EVALUATION OF NOVEL SORPTIVE EXTRACTION TECHNIQUES

Sameer Shamrao Lakade

UNIVERSITAT ROVIRA i VIRGILI

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DOCTORAL THESIS

Supervised by

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Department of Analytical Chemistry and Organic Chemistry

UNIVERSITAT ROVIRA I VIRGILI

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WE STATE

that the present study, entitled "EVALUATION OF NOVEL SORPTIVE EXTRACTION TECHNIQUES", presented by SAMEER SHAMRAO LAKADE for the award of the degree of Doctor, has been carried out under our supervision, at the Department of Analytical Chemistry and Organic Chemistry of the Universitat Rovira i Virgili, and that all the results presented are the result of experiences carried out by the aforementioned doctorate.

Tarragona, September 1st 2017.

Doctoral Thesis supervisors

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"Learning gives creativity,
Creativity leads to thinking,
Thinking provides knowledge,
Knowledge makes you great"

Dr. A.P.J. Abdul Kalam

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DEDICATION

To my Late Grandfather Mr. Meghnath S. Lakade for your support, blessing and encouragement shines through everything I do.

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ABSTRACT

In recent years, one issue of growing environmental concern is the presence of various types of emerging organic contaminants (EOCs) in the different environment compartments, with water being one of the worst affected. This is because modern industrialization, urbanization and contemporary lifestyles have caused many significant changes in the environment that, in turn, affect aquatic and territorial wildlife, as well as human health.

To evaluate the occurrence, distribution and adverse effects on the environment, efficient and reliable analytical methods are needed. The presence of EOCs at low concentrations levels, their high solubility and their interaction with complex environmental matrices make their determination more challenging. The best choice for the determination of these contaminants in environmental waters is liquid chromatography (LC) coupled to a tandem mass spectrometry (MS/MS) based detector.

However, due to the low concentration of these contaminants in environmental samples, a sample preparation technique is needed to extract them from the samples. The most commonly used sorptive extraction techniques are solid-phase extraction (SPE), solid-phase microextraction (SPME), and stir bar sorptive extraction (SBSE), among others, although new extraction techniques are emerging. Therefore, the objective of this Doctoral Thesis is the evaluation and application of novel sorptive extraction techniques for the extraction of EOCs from environmental water samples.

Specifically, this Doctoral Thesis mainly focuses on recently introduced novel extraction techniques including fabric phase sorptive

extraction (FPSE), dynamic FPSE (DFPSE), capsule phase microextraction (CPME) and dispersive solid-phase extraction (d-SPE) using novel hypercrosslinked magnetic particles (MPs), which were evaluated for the extraction of different contaminants, such as pharmaceuticals and personal care products (PPCPs) and sweeteners (SWs), which acted as model compounds. All these extraction techniques are followed by LC-MS/MS for the determination of these contaminants in environmental samples.

The first section is dedicated to the FPSE technique, which is based on the principle of equilibrium extraction. The technique was developed to overcome the limitations of SPME and SBSE techniques. In this technique, a porous surface of cellulose or polyester fabric material is used as a substrate, which is uniformly coated with different materials through sol-gel technology. In equilibrium mode, this fabric material was evaluated for the extraction of a group of PPCPs that covers a wide range of polarities. Four different types of FPSE coatings were evaluated and compared. The best of these, as well as the optimal extraction parameters, were selected for the method development, which was based on FPSE followed by LC-MS/MS. The results obtained were comparable with previously studied SBSE techniques.

In the same section, a new design of the FPSE technique, known as DFPSE, was developed and applied for the extraction of the same group of PPCPs in environmental water samples. DFPSE consists of a 47 mm round fabric flexible disk, which overcomes static FPSE limitation of a long equilibrium extraction time. In DFPSE mode, the sample is percolated through the fabric material using a filtration assembly. Then, the retained analytes are eluted by passing the solvent through the same

assembly. In this study, different parameters affecting the extraction were optimized for the sorbent material in order to increase the extraction recovery of the analytes. The results were compared with static FPSE and other sample preparation techniques. The optimal method was validated and applied to determine these PPCPs in different environmental waters, such as surface and sewage water samples.

In the second section, a recently introduced sample preparation technique known as CPME was evaluated for the first time for the extraction of personal care products (PCPs). In CPME, extraction is carried out with a microextraction capsule (MEC) that consists of two sealed porous membranes, one of which is encapsulated with different polymer/functional moieties and coated by sol-gel technology. The other membrane contains a magnetic rod which allows the device to be spun when placed on a magnetic stirrer. The developed method was applied to determine the occurrence of selected PCPs in environmental water samples.

The last section describes the evaluation of novel hypercrosslinked Q-100 MPs in d-SPE mode. The new sorptive material has the advantages of a hypercrosslinked structure, high surface area and suitable pore size distribution. In view of these features, MPs were evaluated for the retention of a group of SWs, which included very polar compounds. The different parameters affecting extraction were firstly optimized. The d-SPE method was the validated and, later, applied to analyze various environmental samples.

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CHAPTER 1. INTRODUCTION

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Over three quarters of the Earth's surface is covered by water and the rest is taken up by land. As Earth's population continues to grow, people are putting ever-increasing pressure on the water resources. As a result, drinking water, rivers, oceans and other sources of waters are being put under pressure by human activities, causing water to be polluted and therefore affecting its quality. It is well-known that pollution can be of natural or anthropogenic origin because of the relatively recent developments in terms of the industrial revolution, urbanization and modern lifestyles. As the population has grown and, at the same time, industrialization has spread around the world, the problem of pollution has spread with it, affecting air, soil and water, as well as aquatic ecosystems, wild-life, and human health.

Over the last few decades, an increasingly number of organic compounds have been used worldwide in large quantities for production and industrial manufacturing processes, food preservation, and human and animal healthcare, among others reasons. As a result, a wide range of organic pollutants can be found in different environmental compartments, especially in aqueous matrices, causing a risk to surface water quality. In terms of the different organic contaminants, emerging organic contaminants (EOCs) have received special attention in recent years. EOCs include a wide range of different groups, including pesticides, pharmaceuticals and personal care products (PPCPs), veterinary products, nanomaterials, food additives, sweeteners (SWs), industrial by-products and compounds, and many more. Although EOCs have not been identified at significant levels in environmental waters in terms of distribution and concentration in the past, they are now being more widely detected and have the potential to cause known adverse effects on ecological and human health at very low levels (ng/L) [1]. The

various types of EOCs are extensively used in consumer goods, serving useful everyday functions within society. Therefore, the occurrence and fate of the EOCs at very low concentration levels, between ng L^{-1} and µg L^{-1}, in the environment has been reported in a number of publications recent decades [2-4] and reviewed by many authors, demonstrating increasing concern in this respect [1, 5, 6].

Within the large family of EOCs, research has demonstrated that many EOCs are endocrine disrupting compounds (EDCs), which have attracted particular attention due to their effect on endocrine systems, mainly interfering with sexual functions in animals, causing feminization, imposex, decreased fecundity, and developmental abnormalities, at low dosages [7]. Some of these contaminants are found in a wide range of products, such as plastic bottles, detergents, flame retardants, food, toys, cosmetics, etc. [7]. Moreover, recently, the presence of metabolites or transformation products (TPs) of EOCs has emerged as a new challenge of growing concern in environmental analysis. Thus, after the consumption of pharmaceuticals these compounds are excreted or released unchanged and as free or conjugate metabolites. After undergoing different biotic and abiotic processes (such as hydrolysis, photolysis, oxidation, and microbial metabolism) in wastewater treatment plants (WWTPs). The parent compounds or metabolites of the compounds can be found as such or converted to TPs. TPs of some of the compounds, such as salicylic acid, have been reported in environmental water samples, while their parent compounds (in the example, acetylsalicylic acid) have not [8]. In addition, despite being detected at very low concentrations, they may still have potentially harmful effects on the ecosystem and human health [9].

Wastewaters are the most important sources of EOCs entering the environment from domestic, hospital and, industrial waste and waste disposal sites. Because of their continuous release into the ecosystem, they are classified as pseudo-persistent [10]. In fact, the elimination of EOCs at low levels is very difficult and crucial for conventionally designed WWTPs [11]. Some studies have widely demonstrated that, in most cases, different primary, secondary and tertiary treatment included in WWTPs are inefficient for removing the majority of EOCs and their metabolites or TPs, as they are still present in effluent wastewater samples [12-15]. Due to incomplete elimination at WWTPs, EOCs are introduced via this route into rivers and streams used as receiving waters. Therefore, EOCs are not only present in wastewaters, but also some studies have demonstrated their presence in surface, sea and even drinking water samples [16-19]. Fig. 1 shows how the EOCs enter surface water/drinking waters/ground water from several sources, including effluent from WWTPs, leakage from septic tanks and landfill sites, surface water run-off from farm land, agriculture and direct disposal into water courses.

The European Union (EU) Water Framework Directive (WFD) (Directive 2000/60/EC) [20], the Drinking Water Directive (DWD) (Directive 98/83/EC) [21] and its successor, the Ground Water Directive (Directive 2006/118/EC) [22], have established some regulations for protecting the environment. The first Directive (2000/60/EC) [20] on European water policy set up a protocol to define high risk substances to be prioritized, including, organic contaminants: pesticides, polyaromatic hydrocarbon (PAHs) and some chlorinated organic solvents. Subsequently, in 2008, the Environmental Quality Standard Directive

2008/105/EC [23] approved a set of 33 priority substances and their concentration limits.

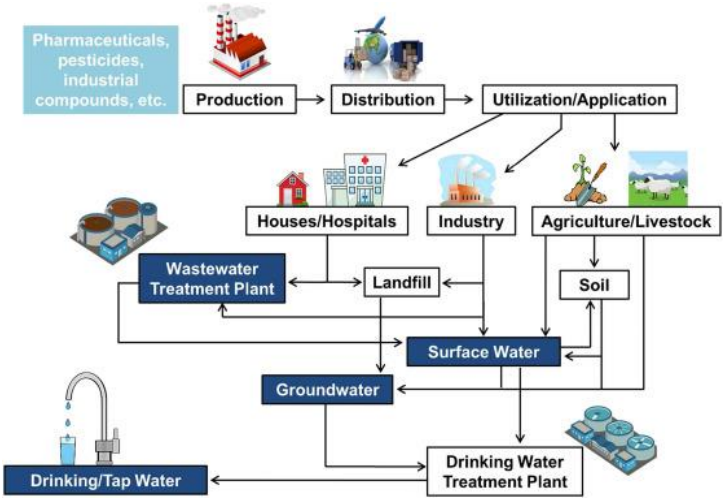

Figure 1. Representative sources and routes of EOCs in the environmental water [11].

Four years ago, the EU Directive 2013/39/EU [24] recommended inclusion on the watch list and treatment options for a group of 45 priority substances to ensure the protection of aquatic compartments and human health. The directive included two pharmaceuticals (the non-steroid anti-inflammatory diclofenac and the synthetic hormone 17-alpha-ethinylestradiol - EE2) and a natural hormone (17-beta-estradiol - E2) in an initial watch list of 10 priority substances for EU monitoring, to be launched within two years. Under Decision 2015/495/EU [25] the watch list of priority substances required to meet EU environmental quality standards was amended including a total of 17 new organic compounds. The directive was updated by including the abovementioned substances (diclofenac, EE2 and E2), as well as three macrolide antibiotics (azithromycin, clarithromycin and erythromycin), as well as other natural hormone (estrone - E1), some pesticides, a UV filter and an antioxidant

commonly used as food additive. These directives are continuously being updated with new regulations for priority substances to be added in the list.

A similar situation has occurred elsewhere in other countries around the world. For instance, in the United States (US), the Environmental Protection Agency (EPA) has set the statutory guideline values for about 125 contaminants in drinking water, 31 of which were considered to be micro-organic pollutants [26]. However, in 2009, the US EPA published a new contaminant candidate list (CCL-3), which includes 3 pharmaceuticals (erythromycin, 17R-ethinylestradiol (EE2), and nitroglycerin), perfluorooctanoic acid and eight hormones [27].

In recent decades, due to the constant increase in public awareness of the impact of these EOCs on the environment, the scientific community has developed new extraction procedures and novel equipment in the field of analysis. Thanks to these new methodological processes, environmental monitoring has made it possible to identify and quantify EOCs in environmental samples. These methods have to provide both high sensitivity and selectivity because of the very low concentration of these contaminants in environmental samples. To achieve this objective, the methods include sample pretreatment, before instrumental determination, which is usually achieved with chromatographic techniques.

Over the past few decades, numerous analytical methods have been reported for the identification and quantification of EOCs based on gas chromatography (GC) and liquid chromatography (LC). These techniques can be used in combination with different types of detectors, such as flame ionization detectors or thermal chemical detectors in the

case of GC, and ultra-violet (UV) or diode array detectors (DAD) for LC. However, in most cases, they are not suitable for detection at low concentration levels. Therefore, current trends are moving towards the use of more sensitive and selective detection systems such as mass spectrometry (MS) or tandem MS (MS/MS). GC is the most preferable technique for determining non-polar and volatile organic compounds. For determining more polar compounds by GC, a derivatization step has to be included prior to the chromatographic separation, in order to reduce the polarity and increase the volatility of the compounds. In contrast, LC can be used for the separation and determination of a wide range of polarities without a derivatization step, for less volatile and thermally labile organic contaminants.

As mentioned above, the majority of EOCs in environmental waters are present at very low concentration levels. Therefore, a sample preconcentration step is included between sampling and determination. This step is usually challenging and a key part of the development of analytical methods, due to the complexity of the matrices, which contain many interfering compounds. In some cases, clean-up steps are also included to eliminate these interfering compounds and decrease the complexity of the sample before the chromatographic technique. There are several techniques used for the extraction of the contaminants in liquid samples. The first classic extraction technique most commonly used for liquid samples was liquid-liquid extraction (LLE). However, due to the large volume of organic solvent required for performing this technique, it is gradually being replaced by other techniques. Solid-phase extraction (SPE), which is a sorptive technique, has been extensively used for the extraction and enrichment of EOCs because of the wide variety of sorbents available. The use of other sorptive techniques, such as solid-

phase microextraction (SPME), stir bar sorptive extraction (SBSE) has increased over the last decade and they are considered suitable alternatives to conventional LLE and SPE, because they reduce the use of organic solvent and are considered to be environmentally friendly.

Apart from the well-established techniques there are other sorptive techniques that have emerged to address some of the limitations and improve applicability. This Doctoral Thesis focuses on the evaluation of new sorptive extraction techniques for the extraction of EOCs from environmental water samples. The Introduction is divided into three sub-sections. In the first, the principal characteristics and applications of EOCs are presented, particularly PPCPs and SWs, which are the target compounds of the studies reported in this Doctoral Thesis. The second sub-section describes the chromatographic techniques used to determine EOCs, and the final sub-section discusses sorptive extraction techniques used for liquid samples.

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1.1. Emerging organic contaminants

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As mentioned earlier, EOCs have been the subject of growing concern in recent years due to continually entering the environment and being detected in the different environmental compartments, especially aqueous samples. They are particularly a cause for concern because of the different classes of EOCs that have been found in environmental waters, such as pharmaceuticals, drugs of abuse, personal care products (PCPs), surfactants, estrogens, food additives and lifestyle compounds. Of these classes, this section describes the group of EOCs focused on the studies reported in this Thesis, namely PPCPs and SWs. The compounds included in each group are discussed in detail, including their chemical properties, ecotoxicological risk and their occurrence in environmental water samples. The structures of the selected analytes can be seen in Appendix II.

PPCPs are a group of thousands of chemicals categorized into chemical classes that are consumed by humans and animals for health or cosmetic reasons, including pharmaceuticals, fragrances, sunscreens, personal-hygiene products and nutritional supplements [28-30]. PPCPs are sub-divided into two more inclusive groups: pharmaceutically active compounds (PhACs) and PCPs.

1.1.1. Pharmaceutically active compounds

PhACs include medically prescribed pharmaceuticals, drugs of abuse, and hormone based compounds. It is estimated that approximately 4,000 different substances use PhACs as ingredients worldwide today, including pain killers, antibiotics, antidiabetics, beta-blockers, contraceptives, lipid regulators, antidepressants, and others [31]. The list of PhACs ingredients increases every day. However, not all

these compounds has been investigated in environmental studies. Pharmaceuticals are not only consumed by humans but also in veterinary applications for livestock, poultry, fish farming, among other, with various drugs commonly given to farm animal to prevent illness and disease and to increase the size of animals.

Pharmaceuticals are used in the diagnosis, treatment, alteration or prevention of abnormal health or structural functional condition in the body. After consumption, not all of these PhACs can be metabolized completely in human and animal bodies, but rather they are excreted as parent compounds, metabolites or conjugates via urine and faeces into environmental systems [32, 33]. A survey of the detailed literature leads to the conclusion that the presence of PhACs is commonly observed in wastewater samples collected from influent, secondary effluent and tertiary effluent from domestic WWTPs, as well as in surface waters at very low concentrations (ng/L) [32, 34], because many of these compounds are not removed after secondary and tertiary WWTP processes. Table 1 lists some examples of each group of the most widely studied PhACs in environmental samples. As mentioned above, the following sections only discuss classes of compounds selected for the studies in this Doctoral Thesis. The analytes selected from the different classes are frequently detected in environmental water samples, mainly because most of them are widely consumed worldwide, with or without prescription.

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) provide analgesic (pain relief), antipyretic (fever reduction) and anti-inflammatory

(inflammation reductions) effects for human and animal species. They are also the most commonly used pharmaceuticals because they are easily available in drug stores or chemists around the world without a medical prescription. Table 1 shows some example of NSAIDs. Because of their chemical structure, most of these pharmaceuticals are weakly acidic (pK_a value between 3 and 7), polar and highly water soluble. Many of these compounds are chiral pharmaceuticals, but they are often administered as racemates. Due to their easy availability and consumption these compounds have been determined in environmental water samples [35-37]. For instance, Gilart *et al.* [36] reported a high concentration of diclofenac in influent (966 ng L^{-1}) and in effluent (641 ng L^{-1}) wastewater.

Table 1. List of some PhACs studied in environmental samples.

Compounds class	**Examples of most common analytes**
Non-steroidal anti-inflammatory drugs	Diclofenac, ibuprofen, naproxen, fenoprofen, ketoprofen, indometacin,
Analgesics	Paracetamol, acetylsalicylic acid, antipyrine
Psychiatric drugs	Diazepam, carbamazepine, primidone, fluoxetine
Beta-blocker	Propranolol, metoprolol, timolol, sotalol, atenolol
Human and veterinary antibiotics	Trimethoprim, erythromycine, lincomycine, sulphamethaxole, chloramphenicol, amoxicillin
Lipid regulators	Bezafibrate, etofibrate, gemfibrozil, fenofibrate
X-ray contrasts	Iopamidol, diatrizoate, iopromide
Steroids and hormones	Estradiol, estrone, estriol, diethylstilbestrol

Analgesics

Another group of the most widely consumed pharmaceuticals without medical prescription is analgesics, which are used for pain relief, with acetaminophen and acetylsalicylic acid (Aspirin) being the most commonly consumed which have been included on the draft list of the European Union's Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) [38]. For instance, Pedrouzo *et al.* [39] demonstrated the presence of salicylic acid (metabolite of acetylsalicylic acid) in samples taken from two WWTPs in the range from 0.009 to 2 µg L^{-1}, and a significantly high level of acetaminophen (19.85 µg L^{-1}) in the samples from both plants.

Psychiatric drugs

This kind of pharmaceuticals often puts the subject in a pleasant and relaxed state because they change the brain functions, resulting in an alteration in mood, perception and consciousness. The most widely prescribed pharmaceuticals in this group are stimulants, antidepressants, antipsychotics and anxiolytics. The most widely used stimulant in the world is caffeine. The most well-known and easy source of caffeine is coffee beans, but it is also found in tea, other beverages and pharmaceuticals. Unlike many other psychoactive substances, it is legal and unregulated in nearly all parts of the world. It is commonly found in environmental water samples because of the high levels of human consumption, which makes this compound a reliable anthropogenic indicator [40, 41]. For instance, Afonso-Olivares *et al.* [41] reported the concentration of caffeine in the range of 0.16 to 4.31 µg L^{-1} in three different WWTPs on the island of Gran Canaria.

Carbamazepine (CBZ) is an anti-epileptic pharmaceutical included in some studies on psychoactive drugs because it is used as an antidepressant as well as for the treatment of seizure disorders, relief of neuralgia and a wide variety of mental disorders [42]. CBZ is used frequently and globally and, because it is very persistent to degradation in WWTPs, it can be found in environmental water samples. The main metabolic pathway in the case of CBZ is oxidation to 10, 11-dihydro-10, 11-epoxycarbamazepine (CBZ-EP) as the most important metabolites, and then, to a lesser extent, hydration to 10, 11-dihydro-10, 11-dihydroxycarbamazepine (CBZ-DiOH) and conjugation of CBZ-DiOH with glucuronide. Miao *et al.* [43] determined CBZ and five of its metabolites or degraded compounds in domestic WWTPs. They reported a concentration of the parent CBZ of 0.036 μg L^{-1}, while its five metabolites were found at concentration up to 0.1 μg L^{-1} in wastewater. In addition, some studies have reported levels up to 0.22 μg L^{-1} in wastewater samples [37, 44, 45].

Another group of psychoactive drugs that has attracted attention is benzodiazepines (e.g. bromazepam, flurazepam, nordazepam and diazepam), the chemical structure of which is the fusion of the benzene ring and diazepine ring. These drugs are frequently prescribed for the pharmacotherapy of epilepsy, convulsions and related disorders. Because of their effects, they are also widely used as psychoactive drugs around the world. Some studies have reported the presence of benzodiazepines detected at ng L^{-1} level in wastewater [46] and river water [47].

Beta-blockers

These are the most frequently prescribed pharmaceuticals and are particularly used to treat cardiac arrhythmias and prevent heart attacks. They are also widely used to treat hypertension. Also known as beta-adrenergic blocking agents, beta-blockers (e.g., atenolol, sotalol, pindolol, timolol, metoprolol, carbazolol, propranolol and betaxolol) are drugs that block norepinephrine and epinephrine (adrenaline) from binding to beta-receptors on nerves. The most widely studied compounds are atenolol, metoprolol and propranolol. They are quite active pharmaceuticals and, as such, a small dose of the beta-blocker provides sufficient blockages. Since they promote lower heart rates and reduce tremors in professional sports activities, beta-blockers have been banned by the International Olympic Committee because they are considered to be anti-doping agents in sports [48]. Some studies have shown the presence of beta-blockers in environmental waters [34, 39, 49, 50]. For instance, Papageorgiou *et al.* [34] reported the comprehensive study containing the seasonal occurrence, removal, mass loading and environmental risk assessment of 55 multi-class PPCPs in WWTPs. Beta-blockers were detected in influent and effluent wastewater samples. Among them, atenolol was determined at the highest concentration of 2,346 ng L^{-1} and 1,707 ng L^{-1} in influent and effluent, respectively. Metoprolol was determined at a higher concentration in effluent 315 ng L^{-1} than influent 96 ng L^{-1} samples, and propranolol was present at low concentrations in influent and effluent (below quantification limit). This suggests that metoprolol might be a metabolite or TP of some other beta-blockers.

1.1.2. Personal care products

Another group of contaminants included on the list of the EOCs are PCPs. The active ingredients included in PCPs used in products for daily use, such as soaps, lotions, cosmetics, sunscreens, fragrances and many more are typically synthetic organic compounds.

Over the last decade, the scientific community has focused more attention on the determination of this group of analytes in different environment compartments, due to their extensive consumption and potential negative impact on the environment, living organisms and human health. Table 2 lists some PCPs classes in terms of their use and associated principle compounds of environmental concern. As stated above, the following sections only discuss the PCPs that were studied in the experimental part of the Doctoral Thesis.

Table 2. List of PCPs studied in environmental samples.

Compounds class	**Examples of analytes**
UV filters	Benzophenone-1, benzophenone-2, benzophenone-3, benzophenone-4, benzophenone-8, methylbenzylidene camphor
Preservatives	Methylparaben, ethylparaben, propylparaben, butylparaben, benzylparaben
Antimicrobials	Triclosan, chlorophene, triclocarban
Insect repellents	N,N-diethyltoluamide
Fragrances	Nitro-, polycyclic and macrocyclic musks

UV filters

These are included in sun creams and other PCPs (shampoo, lipsticks, lotions, etc.) to absorb or reflect some of the sun's ultraviolet (UV) radiation and therefore help to protect us from tanning. The consumption of these products has increased due to growing concern about UV radiation and skin cancer. Moreover, UV filters and ultraviolet light absorbers (UV absorbers or UV light stabilizers) are applied for technical purposes, such as in plastics and other materials to prevent the degradation of polymers and pigments. The EU currently includes 27 UV-filters on the list of the Cosmetics Directive of which 26 are organic UV filters and only one (titanium dioxide) is inorganic, with a further 43 chemicals being listed as UV-filters in ingredients used in cosmetics [51]. UV-filters enter the aquatic environment either directly by being washed off the skin and clothes during recreational activities or indirectly via wastewater and swimming pool waters. Due to the hydrophobic properties of some of these analytes, they have also led to bioaccumulation in fish, sediments and soil [30, 52, 53]. In contrast, some hydrophilic or polar UV filters may act as “pseudo-persistent” compounds, when they are continuously released from WWTPs to a greater extent than their environmental removal. UV filters must be stable when exposed to UV radiation, but recent studies have shown that several organic UV filters undergo degradation, mainly by photolysis, but also resulted in reactions with chlorinated water because the energy absorbed cannot be internally converted quickly enough, so that the molecule remains excited long enough to react chemically [54, 55].

Due to the widespread use of UV-filters in PCPs, some studies have reported their occurrence in different sources of water, such as river

water, wastewater and sea water samples. The most commonly detected organic UV filters in water samples are benzophenones (BP-3, BP-1, BP-8), 2,2-dihydroxy-4-methoxybenzophenone (DHMB), 2-phenylbenzimidazole-5-sulphonic acid (PBSA), 4-methyl-benzylidene camphor (4-MBC), ethylhexyl methoxycinnamate (EHMC), isoamyl methoxycinnamate (IAMC), octocrylene (OC), and octyl dimethyl-p-aminobenzoate (OD-PABA) [3, 18, 30, 52, 56, 57]. For instance, Pintado-Herrera *et al.* [30] reported higher concentrations of OC (up to 1.3 µg L^{-1}) and BP-3 (up to 0.2 µg L^{-1}) in wastewater samples than in seawater (OC at 0.1 µg $L^{-1}$and BP-3 at 0.07 µg L^{-1}) and pore water (OC at 0.2 µg $L^{-1}$and BP-3 at 0.07 µg L^{-1}). In addition, Pedrouzo *et al.* [56] reported a higher concentration of OC, BP-3, DHMB and OD-PABA in influent than effluent wastewater samples and, in the case of river water samples, only BP-3 was detected.

Preservatives

The term “preservatives” refers to the functional name for a wide variety of compounds that help slow or prevent bacterial growth and ensure products remain suitable and safe throughout their shelf-life and the period of use. Preservatives are used in a wide range of products including foods, beverages, pharmaceutical drugs, paints, biological samples and many others. These compounds can be natural or synthetic. Parabens (PBs) are alkyl esters of the para-hydroxybenzoic acid used to inhibit bacterial growth and thus increase the shelf life of a wide variety of products. PBs, which include methylparaben (MPB), ethylparaben (EPB), propylparaben (PrPB), butylparaben (BuPB), isobutylparaben, isopropylparaben, heptylparaben and benzylparaben, are the most commonly used group of preservatives. In particular, MPB, EPB, PrPB

and BuPB are very widely used, individually or in combination, especially MPB and PrPB, which are normally used together because of their synergistic preservative effects [58, 59]. In 2008, under Regulation (EC) No 1333/2008 of the European Parliament, the EU authorized the use of PBs as food additives [60]. In the case of cosmetics, the use of parabens is regulated by Directive 76/768/EEC [51].

Due to the ongoing widespread use of PBs and continuous introduction into the environment through domestic and industrial wastewater, they have recently been found in different types of samples, such as fish, wastewater, surface water, sludge and soil [61-64]. However, several studies have demonstrated that most PBs in aqueous phase are effectively removed during conventional sewage treatments in WWTPs, with an average removal rate over 90% [62, 65]. They have attracted growing attention due to their potential long-term effects on human health and aquatic organisms. Therefore, the occurrence and transportation pathways of these compounds into aquatic ecosystems have received particular attention. Previous studies [62, 66, 67] have also demonstrated their endocrine disrupting activity at environmentally relevant concentrations. Therefore, PBs are increasingly avoided. Kasprzyk-Hordern *et al.* [67] found concentrations of MPB and EPB ranging from 0.010 - 0.030 µg L^{-1} and 0.008 - 0.040 µg L^{-1}, respectively, in river water samples, while, PrPB and BuPB were found below method quantification limits. In addition, Molins-Delgado *et al.* [62] reported that higher concentrations of PBs were observed for PrPB (5.7 µg L^{-1}), MPB (2.46 µg L^{-1}) and BuPB (1.6 µg L^{-1}) in influent wastewater samples. Meanwhile, in effluent wastewater higher concentrations were observed for MPB (0.13 µg L^{-1}) and PrPB (0.083 µg L^{-1}), while BuPB was detected below method detection limits (MDLs).

Antimicrobials

Antimicrobials are chemical agents that slow or stop the growth of micro-organisms or germs on the external surfaces of the body and help prevent infections. Because of these properties, antimicrobials are widely used in PCPs. Triclosan (TCS) and triclocarban (TCC) are the most widely employed as antibacterial and antimicrobial agents, due to their bactericide activity, in consumer products such as soap, toothpaste, creams and mouthwash. They are also suitable for addition to polymers and fibres to give these materials antibacterial properties. They are both relatively hydrophobic, with estimated log octanol-water partition coefficients (log K_{ow}) of 4.8 for triclosan and 4.9 for triclocarban. Because of the wide range of applications and as a consequence of their lipophilic properties, these compounds have become widespread contaminants in the human body and environment. Similar to other EOCs this bactericide as a “down-the-drain” contaminant that is transported in domestic sewage to WWTPs, before eventually being discharged in wastewater effluents into the aquatic environment [68]. TCS can undergo a series of transformation reactions to produce, in some cases, more toxic or bio-accumulative compounds, with the oxidation of TCS being the most favourable. The metabolites or TPs of TCS have been determined in environmental samples in the form of methyl-TCS and three chlorinated derivates [68, 69].

TCC has a two chlorinated phenyl ring structure, as can be seen in Appendix II, which suggests potential resistance to both chemical and biological transformation processes. TCC may have more potential for contaminating surface waters as this compound appears to be more persistent than TCS in WWTPs [70]. Guo *et al.* [71] analysed several

water samples including river water, irrigating water, reclaimed water and domestic water for the determination of the TCS, TCC and methyl-TCS, and, for instance, TCS was only found in the domestic water sample at a concentration of 2.08 µg L^{-1}. Moreover, Gilart *et al.* [72] reported the presence of high concentrations of TCC and TCS in both influent and secondary effluent wastewater samples while, in the tertiary effluent treated sample, TCC and TCS were found below MDLs.

1.1.3. Sweeteners

Sweeteners, also known as 'artificial sweeteners' or 'high intense sweeteners' are commonly used substances that are much sweeter than sucrose. Their sugar equivalence is 30 times sweeter than table sugar. Moreover, they are either not metabolized in the human body or do not significantly contribute to the energy content of foods and beverages.

The history of sweeteners (SWs) started with the discovery of saccharin in 1878. Since then, many other sweet compounds have been developed, mostly by chance. As such, SWs form an important class of food additives with a few having been used as SWs in food products and beverages. Many of them have been banned, due to the emergence of toxicological problems or unsatisfactory properties. The first generation of SWs, such as aspartame (ASP), saccharin (SAC) and cyclamate (CYC), were introduced in the 1950s. A few years later, the second generation of SWs were introduced, including acesulfame (ACE), sucralose (SUC), neotame (NEO) and alitame (ALI) [73]. Over the last three decades, the general perception of SWs has changed due to their low calorific value, high potency or non-nutritive properties to help to prevent body weight gain and, dental cavities, while being suitable for consumption by

diabetics or people who suffer from other metabolic disorders [16, 74, 75]. They may be produced synthetically or isolated from plants. SWs should be clearly classified in sucrose, related carbohydrates and sugar alcohols. Table 3 lists the most widely used sweeteners and their sugar equivalence.

Table 3. SWs classification with examples and the sugar equivalence.

Compounds group	**Examples of analytes**
First generation	Aspartame (200), saccharin (550), cyclamate (30)
Second generation	Acesulfame (200), sucralose (600), neotame (7000-13000), alitame (2500)
Natural source	Glycyrrhizic acid (50), Stevioside (160)

It should be noted that many countries around the world have regulated the different maximum usable dose (MUD) of SWs. In the EU, SWs are evaluated for safety purposes by the European Food Safety Agency (EFSA), prior to authorization for use [76-78]. These regulations enable the gap between the technological developments in the field of SWs to be maintained, while also setting the maximum level or MUD of each SW in the specific category of food. EU directives define which SWs are approved for addition food and beverages. The European Commission regularly revises the list of authorized SWs based on the advice of the EFSA, which takes into account the latest scientific advances in the field.

The US Food and Drug Administration (FDA) has permitted five SWs as food additive (ACE, SAC, ASP, SUC and NEO), while CYC and

neohesperidin dihydrochalcone (NHDC) are not permitted as food additives. Even though stevioside (STV) is extracted from natural sources, as a crude extract of the stevia plant, it is not permitted as a food additive by USFDA. In Australia and New Zealand, all SWs are permitted as food additives, except NHDC, dulcin and glycyrrhizic acid (GLY). In Japan, only five SW (ACE, ASP, GLY, SAC and SUC) are permitted for consumption. Meanwhile, China and Taiwan permit the consumption of ACE, SAC, SUC, ALI, GLY, CYC and ASP, but dulcin and NHDC are not permitted as food additives [79].

Hence, after decades of use, some studies have documented the widespread detection of SWs in different environmental compartments such as wastewaters, surface water, fish, soil and sludge. Therefore, they are considered to be a group of EOCs [80-85]. The six most popular and widely used SWs are ACE, ASP, SUC, SAC, CYC and NHDC. High concentrations of these compounds (especially ACE and SUC) have been found in the aquatic environment, compared to other anthropogenic EOCs [81]. Of the aforementioned SWs, ACE and SUC pass through WWTPs mainly unchanged and so occur in the aquatic environment at higher concentrations (up to several μg L^{-1}). In contrast, CYC and SAC can be partly eliminated at WWTPs at variable removal rates [81, 82, 86]. Therefore, SWs are an indicator of the influence of wastewater on other water sources. The SWs are considered safe for human consumption within regulated concentrations, but their effects on the ecosystem have not yet been studied in depth. However, some scientific research studies have presented data that show that SWs, such as CYC, SAC and ASP, can cause tumours in certain animals [87]. Some studies have reported that exposure to SUC in aquatic species can change aquatic life such as

increasing the swimming speed of *Daphnia magna* [88] and increasing food intake in the case of the marine *Copepode, Calanus glacialis* [89].

Due to the widespread use of SWs, their concentration varies between different regions and countries, up to the microgram per litre level in samples from WWTPs. Focusing on Europe, ACE has been found at higher concentrations than SUC in wastewater, surface water, ground water and tap water in Switzerland [90]. Similarly, Scheurer *et al.* [86] found a higher concentration of ACE (over 2 µg L^{-1}) in German wastewater and surface water. The presence of SUC has been studied in the surface water of 27 European countries [91], as well as in fewer studies in Switzerland [90] and Germany [86] that also included ground water.

In the USA, Ferrer *et al.* [92] found SUC at higher concentrations than ACE and SAC in aquatic environments, whereas Wu *et al*. [81] reported higher concentration of ACE than SUC in well water samples in Canada. In addition, Gan *et al.* [80] determined ACE and SUC at higher concentrations, while SAC and CYC were found at moderately low concentrations in tap water, ground water, river water, sea water, and WWTPs samples in China.

In summary all the selected analytes are present in environmental water samples at very low concentrations ranging from ng L^{-1} to µg L^{-1}. Therefore, to identify and quantify these compounds at such low concentration levels, a suitable extraction technique is required, followed by chromatographic technique. The following sections will focus on the determination techniques used for the selected analytes in these Doctoral studies.

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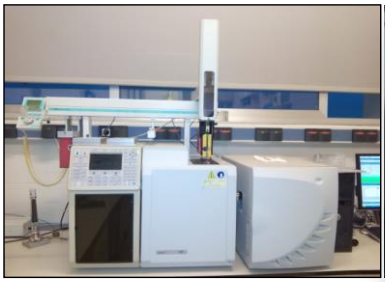
1.2. Determination of emerging organic contaminants



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In the previous section, there was discussion on the different groups of EOCs, particularly PPCPs and SWs, their route into the environment and their occurrence. This section focuses on the techniques used for determining these analytes in environmental water samples.

The determination of these contaminants in water samples involves some difficulty disclosed as: first, the very low concentration levels (µg L^{-1} to ng L^{-1}) at which these contaminants are present; and secondly, the number of matrix components that may interfere. Therefore, it is usually not feasible for the direct injection of the sample to the instrument and in order to achieve better determinations in environmental samples, clean-up and pre-concentration steps are necessary. A wide variety of extraction techniques have been developed for sample preparation and they will be discussed in Section 1.3.

As well as efficient extraction needed, efficient and reliable chromatographic and detection techniques are also required for the determination of EOCs at environmental levels. The most preferred analytical techniques used for separation and identification of EOCs from environmental water are gas chromatography (GC) and liquid chromatography (LC) [18, 57]. Although capillary electrophoresis (CE) has also been reported for the determination of EOCs in environmental waters [93, 94] but far fewer studies are available in comparison to GC and LC. As mentioned above, very low concentrations of EOCs are present in environmental waters and, therefore, mass spectrometry (MS) detectors are used in environmental water samples, as they possess high sensitivity and confirmation power for determining analytes in environmental samples.

Most studies report the development and application of methods that allow the simultaneous determination of the different classes of analytes. The objective is to reduce the cost and times required for sample preparation and also generate broader knowledge of the presence of these contaminants in the environment. However, analysing a broad spectrum of these contaminants (with different physicochemical properties) might involve a compromise, which often results in conditions that are not optimal for studying all the target analytes.

It should be mentioned here that, in this Doctoral Thesis, the methods developed for the compounds of interest in the aqueous samples were based on LC. For this reason, the following section discusses LC in more detail than GC.

1.2.1. Gas Chromatography

Gas chromatography (GC) is the analytical technique most commonly used for the determination of volatile EOCs from environmental waters. Due to its good separation power, GC has become one of the most attractive and powerful techniques for routine analysis of a number of ubiquitous organic contaminants. Thus, GC is used for the determination of certain groups of EOCs, such as PPCPs, but not for SWs because they are thermolabile.

Different types of columns have been used to separate PPCPs, mainly non-polar columns with 5% phenyl-methylpolysiloxane (DB-5, DB-5MS, and HP-5MS or their equivalent). There are some studies available in which, non-polar column from various manufacturers is used to separate PhACs and UV-filters compounds [53, 57, 95, 96]. In regard to

the detection step, there are several detectors available with MS being the most preferred. For instance, Kiguchi *et al*. [95] used the GC-MS for the determination of the derivatized extract of carbamazepine, caffeine and triclosan analytes from urban river water samples.

It is well known that the majority of the PhACs are mainly polar, thermally labile and non-volatile compounds. Therefore, direct analysis of many compounds and mixtures of compounds is difficult because of the interaction between the compounds themselves or between compounds and the column. The derivatization step is included in sample preparation before GC analysis to make them suitable for analysis by decreasing the polarity and increasing the volatility of the compounds. For GC analysis, there are three basic types of derivatization reactions: alkylation, acylation and silylation. There are a number of derivatization agents available for the derivatization of PPCPs, such as bis(trimethylsilyl)trifluoroacetamide (BSTFA) [97], N-(t-butyldimethylsilyl)-N-methyltrifluoroacetamide (MTBSTFA) [95], N-methyl-N-(trimethylsilyl) trifluoroacetamide [98] and acetic anhydride/potassium carbonate [57], among others. Recently, Vila *et al*. [57] determined 14 UV filters in water samples with prior in-vial derivatization with acetic anhydride and potassium carbonate into a water bath kept at 100^{o}C for 15 min, before extraction was performed with direct immersion-SPME in water samples.

