Identification of antibiotics in wastewater: current state of extraction protocol and future perspectives

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ABSTRACT

The release and occurrence of antibiotics in the aquatic environment has generated increased attention in the past few decades. The residual antibiotic in wastewater is important in the selection for antimicrobial resistance among microorganisms and the possibility of forming toxic derivatives. This review presents an assessment of the advancement in methods for extraction of antibiotics with solid phase extraction and liquid–liquid extraction methods applied in different aquatic environmental media. These advanced methods do enhance specificity, and also exhibit high accuracy and recovery. The aim of this review is to assess the pros and cons of the methods of extraction towards identification of quinolones and sulphonamides as examples of relevant antibiotics in wastewater. The challenges associated with the improvements are also examined with a view of providing potential perspectives for better extraction and identification protocols in the near future. From the context of this review, magnetic molecular imprinted polymer is superior over the remaining extraction methods (with the availability of commercial templates and monomers), is based on less cumbersome extraction procedures, uses less solvent and has the advantage of its reusable magnetic phase.

Key words | antibiotics, extraction protocol, quinolones, sulphonamides, wastewaters

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INTRODUCTION

The prevalence of micro-pollutants like pharmaceuticals in the aquatic environment has become an issue of global importance in recent years. Pharmaceuticals are used in human and veterinary medicine as prophylaxis and therapeutics, boosting immunity as well as stimulating and improving the rate of growth in animal production (Luo *et al.* 2014). This is seen as a response to provide for the ever growing human population, to meet an increasing demand (Singer *et al.* 2003; Van Boeckel *et al.* 2015). This increase in antibiotic consumption may facilitate antibiotic resistance development in microorganisms. The treatment of antibiotic resistant bacteria in humans may demand increased doses of antibiotics, the combination of several drugs or the use of entirely new ones (Boehme *et al.* 2010).

Antibiotics are released to the aquatic environment through various routes. After administration to humans, they are excreted partly as incompletely metabolized products (Chang *et al.* 2010) and partly as unchanged active compound via urine and feces, ending up in the sewer system, and are subsequently released into the environment in the effluents after potential wastewater treatment (Kümmerer 2009). The wastewater treatment plants (WWTPs) have been shown to have low capacity towards the removal of antibiotics from the wastewater (Seifrtová *et al.* 2009; Wei *et al.* 2010). Hence, the effluents are major contributors of antibiotics into the aquatic environment. The use of sludge, from WWTPs or on-site sanitation facilities, as fertilizer with active antibiotic components also contributes to release of antibiotics to the soil environment

and can affect the microorganisms present therein (Baguer *et al.* 2000; Kumar *et al.* 2005). Subsequent run-off of organic fertilizers from agricultural land increases the spread of the antibiotics further into the aquatic environment (Michael *et al.* 2013; Pruden *et al.* 2013).

Animal excreta (manure) applied to agricultural fields as fertilizers are a source of contamination, as most of the antibiotics consumed by the animals end up in their excreta in the active form or modified (Toumi *et al.* 2015). Residual antibiotics in animal excreta enter the environment through run-offs from agricultural land or irrigation and are sometimes taken up by plants and transferable via the consumption of such plants (Venglovsky *et al.* 2009; Eggen *et al.* 2011). The active compounds of the antibiotics, or their biologically active metabolites, may also percolate from land or leaking sewers to the groundwater (Frey *et al.* 2015). The presence of these active components in the environment remains a potential risk whether at low (sub-lethal level) or high (toxic level) concentration (Jiang *et al.* 2013).

Quinolones (ciprofloxacin) are among the most used antibiotics in the world, and the wide spread of resistant strains has been well established (Acar & Goldstein 1997; Rocha *et al.* 2017). Lower respiratory tract infections are sometimes not susceptible to ciprofloxacin (Fuller & Low 2005; Pereyre *et al.* 2016; Pribul *et al.* 2017). This trend in bacterial resistance is on the increase, creating a haven of super resistant bacteria to the stronger antibiotics. The same fate of resistance applies to sulphonamide, which has led to reduction in its usage (Enne *et al.* 2001; Alonso *et al.* 2017). One of the causes of antibiotic resistance is the 'misuse of antibiotics', which leads to selection for resistance genes (Lukačišinová & Bollenbach 2017). The presence of these antibiotics in the water and food we consume (Jones *et al.* 2005) may lead to their unintentional misuse and further resistance development (Jones *et al.* 2003). This calls for a holistic approach to mitigate the presence and persistence of antibiotics in the environment from sources such as the wastewater.

Several methods have been developed for identifying and quantifying antibiotics in different aquatic regimes, such as sewage water (Lindberg *et al.* 2005; Li *et al.* 2007; Dorival-García *et al.* 2013), drinking water (Fick *et al.* 2009; Rodríguez *et al.* 2011; Dzomba *et al.* 2014), river water (Senta *et al.* 2008; Agunbiade & Moodley 2014;

Ngumba *et al.* 2016) and groundwater (Batt & Aga 2005; Olaitan *et al.* 2014). Prior to the analysis, the analyte of interest must be concentrated and extracted from the collected samples matrix using sample preparation steps which involve filtration and the use of different analyte-sequestering methods such as solvent extraction (Nabais & Cardoso 1995; Yan *et al.* 2011) and solid-phase extraction (SPE) methods (Dorival-García *et al.* 2013; Errayess *et al.* 2017).

Environmental detection and quantification of antibiotics is essential; hence, the extraction/analysis protocol is a vital part of the chemical risk assessment. The common traditional methods of extraction of antibiotics in wastewater are liquid–liquid extraction (LLE) and SPE. These have several shortfalls in their traditional set-up, including cumbersome procedure, use of expensive glassware, low efficiency in sample clean-up, low specificity towards the target analyte, and reduced recovery when compared with the related recent advanced methods.

Quinolones and sulphonamides are the two types of antibiotics focused on as examples in this review. Their selection is based on the rate of use of these antibiotics in relation to the prevalent diseases and with reference to available data on the rate of production/sales (Van Boeckel *et al.* 2014), their stability in the aquatic environment (wastewater) (Gaugain *et al.* 2013) and the impact of the antibiotics in relation to antibiotic resistance (Rodriguez-Mozaz *et al.* 2015). Their extraction procedures have a good base for comparison of LLE and SPE as well as the advanced states of the extraction methods that use similar detection instrumentation. These criteria were the basis for the screening of research papers for this review.

