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Original Research Article

Determination of Tramadol in Aqueous Samples Using Solid Phase Microextraction Fiber Based on Sol-Gel Coating Reinforced with Multiwall Carbon Nanotube Followed by Gas Chromatography

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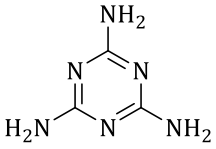
ABSTRACT

In this work, a novel solid phase microextraction fiber based sol-gel coating technology reinforced with carboxylated multiwall carbon nanotube have been prepared, developed, and optimized to determine tramadol in environmental water samples using gas chromatography-flame ionization detector. To reinforce sol-gel and increase in the extraction efficiency of tramadol, the sol-gel coated fiber was reinforced with carboxylated multiwall carbon nanotube. This solid phase microextraction fiber is disposable. Therefore, there is no risk of cross-contamination or carryover. Parameters that affect the extraction efficiency such as pH, extraction time, sample volume, volume of organic solvent, desorption time, and type of nanomaterials were optimized. Under optimized condition, linearity was observed in concentration ranges of 0.01-10 $\mu g L^{-1}$ with correlation coefficient 0.996. Limit of detection (S/N=3) and limit of quantification (S/N=10) were 0.005 and 0.01 $\mu g\ L^{-1}$, respectively. Relative standard deviations (n=5) was 3.13%. Using carboxylated multiwall carbon nanotubes for reinforcement of sol-gel coating leads to increasing extraction efficiency and decreasing the limit of detection. The relative recovery in the real sample (environmental water sample) was 85%. The proposed method can be used as a simple and sensitive method for detection of analgesic drugs such as tramadol in environmental water samples to control the environmental pollution.

GRAPHICAL ABSTRACT



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Introduction

Tramadol (1RS, 2RS)-2-[(dimethylamine) methyl]-1-(3-methoxyphenyl)-cyclohexanol is a centrally acting analgesic drug used for the relief of moderate to chronic pain with no clinically relevant cardiovascular or respiratory depressant activity. Like morphine, tramadol binds to receptors in the brain (opioid receptors) and inhibits reuptake of norepinephrine and serotonin, which appears to contribute to the drug's analgesic effect. Tramadol, like other narcotics used for the treatment of pain, may be abused. Tramadol also interferes with the neuronal release and re-uptake of serotonin and norepinephrine in the descending inhibitory pathways [1, 2]. Its therapeutic plasma concentration is in the range of 100-300 ng mL^{-1}. Tramadol is rapidly and almost completely absorbed after oral administration but its absolute bioavailability is only 65-70% due to first-pass metabolism. This analgesic is rapidly and extensively metabolized in the liver [3]. Pharmaceuticals are widely recognized as environmental contaminants originating in the environment mainly as a result of discharge of raw or treated sewage into surface water. Occurrence of pharmaceuticals in environmental matrices is usually studied because of their possible adverse effects on aquatic life and human. The illicit drugs have been identified as the environmental contaminants [4].

Solid phase microextraction is a well-known and powerful sampling and sample preparation technique which has gained increasing applications in trace analysis in many areas including environmental, food, and drug [5]. Recently, many studies have been reported on the preparation of new kinds of fiber coatings for SPME and their analytical application in the pre-concentration of contaminants from environmental, biological and food samples. Stability, polarity, thickness, surface area of the coating, the amount, and rate of absorption should be considered in the design of SPME fibers. Among the different approaches in coating development, the sol-gel approach is promising because it provides a synthetic technique for both inorganic and organic-inorganic hybrid materials. The sol-gel process can occur under extraordinarily mild conditions. Therefore, it can produce products of various sizes, shapes and forms. Sol-gel offers great advantages compared with the conventional coating techniques: a strong adhesion between the coating and the bed, the coating's porous silica surface structure providing high surfaces areas, and a compatible composition increasing sorbent selectivity. Recently, Malik and coworkers established a convenient pathway to surface coatings using sol-gel technology to overcome important drawbacks of conventional SPME coatings: low recommended operating temperature, instability and swelling in organic solvents, the fiber breakage, and expensive cost [6].

