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Synthesis of active-site rich molybdenum-doped manganese tungstate nanocubes for effective electrochemical sensing of the antiviral drug (COVID-19) nitazoxanide

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HIGHLIGHTS

- The Mo doped MnWO4 NCs were prepared by simple and inexpensive hydrothermal synthesis method.
- A new electrochemical sensor (Mo–MnWO4/GCE) was developed for detection of the COVID-19 drug nitazoxanide (NTZ).
- The Mo–MnWO4/GCE exhibits good electrocatalytic activity towards NTZ detection in biological samples.
- A promising sensing device for detection of drugs by exploring the defect engineering on metal tungstates.

ABSTRACT

Nitazoxanide (NTZ), a promising antiviral agent, is currently being tested in clinical trials as a potential treatment for novel coronavirus disease 2019 (COVID-19). This paper describes a one-pot hydrothermal synthesis to prepare molybdenum (Mo)-doped manganese tungstate nanocubes (Mo–MnWO4 NCs) for the electrochemical sensing of NTZ. The as-prepared Mo–MnWO4 NCs were characterized using various techniques such as XRD, Raman, FE-SEM, FE-TEM, and XPS to confirm the crystal structure, morphology, and elemental composition. The obtained results demonstrate that Mo doping on MnWO4 generates many vacancy sites, exhibiting remarkable electrochemical activity. The kinetic parameters of the electrode modified with Mo–MnWO4 NCs were calculated to be (Ks) $1.1 \times 10^2$ cm$^2$ s$^{-1}$ and (α) 0.97, respectively. Moreover, a novel electrochemical sensor using Mo–MnWO4 NCs was fabricated to detect NTZ, which is used as a primary antibiotic to control COVID-19. Under optimal conditions, the electrochemical reduction of NTZ was determined with a low detection limit of 3.7 nM for a linear range of 0.014–170.2 μM with a high sensitivity of 0.78 μA μM$^{-1}$ cm$^{-2}$ and negligible interference with other nitro group-containing drugs, cations, and anions. The electrochemical sensor was successfully used to detect NTZ in the blood serum and urine samples and achieved high recoveries in the range of 94–99.2% and 95.3–99.6%, respectively. This work opens a way to develop high-performance sensing materials by exploring the introduction of defect engineering on metal tungstates to detect drug molecules for practical applications.

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https://doi.org/10.1016/j.chemosphere.2022.137005
Received 16 August 2022; Received in revised form 18 October 2022; Accepted 23 October 2022
Available online 5 November 2022
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1. Introduction

In recent years, several mixed metal oxides with indeterminate nanostructures have been synthesized and explored for various technological applications such as energy conversion and storage. Their remarkable behavior depends not only on the complex morphology but also on the crystalline properties of the particles in the micro-architecture (Trung et al., 2018). Among the various mixed oxides, transition metal tungstates such as NiWO₄ (Ikram, Javed and Shad, 2021), CoWO₄ (Patil et al., 2021), and CuWO₄ (Roshani, Tadjarodi and Ghaffarinjadeh, 2021) are used widely as electrode materials for various electrochemical applications. Wolframite-structured manganese tungstates (MnWO₄) have attracted considerable attention for important electrochemical applications such as water electrolysis (Selhi et al., 2021), supercapacitors (Mallick et al., 2020), and electrochemical sensors (Eranjaneya et al., 2018), owing to their remarkable advantages such as low cost, high crystallinity, high electrical conductivity, and the presence of numerous oxygen vacancies (Jiang et al., 2016). Moreover, MnWO₄ exhibits strong redox properties and high chemical stability for electrochemical sensors (Eranjaneya et al., 2018). These properties depend strongly on the structural coordination of MnWO₄, because Mn and W atoms are present in octahedral coordination surrounded by oxygen ions (eight), which can lead to a structural disorder, such as oxygen vacancies (Sardar et al., 2021). The presence of such a disturbed structure and the variation of W ion coordination (W⁶⁺) produce localized electronic energy levels with a change in the diverse spin state, leading to the formation of many active sites that increase their electrochemical activity (Li et al., 2022). Thus, Eranjaneya (Eranjaneya et al., 2018) and Ramya et al. (Ramkumar et al., 2022) previously reported the electrochemical sensing behavior of MnWO₄ for the detection of heavy metal ions and tetracycline pollutants. The electrochemical aspects of MnWO₄ are also discussed in the previously published literature (Eranjaneya et al., 2018; Sardar et al., 2021; Vilian et al., 2020). On the other hand, the strategy to improve the electrochemical sensing performance of MnWO₄ is not yet clear. To this end, doping of MnWO₄ with transition metals has been introduced, which in turn can produce many surface sites for the more efficient electrochemical detection of biomolecules.

