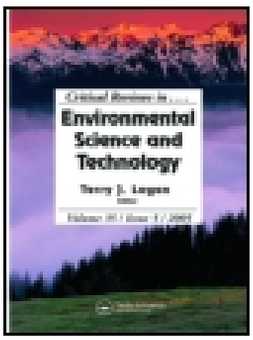

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# A review of extraction methods for the analysis of pharmaceuticals in environmental waters

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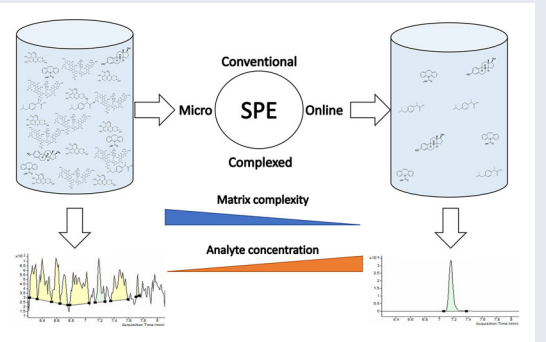
**ABSTRACT**




Pharmaceuticals play a vital role in the prosperity of human and veterinarian health by diagnosing, treating, or preventing diseases. Produced in large quantities for various applications, pharmaceuticals primarily enter the environment through wastewater systems. Historically, the ability to detect pharmaceuticals in environmental waters has been limited. However, growing technological advancements are changing pharmaceutical detection capabilities and our understanding of their occurrence in environmental waters. The analysis of pharmaceuticals in the environment began with simple gas chromatography-mass spectrometry and evolved to using liquid chromatography-tandem mass spectrometry as the dominant method. Many of these methods require sample extraction, with solid phase extraction (SPE) being the most popular. Additionally, miniaturized and online extraction procedures have also attracted a lot of attention. Nevertheless, approaches involving large volume injections without the need for sample enrichment have made significant strides in recent years. The aim of this review is to provide an overview of extraction methods for environmental water samples containing trace levels of pharmaceuticals and how current applications will mold how they are analyzed in the future.

**KEYWORDS** carbamazepine; diclofenac; environmental waters; ion suppression; matrix effects; pharmaceuticals; sample enrichment

## 1. Introduction

Pharmaceuticals are a class of emerging chemical contaminants in aquatic environments that are integral to human and veterinary medicine, where they are applied to diagnose, treat, or prevent disease. By design, each

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pharmaceutical has a specific mode of action, which enables the compounds to be divided into subgroups, including, but not limited to analgesics, anti-inflammatory drugs, antibiotics, contraceptives, beta blockers, lipid regulators, and neuroactive compounds. As populations and our understanding of biological processes grow, the amount and diversity of pharmaceuticals are likely to increase. For example, Fent et al. approximated that over 3,000 different pharmaceuticals were produced for human or veterinary medicine in the European Union during 2006, while a greater number of pharmaceutical production is expected now throughout the world (Fent, Weston, & Caminada, 2006). In many countries, frequently consumed pharmaceuticals are produced in the hundreds of tons per year (Huschek, Hansen, Maurer, Krengel, & Kayser, 2004; Jones, Voulvoulis, & Lester, 2002; Khan & Ongerth, 2004). Due to the volume produced, as well as all the different types, there has been an increase in the attention directed toward the occurrence of pharmaceuticals in the environment.

The detection of pharmaceuticals in the environment began in the 1970s when the US Environmental Protection Agency (EPA) issued the first known report regarding their presence in the environment during 1976 (Garrison, Pope, & Allen, 1976) and then Hignite et al. in 1977 (Higaite & Azarnoff, 1977). During the past decade, various prescription and over the counterdrugs, such as steroidal estrogens and progestogens, non-steroidal anti-inflammatory drugs, antidepressants, antibiotics, and beta blockers, have been reported at trace levels in wastewater effluents, surface and ground waters, as well as in some drinking waters (Daughton & Ternes, 1999; Fent et al., 2006; Heberer, 2002; Loos et al., 2009). Many pharmaceuticals are given to consumers at high levels to ensure a biological response; however, a large proportion of consumed pharmaceuticals are excreted from the body and enter the environment through wastewater effluents (Williams & Cook, 2007). Although this is the most common way pharmaceuticals entering the environment, they are also directly released into wastewater systems from manufacturers (Bound & Voulvoulis, 2005). Consequently, the more pharmaceuticals consumed, the greater the concentrations that will be discharged into the environment, thereby elevating the importance of their occurrence. Since there are numerous species of pharmaceuticals in the environment at trace levels, as well as a wide range of physic-chemical properties, the development of techniques to better quantify these compounds is imperative. While the analytical techniques to detect pharmaceuticals have been widely reviewed (Siddiqui, AlOthman, & Rahman, 2017), sample preparation necessary for analysis still needs to be comprehensively overviewed. The purpose of this paper is to provide a review of the solid phase extraction (SPE) methods for pharmaceuticals in environmental waters.

## 2. Extraction methods for pharmaceuticals in environmental waters

### 2.1. Background

Most pharmaceuticals in environmental waters are often at trace concentrations (sub-μg/L), making them difficult to quantify. Some analytical instruments are not sensitive enough to quantify them directly, requiring a concentration procedure prior to analysis. Figure 1 illustrates the number of publications associated with a couple of popular pharmaceutical extractions methods since the turn of the century. Although, there are other extraction methods that exist, such as liquid-liquid extractions, microwave assisted, ultrasonic, etc. Values were obtained from google scholar with keywords including the extraction method in quotations followed by pharmaceuticals.

In addition to pharmaceuticals being found at low concentrations, matrix effects from environmental samples can often limit ionization due to competition between targeted compounds and interference compounds. When interference compounds are introduced to an ionization chamber along with targeted compounds at greater concentrations and/or have a greater affinity for becoming charged compared to the targeted compound, the available charge could become exhausted, leaving targeted compounds uncharged, called matrix effects. If matrix effects are not properly addressed, it could result in improper data interpretation since the extent of the effects can vary substantially between matrices, leading to artificially decreased concentrations. Therefore, additional clean up steps might be necessary when analyzing pharmaceuticals in the environment.

Recently, strides have been taken to eliminate the need for conventional SPE. Since conventional SPE is off-line, it requires the conditioning, loading, drying, and eluting steps to be done manually before the sample is ready to be evaporated down and raised in the necessary solvent before

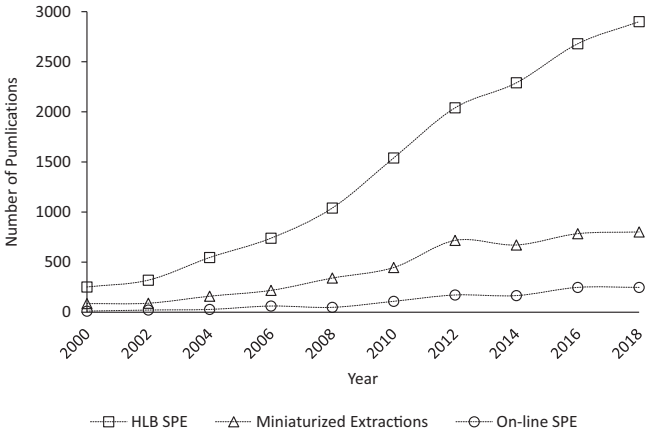


**Figure 1.** Frequency of extraction methods published for pharmaceutical analysis.

instrument injection. This is a high workload and often time consuming; however, only a small fraction of the final extract is necessary for analysis. The dominant methods that are likely to replace conventional SPE are on-line SPE or direct injection, where the extraction is incorporated into the instrument or greater volumes are injected, respectively. Another popular trend over the past two decades, particularly in environmental analysis, is the development of microscale approaches in sample preparation.

