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ORIGINAL ARTICLE

Selective Dispersive Solid Phase Extraction of Sertraline Using Surface Molecularly Imprinted Polymer Grafted on SiO_2/Graphene Oxide

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KEYWORDS

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SiO_2/graphene oxide;
Surface molecular imprinted polymer

ABSTRACT: A surface molecularly imprinted dispersive solid phase extraction coupled with liquid chromatography–ultraviolet detection is proposed as a selective and fast clean-up technique for the determination of sertraline in biological sample. Surface sertraline-molecular imprinted polymer was grafted and synthesized on the SiO_2/graphene oxide surface. Firstly SiO_2 was coated on synthesized graphene oxide sheet using sol-gel technique. Prior to polymerization, the vinyl group was incorporated on to the surface of SiO_2/graphene oxide to direct selective polymerization on the surface. Methacrylic acid, ethylene glycol dimethacrylate and ethanol were used as monomer, cross-linker and progen, respectively. Non-imprinted polymer was also prepared for comparing purposes. The properties of the molecular imprinted polymer were characterized using field emission-scanning electron microscopy and Fourier transform infrared spectroscopy methods. The surface molecular imprinted polymer was utilized as an adsorbent of dispersive solid phase extraction for separation and preconcentration of sertraline. The effects of the different parameters influencing the extraction efficiency, such as sample pH were investigated and optimized. The specificity of the molecular imprinted polymer over the non-imprinted polymer was examined in absence and presence of competitive drugs. Sertraline calibration curve showed linearity in the ranges 1–500 µg L^{-1}. The limits of detection and quantification under optimized conditions were obtained 0.2 and 0.5 µg L^{-1}. The within-day and between-day relative standard deviations (n=3) were 4.3 and 7.1%, respectively. Furthermore, the relative recoveries for spiked biological samples were above 92%.

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INTRODUCTION

"Sertraline is an antidepressant that belongs to a group of drugs called selective serotonin reuptake inhibitors (Supporting Information). Sertraline affects chemicals in the brain that may become unbalanced and cause depression, panic, anxiety, or obsessive-compulsive symptoms. Sertraline is used to treat depression, obsessive-compulsive disorder, panic disorder, anxiety disorders, post-traumatic stress disorder, and premenstrual dysphoric disorder" [1].

Generally the analysis of drugs is an essential issue in treatment and control of patients under treatment. Hence, development of a fast, sensitive and low-cost method is of vital importance. Various analytical methods have been developed for the determination of sertraline including high performance liquid chromatography (HPLC) [2], gas chromatography (GC) [3, 4], and capillary electrophoresis (CE) [5]. However, sample preparation step is usually crucial for the purpose of sertraline detection at low-levels. Liquid liquid extraction [6] and solid phase extraction (SPE) has been frequently employed to isolate and preconcentrate sertraline from complex matrices [7-9].

Nevertheless, LLE requires large volumes of organic solvent and involves multiple time-consuming steps. Although SPE requires a shorter preparation time and less solvent than does LLE, the presence of co-extracted compounds is more serious. It makes very difficult further quantification of the target analytes especially in complex matrices. One way to overcome this disadvantage is by using molecular imprinted strategy [10-12]. Molecular imprinting is a powerful technique to prepare material with highly selective binding cavities which are recognition sites for specific molecule or structurally related compounds [13]. In this process selected functional monomers are polymerized around a target analyte (template) in presence of a crosslinker agent. After elimination of imprinting molecule, three-dimensional structures are left. The formed cavities are complementary in shape, size, and position of functional groups to the analyte molecules. Chemical and mechanical stability, relative ease and low cost of synthesis make these polymers attractive for sample preparation field [14-16]. However, heterogeneous distribution of the binding sites, poor site accessibility, and slow mass transfer rate are drawbacks that limited the practical application of molecular imprinted polymers (MIPs) [17-21].

The exhausting removal of template from bulk-polymerized MIPs is another challenging issue. To overcome these disadvantages, surface molecular imprinting strategy is used [22-24]. Therefore grafting MIPs on large surface area materials, for instance graphene could be a helpful strategy. Graphene has gained much attention in material science owing to its unique properties such as high theoretical surface area [25]. This feature is also mandatory in sample preparation techniques [26-29]. Due to the lack of functional group on graphene surface, it is not effective for further coating. However, hydroxyl and epoxide functional groups on the basal and carboxyl and carbonyl group on the edges could make graphene oxide (GO) a more promising material for surface coating [30]. Since GO could be easily lost during extraction, the improvement of its stability is crucial [31]. Coating an inorganic layer on a nanomaterial surface efficiently improves the nanomateial properties including chemical and colloidal stability and biocompatibility [32]. Among inorganic coatings, SiO_2 can significantly enhance the stability and hydrophilicity of graphene oxide [31, 33].