FACTORS INFLUENCING SAMPLE PREPARATION

All experiments are dependent on the quality of sampling. Sample collection and preparation (preservation, filtration and extraction) are the first steps and an essential part of the analytical procedure, followed by chromatographic separation, detection and data analysis. Proportionately, 80% of the analytical time is used for sampling and sample preparation (Buszewski & Szultka 2012). Sampling generally implies choosing a small fraction of a matrix that is representative of the quality of the whole matrix. Factors such

as frequency and time of sampling, temperature, sampling method and sampling equipment must be critically considered in order to have a good sample for antibiotics analysis (Ort et al. 2010).

A good knowledge of the physicochemical properties of the analytes (antibiotics) is an important precondition in sample preparation (Namieśnik et al. 2005). As highlighted in Table 1, the acid dissociation constant (pKa) is an indicator of the acid–base property of the antibiotics and determines its ionization rate, which enables an effective adjustment of the sample pH for preservation and extraction (Qiang & Adams 2004). Partition coefficient (log P) is an indicator of the degree of hydrophilicity and hydrophobicity of a substance and measures its solubility in two different phases. Antibiotics with high log P are hydrophobic in nature, whereas a low log P is hydrophilic (Pavlović et al. 2007). Cyclic or ring structures of antibiotics can also influence their solubility as well as the level of complexity (the bond structure within the rings) and number of rings. These parameters guide the selection of solvent and extraction media when choosing the extraction method.

It can be inferred that there is a tendency for the solubility of an antibiotic in water to increase with decreasing number of rings in the molecule.
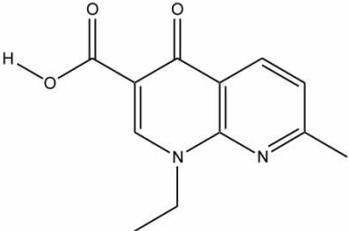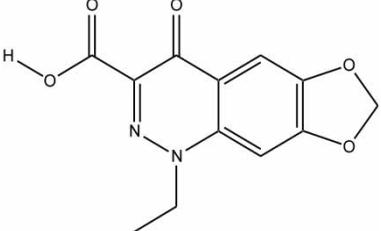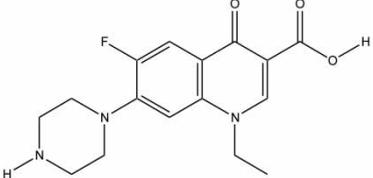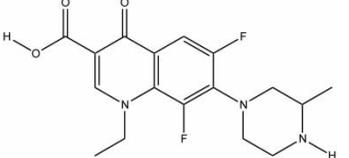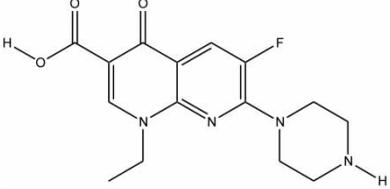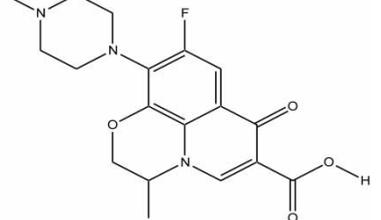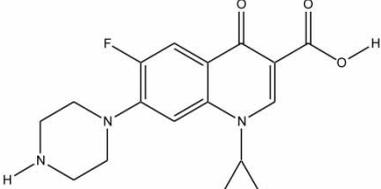
Various models for predicting the solubility of drugs exist, based on parameters such as the log P of the drug, molecular weight and fragment pattern (Sanghvi et al. 2003; Lipinski et al. 2012; Knopp et al. 2015) as well as commercial computational means of predicting the solubility of drugs such as CLOGP (Daylight Chemical Information Systems) and ACD (Advanced Chemistry Development, Inc.). Most of these models require experimental procedures to justify the numerical solubility values assigned to drugs. None of the published models makes use of the number of ring structures to estimate the drug solubility.

Data of the different quinolones and sulphonamides as tabulated in Tables 2 and 3 indicate a relationship between the number of rings and the solubility of the antibiotics. Nalidixic acid (quinolone) and sulfacetamide (sulphonamide) have the smallest number of rings and the highest solubility values in relation to other antibiotics in the table.

Table 1 | Interrelatedness of physicochemical properties of some antibiotics (DrugBank 2017)

Antibiotics	Class of antibiotics	pKa (acid)	Log P	Water solubility mg/mL	Number of rings per antibiotic
Tetracycline	Tetracycline	−2.20	−0.56	1.33	4
Doxycycline		−2.20	−0.72	0.63	4
Oxytetracycline		0.24	−0.99	1.40	4
Amoxicillin	Beta lactam	3.23	0.75	0.96	3
Flucloxacillin		3.75	2.69	0.06	4
Ceftriaxone		3.19	−0.01	0.11	4
Erythromycin	Macrolide	12.44	2.37	0.46	3
Azithromycin		12.43	3.03	0.51	3
Clarithromycin		12.46	3.18	0.22	3
Sulfamethoxazole	Sulphonamides	6.16	0.79	0.46	2
Sulfanilamide Sulfadiazine		−0.25	−0.16	10.4	1
		6.99	0.25	0.60	2
Metronidazole	Imidazole	15.44	−0.15	5.92	1
Albendazole	Benzimidazole	9.51	3.22	0.02	2
Ethambutol	Antituberculosis	14.82	−0.12	7.54	0
Ethionamide		11.89	1.88	0.84	1
Isoniazid		13.61	−0.71	34.90	1

Table 2 | Relating quinolone structure (number of rings) to their solubility in water (DrugBank 2017)

Groups of quinolones	Class	Structure	Number of rings	Solubility in water (mg/mL)
Nalidixic acid	1st generation		2	2.3
Cinoxacin			3	0.96
Norfloxacin	2nd generation		3	1.01
Lomefloxacin			3	0.11
Enoxacin			3	1.09
Ofloxacin			4	1.44
Ciprofloxacin			4	1.35

(*continued*)

