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Khaled Murtada, Fernando de Andrés, Mohammed Zougagh, Ángel Ríos

PII: S0026-265X(19)31922-8
DOI: https://doi.org/10.1016/j.microc.2019.104193
Reference: MICROC 104193
To appear in: Microchemical Journal

Received date: 24 July 2019
Revised date: 18 August 2019
Accepted date: 18 August 2019

Please cite this article as: K. Murtada, F. de Andrés, M. Zougagh, et al., Strategies for antidepressants extraction from biological specimens using nanomaterials for analytical purposes: A review, Microchemical Journal(2018), https://doi.org/10.1016/j.microc.2019.104193

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Strategies for antidepressants extraction from biological specimens using nanomaterials for analytical purposes: A review

Khaled Murtada 1,2, Fernando de Andrés 2, Mohammed Zougagh 2,3, Ángel Ríos 1,2,*

1 Department of Analytical Chemistry and Food Technology, Faculty of Chemical Science and Technology, University of Castilla-La Mancha, Ciudad Real 13071, Spain
2 Regional Institute for Applied Scientific Research (IRICA), Ciudad Real 13071, Spain
3 Department of Analytical Chemistry and Food Technology, Faculty of Pharmacy, University of Castilla-La Mancha, Albacete 02071, Spain

ABSTRACT
Accurate and precise monitoring of antidepressants drugs represents a crucial step for the adequate and personalized treatment of several psychological disorders such as depression, which nowadays represent a social, economic and health major concern. Several chemical, electrochemical, and biological methods have been traditionally developed for the extraction and detection of antidepressants, even though several restrictions such as post-treatment required, elevate costs and limited efficiency. Nanotechnology is a field with a tremendous growth observed in the last two decades, especially regarding their many biological applications, such as antibacterial or as biosensors, as well as in many different applications related to medicine. Lately, nanotechnology has emerged as a promising substitute for the extraction of antidepressants instead of traditional techniques, as nanomaterials can be efficiently used as sorbents due to their small size and their high specific surface area which enhances their high reactivity. In this review article, we provide a general overview on the use of different nanomaterials for the extraction of antidepressants from biological specimens and discuss not only the advantages but also the major limitations of using such nanomaterials. Potential alternatives to overcome these drawbacks are discussed as well.

Keywords: Antidepressants extraction, biological specimens, nanotechnology, nanoparticles, nanocomposites.

*Corresponding author.
E-mail address: angel.rios@uclm.es (Á. Ríos)
1. Introduction

It is estimated by The World Health Organization (WHO) that major depressive disorder currently affects more than 350 million people globally, a currently increasing prevalence due to the population growth and ageing. This disease, therefore, represents the leading cause of disability worldwide and, consequently, possess a remarkable impact not only on each patient’s health, but also has become a social concern as of their consequences in terms of costs (i.e. health systems direct costs, suicide-related and workplace costs) [1–3]. Even though non-pharmacological (psychological) treatments are available, a trend of the increased use, or even the misuse of pharmacological treatments with the different types of antidepressant medication (Table 1) is detected. The antidepressants usually exert their function by inhibiting the reuptake of neurotransmitters (e.g. serotonin, dopamine, noradrenaline or norepinephrine) through selective receptors that way increasing the concentration of specific neurotransmitter around the brain’s nerves. Nevertheless, the role of neurotransmitters at improving mood and emotion is not fully understood [4–6].

Nevertheless, these agents should be prescribed based on the best available evidence, as far as it is widely recognized that each patient under antidepressants treatment should be individually monitored due to the wide interindividual and intraindividual variability observed in their clinical response, and the potential occurrence of side effects frequently detected. The confirmed correlation between plasma concentrations of these drugs and tissue concentrations should therefore be confirmed through this monitoring to obtain evidences on the drug concentration at effector sites in tissue compartments of interest.

Consequently, an accurate therapeutic monitoring of these treatments is required [7–9], not only to ensure the patients therapy compliance, but also to individualize and optimize the dosage regimens, as well as to optimize resources and to improve the overall mental health care as well [1,10–13]. However, the adoption of such monitoring as a routine point of care is quite slow of psychiatrists, even though the awareness on the significance of inter- and intra-patient variability in pharmacokinetics may affect response to antidepressants therapy is currently growing to optimize antidepressant treatment response. TDM can be therefore used to increase the safety of antidepressant pharmacotherapy with certain agents (e.g., tricyclic antidepressants) by avoiding toxic levels of medication, enhancing therapeutic response, and speeding the antidepressant response by improving the dose adjustment and also helping clinicians to confirm adherence to medication [14].

Thus, confirming the levels of the antidepressants prescribed within their corresponding therapeutic range has become essential for treating these diseases, and thus the concentration of these drugs needs to be determined in different biological specimens (i.e. blood, serum, urine, saliva and/or human milk), as confirmed in previous studies (e.g. for the tricyclic...
antidepressant, 100-300 µg L⁻¹ distinct ranges of therapeutically optimal plasma concentration are required) [15,16].

Regarding the quantitative analysis of the antidepressant drugs, several separation and detection techniques have been applied: spectroscopy [17], capillary electrophoresis (CE) [18], capillary electrophoresis coupled with electrospray ionization mass spectrometry (CE-ESI-MS) [19], thin layer chromatography (TLC) [20], gas chromatography coupled with mass spectrometry (GC-MS) [21], liquid chromatography with UV diode array detection (LC-DAD) [22], fluorescence (FL) [23], chemiluminescence (ChL) [24] or electrochemical [25], gas chromatography coupled with flame ionization detection (GC-FID) [26] and liquid chromatography coupled with mass spectrometry (LC-MS) [27]. Mostly, these techniques allow to separate different components from complex mixtures like biological matrices and, additionally, an efficient drug monitoring approach usually requires of efficient techniques for the biospecimen treatment, such as liquid-liquid microextraction (LLME) [28,29], solid-phase extraction (SPE) [30,31], magnetic solid-phase extraction (MSPE) [32], stir bar sorptive extraction (SBSE) [33], pressurized liquid extraction (PLE) [34] or microwave-assisted extraction (MAE) [35]. However, sample preparation is a crucial bottleneck in the whole analytical process and, trying to overcome the limitations linked to this process, continuous progress is being made in this field. For instance, solid phase extraction using cartridge or disk devices are the most common strategies utilized nowadays when sorbent materials are specifically selected depending on the particular physical-chemical properties of the analyte to be determined. The main advantages of SPE over LLE are the possibility of sample concentration, the use of small volumes of organic solvents and the reduced potential for formation of emulsion. Consequently, solid-phase sorbents have aroused increasing interest in research on sample preparation over liquid-liquid extraction, as they allow obtaining higher clean-up and enrichment efficiency in the analysis of trace targets present in complex matrices [36,37], as well as lower volumes of organic solvents are required and less emulsions are formed [38]. In this sense, an interesting review presenting a deep discussion on modern trends in solid phase extraction was previously published [37], as well as revisions on analytical procedures for the determination of different antidepressants were previously published [39-41], also including the enantiomeric analysis of these compounds [42,43].

However, several limitations are also encountered. For instance, the aforementioned extraction techniques require the correct selection of a robust sorbent to be successfully applied under variable conditions. Additionally, the efficiency of extraction, the reusability and disposal of the sorbents with antidepressants must be estimated, representing some of the major issues to consider. Also, performing such techniques is not exempt of difficulties and higher costs. Alternatively, nanotechnology possess certain features which makes this discipline attractive to overcome the drawbacks found when using the conventional extraction
techniques, although the correct selection of the nanomaterials with an adequate conformation or structure must be considered.

