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REVIEW

Up-to-date studies regarding the determination of sertraline by different analytical methods

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Abstract
Sertraline (SER), aka Zoloft, is one of modern antidepressant, it belongs to the selective serotonin reuptake inhibitor class, which functions to raise serotonin levels in the nervous system. SER has both mood-boosting and depressive effects but has bad influence on the gastrointestinal system. The monitor of SER and its major metabolites, desmethyl-SER (DSER) provides useful information that may assist treatments, particularly during adverse reactions or lack of response to the applied therapy. The determination of SER and its metabolites in different samples, like blood, urine, deceased people and water requires various selective, sensitive and reliable analytical methods. These methods would determine and quantify of the whole drug level, as in blood, or unbound form level, as in urine or saliva. The purpose of the current review is to provide a summary of the outcomes of the methods that have been used for the extraction of SER from different sample's types as well as some of the analytical methods that were used for its quantitative analysis. The work targeted the studies of the last decade.

Keyword Sertraline · Ultraviolet–visible spectrophotometry · Voltammetry · Differential pulse voltammetry · Gas chromatography · Liquid chromatography · Thin layer chromatography

1 Introduction

The diagnosis of mental disorder has been growing steadily over the past decades, and is accelerated in the era of COVID-19 as a result of the social isolation during the pandemic. Depression is one of the psychiatric disorders as well as social issue that has had negative influence on human life of different genders and ages [1]. The world health organization (WHO) stated that, it is one of the factors that would lead to increasing mortality. About 280×10^6 people around the globe were estimated to be affected by depression, which could have increased by the COVID-19 pandemic. The elevation of the cases would put pressure on the increasing number of anti-depressants' prescriptions [2, 3]. There are different families of anti-depressants, such as serotonin (SR) reuptake inhibitors, tricyclic anti-depressants, serotonin noradrenaline reuptake inhibitors and monoamine oxidase inhibitors [4].

With regard to the serotonin reuptake inhibitors (SRIs), they are usually used in the first stages of depression treatment for medium to high phases of illness that are related to SR deficiency [5]. The SRIs function by restraining the recovery of SR at the SR transporter, this would lead to increasing SR at the postsynaptic membrane in the serotonergic synapse, which mitigate the gloomy signs of the patients [6, 7]. The mostly used SRIs are citalopram, paroxetine and sertraline (SER). These drugs differ in their structures, but their function is identical. Their use is safe, but the recovery of the patients would differ based on the genetic polymorphisms, however; side effects would be seen like sweating, dizziness, sexual dysfunction and gastrointestinal signs. The respond to the treatment is affected by rate at which these drugs are metabolized by the human body, which is in relation to the genetic polymorphisms [8–10]. The consumption of appropriate amount of the drugs is crucial to ensure that individuals obtain the optimal therapeutic effects, prevent the possible side effects and minimized toxicity. Thus, the drugs amounts must be monitored for best clinical treatments [11, 12]. One of the attempted studies to effectively monitor the SER is by using paper sensor having fluorescent probe and incorporated with graphene quantum dots and tyrosine [13].

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Sertraline (SER), aka Zoloft as in Fig. 1, is an antidepressant, it belongs to the selective serotonin reuptake inhibitor class, which works to raise serotonin levels in the nervous system. SR has both mood-enhancing and depressive effects but has bad influence on the gastrointestinal system. The re-exploitation of serotonin in the brain is specifically inhibition by this medication. SER is considered a strong base compound with pKa = 9.8, so it can react with acids to form salts. Aliphatic amine is the one ionizable site in SER, as in Fig. 1. SER HCl has a thermodynamic solubility of 4.24 mg/mL and a dissociation constant pKa, which is determined by potentiometric titration, of 9.16 ± 0.02 in a mixture of water/methanol. It can be absorbed in the body due to its high lipophilicity value [14].

SER HCl solubility in supercritical CO_2 alone and in the presence of methanol was studied by Sodeifian and Sajadian. The study was evaluated at temperatures of 308–338 K and at pressures of 12–30 MPa by using coupled methods of static analysis and spectrophotometry. It was found that the addition of methanol enhanced the solubility from 0.93×10^{-4} mol fractions to about 0.89×10^{-4} mol fractions [15]. The same group utilized two techniques named as gas anti-solvent (GAS) and rapid expansion of supercritical solution for the synthesis of SER NPs. Both methods influence the SER's dissolution rate with the ability of GAS in reducing SER NPs sizes to 102 ± 11 nm at low pressures, compared to 185 nm for the second method [16].

SER can be found, after its usage, in blood, saliva, urine, plasma, hair and wastewater. The SER is found bounded to proteins in plasma for about 4–9 h after consuming it. Also, it can be ejected to urine and feces. Less than 50% of SER is discarded as metabolites whereas about 14% can be found unchanged in the urine. N-desmethyl-SER (DSER) is the main SER metabolite, and the speed of SER metabolism is reflected by the concentration of its metabolite. SER and DSER can be found in higher concentrations in older adults while smaller concentrations are associated with tobacco smokers [17].

Controlling SER and its metabolite in the body is important, especially when it is administrated to children and pregnant women. It was seen that, variation in the concentration of SER and DSER can differ to about 50% in individuals. Moreover, SER was reported to be metabolized by 5 isozymes, which means its ability to react with other drugs, this required its simultaneous detection alongside DSER [18].

SER is one of the common pollutants found in aquatic ecosystem and it is difficult to be oxidized by natural process, hence the monitor of SER levels in the environment is fatal to estimate its potential impact on human health and the environment. Thus, sensitive and selective techniques for detecting and quantifying SER in various samples are a must.

Various analytical instruments, which have existed in the literature, were used for the detection different drugs in pharmaceutical, industrial and environmental samples [19, 20]. SER is among the drugs being analyzed by analytical methods. These methods are electrochemical methods, spectrophotometric and chromatographic methods. Among the chromatographic methods, liquid chromatography and gas chromatography, each of which is coupled with appropriate detector for sensing SER [21, 22]. Also, spectrometric methods like mass spectrometry (MS) and nuclear magnetic resonance spectrometry (NMR) were used [23, 24]. The chromatographic, spectrometric and spectrophotometric methods are bulky, require tedious sample preparation and special portability which limit their possibility for on-site analysis. On the other hand, electrochemical sensors and techniques provide important information regarding the drugs' electro-activities redox features and metabolisms of the drugs. The electrochemical methods are simple, do not require lengthy sample preparation steps, portable, relatively cheap, provide fast analysis and possess high selectivity and sensitivity [25–27].