### 2.2. Conventional solid phase extraction

Altogether, SPE is by far the most commonly applied technique for enrichment of environmental water samples. An SPE cartridge is packed with a sorbent that has a high affinity for the compounds of interest. Typically, the sorbent binds the target compounds as a filtered aqueous sample is passed through the cartridge. The sorbent can then be washed with an aqueous solution and/or organic solvents to remove unwanted interferences that have also been retained by the sorbent. Subsequently, the sorbent is dried with nitrogen and target compounds are then eluted from the sorbent using organic solvents. The solvents are chosen to ensure the target compounds have a greater affinity for the solvent than for the SPE sorbent. The resulting extract is generally concentrated by evaporation to a volume of one milliliter or less. Finally, eluents can be analyzed. Figure 2 illustrates the typical procedure for conventional SPE.

Many different SPE sorbents have been manufactured to extract organic compounds using a variety of physio-chemical properties. The most commonly used sorbents for environmental analysis include standard C18, Oasis hydrophilic–lipophilic balanced (HLB), Isolute ENV+, Lichrolut EN, and Strata-X polymeric sorbents. Petrovi, Hernando, Silvia Díaz-Cruz, and Barceló (2005) and Hao, Clement, and Yang (2007) reviewed the development of sample preparation and analytical instrumentation for the quantification of pharmaceuticals in environmental waters over a decade ago, and Hernandez (Hernández, Sancho, Ibáñez, & Guerrero, 2007) and Diaz-Cruz (Silvia & Damià Barceló, 2006) also summarized the analytical method of quantifying antibiotics in water samples. Overall, Oasis HLB has been the preferred cartridge since it can simultaneously extract acidic, neutral and basic polar analytes at a wide range of pH values, and can run dry without adversely affecting extraction efficiency (Wong & MacLeod, 2009). These properties increase its application to simultaneously extract various classes of pharmaceuticals from environmental waters, including wastewater and drinking water (Cahill, Furlong, Burkhardt, Kolpin, & Anderson, 2004; Gros, Petrovi, & Barceló, 2006; Renew & Huang, 2004; Vanderford,

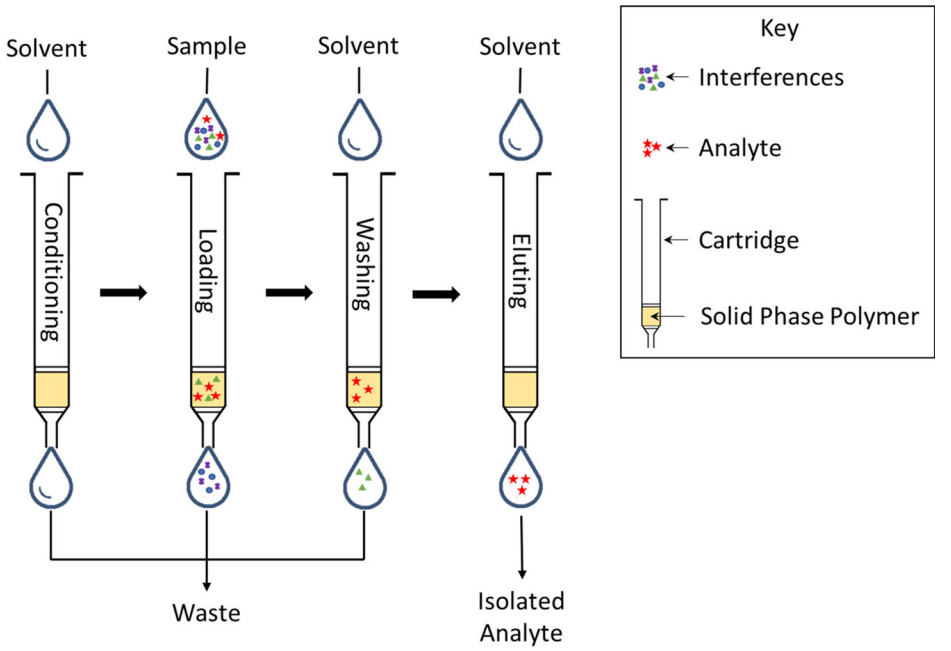


**Figure 2.** Example of a typical conventional SPE procedure.

Pearson, Rexing, & Snyder, 2003; Yang, Cha, & Carlson, 2004; Ye, Weinberg, & Meyer, 2007).

In addition to HLB, there have been a few other mixed sorbents with similar ion exchange and reversed-phase adsorption properties like mixed mode, strong anion-exchange (MAX) and mixed mode, strong cation-exchange (MCX) cartridges, which have been used to analyze pharmaceuticals in water (Kasprzyk-Hordern, Dinsdale, & Guwy, 2007; Kolpin et al., 2002). Batt et al. reported that MCX cartridge recoveries for the majority of their targeted pharmaceuticals ranged between 80% and 125% (Batt, Kostich, & Lazorchak, 2008). Unfortunately, the sorption capabilities of these cartridges are often limited when compared to the HLB cartridge; thus, they might not be efficient enough for large volumes of water or complex environmental matrices. Despite which cartridges are used for aquatic sample enrichment, additional steps including chromatography for separation and further mass quantification has the potential to increase the quality of the data.

### *2.3. Complexed SPE*

Matrix effects mainly occur from co-eluting components from SPE procedures. Hernando reported that up to 60% of signal suppression occurred for beta-blockers and lipid-regulating agents in wastewater using SPE and high performance liquid chromatography-electrospray ionization-tandem

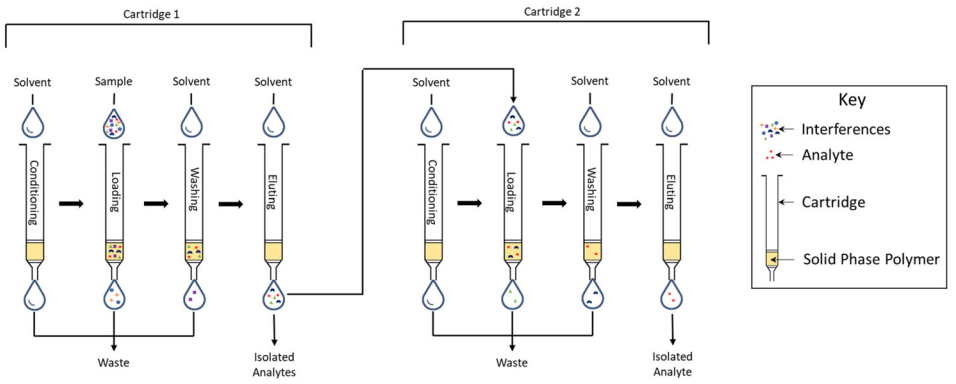


**Figure 3.** Example of a typical complexed SPE procedure.

mass spectrometry (HPLC-ESI-MS/MS) (Hernando, Petrovic, Fernández-Alba, & Barceló, 2004). Matrix effects do not only occur in complicated water matrices like wastewater samples but have also been shown to be just as severe in drinking water samples. Ye et al. found up to 74% ion suppression when analyzing four classes of antibiotics in chlorinated drinking water extracted with HLB cartridges and injected onto an HPLC-ESI-MS/MS, with some chemicals like tylosin experiencing signal enhancement (132%) (Ye et al., 2007).