Recently, metal oxides doped with a high valent metal have been used as dopants (e.g., molybdenum, Mo) to modify the energy level of catalysts and improve their electrocatalytic activity (Jin et al., 2018). Moreover, Mo doping of 3 d-transition metals affects the electronic structure and modulates the electron density, providing a change in the diverse spin state, leading to the formation of many active sites that increase their electrochemical activity (Li et al., 2022). Thus, Eranjaneya (Eranjaneya et al., 2018) and Ramya et al. (Ramkumar et al., 2022) previously reported the electrochemical sensing behavior of MnWO₄ for the detection of heavy metal ions and tetracycline pollutants. The electrochemical aspects of MnWO₄ are also discussed in the previously published literature (Eranjaneya et al., 2018; Sardar et al., 2021; Vilian et al., 2020). On the other hand, the strategy to improve the electrochemical sensing performance of MnWO₄ is not yet clear. To this end, doping of MnWO₄ with transition metals has been introduced, which in turn can produce many surface sites for the more efficient electrochemical detection of biomolecules.

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heated autoclave was allowed to cool to room temperature. The yellow color precipitate was then collected, washed several times with water/ethanol, and dried overnight in a hot air oven. The following equations illustrate the formation of the Mo–MnWO₄ NCs described above:

\[
\text{NaMoO}_2\cdot2\text{H}_2\text{O} + \text{Mn(NO}_3\text{)}_2\cdot6\text{H}_2\text{O} + \text{Na}_2\text{WO}_4\cdot2\text{H}_2\text{O} \rightarrow \text{Mo–MnWO}_4 + 10\text{H}_2\text{O}
\]  

(1)

The overall plausible mechanism for the growth of MnWO₄ NCs is shown in Scheme 1 and is briefly described here. The various steps of the growth illustrate the formation of the desired product. Sodium tungstate monohydrate [Na₂WO₄·2H₂O] was used as a WO₄⁻ ion source, while manganese nitrate hexahydrate [Mn(NO₃)₂·6H₂O] provided Mn²⁺ ions and sodium molybdate monohydrate [NaMoO₄·2H₂O] as Mo⁶⁺ ions. Then the Mo⁶⁺/Mn²⁺ ions react with WO₄⁻ ions during the hydrothermal process to form Mo–MnWO₄ nuclei. This nucleation leads to the formation of particles. Keeping the reactants at 180 °C for 12 h, the nanocubes grow into an elongated crystal-like structure, which develops into Mo–MnWO₄ NCs (Shad et al., 2019). For comparison, (1:2:1 and 1:3:1 ratio (Mn: Mo: WO) Mo-doped MnWO₄ materials were prepared at adding different amounts of Mo by using the same synthesis procedure.

3. Results and discussion

3.1. Synthesis and characterization of Mo–MnWO₄ NCs

A hydrothermal process was used to synthesize Mo–MnWO₄ NCs. Spectral, surface, and morphological characterization plays an important role in understanding the fundamentals and performance of fabricated Mo–MnWO₄ NCs sensors. The Mo–MnWO₄ NCs were characterized by utilizing XRD, Raman, FE-SEM, FE-TEM, and XPS analyses (Figs. 1–5). The crystallites structure of the undoped MnWO₄ and Mo-doped MnWO₄ (Mo–MnWO₄) were characterized by XRD. Fig. 1(A) presents the XRD pattern of the MnWO₄ and Mo–MnWO₄ NCs samples. The distinct diffraction peaks of MnWO₄ at 2θ values of 15.27°, 18.29°, 23.43°, 23.96°, 29.78°, 30.32°, 30.99°, 35.91°, 37.19°, 40.28°, 40.82°, 43.31°, 44.82°, 48.04°, 51.10°, 52.16°, 53.07°, 60.47°, 62.36°, 64.40°, and 67.58° corresponding to hkl planes of (010), (100), (011), (110), (−111), (111), (020), (002), (200), (−102), (121), (112), (211), (020), (130), (−202), (221), (−113), (311), (−231), and (041), respectively. The XRD peaks agree well with the wolframite structure (Fig. 1(A)(a)) of MnWO₄ (space group P2₁/c) and are consistent with the standard card value (ICPDS 01-080-0152) (Harichandran et al., 2020). Similarly, the XRD pattern of Mo–MnWO₄ showed the same diffraction peaks with a slight shift in the diffraction angle values (as shown in Fig. 1(B)(b)). This characteristic shift of the peak positions toward a higher angle (about ~0.1°) indicates the existence of Mo as a dopant in the wolframite structure of MnWO₄. Moreover, the continuous shift of the peak position of all patterns indicates the decrease in the cell volume of the MnWO₄ crystal lattice. The shift of peak position also provides information about the occurrence of lattice distortions on the crystal faces of MnWO₄, which is consistent with Vegard’s law (Samei et al., 2021).