In the present study, sertraline -molecular imprinted polymer was grafted on SiO_2/GO. High surface of GO was used to benefit improved site accessibility of MIP and SiO_2 was employed for better dispersion of synthesized sorbent in water. The dispersive solid phase extraction performance of sertraline and selectivity of sur-

face MIP sorbent has been assessed from biological samples.

MATERIALS AND METHODS

Reagents and Materials

Natural flake graphite, methacrylic acid (MAA), azobisisobutyronitrile (AIBN), sulfuric acid, nitric acid, hydrochloric acid, phosphoric acid, potassium chlorate, trichloroacetic acid (TCA), sodium chloride and sodium hydroxide were all purchased from Merck (Darmstadt, Germany).

HPLC-grade acetonitrile, acetone, methanol, ethanol, and toluene were also obtained from Merck. HPLC-grade water was purchased from Caledon (Ontario, Canada).

γ-Methacryloxypropyl trimethoxysilane (γ-MAPS), ethylene glycol dimethacrylate (EGDMA) was obtained from Sigma-Aldrich (St. Louis, USA). Tetraethyl orthosilicate was purchased from Daejung (Seoul, Korea). Serteraline hydrochloride and ticlopidine hydrochloride were kindly prepared from Tofigh Daru (Tehran, Iran). The urine from a healthy person was collected in disposable polyethylene containers and kept at 4ºC before analysis. A frozen human plasma sample was obtained from the Iranian Blood Transfusion Organization (Tehran, Iran), thawed and allowed to reach room temperature.

Apparatus

An Agilent 1200 series HPLC system including a G1311A quaternary pump and a UV detector was used for the separation and determination of the analyte. Separation was performed on a Zorbax Eclipse XDB-C18 (150 mm, 4.6 mm ID, and 5 µm) column. The solvents used as the mobile phase were acetonitrile and 0.02 M phosphate buffer (pH=2.5). The chromatographic data were collected and recorded using ChemStation software. Direct introduction of the sample was carried out using a Rheodyne manual injector (Rohnert Park, CA, USA) with a 20 mL loop. The column temperature was kept constant at 30 ºC using a thermostatted column compartment. Chromatographic separations were carried out using an isocratic elution with a mixture of acetonitrile and phosphate buffer (40:60). The flow rate was 1 mL min^{-1} and detection was performed at 210 nm.

Sertraline–MIP-SiO_2/GO synthesis

Graphene oxide was prepared according to Staudenmaier's method [34], as mentioned in our previous work [29]. 1 g graphite was carefully added to a mixture containing 18 mL of sulfuric acid and 9 mL of nitric acid, placed in an ice bath. After proper dispersion of graphite powder, 11 g of potassium chlorate was added slowly to the solution. The mixture was stirred at room temperature for 120 h. The resulting product was washed with deionized water until neutral pH was obtained and it was then dried at 60 ºC in a vacuum oven. An amount of 100 mg graphite oxide was added to 100 mL of deionized water. The mixture was placed under ultrasonic condition to unfold graphite oxide sheet and prepare graphene oxide.

Fifty mL of GO aqueous suspension (0.6 mg mL^{-1}) was added into 400 mL of ethanol. After addition of 20 mL of NH3, the mixture was stirred at ambient temperature for 20 min. Following, 1.0 mL of TEOS was added into the mixture. The mixture was homogenized for 5 h at 15000 rpm. After further sonication for 3 h, the suspension was kept overnight at room temperature. Finally, the resulting precipitate was centrifuged and then it washed three times using ethanol and water. The product was dried in a vacuum oven at 60ºC for 24h to obtain SiO_2/GO sheets [35].

In order to obtain γ-MAPS functionalized SiO_2/GO sheets (MAPS- SiO_2/GO), 0.1g of SiO_2/GO and 10 mL γ-MAPS were added into 50 mL of anhydrous toluene. The mixture was refluxed for 24 h under N_2 atmosphere. Subsequently, the product was separated by centrifuga-

tion and it was further washed with toluene and ethanol. The final product was dried overnight at 60 ºC in a vacuum oven. The incorporated vinyl group conducts selective polymerizing onto the SiO_2/GO surface.

