



Boosting Sensitivity with Holmium Tungstate/Reduced Graphene Oxide composites for Electrochemical Detection of Mesalamine

Sundaresan Ruspika^a, Saranvignesh Alagarsamy^a, Tse-Wei Chen^{b,*}, Shen Ming Chen^{a,*}, Ramachandran Balaji^c, Elayappan Tamilalagan^a, Chen-Chi Wang^d, Narendhar Chandrasekar^e, Ming-Chin Yu^{f,g,**}, Heng-Yuan Hsu^{f,g,**}

^a Department of Chemical Engineering and Biotechnology, National Taipei University of Technology, No.1, Section 3, Chung-Hsiao East Road, Taipei, 106, Taiwan

^b Department of Greenery, National University of Tainan, Tainan 700, Taiwan, ROC

^c Department of Electronics and Communication Engineering, Koneru Lakshmaiah Education Foundation, Andhra Pradesh, 522302, India

^d Department of Otorhinolaryngology Head Neck Surgery, Taichung Veterans General Hospital, Taichung, 407, Taiwan

^e Department of BioNano Technology, Gachon University, Seongnam, 13120, Gyeonggi, Republic of Korea

^f Department of Surgery, New Taipei Municipal Tucheng Hospital (Built and Operated by Chang Gung Medical Foundation), New Taipei City, 23652, Taiwan

^g Chang-Gung University, Taoyuan City, 33302, Taiwan

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ABSTRACT

A novel and cost-effective electrochemical sensor was developed for the rapid and sensitive detection of mesalamine using a nanocomposite of rare earth tungstate incorporated with reduced graphene oxide (REW@rGO). The nanocomposite was synthesized and characterized through various analytical and spectroscopic techniques to confirm its successful formation. The synergetic effect between REW and rGO significantly enhanced the electrocatalytic performance, offering a broad linear detection range of 0.01–723 μM a high sensitivity of $1.3406 \mu\text{A} \mu\text{M}^{-1} \text{cm}^{-2}$ and a low detection limit (LOD) of 0.0039 μM . The enhanced electron transfer rate attributed to the large interfacial area of nanocomposite contributed to the sensor's superior performance. These results demonstrated that the REW@rGO-based sensor is a highly efficient platform for the real-time analysis of mesalamine in pharmaceutical and clinical applications.

1. Introduction

Idiopathic ulcerative colitis is an inflammatory chronic disease of the colon requiring both acute and long-term medical treatment to induce and maintain remission [1]. It is recommended that patients with mild to moderate ulcerative colitis be treated with oral mesalazine (5-aminosalicylic acid; MLM) formulations (Asacol, Pentasa, Salofalk, Mesasal, Claversal), pro-drugs (sulfasalazine, olsalazine, balsalazide) and rectal formulations (sulfasalazine, olsalazine, balsalazide). Generally, oral MLM agents have shown safety and efficacy for both short-term and long-term use. Equal doses of MLM have not been shown to have significant differences in efficacy [2]. Despite MLM being an aminosalicylate drug that acts locally in the gut and has several effects, many of which can be detrimental to health [3,4]. This makes it very

important to determine MLM accurately on both clinical and pharmacological levels. Research and development have focused on several analytical techniques recently, including colorimetry, mass spectroscopy, capillary electrophoresis, fluorescence sensors, UV spectrophotometry, electrochemical sensors, and HPLC [5–20]. From these, there is the potential for electrochemical methods to offer low costs, simplicity, fast response times, and good selectivity and sensitivity among those methods. Because of the low sensitivity and small linear range of a bare GC electrode, MLM cannot be detected. For this reason, it is imperative to develop highly sensitive electrodes for the determination of MLM in biological fluids and pharmaceutical samples. Using cobalt stannate/graphene as a sensor, Hwa et al. proposed a technique to measure MLM using electrochemical sensors [21]. Pd-WO₃ with aerogel as an electrochemical sensor, Raj Kumar et al. proposed an amperometric

* Corresponding authors.

** Corresponding authors at: Department of Surgery, New Taipei Municipal Tucheng Hospital (Built and Operated by Chang Gung Medical Foundation), New Taipei City, 23652, Taiwan.

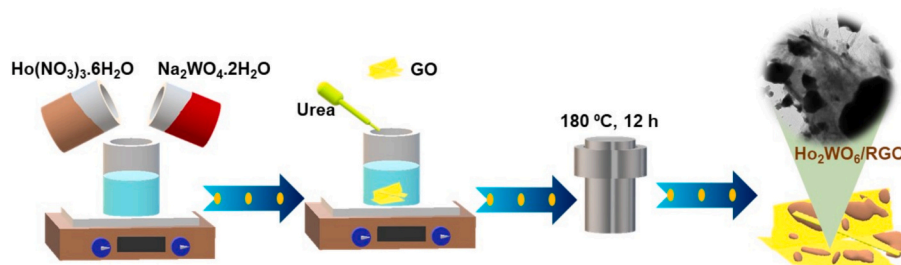
E-mail addresses: twchenchem@gmail.com (T.-W. Chen), smchen78@ms15.hinet.net (S.M. Chen), mingchin2000@gmail.com (M.-C. Yu), smallredshoe@gmail.com (H.-Y. Hsu).

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Scheme 1. Graphical representation of synthesis procedure of $\text{Ho}_2\text{WO}_6/\text{RGO}$.

determination of MLM [22]. ZnCr-LDH/tungsten carbide as an EC sensor, T Kokulnathan et al. developed a disposable strip to determine MLM [23]. Cu-Co bimetallic MOF as a sensor, M Gharagozlou et al. prepared a technique to determine MLM [24]. FSO/SO/g- C_3N_4 as a sensor, SM Babulal, et al. developed a hybrid electrocatalyst to determine MLM [25]. Based on the previously reported sensors, a reusable, sensitive, efficient, and very low-level detector for MLM is still needed.

It is important to understand that the electrocatalyst material is the key component to the electrochemical sensor being able to satisfy practical application needs. Several functional materials on the market these days include ternary metal oxides (TMOs), such as photocatalysts, energy storage materials, biomedical implants, electrochemical sensors, and so forth [26]. As a result of their outstanding structural durability, complex compositions, strong theoretical capacities, ideal band holes, crystallized phases, low charge transfer resistance, fast electron/ion transfer, high basic capacitances, and electronic structures, TMOs have a wide range of intriguing properties. The rare-earth-based nanostructured metal oxides, particularly tungstate, are a vastly understudied group of oxides but have drawn a lot of interest due to their unique properties. Due to the numerous possible uses for tungstate nanoparticles in recent years, such as humidity sensors, optical fiber, scintillation detectors, catalysts, solid-state lasers, photoluminescent products, microwaves, and photovoltaic electrochemical devices, they have become considerably more appealing [27–29]. The higher electrical mobility of W atoms (10^{-7} to $10^{-3} \text{ S cm}^{-1}$) makes metal tungstate nanoparticles an outstanding class of materials [30]. And also in recent years, rare earth compounds have attracted substantial attention due to their potential application in high-performance electronic components. Vanadates, tungstates, and molybdates of the holmium (lanthanide series) have multiple applications due to their electron transitions in the 4f shell [31,32]. Holmium has a plays major role in various applications like ceramic, glass, and phosphor lamps and also it can able to absorb fission bred neutrons [33]. Although HoWO_3 is very effective in the aforementioned applications due to the synergistic interaction between $\text{Ho}(\text{III})$ and WO_3 , one significant limitation is its poor electrical conductivity [34]. In our study, we aim to present a new Ho_2WO_6 as an electrochemical sensor for MLM detection for the first time. To overcome the above limitation, carbon-based materials were introduced such as carbon nanofibers (CNF), graphene oxide (GO) [35], carbon nanotubes, graphitic carbon nitrides (GCNs), reduced graphene oxide (RGO), and graphene aerogel (GA) [36–40]. The reason is because of its electrically conductive, has unique physical and chemical properties, have high strength, high surface area, and fast electron transfer, and are very economical [41–43].

