

MAGNETIC SOLID PHASE EXTRACTION APPLICATIONS COMBINED WITH ANALYTICAL METHODS FOR DETERMINATION OF DRUGS IN DIFFERENT MATRICES REVIEW

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ABSTRACT

Sample preparation procedures are essential for drug analysis in biological fluids, tissues, pharmaceutical preparations, food and environmental matrices. For this purpose different techniques have been used like protein precipitation, liquid liquid extraction (LLE) and solid phase extraction (SPE). Magnetic solid phase extraction (MSPE) has become a highly preferred method due to its advantages as a sample preparation-pretreatment technique when compared to classical methods as a novel type of SPE. Basically, this type of extraction is based on the separation of different analytes from complex matrices based on the use of magnetic nanoparticles (MNPs) as adsorbents. Magnetic solid phase extraction minimizes the use of additional steps which reduces the manipulation of conventional extractions. The main advantages depend on its simplicity, environmentally friendly process, disposable cost, reduced solvent consumption, and short duration. In this review, special attention is paid on drug analysis by using MSPE prior to various analytical methods from biological, environmental and food matrices. MSPE applications, with various types of magnetic adsorbents, and different analytical method combinations were revealed for drug analysis.

Abbreviations: LLE, liquid liquid extraction; SPE, solid phase extraction; MSPE, magnetic solid phase extraction; DLLME, dispersive liquid-liquid microextraction; SBSE, stir bar sorptive extraction; SPME, solid phase microextraction; SFE, supercritical fluid extraction; PFE, pressurized fluid extraction; MAE, microwave-assisted extraction; MSPD, matrix solid-phase dispersion; MNP, magnetic nanoparticle; SPION, superparamagnetic iron oxide nanoparticles; MRI, magnetic resonance imaging; CE, capillary electrophoresis; UV-Vis, ultraviolet-visible; MS, mass spectrometric; PEI, polyethyleneimine; PVA, polyvinylalcohol; PEG, polyethyleneglycol; PVP, polyvinylpyrrolidone; LC, liquid chromatography; GC, gas chromatography; HPLC, high performance liquid chromatography; FLD, fluorimetric detection; CZE, capillary zone electrophoresis; poly(MAA-co-EDMA), poly methacrylic acid co-ethyleneglycol dimethacrylate LOD, limits of detection; LOQ, limit of quantification; SDS, sodium dodecylsulfate; MPTS, 3-methacryloxypropyl trimethoxysilane; CTAB, cetyltrimethylammonium bromide; MWCNTs, multiwalled carbon nanotubes; DBMNPs, diatomite bonding Fe₃O₄ magnetic nanoparticles; EGDMA, ethylene glycol dimethacrylate; DCBI, desorption corona beam ionization; MNGO, magnetic nano graphene oxide; NSAIDs, nonsteroidal anti-inflammatory drugs; UAMDSPME, ultrasound-assisted magnetic dispersive solid-phase microextraction; MRLs, maximum residue limits; SA, sulfonamide; PCL, polycaprolactone; MM-PCL-SPE, microspheres solid-phase extraction; MISPE, molecularly imprinted solid-phase extraction; DMIP, dual-template molecularly imprinted polymer; MOF, metal-organic framework; ZIF-8, zeolite imidazolate framework-8; MSPDE, magnetic solid phase dispersion extraction; MIMM, molecularly imprinted magnetic microsphere.

Keywords: Magnetic solid phase extraction, biological fluids, drug, high performance liquid chromatography, review.

INTRODUCTION

Determination of drugs in biological fluids is vital in therapeutic efficacy, bioavailability, bioequivalence studies and forensic toxicological analysis. Biological fluids like urine, plasma, breast milk, cerebrospinal fluid etc and tissues are complex matrices which cause low selectivity and sensitivity. Selective and efficient sample preparation procedures are necessary for quantitation of low dosages of active drug substances. The separation process prior to instrumental analyses should be effective enough to monitorize drug levels to assess toxicity, adverse effects, inter-actions, therapeutic efficiency, pharmacokinetic calculations and quality control of pharmaceutical formulations.

Sample Preparation Techniques

Drug residues in environmental matrices such as water, food and beverage samples are also very important in order to protect the health and safety of the community. In order to achieve sensitive determinations, like the analytical process, sample preparation (pre treatment process) is also very important. In the analytical process of biological fluids precipitation is also very important because the appropriateness of extraction methods directly affects many critical consequences due to the analysis such as urine, blood, serum, bile, stomach contents, liver secretion etc. Sample preparation involves steps that include the stages of dilution, precipitation, filtration and centrifugation in environmental, biomedical and pharmaceutical analyzes, and covers a large part of the total analysis time. This process can not be ignored because the accuracy of the extraction steps before the successful application of chromatographic methods directly affects the accuracy of the result of the analysis to be performed. Extraction is typically required to separate and enrich the analytes from the matrix components. The main purpose in preparing the sample is to concentrate, stabilize and eventually bring the target analytes in the sample to the optimal conditions for the desired chromatographic or other analysis. Furthermore, choosing the appropriate sample preparation method is vitally important in qualitative and quantitative determination of the target compounds.

Various methods have been developed in extraction of new techniques for sample pre-treatment. Liquid-liquid extraction (LLE), dispersive liquid-liquid microextraction (DLLME), stir bar sorptive extraction (SBSE), solid phase microextraction (SPME), supercritical fluid extraction (SFE), pressurized fluid extraction (PFE), microwave-assisted extraction (MAE), matrix solid-phase dispersion (MSPD), accelerated solvent extraction and the subject of this review solid phase extraction (SPE) can be counted as the most important methods. SPE plays a crucial role in sample pretreatment, replacing the classical LLE, in biological, food and environmental analyses. SPE is recognized as a beneficial alternative to LLE because it overcomes many drawbacks of the later technique (1,2). It provides low solvent consumption, low intrinsic costs and reduction of processing time. Moreover, it is possible to automate the entire process. Furthermore, SPE does not require separation of phases as mandatory for LLE, which causes errors associated with variable/inaccurately measured extract volumes. In addition, other methods may also cause undesirable conditions such as formation of an emulsion phase during extraction, obtaining extracts without the requisite purity, insufficient removal of the solvents and inability to obtain sensitive quantitative results. Another advantageous feature of the SPE that distinguishes it from LLE is the ability to extract a large number of organic analytes from a wide range of samples.

The application of magnetic nanoparticles (MNPs) to SPE

The application of magnetic nanoparticles (MNPs) to SPE has received great interest due to their many unique features. The application of MNPs to the extractions process can reduce the overall extraction time in a serious manner, as mentioned above, by ensuring that the equilibrium analyte and the solid phase is achieved with a small amount of sorbent in a short duration. Currently, MSPE, as a sub group of SPE, is preferred by researchers because of its simplicity, environmentally friendly process, low cost, reduced solvent consumption, and short duration. The MSPE implementing steps are nearly the same in all the cited studies in this article, only the magnetic nanoparticle (MNP) type, amount, particle size, MNP and drug interaction period, elution periods, desorption solvent and amount type vary.

