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Electrochemical codeine sensor based on carbon paste electrode/HKUST-1

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Abstract

In this research, the Cu-MOF (metal–organic framework, HKUST-1) was synthesized via co-precipitation method and it was into the carbon paste electrode and has been investigated in the measurement of codeine. The electrochemical performance of the modified electrode was evaluated by cyclic voltammetry and differential pulse voltammetry. The effective parameters in the sensitivity of the method were optimized. Quantitative measurements and determination of codeine at the surface of the modified electrode were performed by using differential pulse voltammetry. Finally, the ability of the developed method to measure codeine in real plasma samples was investigated. Under the optimal conditions, the linear range was obtained from 2 to 100 μM with a limit of detection of 0.66 μM. The high efficiency of the developed electrode in plasma samples was proved by using high and acceptable accuracy and satisfactory relative recovery percentage. The results in which the recovery values with RSD% for three repeated measurements were in the range of 97–109 (% RSD = 3.75 to 4).

Introduction

Metal–organic frameworks (MOFs) as a type of porous material have attracted much attention due to their remarkable properties, such as regular crystal structures, high surface area, and pores of different sizes. Due to these characteristics, MOFs are widely used in catalysis, drug delivery, gas absorption, energy storage, and sensing purposes [1–3]. Also, in recent years, MOF-derived functional nanomaterials have appeared as state-of-the-art materials for a large different of conceivable usage containing separation, catalysis, storage, analysis [1–8]. These applications arise from their high pore volume and specific surface areas. As one of the most investigated MOFs, HKUST-1 ([Cu3(H2O)2(BTC)3]n, BTC: 1, 3, 5-benzenetricarboxylate) has benefits of open metal sites, facile preparation, high surface area (1925 m² g⁻¹) and an interconnected 3D pore system with pore sizes of 9 Å × 9 Å [9–13]. Both the metallic Cu ion center and the layered structure of HKUST-1 can improve the electron transfer significantly and enhance the catalytic current dramatically. Because of these advantages, here, HKUST-1 was used for the fabrication of an electrochemical sensor for the measurement of codeine [14, 15]. Codeine (3-methylmorphine) is an alkaloid formulated by the methylation of morphine derived from poppy seeds. It is used to control mild to moderate pain, including regular cancer ache, and has antitussive, antistrips, and anti diarrheal properties [16]. The chemical structure of codeine is given in figure 1. Moreover, Codeine is extensively used in cough cold syrup, but it would cause drug addiction, and make mental damage to patient if abused, then even give rise to many issues of social problem. This drug also shows antidiarrheal activity with several side effects such as constipation, sedation and nausea. The increment of drug abuse over the past decades led to the increase of Codeine and other morphine derivatives in drug prescriptions as substitutes and alternative drugs for the management of heroin in some European countries [17, 18].

Various techniques including colorimetric assays, spectrophotometric analysis, electrochemical detection, chromatographic analysis and capillary electromigration techniques have been utilized for the measurement of codeine. MOFs, HKUST-1, Codeine, Electrochemical sensor, Differential pulse voltammetry, Medicine application.
codeine. The use of electrochemistry for measurement of different medicine in various solution and furthermore other functional technologies has much attention has been paid to them. [19–27]. Among the different analytical methods, the electrochemical methods compared to other methods, are powerful detection method due to the intrinsic properties such as sensitivity, low-cost, portability and ease of use [16, 28–34].

Codeine is an electroactive drug that oxidizes, therefore, direct measurement of codeine can be performed. Various electrodes such as glassy carbon electrode, boron doped diamond and carbon paste electrode, have been reported to measure codeine. Electrode modification can reduce the potential excess as well as increase the electron transfer rate in the redox reactions of the desired reduction at the electrode surface [16]. According to the literature, graphene/CoFe2O4 NPs-modified carbon paste [35], TiO2 NPs-modified carbon paste [36], ZnCrFeO4 NPs-modified MWCNT paste [37], CoFe2O4 NPs-modified carbon paste [38], CNT/PdNPs/CPE [39], Zn3SnO4 NPs/graphene-modified carbon paste [40] and CPE/PtNPs/IL [41] electrodes have been utilized for electrochemical measure of this drug and received LOD was in the range of 9–200 nM. In this work, an electrochemical sensor based on modified CPE with CU-MOF was designed for the electrochemical measure of codeine. The limit of detection, linearity range and selectivity of the introducing sensor was also invested by differential pulse voltammetry.

