

ارزیابی غیر مستقیم داروی ضد سرطان کپسیتابین با استفاده از فیبر منخلخل حمایت شده با فوم پلی اورتان/ نانولوله های کربنی عاملدار

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Indirect Determination of Anticancer Drug Capecitabine Using Hollow Fiber Supported Multiwalled Carbon Nanotube Coated on Polyurethane Foam

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چکیده

هدف از این کار اندازه‌گیری غیر مستقیم داروی کپسیتابین به کمک تهیه کمپلکس آن با یون پلاتین (IV) و اندازه‌گیری آن با اسپکترومتری جذب اتمی با کوره گرافیتی است. به این منظور ابتدا کمپلکس کپسیتابین و یون پلاتینیوم تهیه شد و نسبت دارو به فلز با روش‌های مختلف تعیین گردید. در همه روش‌ها مشخص شد که نسبت لیگاند به فلز برای کپسیتابین و پتاسیم هگزاکلروپلاتینات 2:1 (IV) می‌باشد. فرآیند استخراج توسط فیبر منخلخل حمایت‌شده با فوم پلی اورتان/ نانولوله چند دیواره عامل‌دار به عنوان جاذب جامد با سبک میکرواستخراج فاز جامد انجام شد. مقدار یون پلاتینیوم واجذب شده بصورت غیر مستقیم برای اندازه‌گیری غلظت دارو مورد استفاده قرار گرفت. پارامترهای موثر بر روش میکرواستخراج فاز جامد فیبر منخلخل مانند pH فاز دهنده، حجم فاز دهنده، نوع جاذب و حلال واجذبی بهینه شدند. منحنی کالیبراسیون رسم شد و محدوده خطی ۳/۳۲ تا ۹۸/۱۷ میکروگرم بر میلی‌لیتر با حد تشخیص ۰/۳۸ میکروگرم بر میلی‌لیتر بدست آمد. در نهایت روش برای تشخیص و اندازه‌گیری داروی ضد سرطان کپسیتابین در نمونه‌های حقیقی به کار برده شد.

واژه‌های کلیدی

کپسیتابین؛ پتاسیم هگزاکلروپلاتینات (IV)؛ اندازه‌گیری غیرمستقیم؛ اسپکترومتری جذب اتمی با کوره گرافیتی.

Abstract

The aim of this work was indirect determination of anti-cancer drug capecitabine using complexation with platinum (IV) and determination by graphite furnace atomic absorption spectroscopy (GFAAS). For this aim at first, the complex of platinum with capecitabine was performed and the ratio of drug to metal was evaluated with several ways. In the all of these methods, the ligand to metal ratio of the Potassium hexachloroplatinate (IV) and capecitabine complex was found to be 2:1. The extraction process was carried out by the hollow fiber supported functionalized multiwalled carbon nanotubes/ polyurethane foam (fMWCNT/PUF) foam as the solid adsorbent in the solid phase microextraction mode. The amount of desorbed platinum ion has been indirectly used to measure the drug concentrations. Parameters affecting the hollow fiber-solid phase microextraction (HF-SPME) such as pH of the donor phase, donor phase volume, the sorbent type and desorption solvent were optimized. Calibration graph was plotted and a curve with a linear response range of the 3.32 to 98.17 $\mu\text{g mL}^{-1}$ and a detection limit 0.38 $\mu\text{g mL}^{-1}$ was obtained.

Keywords

Capecitabine; SPE Method; Indirect Determination; Graphite Furnace Atomic Absorption Spectroscopy.

1. INTRODUCTION

Cancer phrase refers to a group of tumors in which cells are abnormal and multiply out of control. If the normal cells could not be controlled the rapid growth it can cause even lead to tissue fractures [1]. Capecitabine (CPT), chemically N-4-pentoxycarbonyl-5'-deoxy-5-fluorocytidine (See scheme 1S in the supplementary file), is an

anticancer agent which usually used in the chemotherapy of slowly growing solid tumors such as pancreatic, ovarian, colorectal, and breast [2-4].