Reduced graphene oxide (RGO) has been widely used in the sensor industry because of its superior properties, such as high electrical conductivity, large surface area, and quick electron mobility [44–49]. Its residual oxygen functionalities allow easy integration with metal oxides or biomolecules, forming stable hybrid composites with synergistic effects. [50–52] Increasing the active surface area significantly increases the number of adsorptive sites, which results in improved sensor performance [53]. In addition to electrode fouling, researchers tried to reduce the sensitivity of the nanomaterial by using Nafion as a binder,

instead, they used RGO as a binder to manufacture highly sensitive modified electrodes [45].

We synthesized an electrochemically detectable holmium-nanoplate-encapsulated RGO nanosheet ($\text{Ho}_2\text{WO}_6/\text{RGO}$) utilizing the hydrothermal method followed by the ultrasonication method. To characterize our newly designed $\text{Ho}_2\text{WO}_6/\text{RGO}$ nanomaterial, several spectroscopic approaches have been used. For the electrochemical performance of $\text{Ho}_2\text{WO}_6/\text{RGO}/\text{GCE}$ towards CV, DPV methodologies were used. $\text{Ho}_2\text{WO}_6/\text{RGO}$ demonstrated outstanding electrocatalytic activity, strong conductivity, and a large surface area. We developed a sensor that is sensitive, selective, and stable for detecting MLM. Additionally, the $\text{Ho}_2\text{WO}_6/\text{RGO}/\text{GCE}$ determination of MLM was successful in a human urine and water sample using an appropriate recovery rate.

2. Experimental section

2.1. Chemicals and reagents

Holmium (III) nitrate pentahydrate ($\text{Ho}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$), sodium tungstate dihydrate ($\text{Na}_2\text{WO}_4 \cdot 2\text{H}_2\text{O}$), urea, Ethylene glycol, sodium phosphate monobasic, hydrochloric acid (HCl, 36.5–38.0 %), sodium phosphate dibasic, potassium chloride (KCl, 99.0–100.5 %), potassium ferrocyanide $\text{K}_4[\text{Fe}(\text{CN})_6]$, Sodium hydroxide (NaOH), potassium ferricyanide $\text{K}_3[\text{Fe}(\text{CN})_6]$, Mesalamine were purchased from Sigma Aldrich and used without further purification. PB solution was prepared by mixing Na_2HPO_4 and NaH_2PO_4 with double distilled water (DI) throughout the experiment. Ethanol was used to prepare the stock solution.

2.2. Preparation of $\text{Ho}_2\text{WO}_6/\text{RGO}$ composite

The materials used for the synthesis were mentioned detailly in supplementary section (SI). The nanocomposite $\text{Ho}_2\text{WO}_6/\text{RGO}$ was organized by the facile hydrothermal method. In this typical procedure, stoichiometric ratio of $\text{Ho}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ and $\text{Na}_2\text{WO}_4 \cdot 2\text{H}_2\text{O}$ were dissolved separately in 30 mL of DI H_2O . Then, 0.6 g of urea was dissolved in 30 mL of DI H_2O followed by the addition of 0.8 g of graphene oxide (GO), and the mixture was stirred for approximately 30 min. After that, the suspension was moved to a Teflon-lined autoclave and kept at 180°C for 12 h. After the Teflon was cooled to room temperature and the obtained precipitate was washed with DI water and ethanol centrifuged at 6000 rpm for 15 min. Finally, the resultant product was dried. Hence the product was labelled as $\text{Ho}_2\text{WO}_6/\text{RGO}$. For the comparative study, the similar procedure was followed without adding RGO. A graphical illustration of synthesis of $\text{Ho}_2\text{WO}_6/\text{RGO}$ was depicted in Scheme 1.

2.3. Electrochemical study

Three-electrode cell setups were used for the whole electrochemical investigations. Each experiment was repeated thrice and used an excel sheet to calculate the standard deviation value. The EIS experiment was carried out in a 0.1 M KCl solution containing 5 mM $[\text{Fe}(\text{CN})_6]^{3-/4-}$ (FC system). The 0.1 M PB was used for the CV and DPV.

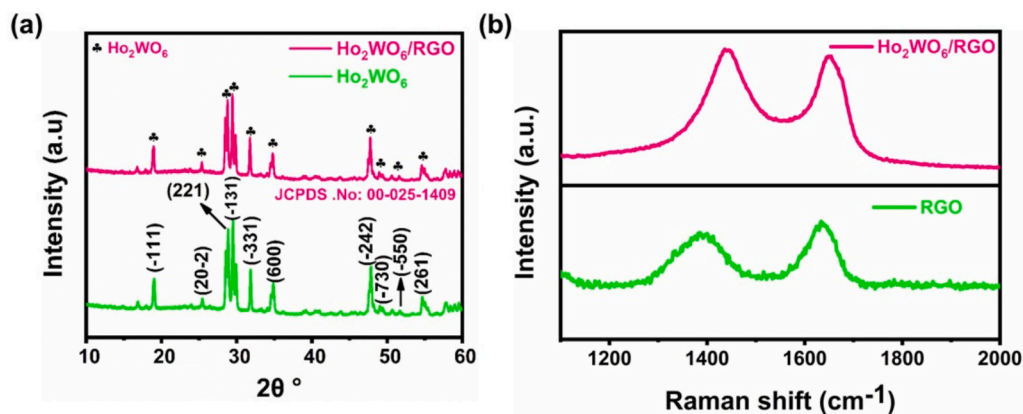


Fig. 1. (a) XRD spectra of Ho_2WO_6 , RGO, $\text{Ho}_2\text{WO}_6/\text{RGO}$ and (b) Raman spectrum of Ho_2WO_6 , $\text{Ho}_2\text{WO}_6/\text{RGO}$.

2.4. Characterization

The prepared nanocomposite's crystallinity was investigated using powder X-Ray diffraction (PXRD, XPERT-PRO, PAN analytical B.V., The Netherlands) and the diffractometer with Cu K α radiation ($k = 1.54 \text{ \AA}$). The structural morphology of the as-synthesized material was captured by Field emission scanning electron microscopy (FE-SEM, Hitachi S-3000H) and Transmission scanning microscopy (HRTEM, H-7600, Hitachi, Japan). The elemental percentage and the chemical composition were investigated by using energy dispersive X-ray (EDX) affiliated with the FE-SEM. The data of the Raman spectrum was collected from the Micro-Raman spectrometer (Raman Dong Woo 500 I, Korea). The chemical and valence states of the composite were examined by X-ray photoelectron spectroscopy (XPS, Thermo ESCALAB 250). The electro-catalytic activity of the as-prepared nanocomposite was analyzed by cyclic voltammetry in CH instrument Company, USA. The three-electrode system used Glassy carbon electrode (GCE) (working area = 0.071 cm^2) as a working electrode, Ag/AgCl (saturated KCl) as a reference electrode, and a platinum wire as a counter electrode. The CV studies were carried out in N_2 saturated (0.1 M PB , pH ~ 7.0) with a scan rate of 50 mVs^{-1} , which is the optimum condition for this entire study.