Nanotechnology is conducted at the nanoscale objects, usually ranging from 1 to 100 nanometer (nm), so the prefix nano represents a key to open many doors [44], as confirmed by their numerous applications in medicine, electronics, food, cosmetic industries, space, as well as in solar cell and water treatment processes [45]. More indeed, nanomaterials have unique physical, thermal, optical chemical, morphological and mechanical characteristics which enable them to be applied in many several applications [46,47]. The distinct benefits offered by nanomaterials in drug extraction can be attributed to their physical stability and the ability to modify the formulating nanomaterials to achieve controlled and selective retention and release of the analytes. Consequently, this ability of sustained release offers an opportunity for successful product lifecycle management by developing new formulations of drugs that are going off-patent.

Consequently, a new perspective on the application of nanomaterials to the extraction of drugs and drug delivery is being considered and new approaches are currently being developed [48,49]. In this sense, antidepressants are drugs with a remarkable frequency of prescription worldwide and, considering the importance of monitoring these pharmacological treatments, new extraction approaches, which are currently being developed and applied, is required. In this review, recent strategies for antidepressants extraction from biological samples using different nanomaterials and their modifications with different capabilities are reviewed and discussed.

2. Mechanisms of antidepressants extraction

The determination of these drugs in biological matrices is required in different contexts, and both the presence of endogenous compounds as well as the low concentration of the analytes make this analysis particularly challenging. Therefore, sample preparation is an important step, and, in this sense, new extraction techniques are being proposed in recent years to overcome the existent difficulties at this part of the analytical process. Several strategies and/or approaches are currently utilized to extract this group of pharmaceuticals from biological matrices, using a variety of materials and combinations [50].

Traditional sorbents have usually been utilized in SPE (e.g. silica, C₈, C₁₈, poly (styrene-divinylbenzene) (PS-DVB), microporous poly (N-vinylpyrrolidone-DVB) polymers, methacrylate-DVB resins and some others, usually used mixed-mode ion-exchange sorbents, including MCX, MAX and WAX, and they have been previously reviewed elsewhere [51]. Moreover, novel solid phase sorbents, including molecularly imprinted polymers (MIPs), carbon nanomaterials, metallic NPs and metal-organic frameworks (MOFs) are also being applied for drugs extraction, including antidepressants [36]. They all have their unique
features, which represent advantages or drawbacks when used as sorbents, but they all have in common their large specific surface area, a property very much appreciated for analytes’ extraction. More recently, an increasing number of publications have been observed regarding liquid-liquid microextraction of antidepressants. Indeed, these analytes have been successfully extracted from biological matrices using dispersive solid phase extraction and deep eutectic solvent-based air-assisted liquid-liquid microextraction [52], liquid-liquid-liquid extraction followed by dispersive liquid-liquid microextraction [53], dispersive liquid-liquid microextraction coupled with green-based agarose gel-electromembrane extraction [54], green sodium sulfate-induced solidification of floating organic droplets-dispersive liquid phase microextraction method [55], or air-dispersed liquid-liquid microextraction [56].

Some previous reviews have been published discussing the extraction approaches for this class of drugs, though mainly focused in environmental samples [57] or in the analysis of a particular group of antidepressants and considering the more classical extraction approaches [58]. On the other hand, several exhaustive revisions have also been performed, basically focused on the use of nanomaterials as sorbents within the field of Bioanalysis, but not focused on this particular class of pharmaceuticals [59].

Adsorption represents the most common mechanism for antidepressants extraction. More precisely, the antidepressant drug is attached on the sorbent’s surface by chemisorption through chemical, usually covalent, bonds to stick the adsorbate to the sorbent, or by physisorption through van der Waals (vdW) interactions between the substrate and adsorbate. In the latter case, an electrostatic interaction occurs among antidepressants and sorbent. Due to pi-pi interaction and hydrogen bonding interaction between the antidepressants and the sorbent, the extraction recoveries of antidepressants can be further improved, wherein the retention behaviour is due to pi-pi interactions and the lack of hydrophobic interactions between the sorbent and antidepressants [60]. Nanomaterials with good adsorption properties have two important characteristics: the innate specific surface-area and capability for selective functionalization of the external surface [61]. High specific surface-area, high adsorption capacity, the absence of any diffusion resistance, the superficial location of atoms, and a high binding capacity due to the increased adsorption capability of the nanomaterials [62,63].

Another common mechanism involved at the extraction of antidepressants is absorption. This mechanism involves the antidepressant molecules crossing the surface and entering the volume of the sorbent material. Again, there can be either chemical and/or physical absorption. The binding properties are essential characteristics and parameters for understanding these sorption mechanisms, so the sorption isotherm has been studied to describe the reciprocal behavior between the sorbent and the solutes. More indeed, four different isotherm models including Langmuir [64], Freundlich [64], Dubinin-Radushkevich
[65] and Temkin [64] are used to evaluate these interactions between the sorbent and the solutes.

The Freundlich isotherm, presented by Freundlich in 1906 [66], was the first isotherm model proposed for sorption processes. This model is applied for the non-ideal sorption on heterogeneous surfaces, as well as for multilayer sorption. The linear form of the Freundlich equation that can be fitted, as defined

$$\log q = \log K_f + \frac{1}{n} \log C_e,$$

where q represents the metal’s uptake per weight unit of sorbent (mg g⁻¹), whereas Cₑ corresponds to the residual concentration at equilibrium of the metal ion in solution (mg L⁻¹), Kᵢ is the sorption capacity (mg g⁻¹), and 1/n the sorption intensity [67].

The Langmuir isotherm describes the adsorption of an analyte or adsorbate onto the adsorbent’s surface assuming of monolayer coverage equivalent in active sites and on a homogeneous surface. Its basic features are represented by the dimensionless constant called the equilibrium parameter (Rₑ), defined as

$$R_L = \frac{1}{1 + K_L C_0},$$

where Kᵢ is the Langmuir constant related to the energy of adsorption (mL mg⁻¹) and C₀ is the initial concentration of the adsorbate (mg mL⁻¹) [68].

On the other hand, the Dubinin-Radushkevich isotherm model explains an empirical adsorption model which is generally applied to express the mechanism of adsorption with Gaussian energy distribution onto heterogeneous surfaces [69]. The Dubinin-Radushkevich isotherm is expressed as follows [70]:

$$\ln q_e = \ln q_m - \beta E^2$$

$$\epsilon = RT \ln (1 + \frac{1}{C_e})$$

$$E = \frac{1}{\sqrt{2B}}$$

where ε is Polanyi potential, β is Dubinin-Radushkevich constant, R the gas constant (8.314 J mol⁻¹ K⁻¹), T is the absolute temperature, and E the mean adsorption energy.

At last, the Temkin isotherm assumes that the fall in the heat of sorption is linear rather than logarithmic, as implied in the Freundlich equation. The adsorption experiment data are thus analyzed by the Temkin isotherm model in the linearized form,

$$q_e = B \ln C_e + B \ln A,$$

where B is equal to RT/b, being b the Temkin constant related to heat of sorption (J mol⁻¹); additionally, A is the equilibrium binding constant corresponding to the maximum binding energy (L g⁻¹), R is the gas constant (8.314 J mol⁻¹ K⁻¹), and T the absolute temperature (K) [71].
At present, the most common kinetic modes are the pseudo-first order, the pseudo-second order and Elovich [72]. The pseudo-first order or the Lagergren kinetic mode describes the sorption rate in the liquid-phase systems [73]. Furthermore, it has been the most widely used kinetic equations. The pseudo-second order kinetics, this model assumes that the overall sorption rate is controlled by the rate of direct adsorption/desorption process [73].