Up to now, various analytical methods have been used for the determination of capecitabine hydrochloride include; HPLC, LC-MS, LC-MS/MS and spectrophotometric methods [5-9].

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Solid phase extraction (SPE) is a separation technique was found to be effective based on some properties of solid sorbents adsorption like ion exchange and chelating, it is used not only to extract traces of organic compound from environmental samples, but also to remove the interfering components of the complex matrices in order to obtain a cleaner extract containing the analytes of interest. A large number of sorbents are available, and the most frequently used group of sorbents are polymer sorbents and graphitized or porous carbon. The nature of the base material and the additional functional groups both affect the way that the sorbents are used. Generally, sorbents are three-dimensional polymeric materials which are manufactured under conditions designed to provide a very porous but rigid material with a high surface area.

Depending on the sample matrix and the task to be performed, SPE can provide several advantages over the other techniques, most remarkably liquid-liquid extraction (LLE), including; low solvent consumption, better extraction efficiency, higher selectivity and reproducibility, the most diverse kind of material, and emulsion formation does not cause problems in the SPE on the contrary, the LLE, etc. [10-13].

The polyurethane foam (PUF) is a class of polymers which due to good properties such as; high surface area, low cost, steadiness in acids and bases, thermal stability so that its structure resistance to heated up to 180 °C, excellent hydrodynamic characteristics, high retention capacity, the resilient property is considered as an excellent sorbent for extraction and preconcentration of organic and inorganic species by conventional methods [4, 14-17]. Polyurethanes derive from the hard the soft segments with $-N=C=O$ and $-OH$ groups respectively [19]. They are in the class of compounds called reaction polymers, which include epoxies, unsaturated polyesters, and phenolics. PUFs having the highly reactive isocyanate group ($-N=C=O$). This group simply react with hydrogen atoms that are attached to atoms more electronegative than carbon. Carboxyl and hydroxyl groups, which are located on the surface of the functionalized carbon nanotubes, are also from this category.

As well as, multi-walled carbon nanotubes (MWCNTs) due to the unique physical properties have attracted scientific interest. These properties include good thermal and electrical conductivity, high strength, tunable morphology, low density, chemical and environmental stabilities, high surface area and mesoporosity [20, 21]. Its properties greatly improved at the nanoscale due to the high surface-to-volume ratio [22, 23].

Various methods have been developed to increase the quantity of surface functional groups and thus improve the MWCNTs surface which most important is chemical oxidation with HNO_3 or H_2SO_4 [24-26].

Graphite furnace atomic absorption spectroscopy technique (GFAAS) used to measure trace amounts of metals and semi-metals. We have to use indirect determination procedure due to in many drugs, like studying the drug, there is no metallic element. The possibility of indirect determination of trace element of drugs even without metal or semi-metal ion is provided with the help of complexation of the drug with a metal ion.

In the present work, an indirect method for detect the trace amounts of capecitabine by GFAAS technique is performed with the use of a sorbent prepared from fMWCNT/PUF supported by hollow fiber with the help of complexation by platinum (IV). The nanocomposite (MWCNTs-PUFIX) increase the extraction efficiency significantly due to increasing the active sites of sorbent. With the aid of the proposed method, we can be abandoned of chromatographic methods problems such as; costly, long analysis time, the need for modern equipment, require purification steps and high purity materials and solvents. The method is used for the determination of tracing amounts of capecitabine drug in real biological samples.

2. EXPERIMENTAL

2.1. Instruments

The sonication of the mixtures and solutions was performed by an Ultrasonic Processor, model UP 400S (Germany) and a Shimadzu FTIR-8400 Fourier transform infrared spectrophotometer (Japan) was used to record the spectra. The voltammetry studies carried out using a Metrohm Model797computrace (Switzerland) with Ag/AgCl, wire platinum and a graphite electrode as a reference, auxiliary and working electrode respectively. A Metrohm pH meter 827 (Switzerland) was used for the pH measurements.

