Iranian Journal of Analytical Chemistry
Volume 10, Issue 1, March 2023 (43-51) Original Research Article

مجله ایرانی شیمی تجزیه
دوره ۱۰، شماره ۱، فروردین ۱۴۰۲ (۴۳-۵۱)

Solid/liquid Phase Microextraction of Anticancer Drug Cisplatin by Using a Hollow Fiber Reinforced with Multiwalled Carbon Nanotube-Ion Exchange Polyurethane Foam, and Determination by Graphite Furnace Atomic Absorption Spectrometry

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Received: 18 March 2023 **Accepted:** 30 April 2023
DOI: 10.30473/IJAC.2023.67414.1264

Abstract
For the first time, hollow fiber-solid liquid phase microextraction (HF-SLPME) using multiwalled carbon nanotube- ion exchange polyurethane foam (MWCNT-PUFIX) as adsorbent along with graphite furnace atomic absorption spectrometry was used to extract and measure the anticancer drug cisplatin. In this method, the nanocomposite dispersed in octanol, is located in the pores and lumen of a porous polypropylene hollow fiber, was used as the extracting phase, this method benefits from high selectivity, high sample purification and enrichment, and reducing the consumption of organic solvents. The major factors affecting the extraction efficiency were investigated. The validation of the method was assessed by linearity, limit of detection, and accuracy calculated as relative recovery percent. The calibration curve was constructed under the optimal conditions was linear in the range of 1.00-55.0 µg/mL and the detection limit was 0.5 µg/mL. This method was successfully used for analysis of biological samples and the obtained results showed that the method has good accuracy and precision.

Keywords
Multiwalled carbon nanotube; Ion exchange polyurethane foam; Cisplatin; Graphite furnace atomic absorption spectroscopy

1.INTRODUCTION

Cis-Diammineplatinum (II) dichloride (Cisplatin) is a chemotherapy drug based on platinum and is often used for ovarian, bladder, head, neck, lung and testicular cancer in humans [1]. Despite of the high efficiency of this drug in the treatment of some cancers, excessive exposure to cisplatin can cause serious side effects, including renal, neurological and gastrointestinal toxicity for patients and even health care workers who are exposed daily during the preparation or administration of chemotherapy [2, 3]. As a result, determination of cisplatin in the patient's body fluid, such as blood or urine, is necessary for effective treatment and dose-dependent study. Several conventional methods for the detection of cisplatin have been reported including, graphite furnace atomic absorption spectrometry [4], liquid chromatography–mass spectrometry [5], and inductively coupled plasma–mass spectrometry (ICP-MS) [6]. Among these methods, GFAAS has a great importance due to its higher tolerance compared to mineral matrices and greater sensitivity as a sensitive, simple and high accuracy technique [7]. Although HPLC and ICP-MS methods are effective methods, the high cost of equipment and consumables, including immunoaffinity columns, consumption time, complexity, and tedious sample preparation steps are some of the disadvantages of these methods. Most of the analytical methods require sample preparation to be compatible with the analytical instrument, which includes the removal of disturbing matrix components and the enrichment of analytes to detectable levels [8]. Different preparation techniques include liquid-liquid extraction (LLE), solid phase extraction (SPE), Solid phase microextraction (SPME) [9], and liquid phase microextraction (LPME) [10] that both LLE and SPE techniques have some drawbacks. Traditional LLE is a laborious and time-consuming process due to the use of large volumes of organic solvents and although SPE uses small amounts of organic solvents, traditional SPE sorbents often lack the selectivity [11]. Hollow fiber protected liquid phase microextraction (HF-LPME) and HF-SLPME were suggested as an efficient and attractive techniques to increase sensitivity [12-14]. In the extraction process known as hollow-fiber solid