The above phenomenon is not surprising, considering that the ionic radius of Mn (0.67 Å) is comparatively higher than that of Mo⁶⁺ and W⁶⁺ (0.59 Å) and (0.60 Å), respectively. The differences in chemical states between Mo⁶⁺/Mo⁵⁺ and Mn²⁺/Mn³⁺ lead to unbound positions and defect sites (vacancies) (Phama et al., 2020). On the other hand, there are no other impurities such as MnO₂, and MoO₂ has not been detected yet, indicating that MnWO₄ retains its original crystal phase after doping process. The corresponding crystal structure of the as-prepared Mo–MnWO₄ consists of building blocks of MnO₂ octahedra with Mn²⁺ ions and WO₄ octahedra with W⁶⁺ (d⁶) ions. The distorted MnO₂ (WO₄) octahedral has common edges and forms zigzag MnO₂ (WO₄) chains by introducing Mo⁶⁺. Moreover, the particle average size of the Mo–MnWO₄ NCs was estimated using the Debye–Scherrer equation (D = kλ/βcosθ). Using the Debye–Scherrer equation, the average particle size of the wolframite-type Mo–MnWO₄ NCs was calculated to be 36 nm, which confirms that Mo doping can reduce the size of MnWO₄.
without significantly altering the crystallinity. It is worthy to note that the crystalline structure of the Mo–MnWO₄ NCs can improve electrocatalytic activity.

Wolframite structured MnWO₄ is thermodynamically stable and belongs to the point group C2h in the Schoenflies notation. This was also confirmed by Raman spectroscopy, which is considered a complementary analysis to XRD. The corresponding Raman spectra of MnWO₄ and Mo–MnWO₄ NCs are shown in Fig. 1(C). According to the group theory, 34 vibrational modes (Γ(k = 0) = 8A_g + 10B_g + 7A_u + 9B_u) are expected after eliminating the acoustic modes in MnWO₄. Of these vibrations, all the even molecular vibrations (i.e., 8A_g and 10B_g) are Raman active, and the odd ones (i.e., 7A_u and 9B_u) are IR active. However, all the peaks below 1000 cm⁻¹ belong to the vibrations of the inorganic phase of MnWO₄. The peak at 133.6 cm⁻¹ (A_g) was assigned to the torsional mode of tungsten (Stella et al., 2015). The peaks at 209 and 330.9 cm⁻¹ were attributed to the symmetric stretching vibrations of an Mn–O and O–Mn–O bond, respectively (Rani et al., 2018). This was followed by a Raman signal at 403.7 cm⁻¹ associated with the in-plane deformation vibration of the W–O bond in the WO₂ (Meziani et al., 2021). The stretching vibrations of the Mn–O–Mn bond belong to the band value of 546.7 cm⁻¹, and the band at 776 cm⁻¹ is mainly associated with the symmetric stretching vibration of the W–O–W bond in the W chain. The most intense peak at 886 cm⁻¹ was also attributed to the symmetric stretching vibration of the W–O bond in MnWO₄. These peaks agree with previous reports of MnWO₄ in the pure form (Meziani et al., 2021; Iliev et al., 2009). Compared to pure MnWO₄, an additional shoulder peak was observed at the beginning of the W–O bond with a value of 852.3 cm⁻¹. The intensity of the shoulder peak (852 cm⁻¹) was higher because the length of the Mo–O bonds is shorter than that of the W–O bonds (Li et al., 2022). These Mo–O bonds in Mo-doped MnWO₄ are expected to lead to structural deformations and promote ion distribution during an electrochemical reaction. In addition, a marginal shift in the peak position to a lower wavenumber was observed upon the introduction of Mo, indicating a decrease in the bond length of Mn–W or Mo–W, resulting in a decrease in cell volume. This result is shown in Fig. 1(D), which is consistent with the XRD analysis. Interestingly, a change in the intensity of the Raman spectra of Mo-doped MnWO₄ was observed in the presence of Mo, suggesting that introducing the dopant may cause the Jahn–Teller distortion. The distortion is also evident in the peak splitting of the XRD patterns in the Mo–MnWO₄ sample. These results show the successful formation of the distorted wolframite structure of Mo–MnWO₄.

Surface morphological analyses were carried out using different magnified FE-SEM (EDAX and elemental mapping) and FE-TEM (FE-TEM and SAED pattern) images of the prepared MnWO₄ and Mo-doped MnWO₄ (Figs. 2 and 3). Fig. 2(A and B) shows the formation of a cubic structure of MnWO₄ with uniform size and shape. The FE-SEM images of Mo–MnWO₄ also show similar morphology to that of MnWO₄. These observations are also shown in Fig. 2(C and D). This result confirms that the structural morphology of MnWO₄ was not changed even after doping with Mo. The FE-SEM-EDAX analysis revealed the presence of Mo, Mn, W, and O elements, which confirmed the distribution of Mo on the
MnWO$_4$ surfaces, as shown in Fig. 2(E and F). The mapping results are also indicated in Fig. S1. Fig. S1 defines the elements such as Molybdenum (Mo), Manganese (Mn), Tungsten (W), and Oxygen (O) which are uniformly dispersed on the as-prepared Mo–MnWO$_4$ without any other products, suggesting that Mo was doped successfully on the MnWO$_4$. The obtained morphology was again studied by FE-TEM analysis (see Fig. 3(A-C)), which is also in good agreement with the FE-SEM. Fig. 3(A-C) shows various magnified images of Mo–MnWO$_4$ indicating the formation of transparent nanocubes of Mo–MnWO$_4$. The appearance of Mo–MnWO$_4$ nanocubes is indicated by the yellow dotted lines in Fig. 3(B and C).

