A Screen-Printed Electrode Modified With Graphene/Co$_3$O$_4$ Nanocomposite for Electrochemical Detection of Tramadol

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In this paper, graphene (Gr)/Co$_3$O$_4$ nanocomposite was synthesized and utilized for the development of a novel electrochemical sensor to detect tramadol. Tramadol determination was examined by linear sweep voltammetry, differential pulse voltammetry, cyclic voltammetry, and chronoamperometry on Gr/Co$_3$O$_4$/SPE in phosphate-buffered saline (PBS). Under the optimized condition, the detection limit of tramadol is 0.03 µM (S/N = 3) in the linear ranges of 0.1–500.0 µM. Furthermore, Gr/Co$_3$O$_4$/SPE was satisfactorily utilized to detect tramadol in tramadol tablet and urine specimens.

Keywords: electrochemical sensor, tramadol, graphene/Co$_3$O$_4$ nanocomposite, screen printed electrode, nanomaterials

INTRODUCTION

Tramadol is a synthetic analog of codeine that acts as a central analgesic. In terms of structure, there is a relationship between tramadol and codeine and morphine. Moreover, it acts as one of the opioid agonists in the body (Abu-Shawish et al., 2010). In addition, it is possible to use tramadol alone or combined with additional non-steroidal anti-inflammatory drugs (NSAIDs) when dealing with patients who have serious chronic pain, depression, spinal cord injuries, low back pain, and post-operative pain (Tetsunaga et al., 2015). Furthermore, it is increasingly being abused by opioid addicts. However, usual dosing requirements for oral consumption of the drug ranges between 50 and 100 mg per 4–6 h, with the maximum dose being 400 mg a day (Thévenin et al., 2008). Overdosing on tramadol can cause vomiting, problems in the central nervous system (CNS) and respiratory system, depression, dizziness, nausea, coma, tachycardia, and seizure (Scott and Perry, 2000). Tramadol is rapidly and nearly completely absorbed in oral usage, but excretion of roughly 10–30% of the parent drug happens un-metabolized in urine (Mohammadpour et al., 2019). Thus, for reasons related to treatment and the drug, it is of special significance to propose a sensitive technique to measure specimens containing of tramadol. At present, many methods have been
employed for measuring tramadol quantitatively, such as high-performance liquid chromatography (Kmetec and Roškar, 2003; Saccamanni et al., 2010), gas chromatography (Ghasemi, 2012), gas chromatography/mass spectrometry (El-Sayed et al., 2013), electrochemiluminescence (Ding et al., 2006), spectrophotometry (Glavanović et al., 2016), capillary electrophoresis (Cunha et al., 2017), and electrochemistry (Ghorbani-Bidkorbeh et al., 2010; Babaei et al., 2011; Chitravathi and Munichandraiah, 2016; Madrakian et al., 2017; Hassannezhad et al., 2019; Hassanvand and Jalali, 2019; Rokheefid and Shishehbor, 2019).

Nevertheless, some of these methods are limited due to complex sample procurement stages and the utilization of organic solvents. Electrochemical techniques have been proposed instead when analyzing drug and biological specimens because of the simplification, speed, inexpensive instruments, higher sensitivity, and precise analytical devices (Mahmoudi-Moghaddam et al., 2014; Prasad and Sreedhar, 2018; Eloheid and Elbashir, 2019; Tan et al., 2020; Xia et al., 2020). Considering the above features to detect diverse significant samples, researchers utilized many procedures for improving the electrode modification in order to enhance selectivity and sensitivity (Beitollahi and Sheikhshoaei, 2012; Soltani et al., 2014; Zhang et al., 2015; Deshmukh et al., 2018; Ghodsi et al., 2018; Mohammadi et al., 2018; Rabiee et al., 2018).

Nanomaterials are defined as substances possessing at least one dimension with ~100 nanometers. They are very interesting materials because of their unique electrical, magnetic, and optical, properties. These emergent features provide the potential for great impacts in medicine, electronics, and other fields (Zhu et al., 2015; Abdussalam-Mohammed, 2019; Elumalai et al., 2019). Now, interest has grown in using nanomaterials for modifying the electrode surface. However, owing to nanomaterials’ very good catalytic features and conductivity, we can use them for enhancing the electron transfer between the electrode surface and target analyte. Moreover, they can be used as the catalyst for increasing the electrochemical reaction (Beitollahi et al., 2008, 2012; Soltani et al., 2014; Zhang et al., 2015; Deshmukh et al., 2018; Ghodsi et al., 2018; Mohammadi et al., 2018; Rabiee et al., 2018).