The Elovich kinetic, this is due to disregarding the rate of desorption which simultaneously occurred. Consequently, practically, the applicability of the Elovich kinetic mode when the system is relatively far from equilibrium, at the initial times of sorption process [73]. Therefore, the adsorption and absorption capability of nanomaterials are investigated and described through different kinetic and isotherm models, and this adsorption efficiency as well as the sorption/desorption kinetics can vary with each nanomaterial utilized for the extraction of antidepressants (Table 2). Many currently existing nanomaterials have been applied for the extraction of antidepressants from biological sources by utilizing different extraction mechanisms which are being further analyzed and their current applications discussed in the following section. The nanomaterials have been widely used for extraction of antidepressants are nanoparticles, nanotubes, nanofibers, nanoshells, nanocomposites, nanorods and polymer-based nanosorbents (Fig. 1). The rate adsorption capacity and efficiency varies with each nanomaterial. Fig. 2 shows the antidepressants sorption mechanism through various nanomaterials.

3. Nanomaterials for antidepressants extraction

Up to now, the nanomaterials used to extract antidepressants comprise nanoparticles, nanotubes, nanofibers, nanoshells, nanocomposites, nanorods and polymer-based nanosorbents, most of which are currently used for antidepressants extraction (Fig. 3). The main parameters involved in these extraction process such as the type of surface modification, the extraction mechanism applied, the biological specimens analyzed, as well as the sample volume and extraction time required, the instrumentation utilized, and the extraction recovery achieved are also included and discussed (Table 3).

3.1. Nanoparticles

Nanoparticles (ranging from 1 to 100 nm) can be either simple or complex nature (metallic, semiconductor, or polymeric nature), and have found numerous fields of application such as medicine, food science and technology, cosmetic industries, or water treatment [74]. Moreover, these materials can be used as adsorbents for an efficient extraction of many drugs in different biological specimens [59]. Due to their uniquely small size, high specific surface-area and excellent catalytic activity, nanoparticles emerged as a promising alternative to conventional methods of treatment for antidepressants extraction from biological specimens,
which often result in tedious, expensive and slightly complex procedures. Thus, metallic nanoparticles (MNP) can be considered as really useful materials in several areas of analytical chemistry as these MNP possess excellent surface area, high adsorption capacity, are susceptible of being modified at relative low temperature and have good conducting properties as well [75]. Currently, different nanoparticles such as Fe₃O₄ [76], TiO₂ [77], Al₂O₃ [78], among others, previously modified with functional coatings, have already been successfully applied as sorbents.

An innovative approach is MSPE, a new type of SPE based on magnetic sorbents. This technique has been increasingly studied for determination of drugs in biological matrices due to several advantages over conventional techniques and the development of new materials [38]. Among them, Fe₃O₄ magnetic nanoparticles (Fe₃O₄ MNPs) have attracted interest wide-ranging due to their outstanding catalytic activities strong magnetism and high specific surface-area [76,79]. In fact, Fe₃O₄ MNPs are becoming important as their role as sorbents remarkably contributes to save time and costs by simplifying the extraction process through their simple isolation from the sample matrix just by applying an external magnetic field. Many synthetic processes have been developed to fabricate these nanomaterials and a coating step (e.g. the use of silica used to allow the introduction of other functional groups) is usually added after their synthesis not only to improve the stability but also to avoid the formation of agglomerates of these NPs. Indeed, a wide variety of coatings can be used to improve selectivity [80,81]. Therefore, these MNPs, including Fe₃O₄ ones, can be considered as excellent sorbents for the extraction of drugs as demonstrated by different studies here reported [82].

The Fe₃O₄ MNPs are widely used for antidepressants extraction [82-88]. First, Markovich et al. synthesized Fe₃O₄ MNPs by reacting aqueous ammonia with an aqueous solution containing FeCl₃ and FeCl₂ at a molar ratio of 2:1 [89]. Since then, different approaches are considered for their synthesis, from physical methods (i.e. size reduction process down to the nanometric range, or the condensation of precursors from either a gaseous or liquid phase) [90], to wet chemical approaches such as oxidation, electrochemical, reactions carried out in constrained environments, supercritical fluid process, sol-gel reactions, hydrothermal, polyol methods, flow injection syntheses, and aerosol/vapor methods. Furthermore, methods using microorganisms, such as the MNPs formed by bio-mineralization have been performed [90].

MNPs synthesis generally requires of remarkable costs; however, when synthesized from natural sources such as microorganisms (i.e. bacteria or fungi) [91,92] the process becomes significantly more economic, as is the case of the synthesis of magnetic/non-magnetic nanocellulose from argan press cake plant [93] and magnetic nanocellulose from olive industry solid waste [94]. When Fe₃O₄ MNPs synthesized from a natural source is compared with MNPs created by co-precipitation.
Bare Fe₃O₄ MNPs have been coated with different materials (e.g. organic compounds, polymers, surfactants, and others) for the simultaneous extraction of antidepressants from biological specimens (Table 3). For instance, when the extraction of antidepressants with pyrrole-coated Fe₃O₄ MNPs was evaluated, a pH-dependent slight variation of their extraction efficiency was detected. Nevertheless, good extraction recoveries, ranging from 85.2 to 118.7% for citalopram, fluoxetine and sertraline were found in human urine and plasma [82]. Fe₃O₄ MNPs has also been ensembled with other nanoparticles to increase the antidepressants extraction ability. In one such case, Fe₃O₄ MNPs had been used with zirconium dioxide (ZrO₂) NPs for the simultaneous extraction of nortriptyline and amitriptyline from human plasma [32]. More specifically, a hydrophobic layer of N-cetylpyridinium surfactant was adsorbed onto the surface of the Fe₃O₄ MNPs@ZrO₂ composites driven by both electrostatic attraction and strong hydrophobic interactions, thus enhancing the extraction of these basic compounds (from 89 to 105%), as this outer surface provides different mechanisms (i.e. chain-chain interactions or hydrophobic with the hydrocarbon chains of the surfactant, hydrogen bonding or electrostatic interaction with the polar groups) for the effective retention of these analytes. Simultaneously, the ZrO₂ and N-cetylpyridinium surfactant-enhanced the endurance of Fe₃O₄ MNPs. Consequently, allow their reuse for repetitive extractions [32]. While bare Fe₃O₄ MNPs, or Fe₃O₄ MNPs in combination with other NPs presented excellent results in adequate antidepressants extraction, these nanomaterials still tend to aggregate in aqueous solution as of their ease of oxidation under ambient conditions, causing a reduction in the extraction capacity of Fe₃O₄ MNPs. However, this issue can be overcome by immobilization of these NMs on substrates/supports, by using an appropriate capping materials or by synthesis of bimetallic nanoparticles (formed by the combination of two different metals) in order to increase their stability as well as to enhance their properties [32].