The first analytical application (and the first use of the term MSPE) was developed in 1999 by Safarikova and Safarik for the separation of a copper phthalocyanine dye using silanized magnetite (3). Compared to the SPE used, sample preparation has been greatly simplified with the use of MSPE because the analyte does not need to be trapped in a column and cartridge. The extraction is carried out only by applying a strong external magnetic field. A solution or suspension containing target analytes in MSPE provides selective adsorption on

the solid surface by direct contact of analytes with magnetic solid phase nanoparticles incorporated therein. In the last years, several papers have described relevant information on the applications of drug analysis with MSPE Aas can be seen in Figure 1a, This figure also indicates the increase in the number of studies in 1990-2016. Figure 1b also shows the distribution of these studies according to subject area (with solid phase extraction keyword) from SCOPUS.

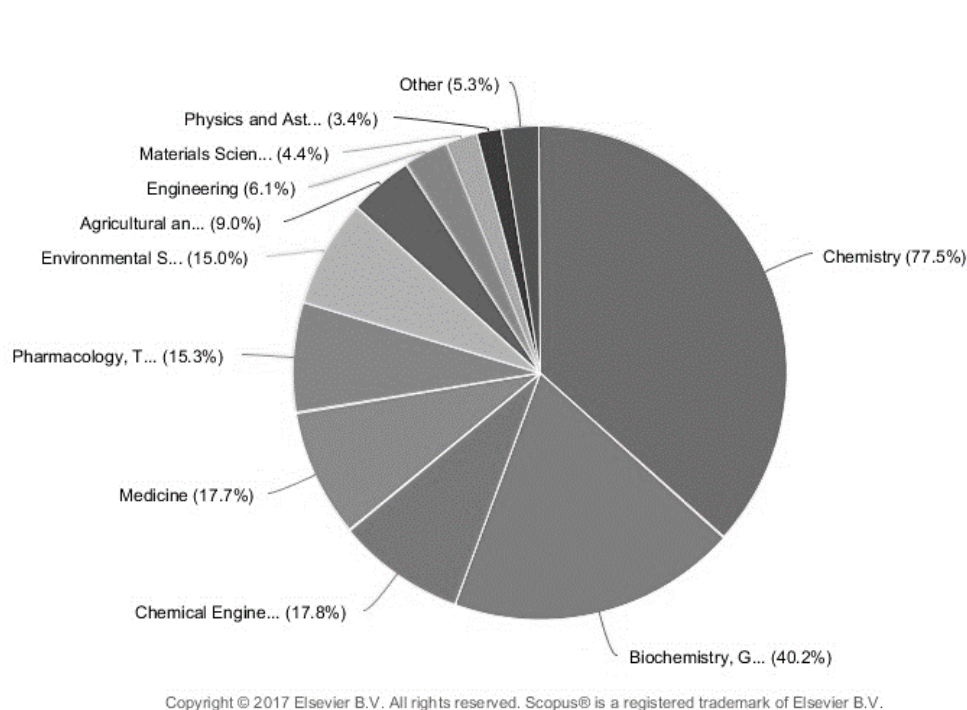
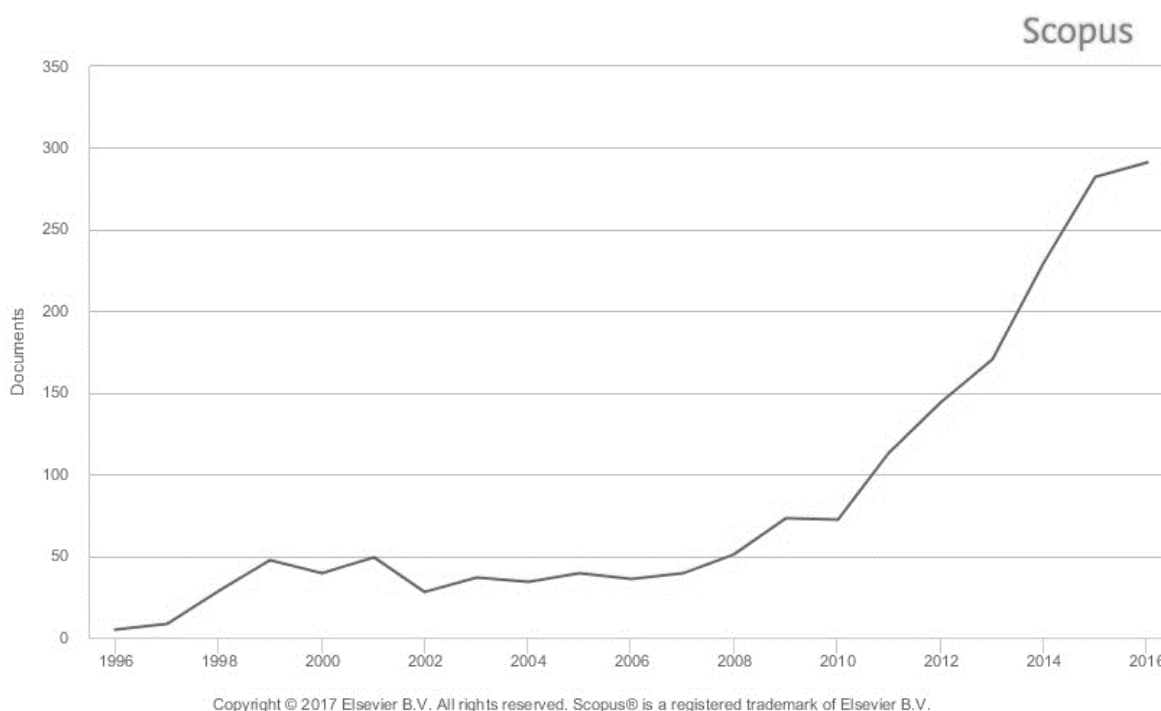


Figure 1. Yearly number of publications of MSPE methods used in drug analysis from 1990 to 2016 (above) Subject area of the publications about drug analysis using MSPE from 1990 to 2016 (below).

Properties of magnetic nanoparticles in MSPE

MNPs exhibit enhanced magnetic and electrical properties such as high coercivity, low Curie temperature, high magnetic susceptibility and especially superparamagnetism. All these unique features provide the advantages of MNPs for various application areas. Superparamagnetism is a phenomenon that emerged in the form of a single magnetic domain when the particle size is reduced to a diameter range. Opposite to paramagnetic counterparts, superparamagnetic materials do not show remnant magnetization when the external magnetic field is removed. Among superparamagnetic iron oxide nanoparticles (SPIONs), maghemite- Fe_2O_3 and magnetite- Fe_3O_4 , are the most intensively studied due to their properties making them useful for a variety of applications including magnetic, catalytic, and biomedical areas. In the clinical area, these particles are used as delivery systems for drugs or genes (4), in medical diagnosis (5), hyperthermia (6), cell separation (7) and magnetic resonance imaging (MRI) contrast enhancement (8) and therapy (9).

Most of these applications require chemically stable, well-dispersible particles with a size smaller than 100 nm and uniform physical and chemical properties. The size and morphology of magnetite NPs could be controlled by varying synthesis methods, shown in Figure 2, such as co-precipitation (10), thermal decomposition (11), solvothermal (polyol) (12), hydrothermal (13), green synthesis (14), microemulsion (15), flow injection (16), Oswald ripening (17), sonochemical (18), electrodeposition (19), microwave (20) and biological (21).

One of the effective approaches for preventing particle agglomeration is to functionalize the surface of the MNPs with polymers or other targeting agents, taking into account their biocompatibility, biodegradability and low toxicity. Surface functionalized SPIONs are a group of novel functional materials, which have been widely used in biotechnology and bioscience.