In this regard, Gr is an ideal nanomaterial for electrochemical processes owing to its larger surface area, reasonable electrical conductivity, and inexpensiveness (Shao et al., 2010). In the fabrication of the electrochemical sensors and biosensors, the Gr-based electrodes have been considered interesting films for the sensing platforms as they cause synergy of the electrocatalytic activities and augment the sensor sensitivity (Zhang et al., 2011). In fact, the Gr sheets are very good host materials to make nanocomposites for high performance electrochemical measurements (Kim et al., 2009; Zhou et al., 2010; Vinodhikumar et al., 2018). Gr nanocomposites display acceptable benefits as one of the sensing platforms in electrochemical sensors (Luo et al., 2012; Thanh et al., 2016; Shahid et al., 2019).

Combining the advantages of the unique features of Gr together with those of GO (the increased absorption capability, larger active site, and wide availability), the Gr/Co3O4 nanocomposite provides stable and sensitive platforms for electroanalysis (Tavuz et al., 2013a,b; Feng et al., 2014). Therefore, we have used Gr/Co3O4 as one of the nanocomposite materials because it has the most reasonable features.

According to studies, the screen-printing technology used for microelectronics has a significant utilization for fabricating electrodes for disposable electrochemical sensors and biosensors (Tangkuaram et al., 2007; Gevaerd et al., 2020). In fact, an SPE enjoys simplified operation, versatility, inexpensiveness, portability, reliability, and lower sizes, and has the capability for mass production. Hence, it has widespread application in the field of electroanalytical chemistry (Nicholas et al., 2018; Khalilzadeh et al., 2020). Moreover, an SPE would avoid the cleaning procedure in contrast to the traditional electrodes, like a glassy carbon electrode (Renedo et al., 2007). SPE resolves the shortcomings of the traditional electrode systems, which require repeated recalibration and are not stable and suitable for on-site analyses, because their completion lasts several hours. Additionally, they require the use of professionals, as they need multiple isolation and washing phases. Therefore, the mentioned disadvantages of the traditional electrode systems resulted in their lower capability in comparison to the SPEs.

We aimed at providing a technique with higher simplification, sensitivity, and speed to electrochemically detect tramadol. Therefore, a Gr/Co3O4/SPE was fabricated by dropping Gr/Co3O4 over SPE to make a voltammetric sensor as well as evaluating tramadol voltammetric behaviors. According to our analysis, Gr/Co3O4/SPE exhibited more robust electrochemical oxidation for tramadol with a more negative potential. The present method was tested and verified using tramadol tablet and urine specimens, showing reasonable precision and recovery. To the best of our knowledge, the detection of tramadol by using Gr/Co3O4/SPE has not been reported yet.

**EXPERIMENTAL**

**Apparatus and Chemicals**

Autolab potentiostat/galvanostat (PGSTAT 302N, Eco Chemie, the Netherlands) was used to measure electrochemicals. The use of General Purpose Electrochemical System (GPES) software aimed at controlling the experimental conditions. Moreover, SPE (DropSens; DRP-110: Spain) possessed three typical graphite counters, unmodified graphite working, and silver pseudo-reference electrodes. Metrohm 710 pH meter was utilized for pH measurements.

Tramadol and other remaining reagents represented an analytical grade. Their preparation was carried out through Merck (Darmstadt, Germany). Orthophosphoric acid and the associated salts with a pH ranging higher than 2.0–9.0 have been utilized to prepare the buffer solutions.

**Synthesizing the Gr/Co3O4 Nanocomposite**

The synthesis of the Gr/Co3O4 composite was done via the chemical deposition of Co3O4 particles over the graphene oxide (GO), which was accompanied by reducing GO to Gr in NaBH4 solution. It is notable that Li et al. fixed synthesis and composition of the Gr/Co3O4 composite (Li et al., 2011). Therefore, we poured the graphite oxide (0.1 g) into 200 mL of ultra-high-purity water and placed it in an ultrasonic bath for 2 h in order to establish
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FIGURE 1 | EDX elemental mapping of (A) carbon, (B) oxygen, and (C) cobalt in Gr/Co$_3$O$_4$ nanocomposite.

FIGURE 2 | EDS spectrum of Gr/Co$_3$O$_4$ nanocomposite.

Preparation of Electrode

The bare SPE was coated by a Gr/Co$_3$O$_4$ nanocomposite. To prepare the Gr/Co$_3$O$_4$ nanocomposite stock solution in 1 mL of aqueous solution, the Gr/Co$_3$O$_4$ nanocomposite (1 mg) was distributed by 30-min ultra-sonication, whereas the Gr/Co$_3$O$_4$ nanocomposite suspension aliquots (5 µl) were cast on working electrodes. Then it was kept until the solvent was evaporated in room temperature.