Another strategy implies the synthesis of amino–functionalized Fe₃O₄ MNPs. For instance, novel Fe₃O₄ MNPs@SiO₂-NH₂ have been synthesized for the extraction of the antidepressant clomipramine from human plasma by ultrasound-assisted dispersive magnetic solid phase extraction [83]. The interaction between this nanosorbent and clomipramine is highly influenced by pH values. Thus, at pH=9.0, and with 37 mg of Fe₃O₄ MNPs, a maximum extraction recovery of 90.6% was obtained mainly due to the sorption by hydrogen bonding of the drug onto the Fe₃O₄ MNPs@SiO₂-NH₂ sorbent.

In another study, Fe₃O₄ MNPs were synthesized by graft copolymerization process of the thermosensitive agent N-isopropylacrylamide and the functional monomer 1-(N,N-bis-carboxymethyl)amino-3-allylglycerol onto Fe₃O₄ MNPs surface modified with 3-mercaptopropyltrimethoxysilane. These so-modified Fe₃O₄ MNPs showed effectiveness for the extraction of dopamine uptake fluvoxamine or the inhibitor of noradrenaline, ranging from 85.5 to 96.5% either from urine, plasma and pharmaceutical samples [95]. At neutral
pH, the best sorption in about five minutes shaking occurred, while lower pH values reduced the obtained extraction results of fluvoxamine, probably by an enhanced protonation of the -NH$_2$ group of the antidepressant drug and the sequent increase of its ionic form and/or its consequent higher water solubility. When pH increased, the antidepressant drug becomes into its neutral form and, therefore, lower water solubility occurred and higher extraction values were favored. Additionally, the sorption rate of fluvoxamine was increased at temperatures below the lower critical temperature of the poly(N-isopropylacrylamide), a result of the increase in driving force with decreasing temperature. The mechanism proposed indicated that this rapid adsorption behavior of fluvoxamine on these grafted Fe$_3$O$_4$ MNPs could be fitted by the Freundlich isotherm model, due to the accessibility of the bonding site in polymers on the CPG-MNP [95].

An additional study used a sorbent synthesized by the polymer-grafted Fe$_3$O$_4$ MNP by the free-radical graft co-polymerization of β-CD/allylamine and N-isopropylacrylamide and modified with 3-mercaptopropyltrimethoxysilane for venlafaxine extraction from plasma, urine and pharmaceutical samples. In this case, pH 5 was selected as optimal for the effective drug sorption, also considering the re-dissolving of Fe$_3$O$_4$ MNPs at alkaline pH. At lower pH values, increased the obtained extraction recovery of venlafaxine, may be due to the weakening of binding force of interaction between the oppositely-charged adsorbate and adsorbent leading to a reduction in sorption capacity.

Overall, novel polymer grafted Fe$_3$O$_4$ MNPs were successfully synthesized and presented as an suitable and efficient sorbent for extraction of venlafaxine with recovery values ranging from 17.6% for plasma to 103.3% for urine sample [96].

3.2. Nanotubes

Nanotubes are one-dimensional (1D) nanostructures with hollow cylindrical tubes which are widely used in pharmacy and medicine as of their variable thermal, physical, electrical, chemical and structural characteristics [97,98]. More indeed, because of their high specific surface-area and capability for pi-pi interactions, their relatively cheap cost, easy accessibility, and their modification/functionization capability [97] these nanomaterials are used as adsorbents for extraction of different drugs, including antidepressants [98]. These particular properties, together with their higher length to act as large platforms for the interactions with the analytes make carbon nanotubes one of the most frequently used sorbents in the recent decades [99-102]. However, the high hydrophobicity surface of CNTs requires of its proper modification for an efficient extraction of antidepressants.

In one such case, CNTs together with ionic liquids have been utilized to extract and to improve the determination of nine antidepressants in human urine by HPLC-UV [103]. More specifically, multiwall carbon nanotubes (MWCNTs) were used SPE sorbent for the pre-concentration of amitryptiline, desipramine, imipramine, trimipramine, clomipramine,
nortryptiline, trazodone, mianserine, and fluoxetine as MWCNTs enable these analytes to remain on their surface bonded by Van der Waals forces or pi-pi interactions. Then, the matrix interferences could be removed just with water, without adding any organic solvent. Additionally, the use of an ionic liquid as an additive for silanol suppression is proposed to improve the chromatographic behavior of these antidepressants, avoiding band tailing of chromatographic peaks. This study showed extraction recoveries from 72.4 to 97%, whereas LODs were determined in the 12.3-90.1 ng mL\(^{-1}\) range [103]. Magnetic adsorption techniques are also employed to simplify and improve the extraction of antidepressants from biological specimens [104,105]. Thus, magnetic multi-walled carbon nanotubes (MMWCNTs) can be easily synthesized by using chemical deposition method of Fe\(_3\)O\(_4\) on the surface of CNTs [106] for their application as a cleaner alternative for antidepressants extraction [107] due to the magnetic properties of these modified carbon nanotubes, they could be easily separated from the matrix and/or from the analytes using magnets, thus enhancing their properties as sorbents.

In this sense, CNTs were modified with magnetic nanoparticles through chemical co-precipitation of FeCl\(_2\) and FeCl\(_3\) in an alkaline solution, and the ionic liquid 1,4 diazabicyclo[2.2.2]octane (DABCO) was attached to their surface. The obtained material is shown to be a selective and effective sorbent for the isolation of several types of antidepressants citalopram, sertraline, fluvoxamine and fluoxetine from human plasma samples with ultrasound-assisted magnetic solid-phase extraction and prior to their determination by LC-UV [108]. The ionic liquid DABCO is an ionic liquid framework and cage-like compound, with a great potential in sample preparation due to its high hydrophobicity and thermo-stability. Furthermore, it is an economic, eco-friendly, and nontoxic organic material. However, this ionic liquid is not usually recovered and, therefore, it would be present in solutions, thus representing a remarkable issue, which can be overcome by immobilizing it on a magnetic surface like magnetic CNTs, to obtain a recoverable, heterogeneous, and reusable derivative of DABCO, as well as to separate the sorbent from the sample matrix. Thus, the antidepressants analyzed were extracted from plasma by hydrophobic and \(\pi\)-cation interactions with recovery values higher than 91% [108].

Besides that, the high mechanical strength, high aspect ratios, high specific surface-area and their excellent electrical and reliability characteristics [109,110] make CNTs ideal to be used as electrodes [111-113]. For instance, the electrochemical behaviour of trazodone was studied at glassy carbon electrode modified with MWCNTs (MWCNT/GCE) [113]. The MWCNTs suspension (15 μL) was then cast onto the GCE and dried in air. The electro-active areas of the MWCNT-modified GCE and the non-modified GCE were obtained by cyclic voltammetry (CV) using 1.0 mM of \(K_3\)Fe(CN)\(_6\), and the MWCNT/GCE showed much better performance than bare GCE. The analytical performance of MWCNT/GCE sensor has been evaluated for
determination and detection of trazodone in urine samples. Under optimal experimental conditions, the dynamic linear range and LOD for trazodone are 0.2–10 µM and 24 nM, respectively. Furthermore, the recovery determined was in the range of 99.15–103.2% for the detection and determination of trazodone in urine samples [113]. In another study, MWCNTs functionalized with the glycine (Gly) amino acid were synthesized using sol-gel technique and held in the pore of a hollow fiber [114] to determine and to extract venlafaxine (VEN) and o-desmethylvenlafaxine (ODV) from biological matrices. The microextraction parameters including pH of donor phase, donor phase volume, the extraction time, stirring rate, and the optimum desorption conditions such as desorption time and the type and volume of solvents were optimized [114].