When coupling GC and MS, two different ionization sources have commonly been used for the determination of PPCPs in environmental waters, namely electron impact (EI) and chemical ionization (CI). The EI source is the most widely used ionization technique in GC-MS and GC-MS/MS analysis. The identification of compounds by comparing the mass spectra obtained with those available in libraries is one of the main

advantages of EI because, in all cases, a voltage of 70 eV is used. However, the larger number of fragment ions caused by EI could potentially decrease the response of quantification ions. Therefore, the sensitivity of target compounds could decrease. CI is an alternative ionization mode used to analyze certain PPCPs to improve detection limits and reduce matrix interferences. This technique is highly sensitive and selective for compounds with electron affinity. Although different gases can be used as reagents, methane is the most widely used. For example, Zhao *et al.* [99] developed a method for the determination of phenolic EDCs and acidic pharmaceuticals using GC-MS with a negative CI source and the sample was derivatized with a pentafluorobenzyl bromide reagent. Recently, soft atmospheric pressure chemical ionization (APCI) has been used in the GC-MS/MS technique. This provided more specific high-mass precursor ions, avoiding potential interferences. For instance, Sales *et al.* [100] developed a method for screening and determining hexabromocyclododecane by GC-APCI-MS/MS. This method achieved better sensitivity and selectivity for the selected analytes and lower MDLs than previous methodologies based on GC and LC coupled with different source and analysers.

Another important part of MS instrumentation is the analyzer. It is used to separate the ions according to the mass to charge (m/z) ratio based on their characteristic behaviour of analytes in electric or magnetic fields. MS takes advantages of this different behaviour to separate the ions of different m/z values in space or time so that their response can be determined. Single quadrupole (Q), ion trap (IT), triple quadrupole (QqQ), and time of flight (TOF) are the four different analyzers commonly used in the determination of EOCs by GC. There are a number of studies available in which the single Q [53, 96, 97], IT [101] and QqQ [57, 100]

are used for the determination of PPCPs in environmental water samples. For example, N. Negreira *et al.* [101] developed a method for the determination of UV-filters in water samples using GC-MS/MS with an IT analyzer. Previously, the analytes were concentrated on the coating of a SPME fibre, on-fibre silylated with an MSTFA derivatization reagent. Very recently, Vila *et al.* [57] have developed a method for UV filters using GC-MS/MS in environmental water samples. The use of GC-MS/MS helps to achieve the low ng L^{-1} MDLs and the detected low concentration of the selected analytes.

Comprehensive two-dimensional gas chromatography (GC x GC) is an approached designed to overcome the problems of separation and quantification of targeted analytes when working with complex environmental samples, as well as obtaining good separation of the stereoisomers. For example, Matamoros *et al.* [102] used GC x GC coupled with TOF-MS for the simultaneous determination of 97 organic contaminants at trace concentration levels in river water samples. The developed methodology was based on SPE followed by GC-port methylation, and it achieved MDLs and limit of quantifications ranging from 0.5 to 100 ng L^{-1} and from 2 to 185 ng L^{-1}, respectively, for all analytes. This technique is commonly used in the characterization of complex samples such as petroleum, food and biological matrices.

In summary, the combination of an extraction technique and GC with MS-based detectors achieved the identification and quantification of non-polar compounds and, by using a derivatization step, some polar compounds can also be determined with good selectivity and sensitivity.

1.2.2. Liquid Chromatography

Liquid chromatography (LC) is the most commonly used technique because of its compatibility with polar, non-volatile and thermally labile EOCs, especially PPCP analytes, as well as helping to overcome some of the limitations of GC discussed above.

Column selection is the most important part of LC for separating the targeted compounds for quantification. Generally, for the separation of PPCPs, reversed phase mode is selected, mainly using C_{18} and C_8 analytical columns [37, 72, 103, 104]. For example, Gilart *et al*. [72] separated 16 PPCPs using a Kromasil 100 C_{18} column (150 mm x 4.6 mm, 5 µm) and the chromatographic separation was achieved in 30 min. Meanwhile, Ferrer, *et al.* [37] used Zorbax Eclipse XDB C_8 (150 mm x 4.5 mm, 3.5 µm) column to separate 100 pharmaceuticals and their degradates in less than 32 min.

In recent years, based on the principle of the Van Deemter equation and growing demand for high throughput analysis, a new trend in LC was developed, known as ultra high performance liquid chromatography (UHPLC). In UHPLC the analytical column packed with sub-2 µm particles (less than conventional LC column particles size of 3 to 5 µm) offers increased speed and improved efficiency compared to conventional LC analysis [45]. UHPLC not only offers a short chromatographic time but also better resolution and narrower peaks that help to prevent the analytes from coeluting with interferences during ionization and can decrease the matrix effect. In this respect, UHPLC has been used to determine PPCPs in different kinds of environmental samples [3, 18, 105]. For example, Gracia-Lor *et al*. [45] separated 17 PPCPs using an Acquity UPLC BEH C_{18} column (50 mm x 2.1 mm, 1.7 µm) in 12 min and a

decrease in the analysis time was achieved because of the sub-2 µm particle size. However, at the same time, back pressure on the system increases according to the decreasing particle size. Therefore, the use of small particles requires the use of a specially designed LC system capable of supporting back pressure of up to 15,000 psi.

To overcome this limitation, fused core particles were introduced, which are usually 2.7 µm in diameter, with a 1.7 µm solid core and a 0.5 µm outer shell of porous silica fused to uniform with three characteristic features over the traditional porous particle: narrow particle size distribution, more consistent in packed beds and a shorter diffusion time. In addition, a larger particle size is available for special applications, with larger pores in fused-core particles [106]. The characteristics of these fused core particles represent a compromise between separation speed and modest operating pressures. Although these fused core particle columns have received widespread attention in the field of pharmaceutical bioanalysis, some studies have also reported separating the analytes from extracts of environmental waters [16, 107]. For instance, Arbeláez *et al.* [16] reported a method for the determination of eight high intense SWs in environmental water using an Ascentis Express RP-amide column (100 mm × 2.1 mm, 2.7 µm particle size) achieving good separation of all analytes in less than 11 min.

Hydrophilic interaction liquid chromatography (HILIC) is a new trend in LC. This is an alternative to conventional reverse phase LC (RPLC) or normal phase LC (NPLC) for determining polar, hydrophilic and ionic analytes, which often requires the use of an ion pairing reagent. The mobile phase used in HILIC is less hydrophilic than the stationary phase, in contrast to RPLC. The mobile phase in HILIC is mainly based on an

organic-aqueous mixture in which the initial state consists of a high percentage of organic solvents that decreases throughout the change in gradient. The organic phase can be selected from the list of polar protic (e.g. methanol, ethanol, isopropanol) or polar aprotic (e.g. acetonitrile, tetrahydrofuran) solvents. Polar protic solvents are both hydrogen bond donors and acceptors, while polar aprotic solvents can only be acceptors. In most cases, acetonitrile is selected as an organic solvent because it provides greater retention and better shaped chromatographic peaks than other solvents [14, 108]. The stationary phases mostly used for HILIC are bared silica, bonded silica phases with aminopropyl, diol or amide groups and polymeric resins modified with functional groups including ion-exchange moieties. There are some studies in which HILIC has been used in environmental water analysis for polar PPCPs and SWs [14, 82, 108, 109]. For example, Salas *et al*. [14] used HILIC-high resolution mass spectrometry to determine SWs in river water, and effluent and influent wastewater, and proposed their separation as an alternative to RPLC.

In the LC technique, the mobile phase is usually composed of two phases: one is the aqueous phase with adjusted pH and other is an organic phase mainly using methanol, acetonitrile or a combination of these two solvents. For instance, in order to obtain sufficient retention for acidic analytes and reproducible retention times, the use of buffer mobile phase at an acidic pH is recommended [34, 73]. It should be taken into account that the mobile phase additives must be volatile when MS is used as the detector, and the most commonly used are formic acid, acetic acid, ammonium hydroxide, ammonium formate and ammonium acetate. In some cases, both the organic phase and aqueous phase are also modified with buffer solutions for better separation and enhanced sensitivity or ionization in MS [73, 80]. For example, Gan *et al*. [80] used a

mobile phase composed of water and acetonitrile, both containing 5 mM ammonium acetate and 1 mM TRIS, for the separation of SWs achieving good separation with increased sensitivity.

Another trend in LC is to increase the temperature in a technique known as high temperature LC (HTLC), which offers similar advantages to UHPLC, such as reducing chromatographic time and the organic solvent used. Another important advantage is that the viscosity of the mobile phase decreases, which results in reduced system back pressure. This system requires a temperature controller and the ability to generate flow rates, while the stationary phase must be stable at high temperature conditions. In HTLC, water can sometimes be used as the sole eluent, thereby moderating certain problems, including toxicity, flammability and costs related to the use of organic solvent, known in short as “green chromatography”. For example, Edge *et al*. [110] used water as the mobile phase at 180^{o}C for separation of pharmaceuticals. However, in spite of those advantages, HTLC is not routinely used for environmental analysis because of the limited availability of stable, high temperature resistant packing materials and the potential degradation of unstable compounds during separation [111].

In LC, various detectors are commonly used such as an ultraviolet (UV) detector [71, 84, 112, 113], diode array detector (DAD) [114-116], fluorescence detector (FD) [17] and electron light scattering detector [117] all of which have been used in the detection of EOCs in water samples. However, with complex samples, an MS-based detector has become the most popular option for ensuring the confirmation of the selected analytes, identification of the intermediate and unknown analytes and quantification at low concentration levels (ng L^{-1}). Some reviews have

been published on the determination of EOCs using LC coupled with an MS-based detector [111, 118, 119]. Table 4 shows examples of the analytical methods (using LC) used for the determination of EOCs in different environmental water samples.

In the case of MS-based detectors, three different types of ionization source or interfaces are mainly used: electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), and atmospheric pressure photoionization (APPI). They are all atmospheric pressure ionization interfaces included in the group of soft ionization sources, since the molecule does not undergo excessive fragmentation while working in positive and negative mode, depending on the target analytes.

Table 4. Analytical methods using LC for the determination of EOCs in water samples.

Analytes	**Analytical method**	**Matrix**	**Ref.**
NSAIDs	LC-UV	Wastewater and surface water	[120]
EDCs	LC-DAD	Wastewater and sea water	[121]
PPCPs, EDCs, SWs	HPLC-ESI-QqQ	Raw, ground and surface water	[103]
PPCPs	HPLC-ESI-QqQ	River, sewage water	[122]
PPCPs	LC-ESI-QqQ	River water and wastewaters	[123]

Table 4. (Cont.)

Analytes	**Analytical method**	**Matrix**	**Ref.**
Pharmaceutical and illicit drugs	LC-ESI-QqQ	Wastewater	[124]
PPCPs	UHPLC-ESI-QqQ	Surface water and wastewater	[45]
Artificial sweeteners	HILIC-ESI-QqQ	Wastewater	[82]
Estrogenic contaminants	LC-IS-IT	River water	[125]
Antibiotics	LC-ESI-TOF	Sea water	[126]
Artificial sweeteners	HILIC-HESI-Orbitrap	River, Wastewater	[14]
Pharmaceuticals and antifungals	UHPLC-HESI-Orbitrap	River water	[127]
Parabens and biodegradable products	LC-ESI-Q-TOF	Wastewater	[65]
Pharmaceutical and their degradates	LC-ESI-Q-TOF	Ground water and wastewater	[37]
Beta-blockers	LC-ESI-Q-LIT	Wastewater	[49]
Acidic pesticides and pharmaceuticals	LC-HESI-LTQ-Orbitrap	Wastewater	[32]
Pharmaceutical and hormones	UHPLC-(Qq-LIT)	Wastewater	[128]

LC, Liquid chromatography; UV, Ultra violet detector; DAD, Diode array detector; ESI, Electrospray ionization; QqQ, Triple quadrupole; UHPLC, Ultra high performance liquid chromatography; HILIC, Hydrophilic interaction liquid chromatography; IS, Ion spray; IT, Ion trap; TOF, Time of flight; Q, Single quadrupole; LIT, Linear ion trap; MS, Mass spectrometry; HESI, Heated electrospray ionization.

ESI is the most common ionization source used in LC-MS, as this interface is suitable and very sensitive for most polar/non-volatile compounds and may offer higher sensitivity than APCI. In contrast, APCI is used for mid-polar or non-polar compounds with a certain degree of volatility. APPI is employed for neutral and non-polar compounds. APPI was introduced as an alternative for the analytes that are poorly or not ionized by ESI and APCI [129]. Some studies [122, 130] have reported that, with APCI, some compounds experience better ionization than more commonly used ESI because the ionization mechanisms are different and can affect efficiency in terms of forming the desired ions in the presence of co-eluting compounds. There are some studies available in which the authors compare the effect of ESI and APCI interfaces on the selected analytes response in environmental water [122, 131]. For example, Tan *et al.* [122] evaluated APCI and ESI sources for PPCP analytes and observed better ionization in APCI with a higher response for non-polar compounds and natural and synthetic hormones than the ESI interface. In the end, the authors selected the APCI interface and developed the method for selected PPCPs in river and sewage water using LC-APCI-MS/MS.

The main drawback of the aforementioned interfaces is that they are susceptible to the matrix effect (ME). This occurs when the analytes and other compounds in the sample enter the ionization source simultaneously, and the ionization efficiency of the analyte can be influenced by decreasing or increasing the signal. Wick *et al.* [131] developed a multi-residue method for a group of EOCs in environmental waters using LC-MS/MS and this study placed special emphasis on the ME encountered in the different sample matrices using ESI and APCI. The results showed that higher ion suppression was observed with the

ESI interface, with less absolute recoveries for the selected analytes compared to the APCI. Nevertheless, in the end, the author decided to use ESI, compensating for the ME using the isotope-labelled surrogate standard. There are some papers in which three different API interfaces have been evaluated on the basis of MDLs and recoveries from different aqueous matrices [129, 132].

In order to eliminate or minimize the ME, several strategies can be used: selective analyte extraction procedures or an effective sample clean-up step, although they may involve longer analysis time. Another effective approach used to compensate for the ME is the calibration method, using either a standard addition, internal standard or matrix-matched curve. To date, several studies have reports different calibration approaches for compensating for the ME [62, 80, 122, 133]. The addition of an internal standard with structurally similar isotopically labelled compounds is relatively simple and less time consuming than other approaches but these are usually expensive or, in some cases, not commercially available. For example, Gan *et al.* [80] developed a method for the determination of SWs in environmental water samples. In river and sea water, they recorded ion suppression between 70% and 86% for different analytes, whereas, in influent and effluent water, the ion suppression ranged from 48% to 62% and 74% to 87%, respectively, and this ME was compensated for using an analogue deuterated internal standard to achieve accurate quantification.

In addition, dilution of the sample is also an option for reducing the ME as the interferences are diluted. However, the analytes are also diluted and so this can affect the sensitivity of the analyte. Another approach for compensating for the ME is the use of the matrix-matched

calibration curve [14, 72], in which the calibration curve is carried out on a similar sample, such as river water or wastewater, not containing the analytes. The main limitations of this approach are that it is matrix dependent and, for each type of matrix, individual calibration curves must be plotted and it may be difficult to find a sample that is free of the analytes of interest. When the concentration found in the sample is low, the response obtained from the blank extract can be subtracted from the spiked sample to construct the matrix-matched calibration curve. However, if the concentration is high, this approach is not suitable.

With respect to the analyzer, over the past decade, single Q, IT, Orbitrap and TOF analyzers have been used to determine EOCs in aqueous samples [14, 45, 92] by LC. There are some papers [134, 135] available in which LC coupled with the single Q analyzer was used for the determination of analytes in environmental samples. However, when complex samples are investigated, insufficient selectivity often compromised the unequivocal identification of the selected analytes. Moreover, the IT mass analyzer allows the instrument to be operated either as an ion trap MS or MS^n, or perform novel scan modes not available on other instruments. In addition, lower limits of quantification are obtained in most cases when the IT analyzer is used for tandem MS. Some studies have reported the application of an IT analyser for the determination of pharmaceutical and estrogenic contaminants in environmental water [125, 128]. Another analyzer used in the determination of EOCs after LC is TOF. The TOF analyzer can achieve 10,000 times higher resolution power than the single Q and IT analyzers. It is operated in full scan mode and forms the spectra, the fragmentation of which enables non-target analytes to be identified. However, one limitation is the lack of sensitivity. A number of studies report the

application of the TOF analyzer for the accurate mass identification and confirmation of EOCs in environmental samples [33, 37].

Of the analyser mentioned above, the Orbitrap analyzer deserves special attention because it is the latest development and another example of high resolution mass spectrometry (HRMS). The most important features of the Orbitrap analyzer are the high resolution power, up to 240,000; high mass accuracy in low ppm range; a mass to charge range up to 6000; and a dynamic range higher than three orders of magnitude. The Orbitrap analyzer operates in full scan mode under high resolution accurate mass conditions and achieves high mass accuracy and selectivity. There are several papers that report the use of an Orbitrap analyzer for the determination of EOCs in environmental samples [14, 127, 136].

However, despite the high resolution of the previously described analyzers for determining low concentration of EOCs, in recent years the most commonly used analyzer is the triple quadrupole (QqQ) because of the higher sensitivity achieved [41, 45, 122, 124, 131] when working in multiple reaction monitoring (MRM) or selective reaction monitoring (SRM) mode. Two or three transitions are selected for each analyte, the most intense of which is used for quantification purpose, while the others are used to confirm the presence of the target analyte in the sample. However, in some cases only one transition is observed because of the structure of the analyte and this can affect the identification of analytes. To overcome this problem, hybrid mass spectrometry or high resolution mass spectrometry instruments have been introduced to provide enough analytical information for accurate identification and improved selectivity.

There are several types of hybrid approaches available, including the quadrupole TOF (Q-TOF), quadrupole linear ion trap (Q-LIT), linear ion trap-Orbitrap (LTQ-Orbitrap) and quadrupole Orbitrap (Q-Orbitrap). When these hybrid HRMS instruments are coupled to LC, selectivity improves and false negatives are reduced. Table 4 summarizes some examples of the hybrid mass spectrometry used for the determination of EOCs in enviromental waters. LC-Q-TOF has rapidly become an important analytical tool and several applications have been reported for the identification of EOCs and their degradation products in environmental samples [65, 137]. For example, González-Mariño *et al.* [65] used LC-Q-TOF for the evaluation of the occurrence and biodegradability of parabens and their chlorination by-products in raw and treated wastewater. However, the main advantage of Q-TOF is the availability of full-spectrum acquisition mode throughout each chromatogram and the accurate mass measurements that provide qualitative information that can be used to ensure the identification of analytes present in the samples. However, the main drawback of Q-TOF is that the sensitivity of the method is lower than QqQ working in MRM mode.

Another hybrid instrument is a quadrupole with a linear ion trap (Q-LIT) which has been applied for the determination of pharmaceuticals in environmental waters [49, 128]. This instrument allows powerful scan combinations that enable rapid identification and confirmation of analytes. For example, Huerta-Fontela *et al.* [128] developed a fast multi-residue method based on UHPLC with Q-LIT for the determination of 49 pharmaceuticals and 6 metabolites from different therapeutic classes in water resources. The benefits of UHPLC combined with Q-LIT acquisition mode for trace determination of pharmaceuticals in the environmental field improve resolution and sensitivity, while reducing the ME.

Of the hybrid MS analysers discussed, another combination is LTQ and Orbitrap. This combination of hybrid instrument provides the advantages of high resolution, mass accuracy, speed and sensitivity. For instance, Bade *et al.* [33] developed a screening method for monitoring pharmaceuticals and illicit drugs in environmental water samples. In this study, the authors used two HRMS instruments, a Q-TOF and LTQ-Orbitrap, from two different laboratories for identification and quantification. They observed that the LTQ-Orbitrap technique was able to identify more compounds without having to search manually for fragment ions. Due to being introduced more recently, this instrument is not used as widely as the aforementioned mass analysers and, therefore, there are fewer studies available for both quantification and confirmation purposes for illicit drugs and metabolites [138], and acidic pesticides and pharmaceuticals [32] in wastewater samples.

From all the above information, it can be concluded that LC coupled with all the aforementioned hybrid mass spectrometry systems are powerful combinations with excellent capabilities for the simultaneous identification, confirmation and quantification of EOCs in environmental samples. These techniques show great sensitivity, similar to that reported in QqQ techniques. However, QqQ under MRM mode is still the instrumental technique of choice, due to the outstanding performance in terms of sensitivity and selectivity when quantification analysis is required. To date, several review articles have summarized its application in environmental water analysis [118, 139].

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EVALUATION OF NOVEL SORPTIVE EXTRACTION TECHNIQUES
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1.3. Extraction techniques

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One of the most important steps in analytical chemistry is sample preparation. This step is of great importance when dealing with trace and ultra-trace levels of target analytes in complex samples. Generally, the sample is not suitable for direct injection into the analytical instrument for chemical analysis. The reason for this incompatibility is based on three main factors: i) the sample compounds may interfere with the determination of target analytes; ii) the concentration of the targeted analytes in the sample may be too low to be detected by the instrument; iii) the sample matrix may not be compatible with the analytical instrument [140, 141]. Due to these reasons, sample preparation plays an important role in the whole analytical procedure since it enables the clean-up of complex matrices, as well as the enrichment of the analytes of interest, which results in the increased sensitivity of the method.

As mentioned above, trace analysis of the EOCs in environmental samples is always challenging due to the complexity and diversity of the sample matrices. The choice of the sample extraction technique depends on the physical state of the sample (solid, liquid or gas) and also on the chemical properties of the analytes (e.g. polarity). To extract organic contaminants from the different types of sample, a variety of extraction techniques have been used. Over the past three decades, in the case of liquid samples, the traditional liquid-liquid extraction (LLE) technique has played a major role in sample clean-up and concentration of the sample. However, the disadvantages of this technique include the use of large volumes of organic solvents, a low degree of automation, emulsion formation and, in particular, the laborious and time-consuming steps involved. The traditional LLE technique has mainly been replaced by SPE [34] and, more recently, also by different sorptive-based extraction techniques, such as SPME [57] and SBSE [4].

SPE is based on a similar principle to LC. SPE is a sorptive-based extraction technique in which a liquid sample flows through the solid-phase sorbent and the compounds are sorbed onto the surface of the sorbent. Then, a small volume of organic solvent elutes the retained analytes. SPE has a number of the advantages over LLE, including complete extraction of the analytes, more efficient separation of interferences from the analytes, the ability to process a small amount of sample, easier automation and, above all, the availability of different sorbents [142]. Moreover, a large variety of the commercially available sorbents and formats makes this technique suitable for the extraction of many compounds with different polarities and from matrices with different physicochemical properties. LLE and SPE are exhaustive traditional sample preparation techniques based on batch equilibrium and flow-through equilibrium, respectively.

Some of the main trends in new extraction techniques involve miniaturization, automation, high throughput performance, on-line coupling with analytical instruments and low-cost operation with an extremely low level of solvent consumption [143]. In addition, inspired by the “green trend”, over the last two decades, a number of microextraction techniques have continuously been developed. The microextraction techniques are divided into two types: liquid-phase and solid-phased. Fig. 2 shows a classification of the microextraction techniques and the different formats that have been developed for analytical applications, based on the same principle of non-exhaustive equilibrium extraction.

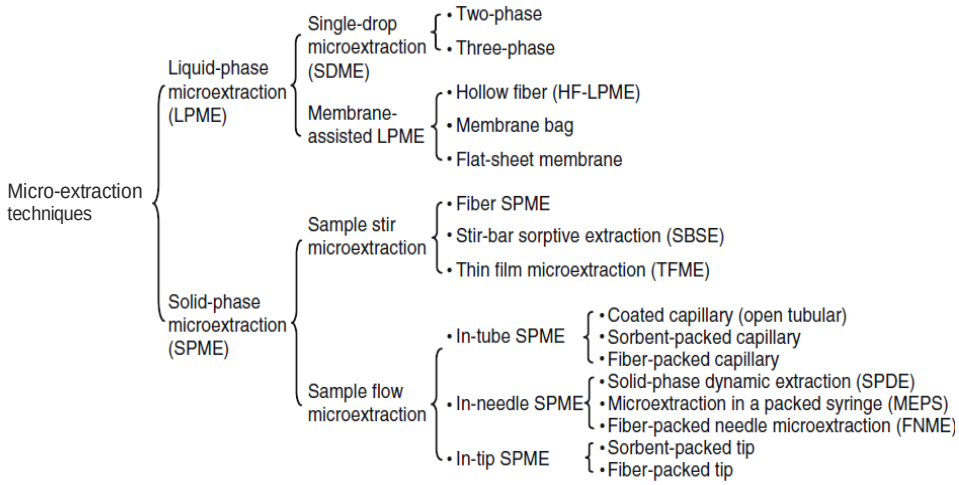

Figure 2. Classification of microextraction techniques [143].

As seen in Fig. 2, liquid-phase microextraction techniques are divided into two formats: single drop micro-extraction (SDME) and membrane-assisted extraction techniques using hollow fibre (HF), membrane bag and flat sheet membrane. SDME is divided into two formats: direct immersion (DI) and headspace (HS) extraction. In most cases, SDME involves two-phase extraction, but three-phase extraction is also possible. Solid-phase microextraction techniques are also divided into two formats: sample stir microextraction and sample flow microextraction. In sample stir microextraction, SPME is the most dominant format and classified into static and flow-through formats (Fig. 2). The static procedures are carried out by stirring the sample with sorbent material coated in fibre SPME, thin film micro extraction and SBSE. As stated earlier, fibre SPME is the most popular format in all techniques in which the sorbent may be either DI into the sample (DI-SPME) or exposed to HS in a closed container (HS-SPME). In the sample

flow microextraction technique, in-needle SPME and in-tip SPME have been developed as an alternative to the in-tube SPME (Fig. 2).

The following sections mainly focus on the most popular sorptive extraction techniques, such as SPE, SPME and SBSE, although novel sorptive extraction techniques that have recently emerged are also discussed.

1.3.1. Solid-phase extraction

In the 1970's SPE was first used for the extraction of analytes with different chemical properties from liquid samples. Initially, solid particles, such as activated carbon and porous polymeric resin, were used as sorbents for the extraction of traces of organic contaminants in water samples [144].

The principle of SPE involves partitioning between a liquid sample or solvent with analytes and a solid sorbent phase. This experimental procedure of sorptive-based extraction technique firstly involves conditioning the sorbent with a suitable solvent, before the removal of the activation solvent by passing a liquid similar in composition to the sample matrix, followed by passing the sample through the solid extracting phase to extract the analyte from the liquid sample. The matrix interference can be removed from the sorbent using a washing solvent. Lastly, the analytes of interest are eluted using a minimal amount of organic solvent. Fig. 3 depicts the schematic protocol of SPE techniques mentioned above.

Various SPE formats have been designed over the years. Nowadays, sorptive materials are commercially available in different

formats, such as free disks (47 mm diameter or the standard filtration size), 96 well plates, SPE pipette tips, SPE cartridges and in dispersive SPE (d-SPE). The most commonly used format in SPE is cartridges, in which a certain amount of extracting material is packed into a polypropylene barrel between two frits. Depending on the type and volume of the sample to be percolated, cartridges are commercially available on the market with different weights, ranging from 10 mg to 10 g. For example, 60 mg [122] and 500 mg [16] SPE cartridges have been used for the extraction of PPCPs [122] and SWs [16] in environmental water samples.

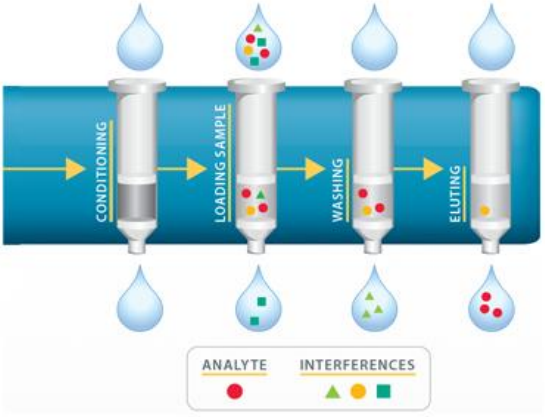

Figure 3. Protocol of SPE technique.

The SPE process can be performed in either on-line or off-line mode. The experimental described above (Fig. 3) is known as off-line SPE. In on-line SPE, the extraction cartridge or pre-column is coupled to the separation technique and is directly connected to the high-pressure pump of the mobile phase, which also acts as the elution solvent [50, 62].

However, the off-line SPE mode is preferred to the on-line mode, mainly because there is no need for specific equipment or conditions.

Different types of commercial sorbents are available for SPE with good extraction efficiencies for retaining a large number of organic contaminants. The selection of the SPE sorbent for extraction purposes depends on understanding the mechanism of interaction between the sorbent and the analyte of interest. The most common retention mechanisms in SPE are based on Van der Waals interactions, hydrogen bonding, dipole-dipole interactions and ion interactions [145]. In turn, this understanding depends on knowledge of the properties of both the solute and the sorbent. Therefore, the development of different sorbents for SPE has become an extensively important objective. Basically, SPE sorbents are classified into two classes: inorganic and organic sorbents. Examples of inorganic supports include magnesium silicate (Florisil), alumina, silica and chemically bonded silica sorbents (similar to packing for LC columns). Magnesium silicate (Florisil) is particularly suitable for cleaning up extracts from fatty foods because it retains some lipids preferentially [85]. The modification of silica particles enables the development of many organic sorbents used for normal phase, reversed-phase and ion-exchange SPE, such as octadecyle (C_{18}), octyl (C_8), ethyl (C_2), phenyl (Ph), cyanopropyl (CN), aminopropyl (NH_2), etc. However, in SPE applications, silica-based sorbents have certain limitations, such as a narrow pH stability range, low recovery for polar compounds and a residual silanol group that can have a negative effect on analyte retention.

Other options for SPE are existing forms of carbon-based sorbents, such as graphite carbon blacks (GCBs) and porous graphite carbons (PGCs). GCBs are commercially available as Carbopack, Carbograph-4

and Envi-carb, and they have been applied for extracting phenolic compounds, pesticides and their degradation products. PGCs in which graphite is immobilized on silica substrates have higher stability than GCBs and greater extraction efficiency than C_{18} sorbents because of the hydrophobic and electrostatic interactions. However, the limitations of these sorbents are that some compounds display irreversible retention [146].

Over the last few decades, there has been growing interest in the development of polymeric sorbents, as they overcome shortcomings of silica-based and carbon-based sorbents. These polymeric sorbents are generally copolymers of polystyrene (PS) and divinylbenzene (DVB), with a macroporous or hypercrosslinked structure containing a relatively high number of active aromatic sites, which allow $\pi-\pi$ interactions. To provide enhanced polarity in the polymer material, polar groups are introduced into the polymeric structure. To do so, two approaches have been assayed: chemical modification of the hydrophobic polymer with polar groups and copolymerization of monomers containing suitable polar moieties. Nowadays, there are several polar sorbents commercially available, but the most well-known and widely used sorbent is Oasis HLB, manufactured by Waters. This material is a macroporous resin based on a poly(N-vinylpyrrolidone-DVB) (PVP-DVB) copolymer with a specific surface area of ~ 800 $m^2\ g^{-1}$. This sorbent has been the optimal choice for the extraction and determination of EOCs with different polarities in environmental water samples and other matrices [14, 37, 45].

There are different types of hydrophilic polymeric sorbents also available commercially, such as Strata X (800 $m^2\ g^{-1}$) from Phenomenex and, Bond Elute Plexa (700 $m^2\ g^{-1}$) from Agilent Technologies, while

other polymers include Isolute ENV+ (1,000 m^2 g^{-1}) from International Sorbent Technology, Super-Select HLB (400 m^2 g^{-1}) from Supelco and Spe-ed Advanta (no data) from Applied Separation. All the aforementioned sorbents are chemically modified sorbents with polar functionality. They have acceptable capability for extracting low to moderate polar organic contaminants including PPCPs and SWs from complex matrices [50, 52, 82, 109]. For instance, Kokotou *et al.* [82] tested two SPE sorbents (Strata X and Isolute® 101) for extracting eight SWs from WWTPs samples and higher recovery values (ranging from 40% to 97%) were provided by Strata X.

In addition, some research groups have focused on the preparation of in-house hydrophilic polymers as SPE sorbents and compared their performance with commercially available sorbents. There are some reviews [147] and books [144] available on in-house hydrophilic sorbent synthesis. They reported that the in-house sorbent significantly outperformed the commercial sorbents (Oasis HLB). For example, Bratkowska *et al.* [148] compared three different in-house synthesized hydrophilic hypercrosslinked polymeric sorbents (HXLPP Polar A, HXLPP Polar B and HXLPP Polar C, which are based on 2-hydroxyethyl methacrylate-paravinylbenzylchloride-DVB copolymer precursor) and the commercially available sorbents LiChrolut EN, Oasis HLB and Isolute ENV+ for the extraction of polar pesticides. Of these, the HXLPP-polar B sorbent showed the highest recovery values (86% to 93%) for all analytes compared to other sorbents, as it is an optimal balance of the specific surface area (850 m^2 g^{-1}) and polar moiety content.

Molecularly imprinted polymers (MIPs) are another type of sorbent designed to establish selective interactions with the target analytes or

class selectivity for family of analytes. As such it has gained the great popularity in the sample preparation of environmental matrices [142]. At present, MIPs are commercially available for a large range of compounds, with brands such as Affinilute MIPs from Biotage, among others. In addition, a number of research groups have prepared them in-house. For instance, Beltran *et al.* [149] synthesized in-house MIPs for the extraction of carbamazepine (CBZ) and two pharmaceuticals from urine and wastewater samples. In this study, two more pharmaceuticals were selected to evaluate the selectivity of the MIPs. The authors reported 85% recovery for CBZ, while the recoveries for the two pharmaceuticals were below 5% in environmental water samples.

Other types of polymeric sorbent developed to enhance both selectivity and extraction capacity using a single material is mixed-mode polymeric ion-exchange or dual-phase sorbent. Mixed-mode polymeric sorbents have been used for the extraction of complex matrices, in which the compounds can be retained by ionic and reversed-phase interactions. These sorbents are classified as cationic or anionic and can be also categorized as strong or weak ion exchangers depending on the ionic group attached to the resin (the most common are sulphonic acid for strong-cation exchangers (SCX), carboxylic acid for weak-cation exchangers (WCX), quaternary amine for strong-anion exchangers (SAX) and secondary amine for weak-anion exchangers (WAX)). Due to their polymeric structure and the acidic and basic functional groups, the range of analytes that can be extracted from complex samples is extended. As well as the material, the pH in the different SPE steps should be controlled. During the sample loading step, selective retention of the analyte is achieved by controlling the sample pH. In the washing step, the proper washing solvent (usually pure organic solvent) is used to disrupt

reversed-phase interactions and remove interferences. In the end, the targeted analytes are eluted from the sorbent using acidic or basic additives in the organic solvents to break down ion-exchange interactions.

The first mixed-mode polymeric sorbents were commercialized by Waters under the product names Oasis MCX (SCX), Oasis WCX (WCX), Oasis MAX (SAX) and Oasis WAX (WAX). All these mixed-mode sorbents are based on an Oasis HLB skeleton based on PVP-DVB, then chemically modified with sulphonic groups for SCX, carboxylic acid for WCX, quaternary amine for SAX and piperazine for WAX. Apart from Waters Corporation, other companies have commercialized similar mixed-mode polymeric sorbents, such as Strata-X sorbents from Phenomenex, Bond Elute Plexa sorbents from Agilent Technologies and Evolute sorbents from Biotage. There are a number of publications in the literature reporting the use of mixed-mode polymeric sorbents for the extraction of EOCs in environmental samples [80, 109, 133]. For instance, Gan *et al.* [80] developed a method for the extraction of seven commonly used SWs in water samples. In this study, 10 different commercial SPE sorbents were tested for the preconcentration of analytes. The most satisfactory recoveries were obtained with CNW Poly-Sery PWAX, with recoveries ranging between 77% and 99% for the selected SWs when 25 mM acetic acid-sodium acetate buffer at pH 4 was used as a wash buffer, and methanol containing 1 mM TRIS was used as the elution solvent.

In recent years, magnetic particles (MPs) have gained popularity in sample preparation due to their desirable characteristics, such as magnetic properties, mechanical and surface properties, easy surface modification, easy operation and high extraction efficiency [150]. There are a number of magnetic materials, including iron (Fe), cobalt (Co),

nickel (Ni), magnetite (Fe_3O_4) and, maghemite (ɣ-Fe_2O_3), with Fe_3O_4 and ɣ-Fe_2O_3 iron-oxide particles being the most frequently used material in sample preparation. Bare iron oxide can be directly used for the separation and preconcentration of some targeted analytes. However, one drawback of these materials is that the particles can easily aggregate because of dipole-dipole interactions, which restrict the application of MPs. To address this issue, surface modification is a very important step for providing various properties to the magnetic materials, such as larger surface area, high pH stability, high adsorption capacity and flexibility for modification. There are several surface modification materials that have been proposed to improve the property of the capacity of MPs, such as silica shell or carbon, surfactants and, polymers, among others [150].

MPs are mainly used in dispersive SPE (d-SPE) the steps of which include: the addition of MPs to the sample solution and stirring the sample solution with the aid of a magnetic stirrer or shaker. After an appropriate equilibrium extraction time, the magnetic material can easily be separated from the sample by applying an external magnetic field. Lastly, the adsorbed analytes are desorbed from the surface of the MPs using an organic solvent. The use of MPs makes this sample extraction procedure very easy and simple. For this reason, several research groups that have developed different types of MPs and used them in d-SPE mode for several applications [151-154] including the extraction and removal of contaminants such as polycyclic aromatic hydrocarbons, antibiotics, drugs and food additives, among others, but not PPCPs. However, one study reports d-SPE of SWs using MPs, but in wine samples [155].

In sample preparation, silica is a widely used material due to its chemical inertness and thermally stability. Silica-modified MPs are stable

under aqueous conditions, where inter particle interactions are easy to control. The magnetic core is protected by a silica material and also prevents direct contact between the magnetic core and additional agents linked to the silica surface, thus avoiding unwanted interactions. There are numerous reports available on silica-modified MPs [156, 157]. For example, silica-coated MPs with an organic metal framework provided remarkable properties, such as high surface area, thermal stability and a uniform core structure. Huo *et al.* [156] developed the method for the determination of polycyclic aromatic hydrocarbons in environmental water samples. In this case in-situ magnetization of MIL-101 microcrystal and MSPE of PAHs was achieved by simultaneously mixing MIL-101 and silica-coated Fe_3O_4 nanoparticles in the sample solution under sonication. Such an organic metal framework based on MIL-101 in combination with HPLC achieved lower MDLs for selected analytes compared to conventional SPE and required a smaller amount of extracting material for extraction.

Another interesting coating material for MPs is carbon, which has attracted increasing attention in sample preparation, because these coating materials have many advantages over silica, such as higher chemical and thermal stability and biocompatibility, as well as the possibility of surface modification and pore creation [158]. This group includes graphitized carbon black, carbon nanotubes (CNTs) and fullerene extraction phases and they display strong adsorption affinity for a wide variety of organic contaminants, as well as being effective over a wide pH range. There are several reports on applications of carbon-modified MPs for sample preparation [126, 159]. For example, Heidari *et al.* [159] reported a method for the determination of the organophosphorus pesticides (OPP) from environmental water samples

by HPLC-UV, in which carbon-coated Fe_3O_4 MPs were used for the preconcentration of OPP from aqueous samples. The method showed good recovery, good linear range, low MDLs and high enrichment factors.

In addition, CNTs have a large surface area and excellent mechanical, electrical and thermal properties. In view of these properties, CNTs have been used in sample preparation. On the downside, CNTs have some shortcomings including poor solubility and difficulty in collect on from aqueous sample, which can cause great inconvenience in their practical uses. These two shortcomings are handled by modification with functional groups. For instance, Guan *et al.* [126] prepared multi-walled carbon nano tubes (MWCNTs-OH) by sol-gel technology and used them for the extraction of several estrogens (including diethylstilbestrol, estrone and estriol) in surface water samples. Under optimized conditions, they achieved extraction recoveries for diethylstilbestrol, estrone and estriol of 96%, 94%, and 52%, respectively.

In surfactant-based coatings, ionic liquid surfactant can lead to the formation of layer of hemimicelles and admicelles on the silica, titanium dioxide and ferric oxyhydroxides materials. Recently, these sorbents have been used in traditional SPE for the extraction of organic contaminants. The surface of mineral oxides formed by the mixture of both hemimicelles and admicelles are termed mixed hemimicelles. Mixed hemimicelles provides different mechanisms for the retention of analytes because of the different characteristics of its parts, as the outer surface consists of hemimicelles (hydrophobic), whereas the inner one consists of admicelles (ionic). Therefore, the special character of mixed hemimicelles in combination with MPs provides advantages such as a high surface area, high chemical stability and good magnetic separation. For example, Zhao

et al. [160] synthesized surfactant-modified MPs for the extraction of phthalate esters from environmental water. Different parameters were optimized for the extraction conditions and, under optimal conditions, extraction recoveries for the selected analytes ranged from 63% to 103%. The method needed 30 mg of the sorbent material for extraction and achieved good sensitivity.

With respect to functionalized MPs, polymer-coated MPs are another important type that can be prepared by coating through covalent bonding or electrostatic interaction, or by encapsulating the MPs. One such example is magnetite (Fe_3O_4), with synthetic or natural polymers. Usually, the covalent bonding reaction is carried out when polypyrrole or MIPs are used as polymeric coatings, whereas electrostatic interaction is carried out in the case of biopolymer such as chitosan, which is the most widely used sorbent for sample preparation. To date, there are several studies available on the extraction of organic contaminants from different types of environmental samples [155, 161-163]. For example, Zhang *et al.* [163] prepared chitosan-coated Fe_3O_4-C_{18} MPs for the extraction and determination of phthalate ester from environmental waters samples. In this study, only 100 mg of sorbent was used to extract the selected analytes from 500 mL of water sample and the MDLs obtained for the analytes were between 12 and 36 ng L^{-1} with extraction recovery ranged from 60% to 100%.