Preparation of Real Sample

Five 50 mg tramadol pills (Amin Co., Iran) were used to prepare a solution by dissolving the pills (250 mg) in water (25 ml) in exposure to ultra-sonication. Then, different dilutions were poured in 25 ml volumetric flasks and reached final volume with PBS at pH of 7.0. The standard addition method was used to measure the tramadol concentrations.

RESULT AND DISCUSSION

Characterization of Nanostructures

The energy-dispersive X-ray spectroscopy (EDX) elemental mapping has been analyzed for the Gr/Co$_3$O$_4$ nanocomposite for the control of distributing the elements found in the nanocomposite (Figure 1). In order to have a clear result, Figures 1A–C shows the independent elemental distribution of C, O, and Co. Figure 1A represents the existence of GO as the carbon materials whereas Figure 1B (O) and Figure 1C (Co) show a big area coverage because of the densely packaged Co$_3$O$_4$ nanoparticles. The presence of all elements (oxygen, carbon, a GO suspension. Then, an aqueous solution (10 mL) of CoCl$_2$ (1.4 g CoCl$_2$.6H$_2$O) was added in this suspension. The mixture was shaken for two hours for completion of the ion exchange. The next stage concerned the drop wise addition of an aqueous solution (10 mL) of NaOH (1 equivalent) to the obtained mix by shaking for another hour. Afterwards, we achieved the solid using centrifugation via the ultrahigh purity water. Next, the product was distributed into ultra-high pure water (25 mL). Hydrogen peroxide (30%, 1.5 mL) was added to the obtained mix. This mix has been sealed into a 50 mL Teflon-lined stainless-steel autoclave. Then, heating was performed to 100$^\circ$C and it was kept at the mentioned temperature for four hours. Notably, we collected the solid product through centrifugation that had been accompanied by a suspension in the ultra-high purity water (25 mL). In addition, we added NaBH$_4$ (0.25 g) into the obtained suspension, and transported it to the autoclave heated to 120$^\circ$C. Finally, we kept it at the above temperature for four hours. Finally, we collected the obtained solid and used ultra-high purity water to wash it. The solid was dried to achieve the Gr/Co$_3$O$_4$ composite. The composite was gained as black powder.
and cobalt) in the Gr/Co₃O₄ nanocomposite was confirmed by EDS analysis (Figure 2). We applied the scanning electron microscope (SEM) for characterizing the morphology of the as-synthesized Gr/Co₃O₄ nanocomposite. A SEM image of the Gr/Co₃O₄ nanocomposite is given in Figure 3.

**Electrochemical Behavior of Tramadol on the Gr/Co₃O₄/SPE**

To study the electrochemical behaviors of tramadol, which was supposed to show dependence on pH, obtaining an optimum pH-value to reach acceptable outcomes is important. Thus, the modified electrode was employed in running the experiments with different pH values varying between 2.0 and 9.0. Eventually, the most desirable results were considered for electro-oxidation of tramadol at a pH of 7.0 (Figure 4).

Figure 5 represents cyclic voltammograms in the presence of 100.0 µM tramadol with the bare SPE (Curve a) and Gr/Co₃O₄/SPE (Curve b). Based on the CV outputs, the greatest oxidation of tramadol on the Gr/Co₃O₄/SPE occurred at 700 mV, which was ∼140 mV more negative than the bare SPE.

**The Scan Rate Effects on the Results**

The association between peak current and scan rate would supply helpful information considering the electrochemical mechanisms. Therefore, the scan rate effects on the peak current of tramadol were examined using LSV, at a range of 10–300 mVs⁻¹ in PBS (0.1 M, pH 7), according to Figure 6. The electrode response of tramadol was a diffusion-controlled procedure, as the oxidation peak current corresponded to the square root of the scan rate (Figure 6 inset).

**Chronoamperometric Analysis**

Chronoamperometric study was used to calculate the diffusion coefficient (D) of tramadol at the surface Gr/Co₃O₄/SPE at an optimum condition. Figure 7 displays the chronoamperometric outputs of the tramadol sample at different concentrations (PBS at pH of 7.0). In addition, Cottrell equation was recommended to perform electroactive moiety chronoamperometric analyses according to the mass transfer restricted conditions (Bard and Faulkner, 2001):

\[ I = nFAD^{1/2}C_0\pi^{-1/2}t^{-1/2} \]

Figure 7A indicates experimental findings regarding I vs. \( t^{-1/2} \), which shows the most acceptable fit for tramadol distinct concentrations. Then, the ultimate slopes relative to the straight lines in Figure 7A could be depicted vs. tramadol concentrations (Figure 7B). Thus, D mean-value equaled to 1.3 × 10⁻⁵ cm²/s with regard to Cottrell equation and resultant slopes.

