Efficient removal of digoxin from aqueous solution using magnetic nanocomposite \((\text{Fe}_3\text{O}_4\text{–GO–SO}_3\text{H})\) as an advanced nano-absorbent

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ABSTRACT

Digoxin separation from pharmaceuticals wastes, is small piece of the larger puzzle in holistic risk assessment. In this study, a novel magnetic nano composite (graphene oxide/\(\text{Fe}_3\text{O}_4\text{–SO}_3\text{H}\)) was synthesized and used as an absorbent for the removal of digoxin from aqueous solution. We utilized UV-Vis spectrophotometry (UV/Vis) for detection and efficient removal of digoxin by magnetic graphene oxide (MGO) in different concentrations. Magnetic absorbent was characterized by thermal gravimetric analysis (TGA), Fourier-transform infrared spectroscopy (FTIR) and X-ray diffraction (XRD). The optimized concentration of absorbent and digoxin were 500 and 1 ppm respectively, in which the optimize reaction time was lasting 10 min. Finally, under optimized condition, MGO was used for the efficient separation of digoxin from aqueous solution.

1. Introduction

Digoxin is a glycosylated steroid-like drug which is extracted from foxglove for the first time in 1930. Other seeds and leaves also contain this drug [1]. According to World Health Organization’s List of Essential Medicines, Digoxin is vital medication in...
health care system. This drug is essential to cure various heart conditions such as atrial fibrillation, atrial flutter, and heart failure [2, 3]. This cardiac glycoside drug is the fifth most commonly prescribed drug in US and costed less than 25 USD per month in 2015 [4]. Ubiquitously, this drug is prescribed in congestive heart failure that inhibits the $\text{Na}^+/\text{K}^+\text{ATPase}$ pump and enhances the intracellular concentration of cytosolic calcium, subsequently. The intracellular $\text{Ca}^{2+}$, then adjusts various physiological events such as cardiac muscle contraction [5, 6]. Beside the importance of digoxin as a widely prescribed drug, the toxic effects of this drug both in environment and medicine cannot be neglected. Wide variety of environmental samples including sewages, ground waters and drinking waters are at risk of pharmaceuticals wastes contamination [7]. Aquatic pollution is particularly troublesome since it affects life-cycle of aquatic organisms, plants and drinking water [8]. Even, very low amount of this wastes is worrisome because their affects accumulates and leading to irreversible changes over the years. Therefore, there is a significant need for detection, separating, and removing them from wastes.

Digoxin separation from pharmaceuticals wastes, is small piece of the larger puzzle in holistic risk assessment. Various surveys have been conducted to filtration and refinement of sewages. Moreover, multiple techniques have been introduced for detection of digoxin in human serum samples such as liquid chromatography (HPLC) [9], immunochemical assays [10] and biosensors [11]. However, there is an urgent need for specific, precise, simple and cost effective method for separation of digoxin from aqueous environments.

Graphene is two-dimensional carbon nanostructures which consisting mechanical, thermal and electrical characteristics [12]. The oxidation product of graphene is graphene oxide (GO), which possesses hydroxyl, epoxide, carboxyl and carbonyl functional groups [13–18]. These functionalized groups not only supply plentiful active attachment sites but also provide excellent adsorption sites for abundant contaminants in aqueous solution [19]. Therefore, multiple functionalised magnetic absorbents has been synthesised and introduced by researchers in order to adsorb and remove various compounds such as proteins [20], metal ions [21] and drugs [22]. Several pharmaceutical companies produce remarkable amounts of toxic pharmacy and their derivatives which are the most important hazard compounds in wastewater. Abundant studies have been conducted to eradicate compounds from environment by taking advantage of organic absorbents [23] such as separation $\text{SO}_2$, NO [24], $\text{CO}_2$ [25], methylene blue [26], Ca, and Mg [27] from aqueous solution. However, fewer researchers have been conducted for pharmacy separation from aqueous solution.