Similarly to the extensive variety of conventional SPE sorbents, nowadays, MPs are also available or prepared with different types of sorbents, such as MIPs and polymeric hypercrossslinked sorbents. The MPs prepared with MIP sorbents give the advantage of selective extraction of the analytes from environmental water samples [151, 164,

165]. For instance, Lin *et al.* [165] prepared magnetic MIPs particles for the selective extraction and determination of estrogens in water samples. This study reported high selectivity, with sorption capacity ranging from 72% to 95% and MDLs from 2.5 to 5.8 ng L^{-1}.

All in all, the SPE technique has been and will continue to be one of the most widely used extraction techniques, thanks to the availability of different materials and formats.

1.3.2. Solid-phase microextraction

Solid-phase microextraction (SPME) is one of most popular microextraction techniques used in sample preparation. This technique was developed by Pawliszyn in 1990 [166] and it become commercially available in 1993. This technique is an alternative for conventional LLE and SPE techniques. It is based on the principle of equilibrium extraction of target analytes between a polymeric stationary phase coated in fused-silica fibre and the matrix. Fig. 4 presents the details of the SPME device. The main steps of the SPME procedure are extraction of the analyte by the SPME coating from the sample solution and desorption of the extracted analytes from the coating. The most widely used form of sampling consists of exposing a thin polymeric-coated fibre directly to the sample solution direct immersion (DI) or the headspace (HS) above sample solution for a predetermined amount of time. The latter is applicable in the case of volatile and semi-volatile species, while the former extraction mode can be applied regardless of analyte volatility. The desorption of the analytes from the coating can be carried out either thermally by direct insertion of the fibre into the GC injector using an appropriate solvent or by coupling to LC with a specific device. Thermal

desorption (TD) is one of the main advantages in the coupling between SPME and GC, which is one of the main reasons for the broad applicability of this coupling (SPME-GC).

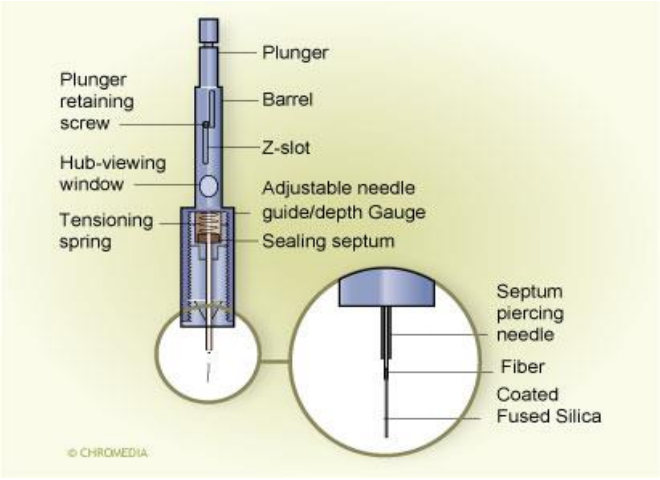

Figure 4. Schematic diagram of a commercial SPME device.

There are several parameters to optimize in the SPME technique, including pH, temperature, ionic strength, agitation speed and sample volume, which affect the equilibrium constant and the equilibration time. Once the fibre is exposed to the sample matrix, the transport of analytes from the matrix to the coating material takes place immediately. The extraction is complete when the analyte concentration has reached distribution equilibrium between the sample matrix and coating material. SPME has routinely been used in combination with GC and GC-MS and successfully applied to a wide variety of compounds, especially for the extraction of volatile and semi-volatile organic compounds from environmental samples [57]. SPME has also been direct coupled with HPLC and HPLC-MS [44] in order to determine weakly volatile or thermally labile compounds not susceptible to GC or GC-MS.

One of the most important variables in SPME is the coating material. There are several commercially available coated SPME fibres on the market, including polydimethylsiloxane (PDMS), polyacrylate (PA), PDMS/divinylbenzene (DVB), carboxen (CAR), and carbowax (CWX), which have all been used for the extraction of PPCPs in environmental water samples [44, 57, 167]. These fibres are available in varying thicknesses and with single coatings or mixtures of copolymers.

One of the limitations of SPME is the determination of polar organic contaminants, but this may be solved with a derivatization step. Derivatization can increase the volatility and reduced the polarity of the same analytes and can therefore improve the extraction recovery, selectivity and detection of the analytes. Three different procedures are currently used: direct derivatization, derivatization on the SPME fiber and derivatization in the GC injection port. Derivatization on the SPME fibre (On-fibre) is often preferred in SPME. For instance, Basaglia *et al*. [167] developed an HS-SPME on-fibre silylation technique for the simultaneous extraction of more polar acidic compounds, such as anti-inflammatories, estrogens, antiseptics and bisphenol A, determined by GC-MS analysis. The optimized operating conditions were an extraction time of 125 min at a temperature of 40^{o}C and a derivatization time of 30.5 min.

In-tube SPME is another format of SPME used in sample preparation, based on the use of an extraction unit that consists of an open tubular fused-silica capillary with an inner surface coating. It is also known as capillary microextraction (CME). This SPME device was developed for coupling with LC or LC-MS. The extraction capillaries have coatings similar to commercially available SPME fibres. The capillary column used for the extraction is placed between the injection loop and

the injection needle of the LC autosampler. In this device, analytes in aqueous matrices are directly extracted and concentrated by the coating in the capillary column through repeated withdrawal and expulsion of the sample solution, before being directly transferred to the GC or LC instrument. The various procedures involved with in-tube SPME, including extraction, concentration, desorption and injection, can be easily automated using a conventional autosampler. This method provides better accuracy, precision and, sensitivity than the off-line manual technique. For instance, Aufartová *et al.* [168] developed an automated in-tube SPME-LC-DAD and fluorescence detector method for the determination of certain estrogens in environmental water samples. Three capillary chromatographic columns (Supel-QTM, CP-Sil 19 CB and CarboxenTM 1006 porous layer open tubular) were evaluated in terms of their extraction recoveries. The authors concluded that the Supel-QTM and CarboxenTM 1006 porous layer open tubular capillary columns are the best candidates for extracting the target analytes. Under the optimal conditions, the obtained recoveries for Supel-QTM and CarboxenTM 1006 porous layer open tubular columns ranged from 80% to 98% and 81% to 100%, respectively, for the selected analytes, which is comparable to the conventional SPE method.

As well as commercially available SPME coatings, nowadays, there are several coating materials developed in-house, such as ionic liquids and MIPs, to exhibit high selectivity for certain groups of compounds and high capacity against the target analytes [169, 170]. For instance, He *et al.* [170] synthesized a MIP material for an SPME device for the extraction and determination of phthalates from aqueous samples by GC-MS. In this study, the authors achieved higher extraction recoveries with the molecular imprinted (MI)-SPME, ranging between 94% and 105% for the

selected analytes, compared to non-imprinted SPME fibre (PDMS) in an extraction time of 30 minute.

1.3.3. Stir bar sorptive extraction

Based on equilibrium extraction, stir bar sorptive extraction (SBSE) was introduced in 1999 by Sandra *et al.* [171], in order to overcome some of the limitations of the extraction techniques that previously existed, particularly in the case of SPME and their low capacity due to the small amount of sorbent. In SBSE, the amount of sorptive phase is 50 to 250 times higher than SPME, which gives greater capacity [4, 172].

The sample preparation procedure for SBSE is the same as that of SPME and the same variables affecting the extraction step must be evaluated as specified in previous section. Fig. 5 shows a schematic diagram of the extraction and desorption of the SBSE technique. Similarly to the SPME technique, SBSE can also work in two different modes: DI-SBSE or HS-SBSE. With respect to the desorption, this can also be TD or LD.

There are some studies reporting the determination of EOCs in the environment using the DI-mode and desorption by TD and LD. For instance, Ramírez *et al.* [96] developed a combination of the SBSE/TD-GC-MS method for simultaneously determining PCPs with a wide range of polarities in different water samples. In this case, the extraction and derivatization steps were carried out at the same time. Different parameters affecting both SBSE extraction and TD were optimized. In contrast, Tanwar *et al.* [4] developed an SBSE/LD/LC-MS/MS method for the determination of NSAIDs in water samples. In this study, the authors

compared the EG-silicone-coated and PDMS-coated SBSE bar for the extraction of the NSAIDs analytes. The best coating was EG-silicone which provided the higher recovery for selected analytes.

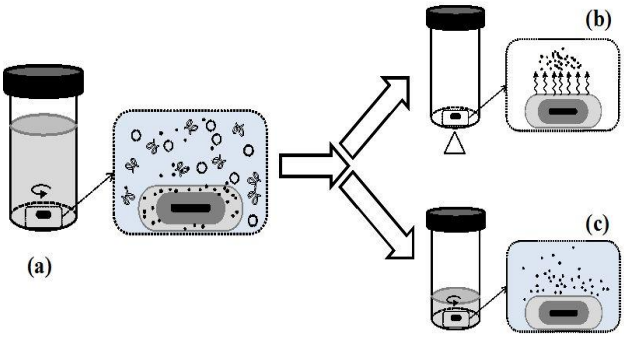

Figure 5. Steps follow in SBSE a) Extraction of analyte b) TD for GC c) LD for LC.

Recently, several reviews have summarized the application of SBSE in environmental, food and biological analysis [173, 174]. The most widely used coating for SBSE is non-polar PDMS. There are several publications available in which the PDMS coating was used for the extraction of EOCs from environmental water samples [13, 72, 96]. However, the main limitation for this coating is lower retention of polar analytes. To overcome this limitation, Gerstel manufactured and marketed new twisters coated with polyethylene glycol (PEG)-modified silicone (EG-Silicone Twister) and polyacrylate (PA) with a portion of PEG Acrylate Twister or PA Twister. For the first time, our research group, used the novel commercially available polar coatings PA and EG-Silicone and compared them to the PDMS coating for the extraction of a wide range of PPCPs from wastewater samples, followed by LC-MS/MS [72]. EG-Silicone SBSE demonstrated good performance in terms of recovery of the less polar compounds (24% to 80%). There are other studies in which these commercial EG-silicone and PA coatings were used for the

extraction of EOCs, such as benzothiazoles UV filters [175] and NSAIDs [4].

Despite the commercial availability of polar coating materials, the scientific research has also focused on the preparation of novel SBSE coatings which enhance the retention of polar compounds from complex matrices. In order to achieve a polar coating, different technologies can be used for synthesizing in-house coatings to provide thermal and mechanical stability for SBSE.

Sol-gel technology is suitable for the preparation of a thick film and the phase obtained has high thermal and mechanical stability and a long life-time, due to the strong chemical bonding between coating and the surface of the glass rod. For example, Ibrahim *et al*. [176] synthesized the sol-gel derived hybrid coating by combining cyanopropyltriethoxysilane (CNPrTEOS) and PDMS for SBSE to extract NSAIDs from water samples. The hybrid coating of PDMS-CNPrTEOS is capable of extracting the less polar compound ketoprofen and the polar compound diclofenac.

Another approach is a monolithic material used as the coating for SBSE, which offers various advantages, such as large pore structure, good permeability, favourable mass transfer characteristics and low cost. In addition, there are a several precursor monomers which can be used to prepare the monolithic coating [177]. For the extraction of polar compounds, several monolithic coatings have been prepared and used for the extraction of EOCs from environmental sample [178-180]. For instance, Gilart *et al.* [178] synthesized and characterized a new in-house polar monolithic coating for the extraction of PPCPs in water samples. The monovinyl monomers, 2-hydroxyethyl methacrylates (HEMA), poly

ethylene glycol monoethylacrylate (PEGMA), were copolymerized with DVB and pentraerythritol triacrylate (PETRA). The newly developed coatings showed a wide range of polarities for the emerging pollutants and the results showed that both poly(HEMA-co-DVB) and poly(PEGMA-co-PETRA) could be used to extract polar and non-polar compounds effectively by SBSE [178]. The morphological and extraction efficiencies of poly(PEGMA-co-PETRA) seem to be satisfactory for application as a novel monolithic coating in SBSE. The above example shows how the polarity of the SBSE coating is enhanced for the retention of polar PPCPs.

In addition, more selective coatings for SBSE based on MIPs have been synthesized and evaluated. There are several studies reporting MIPs synthesized by sol-gel for application SBSE compared to monolithic coatings. For instance, Sheng *et al*. [181] synthesized a dummy MIPs coating for SBSE similar to bisphenol A. When used to extract bisphenol A from aqueous solution, the dummy MIP SBSE method showed high selectivity and high recoveries compared to commercial PDMS.

1.3.4. Fabric phase sorptive extraction

Fabric phase sorptive extraction (FPSE) is a new sorbent-based sorptive extraction technique introduced in 2014 by Kabir and Furton [182]. Similar to the above mentioned sorptive extraction techniques (SPME and SBSE), the FPSE technique is also based on the principle of equilibrium extraction. Fig. 6 shows FPSE material and sample preparation step.

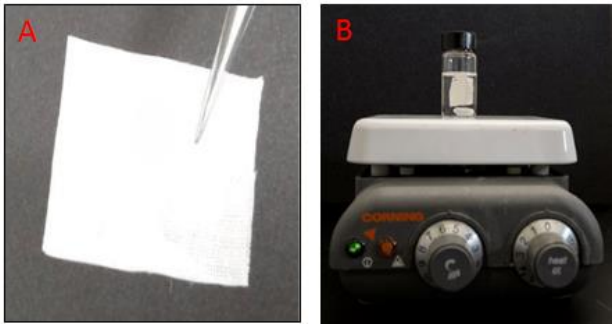

Figure 6. (A) FPSE material; (B) sample preparation.

FPSE consists of a 25 x 20 mm fabric pieces coated with different sorbent chemistries using sol-gel technology. The substrates used in FPSE, such as cellulose, polyester and fibreglass fabric, are not inert like other sorbent-based techniques and, in combination with sol-gel technology, they give more advantages, including a higher amount of sorbent coating, porosity, solvent and chemical stability. The advanced material uses the sol-gel process to create a hybrid organic and inorganic polymeric network to anchor the polymeric network onto the surface of flexible and permeable substrate (cellulose/polyester/fibreglass) materials [183].

FPSE incorporates the advantages of SPME (equilibrium based extraction), exploits the benefits of sol-gel coating technology for microextraction sorbents, enhances the ability to fine tune selectivity parameters using hydrophobic (polyester) or hydrophilic (cellulose) fabric substrate, and augments the primary contact surface area (PCSA) (1000 mm^2) for fast analyte sorbent interaction. Moreover, during desorption, the fabric can be turned in a very small piece hence, small volume of elution solvent is required. FPSE has overcome the two main limitations of the other sorptive extraction techniques (SPME and SBSE), namely the low

sorbent coating capacity and the availability of the different materials [183]. In comparison to PCSA of FPSE with the typical SPME and SBSE, it is obvious that the high surface area of the FPSE coating with high sorbent loading is, an average, 400 and 10 times higher than in the SPME and SBSE, respectively [17, 183].

Similarly to other equilibrium techniques, the FPSE procedure starts with the conditioning and equilibration of the FPSE media with solvent and solution, followed by FPSE media directly being introduced into the glass vial containing the sample for analyte extraction. Once equilibrium is reached, the FPSE media is removed from the glass vial and the retained analytes are back-extracted from the FPSE using a small volume of organic solvent. In the same way as SPME and SBSE, the different variables affecting extraction and liquid desorption have to be evaluated for FPSE.

Sol-gel technology was first introduced for creating surface bonded sorbent coating and monolithic beds for SPME by Malik and co-workers [184]. Since then, this technology has been used in the preparation of different types of materials in different sorptive techniques. Thanks to sol-gel technology and in combination with FPSE, several materials candidates have been prepared and the selectivity and polarity of FPSE depends on the coating material used for the sol-gel polymer coating, which may be hydrophilic or hydrophobic. Table 5 shows the characteristics of the FPSE substrates used in the FPSE method developed.

Table 5. Characteristics of the FPSE media used in the developed methods [183].

Substrate	Sol-gel coating	Sorbent Loading (mg/cm^2)	Polarity
Cellulose/Polyester	PDMDPS[a]	1.93	Non-polar
Cellulose	C_{18}	2.4	Non-polar
Cellulose	PDMS	2.3	Non-polar
Cellulose	PTHF[a]	3.96	Medium-polar
Cellulose	PEO-PPO-PEO	5.68	Polar
Cellulose	Graphene	7.57	Polar
Cellulose	PEG-PPG-PEG[a]	5.68	Polar
Cellulose	PEG	8.64	Highly Polar
Cellulose	CW 20M[a]	8.63	Highly Polar

PDMDPS, poly(dimethyldiphenylsiloxane); PDMS, poly(dimethylsiloxane); PTHF, poly(tetrahydrofuran); PEO-PPO-PEO, poly (ethylene oxide)-block(propylene oxide)-block(ethylene oxide); PEG-PPG-PEG, poly(ethyleneglycol)–block-poly(propylene glycol)–block-poly(ethyleneglycol); PEG, poly(ethyleneglycol); CW-20M, Carbowax 20M; [a] see the structure in Appendix II.

Since 2014, novel FPSE technique have been introduced in diverse fields of analytical chemistry. Table 6 summarized the application of the FPSE media in sample preparation with different modes.

Table 6. Summary of the application of the FPSE media in sample preparation with different modes.

Analytes	Substrate	Sol-gel coating	Matrix	Analytical technique	Ref.
Estrogens	Cellulose	PTHF	Urine, environmental waters	FPSE/LC-FLD	[17]
Antibiotics, amphenicols	Cellulose	PEG	Milk	FPSE/LC-DAD	[114]
NSAIDs	Cellulose	PEG	River and wastewater	FPSE/GC-MS	[35]
Herbicides	Cellulose	PEG	River water	StirFPSE/UPLC-DAD	[185]
Alkyl phenols	Cellulose	PTHF	Environmental waters, soil, sludge	FPSE/LC-UV	[113]
UV Stabilizers	Polyester	PDMDPS	Sewage	FPSE/UHPLC-MS/MS	[3]
Drugs, benzodiazepines	Cellulose	PEG	Blood serum	FPSE/LC-DAD	[116]
Residual UV Stabilizers	Polyester	PDMDPS	Sea water	FPSE/UHPLC-MS/MS	[18]

Table 6. (Cont.)

Analytes	Substrate	Sol-gel coating	Matrix	Analytical technique	Ref.
Flame retardants	Cellulose	PTHF	Wastewater, reservoir water	Magnetic stir-FPSE/LC-DAD	[19]
Flame retardants	Cellulose	PTHF	Wastewater, reservoir water	Stir-bar-FPSE/LC-DAD	[19]
Chemical non-volatile migrants	Cellulose	PTHF	Food stimulants	FPSE/UHPLC-MS	[186]
Volatile compounds	Cellulose	CW-20M	Orange juice	FPSE/UHPLC-QTOF-MS/MS	[187]
Toxic metals	Polyester	PDMDPS	River, costal, ditch water	FDSE/FI-FAAS	[188]
Antibiotics, sulfonamides	Cellulose	PEG	Milk	FPSE/LC-UV	[189]
EDCs	Cellulose	PTHF	Wastewater and urine	FPSE/UHPLC-MS/MS	[190]
Antibiotics, penicillin	Cellulose	PEG	Milk	FPSE/LC-DAD	[191]

FPSE, Fabric phase sorptive extraction; CW-20M, Sol-gel Carbowax 20M; LC, Liquid chromatography; FLD, Fluorescence light detector; DAD, Diode array detector; UV, Ultra violet detector; FDSE-FI-FAAS, fabric disk sorptive extraction- flow injection- flame atomic. absorption spectrometry

To date, FPSE has been mainly applied for the extraction of drugs and PPCPs, before being determined by LC or UHPLC and different types of detector, such as UV, FLD, DAD and MS/MS. For example, in the first application of FPSE reported by Kumar *et al.* [17] a method was developed for the determination of the estrogens (BPA, E2, and EE2) in urine and environmental water samples. The extraction was carried out in batch with a medium polar sol-gel PTHF material and 10 mL of the sample volume was taken for the extraction, while a volume of 500 µL of methanol was used for the desorption of analytes from the fabric. The FPSE/LC-FD method achieved lower MDLs (ranging from 20 to 42 ng L^{-1}) for the selected analytes, compared to previously reported SPE, SPME and SBSE methods.

FPSE is not only applicable to water samples. In the literature, there are some studies available reporting FPSE directly used on food and biological fluid samples, such as milk, juice and blood, to avoid the initial sample pretreatment steps, as well as eliminating potential errors during precipitation, filtration and centrifugation [114]. For example, Samanidou *et al.* [114] developed a simple and fast method for the simultaneous determination of the residue of three amphenicols in raw milk using sol-gel PEG-coated FPSE medium in combination with LC-DAD. In this study, the FPSE effectively eliminated the protein precipitation, a potentially error-prone step during sample preparation. The FPSE material extraction recoveries for the selected antibiotic residues were found to be 44% for thiamphenicol, 66% for florfenicol and 81% for chloramphenicol after an extraction time of 30 min. In another example by the same authors [116], the FPSE material was used for direct immersion in a blood serum sample for the extraction of benzodiazepines, before determination using LC-DAD. In this case, they evaluated three different polarities of FPSE

materials, including sol-gel PDMDPS, sol-gel PTHF and sol-gel PEG. Sol-gel PEG showed the best performance in terms of extraction recovery compared to the other two materials. Under optimal conditions, the absolute recovery for the benzodiazepines examined were found to be 27% for bromazepam, 63% for lorazepam, 42% for diazepam and 39% for alprazolam. The developed method did not require any prior sample pretreatment or clean-up step.

To date, there are only two studies available that combine FPSE with GC [35, 187]. For instance, Racamonde *et al.* [35] developed a method for the determination of four NSAIDs contaminants in environmental water samples by coupling FPSE with GC-MS. In this study, three different sol-gel coatings were evaluated: PDMDPS on a polyester substrate, PTHF and PEG on cellulose substrate. Of these, PEG showed the best performance for the selected NSAIDs analytes.

Some studies have reported different approaches to FPSE in an attempt to increase the contact surface area of the microextraction devices. FPSE is a typical diffusion extraction process and it can be improved by stirring of the whole extraction system simultaneously, including the fabric sorbent medium, as well as the sample. For the first time, Roldán-Pijuan *et al.* [185] proposed a new approach to FPSE in stir-FPSE mode and demonstrated the determination of seven triazine herbicides in environmental water samples. The proposed stir-FPSE technique integrates the FPSE media with a magnetic stirring mechanism. Fig. 7 (i) shows the mode of the extraction device (a) and extraction procedure (b). The optimal conditions for the method were 100 mL of sample stir for 60 min and LD with 1 mL of methanol for 5 min of stirring. Under these conditions, the recoveries were in the range of 22% to 70%.

The method enhanced the extraction efficiencies, as well as reducing the total extraction time due to the design of the device, which provided a high contact surface area for interaction between the analytes and sorbent.

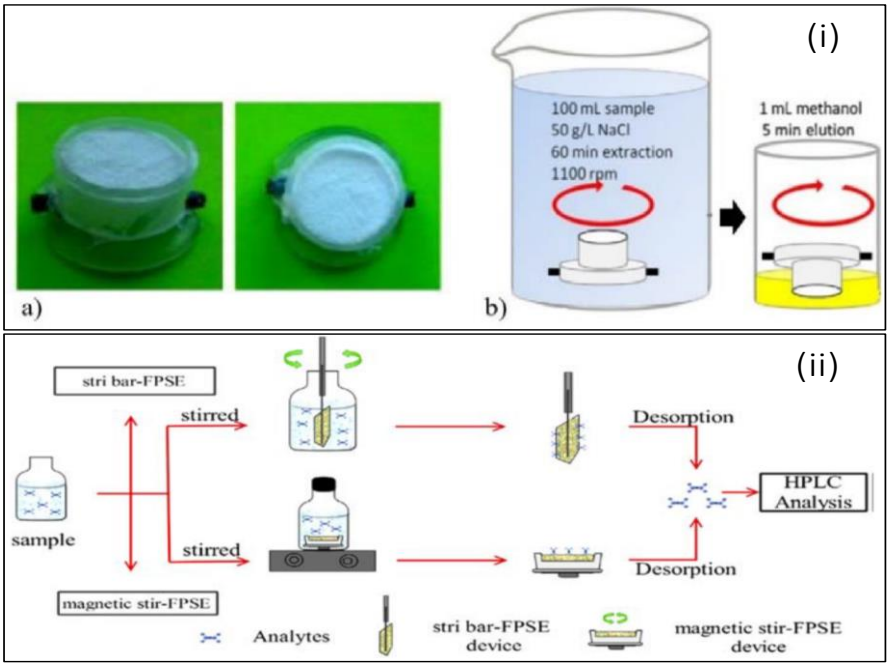

Figure 7. Different approaches to integrate FPSE with stir bars.

Recently, Huang *et al.* [19] proposed two new approaches of the device, stir-bar-FPSE and magnetic stir-FPSE, for the extraction of brominated flame retardant from environmental water samples. Fig. 7 (ii) depicts the schematic diagram of the two extraction procedures. In this study, three different sol-gel coated FPSE media with diverse polarities were prepared and investigated: sol-gel PDMS (non-polar), sol-gel PTHF (medium polar) and sol-gel PEG (highly polar). Better retention was achieved using the sol-gel PTHF material. Under the optimized

conditions, extraction recoveries ranging from 90% to 99% were achieved for selected analytes. The results indicated that both extraction procedures have high extraction capability and fast extraction time due to the performance of stirring and the higher sorbent loading material.

Another strategy for reducing the extraction time and avoiding human intervention was proposed by Anthemidis *et al.* [188], which is known as on-line flow injection fabric disk sorptive extraction (FI-FDSE) or continued dynamic flow injection. In this study the authors took advantage of the easy permeation characteristic of FPSE material to prepare the FDSE. The FDSE consisted of a mini column mode with polypropylene syringe body (1.5 x 4 mm i.d.) being packed in series with FPSE media that was cut into 38 to 40 disks with the same diameter (4 mm). No frits or glass wool were necessary at either end of the column to block the fabric disks. Fig. 8 shows the preparation of the FI-FDSE technique. The prepared mini column provided limited back pressure because of the permeation of the FPSE substrate. Therefore, a high flow-rate can be applied, resulting in a shorter analysis time with higher extraction efficiencies.

Figure 8. (A) FPSE material; (B) preparation of the minicolumn with FPSE disk; (C) FPSE with minicolumn ready for experiment [188].

The FI-FDSE technique was used for the determination of lead and cadmium in environmental water samples in combination with flame atomic absorption spectrometry (FAAS). Initially, four different polarities of materials were examined using the developed FDSE: sol-gel PDMDPS, sol-gel PTHF, sol-gel PEO-PPO-PEO triblock co-polymers and sol-gel graphene. The sol-gel PDMDPS showed better results than the other FPSE media, so it was selected for further optimization studies. The on-line FI-FDSE-FAAS method achieved a 140 and 38 enrichment factor with a preconcentration time of 90 seconds achieving the detection limit for lead and cadmium analytes of 1.8 and 0.4 µg L^{-1}. Comparing dynamic FPSE and FI-FDSE, it can be observed that both modes worked under the same principle of the sample flow through. However, a different size and number of disk materials were used.

FPSE has been effectively employed for the determination of different types of analytes in a range of environmental and biological samples. From all these applications, it was observed that the FPSE technique belonging to an efficient, green and new generation of sample preparation techniques.

1.3.5. Other formats of sorptive extraction techniques

Since 2009, other formats have been designed and employed to extract the analytes from environmental water samples. Fig. 9 shows different sorptive extraction formats and devices. These new formats were designed in-house and include other options for sorptive extractions, such as rotating-disk sorptive extraction (RDSE), stir-rod sorptive extraction (SRSE), stir-cake sorptive extraction (SCSE) and bar adsorptive microextraction (BAµE) or multi-sphere adsorptive microextraction

(MSAμE). The purpose of developing the different formats is to overcome the drawbacks of commercial and in-house coatings for SBSE, primarily to avoid the direct contact of the coating material with the vessel when immersed in the sample and to lengthen the lifetime of the coating material by preventing damage by physical contact. However, these formats have not been widely used and a very limited number of studies are available with those formats.

In the RDSE technique Fig. 9 A, the sorbent material is coated onto the Teflon disk using the sol-gel technique and the disk is rotated with a magnetic stirrer. The sample preparation procedure is the same as for SBSE. This format was the first attempt to improve the extraction recovery of analytes compared to SBSE. PDMS was the only extracting phase used in RDSE. For example, Giordano *et al.* [192] used RDSE formats for the extraction of pesticides in aqueous sample. Under the same optimal conditions, higher extraction recoveries were obtained with RDSE due to the higher contact surface area available for interaction compared to SBSE.

With respect to SRSE Fig. 9 B, it is also an extraction technique with the advantage of reducing the use of the sorbent material in the extraction medium. The device consists of a metal wire with a magnet at one end to which a sorbent-coated glass ending is attached. At the time of extraction, the device is rotated with a magnetic stirrer with a stirring speed far below than that used in SBSE. Lue *et al.* [120] synthesized a polar monolithic material based on poly(4-vinylpyridine-co-ethyleneglycoldimethacrylate) for the stir rod and then applied it for the extraction of NSAIDs from environmental aqueous samples. The method

showed good extraction recoveries for the selected NSAIDs, ranging between 75% and 112%.

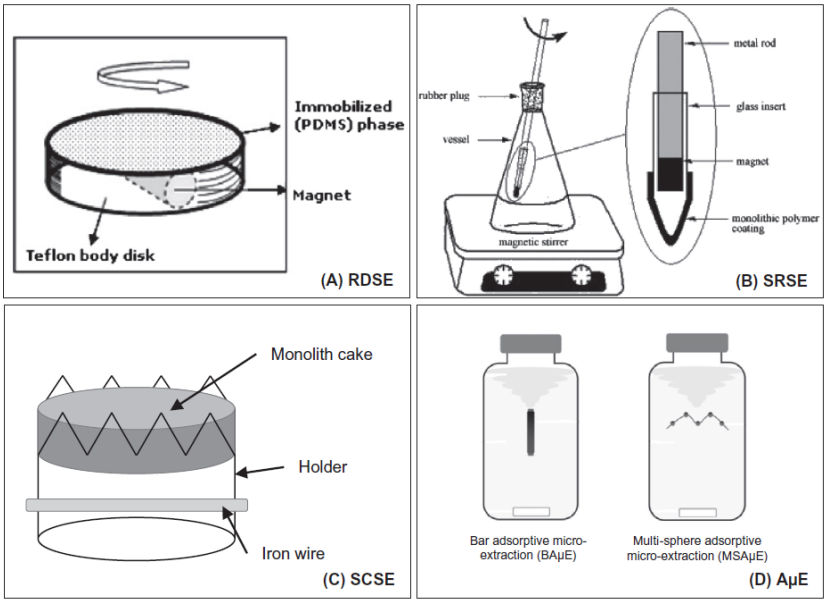

Figure 9. Different formats of sorptive technique and devices: (A) rotating-disk sorptive extraction (RDSE); (B) stir-rod sorptive extraction (SRSE); (C) stir-cake sorptive extraction (SCSE); and (D) adsorptive microextraction (AμE) [173].

The SCSE technique Fig. 9 C was first introduced in 2011. This is a modified replica of the RDSE technique in which a monolithic cake was used as the extraction sorbent. This device consists of a monolithic material that is placed inside a special holder designed for this purpose, and a holder containing the iron wire to stir and enhance the transfer of the analytes. Different types of monolithic materials have been developed for SCSE. For example, Huang *et al.* [193] prepared a monolithic material based on poly(vinylimidazole-divinylbenzene) (VI-DVB) for the extraction of steroid hormones from milk samples.

In addition, Fig. 9 D shows a diagram of both formats of BAμE or MSAμE introduced by Nogueira's research group. They developed a novel BAμE and MSAμE with an activated carbons coating for trace analysis of polar analytes in aqueous media [194]. The application of both BAμE and MSAμE formats obtained higher recoveries for polar analytes and metabolites in water matrices and biological fluids at trace level, whereas the PDMS coating for SBSE was unable to extract them.

As can be seen, different new formats are continuously being developed to improve the performance of sorptive extraction techniques.

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EVALUATION OF NOVEL SORPTIVE EXTRACTION TECHNIQUES
Sameer Shamrao Lakade

1.4. References

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CHAPTER 2. OBJECTIVES

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The objective of the present Doctoral Thesis is the evaluation and application of novel sorptive extraction techniques for the extraction of emerging organic contaminats of a wide range of polarities. These extraction techniques include fabric phase sorptive extraction in static and dynamic mode, capsule phase microextraction and dispersive solid-phase extraction using new hypercrosslinked magnetic particles.

To achieve this objective, different parameters affecting extraction recovery are optimized, including the sorptive materials, in order to increase the retention of polar analytes. The developed methods are then applied for the determination of these contaminants in environmental waters.

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CHAPTER 3. EXPERIMENTAL, RESULTS AND DISCUSSION

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As mentioned earlier, the research of this Doctoral Thesis focuses on the evaluation and application of different types of sorptive extraction techniques for extracting organic compounds. To evaluate the different sorptive techniques a group of EOCs was selected as a model analytes because this group included compounds with a wide range of physicochemical properties. The selected analytes were a group of PPCPs and SWs, the polarities of which cover a broad range from more to less polar.

As previously discussed in the introduction of this Doctoral Thesis, the selected groups of compounds are considered pseudo-persistent because they enter the environment continuously, primarily as a result of high human consumption and excretion as well as inefficient removal from WWTPs. As a result, they are found at very low concentration levels in effluent wastewater and, therefore, in surface water into which effluent water is discharged [1, 2].

This chapter includes the experimental part, results and discussion of the different studies that have been carried out over the course of this Doctoral Thesis. These results have already been published or are in process of being published in international scientific journals. The Doctoral Thesis has been developed in the research group of Chromatography and Environmental Applications at the Universitat Rovira i Virgili in Tarragona, which has more than twenty years' experience in the determination of organic contaminants in different kinds of environmental samples.

The following sections are organized according to the different type of sorptive extraction technique used. Section 3.1 describes the use of the fabric phase sorptive extraction (FPSE) technique in static mode (Section 3.1.1) and dynamic mode (Section 3.1.2) for the extraction of PPCPs. In

Section 3.2, the new capsule phase microextraction (CPME) technique was evaluated for a group of personal care products (PCPs). Lastly, in Section 3.3, dispersive solid-phase extraction (d-SPE) using magnetic particles (MPs) was used to extract SWs. All these extraction techniques were followed by liquid chromatography-tandem mass spectrometry (LC-MS/MS). In each section, a brief introduction is included to establish the context of the research followed by the results presented in paper format. In addition, the most notable results are also discussed after the paper(s). The list of the papers resulting from this Thesis that have been published or are in the process of being published is included in Appendix III.

The first section reports the recently introduced sample preparation technique known as FPSE, which has been successfully employed for the extraction of PPCPs in environmental water sample. Two modes (static and dynamic) were used for the extraction. In static mode, four different types of fabric materials were evaluated for the extraction of PPCPs. The different parameters affecting extraction efficiencies were optimized and compared with commercially available SBSE. The best FPSE material was selected for the development of the method, which was validated and applied to determine PPCPs in environmental samples.

The dynamic FPSE (DFPSE) mode was evaluated for the extraction of the same group of PPCPs. The dynamic mode is designed to overcome the shortcomings of the static FPSE mode in terms of the long equilibrium extraction time. In DFPSE, the sample flows through the FPSE disk material mounted on a filtration assembly and then, the retained analytes are eluted by passing elution solvent through the same assembly. Different parameters affecting the dynamic mode were also optimized and

the results were compared with those obtained with static FPSE, in which the same coating material was also used.

In the second section, a new sample preparation technique, capsule phase microextraction (CPME), which is based on a microextraction capsule (MEC), was evaluated for the extraction of a group of PCPs in environmental samples. Initially, three different types of MEC material were evaluated and the best was selected for further study. The different variables affecting extraction and liquid desorption were optimized and results were compared with commercial and in-house SBSE. Finally, the developed method was applied to environmental water samples.

It should be mentioned that the research on the evaluation of static FPSE was one of the first papers published on this technique, while the studies on dynamic FPSE and CPME were the first to present these techniques. These works were carried out in collaboration with Dr. A. Kabir and Dr. K. G. Furton from Florida International University in Miami (USA), where the MEC and FPSE fabric materials were synthesized.

The third and final section presents new hypercrosslinked MPs used for the extraction by d-SPE of a group of SWs from environmental water samples. This work was done in collaboration with Dr. Q. Zhou and Prof. A. Li, from Nanjing University in Nanjing (China), who prepared the new MPs. To achieve higher extraction recoveries for the selected analytes, different parameters were optimized and the results were compared with previous studies in which conventional SPE was used. The developed method was applied to determine the targeted SWs analytes in river water and effluent wastewater samples.

All the studies reported in this Doctoral Thesis were financially supported by the Spanish Ministry of Economy and Competitiveness of Spain (Projects CTQ2011-24179 and CTQ2014-52617-P).

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3.1. Fabric phase sorptive extraction

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To date, different sample preparation techniques have been used for the extraction of EOCs from liquid samples, as discussed in the introduction to this Thesis. These include a novel sample preparation technique introduced by Kabir and Furton known as FPSE, as part of a new generation of sample preparation techniques that overcome the limitations related of conventional sorptive sample preparation techniques. This technique integrates the benefits of advanced material properties through sol-gel technology with the hydrophobic/hydrophilic properties of the natural or synthetic fabric used as the coating material, and the permeability of the coating material. In addition, because of the flexibility of the FPSE media, it can be introduced directly into the aqueous sample matrix, even in the presence of a high level of matrix interferences. Another advantage of FPSE is its high primary contact surface area (1,000 mm^2) for sorbent-analyte interaction which helps to achieve the equilibrium in a short period of time [1].

Immediately after the introduction of FPSE, the technique has been used in sample preparation because of its advantages, having been widely applied for the extraction of analytes in different type of samples, such as milk, juice, urine, surface water, sea water and wastewater [2-5]. These studies have used different coating materials for FPSE in static mode. At the time of writing, only one study was available in which the automated flow injection mode of FPSE was used [6]. All these studies focused on the extraction and determination of a group of non-polar or mid-polar analytes at trace level in complex samples. However, none of the studies selected a wide range of analyte polarities.

The reason for the development of the methods was the introduction of a new technique with two different modes of sample preparation for

compounds of different polarities. The two different extraction modes that have been evaluated in this section are the static FPSE mode (Section 3.1.1) and dynamic FPSE mode (Section 3.1.2.). It should be highlighted here that this is the first time that these two different modes of FPSE have been studied by our research group and in the scientific world in general for the group of PPCPs analysed. As mentioned earlier, PPCPs have mainly been extracted from liquid samples by SPE [7], SPME [8] and SBSE [9].

The first study presented in this section includes a more detailed evaluation of the different FPSE coatings compared to each other and also to commercial SBSE coatings. Here, different FPSE polarities were tested, including non-polar sol-gel poly(dimethyldiphenylsiloxane) (PDMDPS), medium polar sol-gel poly(tetrahydrofuran) (PTHF), and highly polar sol-gel poly(ethyleneglycol)-block-poly(propyleneglycol)-block-poly-(ethyleneglycol) (PEG–PPG–PEG triblock) and sol-gel Carbowax 20M (CW-20M). The different parameters that affect extraction and liquid desorption in FPSE were also optimized for the four materials to select the best one for further study. The developed method was applied to different kinds of water samples. The results obtained in the static FPSE mode were compared with those obtained with previous studies.

Once the static FPSE mode and its results had been analysed, in the second study, a further step was taken to evaluate the design of the new sample extraction mode known as dynamic FPSE (DFPSE). This mode is a modification of the static FPSE mode that overcomes the main limitation of static FPSE, namely the long extraction time that, in our case, required up to four hours for equilibrium extraction. In DFPSE, the 47 mm circular fabric disk coated with the sorbent material by sol-gel technology

is placed in the filtration assembly for the extraction, with the same assembly being used for the liquid desorption. Fig. 1 shows the DFPSE material and the assembly for sample extraction. DFPSE can be considered as part of a new generation of disk SPE, including the characteristics of flexibility, high sorbent coating, permeability and reusability, as it works based on a similar principle and the same sample treatment procedure. Similarly to the FPSE material, a wide variety of coating materials are available for extraction. However, based on the results of the static FPSE, the same coating (CW-20M) was selected.

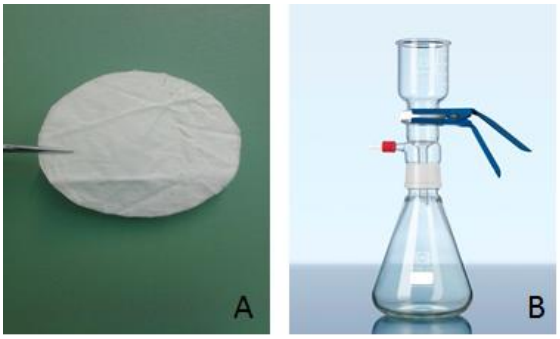

Figure 1. (A) DFPSE material; (B) sample DFPSE extraction assembly.