The surface of the MNPs can be modified by inorganic materials such as amorphous or mesoporous silica (22), metals like Ag, Au, Pd and Pt (26), mannose (27), carrageenan (28) and polymers such as polyethyleneimine (PEI) (29), polyvinylalcohol (PVA) (30), polyethyleneglycol (PEG) (31), and polyvinylpyrrolidone (PVP) (32) to avoid the formation of aggregates and to facilitate the adsorption of various biological ligands.

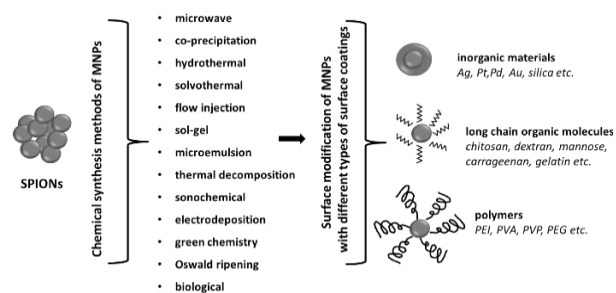


Figure 2: Chemical synthesis methods and surface modification routes of MNPs used in biomedical applications.

Analytical Determination

Generally, at first MNPs were added into the sample and mixed for a few minutes in order to provide the adsorption of the analyte or analytes onto the MNPs' surface. Then by an external magnetic field (by using a magnet) the MNPs accumulated on one side of the test tube and the supernatant were drained easily. Subsequently, MNPs were washed with suitable desorption solvent and the analyte/s were eluted with the solvent. The eluate (extract) can be directly injected to the chromatographic or capillary electrophoretic (CE) system or sometimes direct ultraviolet-visible (UV-Vis) spectrophotometric and fluorimetric and mass spectrometric (MS) procedures can be carried out. The MSPE process was schematized in Figure 3. The pH of the sample medium, the mixing time (MNP and drug interaction period) and the amount, the type of MNPs, the volume of desorption solution and the washing period are the parameters that are optimized for every MSPE study.

In this review article, the MSPE applications for drug analyses are investigated according to their matrix type and divided into subsections as biological, environmental and food matrices. Mostly liquid chromatography (LC) methods were combined with MSPE, also there is gas chromatography (GC), direct UV-Vis spectrophotometry and fluorimetry, MS methods were also presented and two combination with capillary electrophoresis (CE) methods are reported in the literature.

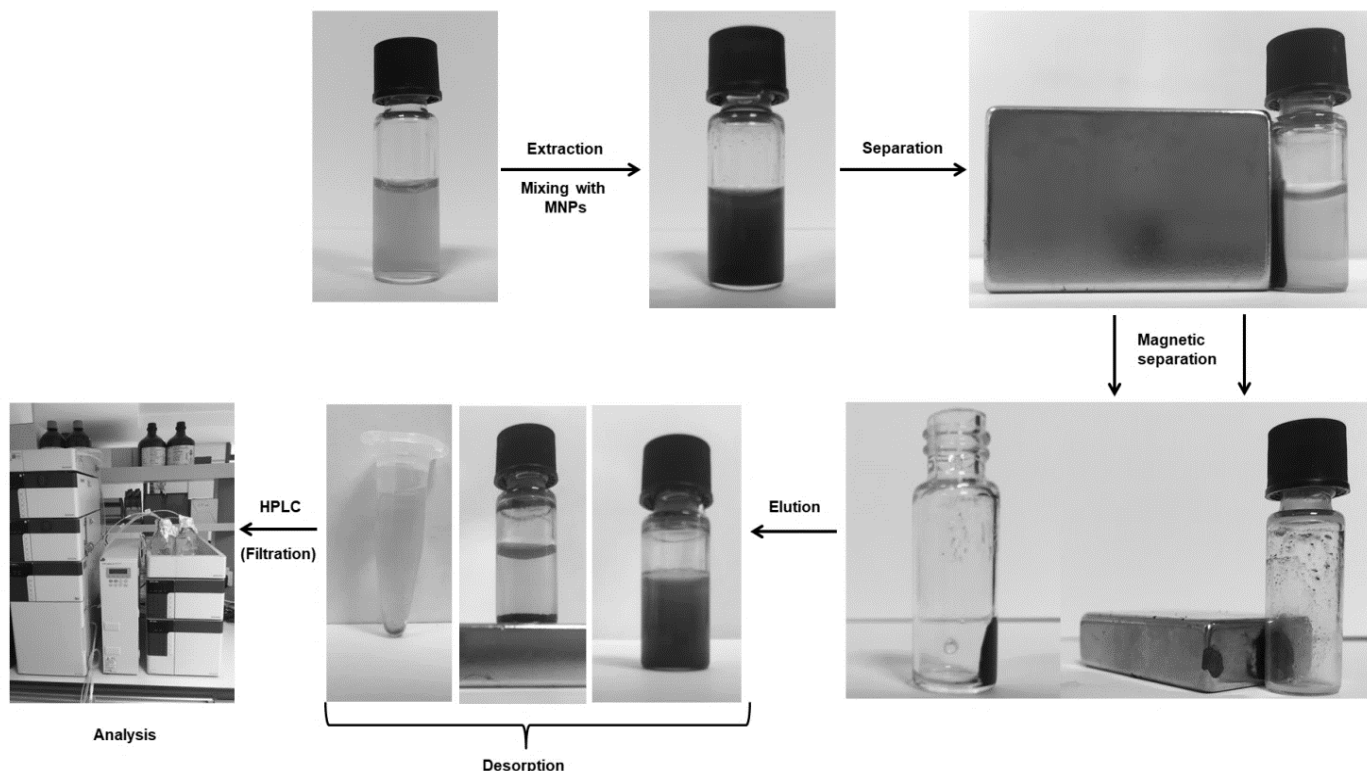


Figure 3: General procedure for MSPE.

Determinations in Biological Matrices

Because the drug concentration is low and the biological fluids are matrix-structured, sample clearance and preconcentration must be performed prior to drug identification. MSPE is a solvent-free, simple, rapid and attractive common sample preparation technique for chromatographic pre-treatment of complex sample matrices for clinical and pharmaceutical analysis due to its advantages. For this purpose, the most widely used types of nanoparticles in SPE are silica, alumina and silica-based sorbents, polymer sorbents, carbon nanoparticles such as graphite, porous carbon or carbon nanotubes (CNTs), molecular imprint polymers, functionalized resins, etc.

Due to its physico-chemical properties, silica is the most advantageous material for coating in bioanalytical use of magnetic cores. However, it is difficult to obtain a completely nanoporous silica coating and thus maintain its stability. Therefore, these structures may be shell-core or mesoporous. However, the solution of the above mentioned stability difficulties seem to be polymer coatings. The use of polymers ensures that the desired colloidal distribution results in a large surface area and stability and biocompatibility (33). In Table 1, the methods are listed with MSPE type, synthesis way and characterization procedures, the combined analytical method and other detailed information.

For the determination of two important anthraquinones, which have several medicinal effects, rhein and emodin were determined in human urine and serum by high performance liquid chromatography (HPLC) with fluorimetric detection (FLD). The Fe₃O₄ and SiO₂ core nanoparticles (NPs), as a mixed hemimicelles based nanosized SPE sorbent were modified by coating with cationic surfactants to prepare the MSPE sorbents. A short shaking time was enough for the required efficiency. By this the MSPE application, the recoveries of both analytes in both matrices (urine and plasma) were around 95% with C 18 column. It is mentioned in this study that good linearities and recoveries with serum and urine samples for both analytes indicate that this proposed method is feasible (34).