Due to the high digoxin toxicity, there is an urgent need for the separation of this drug from the wastes. Multiple techniques have been introduced for digoxin monitoring in biological samples such as liquid chromatography (HPLC) [27], LC–MS/MS assays [28], immunochemical assays [29], and sensing [30]. Most of the methods for digoxin determination are time-consuming, expensive and complex. Moreover, they requires sophisticated experts for sample preparation and cause harmful effects to the environment. Therefore, there is a considerable attention to introduce rapid, sensitive and greener method for digoxin detection and eradication [31].

The goal of this study is to expand an analytical procedure exploiting for the first time the precise extraction based on a novel absorbent aiming at the spectrophotometric determination of digoxin. The procedure was based on formation of magnetic nano composite ($\text{Fe}_3\text{O}_4$–GO–SO$_3$H) and its interaction with digoxin in aqueous solution.

UV-spectrophotometric method enables quantitative measurement of the reflection or transmission properties of digoxin and reveals how much a chemical substance absorbs light by evaluating the intensity of light as a beam of light passes through digoxin solution. This method offers cost effective and time saving alternative to other analytical methods and is more specific than electromagnetic spectroscopy, near ultraviolet, and near infrared techniques [22, 23].

In this study, $\text{Fe}_3\text{O}_4$–GO–SO$_3$H was synthesized and used as a magnetic absorbent for the removal of digoxin from aqueous solution. Then, the peak intensity of UV/vis absorbent was measured in the presence and absence of digoxin by UV-spectrophotometric.

Therefore, simple and fast procedure introduced for digoxin detection and eradication from aqueous solution.

2. Experimental

2.1. Chemical and reagents

Acetone, methanol, dimethyl sulfoxide (DMSO), acetonitrile (ACN), chloroform, carbon tetrachloride, 1,2-dichloroethane (1,2-DCE), and 1,1,2- trichloroethane (1,1,2-TCE) were purchased from Merck. Deionized water was obtained from Ghazi Company (Tabriz, Iran). Digoxin was obtained from Sigma Aldrich. Graphite powder (<$20\mu m$) was purchased from Sigma–Aldrich (St. Louis, USA). $\text{FeCl}_3$-$4\text{H}_2\text{O}$, $\text{FeCl}_3$-$6\text{H}_2\text{O}$, $\text{KMnO}_4$, $\text{BaCl}_2$, $\text{NaNO}_3$, $\text{NaCl}$, $\text{H}_2\text{SO}_4$, $\text{H}_2\text{O}_2$, $\text{NH}_4\text{OH}$ and HCl were purchased from Merck (Darmstadt, Germany). The standard solution of authentic digoxin was prepared
by dissolving an accurate mass of the bulk drug in an appropriate volume of methanol. Additional dilute solutions were prepared daily by accurate dilution just before use. De-ionized (DI) water was used for preparation of aqueous solutions.

2.2. Instruments

UV-1800 UV-VIS Spectrophotometer from Shimadzu, Labnet’s Vortex Mixer VX-200 and New Brunswick Innova 4000 Incubator Shaker were used in this study. The centrifugation was performed on a KUBOTA 6800 centrifuge (KUBOTA Corporation, Japan). X-ray diffraction (XRD) patterns of materials were recorded on a Siemens D 5000 X-Ray diffractometer (Texas, USA) with a Cu Kα anode (λ = 1.54 Å) operating at 40 kV and 30 mA. TEM analysis was conducted on a Carl Zeiss LEO 906 electron microscope operated at 100 kV (Oberkochen, Germany). Fourier transform infrared (FTIR) spectra analysis occurred, in which, stretching vibrations of the (S O) and stretching of OH groups in the SO3H was confirmed in the region of 1036, 1153 and 3367 cm⁻¹, respectively (Figure 2).

XRD was conducted to prove structural properties of Fe3O4–GO–SO3H (Figure 3). Fe3O4–GO–SO3H showed a sharp diffraction peak in 34.90° that originated from GO on its (0 0 2) layer planes. Moreover, Fe3O4 resulted in some low intensity peaks. In general, XRD peaks of absorbent were indexed to (0 0 2), (3 1 1), (4 0 0), (4 2 2) and (5 1 1) planes of a cubic unit cell of magnetite, appearing at 34.90°, 45.53°, 56.21° 64.01° and 67.29°, respectively (Figure 3).