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liquid phase microextraction (HF-SLPME), the acceptor phase is prepared by dispersing the adsorbent, which is prepared as an analyte acceptor in an organic solvent, then transferred to the hollow fiber. After that, the natural process of HF-SLPME is carried out by performing a desorption step, followed by analysis with a graphite furnace. The choice of adsorbent type affects the selectivity and sensitivity of the analysis by using a large number of active adsorption sites and porosity can lead to achieving high pre–concentration. The main advantages of these techniques are high enrichment factor, fast analysis time, simple and low-cost setup, and an environmentally friendly technique [15,11]. Nanocomposites have revolutionized the field of materials science due to their enhanced properties compared to conventional materials. Nanocomposites can significantly increase the absorption capacity and ability to interact with the target analytes and are most used in extraction and pre–concentration processes. Nanocomposites are classified into 1- polymer based including CNT-based nanocomposites and 2- non-polymer [16]. Multi-walled CNTs (MWCNTs) were assembled by several layers of rolled graphite sheets. Because of the large surface area of MWCNTs, they are used as adsorbents [17,18].

This research shows validation of quantitative analysis of the anticancer drug cisplatin through hollow-fiber solid liquid phase microextraction (HF-SLPME) procedure, based on MWCNT PUFIX nanocomposite followed by graphite furnace atomic absorption spectrometry (GFAAS).

2. EXPERIMENTAL

2.1.Materials and reagents

The anti-cancer drug; cisplatin was awarded from Mylan Co. (Tehran, Iran). Ethanol, NaOH, HCl, NaCl, Na2CO3, and other analytical grade reagents were purchased from Merck (Darmstadt, Germany). The Q3/2 Accurel PP polypropylene hollow-fiber (HF) membranes (200 µm wall thickness, 600 µm i.d., 0.2 µm pore size) were obtained from Membrana GmbH (Wuppertal, Germany). The multiwalled carbon nanotubes with 10–40 nm diameters, 1–25 µm length, core diameter 5–10 nm, with the purity of more than 98% was purchased from research institute of the petroleum industry (Tehran, Iran). The stoke solutions were prepared by dissolving a calculated amount of drugs in ethanol/water (50:50, v/v) solution. Working stock solutions were prepared daily from the primary stock solutions.

2.2.Apparatus

In this experiment, a PG-990 atomic absorption spectrometer, with GF-990 graphite furnace power supply were used for analysis of metals in different samples. Monitoring the absorbance of platinum at 265.9 nm and the program for GF-AAS was: drying at 110 °C for 20 s, 180 °C for 10 s, and 350 °C for 10 s, ashing at 1600 °C for 5 s, and atomization at 2700 °C for 2.5 s.

Ultrasonic processor, model UP 400S (Germany) with 60% amplitude and 0.5 s duty cycle was used for dispersion and mixing of all samples. Fourier transform infrared spectrophotometer Shimadzu FTIR-8400 (Japan) was used to determine the functional groups of nanocomposites. pH was measured using a Metrohm 827 pH meter (Switzerland).

2.3.Synthesis of nanocomposite

Poly–hydroxyl polyurethane was prepared by replacing its hydroxyl group with primary amine [19]. Hydroxyl groups act as selective receptors with high binding stability for a wide range of analytes. In this method, commercial polyurethane foam (PUF) was cut into small chips. Then, 1.0 g of PUF chips was soaked in 3 M HCl solution for 24 h. Then the chips were washed with distilled water and placed in a 0.1 M HCl solution and was transferred to an ice bath. PUF was vigorously stirred and 10 mL of ethyl iodide was added dropwise and the product remained in the fridge for 24 h. After that, PUFIX was air dried, and pounded in an agate mortar.

Multi-walled carbon nanotubes were functionalized by sonication in a mixture of nitric and sulfuric acid (70:30; v/v) for 6 h at the 60% duty cycle. To provide the nanocomposite, the synthesized PUFIX and functionalized MWCNT were added to 40 mL of ethanol and the mixture was refluxed for 6 h at a temperature of below 60 °C. MWCNT PUFIX black powder was obtained, which was washed with distilled water and acetone, respectively, and then dried in air. The obtained nanocomposite was crushed in an agate mortar [20].