Various approaches have been applied over the years to try and reduce the impact of matrix effects. A fundamental approach is to remove the matrix components responsible for the interference prior to MS analysis (Reemtsma, 2003). One way to remove the matrix compounds responsible for interference is to apply complexed SPE method, a two-step extraction to further clean up the sample during extraction, as shown in Figure 3. For example, Silica or MAX cartridges can be used after HLB cartridges to reduce the matrix effect when analyzing antibiotics (Hernando et al., 2004; Jia, Xiao, Hu, Asami, & Kunikane, 2009) and glucocorticoids (Jia, Wu, Daniels, & Snyder, 2016). For estrogens, florisil cartridges have been used after HLB cartridges to enhance the analysis of estrogens (Ingrand, Herry, Beausse, & De Roubin, 2003). Recently, molecularly imprinted polymers, which are highly specific, were applied as a cleanup step (Zorita et al., 2008). In addition to clean up steps with SPE, other matrix effects can be correlated to poor chromatographic separation (Kloepfer, Quintana, & Reemtsma, 2005). Ultra-high performance liquid chromatography can reduce some matrix effects that are observed during HPLC by narrowing elution bands (Wong & MacLeod, 2009). Two-dimensional chromatography, such as comprehensive two-dimensional gas chromatography (GC), has been applied where the sample underwent two chromatographic separations (Pascoe, Foley, & Gusev, 2001), resulting in detection limits comparable to HPLC-MS/MS (Matamoros, Jover, & Bayona, 2010). Diluting the

sample can reduce matrix effects; however, it would also increase detection limits (Hernando et al., 2004).

### 2.4. Miniaturized extractions

Recently, a lot of the research community's attention has been drawn toward other sample preparation techniques aimed at making the analysis of pharmaceuticals in environmental samples more efficient and convenient. This can be achieved by reducing the scale of analytical operations as well as that of extraction devices, i.e., miniaturization. Many novel miniaturized approaches have been developed to overcome the disadvantages of conventional liquid-liquid extraction and SPE. This includes the consumption of moderate to large amounts of solvents and reagents, multistep operations and labor-intensity. Some of the most well-received procedures include hollow fiber protected liquid-phase microextraction (HF-LPME), dispersive liquid-liquid microextraction (DLLME), solid phase microextraction (SPME), and magnetic solid-phase extraction (MSPE).

#### 2.4.1. Hollow fiber protected liquid-phase microextraction (HF-LPME)

For HF-LPMEs, analytes of interest are extracted from an aqueous sample solution through a liquid membrane, and retained into the acceptor phase held in the lumen. The extracting (acceptor) phase of this technique is supported by a piece of porous polypropylene hollow fiber, offering stability while still allowing targeted compounds to pass. In a typical HF-LPME configuration, the wall pores of the fiber are impregnated with solvent forming a supported liquid membrane, and the channel (lumen) can be filled with either the same solvent or an aqueous phase. Since the pore size of the hollow fiber membrane is very small (usually 0.2 μm), enhanced clean-up is achieved. After mixing the sample with the liquid membrane, analytes are eluted by passing a targeted higher affinity solvent through the hollow fiber membrane. This process is illustrated in Figure 4.

The suitability of HF-LPME for the determination of acidic drugs in wastewater has been demonstrated (Quintana, Rodil, & Reemtsma, 2004). Altogether, very clean extracts are obtained with HF-LPME with little ion suppression observed during MS analysis. In addition, further applications of HF-LPME, like coupling to HPLC-diode array detector/fluorescence detector, GC-MS and HPLC-MS/MS for the analysis of drugs in wastewaters have also been investigated (Manso, Larsson, & Jönsson, 2014; Ramos Payán, Bello López, Fernández-Torres, González, & Callejón Mochón, 2011; Ramos Payán, Bello López, Fernández-Torres, Callejón Mochón, & Gómez Ariza, 2010). Carbon nanotube reinforced hollow fibers initiated the advance "functionalized hollow fibers" used for HF-LPME.

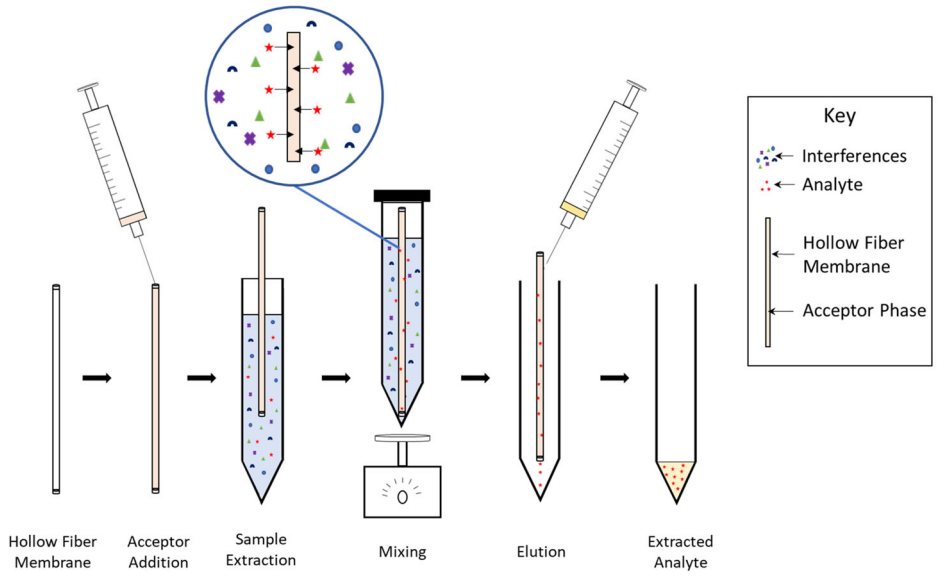


**Figure 4.** Example of a typical HF-LPME procedure.

Ultimately, they have been successfully combined with enhanced electromembrane extraction (in which an electrical potential serves as the driving force) of pharmaceuticals in environmental samples (Hasheminasab, Fakhari, Shahsavani, & Ahmar, 2013; Tahmasebi, Saeed, Davarani, & Asgharinezhad, 2016).

### *2.4.2. Dispersive liquid-liquid microextraction (DLLME)*

DLLME employs a mixture of an extracting solvent and a dispersive solvent for dispersion in an aqueous sample solution through a rapid injection using a syringe. The consequent formation of solvent droplets facilitates mass transfer during the extraction process due to high surface area contact between the extracting phase and the sample phase. Therefore, high enrichment factors are achieved. The extract can be separated by centrifugation or the addition a solvent to clear the emulsion, which can then be withdrawn using a syringe. Figure 5 demonstrates a typical procedure for DLLME.