Another important factor that affects the application of absorbent is thermal stability. Thermal stability of Fe3O4–GO–SO3H was investigated by TGA in dry air (Figure 4). The mass loss (64%) might mainly result from the oxidation of carbon and removal of oxygen containing groups. The distinct mass loss appeared at the temperature higher than 170, indicating as-prepared Fe3O4–GO–SO3H has a good thermal stability and can be used as a suitable absorbent in wastewater treatment (Figure 4).

3. Results and discussion

3.1. Synthesis of graphene oxide (GO)

Hummer method was utilized to prepare GO from purified natural graphite [32] According to modified Hummer method, 0.5 g of graphite powder was added to 50 mL of 98% H2SO4 in an ice bath. Furthermore, in adjusted temperature, shaking solution was mixed with 2 g of KMnO4 slowly and stirred for 2 h at temperatures below 10°C and followed by 1 h shaking at 35°C. So, 50 mL of DI water was used to dilute reaction mixture in temperature below 100°C. After 1 h stirring DI water utilized to diluted solution to approximately 150 mL. Further, in order to change the color of solution to brilliant yellow 10 mL of 30% H2O2 was used. After plenty washing processes the pH of the supernatant become neutral. Finally the resulting solid was dried and brown powder was obtained.

3.2. Synthesis of Fe3O4–GO–SO3H (magnetic adsorbent)

In order to synthesis of Fe3O4–GO–SO3H graphene oxide was mixed with FeCl3·6H2O and FeCl2·4H2O (2:1 mole ratio). Then this solution was ultrasonicated for 30 min, and 20 mL of 30% ammonia solution in DI water was added to above solution. Eventually brown powder of Fe3O4 doped GO is ready to use [33, 34].

3.3. Characterization of absorbent (Fe3O4–GO–SO3H) before adsorption of drug

SEM and TEM microscopy were occurred to reveal morphological characteristics of Fe3O4–GO–SO3H. (Figure 1(A,B)) single atomic layer, thickness nano structures and their dispersity were observed. FESEM analysis confirmed the presence of Fe3O4 on the surface of GO. According to TEM images presence of Fe3O4 nanoparticles on GO structure was appeared as bright dots (Figure 1(B)). Moreover, spherical shape and the distribution of Fe3O4 nanoparticles on GO is obvious in TEM image. Further, FT-IR spectra analysis occurred, in which, stretching vibrations of the (S O) and stretching of OH groups in the SO3H was confirmed in the region of 1036, 1153 and 3367 cm⁻¹, respectively (Figure 2).

XRD was conducted to prove structural properties of Fe3O4–GO–SO3H (Figure 3). Fe3O4–GO–SO3H showed a sharp diffraction peak in 34.90° that originated from GO on its (0 0 2) layer planes. Moreover, Fe3O4 resulted in some low intensity peaks. In general, XRD peaks of absorbent were indexed to (0 0 2), (3 1 1), (4 0 0), (4 2 2) and (5 1 1) planes of a cubic unit cell of magnetite, appearing at 34.90°, 45.53°, 56.21° 64.01° and 67.29°, respectively (Figure 3).

Another important factor that affects the application of absorbent is thermal stability. Thermal stability of Fe3O4–GO–SO3H was investigated by TGA in dry air (Figure 4). The mass loss (64%) might mainly result from the oxidation of carbon and removal of oxygen containing groups. The distinct mass loss appeared at the temperature higher than 170, indicating as-prepared Fe3O4–GO–SO3H has a good thermal stability and can be used as a suitable absorbent in wastewater treatment (Figure 4).