Moreover, the morphology revealed an almost uniform arrangement of the nanocubes, and their particle size only varied slightly during doping, indicating a decrease in cell volume. A particle size distribution of the Mo–MnWO$_4$ NCs determined from FE-TEM analysis showed a significant variation in the size. According to FE-TEM, the average cube size is approximately 33 nm. These results are consistent with the calculation of the particle size measurement in the XRD pattern according to the Debye-Scherrer equation. Moreover, the high-resolution image of the surface lattice of the Mo–MnWO$_4$ NCs shows several distortions/defects due to the presence of Mo on MnWO$_4$, (Fig. 3(D)). The lattice images also show well-defined lattice fringes with spacings of 0.36 and 0.47 nm, corresponding to the planes of the Mo–MnWO$_4$ sample. The surface defects can also be observed in Fig. 3(E). The resulting distorted surface can be attributed to (i) the introduction of high valent Mo atoms, which cause the localized coulombic effect and subtle atomic distortion, and (ii) the unequal Jahn-Teller phenomenon between Mn–W and Mo–W (Sakthivel et al., 2019). At the same time, the lattice distortions prove the existence of more oxygen vacancies due to Mo doping of the MnWO$_4$ lattice. The selected area electron diffraction (SAED) pattern of the Mo–MnWO$_4$ NCs with the corresponding optimistic rings (Fig. 3(F)) was obtained and attributed to the main XRD

Fig. 2. (A–D) FE-SEM images and (E, F) EDAX spectrum of MnWO$_4$ before and after Mo doping.
peak from the (010) and (100) planes of the cubic Mo–MnWO₄ NCs, illustrating the pure crystalline architecture of the NCs.

XPS analysis was carried out to verify the elemental composition and oxidation states of the prepared Mo–MnWO₄ NCs (Fig. 4). The overall XPS survey scan spectrum revealed peaks at 233, 650, 35, and 530 eV in Fig. 4(A), confirming the presence of Mo, Mn, W, and O elements in Mo–MnWO₄. The Mo content in the oxidation product increased gradually. The spectrum of Mo 3 d (Fig. 4(B)), confirmed that Mo exists in two oxidation states (Mo⁶⁺ and Mo⁴⁺) with binding energies around 234.5 and 231.5 eV, corresponding to the subshells of 3d⁵/₂ and Mo⁶⁺ 3d₃/₂, respectively. In addition, a positive shift in the binding energies of Mo (from elemental Mo) was observed, which can be attributed to the...
existence of metallic Mo (Diczhazi et al., 2021). Moreover, the peak spacing of 3.2 eV suggests that Mo$^{4+}$ is in the form of Mo$^{6+}$. As shown in the Mn 2p spectrum (Fig. 4(C)), Mn exhibits binding energies of 652.1, 646.3, 640.8, and 639.4 eV, corresponding to the Mn$^{2+}$ (2p$^{3/2}$) and Mn$^{3+}$ (2p$^{1/2}$) in the spin doublet of Mn peaks. Doping with Mo leads to a positive shift in the binding energies of Mn and a decrease in the peak area of Mn$^{2+}$ and Mn$^{3+}$ valence states, apparently due to a change in the electronic state of MnWO$_4$ (Lu et al., 2018; Xiong and Wang, 2022). The high-resolution spectrum of W 4f was deconvoluted into binding energies of 36.8 and 33.4 eV, which correlated with the spin state of W$^{6+}$ of the subshells W 4f$^{5/2}$ and 4f$^{7/2}$ (Fig. 4(D)).

By contrast, there was no shift in the core spectrum of W, suggesting a similar ionic structure to that of Mo (Jha et al., 2020; Meddar et al., 2012). Moreover, the high-resolution spectrum of O 1s (Fig. 4(E)) revealed the characteristic peaks at binding energies of 529 and 530 eV, which could be assigned to lattice oxygen species originating from the Mn–O–W group (vacancies) and the surface-absorbed oxygen species (bound to the surface), respectively (Sardar et al., 2021). Thus, XPS results confirmed the presence of all elements, including the Mo dopant. Moreover, the positive shift of Mo is likely to result in the transfer of electrons from Mo to the Mn core, leading to increased intrinsic activity and thus higher electrochemical performance towards electrochemical
sensing application (Sukanya and S.M. Chen, 2020). In addition, various compositions of Mo content in Mo–MnWO₄ were also estimated by XPS analysis, and the results are shown in Table S1. The composition result of all ratios of Mo–MnWO₄ confirmed that the W atoms in MnWO₄ are replaced by the introduction of Mo atoms, indicating the successful doping of the MnWO₄ lattice with Mo.