3.3. Nanofibers
Nanofibers usually possess diameters lower than 100 nm and have been widely used in several medical applications [115]. They can be considered as one of the safest nanomaterials due to their extreme length and can be easily incorporated onto into the frequently different media or support/substrate. They also have high porosity, large surface-to-volume ratio, and more functionality. As a consequence, they have been used in airborne nanoscale particles, particulates filtration, , and other applications [116]. In this case, polymer nanofibers have been utilized to prepare electrospun polystyrene nanofibers for direct extraction of the antidepressant and anxiolytic trazodone from human plasma [117]. Electro-spinning was used to produce a polymer this nanoscale fibrous structure, resulting in nanofibers with high aspect ratio and, consequently, larger specific surface. The pH, ionic strength, eluted solvent, fiber packing amount and fiber diameter were additionally optimized for the extraction process. The target compound was then determined by HPLC-UV, and acceptable extraction recoveries of 58.3-75.2% and relative recoveries of 94.6-105.5% were presented, showing the effectiveness of extraction method proposed. Furthermore, the use of this nanomaterial provides a number of advantages in simplifying sample treatment and thus saving costs and analysis time with acceptable sensitivity, selectivity, and reliability [117].

Liquid-liquid extraction, although being highly reproducible and showing high-throughput capacity, it is a labor intensive and time-consuming method. As an alternative to decrease the solvent consumption, a miniaturized format is named liquid phase microextraction (LPME) was developed [118]. More specifically, 8.8 cm length hollow fiber-based liquid phase microextraction (HF-LPME) was successfully applied for the extraction of amitriptyline, imipramine and sertraline in urine and plasma samples [119]. The adsorption experiments were carried out using an accurel Q3/2 polypropylene hollow fiber membrane with a 0.2 µm pore size, 600 µm internal diameter and 200 µm wall thickness and target analytes were then
monitored by HPLC-UV. The study achieved extraction recoveries of 65-68% and enrichment factors up to 300. Overall, the study exhibited excellent performance of the HF-LPME technique for the antidepressant extraction from biological specimens [119].

3.4. Nanoshells
Nanoshells consisted of spherical particles composed by a dielectric core (i.e. silica or ferric oxides, alumina, titanium) and covered by a thin metallic shell (e.g. gold, silver, copper, etc.) with remarkable tendency towards the core to form this adsorbed layer of surfactant molecule [120].
For antidepressants extraction, the core-shell nanoparticles of the type Fe₃O₄ MNPs@ZrO₂ modified at their surface by N-cetylpyridinium have been used for the quantitative extraction by MSPE of amitriptyline and nortriptyline from plasma [32]. The study showed 89 to 105% extraction relative recoveries and detection limits of 0.04 and 0.08 ng mL⁻¹ for amitriptyline and nortriptyline, respectively, due to the enhancement of in adsorption mechanism through chain-chain interactions or hydrophobic, hydrogen bonding or electrostatic interaction with the polar groups, which are more selective and efficient than Fe₃O₄@ZrO₂ or bare Fe₃O₄ NPs. Overall, this MSPE method exhibited selective and efficient extraction of these tricyclic antidepressants, even more considering their stability over a 3-12 pH range and that just 5 mg of sorbent is required to achieve these good recoveries [32].

3.5. Nanocomposites
Nanocomposites have been widely used in medical applications as well as for the extraction of drugs [47,121]. Nanocomposites are defined as solids consisting of a combination of nanomaterials such as polymer [122,123], graphene [124,125], and magnetic polymer [126,127] based nanomaterials, which enhance its overall adsorption capability.
In this regard, a sensitive MSPE method based on Fe₃O₄ MNPs–MgSiO₃ magnetic nanocomposites was developed for extraction of fluoxetine, venlafaxine, sertraline, escitalopram, and paroxetine in serum and urine samples and their subsequent determination at trace levels using LC-UV [128]. In this case, Fe₃O₄ NPs are applied in MSPE due to considerable paramagnetism, a high magnetic saturation, and their synthesis. However, these bare NPs are prone to aggregation and oxidation, apart from not being selective toward complex matrices. To overcome these limitations, this inorganic composite magnetic nanoparticle was prepared to make a selective and appropriate sorbent, also considering that inorganic composite magnetic NPs are easier to prepare and safer. Thus, the Fe₃O₄-MgSiO₃ nanocomposites were synthesized by *in situ* chemical co-precipitation of Fe²⁺ and Fe³⁺, at a 1:2 molar ratio 1:2, in an alkaline solution in the presence of MgSiO₃. This optimized approach required just 12.5 mg of adsorbent at 7.4 pH and using only 1.3 mL of desorption solvent. The recoveries ranged between 72 and 115 %, with RSD lower than 4.75% [128].
In recent years, graphene-based magnetic composites have attracted a great research interest owing to its exceptional properties: huge surface area, large delocalized p-electron system, strong magnetic responsiveness, and excellent mechanical/thermal stability [129]. In one study, the conducting polymer polythionine (PTh) was coated by chemical oxidative polymerization process on the surface of graphene oxide (GO)/Fe₃O₄ NPs to generate a sorbent for the extraction of duloxetine antidepressant from human plasma [130]. First, the GO synthesized was dispersed in water by using ultrasonic radiation and, then, FeCl₃·6H₂O and FeCl₂·4H₂O were added dropwise at room temperature and pH value of 10 to form the GO/Fe₃O₄ MNPs. At basic condition (9.0 pH), the designed MSPE could be reused at least 9 times with an extraction recovery of 87% at its last use. The composition of this sorbent significantly could control the selectivity and efficiency of the extraction process. Indeed, the hydrophilicity of GO along with its high specific surface-area enhances the extraction ability and notable π-electron interaction with hydrocarbon ring structures. Moreover, the high specific surface-area, considerable pi-pi interactions and their excellent physical thermal, chemical and mechanical stabilities make PTh an excellent additive for the sorbent in the extraction of such compounds. The high specific surface-area of the support facilitated the applicability to re-disperse of NPs and preventing the agglomeration [130].

In another study, bovine serum albumin (BSA) conjugated with Fe₃O₄@AuNPs was applied as novel stationary phase at microchip electrophoresis (MCE) for efficient and effective enantioseparation process. First, Fe₃O₄@AuNPs were synthesized by sonochemical synthesis strategy, and the resulting Fe₃O₄@AuNPs are endowed with the excellent properties of the two independent components, such as the high load ability of Au shell and the magnetic nature of Fe₃O₄, which also favors the further immobilization of biomolecules and easy retrieval and separation of the sample from dispersion. Then, BSA was immobilized on the surface of Fe₃O₄@AuNPs through the interaction between Au coating and the amine groups of BSA to form the Fe₃O₄@Au NPs-BSA conjugates, which are subsequently organized by an external magnetic field in the PDMS microchannel. Then, the electrochromatographic enantioselectivity and reproducibility of this so-constructed MCE device were applied to the chiral separation of the amino acids tryptophan and threonine, as well as of the enantiomers of ofloxacin. The results obtained prove the good performance in terms of repeatability and efficiency for the enantiomers separation of this approach [131]. In our previous work [60], a new sorbent based on magnetic multiwalled carbon nanotube poly(styrene-co-divinylbenzene) composite was developed for the MSPE of fluoxetine, venlafaxine, citalopram and sertraline in human urine samples prior to capillary electrophoresis coupled diode array detector (CE-DAD). In comparison with the conventional C₁₈ SPE cartridge, the magnetic composite was smaller in size and easier to be handled during extraction, allowing it to be utilized as a sorbent in dispersive MSPE. The extraction recoveries were > 89.5 % for all analytes, with
LODs ranging from 0.014 to 0.041 µg mL\(^{-1}\). The magnetic sorbent could be re-used at least 10 times without any significant efficiency loss.

