX and ENX was accomplished based on fluorescence quenching of either quantum dot silica-coated nanoparticles or glutathione-capped CdTe, respectively (Chen et al. 2012a, Yang et al. 2016). Another report studied the quenching effect of palladium (II) or sodium dodecyl benzene sulfonate for the fluorescence of PEX (Wang et al. 2014) in acidic and neutral media.

Other spectrofluorimetric methods concerned with the assay of FQs include non-linear variable angle synchronous spectrofluorimetry for the determination of ENX in urine (Murillo Pulgarin et al. 2012) and irradiation of ENX for a few minutes using a high-power UV lamp which drastically increased its fluorescence quantum yield (Espinosa-Mansilla et al. 2007). Use of octadecyl silica membranes for sample pre-concentration and solid substrate for ENX fluorescence line narrowing spectroscopy (Yu et al. 2006) where measurements at liquid helium temperature (4.2 K) were easily made using a cryogenic fiber optic probe. A catalytic-kinetic spectrofluorometric method was described for the determination of traces PFX (Liang et al. 2006b); it was based on the inhibitory effect of PFX on the reaction of H_2O_2 oxidation of rhodamine B catalyzed by Cu^{2+}.

Mass spectrometric methods

The stability of various classes of antibiotics – especially NDA and OXA – was tested in matrix and reference solutions using a straightforward procedure applying mass spectrometric detection (Berendsen et al. 2011). Both drugs were also analyzed by laser diode thermal desorption chemical ionization with tandem mass spectrometry (Lohne et al. 2012). A quasi-MS/MS/MS method was applied to investigate the fragmentation mechanism of FRX, which was analyzed using electrospray mass spectrometry by collision-induced dissociation (Jiao et al. 2009a). The speciation in solutions containing Al^{3+} and FRX was

studied by electrospray mass spectrometry (ESI-MS/MS) and laser desorption ionization (Cvijovic et al. 2012).

Resonance Rayleigh scattering method

A new resonance Rayleigh scattering method for the determination of FRX has been developed (Wang et al. 2010). FRX reacts with Co^{2+} to form chelated cations in Britton-Robinson buffer over the pH range of 4.2–6.8, which further binds with Congo red to form the ion-association complexes, resulting in great enhancement of resonance Rayleigh scattering intensity. The maximum scattering wavelengths are located at 372 and 560 nm. A similar approach for the assay of PFX in tablets, human urine and plasma was also established (Han et al. 2011) where three scattering peaks at 278, 380 and 560 nm appeared. On the other hand, upon using a Britton-Robinson buffer medium, PIA was protonated and reacted with methyl orange to form an ion-pair complex, which then further formed a six-membered ring chelate with Pd (II). As a result, new resonance Rayleigh scattering spectra appeared. The method was applied for the determination of the drug in pharmaceutical formulations and human urine samples (Qiao et al. 2015).

Infrared spectroscopy

Near-IR spectroscopy has been applied to analyze injection samples of PFX. Partial least-squares regression analysis and principal components regression have been utilized to establish the developed method (Xie et al. 2010).

NMR spectroscopy

Non-selective and selective spin-lattice relaxation rates and spin-spin relaxation measurements were used to investigate and characterize interaction processes between FRX and bacterial cells (Waibel and Holzgrabe 2007). The signals of three hydrogens at different moieties of the FRX were considered to get an insight into the complexation behavior.

Chemiluminescence

Dysprosium-sensitized chemiluminescence (CL) reactions have been suggested for the determination of ENX, FRX, PFX and PIA (Sun et al. 2011a). The CL spectra are formed from the narrow characteristic emission of trivalent dysprosium (Dy^{3+}) at 482 and 578 nm through the intermolecular energy transfer from the excited SO to analyte, followed by intra-molecular energy transfer from analyte* to Dy^{3+}. With the FQs including ENX, FRX and RFX, the luminescence and CL properties of Tb^{3+}-FQ and Eu^{3+}-FQ complexes were studied in this contribution (Sun et al. 2011b). An Ag (III) complex CL system was applied for the assay of ENX. The method was applied for the determination of the drug in pharmaceutical preparations, spiked serum and urine samples (Chen and Sun 2010). Another batch-type CL analysis of ENX in pharmaceuticals was described (Karim et al. 2006). On the other hand, the CL determination of PFX was established (Wang et al. 2009a), where the addition of the drug to the Ce^{4+}-Na_2SO_3-H_2SO_4 redox system could improve the CL phenomenon. In another report, the nitrogen atom in PFX was easily protonated in acidic medium and formed ion complexes with $AuCl^{4-}$, the ion-complexes were extracted using dichloromethane, when the ion-complexes entered a reversed micellar system of cetyl trimethyl ammonium chloride containing luminol, and the dissociated $AuCl^{4-}$ reacted with luminol and produced a CL signal (Shi 2008).

Electrochemiluminescence

An electrochemiluminescence (ECL) based on energy transfer from electro-generated triplet sulfur dioxide to PIA was studied (Liang et al. 2006a). A weak ECL from triplet sulfur dioxide was observed when sulfite was electrochemically oxidized in sulfuric acid on a platinum electrode. When PIA was present, the weak ECL was enhanced.

The ECL of the Tb^{3+}-ENX-Na_2SO_3 system in an aqueous solution was reported (Chen et al. 2006). ECL is generated by the oxidation of Na_2SO_3, which is enhanced by the Tb^{3+}-ENX complex. The ECL intensity peak versus potential corresponds to oxidation of Na_2SO_3, and the ECL emission spectra match the characteristic emission spectrum of Tb^{3+}, indicating that the emission is from the excited state of Tb^{3+}.

Flow injection analysis (FIA)

A method for the analysis of ENX by flow injection coupled with CL detection was described, based on the ENX-enhancing effect on a weak CL system of luminol-H_2O_2 in alkaline solution (Du et al. 2012). FIA was also investigated for the assay of ENX using the luminol-H_2O_2 system in the presence of Cu^{2+}. It was observed that the interaction of ENX with Cu^{2+} caused the sensitization of the CL intensity of the system strongly (Alam et al. 2011). On the other hand, the Dy^{3+}-sensitized CL method was developed for the analysis of ENX using flow injection sampling based on the CL associated with the reaction of the Dy^{3+}-Ce^{4+}-$S_2O_3^{2-}$-ENX system and the Dy^{3+}-MnO_4^--$S_2O_3^{2-}$-ENX

system (Sun et al. 2009b). It was also found that the CL reaction between luminol and potassium ferricyanide was significantly sensitized by ENX (Li et al. 2008d). Another FIA method for the determination of ENX was developed based on the inhibiting behavior of ENX on the emission intensity of the CL reaction of luminol-H_2O_2-manganese tetrasulfonatophthalocyanine in a basic medium (Li and Wei 2006).

A new CL reaction system was established for the analysis of FRX. The Dy^{3+}-sensitized CL emission mechanism was investigated by comparing the fluorescence emission with CL spectra (Sun and Li 2011). The CL spectra of the FRX-$KMnO_4$-$Na_2S_2O_3$-$H_6P_4O_{13}$ system are from the narrow characteristic emission of Dy^{3+} at 482 and 578 nm through the energy transfer from the excited SO_2* to analyte, followed by intra-molecular energy transfer from analyte* to Dy^{3+}. Another report based on the enhancement of CL of the luminol-hydrogen peroxide-gold nanoparticles system by FRX was reported for its assay (Wang et al. 2007a).

An FIA method to determine PFX residue in urine and serum was established based on the fact that the presence of Tb^{3+} enhances the luminous intensity of the Ce^{4+}-SO_3^{2-}-PFX system (Ren and Li 2012).

Voltammetric methods

Stripping continuous cyclic voltammetry was presented to determine NDA (Norouzi et al. 2008). The potential waveform was applied to a golden disk microelectrode in a continuous way. It was concluded that the best performance was achieved with the basic parameters set at pH 2, sweep rate of 60 V/s, accumulation potential 100 mV and accumulation time 0.7 s. A square wave adsorptive stripping voltammetric method has also been developed for the individual and simultaneous determination of NDA acid and its main metabolite, 7-hydroximethylnalidixic acid (Cabanillas et al. 2007). Variables that affect accumulation process, such as concentration of perchloric acid, accumulation potential and accumulation time, have been optimized by using an experimental design.

A micro-fluid-enzyme sensor for the quantification of PIA was proposed (Bertolino et al. 2011). PIA has a potential to inhibit topoisomerase II (DNA gyrase) of bacteria. PIA detection in pharmaceutical samples was based on the use of tyrosinase enzyme that was immobilized on 3-aminopropyl-modified-controlled-pore glass packet in a central channel of the microfluidic-enzymic device.