In electrochemical methods, different electrodes like working (sensing), auxiliary and reference electrodes are used. Among which, the working electrodes are the heart of electrochemical analysis. At early times, bare or unmodified electrodes used to sense the analytes but with poor detection at very high potentials. Also, unmodified electrodes have poor selectivity when interferences, that have similar oxidation potential, are present alongside the analytes. Very limited number of studies demonstrated the use of bare electrodes as efficient in sensing the drugs, and they use hanging mercury drop electrode [28], graphite electrode and paper-based electrodes [29, 30]. Moreover, as the analytes would be absorbed onto the working electrode surface, the bare electrodes are not reusable and have poor reproducibility. The solution for the previous problems would be to modify the working electrodes with materials that are easily fabricated, can selectively interact with the analytes and provide remarkable improved physical properties when compared to non-modified electrodes. These materials, or nano materials, should have some functionality and possess enhanced physical, chemical and electrical attributes. The modification

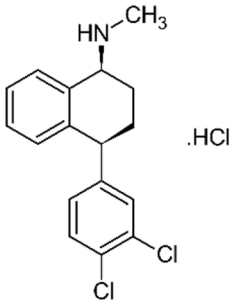

Fig. 1 The structures, chemical formula and molecular weight of sertraline hydrochloride

of the electrodes would be observed in the improved sensing, limit of detection (LOD), selectivity and reproducibility. Both materials and nanomaterials were studies massively in the last decade and found wide applications in electrochemical analysis of SER.

Difficulty in the SER analysis may rely on the sample's types and the low concentration of SER. In this context, different analytical instruments were attempted to answer the questions regarding the identity and quantity of samples' components. The performance of these instruments has been evaluated and compared with each other in terms of linear range, limit of detection (LOD), limit of quantification (LOQ), analysis time and matrix tolerance. The concentrations of SER and DSER in various types of samples have been determined by different analytical methods. They were quantified in samples collected from patients and healthy people as well as in its pure pharmaceutical forms.

Tremendous work is available in the literature regarding the extraction, determination and quantification of SER. This work aims at summarizing the literature studies regarding them, in various samples, for the last decade by some analytical methods.

1.1 Reported preconcentration techniques

The evaluation of the quantity of SER in different sources requires perfect sample preparation steps. Samples preparation is usually a labor-intensive phase of the entire analytical procedure, so the selection of optimum way for sample preparation is the crucial step in setting up an appropriate analytical method for analyzing SER in various samples. The preparation would need preconcentration of the drug. This can be achieved by using different techniques, such as solid-phase extraction (SPE), liquid-phase extraction (LLE), supported liquid extraction (SLE), dispersive liquid–liquid microextraction (DLLME) and protein precipitation. The aim of these techniques is to isolate SER from the matrix (interferants). These techniques would add to the analysis time and cost. They are usually employed when the determination instruments are of chromatographic nature or electrophoresis. Additionally, these methods may expel some compounds of current or future benefits, like metabolites. To overcome these limitations, direct injection of samples containing SER may be used.

The preconcentration methods are not simple, time-ineffective and have low selectivity. SER was detected by many analytical methods, such as spectrophotometric, electroanalytical and chromatographic ones. The last method was massively employed compared with the first two. The sample preparation differs based on the utilized analyzing techniques.

As for SPE, it has been used for the extraction, clean-up and preconcentration of the analytes prior to chromatographic analysis. SPE founds applications for extracting analytes from different sources, such as water, blood, urine and food matrix. In SPE method, cartridges with sorbents that have affinity differences for various analytes in a sample are used. Simply, the cartridge is usually washed with deionized water, conditioned with an appropriate solvent for moistening the sorbent. Thereafter, a solution including analyte and matrix is filled onto the device, then the analyte or impurities from the sample would be retained by the sorbent. Eventually, the analyte or impurities would be eluted from the sorbent. Another form of SPE is SPME which uses a thin fiber with a sorbent to facilitate the adsorption of the analyte. The adsorbed analyte would undergo washing and evaporation treatment, then administrated to GC studies, or reconstituted with the mobile phase for desorption followed by injection into HPLC system [31]. This was applied to human plasma, and the sorbent, silica gel, was modified by amino and butyronitrile groups for improving the extraction efficiency.

SPE found wide applications due to its various kind of sorbents and solvents. It is one of the usually used technique for extracting SER, and antidepressants in general, from wastewater with as low as µg/mL range. During SPE, reversed phase (RP) cation exchange alone or in combination with hydrophilic are chosen. Different polymeric sorbents like Oasis Hydrophilic-Lipophilic Balanced (HLB) RP or Strata were used for SER isolation. Pugajeva et al. demonstrated the use of Oasis HLB or Strata-X for the extraction of SER and other drugs. They concluded that both techniques had similar recoveries, however when acidified eluting solvents were used, the intensity signal reduced in case of Strata-X [32]. SER and DSER were isolated from whole blood by SPE, then derivatized by heptafluorobutyric anhydride. Derivatization enhanced their volatility. During the gas chromatographic analysis, protriptyline was employed as internal standard [33]. SPE is usually performed offline, but it could be linked to HPLC as part of an automated system, so it can be operated online. This mode can make the preparation easier, shorten the analysis time, enhance the recoveries and reproducibility.

LLE is simple and fast in isolating compounds based on their variable solubilities in two immiscible liquids but consume high volumes of solvents. So, LLE makes use of solvents that are immiscible with different polarities. Analytes would distribute between the two liquids according to their affinities. Samples containing the analyte would be placed in a separatory funnel or test tubes and shaken with the liquids for periods of time, then each liquid is eluted separately. The process of mixing, shaking and eluting may occur once or several times for best extraction efficiency. To assure better isolation, if the eluted organic layer contains the analyte, drying step may be required to eliminate any possible water droplets. The solution containing the analyte

would be analyzed directly or undergo dilution process. In most cases, the organic layer is evaporated to dryness and the residue is reconstituted by dissolving in a portion of the mobile phase before liquid chromatographic analysis. As for lipophilic compounds, they have limited solubility in polar solvents like water, therefore organic solvents are alternatively used [34].

SER with other compounds and their metabolites were extracted from human hair and saliva by LLE. The hair samples were washed thoroughly by methanol and dried. Hair strands were then placed in Soxhlet kit and isolated by methanol. As for saliva sample, acetonitrile was used to precipitate proteins as deproteinization was required [34]. Also, SER with other antidepressants were extracted by LLE from plasma, the tert-butyl methyl ether was used as the organic solvent. The extracts were then derivatized by 1-(heptafluorobutyryl) imidazole (HFBI) before being analyzed by gas chromatography [35]. SER and DSER were extracted from human blood by using heptane and isoamyl alcohol with volumes of 98.5: 1.5 (v/v), the extraction efficiency was 85.1%. Also, SER was isolated from human serum by using butyl chloride, the treatment of the sample with sodium carbonate enhanced the efficiency over 90% [36]. Moreover, SER was shown to be extracted from blood samples of deceased by 80:20 (v/v) of ethyl acetate and heptane, respectively [37].