3.3.2. Cyclic voltammogram sensing of NTZ at Mo electrode surface (data not shown). Therefore, a droplet amount of 10 μL (pH 7)). The obtained CV curves are shown in Fig. 5 (B). The lower bar diagram for the current response to the effect of the modifier is up to 10 μL of Mo towards the NTZ. The corresponding CV curves were plotted at a sweep rate of 50 mV/s. The CV curves in Fig. 5(E) indicate that the reduction peak current for NTZ increased linearly with increasing concentration from 100 to 400 μM, indicating the excellent electrocatalytic behavior of Mo–MnWO₄/GCE for the detection of NTZ. This linearity in current response was also inferred from the linear plot between concentration vs. cathodic peak current shown in Fig. 5(F). From this plot, linear regression equation was derived as Ipc = -0.0273 [NTZ/μM] - 4.04; and the coefficient is R² = 0.966. This good linear response indicates that the Mo–MnWO₄/GCE is a highly active electrode for measuring NTZ under acidic pH conditions. To better understand the kinetic parameters, the linear relationship between the log concentration and log cathodic peak current was also derived. The corresponding logarithmic plot between concentration and cathodic peak current gives a linear equation, and the coefficient values of Ipc (μA) = 0.614 [NTZ/μM] – 0.42; R² = 0.984 (Fig. S3). These linear plots show that the detection of NTZ on Mo–MnWO₄/GCE follows a half-reaction kinetic mechanism to detect NTZ. From the above electrochemical results, it is clear that the developed Mo–MnWO₄ modified GCE increases the reduction current as a function of NTZ concentration and exhibits excellent conductivity for the detection of NTZ because of the numerous active catalytic sites formed by Mo doping in the MnWO₄ lattice. To further evaluate the effects of NTZ concentration on Mo–MnWO₄/GCE, a high-sensitivity amperometric analysis was performed as described in Amperometric Section.

3.3.4. Influence of pH on NTZ detection

The effect of protons on the electrochemical reduction of NTZ was studied to estimate their influence on electron transport during electrochemical analysis. The effect of pH on the cathodic current NTZ on Mo–MnWO₄/GCE was investigated by CV analysis using different pH solutions from 3 to 11. The corresponding CV was recorded as shown in Fig. 6(A). The CV curves, show that the cathodic peak current increases from pH 3 to 5 and then decreases at pH 7 to 11, indicating a lack of involvement of protons required during the electrochemical sensing of NTZ. However, the pKa value of NTZ at more acidic pH was reported to be 8.3, indicating that the NTZ molecule is neutral between pH 3 and 5. Moreover, the pH is below the pKa value and the NTZ was protonated, so the unshared electron pairs are prevented from delocalizing from the N atom to the aromatic ring, which decreases the reactivity with free radical (Feng et al., 2022). However, a slight decrease in current response was observed for NTZ at pH 3, which might

3.2. Electrochemical performance of Mo–MnWO₄ NCs

Before the detection process, the quantitative analysis of the interfacial reaction between the electrode and electrolyte was first investigated by electrochemical impedance analysis (EIS). The results characterized by EIS are given in the Nyquist diagram shown in Fig. 5 (A). The EIS showed that the bare GCE (a) has a small semicircle diameter (Rct = 16.98 (Z_re)) along with a straight line, indicating diffusion-driven electron transfer at the electrode-electrolyte interface. At the same time, MnWO₄/GCE (b) and Mo–MnWO₄/GCE (c) show a larger semicircle region (Rct = 359.5 (Z_re) and 380.7 (Z_re)). A large angle of Warburg impedance above the angle of 45° indicates electrostatic repulsion between the redox [Fe(CN)₆]₃/⁴⁻ probe and the negatively charged surface of the metal oxides. The larger diameter of the semicircle represents a large electron transfer resistance compared to unmodified electrodes. The electronic circuit model for the corresponding Nyquist diagram and the Randles equivalent circuit are drawn, as shown in the inset in Fig. 5(A). This Randles equivalent circuit diagram indicates that the redox reaction occurs at the surface of the working electrodes (Mo–MnWO₄/GCE) in a conventional three-electrode electrochemical cell system.

3.3. Optimization of the detection conditions

The electrochemical parameters such as the amount of modifier, the effect of concentration, scan rate, and pH for the detecting NTZ are discussed in the following sections.

3.3.1. Effect of modifier

To better understand the effects on current density and sensitivity parameters, the effect of modifier amount on the electrode surface was investigated. The modifier test was performed by dropping different amounts of the aliquot on the bare GCE surface. Therefore, we investigated the different drop amounts (4, 6, 8, and 10 μL) of Mo–MnWO₄ on the response of 200 μM NTZ using CV analysis (performed at 0.05 M PBS (pH 7)). The obtained CV curves are shown in Fig. 5(B). The lower amount of suspension (4 - 8 μL) leads to a lower current response due to insufficient thickness and particle size of Mo–MnWO₄. The electrochemical activity of NTZ increased with increasing in loading amounts up to 10 μL of Mo–MnWO₄ on the GCE surface, indicating that a larger amount of aliquot is required for the catalysis of NTZ. The corresponding bar diagram for the current response to the effect of the modifier is shown in Fig. 5(C). At the same time, higher loading (more than 10 μL) of Mo–MnWO₄ leads to a decrease in the electrocatalytic activity of NTZ on the modified GCE, because of the aggregation of particles on the electrode surface (data not shown). Therefore, a droplet amount of 10 μL Mo–MnWO₄ was chosen for further studies on the detection of NTZ.