Eight illegal drugs (acetyl codeine, amphetamine, codeine, ethylene dimethacrylate, heroine, ketamine, methamphetamine, 3,4-methylenedioxyamphetamine) were determined in urine by MSPE coupled to capillary zone electrophoresis (CZE) technique with UV-Vis detection. As the extraction sorbent Fe₃O₄/SiO₂/poly(MAA-co-EDMA) magnetic microspheres were used. After adding MNPs, these eight drugs were isolated from the urine matrix by an external magnetic field. After removing the supernatant solution, the magnetic microspheres were washed with ultrapure water twice. Then, analytes were eluted from the sorbent particles with acetone containing 0.5% formic acid. The eluent was evaporated to dryness then dissolved in ultrapure water before applying to the CE system. The limits of detection (LOD) for the eight analytes varied from 0.015 to 0.105 µg/mL (35).

A CE method with FL detection was developed for the determination of alendronate which is a widely used drug substance for osteoporosis and other bone diseases. Prior to CE, as the sample pretreatment procedure, MSPE was used with Al₂O₃ coated Fe₃O₄ nanoparticles. NPs were ultrasonically washed twice with 0.5 mL of 150 mM phosphate buffer solution (pH 9.0) for 5 min, and the supernatant liquid was discarded. A 55 cm length capillary was used with a separation voltage of 24 kV in 5 min until completion the electropherogram. An interesting point in this study is that for the plasma assay prior to SPE a deproteinization procedure using acetonitrile in 1:1 v/v ratio to plasma was utilized. Because of the complexity of plasma and the difficulty to isolate alendronate from plasma proteins, an additional step was conducted before MSPE. Besides, in order to gain high fluorescence after MSPE and before CE injection the analyte was a precolumn derivatized with 2,3-naphthalene dicarboxyaldehyde (36).

Fe₃O₄ nanoparticles were modified with Ag in order to assess an efficient extraction for a cephalosporin antibiotic, ceftriaxone. Following the extraction, the extract was injected to an HPLC system with UV detection by an isocratic elution using a C 18 column. LOD and the limit of quantification (LOQ) were 20 and 60 ng/mL, respectively. The recovery of MSPE was 89% and no other purification was required (37).

To quantify oxymetholone which is an important synthetic anabolic steroid MSPE was used as pre treatment procedure and immediately after spectrophotometric assay was conducted. The amount of oxymetholone and its major metabolite mestanolone are the markers of drug abuse. It is reported as a prohibited substance by World Anti-Doping Agency. In this study Fe₃O₄ was coated with sodium dodecylsulfate (SDS).

MNPs were prepared according to a previously reported procedure (38). After that, Fe₃O₄ treated with SDS solution and the residue of the surfactant was washed with double distilled water. Desorption of the drug was performed with acetonitrile. The method provides a wide range for quantitation with the linearity 15–3300 ng/mL at 530 nm (39).

Letrozole is a third-generation aromatase inhibitor, and it is widely used for malignant breast cancer therapy. In this research, Fe₃O₄ was synthesized by the co-precipitation method (40), and the free-radical graft co-polymerization of 1-(N,N-bis-carboxymethyl carboxymethyl) amino-3-allylglycerol, a functional monomer, and N,N-dimethylacrylamide onto magnetic nano-particle surface modified with (3-mercaptopropyl) trimethoxy silane. The polymer-grafted magnetic nano-sorbent provided efficient extraction for letrozole and after MSPE the extract was directly injected to the HPLC system. C 18 column and the mobile phase of acetonitrile and a phosphate buffer (pH 6.8) (56:44 v/v) at a flow rate of 1 mL/min in isocratic elution mode was completed (41).

By using MNPs modified by tetraethyl orthosilicate and 3-methacryloxypropyl trimethoxysilane (MPTS), the antiepileptic drug substance lamotrigine was isolated from human urine and plasma and determined by HPLC with UV detection. The magnetic molecularly imprinted polymers were prepared by a surface molecular imprinting technique. As a desorption solution, methanol/TFA/acetic acid (96:2:2, v/v/v) was used, the eluate was evaporated and the residue was dissolved in the mobile phase and directly injected into the HPLC system. The sensitivity of the method is 0.7 µg/mL for urine and 0.5 µg/mL for plasma (42).

The MSPE method was developed with magnetic mixed hemimicelles. The MNPs (Fe₃O₄) were synthesized via a simple chemical coprecipitation method (43) and positively charged cetyltrimethylammonium bromide (CTAB) ions were coated to the surface of negatively charged Fe₃O₄ NPs in a basic medium. Then, naproxen was extracted from the matrix by adsorption onto the MNPs. Desorption solvent was chosen as methanol according to the optimization studies. Recoveries were approximately 98.6 for urine and 98.4 for plasma. The extraction processes were completed in eight minutes. The extract was directly injected to HPLC-UV system. C 18 column were used the mobile phase was a mixture of acetonitrile–acetic acid with isocratic elution. Naproxen was detected at 230 nm (44).

Fluoxetine, is a selective serotonin reuptake inhibitor, it is widely used for depression therapy. In order to determine the amount of fluoxetine in human urine magnetic multiwalled carbon nanotubes (MWCNTs) were used as the absorbent. MWCNTs/Fe₃O₄ were synthesized according to previously published methods (45,46). The total extraction time was 25 min. Subsequently, a reaction with a p-acceptor reagent, 2,3-dichloro-5,6-dicyanobenzoquinone was conducted to form a charge transfer complex. Depending on the high molar absorptivity, fluoxetine was determined by spectrophotometry at 470 nm. LOD and LOQ of the developed method were 0.06 and 0.19 mg/mL, respectively (47).

Another MWCNTs study was published for two illegal basic drugs, methamphetamine and ketamine in human urine and whole-blood samples. In this study MWNTs were combined with GC-MS where the ionization source of MS was electron impact. Fe₃O₄ nanoparticles were attached to the MWCNTs' surface by a chemical co-precipitation method (48) with minor adjustments. The extraction time was 10 minutes with high recoveries (49).

In another study a polymer coating application is used for serotonin-norepinephrine reuptake inhibitor class antidepressant drug substance venlafaxine. This time MSPE was combined with spectrofluorimetry in human urine and plasma assays. Desorption solvent was methanol and HCl mixture. The LOQ was nearly 2 ng/mL for both matrices (50).

The second venlafaxine assay by using MSPE in the literature depends on the organic functionalization of Fe₃O₄ with silane-coupling agent 3-methacryloxypropyltrimethoxysilane (KH-570). This agent improves the efficiency of the extraction process by providing cross links. GC-FID was used as the analytical method in hair samples and environmental aqueous samples. The extract was desorbed by methanol and subsequently injected into the GC-FID system for analysis (51).

For the fluorimetric determination of doxazosin and alfuzosin, a mixed micelle surfactant sodium dodecyl sulfate and non-ionic polyoxyethylene (7.5) nonylphenylether were used as the extractant, and diatomite bonding Fe_3O_4 magnetic nanoparticles (DBMNPs) were used as the adsorbent. A two-step extraction technique was used to isolate the drugs from pharmaceutical preparations, urine samples, and plasma samples. In the extraction process micelle solution was mixed with the sample and NaCl solution, then DBMNPs were added and sonicated for 2 min. The DBMNPs were rapidly collected from the tube wall using a strong magnet, and the supernatant was decanted. Ethanol was used to desorb the drugs from the MNPs surface. The extract's fluorescence intensity was measured at 330 with 381 nm emission for doxazosin and 332 with 383 nm emission for alfuzosin. This method provides simple and fast analysis for these two drugs which are effective in hypertension treatment (52).