As for SLE, a cartridge or extraction columns (well-plates) are used. It shares principles of SPE and LLE. Upon loading a sample onto SLE particles, the analyte and impurities, in an aqueous sample, would react with the fine porous particles of the solid support. The solid support would retain the analyte that can be eluted later by using organic solvent. Although SLE are sometimes recommended as better alternative of SPE and LLE, the extraction columns would be used once only, which increases the analysis cost and rise environmental concern [38].

Protein precipitation by organic solvents is one of new and simple methods for sample purification. Commonly, samples are shaken with small amounts of organic solvents like methanol or acetonitrile, followed by centrifugation and the resulted supernatant would be introduced to chromatographic analysis directly, as a single preparation step, or be followed by other sample preparation methods [39]. One of the applications of PP for isolating SER from plasma was reported by Domingues et al. The sample was deproteinized by acetonitrile, the sample volume was half the solvent. About 0.5 mL of the supernatant was dried by evaporation, then dissolved in the mobile phase. The mobile phase consisted of water, formic acid and acetonitrile [39].

When looking at the literature, SPE and LLE were used for the majority of matrix whereas PP is mainly utilized for plasma and blood samples and usually associated with chromatographic methods. Table 1 shows some examples regarding SER extraction methods.

1.2 Electroanalytical methods

Chromatographic methods are usually the first choice for analyzing drugs due to their relative advantages over other methods, such as accurate determination, being able to detect different drugs simultaneously, easily automated with high specificity of the targeted analytes. However, they are costly, consume large solvents' volumes, long analysis time, needs careful maintenance and difficult to be made portable. Electroanalytical methods seem to overcome most of these limitations, especially when electrochemical sensors are employed for quick screening of SER. These methods are based on measuring the electrical response of SER. The literature presented various techniques used for determining SER, such as cyclic voltammetry (CV), differential pulse voltammetry (DPV), linear sweep voltammetry (LSV), square wave voltammetry (SWV) [44], stripping voltammetry, adsorptive stripping differential pulse voltammetry (AdSDPV) [45].

They are derived from voltammetry; in voltammetry, one potential or potential spectrum may be imposed on the working (sensing) electrode, which resulted in oxidizing or reducing the analyte. Mediums having electrolyte support, with minimal or diminished solution resistance, are used for the electrochemical measurements. The mediums are affected by the physical properties of the analyte like its

Table 1 Selected extraction methods reported for sertraline

Analyte	Matrix	Extraction method	Linear range (µg/mL)	LOD (µg/mL)	LOQ (µg/mL)	References
SER and DSER	Whole blood	SPE	$1\times10^{-3}-0.5$	3×10^{-4}	1×10^{-3}	[33]
SER and other drugs	Wastewater	SPME	$0.24\times10^{-3}-3.82\times10^{-3}$	$2\times10^{-6}-13\times10^{-6}$		[40]
SER and other antidepressants	Plasma	LLE	0.005 – 2	0.0025 – 0.05	$0.5\times10^{-5}-1\times10^{-4}$	[35]
SER	Human urine	DLLME	$0.1\times10^{-3}-1\times10^{-3}$	2.5×10^{-6}		[41]
SER and other antidepressants	Blood	SLE	$0.001\times10^{-3}-0.2$	$3\times10^{-7}-3\times10^{-6}$		[42]
SER and DSER	Human plasma	PP	$2.5\times10^{-3}-0.32$ (SER) 0.01 – 1.28 (DSER)		0.031 (SER) 0.125 (DSER)	[43]

solubility, conductivity and reactivity. As for the electrochemical methods, CV, SWV and DPV are reported for SER analysis. With regard to CV, the potential of the sensing electrode is imposed in both forward and backward directions, then the current is recorded for the directions. These currents are anodic or cathodic currents which are linked to oxidizing and reducing the analyte, respectively. As for SWV, the differences in the current between each direction is measured. DPV was noted as the most widely used technique for SER quantification. In DPV, a series of voltage pulses is superimposed onto increased potential of stairsteps or linear sweep voltage. Then, the current would be recorded just before of after every pulse. As for potentiometry, two or three electrodes are utilized in an electrochemical cell. The potential is measured between working and reference electrodes.

Electrodes are the heart of electroanalytical methods because they are the mediator between the analytes and the electrochemical cell. Electrochemical sensors have been used for SER determination as they are cheaper than stationary columns in chromatography, have high selectivity and sensitivity, easily used and modified. There are different electrodes employed as working electrodes for detecting SER, among which are carbon-based electrodes, such as glassy carbon electrode (GCE), carbon paste electrode (CPE), screen printed carbon electrodes (SPCEs), multi-walled carbon nanotubes (MWCNTs) and doped-diamond electrode (DDE). Also, screen printed electrodes (SPE), pencil lead electrodes, platinum electrodes and gold electrodes were used. They were modified by using polymers, metal materials and nano materials as well as functional composites. The modifications would alter the chemical, optical and electrical properties of the interfaces. The modification of these electrodes is explained in the following paragraphs with the evaluation of validation parameters in Table 2.

1.3 Modification with polymers

Polymers are of organic nature having remarkable chemical, physical and electrical features. They are relatively cheap, easily prepared, have large surface area with small dimensions. Polyacetylene was noticed to have good conductivity but poor stability, that paved the way for discovering other conducting polymers with high stability, redox properties and electron transportation, such as polyaniline (PANI), polypyrrole (PPy), polyfluorene (PF) and polythiophene (PTh) [46].

One of famous class of polymers has molecular imprinting which output synthetic recognition spots, this class is known as molecularly imprinted polymer (MIP), that would function like antibodies. These spots are formed inside the polymers or on their surfaces, which would have high selectivity, sensitivity and stabilities. A precipitation polymerization method was used for the synthesis of MIP on SER HCl

Table 2 Selected electroanalytical methods used for the detection of sertraline compound