Another sensitive cathodic stripping voltammetric method has been developed for PIA using the hanging mercury drop electrode as a working electrode versus Ag/AgCl reference electrode (Solangi et al. 2009a). We used 0.1 M hydrochloric acid as medium and 0.1 M potassium chloride as base electrolyte.

An electrochemical sensor based on carbon paste and inclusion of ionic liquid crystal (1-butyl-1-methylpiperidinium hexafluorophosphate) in the presence of sodium dodecyl sulfate for the determination of ENX was prepared (Atta et al. 2015). Different ionic liquids were used and compared. The simultaneous determination of binary mixtures of ENX with either dopamine or epinephrine was demonstrated with good peak potential separations; furthermore, the method was applied for the direct determination of ENX in human urine samples. In another report, a polythionine-modified carbon paste electrode was prepared, and the electrochemical behavior of ENX at this modified electrode was studied by cyclic voltammetry (Gu et al. 2013). Besides, a mercury-free electrochemical method for the assay of ENX was established by using a glassy carbon electrode modified by multi-wall carbon nanotubes functionalized with carboxylic groups (Sun and Xing 2007), where differential voltammograms of ENX were obtained in 0.1 M phosphate buffer of pH 5.91 at 100 mV/s. Another rapid anodic adsorptive voltammetric method was developed for the analysis of trace amounts of ENX at a carbon paste electrode where it was adsorbed on the surface of the electrode in 0.4 mol/l acetate buffer solution (pH 4.5) yielding one oxidation peak at 1.17 V (Yi et al. 2007a).

Concerning FRX, its electrochemical behavior at the glassy carbon electrode was studied by linear scanning voltammetry and cyclic voltammetry (Yu et al. 2012b). In 0.1 M phosphate buffer solution of pH 6.5 containing Cu^{2+} ions, two reduction peaks given by Cu^{2+} ion were observed at −0.136 and −0.728 V, and their peak current decreased with the addition of FRX while keeping their reduction peak potentials unchanged.

The anodic behavior and analysis of PFX on boron-doped diamond and glassy carbon electrodes were investigated using cyclic, linear sweep, differential pulse and square wave voltammetric techniques (Uslu et al. 2008). In cyclic voltammetry, PFX shows one main irreversible oxidation peak and additional one irreversible ill-defined wave depending on pH values for both electrodes. The results indicated that the oxidation of PFX is irreversible and diffusion controlled on the boron-doped diamond electrode and irreversible but adsorption controlled on the glassy carbon electrode. Another highly selective and rapid new anodic adsorptive voltammetric method has been developed for the determination of trace amounts of PFX by using a carbon paste electrode (Yi et al. 2006). PFX was adsorbed on the surface of the electrode yielding an

oxidation peak at 1.03 V using an acetate buffer solution 0.40 M of pH 4.9.

Microbiological assay

Several microbiological assay methods were reported for the determination of FQs of our interest; such methods include fluoroimmunoassay (Mi et al. 2013, Zhang et al. 2013) and enzyme-linked immunosorbent assays (Huet et al. 2006, Iwasaki et al. 2006, Lu et al. 2006, Wang et al. 2006, 2007b, Adrian et al. 2008, Burkin 2008, Li et al. 2008a, Scortichini et al. 2009, Chang et al. 2011, Jiang et al. 2011, 2013, Sheng et al. 2011, Fan et al. 2012, Wen et al. 2012, Tao et al. 2013, Tian et al. 2013, Zhao et al. 2013).

Separation techniques

Capillary electrophoresis (CE)

The literature survey revealed several CE methods for the assay of FQs; such methods could be summarized as follows.

The applicability of capillary zone electrophoresis for the separation of ENX with five other quinolones in acidic background electrolyte was studied (Rusu et al. 2015b). Furthermore, the migration behavior and separation of 13 quinolone antibacterials including ENX were investigated by CE (Rusu et al. 2015a). It was proved that the electrophoretic mobility of ionized quinolones can be described with Offord's equation, and the migration order depends on their charge-to-mass ratios. Meanwhile, molecularly imprinted polymers were evaluated as sorbent for the construction of an in-line solid phase extraction analyte concentrator in CE coupled with mass spectrometry for the determination of eight regulated veterinary quinolones in bovine milk samples (including ENX and OXA) (David et al. 2014). Different parameters affecting the analyte concentrator performance, such as sample pH, volume and composition of the elution plug and injection time, were studied. Single drop microextraction coupled with CE for the analysis of six FQs including ENX was developed. The method was eventually applied for the extraction and pre-concentration of FQs in human urine samples (Gao et al. 2011a). Another method for the simultaneous determination of ENX and ofloxacin was established using CE coupled with ECL detection based on the ECL enhancement of tri(2,2-bipyridyl)ruthenium(II) (Liu et al. 2010). A method for the simultaneous separation and detection of six 4-quinolones including ENX by capillary zone electrophoresis was developed. The most suitable running buffer was found to be 30 mM sodium borate-10 mM NaH_2PO_4 (pH 8.5), and the optimal applied voltage, temperature and UV detection wavelength were 18 kV, 25°C and 278 nm, respectively (Li et al. 2009b). Another CE method was developed for the simultaneous assay of tetracaine, proline and ENX in human urine with ECL detection. The effects of applied voltage signal, the potential of working electrode, pH value, the flow rate of carrier solution, concentration of $Ru(bpy)_3^{2+}$ and the ECL intensity of the drugs were investigated in detail (Sun et al. 2010b). Another CE method was developed for the simultaneous determination of five quinolone antibacterials including ENX. At the detection wavelength of 268 nm, the electrophoresis parameters were optimized where the buffer was 15 mM sodium borate-15 mM potassium dihydrogen phosphate at pH 8.8, the applied voltage was 8 kV and the sampling time was 20 s (Tian et al. 2009). Meanwhile, a CE-potential gradient detection method was developed for the determination of ENX together with RFX and moxifloxacin. The FQs were baseline separated within 3.5 min with background electrolyte composed of 50 mM acetic acid and 6 mM potassium hydroxide at pH 3.7 (Fan et al. 2009). The influence of bovine serum albumin as an additive on the CE-potential gradient determination of five quinolones including ENX was described with 10 mg/l of bovine serum albumin present in the buffer of 30 mM Tris and 3 mM H_3PO_4 at pH 9 (Qin et al. 2009). Another CE coupled to a self-made conductometric detector was developed for the separation and detection of five quinolones including ENX in a buffer containing bovine serum albumin in 30 mM Tris, 3 mM phosphoric acid at pH 9 (Liu et al. 2008c). Another method for the effective assay of eight FQs including ENX in human urine was reported. The method applied a voltage of 22 kV, using a mixture of 4×10^{-2} M $Na_2B_4O_7$ and 0.1 M H_3PO_4 (pH 9.15) as running buffer, and detecting by using a diode array detector at wavelength 278 nm (Sun et al. 2008a). A rapid CE coupled with potential gradient detection for the determination of four quinolones, namely, ENX in a mixture with ofloxacin, FRX and pazufloxacin, was described. Separation was performed in a fused-silica capillary using a buffer of 30 mM Tris and 4 mM phosphoric acid at pH 8.9 (Fan et al. 2007). The interactions between FQs and human serum albumin were investigated by affinity CE. Based on the efficient separation of several FQs (including ENX) using a simple phosphate buffer (Zhang et al. 2007b), a simple method was developed for the effective separation of ENX, PFX together with other FQ residues in porcine tissues by CE with a diode array detector. A mixture consisted of 25 mM

NaH_2PO_4, 25 mM $Na_2B_4O_7$ and 25 mM H_3BO_3 (pH 9) was used as a running buffer (Sun et al. 2007).

Regarding PIA, a novel method was developed and validated for the separation and simultaneous quantitation of seven structurally different drugs: PIA and ofloxacin, pseudoephedrine, piroxicam, thiamin, pyridoxine and cyanocobalamin by capillary zone electrophoresis (Solangi et al. 2009b). The coupling of $Ru(bpy)_2^{3+}$-based ECL detection with CE was developed for the simultaneous determination of proline and PIA in human urine (Sun et al. 2010a). A specific pressure-assisted CE-MS method is described for the analysis of PIA in combination with danofloxacin, enrofloxacin, flumequine and ofloxacin. The most suitable electrolyte was 60 mM $(NH_4)_2CO_3$ at pH 9.2. Using this method, the FQs were analyzed in fortified samples of chicken and fish (Juan-Garcia et al. 2006). One report used narrow-bore fused-silica capillaries to perform high-efficiency separation of PIA and NDA using a buffer composed of 40 mM sodium tetraborate and 5% methanol as organic modifier (Rusu et al. 2011).