DLLME has been demonstrated for the analysis of anti-inflammatory pharmaceuticals in river water and tap water (Zgoła-Grześkowiak, 2010), in which sonication for forming a dispersion and a two-step extraction were found to be beneficial for high recoveries of the analytes. The prominent role of ultrasonication in DLLME has been shown to significantly enhance the recovery of targeted compounds (Guan et al., 2016; Yan, Wang, Qin, Liu, & Du, 2011). Yao et al. used functionalized ionic liquids as the extraction solvent in DLLME toward fourteen pharmaceuticals in water samples (Yao, Li, Twu, Pitner, & Anderson, 2011). Ionic liquids with different

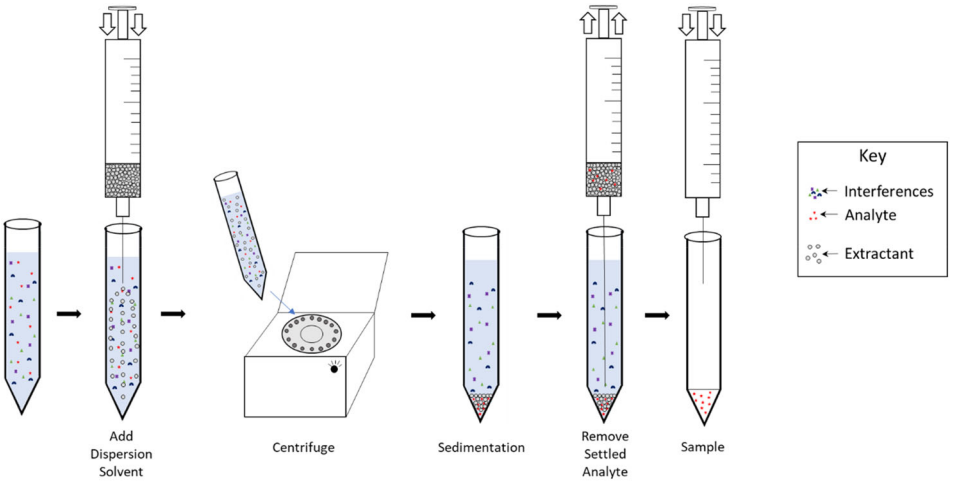


**Figure 5.** Example of a typical DLLME procedure.

functional moieties displayed a strong preference for extracting compounds with amine or acid groups. Thus, the selectivity and sensitivity of using ionic liquids in DLLME for pharmaceutical compounds analysis can be tuned and modulated by appropriate design of ionic liquids.

Ge and Lee reported a new extraction mode which applied μ-SPE (a device comprising a membrane envelope containing a sorbent) immediately after DLLME to retrieve the extraction solvent and further concentrate the extracted drugs (Ge & Lee, 2013). Montesdeoca-Esponda et al. introduced a micellar solution of a surfactant as the extraction solvent and chloroform as the dispersive solvent, to DLLME technology (Montesdeoca-Esponda, Mahugo-Santana, Sosa-Ferrera, & Santana-Rodríguez, 2015). Five pharmaceutical compounds of different nature could be simultaneously extracted and preconcentrated from wastewater samples in a very short time. To obtain a better insight into fundamental parameters affecting the extraction, Nojavan et al. studied the influence of high- and low-density organic solvents on the extraction efficiencies of seven basic pharmaceutical compounds in ultrasound-assisted DLLME (Nojavan, Gorji, Davarani, & Morteza-Najarian, 2014). The advantages of DLLME, such as easy operation, rapidity and high recovery, as well as other variables that can be regulated to improve extraction efficiency, makes this technique exceedingly suitable for pharmaceutical analysis.

### *2.4.3. Solid phase microextraction (SPME)*

SPME is a simple, solvent-free, reliable and flexible sample preparation method that integrates preconcentration and clean-up into one step and results in considerable reduction in solvent consumption and operation time. This technique relies on the extraction of targeted compounds using

a coating phase that has been immobilized on fused silica or metal fiber. The SPME device will employ a needle to pierce a septum of the sample vial, expose the coating phase to the sample with the fiber attachment, and then will be withdrawn from the septum. Afterwards, the analytes can be directly desorbed onto the analytical column. An illustration of typical SPME steps is shown in Figure 6. Similarly, stir bar sorptive extraction (SBSE) is conducted by applying a stir bar with a sorbent coating. Due to a larger sorbent phase, SBSE is generally able to achieve higher sensitivity, but the mass transfer in SBSE is slower due to the thicker sorbent coating. However, more options of fiber coating phases including commercial and laboratory-made are available for SPME than for SBSE.

In recent years, novel materials have been fabricated in-house (i.e., they are not commercially available) for the sorptive phases of SBSE and employed for environmental pharmaceutical monitoring (Acta, 2013; Bratkowska, Fontanals, Cormack, Borrull, & Marcé, 2011; Fan, Mao, He, Chen, & Hu, 2014; Peng, 2014). Due to its intrinsic features, SPME has a broader application range in the pharmaceutical analysis field. Commercially available coatings have shown promise, for example, a fiber coating of polydimethylsiloxane/divinylbenzene was applied to the extraction of non-steroidal anti-inflammatory drugs in river water, and subjected to direct desorption to the chromatographic system by the LC-SPME interface (García et al., 2009; Vera-Candioti, García, Martínez Galera, & Goicoechea, 2008). Sarafraz-Yazdi et al. prepared an SPME fiber containing a stationary phase of hydroxyl-terminated poly(ethylene glycol)

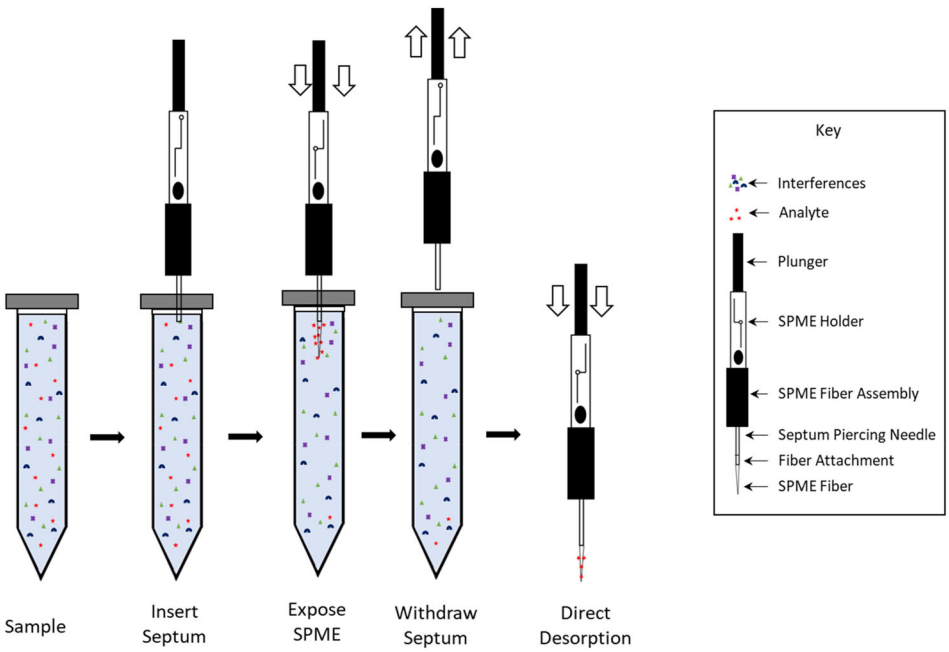


**Figure 6.** Example of a typical SPME procedure.

grafted via covalent functionalization of multiwalled carbon nanotubes by sol–gel technology (Acta, Sarafraz-Yazdi, Amiri, Rounaghi, & Eshtiagh-Hosseini, 2012). With this chemically bonded coating phase, three drugs could be determined by GC-flame ionization detection from wastewater with high selectivity and sensitivity. Derivatization is a good way to increase the instrumental response to polar drugs such as phenolic, acidic and amine compounds.