2.5. Fabrication of $\text{Ho}_2\text{WO}_6/\text{RGO}/\text{GCE}$

As prepared $\text{Ho}_2\text{WO}_6/\text{RGO}$ has dispersed (3 mg/ml) in DI water through ultrasonication for about 1 h. Before the fabrication, GCE was cleaned using alumina powder and thoroughly washed with water, and ethanol to obtain a well-cleaned GCE. The dispersed catalyst was used to

fabricate the bare GCE and used for the investigation of electrochemical experiments. The average loading of $\text{Ho}_2\text{WO}_6/\text{RGO}$ on GCE is 0.253 mg cm^{-2} , calculated from the below equation. The corresponding loading on the electrode surface was:

$$\text{Loading} = \frac{m}{A_{\text{geo}}} = \frac{0.018 \text{ mg}}{0.071 \text{ cm}^2} \approx 0.254 \text{ mg cm}^{-2}$$

A_{geo} stands for the geometric area of the working electrode (in cm^2), m (C^*V) refers to the mass of the deposited modifier (mg) on the electrode surface. Thus, the average loading of $\text{Ho}_2\text{WO}_6/\text{RGO}$ on GCE is 0.254 mg cm^{-2} .

3. Result and discussions

3.1. Characteristics of $\text{Ho}_2\text{WO}_6/\text{RGO}$

The crystal structure of the synthesized Ho_2WO_6 , RGO, and $\text{Ho}_2\text{WO}_6/\text{RGO}$ was characterized by X-ray photoelectron spectroscopy. XRD spectra of Ho_2WO_6 , RGO, and $\text{Ho}_2\text{WO}_6/\text{RGO}$ were depicted in Fig. 1a. Evidently, the diffraction peaks of Ho_2WO_6 were indexed at 2θ values at $18.9, 28.7, 29.4, 31.7, 34.7, 47.7, 49.02, 50.4$, and 54.5° belongs to the planes $(-111), (221), (-131), (-331), (600), (-242), (-730), (-550)$ and (261) which indicated the crystallinity of the Ho_2WO_6 (JCPDS. No: 00-025-1409). In the XRD spectra of $\text{Ho}_2\text{WO}_6/\text{RGO}$, the existence of peaks of Ho_2WO_6 was found whereas the peak of RGO was not found due to the high intensity of Ho_2WO_6 . The average crystalline size of the $\text{Ho}_2\text{WO}_6/\text{RGO}$ was calculated by using the Debye Scherrer's formula as 8.76 nm .

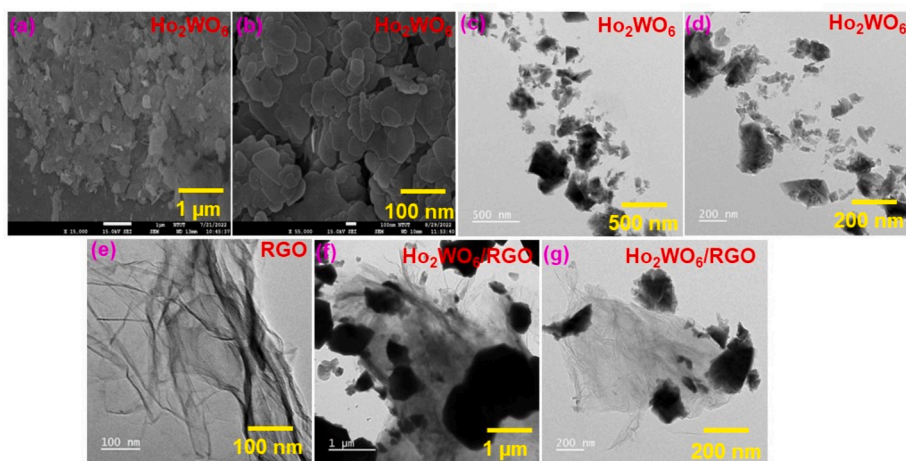


Fig. 2. (a, b) FESEM images of Ho_2WO_6 , TEM images of (c, d) Ho_2WO_6 , (e) RGO, (f, g) $\text{Ho}_2\text{WO}_6/\text{RGO}$.

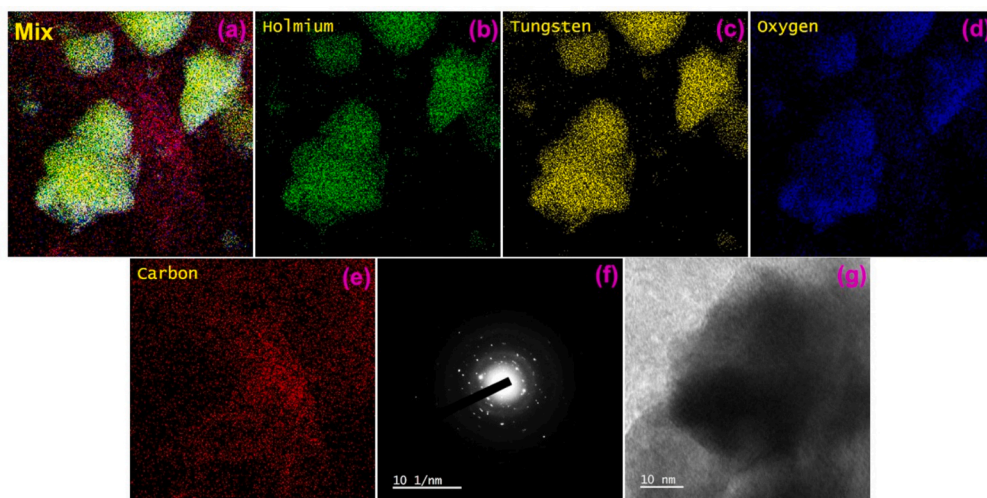


Fig. 3. EDX mapping images of (a) overall mapping, (b) Ho (green), (c) W (yellow), (d) O (blue), (e) C (red), (f) SAED pattern of Ho₂WO₆/RGO, (g) HR-TEM images of Ho₂WO₆/RGO.

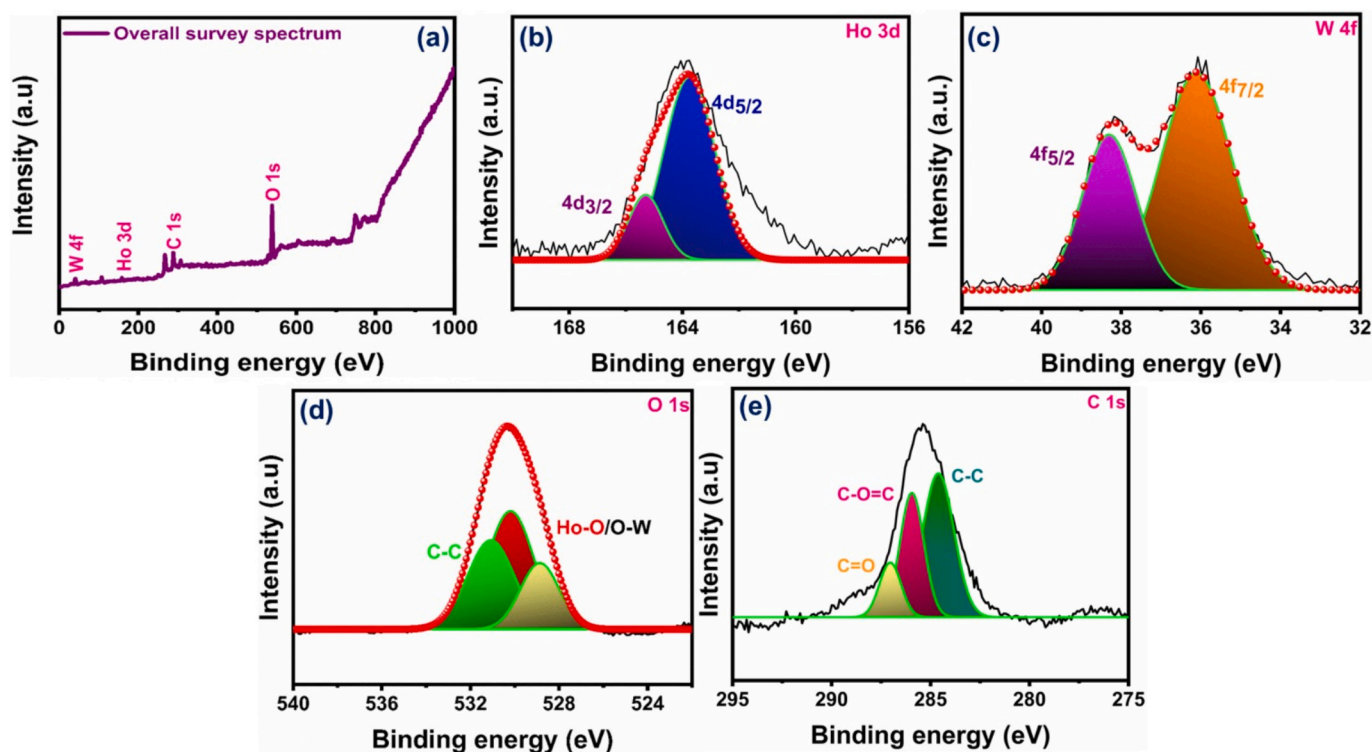


Fig. 4. XPS spectra of Ho₂WO₆/RGO (a) overall survey spectra, high-resolution spectra of (b) Ho, (c) W, (d) O, and (e) C.