For the analysis of OXA, a magnetic solid-phase extraction method combined with CE for the simultaneous determination of the concerned drug with other FQs using (S)-(+)-6-methoxy-α-methyl-2-naphthaleneacetic acid as internal standard in milk samples was developed (Ibarra et al. 2012). OXA together with other FQs was also assayed in bovine and porcine plasma, bovine milk using CE (Francisco et al. 2006, Hermo et al. 2011).

Several other methods were reported for the quantitation of FRX. Field-enhanced sample injection for sample stacking prior to the CE separation was developed inside a bubble cell capillary for highly sensitive detection of five typical FQs in bovine milk of which we concern FRX (Deng et al. 2014). Ethylene diamine was proposed as the main component for the antibiotics separation. A rapid method for the determination of residues of FRX with other three FQs in blood samples was developed. The method was based on matrix solid-phase dispersion extraction followed by CE with UV detection. 1-Butyl-3-methylimidazolium tetrafluoroborate was used as the background electrolyte (Li et al. 2011). A CE method based on ECL detection with $Ru(bpy)_3^{2+}$ was developed for the simultaneous determination of FRX and proline in human urine. The most favorable resolution and high sensitivity were obtained using a 15 mM phosphate buffer at pH 9.6 with the detection potential at 1.15 V (Sun et al. 2009a). FRX was also determined with other FQs by CE using silica nanoparticles as running buffer additive (Wang et al. 2009b). A method for the simultaneous separation of FQs (including FRX) and tetracyclines by CE was developed. The UV detection wavelength was 262 nm, the running buffer consisted of 50 mM NaB_4O_7-200 mM H_3BO_3 with pH 8.41 and the separation voltage was at 18 kV (Shen et al. 2012). FRX together with eight FQs was separated by CE-UV based on poly(methacrylic acid-co-ethylene glycol dimethacrylate) monolith microextraction coupled with an online preconcentration technique of field-amplified sample stacking (He et al. 2010a).

For the assay of PFX, novel methods to determine its pharmacokinetics in urine of healthy adults were developed. The proposed methodologies were based on the ECL of tris(2,2′-bipyridine)ruthenium (II) at a platinum electrode (Li et al. 2008b, Deng et al. 2009).

The determination of five FQs, namely, RFX, ciprofloxacin, enrofloxacin, gatifloxacin and moxifloxacin, in acidic buffer by a CE-capacitively coupled contactless conductometric detection technique was prescribed. The separation was carried out in a fused-silica capillary using a buffer composed of 10 mM tartaric acid, 14 mM sodium acetate and 15% (v/v) methanol at pH 3.8 (Yang and Qin 2009).

A Micellar electrokinetic capillary chromatography (MEKC) method was developed using 1-butyl-3-methylimidazolium hexafluorophosphate (BMIM) PF6 as a modifier for separating ENX together with other seven FQs. Under the optimal conditions of 10 mM sodium borate, pH 7.1, 1.7% (w/w) SDS, 1.5% (w/w) [BMIM] PF6 with 18 kV as running voltage, the eight investigated FQs were baseline separated within 15 min (Chen et al. 2012b).

Another MEKC method has been developed for the simultaneous separation of seven FQs including FRX. Baseline separation was achieved in a carrier electrolyte containing 1% (v/v) heptane, 100 mM SDS, 10% (v/v) 1-butanol and 8-mM phosphate-sodium tetraborate buffer at pH 7.3 (Wei et al. 2008).

Thin layer chromatography (TLC)

The densitometric analysis of NFX in microemulsions was developed and validated. The compact spot for NFX was found at an R_f value of 0.39 ± 0.02 at an absorption wavelength of 288 nm using a mobile phase consisting of chloroform:methanol:formic acid (7.5:2.0:0.5, v/v) (Kumar et al. 2010). Another work described the HPTLC method for the analysis of NFX and mometasone furoate in topical cream. The separation was carried out using dichloroethane:di-ethyl ether:ammonia:methanol:ethyla cetate (6:3:0.2:1.75:3.5, v/v) as the mobile phase. The densitometric scanning was carried out at 254 nm (Amol et al. 2010). PIA and PFX together with other FQs were separated with TLC using either buffer (pH = 5.5)-methanol, or

Table 2: Reported HPLC methods for the determination of FQs.

Name	Matrix	Column	Mobile phase	Detection	References
NDA and metronidazole	Tablets	C_{18}	Mixed phosphate buffer (pH 4.5; $KH_2PO_4 + K_2HPO_4$):methanol:acetonitrile; 30:50:20 v/v	UV detection	Kumar et al. 2015
Seven FQs including NDA, OXA	Gilthead sea bream	C_{18}	Gradient elution using 0.1% trifluoroacetic acid (pH = 1), acetonitrile and methanol	Tandem mass spectrometry	Evaggelopoulou et al. 2014
Nineteen FQs including NDA, OXA, PIA, ENX, FRX, PFX	Environmental water samples	C_{18}	Gradient elution using 0.02% aqueous formic acid and acetonitrile	Tandem mass spectrometry	Lombardo-Agüí et al. 2014
NDA, OXA with other classes of antibiotics	Fresh egg samples	C_{18}	Gradient elution using (methanol-acetonitrile 8:2, v/v) and (0.1% formic acid)	Tandem mass spectrometry	Piatkowska et al. 2014
NDA, OXA, PMA, PIA, ENX together with other FQs and β lactams	Raw cow milk	C_{18}	Gradient elution using 50 mM aqueous ammonium formate pH 4 and methanol	MS/MS	Junza et al. 2014
FRX	Human plasma	C_{18}	Acetonitrile-0.1% trifluoroacetic acid-water (20:20:60)	UV detection	Song-feng et al. 2015
NFX	Bulk powder	C_{18}	0.05% v/v trifluoroacetic acid and acetonitrile (65:35 v/v)	UV detection	Ayyagari et al. 2014
Several quinolones (NDA, FRX, PFX) with sulfonamides	Milk samples	C_{18}	Gradient elution using acetonitrile and 0.1% formate	Tandem mass spectrometry	Cao et al. 2013
Nineteen quinolone antibiotics including OXA	Cosmetics	C_{18}	Methanol:acetonitrile (85:15, v/v)-0.05 M phosphate buffer (pH 3.6) under gradient elution	Diode array detection	Chen et al. 2013
Some quinolones including PIA and PFX	Tap water and human urine	C_{18}	Gradient elution with of 10 mM sodium citrate at pH 4 (solvent A) and acetonitrile (solvent B)	Fluorescence detection	Francisco et al. 2013
Ten quinolones (NDA) and eight cephalosporins	Milk samples	C_{18} column	Gradient elution using a mobile phase of 0.1% TFA in water and 0.1% TFA in ACN	MS/MS	Karageorgou et al. 2013
Quinolone antibacterials (NDA, OXA)	Sewage sludge	C_{18}	Gradient mobile phase consisting of 0.2% (v/v) formic acid aqueous solution (solvent A) and methanol (solvent B)	MS/MS	Dorival-Garcia et al. 2013a
Thirty-one antibiotics including NDA and ENX	Drinking water, surface water and reclaimed waters	C_{18}	Gradient elution using a mobile composed of water, methanol, acetonitrile, 0.1% formic acid	MS/MS	Panditi et al. 2013
Eighty-four veterinary drug residues (benzimidazoles, FQs: ENX, OXA, NDA, nitroimidazoles, β-lactams, macrolides, triphenylmethane dyes, sulfonamides and tetracyclines)	Chicken muscles and tissues	C_{18}	Gradient elution using a mobile composed of 0.1% formic acid in water, 0.1% formic acid in acetonitrile	MS/MS	Biselli et al. 2013
Thirty-four antibacterial drugs (aminoglycosides, β-lactams, fluoroquinolones including OXA, NDA, macrolides, sulfonamides, trimethoprim and tetracyclines)	Fish samples	C_{18}	Gradient elution using a mobile composed of (A): acetonitrile; (B): 0.025% Heptafluorobutyric in water	Tandem mass spectrometry	Gbylik et al. 2013

Table 2 (continued)