For the determination of p-nitroaniline treated amoxicillin in human urine samples, dibenzo-18-crown-6 modified magnetic-multiwalled carbon nano tubes, which are synthesized and characterized, were used prior to its spectrophotometric determination; on the other hand the conditions (such as pH, amount of the adsorbent) etc. of extraction process were optimized. Recovery was 99.9% (53).

A study describes a method for the determination of codeine in human urine by spectrofluorimetry. Fe_3O_4 was used as a core and polymeric adsorbent was synthesized with aminoimide monomer as the functional monomer and ethylene glycol dimethacrylate (EGDMA) as the cross-linker, and ammonium persulfate as the initiator. 97.7 % recovery was achieved. After the extraction process at 214 nm emission and 348 nm excitation ng/mL level codeine was determined in urine (54).

Pyrrrole-coated Fe_3O_4 magnetic nanoparticles were prepared and used for the extraction of antidepressant drug substances citalopram, sertraline and fluoxetine. After isolation of these drugs, the determination was assessed by MS, the ionization source was desorption corona beam ionization (DCBI). DCBI-MS analysis was very short with 3 min of duration. The most interesting point in this study is the absence of desorption step for MSPE. Besides as direct detection was possible with DCBI-MS, no separation process like chromatography was required (55).

A new method was described for the determination of methamphetamine from urine samples using MSPE combined with HPLC-UV. The sorbent was a magnetic nano graphene oxide (MNGO) and it was synthesized by Hummer's method (56). The mobile phase of acetonitrile/phosphate buffer solution was used in isocratic mode with C 18 column. Drug free samples from the volunteers and drug positive samples from related drug abuse centers were both centrifuged to provide the sedimentation of lipidic solid components. The supernatant was subjected to MSPE and the MSPE conditions were optimized. Acetone was preferred as the desorption solvent. MNGO was more efficient in comparison with pure Fe_3O_4 . The reason is the higher surface area and the presence of polar groups on the surface. This method is feasible for forensic analysis with the LOQ of 100 ng/mL (57).

In another method, amphetamine and methadone were determined simultaneously in human urine. The LOQ was 100 ng/mL for both analytes. This method is also useful to evaluate drug abuse. Magnetic graphene oxide was used as the sorbent. Its way of synthesizing and characterization were explained in previous works (58-60). A centrifugation step was applied before MSPE in order to provide the precipitation of lipidic constituents of urine. The recovery values were 94% for amphetamine and 96% for methadone after this efficient extraction reverse phase HPLC with UV detection (61).

Magnetic ethylenediamine-functionalized graphene oxide nanocomposite was used as the extraction sorbent for the extraction of cow milk, human urine, river, and water samples for the determination of two of the NSAIDs, naproxen and ibuprofen. This study is related to all the subsections of this review article with different matrices applying ultrasound-assisted magnetic dispersive solid-phase microextraction (UAMDSPME) technique (62,63). In this technique the MNPs were dispersed in water by a compact hand-held ultrasonic and urgently injected into the sample solution for extraction. For urine samples the recovery was 86.4% for naproxen and 88.6% for ibuprofen. C18 analytical column (6.4 mm \times 250 mm, 5.1 μm) and the mobile phase of acetonitrile/ formic acid-sodium formate buffer (pH 4)/methanol (20:40:40, v/v/v) was delivered at a flow rate of 1.0 mL/min. The photodiode-array detector was set at the wavelength of 225 nm (64).

Amlodipine and carvedilol are generally used as a combination in pharmaceutical formulations for hypertensive therapy. Fe_3O_4 NPs were synthesized and coated with sodium dodecyl sulfate (SDS) and used as an extraction sorbent. Desorption solvent was acetonitrile and 20 μL of the eluate was injected to the HPLC-UV system. The recovery was calculated by the following equation: $\text{Recovery}\% = [(C_{\text{found}} - C_{\text{real}})/C_{\text{added}}] \times 100$ where c_{found} , c_{real} and c_{added} are the concentrations of analytes measured in spiked samples after MSPE, analytes in real samples after MSPE and the known amount of standards added to the real sample, respectively. The recovery was about 90 % (65).

MNPs with phenyl functionalized core and a hydrophilic methylcellulose coating were synthesized by the solvothermal method and used for the sample preparation of sildenafil and its metabolite desmethylsildenafil prior to liquid chromatographic determination in plasma and urine. No other pretreatment procedure was required and sensitive analysis were provided for this widely used drug and its major metabolite in ng/mL level (66).

In the bioassay, MNPs are used to isolate inorganic and organic compounds from biological samples, as shown in the studies detailed above. Table 1 summarizes information on the application of MNPs for the isolation and enrichment of analytes from biological samples. Analytical examination of biological specimens containing complex matrices that preclude direct analysis of blood, urine, saliva, bile, sperm etc. is a major challenge for analysts. Biological samples were usually detected by treating with the surface functionalized MNPs to target analytes.

Table 1: The main parameters of MSPE and analytical process combination of drug determinations in biological samples.