3.4. Characterization of Fe3O4–GO–SO3H after adsorption of digoxin

XRD and FT-IR was conducted to prove structural properties of Fe3O4–GO–SO3H (Figures 2 and 3). Another important factor that affects the application of adsorbent is its thermal stability. The FTIR spectra of the Fe3O4–GO–SO3H and digoxin/Fe3O4–GO–SO3H, were shown in Figure 5. The FTIR spectrum of absorbent showed a peak between 500 and 750 cm⁻¹ (Fe–O), verifying the existence of Fe3O4, and they both presented the peaks around 1609 cm⁻¹ (C=O stretching vibrations of –COOH) and 3420 cm⁻¹ (–OH), which confirmed the presence of GO. Moreover, according to previous studies conducted by previous researchers, bare GO reveals plenty characteristic bands at 1719,
1222, and 1060 cm\(^{-1}\), which are ascribed to the GO carbonyl stretching, O–H deformation vibration, and C–OH and C–O stretching, respectively. The infrared spectrum of pure digoxin revealed absorption bands at \(\sim\)3400 cm\(^{-1}\) related to -OH stretching vibration; at \(\sim\)3000–2900 cm\(^{-1}\) equivalent to C–CH\(_2\) and CH\(_2\) stretching vibration; at \(\sim\)1750 cm\(^{-1}\) corresponding to -C\(=\)O stretching vibration; at \(\sim\)1400 cm\(^{-1}\) attributed to conjugated C= C of aromatic groups; at \(\sim\)1300 cm\(^{-1}\) equivalent to the bending mode of -CH3 and at \(\sim\)1200–1000 cm\(^{-1}\) corresponding to skeletal aromatic ring vibration. The FTIR results reported for pure digoxin were similar to those previously described.

The XRD spectra were recorded in a range of 2\(\theta\) from 5\(^{\circ}\) to 50\(^{\circ}\) and show (001) diffraction peak at 2\(\theta\) = 11.0\(^{\circ}\) for GO, indicating the distance between graphene layers. The XRD pattern of MGO is very similar to that of the pristine Fe\(_3\)O\(_4\), with diffraction peaks which can be indexed as the characteristic (200), (311), (400), (422), (511) and (440) reflections of the pure cubic spinel crystal structure of Fe\(_3\)O\(_4\) (JCPDS no. 19– 0629).
The thermal stability of Fe₃O₄–GO–SO₃H was investigated by TGA in dry air (Figure 4). The mass loss (64%) might mainly result from the oxidation of carbon and removal of oxygen containing groups. The distinct mass loss appeared at the temperature higher than 210, indicating as-prepared Fe₃O₄–GO–SO₃H has a good thermal stability and can be used as a suitable absorbent in wastewater treatment (Figure 4). As can be seen, a weight loss of 30% at 250 °C due to the water content. Compared curves a (Fe₃O₄–GO–SO₃H) and b (digoxin-Fe₃O₄–GO–SO₃H), more decreasing of weight 4.6% appeared which was shown in range of 300 to 350 °C, and attributed to the coating of digoxin.
3.5. Adsorption study

All experiments were performed by providing 500 ppm of Fe₃O₄–GO–SO₃H as absorbent. Then different concentrations of aqueous solution of absorbent (10-20-40-80-100-500 ppm) was provided from main stock by DI water. In order to carry out the absorption process, the pre-prepared digoxin solutions was incubated with absorbent for 1 h. In the following step, incubated solutions were centrifuged for about 15 min in 1000 rpm. Finally, deposited of adsorption sediment was collected. Then, the UV/Vis spectra of digoxin and absorbent was recorded at various concentrations (Figures 5 and 6). So, the absorbent concentration, amount of digoxin and incubation time were optimized as

Figure 5. UV/Vis spectra (A) and histogram (B) of absorbent in different concentration (1, 050, 100, 300, 500 ppm). (n = 3).

Figure 6. UV/vis spectra (a) and histogram (b) of digoxin in the presence of Fe₃O₄–GO–SO₃H in different concentration (0.5, 1, 5, 10, 20 ppm). (n = 3).
500 ppm and 1 ppm at 10 min, respectively (Figure 7). Finally, deposited of adsorption sediment was collected.

3.5.1. Optimization of digoxin and absorbent concentration and reaction time

In order to optimize the reaction condition occurred between digoxin and absorbent, a multiple concentrations of absorbent (10-20-40-80-100 ppm) and digoxin (0.5, 1, 5, 10, ppm) was made. Successive, reactions were performed with different concentrations of digoxin at different incubation times. The optimize saturation point of absorbent concentration in which absorbent is saturated was estimated as 500 ppm. Furthermore, the minimum amount of digoxin that absorbed was estimated as 1 ppm (Figures 5 and 6). Incubation time was the other important factor which was optimized in 10 min (Figure 7).