$$D = \frac{K\lambda}{\beta \cos \theta} \quad (1)$$

Raman spectroscopy is widely used for the characterization of carbon materials. The presence of RGO in the composite Ho₂WO₆/RGO was confirmed by Raman analysis. Fig. 1b depicts the Raman spectra of Ho₂WO₆, Ho₂WO₆/RGO. The estimated I_D/I_G value for RGO was calculated to be 0.84, and for Ho₂WO₆/RGO was calculated to be 0.85. The value of the disorder degree for Ho₂WO₆/RGO was higher than Ho₂WO₆ which proves the synthesized material had more defects and loss of sp² domains. The successful formation of Ho₂WO₆/RGO was confirmed.

The morphology of the Ho₂WO₆ and Ho₂WO₆/RGO was experimented with using FE-SEM and HR-TEM. As shown in Fig. 2(a, b), the

Ho₂WO₆ exhibits a nanoplate-like structure. Also, the HRTEM image displayed in Fig. 2(c, d) shows a plate-like structure similar to the FESEM image. A wrinkled and sheet-like structure of RGO was depicted in Fig. 2(e). Fig. 2(f, g) outlines that the nanoplate-like Ho₂WO₆ gets wrapped over the surface of RGO. The agglomeration of the Ho₂WO₆ was prevented in the composite and it will be beneficial for the sensor detection of MLM. The results demonstrated the successful synthesis and good interaction between the Ho₂WO₆ and RGO. In addition, the elemental mapping in Fig. 3 displays the homogeneous distribution of Ho, W, O, and C components. Fig. 3a displays the overall mapping, and Fig. 3(b–e) displays the individual distribution of elements holmium, tungsten, oxygen, and carbon. Fig. 3f displays the SAED pattern of Ho₂WO₆/RGO composite which specifies the crystallinity of the

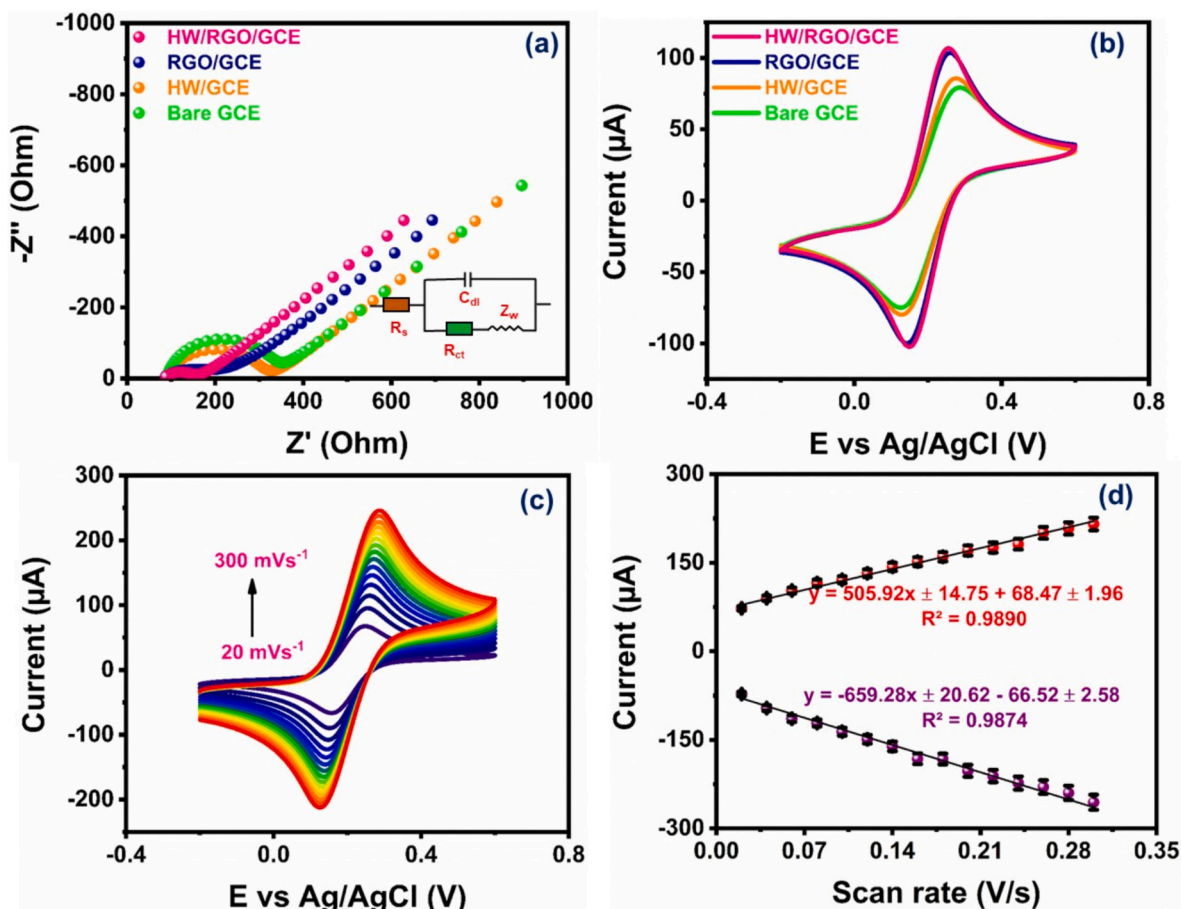


Fig. 5. (a) EIS Nyquist plots for modified electrodes (b) obtained CV current response for unmodified and modified electrodes at a scan rate 50 mVs^{-1} , (c) CV curves of $\text{Ho}_2\text{WO}_6/\text{RGO}/\text{GCE}$ at different scan rates, (d) linear plot vs different scan rates. And these all experiments were performed in $0.005 \text{ M} [\text{Fe}(\text{CN})_6]^{3-/4-}$ with 0.1 M KCl solution.

synthesized material. Fig. 3g displays the HRTEM image of the $\text{Ho}_2\text{WO}_6/\text{RGO}$ having a lattice distance of 0.3347 nm . The $\text{Ho}_2\text{WO}_6/\text{RGO}$ was synthesized successfully, and the Ho_2WO_6 gets connected to the RGO via a synergetic effect.