**Calibration Curve**

The DPV method explored the association of the peak current with tramadol at different concentrations. As shown in Figure 8,
the DPVs of Gr/Co$_3$O$_4$/SPE in the presence of different concentrations of tramadol was recorded in the concentration ranging from 0.5 to 500.0 µM. The detection limit 30.0 nM was established for analysis of tramadol at the surface of Gr/Co$_3$O$_4$/SPE. The response time was ∼13 s.

The comparison study of the results for the determination of tramadol with different modified electrodes in the literature are listed in Table 1. The novel sensor presented in this study exhibits outstanding analytical performance for the determination of tramadol. The comparative data showed excellent efficiency of the proposed sensor over some earlier reported sensors. Thus, the fabricated electrode was appropriate for the determination of tramadol with the advantages of facile fabrication, ease of use, and low cost.
TABLE 1 | Comparing performances of the purposed electrochemical sensor with others for determination of tramadol.

| Electrochemical sensor | Method | Linear range (µM) | Limit of detection (µM) | References |
|------------------------|--------|-------------------|-------------------------|------------|
| CNPs/GCE\textsuperscript{a} | DPV | 10–1000 | 5 | Ghorbani-Bidkorbeh et al., 2010 |
| MWCNTs/GCE\textsuperscript{b} | DPV | 2–300 | 0.36 | Babaei et al., 2011 |
| Au NPs/cysteic acid/GCE\textsuperscript{c} | SWV\textsuperscript{d} | 0.5–63.5 | 0.17 | Hassannezhad et al., 2019 |
| g-C\textsubscript{3}N\textsubscript{4}/Fe\textsubscript{3}O\textsubscript{4}/CPE\textsuperscript{e} | DPV | 0.2–14.0 and 14.0–120.0 | 0.1 | Hassanvand and Jalali, 2019 |
| Au NPs/GrN/CPE\textsuperscript{f} | DPV | 1.0–100.0 | 0.82 | Rokhsifeld and Shishhehbore, 2019 |
| Magneto LDH/Fe\textsubscript{3}O\textsubscript{4}NPs/GCE\textsuperscript{g} | DPV | 1–200 | 0.3 | Madrakian et al., 2017 |
| PNB/GCE\textsuperscript{h} | DPV | 1–310 | 0.5 | Chitravathi and Munichandraiah, 2016 |
| Gr/Co\textsubscript{3}O\textsubscript{4}/SPE | DPV | 0.1–500.0 | 0.03 | This work |

\textsuperscript{a}Carbon nanoparticles modified glassy carbon electrode.
\textsuperscript{b}Multiwalled carbon nanotube modified glassy carbon electrode.
\textsuperscript{c}Au nanoparticles/cysteic acid modified glassy carbon electrode.
\textsuperscript{d}Square wave voltammetry.
\textsuperscript{e}Graphitic carbon nitride/Fe\textsubscript{3}O\textsubscript{4}nanocomposite modified carbon paste electrode.
\textsuperscript{f}Au nanoparticles/graphene nanosheet modified carbon paste electrode.
\textsuperscript{g}Magneto layer double hydroxide/Fe\textsubscript{3}O\textsubscript{4}nanoparticles modified glassy carbon electrode.
\textsuperscript{h}Poly(Nile blue) modified glassy carbon electrode.

TABLE 2 | The application of Gr/Co\textsubscript{3}O\textsubscript{4}/SPE for determination of tramadol in tramadol tablet and urine samples (n = 5).

| Sample    | Spiked | Found | Recovery (%) | R.S.D. (%) |
|-----------|--------|-------|--------------|------------|
| Tramadol tablet | 0      | 5     | -            | 3.5        |
| 2.5       | 7.3    | 97.3  | 2.7          |
| 7.5       | 12.8   | 102.4 | 2.3          |
| 12.5      | 17.9   | 102.3 | 2.3          |
| 17.5      | 22.3   | 99.1  | 1.9          |
| Urine     | 0      | 5.1   | 2.7          |
| 10        | 9.8    | 98    | 1.9          |
| 15        | 15.5   | 103.3 | 3.4          |
| 20        | 19.8   | 99    | 1.9          |

All concentrations are in µM.

Stability and Repeatability of Gr/Co\textsubscript{3}O\textsubscript{4}/SPE

The stability of Gr/Co\textsubscript{3}O\textsubscript{4}/SPE was evaluated using records of the oxidation signal of 40.0 µM tramadol over 2 weeks. A 2.5% deviation was identified with compression of the first oxidation signal of tramadol after 2 weeks, indicating good stability of Gr/Co\textsubscript{3}O\textsubscript{4}/SPE as a voltammetric sensor.