Experimental section

Materials
Analytical grade chemicals were used in all experiments and no further treatments were performed on them prior to tests. The main chemicals used were Cu(NO3)2 and H3BTC. Also, codeine were purchased from rouzdarou Co.

Synthesis of HKUST-1
At first, 1 g Cu(NO3)2 were added into deionized water (25 ml). Followed by added solution H3BTC (2 g in 50 ml water) drop-by-drop, followed by 60 min of stirring at the room temperature. Afterward, the precipitate was collected through centrifugation at 5000 rpm. The produced was rinsed using water and ethanol [1].

Apparatus
The FE-SEM device model (Mira3 TESCAN) was employed for recording SEM images. X-ray diffraction (XRD) patterns of the active materials were recorded on a PANalytical, X’PertPRO instrument with Cu-Kα (λ = 1.5406 Å) radiation. Cyclic voltammetry (CV), differential pulse voltammetry studies were performed using a μ-Autolab PGSTAT coupled with a frequency response analyzer equipped with a NOVA software.

Preparation of modified sensor
A combination of graphite (0.15) and HKUST-1 nanomaterial (0.05 g) in oil were mixed to form a paste. The prepared paste was placed in to a syringe tube and every time we wanted to use it, the surface was refreshed. The electrode was connected to the device with a copper wire.
Result and discussions

XRD and FE-SEM analysis

Figure 2 shows typical x-ray diffraction spectrum (XRD) of the HKSUT-1. Significant deflection peaks of HKSUT-1 are located at 2θ values of approximately 8.08, 10.36, 11.64, 13.48, 14.7, 19.28, 25.92, and 28.92, and were attributed to the (200), (220), (222), (400), (331), (440), (731) and (751) crystal orientations respectively (JCPDS card no: 00–062–1183) [1]. The typical morphology of HKUST-1 nanoparticles was investigated by the FESEM. As can be seen, the HKSUT-1 particles with size distributions into the range below 100 nm are nanoscale, spherical and homogeneous.

Electrochemical test

To assess the electrochemical behavior of 50 μM codeine on the CPE and CPE/HKUST-1 in phosphate solution (0.1 M, pH = 4.0) was used with scanning rates of 50 mV/s. Figure 3 demonstrates that can be seen, oxidation peak for codeine at the CPE and CPE/HKUST-1 surface appeared with a current (I_p) of 20 μA (at 1.18 V) and 52 μA (at 1.16 V), respectively. The effect of HKUST-1 nanoparticles on the active surface of CPE was investigated by Randles-Sevcik equation. The active surface area of modified electrode increase about 1.7 times compared with the CPE.
The effect of pH on codeine oxidation at the CPE/HKUST-1 surface was performed by cyclic voltammetry. Codeine voltammograms with different pHs are shown in figure 4(a). The shift of the Codeine peak oxidation potential at the Codeine surface indicates that this drug is sensitive to pH and this parameter can play a very important role in the electrochemical measurement of this drug. Also current diagram versus of pH showed that the highest oxidation current is related to pH = 4, so this optimal pH was used. The potential diagram versus of the pH was also plotted according to figure 4(b), that line slope is close to that of the Nernst line, therefore the number of electrons and protons transferred in Codeine oxidation is equal. The electrochemical mechanism for this drug interaction is in accordance with figure 4(c) [39]. The pKa values of 8.2 for the codeine showed that while the carbocyclic moiety is almost deprotonated at acidic. Moreover, the observation of the almost irreversibility behavior for the electro-oxidation of codeine in optimized pH value acidic.

Using the effect of potential scan rate on the cyclic voltammograms of the codeine, it is possible to investigate the diffusion or adsorption of analyte on the modified electrode. For this purpose, cyclic voltammograms were recorded at different scan rates in the range of 10 to 150 mV s\(^{-1}\) and the results are reported in figure 4. As shown in figure 5, there is a linear relationship between the current intensity and the square of the potential scan rate, indicating that the reaction has a diffusion-controlled mechanism. In addition, based on the results obtained Tafel plot (log I versus E) Curve and the slope of the equation gives the value of the electron transfer coefficient (\(\alpha\)) for codeine is equal to 0.62.