In SPME, the derivatization can take place in the sample solution, in the coating phase, or in the GC injection port. In situ derivatization of acidic drugs in aqueous samples were conducted together with the SPME procedure, either in the headspace or direct immersion mode, after which the extracts were subjected to thermal desorption in a GC injector (Araujo, 2008; de Lima Gomes et al., 2011). Another promising feature of SPME is its ease to be automated and coupled with chromatographic instruments. Huang et al. developed an automated derivatization SPME for the simultaneous determination of eight acid pharmaceuticals in water samples (Huang et al., 2015). The derivatization and extraction procedures were performed on a commercial autosampler coupled with GC, by which rapid and sensitive analysis of pharmaceuticals could be achieved.

#### *2.4.4. Magnetic solid phase extraction (MSPE)*

Lastly, magnetic separation, based on dispersive SPE (d-SPE), is a convenient miniaturized preconcentration technique developed for the analysis of environmental contaminants. MSPE is a noteworthy improvement of the d-SPE technique in which the extraction occurs when a more uniform sorbent dispersion is formed in a sample solution. Compared to SPE, MSPE can provide increased contact area between the analytes and the sorbents, is easy to conduct, saves time and reduces waste. Thanks to various synthetic strategies available for use, functionalized magnetic materials with high adsorption capability has led to the development of efficient determination methods for pharmaceuticals in the environmental waters. Generally, the magnetic material will be added to the sample, vortexed, and then separated from the mixture with a magnetic while the sample is decanted. A higher affinity solvent will then be added to the vial to separate the analytes from the magnetic material, as shown in Figure 7.

The innovation concerning the design and preparation of the surface coatings of magnetic sorbents is mainly focused on surfactants, carbon nanostructures, polymers, etc. Perez et al. prepared oleate coated $Fe_3O_4$ magnetic nanoparticles which could extract macrolide antibiotics in water samples from different sources by MSPE (Pérez, Albero, Férriz, & Tadeo, 2017). Aguilar-Arteaga et al. compared the performance of different alkyl chains covered magnetite microspheres in the extraction of four non-steroidal anti-

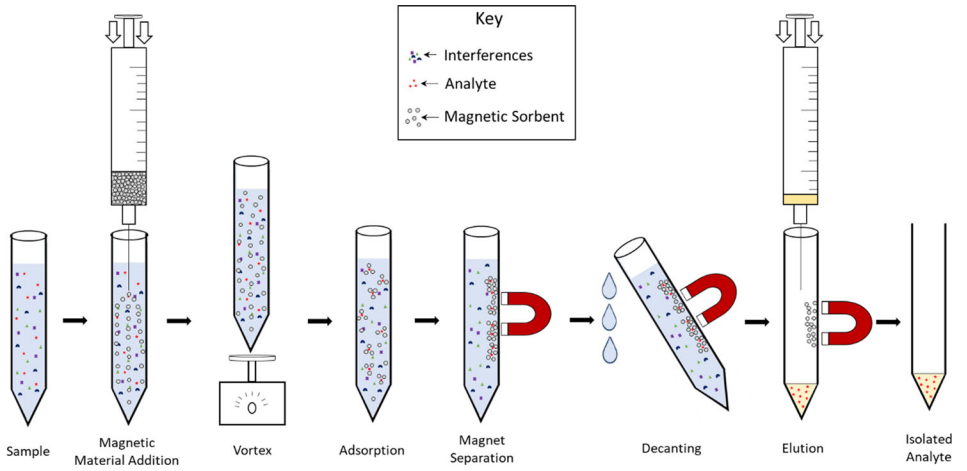


**Figure 7.** Example of a typical MSPE procedure.

inflammatory drugs (Aguilar-Arteaga, Rodriguez, Miranda, Medina, & Barrado, 2010). MSPE has also been shown that polar chains or highly hydrophobic chains are not conducive for the preconcentration of these drugs, and the best functional group was octyl. Ye et al. investigated the non-ionic surfactants, including Tween- and Span-series materials, as the coatings of magnetic nanoparticles for the restricted-access extraction of steroid hormones (Ye, Wang, Xu, Shi, & Xu, 2012). The macromolecules present in a complex sample matrix could be excluded due to the shielding effect of the surfactant coating. Another study made use of the host-guest interaction between the target compound of gemfibrozil and the β-cyclodextrin-grafted graphene oxide magnetic nano-hybrid to extract the gemfibrozil from wastewater samples (Abdolmohammad-Zadeh & Talleb, 2015). High selectivity was obtained for ultra-trace analysis of gemfibrozil in this work. Magnetic molecularly imprinted polymers with $Fe_3O_4$-chitosan as the core was synthesized by Qin, Su, Wang, and Gao (2015), and exhibited good selective recognition of sulfonamides from sewage samples. Tang et al. proposed an automated extraction approach of several acidic drugs using $Fe_3O_4$-layered double hydroxide core-shell microspheres which were dissolvable and could be separated from the sample solution via the magnetism applied at the exterior bottom of the sample vial (Tang, Chia, Chang, & Lee, 2014). After separation, the microspheres (now containing the analytes) were simply dissolved to form the extract that was directly analyzable. All the steps involved could be realized automatically by using a commercial autosampler. Notwithstanding the good extraction performances of MSPE implied in the preceding discussion, its robustness for batch processing applications still needs to be evaluated, and improvements are still needed to enable the technology to be a viably routine alternative to conventional SPE.

### 2.5. On-line solid phase extraction

The development of on-line SPE has made it possible to process samples in a very short time, increasing sample throughput. For on-line technology, the SPE cartridge is installed in the injection valve instead of the injection loop; therefore, the preconcentrated analytes are directly eluted onto the analytical column (Buchberger, 2007). By coupling SPE to the LC system with column-switch technology, all the traditional evaporation and reconstitution steps can be reduced (Figure 8). Rodriguez-Mozaz et al. gave a review on the advantages and limitations of on-line SPE, as well as their application for emerging contaminants (Rodriguez-Mozaz, Lopez De Alda, & Barceló, 2007). Some of the advantages of on-line SPE compared to traditional SPE include smaller required sample volumes, reusable cartridges, decreased volume of solvents, decreased time commitment, all leading to an overall lower cost for sample processing. Recently, fully automated on-line SPE procedures with multiuse cartridges are commercially available, such as the Prospekt technology with the Symbiosis model. These units are fully automated and are capable of unattended analysis of 1152 samples (Rodriguez-Mozaz et al., 2007) and have been used for analyzing antibiotic residues in wastewater samples (Choi, Kim, Kim, & Kim, 2007).