2.2. Chemicals and reagents

The capecitabine awarded from Osvah pharma Co (Tehran, Iran). All reagents and organic solvents were purchased from Merck (Darmstadt, Germany) and Sigma-Aldrich (United States) in analytical grade. For preparing of stock drug solutions, necessary amount of the drug was dissolved in ethanol. Multi-walled carbon nanotubes were purchased from Research Institute of the Petroleum Industry (RIPI), (Tehran, Iran) with specifications contains 10–40 nm diameters, core diameter 5–10 nm, BET

surface area (SBET) 40–600 m² gV⁻¹, bulk density 0.1 g cm⁻³ with 98% < purity. And the polypropylene hollow fiber membrane obtained from Membrana (Wuppertal, Germany) with wall thickness 200 nm, the inner diameter 600 nm.

2.3. Preparation of the fMWCNT/PUF adsorbent

After several attempts at fabricating a MWCNT coating on PUF, it was apparent the as-received MWCNTs would not yield an appropriate coating on PUF. Attempts to coat using raw MWCNT solution resulted in a substrate with an inhomogeneous light gray color, which indicated a coating with a low concentration of un-distributed MWCNTs. To improve MWCNT stability in water and improve adhesion to the substrate,

MWCNTs were acid functionalized.

The acid functionalized MWCNT-PUF formed a suspension that remained stable in water for more than a week. The functionalized MWCNT-based coated PUFs where a homogenous dark gray color, indicating that using the fMWCNT/PUF increased both MWCNT retention and degree of distribution.

For functionalization of the MWCNT, 1.0 g of this powder was sonicated in a mixture of (30:70) nitric and sulfuric acid for 6h by 60% amplitude and 0.5 S cycles. For the treatment of commercial PUF, 1 g of foam was shaved so fine and soaked in HCl 3M. After 24h washed with distilled water, sprinkled on HCl 0.1 M solution and was cooled in an ice bath.

For preparing ion exchange polyurethane foam (PUFIX), during strong stirring, 10 mL of ethyl iodide added dropwise to PUF and was left for 24 h in the fridge [10]. The product after drying at the room temperature completely powdered with an opal mica.

In the last step, the PUFIX and functionalized MWCNT were refluxed in 40 mL of ethanol for 6h at 50 °C. The black powder MWCNT-PUFIX was obtained and washed with distilled water and acetone respectively. It was dried at room temperature and blended in an agate mortar.

The FTIR spectra of synthesized sorbent steps by step were investigated, the structure of nanocomposite was studied by SEM imaging. The synthesized nanocomposite used for extraction and measurement of anti-cancer drug, capecitabine.

2.4. Extraction process of platinum and its complexes

For study of the extraction process at first, platinum (IV) solution with the concentration of 10 µg mL⁻¹ was prepared from potassium hexachloro platinate (K₂PtCl₆). The 2 cm

segments of polypropylene hollow fibers packed ultrasonically with the mixture of octanol/nanocomposite, and then was placed in the donor phase and the solution stirred for 30 minutes at 200 RPM. In the desorption process hollow fiber was transferred to the extraction solvent and stirred for 15 minutes at 300 RPM. Desorption solvent was injected into the GFAAS. Since the objective of this study was indirect measurement of the drug capecitabine via complexation with the platinum, the ratio of metal to ligand complex by taking three methods of UV-Vis spectroscopy, differential pulse voltammetry and GFAAS was investigated.

2.4.1. Determining the stoichiometry of metal-drug complexes

One of the most common methods for defining the stoichiometry of the metal-ligand complexes is the mole-ratio method in which the amount of one component, proved to be kept, while the amount of the other substance changes. To perform the mole ratio method, the moles of capecitabine in the solution was constant and the platinum ion mole was changed. Absorbance is monitored at the maximum complex wavelength. Using the mole ratio method, 1:2 complex of platinum (IV): capecitabine was proposed.

2.4.2. Investigation of the composition of complex with GFAAS technique

To study the stoichiometry of complex, extraction process was done in the presence of various metal-drug ratios: 1: 1, 1: 2, 1: 3 and 2: 3 metal to drug ratios. The adsorption and desorption processes were done under the optimum conditions. The 1:2 ratio of metal to drug was confirmed due to the best extraction efficiency was achieved in this ratio. The best extraction efficiency is achieved in this ratio. The results are summarized in Table 1S in the supplementary file.