Analyte	Detection method	Electrode	Sample	Linear range (μmol/mL)	Detection limit (μmol/mL)	References
SER	CV, SWV	Modified Au electrode	Tablets and human serum	$0.1\times10^{-3}-0.9\times10^{-3}$	0.026×10^{-3}	[49]
SER		Modified SPCE	Tablets and human serum	$5\times10^{-6}-7.5\times10^{-4}$	1.99×10^{-9}	[51]
SER	DPV	Modified SPE with $ZnFe_2O_4$	Tablets and human serum	$0.07\times10^{-3}-300\times10^{-3}$	0.02×10^{-3}	[60]
SER	DPV	Modified SPE with La_2O_3/Co_3O_4	Tablets and human serum	$5\times10^{-3}-400\times10^{-3}$	0.001	[61]
SER	CV, DPV	Modified SPE with La^{3+}/ZnO	Tablets	$0.5\times10^{-3}-150\times10^{-3}$	0.15×10^{-3}	[62]
SER	DPV	Modified graphene SPE	Urine	$0.1\times10^{-3}-550\times10^{-3}$		[63]
SER	DPV	Modified GCE	Tablets		25×10^{-6}	[64]
SER	DPV	Modified GCE with Fe_3O_4@MCM-48-SO_3H/MWCNTs	Human blood and urine	$0.1\times10^{-3}-85\times10^{-3}$	0.025×10^{-3}	[65]
SER	CV, DP AdSV	Modified GCE with IL/NiO NPs	Tablets and human serum	$0.21\times10^{-3}-85\times10^{-3}$	0.047×10^{-3}	[66]
SER	CV, SWV	Modified CPE with CNT/Cs/SDS	Tablets and human plasma	$0.06\times10^{-3}-15\times10^{-3}$	0.0092×10^{-3}	[67]
SER	CV, DPV	Modified Pt with MIP and graphene	Human serum	$0.01\times10^{-3}-1\times10^{-3}$	0.007×10^{-3}	[68]
SER	CV, DPV	Modified SPCE with MIP and graphene	Tablets and human serum	$0.005\times10^{-3}-0.075\times10^{-3}$	0.002×10^{-3}	[51]
SER	CV	Modified GCE with Ni^{2+}-levodopa and Au NPs	Human serum	$0.05\times10^{-3}-5.5\times10^{-3}$	0.095×10^{-3}	[73]
SER	CV, DPV	Modified PGE with Cu-MOF	Tablets and human blood	$0.05\times10^{-3}-2.67\times10^{-3}$	0.038×10^{-3}	[74]

as a template, methacrylic acid was used as functional monomer and ethylene glycol dimethacrylate for cross-linking. The SER MIP was dispersed in dibutyl sebacate plasticizer, then embedded in PVC. The developed sensor had a linear response towards SER HCl in 0.001 – 0.01 µmol/mL concentration range with LOD of 0.0008 µmol/mL [47].

SER membranes were developed and tested for their ability to detect SER. Khater et al. constructed membrane sensors by using hetero-polyacids, such as silicotungstic acid, silicomolybdic acid and phosphomolybidic acid as ion associating materials. They showed low response time of 10 s with linear range of 0.00001–0.01 µmol/mL. These sensors were applied on SER pure powder and its tablets, they had fascinating selectivity towards SER^+ even when interferants ions and molecules are present [48].

Gold electrodes were coated with cyclodextrin (CD) as CD increases SER solubility and improve its bioavailability. This modification enhanced the electrode sensitivity by five-folds compared to bare Au electrode [49]. Also, 2-hydroxypropyl)-β-cyclodextrin (HPβCD) was coated onto Au electrode which improved its SER quantification. The SWV measurement showed linearity of the anodic current peaks within 0.0001–0.0005 µmol/mL concentration span, and 2×10^{-11} µmol/mL as LOD [50].

An electrochemical sensor was developed for detecting SER by modifying SPCE with a thin layer of molecularly imprinted polymer (MIP)/graphene suspension. This treatment showed better adsorption when compared to bare SPCE. The sensor was applied for detecting SER in tablets and human serum and had a linear response in the nM range with recoveries up-to 101% [51].

Very recently, SER was used as a template for the fabrication of MIP that can extract SRIs from wastewater. 72.6 mg/g and 3.7 were reported as maximum capacity of MIP for SER and maximum imprinting factor, respectively. The performance of the MIP was stable around neutral pH. These MIP showed higher sorption than activated carbon, although the latter has higher surface area [52].

SER alongside other SRIs drugs showed ability in reducing the oxidation current of serotonin when using Jackson waveform. Carbon-fiber microelectrodes surfaces were coated by electrodepositing Nafion. Their use in the study speeded the analysis time, further lowered both the peak current and the background charging current [53].

1.4 Modification with carbon nanomaterials

These materials are derived from different sources with variable morphologies, they also have unique chemical and biological features like enhanced electrical conductivity, being reusable, highly biodegradable, chemically stable, easily functionalized and have high surface-to-volume ratio [54–57]. Various electrochemical studies utilized carbon nanomaterials, e.g. carbon nanotubes (CNs), graphene and carbon nanoparticles (C-NPs) for detecting SER.

1.5 Modification with metal or metal oxide nanomaterials

This kind of nanomaterials has fascinating catalytic, optical and electrical properties which would enhance the redox processes. Moreover, some metals, like Ni, Zr, Ti, Zn, Fe and Cu, and their oxides have high electrical conductivity, large surface area, high chemical stability, and wider electrochemical working potential [58, 59]. Zinc ferrite is one of the metal oxides NPs used for modifying working electrodes, due to large surface area, less toxicity of Zn^{2+}, fast sensing and high reactivity of iron oxide NPs [57]. Screen printed electrode (SPE) was modified by $ZnFe_2O_4$ for the electro-catalytic oxidation of SER. The modification improved the electron transport ability of SPE. This affect was observed by running DPV measurement in 0.1 M phosphate buffer solution (PBS) at neutral pH, the SER was oxidized at potential lower by 350 mV compared to unmodified SPE [60].

Due to low toxicity of lanthanum ions and high catalytic property of its oxides, a nano-composite of La_2O_3/Co_3O_4 was employed for modifying SPE, then DPV used for detecting SER in tablets and urine samples. The improved electrode surface facilitated the oxidation process towards lower positive potentials [61].

A standard addition method was adopted during the detection of SER in tablets by using a modified SPE with feather-like composite of La^{3+} and ZnO nano-flowers. Upon using CV and DPV, the composites showed good catalytic activity towards SER and lowered the SER's oxidation potential by about 280 mV. The modified electrode had good linearity in µM concentration range [62]. The synergetic effect of these La^{3+} and the nano-flowers provides enhanced sensitivity for the SER oxidation whereas the modified SPE by $ZnFe_2O_4$ has higher electrocatalytic and sensitivity.

Graphene SPE modified with ZnO nanoflowers showed excellence electrochemical catalytic activity of SER when using DPV for pharmaceuticals and urine samples. SER was analyzed alongside imipramine and the electrode exhibited high linearity. Also, the modification improved the peak separation between the two drugs to be 200 mV [63]. Very recently, GCE was treated by carboxylated GO nanosheets and $AgVO_3$ nanowires composite that were prepared by hydrothermal method. The surface of the modified electrode had a 3D matrix with an increase in the porosity, which showed excellent oxidation of SER in pharmaceutical tablets [64].