3.3.2 Cyclic voltammetry sensing of NTZ at Mo–MnWO₄/GCE

Cyclic voltammetry (CV) analysis was conducted to study the electrochemical behavior and the mechanism for the detection of NTZ on various modified electrodes, including bare GCE, MnWO₄/GCE, and Mo–MnWO₄/GCE. The CV experiments were performed in the presence of Na₂-saturated 0.05 M PBS (pH 7) containing 200 μM NTZ at a sweep rate of 50 mV/s, as shown in Fig. 5(D). As can be observed in the figure, a low current response (~0.58 μA at ~0.55 V) was observed for bare GCE in the presence of 200 μM NTZ. In addition, the current response of NTZ on MnWO₄/GCE was improved slightly to ~7.89 μA at ~0.57 V potential, most likely due to abundant oxygen vacancies and the higher conductivity of W. While a strong current response (~10.45 μA) was observed for NTZ on Mo–MnWO₄/GCE at a potential of ~0.56 V, which could result from the direct reduction of NTZ into a hydroxylamine derivative by the 2e⁻/H⁺ transfer process. In the reverse scan, there was no oxidation peak for NTZ was observed, confirming that the electrochemical detection of NTZ is irreversible. However, the current response for NTZ at Mo-doped MnWO₄/GCE is much higher than that of other electrodes. In this case, it may be caused by the higher Mo redox activity, which distorts the MnWO₄ NCs to create more active catalytic sites. To compare the electrochemical activity, CV analysis was also performed for different concentrations of 1:2:1 and 1:3:1 ratio (Mn: Mo: W) Mo doped MnWO₄/GCE and the corresponding results are shown in Fig. S2. The overall electrochemical reduction mechanism for the detection of NTZ on Mo–MnWO₄/GCE is shown in Scheme 2. In addition, to the electrochemical performance of Mo–MnWO₄ NCs makes it an excellent material for the detection of NTZ owing to the presence of metals with multiple oxidation states (Mo and Mn), as well as the ability of the metal tungstate to generate excellent redox activity. This allows for a superior electrocatalytic activity for the detection of NTZ.
provided a corresponding linear regression equation and a correlation role in the NTZ reduction. On this basis, a linear curve between the pH of the pH varied between 9.0 and 11.0, indicating that protons perform a role in the electrochemical reduction of NTZ shifted slightly to more negative values when the pH varied between 9.0 and 11.0, indicating that protons perform a role in the NTZ reduction. On this basis, a linear curve between the pH of the electrolyte and the peak potential was constructed (Fig. 6(C)) which provided a corresponding linear regression equation and a correlation coefficient of $I_{pc} (\mu A) = -0.034$ [NTZ/μM] − 0.396; $R^2 = 0.9394$. The obtained slope was lower than the theoretical Nernst slope of 0.059 mV/n, indicating that an unequal number of electrons and protons were involved in the electrochemical reduction of NTZ (Bard et al., 2022). As a result of the protonation of the NTZ residue at the surface of the Mo–MnWO$_4$ modified electrode, there is a difference in the slope, which can be explained by the complexity of the protonation process. Hence, the pH optimized to be 5.0 was chosen for the other sensor measurements (concentration, scan rate, and determination studies) of NTZ on the Mo–MnWO$_4$ modified electrodes.

3.3.5. Effect of scan rate on NTZ at Mo–MnWO$_4$/GCE

The scan rate test is considered the most important parameter in the kinetic mechanism of each electrochemical sensor. To investigate the scan rate test of the reduction of NTZ on Mo–MnWO$_4$/GCE, the CV analysis was performed in the presence of 0.05 PBS (pH 5) containing 200 μM NTZ and recorded at different scan rates of 20–200 mV/s as shown in Fig. 6(D). Fig. 6(D) clearly shows the trend of a slight increase in cathodic current response with the increase in scan rate from 20 to 200 mV/s. A slight increase in the current response was observed for the reduction of NTZ during the variation of the scan rate from a lower to a higher scan rate, which is mainly related to the occurrence of sudden deprotonation of NTZ at the surface of the Mo–MnWO$_4$ modified electrode; this phenomenon has already been explained in pH Section. Furthermore, the slight shift of the peak potential to negative values with respect to the scan rate indicates the irreversible nature of the electrode reaction. However, the linear relationship between the cathodic peak current and scan rate shown in Fig. 6(E) indicates that the reduction of NTZ is an adsorption-controlled process, and it gives a slope from the regression equation $I_{pc} (\mu A) = -0.021$ [mV/s] − 2.382, along with a correlation coefficient of $R^2 = 0.996$. However, the linear plot of the cathodic peak current vs. square root of the scan rate proved that the reduction of NTZ also follows a diffusion-controlled process (Fig. 6(F)). Moreover, the linear trend gives a slope value of 0.41 from the linear regression equation and a correlation coefficient of $I_{pc} (\mu A) = -0.4108$ [mV/s]$^{1/2}$−0.6249; $R^2 = 0.9916$. From this observation, it can be concluded that the reduction of NTZ consists of a mixed diffusion and adsorption-controlled process that depends on the scan rate. Subsequently, the electrochemical kinetics was explained by various parameters such as the charge transfer coefficient ($\alpha$) and the standard heterogeneous rate constant (K). Following Bard and Faulkner, the concept $E_p - E_{p/2}$ was used to calculate $\alpha$. These values are substituted into the equation ($E_{p} - E_{p/2} = (47.7/\alpha n)$ mV) to calculate $\alpha$ and $n$. By applying the above equation, the value of $\alpha$ was calculated to be 0.97 ($n = 3$). In addition, the participation of electrons ($n$) in the electrocatalytic reduction of NTZ was determined to be 3. From this calculation, two electrons ($n_a = 2$) and one proton ($m = 1$) are involved in the rate-determining step of the electroreduction process of the -NO$_2$ group, i.e., the ratio (m/n) = 1/2. Accordingly, the $\alpha$ value of 0.97 and the slope value (34 mV/ph) of the plot ($E_{p}$ vs. $E_{p/2}$) indicate the irreversible nature of the electrode process of NTZ at the Mo–MnWO$_4$ modified GC electrode. Subsequently, the heterogenous rate constant terms are mentioned in the Supporting Information (Figure S4, S2.1.4).