Name	Matrix	Column	Mobile phase	Detection	References
Two hundred and twenty undesirable chemical residues including PIA, PFX, ENX, OXA, NDA	Infant formulae	C_{18} column	Methanol containing 0.1% (v/v) formic acid and water containing 0.1% (v/v) formic acid/0.5 mM ammonium acetate	Tandem mass spectrometry	Zhan et al. 2013
Seven veterinary drugs, including furazolidone, 4 sulfonamides, OXA, NDA	Aquatic products	C_{18} column	Gradient elution with mixtures of acetonitrile and 0.08 M acetic acid	UV detection	Meng et al. 2012
Fifty-three antibiotic residues including OXA, NDA, PIA	Hospital and urban wastewaters	C_{18} column	Solvent (A) acetonitrile, solvent (B) HPLC grade water acidified with 0.1% formic acid	Tandem mass spectrometry	Gros et al. 2013
Thirty-six antibiotics from seven different chemical classes (aminoglycosides, macrolides, lincosamides, sulfonamides, tetracyclines, FQs including ENX, OXA, NDA and trimethoprim	Chicken meat	Phenyl column	Gradient elution using solvent (A) 1 mM heptafluorobutyric acid + 0.5% formic acid in water and (B) 0.5% formic acid in acetonitrile/methanol (1:1, v/v)	Tandem mass spectrometry	Bousova et al. 2013
Seventy-two veterinary residues including NDA, FRX	Shrimps samples	C_{18} column	Gradient elution with acetonitrile and 0.1% formic acid	Tandem mass spectrometry	Bu et al. 2012
Fifty-four veterinary drug residues of six families including sulfanilamide, nitroimidazoles, macrolide antibiotics, lincosamides, praziquantel, FQs including NDA, OXA, ENX	Pork meat samples	C_8 column	Gradient elution with acetonitrile, methanol and formic acid	MS/MS	Xie et al. 2012
FQs including NDA, OXA, PIA, ENX, PMA	Urban waste waters	C_{18} column	Gradient mobile phase consisting of 0.2% (v/v) aqueous formic acid solution (solvent A) and methanol (solvent B)	MS/MS	Dorival-Garcia et al. 2013b
Seven quinolone antibacterials including OXA, NDA	Tissue of Atlantic salmon	C_{18} column	0.1% trifluoroacetic acid (pH 1), acetonitrile and methanol	Photodiode array detector	Evaggelopoulou and Samanidou 2013
Veterinary drug residue anal. (sulfonamides, tetracyclines and FQs including OXA, ENX, NDA	Animal urine samples	C_{18} column	Gradient elution using mobile phase of acetonitrile and formic acid	Mass spectrometry	Kaufmann and Walker 2013
Two hundred and fifty-five veterinary drug residues and contaminants of different classes including PIA, PFX, ENX, OXA, NDA	Milk samples	C_{18} column	Gradient elution using mobile phase composed of: 0.1% (v/v) formic acid in water containing 0.5 mM (v/v) ammonium acetate, methanol containing 0.1% (v/v) formic acid	Tandem mass spectrometry	Zhan et al. 2012
Eight FQs including OXA, NDA	Ground water	C_{18} column	H_3PO_4 (50 mM) and acetonitrile in different ratios	Fluorescence detection	Vazquez et al. 2012
Forty-two pesticides and veterinary drugs including NDA, OXA	Milk samples	C_{18} column	Gradient elution using a mobile phases of acetonitrile and water containing 0.1% formic acid	Mass spectrometry	Gao et al. 2012
FQs including NDA, OXA	Egg samples	Luna C_8	Gradient elution using a mobile phases of acetonitrile (A) and 0.02 M oxalic acid, pH = 4.0 (B)	MS/MS	Gajda et al. 2012

Table 2 (continued)

Name	Matrix	Column	Mobile phase	Detection	References
FQs including OXA, NDA	Surface waters	C_{18} column	Phosphoric acid and 5% methanol	Fluorescence detection	Garcia et al. 2012
FQs: cinoxacin, OXA, NDA, flumequine	Underground water, river and sea water	C_{18} column	Gradient elution using a mobile phases of (A): 0.1% formic acid and 10% methanol in and (B): 100% methanol	Mass spectrometry	Wang and Wang 2012
Tetracyclines, quinolones (OXA, NDA) and sulfonamides	Meat samples	C_{18} column	Gradient elution using solvent A (aqueous solution 0.1% formic acid) and solvent B (acetonitrile with 0.1% formic acid)	Tandem mass spectrometry	Bittencourt et al. 2012
Several FQs including PIA, OXA, NDA, PMA	Fish samples	C_{18} column	Mixtures of methanol-acetonitrile-10 mM citrate buffer at pH 4.5, delivered under optimum gradient program	Photodiode array and fluorescence detection	Canada-Canada et al. 2012
Thirty-seven antibiotic substances from the six antibiotic groups: macrolides, lincosamides, quinolones (NDA, OXA, ENX), tetracyclines, pleuromutilines and diamino-pyrimidine derivatives	Honey samples	C_{18} column	Gradient elution using A: water (with 0.2% formic acid) and B: acetonitrile (with 0.2% formic acid)	Tandem mass spectrometry	Bohm et al. 2012
Fifteen kinds of FQs including ENX, FRX, PFX, NDA	Food of animal origin	C_{18} column	Three gradient system with methanol/acetonitrile/0.02 M citric acid and 0.03 M ammonium acetate	UV detection	Yu et al. 2012c
Nine quinolones including OXA, NDA	Honey samples	C_{18} column	Solvent mixture of acetonitrile (25%) and SDS solution (75%) (pH 2.5)	Fluorescence detection	Du et al. 2011
Twenty-three antibiotics of different classes: sulfonamides, tetracyclines, macrolides, β lactams, diaminopyrimidines, nitro-imidazoles, FQs including NDA, OXA, PIA, ENX	Environmental water samples	C_{18} column	Gradient elution using UP-water + 0.1% formic acid (A) and acetonitrile + 0.1% formic acid (B)	MS/MS	Dinh et al. 2011
Forty-seven pharmaceuticals of different classes including PFX, OXA, NDA, PIA	Environmental and wastewater	C_{18} column	Gradient elution using: water/methanol, 0.1 mM ammonium acetate and 0.01% formic acid	MS/MS	Gracia-Lor et al. 2011
Thirty-three analytes from 13 classes of antibiotics: tetracyclines, FQs; (NDA, OXA), penicillins, macrolides, sulfonamides, quinoxalines, phenicols, lincosamides, diaminopyrimidines, polypeptides, streptogramins and pleuromutilins	Animal feeds	C_{18} column	Gradient elution with A: water with 0.1% formic acid and B: mixture of acetonitrile/methanol (70/30, v/v) with 0.1% formic acid	MS/MS	Boscher et al. 2010
Eighteen FQs including ENX, OXA, NDA, PMA and PIA	Milk, chicken, pork, fish and shrimp	C_8 column	Gradient elution using 20 mM ammonium formate in 0.1% formic acid-acetonitrile	MS/MS	Chang et al. 2010
FQs including PIA, ENX, OXA, NDA	Fish tissues	C_{18} column	Gradient elution using 0.2% formic acid in water as solvent A and 0.2% formic acid in acetonitrile as solvent B	Fluorescence detection	Zhang et al. 2010

Table 2 (continued)