1.6 Modification with carbon–metal or metal oxide nanocomposite

The composites consist of different nanomaterials, each of which have individual optical, physical, chemical and electrical properties, and the final composite could be a combination of their advantages. This type of modifiers has carbon as the backbone and facilitates the electricity conduction between the loaded material and the bare electrode. Electrons are exchanged between the analytes and the metal/metal oxide material, the latter are semiconductors not having very high conductivity like metals, however; they have high electrocatalytic capability [54].

The mobile composition of matter (MCM) has materials with mesopores. There are two general adsorbents with mesopores named as MCM-41 and MCM-48, the latter is of cubic structure and widely used for the fabrication of sensors when compared to MCM-41. This is due to its higher surface area, higher pore capacity, being thermally stable and has better catalytic property. GCE was modified by a composite that had iron oxide NPs, MCM-48 and MWCNTs. The modified electrode had high selectivity towards SER even in the presence of serotonin. This ability was due to higher surface area of the composite and the charged electrode [65].

Ionic liquids (ILs) consist of anions and cations of organic and inorganic nature were used as solvents and for modifying electrodes, due to them being chemically stable, have low vapor pressure, thermally stable and having good ionic conductivity. Ehzari et al. modified GCE by coating its surface with MWCNTs and IL. This was followed by electrodepositing NiO NPs onto it. SER was analyzed in the presence of clozapine. The electrochemical process produced weak peaks for bare GCE which overcome by the modification process. This led to obvious anodic and cathodic peaks regarding the two drugs [66].

The surfactants like sodium dodecyl sulfate (SDS) was used for improving the electron transfer and the accumulation of the targeted analytes at the electrode surface. Stemming from this, Atty et al. combined the advantages of Cs, MWCNTs and SDS onto modifying CPE. The modified electrode produced higher anodic peak current when detecting SER and paracetamol over bare one [67].

1.7 Modification with carbon-polymer composite

The composites consist of polymers whose performance was enhanced by incorporating carbon. SER was detected in human serum by modified Pt electrode. The electrode was treated with molecularly imprinted polymer (MIP) and graphene NPs. SER HCl was the template upon which the MIP was made with a mixture of ethylene glycol dimethyl acrylate and methacrylic acid. The modified sensor had improved absorption towards SER. The utilization of graphene introduced higher surface area and enhanced conductivity to MIP with made it perfect in selectivity and electrical sensing [68]. Similar sensor was constructed by Khosrokhavar et al., in which SPCE was loaded with a layer of MIP and graphene suspension. MIP provided good selectivity towards SER whereas graphene introduced larger surface area and electrical conductivity to the electrode. Two inks named silver and carbon inks were used. The former ink had 97% silver and 3% PVC, whereas the latter ink had 80% graphite, 8% PVC and 12% dibutyl phthalate, each of which inks were made in 1:1 v/v with acetone-cyclohexanone solution. This modification made SPCE of high adsorption ability and sensitivity of 177.25 µmol/L [51].

Khater et al. employed modified CPE, polymeric membrane and SER tetraphenylborate for detecting SER HCl. The electrode responded at wide linear concentration range 0.01–10 µmol/mL with about 2.8×10^{-3} µmol/mL as LOD. It was seen that treating PVC with different plasticizer and additives influence the electrode surface and its ability to oxidize SER [69]. Zamani and Yamini determine SER and other tricyclic antidepressants in different biological samples by using solid-phase microextraction (SPME) method. In their work, SPME fibers were coated by PEDOT-GO upon electrodeposition process. PEDOT offers better electrical conductivity whereas the fibers works as acceptor-electrode [70].

There are different advantages when using plasticized PVC membrane, such as extending the LOD of the used electrochemical method, prevent or mitigate the electrode fouling and minimize the effect of possible interferences [71]. Very recently, Saber et al. reported using potentiometric ion-selective electrode based on PVC membrane for detecting SER in pharmaceutical preparations and human urine. The membrane was prepared by dissolving PVC powder, ion complex and o-nitrophenyl octyl ether in tetrahydrofuran. The sensor had linearity range of 1×10^{-8}–0.01 mol/L with LOD of 7×10^{-8} mol/L when detecting SER [72].

1.8 Modification with carbon–metal-polymer composite

The couple of metal to polymers has gained attention in biomedical research. This is due to their electrocatalytic ability for the oxidation of different molecules, such as carbohydrates, amino acids and amines. Some amino acids like L-3,4-dihydroxyphenylalanine was found to act as ligands during the deposition of metal-polymer onto electrodes' surfaces. Species of nickel oxyhydride would behave as mediator during the electro-oxidation process between the electrode surface and the analytes [73]. Shoja et al. bounded Au NPs onto MWCNTs, then electropolymerized Ni^{2+}-levodopa in alkaline solution onto the electrode. Stemming from the synergistic effect of the NPs and CNTs provides bed for

immobilizing Ni^{2+}-levodopa. The Ni^{2+} and Ni^{3+} active sites enhanced the electrocatalytic oxidation of SER [73]. Furthermore, a pencil graphite electrode (PGE) was modified by exfoliation in a solution containing melamine and ammonium sulfate, by using potentiostatic method. Then, a chronoamperometry technique was used for depositing Cu-based metal organic framework (Cu-MOF) onto the modified PGE. The whole process improved the electro-catalytic of the PGE towards SER oxidation. The study showed that modified PGE had linearity response with 0.456 μA/μM cm^2 sensitivity [74].

SER was detected in its cationic form in drinking and river water samples by modified pencil lead electrode. The electrode was treated with electrodeposition of a conductive polymer known as 3,4-ethylenedioxythiophene (PEDOT-C_{14}). This was followed by submerging in a plasticized poly(vinyl chloride) (PVC) membrane. SER was simultaneously detected alongside other serotonin reuptake inhibitors by using ion transfer stripping voltammetry (ITSV). The electron transportation between the analyte and the membrane was facilitated by the used polymer, this resulted in response of ionic current with no need for ion electrolysis. The electrode showed a linearity response in 100–1000 nm and 35 nm as LOD [75].

Overall, modified electrodes overcome bare electrodes due to improved surface properties, after the modifications, like larger surface areas, many surface's functional groups, improved SER adsorption, enhanced catalytic oxidation and enhanced selectivity. However, the modification may lead to short-term stability and contamination of the original electrode surface. Potentiometric sensors have become a common analytical tool in a variety of disciplines, including clinical and environmental investigation, physiology and process control. Imprinted polymers have piqued the curiosity of scientists working on electrochemical sensor development during the last decades. The major potential benefits of utilizing molecularly imprinted polymers (MIPs) instead of natural receptors and enzymes stems from their improved stability, cheap cost, excellent selectivity, and ease of production.

