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Innovative electrochemical sensor for the precise determination of the new antiviral COVID-19 treatment Favipiravir in the presence of coadministered drugs

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1. Introduction

During the year 2020, the world faced the worst public-health crisis in past hundred years, COVID-19 pandemic. Coronaviruses are large genome viruses of the Nidovirales order, with a positive-strand RNA [1]. European and almost all countries have applied non-pharmaceutical involvements, like school closure and national lockdown that lead to huge economic crises [2]. Regardless of the major efforts to stop its spread, COVID-19 has affected considerable health and financial burden, stressing the urgent need for antiviral treatments [1]. Great efforts have been devoted to the development of an antiviral agent for the halt of the progression of this ailment. During the pandemic influenza in Japan 2014, Favipiravir (FAV) was approved for the treatment of that ailment which showed high potential for the in vitro activity against the acute respiratory syndrome coronavirus-2 [3]. FAV was first applied as a medication against COVID-19 in China-Wuhan, at the red zone of the pandemic origin. After that as the pandemic been in Europe, FAV got approval for emergency use in Italy, and currently has been in use in Japan, Russia, and many other countries around the globe including Egypt [4]. The main advantages of using FAV to treat a new indication, a process called “drug repurposing,” are that FAV is available in high doses and the safety measurements have previously been conducted on a high patients number [5,6]. Accordingly, the approved medical agent FAV has the potential to be rapidly used on a large scale and be used as a first line of protection to administer to suspect or contact cases during a pathogen lockdown [5].

Based on the above mentioned facts, there is urgent need to develop a sensitive, reliable, fast, low expensive analytical method to trace and determine FAV individuality in the presence of coadministered drugs. By reviewing the previously published works regarding the determination of FAV, only few methods have been reported for the determination of FAV including HPLC method [7], and spectrofluorometric method [8]. One electrochemical method has been reported for the single determination of FAV [9].

The MnO2 nanomaterials have been used in different applications fields of industry quality control and clinical analysis laboratories for the FAV determination.
conductivity, the conductivity of MnO₂ nanomaterials were further enhanced, reduce the equivalent resistance and charge-transfer resistance [10–12]. Graphene nanostructured materials have received great attention in the past recent years as these materials offer high conductivity, excellent mechanical characteristics, high chemical/thermal stability, with tremendous surface area [13–16].

So, due to the urgent need to develop a fast, precise and sensitive strategy for the sensitive determination of FAV, we have fabricated the present electrochemical protocol. In this work, hydrothermal one-pot strategy was developed to prepare directly MnO₂-rGO nanocomposite using graphene oxide (GO). To the best of our knowledge, there were no literature reporting the use of MnO₂-rGO nanocomposite for the modification of screen-printing electrodes (SPE) for the electrochemical determination of FAV.

2. Experimental

The whole data and description of the used chemicals, apparatus, and methods are described in the electronic supplementary information (ESI) section S2.

3. Results and Discussion

3.1. Characterisation of MnO₂-rGO nanocomposite

The structural morphology of the prepared MnO₂-rGO nanomaterial is displayed in Fig. 1A. TEM photo is used to examine the structural morphology of MnO₂-rGO. TEM displays the structure of graphene with transparent layers and the manganese oxide distribution on its surface. (Fig. 1A). The MnO₂-rGO provided high surface area over the common graphite. The bulky particles of the graphite material is displayed in Fig. 1A. TEM photo is used to examine the structural morphology of the prepared material. Fig. 1B shows the EDX of nanocomposite, indicating the presence of Mn, O, and C.

The non-destructive method XRD is a beneficial tool in the description of MnO₂. Inset in Fig. 1B shows different peaks at 2θ 18.10°, 29.0°, 31.14°, 37.50°, 44.54°, 50.68°, 59, 98° and 64.70° [11]. The sharp peaks are confirming the stability of MnO₂ crystalline nanoparticles. The peaks are correlated to 200, 310, 110, 002, 210, 512, 521 and 541 planes of crystalline MnO₂ [17–19], Fig. 1C.

Field Emission Scanning Electron Microscopy (FE-SEM) Fig. 1D displays the hydrothermal synthesized MnO₂ nanoparticles of a spherical shape that covered the rGO surface. Fig. S1 depicts the FTIR spectra of GO, the C=C stretching and C–O–C epoxy stretching peaks appeared at 1642 and 1225 cm⁻¹, while the bands at 1725 and 1054 and 3224–3350 cm⁻¹ correspond to C=O stretching, C–O in alkoxy group and OH for the adsorbed H₂O. These FTIR indicate the graphite oxidation [20–23]. While for MnO₂-rGO nanocomposite, epoxy, alkoxy and carbonyl peaks were decreased because of the reduction of GO. Moreover, the clear events at 582 and 468 cm⁻¹ are recognized for the MnO₂ nanoparticles that completely cover the reduced graphene sheets [24].