3.5.2. Optimization of digoxin and absorbance concentration and reaction time

In order to optimize the reaction condition occurred between digoxin and absorbent, multiple concentrations of absorbent (10-20-40-80-100 ppm) and verity digoxin solutions (0.5, 1, 5, 10, ppm) was mixed. Successive, reactions were performed with different concentrations of digoxin at different times. The optimize saturation point of absorbent concentration in which absorbent is saturated was estimated 500 ppm. Furthermore, the minimum amount of digoxin that absorbed was estimated 1 ppm. Incubation time was the other important factor which were optimized in 10 min.

UV-Vis spectrophotometry was used in this work for determination absorbance of digoxin by Fe₃O₄–GO–SO₃H in different concentrations. The magnetic absorbent was mixed with different concentrations of digoxin and the analyte was adsorbed by Fe₃O₄–GO–SO₃H as absorbent. Then, UV/Vis spectra response of Fe₃O₄–GO–SO₃H in different amount of absorbent (1, 050, 100, 300, 500 ppm), in different concentration of digoxin (0.5, 1, 5, 10, 20 ppm) and in different incubation time (1, 015, 202, 530 min) were analyzed. By increasing the amount of absorbent, the intensity of UV/Vis absorption of digoxin increased respectively, which revealed the proper potential of Fe₃O₄–GO–SO₃H as efficient absorbent to removal of digoxin based on linear relationship of absorbents amount and its application. Moreover, in the presence of a constant amount of absorbent and various concentrations of digoxin, the intensity of UV/Vis absorption peaks decreased by increasing the concentration of digoxin, which indicates the saturation ability of Fe₃O₄–GO–SO₃H absorbent. On the other hand, by increasing the incubation time of digoxin and Fe₃O₂–GO–SO₃H reaction, the intensity of UV/Vis peaks of absorbent were decreases, which also indicates the saturation of the absorbent.

Figure 7. UV/vis spectra response (a) and histogram (b) of digoxin in the presence of Fe₃O₄–GO–SO₃H in different time of incubation (1, 015, 202, 530 min). (n = 3).
Adsorption is often regarded as a common method for the removal of pollutants in gas and liquid phases. Several strong points of this approach include cost-effectiveness and high performance. Thanks to the good reusability of absorbents, the overall cost can be reduced. Moreover, the adsorption is highly compatible with organic-derived hazardous wastes including digoxin contaminant. Therefore, the IBU degradation by the adsorption process has been rapidly developed. According to the above discussed example, in the adsorption process, solid adsorbents play a decisive role in removing the contaminants. Heterogeneous materials have undergone a long history, especially nanostructured graphene based magnetic nanomaterials. Thanks to the high surface area along with open metal sites, these materials have been considered as ideal platforms towards removal of drug residues.

Comparison of the performance of $\text{Fe}_3\text{O}_4$–GO–SO$_3$H with previous reports indicated that, proposed adsorb has various advantage such as magnetic properties, high surface are and excellent electrostatic interaction which lead to efficient removal of digoxin from aqueous solution. Due to existence of $\text{Fe}_3\text{O}_4$NPs as magnetic core, this adsorbent can be separated using simple external magnetic and there is no need to high cost method for the removal of adsorbent from sample solutions. Also, high surface area of GO lead to dense loading of digoxin on the surface of nanocomposite (adsorbent) and high yield of reaction was obtained. On the other hand acidic agent on the structure of adsorbent is important item which lead to electrostatic interaction with the candidate contamination (digoxin). Therefore, purposed adsorbent is an excellent candidate than other materials for this purpose. According to the magnetic studies $\alpha$-Fe$_3$O$_4$–GO–SO$_3$H, nanocomposites exhibit a ferromagnetic behavior with small coercivity and remnant magnetization at room temperature, which is desirable for many practical applications, such as water purification systems, as it can be removed from the contaminated water. The hybrid material was separated after being exposed to the magnetic field. However, additional studies should be done since $\alpha$-Fe$_3$O$_4$ nanoparticles reduce the adsorption capability of GO-SO$_3$H. The magnetization is probably enough to allow magnetic separation in laboratory-scale systems but might not be high enough to allow separation in large wastewater volumes.