Similarly to static FPSE, different parameters were optimized to obtain high extraction recoveries. This new sample preparation mode decreases extraction time because of the availability of a large surface area for interaction, while keeping all other features the same. Thus, in this study, the performance of the new sorptive extraction was evaluated for the same analytes used in the static FPSE mode. It should be mentioned that our research group is the first to present the dynamic mode of FPSE.

Due to the very low concentration and the wide range polarities of the PPCPs in the environmental water sample, both extraction modes

were followed by LC-(ESI)MS/MS for the determination of PPCPs in environmental waters.

The results obtained from these studies were published in *Talanta 144 (2015) 1342-1351* and the *Journal of Chromatography A 1456 (2016) 19-26* and are presented in the following sections.

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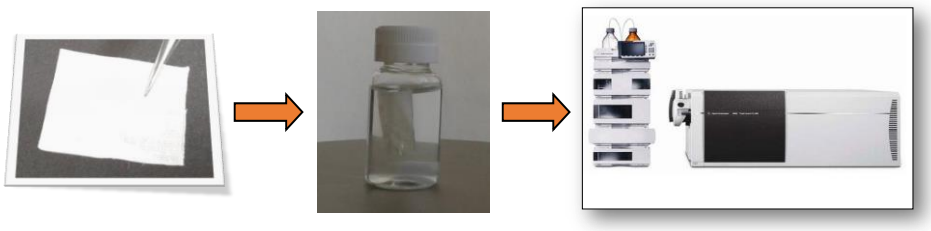
3.1.1. Comparative study of different fabric phase sorptive extraction sorbents to determine emerging contaminants from environmental water using liquid chromatography–tandem mass spectrometry



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COMPARATIVE STUDY OF DIFFERENT FABRIC PHASE SORPTIVE EXTRACTION SORBENTS TO DETERMINE EMERGING CONTAMINANTS FROM ENVIRONMENTAL WATER USING LIQUID CHROMATOGRAPHY–TANDEM MASS SPECTROMETRY

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Abstract

A new sorptive extraction technique, fabric phase sorptive extraction (FPSE), using different coating chemistries: non-polar sol–gel poly(dimethyldiphenylsiloxane) (PDMDPS), medium polar sol–gel poly (tetrahydrofuran) (PTHF), and polar sol–gel poly(ethylene glycol)–block-poly(propylene glycol)–block-poly(ethylene glycol) (PEG–PPG–PEG triblock) and sol–gel Carbowax 20M were evaluated to extract a group of pharmaceuticals and personal care products (PPCPs) with wide range of polarity from environmental aqueous samples. Different parameters affecting FPSE such as sample pH, stirring speed, addition of salt, extraction time, sample volume, elution solvent and desorption time were optimized for each sorbent coated FPSE media. Under optimum conditions, FPSE media coated with sol–gel Carbowax 20M provided the highest absolute recoveries (77–85%) for majority of the analytes with the exception of the most polar ones. Nevertheless, all four sorbents offered better recovery compared to the commercially available coating for stir-bar sorptive extraction based on Ethylene Glycol/Silicone (EG/Silicone). The method based on FPSE with sol–gel Carbowax 20M media and liquid chromatography-(electrospray ionization) tandem mass spectrometry (LC-(ESI) MS/MS) was developed and validated for environmental water samples. Good apparent recoveries (41-80%), detection limits (1-50 ng L^{-1}), repeatability (%RSD<15%, n=5) and reproducibility (% RSD<18%, n=5) were achieved.

Keywords: fabric phase sorptive extraction (FPSE), carbowax 20M sorbent, liquid chromatography–tandem mass spectrometry, pharmaceuticals and personal care products (PPCPs), environmental water samples

1 INTRODUCTION

Effective sample preparation strategy as well as highly sensitive analytical instrument is indispensable to determine low concentrations of contaminants in the environmental samples. Among them, different types of emerging organic contaminants (EOCs) are found at concentration levels from ng L^{-1} to µg L^{-1} in environmental samples such as wastewater and surface water. In addition, these EOCs are grouped in different types of compounds with wide range of physicochemical properties. An example of this is the pharmaceutical and personal care products (PPCPs) group, whose polarities differ broadly from polar to non-polar [1-3].

Several extraction techniques are used to clean-up and pre-concentrate these analytes from a wide variety of sample matrices. Over the last few years, different sorptive extraction techniques such as, solid-phase extraction (SPE), solid phase microextraction (SPME) and stir bar sorptive extraction (SBSE) have been commonly used in liquid sample treatment [4-8]. The efficiency of sorption primarily depends upon the characteristics of the sorbent material used as well as the physicochemical properties of the analytes [5,9,10]. Among all the sample preparation technique, SPE is the most commonly used due to the wide variety of extraction phases available [5,11]. SPME, predominantly used in combination with gas chromatography, has also been established due to the availability of different types of fibers [12-14]. However, the main limitation of SPME is the low sample capacity due to the small sorbent loading constrained by the shape and size of the fiber support.

To overcome this limitation, SBSE emerged [4,11]. The main limitation of SBSE is that, till very recently, only one non-polar coating based on poly(dimethylsiloxane) (PDMS) was commercially available, which showed excellent performance for the sorption of non-polar analytes but most of the

polar analytes were not retained at all or retained poorly [15-17]. Nevertheless, in the last years, two new SBSE polar coatings have been commercially available and trademarked as Acrylate Twister® (based on polyacrylate with proportion of polyethylene glycol) and EG/Silicone Twister® (based on polyethylene glycol modified with silicone). Till date, these new coatings have been evaluated for the extraction of PPCPs [18] and benzothiazoles [19] from wastewater samples, and volatile organic compounds (VOCs) in oil, perfume and coffee samples [20] with better extraction performances than those obtained with the PDMS coating [18,20]. Different polar coatings and device formats have also been developed in-house using different synthetic strategies, mainly based on monolithic approaches [21,22] or sol-gel technology [23-25].

Recently, a new sorptive extraction technique, fabric phase sorptive extraction (FPSE), has been introduced [26,27]. FPSE consists of 25 x 20 mm^2 fabric pieces coated with different sorbent chemistries using sol-gel technology. The amount of sorbent material, which is on an average 10 times higher than in the SBSE, is uniformely distributed on the cellulose/polyester/fiber glass fabric substrate. Due to the high primary contact surface area (1000 mm^2) of FPSE media, inherently porous sol-gel sorbent coating, high volume of sorbent loading in the form of ultra-thin porous film, and the strong chemical bonding between the substrate and the sorbent, FPSE demonstrates remarkably fast extraction kinetic, extraordinary extraction sensitivity as well as high solvent and chemical stability. FPSE incorporates the advantages of equilibrium based extraction, exploits the benefits of sol-gel coating technology, utilizes the permeability of fabric substrate and increases the primary contact surface area for rapid analyte-sorbent interaction. A large number of sorbent chemistries are available which include: sol-gel poly(dimethylsiloxane), sol-gel poly(dimethyldiphenylsiloxane), sol-gel poly(diphenylsiloxane), sol-gel C_{18},

sol-gel C_8, sol-gel graphene, sol-gel poly(tetrahydrofuran), sol-gel poly(ethylenglycol), sol-gel Carbowax 20M and sol-gel poly(ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene glycol) [26].

To date, only a few studies have reported the use of FPSE technique. For example, Kumar et al. [27] demonstrated the suitability of sol-gel poly(tetrahydrofuran) (PTHF) coated FPSE media to extract bisphenol A, 17β-Estradiol and 17α-ethynylestradiol from urine and different types of water samples. Samanidou et al. [28] reported the extraction of highly polar amphenicol antibiotics directly from raw milk using sol-gel short-chain poly(ethylene glycol) (PEG) coated FPSE media and demonstrated a substantial simplication in the sample preparation compared to matrix solid-phase dispersion. Racamonde et al. [29] also used sol-gel PEG coated FPSE media to determine non-steroidal anti-inflammatory drugs in different type of environmental water samples. Roldán-Pijuán et al. [30] used the same FPSE technique with integrated magnetic stirring mechanism known as stir FPSE to determine triazines herbicides in environmental water samples. However, none of the FPSE studies have dealt with contaminants with wide polarity range at trace concentration levels present in complex matrices. At present, there is a long-standing demand for a simple, green, and robust sample preparation and analysis technique that can simultaneously handle polar, medium polar, and non-polar analytes at their low level concentrations present in complex samples. The aim of the present study is to compare four FPSE coating chemistries: non-polar PDMDPS, medium polar PTHF, polar PEG-PPG-PEG triblock and polar Carbowax 20M to extract a group of PPCPs (log K_{ow} values range from -0.6 to 6.1) from environmental water samples. The selection of the best sorbent material for the target PPCPs was followed by the development of an analytical method to determine the selected compounds in river and waste waters by FPSE/LC-MS/MS.

2 MATERIALS AND METHODS

2.1 Reagents and chemicals

The reagents used in the preparation of FPSE media were of analytical grade. Sol-gel active polymers poly(tetrahydrofuran) (PTHF) and poly(ethylene glycol) (Carbowax 20M), poly(ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene glycol) were purchased from Sigma-Aldrich (Saint Louis, MO, USA); poly(dimethyldiphenylsiloxane) (PDMDPS) was purchased from Gelest (Morrisville, PA, USA). Acetone, methylene chloride (CH_2Cl_2), methyltrimethoxysilane (MTMOS), 3-cyanopropyltriethoxysilane (3-CPTEOS) and trifluoroacetic acid (TFA) were purchased from Sigma-Aldrich. Sodium hydroxide (NaOH) and hydrochloric acid (HCl) were purchased from Thermo Fisher Scientific (Milwaukee, WI, USA). Substrates for fabric phase sorptive extraction media were obtained from Jo-Ann Fabric (Miami, FL, USA).

Unlike other material synthesis, sol-gel synthesis of extraction sorbents does not require a lot of sophisticated equipment. An Eppendorf Microcentrifuge Model 5415 R (Eppendorf North America Inc., Hauppauge, NY, USA) was used to centrifuge different sol solutions in order to obtain particle free sol solutions. A Fisher Scientific Digital Vortex Mixture (Fisher Scientific, Pittsburg, PA, USA) was employed for thorough mixing of different solutions. Bubble-free sol solutions were obtained using a 2510 BRANSON Ultrasonic Cleaner (Branson Ultrasonics, Danbury, USA). A Barnstead Nanopure Diamond (Model D11911) deionized water unit (Dubuque, IA, USA) was used to obtain ultra-pure deionized water (18.2 MV cm $^{-}$1) for sol–gel synthesis and substrate treatment in the USA lab.

The representative PPCPs: paracetamol (PARA), caffeine (CAFF), antipyrine (APy), propranolol hydrochloride (PROP), methylparaben (MPB),

carbamazepine (CBZ), propylparaben (PrPB), 2,4-dihydroxybenzophenone (DHB), benzylparaben (BzPB), 2,2-dihydroxy-4-4methoxybenzophenone (DHMB), diclofenac (DICLO), 3- benzophenone (BP-3), triclocarban (TCC), triclosan (TCS) were purchased from Sigma-Aldrich (Steinheim, Germany). Table 1 shows the relevant physicochemical properties of the selected PPCPs.

Table1. General parameters of Log K_{ow}, pK_a, and t_R, and LC–(ESI)MS/MS acquisition parameters in MRM mode for each analyte.

Analyte	log K_{ow}*	pK_a*	t_R(min)	Precursor ion (m/z)	Cone voltage (V)	Product ion (m/z) (Collision energy (eV))	
						Quantification	Confirmation
PARA	0.5	9.2	3.87	152	100	110 (15)	93 (25)
CAFF	-0.6	13.4	4.37	195	125	138 (15)	110 (25)
APy	1.4	13.3	6.70	189	100	145 (30)	115 (30)
PROP	2.9	9.5	7.57	260	125	116 (15)	183 (15)
MPB	1.9	8.3	9.45	151	80	92 (15)	136 (5)
CBZ	1.9	13.7	11.0	237	150	193 (35)	179 (35)
PrPB	2.9	8.2	13.1	179	100	92 (15)	136 (5)
DHB	3.2	7.7	13.9	213	130	135 (15)	169 (5)
BzPB	3.6	8.2	14.7	227	100	92 (10)	136 (20)
DHMB	4.3	7.1	15.3	243	80	123 (15)	93 (15)
DICLO	4.5	4.2	16.4	294	75	250 (5)	214 (15)
BP-3	4.0	7.6	18.0	229	130	151 (15)	105 (15)
TCC	6.1	12.7	19.2	313	130	160 (5)	126 (15)
TCS	5.3	7.9	19.5	287	18	35 (8)	
				289	18		35 (8)

* Log K_{ow} calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02 (© 1994–2012 ACD/Labs)

All PPCPs standards were high purity grade (>98%). Stock solutions of individual standards were prepared in methanol (MeOH) at concentration of 1000 mg L^{-1}. A mixture of standards of all compounds at 50 mg L^{-1} was prepared in methanol. Working standard solution prepared weekly by diluting with mixture of ultra-pure water pH 3 and acetonitrile (ACN) (80:20). These solutions were stored at 4ºC. HPLC grade MeOH, and ACN was supplied from Scharlab (Barcelona, Spain), and formic acid (HCOOH) 95% and

sodium chloride (NaCl) were from Sigma-Aldrich (Steinheim, Germany). Ultra-pure water was obtained from a water purification system (Veolia Waters, Barcelona, Spain).

2.2 Preparation of sol-gel poly(dimethyldiphenylsiloxane) (sol-gel PDMDPS), sol-gel poly(tetrahydrofuran) (sol-gel PTHF), sol-gel poly(ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene glycol) (sol-gel PEG-PPG-PEG) and sol-gel Carbowax 20M coated fabric phase sorptive extraction media

Preparation of fabric phase sorptive extraction media coated with any sol-gel derived sorbent involves a number of sequential steps including: (a) selecting and pretreating the substrate; (b) design and preparation of sol solution for coating; (c) sol-gel coating on the treated substrate; (d) conditioning and aging of the sol-gel coated FPSE media; (e) post-coating cleaning of the sol-gel coated FPSE media.

2.2.1 Selecting and pre-treating the substrate for sol-gel coating

The substrate selection for sol-gel coating is primarily dependent on: (a) the hydrophilicity or hydrophobicity of the analyte(s) of interest; (b) the strategy used in analyte back-extraction after preconcentrating onto the FPSE media. If solvent mediated back-extraction is used, fabric substrates such as cellulose, polyester are preferred. On the other hand, if thermal desorption is used, glass fiber based fabric is the best option. Once the substrate selection is made, a chemical clean-up procedure needs to be applied in order to remove external dirt, particulates, and the residues of fabric finishing chemicals such as starch, dye, fillers, etc. and to activate surface hydroxide groups before administering the sol-gel coating process. This fabric treatment regimen is a modified form of a standard industrial

process known as “mercerization” [31]. A detailed account of the fabric treatment process is described elsewhere [27].

2.2.2 Design and preparation of the sol solutions for substrate coating

The design of the sol solution primarily depends on the physicochemical properties of the target analytes and includes selection of: (a) organic polymer; (b) inorganic or organically modified inorganic polymer; (c) solvent/solvent system; (d) catalyst; (e) water content; and (f) relative molar ratio of the ingredients. Considering the wide polarity range of the selected PPCPs, a nonpolar PDMDPS, a medium polar PTHF, a relatively polar PEG-PPG-PEG copolymer, and a highly polar Carbowax 20M were selected as potential organic polymer candidates for the sol solution. PDMDPS possesses 14-18% diphenyl containing blocks in the polymer back-bone which should offer π-π interactions, in addition to other intermolecular interactions, towards the target analytes during extraction. PTHF is a hydroxyl-terminated polar polymer frequently used in synthesizing inorganic-organic hybrid materials. Due to the presence of less number of C-O-C linkages into the polymer chain compared to poly(ethylene glycol), PTHF is a medium polarity polymer. PEG-PPG-PEG is an amphiphilic block terminal copolymers containing sol-gel active functional groups in both the ends. The selectivity of the block copolymer originates from the hydrophilic segment of PEG and hydrophobic segment of PPG. Carbowax 20M is a polar polymer with diversified applications in foods, cosmetics, pharmaceuticals, biomedicines, etc. Due to the high polarity of PEG, a number of polar microextraction sorbents as well as gas chromatographic stationary phase have been developed.

Another major decision in sol solution design is choosing the appropriate inorganic/organically modified inorganic precursor. The integrity of the hybrid organic-inorganic sorbents largely depends on the sol-gel

precursor and/or the sol-gel reaction and processing conditions. Although tetraalkoxysilanes are commonly used as the sol-gel precursors, Malik and co-workers introduced methyltrimethoxysilane (MTMS) in the sol-gel coating technology [32] in order to minimize cracking and shrinking of sol-gel coating. Since then, hundreds of new sol-gel sorbents have been developed using this precursor [33]. The presence of a nonpolar methyl group in MTMS reduces the overall polarity of the hybrid sorbent, regardless of the polarity of the organic polymer employed. As such, it is counter-intuitive to use MTMS as a precursor when enhancing polarity of the composite material is the goal. Herein, we used 3-cyanopropyltriethoxysilane (3-CPTEOS) as the precursor to increase the polarity of sol-gel Carbowax 20M. A number of research groups have used this precursor along with nonpolar polymers to increase the polarity of the composite material [32,34]. The relative molar ratio of sol solution ingredients were designed based on a previously described formulation [35]. However, due the fact that different polymers have different average molar mass, molar ratio of polymers to other sol solution ingredients varied significantly. Also, in order to have a homogenous sol solution, on one hand, CH_2Cl_2 was used for sol-gel PDMDPS and sol-gel PTHF. On the other hand, an equimolar mixture of CH_2Cl_2 and acetone was used for sol-gel PEG-PPG-PEG and sol-gel Carbowax 20M. The molar ration between precursor: solvent: catalyst: water (1: 3.90: 1.31: 0.30) were kept constant in all the sol solutions. The molar ratio between the precursor and PDMDPS, PTHF, PEG-PPG-PEG, and Carbowax 20M were 1:0.1, 1:0.4, 1:0.05, and 1:0.02, respectively. Exact sol solution composition for individual coating can be found elsewhere [27].

2.2.3 *Sol-gel coating process*

Preparation of a sol solution for a specific sol-gel coating is followed by the sol-gel coating on the treated substrate. The sol-gel coatings on the

substrates were carried out for a duration of 4 hours. The sol-gel coating process, conditioning and aging of the sol-gel coated FPSE media and the final cleaning of the sol-gel coated FPSE media are described in our previous reports [27].

2.3 Fabric phase sorptive extraction

The FPSE conditions were optimized for each fabric media. Before using it for extraction, the FPSE media was conditioned and equilibrated by immersing in MeOH for 5 min and then dried by air. For the extraction, the FPSE media was immersed into a 12 mL glass vial having 10 mL of sample adjusted to pH 3 and containing 10% of NaCl (w/v). The sample was stirred for 4 h at room temperature. After extraction, the FPSE media was removed from the sample and dried with lint-free tissue. For liquid desorption (LD), the FPSE media was introduced into a 5 mL glass vial containing 1 mL of MeOH and placed in an ultrasonic bath for 5 min. The extract was evaporated to dryness under gentle stream of nitrogen. The residue obtained was re-dissolved in 1 mL of solution of ultra-pure water at pH 3 and ACN (80:20, v/v). Then, the extract was injected to LC-(ESI) MS/MS. After every use, the FPSE media was cleaned three times with 2 mL MeOH in the ultrasonic bath for 5 min, then dried and stored in the air tight glass vial till the next experiment.

2.4 Liquid chromatography-tandem mass spectrometry (LC-(ESI)MS/MS) analysis

The chromatographic determination was performed with a 1200 Agilent liquid chromatography, equipped with an automatic injector, a degasser, a quaternary pump, a column oven, and a 6410 series triple quadrupole mass spectrometer using electrospray ionization (ESI) (Agilent Technologies, Waldron, Germany).

The chromatographic column was a Kromasil 100 C_{18} (150 mm × 4.6 mm i.d., 5 µm) from Teknokroma (Barcelona, Spain). ACN and ultra-pure water adjusted to pH 3 with HCOOH were used as the mobile phase. The gradient started at 20% ACN, which was increased to 80% ACN in 15 min, then to 100% ACN in 8 min and kept constant for 1 min. Finally, it returned to the initial conditions in 2 min. The chromatographic separation was achieved in less than 20 min. The temperature of the chromatographic column was maintained at 40ºC and the flow-rate was 0.6 mL min^{-1}, and 50 µL were injected to LC-(ESI)MS/MS.

The LC-MS/MS parameters were based on a previous study [18] and optimized by injecting each compound at 1 µg L^{-1} in mixture of ultra-pure water pH 3 and ACN (80:20, v/v) individually in flow injection analysis (FIA). Depending on the acidic or basic properties of compounds, positive $[M+H]^+$ or negative $[M-H]^-$ ESI mode were used. PARA, CAFF, APy, PROP, CBZ and BP-3 were acquired in positive ionization mode and MPB, PrPB, DHB, BzPB, DHMB, DICLO, TCC and TCS were in negative ionization mode. The optimal conditions for analytes were as follows: nebulizer pressure of 45 psi, drying gas (N_2) flow-rate of 12 L min^{-1}, source temperature of 350ºC and a capillary potential of 4000 V. Ionization mode, cone voltage and collision energies were optimized for each analyte in order to obtain two multiple reaction monitoring (MRM) transitions. The optimized parameters are summarized in Table 1.

All selected compounds showed good linearity ($R^2 \geq 0.999$) by direct injection with a linear range of 0.1 - 50 µg L^{-1}, except for TCS which were of 2 - 50 µg L^{-1}. The instrumental limit of detection (LODs), calculated as signal-to-noise ratio (S/N) of 3 ranged from 0.01 - 0.5 µg L^{-1}. The instrumental limits of quantification (LOQs) were calculated as the concentration of the lowest point of the calibration curve.

2.5 Sampling

River water samples were collected from the Ebre River in Spain. Influent and effluent wastewaters were collected from the domestic wastewater treatment plant (WWTP) from Tarragona (Spain). All water samples were filtered using Magna, nylon supported 0.45 μm membrane (Fisher brand, Loughborough, UK), acidified to pH 3 with HCl and stored at 4ºC until analysis.

3 RESULTS AND DISCUSSION

3.1 Chemistry of the FPSE substrates and the sol-gel coatings

A large number of commercially available natural and synthetic fabrics can be used as the potential candidates as substrate for FPSE which includes cellulose, polyester, nylon, fiber glass and polyamide. All these fabrics either contain readily available sol-gel active functional groups or may have the capability to contain sol-gel active functional groups *via* surface modification. However, polyester and cellulose fabrics inherently possess sol-gel active functional groups and therefore both fabrics were selected as the substrates for sol-gel coating. Cellulose fabric is known to be hydrophilic and polyester fabric hydrophobic [27]. Since both the substrate and the sol-gel coating contribute to the final selectivity and polarity of the resulting extraction media, a relatively non-polar organic polymer PDMDPS was used as the organic polymer to coat hydrophobic polyester substrate in order to create a non-polar extraction media. Poly THF is medium polar, whereas, PEG-PPG-PEG triblock and Carbowax 20M polymers are considered as highly polar polymers. As such, they were used to coat hydrophilic cellulose substrate in order to develop extraction media with medium and high polarities.

The chemical reactions involving the sol-gel coating process are well studied and widely reported [32]. The creation of sol-gel hybrid organic-

inorganic coating on the substrate involves: (1) controlled catalytic hydrolysis of the sol-gel precursor; (2) polycondensation of hydrolyzed precursor, leading to a growing three-dimensional sol-gel network; (3) random incorporation of sol-gel active polymers into the evolving sol-gel network; (4) chemical immobilization of the growing sol-gel network to the flexible cellulose and polyester substrates *via* condensation. A general reaction scheme for creating sol-gel hybrid organic-inorganic coating on the substrate is shown in Fig 1.

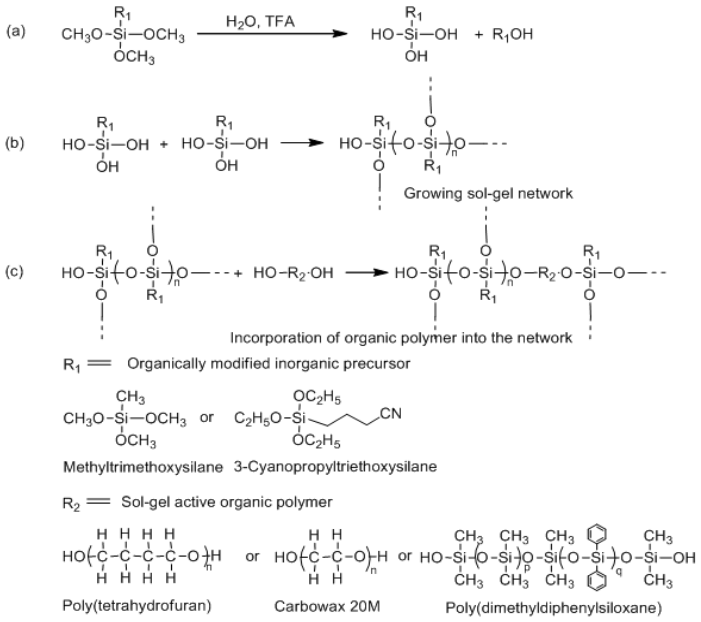

Fig. 1. Chemical reactions involved in the synthesis of sol-gel hybrid inorganic-organic polymeric network.

During the polycondensation, the growing sol-gel network reacts with available surface hydroxyl groups of cellulose or polyester microfibrils, resulting in a covalently bonded sol-gel hybrid coating uniformly distributed throughout the substrate matrix with chemical stability as well as highly accessible active sites for efficient and fast analyte extraction. A schematic

representation of sol-gel Carbowax 20M coated FPSE media is demonstrated in Fig 2.

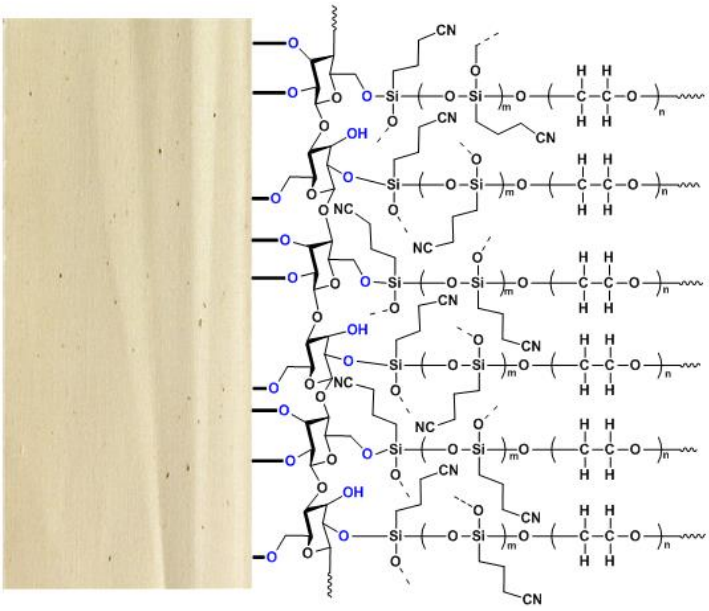

Fig. 2. Schematic representation of sol-gel Carbowax 20M coated FPSE media.

3.2 Optimization of FPSE procedure

As the selected analytes possess wide range of polarity, four different FPSE media that covers different polarity (i.e. non-polar with PDMDPS, mid-polar with PTHF, and more polar with PEG-PPG-PEG triblock and Carbowax 20M) were studied and compared. Firstly, different parameters affecting FPSE were optimized for each FPSE media in order to obtain the maximum extraction efficiency with each fabric coating. The extraction parameters optimized were pH, addition of salt, stirring speed, extraction time and volume of sample. After extraction, desorption of analytes is also a crucial step in FPSE; in this case, LD was used since the material can be folded so

that the volume required is low. In LD, parameters such as mode of desorption, solvent and desorption time were also optimized.

These parameters were optimized under following initial experimental conditions: 10 mL of ultrapure water adjusted at pH 3 with HCOOH, spiked at 0.2 µg L^{-1} for all the compounds and 1 µg L^{-1} for triclosan with the mixture of analytes stirring at 900 rpm for 1 h at room temperature and the LD was performed by soaking the fabric sorbent in 1 mL of MeOH for 10 minutes. These conditions were selected from previous experience in SBSE [18], where the same compounds were extracted. The optimization experiments were carried out with all four FPSE media: sol-gel PDMDPS, sol-gel PTHF, sol-gel PEG-PPG-PEG triblock copolymer and Carbowax 20M. Thus, in the next section, we discuss in general the results of each fabric sorbent and in more detail, the ones from the Carbowax 20M sorbent because this sorbent provided the best results.

3.2.1 Liquid desorption conditions

LD consisted of immersing the FPSE media in suitable organic solvent to release the extracted analyte from the extraction media. The extracted aliquots were evaporated to dryness and the residue redissolved in 1 mL of ultra-pure water at pH 3 and ACN (80:20, v/v). No significant losses of the analytes during the evaporation step were observed (1-3%).

Two desorption volumes (5 mL and 1 mL) were tested, and when 5mL were used no improvement in the results were observed. It should be highlighted that only 1mL of desorption solvent was necessary to completely cover the fabric sorbent. This small volume contributed to enhance the sensitivity of the method as well as required less time during the evaporation step, and therefore, 1mL was selected as desorption volume.

The modes to desorbed the analytes from FPSE were first tested by soaking the fabric sorbent in desorption solvent with and without sonication. As expected, we observed an increase in recovery of 12–15% when sonication was applied.

To ensure the complete desorption of the analytes, different solvents were tested: MeOH, ACN and a mixture of MeOH/ACN (50:50, v/v). When 1 mL of these desorption solvent was evaluated, it was observed that MeOH showed better recoveries (increase in ~ 5%) compared with ACN and MeOH/ACN (50:50, v/v) for all of the compounds. Therefore, sonication with 1 mL of MeOH was chosen as the desorption conditions. Desorption time was also investigated between 5 and 15 min, and sonication for 5 min was enough to desorb all the analytes from the sol-gel PDMDPS, sol-gel PTHF, sol-gel Carbowax 20M sorbents. However, sol-gel PEG-PPG-PEG triblock sorbent needed 15 min to desorb all analytes from fabric sorbent. Therefore, 5 min was selected as the optimal desorption time for three fabric sorbent, except for PEG-PPG-PEG triblock which was 15 min.

3.2.2 *Extraction conditions*

Once desorption conditions had been optimized, parameters affecting the extraction process such as sample pH, salt addition, agitation speed and extraction time were evaluated.

The sample pH is necessary to be controlled to promote the non-ionic form of analyte with acidic or basic functionalities, and, therefore, to increase retention towards the FPSE sorbent. The extraction was investigated at different pH values (3, 5, 7 and 9) since the studied analytes possess different pK_a values (Table 1). Fig. 3 shows the extraction recovery attained for a group of selected analytes when sol-gel Carbowax 20M sorbent was used with the samples adjusted at the different pHs. As can be seen, the

recoveries at all different pHs are similar for all the selected compounds, with the exception of DICLO and TCC, whose recoveries decreases at pH 9 and pH 7, respectively. Similar trends were observed with the other three FPSE sorbents (sol-gel PDMDPS, sol-gel PTHF and sol-gel PEG-PPG-PEG triblock). Overall, sample adjusted at pH 3 showed the best recoveries during the extraction of the analytes for all four FPSE sorbents.

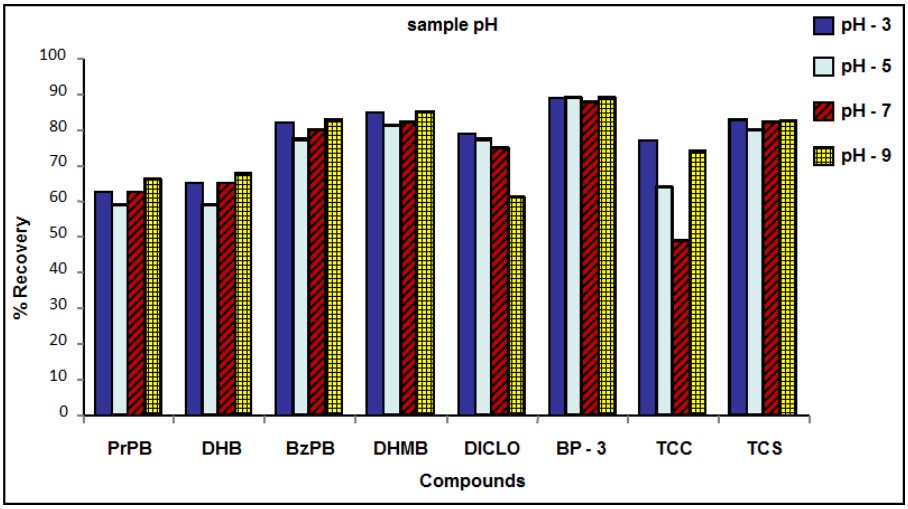

Fig. 3. Effect of sample pH on extraction recovery for a representative group of compounds using Carbowax 20M sorbent in FPSE. (%RSD (n=3) were lower than 12%).

The effect of ionic strength in the recovery of compounds was performed by adding NaCl from 0% to 20% (w/v) to the aqueous solution. For the sol-gel Carbowax 20M sorbent, it was observed that the recoveries decreased (~ 10% on average) with 5% NaCl addition and then increased (~ 30% on average) to the maximum with 10% NaCl addition. This effect may be attributed to the salting-out effect and the electrostatic interaction between polar molecules and salt ions in the solution [36]. With addition of higher percentage (15% and 20% of NaCl), the recoveries started to decrease. The similar behavior was observed with the sol-gel PTHF sorbent. However, in

the case of sol-gel PDMDPS and for the most non-polar analytes (BzPB, DHMB, DICLO, BP-3, TCC and TCS) the best recoveries were achieved when 15% of NaCl was added to the sample instead of 10% of NaCl. For the sol-gel PEG-PPG-PEG triblock sorbent the recovery remains the same as the percentage of salt addition increases. Therefore, for sol-gel Carbowax 20M and sol-gel PTHF sorbent 10% of salt was added to the sample, for sol-gel PDMDPS sorbent 15% salt was added whereas for sol-gel PEG-PPG-PEG triblock sorbent no salt was added.

Three agitation rates (300, 600 and 900 rpm) were tested to optimize the stirring speed. The results obtained with an agitation rate of 900 rpm were better (increase of 5-20%) than those obtained at lower rpm for all fabric sorbents. Experiments at higher level of stirring were not feasible since the agitation was not uniform.

Sample volume usually affects both the extraction time and extraction efficiency. In order to select the optimum sample volume, different sample volumes (10, 20 and 30 mL) of standard solution of the analytes were tested. When 20 and 30 mL of a standard solution were extracted, the recoveries decreased significantly (between 10-30%) for all FPSE sorbents. For this reason, 10 mL of sample was selected for further analysis.

The extraction time is also an important parameter in order to determine the time required to reach extraction equilibrium. It was tested from 1 to 8 hours for all four fabric sorbents. Fig. 4 shows the extraction time profile for a representative group of analytes when sol-gel Carbowax 20M sorbent was tested. As can be seen in this Figure, from 1 to 3 hours there is an increase in recovery for most of the compounds; at 4 hours, a significant increase in recovery of TCC, BzPB and PrPB was observed; at time higher than 4 hours MPB and CBZ increased their recoveries. However, as a compromise, 4 hours were selected as optimum time in order to not make

longer the time of analysis. Although it may seem a long extraction time compared to other techniques, the possibility of doing several extractions simultaneously reduces the whole time of analysis for a set of samples.

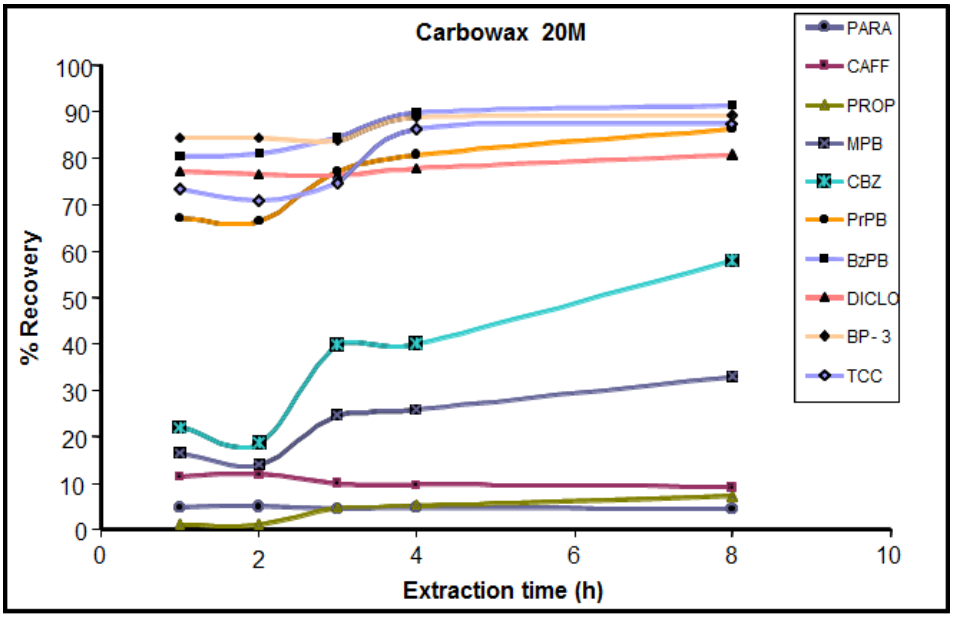

Fig. 4. Effect of the extraction time on the extraction recovery for a representative group of analytes using Carbowax 20M sorbent in FPSE. (%RSD (n=3) were lower than 10% for %R>10%).

The optimal extraction conditions for the different sorbents tested were as follows: 10 mL of sample adjusted at pH 3, containing 10% of NaCl (15% for sol-gel PDMDPS and without salt for sol-gel PEG-PPG-PEG triblock sorbent), extracted at room temperature by stirring at 900 rpm for 4 h extraction time; and for the LD the fabric sorbent was sonicated in 1 mL of MeOH for 5 min (15 min for sol-gel PEG-PPG-PEG triblock sorbent). The extract was evaporated to dryness under gentle nitrogen stream. The residue obtained was re-dissolved in 1 mL of mixture of ultra-pure water at pH 3 and ACN (80:20, v/v).

3.3 Comparison of FPSE sorbent chemistries

As mentioned, all parameters were optimized for each FPSE sorbent in ultra-pure water and the extraction recoveries (%) under optimal conditions are detailed in Table 2. From the results, it can be observed that the less polar compounds have better recoveries than the most polar ones for all four sorbents.

Comparing the results for the different sorbent, it can be seen that sol-gel PDMDPS coating achieved recoveries from 25% to 75% for slightly mid-polar to non-polar analytes such as BzPB, DHMB, DICLO, BP-3, TCC and TCS, whereas sol-gel PTHF coated FPSE media showed better recoveries for these compounds and also for PrPB and DHB. A similar trend was observed for sol-gel PEG-PPG-PEG triblock coated media. In any case, the best results were obtained for sol-gel Carbowax 20M FPSE media, with acceptable recoveries (between 24 and 85%) for all compounds with the only exception of the most polar ones (PARA, CAFF, APy and PROP). It should be taken into account that FPSE is not an exhaustive extraction technique but an equilibrium one.

When the results obtained by the novel technique of FPSE are compared with those obtained in a previous study [18] where SBSE with EG/Silicone was evaluated for the same compounds (results included in Table 2), it can be concluded that FPSE provided better recoveries. In particular, when comparing sol-gel Carbowax 20M coating results a very significant increase in recoveries for most of the compounds are observed. In principle, both EG/Silicone and Carbowax 20M own the same functional groups as both are based on ethylene glycol structure. Nevertheless, the better recoveries achieved with the FPSE with sol-gel Carbowax 20M media can be explained by the higher primary contact area in FPSE media, advanced material properties of sol-gel derived material, complementary

hydrophilic affinity by the fabric substrate and increased analyte diffusion due to the permeable FPSE media.

Table 2. Extraction recovery values (%) (n=3) obtained from different FPSE sorbents when 10 mL of ultra-pure water spiked with 0.2 µg L^{-1} with analyte mixture were extracted with PDMDPS, PTHF, PEG-PPG-PEG and Carbowax 20M sorbents.

Analyte	Extraction recovery (%)				
	PDMDPS	PTHF	PEG-PPG-PEG	Carbowax 20M	SBSE-EG/Silicone[a]
PARA	5	5	-	5	-
CAFF	13	12	1	9	-
APy	7	5	2	4	< 1
PROP	2	< 1	2	4	2
MPB	3	6	14	24	1
CBZ	8	2	15	39	< 1
PrPB	4	43	51	77	10
DHB	7	37	58	75	24
BzPB	25	64	59	84	39
DHMB	32	76	58	85	26
DICLO	34	70	55	76	< 1
BP-3	64	86	62	83	45
TCC	75	81	50	74	59
TCS	75	87	53	80	80

%RSD (n=3) were lower than 10%for % R> 10%.