The chemical composition of the prepared $\text{Ho}_2\text{WO}_6/\text{RGO}$ was analyzed using X-ray photoelectron spectroscopy (XPS). Fig. 4a depicts the full survey spectrum of $\text{Ho}_2\text{WO}_6/\text{RGO}$ and shows the peaks for Ho, W, O, and C demonstrating the existence of those elements. In Fig. 4b, the peaks of Ho splits into two as 165.2 and 163.7 eV belongs to $4d_{3/2}$ and $4d_{5/2}$ [54]. The $4f_{5/2}$ and $4f_{7/2}$ of W were located at 38.3 and 36.1 eV respectively [55]. In the spectrum of O $1s$, the peaks were at 531.0 , 530.2 , and 528.8 eV , whereas the peak at 531.07 eV corresponds to the $\text{C}=\text{O}$, and the peaks at 531.0 and 530.2 belong to the $\text{Ho}-\text{O}$ or $\text{W}-\text{O}$ respectively [37]. The appearance of peaks at 287.0 , 285.9 , and 284.6 eV corresponds to the $\text{C}=\text{O}$, $\text{C}-\text{O}=\text{O}$, and $\text{C}-\text{C}$ respectively [37]. These peaks strongly validate the existence of Ho, W, O, and C in the prepared composite by enumerating the peaks in the position.

3.2. Electrochemical characterization of the $\text{Ho}_2\text{WO}_6/\text{RGO}/\text{GCE}$

3.2.1. Electrochemical impedance and kinetics investigation

EIS analysis is conducted to identify the conductive nature of Ho_2WO_6 -based modified working electrodes and bare GCE. The EIS experiment is performed under $[\text{Fe}(\text{CN})_6]^{3-/4-}$ (5 mM concentration) in the presence of potassium chloride (0.1 M concentration) with $0.1\text{--}100 \text{ kHz}$ frequency ($I = 10 \text{ mV}$). Fig. 5 shows the obtained EIS plots for $\text{Ho}_2\text{WO}_6/\text{RGO}/\text{GCE}$ (pink), RGO/GCE (blue), $\text{Ho}_2\text{WO}_6/\text{GCE}$ (yellow), and bare GCE (green). The corresponding Randles-circuit model

involved in EIS studies is shown as an inset in Fig. 5, R_s is an electrolyte resistance, R_w is Warburg impedance and C_{dl} denotes double-layer capacitance. Upon comparing with bare, Ho_2WO_6 , and RGO/GCE , the $\text{Ho}_2\text{WO}_6/\text{RGO}/\text{GCE}$ displayed a small semi-circle which shows a lower resistance at a higher frequency and expresses superior charge transfer capability. This is mainly because of the rapid charge transfer between Ho_2WO_6 and RGO in the working electrode. The R_{ct} value of $\text{Ho}_2\text{WO}_6/\text{RGO}/\text{GCE}$, RGO/GCE , $\text{Ho}_2\text{WO}_6/\text{GCE}$, and bare GCE are as follows 74.93 , 110.52 , 237.68 , and 265.74Ω .

Fig. 5(b) showcases the detailed CV current responses of bare and other modified working electrodes ($\text{Ho}_2\text{WO}_6/\text{RGO}$, RGO , $\text{Ho}_2\text{WO}_6/\text{GCE}$). The accumulation of ions and charges appearing in the electrolyte-electrode interface is predominantly due to the large surface area of $\text{Ho}_2\text{WO}_6/\text{RGO}/\text{GCE}$ than other modified electrodes. The highest redox current response was obtained for $\text{Ho}_2\text{WO}_6/\text{RGO}/\text{GCE}$, than the others, which showed the lowest peak current values. This study proves that $\text{Ho}_2\text{WO}_6/\text{RGO}/\text{GCE}$ exhibits superior electrical conductivity and active surface area, further it was calculated using Eq. (1).

$$I_p = (2.69 \times 10^5) n^{3/2} D^{1/2} A \nu^{1/2} C \quad (2)$$

Eq. (1) represents the Randles-Sevcik equation which is used to estimate the Electrochemically Active Surface Area of modified electrodes under the increasing scan rate conditions from 20 to 300 mVs^{-1} (Fig. 5c). The Randles-Sevcik equation confirms a larger electroactive surface area, while the $4f$ electron transitions of Ho^{3+} contribute to enhanced charge transfer. Fig. 5d shows the linear relationship between the square root of the scan rate and redox peak currents. The results show that $\text{Ho}_2\text{WO}_6/\text{RGO}/\text{GCE}$ exhibits higher cathodic to anodic peak

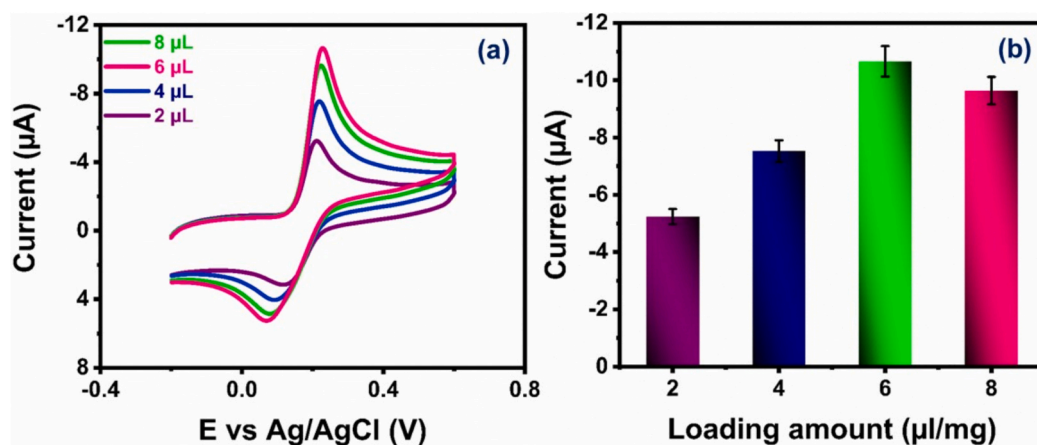


Fig. 6. (a) CV plot for 100 μM of MLM in N₂ saturated 0.1 M PBS at a scan rate of 50 mV/s using different loading amounts of Ho₂WO₆/RGO/GCE, (b) corresponding bar diagram of current response of different loading amounts.