Name	Matrix	Column	Mobile phase	Detection	References
FQs including (OXA, NDA)	Porcine muscle, table eggs and milk	C_{18} column	Gradient mobile phase composed of acetonitrile and 0.01 M oxalic acid buffer at pH 3.5	Fluorescence detection	Cho et al. 2010
FQs: NDA, ENX, PFX	Aquatic products	C_{18} column	Water and acetonitrile (contains 0.4% formic acid)	Tandem mass spectrometry	Kang et al. 2008
OXA, NDA and flumequine	Milk samples	C_{18} column	0.1% phosphoric acid and acetonitrile with gradient elution	UV detection	Zeng et al. 2009
Some FQs including OXA, NDA, PMA	Swine muscles	C_{18} column	Acetonitrile: 0.05 M sodium dihydrogen phosphate (pH 2.5) (35:65, v/v) containing 3.7 mM SDS	Diode array detection	Tsai et al. 2009
Forty-seven substances of the antibiotic groups tetracyclines, FQs (OXA, NDA, ENX), macrolides, sulfonamides, diaminopyrimidine derivatives and lincosamides	Milk samples	C_{18} column	Gradient elution using A (water with 0.2% formic acid) and B (acetonitrile with 0.2% formic acid)	Mass spectrometry	Bohm et al. 2009
FQs including NDA, OXA	Animal feeds	C_{18} column	Gradient elution with acetonitrile and o-phosphoric acid 25 mM at pH 3	Fluorescence detection and photodiode array	Galarini et al. 2009
Nineteen kinds of FQs: NDA, OXA, ENX, FRX, PFX	Animal foods	C_{18} column	0.1% formic acid-methanol system as the mobile phase with a linear gradient elution program	Tandem mass spectrometry	Li et al. 2008c
Eleven FQs including OXA, NDA	Chicken, pork, fish and shrimp	C_{18} column	Linear gradient elution of 0.1% formic acid and acetonitrile	Fluorescence detection	Chang et al. 2008
OXA, ENX, PFX, NDA, PIA together with other FQs	Pig and fish	C_{18} column	0.1% formic acid-methanol with a linear gradient elution	MS/MS	Li et al. 2009c
Nineteen quinolones residues including OXA, FRX, ENX, PIA, PFX, NDA	Honey samples	C_{18} column	Linear gradient elution program of methanol and 0.1% formic acid solution	MS/MS	Ding et al. 2009
Eighty-nine compounds including NDA, OXA	Milk samples	C_{18} column	Gradient system of 0.1% formic acid-acetonitrile containing 0.1% formic acid	MS/MS	Fujita et al. 2008
Five antibiotic groups: FQs: (OXA, NDA, PIA, ENX), sulfonamides, nitro-imidazole and diaminopyrimidine	Natural waters	C_{18} column	Gradient elution with ultra-pure water (solvent A) and acetonitrile (solvent B), both solvents acidified with 0.01% formic acid	Tandem mass spectrometry	Tamtam et al. 2009
Twenty FQs (PIA, FRX, PFX, ENX, OXA, NDA, PMA)	Influent, effluent and river waters	C_{18} column	Gradient elution with methanol (A) and purified water containing 0.1% formic acid (v/v) (B)	Tandem mass spectrometry	Xiao et al. 2008
Twelve FQs, such as PFX, OXA, NDA	Egg samples	C_{18} column	Acetonitrile-citric acid/ammonium acetate buffer in water as the mobile phase using a linear gradient elution program	Fluorescence detection	Liao et al. 2008b
Seven quinolones (OXA, NDA)	Gilthead sea bream	C_{18} column	Gradient elution using a mixture of 0.2% (v/v) formic acid, methanol and acetonitrile	MS/MS	Samanidou et al. 2008
Twelve quinolones (NDA, OXA)	Muscles, liver, chicken eggs, milk, prawn and rainbow trout	C_{18} column	Gradient system of 0.1% phosphoric acid-acetonitrile	Fluorescence detection	Chonan et al. 2008

Table 2 (continued)

Name	Matrix	Column	Mobile phase	Detection	References
Several FQs such as NDA	Urine, ground water, hospital wastewater and chicken muscle	C_{18} column	Citrate buffer (0.001 M) of pH 4.5, methanol and acetonitrile using gradient elution	UV detection	Kumar et al. 2008
Ten quinolones: ENX, OXA, NDA	Bovine liver and porcine kidney	C_{18} column	Gradient elution using a mixture of TFA 0.1%-acetonitrile-methanol	Photodiode array	Christodoulou et al. 2008
Ten quinolones: ENX, OXA, NDA	Various tissues of food-producing animals	C_{18} column	0.1% TFA-methanol-acetonitrile using a gradient program	Photodiode array	Christodoulou et al. 2007b
Ten FQs (ENX, OXA, NDA)	Chicken muscle and egg yolk	C_{18} column	Gradient elution using a mixture of 0.1% trifluoroacetic acid-acetonitrile-methanol	Photodiode array	Christodoulou et al. 2007a
Ten FQs (ENX, OXA, NDA)	Cow's milk	C_{18} column	Mixture of TFA 0.1%-acetonitrile-methanol delivered by a gradient program	Photodiode array	Christodoulou and Samanidou 2007
OXA, NDA	Shrimp samples	C_8 column	60% oxalic acid (0.01 M), 30% acetonitrile and 10% methanol (v/v/v)	Fluorescence, mass spectrometry	Karbiwnyk et al. 2007
Fifteen FQs (PIA, ENX, OXA, NDA, PMA)	Urine and pharmaceutical samples	C_{18} column	Mixtures of methanol-acetonitrile-10 mM citrate buffer at pH 3.5 and 10 mM citrate buffer at pH 4.5, delivered under an optimum gradient program	Diode array and fluorescence detection	Canada-Canada et al. 2007
Sixty-three veterinary drugs including OXA	Bovine, porcine and poultry muscles	C_{18} column	0.1% formic acid-acetonitrile in a gradient mode	Tandem mass spectrometry	Tagiri-Endo and Yanagita 2007
OXA	Fish farms	C_{18} column	Mixture of acetonitrile and orthophosphoric acid	Fluorescence detection	Pouliquen et al. 2006
Flumequine and oxolinic acid	Aquatic sediments and agricultural soils	C_8 column	10 mM oxalic acid buffer at pH 4-acetonitrile (65:35, v/v)	Fluorimetric detection	Prat et al. 2006
Eighteen drugs of different classes including NDA, OXA	Raw shrimp, meat samples	Phenyl column	A: 5% (v/v) acetonitrile/water, with 0.1% formic acid; B: 85% (v/v) acetonitrile/water with 0.05% formic acid. Two gradients were used	Mass spectrometry	Li et al. 2006b
Several quinolones (ENX, OXA, NDA)	Soil samples	C_{18} column	Linear gradient elution using: A (3.16 mM formic acid, pH 2.5) and B (acetonitrile)	UV detection	Turiel et al. 2006
Sulfonamides and quinolones residues (OXA)	Milk samples	C_{18} column	Gradient elution using acetonitrile and 0.1% formate in water	Tandem mass spectrometry	Cao et al. 2013
Fifty antimicrobials from 13 different families including OXA	Animal feeds	C_{18} column	Gradient elution using A (5 mM aqueous formic acid), B (50 mM aqueous formic acid/acetonitrile (10/90, v/v)	Tandem mass spectrometry	Borras et al. 2013
Twenty-nine veterinary drugs residues including 6 quinolones (OXA), 14 sulfonamides, 3 nitrofurans and 6 macrolides	Animal feed samples	C_{18} column	Acetonitrile and water (containing 0.1% formic acid) in gradient elution	Tandem mass spectrometry	Liu et al. 2013
Twenty-five antibiotics: 11 sulfonamides and 14 FQs (PIA, FRX, PFX, OXA)	Mineral and run-off waters	C_{18} column	Gradient elution using 0.3% (v/v) formic acid in Milli-Q water as mobile phase A and acetonitrile as mobile phase B	Diode array detection	Herrera-Herrera et al. 2013

Table 2 (continued)