Table 2 | continued

Groups of quinolones	Class	Structure	Number of rings	Solubility in water (mg/mL)
Levofloxacin	3rd generation		4	1.44
Sparfloxacin			4	0.11
Gatifloxacin			4	0.63
Moxifloxacin			5	0.17
Trovafloxacin	4th generation		5	0.07
Alatrofloxacin			5	0.04
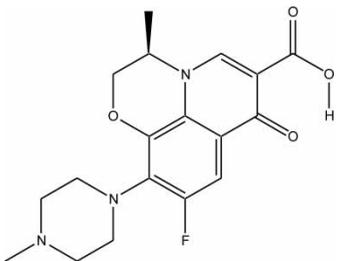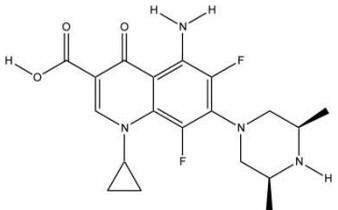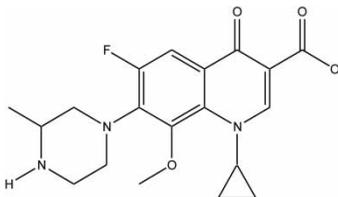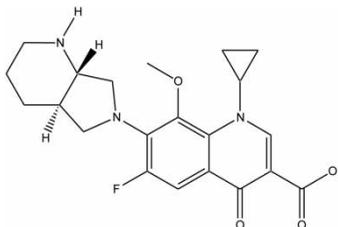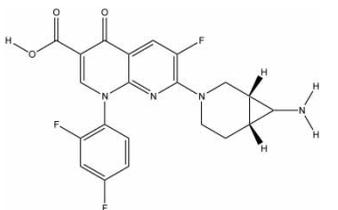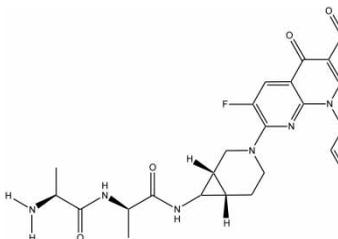
Table 3 | Relating sulphonamide structure (number of rings) to their solubility in water (DrugBank 2017)

Groups of sulphonamide	Class	Structure	Number of rings	Solubility in water (mg/mL)
Sulfacetamide	Short acting		1	4.21
Sulfadiazine			2	0.60
Sulfafurazole			2	0.31
Sulfadoxine	Intermediate acting		2	0.30
Sulfamethoxazole			2	0.46
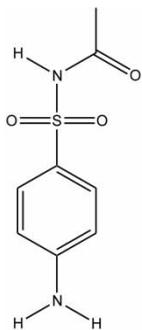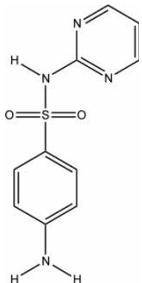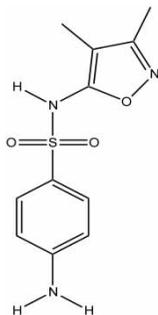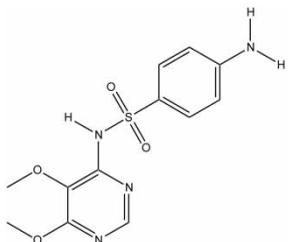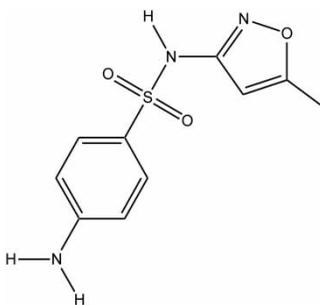
(*continued*)

Table 3 | continued

Groups of sulphonamide	Class	Structure	Number of rings	Solubility in water (mg/mL)
Sulfamoxole			2	0.27
Sulfadimethoxine	Long acting		2	0.28
Sulfadoxine	Ultra long acting		2	0.30
Sulfametopyrazine			2	0.41
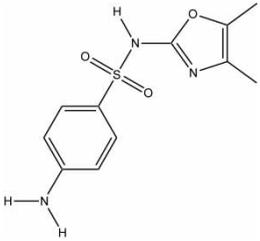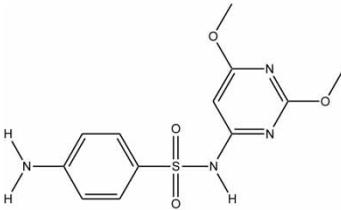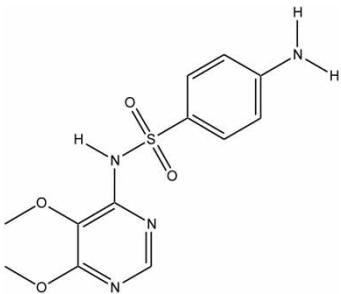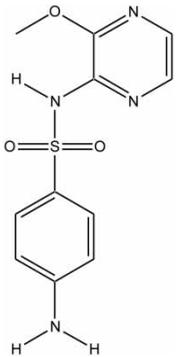
Sulphonamide and quinolone extraction techniques from wastewater

In the fight against bacterial infection, sulphonamides were the pioneer group of drugs that achieved great success. The simplest and oldest form of sulphonamides is sulphanilamide, and all others are its derivatives, while quinolones are derivatives of nalidixic acid (Figures 1 and 2).

Sulphonamides and quinolones are mostly insoluble in water (Tables 2 and 3) at neutral pH and become more soluble in an acidic environment with high stability (Luo *et al.* 2011). The frequency of use of these antibiotics and their stability account especially for their detection in the aquatic environment (Senta *et al.* 2008).

SPE and LLE are widely used as a pre-concentration step. In SPE, analytes are extracted from liquid sample, based on the polarity of the compound. The analytes are
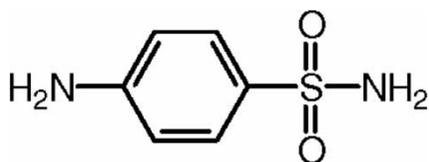
Figure 1 | Sulphanilamide.
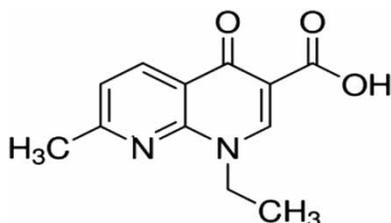
Figure 2 | Nalidixic acid.

retained on the sorbent, based on their affinity, and subsequently eluted for instrumental analysis. SPE makes use of a solid phase and a mobile phase to separate analytes based on their different degrees of affinity for the liquid or solid phase. SPE has been widely used with excellent recoveries (Mutavdžić Pavlović *et al.* 2010; Dorival-García *et al.* 2013; Płotka-Wasylka *et al.* 2016), but is time consuming (conditioning, sample loading, washing and elution), especially when the sample volume is large (Płotka-Wasylka *et al.* 2016).

LLE or solvent extraction is an extraction process that makes use of two immiscible solvents to separate compounds based on their relative solubility (Soniya & Muthuraman 2015). To the best of our knowledge, LLE has not been extensively used for the extraction of both sulphonamides and quinolones in recent years (after 2000). The drawbacks in pre-concentration have mainly been resolved. The use of a small volume of solvent in LLE enhances the efficiency and environmental friendliness (Gjelstad & Pedersen-Bjergaard 2013; Xing *et al.* 2015) and, in SPE, time required has been reduced in its further development with magnetic solid phase extraction (MSPE) and molecular imprinted polymers (MIPs) (Li *et al.* 2015).