Sol-gel chemistry can overcome this problem by providing efficient incorporation of organic component into the inorganic polymeric structure in solution under very mild thermal conditions. The porous structure of the sol-gel coating offers a high surface area; allowing high extraction efficiency and the coating composition can be altered with a relative ease to give different selectivity characteristics. Strong adhesion of the coating onto the support due to chemical bonding is a very important characteristic which increases the coating stability toward organic solvents and high desorption temperatures [7]. The nanotubes presence caused a substantial enhancement of silica coating fracture toughness on coatings deposited on grounded substrates, but it was not as effective on polished substrates because of the low adhesion of the coating to the substrate. Bridging phenomena caused by the multiwall carbon nanotube was observed, indicating that an effective load transfer between the silica matrix and the nanotube reinforcement was further achieved [8]. Chemical functionalization of the MWCNT surface increases interfacial interaction between MWCNTs and the polymer matrix, enhances adhesion of the MWCNTs in various organic solvents and polymers, reduces the tendency to agglomerate, and improves dispersion [9]. The –COOH grafted onto the surface of the MWCNT enhances its dispersion

and compatibility [6]. Previously reported chromatographic methods for the tramadol quantification were HPLC with diode-array detection [10, 11] and fluorescence detection [12, 13]. Capillary gas chromatography (GC) was also used to determine tramadol [14-17].

In this work we propose the preparation of novel SPME fibers by sol-gel technology reinforced with carboxylated multiwall carbon nanotube to detect tramadol in environmental water samples using gas chromatography-flame ionization detector (GC-FID).

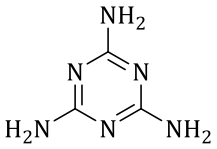

Figure 1: Chemical structure of tramadol hydrochloride

Materilas and Methods

Tramadol hydrochloride (Figure 1) with purity greater than 99% was purchased from Tolid Darou Co. (Tehran, Iran). Trifluoroacetic acid (TFA), Methyltrimethoxysilane (MTMOS), NaOH, NaCl, HCl, acetone (analytical grades), and methanol (HPLC grade) were purchased from Merck. Multiwall carbon nanotube (~95% purity) was supplied from Sanate Naft Research Institute.

Instruments

The gas chromatographic system comprised a Varian 3800 CP gas chromatography (Palo Alto, CA, the USA) equipped with a flame ionization detector. The GC was fitted with CP-Sil 8 (5% biphenyl+95% poly dimethyl siloxane) fused-silica capillary column (30m×0.32mm i.d. and 0.25µm film thickness). Nitrogen (99.999%) was employed as carrier gas and its flow rate was adjusted to 1.5 ml min^{-1}. Temperature of injector and detector were 280°C. The following temperature program was employed: 150°C for 1 min, increased to 250°C at 8°C min^{-1}, and held for 2 min.

Preparation of standard solutions

Stock solutions of tramadol were monthly prepared at concentrations of 1000 mg L^{-1} in methanol and water and kept at 4 °C. The working standard solutions were prepared by diluting the stock solutions in the concentration of 10 mg L^{-1} for both solvent mediums.

Carboxylation treatment of MWCNTs

Firstly, acid treatment method is as follows. The MWCNTs were immersed in a 65% solution of 3:1 mixture of 98% H_2SO_4 and 68% HNO_3, and the suspension was heated at 100°C for 30 min. Then, they were washed several times with deionized water on a filter paper with the pore size of 1 µm (ADVANTEC MFS, C100A047A), and they were dried in a vacuum oven at 90°C for 1 day. Through this process, MWCNTs were oxidized and purified by eliminating impurities such as amorphous carbons, graphite particles, and metal catalysts [18].

Fabrication of the SPME fiber

Before coating process, to remove the polyimide layer from a 1 cm segment of the fiber at one of a 3 cm long fused silica fiber ends, this layer was burnt off using a naked flame. Then the fiber was dipped into 1 M NaOH solution for 1 h, to expose the maximum number of silanol groups on the surface of the fiber, and cleaned with water. Then, it was placed into 0.1 M HCl solution for 30 min to neutralize the excess NaOH. Thereafter, it was cleaned again and dried. Next, 25 mg of carboxylate functionalized MWCNTs was dissolved in 400 µL MTMOS. Then, 50 µL distilled water and 50 mg Polymethylhydrosiloxane (PMHS) were added. The mixture was agitated thoroughly by sonication for 30 min in a glass vial. After that, 50 µl TFA was added to the resulting solution with ultrasonic agitation for 10 min and stable sol solution was formed [19].

In the aging and gelation process, the prepared fiber was placed in a desiccator at room temperature for 24 h and the prepared fibers were conditioned at 50-150 °C for 6 h in the GC oven with gradually rising temperature program [20].

Solid phase microextraction procedure

For each analysis, 15 mL water sample was added into the sample vial. The SPME fiber was then immersed in the aqueous solution at ambient temperature (25 °C). The vial was sealed with rubber septa to prevent sample evaporation. The vial was placed in a shaker for 10 min. After extraction, the SPME fiber was removed and aqueous solution was decanted from the vial. Then, 0.5 ml methanol was added into the sample vial and the fiber was immersed in the organic solvent. The vial was placed in a shaker for 30 min. Subsequently, 1 µL of organic solvent was injected into the GC–FID.