3.2. Electrochemical characterisation of the SPE modified with MnO₂-rGO nanocomposite

Next, the electrochemical characteristics of the developed platforms were depicted in 5.0 mM potassium ferricyanide (K₃Fe(CN)₆) in 0.1 M KCl. MnO₂-rGO/SPE (1:1) performance was compared to the bare SPE, and GO/SPE, Fig. 2A. The redox peaks for MnO₂-rGO/SPE were 3.33, and 1.62 times higher than those of SPE, and GO/SPE, respectively, which could be attributed to the increase in the surface area of MnO₂-Gr compared to GO. The impedance spectroscopy (EIS) is a potent method for proper specification of the different parameters like mass transport and kinetic as well as the coefficient of charge transfer.

Fig. 2B displays the electrochemical impedance spectroscopy (EIS) plot of bare SPE, GO/SPE, and MnO₂-Gr/SPE platforms, which were detected in 5.0 mM potassium ferricyanide (K₃Fe(CN)₆) in 0.1 M KCl. A simple corresponding circuit model was applied to adequate the obtained data.

Rs, C and R_CT symbolize solution resistance, a capacitance for the double-layer and electron transfer resistance, respectively. ZW is a Warburg-type impedance coupled to R_CT, which represents the bulk diffusion. A semicircle with a Warburg-type line was shown in the spectra. The reduction in the semicircle diameter was indicated in the Nyquist plot for the electrochemical platforms GO/SPE and MnO₂-rGO/SPE, indicating an enhancement of charge transfer kinetics for those sensors comparing to the unmodified bare SPE.

The capacitance (C) was in parallel with the R_Ct and W impedance. The resistance of charge transfer R_Ct was valued to be 5970.0 Ω for the unmodified SPE, while it diminished to 4880.0, and 1600.0 Ω for GO/SPE, and MnO₂-rGO/SPE, respectively, indicating the significantly lower R_Ct value at the MnO₂-rGO/SPE. The obtained cyclic voltammograms data were in a good agreement with the previous data gained from the electrochemical impedance measurements, showing that MnO₂-rGO offers high area along with good electron conduction.

The value of resistance of charge transfer R_Ct can be applied to estimate the rate constant of the electron transfer (kₜ) through the MnO₂-rGO/SPE. Using the following equation [25]:
the electrochemical impedance of each electrode.

\[ k^0 = \frac{RT}{FAC} \]

where \( R \) is defined as the universal gas constant, \( T \) is the thermodynamic temperature (298.15 K), \( F \) is the Faraday’s constant (96485 C mol\(^{-1}\)), \( A \) is the sensor area and \( C \) is the electroactive species concentration in the electrolyte medium. Heterogeneous electron transfer rate constant \( (k^0) \) were estimated and the calculated values were: 1.08 × 10\(^{-4}\), 1.10 × 10\(^{-4}\), and 1.75 × 10\(^{-7}\) cm s\(^{-1}\) for the bare SPE, GO/SPE, and MnO\(_2\)-rGO/SPE, respectively.

By comparing the \( k^0 \) constant values, the highest value of \( k^0 \) that is related to MnO\(_2\)-rGO/SPE indicates the effect of MnO\(_2\)-rGO nanomaterial for the enhancement of electron transfer kinetics throughout the electrode surface.

3.3. Electrochemical detection of Favipiravir with the SPE modified with MnO\(_2\)-rGO nanocomposite

Fig. 3A displays the characteristic SWV of 5.5 × 10\(^{-4}\) M FAV in pH 7.0B.R. buffer at unmodified SPE, GO/SPE, and MnO\(_2\)-rGO/SPE. Upon adding 1.0 mM FAV, the unmodified SPE showed an anodic peak current of 14.70 \( \mu \)A at 1.27 V, which related to the oxidation of FAV. As can be seen in Fig. 3A, the value of the current of the electrode rises due to the addition of GO, where the anodic peak appears at 1.25 V with a current value of 18.10 \( \mu \)A. After modification of the sensor with MnO\(_2\)-rGO, the peak current increased to 25.14 \( \mu \)A at 1.14 V. Consequently, the successful application of MnO\(_2\)-rGO for the determination of FAV enhanced the analytical signal, due to a higher electron transfer with high electrical conductivity.