Improvements in the traditional LLE and SPE methods are aimed at enhancing the speed and reducing the costs in the sample pre-concentration and adaptation to the analytical instrument to be used (Thurman & Snavely 2000; Hanson 2013; Wen *et al.* 2014; Ahmad *et al.* 2015). These

advancements are exemplified in relation to efficiency and frequency of use with dispersive liquid–liquid micro-extraction (DLLME) and hollow-fiber liquid-phase microextraction (HF-LPME) for the LLE extraction and with MSPE and MIP for the SPE (Tables 4 and 5) (Vas & Vekey 2004; Prieto *et al.* 2011; Wen *et al.* 2014; Ebrahimpour *et al.* 2015). DLLME is a process in which two immiscible solvents (organic and aqueous) are used for the extraction of organic compounds from water samples, while HF-LPME involves the use of an acceptor solution concealed in a polypropylene fiber in an organic solvent (Sharifi *et al.* 2016).

Matrix effect on recovery

Matrix effect is the interference experienced as a result of the presence of other compounds that are not of interest when analyzing for the target substances at the instrumental detection point (Matuszewski *et al.* 2003; Petrović *et al.* 2005). The source of the samples is a determinant for the constituents, where, for example, wastewater from an animal farm will have different constituents compared with wastewater from a pharmaceutical company. Evaluation of the matrix effect is very important to ensure reliable analysis where co-elution of compounds can lead to signal enhancement or suppression and analytical inaccuracy (Bolong *et al.* 2009).

Several papers on matrix effect evaluation have been published (Lamble & Hill 1998; Matuszewski *et al.* 2003; Hamid & Eskicioglu 2012), and the most reliable with regard to antibiotics in water samples is the one where an isotope-labelled internal standard (surrogate) has been used (Zwiener & Frimmel 2004). These surrogates are not commercially available, and other methods, such as an external calibration method (addition of pure standard of analyte of interest at a fixed concentration) and standard addition method (addition of pure standard of analyte of interest at varying concentration), are used (Gros *et al.* 2006). In Table 4, Dasenaki & Thomaidis (2015) and Ye *et al.* (2007), compensated for the matrix effects using the standard addition method, while Pedrouzo *et al.* (2008) compared the use of both internal and external standard and obtained better results with the use of an internal standard. MIP posesses high selective properties, which enable reduction of the matrix

Table 4 | Comparisons between different extraction methods for the determination of sulphonamide in wastewater (extraction method abbreviations are given as a footnote to Table 5)

Extraction methods	Extraction time (min) per sample volume (mL)	Solvent consumed per sample (mL)	Limit of detection (ng/L)	Matrices (sample source)	Percentage recovery (%)	References
SPE-HPLC-MS/MS	*/50 mL	12	6.6–22.0	[a.] Wastewater influent [b.] Wastewater effluent	[a.] 38.5–78.1 [b.] 42.2–79.0	Dasenaki & Thomaidis (2015), Pedrouzo et al. (2008), Ye et al. (2007), Peng et al. (2008) and Agunbiade & Moodley (2014)
SPE-HPLC-MS	8 min/100 mL 20 min/250 mL	9	20	[a.] Wastewater influent [b.] Wastewater effluent	[a.] 25.0–56.0 [b.] 27.0–53.0	
SPE-HPLC-MS/MS	167 min/500 mL	9	1–3	Raw wastewater	23.1–87.0	
SPE-HPLC-DAD	100 min/500 mL 30 min/150 mL	29	70–80 200–250	[a.] Wastewater influent [b.] Wastewater effluent	[a.] 64.0–72.0 [b.] 65.0–71.0	
SPE-HPLC-DAD	100 min/500 mL	28	310	Environmental water (river water)	87.4–92.5	
MIP-HPLC-MS/MS	25 min/500 mL	11	380–1,320	Environmental water (river, lake, sewage water)	76.8–32.8	Chen et al. (2013), Lian et al. (2014) and Qin et al. (2012)
MIP-HPLC-DAD	16 min/4 mL	4	50	Sea water	88–79.2	
MIP-HPLC-DAD	333 min/500 mL	7	4.1–19.3	Wastewater influent	84.1–98.6	
MSPE-HPLC-UV	15 min/500 mL	6.5	20–30	Environmental water (sewage effluent, tap water, lake water)	70–102	Sun et al. (2009), Li et al. (2007) and Tolmacheva et al. (2016)
MSPE-HPLC-UV	35 min/150 mL	4.5	150–350	River water	89–113	
MSPE-HPLC-AD	10 min/100 mL	2.5	0.2–0.3	River water	84–105	
DLLME-HPLC-DAD	13 min/5 mL	1.94	[+]350–10,500	Run off water	78–117	Herrera-Herrera et al. (2013), Xu et al. (2011) and Song et al. (2014)
DLLME-HPLC-FD	12 min/10 mL	1.05	10–20	River water	95–110	
MA-DLLME-HPLC-UV	1.5 min/2 mL	**0.1	330–850	Environmental water (tap, pool, lake, river water)	75.1–115.8	
HF-LPME-HPLC-DAD-FD	360 min/50 mL	0.05	[+]1,000–15,000 for DAD detection 300–33,000 for FD detection	Environmental water (wastewater influent, effluent, river water, tap water)	36.2–101	Payán et al. (2011b), Tao et al. (2009) and Yudthavorasit et al. (2011)
HF-LPME-HPLC-UV	480 min/4 mL	4.03	100–400	Environmental water (fish, duck, pig farm water, river water)	82.2–103.2	
HF-LPME-UHPLC-MS/MS	60 min/20 mL	0.02	10–250	River water	79–118	

*Extraction time was not stated.

**0.16 g of ionic liquid was dissolved in 0.1 mL of acetonitrile.

[+]Poor detection limit as a result of the use of a less sensitive detector (DAD).