The FTIR spectrum of PUF, PUFIX, primary and functionalized multi-walled carbon nanotubes were recorded and analyzed. Also, scanning electron microscope (SEM) imaging of MWCNT-PUFIX was performed.

3.RESULTS AND DISCUSSION

3.1.Characterization of synthesized nanocomposite

Infrared spectroscopy (FT-IR) was performed to confirm the functional groups in all synthesis steps. FT-IR spectrum of the nanocomposite is shown in Figures 1.

In PUF and PUFIX spectra, the observed stretches of 3270, 2770 and 1580 cm-1 are related to free NH groups, NH of urethane group, aliphatic hydrocarbon and urethane groups (-NHCOO-), respectively. Next, the infrared spectrum of the

DOI: 10.30473/IJAC.2023.67414.1264

initial and functionalized MWCNT was studied. The stretching band at 2751 cm-1 indicates the presence of aliphatic hydrocarbon, and the vibration at 1645 cm-1 is related to the C=C bond. Bands at 1519 and 1415 cm-1 are related to the presence of NO2, which was created as a result of functionalization by nitric acid and sulfuric acid [21]. The disappearance of some bonds in the spectrum of MWCNT-PUFIX indicates the joining of these groups to functional groups on the surface of carbon nanotubes [22].

In the infrared spectrum of MWCNT-PUFIX, the peak at 2326 cm-1 corresponds to the NH group, 1716 cm-1 corresponds to the carboxyl group, and 1519 and 1418 cm-1 refers to the NO2, in the urethane group. The slight change in the partial bands indicates the formation of bonding. Also, the presence of a peak at 1255 cm−1 confirms the presence of type III amine and the peak at 1645 cm−1 is related to the C=C bond. [23,24].

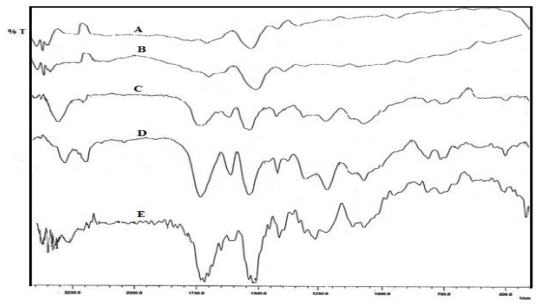

Fig. 1. FTIR spectrum of MWCNT (A), functional MWCNT (B), PUF (C), PUFIX (D) and synthesized nanocomposite(E)

3.2.SEM analysis

The morphology of the synthesized MWCNT-PUFIX adsorbent was evaluated by electron microscopy. The obtained image shows the multi-walled carbon nanotubes are wrapped around the nanoparticle, which creates a suitable surface for transferring the analyte to the nanocomposite and increases the extraction. SEM image of synthesized nanocomposite is shown in Figure 2.