For the preparation of sertraline–MIP, 0.08 g of MAPS-SiO_2/GO was added into 20 mL of ethanol. 0.25 mmol of sertraline, 1.00 mmol of the functional monomer MAA, 5.00 mmol of cross-linker EGDMA, and 20 mg of initiator AIBN was mixed with the suspension. The solution was purged with nitrogen for 15 min. Subsequently the temperature was raised to 60ºC and the reaction was allowed to proceed for 24 h while stirring. The resultant polymer was washed several times with methanol and ethanol to remove the template completely. The remaining polymer was dried under vacuum at 50ºC for 24h [36]

The corresponding non-imprinted polymer (NIP) was prepared by the same procedure but in the absence of the template.

Dispersive solid phase extraction procedure

A volume of 10.0 mL of sample (pH=12) containing 500 µg L^{-1}sertraline and 20% (w v^{-1}) NaCl was transferred into a test tube. Then, 30 mg of MIP sorbent was added and the mixture was stirred for 5 min at room temperature. Subsequently the sorbent was isolated from the solution by centrifugation. After decanting the solution, 1 mL of ethanol was used to carry out the desorption process for 2 min while stirring. The solution was centrifuged and the eluent was transferred into a vial. This solution was dried using a gentle flow of nitrogen gas. The residue was dissolved in 100 µL of methanol and then injected into the HPLC system.

For the purpose of comparison, same extraction procedure was used for DSPE using non-Imprinted polymer.

To do extraction from biological samples, urine sample was also diluted two times and then the extraction process was performed. An amount of 3 mL human plasma sample was mixed with 125 µL hydrochloric acid and 400 µL TCA (167 mg mL^{-1}), respectively. Subsequently, the sample was centrifuged at 10000 rpm for 5 min to remove precipitated proteins. The supernatant was diluted four times and then extraction procedure was conducted.

RESULTS AND DISCUSSION

Characterization of MIP-SiO_2/GO

The X-ray diffraction pattern for GO displayed a peak at 2θ= 12.09 º (Supporting Information) which was in accordance with literatures [37].

The GO, SiO_2/GO, γ-MAPS-SiO_2/GO and MIPs-SiO_2/GO were characterized by FTIR spectroscopy as shown in Figure 1. The FTIR spectrum for GO showed bands at 1729, 1254 and 1057 cm^{-1}. These bans are attributed to stretching vibration of carbonyl, C-OH, and C-O groups, respectively. Moreover, the broad band at 3439 cm^{-1} is corresponding to stretching vibration of hydroxyl group. For SiO_2/GO, the bands at 1083 and 462 cm^{-1} are related to asymmetric vibration and bending vibration of Si-O-Si. It is worth mentioning that stretching vibration of C-O-Si is also appeared at 1083 cm^{-1}. The observed bands at 943 and 802 cm^{-1} are attributed to stretching vibration of Si-OH and symmetric vibration of Si-O-Si. The band at 1726, relating to carbonyl group is appeared at lower intensity. γ-MAPS-SiO_2/GO spectrum displays clearly the characteristic peaks at 1723 and 1625 cm^{-1} which are assigned to C=O and C=C stretch vibration, respectively. These bands corroborate successful introduction of γ-MAPS on to the SiO_2/GO. The main bands in MIPs-SiO_2/GO situating at 1729, 1248, 1156 cm^{-1} are assigned to C=O stretching vibration of carboxylic ester and carboxyl group along with symmetric and asymmetric stretching vibration of C-O, related to ester group [36, 38]. These spectra validate step by step synthesis of MIP-SiO_2/GO.

The morphology of GO, SiO_2/GO, MAPS- SiO_2/GO and MIPs-SiO_2/GO was investigated by field emission-

scanning electron microscopy (FE-SEM) images. According to Figure 2, the thickness of GO sheets was in the range of 24-54 nm. These nanosheets could prepare a large surface area for further coverage by SiO_2 and MIPs-SiO_2. The presence of fine particles on graphene sheet could be attributed to the formation of SiO_2 particles. Higher aggregation of particles formed could be assigned to the incorporation of vinyl group on SiO_2 surface in the third image. The distinctive surface morphology in the last FE-SEM image could be evidence of MIP formation. Thus the FE-SEM images confirm appropriate coverage of GO nanosheets in each step. Moreover, the MIP particle sizes prove the formation of nano-sized structures.