To date, several on-line SPE analytical methods on pharmaceuticals have been published. Galera et al developed a method using on-line SPE and LC fluorescence detectors to analyze 5 β-blocker drugs in groundwater (Galera, Vázquez, Vázquez, García, & Amate, 2011), and Pozo et al. utilized on-line SPE-LC-MS/MS to analyze 16 antibiotics in water by injecting small water samples (9.8 mL) directly onto the system. The detection limits were as low as 0.4–4.3 ng/L, with no impact from matrix effects (Pozo et al., 2006).. Viglino et al. also used online SPE-LC-MS/MS to quantify pharmaceuticals,

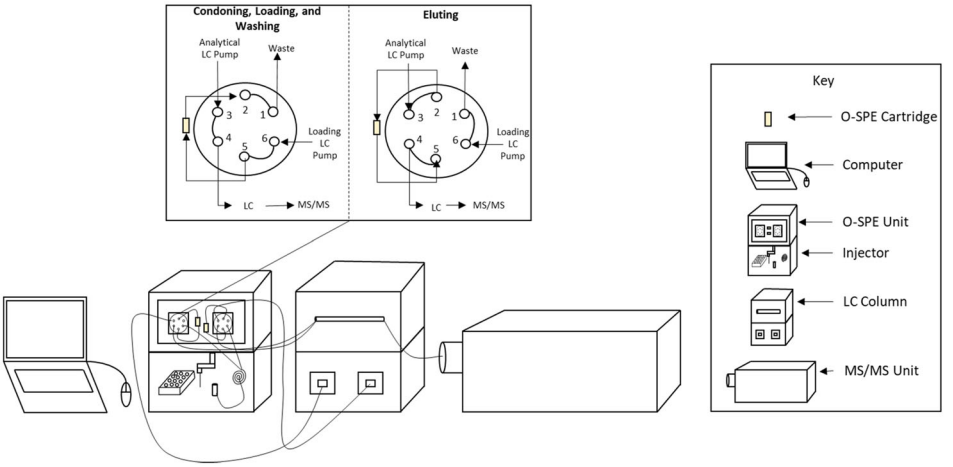


Figure 8. Example of a typical on-line SPE procedure for liquid chromatography.

pesticides, and some metabolites in wastewater, drinking water, and surface water. The injection of only 1 mL was required, with a total analysis time of 20 min and method detection limits ranging from 2 to 24 ng/L. At least 200 samples could be analyzed without affecting the performance of the preconcentration column (Viglino, Aboulfadl, Mahvelat, Prévost, & Sauvé, 2008). Similar research was conducted by Stoob et al. to simultaneously investigate sulfonamide antibiotics and pesticides with surface water samples of only 18 mL (Stoob, Singer, Goetz, Ruff, & Mueller, 2005). On-line SPE with renewable sorbents has been described by Quintana, Miro, Estela, and Cerdà (2006). Recently, Garcia-Ac et al. used Strata-X on-line SPE and TOF confirmation to analyze 14 pharmaceuticals in water, with detection limits for all target chemicals between 0.6 to 6 ng/L and 0.4 to 3 ng/L in surface water and drinking water, respectively (Garcia-Ac et al., 2009). A new trend in environmental analytical chemistry with the development of modern analytical technology is to simultaneously determine various classes of chemicals by early warning or on-site monitoring. On-line SPE methodology will play an important role for trace analysis of pharmaceuticals in the future.

### 2.6. No extraction—large volume injection

Conventional injection volumes for LC-MS and GC-MS are usually below 5 µL due to the limit of volume expansion into the liner (GC) and matrix effect or peak quality for LC-MS. Conventional sample preparation usually involves a very large enrichment (e.g., 100–2000 fold) due to the low concentration (ng/L) levels of most target compounds in environmental waters. Large volume injection has certainly shortened part of the sample preparation procedure, which has led to an increase in the instrument sensitivity, lowered detection limits, along with a decrease in the investment of time, labor and cost. For GC systems, large volume injection can be achieved by using programable temperature vaporization and retention gap, or solvent re-condensation to process the expanded solvents. The GC injection volume can be increased from 1–2 µL to 20 µL (Carpinteiro, Ramil, Rodríguez, & Nogueira, 2012; Schmarr, Koschinski, Sang, & Slabizki, 2012; Walorczyk, 2012).

For LC, large volume injection can be achieved by inserting a larger sample loop, as well as optimizing the solvent composition of the injection sample extracts to be similar to the initial mobile phase (Figure 9). Large volume LC injections can range from 100 to 200 µL of sample being directly injected onto the column, compared to conventional MeOH injections of less than 5 µL. This increase in injection volume can increase the ion sensitivity by 20–100 fold (Kowal, Balsaa, Werres, & Schmidt, 2012; Medvedovici, Udrescu, Albu, Tache, & David, 2011). As discussed

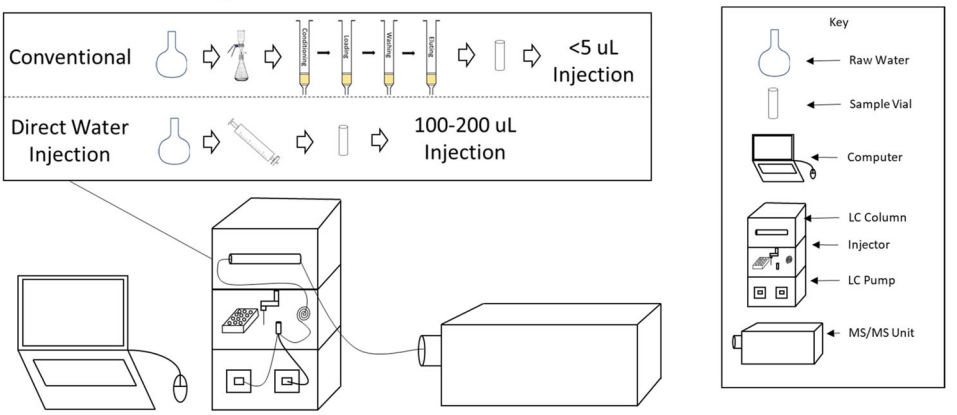


**Figure 9.** Example of a typical direct water injection procedure for liquid chromatography.

previously, on-line SPE is another powerful way to achieve large volume injection, since the samples can be directly injected into the LC-MS/MS (Busetti et al., 2012; Regueiro, Martín-Morales, Álvarez, & Blanco, 2011). Therefore, samples go through two-coupled "column" separations, on- line SPE cartridge as the first column and LC analytical column as the second column. Target compounds of varying polarity, as well as the sample matrix, can achieve good separation during the flow of the mobile phase, saving time and money compared to from off-line, while avoiding matrix effects.