4. Conclusion

In this study, $\text{Fe}_3\text{O}_4$–GO–SO$_3$H was synthesized and utilized to absorption and removal of digoxin from aqueous solution. $\text{Fe}_3\text{O}_4$–GO–SO$_3$H (adsorbent) was characterized by Scanning electron microscopy (SEM), Transmission electron microscope (TEM), thermal gravimetric analysis (TGA), Fourier-transform infrared spectroscopy (FTIR) and X-ray diffraction (XRD). All characterization analyses confirmed the adsorption ability of $\text{Fe}_3\text{O}_4$–GO–SO$_3$H and separation of digoxin by candidate absorbent. The optimized concentration of absorbent and digoxin were 500 and 1 ppm respectively, in which the optimize reaction time was lasting 10 min. Therefore, this simple, cost effective and reliable method for the separation of digoxin from aqueous solution, could pave a new way for solving small piece of the larger puzzle in holistic risk assessment.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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References

1. Hollman A. Drugs for atrial fibrillation. Digoxin comes from Digitalis lanata. BMJ. 1996;312(7035): 912.
2. Salamon JN, Kelesidis I, Msaouel P, et al. Outcomes in World Health Organization group II pulmonary hypertension: mortality and readmission trends with systolic and preserved ejection fraction-induced pulmonary hypertension. J Card Fail. 2014; 20(7):467–475.
3. Khand AU, Rankin AC, Martin W, et al. Carvedilol alone or in combination with digoxin for the management of atrial fibrillation in patients with heart failure? J Am Coll Cardiol. 2003;42(11):1944–1951.
4. Saunders K, Amerasinghe A, Saunders K. Dose of digoxin prescribed in the UK compared with France and the USA. The Lancet. 1997;349(9055): 833–836.
5. Rasmussen HH, Okita GT, Hertz RS, et al. Inhibition of electrogenic Na (+)-pumping in isolated atrial tissue from patients treated with digoxin. J Pharmacol Exp Ther. 1990;252(1):60–64.
6. Konstantinou DM, Kavrounis H, Giannakoulas G. Digoxin in heart failure with a reduced ejection fraction: a risk factor or a risk marker? Cardiology. 2016;134(3):311–319.
7. Kasprzyk-Hordern B, Dinsdale RM, Guwy AJ. Illicit drugs and pharmaceuticals in the environment: forensic applications of environmental data, part 2: pharmaceuticals as chemical markers of faecal water contamination. Environ Pollut. 2009;157(6):1778–1786.
8. Arenas-Sánchez A, Rico A, Vighi M. Effects of water scarcity and chemical pollution in aquatic ecosystems: state of the art. Sci Total Environ. 2016; 572:390–403.
9. Sistik P, Urinovska R, Brozmanova H, et al. Routine therapeutic drug monitoring of haloperidol in human serum by liquid chromatography-tandem mass spectrometry. Clin Ther. 2017;39(8):e84–e85.
10. Dodig S. Interferences in quantitative immunochemical methods. Biochem Med. 2009;19(1):50–62.
11. Feng J, Jester BW, Tinberg CE, et al. A general strategy to construct small molecule biosensors in eukaryotes. Elife. 2015;4:e01066.
12. Liu G, Jin W, Xu N. Graphene-based membranes. Chem Soc Rev. 2015;44(15):5016–5030.
13. Yola ML, Atar N, Üstündag Z, et al. A novel voltammetric sensor based on p-aminophenol functionalized graphene oxide/gold nanoparticles for determining quercitin in the presence of ascorbic acid. Electroanal Chem. 2013;698:9–16.
14. Lütfi Yola M, Kumar Gupta V, Eren T, et al. Novel electro analytical nanosensor based on graphene oxide/silver nanoparticles for simultaneous determination of quercitin and morin. Electrochim Acta. 2014;120:204–211.
15. Lütfi Yola M, Eren T, Atar N. A sensitive molecular imprinted electrochemical sensor based on gold nanoparticles decorated graphene oxide: application to selective determination of tyrosine in milk. Sens Actuat B. 2015;210:149–157.