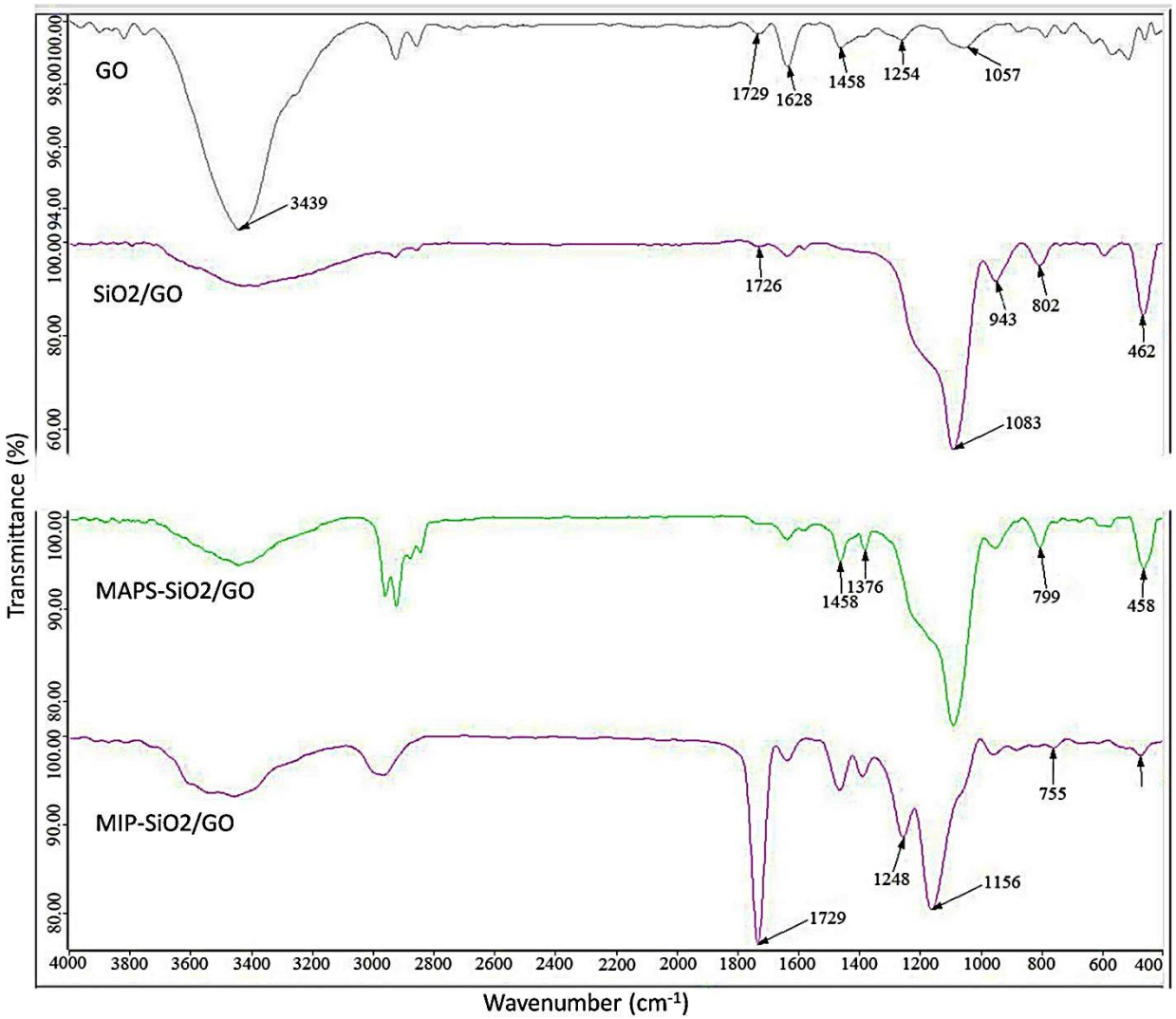

Figure 1. FT-IR spectra of GO, SiO_2/GO, MAPS- SiO_2/GO and MIP-SiO_2/GO

Optimization process

The optimization of the parameters affecting the extraction of sertraline using the MIP-SiO_2/GO sorbent was performed by univariate strategy. The peak area was used to study the influence of sample pH, sorbent amount, the ionic strength, extraction time, type and volume of elution solvent and elution time on the extraction efficiency.