[a] Recovery values (%) obtained when 50 mL of ultra-pure water spiked with 4 µg L^{-1} with analyte mixture were extracted with SBSE-EG/Silicone coating [18].

Once the different FPSE sorbents had been evaluated for the extraction of the PPCPs from ultra-pure water, the four FPSE media were evaluated for the extraction of these compounds from more complex samples, such as effluent wastewater. Extraction recoveries for the four FPSE media were similar to those obtained with ultra-pure water. For instance, the recoveries for sol-gel Carbowax 20M were between 30 and 95% for all compounds with the only exception of the most polar ones (PARA, CAFF, APy and PROP), and therefore, sol-gel Carbowax 20M was

selected for the method development and validation because of the higher recoveries obtained. At this point, it should be mentioned that the four most polar compounds (namely PARA, CAFF, APy and PROP) were not included in the following method development since these compounds were hardly recovered.

3.4 Method Validation

A common drawback when quantifying using LC–MS/MS with an ESI source is the matrix effect (ME) expressed as percentage decrease (ion suppression) or increase (enhancement) arising from compounds present in the matrix sample. It was calculated as:

$$ME\ (\%) = -\ [100 - (c_b/c_a \times 100)]$$

Where, c_b is the concentration measured in the post-extraction spiked sample and c_a is the concentration of the standard. If the ME (%) = 0 no matrix effect is present, if ME (%) < 0 there is ion suppression and if ME (%) > 0 there is ion enhancement is present.

The apparent recovery ($\%R_{app}$) is referred to the recovery in the whole analytical process, including extraction recovery and ME. It was calculated as:

$$\%R_{app} = (c_b/c_a) \times 100$$

Where, c_b, and c_a are the concentration measured in the pre-extraction spiked sample, and the concentration of the standard, respectively.

Both values were evaluated for river, influent and effluent waste water samples spiked at both 0.2 μg L^{-1} (1 μg L^{-1} for triclosan) and 5 μg L^{-1}, and similar results were obtained at both levels. To do this, first a blank sample was analyzed in order to subtract the possible signal of analytes present in the samples. Ion suppression was observed in all cases, with the exception

of BP-3 and CBZ that presented ion enhancement in river samples. Table 3 shows the results for each sample spiked at 0.2 µg L^{-1} and, even for the influent sample, which is more complex, the ME was acceptable. In order to better quantify the samples, the matrix-matched calibration was applied.

Table 3. Matrix effect (%) and apparent recovery (%R_{app}) obtained from different sample matrices when 10 mL of sample spiked at 0.2 µg $L^{-1}$with the analyte mixture were analyzed by FPSE using Carbowax 20M coated media followed by LC-MS/MS.

Analyte	Effluent water		Influent water		River water	
	ME (%)	R_{app} (%)	ME (%)	R_{app} (%)	ME (%)	R_{app} (%)
MPB	-32	9	-36	14	-21	27
CBZ	-29	20	-17	32	48	92
PrPB	-34	43	-39	41	-22	65
DHB	-24	55	-32	44	-14	74
BzPB	-31	67	-36	45	-28	65
DHMB	-27	74	-26	50	-21	67
DICLO	-37	44	-29	52	-16	73
BP-3	-16	80	-14	59	8	93
TCC	-23	58	-24	57	-19	59
TCS [a]	-39	47	-38	43	-29	54

%RSD (n=3) were lower than 15% for % R_{app}> 20%.
[a] spiked at 1 µg L^{-1}.

In an analogous trend, % R_{app} (Table 3) for each compound is similar for the three samples analyzed, and they are slightly lower to the extraction recoveries, which is mainly attributed to the ME.

Table 4 includes the validation parameters for the effluent wastewater sample and good linearity was observed for the range specified in the table with determination coefficient (R^2) values greater than 0.998. The method LODs of different analytes calculated by S/N ≥ 3 ranged from 1 - 10 ng L^{-1},

except for TCS (50 ng L^{-1}), the method LOQs were calculated the lowest point of the calibration curve and ranged between 10 - 50 ng L^{-1} for all the compounds, with the exception of TCS which was 200 ng L^{-1}. In most of the compounds, these LODs were lower than those obtained in the previous study [18] using SBSE and the same LC-MS/MS instrument, where LODs of 5 - 10 ng L^{-1} were obtained. The repeatability and reproducibility between days of five samples spiked at 0.2 µg L^{-1} (1 µg L^{-1} for triclosan), expressed as % relative standard deviation (% RSD), were lower than 15% and 18%, respectively.

Table 4. LODs, LOQs, linear range, repeatability and reproducibility between days obtained when 10 mL of effluent wastewater sample spiked at 0.2 µg $L^{-1}$of each analyte were analyzed by FPSE using Carbowax 20M media followed by LC-MS/MS.

Analyte	LODs (ng L^{-1})	LOQs (ng L^{-1})	Linear range (ng L^{-1})	Repeatability (%RSD, n=5)	Reproducibility (%RSD, n=5)
MPB	10	50	50 - 10000	8	9
CBZ	10	50	50 -10000	7	7
PrPB	2	20	20 - 10000	6	8
DHB	5	50	50 - 10000	6	13
BzPB	1	20	20 - 10000	8	15
DHMB	2	20	20 - 5000	9	15
DICLO	1	20	20 - 5000	10	13
BP-3	2	20	20 - 5000	7	12
TCC	3	10	10 - 1000	8	18
TCS[a]	50	200*	200 - 10000	15	12

[a] spiked at 1 µg L^{-1} under the same conditions.

The results obtained in the validation process demonstrated the good performance of the FPSE/LC-MS/MS method developed using the Carbowax 20M sorbent.

3.5 Analysis of real samples

In order to demonstrate the application of the new method, different samples from Ebre River, effluent and influent waste water were analyzed. Three different samples from the same location and at different sampling period were analyzed in triplicate. Results for waste water samples are included in Table 5. As can be seen, all analytes were present in the collected samples, although in some cases at concentration below the LOQ and TCS were not detected in any of the effluent samples. Those analytes found at higher concentrations were MPB, CBZ, DICLO, and BP-3 in waste water samples. Their presence was confirmed by retention time and ion ratio between qualification and quantification ions.

Table 5. Concentration range of analytes found in three effluent and influent wastewater samples by FPSE using Carbowax 20M media followed by LC-MS/MS.

Analyte	Concentration (ng L^{-1})	
	Effluent water	Influent water
MPB	111 - 170	87 - 187
CBZ	189 - 323	289 - 344
PrPB	28 - 49	55 - 227
DHB	<LOQ	129 - 217
BzPB	<LOQ	<LOQ
DHMB	<LOQ	<LOQ
DICLO	57 - 763	205 - 776
BP-3	93 - 168	160 - 356
TCC	21 - 39	<LOQ - 62
TCS	n.d.	<LOQ

n.d: not detected.

As regards the river samples, only BP-3 was quantified between LOQ and 26 ng L^{-1}, and MPB and PrPB were found at concentration below the LOQ in one sample.

These results agree with those obtained in previous studies where the samples from the same WWTP [18,37,38] and river [37,38] were analyzed. As an example, Fig. 5 shows the chromatogram of one effluent sample analyzed where all target analytes were found except TCS.

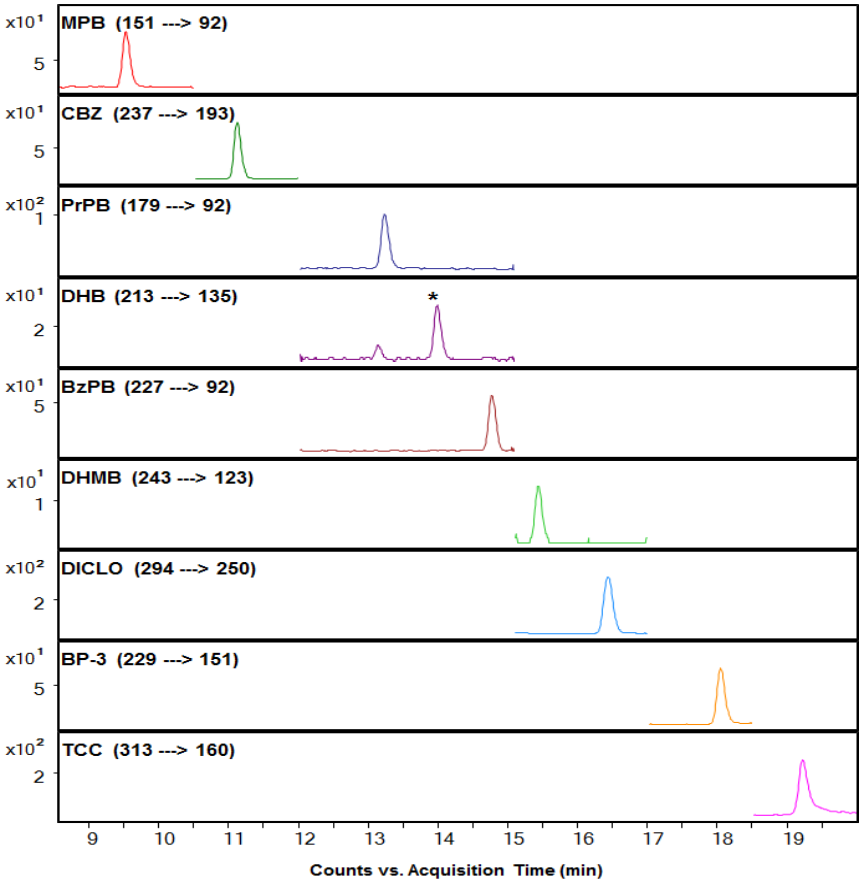

Fig. 5. MRM chromatogram of an effluent WWTP sample analyzed by FPSE/LC-MS/MS. For experimental conditions see the text. * Denotes the peak of DHB.

When the values in influent and effluent samples were compared, it can be seen that, as expected, concentrations were lower in effluent samples due to the treatment process but the elimination was different for each compound. It should be mentioned that the samples were grab samples and

the elimination efficiency cannot be calculated, but the trend for some compounds clearly agree with those described in the literature. For instance, it is known that elimination efficiency for CBZ and DICLO are very low [39] and values are similar in influent and effluent samples.

4 CONCLUSIONS

A new extraction technique, FPSE, was evaluated for the extraction of a group of PPCPs of wide range of polarity from environmental waters. Four different FPSE sorbents (sol-gel PDMDPS, sol-gel PTHF, sol-gel PEG-PPG-PEG triblock copolymer and sol-gel Carbowax 20M) for the new sorptive extraction technique were compared. Sol-gel Carbowax 20M provided the best FPSE performance for the extraction of selected PPCPs. The sol-gel Carbowax 20M coated FPSE media substantially improved the extraction efficiencies for the analytes with wide range of polarity compared to those obtained in previously studied SBSE-EG/Silicone coating, mainly due to the advanced material properties of sol-gel derived material, larger primary contact surface area of FPSE media, and synergistic selectivity enhancement by the polar Carbowax 20M polymer, polar 3-CPTEOS precursor and strong hydrophilic property of cellulose fabric substrate.

When Carbowax 20M coated FPSE media was used for the extraction of selected PPCPs from 10 mL of river water, effluent and influent wastewater samples, recoveries of target analytes and ME were acceptable taken into account the complexity of the sample. The combination of FPSE with LC-(ESI) MS/MS provided an efficient, simple and sensitive method for the determination of PPCPs from environmental water samples at low levels and it is an economical and green alternative to the other extraction techniques such as SBSE or SPE.

Acknowledgments

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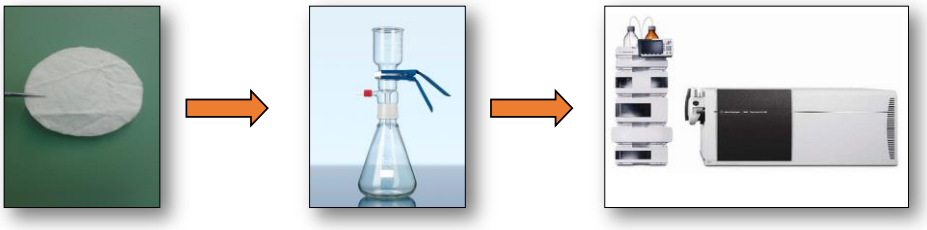
3.1.2. Dynamic fabric phase sorptive extraction for a group of pharmaceuticals and personal care products from environmental waters



UNIVERSITAT ROVIRA I VIRGILI
EVALUATION OF NOVEL SORPTIVE EXTRACTION TECHNIQUES
Sameer Shamrao Lakade

DYNAMIC FABRIC PHASE SORPTIVE EXTRACTION FOR A GROUP OF PHARMACEUTICALS AND PERSONAL CARE PRODUCTS FROM ENVIRONMENTAL WATERS

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Abstract

This paper describes for the first time the use of a new extraction technique, based on fabric phase sorptive extraction (FPSE). This new mode proposes the extraction of the analytes in dynamic mode in order to reduce the extraction time. Dynamic fabric phase sorptive extraction (DFPSE) followed by liquid chromatography-tandem mass spectrometry was evaluated for the extraction of a group of pharmaceuticals and personal care products (PPCPs) from environmental water samples. Different parameters affecting the extraction were optimized and best conditions were achieved when 50 mL of sample at pH 3 was passed through 3 disks and analytes retained were eluted with 10 mL of ethyl acetate. The recoveries were higher than 60% for most of compounds with the exception of the most polar ones (between 8% and 38%). The analytical method was validated with environmental samples such as river water and effluent and influent wastewater, and good performance was obtained. The analysis of samples revealed the presence of some PPCPs at low ng L^{-1}concentrations.

Keywords: dynamic fabric phase sorptive extraction (DFPSE); sol-gel carbowax 20M material; liquid chromatography-tandem mass spectrometry; pharmaceuticals and personal care products (PPCPs); environmental water samples

1 INTRODUCTION

Pharmaceuticals and personal care products (PPCPs) are extensively used in our day-to-day life and, after their consumption, they often enter into the environment, mainly from household water because of their ability to pass through the wastewater treatment plants. Their presence may affect human and aquatic life, as they are known to be hazardous and may be accumulated in various environmental compartments due to their continuous release into the environment. Consequently, these compounds are frequently found in waste, surface and even ground water [1–5]. Thus, they are considered to be contaminants of emerging concern.

Due to the growing interest in determining contaminants at low concentration levels in complex matrices, many different extraction techniques have been developed for liquid samples. In the last years, solid-phase extraction (SPE) has become the technique of choice [6–8], although some other techniques have been success-fully applied, such as solid-phase microextraction (SPME) [9,10] and stir bar sorptive extraction (SBSE) [11,12], among others. However, the most important drawbacks of these techniques [13–15] are the low sorbent present in the fibres of SPME, and the limited number of available sorbent type and slow analyte diffusion rate through polymeric coating in SBSE. A novel sorptive extraction technique, fabric phase sorptive extraction (FPSE), was recently introduced by Kabir and Furton [16]. This technique consists of the use of a flexible fabric substrate surface coated with different polymers/functional moieties using sol-gel technology so that high primary contact surface area is available for extraction. These unique sorbent chemistries have been developed to cover wide range of analyte polarities and include sol-gel Carbowax 20M [17], sol-gel poly(tetrahydrofuran) [18], sol-gel poly(dimethyldiphenylsiloxane) [19,20], among others. The sol-gel coated FPSE medium (25 × 20 mm^2) can be

directly introduced into the sample for the analyte extraction and, once equilibrium is reached, the analytes retained on the extraction medium can be back-extracted using a small volume of organic solvent [21].

To date, FPSE has been applied to extract several analytes from different samples, such as benzotriazole UV stabilizers in sewage samples [22], alkyl phenols in aqueous and soil samples [23], benzodiazepines in blood samples [24], estrogens in urine and environmental water samples [18], polar antibiotic in raw milk [25], non-steroidal anti-inflammatory drugs [19] and triazine herbicides in environmental water samples [20]. Our research group evaluated FPSE for the extraction of a group of PPCPs followed by liquid chromatography-tandem mass spectrometry (LC–MS/MS) with satisfactory results [17]. However, the main drawback of FPSE was the extraction time (up to four hours) required to reach the extraction equilibrium. To overcome this long extraction time, anew mode of the FPSE approach is proposed, called dynamic fabric phase sorptive extraction (DFPSE). DFPSE uses 47 mm circular disks of FPSE media coated with sorbent material of different polarities using sol–gel coating technology. In the new extraction mode of FPSE, the sample is percolated through the FPSE disks installed on a filtration assembly. Following the extraction of the target analytes into the FPSE disks, the retained analytes are eluted by passing a volume of the elution solvent through the same assembly. This configuration may decrease the equilibrium time while maintaining the rest of features.

The present work describes for first time the use of the DFPSE technique whose performance efficiency was evaluated using a group of PPCPs in environmental water samples. In this study, different parameters affecting the dynamic extraction mode were optimized and the results were compared with those obtained with static FPSE, where the sol-gel Carbowax 20M coated media were also used [17]. Subsequently, a method was

developed based on the new DFPSE mode followed by LC–MS/MS and it was validated for the determination of PPCPs from river and wastewater samples.

2 MATERIALS AND METHODS

2.1 Reagents and standards

Substrates for fabric phase sorptive extraction (FPSE) media (unbleached Muslin, 100% cellulose cotton fabric) were purchased from Jo-Ann Fabric (Miami, FL, USA). Poly(ethylene glycol) (Carbowax 20 M) polymers, acetone, dichloromethane, methyltrimethoxysilane (MTMS), trifluoroacetic acid (TFA) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Sodium hydroxide (NaOH) and hydrochloric acid (HCl) were purchased from Thermo Fisher Scientific (Milwaukee, WI, USA).

The reagents for the analytical evaluation were: paracetamol (PARA), caffeine (CAFF), antipyrine (APy), propranolol hydrochloride (PROP), methylparaben (MPB), carbamazepine (CBZ), propylparaben (PrPB), 2,4-dihydroxybenzophenone (DHB), benzylparaben (BzPB), 2,2-dihydroxy-4-4-methoxybenzophenone (DHMB), diclofenac (DICLO), 3-benzophenone (BP-3), triclocarban (TCC) and triclosan (TCS) and all of them were purchased from Sigma-Aldrich (Steinheim, Germany). Stock solutions of individual standards were prepared by dissolving each compound in methanol (MeOH) at concentration of 1000 mg L^{-1}. A mixture of standards of all compounds at 50 mg L^{-1} was prepared in MeOH every month. Working standard solutions were prepared weekly by diluting with mixture of ultrapure water at pH 3 and ACN (80:20, v/v). All the solutions were stored at 4^{o}C. Ultrapure water was obtained from a water purification system (Veolia Waters, Barcelona, Spain) and the elution solvent was evaporated using the miVac Duo system (Genevac, Ipswich, United Kingdom). HPLC grades MeOH, acetonitrile

(ACN) and ethyl acetate (EtOAc) were supplied by Scharlab (Barcelona, Spain). Sodium chloride (NaCl) and formic acid (HCOOH) (95% purity) were purchased from Sigma-Aldrich.

2.2 Preparation of FPSE media

Preparing the substrate for sol-gel coating, design and preparation of the sol-gel coating solution, applying the sol-gel coating on the pre-treated substrate, conditioning and ageing of the sol–gel coated FPSE media, and the post-coating cleaning of the FPSE media are the sequential steps that are followed to create an inherently porous sol-gel coated permeable FPSE media. A detailed account one very steps mentioned herein are described elsewhere [17]. However, a summary of the entire process is given below. Selection of the suitable FPSE media takes into consideration the hydrophobicity or hydrophilicity of the target analytes. Considering the fact that majority of the selected PPCPs are either highly polar (PARA, CAFF, APy, MPB, CBZ) or moderately polar (PROP, PrPB, DHB, BzPB), a hydrophilic substrate would have been a suitable choice as the substrate may synergistically complement to the overall polarity and the selectivity of the FPSE media. As such, 100% cotton cellulose, being a hydrophilic substrate, was selected as the substrate for sol–gel coating. The cellulose fabric support was treated with NaOH solution to activate surface hydroxide groups, neutralized with dilute HCl, washed with deionized water and dried in an inert atmosphere prior to the sol-gel coating. Due to the good results obtained in previous study [17] using FPSE, a polar polymer Carbowax 20M was selected as the organic polymer from a large number of polymer candidates. Methyltrimethoxysilane (MTMS) was used as the sol-gel precursor in order to prevent from shrinking and cracking of the sol-gel coating often seen when trimethoxysilane or triethoxysilane are used as the sol-gel precursor. In addition to prevent the sol–gel coating from cracking and shrinking, MTMS also exerts London dispersion type of intermolecular interaction via methyl

functional groups towards the target analytes. TFA was used as the sol-gel catalyst. Formation of a homogeneous sol solution incorporating all the sol solution ingredients is of prime importance to the success of a sol-gel coating. An equimolar mixture of dichloromethane and acetone was needed to prepare homogeneous sol solutions for sol–gel Carbowax 20M coatings. The molar ratio between the sol–gel precursor and Carbowax 20M was kept at1:0.02. The molar ratio between sol–gel precursor, solvent, catalyst, and water was maintained at 1:3.90:1.31:0.30, respectively.

Sol-gel coating was carried out via dip coating technique. The pre-treated substrates were kept submerged in the sol solution for four hours and then sol solution was discarded and the coated fabrics were transferred into a desiccator for conditioning and ageing of the sol-gel coating. The coated FPSE media were then rinsed with a mixture of dichloromethane: acetone (50:50; v/v) under sonication for 30 min to remove unreacted sol solution ingredients as well as other sol-gel reaction intermediates or by-products from the FPSE media. Finally, after drying the FPSE media in an inert environment, they were cut into 47 mm diameter FPSE disks.

2.3 Dynamic fabric phase sorptive extraction

The DFPSE conditions were optimized using sol-gel Carbowax20M coated FPSE media. Prior to any extraction, the FPSE disks, placed in the filtration assembly, were conditioned and equilibrated by passing 10 mL MeOH followed by 10 mL of ultrapure water, and then dried by applying vacuum. For the extraction, 50 mL of sample (25 mL for influent wastewater) adjusted to pH 3 with HCOOH and containing 10% of NaCl (w/v) were loaded. Then, the sample was left for 10 min in contact with the FPSE disk for the retention of analytes. After 10 min, a vacuum was applied to pass the sample through the FPSE disk completely, and then to dry the FPSE media. The retained analytes were eluted by passing 10 mL of EtOAc through the

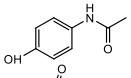
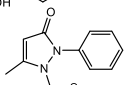
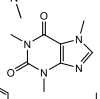
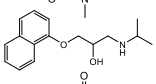
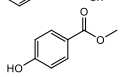
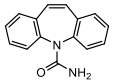
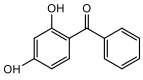
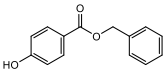
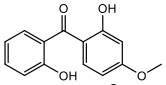
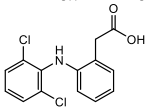
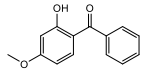
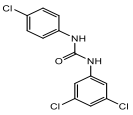
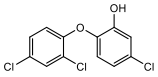
same assembly and they were collected in a receiver flask. The extract was evaporated to dryness in a miVac concentrator. Prior to LC-(ESI)MS/MS injection, the residue obtained was redissolved in 1 mL of ultrapure water at pH 3 and ACN (80:20, v/v) solution. After each use, the FPSE disk was cleaned twice with 5 mL of MeOH in the ultrasonic bath for 5 min, then dried and stored in the glass vial until the next experiment.

All water samples including river water and influent and effluent water from wastewater treatment plant (WWTP) were collected using pre-cleaned plastic bottles. Prior to the extraction, these samples were filtered through nylon supported 0.45 µm membrane filters (Fisher, Loughborough, UK) to eliminate any particulate matter present, then acidified to pH 3 with HCOOH and stored at 4ºC until analysis.

2.4 Liquid chromatography-tandem mass spectrometry analysis

To analyze the extracts a 1200 series liquid chromatography coupled to a 6410 series triple quadrupole mass spectrometer with an electrospray ionization (ESI) interface, and equipped with an automatic injector, a degasser, a quaternary pump and a column oven from Agilent Technologies (Waldron, Germany) was used. The optimized parameters for LC and (ESI) MS/MS were taken from a previous study [17]. The column used for chromatographic separation was the reversed-phase Kromasil 100 C_{18} (150 mm × 4.6 mm i.d., 5 µm) from Teknokroma (Sant Cugat del Vallès, Spain). The temperature of the chromatographic column was maintained at 40ºC and the flow-rate was 0.6 mL min^{-1}. The mobile phase consisted of ACN and ultrapure water adjusted to pH 3 with HCOOH. The gradient started at 20% ACN, which was increased to 80% ACN in 15 min, to 90% ACN in 7 min, to 100% in1 min and kept constant for 8 min. Finally, it was returned to the initial conditions in 3 min, which were held for 8 min to equilibrate the column for further analysis. 50 µL of the extract were injected into LC-(ESI) MS/MS.

Table 1. General parameter of structures, t_R, pK_a and LC-(ESI)MS/MS acquisition parameters in MRM mode for each analyte.

Analyte	Structure	t_R min	Log K_{ow}[a]	pK_a[a]	Cone voltage (V)	MRM Transition (collision energy (ev))	Ionization mode (ESI)
PARA		3.9	0.5	9.2	100	152 > 110 (15) 152 > 93 (25)	+
CAFF		4.4	-0.6	13.4	125	195 > 138 (15) 195 > 110(25)	+
APy		6.7	1.4	13.3	100	189 >145 (30) 189 >115 (30)	+
PROP		7.6	2.9	9.5	125	260 > 116 (15) 260 > 183 (15)	+
MPB		9.5	1.9	8.3	80	151 > 92 (15) 151 > 136 (5)	–
CBZ		11.0	1.9	13.7	150	237 > 193 (35) 237 > 179 (35)	+
PrPB		13.1	2.9	8.2	100	179 > 92 (15) 179 > 136 (5)	–
DHB		13.9	3.2	7.7	130	213 > 135 (15) 213 > 169 (5)	–
BzPB		14.7	3.6	8.2	100	227 > 92 (10) 227 > 136 (20)	–
DHMB		15.3	4.3	7.1	80	243 > 93 (15) 243 > 123 (15)	–
DICLO		16.4	4.5	4.2	75	294 > 250 (5) 294 > 214 (15)	–
BP-3		18.0	4	7.6	130	229 > 151 (15) 229 > 105 (15)	+
TCC		19.2	6.1	12.7	130	313 > 160 (5) 313 > 126 (15)	–
TCS		19.5	5.3	7.9	18	287 > 35 (18) 289 > 35 (18)	–

[a] Calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02 (© 1994-2012 ACD/Labs).

The analyses were performed in MRM mode in positive or negative ionization mode. The optimized ESI parameters were as follows: N_2 flow rate of 12 L min^{-1}, capillary voltage of 4000 V, nebulizer pressure of 45 psi (N_2) and source temperature of 350°C. The cone voltage and collision energies for all of the compounds were between 18 and 200 V, and 5 and 35 eV, respectively (optimal values are summarized in Table 1). The confirmation of the presence of the compound was performed by comparing the retention time and ratios of two MRM transitions with those from the standard.

Using the LC–MS/MS in MRM mode, linear range for the selected analytes was between 0.1 and 50 µg L^{-1}, except for TCS, which were between 2 and 50 µg L^{-1}. The lowest points of the calibration curve were considered as the instrumental limits of quantification (ILOQs). The instrumental limits of detection (ILODs), calculated as a signal-to-noise ratio (S/N) of 3 ranged from 0.02 to 0.5 µg L^{-1}.

3 RESULTS AND DISCUSSION

3.1 Optimization of DFPSE procedure

In our previous study, the static FPSE technique was used for the extraction of PPCPs from environmental water samples. In that study, we evaluated several FPSE media coated with sorbents having different polarities: non-polar sol-gel poly(dimethyldiphenylsiloxane) (PDMDPS), mid polar sol-gel poly(tetrahydrofuran) (PTHF), and polar sol-gelpoly(ethyleneglycol)-block-poly(propyleneglycol)-block-poly(ethyleneglycol)-(PEG-PPG-PEG triblock) and sol–gel Carbowax 20M. Sol–gel Carbowax 20M provided the highest recoveries for the analytes tested [17] and therefore, this extraction medium was selected for the present study.

Taking advantage of the previous information, the dynamic extraction mode was evaluated for the same group of PPCPs. In order to obtain high extraction efficiencies for the DFPSE, several parameters were optimized: extraction time, ionic strength, sample volume and number of FPSE disks. For the desorption, elution solvent and its volume were optimized. Initial experimental conditions were: 10 mL of ultrapure water adjusted to pH 3 with HCOOH spiked at 2 μg L^{-1} with the mixture of analytes percolated through the FPSE disk using the filtration assembly. For the elution of the retained analytes, two times 5 mL of MeOH were passed. These two 5 mL fractions of the eluted solvent were evaporated and the residue was re-dissolved in 1 mL of ultrapure water at pH 3 and ACN (80:20, v/v) before injecting into LC-(ESI) MS/MS.

3.1.1 Extraction conditions

The effect of sample pH on the extraction efficiency had already been investigated in our previous study at pH 3, 5, 7 and 9 [17], with better results being obtained under acidic conditions at pH 3 for the extraction of PPCPs from water sample. Therefore, this value was selected for the current study.

At initial conditions, the recoveries were not very high, so attempts were made to increase the retention of the analytes by increasing the contact time, leaving the sample in contact with the FPSE disk before applying the vacuum. The contact time was optimized from 10 to 60 min. The results showed that the extraction efficiencies increased about 10% in recoveries when the extraction time was 10 min but they did not improve significantly with higher contact time. In addition, extended extraction time was not suitable for the desirable routine analysis method, and the aim of this new mode was to reduce extraction time. Therefore, an extraction time of 10 min was selected for subsequent analyses, with better results and much shorter time being necessary compared to the 4 h needed in static FPSE [17], or even

compared to some commercially available and in-house SBSE materials [11,12,26].

The ionic strength effect was evaluated by adding NaCl from 0% to 20% (w/v) in the sample. It was observed that the extraction efficiencies increased when the concentration of NaCl increased from 0% to 10%, but decreased when the concentration of NaCl was raised to 20%, except in the case of APy, PROP, MPB and CBZ. Extraction efficiencies increased due to the salting-out effect and electrostatic interaction between polar molecules and salt ions in the solution [27]. Therefore, the addition of 10% of NaCl was chosen to provide the best results for further studies, which also agreed with the results obtained with static FPSE [17].

In order to improve analyte recoveries, the number of FPSE disks used for the extraction of PPCPs was increased. Here, the effect of extraction recovery was evaluated when one or three FPSE disks were used. It was observed that the number of FPSE disks increased the percentage of recovery (increasing between 5% and 20%) for all of the analytes. Thus, three FPSE disks were selected for the further studies. The next step was to determine the sample volume that could be loaded. To do this, volumes of 10, 25, 50 and 100 mL of ultrapure water spiked with the analyte mixture were tested. Fig. 1 shows that, when the sample volume was increased from 10 mL to 25 mL, the recoveries decreased (~8% on average) for the PARA, CAFF, APy, PROP, MPB and CBZ. When 50 mL and 100 mL of sample volume were extracted, the recoveries decreased between 5% and 25% for the all of the analytes and, therefore, 50 mL of sample volume was selected as a compromise between recoveries and the sensitivity of the method.

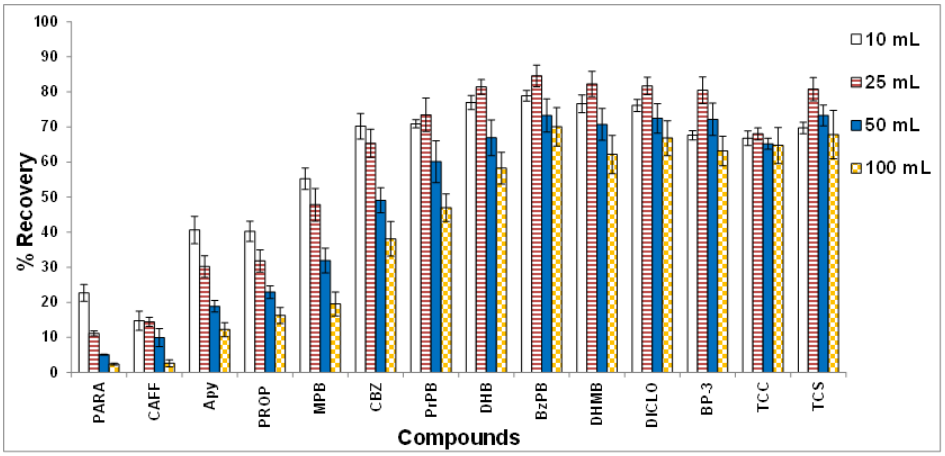


Fig. 1. Effect of the sample volume on extraction recovery of analytes using sol-gel Carbowax 20M material in DFPSE.

3.1.2 Solvent desorption conditions

Different solvents used to back-extract the analytes retained in the FPSE disks were tested. Apart from MeOH, 5 mL of other sol-vents such as ACN, mixture of MeOH/ACN (1:1, v/v) and EtOAc were tested. All the solvents tested showed similar results for the studied analytes, which included different polarities, but EtOAc took less time to be evaporated and, therefore, this was the selected elution solvent.

For determining the volume of the elution solvent, three fractions of 5 mL of EtOAc were passed through the FPSE disks and recoveries up to 65% were obtained in the first fraction of 5 mL. However, some analytes (recoveries ranging from 10% to 15%) still appeared in the second fraction. Furthermore, when 5 mL of solvent volume was additionally passed through the FPSE disks, no significant increase in recovery was observed. Therefore, 10 mL of EtOAc was chosen as the optimal volume for elution.

The 10 mL of EtOAc was evaporated to dryness in a miVac concentrator and the residue re-dissolved in 1 mL of ultrapure water at pH 3

and ACN (80:20, v/v) before being injected into LC. No significant losses were observed during this step (less than 5% losses). To check for the possible carryover effect, the FPSE disks were washed with 5 mL of MeOH in a sonication bath for 5 min twice and, when analyzed, after evaporation and reconstitution, no carryover was observed. In addition, each FPSE disk can be used for several times (more than 20) for the extraction of water samples.

To summarize, the optimal extraction conditions for the DFPSE-Carbowax 20M coated FPSE disks were as follows: (a) load 50 mL of sample adjusted to pH 3 with HCOOH, containing 10% of NaCl (w/v) on three FPSE disks placed in the filtration assembly; (b) let the sample be in contact with the media for 10 min to enhance the retention of the analytes and then apply vacuum to draw sample through FPSE disks; (c) dry the FPSE disks; (d) elute the retained analytes by passing 10 mL of EtOAc; (e) evaporate the extract to dryness, and redissolve it in 1 mL of the mixture of ultrapure water at pH 3 and ACN (80:20, v/v); (f) inject 50 µL into LC-(ESI)MS/MS instrument. When comparing these optimal conditions to the ones of static FPSE [17], these DFPSE conditions involve higher sample volume (from 10 mL in FPSE to 50 mL in DFPSE), which leads to higher sensitivity, and shorter extraction time (from 240 min in FPSE to 10 min in DFPSE).

Different extraction techniques had been evaluated for the PPCPs, but they still had certain drawbacks, such as the extraction time of over an hour [11, 26, 28] and the low recoveries for the most polar analytes. For instance, when using SBSE with commercial coating based on EG/Silicone [11] the recoveries for the most polar analytes (PARA, CAFF, APy and PROP) were not higher than 2% when 50 mL of sample were extracted, whereas when in-house SBSE coating based on poly(PEGMA-co-PETRA) [26] was used to extract these analytes from 50 mL of sample, recoveries were between 2 and 19%. Therefore, DFPSE mode provided promising results.

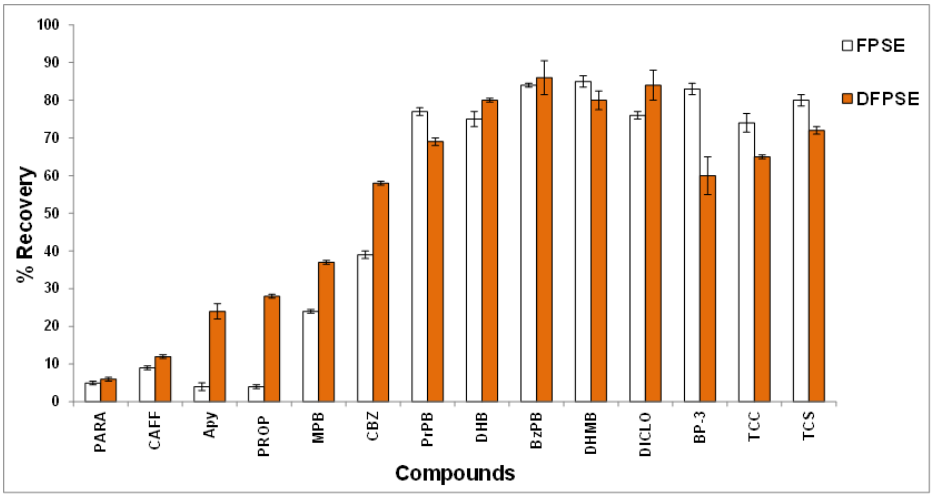


Fig. 2. Recovery obtained by FPSE and DFPSE at optimum conditions of each technique using Carbowax 20M. FPSE: 10 mL of ultrapure water spiked at 0.2 µg $L^{-1}$of each analyte [17]. DFPSE: 50 mL of ultrapure water spiked at 0.6 µg $L^{-1}$of each analyte.

3.2 Evaluation and validation of DFPSE with environmental samples

After optimization, DFPSE was applied for the extraction of the PPCPs from environmental water samples, such as river water, and effluent and influent samples from WWTP. Due to the low recoveries obtained for PARA and CAFF, the method was validated excluding these two analytes.

When working in the electrospray ionization mode in LC–MS/MS, the matrix effect (%ME) is one of the main problems that arises in the quantification of the analytes in complex samples. This can result in the suppression or enhancement of analyte response, leading to erroneous quantification. %ME was calculated as the ratio of the signal of each analyte when it was spiked in the sample (river water, effluent or influent wastewater) after extraction by DFPSE and their signal in standard solution. Apparent recovery (%R_{app}) was calculated as the ratio of the signal of each analyte in the sample spiked before DFPSE and the signal of each analyte in standard solution. As is known, the %R_{app} includes the extraction recovery and the ME.

Table 2. $\%R_{app}$ and %ME of PPCPs in river, effluent and influent WWTP sample by DFPSE extraction techniques (n=3).

Analyte	River [(a)]		Effluent WWTP [a]		Influent WWTP [b]	
	% R_{app}	%ME	% R_{app}	%ME	% R_{app}	%ME
APy	10	-13	8	-11	3	-7
PROP	26	-15	5	-7	3	-9
MPB	30	-25	16	-13	12	-27
CBZ	53	-10	13	-26	8	-11
PrPB	64	-22	31	-28	20	-49
DHB	68	-22	38	-23	21	-52
BzPB	70	-24	50	-21	33	-46
DHMB	76	-5	64	9	39	-28
DICLO	49	-24	50	-32	23	-50
BP - 3	52	-26	52	-34	45	-37
TCC	49	-20	29	-30	5	-52
TCS	43	-26	32	-36	12	-48

[a] 50 mL spiked at 0.6 µg L^{-1}
[b] 25 mL spiked at 1.2 µg L^{-1}

The %ME and $\%R_{app}$ were calculated when 50 mL of river and effluent wastewater was spiked at 0.6 µg L^{-1}. When an influent sample was analyzed, the sample volume was decreased to 25 mL, due to complexity of the sample. Previously, each sample was analyzed without spiking and the results of the analytes present in the sample were subtracted to determine %ME and $\%R_{app}$. The %ME and $\%R_{app}$ for all three samples are shown in Table 2. While dealing with different water samples, ion suppression was observed, with the exception of DHMB, with 9% enhancement when analyzing effluent wastewater samples. The %ME values are acceptable and range from −5% to −26% for river samples, and from −7% to −36% for effluent samples. As expected, when dealing with influent sample, the %ME values were higher, up to −52%. In all of the samples, the analytes that were most affected by ion suppression were the last compounds to be eluted, due to the co-elution of these compounds with organic components of the matrix. These ME results are inline of other studies that determine these PPCPs in

complex matrices, such as the one obtained in a previous study [17]. The $\%R_{app}$ (detailed in Table 2) were acceptable if the above values of %ME are taken into account. In addition, in influent samples, as expected the $\%R_{app}$ values decrease for all the compounds. In all of the samples, the compounds that showed the lowest $\%R_{app}$ were APy and PROP, since they also showed low recoveries in ultrapure water. In view of this, APy and PROP were also discarded for the validation in wastewater samples.

Table 3. Linear range, LODs, LOQs, repeatability, reproducibility between days obtained when 50 mL of spiked effluent wastewater sample analyzed by DFPSE followed by LC–MS/MS.