Table 5 | Comparative study of different types of extraction methodologies for the determination of fluoroquinolones in water

Extraction methods	Extraction time (min) per sample/volume (mL)	Solvent consumed per sample (mL)	Limit of detection (ng/L)	Matrices (sample source)	Percentage recovery (%)	References
SPE-UPLC-MS/MS	36 min/100 mL	23	20–40	Wastewaters (WWTP)	98.5–103.9	Senta et al. (2008), Wang et al. (2010) and Dorival-García et al. (2013)
SPE-HPLC-MS/MS	40 min/200 mL	14	6.5–13.2	Wastewater (primary effluent)	53–60	
SPE-HPLC-MS/MS	250 min/500 mL	12	0.09–0.25	Tap water	61.4–91.3	
ONLINE-MISPE-LC-FLD	30 min/25 mL	17.5	1–11 1–12	Drinking water Fish farm water	62–102	Rodríguez et al. (2011), Luaces et al. (2013) and Lian & Wang (2016)
MISPE-FI-CL	10 min/10 mL	3	270	Environmental water (mineral, tap and river water)	84–119	
MISPE-HPLC-FD	20 min/5 mL	2	200	Sea water	75.2–112.4	
MSPE-HPLC-DAD	17 min/50 mL	0.5	50–120	Environmental water (lake water, reservoir water)	72.0–118	Liu et al. (2016), Huang et al. (2013) and Wu et al. (2016)
MSPE-HPLC-DAD	60 min/50 mL	0.5	200–1,460	Environmental water (lake water, reservoir water, surface water)	52.1–104.5	
MSPE-HPLC-UV	9 min/10 ml	0.4	200–1,000	Environmental (tap water, river and lake)	83.5–103.0	
DLLME-LC-UV	7 min/8 mL	0.6	140–810	Wastewater (wastewater from pharmaceutical factory)	82.7–110.9	Yan et al. (2011), Vázquez et al. (2012) and Guan et al. (2016)
DLLME-LC-FD	19 min/10 mL	0.5	0.8–13	Ground water	85–107	
DLLME-UHPLC-MS/MS	12 min/5 mL	1.2	6–9.1	Environmental water (tap water, river water, running water, wastewater)	76.8–100	
HF-LPME-UHPLC-MS/MS	60 min/20 mL	0.02	10–250	River water	78–118	Yudthavorasit et al. (2011), Payán et al. (2011a) and Denadai & Cass (2015)
HF-LPME-HPLC-DAD-FD	330 min/50 mL	0.05	0.3–16	Environmental water (river water, wastewater)	97–100	
HF-LPME-LC-QqQ-MS/MS	4.5 min/0.5 mL	0.05	5.3–31.8	Environmental water (surface and wastewater)	79.5–112	

Abbreviations for extraction methods: SPE-HPLC-MS/MS (solid phase extraction – high performance liquid chromatography tandem mass spectrometry); SPE-HPLC-DAD (solid phase extraction – high performance liquid chromatography – diode array detection); MIP-HPLC-MS/MS (molecular imprinted polymer high performance liquid chromatography tandem mass spectrometry); MIP-HPLC-DAD (molecular imprinted polymer high performance liquid chromatography diode array detection); MSPE-HPLC-UV (magnetic solid phase extraction – high performance liquid chromatography – ultraviolet light detection); MSPE-HPLC-AD (magnetic solid phase extraction – high performance liquid chromatography – amperometric detection); DLLME-HPLC-FD (dispersive liquid–liquid microextraction – high performance liquid chromatography – fluorescence detection); MA-DLLME-HPLC-UV (microwave assisted dispersive liquid–liquid microextraction – high performance liquid chromatography – ultraviolet light detection); HF-LPME-HPLC-DAD-FD (hollow-fiber liquid phase microextraction – high performance liquid chromatography – diode array detection tandem fluorescence detection), HF-LPME-HPLC-UV (hollow-fiber liquid phase microextraction – high performance liquid chromatography – ultraviolet light detection); HF-LPME-UHPLC-MS/MS (hollow-fiber liquid phase microextraction – ultra high performance liquid chromatography tandem mass spectrometry); HF-LPME-LC-QqQ-MS/MS (hollow-fiber liquid phase microextraction – ultra liquid chromatography triple-quadrupole tandem mass spectrometry); MISPE-FI-CL (molecularly imprinted polymer solid phase extraction – flow-injection chemiluminescence); ONLINE-MISPE-LC-FLD (online molecular imprinted solid phase extraction – liquid chromatography fluorescence detection); DLLME-LC-UV (dispersive liquid–liquid microextraction – liquid chromatography – ultraviolet light detection); DLLME-UHPLC-MS/MS (dispersive liquid–liquid microextraction – ultra high performance liquid chromatography tandem mass spectrometry).

effect significantly via targeted analyte sorbents. Chen et al. (2013) used external calibration to evaluate the reduction of the matrix effect of the MIP extract. Out of the papers reviewed, 25 made use of external calibration, while four utilized surrogate standards (Castiglioni et al. 2005; Senta et al. 2008; Wang et al. 2010; Dorival-García et al. 2013) and one (Renew & Huang 2004) used both surrogate and standard addition methods. Despite the different sample sources, the recovery results presented here are reliable based on the use of one form of matrix check for result validation.

Solid phase extraction

SPE is currently more frequently used for sample clean-up in wastewater than previously due to enhanced ease of use and commercially available solid-phase sorbents with extraction kits including extraction manifolds. Sorbents packed in a cartridge are placed on the manifold, and the appropriate extraction solvent is used in the four-step extraction process. These steps are essentially: (1) conditioning of sorbent; (2) loading of sample; (3) washing of impurities (not in all cases); and (4) elution of the analyte.

Different types of sorbent can be used for the separation. The choice mainly depends on the chemical characteristics (polarity and functional group) of the analyte and the interaction of the functional groups of the analyte with the sorbent (Babić et al. 2006; Chen et al. 2010; Mutavdžić Pavlović et al. 2010; Płotka-Wasylka et al. 2016). Different sorbents have been used for the determination of many organic compounds, including different pharmaceuticals in water/wastewater environments (Renew & Huang 2004; Tong et al. 2009; Jelic et al. 2011).

Mainly the polymeric based sorbents (e.g. Oasis HLB and strata X) and the silica-based sorbents (e.g. Strata C18-E and C8) are preferred in wastewater analysis (D'Archivio et al. 2007; Mutavdžić Pavlović et al. 2010; Masiá et al. 2014). The polymeric based sorbents are preferred due to their compatibility with most analytes and their ability to perform within a broad pH range (Karthikeyan & Meyer 2006; Jiang et al. 2013; Cheng et al. 2015; Skendi et al. 2016). The silica-based sorbents are restricted to more specific pH values within the neutral range. The silica in

the sorbent is unstable at both low and high pH values, where it tends to hydrolyze and thereby reduce the efficiency of the extraction process (Kirkland et al. 1997). Comparative assessments of sorbent efficiency have been carried out for optimal use in relation to the particular analyte of interest (Mutavdžić et al. 2006; Mutavdžić Pavlović et al. 2010; Tayeb et al. 2015). Table 6 lists a few examples of the polymeric and silica-based sorbents used in the extraction of sulphonamides and fluoroquinolones from wastewater and aquatic recipients. Hartig et al. (1999) utilized LiChrolut EN SPE catridges, which are polymeric sorbents, for the extraction of sulphonamides in secondary effluent and obtained a recovery between 77 and 100%. The polymeric sorbent Oasis hydrophilic-lipophilic (HLB) was used by Tong et al. (2009) for the extraction of 13 antibiotics, including sulfamerazine and ofloxacin. They obtained a recovery of over 90% for sulfamerazine, while the efficiency was much lower, 65%, for ofloxacin (Table 6). Non-specific/generic extraction methods tend to be advantageous (high recovery) to many antibiotics, while some may render low recoveries and require specific treatment, such as, for example, for ofloxacin (Table 6).