## 3. Method comparison

The performance of these extraction methods was further investigated for the positively ionized pharmaceutical carbamazepine and the negatively ionized pharmaceutical diclofenac. A comparision of methods for carbamazepine in surface water and wastewater is presented in Tables 1 and 2, respectively. While the a comparison of methods for diclofenac in surface water and wastewater is presented in Tables 3 and 4, respectively. Altogether, traditional SPEs offer the widest range of analytes but are the most labor-intensive and require the largest sample and solvent volumes. These methods utilize cartridges packed with sorbents that have high affinities for pharmaceuticals. Thus, when the water sample passes through the cartridge, targeted pharmaceuticals can be retained and then eluted. Complexed SPEs can be applied to further reduce matrix effects but entail additional labor. Complex SPE methods apply multiple SPE cartridges in tandem. The additional cartridge is responsible for further reduction of non-targeted compounds co-eluting with pharmaceuticals. Miniaturized extractions reduce the sample and solvent volumes; however, they do not have the robustness for high throughput. The miniaturized methods employ various solid phase techniques using small water sample volumes

**Table 1.** Comparison of sample extraction methods for carbamazepine in surface waters.

| Technique | Method | Labor Intensity | Extraction Labor Time (min) | Sample Volume | Conditioning/Washing Solvent & Volume | Eluention Solvent & Volume | Recovery (%) | Instrument | Reference |
|---|---|---|---|---|---|---|---|---|---|
| Traditional solid phase | HLB | High | ~65* | 1 L | 5 mL MTBE<br>5 mL MeOH<br>5 mL Water | 5 mL MeOH<br>5 mL (10/90) MeOH/MTBE | 117 | UHPLC-MS/MS | (Anumol, Merel, Clarke, & Snyder, 2013) |
| | Isolute ENV+ | | ~70* | 1 L | 5 mL N-Hexane<br>5 mL Ethyl Acetate<br>10 mL MeOH<br>10 mL Water | 30 mL MeOH | 104 | GC-MS | (Weigel, Kallenborn, & Hühnerfuss, 2004) |
| | Lichrolut EN | | ~70* | 1 L | 5 mL N-Hexane<br>5 mL Ethyl Acetate<br>10 mL MeOH<br>10 mL Water | 30 mL MeOH | 100 | GC-MS | (Weigel et al., 2004) |
| | Strata-X polymeric | | ~105* | 1 L | 5 mL Acetone<br>5 mL MeOH<br>5mL Water (pH = 3.6) | 10 mL Acetone<br>10 mL MeOH | 89 | HPLC-UV | (Patrolecco et al., 2013) |
| | C18 | | ~30* | 250 mL | 20 mL MeOH<br>1L Water (4g KCO3 + 10 mL Ac. Acid; pH = 5.4) | 1.6 mL MeOH | 100 | LC-MS/MS | (Zuehlke, Duennbier, & Heberer, 2004) |
| Miniaturized | HF-LPME | Medium | ~60 | 1 L | – | 15 mL Octanol | 114 | LC-MS/MS | (Salvatierra-Stamp, Muñiz-Valencia, Jurado, & Ceballos-Magaña, 2018) |
| | DLLME | | ~10 | 10 mL | – | 120 uL Octanol<br>750 uL Acetone | 103 | LC-MS/MS | (Caldas, Rombaldi, De Oliveira Arias, Marube, & Primel, 2016) |
| | SPME | | ~200 | 10 mL | Any volume of DCM | 1 mL DCM | 103 | LC-MS/MS | (Teo et al., 2016) |
| On-line solid phase | Hypersil GOLD™ | Low | ~20 | 1 mL | Any volume of MeOH | 5 mL MeOH | 103 | LC-MS/MS | (Viglino et al., 2008) |
| | PLRP-s | | ~4 | 1.7 mL | 2 mL (5% ACN/0.1% Ac. Acid) | <1 mL ACN | 99 | UHPLC-MS/MS | (Anumol & Snyder, 2015) |
| | HySphere Resin GP | | ~30 | 2.5 mL | 2 mL of Water<br>2 mL of MeOH | 2 mL MeOH | 118 | HPLC-MS/MS | (López-Serna, Pérez, Ginebreda, Petroví, & Barceló, 2010) |
| No extraction | Direct Large Volume Injection | None | – | 100 uL | - | – | 91 | UHPLC-MS/MS | (Boix et al., 2015) |

*Additional 30–60 min will be necessary for drying the cartridge.

**Table 2.** Comparison of sample extraction methods for carbamazepine in wastewater.

| Technique | Method | Labor Intensity | Extraction Labor Time (min) | Sample Volume | Conditioning/Washing Solvent & Volume | Eluention Solvent & Volume | Recovery (%) | Instrument | Reference |
|---|---|---|---|---|---|---|---|---|---|
| Traditional s olid phase | HLB | High | ~65* | 1 L | 5 mL MTBE<br>5 mL MeOH<br>5 mL Water | 5 mL MeOH<br>5 mL (10/90) MeOH/MTBE | 98 | UHPLC-MS/MS | (Anumol et al., 2013) |
| | Strata-X polymeric | | ~105* | 1 L | 5 mL Acetone<br>5 mL MeOH<br>5mL Water (pH = 3.6) | 10 mL Acetone<br>10 mL MeOH | 87 | HPLC-UV | (Patrolecco et al., 2013) |
| | C18 | | ~30* | 250 mL | 20 mL meOH<br>1L Water(4g KCO3 + 10 mL Ac. Acid; pH = 5.4) | 1.6 mL MeOH | 100 | HPLC-MS/MS | (Zuehlke et al., 2004) |
| Miniaturized | DLLME | Medium | ~5 | 16 mL | – | 200 uL Chloroform 100 uL NaCl | 107 | HPLC-DAD | (Montesdeoca-Esponda et al., 2015) |
| | SPME | | ~60 | 10 mL | – | – | 99 | GC-MS | (Antoniou, Koukouraki, & Diamadopoulos, 2009) |
| | MSPE | | ~45 | 10 mL | 5 mL MeOH<br>5 mL Water | 0.5–1 mL ACN | 100 | HPLC-DAD | (Lekota, Dimpe, & Nomngongo, 2019) |
| On-line solid phase | Hypersil GOLD™ | Low | ~20 | 1 mL | Any volume of MeOH | 5 mL MeOH | 99 | HPLC-MS/MS | (Viglino et al., 2008) |
| | PLRP-s | | ~4 | 1.7 mL | 2 mL (5% ACN/0.1% Ac. Acid) | <1 mL ACN | 95 | UHPLC-MS/MS | (Anumol & Snyder, 2015) |
| | HySphere Resin GP | | ~30 | 2.5 mL | 2 mL of Water<br>2 mL of MeOH | 2 mL MeOH | 130 | HPLC-MS/MS | (López-Serna et al., 2010) |
| No extraction | Direct Large Volume Injection | None | – | 80 uL | - | – | 102 | HPLC-MS/MS | (Anumol, Wu, Marques dos Santos, Daniels, & Snyder, 2015) |

*Additional 30–60 min will be necessary for drying the cartridge.