Analytes	Linear range (ng L^{-1})	LODs (ng L^{-1})	Repeatability[a] (%RSD.n=5)	Reproducibility[a] (%RSD.n=5)
MPB	50 - 1000	4	11	17
CBZ	50 – 1000	4	19	19
PrPB	50 – 1000	2	12	20
DHB	50 – 1000	2	11	15
BzPB	50 – 1000	2	14	15
DHMB	50 – 1000	2	6	13
DICLO	50 – 1000	2	6	7
BP - 3	100 - 1000	2	16	13
TCC	50 – 1000	8	2	13
TCS	100 - 1000	20	6	8

[a] Spiked at 200 ng L^{-1}

The analytical method based on DFPSE/LC–MS/MS was validated with effluent wastewater samples in terms of linearity, repeatability, reproducibility, limits of detection (LODs), and limits of quantification (LOQs) and results are shown in Table 3. The calibration curve was built using the matrix-matched calibration approach at 5 concentration levels in duplicate, and the analytes showed good linearity with determination coefficient (R^2) values greater than 0.993. The LOQ obtained from the lowest point of the calibration curve ranged between 20 and 50 ng L^{-1} for all compounds, with the exception of

BP-3 and TCS (100 ng L^{-1}). The LODs were estimated on the basis of the instrumental LODs and $\%R_{app}$ because all of these compounds were present in the sample. The intra-day repeatability (n=5) and inter-day reproducibility (n=5) for all compounds expressed as relative standard deviation (%RSD) of 50 mL effluent wastewater sample spiked at 200 ng L^{-1} were lower than 19% and 20%, respectively

3.3 Analysis of environmental water sample

The DFPSE/LC–MS/MS method was applied to determine the presence of these PPCPs in three kinds of matrices, which were taken on three different days and analyzed in triplicate.

In view of the differences in the $\%R_{app}$, mainly for influent wastewater samples compared to river and effluent wastewater samples, and in order to provide more accurate results, firstly, a matrix-matched calibration curve was prepared for each kind of sample to be analyzed (i.e. river water and influent wastewater samples) in a similar range to the one previously reported in the validation for effluent wastewater samples.

Table 4 includes the concentration found in river water, and effluent and influent wastewater samples. As can be seen, when analyzing river water samples, only MPB (<LOQ-64 ng L^{-1}) and DHMB (45-64 ng L^{-1}) were found, while the other PPCPs were not detected. These values are comparable to previous studies in which samples from the same river were analyzed [12, 29, 30].

Similarly, effluent and influent wastewater samples were analyzed. It can be seen that, all of the analytes were present in both wastewater samples. In effluent samples, some analytes, such as MPB, CBZ, DHMB and DICLO, were quantified in all of the samples, whereas the other analytes

were found at concentrations lower than the LOQ. In influent samples, the highest concentrations found were for CBZ, PrPB, DHB and DICLO, while BzPB, BP-3, TCC and TCS were found at concentrations below the LOQ, except in the case of MPB and DHMB, which were in the ranges of <LOQ-257 ng L^{-1} and <LOQ-28 ng L^{-1}, respectively. As expected, most of the analytes were found at higher concentrations in influent rather than effluent wastewater due to the wastewater treatment, except CBZ and DICLO, which were found at similar concentrations in both effluent and influent samples. The concentrations found of these PPCPs are in line with those found in the same kind of samples [12, 17, 29, 31].

Table 4. Concentration (ng L^{-1}) of found in river, effluent and influent in WWTP sample (n=3).

Analyte	River	Effluent WWTP	Influent WWTP
APy	nd	nd	nd
PROP	nd	nd	nd
MPB	<LOQ-64	51 - 62	< LOQ - 257
CBZ	nd	189 - 306	119 - 343
PrPB	nd	< LOQ	425 - 660
DHB	nd	< LOQ	261 - 324
BzPB	nd	< LOQ	< LOQ
DHMB	45-64	55 - 76	< LOQ - 28
DICLO	nd	203 -420	177 - 241
BP - 3	nd	< LOQ	< LOQ
TCC	nd	< LOQ	< LOQ
TCS	nd	< LOQ	< LOQ

nd: not detected

4 CONCLUSIONS

A novel dynamic mode of FPSE is presented for the first time. DFPSE with sol-gel Carbowax 20M material was successfully applied for the extraction of a group of PPCPs from environmental water samples with

shorter equilibrium time and higher retention than static FPSE for some analytes extracted.

The optimization of different parameters, such as using three FPSE disks and leaving the sample for 10 min before applying the vacuum, was positive in terms of achieving good extraction recoveries of the analytes.

The combination of the new DFPSE with LC–MS/MS provided an efficient, rapid, simple and sensitive method for the determination of PPCPs at low levels of concentration in complex environmental samples. The results of these studies encourage us to further test this new mode with other target compounds in different kind of samples.

Acknowledgments

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3.1.3. Discussion of results

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Although the results of the experimental part of the studies included in this section have been already discussed separately in their respective papers, the following section discusses the most important aspects of both of them.

The previous studies focused on two different approaches, static and dynamic mode, for the evaluation of FPSE as an alternative to other sorptive extraction techniques. The developed FPSE methods using both approaches are the first studies for analytes of a wide range of polarities. Before applying them, different parameters were optimized. Table 1 compares the optimized FPSE parameters for the static and dynamic FPSE modes.

Table 1. Optimized FPSE conditions for static and dynamic mode.

	Variables	Static FPSE	Dynamic FPSE
Extraction	Fabric phase	Carbowax 20M	Carbowax 20M
	Size of fabric	25 x 20 mm	47 mm Ø
	Fabrics used	1	3
	Sample pH	3	3
	Sample volume (mL)	10	50
	Ionic strength (%)	10	10
	Stirring rate (rpm)	900	-
	Extraction time (min)	240	10
Liquid desorption	Elution solvent	Methanol	Ethyl acetate
	Elution volume (mL)	1	10
	Elution time (min)	10	-
	Elution modality	Ultra-sonication	Percolation

The most common features observed in Table 1 are that the same material for extraction, sample pH and ionic strength were used in both

modes of extraction. The reason for this is that, in the first study, four different coatings of the FPSE material were evaluated and compared, covering a range of different polarities (i.e. non-polar with sol-gel PDMDPS, mid-polar with sol-gel PTHF, and more polar with sol-gel PEG-PPG-PEG triblock and sol-gel CW-20M). Based on this comparison, the CW-20M material provided the best results and so it was selected for further study.

There are different studies [1-3] available in the literature that have also evaluated different types of FPSE coating materials for the extraction of analytes. They eventually selected the FPSE coating material that provided the best performance for the selected analytes. For instance, Aznar *et al.* [3] evaluated five FPSE media coated with different sol-gel sorbent chemistries, including long-chain PDMS, short-chain PDMS, poly PTHF, CW-20M and triblock copolymer PEG-PPG-PEG, all of which have different polarities, for the extraction of monoterpenes and terpenoids analytes from orange juice. Of these, CW-20M coated FPSE media was found to be the most efficient for extraction.

With respect to the sample, the adjustment of the pH to 3 and the addition of 10% of salt were the conditions adapted for DFPSE, based on the previous results of the optimized FPSE method.

It is well known that the higher the amount of extracting material used, the higher the capacity and extraction recoveries achieved. The dimension and amount of coated extracting material in the case of static FPSE and DFPSE are different and they also differ from the commercial stir bars. Fig. 2 shows the dimensions and specific surface areas for SBSE, FPSE and DFPSE.

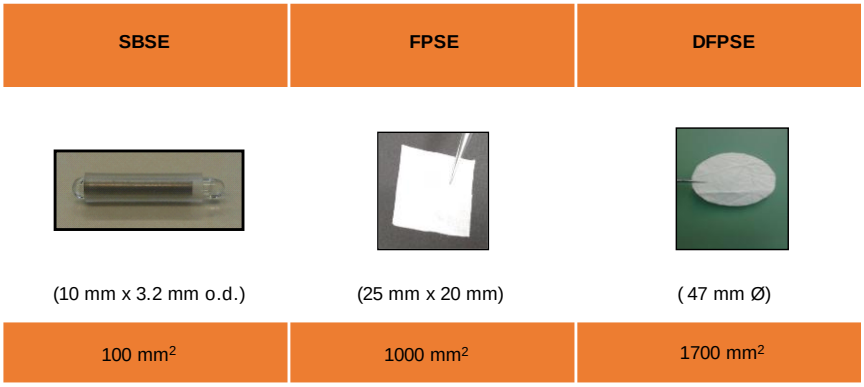

Figure 2. Comparison of the dimension and surface area for the sorptive techniques.

For instance, as mentioned earlier, FPSE material is available in 25 x 20 mm^2 format and the amount of the coating material on FPSE is 10 times higher than commercial stir bars with a length of 10 mm (also available in 20 mm format) and a thickness of 0.5 mm. However, DFPSE consists of 47 mm diameter round fabric disk, which has a higher amount of contact surface area than FPSE and SBSE. It can also be observed from Table 1 that, in the case of static FPSE, a single piece of fabric material is used for extraction, whereas, in DFPSE, three round disks had to be used for the extraction to reach acceptable recoveries. Therefore, due to the use of the three round disks and availability of the higher contact surface area for the interaction, DFPSE took less time (10 min) for the equilibrium extraction to achieve similar recoveries for mid-polar and non-polar analytes (ranging from 38% to 86%) compared to static FPSE, which required 240 min. In addition, it should be mentioned that, in static FPSE mode, two or more pieces of the FPSE material can also be used to increase the extraction recovery of analytes. In such a case, however, liquid desorption would have not been as straightforward as it is under the conditions presented (see Table 1). In addition, it should also be noted

that, in DFPSE, a higher number of fabric disks was also tested but it was observed that the sample percolation took longer and there was a negligible difference in terms of the extraction recovery of the analytes. Thus, this option was ruled out since the aim of the method development was also to reduce the sample preparation time.

With respect to liquid desorption conditions, the most important parameter is the selection of the desorption solvent. The selected pure organic solvent depends on the aim of the elution of retained compounds from the sorbent material and also on the time required to concentrate it. For instance, in the case of DFPSE, ethyl acetate solvent was chosen because it fulfils all the requirements of the elution solvent mentioned above and gives similar recovery results to MeOH.

As stated earlier, both modes of sample preparation technique achieved similar extraction recoveries. The matrix effect (ME) was also studied for both FPSE modes in environmental water samples and the results showed that similar values of ME were obtained for most of the analytes. In addition, the ME values obtained were acceptable and comparable with other studies in which other extraction techniques used [4, 5].

Different volumes of the sample were evaluated according to the FPSE size and amount (Fig. 2). For static FPSE (25 x 20 mm^2), the sample volume of 10 mL was selected while for DFPSE (47 mm^2 Ø), the sample volume was fixed at 50 mL. With this different sample volume, the results in terms of MDLs ranged between 1 and 10 ng L^{-1} (except for TCS, at 50 ng L^{-1}) in static FPSE mode, and between 2 and 8 ng L^{-1} (except TCS at 20 ng L^{-1}) in DFPSE mode. Moreover, the MDL values of the selected analytes obtained from both FPSE modes were lower than those

in previously reported methods using commercial [4] and in-house SBSE [6].

Lastly, the developed methods based on FPSE were used for the analysis of environmental water samples, including river water, and influent and effluent wastewater. In the river water samples, both methods only showed the presence of MPB, DHMB and BP-3. In contrast, all the analytes were present in effluent and influent wastewater. The analytes present in the highest concentrations were MPB, CBZ, DICLO and BP-3. The concentrations obtained with these studies were in concordance with previous studies in where similar samples were analyzed [4, 7].

One limitation observed during the extraction of the selected compounds was the lower extraction recoveries obtained for the most polar analytes. However, the solution to this issue should be the focus of future research in preparing different types of coating materials to improve the technique, as well as looking for more selective materials in order to increase the selectivity of the method.

The results obtained therefore confirm that FPSE in both static and dynamic modes is an alternative to other techniques for extracting a broad group of PPCPs from environmental water samples. In addition, their applicability can be broadened to other types of analytes in different kinds of samples.

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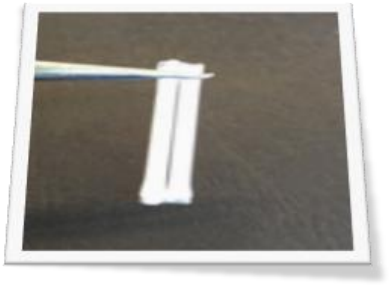
3.2. Capsule phase microextraction



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In the previous section, the FPSE technique in two different modes was presented as an alternative sample extraction technique for various kinds of compounds. However, in the case of static FPSE, a separate magnetic stir bar is required to stir the fabric materials [1]. In order to overcome this drawback of this technique, this year Kabir and Furton have introduced a new sample preparation technique known as capsule phase microextraction (CPME) and registered the technique in a United States patent application [2]. In CPME, the analytes are extracted by a microextraction capsule (MEC). The MEC has two porous polypropylene membrane tubes: one holding the sorbent coating crochet thread by sol-gel technology, and another holding a cylindrical magnetic rod to allow the device to be rotated when placed on a magnetic stirrer and diffuse the sample matrix for fast analyte-sorbent interaction. Both tubes are attached to each other by heat sealing. Fig. 3 shows the formats of MEC and the sample preparation step.

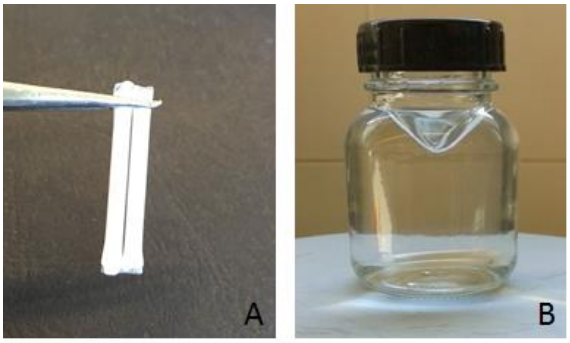

Figure 3. (A) Microextraction capsule; (B) CPME extraction.

The advantages of MEC are that the porous tube allows easy permeation and interaction between the aqueous sample containing the target analyte(s) and the coated material, as well as protecting the coated material from contamination. Moreover, sol-gel technology helps to coat

the high volume of organic and inorganic sorbent in the form of an ultra-thin film on substrate (220 mm^2) and forms strong chemical bonds between the substrate and the sorbent.

The principle of the CPME is based on equilibrium extraction and the sample preparation procedure is similar to the SBSE technique. In fact, it can be considered a modified version of SBSE and its design overcomes the limitations of the commercial and in-house prepared SBSE by enlarging the primary contact surface area available for interaction. In addition, the main feature of MEC, because of the encapsulation of coating materials in a porous tube, is the prevention of the shading of the coating material when stirring at high speeds (more than 1,000 rpm) and preventing damage through physical contact. Consequently, the MEC device can be used to perform more than 30 experiments. All the aforementioned characteristics make CPME an easy and robust sample preparation technique.

Several materials are available as coating phase including sol-gel PDMS, sol-gel PDMDPS, sol-gel C_8, sol-gel C_{18}, sol-gel poly(diphenylsiloxane), sol-gel graphene, sol-gel PTHF, sol-gel poly(ethyleneglycol), sol-gel CW-20M, sol-gel UCON (UCON), sol-gel poly(polycaprolactone-dimethylsiloxane-caprolactone) (PCAP-DMS-CAP). These different coatings may be used for the extraction of target analytes from different types of samples, such as biological, food, environmental, and forensic samples.

Various interesting attempts have been reported in regards to increasing extraction kinetics by expanding the contact surface area and reducing the equilibrium extraction time of the FPSE and SBSE techniques, as discussed earlier in Section 1.3. With regard to FPSE,

different formats have been used for extraction purpose, including stir-FPSE [3], magnetic stir-FPSE and stir-bar FPSE [4]. For instance, Huang *et al*. [4] designed two different formats of extraction techniques, including stir-bar FPSE and magnetic stir-FPSE, for the extraction of brominated flame retardants in water samples. In this study, the optimal extraction time selected for stir-bar FPSE and magnetic stir-FPSE were 10 and 15 min, respectively. It seems that the working principle of CPME and magnetic stir-FPSE is the same but the design of the formats is different, as can seen in Fig 7 (ii) in Section 1.3.4. In addition, there are studies [5, 6] available in which different formats, including rotating-disk sorptive extraction and stir-rod sorptive extraction among others, have been designed to solve the drawbacks of SBSE and improve the extraction efficiency of the technique discussed in Section 1.3.5 of the introduction.

As mentioned earlier, this is a recently introduced technique in sample preparation so there is no literature available on this technique at the time of writing. It should be emphasized here that ours is the first group to evaluate this technique and, to do so, a wide range of polarity groups of personal care products (PCPs) were selected in environmental water samples. The extracts were injected into LC-(ESI)MS/MS for the determination of the compounds.

In this study, different polarities of coating materials were evaluated initially, such as highly polar sol-gel CW-20M, medium polar sol-gel UCON and polar and non-polar segment of sol-gel PCAP-DMS-CAP. It should be noted that, in the present study, the new sol-gel coating of UCON and PCAP-DMS-CAP materials were tested for first time, the structure of which is shown in Appendix II. The best one was selected and the results of recoveries were compared with commercial and in-house

SBSE coatings. In the end, the developed method was applied to analyze different types of environmental water samples.

The paper discussing the results of the present study has been submitted for publication in *Talanta*.

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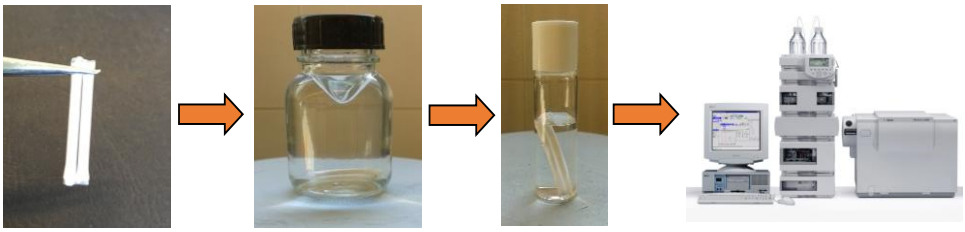
3.2.1. Novel capsule phase microextraction in combination with liquid chromatography-tandem mass spectrometry for determining personal care products in environmental waters



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NOVEL CAPSULE PHASE MICROEXTRACTION IN COMBINATION WITH LIQUID CHROMATOGRAPHY-TANDEM MASS SPECTROMETRY FOR DETERMINING PERSONAL CARE PRODUCTS IN ENVIRONMENTAL WATER

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Abstract

A novel sample preparation technique known as capsule phase microextraction (CPME) is presented here. The technique utilizes a miniaturized microextraction capsule (MEC) as the extraction medium. The MEC consists of two conjoined porous tubular polypropylene membranes, one of which encapsulates the sorbent through sol-gel technology, while the other encapsulates a magnetic metal rod. As such, MEC integrates both the filtration and stirring mechanisms into a single device. Three different sol-gel sorbents were prepared, with sol-gel UCON, sol-gel poly(caprolactone-dimethylsiloxane-caprolactone) (PCAP-DMS-CAP) and sol-gel Carbowax 20M (CW-20M), using methyltrimethoxysilane (MTMS) as the inorganic precursor and UCON®, (PCAP-DMS-CAP) and CW-20M as the organic polymer, respectively. Of the three sol-gel sorbents, MEC with the sol-gel CW-20M sorbent demonstrated the best extraction performance for the selected PCPs. The extraction conditions for sol-gel CW-20M MEC were optimized, including sample pH, stirring speed, addition of salt, extraction time, sample volume, elution solvent and elution time. Under the optimal conditions, sol-gel CW-20M MEC provided the highest recoveries, ranging between 47% and 90% for all analytes, except for ethylparaben, which showed a recovery of 26%. The CPME method based on sol-gel CW-20M MEC followed by liquid chromatography-tandem mass spectrometry (LC-MS/MS) was developed and validated for the extraction of PCPs from river water and effluent wastewater samples.

Keywords: capsule phase microextraction (CPME); microextraction capsule (MEC); personal care products (PCPs); environmental water samples; emerging organic contaminants (EOCs)

1 INTRODUCTION

Over the past few decades, there has been a large number of sample preparation techniques developed to extract personal care product (PCPs) from aqueous samples, including liquid-liquid extraction [1], solid-phase extraction (SPE) [2], solid-phase micro extraction (SPME) [3], stir bar sorptive extraction (SBSE) [4] and recently introduced fabric phase sorptive extraction (FPSE) [5-7], among others. As well as the most commonly used SPE techniques, sorptive extraction techniques have proven to be an interesting and environmentally friendly alternative for the extraction of these compounds. Of these, SBSE is considered to be a more promising technique than SPME because of the large volume of extracting phase coating. The SBSE approach is based on the use of a stir bar initially coated with polydimethylsiloxane (PDMS), a material with a higher affinity for non-polar compounds [4, 8], displaying limitations for extracting more polar compounds. To overcome this limitation, new strategies have been proposed, such as derivatization [9], the availability of two commercial polar coatings [9, 10] and synthesized in-house polar polymers [11, 12] to recover compounds with higher polarity.

Recently, Kabir and Furton [13] have introduced a new sample preparation technique known as capsule phase microextraction (CPME) in an attempt to mitigate the inherent limitations of SBSE techniques. CPME is a based on the principle of equilibrium extraction. It uses microextraction capsules (MEC) consisting of porous, flexible tubular polypropylene membranes of 0.2 µm pore size and 5.5 mm internal diameter to encapsulate different polymer/functional moieties coated onto cellulose fabric or in the form of a monolithic bed by sol-gel technology. MECs are designed to have two fused porous tubes: one to accommodate the sorbent and the other for holding the magnetic rod, which allows the device to be rotated at a set

speed under the magnetic stirrer and significantly increase the mass transfer kinetic between the sample and MEC. The character of the porous membrane enables easy permeation of analytes in an aqueous sample to interact with sol-gel coated sorbents and protect the sorbent from contamination. With the help of sol-gel technology, a high volume of sorbent loading in the form ultra-thin porous film and strong chemical bonding between the substrate and the sorbent are achieved. In addition, MEC shows fast extraction kinetics and sorbent protection via encapsulation into a porous tubular membrane. A variety of sorbent chemistry options are available, including sol-gel poly(dimethylsiloxane), sol-gel poly(dimethyldiphenylsiloxane), sol-gel poly(diphenylsiloxane), sol-gel C_8, sol-gel C_{18}, sol-gel poly(dimethylsiloxane), sol-gel graphene, sol-gel poly(tetrahydrofuran), sol-gel poly(ethyleneglycol), sol-gel Carbowax 20M (CW-20M), sol-gel UCON and sol-gel poly(polycaprolactone-dimethylsiloxane-caprolactone) (PCAP-DMS-CAP) [13].

The aim of the study was to evaluate the performance of this novel CPME technique. To achieve this aim, a group of PCPs was selected in order to cover a wide range of polarity in the target list of compounds. PCPs are a diverse group of chemicals used in human healthcare treatments, detergents, cosmetics among others. The main route by which PCPs enter the environment is by being directly released into surface waters by emission from wastewater treatment plants (WWTPs) or during recreational activities. For this, they are of environmental interest because of the continuous introduction of PCPs and their bioactive metabolites into the environment, which may lead to high, long-term concentrations and promote continual but unnoticed adverse effects on the entire life of aquatic organisms, as well as human health [14-17]. Initially, different polarities of MEC materials were evaluated, such as sol-gel CW-20M, sol-gel UCON and sol-gel (PCAP-DMS-CAP), while the different parameters affecting the extraction and solvent

desorption were optimized. The obtained results were compared with those achieved using commercially available and in-house SBSE, as well as different extraction modes of FPSE. Lastly, the developed method based on CW-20M MEC followed by LC-ESI-MS/MS was validated and applied to determine PCPs in river water and samples from wastewater treatment plants (WWTPs).

2 MATERIALS AND METHODS

2.1 Reagents and standards

Red Heart Fashion crochet thread 3 size, 100% mercerized cotton was purchased from Walmart at Kendall (Miami, FL, USA). Cylindrical magnets (1/16 inch diameter x ¾ inch) were purchased from K&J Magnetics, Inc. (Pipersville, PA, USA). All chemicals used during the preparation of the MECs were of analytical grade or higher. Acetone (Act) (HPLC grade), dichloromethane (anhydrous), methyltrimethoxysilane (MTMS) (98%), UCON® and trifluoroacetic acid (TFA) (99%) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Sodium hydroxide and hydrochloric acid were purchased from Thermo Fisher Scientific (Milwaukee, WI, USA). CW-20M was purchased from Alfa Aesar (Ward Hill, MA, USA). Accurel® PP S6/2 hydrophobic capillary membranes were purchased from 3M Inc. (St. Paul, MN, USA). PCAP-DMS-CAP polymer was purchased from Gelest Inc. (Morrisville, PA, USA).

The standards of the PCPs: 2-phenylbenzimidazole-5-sulphonic acid (PMDSA), methylparaben (MPB), ethylparaben (EPB), propylparaben (PrPB), 2,4-dihydroxybenzophenone (DHB), benzylparaben (BzPB), butylparaben (BuPB), 2,2-dihydroxy-4-4 methoxybenzophenone (DHMB), benzophenone-3 (BP-3), triclocarban (TCC), triclosan (TCS), octocrylene (OC), octyldimethyl-

p-aminobenzoic acid (OD-PABA) were of high purity (> 98%) and purchased from Sigma-Aldrich (Steinheim, Germany).

Stock solutions of individual standards were prepared by dissolving each compound in methanol (MeOH) at a concentration of 1,000 mg L^{-1} and then stored at 4°C. Only the PMDSA solid need to be dissolved in (30:70) water/MeOH. A mixture of all compounds at 50 mg L^{-1} was prepared in MeOH. Working standard solutions were prepared weekly by diluting with a mixture of ultrapure water pH 3 and MeOH (80:20). These solutions were stored at 4°C.

HPLC grade MeOH and acetonitrile (ACN) were supplied by Scharlab (Barcelona, Spain) and formic acid (HCOOH) 95% was used to adjust the pH of sample and mobile phase. Sodium chloride (NaCl) was purchased from Sigma-Aldrich. Ultrapure water was obtained from a water purification system (Veolia Waters, Barcelona, Spain), and concentration of the elution solvent carried out using the miVac Duo system (Genevac, Ipswich, United Kingdom).

2.2 Preparation of microextraction capsule

MECs were prepared using (a) Accurel® S6/2 tubular membranes; (b) sol-gel sorbent coated 100% cellulose cotton fibre segments; and (c) cylindrical magnet rods. The preparation of sol-gel sorbent coated cellulose fibre and the assembling process of MEC are described in the following sections.

2.2.1 Preparation of cotton fibre for sol-gel coating

A 3 size crochet thread was first soaked with deionized water for 30 min in a heated water bath at 40°C under constant sonication. The crochet thread was then further washed with deionized water and the clean thread

was subsequently immersed in 1M NaOH solution for 1 h at 40°C under constant sonication. The thread was then washed multiple times with deionized water and then treated with 0.1M HCl solution at 40°C. The base-treated and acid-neutralized crochet thread was washed several times with deionized water. The thread was then dried in a vacuum oven at 60°C overnight. The clean and dry crochet thread was subsequently stored in an airtight glass container until it was coated with sol-gel sorbent.

2.2.2 Sol-gel coatings on cotton fibre

Three different sol solutions were prepared to create sol-gel CW-20M, sol-gel UCON and sol-gel PCAP-DMS-CAP sorbent coating. Sol solutions were prepared by sequentially dissolving 5 g of organic polymer (CW-20M/ UCON®/ PCAP-DMS-CAP), 5 mL of organically modified sol-gel MTMS precursor, 5 mL of dichloromethane, 5 mL of acetone, 2 mL of TFA containing 5% water (v/v) as the sol-gel catalyst. The sol solution mixture was vigorously vortexed using Fisher Scientific Digital Vortex Mixer (Pittsburgh, PA, USA) for 5 min and sonicated for 5 min. Subsequently, the sol solution was centrifuged at 8,000 rpm for 15 min using an Eppendorf Centrifuge Model 5415 R (Hauppauge, NY, USA), and the clear, particulate-free sol solution was transferred into a 30 mL amber reaction glass bottle.

The pre-treated crochet thread was then immersed in the sol solution at room temperature, with the crochet thread being kept immersed in the sol solution for 4 h. On completion of the coating period, the crochet thread was removed from the reaction glass bottle and transferred into a desiccator for 2 h. The sol-gel coated crochet thread was then thermally conditioned at 50°C in an in-house conditioning device under a continuous helium flow for 24 h. Subsequently, the conditioned sol-gel coated crochet thread was thoroughly rinsed with MeOH-Act mixed solvent system (50:50 v/v) at 40°C under constant sonication. Finally, the sol-gel coated crochet tread was dried in the

conditioning device for 2 h under a continuous helium gas flow. The sol-gel coated crochet thread was stored in an airtight glass container until use in the preparation of the microextraction capsule.

2.2.3 Preparing Accurel® S6/2 tubular membranes and assembling the MECs

Accurel® PP S6/2 capillary membranes were first cut into 30 mm pieces. They were then rinsed with dichloromethane followed by air drying at room temperature for 30 min. The membranes were stored in an airtight glass bottle.

The MEC was assembled by inserting a 30 mm sol-gel coated crochet thread into one Accurel® S6/2 tubular membrane and the cylindrical magnet into the other Accurel® S6/2 tubular membrane, followed by impulse heat sealing (Pasco, Inc., Rocky Mount, MO, USA) of both sides of the Accurel® S6/2 tubular membranes. As a result, a new MEC device was created. A Philips XL30 scanning electron microscope equipped with an EDAX detector was used to obtain SEM images of the Accurel® S6/2 tubular membrane, uncoated crochet thread and sol-gel CW-20M coated crochet thread.

2.3 Capsule phase microextraction conditions

The optimal extraction conditions for the CW-20M MEC were as follows: MEC was conditioned and equilibrated with 5 mL of MeOH and 5 mL of water magnetically stirred for 5 min each. Then, a cleaned MEC was immersed into a glass vial containing 50 mL of sample adjusted to pH 3 and containing 15% of NaCl (w/v). The sample was stirred at a speed of 600 rpm for 2 h at room temperature. After extraction, the MEC was removed from the sample by using magnetic tweezers and dried with lint-free tissue paper. For liquid desorption (LD), the MEC was introduced into a glass vial containing 5 mL of MeOH:ACN (1:1) and placed in an ultrasonic bath for 10 min. The

extract was evaporated using miVac concentrator (Genevac, Ipswich, UK) to approximately 100 µL. The final extract was diluted to 1 mL with a solution of ultrapure water at pH 3 and ACN (80:20, v/v). Then, the extract was injected for LC-(ESI)MS/MS.

After each use, the MEC was cleaned with 10 mL of MeOH:ACN (1:1, v/v) in the ultrasonic bath for 10 min. This step was repeated twice with a fresh portion of the solvent mixture, then dried and stored in the air tight glass vial until the next experiment. The MEC was reused more than 30 times with environmental samples.

The performance of the method was tested on three different types of environmental water samples. The river water samples were collected from the River Ebro in Catalonia. The influent and effluent wastewater samples were collected from an urban WWTP in the Tarragona area. All samples were collected using pre-cleaned plastic cans and filtered through 1.2 µm glass fibre filters (Fisher brand, Loughborough, UK) followed by a 0.45 µm nylon supported membrane filter (Fisher brand) to eliminate the particulate matter. The samples were then acidified to pH 3 with HCOOH to prevent microbial growth and stored at 4°C until analysis.

2.4 Liquid chromatography-tandem mass spectrometry analysis

The Agilent model 1200 series LC was used, coupled to a 6410 series triple quadrupole mass spectrometer (MS/MS) with an electrospray ionization (ESI) interface, and equipped with an automatic injector, a degasser, a quaternary pump and a temperature controlled column compartment from Agilent Technologies (Waldbronn, Germany). The chromatographic separation was achieved on a reversed-phase Kromasil 100 C_{18} (150 mm X 4.6 mm i.d., 5 µm) column from Teknokroma (Sant Cugat del Vallès, Spain). ACN and ultrapure water adjusted to pH 3 with HCOOH were used as mobile

phase. The gradient started at 15% ACN, which was increased to 90% ACN in 12 min, then to 100% ACN in 8 min and kept constant for 8 min. Finally, it returned to the initial conditions in 2 min, which were then held for 6 min to equilibrate the column for the next analysis. Under the optimal conditions, all the compounds were eluted within 21 min. A flow rate of 0.6 mL min^{-1} was used and the temperature of the chromatographic column was kept at 40°C. The injection volume was 50 µL.

The LC-MS/MS parameters were optimized by injecting each compound at 1 mg L^{-1} in a mixture of ultrapure water at pH 3 and ACN (80:20, v/v) individually in flow injection analysis (FIA). The studied compounds were divided individually or in groups into six windows depending on their negative or positive ESI ionization mode. The optimal conditions for analytes were as follows: a nitrogen flow rate of 12 L min^{-1}, a spray potential of 4,000 V, a nebulizer pressure of 45 psi (N_2) and source temperature of 350°C. The cone voltage and collision energies for all compounds were from 18 to 200 V and 5 to 35 eV, respectively. The two most intensive transitions between parent ion and product ions were selected for quantification and identification in MRM mode. The optimal values of LC-(ESI)MS/MS parameters are summarized in Table S1 (supplementary information). The retention time and the ratio of two MRM transitions were compared with standard solution to confirm the presence of the compound.

All selected compounds showed good linearity ($R^2 \geq 0.9996$) in LC-(ESI)MS/MS and the linear ranges were 0.1-50 µg L^{-1} for PMDSA, MPB, EPB, PrPB and OD-PABA, and 0.5-50 µg L^{-1} for BzPB, BuPB, DHMB, BP-3,TCC and OC, and 2-50 µg L^{-1} for TCS. The instrumental limit of detection (ILODs), calculated as a signal-to-noise ratio (S/N) of 3 ranged from 0.01-0.5 µg L^{-1}. The lowest points of the calibration curve were taken as the instrumental limits of quantification (ILOQs).

3 RESULTS AND DISCUSSION

3.1 Development of MEC

The primary objective of the current project is to design and produce a microextraction device that (a) possesses a built-in magnet to diffuse the analytes in the sample matrix; (b) protects the extracting sorbent from being contaminated by matrix interferents; (c) provides a high primary contact surface area (PCSA) in order to achieve fast extraction equilibrium; (d) enables elution/back-extraction of the extracted analytes into a small volume of organic solvent to eliminate solvent evaporation and sample reconstitution. All these criteria were met by the MEC. Fig 1 (a-c) shows the photographic images of the different building blocks of MEC. Scanning electron microscopy images of the Accurel® PP membrane, uncoated crochet thread, and sol-gel CW-20M coated crochet thread are presented in Fig 1 (d-e). The 0.2 µm pore size of the membrane allows rapid diffusion of the sample containing the analyte(s) of interest into the sol-gel coated crochet thread for rapid analyte-sorbent interaction and subsequent extraction and preconcentration into the extraction sorbent, while effectively protecting the sorbent from contamination from matrix interferents. The built-in magnet, as the integral part of the MEC enables the device to spin on a magnetic stirrer, thus eliminates the necessity of using an external magnet. The sol-gel coating on the crochet thread forms a thin layer of sol-gel sorbent. Dozens of individual strings conjoined together in the crochet thread retain a thin film of sol-gel coating. As such, the overall sorbent loading in a MEC is fairly high.

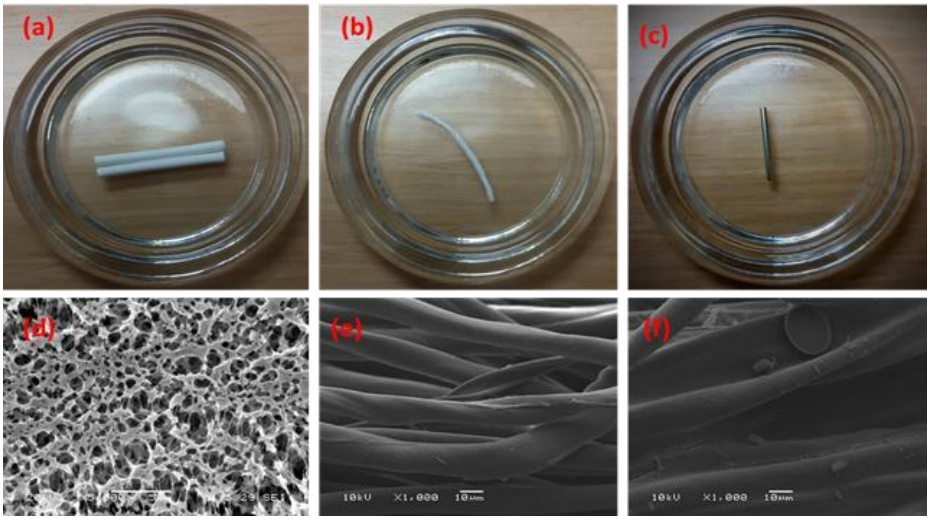

Figure 1. Components of microextraction capsule and their scanning electron microscopy images: (a) image of porous polypropylene tubes; (b) sol-gel CW-20M coated cellulose fiber segment; (c) a cylindrical magnet rod; (d) scanning electron microscopy image of polypropylene tube surface at 5000x magnifications; (e) scanning electron microscopy image of cellulose fiber surface before sol-gel CW-20M coating at 1000x magnifications; (f) scanning electron microscopy image of cellulose fiber surface after sol-gel CW-20M coating at 1000x magnifications.

3.2 Optimization of MEC procedure

The CPME procedure consists of two consecutive steps: extraction and liquid desorption. Different parameters were optimized for these two steps in order to achieve higher extraction recoveries and short equilibrium time for PCPs. The initial experimental conditions were: 25 mL of ultrapure water adjusted to pH 3 with HCOOH spiked at 2 µg L^{-1} with the mixture of PCPs, stirred at 600 rpm for 60 min, then desorption was carried out twice with 10 mL of MeOH and stirring for 10 min. These two 10 mL elution fractions were evaporated using the miVac concentrator to approximately 100 µL and diluted with 1 mL of ultrapure water at pH 3 and ACN (80:20, v/v). The 50 µL extract was injected for LC–(ESI)MS/MS.

Three different MEC coated with sol-gel CW-20M (highly polar), sol-gel UCON (medium polar) and sol-gel PCAP-DMS-CAP (block copolymer of polar and non-polar segment) were initially evaluated with initial experimental conditions as described above. The goal of this experiment was to select the best MEC sorbent chemistry suitable for the extraction of PCPs in aqueous sample. Table 1 shows the extraction recoveries of PCPs achieved when the three MEC with different sorbent coatings were tested.

Table 1. % Extraction recovery value (n=3) obtained when 25 mL of ultra-pure water spiked with 0.2 µg L^{-1} of each analytes were extracted with three different MECs.

Analyte	% Extraction recovery		
	CW-20M	UCON	PCAP-DMS-CAP
PMDSA	0	0	0
MPB	0	0	0
EPB	7	8	8
PrPB	13	10	9
DHB	24	22	20
BzPB	36	27	24
BuPB	29	29	29
DHMB	40	37	34
BP-3	58	47	44
TCC	60	22	28
TCS	74	62	62
OC	81	20	17
OD-PABA	89	39	42

Of these, sol-gel CW-20M MEC showed better extraction recoveries for polar compounds such as OC and OD-PABA, with values of 81% and 89%, respectively, while the non-polar compounds such as TCC and TCS, had values of 60% and 74%, respectively. In view of these results, sol-gel CW-20M MEC was selected for the further studies. It should be noted that, hereinafter, sol-gel CW-20M MEC is denoted as MEC.

3.2.1 Extraction conditions

Initially, the pH of the sample was tested by performing experiments with the sample adjusted to pH values of 3, 5 and 7. It was observed that, for most of the compounds, negligible differences in extraction recoveries were observed when increasing the pH from 3 to 5 and 7. However, in the case of TCC, TCS, OC and OD-PABA, when the pH was increased from 3 to 5, the extraction recoveries decreased by between 10% and 40% (especially for OC, 40%), and the extraction recoveries remained constant when further increasing the pH from 5 to 7 for the same analytes. In view of these results, the most suitable pH for the extraction was 3 and it was selected for further analysis.

The agitation speed was also studied. As well as 600 rpm, two different agitation speeds (300 and 900 rpm) were tested and similar extraction recoveries were obtained with the three speeds. Therefore, an agitation speed of 600 rpm was selected for further studies.

To test the effect of salt (NaCl) on the extraction recoveries, the addition of 5%, 10%, 15% and 20% (w/v) of salt were evaluated. The results are shown in Fig 2 and, as a trend, it can be observed that, when the concentration of salt increased from 0% to 15%, the recovery values for the most polar analytes (EPB, PrPB, DHB, BzPB, BuPB, DHMB, and BP-3) increased, whereas the recovery values decreased for the most apolar analytes (TCC, TCS, OC and OD-PABA). This behavior is well known due to the salting-out effect and the electrostatic interaction between polar molecules and salt ions in the solution [18, 19]. When the concentration of salt was further increased to 20%, the extraction recoveries increased by less than 10% in the case of EPB, PrPB, DHB, BzPB, BuPB, TCC, and OD-PABA, while recoveries decreased for BP-3 and TCS, and no difference in recoveries was observed for DHMB and OC. In view of this, a salt addition of

15% was selected in order to take advantage of the increased recoveries for the polar analytes, as the recovery of the apolar analytes remained at 60%, despite not using the optimal salt conditions.