The highest recovery on the SPE was generally below 100% except for Dorival-García et al. (2013), which had a recovery of 103%. The advanced methods often gave 100% and above. The presence of phthalates from the SPE cartridges usually accounts for the above 100% recovery rates (Table 6). Since the choice of sorbent for SPE is based partly on economic considerations, further developments of the analytical procedure should account for this as well. The percentage recovery is calculated from the ratio of the experimental concentrations to the theoretical concentration of the antibiotics with reference to matrix effect elimination.

Modification and advancement in SPE (Whang et al. 2012; Xu & Lee 2012; Zhu et al. 2013; Li et al. 2015) has included sorbent coating to enhance the performance, as exemplified by magnetic coatings (Yu et al. 2013; Zhang & Anderson 2014) and micro extraction fibers (Bagheri et al. 2012; Pelit et al. 2015). High recoveries have been obtained with magnetic adsorbents (MSPE), such as magnetic molecular imprinted polymer (MMIP) (Mehdinia et al. 2011; Herrero-Latorre et al. 2015). These modifications have

Table 6 | Recovery of common SPE sorbents used for sulphonamide and fluoroquinolones

Sorbent packaging	Sorbent mass/ sample volume	Matrices (sample source)	Antibiotics	Percentage recovery	Reference
Oasis Hydrophilic–lipophilic (HLB) balanced	60 mg/50 mL	Wastewater (swine wastewater)	Sulfamerazine Ofloxacin	93%–98% 58–63%	Tong *et al.* (2009)
Oasis Hydrophilic–lipophilic (HLB) balanced	60 mg/150 mL	Wastewater (municipal wastewater influent)	Sulfapyridine	66–110%	Shaaban & Górecki (2012)
Anion-exchange cartridge (Isolute) + hydrophilic–lipophilic balanced (HLB)	500 mg + 500 mg/1,000 mL	Wastewater (municipal wastewater effluent)	Ciprofloxacin Oxofloxacin	90–154% 62–123%	Renew & Huang (2004)
Oasis Cation exchanger (MCX)	60 mg/500 mL	Wastewater (municipal wastewater effluent)	Ciprofloxacin Oxofloxacin	36–28% 3–25%	Castiglioni *et al.* (2005)
Oasis Hydrophilic–lipophilic (HLB) balanced	500 mg/100 mL	Wastewater (municipal wastewater effluent)	Ciprofloxacin Oxofloxacin	99–100% 99–102%	Dorival-García *et al.* (2013)
(a) Strata C8 (b) Strata C18-E	200 mg/100 mL	Wastewater (water municipal wastewater effluent)	Sulfadiazine Sulfamerazine	(a) 37–47% (b) 28–40% (a)92–94% (b)73–78%	Mutavdžić Pavlović *et al.* (2010)
LiChrolut EN SPE cartridges	200 mg/1,000 mL	Environmental water (water municipal wastewater effluent)	Sulfathiazole Sulfadiazine Sulfamerazine Sulfapyridine	77–100% 88–107% 83–117% 77–97%	Hartig *et al.* (1999)
(a) Strata C8 (b) Strata C18-E	200 mg/100 mL	Wastewater (water municipal wastewater effluent)	Norfloxacin Sulfamerazine	(a)54–62% (b)84–95% (a)71–74% (b)97–99%	Mutavdžić Pavlović *et al.* (2010)

Note: Analysis utilized LC-MS/MS for the analysis and recovery percentages (ratio of experimental concentration to theoretical concentration).

partly taken over the traditional use of the SPE in sample pre-treatment.

Magnetic solid phase extraction

In the MSPE method, magnetic particles (MPs) are used as adsorbents. They are not packed into cartridges as in the traditional SPE, but are dispersed in the sample solutions to adsorb the analytes. A larger surface area to volume ratio is achieved, resulting in higher extraction efficiency. The ease of preparation of the MP adsorption step encourages its use (Šafaříkovà & Šafařík 1999). An external magnet is applied to collect the MPs and separate these from the liquid phase, as shown in Figure 3. This procedure excludes the need for time consuming centrifugations or filtrations of the sample during the clean-up process. It is a time and labor effective approach, overcoming the setbacks of the traditional SPE procedure, especially the sample loading step (Li *et al.* 2015). The MPs frequently used are ferrite- or iron-oxide nanoparticles and Fe_3O_4 (crystalline iron oxides of maghemite or magnetite). Other types of MPs include silica-based MPs used in the purification of DNA (Rittich & Španová 2013), alumina coated nanoparticles used for metal/metalloid pre-concentration and/or separation (Giakisikli &

Anthemidis 2013), MMIP (Chen *et al.* 2010) and also polydimethylsiloxane (PDMS) used for the determination of phthalate diesters in water samples (Jeddi *et al.* 2014).

After completion of the extraction process, the extract is subjected to further analysis, such as liquid chromatography-tandem mass spectrometry (LC-MS/MS), in order to detect and determine the analytes quantitatively and qualitatively. The reusability of the magnetic sorbent is ensured by regenerating it through washing with an organic solvent such as methanol (Sarafraz-Yazdi *et al.* 2015). The separation of MPs depends on the type of MPs (sorbents), and is connected with the interaction of analyte molecules with the surface functional groups of the sorbents, in a similar manner as the traditional extraction in the solid phase (Aguilar-Arteaga *et al.* 2010).