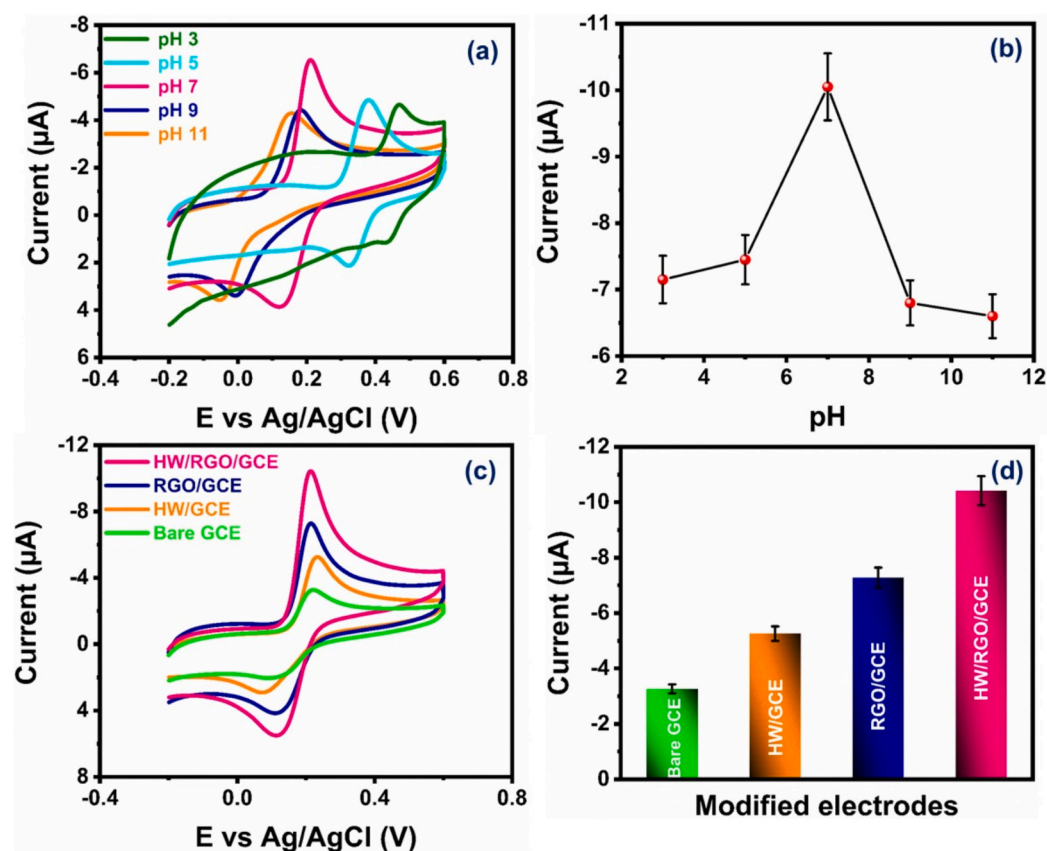


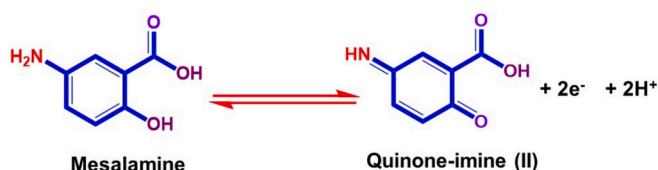
Fig. 7. (a) CV response of Ho₂WO₆/RGO/GCE for MLM detection at different pH using 100 μM of MLM in N₂ saturated 0.1 M PBS at a scan rate of 50 mV/s, (b) dependence plot of current response for different pH, (c) CV response of MLM detection for different modified electrodes using 100 μM of MLM in N₂ saturated 0.1 M PBS at a scan rate of 50 mV/s, (d) bar diagram of current response of different modified electrodes.

current values. This is due to the rapid redox reaction on the surface of Ho₂WO₆/RGO/GCE. The estimated EASA values for Ho₂WO₆/RGO/GCE, RGO/GCE, Ho₂WO₆/GCE, and bare GCE are as follows: 211, 208, 163, 156 cm². Among them, Ho₂WO₆/RGO/GCE displayed a superior value, proving its enhanced electrocatalytic activity, which is ideal for the sensing of MLM.

3.2.2. Different loading amounts

Ho₂WO₆/RGO/GCE catalyst loading optimization studies have been conducted in the presence of MLM and its corresponding CV responses

are shown in Fig. 6a. It is evident that 6 μL/mg displayed a higher peak current than other modified electrodes. This results in an expanded electroactive surface area and enhanced electron transfer pathways. However, excessive loading can lead to particle clustering, which may obscure active rGO sites and reduce conductivity, conversely, insufficient. The respective bar graph showing the peak current responses corresponding to the loading amount is shown in 6b. Table.S1 represents the average loading amount of the Ho₂WO₆/MCT on the GCE surface.



Scheme 2. Electro-oxidation mechanism of MLM.

3.2.3. Effect of pH on MLM detection

The reaction effect of pH during the electrochemical sensing of MLM is investigated through CV analysis by altering the pH values from 3 to 11 upon the addition of 100 μM MLM. Fig. 7a shows the obtained CV signals of MLM during different pH conditions. It is evident from the data that when the pH increases, a shift in the peak potentials of MLM is witnessed. It is due to the activity of protons during the MLM electrochemical oxidation, an aromatic amine and hydroxyl functional group, which undergoes electrochemical oxidation. At the optimised pH 7.0 Fig. 7b, the amino group of MLM is oxidised to form a quinone-imine structure via a two-electron and two-proton transfer process. The enhanced electrocatalytic activity of the $\text{Ho}_2\text{WO}_6/\text{RGO}$ nanocomposite arises from several factors, the Ho^{3+} centers promote electron transfer through their 4f orbital interactions; the WO_6 moieties provide redox-active sites that catalyze oxidation; and the RGO sheets increase the electroactive surface area, minimize nanoparticle agglomeration, and facilitate rapid charge transport. The observed pH-dependent shift in oxidation potential (as shown in Fig. 7) confirms the involvement of protons in the redox reaction. Scheme 2 has been added to visually represent the oxidation pathway of mesalamine [21].

3.2.4. Effect of different modified electrodes

The electrochemical performance of bare and modified GCE ($\text{Ho}_2\text{WO}_6/\text{RGO}/\text{GCE}$, RGO/GCE , $\text{Ho}_2\text{WO}_6/\text{GCE}$, bare GCE) in the presence of MLM 100 μM under 0.1 M PBS condition is investigated. It is displayed in Fig. 7c. In the experiment, bare electrode GCE exhibited the lowest peak current I_{pa} owing to low surface area and slow mobility of charge carriers. On the other hand, $\text{Ho}_2\text{WO}_6/\text{RGO}/\text{GCE}$ showed the highest peak current for MLM proving its superior electrocatalytic performance and enhanced surface area. The highest peak current for $\text{Ho}_2\text{WO}_6/\text{RGO}/\text{GCE}$ is due to 2 primary reasons. 1: Agglomeration of Ho_2WO_6 is reduced drastically as it is distributed on either side of RGO in the composites 2: The electrocatalytic property of RGO is boosted by Ho_2WO_6 nanostructures as they have strong electrostatic interaction and synergistic communication. This ultimately results in rapid charge transfer and aids in the high-performance detection of MLM. Fig. 7d represents the bar diagram for the current response of the different modified electrodes.

3.2.5. Effect of concentration and scan rate

The CV signals for $\text{Ho}_2\text{WO}_6/\text{RGO}/\text{GCE}$ in the presence of varying concentrations of MLM from 20 to 100 μM under the 0.1 M PBS pH 7 conditions with a constant scan rate of 50 mVs^{-1} (Fig. 8). The results indicate that the oxidation peak current increases periodically upon increasing the concentration of MLM. The relationship between the oxidation peak current values and MLM concentrations is linear as seen in Fig. 8b, and $R^2 = 0.9981$ is also shown. To further prove the enhanced electrocatalytic kinetic property of the prepared $\text{Ho}_2\text{WO}_6/\text{RGO}/\text{GCE}$ for the electrochemical detection of MLM, CV studies are done. The CV responses using $\text{Ho}_2\text{WO}_6/\text{RGO}/\text{GCE}$ for the varying scan rate from 20 to 300 mVs^{-1} in the presence of MLM (Fig. 8c). The linear increase in peak