Examination of the modified SPE anti-fouling features regarding tramadol oxidation and the corresponding products carried out through CV for the modified SPE prior and subsequent to application when tramadol was present. CVs were recorded when tramadol was present following cycling the potential 15 times at a 50 mV s\textsuperscript{-1}. The currents were reduced by more than 2.3 %, while the peak potential faced no alterations.

Analyzing the Real Samples

Finally, Gr/Co\textsubscript{3}O\textsubscript{4}/SPE performance as a new electrochemical sensor used to analyze tramadol in tramadol tablet and urine samples was evaluated. Table 2 indicates the collected data and, according to the recovery data, Gr/Co\textsubscript{3}O\textsubscript{4}/SPE could be regarded as a sensitive sensor to analyze tramadol in actual samples.

CONCLUSIONS

We used a simplified procedure to synthesize Gr/Co\textsubscript{3}O\textsubscript{4} and characterized it by EDX and SEM. Then, it was utilized for the electrochemical detection of tramadol. The modified electrode exhibited good electrocatalytic activity and sensitivity. Linear response of its peak current on tramadol concentrations ranged between 0.1 and 500.0 µM, and LOD was 0.03 µM. Finally, the modified electrode was substantially used for tramadol analysis in the real specimens. The proposed method offers a sensitive approach to detect tramadol in drug and biological formulations.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

All authors have contributed to the scientific discussion, investigation, analysis, and manuscript writing and editing.

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REFERENCES

Abdussalam-Mohammed, W. (2019). Review of the rapetive applications of nanotechnology in medicine field and its side effects. J. Chem. Rev. 1, 243–251. doi: 10.33945/SAMI/JCR.2019.3.5

Abu-Shawish, H. M., Ghalwa, N. A., Zaggout, F. R., Saadeh, S. M., Al-Dalou, A. R., and Abou Assi, A. A. (2010). Improved determination of tramadol hydrochloride in biological fluids and pharmaceutical preparations utilizing a modified carbon paste electrode. Biochem. Eng. J. 48, 237–245. doi: 10.1016/j.bej.2009.10.019

Babari, A., Taheri, A. R., and Afraisiabi, M. (2011). A multi-walled carbon nanotube-modified glassy carbon electrode as a new sensor for the sensitive simultaneous determination of paracetamol and tramadol in pharmaceutical preparations and biological fluids. J. Braz. Chem. Soc. 22, 1549–1558. doi: 10.1590/S0103-50532011008000020

Bard, A. J., and Faulkner, L. R. (2001). Electrochemical Methods: Fundamentals and Applications. 2nd ed. New York, NY: Wiley.

Beitollahi, H., Dourandish, Z., Tajik, S., Ganjali, M. R., Norouzi, P., and Tajik, S. (2008). Fast determination of codeine, orphenadrine, promethazine, scopolamine, tramadol, and paracetamol in pharmaceutical formulations by capillary electrophoresis. J. Sep. Sci. 31, 1815–1823. doi: 10.1002/jssc.200601275

Cunha, R. R., Ribeiro, M. M., Muñoz, R. A., and Richter, E. M. (2017). Voltammetric determination of tramadol, paracetamol and caffeine using poly (Nile blue) modified glassy carbon electrode. J. Electroanal. Chem. 764, 93–103. doi: 10.1016/j.jelechem.2017.06.060

Chitravathi, S., and Munichandraiah, N. (2016). Determination of acetaminophen with dysprosium tungstate nanoparticles in voltammetric determination of epinephrine in the presence of acetylcholine. J. Rare Earth. 36, 750–757. doi: 10.1016/j.jre.2018.01.010

Ding, S. N., Xu, J. J., Zhang, W. J., and Chen, H. Y. (2006). Tris (2,2′,4,4′,6,6′-hexafluoro-3,3-diacylamino-3′-acetic acid). Chinese Chem. Lett. 25, 511–516. doi: 10.1016/j.ccl.2014.01.004

Elumalai, D., Sathiyaraj, M., Vimalkumar, E., Kaleena, P. K., Hemavathi, M., and Venkatesh, P. (2019). Bio fabricated of silver nanoparticles using Ocimum basilicum and its efficacy of antimicrobial and antioxidant activity. Asian J. Green Chem. 3, 103–124. doi: 10.22034/ajgc.2018.67295

Feng, Z. L., Yao, Y. Y., Xu, J. K., Zhang, L., Wang, Z. F., and Wen, Y. P. (2014). One-step co-electrodeposition of graphene oxide doped poly (hydromethylated-3,4-ethylenedioxythiophene) film and its electrochemical studies of indole-3-acetic acid. Chinese Chem. Lett. 25, 511–516. doi: 10.1016/j.ccl.2014.01.004