1.9 Spectrophotometric methods

As for spectrophotometric methods, the interaction of the analytes with the light facilitates their detection. Spectrophotometers consist of light sources which are lamps emitting radiation in the ultraviolet (UV), visible (Vis) and infrared (IR) ranges. SER was observed to have maximum absorbance (λ_{max}) in the UV region. SER had λ_{max} as 273 nm in aqueous medium [76]. The molar absorptivity was calculated to be 5.5×10^{-4} l $mole^{-1}$ cm^{-1} [77]. The absorbance can be extended to the visible region upon reacting with colorants like chloranilic acid, that form purple color having λ_{max} around 527.5 nm [78].

The establishment of a calibration curve is crucial for instrumental methods. As for spectrophotometry, solutions with different concentrations of the analyte can be prepared, then their absorbance would be measured following Beer's law. Under optimal conditions of the used procedure and the resulted best follow of the Beer's law in terms of the correlation coefficient between the solutions' concentrations and their absorbance values, the straight-line equation; $y = ax \pm b$ can be utilized for the determination of unknown SER concentration in different samples. In that equation, y is the absorbance value, x denoted the analyte concentration, a is the slope whereas b is the y-intercept, can be used to determine the unknown concentration in the studied sample.

It the use of UV–Vis spectrophotometry alone, the analysis of tablets requires weighing, crushing by using a pestle and a mortar. They should be homogenously powdered. Then, a required amount of the powder is weighed and dissolved in an appropriate solvent, filtered by using Whatman paper, an aliquot of the filtrate would be subjected to extraction method to isolate the analyte. The final solution after the extraction may contain small volume of the organic extraction solvent, hence heating the solution may be required to remove the extraction solvent.

SER and fluoxetine (FX) were determined together in pharmaceutical tablets and biological liquids by Hasanjani et al. Although the spectral overlap between the two drugs, when conducting conventional absorbance measurement, required initial isolation of each one prior to the analysis, the use of multivariate techniques beside adaptive neuro-fuzzy inference system (ANFIS) overcome this issue. SER absorbance was measured in 200–300 nm range at 10–120 μg/mL concentration range [79]. Extended work by the same group determined SER and FX by using standard addition method and net analyte signal concept (NASC). The NASC do not need calibration curves neither prediction steps. This approach had LOD of 0.20 μg/mL for SER [80]. Similar study was reported for simultaneous determination of SER and FX by UV–VIS spectrophotometry. The absorbance of the two compounds was measured in the wavelengths of 200–300 nm. The spectrophotometer was linked to Artificial Neural Networks (ANN) for reducing possible overlaps between the two drugs [81].

The interaction between SER and some dyes like eosin Y was studied in aqueous medium at neutral pH by spectrophotometric methods. The optical and fluorescent measurements demonstrated that the interaction is exothermic, which was proved by positive entropy and negative enthalpy changes [82].

Ratnia et al. estimated SER HCl in pharmaceuticals by spectrophotometry. Stock solutions of SER HCl were prepared with 1:1 v/v of aqueous methanol and the UV

measurement was performed at 273 nm [77]. Tablets containing SER were crushed and powdered, a known amount is then weighed, extracted with CH_3OH and filtered before conducting spectrophotometer measurements at 273 nm [83]. Lotfi et al. reported developed spectrofluorimetric method for detecting SER in pharmaceuticals and human-based samples. The method required enhancing the fluorescent signal of SER by using 1,10-phenanthroline-terbium probe and Ag NPs. The method had linearity over 0.001–3 mg/L, LOD and LOQ of 2.9×10^{-4} mg/L and 9.8×10^{-4} mg/L, respectively [84]. In 2020, Patel and Mashru developed three statistical methods and linked to UV spectrophotometric methods for simultaneous determination of SER and Brexpiprazole in pharmaceuticals. The methods were vireo's method, absorption ratio method whereas the third method depended on zero crossing second derivative spectrometry. The UV measurement showed linearity range for SER in 20–140 µg/mL [85].

Laghari et al. detected SER alongside other antidepressant by colorimetry. The probe had Ag NPs stabilized by citrate. The binding of the antidepressant would induce aggregation and change color. The response was linear over 2–10 µg/mL with 0.39 µg/mL as LOD for SER [86]. The same team further constructed an optical sensor having citrate-Au NPs and applied it for detecting SER and FX in micellar and aqueous solutions, then applied for real detection in human urine and blood serum as well as in tablets. SER and FX produced H-bonding that force the Au NPs to aggregate and causing the color to change. Under optimium conditions, the sensor had LOD for SER and FX as 0.511–0.543 nM and 0.041–0.047 nM in aqueous and micellar mediums, respectively [87].

Sayqal and Saber determined SER in pharmaceuticals by simple and developed spectrophotometric methods. The methods relay on forming ion-pair complexes between SER and different reagents. SER was interacted, in buffer solution of 2.0–8.0 pH, with methyl orange (MO), methyl green (MG), methyl blue (MB), phenol red (PR) and bromophenol red (BR) which produced colored complexes having λ_{max} at 553, 647, 668, 717 and 747 nm. The absorbance regarding the complexes was linear within 2–16 µg/mL [88]. Some spectrophotometric methods presented in the literature regarding the determination of SER is shown in Table 3.

1.10 Chromatographic methods

The chromatographic methods relay on the distribution of the analytes between a stationary phase and a mobile phase. HPLC coupled with UV or MS would be seen as preferable for the isolation and quantification of SER and DSER. The stationary phases are mainly C18 column whereas the mobile phases are mainly composed of low acidity buffers and organic solvents. Moreover, internal standards are added to eliminate possible volume errors and to improve the validity of these methods.

Samples must be volatile and thermally stable if want to be subjected to GC analysis. Derivatization is required when samples are not volatile. This process would add to the analysis cost which is one of the limitations of GC usage. A group of antidepressants, among which is SER, were determined and quantifies by using GC–MS. They were extracted from blood samples by hollow-fiber liquid-phase microextraction. HF-LPME was proven to overcome LLE and SPME disadvantages in terms of high solvent consumption,

Table 3 Some of the sertraline spectrophotometric methods

Analyte	Sample	Detection method	Wavelength max (nm)	Linearity/LOD/LOQ (µg/mL)	References
SER and FX	pharmaceutical tablets and biological liquids	UV spectrophotometry	NR	10 – 120 for SER	[79]
SER and FX	Plasma	UV spectrophotometry	355	LOD: 0.20 for SER	[80]
SER HCl	Pharmaceuticals	UV spectrophotometry	273		[77]
SER	Pharmaceuticals	Spectrofluorimetric		0.001 – 3, LOD: 2.9×10^{-4}, LOQ: 9.8×10^{-4}	[84]
SER and Brexpiprazole	Pharmaceuticals	UV spectrophotometry		20 – 140 for SER	[85]
SER and other antidepressants		Colorimetry		2 – 10, LOD: 0.39 for SER	[86]
SER and FX	Human urine and blood serum	UV spectrophotometry		LOD:0.511 – 0.543 for SER, LOD: 0.041 – 0.047 for FX	[87]
SER	Pharmaceuticals	UV spectrophotometry	553, 647, 668, 717 and 747 nm	2 – 16	[88]

expensiveness and short lifetime. Santos et al. used dodecane as extraction solvent and the extraction pH was maintained by using formic acid and sodium hydroxide solutions. During the analysis, the method had linear response over 0.02–1.2 µg/mL and LOQ was less than 0.02 µg/mL [89].