A step forward would be the microextraction procedure, a remarkable alternative simple, inexpensive and reproducible, even though some disadvantages are also present: fiber breakage, bending of the syringe needle and stripping of coating. On the other hand, in dispersive solid phase microextraction (DSPME), no fiber is utilized, and the selected synthesized sorbent is directly dispersed in the sample solution. Consequently, the aforementioned disadvantages of traditional SPME do not occur. For DSPME, the selection or preparation of a suitable SPME sorbent is a key factor as the selectivity and efficiency of analyte extraction depends on this material and of the interactions between it and the analyte.

A step forward in this direction has been taken by Ghorbani et al., who used ultrasonic assisted magnetic dispersive solid phase microextraction (UAMDSPME) to extract venlafaxine, atomoxetine and duloxetine from urine for their subsequent determination by HPLC-DAD [132]. More precisely, they synthesized magnetic p-Phenylenediamine functionalized reduced graphene oxide Quantum Dots@Ni nanocomposites (MrGOQDs–PD@Ni) as a novel SPME sorbent and studied its performance on the extraction efficiency of these three antidepressants. The efficiency of extraction was in this case determined to be mainly influenced by the amount of sorbent, pH of sample solution and desorption time, and the MrGOQDs–PD@Ni as SPME sorbent was found to be more effective than magnetic graphene oxide (MGO@Fe\(_3\)O\(_4\)) and magnetic reduced graphene oxide (MrGO@Ni) sorbents. More precisely, the electrostatic interaction between the analytes, positively charged, and MrGOQDs–PD@Ni sorbent (with negative charges) is advantageous when compared with the hydrogen bond between the analytes and the MGO sheet, whereas MrGO sorbent is able to produce minimal interaction with the analytes as of their lower number of hydroxyl, ether and carboxyl functional groups [132].

3.6. Nanorods

Nanorods are nanoscale objects (10\(^{-9}\) m) within a 1-100 nm size range. They can be synthesized by direct chemical synthesis from different metals such as gold [133], silver [134], or from semiconducting materials [135].

In one such case, arrays of SnO\(_2\) nanorods were fabricated to be applied at a solid phase microextraction (SPME) fiber method for the extraction of some polar selective serotonin reuptake inhibitors drugs, fluoxetine and citalopram, in human plasma and urine [136]. The pH, extraction time, the ion strength, and desorption time were optimized by using a Box-Behnken design and the response surface equations were developed. The optimum conditions for the plasma analysis thus obtained included a 30% w/v salt percentage, 6.5 µL from a 1M solution NaOH, 10 min required for the extraction and 30 min for desorption of the drugs,
whereas 100 µL from a 1 M NaOH solution, 18 min for extraction and 23 min as optimum desorption time (23 min) were applied for drugs extraction from urine samples [136]. Good reproducibility (RSD < 10%) as well as acceptable recoveries (79-94%) were found for the method proposed [136].

3.7. Polymer-based nanosorbents
Polymer-based nanosorbents such as those based on organic [137,138], inorganic and hybrid polymers [139,140], as well as on molecularly imprinted polymers (MIPs) [141,142] have been successfully applied in for drugs extraction with medical purposes [143].

Thus, a selective and sensitive MIP based on magnetic chitosan/GO method was developed for the spectrophotometric analysis of fluoxetine in urine, water and pharmaceutical samples [144]. For this purpose, a sorbent of MIP was synthesized using magnetic chitosan/GO as supporting material to provide multi-imprinting sites, high specific surface area, and ease of separation of magnetic nanomaterials. The synthesized polymer was characterized, and its capability of this sorbent for extracting fluoxetine was examined by optimizing the main factors affecting the extraction efficiency of fluoxetine. This method was successfully applied to the separation, preconcentration and determination of fluoxetine in the aforementioned matrices, with satisfactory recoveries (95.7–104%) [144].

Another selective method was developed for determination and extraction of amitriptyline from water and plasma samples using nano-sized molecularly imprinted polymer (MIP) with ultrasound-assisted extraction (UAE). The nano-sized amitriptyline imprinted polymer particles were synthesized using suspension polymerization in silicon oil. All main factors affecting the extraction and determination of amitriptyline were investigated and optimized such as, pH, sample volume, nature and volume of concentrative solvent, temperature, and ultrasound time. The relative recovery values ranged from 82.4 to 92.3% [145]. On the other hand, non-nanosized polymer have been used for the extraction of antidepressants in biological sample. In our previous work, a simple method based on poly(styrene-co-divinylbenzene) was developed for extraction of seven types of antidepressants (mirtazapine, bupropion, agomelatine, fluoxetine, , paroxetine, citalopram and trazodone) in human blood samples prior to their determination by capillary liquid chromatography-mass spectrometry (CLC-MS) [146].

4. Future perspectives
Most of the methods here discussed were performed at a laboratory, and no green synthetic materials were utilized. Even considering the reusability of many nanomaterials and the low reagents consumption associated to their application, these alternative green compounds and methods should be considered as future approaches to be developed. In this sense,
supercritical carbon dioxide (sc-CO$_2$) used to prepare nanomaterials may be further developed [147,148]. More indeed, produced nanomaterials of natural products such as the clay-based halloysite nanotubes could also be used for antidepressants extraction from biological specimens [149-151]. Consequently, these nanomaterials represent an eco-friendly, economic, and remarkably efficient, thus a highly suitable alternative, also considering their potential tunable surface chemistry [152-154] for biological applications and, more specifically, as potential excellent adsorbents for antidepressants. Additionally, new kind of nanomaterials applicable at wide pH ranges could also represent a remarkably interesting alternative to applied for antidepressants extraction from biological samples, even considering the different pH values usually existent in the different biological matrices to be monitored. On the other hand, all of these methods here resumed and discussed are applied as sorbents for solid phase extraction approaches, while alternative extraction strategies such as liquid-liquid microextraction or, more interestingly, supercritical fluid extraction are not considered when antidepressants are to be extracted from biological samples for their subsequent determination.

With regard to supercritical fluid extraction (SFE), sc-CO$_2$ was proven to be a green alternative to organic extraction liquids, as it is no flammable and it does not leave environmentally hazardous waste. Moreover, greater potential effectiveness, mild extraction conditions and short analysis times of SFE is derived from the rapid diffusion (gas-like) of the analytes in the fluid and the liquid-like solvation capacity of the supercritical fluids, thus enhancing its preconcentration effect, as well as its quantitiveness, expeditiousness, simplicity and selectivity [155]. All of these advantages could even be reinforced if nanomaterials were added to this extraction approach as of potential improvement of selectivity, rapidness and reduction of time and costs could be obtained.

Nevertheless, some difficulties must be overcome when SFE is to be used as of the challenging extraction of polar analytes, the rate of extraction efficiency obtained when spiked and natural samples are analyzed, and the clean-up process usually required before the analytes’ measurement.