The mechanism of the MSPE is based on the different types of interaction between the analyte and the magnetic sorbent; ionic, dipole-dipole, dipole-induced dipole, hydrogen bonding and dispersion forces (Wierucka & Biziuk 2014; Shi & Ye 2015). Similarly to the traditional SPE, the reverse-phase sorbent of the MSPE is a weak polar or non-polar compound, and the interactions are mostly with hydrophobic compounds through Van der Waal forces. In the normal phase sorbent, polar compounds
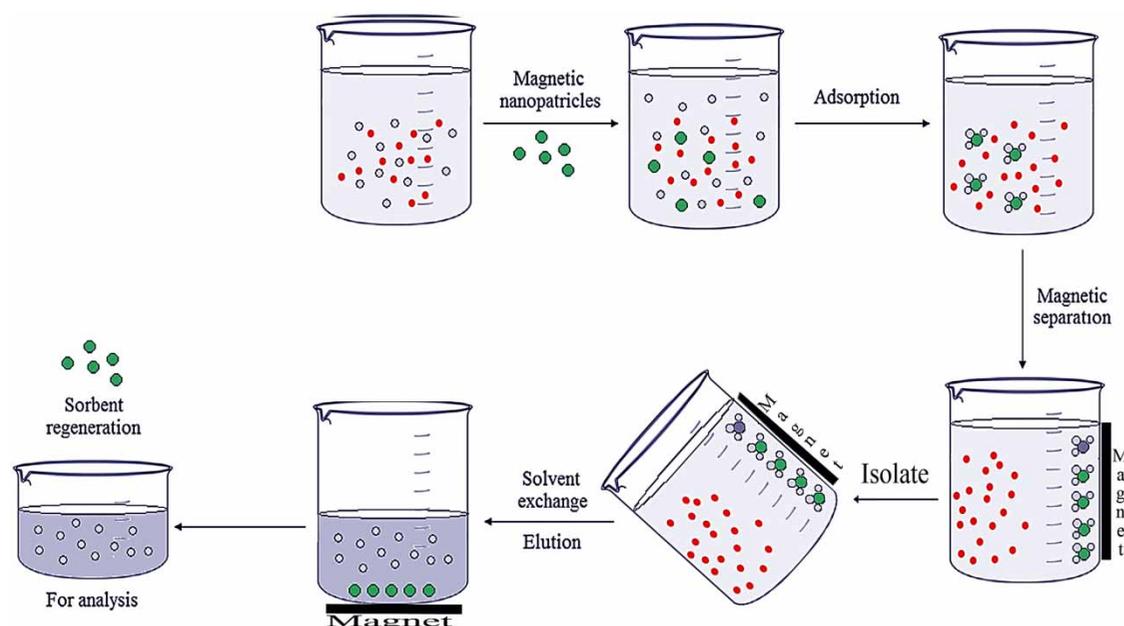

Figure 3 │ Application for enriching analyte as MSPE-NP sorbent (Wierucka & Biziuk 2014).

are used as the stationary phase, and the mobile phase is non-polar. The interaction is based on hydrogen bonding, dipole-dipole interactions and π-π interactions. A good knowledge of the analyte of interest, such as ionization and solubility, will guide in the selection of sorbent for the extraction protocol. These properties would determine the level of affinity for the sorbent and the extraction efficiency of the analyte from the sample solution (Wierucka & Biziuk 2014).

Another important factor is the choice of the eluting solvent. To ensure effective and quantitative elution, the solvent should have the right elution strength that matches the desired analyte (Sun *et al.* 2009). The amount of solvent and time used for the MSPE is generally small when compared with other types of SPE and LLE (Tables 4 and 5). Sun *et al.* (2009) made use of a magnetic hemimicelles solid phase extraction (MMHSPE) for several sulfonamides from environmental water samples (Sun *et al.* 2009). The process was time effective, making use of 15 min/500 mL with low solvent consumption of 6.5 mL. In addition, a recovery of close to 100% with low standard deviation (within 1–6%) was recorded, indicating a better result when compared with other SPE processes used in the same category.

In addition to the better yield, the high efficiency of the regenerated MPs makes MSPE economical and unique in a wastewater environmental analyte clean-up process (Šafaříkovà & Šafařík 1999).

Molecular imprinted polymer

Another methodological extraction SPE-based alternative is the MIP. These are polymers that have been processed using the molecular imprinting technique, which leaves cavities in the polymer matrix with an affinity for a chosen 'template' molecule (Figueiredo *et al.* 2016). MIPs are prepared by forming complexes with a template molecule (target molecule or its derivatives) and a functional monomer(s) that either covalently or non-covalently links with the template molecule followed by co-polymerization in the presence of cross-linker (Takeuchi & Sunayama 2014). The efficiency of this method has been proven by many researchers; for example, Luaces *et al.* (2013) prepared fluoroquinolone-selective MIP beads for the determination

of trace amounts of enrofloxacin in environmental waters, and a recovery of 84–119% was recorded. Other records of the use of MIP in the determination of sulphonamides and quinolones are listed in Tables 4 and 5.

MMIPs are produced by coating MIPs with MPs such as Fe_3O_4. The MMIPs possess the template-binding property of the MIP and the magnetic property of the MPs, hence making it a multifunctional method of extraction (Tan & Tong 2007; Zhou *et al.* 2010). The main difficulty encountered in the use of MIPs is the production, which includes template bleeding and cumbersome synthesis procedures (Figueiredo *et al.* 2016). Careful laboratory methods (synthesis of selective template) are currently being used for the production of templates (Luaces *et al.* 2013; Lian *et al.* 2014), but commercial availability of the imprinted polymer would make the use of MIPs much easier and faster. The possibility of making use of an external electrical current to generate the magnetic force needed in this extraction method, with the aim of generating an appropriate force to attract a particular analyte (based on their ionic charges) at a particular time, will greatly enhance the speed and efficiency of this method in the very near future.

Liquid–liquid extraction

As a result of the advancement in SPE (e.g., MSPE, MIP), conventional LLE is currently infrequently used, mainly due to three drawbacks: (1) time consuming extraction period; (2) cumbersome procedure and use of expensive glassware; (3) large quantity of extraction solvent needed.

Due to these drawbacks, literature references are limited on traditional LLE for clean-up of antibiotics in wastewater, especially for antibiotics like quinolones and sulphonamides. Specifically, after the year 2000, so far as we can ascertain, there is little or no available literature for the extraction of quinolones and sulphonamides in wastewater using LLE.

LLE is, however, still undergoing further development, as demonstrated by Leong *et al.* (2014) and others in the use of miniaturized pre-concentration techniques, and the use of dispersive liquid and phase extractions (Leong *et al.* 2014; Ahmad *et al.* 2015; Bendicho *et al.* 2015).

Micro-extraction techniques are environmentally friendly, less expensive and simple to operate, which has renewed the interest in a miniaturized LLE method. The improvements involve the reduction of the acceptor to donor phase ratio, thereby miniaturizing the solvent use (Sarafraz-Yazdi & Amiri 2010) in the liquid-phase micro extraction (LPME) method. Several alternative methodological approaches exist: HF-LPME, DLLME and pressurized liquid extraction (PLE) are a few examples. PLE is an advanced form of LLME, not further detailed here (Li *et al.* 2013; Vazquez-Roig & Picó 2015). The extracts from the PLE method are mostly enhanced by a further clean-up procedure, which governs the recovery (Vazquez-Roig & Picó 2015).