Name	Matrix	Column	Mobile phase	Detection	References
Twenty-nine veterinary drugs, FQs (OXA), sulfonamides, macrolides, nitrofuran	Feed samples	C_{18} column	Gradient elution program of methanol and water (containing 0.2%formicacid)	Mass spectrometry	Li et al. 2012
Twenty-nine veterinary drug:14 sulfonamide drugs, 3 nitrofuran drugs, 6 macrolide drugs, 6 FQs such as OXA	Feed premix samples	C_{18} column	Methanol and water (containing 0.1% formic acid) in gradient elution	MS/MS	Liu et al. 2012a
Twenty-nine veterinary drugs: sulfonamides, macrolides and nitrofurans, FQs (OXA)	Compound feeds	C_{18} column	Gradient elution with the mobile phases of methanol and 0.1% (v/v) formic acid solution	Tandem mass spectrometry	Zhao et al. 2012
One hundred and twenty drug analytes from 11 different classes including OXA	Bovine kidney	C_{18} column	Gradient elution using (A) 0.1% aqueous formic acid and (B) 0.1% formic acid in acetonitrile	Tandem mass spectrometry	Schneider et al. 2012
Thirty-two veterinary drug residues belonging to several families including OXA	Fish samples	C_{18} column	Gradient elution using 0.1% formic acid in acetonitrile (eluent A) and 0.1% formic acid in water (eluent B)	Tandem mass spectrometry	Lopes et al. 2012b
Eight quinolones of veterinary use (OXA)	Bee products	C_{18} column	0.02% formic acid solution and acetonitrile	Mass spectrometry	Lombardo-Agüí et al. 2012
Twenty veterinary drug residues belonging to several classes: sulfonamides, macrolides, anthelmintics, diamino derivatives, FQs (OXA)	Chicken muscles	C_{18} column	Gradient elution using 0.1% (v/v) formic acid in acetonitrile (eluent A) and 0.1% (v/v) formic acid in water (eluent B)	Tandem mass spectrometry	Lopes et al. 2012a
Eight quinolone residues OXA	Chicken tissues	C_{18} column	0.1% trifluoroacetic acid aqueous solution (pH 3), methanol and acetonitrile (82:12:6 v/v)	Fluorescence detection	Xia and Peng 2011
Fifteen FQs such as: OXA, ENX, FRX	Raw bovine and skimmed milk	C_{18} column	Gradient elution using mobile phase consisting of (A) ultra-pure water and (B) acetonitrile, both acidified with 0.2% formic acid	Tandem mass spectrometry	Kantiani et al. 2011
Twelve FQs (PIA, OXA, FRX, PFX)	Different infant and young children powdered milks	C_{18} column	Gradient elution using water containing 0.1%–0.2%, v/v formic acid as mobile phase A, methanol and acetonitrile (both with and without 0.1% v/v formic acid) as mobile phase B	MS/MS	Herrera-Herrera et al. 2011
Six antibiotic residues including tetracyclines, sulfanilamides and FQs: OXA, ENX, FRX	Coastal waters	C_{18} column	Binary eluent containing methanol and water with 0.1% formic acid	MS/MS	Na et al. 2011
Nine quinolones such as OXA	Egg matrices	C_{18} column	Mobile phase A: an aqueous solution of 0.01 M oxalic acid, mobile phase B: acetonitrile, applying gradient elution	Fluorescence detection	Jimenez et al. 2011a
Several FQs: OXA, PIA, PMA	Bovine and porcine plasma	C_8 column	Gradient program with mobile phase that combined solvent A (10 mM citric acid-acetonitrile (91:9, v/v), adjusted with NH_3 and solvent B (acetonitrile)	UV detection, mass spectrometry and tandem mass spectrometry	Hermo et al. 2011

Table 2 (continued)

Name	Matrix	Column	Mobile phase	Detection	References
Forty-one antimicrobial agents belonging to seven families (sulfonamides, diaminopyridine derivates, quinolones: OXA, tetracyclines, macrolides, penicillins and lincosamides)	Egg matrices	C_{18} column	Gradient elution using mobile phase A: an aqueous solution of 0.02% formic acid and 1 mM oxalic acid, and mobile phase B: acetonitrile with 0.1% formic acid	Tandem mass spectrometry	Jimenez et al. 2011b
Twenty-four important veterinary drugs including aminoglycosides, β-lactams, lincosamides, macrolides, FQs: OXA, sulfonamides, tetracyclines and amprolium	Chicken muscles	C_{18} column	50 mM ammonium formate in water at pH 2.5 (mobile phase A) and acetonitrile (mobile phase B) using gradient elution	MS/MS	Chiaochan et al. 2010
Nitroimidazoles, sulfonamides and FQs: OXA, ENX, FRX, PFX	Honey samples	C_{18} column	Gradient solvent system (acetonitrile-methanol-formic acid solution)	Tandem mass spectrometry	He et al. 2010b
FQs: OXA	Fish muscles	C_{18} column	0.065 M sodium dodecyl sulfate, 12.5% propanol and 0.5% triethylamine buffered at pH 3	Fluorescence detection	Rambla-Alegre et al. 2010
Fifteen FQs: OXA, FRX	Honey samples	C_{18} column	Gradient solvent system (acetonitrile-0.1% formic acid)	Electrospray ionization, tandem mass spectrometric	He et al. 2010c
Thirty-eight compounds from a variety of drug classes including OXA	Four species of fish	Phenyl column	Gradient elution using mobile phase A: 0.1% formic acid with 10 mM NaOH in water and B: acetonitrile	Mass spectrometry	Smith et al. 2009
Seven trace FQs: OXA	Milk, egg, chicken and fish	C_{18} column	A mixture of formic acid solution and acetonitrile was used in gradient elution	Mass spectrometry	Zheng et al. 2009
Several FQs such as OXA and sulfonamides	Swine and chicken muscle tissues	C_{18} column	Formic acid solution-acetonitrile system as mobile phase with a linear gradient elution program	UV detection and fluorescence detection	Li et al. 2009d
Nine quinolones including OXA	Porcine, chicken and bovine muscles	C_8 column	Gradient elution using a mobile phase of 200 mM ammonium acetate buffer (pH 4.5) and acetonitrile	Fluorescence detector	Lee et al. 2009
Oxolinic acid and flumequine	Pure form	C_{18} column	Water-acetonitrile (2:1, v/v) at pH 2.5	Fluorescence detection	Feas et al. 2009
Flumequine and oxolinic acid	Eel tissues	C_8 column	0.01 mol/l oxalic acid and acetonitrile (65:35)	Fluorescence detection	Liu et al. 2009
Several FQs as OXA	Tilapia fillets	C_{18} column	Gradient elution using water and acetonitrile, both containing 0.1% of acetic acid	Tandem mass spectrometry	Paschoal et al. 2009
Several FQs as PFX, OXA	Chicken muscles	C_{18} column	Gradient elution (acetonitrile and water as mobile phases)	Fluorescence detector	Lin 2009
FQs including OXA, ENX, FRX	Honey samples	C_{18} column	Methanol-ammonia solution (19:1, v/v)	Tandem mass spectrometry	Cao et al. 2008
Seven quinolone antibacterials: OXA	Whole eggs	C_{18} column	Gradient elution using component A (acetonitrile) and component B (water). Both components were acidified with 20 mM formic acid	Tandem mass spectrometry	Bogialli et al. 2009

Table 2 (continued)

Name	Matrix	Column	Mobile phase	Detection	References
OXA with other FQs	Bovine milk samples	C_{18} column	Formic acid solution 0.1% (v/v) and acetonitrile using linear gradient elution	Mass spectrometry	Zafra-Gomez et al. 2008
OXA with other FQs	Pig liver	C_8 column	0.005 M ammonium acetate and formate solution and acetonitrile (86:14, v/v) at pH 2.5 using gradient elution	Mass spectrometry	Hermo et al. 2008
Several veterinary drugs including OXA	Livestock foods and fish	C_{18} column	0.1% formic acid-acetonitrile	Tandem Mass spectrometry	Kai et al. 2007
OXA and other FQs	Pig kidney	C_8 column	Acetonitrile and 10 mM citrate buffer of pH 4.5 using linear gradient elution	Fluorescence detection	Hassouan et al. 2007b
PIA, OXA with other FQs	Fish, chicken muscle, chicken liver and pig kidney	C_{18} column	Phosphoric acid:water:triethylamine:acetonitrile	Photodiode array and fluorescence detection	Romero-Gonzalez et al. 2007
OXA and other FQs	Egg samples	C_{18} column	Acetonitrile and 10 mM citrate buffer solution of pH 4.5 using linear gradient elution	Fluorescence detection	Hassouan et al. 2007a
Nine quinolones such as OXA	Bovine muscles	C_{18} column	Water/acetonitrile mixtures containing acetic acid	Tandem mass spectrometry	Rubies et al. 2007
OXA	Serum and muscles of the Chinese mitten crab	C_{18} column	Acetonitrile and 0.02 M phosphate buffered saline pH 3 (25:75)	Fluorescence detection	Tu et al. 2006
OXA	Fish farms	C_{18} column	Acetonitrile and aqueous orthophosphoric acid solution	Fluorescence detection	Pouliquen et al. 2006
Antibiotics including sulfonamides, macrolides, quinolones (OXA), tetracyclines and trimethoprim	Chlorine-disinfected drinking water	C_{18} column	Acidified methanol (0.1% formic acid)	Tandem mass spectrometry	Ye et al. 2007
Oxolinic acid and flumequine	Aquatic sediments and agricultural soils	C_{18} column	65% aqueous oxalic buffer at pH 4 and 35% acetonitrile	Fluorescence detection	Prat et al. 2006
OXA with erythromycin, fungicides and parasiticide	Edible portion of salmon	C_{18} column	Gradient elution using acetonitrile as solvent A and 0.1% formic acid in water (pH 3.5) as solvent B	Mass spectrometry	Hernando et al. 2006
Several FQs such as OXA	Chicken muscles	C_8 column	Gradient elution using 0.02 M ammonium acetate solution adjusted at pH 2.5 using formic acid/acetonitrile (86:14)	Mass spectrometry	Bailac et al. 2006
Some FQs such as OXA	Pig muscles	C_8 column	0.005 M ammonium acetate and formate solution and acetonitrile (86:14, v/v) at pH 2.5 with gradient elution	Tandem mass spectrometry	Hermo et al. 2006
Ten quinolones such as OXA, NDA, PFX, PIA and penicillins	Groundwater and surface waters	C_{18} column	8 mM ammonium acetate at pH 2.5 adjusted with formic acid (A) and acetonitrile with 0.1% formic acid (B) with gradient elution	Electrospray tandem mass spectrometry	Pozo et al. 2006
FQs such as OXA	Bee products	C_{18} column	0.02% aqueous formic acid solution and acetonitrile	MS/MS	Lombardo-Agüí et al. 2012