**Chronoamperometry**

Thecottrell relationship was used to calculate the diffusion coefficient of codeine on the CPE/HKUST-1 surface by chronoamperometry. For this purpose, amperograms of different concentrations of codeine on the surface of CPE/HKUST-1 were drawn by chronoamperometry method at a potential of 1.3 V for a period of 30 s. Then, by drawing the current diagram according to the \(t^{\frac{1}{2}}\) and according to the slope of their line (figure 6(b)) and drawing figure 6(c), the penetration coefficient for the codeine was equal to \(3.62 \times 10^{-6} \text{ cm}^2\text{s}^{-1}\) \([42, 43]\). In Cottrell relation, \(A, n, C, F\) are the electrode surface area, the number of electrons, concentration, and Faraday constant, respectively

\[
I = nFACD^{1/2}/\pi^{1/2}t^{1/2} \quad \text{(Cottrell relation)}
\]

Different concentrations of codeine were measured at the surface CPE/HKUST-1 and pH = 4 by DPV method. The results are shown in figure 7. As the concentration increases, the oxidation current also increases. The linear relationship of current with concentration was obtained in the concentration range of 2–100 μM. The detection limit of codeine at the surface of CPE/HKUST-1 was also obtained according to LOD = 3 S m\(^{-1}\) equal to 0.66 μM. A comparison of codeine measurement performance of previously reported with the CPE/HKUST-1 sensor is given in table 1. The electrochemical measurements of codeine were investigated in the presence of the various compounds. The interference threshold is considered as the concentration of the interfering species that changes the codeine signal by more or less than 5%. The results (table 2) showed that the studied compounds had no effect on sensor response.
Figure 4. Effect pH on the oxidation peak codeine, (a) CVS, (b) Ep versus pH and (c) Electrochemical mechanism of codeine.

Table 1. Comparison of the performance of different sensor for codeine measurement.

| Electrode                        | Method | Linear range (μM) | LOD (μM) | References |
|----------------------------------|--------|-------------------|----------|------------|
| Psi/Pd/CNTPE                     | DPV    | 1–700             | 0.3      | [39]       |
| PB/Pd-Al                         | DPV    | 2–50              | 0.8      | [44]       |
| NiNPs/carbon black/GCE           | SWV    | 0.83–38.5         | 0.48     | [45]       |
| SWCNT/carbo ceramic electrode    | DPV    | 0.4–300           | 0.25     | [46]       |
| CPE/HKUST-1                      | DPV    | 2–100             | 0.66     | This Work  |

Table 2. Investigate selectivity in measuring codeine.

| Compounds                        | $I_{\text{inter}}$ (μM) |
|----------------------------------|-------------------------|
| Ascorbic acid, Uric acid, Dopamine| 100                     |
| $\text{H}_2\text{O}_2$, Citric acid, L-cysteine | 150                     |
| NaCl, Na$_2$HPO$_4$, CuCl$_2$   | 1000                    |
The performance of the CPE/HKUST-1 for detection of codeine were examined in the serum samples. Three concentrations of codeine was add to the real sample. The recovery values in the range of 96%–99% in added samples with different codeine (table 3), indicating that the CPE/HKUST-1 has an acceptable accuracy to measurements of codeine in real serum samples.

**Conclusion**

In summary, an electrochemical sensor for detection of codeine was developed based on the simple and economic technique. The response of this electrochemical sensor was based on the changes of interfacial properties of sensing platform by interaction between the codeine in the solution and the HKUST-1 on the carbon paste electrode. Since MOFs are a good choice for electrode modification. With the modification of the electrode by HKUST-1, the oxidation current has increased several times and its starting potential occurs at in lower values. Therefore, the improvement in the electrochemical behavior of codeine is due to the acceleration of electron transfer due to the increase in surface area by HKUST-1. The fabricated CPE/HKUST-1 shows

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**Table 3.** The measurement of codeine in human blood serum.

| Add (μM) | Obtained (μM) | Recovery (%) | RSD (%) |
|----------|---------------|--------------|---------|
| 5        | 4.86          | 97.20        | 3.87    |
| 10       | 9.89          | 98.90        | 4.03    |
| 25       | 24.79         | 99.16        | 3.75    |

**Figure 5.** Cyclic voltammograms of codeine on the modified electrode surface at different scan rates (a), I versus υ^{1/2} (b) and E versus Log I (c).
Figure 6. Chronoamperometry for various concentration of codeine at surface CPE/HKUST-1 in solution (pH = 4.0).

Figure 7. DPVs (a) and calibration (b) curve of codeine.
acceptable selectivity in measurements of codeine, detection limit as 0.66 μM, and a wide linear range from 2 to 100 μM. The codeine quantification in blood serum samples was successfully performed.

Data availability statement

All data that support the findings of this study are included within the article (and any supplementary files).

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