5. Conclusion

Antidepressants drugs are widely prescribed for the treatment of psychological disorders such as depression and therefore their monitoring in biological specimens is important considering that they need to be accurately monitored. Antidepressants extraction does not occur through common processes for biological specimens. Traditional techniques used for antidepressants extraction such as adsorption, and other chemical and biological techniques. However, these techniques have several restrictions. Nanomaterial is an ideal alternative to extract the antidepressants over the traditional techniques, as it is a secure, clean and energy efficient
method. Nanomaterials have been widely used for antidepressants extraction, such as nanoparticles, nanotubes, nanofibers, nanoshells, nanocomposites, nanorods and polymer-based nanosorbents. Many advantages associated with these materials are large surface-area, good catalytic activity, easy synthetic routes, and good optical, physical, electrical and mechanical properties. The nanomaterials have either been extensively used as sorbents due to their high specific surface areas. The nanoparticles were used without any functionalization, modification or immobilized on a support/substrate. Efficient antidepressants extraction recoveries have been accomplished using these nanomaterials at differing functionalization/modification, extraction type, biological specimens, linear range, LODs, instrumentation and extraction recovery. The concentration of antidepressants extracted have been determined through different techniques such as, spectrophotometry, and chromatography techniques. Antidepressants extraction recoveries as high as 100% have been accomplished using different types of nanomaterials. However, these nanomaterials have several restrictions such as toxicity of different classes of nanomaterials and particle agglomeration. The nanomaterials are generally expected to be unstable at different conditions. Use of novel and eco-friendly materials such as nanotubes and their composites for antidepressants extraction may lead up to an improvement in antidepressants extraction efficiency. The development of further techniques that overcome the restrictions of nanomaterials may become the real ‘silver bullet’ needed for efficient and effective antidepressants extraction from biological specimens.

Acknowledgments
The Spanish Ministry of Economy and Competitiveness (MINECO) and JICC Castilla-La Mancha are gratefully acknowledged for funding this work with Grants CTQ2016-78793-P and JCCM SBPLY/17/180501/000262, respectively.

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Figure captions

Fig. 1. Nanomaterials used in antidepressants extraction.

Fig. 2. Antidepressants extraction mechanism using different nanomaterials.

Fig. 3. Classification of nanomaterials used for antidepressants extraction.
Table 1. Classification of the main types of antidepressants.

<table>
<thead>
<tr>
<th>Class of antidepressants</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>Citalopram, fluoxetine</td>
</tr>
<tr>
<td>Serotonin-norepinephrine reuptake inhibitors</td>
<td>Duloxetine, venlafaxine</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>Desipramine, imipramine</td>
</tr>
<tr>
<td>Monoamine oxidase inhibitors</td>
<td>Phenelzine, tranylcypromine</td>
</tr>
<tr>
<td>Reversible inhibitors of monoamine oxidase A</td>
<td>Moclobemide, toloxatine</td>
</tr>
<tr>
<td>Tetracyclic antidepressants</td>
<td>Mirtazapine, setiptiline</td>
</tr>
<tr>
<td>Noradrenergic and specific serotonergic antidepressants</td>
<td>Aptazapine, mianserin</td>
</tr>
</tbody>
</table>
Table 2. Isotherm and kinetic models of different nano-sorbents used for antidepressants extraction form biological specimens.

<table>
<thead>
<tr>
<th>Adsorbent</th>
<th>Isotherm model</th>
<th>Kinetic model</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIPs based on magnetic chitosan/GO</td>
<td>Langmuir, Freundlich, Temkin, and Dubinin-Radushkevich</td>
<td>Pseudo-first-order, pseudo-second-order, Elovich and intra particle kinetic</td>
<td>[144]</td>
</tr>
<tr>
<td>The surface grafting of poly[β-CD/allylamine-co-N-isopropylacrylamide] onto modified Fe₃O₄ MNPs by 3-mercaptopropyltrimethoxysilane</td>
<td>Langmuir and Freundlich</td>
<td>–</td>
<td>[96]</td>
</tr>
<tr>
<td>RAMIP-BSA</td>
<td>Langmuir and Freundlich</td>
<td></td>
<td>[156]</td>
</tr>
<tr>
<td>Imz ionic liquid-modified Fe₃O₄@SiO₂ NPs</td>
<td>Freundlich</td>
<td>–</td>
<td>[84]</td>
</tr>
<tr>
<td>PNCBCA grafted to Fe₃O₄ MNPs</td>
<td>Freundlich</td>
<td></td>
<td>[95]</td>
</tr>
<tr>
<td>MIPs coated Fe₃O₄ MNPs</td>
<td>Langmuir and Freundlich</td>
<td>–</td>
<td>[157]</td>
</tr>
</tbody>
</table>

MIPs: Molecularly imprinting polymers, GO: Graphene oxide, MNPs: Magnetic nanoparticles, Imz: Imidazolium, RAMIP-BSA: Restricted access molecularly imprinted polymer-bovine serum albumin, NPs: Nanoparticles and PNCBCA: Poly[N-isopropylacrylamide-co-1-(N,N-bis-carboxymethyl)amino-3-allylglycerol].

Table 3. Efficiency of the extraction of antidepressants from biological specimens by using different nanomaterials.

<table>
<thead>
<tr>
<th>Nanomat erial</th>
<th>Type</th>
<th>Surface modification</th>
<th>Extraction technique</th>
<th>Sample mat</th>
<th>Analyte(s) extracted</th>
<th>Sample volu</th>
<th>Extraction time</th>
<th>Determination</th>
<th>Recovery (%)</th>
<th>Ref.</th>
</tr>
</thead>
</table>