Results and Discussion

Sample pH

The pH value plays an important role in this technique. A suitable pH can improve the extraction efficiency and reduce matrix interferences. To extract the basic compounds into the solid phase from the aqueous phase, the pH of the feed was basified to convert the analytes into their molecular form [21-24]. The pH range of 2-8 was investigated and observed that, due to the dissociation constant (pK_a) values of tramadol (9.41), in the pH values less than 6, the amount of tramadol extracted was significantly reduced. In the pH values higher than 6, the amount of tramadol extracted was also reduced (Figure 2). At pH=6, tramadol was in molecular form and adsorbed onto the SPME fiber and at lower values of pH tramadol was in ionic form. Therefore, pH = 6 was selected as optimal pH for next experiments.

Extraction time

Mass-transfer is a time-dependent process, and its rate affects the equilibrium conditions. Since SPME is an equilibrium extraction mode, the maximum amount of analyte extracted by the sorbent is achieved at equilibrium. Sol-gel is a porous material in which mass transfer is a process of diffusion through the pores. Therefore, the porosity of the sol-gel should strongly affect the equilibrium time for analyte extraction [6]. The extraction times between 5-20 min were evaluated and observed that extraction efficiencies are maximums in 10 min (Figure 2). Mass transfer between the solution and fiber was completed for extraction time of 10 min. Thus, 10 min was chosen as the optimal extraction time.

Sample volume

Clearly, by increasing the sample volume results in increasing the extraction efficiency. To study this effect, the volumes of 5-20 mL were examined. Figure 3 depicts that better extraction efficiencies were achieved at 15 mL of sample volume and chosen for the subsequent experiments.

Volume of organic solvent

Volume of organic solvent has a significant effect on the extraction efficiencies in this solid phase microextraction. Therefore, the volume of organic solvent (methanol) should be optimized. Extraction was performed from 0.25 to 2 mL of the organic solvent. Figure 3 illustrates that the peak area was maximum at 0.5 mL of the organic solvent. Therefore, 0.5 mL of the organic solvent was selected as optimal volume of organic solvent.

Desorption time

To obtain the optimal desorption time, desorption times 5-50 min were further evaluated. Results showed that, desorption of analyte was almost complete in 30 min. After 30 min, the analyte was extracted from solvent to fiber (Figure 4). Therefore, 30 min was selected as optimal desorption time.

Types of nanomaterials

To obtain a better nanomaterial for reinforcement of sol-gel and high pre-concentration of analyte, four typical of nanomaterials were evaluated. Results indicated that MWCNTs exhibited better extraction efficiency than other nanomaterials in this solid phase microextraction method and selected as optimal nanomaterials for reinforcement of sol-gel (Figure 4).

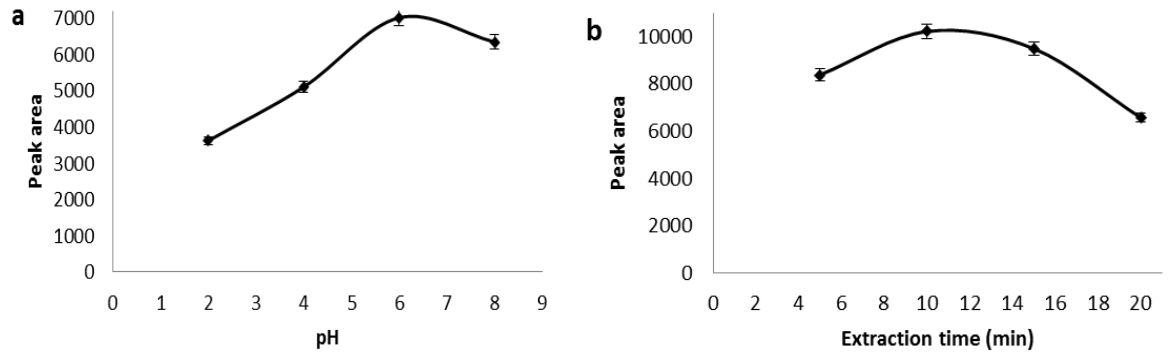

Figure 2: Optimization of pH and extraction time, (a) effect of sample pH on the peak area of tramadol, concentration level at 10 mg L^{-1}; sample volume, 5 mL; volume of organic solvent, 2 mL; extraction time, 10; desorption time, 10 min and (b) effect of extraction time on the peak area of tramadol, concentration level at 10 mg L^{-1}; sample pH, 6; sample volume, 5 mL; volume of organic solvent, 2 mL; desorption time, 10 min