2.4.3. Determination of the stoichiometry of complex by differential pulse voltammetry (DPV)

For this study, 2 mL of 10 µg mL⁻¹ capecitabine was transferred to the voltammetry cell and then regular amounts of platinum were added sequentially. The results showed increasing the platinum ion from 0 to 1 mL (concentration of 10 µg mL⁻¹) led to decrease the peak current of free capecitabine, But after the 1:2 metal / drug mole ratio, increasing the metal ion did not affect the peak height. The result was shown in the supplementary file, Fig. 1S.

3. RESULT AND DISCUSSION

3.1. Characterization of synthesized nanocomposite by FT-IR and SEM

The FT-IR spectrum of MWCNT- PUFIX has performed for verification the functional groups

(Fig. 1a). As it can be seen in spectrums of PUF and PUFIX, the feature of 1580.4 cm^{-1} corresponds to the absorption of urethane ($-\text{NHCOO}-$) group stretching. The bands of 1724.2 and 1072.3 cm^{-1} refer to carbonyl group that shifted to lower energy because of conjugation; two bands at 1527.5 and 1410 correspond to the NO_2 group.

The MWCNTs have some peaks, bands at 1519.8 and 1415.2 cm^{-1} , indicating that NO_2 group introduced to the sidewall of MWCNTs. The NH_2 stretching band appears at 3480 cm^{-1} [27]. Some of the bonds between the MWCNT and PUFIX disappeared in the spectrum of MWCNT-PUFIX, reflecting joining of these groups of the surface functional groups of carbon nanotubes [28].

Scanning electron microscopy (SEM) imaging provided for observing the particle size and surface morphologies of synthesized nanocomposite (Fig. 1b). As expected, after reflux, PUFIX particles coated by a layer of MWCNTs. The porous structure provides the bunch of sites for capturing analyte, which results in the increase of the pre-concentration and extraction efficient.

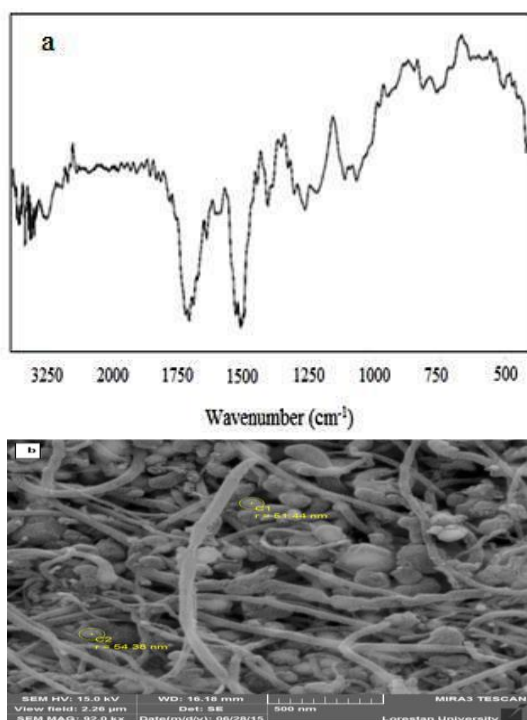


Fig. 1. a) FTIR spectrum and b) SEM imaging of synthesized MWCNT-PUFIX nanocomposite. The average size of nanocomposite is 53 nm.

3.2. Optimization of experimental factors

3.2.1. Effect of pH

The effect of pH on the extraction recovery was studied by GFAAS technique on the range over the 3.0- 9.0. The results showed the

environmental pH is effective in the extraction recovery of the complex. As can be observed in Fig 2, the most extraction recovery was observed at pH 5.0.

The reason for this result can be the value of pH ZPC that is in the basic region (about pH 8.0- 9.0) for the PUFIX-MWCNT and is based on terminal groups. At pH lower than that of pH ZPC, the surface of the PUFIX-MWCNT is positively charged and the hydrogen bonds can occur between the nitrogen atoms of the PUF and the protons of the CH_2 groups in the capecitabine chain, which can increase the extraction efficiency [10, 29]. Therefore, it was considered for further experiments.