Sample pH

Since Sertraline is a basic compound (pKa=9.5) [39], sample pH was examined in the range of 6-12. The highest extraction efficiency was achieved at pH 12 (Figure 3a). MIP extracts sertraline through both specific, via cavities, and non-specific interactions, via hydrogen bonding and π-π interaction to the backbone. At higher pH, neutrality of amine group could help establishing stronger hydrogen bonding to the oxygen atoms in the framework and substantially improve the extraction efficiency. However, protonation of amine group at pH 10 is responsible for lower extraction efficiency.

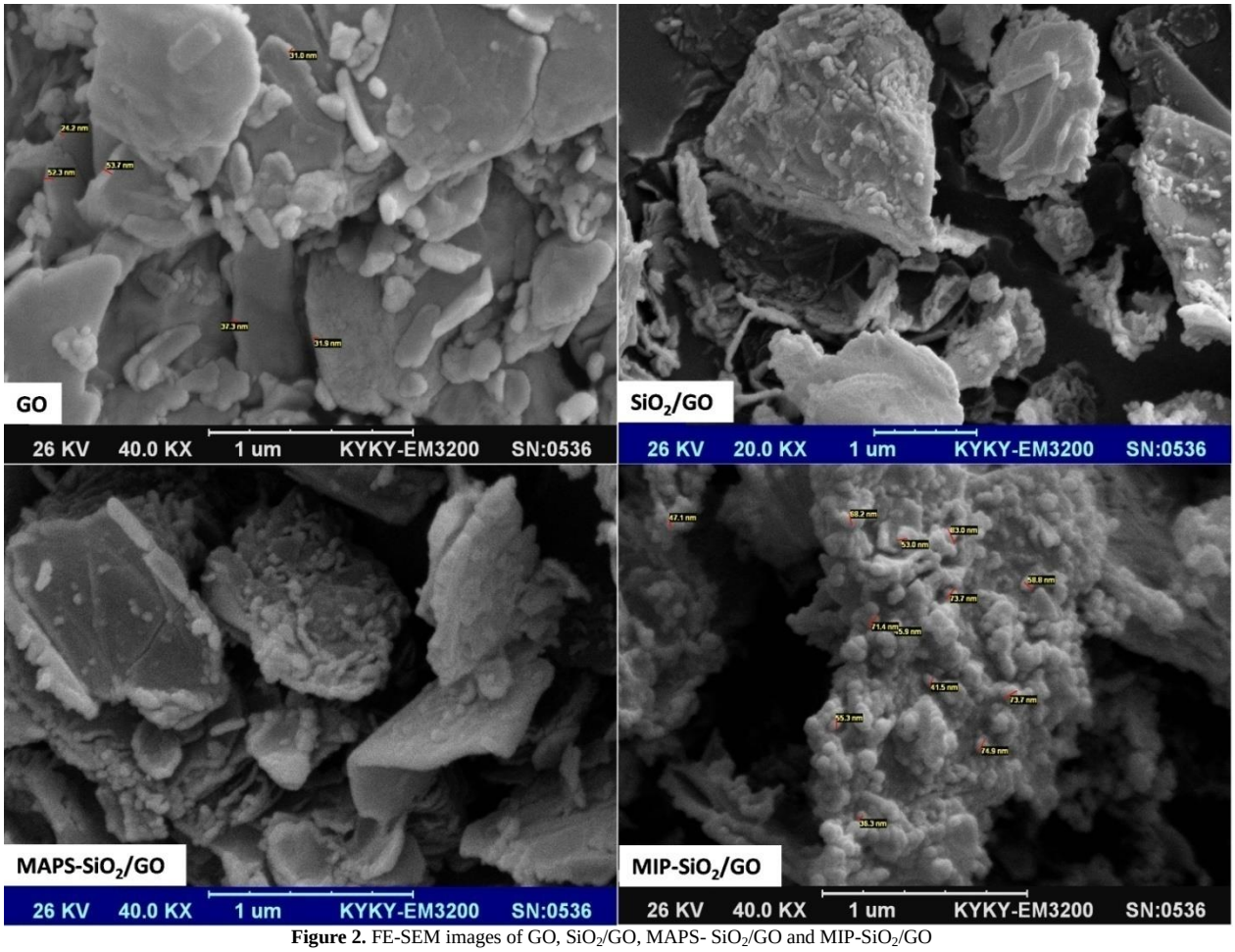

Figure 2. FE-SEM images of GO, SiO_2/GO, MAPS- SiO_2/GO and MIP-SiO_2/GO

Sorbent amount

The extraction capacity and its sensitivity are impacted by the sorbent amount. This parameter was studied in the range of 10 to 50 mg and the best results were obtained at 30 mg. No significant changes in extraction efficiency were observed as the amount of sorbent was increased further.