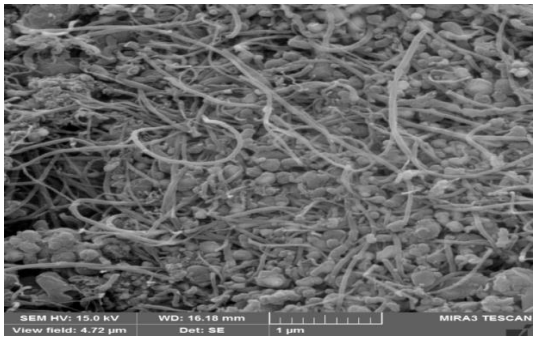

Fig. 2. SEM image of synthesized nanocomposite

3.3.HF-SLPME procedure

Polypropylene hollow fiber was cut into 15.0 mm long pieces. To remove impurities, washed with distilled water and acetone, respectively, and dried in air. One end of the hallow fiber was heat-sealed. A certain amount of the synthesized adsorbent was dispersed ultrasonically in the organic solvent of octanol for 10 min with a cycle of 0.5 s and 60% duty cycle. Then the dispersed adsorbent was injected into the prepared hollow fiber by a syringe, and the other end of the hollow fiber was sealed by heating. The hollow fiber was washed with distilled water and dried. The prepared hollow fiber was placed in the sample solution for a certain period of time with 600 rpm agitation. After the extraction, the hollow fiber was transferred into a small glass vial and sonicated with 1 mL of 50% water/ethanol solution. The hollow fiber was removed and the desorption solvent was injected into the graphite furnace atomic absorption spectrometer.

3.4.Selection of Organic Solvent

One of the important steps in the microextraction process is the selection of an appropriate organic solvent (desorption solvent). Consequently, several factors must be considered. First, the high partition coefficient of the analyte in the organic solvent and in the pores of the hollow fiber. Also, the solubility in water should be as low as possible (immiscible with donor solutions) and the organic solvent should have a high boiling point so that it does not evaporate during the experiment. In addition, MWCNTs should be well dispersed in the organic solvent. On the other hand, carbon nanotubes are insoluble in all solvents due to their high inter-tube attraction energy and therefore aggregate in organic solvents [25]. One approach is surface functionalization of carbon nanotubes. Also, the diameter of carbon nanotubes is large enough to easily accommodate octanol molecules. As a result, it is compatible with hollow fiber. In this work, according to the latest research findings, 1-octanol has been chosen as an organic solvent.

3.5.Optimization of HF-SLPME

Considering that the extraction performance in the HF-SLPME method depends on important experimental variables that affect the extraction efficiency, they should be optimized to obtain a sensitive extraction method with high repeatability.

The Taguchi method can create effective experimental design to reduce the volume of calculations, to obtain the optimal conditions, and to achieve maximum extraction efficiency.

Taguchi method

Taguchi experimental design was used in order to obtain the optimum conditions for determination of cisplatin. In this study, an L27 design was used to verify the effects of six controllable factors including sample pH, MWCNT-PUFIX amount,

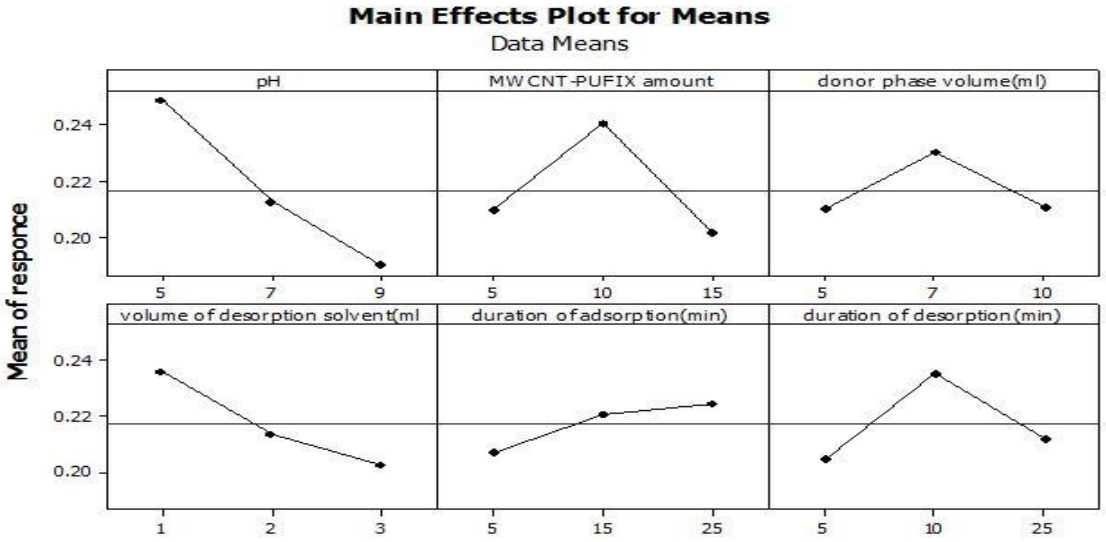

Fig. 3. Main effects plot for means

Table 2. ANOVA of the extraction of cisplatin.