3.4. Validation of the proposed method

The analytical parameters such as LOD, sensitivity, and specificity, as well as the linear range, were validated using a highly sensitive electrochemical technique.

3.4.1. Determination of NTZ by amperometric (i-t) techniques

Compared to CV analysis, the amperometric (i-t) technique is considered a more sensitive method. It is used to determine the lowest concentration and analytical parameters such as the limit of detection (LOD), linear range, and sensitivity. For this purpose, amperometric (i-t) analysis was performed in the presence of N$_2$-saturated 0.05 M PBS (pH 5), followed by the addition of NTZ at different concentrations. In addition, a rotating ring disk electrode (RRDE) modified with Mo–MnWO$_4$ was used as the working electrode to perform the amperometric analysis. Fig. 7(A) shows the relative amperometric current response for the successive addition of different NTZ concentrations (0.014–170.2 μM) at an identical time interval (50 s) to the continuously stirred 0.05 M PBS electrolyte (rotation speed of 1500 rpm) at an applied potential of −0.56 V. As shown in Fig. 7(A), the current response...
increases gradually from lower to higher with the increase in NTZ concentration. A steady-state current response was observed for less than 5 s, indicating the rapid electrochemical behavior of Mo–MnWO<sub>4</sub>/RRDE for the detection of NTZ. Fig. 7 (B) shows a linear plot between the NTZ concentration and the resulting reduction current. The reduction of NTZ shows a linear response range of 0.014–170.2 μM, together with a linear regression equation \(I_{pc} = 0.154 + 0.970\), and a correlation coefficient of \(R^2 = 0.995\). The lower detection limit for the detection of NTZ was calculated using equation (Patil et al., 2021),

\[
\text{LOD} = 3S_b/m
\]

(3)

From the linear range, LOD was calculated to be 3.7 nM (S/N = 3) using the above equation and “m” is the slope value obtained from the linear plot and “\(S_b\)” is the standard deviation of the three blank signals. The sensitivity of the Mo–MnWO<sub>4</sub>/RRDE was reported to be 0.78 μA μM<sup>-1</sup> cm<sup>-2</sup>. Moreover, the obtained analytical factors such as LOD, sensitivity, and linear ranges of the developed sensor were compared with the previously reported modified electrodes for NTZ sensors and are listed in Table S2. Compared with previous reports, we found that the Mo–MnWO<sub>4</sub>/RRDE showed improved and comparable
electrochemical performance for NTZ detection. This remarkable sensor performance can be attributed to the presence of multivalent transition metals (Mo and Mn) and the high conductivity of W in the wolframite structure, which provides excellent redox activity and improves the electrocatalytic activity in the reduction of NTZ.