A group of SRIs including SER were determined by Papoutsis et al. in blood samples by using GC–MS. The analytes were extracted by SPE onto 30 m length HP-5MS capillary column with 0.25 mm diameter. He was used as a carrier gas. The sample was prepared by centrifuging blood with phosphate buffer. Methanol and phosphate buffer were used for conditioning Bond Elut LRC Certify cartridges. Blood sample was placed in the cartridge and the sorbent was cleaned by washing with water, CH_3COOH and methanol. This was followed by drying the SPE under vacuum. A mixture of ammonium hydroxide, ethyl acetate and isopropanol with v/v/v of 3: 85: 12 was used for eluting the analytes. Then, the eluted solution was dries, reconstituted, derivatized with heptafluorobutyric anhydride before injecting in the GC system. The method had response in linear range over 5–1000 µg/L with LOQ down to 0.30×10^{-3} µg/mL [90].

SER was derivatized by using N-Methyl-N-trimethylsilyltrifluoroacetamide (MSTFA) and 1% of 2,2,2-Trifluoro-N-methyl-N-(trimethylsilyl)-acetamide, Chlorotrimethylsilane (TMCS) to enhance its volatility [91].

The release of the drugs like SER to the environment would cause unwanted consequences on the ecological system, for example SER was found to accumulate in mussels at Catalan coast. The control of their concentrations is important. To do so, SER was quantified in water and wastewater samples [92]. The presence of SER and other drugs in wastewater would make its purification costly, also part of the wastewater may find its route to groundwater, to plants and animals and to human. SER was also detected in some type of fish with concentrations span of 1×10^{-3}–0.1 µg/mL. It altered circadian rhythms and diurnal activity patterns [93]. HPLC triple-quadrupole tandem MS was used by Borova et al. to determine SER and over 60 drugs in wastewater samples. The instrument response was linear in 0.1×10^{-3}–0.1 µg/mL [94].

A group of researchers analyzed hair samples for the detection of 24 antidepressants and validated the used HPLC-tandem MS. The drugs were extracted by acetonitrile, methanol and ammonium formate solutions prior to SPE. The separation was done by using BEH C18 column while acetonitrile and ammonium acetate were used the mobile phase. SER concentration in the hair sample spans $0.05\times10^{-3}-0.1\times10^{-3}$ µg/mg [95]. Ultra-high performance liquid chromatography (UHPLC) with tandem MS was developed and validated for the analysis of over hundred analytes, having different acidity and basicity nature, in 2-cm hair segments of postmortem. Hair samples were washed then incubated for ¾ day in a mixture of acetonitrile, methanol and ammonium formate at pH 5.3 for drugs' extraction. The analysis showed that LOQ for acidic and neutral analytes was 0.4–500 pg/mg, whereas it was $0.05\times10^{-6}-0.5\times10^{-6}$ µg/mg for basic analytes [96]. Papaseit et al. analyzed hair segments of atomoxetine-treated people by HPLC-tandem MS and found SER presented in one case [97].

Marchel et al. reported a case demonstrating the analysis of SER in children hair by immunoassay and HPLC–MS. Children were intoxicated with consuming narcoleptic drugs. Their blood and urine samples were found to contain SER, quetiapine and their metabolites like DSER. The hair was cut to 2 cm strands, washed by dichloromethane and methanol, injected with internal standards and incubated with M3 buffer reagent at 100 °C for 60 min. After cooling the samples, 0.1 mL of the extract was mixed with 0.9 mL water, then 10 µL of the diluted solution was analyzed by HPLC-tandem MS. The separation was done in RP with two mobile phases; 0.1% HCOOH in water and 0.1% HCOOH in acetonitrile [98]. The hair of patients who had previous dosage of SER and citalopram was cut to 1 cm segments and the shaft was analyzed by HPLC-tandem MS. The obtained concentrations were in disagreement with the dosage history [99]. The hair samples of about 234 people who had headache and previous drug treatment were analyzed. Samples were collected from people who were subjected to drugs treatment 30 days earlier. About 3-com hair segments were analyzed for around 50 drugs were detected by HPLC-tandem MS [100].

In an attempt to reduce analysis time, a group of researchers utilized ultra-fast high-throughput direct injection HPLC-tandem MS for determining SER with another 134 compounds. The method required only five minutes run time. They used about 10 µL of filtered sample/ injection on biphenyl column. The LOD was in ng/L [101]. Furthermore, two-dimensional HPLC-tandem MS with stationary phases of RP C18, as for one dimension, and C12 for two dimensions. Pugajeva team were able to quantify multiple drugs including SER with 0.1–50 µg/mL as LOQ [32].

The use of HPLC–MS is preferable over GC–MS as the former allows the determination of analytes with wider spectrum of polarities, samples of low volatility or poor thermal stability. Some chromatographic methods presented in the literature regarding the determination of SER is shown in Table 4.

Diode array detector is another detector coupled with HPLC for detecting SER. Wróblewski et al. used C18 column in SPE for isolating SER and other psychotropic drugs from human serum. Then used polar-RP-HPLC–DAD for the quantification. An acidic mobile phase consisted of CH_3OH, H_2O, diethylamine and acetate buffer was used for eluting the drugs [102]. HPLC–DAD confirmed the presence

Table 4 Some of the sertraline chromatographic methods

Method	Analytes	Sample	Extraction method	Linear range (µg/mL)	LOD (µg/mL)	LOQ (µg/mL)	References
HPLC-tandem MS	SER	Plasma	SPE	$5\times10^{-3}-0.325$	1.65×10^{-3}	5×10^{-3}	[105]
HPLC–ESI–MS	SER	Human milk	SPE	$5\times10^{-3}-0.5$	6.6×10^{-4}	2×10^{-3}	[106]
UHPLC-tandem MS	SER	Whole blood	LLE	$7.6\times10^{-3}-0.92$	2.5×10^{-3}	7.6×10^{-3}	[37]
HPLC-tandem MS	SER	Plasma	SPME	5×10^{-3}–0.325	1.65×10^{-3}	5×10^{-5}	[31]
HPLC-tandem MS	SER	Plasma	Precipitation with acetonitrile	$2.5\times10^{-3}-0.405$	8.25×10^{-4}	2.5×10^{-3}	[39]
HPLC–DAD	SER	Human serum	SPE	0.5 – 6			[102]
HPLC–DAD	SER	Aqueous samples	FPSE	$1.9\times10^{-3}-10.7\times10^{-3}$	1.12×10^{-3}	3.36×10^{-3}	[104]

of traces of SER and DSER in blood and urine samples of intoxicated person [103]. Jiménez-Holgado et al. determined SER and other antidepressant drugs in aqueous samples, collected from the environment, by HPLC–DAD. Three different fabric media and two sol–gel sorbents were studies for the drugs extraction by fabric phase sorptive extraction (FPSE). The coating of PEG 300 sol–gel sorbent onto microfilter glass filter was the best performing FPSE device. During the analysis by HPLC–DAD, the 245 nm was selected for detecting SER by UV detector [104].