Gevaerd, A., Banks, C. E., Bergamini, M. F., and Marcolino-Junior, I. H. (2020). Nanomodified Screen-Printed Electrode for direct determination of aflatoxin B1 in malted barley samples. Sens. Actuat. B Chem. 307:127547. doi: 10.1016/j.snb.2019.127547

Ghasemi, E. (2012). Optimization of solvent bar microextraction combined with gas chromatography mass spectrometry for preconcentration and determination of tramadol in biological samples. J. Chromatogr. A 1251, 48–53. doi: 10.1016/j.chroma.2012.06.060

Ghodsi, J., Rafati, A. A., and Shoja, Y. (2018). Determination of acetaminophen using a glassy carbon electrode modified by horseradish peroxidase trapped in MWNTs/silica sol-gel matrix. Adv. J. Chem. 1, 39–55. doi: 10.2988/88/SAMI/AJCA.2015.8.3959

Ghorbani-Bidkorbeh, F., Shahrokhsian, S., Mohammadi, A., and Dinavard, R. (2010). Simultaneous voltammetric determination of tramadol and acetaminophen using carbon nanoparticles modified glassy carbon electrode. Electrochim. Acta 55, 2752–2759. doi: 10.1016/j.electacta.2009.12.052

Glavanovic, S., Glavanovic, M., and Tomisić, V. (2016). Simultaneous quantitative determination of paracetamol and tramadol in tablet formulation using UV spectrophotometry and chemometric methods. Spectrochim. Acta A Mol. Biomol. Spectros. 157, 258–264. doi: 10.1016/j.saa.2015.12.020

Hassannezhad, M., Hosseini, M., Ganjali, M. R., and Arvand, M. (2019). A graphite carbon nitride (gC3N4/Fe3O4) nanocomposite: an efficient electrode material for the electrochemical determination of tramadol in human biological fluids. Anal. Methods 11, 2064–2071. doi: 10.1039/C9AY00146H

Hassanvand, Z., and Jalali, F. (2019). Gold nanoparticles/cysteic acid modified electrode for simultaneous electrochemical determination of tramadol and paracetamol. Anal. Biochem. Res. 6, 393–404. doi: 10.22036/abcr.2019.170247.1305

Khalilzadeh, M. A., Tajik, S., Beitollahi, H., and Venditti, R. A. (2020). Green synthesis of magnetic nanocomposite with iron oxide deposited on cellulose nanocrystals with copper (Fe3O4@CNC/Cu): investigation of catalytic activity for the development of a venlafaxine electrochemical sensor. Ind. Eng. Chem. Res. 59, 4219–4228. doi: 10.1021/acs.iecr.9b06214

Kim, K. S., Zhao, Y., Jang, H., Lee, S. Y., Kim, J. M., Kim, K. S., et al. (2009). Large-scale pattern growth of graphene films for stretchable transparent electrodes. Nature 457, 706–710. doi: 10.1038/457719a

Kmetec, V., and Roskar, R. (2003). HPLC determination of tramadol in human breast milk. J. Pharm. Biomed. Anal. 32, 1061–1066. doi: 10.1016/S0731-7085(03)00209-7

Li, B., Cao, H., Shao, J., Li, G., Qu, M., and Yin, G. (2011). CoO4@graphene composites as anode materials for high-performance lithium ion batteries. Inorg. Chem. 50, 1628–1632. doi: 10.1021/ic1023086

Li, D. W., Li, Y. T., Song, W., and Long, Y. T. (2010). Simultaneous determination of dihydroxybenzene isomers using disposable screen-printed electrode modified by multiwalled carbon nanotubes and gold nanoparticles. Anal. Methods 2, 837–843. doi: 10.1039/c0ay00076k

Li, Y., Zhao, X., Liu, X., Zhang, L., Liu, H., and Wang, H. (2016). Electrochemical determination of bisphenol A at ordered mesoporous carbon modified nano-carbon ionic liquid paste electrode. Talanta 148, 362–369. doi: 10.1016/j.talanta.2015.11.010

Luo, L., Zhu, L., and Wang, Z. (2012). Nonenzymatic amperometric determination of glucose by CuO nanocubes–graphene nanocomposite modified electrode. Bioelectrochemistry 88, 156–163. doi: 10.1016/j.bioelechem.2012.03.006

Madrakian, T., Alizadeh, S., Bahram, M., and Afkhami, A. (2017). A novel electrochemical sensor based on magneto LDH/Fe3O4 nanoparticles/graphene carbon electrode for voltammetric determination of tramadol in real samples. Ions 23, 1005–1015. doi: 10.3391/i1581-016-1871-2