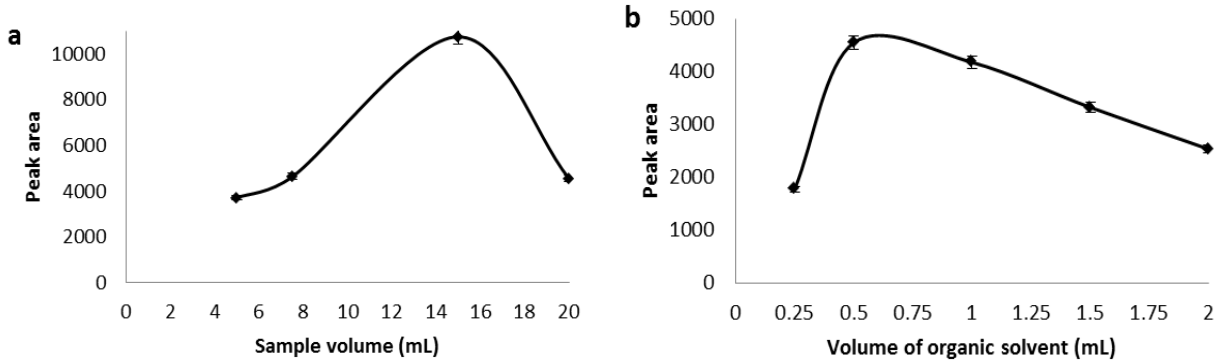

Figure 3: Optimization of sample volume and solvent volume, (a) effect of sample volume on the peak area of tramadol, concentration level at 10 mg L^{-1}; sample pH, 6; volume of organic solvent, 2 mL; extraction time, 10; desorption time, 10 min, (b) effect of solvent volume on the peak area of tramadol, concentration level at 10 mg L^{-1}; sample pH, 6; sample volume, 15 mL; extraction time, 10; desorption time, 10 min

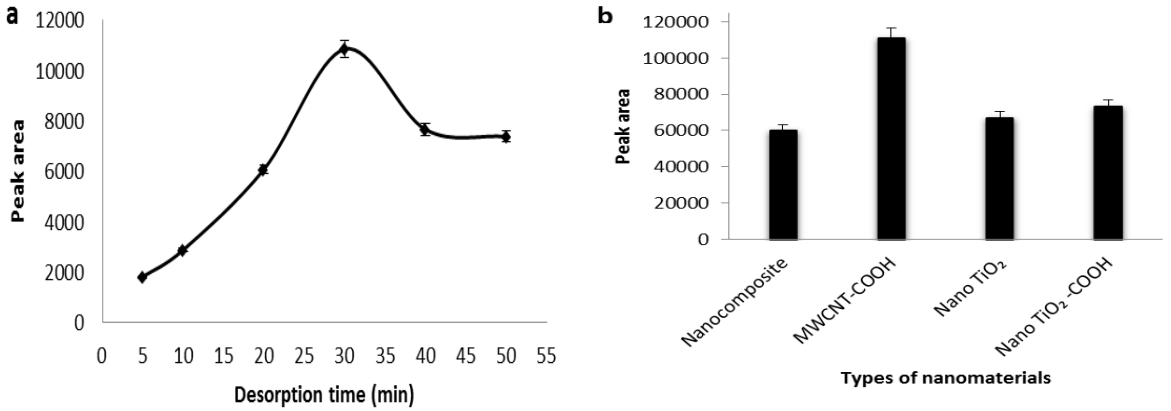

Figure 4: Optimization of desorption and types of nanomaterials, (a) desorption time on the peak area of tramadol, concentration level at 10 mg L^{-1}; sample pH, 6; sample volume, 15 mL; volume of organic solvent, 0.5 mL; extraction time, 10 and (b) effect of types of nanomaterials on the peak area of tramadol, concentration level at 10 mg L^{-1}; sample pH, 6; sample volume, 15 mL; volume of organic solvent, 0.5 ml; extraction time, 10; desorption time, 30 min

Validation of the method

To evaluate the analytical characteristics of SPME reinforced with carboxylated multiwall carbon nanotubes technique, using the optimized parameters, the figures of merit of this method including the corresponding regression equation, correlation coefficient (R^2), limit of detection (LOD), and linear dynamic range (LDR) were investigated to estimate the efficiency and its feasibility in the application of environmental sample analysis. The calibration curve for tramadol was obtained in the concentration range of 0.01-10 µg L^{-1} in aqueous solutions. The results are listed in Tables 1. Figures of merit of the present method were compared with those of other methods to determine tramadol (Table 2).