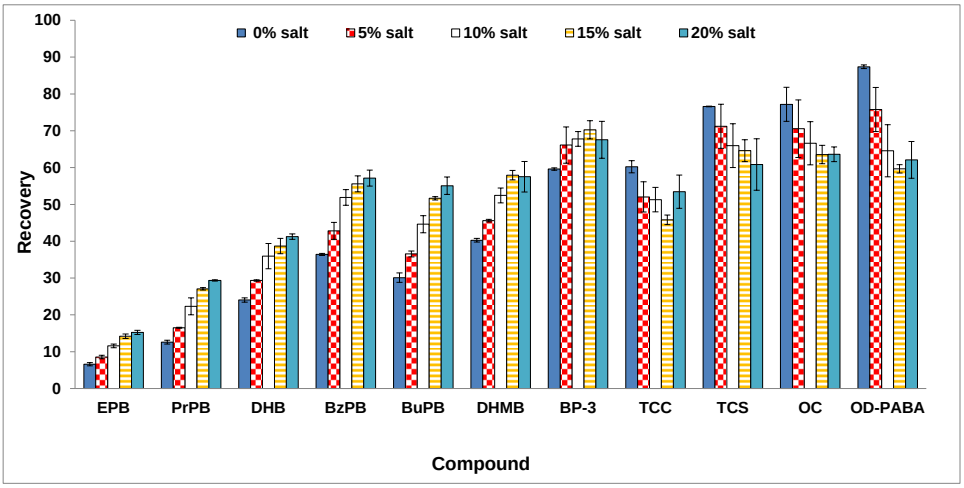

Figure 2. Effect of the NaCl addition on the extraction of the analytes using CW-20M MEC (%RSD (n=3) were lower than 20%).

Next, the effect of sample volume on the extraction recovery was investigated with 50 and 100 mL volumes of ultrapure water. The extraction recoveries decreased by between 10% and 30%, when the sample volume was increased from 25 mL to 50 mL. A further decrease in the recoveries was observed when sample volume was increased to 100 mL. Therefore, 50 mL was selected for the following analysis as a compromise between recoveries and the sensitivity of the method.

The effect of the extraction time on the recovery was also evaluated by stirring the sample at different time intervals from 30 min to 300 min, with the results shown in Fig 3. As can be observed, the extraction recoveries increased when the extraction time increased from 30 min to 120 min for all analytes, but a further increase in extraction time from 120 min to 300 min did not result in any substantial improvement. Thus, considering the sample

extraction time and recoveries obtained, 120 min was selected as extraction time.

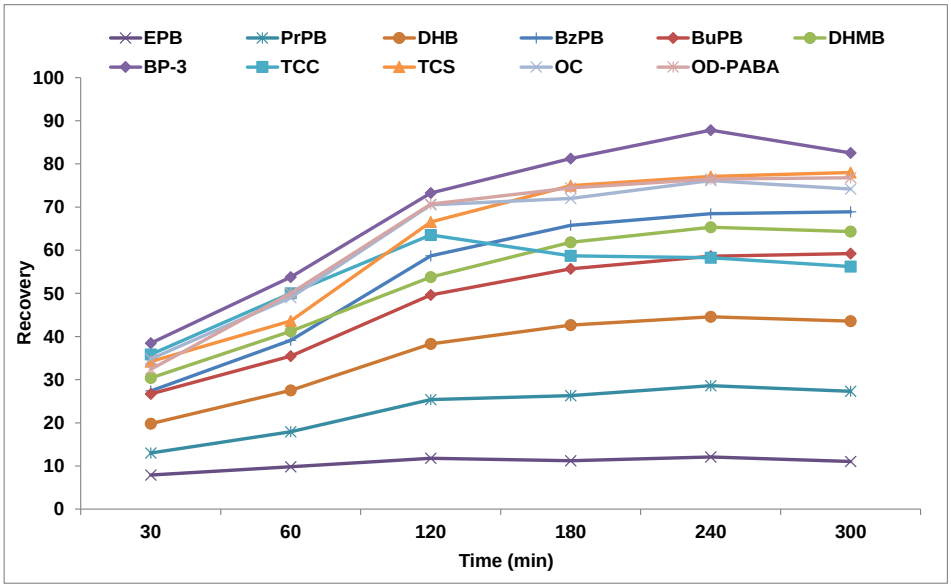

Figure 3. Effect of the extraction time on the extraction of the analytes using CW-20M MEC (%RSD (n=3) were lower than 20%).

To summarize, the optimized conditions for CPME are as follows: 50 mL of sample adjusted to pH 3 with the addition of 15% of salt, stirred at 600 rpm for 120 min at room temperature.

3.2.2 Liquid desorption conditions

For the liquid desorption (LD), the most frequently tested parameters to be evaluated are: elution solvent, elution modality, elution volume and time. In the case of the elution solvent, as well as MeOH, other solvents such as ACN and the mixture of MeOH:ACN (1:1, v/v) were evaluated. When 10 mL of these solvents were used, it was observed that MeOH and ACN showed similar extraction recoveries for all the compounds. However, with mixture of MeOH:ACN (1:1) the extraction recoveries slightly improved compared to

MeOH and ACN. Therefore, a mixture of MeOH:ACN (1:1, v/v) was selected for the LD in further experiments.

After the selection of LD solvent, the elution mode (stirring and ultra-sonication) and elution volume (5 and 10 mL) were tested for desorption of PCPs from MEC. From the results, it was observed that, in stirring mode, 5 mL of elution solvent was not enough to completely desorb all the analytes, with up to 10 mL of elution solvent being required. However, in ultra-sonication mode, the analytes were completely desorbed with only 5 mL of elution solvent, because the analytes recoveries were up to 5% in the next 5 mL of solvent, with similar recoveries as in stirring mode with 10 mL of solvent. Therefore, based on these results, an elution volume of 5 mL in ultra-sonication mode was selected.

Furthermore, the desorption time was also tested in the range of 5 to 15 min. It was observed that, when the elution time was increased from 5 to 10 min, the extraction recoveries increased by between 2% and 9% for all analytes. After increasing the desorption time to 15 min, the extraction recoveries remained constant. In view of these results, 10 min was maintained as the optimal desorption time to ensure the complete desorption of analytes.

In order to enhance the overall sensitivity of the CPME method, the 5 mL of elution solvent from LD was evaporated to approximately 100 µL and the extract was diluted to 1 mL with ultrapure water at pH 3 and ACN (80:20, v/v), before being injected for LC. It should be noted that, up to 25%, losses for some analytes were observed during the evaporation to dryness and, for this reason, the elution solvent was just evaporated to ~200 µL.

Under the optimal conditions, the recovery for each of the analytes in ultrapure water is shown in Table 2. The MEC method was able to extract

most of the compounds, with recovery values in the range of 47% to 90%, except for EPB, for which the value was 26%, and PMDSA and MPB, which were below 4%.

Table 2. Extraction recovery value % (n=3) obtained when 50 mL of ultra-pure water spiked with 0.2 µg L^{-1} of each analyte were extracted with CW-20M MEC material and SBSE-EG/Silicone.

Analyte	Extraction recovery (%R)			
	CW-20M MEC	SBSE-EG/Silicone[a]	SBSE-PA coating[a]	Poly(PEGMA-co-PETRA)[b]
PMDSA	4	n.d.	n.d.	n.d.
MPB	3	1	2	20
EPB	26	n.d.	n.d.	n.d.
PrPB	47	10	2	38
DHB	56	24	9	55
BzPB	73	39	14	64
BuPB	71	n.d.	n.d.	n.d.
DHMB	85	26	9	56
BP-3	90	45	10	55
TCC	64	59	43	51
TCS	67	80	42	55
OC	73	n.d.	n.d.	n.d.
OD-PABA	77	n.d.	n.d.	n.d.

% RSD (n=3) were lower than 10% for %R>15%. For the experimental conditions, see text.
[a] Recovery values (%) obtained when 50 mL of ultra-pure water spiked with 4 µg L^{-1} with analyte mixture were extracted with SBSE-EG/Silicon coating [10].
[b] Recovery values (%) obtained when 50 mL of ultra-pure water spiked with 2 µg L^{-1} with analyte mixture were extracted with SBSE-poly(PEGMA-co-PETRA) coating [11].
n.d.: not determined.

The performance of MEC was compared with two commercially available polar stir bars SG/Silicone Twister® and PA coating Twister® [10] and in-house SBSE coating based on poly(PEGMA-co-PETRA) [11], which were previously tested for the extraction of PPCPs from environmental samples. Table 2 shows the results obtained under optimal conditions (note that the extraction volume is 50 mL in all instances) with the commercial and in-house stir bars. The obtained extraction recoveries with the commercial

EG/Silicon Twister® and PA coating Twister® stir bars were lower for all the compounds, except in the case of TCS, which was higher with EG/Silicon than the recovery obtained by MEC. Furthermore, the extraction time for the commercial SBSE was 4 hours, while the MEC extraction time was 2 hours. In contrast, the extraction time of the in-house coated poly(PEGMA-co-PETRA) was shorter (1 hour), but the recoveries achieved were lower than those obtained with the MEC material for all the common analytes studied. These better results can be explained by the sol-gel technology and the higher contact surface area available for interaction with the analytes, as well as a significant contribution from the porous tubular membrane, which might provide hydrophilic affinity, while the porous membrane enabled easy permeation.

CPME results can also be compared to the those obtained in previous studies in which the same CW 20M material was evaluated in other extraction modes, such as FPSE [5] and dynamic FPSE [20]. In general, the extraction recoveries obtained with CPME for the selected PCPs were comparable with static FPSE and dynamic FPSE modes when 10 mL and 50 mL of sample volume was extracted, respectively, although, for the compounds MPB, PrPB and DHB, the recoveries achieved with FPSE or DFPSE were higher (c. 40%, 80% and 75%, respectively). However, the straightforward, easy-to-use format and the set-up designed used for CPME overcame these differences in recovery. Thus, the overall results obtained with CPME were promising and encouraged us to perform tests it in real samples.

3.3 Method validation

After the CPME method optimization, the applicability of the new device CW-20M MEC was evaluated on real matrices. The assays were performed on river water and wastewater samples. At this point, it should be

noted that, due to the low extraction recovery of PMDSA and MPB, the method was validated excluding these two analytes.

The apparent recovery (%R_{app}) and the matrix effect (%ME) were determined for 50 mL of river water and 25 mL of effluent wastewater using sample spiked at two concentration levels (0.04 µg L^{-1} and 0.4 µg L^{-1} for river water, 0.08 µg L^{-1} and 0.8 µg L^{-1} for effluent wastewater). A lower volume of effluent wastewater was used than river water due to the complexity of the matrix and to obtain similar recoveries to ultrapure water. Firstly, a blank sample of river water and effluent wastewater was analyzed and the areas of the analytes present in the blank extract of sample were subtracted to determine %R_{app} and %ME. In each case, samples were analyzed in triplicate and the results of %R_{app} and %ME for these two samples at the two concentration levels are shown in Table 3.

The %R_{app} was calculated as the ratio of the signal of each analyte in the sample spiked before MEC and the signal of each analytes in standard solution. It is well-known that %R_{app} includes the extraction recovery and %ME. In Table 3, it can be observed that similar recoveries were obtained for both river water and effluent wastewater samples, which were slightly lower than those achieved in ultrapure water, mainly due to the ME.

The significant drawback of ESI coupled with MS/MS is the %ME. In LC-MS/MS, it is observed that co-extracted matrix components can affect analytes ionization in analysis employing electrospray interfaces, while suppression or enhancement of the signal occurs. The %ME was calculated as the ratio of the signal of each analyte when it was spiked in the sample after extraction by MEC and their signal in standard solution. Ion suppression was observed in river water and effluent wastewater samples. The resulting ion suppression in river water samples ranged from -18 to -38% for all analytes, except OD-PABA (-46%), which was the most affected compound.

In the case of effluent wastewater samples, the ion suppression ranged from -14 to -39% for all analytes, except for EPB and PrPB, which were most affected, with values between -49% and -42%, respectively, at the two concentration levels. In view of these general values, the %ME obtained for the selected analytes can be considered acceptable.

Table 3. $\%R_{app}$ and %ME of PCPs in river and effluent water samples by CW-20M MEC extraction technique.

Analyte	River water[a]				Effluent water[b]			
	0.04 (µg L^{-1})		0.4 (µg L^{-1})		0.08 (µg L^{-1})		0.8 (µg L^{-1})	
	$\%R_{app}$	%ME	$\%R_{app}$	%ME	$\%R_{app}$	%ME	$\%R_{app}$	%ME
EPB	14	-30	19	-26	19	-49	11	-49
PrPB	23	-33	27	-36	28	-42	21	-42
DHB	34	-23	30	-33	30	-39	23	-38
BzPB	43	-33	39	-38	35	-41	29	-39
BuPB	27	-28	39	-32	35	-34	28	-40
DHMB	45	-18	33	-28	35	-25	27	-32
BP-3	57	-25	40	-23	45	-25	33	-28
TCC	63	-22	60	-22	60	-18	56	-14
TCS	n.a.	n.a.	57	-24	n.a.	n.a.	34	-32
OC	49	-27	43	-33	62	-17	54	-17
OD-PABA	34	-46	37	-44	32	-36	28	-33

[a] 50 mL river water
[b] 25 mL effluent wastewater
n.a. not available since the concentration is below its LOQ.

Then, the whole analytical procedure based on CW-20M MEC/LC–MS/MS was tested for other validation parameters of the method with river water and effluent wastewater. For each type of sample, the linear range, limits of detection (LODs), limits of quantification (LOQs), repeatability and reproducibility between days were evaluated. In view of the results from the ion suppression study, a matrix-matched calibration curve was made at six different concentration levels in duplicate for river water (50 mL) and effluent

wastewater (25 mL) to perform accurate quantification. In the case of river water, all the compounds showed good linearity in the range between 10 and 5,000 ng L^{-1}, except for TCS (100-5,000 ng L^{-1}), with a determination coefficient (R^2) greater than 0.9996. When effluent wastewater was analysed, satisfactory linearity was obtained for all the compounds, ranging from 20 to 5,000 ng L^{-1}, except for DHMB (40-5,000 ng L^{-1}) and TCS (200-5,000 ng L^{-1}), with a determination coefficient (R^2) greater than 0.9993.

In both samples, the LODs were calculated on basis of a signal-to-noise ratio of 3, and when the analytes (PrPB, DHM, DHMB and BP-3) were present in the blank extract of both samples. The LODs were calculated on the basis of instrumental LODs and $\%R_{app}$; and LOQs were obtained from the lowest point of the calibration curve. The LODs in river water ranged between 2 and 5 ng L^{-1} for all compounds, except for TCS (10 ng L^{-1}), while the LODs in effluent wastewater ranged between 3 and 7 ng L^{-1} for all compounds, except for TCS (20 ng L^{-1}). The repeatability of the method on the same day and reproducibility between days, expressed as relative standard deviation (%RSD) of five replicates of samples spiked at a concentration level of 100 ng L^{-1} for river water and 200 ng L^{-1} in effluent wastewater, were lower than 20% and 19%, respectively, in both types of sample. The validation data obtained by the CW-20M MEC followed by LC-MS/MS method provided satisfactory results to be able to determine the studied analytes at low concentrations levels in environmental samples.

3.4 Analysis of real samples

The developed CPME method was used to determine the presence of PCPs in two different kinds of environmental water sample (river water and effluent wastewater). Three different samples of each sample matrix were analysed in triplicate. The confirmation of the analytes in the sample was carried out by calculating the peak area ratios between the quantifier and

qualifier transitions and retention time, when compared with a reference standard. Table 4 shows the concentration of the PCPs determined in the both samples.

Table 4. Concentration range of analytes found in river and effluent wastewater samples analyzed by CW-20M MEC/LC-MS/MS.

Analyte	Concentration (ng L^{-1})	
	River water	Effluent water
EPB	n.d.	n.d
PrPB	n.d	26 - 43
DHB	< LOQ	< LOQ
BzPB	n.d	n.d
BuPB	n.d	n.d
DHMB	14 - 93	<LOQ - 122
BP-3	36 - 93	95 - 142
TCC	n.d	n.d
TCS	n.d	n.d
OC	n.d	n.d
OD-PABA	n.d	n.d

n.d., not detected

In the analysed effluent wastewater samples, most of the analytes were not detected in any sample except PrPB, DHB, DHMB and BP-3, which were detected in all samples. Of these, the highest concentrations found were for PrPB, DHMB and BP-3. DHB was also detected in all the samples, but could not be quantified as the levels were lower than the LOQs. For example, Fig. 4 shows the MRM chromatogram from the analysis obtained under optimal conditions from one of the effluent wastewater samples.

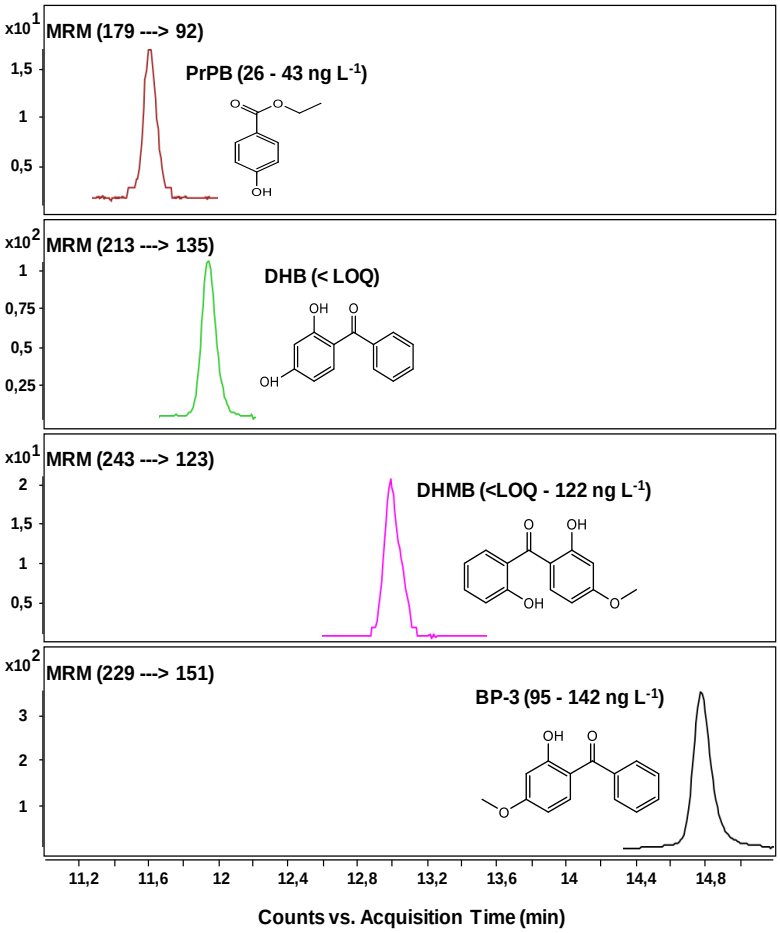

Figure 4. MRM chromatogram of an effluent sample. For experimental conditions see section 2.3.

In the case of river water samples, the highest concentrations were found for DHMB and BP-3, which were in the range of 14 - 93 ng L^{-1} and 36 - 93 ng L^{-1}, respectively, while DHB was detected in all samples, but at concentrations below LOQs.

The ranges of concentrations of PCPs were in line with those found in the samples from the same river water [2, 12, 20] and effluent wastewater [2, 4, 5] analyzed.

4 CONCLUSIONS

A novel sample preparation technique known as capsule phase microextraction (CPME) was successfully developed and evaluated for the first time. The device used in CPME, a microextraction capsule (MEC), encapsulates high efficiency sol-gel hybrid organic-inorganic sorbent coated cellulose fibre segment and a cylindrical magnet in porous tubular polypropylene membranes. The incorporation of a cylindrical magnet inside the MEC enables the device to diffuse the analytes in the sample matrix using a magnetic stirrer to achieve fast extraction equilibrium. The sol-gel sorbent coated on cellulose fibre results in a large contact area for rapid sorbent-analyte interaction and enables satisfactory recoveries to be achieved in the case of PCPs in environmental samples in an acceptable equilibration time.

Of the different MEC evaluated (sol-gel UCON, sol-gel PCAP-DMS-CAP and sol-gel CW-20M), CW-20M MEC showed the best performance for the extraction of the group of PCPs evaluated. Better recoveries were achieved after the optimization of the different parameters affecting extraction and liquid desorption. The combination of CW-20M MEC material with LC-(ESI)MS/MS provided an efficient, simple and sensitive method for determination of PCPs at low concentration levels in environmental samples.

The proposed CPME technique could be extended to extract other target compounds in different sample matrices in future.

Acknowledgments

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Supplementary information

Table S1. Analyte, t_R (min), log $K_{o/w}$, MRM conditions and proposed products ion for determination of PCPs.

Analytes	t_R (min)	log $K_{o/w}$	Ionization mode	Precursor ion (m/z)	Cone voltage (V)	Quantifier		Qualifier	
						Product ion (m/z)	Collison energy (eV)	Product ion (m/z)	Collison energy (eV)
PMDSA	5.16	0.4	Positive	275	200	194	35	211	25
MPB	9.14	1.9	Negative	151	80	92	15	136	10
EPB	10.39	2.5	Negative	165	100	92	15	136	10
PrPB	11.59	2.9	Negative	179	100	92	15	136	10
DHB	12.05	3.2	Negative	213	130	135	15	169	10
BzPB	12.53	3.6	Negative	227	100	92	20	136	10
BuPB	12.69	3.6	Negative	193	100	92	15	137	10
DHMB	13.03	4.3	Negative	243	80	93	15	123	15
BP-3	14.79	4.0	Positive	229	100	151	15	105	15
TCC	15.41	6.1	Negative	313	130	160	10	126	15
TCS	15.62	5.3	Negative	287/289	18	35	5	35	5
OC	16.37	6.9	Positive	384	130	272	5	228	5
OD-PABA	19.94	5.8	Positive	278	130	166	20	151	20

Log $K_{o/w}$ calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02 (© 1994-2012 ACD/Labs).

3.2.2. Discussion of results

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A novel approach to the sample preparation technique has been described in this section. The purpose of this study was to introduce a new format of sample preparation technique, to evaluate its extraction performance for compounds with a wide range of polarities, and compare its results with those obtained with commercial and in-house SBSE.

The design of the CPME technique overcomes some of the limitations of the commercial and in-house SBSE, as well as FPSE techniques, as discussed in the introduction of Section 3.2. For instance, CPME avoids direct physical contact with the encapsulated porous coating material, which is available in a format larger than 20 mm. As a result, a higher amount of sorptive material coated by sol-gel technology is exposed for retaining the analytes. In contrast, SBSE is available in formats up to 20 mm in length and 0.5 mm in thickness. This means that the CPME coating area is twice the size of the commercial SBSE. Fig. 4 shows the comparison of SBSE and CPME in terms of size and coating material. Another advantage of the CPME design is that it avoids contamination of the coating material by encapsulation in a porous membrane.

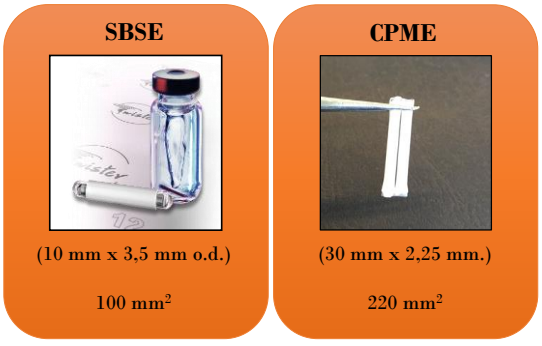

Figure 4. Comparison of the dimension and surface area.

As can seen in the presented paper, three MEC coating materials with different polarities were initially evaluated for the extraction of PCPs. It should be noted that, as well as those already tested in the FPSE technique (PDMS, PDMDPS and CW-20M), our study also tested new coatings based on sol-gel technology for the first time (UCON and PCAP-DMS-CAP). Similar recoveries for PCPs were obtained with UCON and PCAP-DMS-CAP because the chemistry of the two coatings are similar, while the CW-20M coating showed higher recoveries for the less polar compounds. However, when comparing the recovery results obtained for MEC CW-20M in this study and previous studies of FPSE and DFPSE in which the same CW-20M coating material was used for PPCP extraction, it was observed that CPME showed similar extraction recoveries for some PCPs, except in the case of MPB, PrPB and DHB, for which lower recoveries were recorded. With respect to the matrix effect (ME), the values obtained with the MEC material were comparable with the previous studies and acceptable [1, 2].

In comparison to commercial and in-house SBSE based on EG/Silicone Twister®, PA coating Twister® and poly PEGMA-co-PETRA coatings, the CW-20M material retained a broad range of PCPs analytes with higher recovery values. The higher specific surface area available for interaction in CPME (220 mm^2) than in SBSE (100 mm^2) also contributed to higher recoveries. Another feature is that the equilibrium extraction time was two hours, as mentioned previously, which is shorter than the time required for the commercial and in-house SBSE [3, 4] or the previous study of static FPSE, both of which took up to 4 hours to reach equilibrium.

The good performance of the CPME technique in combination with LC-MS/MS enables low MDLs to be obtained for the selected PCPs. These MDLs were similar to those obtained in our previous studies of FPSE in which the same CW-20M material was used, and also comparable to MDLs achieved using other commercial and in-house SBSE techniques [2-4].

Therefore, when applied for determining PCPs in river water and samples from WWTPs, the developed CW-20M CPME method enables the quantification of PCPs at low ng/L levels. The most common compounds found in river water and effluent wastewater samples were PrPB, DHMB and BP-3. The results agreed with the numerous studies carried out by our research group [1, 2, 5], which reported the presence of these PCPs in environmental samples, and were in line with other studies [6, 7].

However, it should be mentioned that one limitation of CPME compared to SBSE is that desorption by TD is not possible. As mentioned earlier, CPME is made from cellulose cotton fibre and encapsulated in a polypropylene membrane. Therefore, the retained analytes have to be eluted by LD because of the possibility of burning or melting the material at higher temperatures.

The results obtained from the first study on MEC pave the way for this technique to be applied to different compounds and matrices. In addition, future research should focus on improving the MEC coating to enhance selectivity.

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3.3. Magnetic particles for dispersive solid-phase extraction

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The previous two sections presented new designs in sorptive extraction techniques applied for the extraction of pharmaceuticals and personal care products from environmental water samples. In order to explore new sorptive materials, this section presents an study of the use of magnetic particles (MPs) as a sorptive material in dispersive solid-phase extraction (d-SPE) mode.

As already discussed in the Thesis introduction, MPs have received increasing attention in the field of sample preparation for different kinds of matrices. This is because of the advantages they offer, including easy dispersion in the sample, shorter equilibrium extraction time and easy separation by applying an external magnetic field. MPs have also been coated with different types of inorganic and organic materials, such as silica, carbon, polymer, etc., and applied as sorptive materials [1]. To date, MPs in dispersive mode have been also used for the extraction and removal of contaminants in environmental water samples [2-5].

In view of the advantages of applying MPs, recently Dr. Qing Zhou synthesized two sets of MPs: Q-100 MPs, which are hypercrosslinked, and Q-80 MPs, which are macroporous polymers. Both Q-100 MPs and Q-80 MPs demonstrated their performance in the removal of antibiotics from aqueous solution [6]. In this study, the authors observed that Q-100 MPs showed better retention of the contaminants and was more reusable than the other particles, including Q-80 MPs. This is because Q-100 MPs have the hypercrosslinked structure, which lead to suitable pore size distribution, high surface area (~1,150 m^2/g) and 100-150 micron particle size. In contrast, Q-80 MPs have a smooth macroporous structure and lower surface area (~ 780 m^2/g) than Q-100 MPs. Based on these satisfactory results, in order to enlarge the application field of Q-100 MPs,

it was decided to evaluate them as material for d-SPE in a collaborative study between the two research groups.

Taking into account these properties, the objective of this study is to evaluate the retention behaviour of Q-100 MPs in d-SPE mode for the extraction of SWs from environmental water samples. In this study, a challenging group of EOCs as SWs was selected [7-9]. They are widely applied in food, beverages, pharmaceuticals and cosmetic products. Therefore, they are found in the different compartments of the environment at high concentration levels. To date, there are several well-established methods for extracting SWs, most of which are based on SPE [7, 9-11]. In some methods, different copolymer sorbents are used for the extraction of SWs from water samples and it has been found that, due to the high polarity of the SWs, some of these sorbents fail to retain them [7, 11]. The selected SWs cover a wide range of polarities and the most polar analytes needed a retentive material, such as Q-100, to enable suitable retention. In this study, different parameters affecting the extraction and elution were optimized. The method was validated and applied to analyze different environmental samples including river water, and effluent and influent sewage.

The paper discussing the results of the present study has been submitted for publication in the *Journal of Separation Science.*

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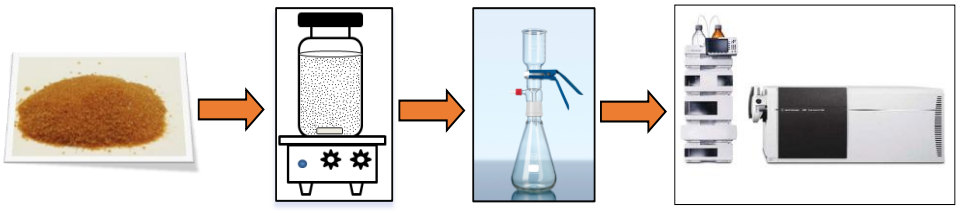
3.3.1. Hypercrosslinked magnetic particles to extract sweeteners from environmental samples



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HYPERCROSSLINKED MAGNETIC PARTICLES TO EXTRACT SWEETENERS FROM ENVIRONMENTAL SAMPLES

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Abstract

This work presents a new extraction material, namely Q-100, based on hypercrosslinked magnetic particles (MPs) that was tested in dispersive solid-phase extraction (d-SPE) for a group of sweeteners (SWs) from environmental samples. The hypercrosslinked Q-100 MPs had the advantage of suitable pore size distribution and high surface area, and showed good retention behaviour towards SWs.

After the optimization of the d-SPE parameters, Q-100 showed suitable apparent recovery (%R_{app}), ranging in the case of river water sample from 21% to 88% for all the SWs, except for alitame, for which the %R_{app} was 12%. The validated method based on d-SPE using Q-100 followed by LC-MS/MS provided good linearity and limits of quantification (LOQs) between 0.01 and 0.05 µg L^{-1}.

The method was applied to analyze samples from river water and effluent wastewater and four SWs (acesulfame, saccharin, cyclamate and sucralose) were found in both types of samples. In effluent water, higher concentrations of acesulfame, sucralose and saccharin were quantified at 17.87 µg L^{-1}, 4.91 µg L^{-1} and 0.18 µg L^{-1}, respectively. Meanwhile, in river water, the same compounds were found at concentrations between 0.09 µg L^{-1} and 0.39 µg L^{-1}. In both samples, the levels of cyclamate detected were below LOQ.

Keywords: sweeteners; hypercrosslinked magnetic particles; dispersive solid-phase extraction; liquid chromatography-tandem mass spectrometry

1 INTRODUCTION

Currently, the consumption of synthetic sweeteners (SWs) is increasing because of their low calorific value, high potency and non-nutritive properties to help to prevent body weight gain, dental cavities and diabetes [1]. They are the largest class of additives in the food industry and are purposely added to food, beverages, personal care products and so on to provide a sweet flavour or as a preservative. In the 1950s, the first generation of SWs was introduced, including aspartame (ASP), saccharin (SAC) and cyclamate (CYC). Subsequently, the second generation of SWs included acesulfame (ACE), sucralose (SUC), neotame (NEO) and alitame (ALI) [2]. In the last decade, ACE, ASP, CYC, SAC, SUC, neohesperidin-dihydrochalcone (NHDC) have been permitted by the European Union (EU) for use in foodstuffs [3]. Moreover, consumption has also increased in the case of SWs of natural origin, such as stevioside (STV) and glycyrrhizic acid (GLY) [1]. Since December 2011, the EU has permitted the use of steviol glycosides in foodstuffs [4]. Due to high consumption, the occurrence of SWs in the aquatic environment has already been demonstrated in previous studies and they are therefore considered as emerging organic contaminants (EOCs) [5-7]. The major source of discharging EOCs in environment water is wastewater treatment plants (WWTPs). Some studies [7, 8] have demonstrated that SWs are inadequately removed from WWTPs. As such, they remain in environment and their presence affects the physiology and locomotion behaviour of aquatic species [9], though they are considered nontoxic to humans within regulated concentrations [10, 11]. Therefore, recent research has focused on studying the environmental occurrence, fate and ecotoxicological effect of SWs [8, 9, 11].

To date, a large number of papers about the determination of SWs in environmental water have been published. Most of these are based on solid-

phase extraction (SPE), either in off-line [6, 12] or on-line [13] mode, followed by liquid chromatography (LC). Another SPE mode is the dispersive (d-SPE) one, which has been already used for extracting target compounds by dispersing a few mg of sorbent into liquid samples [14]. d-SPE has also been used to cleanup extracts from QuEChERS extraction [15].

As well as the most commonly applied silica- [16] and polymeric-based sorbents [17], magnetic particles (MPs) have been also applied in d-SPE, in which they are dispersed in aqueous samples, shortening the equilibrium time and being easily removed from aqueous sample by applying a magnetic field rather than centrifugation or filtration [18]. Numerous MPs have been developed through the incorporation of different functional groups (silica, carbon, surfactants and polymers), which are used in different analytical applications [18, 19], which include the extraction of compounds such as endocrine disruptors [20], drugs [21] and food additives including some SWs [22]. In fact, this is the only study [22] dealing with the extraction of SWs, but from red wine samples.

Recently, a novel Q-100 hypercrosslinked MPs was developed and demonstrated efficient removal of antibiotics from water from a WWTP [23]. An important feature of the Q-100 material are the hypercrosslinked structure, which leads to suitable pore size distribution and high surface area. In view of these characteristics, the aim of this study was to evaluate the retention behaviour of Q-100 as material for extraction of a broad group of SWs from environmental water samples using the d-SPE technique followed by LC-tandem mass spectrometry (LC-MS/MS).

2 MATERIALS AND METHODS

2.1 Reagents and standards

Analytical reagent grade ferrous ferric oxide (Fe_3O_4), ferric chloride hexahydrate ($FeCl_3$,$6H_2O$), ferrous chloride tetrahydrate ($FeCl_2$, $4H_2O$), aqueous ammonia (28 wt%), benzoperoxide (BPO), toluene, 1,2-dichloroethane (DCE), oleic acid (OA), acetone and methanol (MeOH) were purchased from Shanghai Chemical Reagent Corp. (China). Polyvinyl alcohol (PVA) and divinylbenzene (DVB, 80 wt%) were purchased from Sigma-Aldrich and J&K Chemical Co. Ltd, China.mn to remove the inhibitors.

HPLC grade acetonitrile (ACN) and MeOH were supplied by Scharlab (Barcelona, Spain). Hydrochloric acid (HCl) and formic acid (HCOOH) 95% used to adjust the pH of the sample and mobile phase were purchased from Merck (Darmstadt, Germany). Ammonium hydroxide (NH_4OH) was purchased from Sigma-Aldrich (Steinheim, Germany). Ultrapure water was obtained using an ultrapure water purification system Veolia Waters (Sant Cugat del Vallès, Spain).

The individual SW standards were supplied by Sigma-Aldrich and they were: ACE, SAC, CYC, ASP, SUC, ALI, NHDC, STV, NEO and GLY. All the above standards were 99% purity except GLY, which was 70% purity. The chemical structures and properties of all SWs are described in Fig. 1S (supplementary information).

Stock solutions of individual standards were prepared by dissolving of pure compound in MeOH at a concentration of 1,000 mg/L, and then stored at -20^{o}C in amber glass bottles. Mixed standard solutions at a concentration of 50 mg/L were prepared every month by dilution of stock solutions in MeOH and stored at 4^{o}C. Mixed standard working solutions were prepared daily

from mixed standard solutions by appropriate dilution with water:MeOH (9:1, v/v).

2.2 Preparation of hypercrosslinked Q-100 magnetic particles

The hypercrosslinked MPs Q-100 were prepared through the copolymerization reaction reported in a previous work [23]. Briefly, the Fe_3O_4 nanoparticles were prepared through coprecipitation reaction, and coated by OA under a nitrogen atmosphere. The oil phase containing the monomer DVB, the initiator BPO, the porogen toluene and the magnetic core, OA-Fe_3O_4, was stirred at 80ºC in the aqueous phase, which consisted of PVA and sodium sulphate dissolved in distilled water. Afterwards, the obtained MPs were dried and hypercrosslinked in 1, 2-DCE at 90ºC for 18 h using anhydrous ferric chloride as catalyst. The obtained Q-100 particles were rinsed and dried, and their surface area was ~1,150 m^2/g, with particle size of 100-150 µm.

2.3 Dispersive solid-phase extraction

For the d-SPE procedure, 100 mg of Q-100 MPs were introduced into a glass vial, and the sample volume (50 mL for river waters and 25 mL for wastewater samples) adjusted to pH 2 with HCl was added to the glass vials. The solution was stirred for 30 min at 900 rpm aided by a magnetic stirrer. After 30 min, the MPs were separated out from the water sample using the filtration assembly and then dried under vacuum for 15 min. Finally, the retained analytes were eluted from the MPs by passing 5 mL of MeOH and 5 mL of 2% NH_4OH in MeOH solvent through the same assembly. The elution solvent was evaporated using a Genevac miVac Duo system concentrator (Ipswich, United Kingdom) and the dried residue was resuspended with 1 mL of water:MeOH (9:1 v/v) prior to injecting into LC-MS/MS.

To avoid carryover, the Q-100 MPs were cleaned after each use by twice passing 5 mL of MeOH and 5 mL of 2% NH_4OH in MeOH solvent through the same assembly, and then they were dried.

2.4 Liquid chromatography-tandem mass spectrometry analysis

A liquid chromatography-ultra violet detector (LC-UV) instrument was used during the optimization of the d-SPE. The chromatographic analyses were carried out using a model 1200 series HPLC system from Agilent Technologies (Waldbronn, Germany) equipped with a degasser, an automatic injector, a column oven and a UV detector. The column used was a Zorbax Eclipse XDB-C_8 (150 mm × 4.6 mm i.d., 5 µm) from Agilent. The column temperature was maintained at 25ºC. The mobile phase flow-rate was set 0.6 mL/min and the sample volume injected was 50 µL. The mobile phase consisted of ultrapure water adjusted to pH 2.5 with HCl and ACN. The gradient started at 5% ACN, which was increased to 40% ACN in 13 min, then to 100% in 11 min and kept constant for 3 min. Finally, it was returned to the initial conditions in 2 min, which was held for 8 min to equilibrate the column for further analysis. All the compounds were eluted in 20 min and the total run time was 29 min.

Once the d-SPE was optimized, the method was validated with an Agilent 1200 series LC coupled to a 6410 series triple quadrupole mass spectrometer with an electrospray ionization (ESI) interface from Agilent Technologies. The chromatographic conditions used in the LC-MS/MS instrument were the same as for the LC-UV, except that the aqueous mobile phase was adjusted to pH 3 with HCOOH. The analyses were performed in multiple reaction monitoring (MRM) and negative ionization mode. The operating optimized ESI parameters were as follows: N_2 flow rate 12 L/min, capillary voltage of 4,000 V, nebulizer pressure of 45 psi (N_2) and source temperature of 350ºC. Three MRM transitions (one as a quantifier, two as

qualifiers) were selected for each analyte. Just in the case of CYC and SUC, two MRM transitions were monitored due to their poor fragmentation. All information is summarized in Table 1.

Under the LC-MS/MS conditions, the 10 SWs showed good linearity (determination coefficients R^2>0.9993) in the range of 0.2-50 µg L^{-1} for ACE, SUC, ALI, STV, and GLY, and 0.5-10 µg L^{-1} for SAC, CYC, ASP, NEO, and NHDC. The instrumental limits of detections (ILODs) were evaluated as a signal-to-noise ratio (S/N) of 3:1 and ranged from 0.05-0.5 µg L^{-1}.The lowest points of the calibration curve were taken as the instrumental limits of quantifications (ILOQs).

2.5 Sampling

The surface water samples from River Ebro were collected from three different locations and the wastewater samples were collected from the influent and effluent wastewater treatment plants (WWTPs) Tarragona and Reus cities (Spain). All samples were filtered by using 1.2 µm glass fibre filters followed by a nylon supported 0.45 µm membrane filters, both from Fisher (Loughborough, UK). The samples were then stored at 4ºC until analysis.

Table 1. General LC-(ESI)MS/MS parameters for each analyte.