Analyte	Matrix	MNP type	MNP synthesis method	MNP characterization	MSPE recovery %	Desorption solvent/elution process	Additional step before or after MSPE	Combined analytical method	Ref
rhein emodin	urine plasma	CTAB coated Fe ₃ O ₄ /SiO ₂	coprecipitation	TEM, IR	95	acetonitrile:1% acetic acid	—	HPLC-FLD	-42
ketamine amphetamine opiates (8 illegal drugs)	urine	Fe ₃ O ₄ /SiO ₂ /poly (MAA-co-EDMA)	precipitation, polymerization (61)	XRD, TEM, FTIR	85.4-110.1	acetone:0.5% formic acid	—	CZE-UV-Vis	-43
alendronate	urine plasma	Al ₂ O ₃ coated Fe ₃ O ₄	—	—	104.5 urine 101.5 plasma	Na ₅ P ₃ O ₁₀ solution (pH 9.0).	derivatization for FLD after MSPE	CE-FLD	-44
ceftriaxone	plasma	Ag coated Fe ₃ O ₄	coprecipitation	XRD, TEM, FTIR, UV-Vis	89	0.05 M phosphate buffer	—	HPLC-UV	-45
oxymetholone mestanolone	urine	SDS coated Fe ₃ O ₄	coprecipitation (38)	XRD, TEM, FTIR	99.7	acetonitrile	—	UV-Vis	-47
letrozole	serum urine	polymer-grafted Fe ₃ O ₄	coprecipitation (40)	XRD, TEM, FTIR, SEM, TGA	95 urine 81.5 serum	acetonitrile:TFA (94:1.5(v/v))	—	HPLC-UV	-49
lamotrigine	urine plasma	Fe ₃ O ₄ @SiO ₂	surface molecular imprinting,	XRD, SEM, FTIR, TGA	97.5 urine 96.8 plasma	methanol:TFA: acetic acid (96:2:2, v/v/v)	—	HPLC-UV	-50
naproxen	urine plasma	CTAB coated Fe ₃ O ₄	coprecipitation (43)	FTIR, TEM, XRD	98.9 urine 98.4 plasma	methanol: acetonitrile (1:5)	—	HPLC-UV	-52
fluoxetine	urine	MWCNTs/Fe ₃ O ₄	MWCNT oxidation (45) coprecipitation (46)	FTIR, TEM, XRD	99.4	acetonitrile	charge transfer complexation (after MSPE)	UV-Vis	-55
methamphetamine ketamine	urine whole blood	MWCNTs/Fe ₃ O ₄	coprecipitation (48)	TEM, XRD	86.6 urine 81.4 blood for MA 93.6 urine	ethyl acetate	protein precipitation (before MSPE)	GC-MS	-57
venlafaxine	urine serum	EGDMA coated Fe ₃ O ₄	polymerization onto magnetic core	FTIR, VSM, XRD, TEM	—	methanol:HCl	—	spectro fluorimetry	-58
venlafaxine	hair river water surface water	silanized Fe ₃ O ₄	coprecipitation	FTIR, XRD, TEM	89.4 hair 93.4 river water 95 surface water	methanol	washing and incubation (before MSPE)	GC-FID	-59
doxazosin alfuzosin	urine plasma	diatomite bonding Fe ₃ O ₄	—	—	85.2-118.7-both matrices	—	—	MS	-60
amoxicillin	urine	surface modified MWCNTs	surface modification	FTIR, XRD, TEM	99.9	—	formation of a colored azo-derivative (after MSPE)	UV-Vis	-61
codeine	urine	EGDMA coated Fe ₃ O ₄	solvothermal reduction	FTIR, XRD, TEM	98	methanol	—	spectro fluorimetry	-62
citalopram, sertraline fluoxetine	urine plasma	pyrrole coated Fe ₃ O ₄	—	FTIR, TEM	—	—	—	DCBI-MS	-63
methamphetamine	urine	graphene oxide coated Fe ₃ O ₄	graphene oxidation (56), coprecipitation	FTIR, SEM, XRD, VSM	91.7	acetone	—	HPLC-UV	-65
amphetamine methadone	urine	graphene oxide coated Fe ₃ O ₄	graphene oxidation (58-60) coprecipitation	—	93.87 amphetamine 96.58 methadone	acetonitrile	—	HPLC-UV	-69
naproxen ibuprofen	cow milk human urine river well water	functionalized graphene oxide coated Fe ₃ O ₄	graphene oxidation precipitation (62, 63)	FTIR	86.4-104.6 naproxen 88.6-95.8 ibuprofen	methanol	ultrasonication centrifugation	HPLC-DAD	-72
amlodipine carvedilol	urine	SDS coated Fe ₃ O ₄	coprecipitation	TEM	85.06 amlodipine 88.6 carvedilol	acetonitrile	—	HPLC-UV	-73
sildenafil	urine plasma	methylcellulose coated Fe ₃ O ₄	solvothermal method	FTIR, TGA	—	methanol:water: CH ₃ COOH	—	HPLC-DAD	-74

Determinations in Environmental Matrices

One of the most important consequences of the developments in microbiology is that it opens the way of making antibiotics through synthesis. Since the discovery of antibiotics, a broader set of natural microbial compounds has been described in several medical, veterinary and agricultural applications with antibacterial, antifungal, antiviral, antitumor or pesticidal activities. This has led to the accumulation of antibiotic residues in the environment, along with the widespread use of antibiotics in various areas. For example, allergic reactions to antibiotics can put the immune system at risk, as antibiotic residues can cause a harmful effect on human and animal health and to smaller extent plants. In many countries monitoring obligations have been established to determine antibiotic levels in food and water. The studies carried out in order to determine drug pollutants in environmental matrices by magnetic solid phase extraction methods are summarized in Table 2 and the details are examined below.

Sulfonamide (SA) antibiotics can easily contaminate environmental water because of their anionic characteristics. To determine the level of exposure, a new HPLC method was developed. Before the chromatographic process, MSPE

was applied to waste water samples by using graphene coated Fe₃O₄ as the extraction sorbent. By using graphene the surface was widened and high recoveries were provided. The LOD for three SA antibiotics (sulfadiazine, sulfamerazine, sulfamethoxazole) ranged from 0.43 to 0.57 ng/mL. This sensitive analysis did not require any pretreatment procedure other than MSPE (67).

Ten SA antibiotics were determined from commercial milk samples by using MSPE combined with LC-MS-MS. The MNPs were graphene oxide coated Fe₃O₄. They were synthesized according to Hummer's method (35) and characterized by FTIR and TEM. This method provides the evaluation of milk quality as a food product (68).

Dopamine has a self-polymerization capacity in the aqueous phase and depending on this property it provides the formation of a surface-adhesive film onto the Fe₃O₄ core. By using this combination as a MSPE sorbent, 12 estrogenic compounds were isolated from mineral, tap and wastewater samples and determined by ESI sourced LC-MS. Validation of the entire method was carried out, obtaining good repeatability and reproducibility while LODs and LOQs are in the range of 0.01–0.34 ng/L (69).

Seventeen β -estradiol exist in lake water, river water and effluent, which causes a potential risk for environmental and human health and this were investigated by an HPLC-UV assay. A pretreatment procedure was carried out by using aldehyde groups to the surface of amino-functionalized magnetic nanoparticles that are imprinted with gelatin. UV detection provides sensitive analysis in ng/mL levels in this study (70).

In another method raniditine was determined in well and tap water samples and human plasma. MSPE was used for sample pretreatment and also for preconcentration in aquatic samples. Fe_3O_4 NPs were modified by SDS as a sorbent. The structure of the sorbent was characterized with SEM. In 5 minutes, the extraction was performed by using methanol as the desorption solvent. Before extraction of the plasma samples, protein precipitation was also performed. The extraction recovery in human plasma and different matrixes of waters were investigated and values of 89.0% to 103.4% were obtained. The determinations were carried out spectrophotometrically at 320 nm in $\mu\text{g/mL}$ level (71).

For the determination of an important antiviral drug, active substance lamivudine, which is widely prescribed in HIV infections, an HPLC-DAD method was developed by using MMWCNTs prepared by assembling Ni. By this modification the adsorption ability of the sorbent improved and efficient extraction procedures were performed in human urine and environmental water samples (river water). There is an additional novelty in this study depending on the desorption solvent. The extracted lamivudine was desorbed using ionic liquid (IL) which are known as "Green solvents" as substitutes of volatile organic solvents. The ILs are the salts in a liquid state and have attracted great attention due to their unique chemical and physical properties such as nonvolatility that preserves the environment and high adsorption capacity. The recoveries were

above 90%. C 18 (150 mm 4.6 mm, 5 mm) column and phosphate buffer (pH 3.5)–MeOH (92:8, v/v) were used as the mobile phase. The detection wavelength was set at 270 nm (72).

17 natural estrogenic compounds, including four steroid estrogens, six mycoestrogens, and seven phytoestrogens, in river water samples were determined by electrospray ionization sourced LC-MS/MS. C 18 column was used with the mobile phase composed of water and acetonitrile in gradient elution mode with a flow rate of 0.3 mL/min. In order to enrich the samples, MSPE was applied before the chromatographic process by using poly dopamine coated Fe_3O_4 . The elution was performed with 5 mL methanol twice (73).

In another study, the sulfonamide antibiotics assay from environmental water samples were detected with Fe–pamoate porous complex attached to silica-coated microspheres. For preconcentration and pretreatment, Prior to HPLC analysis, high recoveries were obtained with this MSPE in water samples. UV detection and reverse phase chromatography were applied for the quantitation for the extraction and enrichment of SAs in tap, river and rain water samples (74).