Real sample

To evaluate the efficiency and applicability of this method, environmental water samples collected from wells water in the Kashmar, spiked with tramadol at a concentration of 10 µg L^{-1} was investigated and relative recoveries of 85% was obtained. The obtained chromatogram (Figure 5) revealed that the tramadol peak was not interfered by other matrix compartments.

Table 1: Figures of merit of the proposed method in determining tramadol in environmental water samples

LDR [a] (µg L^{-1})	Regression equation	R^2 [c]	LOQ [d] (µg L^{-1})	LOD [e] (µg L^{-1})	%RSD [f] (n=5)	Relative recovery (%100)[g]
0.01-10	y = 40509x+1081 [b]	0.996	0.01	0.005	3.13	85

[a]Liner dynamic range.
[b]Y and x are peak area and concentration of the analyte (µg L^{-1}), respectively.
[c]Correlation coefficient.
[d]Limit of quantification.
[e]Limit of detection.
[f]Relative standard deviations.
[g]Recovery after spiked amount of analyte.

Table 2: Comparison of figures of merit of the present method with other reported methods for determination of tramadol

No.	Date	Matrix	Extraction	LOD	r	RSD	Reference
1	2003	Hair	SPME	0.5 ng mg^{-1}	0.996	9.8	[25]
2	2004	plasma	SPME	1.1 µg L^{-1}	0.974	3.2	[26]
3	2005	plasma	SPME	0.2 ng mL^{-1}.	0.998	4.47	[27]
4	2008	beverage	LPME	0.12µg L^{-1}	0.999	6.29%,	[28]

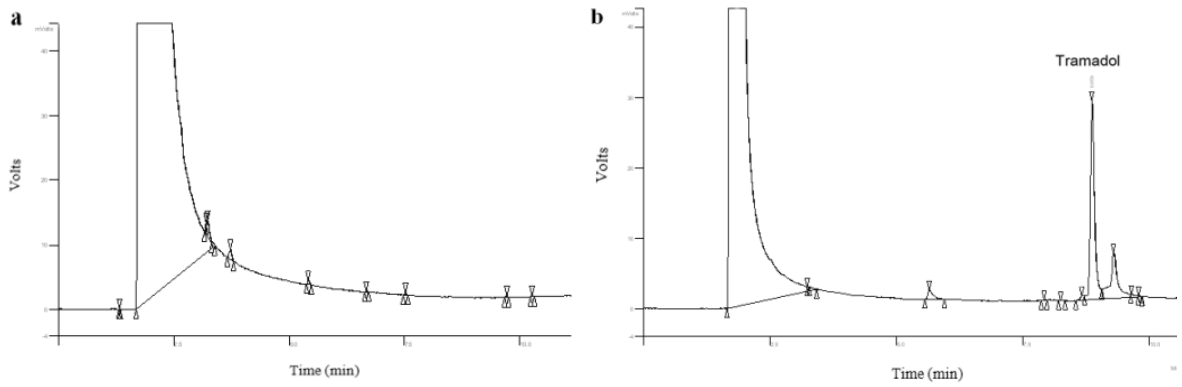

Figure 5: A typical GC-FID chromatogram from wells water in the Kashmar (Iran), (a) after SPME under optimal conditions (before spiking) and (b) Chromatogram of wells water in the Kashmar spiked with 10 µg L^{-1} of tramadol

Conclusion

In this work, a novel solid phase microextraction (SPME) fiber based sol-gel coating technology reinforced with carboxylated multiwall carbon nanotube (MWCNT) have been prepared, developed, and optimized to determine tramadol in environmental water samples using gas chromatography-flame ionization detector (GC-FID). The proposed method is a very useful analysis technique for analyzing trace analgesic drugs such as tramadol that provide a rapid and reliable extraction of tramadol in environmental water samples using carboxylated multiwall carbon nanotubes for reinforcement of sol-gel coating technology leads to increase the peak area of analyte in chromatograms of GC-FID, extraction efficiency, and decreasing the detection limit. This SPME fiber is disposable, so there is no risk of cross-contamination or carryover. In addition, fiber preparation is very simple, fast, and usable for extraction and pre-concentration of trace quantities of tramadol in environmental water samples. The proposed method can be used as a simple and sensitive method for detection of analgesic drugs such as tramadol in environmental water samples to control environmental pollutions.

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Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

There are no conflicts of interest in this study.

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