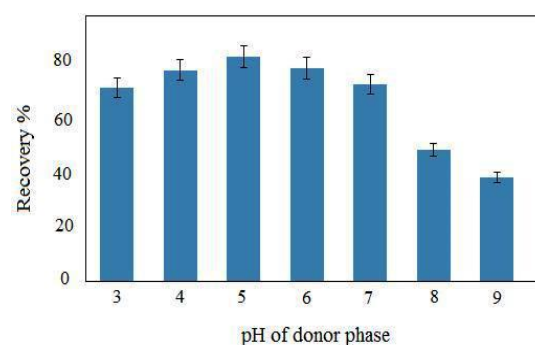


Fig. 2. The investigation of pH of donor phase influence on the complex recovery by GFAAS technique.

3.2.2 Effect of donor phase volume and the sorbent amounts

To study and compare its performance of nanocomposite filled hollow fiber with the calcined graphite rod, experiments were performed in which 2cm pieces of graphite and hollow fiber was used. The calcined graphite rod had good performance for extraction of metal alone and the complex, although the preparation process of this was simple. But nanocomposite filled hollow fiber showed more recovery of extraction due to functional groups at nanocomposite while connected to terminal groups of the complex. Results are displayed in Table 2S in the supplementary file.

As is clear from the results, filled hollow fiber with nanocomposites performed better in different situations so that is almost twice the efficiency of calcined graphite. The volume of donor phase was investigated and the results showed that the volume of 2 mL was the best. So in the next steps were used filled hollow fiber as a sorbent and a volume of 2 mL donor phase.

3.2.3 Effect of desorption solvent

Desorption solvent in extraction process has an important role because if properly selected,

Table 1. Figures of merit for capecitabine determined by the proposed method.

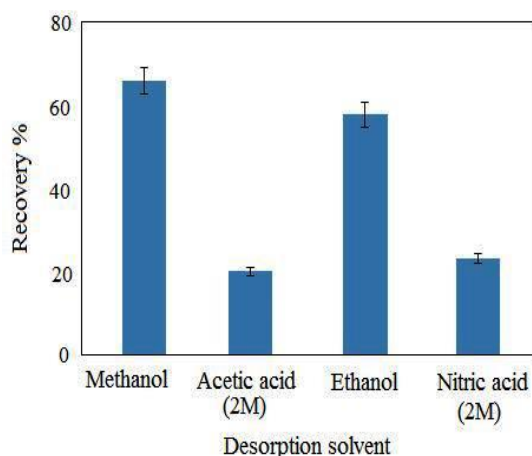
Analyte	Linear range ($\mu\text{g mL}^{-1}$)	Correlation curve (R^2)	LOD ($\mu\text{g mL}^{-1}$)	LOQ ($\mu\text{g mL}^{-1}$)	RSD
Capecitabine	3.32 to 98.17	0.965	0.38	1.28	0.059

Table 2. Comparison between previous studies and proposed method.

Method	LOD $\mu\text{g mL}^{-1}$	LOQ $\mu\text{g mL}^{-1}$	R^2	RSD %	Ref
Electrochemistry by Glassy Carbon Electrode	1.13×10^{-7} *	3.78×10^{-7} *	-	1.01	29
RP-HPLC	0.005	0.014	0.9990	2.0	5
improved RP-HPLC	0.169	0.513	-	2.0	30
Eco friendly HPLC-UV	-	0.050	0.9999	6.9	31
Bioanalytical RP-HPLC	0.300	0.600	0.9987	5.0	32
RP-HPLC	0.05	0.190	0.9990	-	33
RP-HPLC	0.088	0.260	0.9970	0.5	34
RP-HPLC	0.600	1.900	0.9990	0.1	35
pH independent spectroscopic	0.662	2.000	0.9987	-	36
Indirect determination by GFAAS	0.380	1.280	0.9650	5.9	Present work

*Molarity

facilitate the final analyte transition to receiver phase. Organic solvents can usually have a good effect. In this process, different solvents were investigated. As can be seen in Fig. 3, the highest extraction efficiency was observed in the presence of methanol as a solvent so it was determined as optimum desorption solvent.