1.11 Thin layer chromatography (TLC)

Different samples can be analyzed, by using the same plate, in parallel simultaneously. This would benefit in reducing the analysis time and cost. The combination of this method with MS, by using TLC-MS interface, or UV spectrophotometry can make the identification easier through UV densitometry.

SER was quantified by HPTLC in human serum by Mennickent et al. SER was extracted by LLE using a mixture of diethyl ether and chloroform (3:1, v/v) as solvents. Carbamazepine was the internal standard. The separation was performed onto silica gel plate as stationary phase. The mobile phase consisted of toluene, ethyl acetate, methanol and glacial acetic acid. The method showed a linearity in the concentration range of 1–70 ng/band. 0.12 ng/band and 0.25 ng/band were reported as LOD and LOQ, respectively [107].

SER was detected in tablets and house formulations by HPTLC with densitometry. The stationary phase was silica gel coated on Al plate. The mobile phase consisted of toluene, ethyl acetate and ammonia in the volume ratios of (1:5:0.1). The calibration plots were linear in 25–2000 ng/spot. SER was subjected to different processes like hydrolysis in different pH mediums, degradation and heat treatment [108]. Also, the isolated SER with other antidepressants were reacted with free Cl_2 to yield corresponding chloramines. They were then interacted with o-tolidine for producing blue spots. SER has LOD of 0.1 µg [109]. A mixture of 2-propanol and dichloromethane with (70:30, v/v) was used to isolate SER and other antidepressants. The stationary phase was silica plate on which SER had Rf of 0.68. Different metal cations were used and their effect on the separation degree of the antidepressant was evaluated, this was done as impregnated plates. The drugs underwent SPE by using 0.05 M phosphate buffer at pH 9. Methanol spiked with 0.1% acetic acid was the eluting solvent [110].

A group of scientists made use of pre-made silica gel plate for studying the effect of using different mobile phases for the separation of antidepressant. The drugs were dissolved in alcohol to make 1% concentration, then 0.05 mL was placed on the plate. Plates were heated at 55 °C to enhance the separation. The colorless spots were treated by UV radiation and detection was at 254 nm [111].

Parys et al. conducted a systematic study on the separation of SER and fluoxetine by TLC-densitometry. Four different chromatographic plates and three mobile phases were utilized in two TLC techniques, known as adsorption (NP-TLC) and partition (RP-TLC). It was observed that best LOD and LOQ for SER in NP-TLC were obtained by using a silica gel 60, as the stationary phase, with a mobile phase having (10:9:1, v/v) of acetone, toluene and ammonia, respectively. SER had LOD and LOQ of 0.079 µg/spot and 0.239 µg/spot, respectively. As for RP-TLC, SER had LOD and LOQ of 0.037 µg/spot and 0.112 µg/spot, respectively, which was determined from silanized silica gel 60 F254 plate in combination of methanol and water (9:1, v/v) [112]. Another study to find better mobile phase for the separation between SER and fluoxetine, in pharmaceutical formulations, was conducted. It found a mixture of ammonia, acetone and chloroform facilitated the separation based on RF values and the spectro-densitograms. SER was highly stable than fluoxetine. The drugs were found linear response by the method in 0.6–3 µg/spot for SER and 0.5–5 µg/spot for fluoxetine. SER had LOD and LOQ of 0.054 µg/spot and 0.162 µg/spot, respectively [113]. Lately, SER HCl was simultaneously quantified with brexpiprazole, in tablets and synthetic mixture, by using Al plate coated with silica gel. A mixture of trimethylamine, hexane, toluene and propanol with (v/v)

of 0.1:2:1:7 was used as a mobile phase. The absorbance of the isolated drugs was then measured at 254 nm [114].

2 Conclusion and future viewpoints

The determination of SER and its main metabolite DSER permits primarily control of its levels in the different sources, among which is the human body, that is highly significant when the body does not respond to the drug therapy. Quantifying SER and DSER permits the dosage optimization and evaluate its possible toxicology. This literature review presents several extraction methods and analysis methods regarding SER presence in different environments. Both SPE and LLE found to be widely used for SER isolation. A suitable modification of the sorbents would enhance and facilitates simultaneous segregation of many analytes that have comparable structure and action. This permits methods' evolution, considerably minimizing the utilization of toxic organic solvents and conserving the environment.

The current work emphasized the SER determination from 2013 to 2023. Surveying the literature revealed that different analytical techniques were used for SER determination, such as liquid chromatography, gas chromatography, thin layer chromatography, UV–visible spectrophotometry and electroanalytical methods. Among these methods, liquid chromatography coupled with mass spectrometry provides the best sensitivity and reliability of the measurements; however, it would be considered the most expensive method.

When comparing the analytical methods, chromatographic methods are preferable over the others as they can determine trace analyte concentrations and best fit for wide range of samples. However, chromatographic methods demand lengthy sample preparation, consume high volumes of solvents that is not eco-friendly, not time efficient, need specialized persons for its operation and maintenance. Besides, they are not easily transformed to portable devices which may hinder its widespread in on-site analysis. On the other hand, sensors would be suitable for SER analysis due to their simple fabrication, easily modified, comparatively the cheapest, consume low volumes of solvents and can be easily made portable. Sensors are comparatively new with respect to the other analytical methods, so there still a room for their advancement by modifying the features of the components of the working electrodes. This modification can be through the use of nanomaterials with improved optical and electrical aspects, the use of 2D inorganic compounds (like Mxenes), 3D-printed sensors and metal organic frameworks for modifying the present electrodes needs consideration. The use of lab-on-chip technology may reduce the sensor fabrication cost. Also, the use of eco-friendly products, such as cotton and paper for isolating SER during preconcentration process, would lower the analysis cost. As for spectrophotometric methods, they require samples to be colored and usually detect analytes at higher concentrations and have poor absorbance detection for transparent samples.

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Declarations

Conflict of interest The authors declare no conflict of interest.

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