A new polycaprolactone (PCL) coated Fe_3O_4 nanocomposite was synthesized and used as a sorbent for magnetically mediated PCL microspheressolid-phase extraction (MM-PCL-SPE) prior to gas chromatography-flame ionization detection (GC-FID) for the determination of progesterone hormone in biological and environmental matrices (tap water, urine, and hospital waste water). The nanomagnetite core of the sorbent was synthesized by a co-precipitation method. Magnetic nanoparticles (MNPs) were then microencapsulated with PCL microspheres using emulsion polymerization. High recoveries for all types of samples were achieved (75).

Table 2: The main parameters of MSPE and analytical process combination of drug determinations in environmental samples.

Analyte	Matrix	MNP type	MNP synthesis method	MNP characterization	MSPE recovery %	Desorption solvent/elution process	Additional step before or after MSPE	Combined analytical method	Ref
sulfadiazine sulfamerazine sulfamethoxazole	waste water	graphene oxide coated Fe_3O_4	solvothermal	FTIR, XRD, TEM	95.8	acetonitrile:5% ammonium hydroxide	—	HPLC-DAD	-67
sulfonamide antibiotics (10 samples)	milk	graphene oxide coated Fe_3O_4	graphene oxidation, coprecipitation	FTIR, TEM	73.4 - 97.4	acetonitrile:5% ammonium hydroxide	—	LC-MS/MS	-68
estrogenic compounds (12 samples)	mineral water tap water waste water	dopamine coated Fe_3O_4	coprecipitation	FTIR, XRD, TEM, SEM, XRP, VSM	72-116	methanol	—	LC-MS	-69
17 β -estradiol	environmental water	amino and aldehyde-functionalized Fe_3O_4	molecular imprinting technique	FTIR, XRD, TEM	88.3-99.1	ethanol:acetic acid (96:4)	—	HPLC-UV	-70
raniditine hydrochloride	human plasma aquatic water	SDS coated Fe_3O_4	surfactant assisted coprecipitation	SEM	89-103.4	methanol	protein precipitation for plasma samples	UV-vis	-71
lamivudine	human urine river water	Ni/MWCNTs	precipitation onto MWCNTs	TEM, XRD, VSM	>90%	ILs: Na_3PO_4	—	HPLC-DAD	-72
estrogens, phytoestrogens, mycoestrogens	river water	polydopamine coated Fe_3O_4	coprecipitation	SEM, FTIR, ATR	>70 %	methanol	—	LC-MS/MS	-73
sulfadiazine sulfamerazine sulfadimidine sulfisoxazole sulfathiazole	environmental water	silica-coated Fe_3O_4	solvothermal	TEM, FTIR	86.3-98.9	acetone:5% ammonium hydroxide	—	HPLC-UV	-74
progesterone	serum tap water urine hospital waste water	polycaprolactone coated Fe_3O_4	coprecipitation emulsion polymerization	SEM, FTIR			—	GC-FID	-75

Determinations in Food Matrices

Today, food production processes are becoming global and it is becoming difficult to control food safety and quality. For this reason, national and international regulatory committees identify and supervise relevant aspects. In the European Union, maximum residue limits (MRLs) have been established for antibacterial substances in animal-derived foods and the limits for use as feed additives have been established. For example, in the production of high quality raw milk and dairy products, antibiotic detection is carried out in various ways and controlled. Although antibiotics are classified by type of bacteria, type of activity or chemical structure, there is no method to determine all types of antibiotics. In this sense, increasing speed in detection and control has become an alternative to magnetic solid state separation in efficient new methods, which allows for high and selective separation in analytical methods. A detailed table

(Table 3) has been prepared and the details of the studies in the table are explained below.

In a study, a new method was developed for the quantitation of three tetracycline and quinolone veterinary antibiotics (oxytetracycline, tetra-cycline, chlortetracycline and three acidic quinolones, such as oxolinic acid, nalidixic acid and flumequine) in meat samples. The drug residues are very important for human health. The LOD values of the method are 1.0, 1.5, 3.8, 0.25, 0.7 and 1.2 ng/mL, which correspond to 3.3, 5.0, 12.7, 0.8, 2.3 and 4.0 $\mu\text{g/kg}$ —for oxytetracycline, tetracycline, chlortetra-cycline, oxolinic acid, nalidixic acid and flumequine, respectively. This quantitation level is feasible for meat analysis of food products. Ultra-high performance liquid chromatography (UHPLC) was applied with reverse phase chromatography and gradient elution profile. Detection was performed fluorimetrically.

As an advantage of UHPLC, the analysis was completed in a short time and the resolution of peaks was high enough by the effect of 1.7 μm particule sized column. Prior to UHPLC, MSPE was applied with europium- and terbium-coated Fe_3O_4 as sorbents. Besides, prior to MSPE homogenization and protein precipitation steps were carried out in order to facilitate MSPE (76).

Natamycin, which is widely used as an additive for food products to prevent the microbial contamination, was determined in jam samples by HPLC with UV-Visible detector. MSPE combined with HPLC was used in order to eliminate the possible interferences that may occur because of the complicated components of jam such as lipidic and protein based ingredients. Prior to MSPE homogenization and LLE were also applied to samples. As the sorbent of SPE $\text{Fe}_3\text{O}_4/\text{SiO}_2/\text{poly}$ (acrylamide- N , N' -methylene bisacrylamide) microspheres modified with non-ionic triblock copolymer surfactant were synthesized and used. For different jam samples a recovery range of 78.8–93.4% was achieved. Reverse phase HPLC was preferred and the quantitations were carried out at 304 nm. Retention time is about 3.5 min for the analyte (77).

Five sulfonamides, including sulfamerazine, sulfamethizole, sulfadoxine, sulfamethoxazole and sulfisoxazole in various milk samples were determined by HPLC with UV detection. C18 column (4.6 mm, 150mm, 5 μm) and as a mobile phase acetonitrile, water (25:75) was used. The chromatogram was completed in 8 min with good resolution. Prior to HPLC analysis, protein precipitation and MSPE were applied for pretreatment and enrichment. Graphen coated magnetide was used as the sorbent and synthesized according to Hummers' method. MSPE was conducted immediately after homogenization and protein precipitation of milk samples. This method provides recoveries in a range of 62.0–104.3% for different meat samples (78).

Sulfadiazine and sulfathiazole were determined by another MSPE-HPLC combination. Fe_3O_4 was used as the extraction sorbent and provided an efficient extraction with 92.9–102.4% recovery for both analytes from various cow milk samples that were purchased from markets. A protein precipitation pre-treatment procedure was applied before MSPE. SPE was carried out nearly in 6 min. The extract was evaporated and the residue was dissolved in the mobile phase.

The analytes were desorbed from the surface of MNPs by shaking with acetonitrile for 1 min. C 18 column at 40°C and acetonitrile water combination (98:2) was used as the mobile phase. The analyte peaks were observed at 270 nm (79). Another study reported a MISPE-HPLC method based on determination of amphenicol antibiotics in egg, water, chicken blood. Molecular imprinting was applied to synthesise a magnetic mesoporous dual-template molecularly imprinted polymer ($\text{Fe}_3\text{O}_4@\text{mSiO}_2@\text{DMIP}$) with chloramphenicol (CAP) and florfenicol (FF) as the templates. The obtained dual template MIP was showed high adsorption capacity and good specific recognition performance for CAP and FF (80).