**Fig. 3.** Results for desorption solvent effect on the extraction efficiency.

3.3. Method validation

After optimizing the important factors in the extraction process, the calibration curve was plotted for this study, in about 10 concentrations with three times repeated. The results are shown in Table 1 while important figures were calculated such as; LOD and LOQ, the Correlation curve and RSD. A study was also carried out to compare the current method with

previous methods and the results are shown in Table 2.

3.4. Real samples

The pH of bulk urine was adjusted to pH of 5.0 with HCl 4M and then was diluted tenfold with the phosphate buffer at pH 5 [37].

The nail sample was prepared by washing the 0.1 grams of nail with deionized water and acetone respectively, and drying and solving in the 1M of sulfuric acid.

Specified amounts of analyte were spiked to nail, urine and laboratory wastewater and the extraction process were performed. The results are presented in Table 3.

Table 3. Investigation of real samples by the proposed method.

Sample	RR %*	RSD
Urine	101.74	0.047
Nail	74.14	0.101
Laboratory waste	87.98	0.064

*Relative Recovery%

4. CONCLUSION

Nowadays the ways to study and measure very low doses of anticancer drugs has special importance. Often medication review by chromatography and especially HPLC have done that are requiring high purity solvents, ultra-pure gasses, different columns and different detectors. The proposed method in this study provided possibility by the indirect measure of anticancer drug capecitabine to help with the platinum complex by furnace atomic absorption method. In

the process parameters affecting the extraction and determination of drug were studied and optimized. Finally, to ensure the true method of drug real samples was measured with good precision and accuracy.

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We wish to draw the attention of the Editor to the following facts which may be considered as potential conflicts of interest and to significant financial contributions to this work.

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

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REFERENCES

- [1] I. Amjadi, M. Rabiee and M.S. Hosseini, Anticancer Activity of Nanoparticles Based on PLGA and its Co-polymer: In-vitro Evaluation, *Iran. J. Pharm. Res.* 12 (2013) 623-634.
- [2] R.M. Alagar, S. Anusha, D. Banji, K.N.V. Rao and D. Selva Kuamar, Analytical method development and validation of anticancer drugs (Imatinib and Capecitabine) by RP-HPLC method, *Asian J. Res. Chem. Pharm. Sci.* 3 (2015) 51 - 65.
- [3] P.R. Subbarayan, M. Sarkar, G. Nelson, E. Benitez, S. Singhal and B. Ardalan, Chronic Exposure of Colorectal Cancer Cells in Culture to Fluoropyrimidine Analogs Induces Thymidylate Synthase and Suppresses, *Anticancer. Res* 30 (2010) 1149-1156.
- [4] R. Akbari and H. Akbari Javar, Efficacy of Capecitabine and 5- Fluorouracil (5-FU) on the human breast cancer cell line (MCF7) – effect of concentration, *Am. J. Res. Commun* 1 (2013) 75-91.
- [5] V. Rajesh, B. Anupama, V. Jagathi and P. Saipraveen, Simultaneous estimation of Gemcitabine Hydrochloride and Capecitabine Hydrochloride in combined tablet dosage form by RP-HPLC method, *E-J. Chem* 8 (2011) 1212-1217.
- [6] A. Morikawa, D.M. Peereboom, H.R. Thorsheim and R. Samala et al, Capecitabine and lapatinib uptake in surgically resected brain metastases from metastatic breast cancer patients: a prospective study, *Neuro. Oncol.* 17 (2015) 289–295.
- [7] M. Meloun, Z. Ferencikova, A. Vrana A, Determination of the thermodynamic dissociation constant of capecitabine using spectrophotometric and potentiometric titration data, *J. Chem. Thermodynamics* 43 (2011) 930-937.
- [8] P. Singhal, P.A. Shah, J.V. Shag, P. Sharma and P.S. Sgrivastav, Determination of Capecitabine – an anticancer drug in dried blood spot by LC-ESI-MS/MS, *Int. J. Pharm. Pharma. Sci* 7 (2015) 238-245.
- [9] E. Piorkowska, M. Kaza, J. Fitatiuk, I. Szlaska, T. Pawinski and P.J. Rudzki, Rapid and simplified HPLC-UV method with on-line wavelengths switching for determination of capecitabine in human plasma, *Pharmazie* 69 (2014) 500-505.
- [10] E.A. Mohamed, I. Ishaq and A. Abdul-Rahman, Synthesis, characterization of carbon poly urethane powder and its application for separation and spectrophotometric determination of platinum in pharmaceutical and ore samples, *Talanta* 121 (2014) 113-121.
- [11] N. Abd-Talib, S.H. Mohd-Setapar and A.K. Khamis, The Benefits and Limitations of Methods Development in Solid Phase Extraction: Mini Review, *Jurnal Teknologi* 69 (2014) 69-72.
- [12] A. Zwir-Ferenc and M. Bizziuk, Solid Phase Extraction Technique – Trends, Opportunities and Applications, *Polish J. Environ. Stud.* 15 (2006) 677-690.
- [13] Steve Zdravkovic, Solid phase extraction: Realizing the advantages of an underutilized technique, www.ppd.com (2017).