One of the important factors that affect the electrochemical process is the solution pH. Different pH values were tested using 5.5 × 10\(^{-4}\) M FAV, Fig. 3B. Upon varying the pH from 2.0 to 9.0, the FAV oxidation peak was shifted towards lower potentials values, i.e. more negative values, which might be explained as reduction–deprotonation of FAV [26]. The relation between the peak potential \( (E_p) \) and pH values of the buffer solution was linear as: \( E_p (V) = 1.558 V - 0.046 V \text{ pH}^{-1} \), \( (R^2 = 0.9845) \). The slope value follows Nernst behavior where the included number of electrons and protons are equal during the electrochemical oxidation of FAV. Furthermore, the physiological pH 7.0 was selected as the optimum working one.

Chronoamperometric measurements (CA) at 1.23 V for 20 s were performed for the determination of diffusion coefficient \( (D) \) applying Cottrell’s law [27], Fig. 4. The calculated \( D \) value was found to be 4.67 × 10\(^{-5}\) cm\(^2\) s\(^{-1}\) for FAV at MnO\(_2\)-rGO/SPE in 0.04 M B.R. buffer (pH 7.0).

3.4. Analytical performance of the SPE modified with MnO\(_2\)-rGO nanocomposite

For the determination of FAV, SWV experiments were done using MnO\(_2\)-rGO/SPE in solutions of varying FAV concentrations using pH 7.0B.R. buffer. As depicted in Fig. 5A, the calibration curve is drawn as peak current \( I_p \) vs. FAV concentration. For the range 1.0 × 10\(^{-8}\)–5.5 × 10\(^{-5}\) M, the regression equation was \( I_p(\mu A) = 0.048C - 1.10; (R^2 = 0.9990) \). The calculated values for the limit of detection (LOD) and limit of quantification (LOQ) were found to be 9.0 × 10\(^{-7}\) and 2.9 × 10\(^{-5}\) M, respectively.

To check the specificity of MnO\(_2\)-rGO/SPE, its electro-analytical response was examined for the determination of FAV in the existence of co-administered COVID-19 drugs including fingolimod, remdesivir, and hydroxychloroquine (HCQ). Fingolimod and remdesivir did not show any electrochemical activity using MnO\(_2\)-rGO/SPE. Paracetamol (PAR) also is prescribed for COVID 19 patients for fever control. Fig. 6A shows voltammetric response of FAV in presence of PAR as the peak at 0.43 V is corresponding to PAR, while the other at 1.23 V is due to FAV oxidation. These findings are indicating that the simultaneous determination of the co-administered drugs of FAV is practicable using the MnO\(_2\)-Gr/SPE platform. While for testing hydroxychloroquine (HCQ), two separated peaks appeared at 1.01 and 0.81 V at pH 7. Upon adding 5.5 × 10\(^{-4}\) M FAV, FAV well-separated peak appeared at 1.23 V, Fig. 5B. Comparing to the published electrochemical work [9], our sensor offers wide range of linearity and sensitive determination of FAV alone and the presence of different coadministered drugs were demonstrated for the first time.

3.5. Repeatability, reproducibility, and storage stability of the MnO\(_2\)-rGO/ SPE electrochemical sensor

The MnO\(_2\)-rGO/SPE sensor showed high repeatability and reproducibility for FAV analysis. Five determinations of 1.0 × 10\(^{-5}\) M FAV were performed for a single MnO\(_2\)-rGO/SPE (intra-day repeatabil-
Fig. 3. (A) SWV of $5.5 \times 10^{-4}$ M FAV in B.R. buffer solution pH 7.0 at a SR of 0.1 V s$^{-1}$ at SPE, GO/SPE, and MnO$_2$-rGO/SPE electrodes, (B) SWV of $5.5 \times 10^{-4}$ M FAV at different pH values using MnO$_2$-rGO/SPE at $v = 0.1$ V s$^{-1}$, $P_W = 0.50$ V, $P_H = 0.25$ V, $S_H = 0.02$ V. The inset: the plot of $I_p$ versus pH.

Fig. 4. CA measurements for the oxidation of FAV concentrations using MnO$_2$-rGO/SPE in B.R buffer pH 7.0, with a $P_s = 500$ mV. Inset displays the variant of CA currents at $t = 20$ s vs. [FAV].
ity). The relative standard deviation (RSD) for five determinations of FAV was 1.37%. Furthermore, the series of five different MnO2-rGO/SPE sensors made-up in the same procedure (inter-day reproducibility) have showed the response with an RSD of 1.53% during the electroanalytical determination of 1.0 x 10^{-5} M FAV (Fig. S2).