<table>
<thead>
<tr>
<th>Nanoparticles</th>
<th>rix</th>
<th>me (mL)</th>
<th>(min)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fe₃O₄ MNPs</td>
<td>CTAB</td>
<td>SPME</td>
<td>Urine</td>
<td>Amitriptyline, nortriptyline, imipramine, and doxepin</td>
</tr>
<tr>
<td>Hydrophobic Fe₃O₄ MNPs</td>
<td>dµSP E</td>
<td>Plasmas and urine</td>
<td>Doxepin, nortriptyline, and amitriptyline</td>
<td>0.5</td>
</tr>
<tr>
<td>Fe₃O₄@SiO₂-Imz NPs</td>
<td>MSPE</td>
<td>Serum</td>
<td>Amitriptyline and nortriptyline</td>
<td>300</td>
</tr>
<tr>
<td>Poly[N-isopropylacrylamide-co-1-(N,N-bis-carboxymethyl)aminomethyl]allylglycerol</td>
<td>SPE</td>
<td>Plasma</td>
<td>Fluvoxamine</td>
<td>1</td>
</tr>
<tr>
<td>Poly[β-CD/allylamine-co-N-isopropylacrylamide]</td>
<td>SPE</td>
<td>Urine</td>
<td>Venlafaxine</td>
<td>1</td>
</tr>
<tr>
<td>Fe₃O₄ MNPs@SiO₂-NH₂</td>
<td>UAD M-SPE</td>
<td>Plasma</td>
<td>Clomipramine</td>
<td>23</td>
</tr>
<tr>
<td>Grafting of β-cyclodextrin/allylamine on Fe₃O₄ MNPs modified with 3-</td>
<td>dMSP E</td>
<td>Plasma and urine</td>
<td>Sertraline</td>
<td>NS</td>
</tr>
<tr>
<td>MIN</td>
<td>Grafting on silica beads</td>
<td>SPE</td>
<td>Urine</td>
<td>Citalopram, desmethylcitalopram and didesmethyl citalopram</td>
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<tr>
<td>Fe₃O₄ MNPs</td>
<td>Py</td>
<td>MSPE</td>
<td>Plasma and urine</td>
<td>Citalopram, sertraline and fluoxetine</td>
</tr>
<tr>
<td>Fe₃O₄ MNPs</td>
<td>SDS</td>
<td>MSPE</td>
<td>Urine</td>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Fe₃O₄ MNPs</td>
<td>based on MCM-41</td>
<td>MuSPE</td>
<td>Plasma and urine</td>
<td>Amitriptyline and chlorpromazine</td>
</tr>
<tr>
<td>Fe₃O₄ MNPs</td>
<td>SiO₂@N₃</td>
<td>EA-DM-μSPE</td>
<td>Urine</td>
<td>Amitriptyline and nortriptyline</td>
</tr>
<tr>
<td>Fe₃O₄ MNPs</td>
<td>SiO₂@C₇/NH₂ nano-particles</td>
<td>MSPE</td>
<td>Plasma and urine</td>
<td>Imipramine and desipramine</td>
</tr>
<tr>
<td>Nanotubes</td>
<td>MWCNTs</td>
<td>MWCNTs/Fe₃O₄ MNPs/PS-DVB</td>
<td>MSPE</td>
<td>Urine</td>
</tr>
<tr>
<td>MWCNTs</td>
<td>CNTs with ionic liquid</td>
<td>SPE</td>
<td>Urine</td>
<td>Fluoxetine, desipramine and mianserine</td>
</tr>
<tr>
<td>CNTs</td>
<td>Magnetic CNTs coated DABCO</td>
<td>UA-MSPE</td>
<td>Plas ma</td>
<td>Citalopram, sertraline, fluvoxamine and fluoxetine</td>
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<tr>
<td>MWCNTs</td>
<td>Gly-MWCNTs</td>
<td>HF-SPME</td>
<td>Urine</td>
<td>Venlafaxine, o-desmethylvenlafaxine</td>
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<tr>
<td>MWCNTs</td>
<td>MWCNTs/Fe₃O₄ MNPs</td>
<td>MSPE</td>
<td>Urine</td>
<td>Fluoxetine</td>
</tr>
<tr>
<td>MWCNTs</td>
<td>Monolithic polymethacrylate</td>
<td>µSPE</td>
<td>Urine</td>
<td>Mianserine, trimipramine, desipramine and amitriptyline</td>
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<td>Nanofibers</td>
<td>EPS</td>
<td>SPE</td>
<td>Plas ma</td>
<td>Trazodone</td>
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<td>Hollow fiber</td>
<td>Hollow fiber-based LPME</td>
<td>LPM E</td>
<td>Plas ma and urin e</td>
<td>Amitriptyline, imipramine and sertraline</td>
</tr>
<tr>
<td>Hollow fiber</td>
<td>Hollow fiber-based LPME</td>
<td>LPM E</td>
<td>Plas ma</td>
<td>Fluoxetine and norfluoxetine</td>
</tr>
<tr>
<td>Nanoshells</td>
<td>Fe₃O₄ MNPs @ZrO₂ core shell</td>
<td>N-cetylpyridinium</td>
<td>MSPE</td>
<td>Amitriptyline, nortriptyline</td>
</tr>
<tr>
<td>Nanocomposites</td>
<td>MG(11 hexadecyl-3-methylimidazolium bromide</td>
<td>hemimicelle dµSPE</td>
<td>Urine</td>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Fe₃O₄ MNPs</td>
<td>Fe₃O₄ MNPs@PPy</td>
<td>dµSPE</td>
<td>Plas ma and</td>
<td>Citalopram, sertraline</td>
</tr>
<tr>
<td>Fe$_3$O$_4$ MNPs</td>
<td>Fe$_3$O$_4$-MgSiO$_3$</td>
<td>MSPE</td>
<td>Serum and urine</td>
<td>Venlafaxine, escitalopram, paroxetine, sertraline and fluoxetine</td>
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<td>--------------------------------------------------------</td>
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<tr>
<td>Fe$_3$O$_4$ MNPs</td>
<td>PU</td>
<td>MSPE</td>
<td>Plasma and urine</td>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Gr/CT</td>
<td>–</td>
<td>HS-SPME</td>
<td>Plasma, milk, urine and hair</td>
<td>Imipramine, desipramine and clomipramine</td>
</tr>
<tr>
<td>PDA-Ag-PPy</td>
<td>–</td>
<td>MEPS</td>
<td>Urine</td>
<td>Amitriptyline, imipramine and citalopram</td>
</tr>
<tr>
<td>PA</td>
<td>PA and PS-DVB</td>
<td>DPX</td>
<td>Plasma</td>
<td>Fluoxetine and norfluoxetine</td>
</tr>
<tr>
<td>GO/Fe$_3$O$_4$ MNPs@PTh</td>
<td>GO/Fe$_3$O$_4$ MNPs</td>
<td>MSPE</td>
<td>Plasma</td>
<td>Duloxetine</td>
</tr>
<tr>
<td>IN-Th copolymer</td>
<td>–</td>
<td>SPME</td>
<td>Plasma</td>
<td>Amitriptyline, imipramine and chlorpromazine</td>
</tr>
<tr>
<td>Nanostructured Cu-Cr-Al</td>
<td>Layered double hydroxide/polythiophene</td>
<td>SPME</td>
<td>Plasma and urine</td>
<td>Chlorpromazine and perphenazine</td>
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<tr>
<td><strong>Nanostructures</strong></td>
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<tr>
<td>SnO$_2$</td>
<td>–</td>
<td>SPME</td>
<td>Plasma and urine</td>
<td>Citalopram and fluoxetine</td>
</tr>
<tr>
<td>RAMIPs</td>
<td>–</td>
<td>SPE</td>
<td>Plasma</td>
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<td>Urine</td>
<td>Fluoxetine</td>
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<td>–</td>
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Highlights

- Nanomaterials are used as nano-sorbents for antidepressants extraction in various biological specimens.
- Nanomaterials provide high surface area and high sorption capacities compared to micro-scale sorbents.
- The use of carbon nanotubes in antidepressants sample preparation.
- Polymer based nano-sorbents.
Nanomaterials for antidepressants extraction

- Nanotubes
- Nanocomposites
- Nanoparticles
- Polymer-based nanosorbents
- Nanofibers
- Nanoshells
- Nanorods
Figure 2

Nanoparticles + Nanoshells + Nanotubes + Nanocomposites + Nanofibers + Nanorods + Polymer-based nanosorbents

Antidepressants

Extraction Mechanism

Sorption of antidepressants on nanomaterials
Antidepressants Extraction using Nanotechnology

- Nanoparticles
  - Fe₃O₄ NPs
  - Fe₃O₄@SiO₂ NPs
  - Chitosan NPs
  - Molecularly imprinted NPs
- Nanotubes
  - Carbon nanotubes
  - MWCNTs/styrene-divinylbenzene copolymer
- Nanofibers
  - Electrosyn polystyrene nanofibers
  - Polypropylene hollow fiber
- Nanoshells
  - Fe₃O₄@ZrO₂@N-cetylpyridinium core-shell NPs
- Nanocomposites
  - GO/Fe₃O₄@polythionine
  - Polypyrrole/MNPs
- Nanorods
  - SnO₂
  - Fe₃O₄-MgSiO₃
  - Magnetic polyurethane
  - Graphene/polyaniline
  - Polydopamine, Ag NPs, and polypyrrole
  - Polyaniline/styrene-divinylbenzene copolymer
- Polymer-based nanosorbents
  - MIPs/Poly(methacrylic acid)
  - MIPs based on magnetic chitosan/GO

Figure 3