- [14] J. Vinhal, C. Lima and R. Cassella, Polyurethane foam loaded with sodium dodecyl sulfate for the extraction of 'quat' pesticides from aqueous medium: Optimization of loading conditions, *Ecotoxi. Env. Safety* 131 (2016) 72-101.
- [15] J. Li, B. Wang, K. Chen, X. Tian, J. Zeng, J. Xu and W. Gao, The Use of Lignin as Cross-linker for Polyurethane Foam for Potential Application in Adsorbing Materials, *bioresources* 12 (2017) 8653-8671.
- [16] E.A. Moawed, N. Burham and M.F. El-Shahat, Separation and determination of iron and manganese in water using polyhydroxyl polyurethane foam, *J. Assn. Arab. Univ. Basic. Appl. Sci* 14 (2013) 60-66.
- [17] O.S.H. Santos, M. Coelho da Silva and M.I. Yoshida, Synthesis and performance of different polyurethane foams as oil sorbents, *J. app. Polymer. Sci* 134 (2017) 45409-45416.
- [18] M.M. El-Bouraiie, Preconcentration and determination of copper (II) and silver (I) onto polyurethane foam functionalized with salicylate, *Sustain. Environ. Res* 25 (2015) 171-176.
- [19] K. Bouchemal, S. Briancon, E. Perrier, H. Fessi, I. Bonnet and N. Zydowicz, Synthesis and characterization of polyurethane and poly (ether urethane) nanocapsules using a new technique of interfacial polycondensation combined to spontaneous emulsification, *Int. J. Pharm* 269 (2004) 89-100.
- [20] D. Rosenthal, M. Ruta, R. Schlogl and L. Kiwi-Minsker, Combined XPS and TPD study of oxygen-functionalized carbon nanofibers grown on sintered metal fibers, *Carbon* 48 (2010) 835-1843.
- [21] M.O. Ogasawara, M. Takaya and M. Yamada, Exposure Assessment of MWCNTs in Their Life Cycle, *J. Phys: Conf. Series* 617 (2015) 1-8.
- [22] M. Deborah, A. Jawahar, T. Mathavan and M. Kumara Dhas, A. Milton Franklin Benial, Preparation and Characterization of Oxidized Multi-Walled Carbon Nanotubes and Glycine Functionalized Multi-Walled Carbon Nanotubes, *Fullerene. Nano. Carbon. Nanostruct* 23 (2015) 583-590.
- [23] A. Sengupta, N. Gupta, MWCNTs based sorbents for nuclear waste management: A review, *J. Environ. Chem. Eng.* 5 (2017) 5-13.
- [24] D.K. Seo, J.P. Jeun, H.B. Kim and P.H. Kang, Preparation and characterization of the carbon nanofiber mat produced from electrospun pan/lignin precursors by electron beam irradiation, *Adv. Mater. Sci* 28 (2011) 31-34.
- [25] F.M. Fernandes, R. Araujo, M.F. Proenca, C.J.R. Silva and M.C. Paiva, Functionalization of carbon nanofibers by a Diels Alder addition reaction, *J. Nanosci. Nanotechnol* 7 (2007) 3514-3518.