Source	DF	Sum of sqrs.	Mean of sqrs.	F	P (%)
pH	2	0.01590	.00795	6.11	40.1
MWCNT-PUFIX amount	2	0.00778	0.00389	2.37	20.6
donor phase volume (ml)	2	0.00240	0.00120	0.64	6.4
volume of desorption solven t(ml)	2	0.00513	0.00256	1.47	13.6
duration of adsorption (min)	2	0.00161	0.00080	0.42	4.2
duration of desorption (min)	2	0.00471	0.00236	1.33	12.5
Error	2	0.00101	0.0004		2.6
Total	14	0.03854			100

DF: Degree of freedom

duration of adsorption and desorption, donor phase volume and volume of desorption solvent at three levels (Table 1).

The S/N ratio calculation results for determination of cisplatin are shown in Table S1 and Figure 3. Response is depicted in Table S2. The analysis of variance (ANOVA) which is a useful statistical test was used to investigate the influence and confidence of the processing parameters on the extraction performance. ANOVA can specify the percentage and contribution of each controllable factor on the extraction percentage of cisplatin. Summary results of the ANOVA are shown in Table 2.

3.6.Effect of pH

The pH of the solution plays a main role on the extraction of analytes. According to Taguchi design, the effect of pH on cisplatin extraction was studied.

According to Figures 3 and 4 and based on ANOVA results, the effect of pH on the analytical signal of cisplatin was significant and is maximized at pH 5. According to the pKa reported for cisplatin (pKa=6.6) [27], at lower pH values, the analyte is in neutral form and neutral species can diffuse through the membrane from the donor phase [28].

Table 1. Taguchi L_{27} design factors and levels.

Factor	Level 1	Level 2	Level 3
pH	5	7	9
MWCNT-PUFIX amount (mg)	5	10	15
donor phase volume (mL)	3	7	10
volume of desorption solvent (mL)	1	2	3
Duration of adsorption (min)	5	15	25
Duration of desorption (min)	5	10	25

In (table 2), the sum of squares of the influential pH factor and their interactions and effective percentage are reported. The importance of the studied factor will be better understood by observing the main effects plot (Figure 3), where the steeper slope of this line indicates the larger

main effects. The effect of optimized parameters on the HF-SLPME extraction can be seen in Figure4.

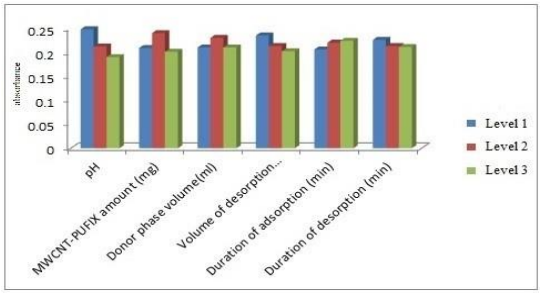

Fig. 4. Effect of the optimized parameters on the HF-SLPME extraction

3.7.Effect of MWCNT-PUFIX amount

According to the results, initially increasing the amount of MWCNT-PUFIXs increases the adsorption of platinum ions on nanocomposites. As a result, it improves the extraction efficiency, but at higher amounts, this efficiency decreases, which is due to the negative effect of crowding of molecules. Therefore, the optimal amount of nanocomposite was obtained to be 10 mg.