Extraction Time

The extraction time was investigated in the range from 2 to 30 min. The results are shown in Figure 3b, which demonstrates that as the extraction time increased to 5 min, the peak areas increased sharply. Prolonged extraction time did not increase the peak areas of target analyte. Therefore extraction time was fixed at 5 min.

Salt effect

The extraction efficiency is dependent on the partition coefficient of analyte between the sample and extracting media. This coefficient can be altered by adding a salt, known as the salting-out effect. Thus, the effect of ionic strength was studied to obtainthe optimal conditions for the extraction of sertraline. Several solutions containing different concentrations of sodium chloride salt (0 to 20% (w v^{-1})) were prepared and extractions were con ducted. According to Figure 3c, the most suitable extraction performance was found at a value of 20% salt.

Desorption condition

In order to optimize desorption process; three solvents including acetone, ethanol, and methanol were studied as elution solution. Ethanol provided the best results and possessed higher desorption capabilities among these solvents.

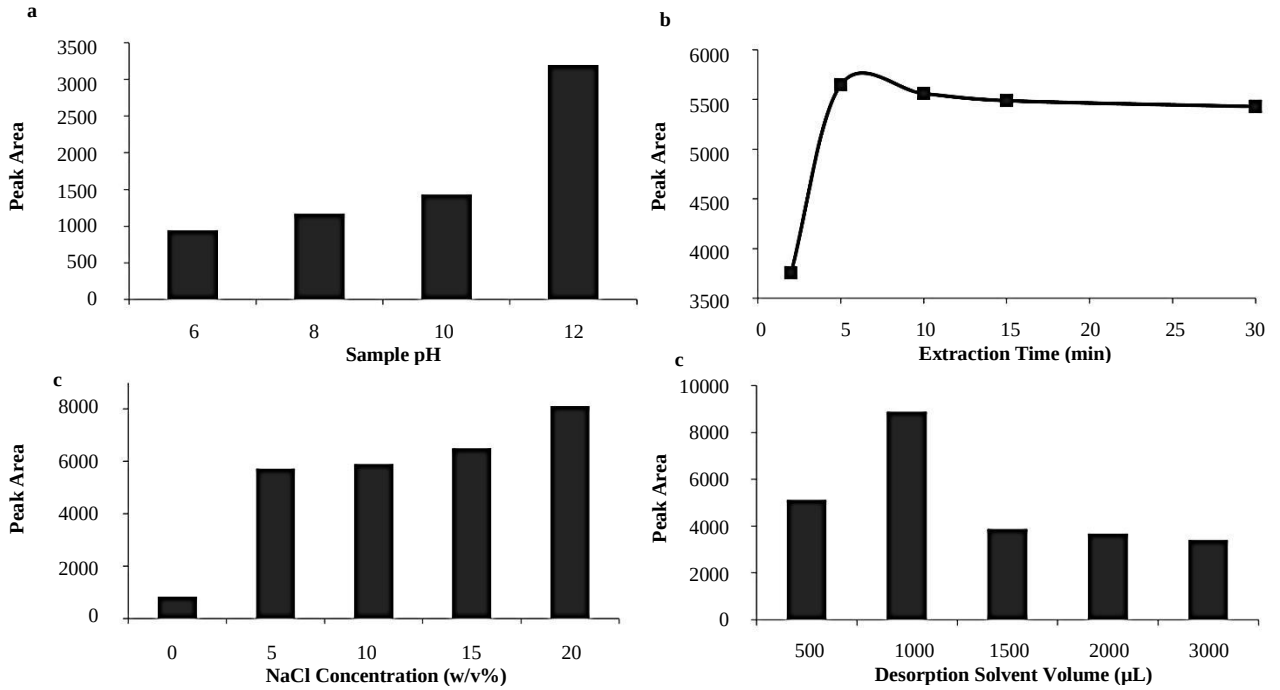

Figure 3. Effect of a) sample pH, b) extraction time, c) solution ionic strength and d) desorption solvent volume on dispersive solid phase extraction performance of sertraline. Extractions were performed from 10 mL aqueous sample solution, spiked with sertraline at 500 µg L^{-1}

A study on the volume of the elution solvent showed a gradual increase in extraction efficiency as the volume of methanol was increased from 500 to 1000 µL (Figure 3d). Further volume increase led to decrease in performance due to the losing analyte during evaporation step. Thus, elution was performed using 1 mL methanol in further experiments.