- [26] H.H. Cho, K. Wepasnick, B. A. Smith, F. K. Bangash, D. H. Fairbrother and W. P. Ball, Sorption of Aqueous Zn [II] and Cd [II] by Multiwall Carbon Nanotubes: The Relative Roles of Oxygen-Containing Functional Groups and Graphenic Carbon, *Langmuir* 26 (2010) 967-981.
- [27] J.D. Gelder, K.D. Gussem, P. Vandenabeele and L. Moens, Reference database of Raman spectra of biological molecules, *J. Raman. Spectrosc.* 38 (2007) 1133-1147.
- [28] H. Sone, B. Fugetsu and S. Tanaka, Selective elimination of lead (II) ions by alginate/polyurethane composite foams, *J. Hazard. Mater* 162 (2009) 423-429.
- [29] S.S. Kalanur, J. Seetharamappa, G.P. Mamatha, M.D. Hadagali and P.B. Kandagal, Electrochemical Behavior of an Anti-Cancer Drug at Glassy Carbon Electrode and its Determination in Pharmaceutical Formulations, *Int. J. Electrochem. Sci.* 3 (2008) 756-767.
- [30] P. Ravisankar, G.D. Rao, M.N. Kumar and M.K. Chaitanya, An improved RP-HPLC method for the quantitative determination of capecitabine in bulk and pharmaceutical tablet dosage form, *Der. Pharmacia. Lettre* 5 (2013) 249-260.
- [31] S. Hassanlou, M. Rajabi, A. Shahrasbi and M. Afshar, Development and Validation of an Ecofriendly HPLC-UV Method for Determination of Capecitabine in Human Plasma: Application to Pharmacokinetic Studies, *S. Afr. J. Chem.* 69 (2016) 174-179.
- [32] S. Jayaseelan, S. K. Bajivali, U. Ramesh, V. Sekar, P. Perumal, Bioanalytical Method Development and Validation of Capecitabine by RP-HPLC Method, *Int. J. Chem. Tech. Res.* 2 (2010) 2086-2090.
- [33] K. Srinivasu, J.V. Rao, N.A. Raju and K. Mukkanti, RP-HPLC Method for the Estimation of Capecitabine in Tablet Dosage Forms, *Asian. J. Chem.* 22 (2010) 3255-3259.
- [34] K.R. Kumar, CH.M.M. Rao, CH.B. Rao, K.B.C. Sekhar and P.G. Reddy, RP-HPLC Method Development and Validation for Estimation of Capecitabine in Capsules, *Int. J. Chem. Tech. Res.* 2 (2010) 307-311.
- [35] N.S. Rao, D. Venkataramana, P. Srinivas and P. Anitha, RP-HPLC Method for

Determination of Gemcitabine Hydrochloride and Capecitabine Hydrochloride in Combined Tablet Dosage Form, *Indo. Am. J. Pharm. Res.* 4 (2014) 5134-5139.

- [36] S.H. Patel and P.U. Patel, Development and validation of pH independent spectroscopic method for determination of Capecitabine, *Der. Pharmacia. Sinica.* 6 (2015) 19-23.
- [37] Z. Es'haghi, A. Nezhadali, S. Bahar, S. Bohlooli and A. Banaei, [PMIM] Br@ TiO₂ nanocomposite reinforced hollow fiber solid/liquid phase microextraction: An effective extraction technique for measurement of benzodiazepines in hair, urine and wastewater samples combined with high-performance liquid chromatography, *J. Chromatogr. B* 980 (2015) 55-64.