3.8.Effect of donor phase volume and volume of desorption solvent

The microextraction techniques provides significant enrichment factor because the analyte is extracted from a relatively large volume of donor phase into a very small volume of desorption solvent. According to the following equation, Ca,final is the final concentration of analyte in the acceptor solution, Cs,initial is the initial analyte concentration within the sample, Va is the volume of the acceptor solution and Vd is the volume of donor phase.The enrichment factor in LPME is basically determined by the analyte recovery as well as the donor phase volume. As the donor phase volume increases, the enrichment factor also increases [29,30], However, large sample volume can lead to lower extraction efficiency due to weaker mass transfer kinetics. According to the obtained results, 7 ml was chosen as the optimum volume for the donor phase and 1 mL for the desorption solvent.

$EF = (Ca, final / Cd, initial) = (Vd / Va) \times R / 100$

3.9.Effect of duration of adsorption

The extraction time influences the partition of the target analytes between the sample solution and the acceptor phase in the lumen of the fiber. In fact, the longer equilibration times do not have any significant effect on the microextraction efficiency [25]. Extraction times were investigated at the range of 5,15, 25 min (Figure 4). According to the results, the best extraction has been occurred at 25 min.

3.10.Analytical figures of merits

By using the figures of merit of each analytical method, the efficiency of different methods can be compared with each other as well as evaluating the ability of an analytical method for special applications. The analytical performance of the proposed HF-SLPME method was investigated under the optimal conditions obtained above. The calibration curve was obtained after pre–concentration by the proposed HF-SLPME method via 20 µL injection of 0.5–65 mg mL−1 of standards of cisplatin into the GFAAS system. The limits of detection (LOD) was calculated according to the equation 3s/m, where s and m are the standard deviation of the blank signals of four replicates and the slope of the linear calibration graph, respectively. The results are summarized in Table 3. The proposed procedure comparing the other methods for quantitative determination of cisplatin was summarized in Table 4. It shows that our proposed method has wide linear dynamic ranges, low LODs and good precisions.

3.11.Real sample analysis

To evaluate the capability of this extraction technique in biological samples, this technique was employed to measure cisplatin drug in nail and urine samples. The accuracy and precision of the method were examined by extracting under the optimum conditions and expressed as relative recovery percent. The results are summarized in Table 5.

3.12.Nail sample

In this method, water and acetone solution (1:1; v/v) was used to clean the nail surface and remove all pollutants (fats and lipids) [38]. 0.01 g of clean and dried nail was weighed and soaked in 1.0 mL of concentrated HCl for 24 h. 0.1 mL of this mixture was diluted with 25 ml of 0.05 M carbonate buffer at pH 5.0. The extraction process was then performed by spiking specific volumes of analyte standard solutions through the standard addition method, and the relative recovery was calculated.

3.13.Urine sample

The urine sample is often diluted with an optimal buffer because it does not require pretreatment. A strong acid or base is usually added to the urine to adjust the optimal pH. Urine pH was checked and adjusted to optimal pH Then 1.0 ml of the urine sample was diluted tenfold with carbonate buffer (0.05 M) at pH 5.0 and the extraction process was performed by HF-LPME method. Certain amounts of analyte were spiked and the absorbance of the final solution was measured.

DOI: 10.30473/IJAC.2023.67414.1264

Table 3. Figures of merit for the extraction of cisplatin using the proposed method

Analyte	Linearity DLR (µg mL^{-1})	R^2	LOD (µg mL^{-1})	LOQ (µg mL^{-1})	RSD% (n=4)
cisplatin	1-55	0.9966	0.5	1.7	5.7

Table 4. A comparison between previously reported extraction method and the proposed method for Cisplatin determination

Method	**Range**	**LOD**	**Ref**
HPLC	0.025-2.00 µg/mL	0.008 µg/mL	[31]
chromatography	6.0–60.0 µg/mL	2.00 µg/mL	[32]
UV-Vis spectrophotometer	10.0 – 5750.0 µg L^{-1}	4.2 µg L^{-1}	[33]
UV-Vis spectrophotometer	0.25-6.0 µg	0.12 µg	[34]
HPLC coupled with tandem mass spectrometry	3–3000 ng mL^{-1}	1 ng mL^{-1}	[35]
adsorptive transfer stripping and pulse voltammetry	0.5 and 5 µM	500 nM	[36]
Cyclic Voltammetry	0.2–110 µM	90 nM	[37]
GFAAS	1-55 µg/mL	0.5 µg/mL	This work