Mahmoudi-Moghaddam, H., Beitollahi, H., Tajik, S., Malakootian, M., and Karim-Maleh, H. (2014). Simultaneous determination of hydroxyamine and phenol using a nanostructure-based electrochemical sensor. Environ. Monit. Assess. 186, 7431–7441. doi: 10.1007/s10661-014-3938-8

Moghaddam, H. M., Beitollahi, H., Tajik, S., Sheikhshoae, I., and Biparva, P. (2015). Fabrication of novel TiO2 nanoparticles/Mn (III) salen doped carbon paste electrode: application as electrochemical sensor for the determination of hydrazine in the presence of phenol. Environ. Monit. Assess. 187, 1–12. doi: 10.1007/s10661-015-5629-9

Mohammadi, S., Taheri, A., and Rezayat-Zad, Z. (2018). Ultrasensitive and selective non-enzymatic glucose detection based on pt electrode modified by carbon nanotubes/graphene oxide/nickel hydroxide-Nafion
hybrid composite in alkaline media. *Prog. Chem. Biochem. Res.* 1, 1–10. doi: 10.29088/SAMI/PCBRR.2018.1.110

Mohammadpour, A., Ashkezari, M. D., Farahmand, B., and Shokrzadeh, M. (2019). Demographic characteristics and functional performance of the kidneys and hearts of patients with acute trimalad toxicity. *Drug Res.* 69, 207–210. doi: 10.1055/a-0646-3918

Nicholas, P., Pittson, R., and Hart, J. P. (2018). Development of a simple, low cost chronoamperometric assay for fructose based on a commercial graphite-nanoparticle modified screen-printed carbon electrode. *Food Chem.* 241, 122–126. doi: 10.1016/j.foodchem.2017.08.077

Prasad, P., and Sreedhar, N. Y. (2018). Effective SWCNTs/Nafion electrochemical sensor for detection of dicationic pesticide in water and agricultural food samples. *Chem. Methods* 2, 277–290. doi: 10.22034/cmec.2018.63835

Rabiee, N., Safarkhani, M., and Rabiee, M. (2018). Ultra-sensitive electrochemical on-line determination of Clarithromycin based on Poly (L-Aspartic acid)/graphite oxide/pristine graphene/glassy carbon electrode. *Asian J. Nanosci. Mater.* 1, 63–73. doi: 10.26655/ajnanomat.2018.3.3

Renedo, O. D., Alonso-Lomillo, M. A., and Martinez, M. A. (2007). Recent developments in the field of screen-printed electrodes and their related applications. *Talanta* 73, 202–219. doi: 10.1016/j.talanta.2007.03.050

Rokhsheid, N., and Shishehbore, M. R. (2019). Synthesis and characterization of an Au nanoparticles/graphene nanosheet nanocomposite and its application for the simultaneous determination of tramadol and acetaminophen. *Anal. Methods* 11, 5150–5159. doi: 10.1039/C9AY01497G

Saccomanni, G., Del Carlo, S., Giorgi, M., Manera, C., Saba, A., and Macchia, M. (2010). Determination of tramadol and metabolites by HPLC-FL and HPLC-MS/MS in urine of dogs. *J. Pharm. Biomed. Anal.* 53, 194–199. doi: 10.1016/j.jpba.2010.03.016

Scotch, L. J., and Perry, C. M. (2000). Tramadol. *Drugs* 60, 139–176. doi: 10.2165/00003495-200060010-00008

Shahid, M. M., Ramesh Kumar, P., Numan, A., Shahabuddin, S., Alizadeh, M., Khiew, P. S., et al. (2019). A cobalt oxide nanocubes interleaved reduced graphene oxide nanocomposite modified glassy carbon electrode for amperometric determination of serotonin. *Mater. Sci. Eng. C* 100, 388–395. doi: 10.1016/j.msec.2019.02.107

Shao, Y., Wang, J., Wu, H., Liu, J., Aksay, I. A., and Lin, Y. (2010). Graphene based electrochemical sensors and biosensors: a review. *Electroanalysis* 22, 1027–1036. doi: 10.1002/elan.200900571

Soltani, H., Beitollahi, H., Haleh Mehrjardi, A. H., Tajik, S., and Torkzadeh-Mahani, M. (2014). Voltammetric determination of glutathione using a modified single walled carbon nanotubes paste electrode. *Anal. Bioanal. Electrochem.* 6, 67–79.