Hollow-fiber liquid-phase microextraction

In HF-LPME, a hollow fiber containing an organic solvent is used to prevent direct mixing of acceptor solution with the sample solution (Hu *et al.* 2013), as illustrated in Figure 4, with the vial filled with the aqueous sample. A porous rod (typically made of polypropylene) placed in a glass vial is used as the main component in HF-LPME (Psillakis & Kalogerakis 2003). Before extraction, the porous rod (HF) is immersed in an organic solvent to immobilize this in the pores, and excess solvent is removed. A hydrophobic solvent is used as a thin barrier within the wall of the HF to ensure that the organic does not mix with the aqueous sample during the extraction process. Depending on the type of phase involved in HF-LPME, the acceptor solution can be either an 'organic solvent' in the hollow fiber, which makes it a two-phase extraction process, or an acidic or alkaline 'aqueous solution', which makes it a three-phase extraction process.

In the two-phase extraction process, the targeted analytes are extracted from the aqueous sample into the organic solvent (acceptor solution) present both in the porous HF wall and inside the core of the HF. In the three-phase process, the analytes are extracted from the aqueous sample via the organic solvent in HF pores, then into the aqueous acceptor solution in the core of the HF (Sarafraz-Yazdi & Amiri 2010).

The HF-LPME process has proven to be a simple, low cost, small solvent use sample preparation technique. The low solvent consumption is exemplified in the extraction of sulphonamides and quinolones in Tables 4 and 5. More specifically, Yudthavorasit *et al.* (2011) made use of 0.02 mL of solvent for the pre-concentration of 11 antibiotics, which included sulphonamides and quinolones, in 20 mL water samples. With this method, an excellent percentage recovery of 79–118% was recorded. Based on the assesment of the solvent consumed by other methods, HF-LPME uses the least solvent.

A prolonged contact time of 60 min and above between the aqueous sample and HF-LPME must be ensured to achieve maximum extraction of the intended analyte. This makes the process time consuming for the extraction of sulphonamides and quinolones when compared with other methods.

Dispersive liquid–liquid micro-extraction

The DLLME technique is generally based on the dispersion of extracting solvent in a sample matrix, and it is composed
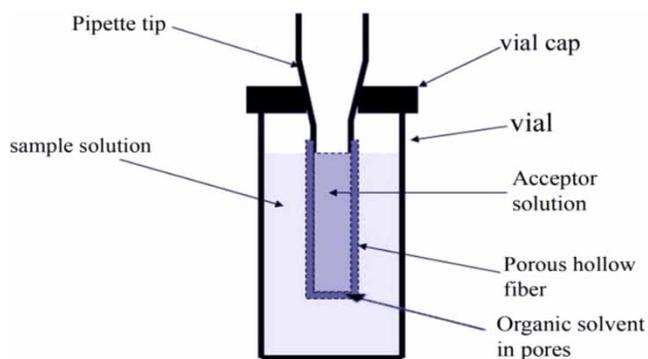

Figure 4 | Hollow-fiber liquid-phase microextraction (HF-LPME) (Gjelstad & Pedersen-Bjergaard 2013).

of a disperser solvent (an amphiphilic compound) that is applied to an aqueous sample to form a turbid solution. Extraction is achieved due to the large contact surface area between the droplets of the extractant solvent and the sample. After the introduction of the extractant, the sample mixture is centrifuged and the extraction solvent usually sediments at the bottom of the tube, after which it is drawn up with a micro syringe for further analysis (Herrera-Herrera *et al.* 2013). The simple extraction process and low consumption of organic solvent make the DLLME a good method of extraction. The main drawbacks of DLLME are its inability to extract hydrophilic compounds into the extraction solvent, the volume of samples restricted to the volume of the vial, and time spent in centrifugation (Tables 4 and 5). A maximum volume of 10 mL is mostly used for the analysis (Tables 4 and 5) and a larger volume would mean longer time of extraction. Current further developments deal with some of these constraints, where the centrifugation (which prevents automation) is replaced with the use of a process referred to as the ionic liquid-based DLLME, and the hydrophilic limitation is being investigated via the use of ion-pair based emulsification liquid phase micro extraction (IP ELPME) (Ebrahimpour *et al.* 2015).

SOCIETAL IMPACT

The release and persistence of antibiotic residues in the wastewater, receiving water bodies and the environment lead to the emergence of antimicrobial resistance among environmental isolates. This also triggers selection for antibiotic resistant genes. Quantitative and qualitative analysis of antibiotics in the environment is, therefore, vital for effective planning against the result of an ecological resistance pool effect and spread to humans through several transmission routes.

Different approaches have been employed by many researchers to quantify the antibiotic residues in the environment, mainly in the aquatic environment. Despite this being an issue of global concern, few reports are available on this study area, particularly from developing countries. This review presents a critical assessment of advances in methods of extraction evaluation for antibiotic micropollutants in wastewater with a focus on sulphonamides and

quinolones. A comparative analysis on these antibiotics in wastewater was done, using the few available reports, with a view to identifying quick and effective ways of extracting and quantifying them in the environment. Structural elucidation of various antibiotics with respect to their physiochemical properties was correlated with their solubility, towards enhancing the extraction protocols. Funding of research is mostly a great challenge; with the level of finance of developing nations in mind, and the fact that resistant bacteria are not boundary restricted, there is a need to develop an efficient and cost-effective method towards the quantification/identification of antibiotics in the environment. Valuable perspectives for improvement in these protocols based on a few existing gaps were presented.

CONCLUSION AND FUTURE TRENDS

The progress in the advancement in extraction methods over the last years is well documented and is constantly being updated in the literature.

The improvement in the LLE (DLLME, HF-LPME) has greatly reduced the volume of solvent used in the extraction process, thereby decreasing its environmental impact. However, the inability to reuse the solvent used in the process of extraction is a disadvantage, due to higher costs. Also, the centrifugation process of DLLME prevents direct automation, albeit several modalities are being researched (Herrera-Herrera *et al.* 2013).

MIP processes are very selective and sensitive for analytical methods, and the fact that they can be used to solve selectivity/sensitivity problems in a less cumbersome way makes them an efficient process of extraction, while the non-availability of commercial template and monomers makes the process less practicable. The polymers used in MIP are not like the conventional SPE sorbents that are universal, as the imprinted polymers must be synthesized for the specific analyte or class of analytes to be extracted.

The possibility of having a more robust and advanced sample preparation technique, which will utilize a highly selective filtration system, with an onsite filtration ability and a hybrid extraction method, which will involve an advanced method of both LLE and SPE, will create a less cumbersome process for the analytical chemist. An

automated highly sensitive and rugged analytical system that will be able to analyze samples with little or no pre-instrumental treatment, enhancing analyte quantification through reduction in analyte lost, will be of future interest.

FUNDING

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