Table 2 (continued)

Name	Matrix	Column	Mobile phase	Detection	References
PIA with other FQs	Pharmaceuticals	C_{18} column	0.15 M sodium dodecyl sulfate, 2.5% propanol and 0.5% triethylamine at pH 3	UV detection	Collado-Sanchez et al. 2010
PIA, ENX, FRX, PFX	Human urine	C_{18} column	Acetonitrile:0.02 M tetrabutyl ammonium bromide (9:91, v/v) adjusting pH 2.87 by trifluoroacetic acid buffer	Diode array detector	Sun et al. 2008b
Thirty-one antimicrobials including β-lactams, lincosamides, macrolides, quinolones (PIA), sulfonamides, tetracyclines, nitroimidazoles and trimethoprim	Cattle and pig meat	C_{18} column	Gradient elution using component A: methanol with 10 mM formic acid, and B: water with 10 mM formic acid	MS/MS	Carretero et al. 2008
Fifty antibiotic drugs including chloramphenicol, sulfonamides, FQs (ENX), tetracyclines and macrolides	Sewage sludge	C_{18} column	0.1% formic acid-methanol or acetonitrile-water by gradient elution	MS/MS	Wang et al. 2013
Ten kinds of antibiotics such as ENX, PFX	Cosmetics	C_{18} column	Acetonitrile-0.05 M ammonium dihydrogen phosphate	UV detection	Yang et al. 2012
One hundred and nineteen pharmaceuticals including ENX	Sewage sludge	C_{18} column	Mobile phase composed of (A) 0.01% NH_4OH and (B) acetonitrile, using gradient elution	Mass spectrometry	William and Emmanuelle 2013
Fifty-eight pharmaceuticals including ENX	Environmental waters	C_{18} column	0.1% formic acid + 0.02% trifluoroacetic acid using gradient elution	Electrospray tandem mass spectrometry	Lopez-Serna et al. 2012
Ten FQs such as ENX, FRX, PFX	Grass carp	C_{18} column	Gradient elution program with acetonitrile and water (containing 0.05% formic acid)	Mass spectrometry	Liu et al. 2012b
Two FQs (ENX and lomefloxacin), sulfonamides and tetracycline	Animal tissues matrix	C_{18} column	Acetonitrile-dichloromethane (1:1, v/v). acetonitrile and acetic acid (0.1%) were combined in a gradient elution	Diode array detection	Yu et al. 2012a
ENX	Estuarine and coastal seawater	C_{18} column	Acetonitrile and water containing 0.2% formic acid	Tandem mass spectrometry	Yang et al. 2011
Some antibiotics such as ENX, PFX	Milk samples	C_{18} column	Gradient elution using a mobile phase consisting of acetonitrile (A) and aqueous solution: 2.9 mM [1-ethyl-3-methylimidazolium tetrafluoroborate], 0.7 mM ammonium acetate-acetic acid, pH = 2.70) (B)	UV detection	Gao et al. 2011b
Twenty antibiotic residues including cephalosporins, macrolides, quinolones: ENX, FRX	Milk and powdered milk	C_{18} column	Acetonitrile (containing 0.2% formic acid)-0.006 M ammonium acetate	Tandem mass spectrometry	Wang et al. 2011
Twelve FQs such as ENX, FRX, PFX	Honey samples	C_{18} column	Mobile phase (pH 2.5) consisted of methanol and 1% aqueous formic acid (29:71, v/v) in gradient elution	Diode array detector	Yu et al. 2011
ENX and its related substances	Pure form	C_{18} columns	0.025 M phosphoric acid solution-methanol-acetonitrile in gradient elution	UV detection	Du and Cao 2011

Table 2 (continued)

Name	Matrix	Column	Mobile phase	Detection	References
Nineteen antibiotics, including tetracyclines, sulfonamides, macrolides, quinolones (ENX) and β-lactam antibiotics	Environmental water samples	C_{18} columns	Methanol-0.1% formic acid as mobile phase in gradient elution	MS/MS	Lu et al. 2010
Norfloxacin and ENX	Serum and urine	C_{18} column	20 mM sodium dihydrogenphosphate (pH 3) and acetonitrile (85:15, v/v)	UV detection	Kobayashi et al. 2011
Seventy-four pharmaceuticals including ENX	Environmental waters and sewage	C_{18} column	Acetonitrile/0.1% (v/v) formic acid in a gradient elution	Electrospray tandem mass spectrometry	Lopez-Serna et al. 2010
Twenty-eight antibiotics residues including FRX, ENX, PFX	Honey samples	C_{18} column	Phase A [methanol (containing 0.4% formic acid)-acetonitrile, 65:35] and phase B (0.4% formic acid solution in gradient elution)	Tandem mass spectrometry	Zuo et al. 2009
Norfloxacin, ciprofloxacin and ENX	Pure form	C_{18} column	15 mM sulfuric acid and 35% (v/v) methanol	Fluorescence detection	Song et al. 2008
FRX, ENX and other FQs	Chicken tissues	C_{18} column	Formic acid solution and acetonitrile	Fluorescence detection	Ma et al. 2008
ENX, ELR with other FQs	Pure form	C_{18} column	11 mM tetrabutyl ammonium bromide solution:acetonitrile (96:4) of pH 4.2	UV detection	Shi et al. 2009
Enoxacin and related substances	Pure form	C_{18} column	Sodium dodecanesulfonate-methanol-acetonitrile (45:30:25, pH 3 adjusted by triethylamine)	UV detection	Yi et al. 2007b
Some residual antibiotics: sulfonamides, FQs (ENX, FRX)	Chicken tissues	C_{18} column	Gradient elution program of acetonitrile and water (containing 0.05% formic acid)	Electrospray tandem mass spectrometry	Liu et al. 2008a
Enoxacin	Human serum	C_{18} column	Acetonitrile: 0.05 M citric buffer (15:85, pH 3.5)	UV detection	Sun et al. 2006
PFX, ENX and other FQs	Pure form	C_{18} column	Acetonitrile: methanol: 1% trifluoroacetic acid (4:7:89)	Fluorescence detection	Yu and Bi 2007
ENX, FRX and other FQs	Pork samples	C_{18} column	Acetonitrile (containing 0.1% phosphatic acid)	UV detection	Hou et al. 2007
Enoxacin gluconate and related substances	Enoxacin gluconate injection	C_{18} column	0.01 M citric acid (pH 3.5)-methanol-acetonitrile (78:12:10) or acetonitrile-phosphate buffer-0.05 M tetrabutyl ammonium bromide (5:37.5:1)	UV detection	Gao 2007
Norfloxacin, ciprofloxacin and ENX	Pure form	C_{18} column	15 mM H_2SO_4 and 35% methanol (v/v)	Fluorescence detection	Zhang et al. 2007a
Three sulfonamides and seven fluoroquinolones ENX, FRX	Pork samples	C_{18} column	Methanol-0.02 M phosphate buffer-triethylamine (25.5/74.5, v/v, pH 2.8)	Diode array detector	Liu et al. 2006
Several FQs such as ENX	Environmental waters	C_8 column	5 mM ammonium formate (pH 3)/acetonitrile (85/15, v/v)	Tandem mass spectrometry	Mitani and Kataoka 2006
Several FQs such as ENX	Urine and serum	C_{18} column	Tetrahydrofuran (8%) and phosphate buffer (pH 3, 30 mM, 92%)	Fluorescence detection	Espinosa-Mansilla et al. 2006

Table 2 (continued)