Name	Abbreviation	t_R (min)	Cone Voltage (V)	Precursor ion (m/z)	Collision energy (eV)	Product Ion	Ion ratio	window set
Asesulfame-K	ACE	6.9	80	162.1	10	**82.1**		
					35	78	32	1
					70	64	7	
Saccharin-Na	SAC	8.5	120	182	35	**42**		
					15	105.9	51	
					15	62	11	2
Cyclamate-Na	CYC	8.9	120	178.1	30	**80**		
					25	96	1	
Aspartame	ASP	10.6	120	293.1	10	**200**		
					10	217.02	44	
					5	261	90	
Sucralose	SUC	10.7	120	433	10	**396.9**		3
					10	358.9	5	
Alitame	ALI	11.7	120	330.1	10	**312.1**		
					15	295	26	
					20	167.1	17	
Neohesperidin dihydrochalcone	NHDC	14.5	240	611.2	45	**303.1**		
					55	125	43	
					70	166	48	4
Stevioside	STV	15.2	160	839.3	35	**641.2**		
					70	479	19	
					85	317.1	7	
Neotame	NEO	16.2	120	377.2	15	**200**		
					10	345.1	43	
					20	301.1	25	
Glycyrrhizin acid	GLY	18.2	280	821.4	45	**350.9**		5
					55	192.8	34	
					65	112.8	32	

In bold means quantifier

3 RESULTS AND DISCUSSION

3.1 Optimization of d-SPE procedure

For the d-SPE procedure, several parameters were optimized including extraction time, sample pH and volume, the amount of Q-100 MPs, elution solvent and its volume. These parameters were optimized by LC-UV (conditions described in Section 2.4), and this did not include the compounds CYC and SUC because they do not absorb in the UV range due to the lack of a chromophore group. Initial experimental extraction conditions were: 10 mL of ultrapure water adjusted to pH 3 with HCOOH spiked at 5 µg L^{-1} with the mixture of analytes placed in a ~10 mL glass vial. Then, 50 mg of Q-100 MPs were transferred into a vial and the solution was stirred at 900 rpm, aided by a Teflon-coated magnetic stir bar for 30 min at room temperature for the sorption of the analytes. After sorption, the Q-100 MPs were separated from the sample using the filtration assembly instead of applying an external magnetic field, due to the Q-100 particles' own limited magnetization. For the elution of the retained analytes, 3x5 mL of MeOH were passed through the particles in the filtration assembly. The three collected fractions were evaporated to dryness and the residue re-dissolved in water:MeOH (9:1) mixture before injection into the LC system.

3.1.1 Extraction conditions

The recoveries at sample pH 2, 3 and 7 were compared in order to evaluate the effect of pH on extraction recoveries of the SWs, since they possess different physicochemical characteristics (see Fig. S1 for details). As Fig. 1 shows, comparing pH 3 and 7, the recoveries were only 10% to 15% lower at pH 7 than at pH 3. In contrast, when decreasing the pH from 3 to 2, the compounds ACE, SAC, ASP, ALI and GLY presented higher extraction recoveries at pH 2, while no significant decrease was observed for the rest of

the compounds. Therefore, considering these results, pH 2 was chosen for further experiments.

To investigate the sample volume, 50 and 100 mL of ultrapure water spiked with mixture of SWs were tested, and it was observed that recoveries decreased (by 10% to 20%) for all analytes when the sample volume increased from 10 mL to 50 mL, although the sensitivity of the method increases. It was also observed that from 50 mL to 100 mL of sample, the recoveries further decreased from 5% to 15% for all compounds. Therefore, as a compromise between the sensitivity and recoveries of the method, a sample volume of 50 mL was selected.

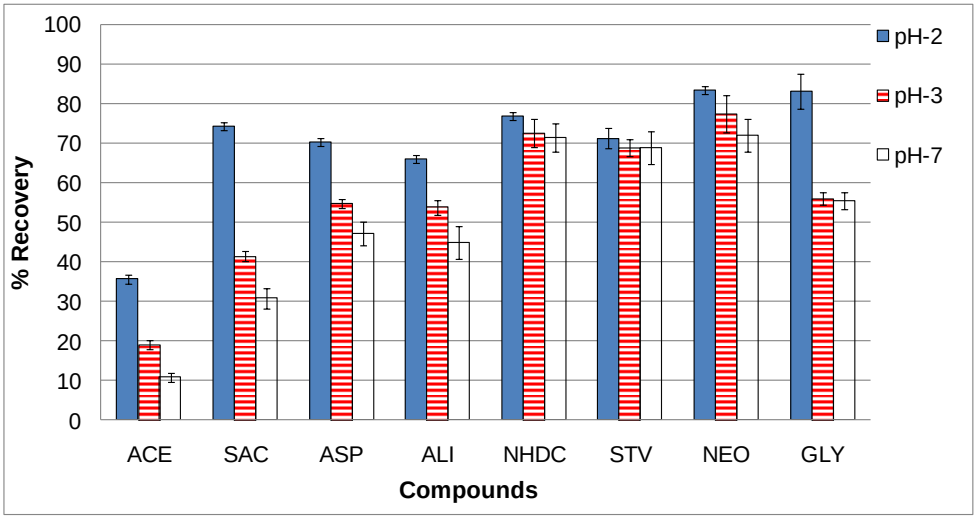

Figure 1. Effect of the sample pH on extraction recovery of analytes using Q-100 MPs in d-SPE (%RSD (n=3) were lower than18%).

The amount of MPs was tested at 50 mg, 100 mg and 150 mg. When the amount of MPs increased from 50 mg to 100 mg, the extraction recoveries increased from 5% to 35% for all compounds. However, when increasing from 100 mg to 150 mg, the MPs formed agglomerates instead of

being dispersed in the sample, and the recoveries did not increase more than 10%. Thus, 100 mg of MPs was selected for further experiments.

The effect of extraction time on the extraction recovery was tested by stirring the sample for 30 and 60 min. The results showed that, in the case of 60 min extraction, recoveries of analytes did not increase more than 10% compared to 30 min. In addition, for routine analysis, an extended extraction time was not suitable, and 30 min was selected.

To sum up, the optimal conditions for SW extraction were 50 mL of sample adjusted to pH 2 with 100 mg of Q-100 MPs stirred at 900 rpm for 30 min.

3.1.2 Elution conditions

Due to the low magnetization of the particles, the elution was carried out in the filtration assembly, which was used to separate the particles from aqueous sample, while the retained analytes were eluted by passing a volume of the elution solvent through the same assembly.

The elution strength of MeOH and ACN was compared and, under the same conditions, ACN provided lower extraction recoveries compared to MeOH. Therefore, MeOH was maintained.

As regards the volume, three fractions of 5 mL MeOH each were passed through the Q-100 MPs. With the first 5 mL, recoveries ranged from 56% to 78% for all the analytes, except ACE (12%), ASP (44%) and ALI (43%). In the second fraction of MeOH, the recoveries were between 5% and 10% for all the compounds. Lastly, with the third fraction of MeOH, no improvement in recoveries was observed. In this respect, previous studies dealing with the extraction of SWs by SPE [6, 24] also pointed out that the use of pure MeOH and ACN was not sufficient to elute out certain SWs, such

as ACE, SAC, NEO and STV. The improvement in the recoveries of these compounds had been achieved with basic additives (i.e. NH_4OH) in the solvent [6, 24]. Thus, when 5 mL of MeOH followed by 5 mL of 2% NH_4OH in MeOH were used, the extraction recoveries increased from 16% to 40% for the above mentioned analytes, while the rest of analytes did not show any improvement. Thus, all the studied SWs can be desorbed with recoveries up to 75%, except ACE (32%), ASP (60%) and ALI (50%). Considering the obtained results, 5 mL of MeOH followed by 5 mL of 2% NH_4OH in MeOH (10 mL volume) was chosen.

The 10 mL of elution solvent was evaporated to dryness using a miVac concentrator and the residue was re-dissolved in 1 mL of ultrapure water and MeOH (9:1, v/v) before injecting to LC. During this step, less than 5% losses were observed for all compounds.

After the optimization of the d-SPE procedure, the conditions used for further application in real samples were as described in Section 2.3. Under the optimal conditions, the extract from d-SPE was injected into the LC-MS/MS, in which CYC and SUC could be monitored and provided recovery values of 36% and 98%, respectively. Thus, on the whole, the recovery values (%) for each analyte in ultrapure water were in the range of 60% to 98% for all compounds, expect for ACE, CYC and ALI, which were 32%, 36% and 50%, respectively. A possible explanation could be that the MPs coated with non-polar polystyrene-based material was not able to retain the more polar analytes.

In fact, the present results are comparable to those obtained in a previously studies [6, 24, 25], where higher amount of the commercial available Oasis HLB (500 mg) [24] and HR-X (500 mg) [25] sorbent were evaluated for the extraction of SWs in 100 mL [24] and 500 mL [25] of water sample. It is clear from the results that, with a small amount of Q-100

material, better recoveries might be achieved because of the hypercrosslinked structure of Q-100 that provides high surface area to interact with the extracted analytes.

3.2 Method validation

The Q-100 material was applied for the extraction of the SWs from environmental water samples, including river water, and effluent and influent samples from a WWTP.

Table 2 shows the apparent recovery (%R_{app}) and matrix effects (%ME) that were calculated for each kind of sample. Sample volumes of 50 mL for river water and 25 mL for effluent and influent wastewaters were selected due to the complexity of the matrix and to reduce the %ME. The %R_{app} and %ME were calculated at low and high concentration levels for all matrices except influent wastewater, which was just calculated at the high concentration level. Firstly, non-spiked samples were analyzed in order to subtract the signal of existing analytes.

The %R_{app} were calculated by comparing the responses of pre-spiked sample with the responses of pure standard solution at same concentration. As can be seen in Table 2, in river water samples at both levels of concentration, it was observed that %R_{app} were higher than 70% for all the analytes, except for ACE, CYC, ASP, which were between 21% and 33%, and ALI, which was below 12%. In effluent wastewater at both levels, it was also observed that %R_{app} for ACE, CYC, ASP and NHDC were below 24% and, for rest of analytes, ranged from 30% to 69%. As expected, lower values of %R_{app} were obtained in influent wastewater than in river and effluent wastewater due to the complexity of matrix. The obtained %R_{app} for all studied analytes ranged from 18% to 45%, except for CYC, ASP and NHDC, which were below 10%.

Table 2. $\%R_{app}$ and %ME of SWs in river and effluent wastewater samples by d-SPE extraction techniques.

Analyte	River water (50 mL)				Effluent (25 mL)				Influent (25 mL)	
	spiked at 0.05 (µg L^{-1})		spiked at 0.5 (µg L^{-1})		spiked at 0.1 (µg L^{-1})		spiked at 1 (µg L^{-1})		spiked at 0.4 (µg L^{-1})	
	% R_{app}	% ME	% R_{app}	% ME	% R_{app}	% ME	% R_{app}	% ME	% R_{app}	% ME
ACE	31	-3	27	-21	20[a]	-26	24[b]	-21	18[b]	-23
SAC	70	-6	75	-4	69	-9	63	-14	34	-39
CYC	21	-29	27	-33	5	-49	16	-46	4	-27
ASP	30	-35	33	-36	19	-52	18	-74	2	-57
SUC	84	-21	78	-24	43[a]	-37	50[b]	-31	45[b]	30
ALI	12	-13	11	-15	38	-39	42	-32	25	-74
NHDC	70	-27	72	-20	24	-61	23	-70	9	-88
STV	88	-16	84	-12	43	-56	30	-65	22	-78
NEO	72	-27	75	-28	35	-64	30	-68	20	-78
GLY	85	-29	69	-22	66	-20	57	-34	23	-63

[a] Spiked at 1 µg L^{-1} (n=3)
[b] Spiked at 2 µg L^{-1} (n=3)

The ME was evaluated in the three types of matrices and was calculated by comparing the signal response obtained when spiking a sample after extraction with the signal response obtained from a standard solution at the same concentration. If the %ME=0, no ME is present, if %ME<0, there is ion suppression and if %ME>0, there is ion enhancement. Ion suppression was observed for all analytes in all matrices (data shown in Table 2). In river water, similar ion suppression was observed at the two levels of concentration, which was less than 36% for all analytes. However, in effluent wastewater samples ion suppression was higher with values from 37% to 65% for all analytes, except for ACE and SAC, which had values lower than 26% and 14%, respectively. In the case of influent wastewater, high ion suppression was observed for ASP, ALI, NHDC, STV, NEO and GLY (values ranged from 63% to 88%) but, for the other analytes, the values of ion suppression ranged from 23% to 39%, which is fairly good and similar to river and effluent matrices. These results might be attributed to the high content of compounds in the sample that are strongly retained by Q-100 MPs, and eventually affect the analytes' ionization.

Then, the analytical method based on d-SPE/LC–MS/MS was validated for river water samples including the following parameters: linearity, repeatability, reproducibility, limits of detection (LODs), and limits of quantification (LOQs), and the results are shown in Table 3.

The linear range of matrix-matched calibration curve was very suitable, ranging from 0.01 to 0.05 to 1 µg L^{-1} (details in Table 3) with determination coefficients (R^2) greater than 0.9996. The LODs for the compounds present in the river sample (ACE, SAC, CYC and SUC) were calculated on the basis of the ILODs and applying $\%R_{app}$, and they ranged between 0.004 and 0.02 µg L^{-1}. LODs for rest of the compounds were calculated as S/N 3:1, and ranged between 0.001 and 0.005 µg L^{-1}. The LOQs were selected as the lowest point of calibration curve, between 0.01 and 0.05 µg L^{-1}. The

repeatability and reproducibility between days were both measured at two different concentration levels (0.05 µg L^{-1} and 0.5 µg L^{-1}) and the results are summarized in Table 3.

Table 3. LODs, linear range, repeatability and reproducibility between days obtained when 50 mL of river water sample spiked at 0.05 µg L^{-1} and 0.5 µg L^{-1} of each analyte were analyzed by d-SPE/LC–MS/MS.

Analyte	LODs (µg L^{-1})	Linear range (µg L^{-1})	Repeatability (%RSD, n=5)		Reproducibility (%RSD, n=5)	
			0.05 (µg L^{-1})	0.5 (µg L^{-1})	0.05 (µg L^{-1})	0.5 (µg L^{-1})
ACE	0.006[a]	0.05 - 1	16	6	13	15
SAC	0.01[a]	0.05 - 1	7	3	16	12
CYC	0.004[a]	0.02 - 1	15	2	18	10
ASP	0.002	0.02 - 1	14	6	17	15
SUC	0.02[a]	0.05 - 1	12	7	14	14
ALI	0.005	0.01 - 1	8	19	19	14
NHDC	0.001	0.01 - 1	5	8	7	7
STV	0.001	0.01 - 1	6	3	3	7
NEO	0.001	0.01 - 1	5	3	4	7
GLY	0.003	0.02 - 1	9	6	10	4

[a] Calculated from instrumental LODs considering apparent recovery

3.3 Application to environmental samples

To evaluate the applicability of the d-SPE/LC–MS/MS method, three different samples of river and effluent wastewater were analyzed in triplicate and the quantitative results are shown in Table 4. The concentration of the analytes in effluent samples was calculated using the instrumental calibration curve and applying the corresponding $\%R_{app}$, whereas, for quantifying the concentration of the analytes in river water samples, the matrix-matched calibration curve was used. The identification of compounds in the sample was based on the retention time and ratios between the quantifier and

qualifier transitions, when compared with reference standards.ACE, SAC, CYC, and SUC were found in all river and effluent water samples analyzed. However, the rest of SWs were not detected in any of the samples analyzed, which is in line with previous studies [6, 24].

Table 4. Concentration of the analytes in μg L^{-1} when river and effluent water by d-SPE followed by LC–MS/MS were analyzed (N=3).

Analyte	River	Effluent
ACE	0.37 - 039	15.10 - 17.87
SAC	0.14 - 0.23	0.12 - 0.18
CYC	below LOQ	below LOQ
SUC	0.09 - 0.21	4.66 - 4.91

As regards river water, trace levels of ACE, SAC and SUC were found, whereas CYC was detected at a concentration below its LOQ. As for effluent wastewater, the same analytes were present, but at higher concentrations except in the case of SAC, which was at a lower concentration, similar to that found in river, and CYC, which was also found at a concentration below its LOQs in the majority of the samples. The fact that these analytes were present in river water could be explained for their incomplete elimination at WWTPs. The concentrations detected in this study were similar to previous studies [6, 24] in which water supplied from the same WWTPs was analysed, although higher concentration levels were found in wastewater samples in North-West Spain [12] and Switzerland [26].

4 CONCLUSIONS

The evaluated new material Q-100 MPs with hypercrosslinked properties provided high retention features with respect to SWs. However, the limited magnetization should be addressed to be able to exploit Q-100 MPs fully.

Under optimized conditions, the recoveries of analytes in different environmental samples were satisfactory. From the results obtained, the optimal d-SPE was comparable with previous results obtained with SPE using commercially available sorbents.

The developed method based on d-SPE/LC-MS/MS was successfully validated in river water sample and applied to the determination of SWs in river water samples and effluent wastewater samples, where ACE and SUC were the analytes found at higher concentrations.

Acknowledgments

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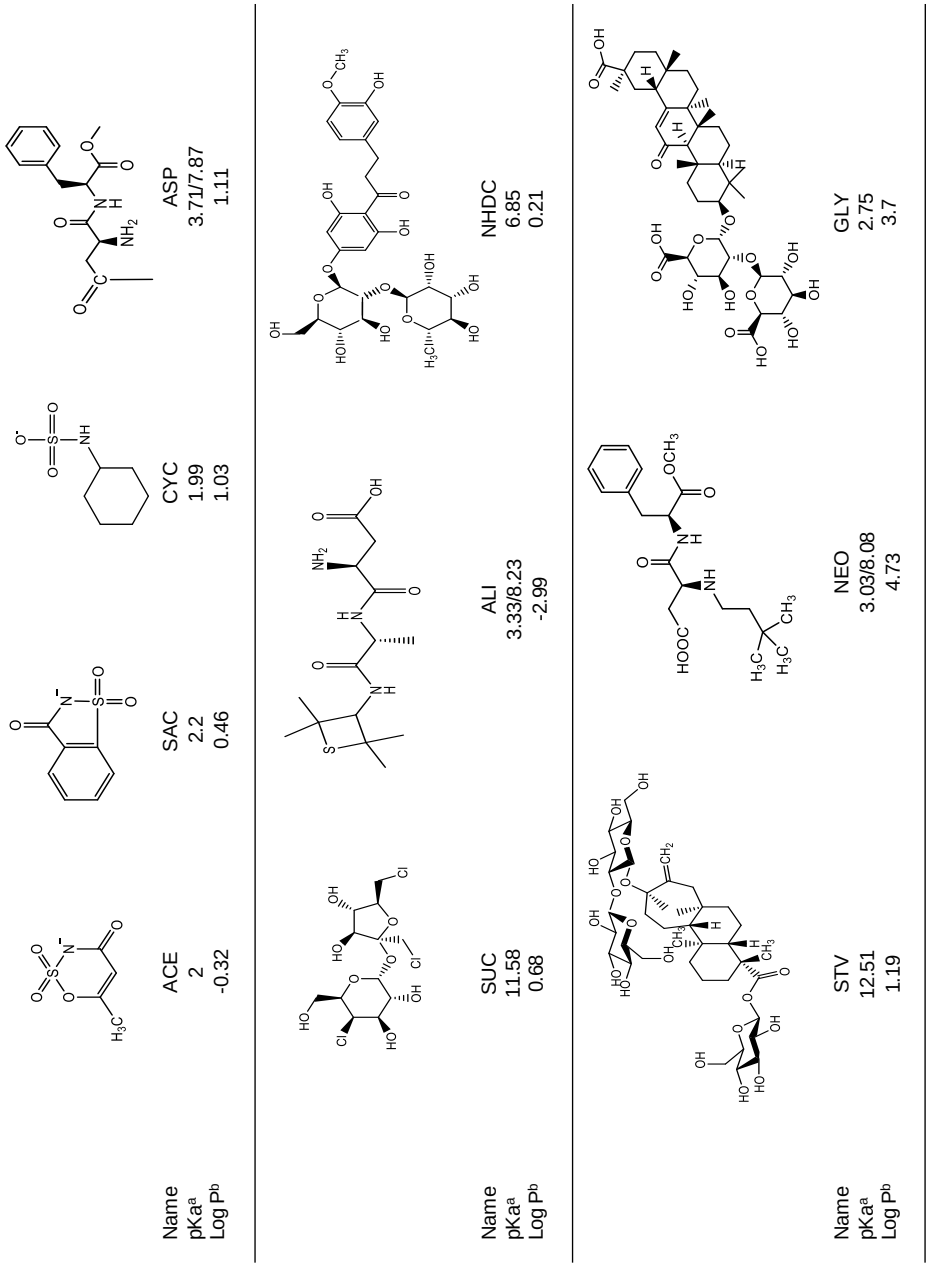
Figure 1 Supplementary- Structure and properties of ten SWs.



3.3.2. Discussion of results

UNIVERSITAT ROVIRA I VIRGILI
EVALUATION OF NOVEL SORPTIVE EXTRACTION TECHNIQUES
Sameer Shamrao Lakade

In this present section, a new sorptive material was introduced for a well-known extraction technique, d-SPE. The advantages of the new hypercrosslinked Q-100 MPs have already been discussed in the introduction to Section 3.3.

In this study, SWs were chosen because they have a wide range of polarities and they are structurally very complex compounds. Although there are several analytical methods that have been developed for the determination of these compounds in aqueous sample [1-3], their determination is still challenging and MPs have not been yet applied to extract there from environmental samples. However, there is one study [4] in which the authors used the d-SPE technique for the extraction of food additives from wine samples, selecting certain SWs similar to the present study, but the sample was different. In this case, the authors used 1 mL of wine sample adjusted to pH 1 and 15 mg of an improved ethylenediamine-functionalized magnetic polymer for the extraction. After 1 minute of extraction time, the retained analytes were eluted using 0.5 mL of elution solvent and the recovery obtained ranged from 78% to 98% for the selected SWs. Although the recoveries were almost completed, it should be remembered that just one millilitre was extracted.

At the beginning of the evaluation experiment, a significant limitation of Q-100 MPs was observed in relation to the fact that these MPs could not be separated from the sample by applying an external magnetic field due to lack of magnetization. There are some studies [5, 6] available that cover different strategies to improve the magnetization properties of the particles by introducing iron oxide to the desired material by co-precipitation, micelle synthesis, hydrothermal synthesis and thermal desorption reaction. However, in the present study, the synthesis

approach was not taken further. Instead, the design of the process was changed using a filtration assembly for both separations of particles from the sample and in the elution step.

Despite of the lack of magnetization, satisfactory retention was observed for a broad group of selected SWs, due to the hypercrosslinked structure, which leads to larger surface area. After achieving satisfactory results, the different parameters that affect retention and elution were optimized. Under the optimal conditions, the obtained recovery results were similar for some analytes when compared to previous studies by our research group, in which conventional SPE was used [1, 2].

It is well known that a higher amount of sorbent material improves extraction recovery. However, in the present study, 100 mg of the sorbent was chosen because the larger amount of MPs formed agglomerates in the water sample and inhibited the extraction of the analytes, which is another limitation of this material.

With regard to the recovery results, when 100 mg of sorbent and 50 mL of sample volume was used, the values obtained were similar for all analytes, except ACE, CYC and ALI, to those in another study [3], in which 200 mg of the commercially available Oasis HLB cartridge and the same sample volume (50 mL Ultrapure water) were applied. In that study, recoveries ranged from 73% to 102% for all compounds. In addition, Kokotou *et al.* [7] extracted similar SWs compounds from 50 mL of ultrapure water sample adjusted to pH 3 using the commercially available Strata X SPE cartridge (200 mg). The analytes were then eluted from the cartridge with 3 x 3 mL of MeOH. The recoveries reported were between 67% and 97% for all analytes, except for CYC, which was 40%. In fact, in our study, a low recovery was also obtained for the CYC.

With respect to the ME, the values obtained were below 35% for all analytes in the river water sample. In the case of effluent and influent wastewater samples, a high %ME (over 50%) was observed for some analytes.

When the developed d-SPE method was applied to analyzed river water sample, the determination of SWs was carried out using the matrix-matched calibration method. However, in the case of wastewater samples, they were determined with the external calibration method and taking the extraction process into consideration, because these compounds were present at a high concentration in the samples. The results of the present study were in line with previous studies [1, 2] by our research group in which samples from the same origin were analyzed, and were also similar to studies by other research group studies [7, 8].

The above mentioned limitations of MPs, such as low magnetization and the formation of agglomeration, could be overcome through future research focusing on improving the magnetization of MPs and developing new sorbents with enhanced retention features.

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CHAPTER 4. CONCLUSIONS

UNIVERSITAT ROVIRA I VIRGILI
EVALUATION OF NOVEL SORPTIVE EXTRACTION TECHNIQUES
Sameer Shamrao Lakade

The most important conclusions derived from the studies presented in this Doctoral Thesis can be summarized as follows:

1. Different novel sorptive extraction techniques, namely fabric phase sorptive extraction (FPSE), dynamic FPSE (DFPSE) and capsule phase microextraction (CPME), were applied for the first time and proved to be an alternative to well-established sorptive extraction techniques.

2. The successful application of FPSE was demonstrated for the extraction of a group of pharmaceuticals and personal care products (PPCPs) with high recoveries from environmental water samples.

3. To achieve these high recoveries, the different FPSE extraction parameters were optimized and it needed up to four hours to reach equilibrium.

4. DFPSE, which is a modification of FPSE using a filtration assembly, overcomes the long extraction time required in FPSE, resulting in a significant reduction from 4 hours to 10 minutes.

5. The CPME technique, which uses a microextraction capsule (MEC), is another novel extraction technique that overcomes some of the limitations of FPSE, DFPSE and SBSE techniques, with a porous permeable polypropylene tube protecting the sorbent coating from contamination.

6. Of the different materials evaluated, Carbowax 20M (CW-20M) was selected in both FPSE modes and CPME, since CW-20M presents polar properties and, therefore, better retention capabilities for the polar analytes studied.

7. The new hypercrosslinked Q-100 magnetic particles (MPs) were successfully evaluated for the retention of sweeteners (SWs) from aqueous samples using dispersive SPE (d-SPE).

8. Q-100 MPs own hypercrosslinked structure and high surface area, which enhances the retention of the selected analytes. However, the lack of magnetization features is an issue that should be resolved in order to provide an attractive method.

9. The methods developed in the Doctoral Thesis based on novel sorptive extraction techniques followed by LC-MS/MS to determine PPCPs and SWs enable their determination at low concentration levels in environmental water samples.

10. The results obtained from the pioneering evaluation of FPSE, DFPSE and CPME encourage us to test them for different types of analytes in varied ranged of samples.

APPENDIX

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Appendix I. List of abbreviation

ACE	Acesulfame
ALI	Alitame
APPCI	Atmospheric pressure chemical ionization
APPI	Atmospheric pressure photoionization
APy	Antipyrine
ASP	Aspartame
BAμE	Bar adsorptive microextraction
BP-3	3-Benzophenone
BuPB	Butylparaben
BzPB	Benzylparaben
CAFF	Caffeine
CBZ	Carbamazepine
CI	Chemical ionization
CNPrTEOS	Cyanopropyltriethoxysilane
CPME	Capsule phase microextraction
CW-20M	Sol-gel Carbowax 20M
CYC	Cyclamate
DAD	Diode array detector,
DHB	2,4-dihydroxybenzophenone
DHMB	2,2-dihydroxy-4-4-methoxybenzophenone
DICLO	Diclofenac
DI-SPME	Directly immersion-solid phase microextraction
d-SPE	Dispersive solid-phase extraction
DVB	Divinylbenzene
EDC	Endocrine disruptive compounds
EI	Electron impact
EFSA	European Food Safety Agency
EHMC	Ethyllhexyl methoxycinnamate
EOCs	Emerging organic contaminants

EPA	Environmental Protection Agency
EPB	Ethylparaben
FDSE-FI-FAAS	Fabric disk sorptive extraction- flow injection- flame atomic absorption spectrometry
FLD	Fluorescence light detector
FPSE	Fabric phase sorptive extraction
GC	Gas chromatography
GCBs	Graphite carbon blacks
GLY	Glycyrrhizin acid
HEMA	2-hydroxyethyl methacrylates
HF	Hollow fiber
HILIC	Hydrophilic interaction liquid chromatography
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
HS-SPME	Head space-solid phase microextraction
HXLPP	Hypercrosslinked precipitation polymerization
HTLC	High temperature liquid chromatography
IAMC	Isoamyl methoxycinnamate
IT	Ion trap
LC	Liquid chromatography
LD	Liquid desorption
LLE	Liquid-liquid extraction
MDLs	Method detection limits
ME	Matrix effect
MIPs	Molecular imprinted polymers
MPB	Methylparaben
MPs	Magnetic particles
MRM	Multiple reaction monitoring
MS	Mass spectrometry
MSAμE	Multi-sphere adsorptive microextraction
MUD	Maximum useable dose

NEO	Neotame
NHDC	Neohesperidindihydrochalcone
NPLC	Normal phase liquid chromatography
NSAID	Nonsteroidal anti-inflammatory drugs
OC	Octocrylene
OCs	Organic contaminants
OD-PABA	Octyldimethyl-p-aminobenzoic acid
OPP	Organophosphorus pesticides
PA	Polyacrylate
PAH	Poly aromatic hydrocarbon
PARA	Paracetamol
PBs	Parabens
PCAP-DMS-CAP	Sol-gel poly(polycaprolactone-dimethylsiloxane-caprolactone)
PCP	Personal care products
PDMDPS	Poly(dimethyldiphenylsiloxane)
PDMS	Poly(dimethylsiloxane)
PEG	Poly(ethylenglycol)
PEGMA	Poly ethylene glycol monoethylacrylate
PEG-PPG-PEG	Triblock Poly(ethylene glycol)–block-poly(propylene glycol)–block-poly(ethylene glycol)
PEO-PPO-PEO	Poly (ethylene oxide)-block(propylene oxide)-block(ethylene oxide)
PGCs	Porous graphite carbons
PhACs	Pharmaceutical active compounds
PMDSA	2-phenylbenzimidazole-5-sulphonic acid
Poly(VP-co-EDMA)	Poly(4-vinylpyridine-co-ethylene glycol dimethacrylate)
PPCPs	Pharmaceuticals and personal care products
PROP	Propranolol
PrPB	Propylparaben

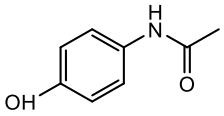
PS	Polystyrene
PTHF	Poly(tetrahydrofuran)
PTHF	Sol-gel Polytetrahydrofluride
PUFs	Polyurethane foam
PVP	Poly (N-vinylpyrrolidone)
Q	Single quadrupole
QqQ	Triple quadrupole
RDSE	Rotating-disk sorptive extraction
RPLC	Reverse phase liquid chromatography
SAC	Saccharin
SAX	Strong anion exchanger
SBSE	Stir bar sorptive extraction
SCSE	Stir-cake sorptive extraction
SCX	Strong cation exchanger
SDME	Single drop microextraction
SPE	Solid-phase extraction
SPME	Solid phase microextraction
SRM	Selective reaction monitoring
SRSE	Stir-rod sorptive extraction
STV	Stevioside
SUC	Sucralose
SWs	Sweeteners
TCC	Triclocarban
TCS	Triclosan
TD	Thermal desorption
TOF	Time of flight
TPs	Transformation products
UCON	Sol-gel UCON
UHPLC	Ultra high performance liquid chromatography
US	United State
UV	Ultra-violet detector

VI-DVB	Poly(vinylimidazole-divinylbenzene)
WAX	Weak anion exchanger
WCX	Weak cation exchanger
WWTPs	Wastewater treatment plants

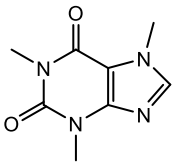
Appendix II. Chemical structure of compounds and sorbent materials

Pharmaceutical Active compounds (PhAc)

Paracetamol



Caffeine



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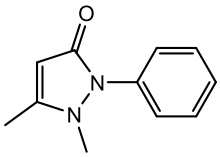
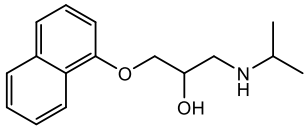
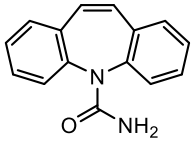


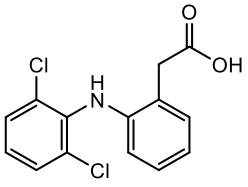
Propranolol



Carbamazepine

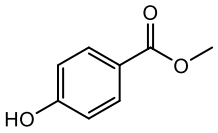


Diclofenac

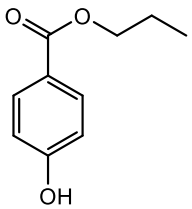


Personal care products (PCPs)

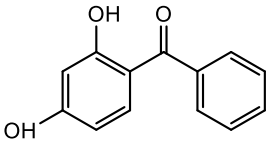
Methylparaben



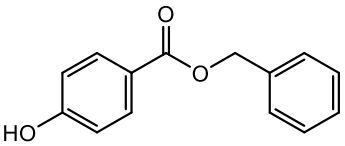
Propylparaben



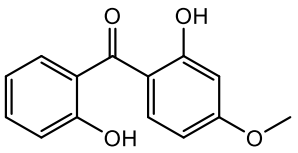
2,4-Dihydroxybenzophenone



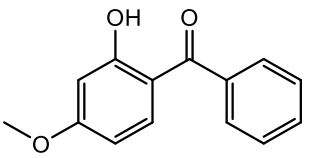
Benzylparaben



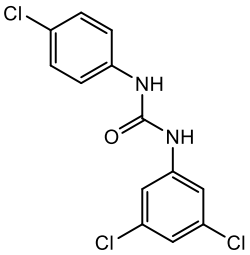
2,2-Dihydroxy-4-4-methoxybenzophenone



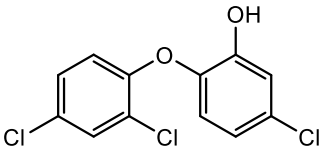
3-Benzophenone



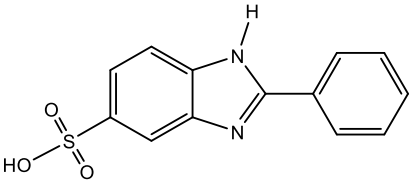
Triclocarban



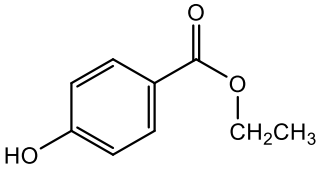
Triclosan



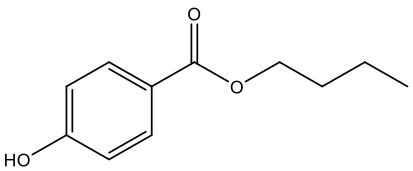
2-Phenylbenzimidazole-5-sulphonic acid



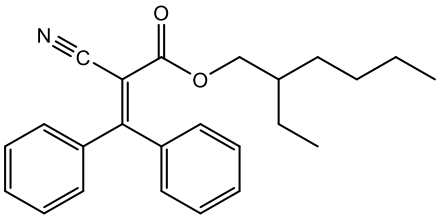
Ethylparaben



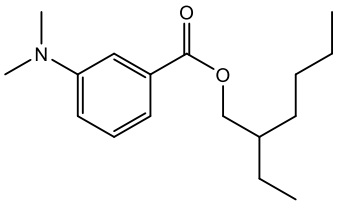
Butylparaben



Octocrylene

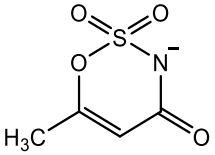


Octyldimethyl-p-aminobenzoic acid

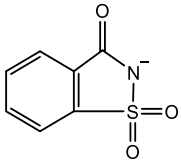


Sweeteners

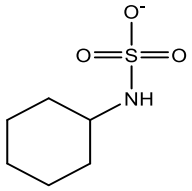
Acesulfame



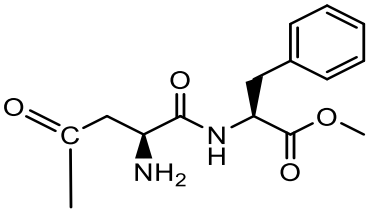
Saccharin



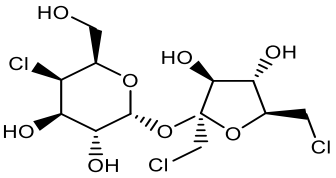
Cyclamate



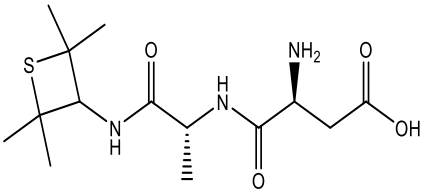
Aspartame



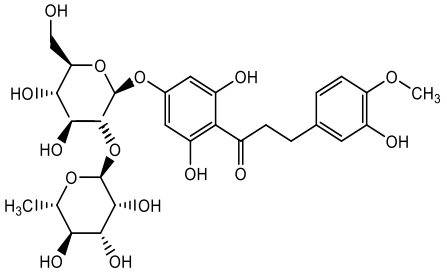
Sucralose



Alitame



Neohesperidin dihydrochalcone



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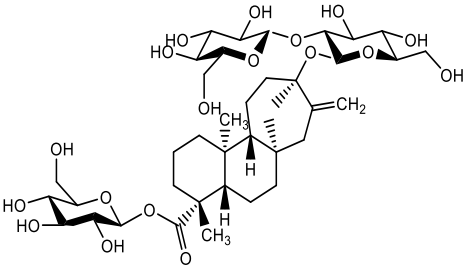
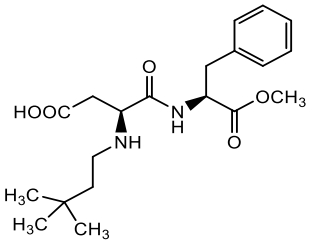
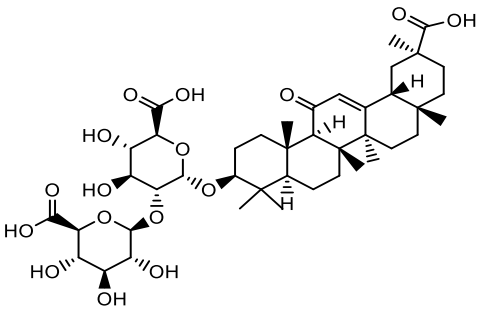


Neotame

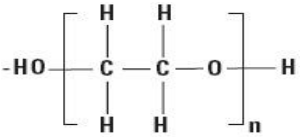


Glycyrrhizin acid

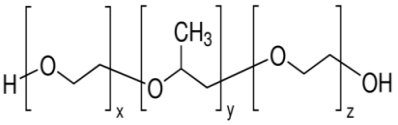


Sorbent materials

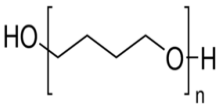
Sol-gel CW-20M



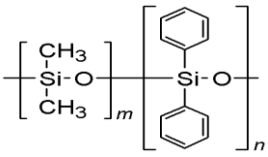
Sol-gel Triblock (PEG-PPG-PEG)



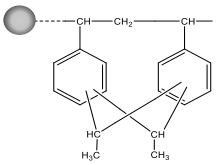
Sol-gel PTHF



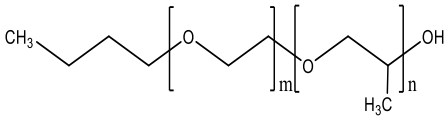
Sol-gel PDMDPS



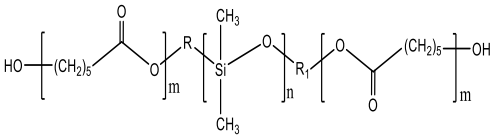
Hypercrosslinked Q-100



Sol-gel UCON



Sol-gel PCAP-DMS-CAP



Appendix III. List of publications

The list of publications obtained in this present Thesis, included in the section of experimental part, which are already published or submitted for publications in different scientific journals are listed below.

1. Sameer S. Lakade, Francesc Borrull, Kenneth G. Furton, Abuzar Kabir, Rosa Maria Marcé, Núria Fontanals, *Novel capsule phase microextraction in combination with liquid chromatography-tandem mass spectrometry for determining personal care products in environmental water, Talanta 2017 (submitted).*

2. Sameer S. Lakade, Qing Zhou, Francesc Borrull, Núria Fontanals, Rosa Maria Marcé, *Hypercrosslinked magnetic particles to extract sweeteners from environmental samples, J. Sep. Sci. 2017 (submitted).*

3. Sameer S. Lakade, Francesc Borrull, Kenneth G. Furton, Abuzar Kabir, Rosa Maria Marcé, Núria Fontanals, *Dynamic fabric phase sorptive extraction for a group pharmaceuticals and personal care products, J. Chromatogr. A 1456 (2016) 19-26.*

4. Sameer S. Lakade, Francesc Borrull, Kenneth G. Furton, Abuzar Kabir, Núria Fontanals, Rosa Maria Marcé, *Comparative study of different fabric phase sorptive extraction sorbents to determine emerging contaminants from environmental water using liquid chromatography–tandem mass spectrometry, Talanta 144 (2015) 1342-1351.*

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