Tan, C., Zhao, J., Sun, P., Zheng, W., and Cui, G. (2020). Gold nanoparticle decorated poly(pyrrole)/graphene oxide nanosheets as a modified electrode for simultaneous determination of ascorbic acid, dopamine and uric acid. *New J. Chem.* 44, 4916–4926. doi: 10.1039/D0NJ00016E

Tangkuaram, T., Poncho, C., Kangkasomboon, T., Katikawong, P., and Veerarsi, W. (2007). Design and development of a highly stable hydrogen peroxide biosensor on screen printed carbon electrode based on horseradish peroxidase bound with gold nanoparticles in the matrix of chitosan. *Biosens. Bioelectron.* 22, 2071–2078. doi: 10.1016/j.bios.2006.09.011

Tetsunaga, T., Tetsuna, T., Tanaka, M., and Ozaki, T. (2015). Efficacy of tramadol–acetaminophen tablets in low back pain patients with depression. *J. Orthop.* Sci. 20, 281–286. doi: 10.1007/s00776-014-0674-4

Thanh, T. D., Balamsurugan, J., Lee, S. H., Kim, N. H., and Lee, J. H. (2016). Effective seed-assisted synthesis of gold nanoparticles anchored nitrogen-doped graphene for electrochemical detection of glucose and dopamine. *Biosens. Bioelectron.* 81, 259–267. doi: 10.1016/j.bios.2016.02.070

Thévenin, A., Beloelj, H., Blanie, A., Benhamou, D., and Mazoit, J. X. (2008). The limited efficacy of tramadol in postoperative patients: a study of ED80 using the continual reassessment method. *Anesth. Analg.* 106, 622–627. doi: 10.1213/ane.0b013e31816053aa

Vinodkumar, G., Ramya, R., Vimalan, M., Potheher, L., and Cyprak, Peter, A. (2018). Reduced graphene oxide based on simultaneous detection of neurotransmitters. *Prog. Chem. Biochem. Res.* 1, 40–49. doi: 10.29088/SAMI/PCBRR.2018.1.4049

Xia, Y., Zhao, F., and Zeng, B. (2020). A molecularly imprinted copolymer based electrochemical sensor for the highly sensitive detection of L-Tryptophan. *Talanta* 206, 120245. doi: 10.1016/j.talanta.2019.120245

Yang, Y., Asiri, A. M., Du, D., and Lin, Y. (2014). Acetylcholinesterase biosensor based on a gold nanoparticle-poly(pyrrole)-reduced graphene oxide nanocomposite modified electrode for the amperometric detection of organophosphorus pesticides. *Analyst* 139, 3055–3060. doi: 10.1039/c4an00068d

Yavuz, E., Tokaloglu, S., Sahanj, H., and Patat, S. (2013a). A graphene/Co3O4 nanocomposite as a new adsorber for solid phase extraction of Pb (II), Cu (II) and Fe (III) ions in various samples. *Rsc Adv.* 3, 24650–24657. doi: 10.1039/c3ra5111a

Yavuz, E., Tokaloglu, S., Sahanj, H., and Patat, S. (2013b). Ultralayered Co3O4 as a new adsorber for preconcentration of Pb (II) from water, food, sediment and tobacco samples. *Talanta* 115, 724–729. doi: 10.1016/j.talanta.2013.06.042

Zhang, Y., Sun, X., Zhu, L., Shen, H., and Jia, N. (2011). Electrochemical sensing based on graphene oxide/Prussian blue hybrid film modified electrode. *Electrochim. Acta* 56, 1239–1245. doi: 10.1016/j.electacta.2010.11.011

Zhang, Y., Zeng, G. M., Tang, L., Chen, J., Zhu, Y., He, X. X., et al. (2015). Electrochemical sensor based on electrodeposited graphene-Au modified electrode and nanoAu carrier amplified signal strategy for attomolar mercury detection. *Anal. Chem.* 87, 989–996. doi: 10.1021/ac503472p

Zheng, W., Wu, H., Jiang, Y., Xu, J., Li, X., Zhang, W., et al. (2018). A molecularly-imprinted-electrochemical-sensor modified with nano-carbon-dots with high sensitivity and selectivity for rapid determination of glucose. *Anal. Biochem.* 555, 42–49. doi: 10.1016/j.ab.2018.06.004

Zhou, Y. G., Chen, J. J., Wang, F. B., Sheng, Z. H., and Xia, H. (2010). A facile approach to the synthesis of highly electroactive Pt nanoparticles on graphene as an anode catalyst for direct methanol fuel cells. *Chem. Commun.* 46, 5951–5953. doi: 10.1039/c00394h

Zhu, C., Yang, G., Li, H., Du, D., and Lin, Y. (2015). Electrochemical sensors and biosensors based on nanomaterials and nanostructures. *Anal. Chem.* 87, 230–249. doi: 10.1021/ac503863

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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