16. Lütfi Yola M, Atar N, Eren T, et al. Sensitive and selective determination of aqueous triclosan based on gold nanoparticles on polyoxometalate/reduced graphene oxide nanohybrid. RSC Adv. 2015;5(81): 65953–65962.
17. Lütfi Yola M, Atar N, Eren T, et al. Direct-methanol fuel cell based on functionalized graphene oxide with mono-metallic and bi-metallic nanoparticles: electrochemical performances of nanomaterials for methanol oxidation. Electroanalysis. 2016; 28(3):570–579.
18. Voiry D, Yang J, Kupferberg J, et al. High-quality graphene via microwave reduction of solution-exfoliated graphene oxide. Science. 2016;353(6306): 1413–1416.
19. Rashid Z, Naeimi H, Zarnani A-H, et al. Facile fabrication of nickel immobilized on magnetic nanoparticles as an efficient affinity adsorbent for purification of his-tagged protein. Mater Sci Eng C Mater Biol Appl. 2017;80:670–676.
20. Wu N, Wei H, Zhang L. Efficient removal of heavy metal ions with biopolymer template synthesized mesoporous titania beads of hundreds of micrometers size. Environ Sci Technol. 2012;46(1): 419–425.
21. Zhou L, Gao C, Xu W. Magnetic dendritic materials for highly efficient adsorption of dyes and drugs. ACS Appl Mater Interfaces. 2010;2(5):1483–1491.
22. Yang T, Hu X, Zhang P, et al. Study of pretreatment of quinoline in aqueous solution using activated carbon made from low-cost agricultural waste (walnut shells) modified with ammonium persulfate. Water Sci Technol. 2019;79(11):2086–2094.
23. Zhao Y, Guo T-x, Chen Z-y, et al. Simultaneous removal of SO2 and NO using M/NaClO2 complex absorbent. Chem Eng J. 2010;160(1):42–47.
24. Bonenfant D, Mimeault M, Hausler R. Determination of the structural features of distinct amines important for the absorption of CO2 and regeneration in aqueous solution. Ind Eng Chem Res. 2003;42(14):3179–3184.
25. Yang S-T, Chen S, Chang Y, et al. Removal of methylene blue from aqueous solution by graphene oxide. J Colloid Interface Sci. 2011;359(1):24–29.
26. Zhu D, Wu L, Wang B, et al. Determination of Ca and Mg in aqueous solution by laser-induced breakdown spectroscopy using absorbent paper substrates. Appl Opt. 2011;50(29):5695–5699.
27. Kim HM, Park J-H, Long NP, et al. Simultaneous determination of cardiovascular drugs in dried blood spot by liquid chromatography-tandem mass spectrometry. J Food Drug Anal. 2019;27(4): 906–914.
28. Keane S, Wallace G, Munday C, et al. Sensitive and robust LC-MS/MS analysis of digoxin in human plasma through optimization of in-source adduct formation. Bioanalysis. 2018;10(17):1401–1411.
29. Datta P. Immunoassay design for screening of drugs of abuse. Critical issues in alcohol and drugs of abuse testing. Netherlands: Elsevier; 2019. p. 121–128.
30. Nikfarjam A, Rezayan AH, Mohammadkhani G, et al. Label-free detection of digoxin using localized surface plasmon resonance-based nanobiosensor. Plasmonics. 2017;12(1):157–164.
31. Tatar S, Sağlık S. Comparison of UV-and second derivative-spectrophotometric and LC methods for the determination of valsartan in pharmaceutical formulation. J Pharm Biomed Anal. 2002;30(2): 371–375.
32. Bouhsain Z, Garrigues S, de la Guardia M. PLS-UV spectrophotometric method for the simultaneous
determination of paracetamol, acetylsalicylic acid and caffeine in pharmaceutical formulations. Fresenius' J Anal Chem. 1997;357(7):973–976.

33. Hummers WS Jr, Offeman RE. Preparation of graphitic oxide. J Am Chem Soc. 1958;80(6):1339–1339.

34. Hasanzadeh M, Shadjou N. (Fe3O4)-graphene oxide-SO3H as a new magnetic nanocatalyst for electro-oxidation and determination of selected parabens. J Nanosci Nanotechnol. 2013;13(7):4909–4916.