Name	Matrix	Column	Mobile phase	Detection	References
Eleven classes of antibiotics including FRX	Surface waters and sludge	C_{18} column	Gradient elution using (A): 5 mM oxalic acid, 0.1% formic acid, with 5 mM ammonium acetate and (B): acetonitrile	Tandem mass spectrometry	Zhou et al. 2012
Fleroxacin	Fleroxacin and glucose injection	C_{18} column	Triethylamine and phosphoric acid-acetonitrile (83:17)	UV detection	Song and Hao 2011
Twenty-two antibiotics (quinolones, sulfonamides and macrolides)	Fish samples	C_{18} column	Methanol-acetonitrile (1:1, v/v)	MS/MS	Li et al. 2010
Fleroxacin and other FQs	Chicken breast muscle	C_{18} column	Aqueous solution of 54 mM formic acid and 10 mM ammonium acetate and acetonitrile in gradient elution	Tandem mass spectrometry	Xu et al. 2011
FRX and other FQs	Soil samples	C_{18} column	Gradient elution using A: 25 mM H_3PO_4 and B: acetonitrile	Fluorescence detection	Sturini et al. 2010b
Twenty-two antibiotics including FRX	Environmental water samples	C_{18} column	A: methanol-acetonitrile (1:1, v/v) and B: 0.3% formic acid/water (containing 0.1% ammonium formate, v/v; pH 2.9) in gradient elution	Tandem mass spectrometry	Gao et al. 2010
Several FQs such as FRX	Water samples	C_{18} column	Mixture of 0.25% formic acid and 10 mM ammonium acetate and acetonitrile using gradient elution	Tandem mass spectrometry	Chen et al. 2010
Several FQs such as FRX	Bovine, ovine and caprine milk	C_{18} column	5 mM BMIM-BF4, 10 mM ammonium acetate at pH 3 and 13% (v/v) acetonitrile using gradient elution	Fluorescence detection	Herrera-Herrera et al. 2009
Fleroxacin, levofloxacin, norfloxacin and ciprofloxacin	Human serum	C_{18} column	Mixture of isoleucine and $CuSO_4$:methanol (80:20, v/v)	Fluorescence detection	Wang et al. 2008
Fleroxacin	Fleroxacin and glucose injection	C_{18} column	Triethylamine and phosphoric acid-acetonitrile (82:18)	UV detection	Zhu et al. 2008
Fleroxacin	Human plasma	C_{18} column	Water solution including L-isoleucine and $CuSO_4$:methanol (80:20, v/v)	Fluorescence detection	Wang and Bai 2007
FRX with other FQs	Water samples	C_{18} column	5 mM BF4 and 10 mM ammonium acetate at pH 3 with 13% acetonitrile	Fluorescence detection	Herrera-Herrera et al. 2008
Fleroxacin	Human blood plasma	C_{18} column	1% triethylamine at pH 4.8 and acetonitrile (80/20, v/v)	Fluorescence detection	Fang et al. 2007
Nadifloxacin	Cream dosage forms	C_{18} column	Acetonitrile: tetrahydrofuran-0.025 M ammonium dihydrogen phosphate (35:5:60, pH 3)	UV detection	Zhang et al. 2006a
Pefloxacin mesylate	Bulk drug and in tablets dosage form	C_{18} column	Methanol-buffer (30:70, v/v)	UV detection	Agrahari et al. 2013
Eight kinds of quinolones such as PFX	Veterinary drugs preparations	C_{18} column	Phosphoric acid-pure water-triethylamine-acetonitrile as mobile phase at a gradient elution	Fluorescence detection	Zhao and Fan 2012
Several FQs such as PFX	Whole eggs	C_{18} column	Acetonitrile-0.1% formic acid (13:87)	MS/MS	Tian et al. 2010

Table 2 (continued)

Name	Matrix	Column	Mobile phase	Detection	References
Five fluoroquinolones including PFX	Waste water	Phenyl column	Methanol or acetonitrile was used as the organic modifier (solvent A) and 10 mM acetate buffer (pH 9) was used as solvent B applying gradient elution	MS and fluorescence detection	Seifrtova et al. 2010
Pefloxacin, norfloxacin, ciprofloxacin and ofloxacin	Pharmaceutical preparations and human serum	C_{18} column	Water-acetonitrile (50:50, v/v) mobile phase of pH 2.9 adjusted with phosphoric acid	UV detection	Siddiqui et al. 2009
PFX and other FQs	Chicken muscle	C_{18} column	Methanol/acetonitrile/0.2% formic acid (15/15/70, v/v/v)	MS/MS	Chen et al. 2008b
Seventy-six pharmaceutical agents of nine classes of drugs including PFX	Slaughterhouse waste water	C_{18} column	Water-acetonitrile using gradient elution	Tandem mass spectrometry	Shao et al. 2009
Nine fluoroquinolone residues including PFX	Milk samples	C_{18} column	Methanol/acetonitrile/0.2% formic acid	MS/MS	Chen et al. 2008a
Pefloxacin mesilate and its related substance	Tablets	C_{18} column	Acetonitrile-mixture of cetytrimethylammonium bromide with boric acid solution-2,2′-thiodiglycol (30:70:0.2, v/v/v)	UV detection	Li et al. 2009a
Pefloxacin	Bulk material, tablets and human plasma	C_{18} column	Acetonitrile: 0.025 M phosphoric acid solution (13:87, v/v); pH 2.9	UV detection	Gauhar et al. 2009
PFX together with other FQs	Royal jelly samples	C_{18} column	Methanol/acetonitrile/0.1% trifluoroacetic acid (8:4:88, v/v/v) pH 2.5	Fluorescence detection	Zhou et al. 2009
Related substances and contents in pefloxacin mesylate	Pefloxacin mesylate injection	C_{18} column	0.04 M potassium dihydrogen orthophosphate-acetonitrile-0.05 M tetrabutyl ammonium bromide (80:9:8) pH 2.5	UV detection	Li et al. 2006a
PFX and other FQs	Fish and shellfish muscle	C_{18} column	0.1 M phosphoric acid and acetonitrile (91:9, v/v)	Fluorescence detection	Jo et al. 2006
PFX and other FQs	Pharmaceutical preparations	C_{18} column	Water: acetonitrile (80:20, v/v) with 0.3% of triethylamine and pH 3.3	UV detection	Santoro et al. 2006
RFX and other FQs	Milk samples	C_{18} column	Methanol-10 mM ammonium acetate solution (25:75)	MS/MS	Jiao et al. 2009b

ACN, acetonitril; BMIM, 1-butyl-3-methylimidazolium hexafluorophosphate; ENX, enoxacin; FQs, fluoroquinolones; FRX, fleroxacin; HPLC, high performance liquid chromatography; NDA, nalidixic acid; NFX, nadifloxacin; OXA, oxolinic acid; PFX, pefloxacin; PIA, pipemidic acid; PMA, piromidic acid; TFA, trifluoroacetic acid.

40:10 (v/v) or acetonitrile-water-acetic acid, 6:40:4 (v/v/v) (Bober 2008).

Gas chromatography (GC)

Derivatization of some pharmaceutical substances for GC analysis including NDA was performed using many derivatizing reagents of different types; the derivatization was followed by the GC/MS detection of the resultant products. The number of labile hydrogen atoms in the initial molecules substituted by the structural fragments of derivatizing reagents was determined (Gulyaev and Revel'skii 2010).

High performance liquid chromatography

Several HPLC methods were developed to separate FQs in pure form, pharmaceutical preparations, biological fluids, environmental samples, cosmetics, animals' tissues and so on. Such methods are abridged in Table 2.

Conclusions

The analysis of some selected 4-quinolone drugs from the first and second generation since 2006 up till now has been fully covered by the comprehensive review. Different analytical techniques were summarized to facilitate the literature reviewing effort that many researchers perform to get up-to-date knowledge about this category of antibacterial agents. In spite of that numerous analytical tools were suggested for their determination, it was noticed that separation techniques constitute the main core for their quantitative measurement. This could be attributed to the fact that FQs exist in the form of a mixture in many samples whether it is *per se* pharmaceutical formulation, biological and environmental samples, cosmetics, animal tissues and feed-premix samples. CE and HPLC are two principal methods for the assay of such class. In spite of that CE is characterized by its high separation efficiency owing to the use of narrow tubes in the apparatus, besides its simple instrumentation which does not need experienced staff, HPLC is more spread because it is superior to CE in many aspects. Small pH changes affect a molecule's charge and flow in CE; thus, small variations in pH have a greater impact in CE than in HPLC. Compared with HPLC, the control of the pH is critical in CE, and there are many factors, including temperature, that affect pH. Moreover, band broadening, poor repeatability and lower sensitivity are other limitations of CE. Thus, the reason of such numerous reports in this review applying HPLC for FQ assay could be inferred.

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