The desorption time was investigated by increasing the stirring time from 1 to 6 min. The results showed that 2 min was enough to elute the sertraline from the sorbent.

Selectivity performance of sertraline–MIP

The selectivity performance of the synthesized sertraline-surface MIP was examined and compared with NIP under optimized conditions. This study was performed under both uncompetitive and competitive conditions.

The extraction performance of MIP and NIP at concentration level of 50 µg L^{-1} was assessed. The adsorption recovery of MIP was 1.5 times higher than it was for the NIP. Despite the lower extraction recovery of NIP, its

capability in extraction of sertraline reveals that MIP extract sertraline through both specific, via cavities, and non-specific interactions [40].

The specificity of the MIP over the NIP was assessed in presence of ticlopidine as competitive drug having aromatic ring moiety and N-H bond. While the selectivity of MIP toward sertraline is sensible, no serious difference in selectivity performance is observed for ticlopidine using NIP (Figure 4).This observation confirms presence of selective recognition sites in the structure of MIP sorbent. The selectivity factor (α) is defined as the ratio of adsorbed template molecule amount to that of for analogue molecule [41]. As the selectivity factor increases, the more MIP selectivity will result. The α value was found 5.8 that confirm plausible selectivity of MIP sorbent.

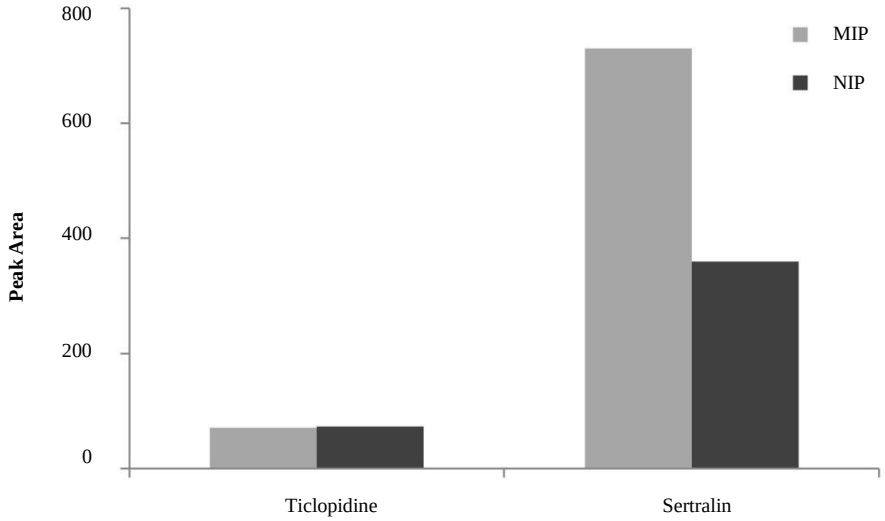

Figure 4. MIP and NIP selectivity performances of sertraline in presence of a competitive drug at concentration of 20 µg L^{-1}. Extractions were carried out in 5 min using 30 mg sorbent from 10 mL aqueous sample solution (pH=12). Desorption process was performed for 2 min using 1 mL methanol

Analytical figures of merit

From the results obtained in the optimization procedure, the surface MIP-DSPE method was assessed and a reasonable enrichment factor of 56 was achieved for sertraline. Calibration curve was constructed to estimate the linear range, correlation coefficient, and limits of detection and quantification for sertraline using the proposed method. The wide dynamic range of 1–500 µg L^{-1}, along with good R^2 value (0.996) was observed. The limits of detection and quantification were quantified 0.2 and 0.5 µg L^{-1}, as three and ten times the signal to noise ratio, respectively. The amount of within-day and between-day precision of the method were assessed based on RSD% (n=3) values and they were 4.3 and 7.1% at concentration of 50 µg L^{-1}, respectively.

Comparing the developed Surface MIP-DSPE-HPLC-UV method to LLE/HPLC-ESI-MS and cartridge-based SPE [42, 43], the developed method demonstrates wider dynamic range and comparable RSD% value (Table 1). Furthermore, the proposed method presented more rapid sample clean-up method, probably because of the dispersion of surface MIP-based sorbent in the solution and facile accessibility of cavities. Moreover, the LOD value for the proposed procedure is much better than those obtained for bulk MIP-SPE method. In addition, the obtained LOQ, using a simple HPLC-UV system, is comparable to what obtained by LLE/HPLC-ESI-MS. All these features verify the applicability of proposed method for extraction and determination of sertraline.