Fluoroquinolone drugs in foods of animal origin were analyzed with magnetic graphene as the novel sorbent combined with HPLC. Results showed that this method achieved high absorption capacities, high recoveries, high enrichment, high sensitivities, satisfactory purification effects and excellent reusability (81).

In the literature, it is also found other functionalizing special molecules like organo frames or molecularly imprinted polymers adsorbed onto the surface of the MNPs for the selective interaction with a particular compound or a family of compounds in food stuff. Exemplarily a to determine four estrogens, novel molecular imprinted film coating by using magnetic ZIF composite ($\text{Fe}_3\text{O}_4@\text{ZIF-8}$) as carrier was fabricated for solid phase microextraction in 24 food samples by HPLC-DAD in a study (82). In another, to testify the feasibility of the magnetic composites in sample preparation, magnetic MIPs were applied as sorbents for MSPE combined HPLC-UV of fluoroquinolones (FQs) in milk samples (83).

In the above examples of the use of magnetic nanoparticles in the environment for solid phase extraction, 17 estrogens is also studied for the determination of the amount in milk. In this study novel monodisperse molecularly imprinted layer was coated on magnetic $\text{Fe}_3\text{O}_4@\text{NH}_2$ by combining surface molecular imprinting technique (84). Similarly, in a study showed that magnetic dispersion extraction using molecularly imprinted magnetic microspheres (MIMMs) is a powerful tool for food-sample pretreatment with high selectivity and a simplified procedure for the selective clean-up and enrichment of tetracycline antibiotics from milk samples (85).

Table 3: The main parameters of MSPE and analytical process combination of drug determinations in food samples

Analyte	Matrix	MNP type	MNP synthesis method	MNP characterization	MSPE recovery %	Desorption solvent/elution process	Additional step before or after MSPE	Combined analytical method	Ref
oxytetracycline tetracycline chlortetracycline oxolinic acid nalidixic acid flumequine	meat	Eu and Tb coated Fe_3O_4	precipitation	XRD, TEM, XPS	61.5–102.6	acetonitrile	homogenization, centrifugation	UHPLC/FL	-76
natamycin	jam	surfactant functionalized $\text{Fe}_3\text{O}_4/\text{SiO}_2/\text{poly}$ (acryl amide- N , N' methylene bisacrylamide) composite	solvothelmal sol-gel	SEM, TEM, FTIR, XRD, VSM	78.8–93.4	acetonitrile:water (40:60): 0.1% TFA	LLE, homogenization	HPLC-UV	-77
sulfamerazine sulfamethizole sulfadoxine sulfamethoxazole sulfisoxazole	milk	graphene coated Fe_3O_4	graphene oxidation, coprecipitation	SEM, FTIR, XRD, VSM, UV- vis spectrometry	62.0–104.3	methanol:5% acetic acid	protein precipitation	HPLC-UV	-78
sulfadiazine sulfathiazole	milk	Fe_3O_4	commercially purchased	_____	92.9–102.4	acetonitrile	protein precipitation	HPLC-UV	-79
chloramphenicol florfenicol	egg chicken blood	$\text{Fe}_3\text{O}_4@\text{mSiO}_2@\text{DMIP}$	coprecipitation	SEM, FTIR	88.3–99.1	acetonitrile and water (70:30)	_____	HPLC-UV	-80
ofloxacin pefloxacin lomefloxacin ciprofloxacin enrofloxacin difloxacin sarafloxacin	egg bovine milk chicken muscle	magnetic graphene	commercial	_____	82.4–108.5	acetonitrile:0.05% phosphoric acid-triethylamine (pH 3.0)	_____	HPLC	-81
4 estrogens	Fish, pork	$\text{Fe}_3\text{O}_4@\text{ZIF-8}@\text{MIP}$	calcination precipitation	_____	74–97	water:acetonitrile, gradient elution	_____	HPLC-DAD	-82
Ofloxacin Lomefloxacin ciprofloxacin	milk	$\text{Fe}_3\text{O}_4\text{-MIP}$	hydrothermal	SEM	94.0–124.4	20 mM phosphate buffer (pH 2.5)/acetonitrile/ methanol (80.5:8.5:11.)	_____	HPLC-UV	-83
17 beta-estradiol	environmental water	amino and aldehyde- functionalized Fe_3O_4	molecular imprinting technique	FTIR, XRD, TEM	88.9–92.1	ethanol: acetic acid (96:4)	_____	HPLC-UV	-84
tetracyclines	milk	surface-modified Fe_3O_4	molecular imprinting technique	TGA, VSM	74.5–93.8	methanol/acetonitrile/oxalic acid	_____	HPLC-UV	-85

CONCLUSION

In this paper, MSPE and analytical method combinations, used for the determination of drugs in biological fluids, environmental matrices and food products, were reviewed in detail. Pre treatment/sample preparation procedure has vital importance in such complicated matrices. In all the investigated studies in this review, it was observed that, by using MNPs as an adsorbent in SPE, good recoveries were provided with simple, fast and environmentally friendly processes at room temperature. Besides, with this type of extraction, cost and solvent consumption were significantly reduced. As MNPs, various types of nanocomposites were used based on Fe_3O_4 . Mostly, graphene and other carbon derivated materials such as carbon nanotubes and graphite coated Fe_3O_4 were observed. Polymeric modifications and surface functionalization attachments were also found in a respectable number of studies for all types of matrices. Generally, the research studied meat and milk samples as food matrices. MSPE occasionally causes an additional pre treatment requirement such as protein precipitation and LLE especially in meat samples. As for the biological samples, mostly we observed serum, plasma and urine. River and tap water are the main environmental samples that we observed in the literature survey. For the synthesizing process, mostly coprecipitation, aggregation, solvothermal and surface imprinting techniques were used and the magnetic products were characterized with some of the mentioned methods: SEM, TEM, FTIR, XRD, VSM, UV-Vis spectrometry, and TGA. Overwhelmingly HPLC combined to MSPE applications with different detectors such as DAD, UV-Vis, fluorimetry, and MS. In GC combinations MS and FID detections were used. There are two CE combinations reported in this review with UV and FL detections. Directly UV-Vis spectrometry, fluorimetry and MS applications were also existent in the literature.

In the literature survey, different drugs were analysed by MSPE-analytical method combinations and the number of these kinds of methods increased consistently because of the advantages of MSPE. Sensitive quantitations were performed, which enable bioavailability, bioequivalence studies for biological matrices and which are able to measure environmental contamination and food quality.

MNPs are used for separation of almost all analytes, whether simple or complex. The excellent properties of MNPs, together with the advantage for use, enhance the functionalization of their surfaces. More attention should be paid to improving existing MNP synthesis methods for this, in order to develop new coatings to achieve multifunctional MNPs. The development of new designs that will enhance the interaction between the analyte and MNP surface will improve the physicochemical properties of MNPs. Development of appropriate analytical procedures for the synthesis and functionalization of MNPs and study of the conditions of the extraction process are also necessary. As a next step in the synthesis of new materials for SPE, various functionalized polymers like molecular imprinting polymers and highly cross-linked sorbents should be developed with increased. Subsequently, the development of miniaturized devices containing these new types of materials can increase the use of high-efficiency systems operating with fast and accurate analytical methods for sample preparation and analysis. Finally, there is still much to be done to develop innovative MSPE systems so that NPs can be used in routine laboratory analyze of large numbers of samples.

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