**Table 3.** Comparison of sample extraction methods for diclofenac in surface waters.

| Technique | Method | Labor Intensity | Extraction Labor Time (min) | Sample Volume | Conditioning/Washing Solvent & Volume | Eluention Solvent & Volume | Recovery (%) | Instrument | Reference |
|---|---|---|---|---|---|---|---|---|---|
| Traditional solid phase | HLB | High | ~65* | 1 L | 5 mL MTBE<br>5 mL MeOH<br>5 mL Water | 5 mL MeOH<br>5 mL (10/90) MeOH/MTBE | 96 | UHPLC-MS/MS | (Anumol et al., 2013) |
| | Isolute ENV+ | | ~70* | 1 L | 5 mL N-Hexane<br>5 mL Ethyl Acetate<br>10 mL MeOH<br>10 mL Water | 30 mL MeOH | 62 | GC-MS | (Weigel et al., 2004) |
| | Lichrolut EN | | ~70* | 1 L | 5 mL N-Hexane<br>5 mL Ethyl Acetate<br>10 mL MeOH<br>10 mL Water | 30 mL MeOH | 38 | GC-MS | (Weigel et al., 2004) |
| | Strata-X polymeric | | ~105* | 1 L | 5 mL Acetone<br>5 mL MeOH<br>5mL Water (pH = 3.6) | 10 mL Acetone<br>10 mL MeOH | 94 | HPLC-uv-FI | (Patrolecco et al., 2013) |
| | C18 | | ~150* | 100 mL–2000 mL | 5 mL of ACN<br>5 mL of MeOH<br>5 mL of Water (pH = 2) | 5 mL Acetone<br>10 mL MeOH | 72 | LC-DAD-MS | (Kot-Wasik, Dębska, Wasik, & Namieśnik, 2006) |
| Miniaturized | HF-LPME | Medium | ~60 | 1 L | 3 mL MeOH | 5 mL MeOH | 100 | HPLC-DAD-FI | (Larsson, Petersson, Rylander, & Jönsson, 2009) |
| | DLLME | | ~10 | 10 mL | – | 120 uL Octanol<br>750 uL Acetone | 104 | LC-MS/MS | (Caldas et al., 2016) |
| | SPME | | ~60 | 20 mL | – | – | 95 | GC-FID | (Acta et al., 2012) |
| | MSPE | | ~20 | 50 mL | – | 2 X 0.2 mL of 1% Methanoic acid | 91 | UHPLC-MS/MS | (Wang et al., 2017) |
| On-line solid phase | Hypersil GOLD™ | Low | ~20 | 1 mL | – | 2 mL ACN | 98 | LC-MS/MS | (Idder, Ley, Mazellier, & Budzinski, 2013) |
| | PLRP-s | | ~4 | 1.7 mL | 2 mL (5% ACN/0.1% Ac. Acid | <1 mL ACN | 99 | UHPLC-MS/MS | (Anumol & Snyder, 2015) |
| | HySphere Resin GP | | ~30 | 2.5 mL | 2 mL of Water<br>2 mL of MeOH | 2 mL MeOH | 100 | HPLC-MS/MS | (López-Serna et al., 2010) |
| No extraction | Direct Large Volume Injection | None | – | 100 uL | - | – | 105 | UHPLC-MS/MS | (Boix et al., 2015) |

*Additional 30–60 min will be necessary for drying the cartridge.

**Table 4.** Comparison of sample extraction methods for diclofenac in wastewater.

| Technique | Method | Labor Intensity | Extraction Labor Time (min) | Sample Volume | Conditioning/Washing Solvent & Volume | Eluention Solvent & Volume | Recovery (%) | Instrument | Reference |
|---|---|---|---|---|---|---|---|---|---|
| Traditional solid phase | HLB | High | ~65* | 1 L | 5 mL MTBE<br>5 mL MeOH<br>5 mL Water | 5 mL MeOH<br>5 mL (10/90) MeOH/MTBE | 64 | UHPLC-MS/MS | (Anumol et al., 2013) |
| | Lichrolut EN | | ~120* | 1L | 6 mLHexane<br>6 mL Acetone<br>6 mL Water (pH = 2) | 1 mL Acetone<br>2 mL MeOH<br>2 mL Acetone | 85 | HPLC-MS | (Farré et al., 2001) |
| | Strata-X polymeric | | ~105* | 1 L | 5 mL Acetone<br>5 mL MeOH<br>5 mL Water (pH = 3.6) | 10 mL Acetone<br>10 mL MeOH | 90 | HPLC-UV | (Patrolecco et al., 2013) |
| | C18 | | ~30* | 250 mL (pH = 6.3 Citric Acid) | 2 X 5 mL MeOH<br>2X 5 mL Water (pH = 6.3 Citric acid) | 3 X 2 mL MeOH | 81 | HPLC-MS/MS | (Stülten, Zühlke, Lamshöft, & Spiteller, 2008) |
| Miniaturized | HF-LPME | Medium | ~20 | 50 mL (pH = 2) | Any volume of Dihexyl Ether | 50 uL Acceptor Phase (pH = 12.5) | 72 | HPLC-MS/MS | (Ramos Payán et al., 2010) |
| | DLLME | | ~15 | 4.5 mL (pH = 2 HCl) | – | 1 mL MeoH<br>300 uL Toluene | 65 | HPLC-UV | (Sarafraz-Yazdi, Assadi, Es'haghi, & Danesh, 2012) |
| | SPME | | ~60 | 20 mL | – | – | 92 | GC-FID | (Acta et al., 2012) |
| | MSPE | | ~30 | 0.2-0.5-1 L (pH = 3) | – | 1 mL MeOH | 96 | HPLC-UV | (Aguilar-Arteaga et al., 2010) |
| On-line solid phase | Hypersil GOLD™ | Low | ~10 | 10 mL | Any volume of Water and MeOH | 5 mL MeOH | 97 | HPLC-MS/MS | (Gusmaroli, Insa, & Petrovic, 2018) |
| | PLRP-s | | ~4 | 1.7 mL | 2 mL (5% ACN/0.1% Ac. Acid) | <1 mL ACN | 111 | UHPLC-MS/MS | (Anumol & Snyder, 2015) |
| | HySphere Resin GP | | ~30 | 2.5 mL | 2 mL of Water<br>2 mL of MeOH | 2 mL MeOH | 95 | HPLC-MS/MS | (López-Serna et al., 2010) |
| No extraction | Direct Large Volume Injection | None | – | 80 uL | - | – | 100 | HPLC-MS/MS | (Anumol et al., 2015) |

*Additional 30–60 min will be necessary for drying the cartridge.

(uL). On-line SPEs offer reusable cartridges and less labor but have a limited range of analytes. These methods incorporate an SPE cartridge between the sample injector and analytical column. Therefore, preconcentrated analytes are directly eluted onto the analytical column. Lastly, no extraction methods offer the lowest cost and labor requirement, but also have the greatest matrix effects. These methods inject water samples directly onto the analytical column. By increasing the sample loop of an injector, it negates the need for extraction by increasing injection volume size.

## 4. Concluding remarks

Pharmaceuticals have become an integral part of human health care and as their production and consumption increase, so does their occurrence in environmental waters. Despite being detected in the environment since the 1970s, pharmaceuticals did not start gathering attention until they were found to be widespread within U.S streams from 1999 to 2000 (Kolpin et al., 2002). This led to the development of analytical and biological methods to monitor pharmaceuticals within the environment. Pharmaceutical analysis originated from GC-MS and evolved into liquid chromatography-tandem mass spectrometry. Although TOF-MS (Marchese, Gentili, Perret, Ascenzo, & Pastori, 2003; Petrovic, Gros, & Barcelo, 2006; Stolker et al., 2004), quadrupole ion trap (Batt et al., 2008; Seitz et al., 2006), and even ion chromatography (Sacher, Raue, & Brauch, 2005), or capillary electrophoresis (Ahrer, Scherwenk, & Buchberger, 2001), have been attempted in recent years, LC-MS/MS is currently the primary choice in pharmaceutical analysis due to the greater sensitivity. In order to maximize the selectivity and sensitivity of such advanced analytical techniques, sample preparation plays a pivotal role. While conventional SPE is the predominant extraction method in environmental analysis, complexed extraction including clean up procedures is often necessary for the detection of pharmaceuticals with high ion suppression. The future direction of sample preparation likely focuses on reducing solvent/reagent consumption, labor intensity, and length of procedures. Miniaturization and on-line extraction techniques, as well as bypassing extractions with large volume injections, can be examples. Ultimately, the development of sensitive and selective instruments can help reduce/eliminate sample preparation steps.

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