Table 1. Some analytical data obtained for MIP-DSPE of sertraline and HPLC-UV method

Method	LDR[a]	LOD[b]	LOQ[c]	RSD[d]%	Ref
Surface MIP-DSPE-HPLC-UV	1-500 µg L^{-1}	0.2 µg L^{-1}	0.5 µg L^{-1}	4.3	This work
LLE/HPLC-ESI-MS	0.5-25.0 ng mL^{-1}	---	0.5 ng mL^{-1}	7.8	42
SPE/HPLC-DAD	35-1500 ng mL^{-1}	10 ng mL^{-1}	---	1.8	43

[a] Linear dynamic range
[b] Limit of detection
[c] Limit of quantification
[d] Relative standard deviation

The proposed method was also applied to the analysis of biological samples. The recovery test was performed by spiking each sample with 20 and 50 µg L^{-1} of sertraline for urine and plasma samples, respectively. Figure 5 shows chromatograms obtained from plasma sample extracted before and after spiking with analyte. As illustrated, the chromatograms confirm the absence of sertraline in the non-spiked biological samples. The relative recoveries for the urine and plasma samples were satisfactory, with values of 96and 92%, respectively.

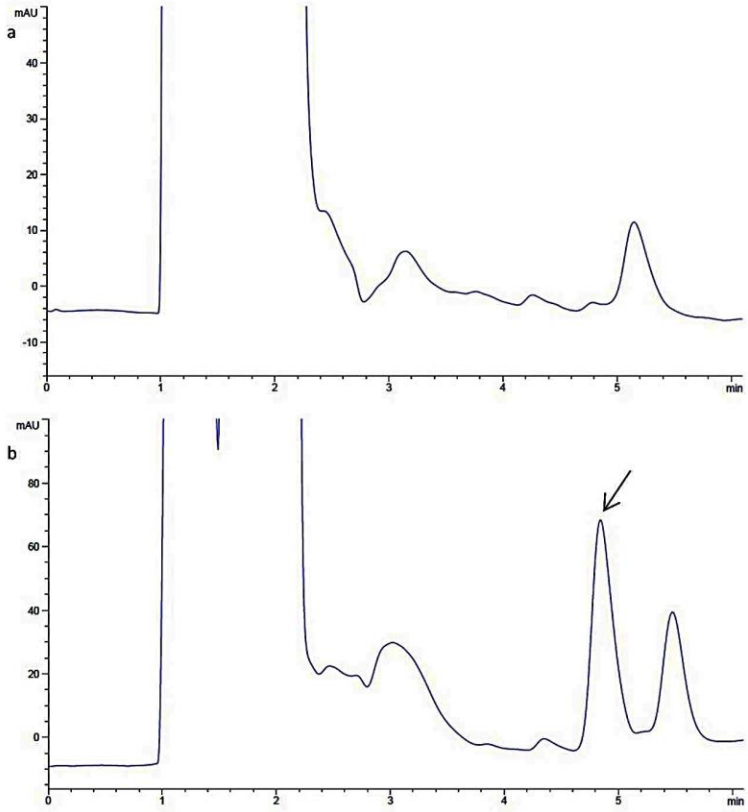

Figure 5. HPLC chromatograms obtained after dispersive solid phase extraction of plasma sample a) unspiked and b) spiked at concentration level of 50 µg $L^{-1}$of sertraline, under optimized condition. The peak at 4.8 min is corresponding to sertraline

CONCLUSIONS

The DSPE method, using MIP-SiO_2/GO as an adsorbent, proposed a reliable and robust methodology for selective trace analysis of sertraline in biological samples. SiO_2 coating improved hydrophilicity and dispersion property of sorbent during extraction. Due to the surface cavities location and good site accessibility, the prepared sertraline-MIP-SiO_2/GO sorbent proved fast

recognition of sertraline. Moreover, the specificity examination of the molecular imprinted polymer over the non-imprinted polymer confirmed the presence of selective recognition sites and plausible selectivity of molecular imprinted polymer sorbent. Although hydrophobic and hydrogen bonding interactions generally possess an important effect in the recognition of competitive drugs using MIP, steric hindrance has a leading role in making interaction to specific sites.

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