3.4.2. Studies on interference, reproducibility, and stability

Before presenting the practical application of the proposed Mo–MnWO₄ sensor, some factors such as interference ability, reproducibility, and stability were investigated using amperometric analysis. First, the anti-interference ability of the Mo–MnWO₄/RRDE was examined using an amperometric technique with various interfering compounds, including biomolecules, nitro compounds, cations, and anions. A 30-fold excess concentration of similar antiviral drugs such as ribavirin (Rib), tenofovir (Ten), favipiravir (Fav), domperidone (Dom), ciprofloxacin (Cip), and 4-nitrophenol (4-NP) was added. A 50-fold excess of biomolecules (ascorbic acid (AA), uric acid (UA), glucose (Glu), and hydrogen peroxide (H₂O₂)) and some cations such as Na⁺, K⁺, Zn²⁺, Mn²⁺, Cd²⁺, Ca²⁺, Fe³⁺, Cr³⁺, and Pb²⁺, were added. During amperometric analysis, the chemical structures of the selected interfering compounds and the corresponding interfering signals were also recorded, as shown in Fig. 7(C and D). However, no significant current...
responses for these interfering compounds can be seen in Fig. 7(C and D). Despite having a similar structure to NTZ, it does not affect the reduction current because the electronic charge around NTZ is unevenly distributed, which is not comparable to the interfering molecules (Fig. 7 E)). Moreover, the energy of the highest occupied orbital determines the case of electron donation by the catalytically active sites in the MnWO₄ lattice after Mo doping. At the same time, an excellent current response to the addition of NTZ was observed (Fig. 7(C)), indicating excellent selectivity of the proposed Mo–MnWO₄ sensor. To confirm the above phenomena, a CV analysis was performed for the interfering substances 4-NP and chloramphenicol (CAP); the results are shown in Fig. 55. The CV curves show that the current response for both interfering species is lower than the NTZ and shows a slight shift in the reduction peak potential. The above CV results also confirm the excellent selectivity of the proposed Mo–MnWO₄ sensor. The CV technique was used to investigate the reproducibility of Mo–MnWO₄/GCE. The reproducibility test experiment was performed in the presence of three Mo–MnWO₄ modified electrodes (GCE) that were independently tested for NTZ detection (200 μM). These modified electrodes were immersed in 0.05 M PBS (pH 5) at 50 mV/s. The reproducibility results are shown in Fig. 56. They show that a reproducible current is present and the relative standard deviation (RSD) of NTZ is less than 1%. The results show that the proposed Mo–MnWO₄/GCE has acceptable reproducibility for NTZ detection. Subsequently, the reproducibility of the Mo–MnWO₄ sensor was tested using CV analysis. The reduction peak current for NTZ (100 μM) was measured 8 times under the same operating conditions using the same Mo–MnWO₄ modified GCE, and the following results are shown in Fig. 57. The reduction peak current for NTZ showed a small current variation after the 8th measurement, indicating an acceptable reproducibility behavior of the proposed sensor. In addition, the stability of the developed Mo–MnWO₄ sensor was investigated under the same experimental conditions (0.05 M PBS (pH 5)) and a scan rate of (50 mV/s). The electrochemical stability tests were performed in the presence of NTZ (200 μM) at regular time intervals from days 1–15. The result showed that the sensor still exhibited 93% of its original reduction current after 15 days of storage. Thus, the Mo–MnWO₄/GCE has excellent storage stability for the electrochemical measurement of NTZ. Therefore, all analytical test results proved that the developed sensor (Mo–MnWO₄) is more suitable for the electrochemical sensing of NTZ.

3.4.3. Practical application

To validate the practicality of the electrode modified with Mo–MnWO₄, a series of real samples including human blood serum and urine samples were analyzed. The optimization of real samples is important for practical usage. Therefore, the blood serum (Sigma-Aldrich) and urine samples were collected directly from healthy patients and stored in a refrigerator to avoid contamination. The blood serum and urine samples were diluted with an appropriate amount of electrolyte to perform a recovery experiment. The diluted samples were used directly for analysis of the real sample analysis using the CV. However, since the blood serum and urine sample do not contain NTZ, a known concentration of NTZ was added to the diluted urine sample. The detection of NTZ in both samples was examined using the standard method. The recoveries of the spiked blood serum and urine samples were ranged from 94 to 99.2% and 95.3–99.6%, as listed in Table S3. These recoveries were satisfactory and indicate that the constructed modified electrode with Mo–MnWO₄ NCs is more suitable for the electrochemical sensing of NTZ.

4. Conclusion

In summary, we successfully introduced Mo doping of the MnWO₄ lattice using a one-pot hydrothermal synthesis process. The physical and structural properties were characterized by XRD, Raman, FE-SEM, FE-TEM, and XPS analyses. The prepared Mo–MnWO₄ NCs were used to modify a GCE and applied for the detection of the antiviral drug (NTZ). XRD and FE-TEM analyses showed that Mo doping significantly affects the lattice by creating several distortions or defects without affecting the morphology. The subsequent EIS measurements to determine the Rct show a better electrical conductivity behavior for Mo–MnWO₄ NCs. On the other hand, the electrochemical CV measurements also showed impressive electrocatalytic activity for NTZ detection. The sensitive amperometric technique also revealed a lower detection limit of 3.7 nM and high sensitivity of 0.78 μA μM⁻¹ cm⁻² for NTZ detection, indicating that the proposed Mo–MnWO₄ NCs are more suitable for antiviral drug detection. Moreover, the practical application of the Mo–MnWO₄ NCs sensor was demonstrated by the excellent reproducible and appreciable results. Furthermore, the recoveries in the analysis of real samples, both in human blood serum and urine samples, proved the excellent practicality of the proposed Mo–MnWO₄ modified electrode. Therefore, these Mo–MnWO₄ results open an exciting new avenue for exploring a defect strategy on metal tungstates for enhancing electrochemical finding of drug molecules in biological samples.

Credit author statement

Ramaraj Sukanya; Conceptualization, Experiments implementation, Data recording, Paper writing, review, and editing. Sonaimuthu Mohandoss; Paper review, editing, Project administrator, and Funding acquisition: Yong Rok Lee; Conceptualization, Experiments implementation, Paper review, editing, Project administrator, and 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.

Data availability

Data will be made available on request.

Acknowledgments

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIT) (2021R1A2B5B02002436 and 2021R1F1A1061566).

Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.chemosphere.2022.137005.

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