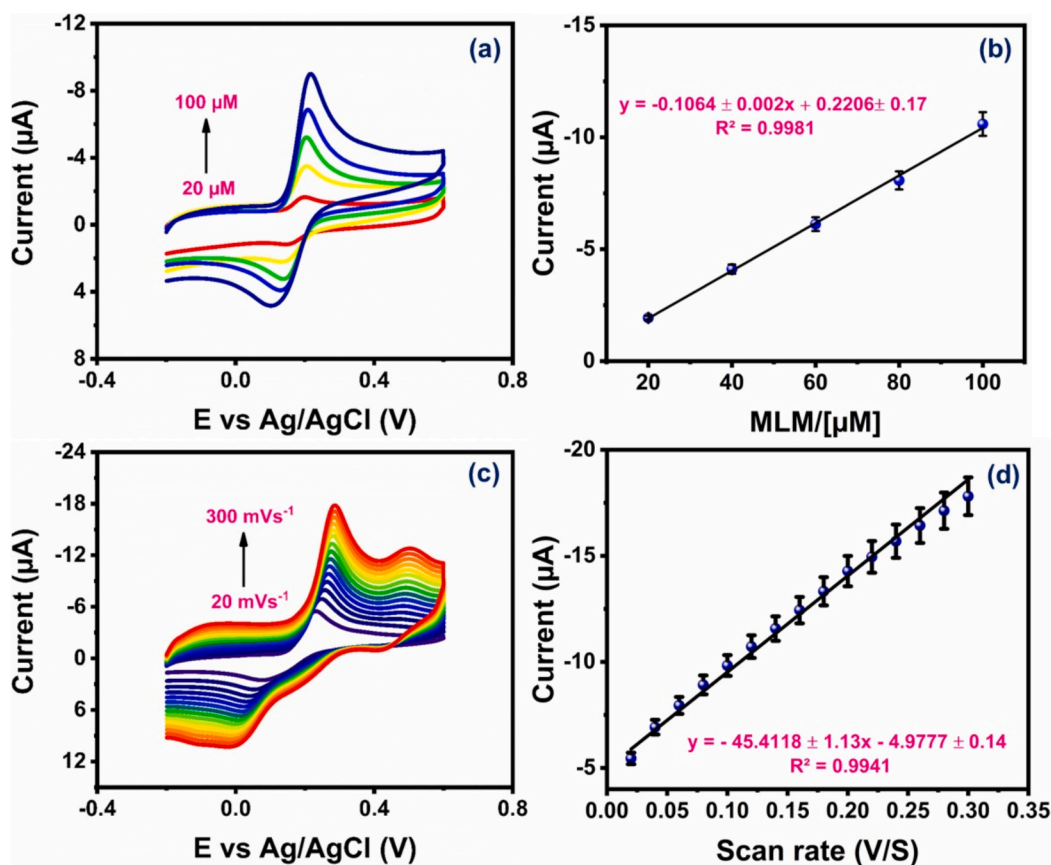


Fig. 8. a) CV response of $\text{Ho}_2\text{WO}_6/\text{RGO}/\text{GCE}$ using different concentration of MLM in N_2 saturated 0.1 M PBS at different concentrations, (b) corresponding linear plot of MLM concentration, (c) CV response of $\text{Ho}_2\text{WO}_6/\text{RGO}/\text{GCE}$ using 100 μM of MLM in N_2 saturated 0.1 M PBS at scan rate (20 mV/s –300 mV/s), (d) corresponding linear plot for scan rate vs current.

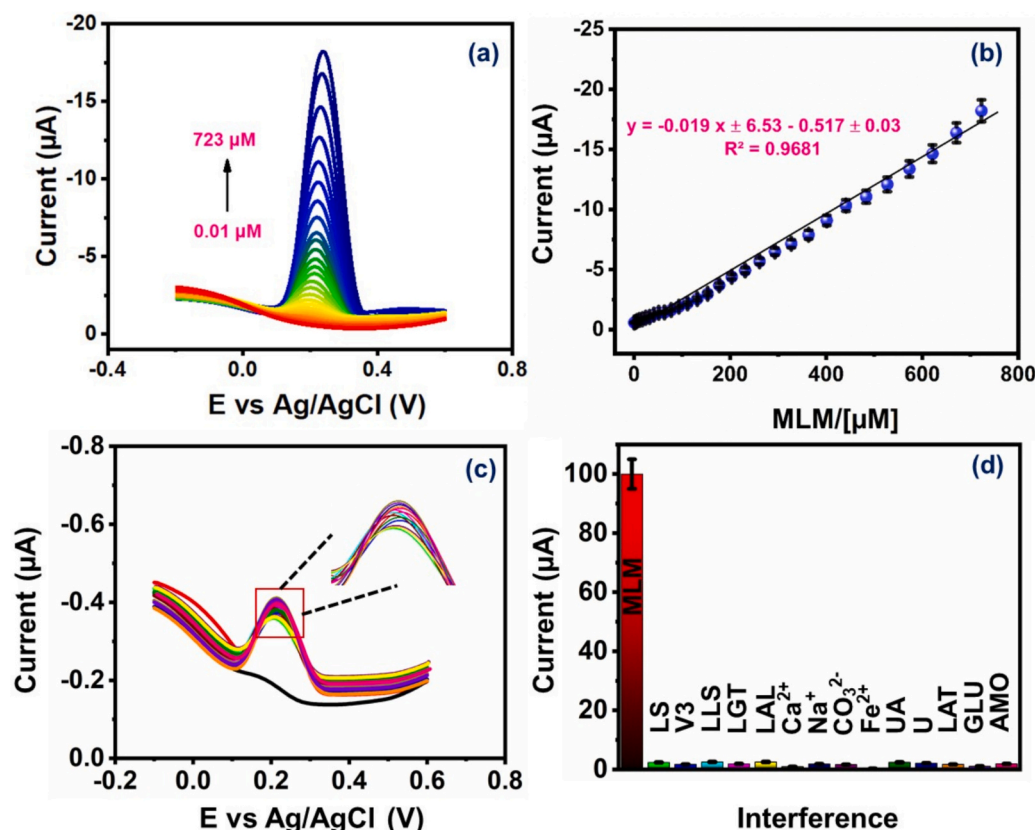


Fig. 9. (a) DPV response of $\text{Ho}_2\text{WO}_6/\text{RGO}/\text{GCE}$ for the different concentration of MLM detection at an increasing concentration in N_2 saturated 0.1 M PBS at a scan rate of 50 mV/s, (b) linear plot of $\text{Ho}_2\text{WO}_6/\text{RGO}/\text{GCE}$ for current response against increasing concentration, (c) DPV response of $\text{Ho}_2\text{WO}_6/\text{RGO}/\text{GCE}$ at different interfering reagents, (d) bar diagram for the current response of different interfering compounds.

Table 1

Summary of linear range, LOD of $\text{Ho}_2\text{WO}_6/\text{RGO}/\text{GCE}$ for detection of MLM compared with the previously reported results.

Electrodes	Linear range (μM)	LOD (μM)	Method	References
PCR-CPE	80–200	0.112	CV	[56]
$\text{Co}_2\text{SnO}_4/\text{rGO}$	0.029–5.78, 15.69–1326.07	0.0049	DPV	[21]
$\text{Co}/\text{Cu-BTC}/\text{SiO}_2$	0.05–200	0.01	DPV	[24]
$\text{FSO}/\text{SO}/\text{g-C}_3\text{N}_4/\text{GCE}$	0.05–1749.4	0.0075	DPV	[25]
ds-DNA/PPy/SL-C/ La^{3+} -doped CuO/ PGE	0.03–100	0.009	DPV	[57]
GO/MIP/GCE	2–20, 20–150	0.97	DPV	[5]
ZIF-67/CPE	0.03–50	0.01	DPV	[58]
CNTs-N/GCE	0.05–2.5	0.012	AdSWV	[19]
$\text{Ho}_2\text{WO}_6/\text{RGO}/\text{GCE}$	0.01–723	0.0039	DPV	This work

current is witnessed as the scan rate increases and it is shown in a linear graph between the scan rate Vs. current with $R^2 = 0.9941$ (Fig. 8d). The electro-catalytic redox reaction that MLM goes through over the $\text{Ho}_2\text{WO}_6/\text{RGO}/\text{GCE}$ electrode is an adsorption-controlled electrode process.

3.2.6. DPV investigation for the MLM sensing

Furthermore, to investigate MLM sensing in low concentrations, differential pulse voltammetry (DPV) analysis is adopted. Varying concentration from low to high of MLM is introduced into 0.1 M PBS and its responding DPV signals are displayed in Fig. 9a. DPV measurements for Mesalamine detection were performed using the following conditions:

initial potential -0.1 V, final potential 0.6 V, pulse width 0.05 s, and pulse period 0.2 s. These parameters were applied consistently throughout the study and provided stable and reproducible analytical responses. Peak current (I_{pa}) periodically increased upon increasing the concentration of MLM from 0.01 to $723 \mu\text{M}$. The linear relationship between the peak current and concentration of MLM is shown in Fig. 9b with $R^2 = 0.9681$. From this investigation, we can clearly understand the superior electrocatalytic activity of $\text{Ho}_2\text{WO}_6/\text{RGO}/\text{GCE}$. The estimated LOD ($3 S/Q$: S-standard deviation, q-slope value from the calibration plot) for the proposed electrochemical sensor is $0.0039 \mu\text{M}$. Then the sensitivity is estimated to be $1.3406 \mu\text{A} \mu\text{M}^{-1} \text{cm}^{-2}$. In regard to this impressive $\text{Ho}_2\text{WO}_6/\text{RGO}/\text{GCE}$ performance, they can be recommended for real-time analysis. Table 1 shows the proposed sensor performance with other reported literature for MLM detection.