After the preliminary determination of FAV, the MnO2-rGO/SPE sensor was kept in the buffer (pH = 7.0) at 25 °C. The FAV electrochemical response was checked regularly over 4 weeks (Fig. S2). So, four sensors prepared in the same manner were tested in parallel (n = 3). After four weeks, the final current decreased by 12% of the initial current value that proposes the sensor was rationally stable through the checking period. The high stability of the sensor can be gained because of the hydrophobic property of the graphene materials [28–30], which prevents the formation of a water film on the sensor surface.
3.6. Interference studies

Croscarmellose sodium, sodium lauryl sulphate, titanium dioxide, sodium dihydrogen orthophosphate (H₂NaO₆P), talc, castor oil, mannitol, cellulose, magnesium oxide, and povidone, were examined in order to check any change in the FAV electrochemical signal. Using 1.0 × 10⁻⁵ M FAV in a pH 7.0 B.R. buffer (0.04 M) solution, each was added, and the magnitude of the anodic peak current was monitored. From the chosen potential interfering substances, none were found to interfere with the electroanalytical sensing of FAV. The tolerance limit was less than ± 5.0% for each interfering substance. Correspondingly, it was found that the use of 40-fold of inorganic ions (e.g. Mg²⁺, K⁺, Zn²⁺, Na⁺, Fe³⁺, Ca²⁺, Cl⁻, NO₃⁻ and SO₄²⁻) did not affect the electrochemical response, as shown in Fig. S3.

In addition, the important commonly interfering materials in the biological fluids ascorbic acid (vitamin C, AA) and uric acid (UA) have been tested in the presence of 1.0 × 10⁻⁵ M FAV. Also, the precursor of dopamine, levodopa (LEVO) has been checked. From the chosen potential interfering substances, none were found to interfere with the electroanalytical sensing of FAV. The tolerance limit was less than ± 5.0% for each interfering substance. Correspondingly, it was found that the use of 40-fold of inorganic ions (e.g. Mg²⁺, K⁺, Zn²⁺, Na⁺, Fe³⁺, Ca²⁺, Cl⁻, NO₃⁻ and SO₄²⁻) did not affect the electrochemical response, as shown in Fig. S3.

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Table 1

| Sample         | Added (µM) | Found (µM) | Recovery% ± R.S.D |
|---------------|------------|------------|-------------------|
| Plasma        | 12.00      | 11.82      | 98.50 ± 0.46      |
|               | 55.00      | 54.03      | 98.23              |
|               | 120.00     | 118.92     | 99.10              |
|               | 150.00     | 148.80     | 99.20              |
| Recovery% ± R.S.D |           |            | 98.75 ± 0.46      |
| Invisiram® Tablet | 12.00      | 11.88      | 99.00              |
|               | 55.00      | 54.50      | 99.10              |
|               | 120.00     | 118.52     | 98.77              |
|               | 150.00     | 148.99     | 99.33              |
| Recovery% ± R.S.D |           |            | 99.05 ± 0.23      |

3.7. Analysis of FAV in real samples

The practicability of MnO₂-rGO/SPE for the determination of FAV in real samples were tested using SWV technique. The standard addition method was used to evaluate the analytical performance of the sensor for FAV determination. The recovery experiment was presented in Table 1, which confirm that, the MnO₂-rGO/SPE is very sensible for the determination of low and high concentrations of FAV in different real samples.

4. Conclusion

In the current study, we have described for the first time, the electrochemical determination of FAV with screen-printed electrode modified with MnO₂-rGO nanocomposite. The developed electrochemical platform showed outstanding electrocatalytic activity towards the sensitive determination of FAV with low values of detection and quantification limits along with wide linear range. Furthermore, FAV was selectively determined using MnO₂-rGO/SPE platform in the presence of co-administered drugs with high recovery values. Based on the obtained results for the oxidation of FAV, the quantitative determination of FAV in pharmaceutical preparation and human fluids samples was achieved by a simple, rapid, selective and sensitive SWV technique. Furthermore, along with the excellent characteristics of high accuracy, sensitivity, and reproducibility, the developed sensor offers appropriate simple platform for the sensitive determination of FAV in the clinical work.

CRediT authorship contribution statement

Mona A. Mohamed: Investigation. Ghada M. G. Eldin: Investigation. Sani M. Ismail: Investigation. Nadia Zine: Writing - original draft preparation. Abdelhamid Elaissari: Conceptualization. Nicole Jaffrezic-Renault: Writing - review and editing. Abdelhamid Errachid: Funding acquisition, Writing - review and editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Fig. 7. SWVs using a MnO₂-rGO/SPE in a pH 7.0B-R buffer containing 5.0 × 10⁻⁵ M FAV, 5.0 × 10⁻³ M AA, UA and LEVO, respectively, for each at scan rate: 0.1 V s⁻¹, P_H = 0.25 V, P_W = 0.50 V, S_H = 0.02 V.
Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jelechem.2021.115422.

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