Table 5. Analytical results for determination of Cisplatin in the real samples

Real sample	Spiked conc. (µg/mL)	Measured conc. (µg/mL)	RR%	RSD%
Nail	0	ND	-	-
	0.5	0.42	84.01	5.71
	1.0	1.08	108.04	6.43
Urine	0	ND	-	-
	0.5	0.53	106.10	3.82
	1.0	0.90	90.14	4.97

ND: not detected

4.CONCLUSION

In the present study, a solid liquid-phase microextraction method based on hollow-fiber in combination with GFAAS analysis was developed and successfully applied using the Taguchi method to determine optimal HF-SLPME for extraction and pre-concentration of cisplatin from aqueous samples. This developed method has some advantages such as simplicity, ease of operation, low cost of the extraction device, safety and environmentally friendly due to the minimal use of organic solvents, minimum carryover as the hollow fiber is cheap enough to be discarded or disposed after single use and cross-contamination, selectivity, sensitivity and high pre-concentration by using a nanocomposite with high porosity and a large active adsorption sites. This method can be successfully applied to the pre-concentration and determination of cisplatin in biological samples. since it is important to measure anticancer drugs, including cisplatin, in small amounts continuously and quickly, the use of the above method, which was performed for the first time with the HF-SLPME method using a graphite furnace, can be very effective and efficient.

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DOI: 10.30473/IJAC.2023.67414.1264

میکرواستخراج فاز جامد/ مایع داروی ضد سرطان سیس پلاتین با استفاده از فیبر توخالی تقویت شده با فوم تبادل یون پلی اورتان و نانولوله کربنی چند دیواره و تعیین مقدار آن با طیف سنجی جذب اتمی با کوره گرافیت

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تاریخ دریافت: ۲۷ اسفند ۱۴۰۱ **تاریخ پذیرش:** ۱۰ اردیبهشت ۱۴۰۲

چکیده

برای اولین بار، میکرواستخراج فاز مایع –جامد با فیبرتوخالی (HF-SLPME) با استفاده از فوم تبادل یونی پلی اورتان و نانولوله کربنی چند دیواره (MWCNT-PUFIX) به عنوان جاذب همراه با طیف سنجی جذب اتمی کوره گرافیتی برای استخراج و اندازه گیری داروی ضد سرطان سیس پلاتین استفاده شد. در این روش نانوکامپوزیت پراکنده شده در اکتانول، در منافذ و مجرای یک فیبر توخالی پلی پروپیلن قرار گرفت، و به عنوان فاز استخراج کننده آز آن استفاده شد. این روش از گزینش پذیری بالا، خالص سازی و غنی سازی نمونه بالا و کاهش مصرف مواد آلی بهره می برد. عوامل اصلی موثر بر راندمان استخراج مورد بررسی قرار گرفتند. روش با خطی بودن، حد تشخیص و دقت محاسبه شده به عنوان درصد بازیابی نسبی ارزیابی شد. منحنی کالیبراسیون در شرایط بهینه به صورت خطی در محدوده ۵۵-۱ میکروگرم بر میلی لیتر و حد تشخیص ۰,۵ میکروگرم بر میلی لیتر رسم شد. این روش با موفقیت برای تجزیه نمونه های بیولوژیکی مورد استفاده قرار گرفت و نتایج به دست آمده نشان داد که روش از صحت و دقت خوبی برخوردار است.

کلید واژه ها

نانولوله کربنی چند دیواره؛ فوم تبادل یونی پلی اورتان ؛ سیس پلاتین؛ طیف سنجی جذب اتمی کوره گرافیت

DOI: 10.30473/IJAC.2023.67414.1264