3.2.7. Interference studies

To evaluate the selectivity of the $\text{Ho}_2\text{WO}_6/\text{RGO}/\text{GCE}$ sensor, an interference study was conducted using DPV in 0.1 M PBS (pH 7), with all tests performed at $1 \mu\text{M}$ MLM and $100 \mu\text{M}$ concentrations of potential interferents, in accordance with the reviewer's suggestion. The interfering species included biologically and clinically relevant compounds such as lactose (LS), vitamin B3 (V3), L-lysine (LLS), L-glutamine (LGT), L-alanine (LAL), Ca^{2+} , Na^+ , Cl^- , CO_3^{2-} , uric acid (UA), urea, ammonia, glucose, lactate, and Fe^{3+} . As shown in Fig. 9c and d, no significant overlapping peaks or current changes were observed in the presence of these interferents, indicating minimal interference with the MLM signal. These results confirm the excellent selectivity and practical reliability of the $\text{Ho}_2\text{WO}_6/\text{RGO}/\text{GCE}$ sensor for mesalamine detection, even under realistic biological conditions with high interferent concentrations.

Table 2

MLM determination spiked in blood serum and human urine.

Real sample	Added (μM)	Found (μM)	HP-LC spectroscopy	Recovery (%)		RSD (%)	
				DPV	HPLC	DPV	HPLC
Blood serum	5	4.90	4.72	98	96.1	1.17	2.22
	10	9.89	9.36	98.9	97.7	1.32	2.46
	15	14.99	14.21	99.9	98.1	1.52	2.38
Human urine	5	4.99	4.31	99.8	95.32	1.47	1.62
	10	9.96	9.52	99.6	96.23	1.36	2.43
	15	14.99	14.42	99.9	97.71	2.85	3.31

3.2.8. Repeatability, reproducibility, and stability

Some important properties like sensor repeatability, reproducibility, and stability are investigated before probing for real-world samples. All these properties are investigated using the DPV technique. For the repeatability studies, $\text{Ho}_2\text{WO}_6/\text{RGO}/\text{GCE}$ is analyzed in a 0.1 M PBS pH 7 system with the inclusion of 100 μM of MLM. Four consecutive DPV runs were performed using $\text{Ho}_2\text{WO}_6/\text{RGO}/\text{GCE}$ for MLM detection and are presented in Fig. S2a. As it is clear from the investigation, there is no peak current loss even after the four runs (Fig. S2d). The RSD value was calculated to be 1.52 %, which indicates the sensor possesses good repeatability. A similar experiment is performed for reproducibility studies with five freshly modified electrodes with $\text{Ho}_2\text{WO}_6/\text{RGO}$, and it is shown in Fig. S2b. Only a negligible peak current reduction is seen for the five electrodes (Fig. S2b), and this proves $\text{Ho}_2\text{WO}_6/\text{RGO}/\text{GCE}$ sensor is reproducible for MLM sensing. The RSD value was calculated to be 1.14 %, which indicates the sensor possesses excellent reproducibility. Finally, storage stability studies are done to understand the durability of fabricated $\text{Ho}_2\text{WO}_6/\text{RGO}/\text{GCE}$. Through DPV analysis, studies are conducted similar to repeatability and reproducibility. For the period of 12 days, the stability studies are done and are shown in Fig. S2c. From this analysis, we can understand that till 20 days, there was only very minimal current loss with an RSD of 1.43 % and proven superior stability of the $\text{Ho}_2\text{WO}_6/\text{RGO}/\text{GCE}$ for MLM sensing.

3.2.9. Real sample analysis

To evaluate the practical applicability of the fabricated $\text{Ho}_2\text{WO}_6/\text{RGO}/\text{GCE}$ sensor, differential pulse voltammetry (DPV) was performed on real samples including human blood serum and urine. Blood serum was collected approximately 3 h after oral administration of mesalamine, corresponding to its expected peak plasma concentration ($\sim 3 \mu\text{M}$). Both serum and urine samples were diluted 20-fold with 0.1 M PBS (pH 7.0) prior to analysis. This dilution was essential to (i) bring mesalamine concentrations within the linear detection range of the sensor, and (ii) minimize matrix effects that could interfere with electrochemical measurements. Blank DPV scans of the diluted serum and urine confirmed no significant interfering peaks at the oxidation potential of mesalamine (Fig. S3a, b). Standard additions of mesalamine were performed in 5–15 μM increments up to 5 μM , reflecting physiologically relevant levels. The corresponding DPV signals (Fig. S3a, b) exhibited clear, concentration-dependent responses. For validation, the sensor results were cross-checked with a standard HPLC method, and comparative data are presented in Table 2. The statistical analysis demonstrates that for blood serum samples, there was no significant difference between the DPV and HPLC results ($p > 0.05$), confirming strong agreement between the two analytical methods (Table S1). For urine samples, the t -test revealed a statistically significant difference ($p < 0.05$), though the F-test indicated no significant variance difference ($p > 0.05$), implying comparable precision between both techniques. The slightly higher values observed in the DPV method can be attributed to its superior electrochemical sensitivity and higher surface-active sites of the $\text{Ho}_2\text{WO}_6/\text{RGO}$ electrode rather than systematic bias. These findings confirm that $\text{Ho}_2\text{WO}_6/\text{RGO}/\text{GCE}$ offers reliable, sensitive, and selective detection of mesalamine in real biological matrices.

4. Conclusion

In this study, we prepared a novel rare earth metal tungstate composed of $\text{Ho}_2\text{WO}_6/\text{RGO}$ via a hydrothermal route for the electrochemical sensor detection of MLM. The resulting $\text{Ho}_2\text{WO}_6/\text{RGO}$ was characterized by various methods and used as a promising catalyst in electrochemical sensing. Owing to its enhanced electrochemical properties, they show a low LOD of 0.0039 μM , a wide linear range of 0.01–723 μM . These satisfactory results were due to the synergetic effect between the Ho_2WO_6 and RGO, which enhances the fast electron transfer ability. Thus, the developed sensor exhibits good stability, better sensitivity towards MLM detection, and easy synthesis. Accordingly, the tremendous recovery results of MLM in real samples show an excellent ability towards practical applicability. This research provides real-time applications and cost-effectiveness for the MLM with high sensitivity, selectivity and anti-fouling properties. This material and detection strategy hold strong potential for translation into next-generation, real-time analytical and biomedical sensing applications.

CRediT authorship contribution statement

Sundaresan Ruspika: Writing – review & editing, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Saranvignesh Alagarsamy:** Writing – review & editing, Writing – original draft, Software. **Tse-Wei Chen:** Visualization, Methodology, Funding acquisition, Formal analysis. **Shen Ming Chen:** Project administration, Funding acquisition, Visualization, Reviewing. **Ramachandran Balaji:** Writing – review & editing, Writing – original draft, Validation. **Elayappan Tamilalagan:** Software. **Chen-Chi Wang:** Visualization. **Narendhar Chandrasekar:** Writing – review & editing, Writing – original draft. **Ming-Chin Yu:** Visualization. **Heng-Yuan Hsu:** Visualization, Funding acquisition.

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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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cej.2025.170196>.

Data availability

Data will be made available on request.

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