An efficient electrochemical sensor based on CeVO₄-CuWO₄ nanocomposite for methyldopa

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Abstract
A novel modified electrode based on cerium vanadate and copper tungstate (CeVO₄-CuWO₄) nanocomposite was prepared as a sensitive sensor for the methyldopa. The prepared nanocomposite was characterized by x-ray diffraction (XRD), energy dispersive x-ray spectroscopy (EDX), Fourier transform infrared spectroscopy (FT-IR), and scanning electron microscopy (SEM) methods. The cyclic voltammetry (CV) and differential pulse voltammetry (DPV) techniques were applied for the evaluation of the electrochemical performance of the sensor. The enhanced active surface area, electro-catalytic activity, and expedient conductivity provided by the CeVO₄-CuWO₄ nanocomposite led to the peak current increment with a well-resolved anodic peak for methyldopa in the presence of potential interferences. The CeVO₄-CuWO₄ nanocomposite-based modified electrode successfully measured methyldopa over a wide concentration range of 0.02–400 μM with the low limit of detection (LOD) of 0.006 μM. The findings of the methyldopa sensing in human serum samples verified the proper efficiency of the proposed sensor.

1. Introduction
As a catecholamine derivative, methyldopa (scheme 1) is an effective antihypertensive agent [1, 2]. It is extensively applied to reduce moderate hypertension, especially during the pregnancy period. In adrenergic nerve endings, methyldopa targets central α-adrenoceptors through its metabolite, α-methylnorepinephrine [3]. Methyldopa inhibits the aromatic L-amino acid decarboxylase enzyme, DOPA decarboxylase, therefore prevents the conversion of L-DOPA into dopamine that is a precursor for the epinephrine and norepinephrine synthesis.

The drop in the blood pressure can be obtained by the effect of methyldopa on α2-adrenoreceptor agonists. The methyldopa metabolism with a half-life of about 2 h occurs in the liver and intestines, while with its metabolites, it is expelled through the urine [3]. Sleepiness, liver issues, damaging red blood cells, and allergic reactions are some side effects of methyldopa [4]. This is obvious that the accurate quantification of methyldopa is very important for controlling its dosage because of stated complications [5, 6].

Diverse analytical techniques have been used for the measurement of methyldopa in biological fluids and pharmaceutical products. They involve high-performance liquid chromatography [7], titrimetric analysis [8], gas chromatography [9], nuclear magnetic resonance spectroscopy [10], kinetic procedures [6], fluorometric analysis [11], spectrophotometry [12], chemiluminescence [13], reflectance spectroscopy [14], mass spectrometry [15], and so on. Nearly all these methods have limitations such as high costs, long analysis times...
and difficult control of the conditions, complicated pretreatments, and possible interfering substances. Besides, low selectivity and sensitivity make these methods inappropriate for standard analysis. To resolve these problems, electrochemistry-based methods can be employed considering their lower cost, speediness, portability, reasonable selectivity, simple preparation process, suitable accuracy, and precision [16–21]. Several electrochemical methods have been reported for the detection of active pharmaceutical ingredients in biological fluids, which include voltammetry, potentiometric, amperometric, etc [22–24]. In traditional electrodes, oxidation-reduction reactions require a high overpotential because of the sluggish electron transfer process [17, 25–27]. Therefore, it is necessary to increase the performance of these types of electrodes. Electrode surface modification decreases the over-potentials and increases the electron transfer rate.

Nanotechnology has made tremendous changes in the modification of electrode surfaces [28]. Among the nanoparticles, nano metals and metal oxides have offered outstanding conductivity and catalytic capabilities facilitating the electron transfer kinetics, which is an important parameter in the electrochemical reactions [29].

In this work, a nanocomposite of cerium vanadate and copper tungstate was synthesized and utilized for the development of a methyldopa electrochemical sensor. The glassy carbon electrode (GCE) was employed here because among the various promising electrodes applied in the electrochemical measurement, it revealed suitable stability and resistance [25, 26, 30–35]. As rare earth vanadate, cerium vanadate (CeVO₄) offers multiple redox features, which originate from the special electronic configuration and different oxidation states [36]. CeVO₄ has been applied as catalyst and photocatalyst [37, 38], in gas sensors [39, 40], in batteries [41, 42], and utilized in electrochromic applications [43, 44]. Concerning the recent reports, CeVO₄ is the safest material for anode of lithium-ion batteries (LIBs) due to its slight insertion potential, elevated power/energy density, and high reversible capacity [42, 45–47]. Copper tungstate (CuWO₄) is one of the most promising photo-anode for photocatalytic degradation of the organic pollutants [48], gas sensors [49], and water splitting [50] due to its narrow bandgap (2.2–2.4 eV). Moreover, CuWO₄ belongs to n-type semiconductors that create positive holes in the valence band, which move to the surface to perform many oxidation processes [51]. Recently, CuWO₄ nanocomposites are more interested in researches because of their good chemical stability, selectivity, and better current densities in addition to the smaller bandgap [52]. In this work, to further improve the limit of detection, linear concentration range, and sensitivity, an electrochemical sensor based on a nanocomposite of cerium vanadate and copper tungstate was prepared for the electrochemical measurement of methyldopa in pharmaceutical and biological samples.

2. Experimental

2.1. Chemicals

Cerium nitrate, ammonium vanadate, copper nitrate, sodium tungstate, ascorbic acid, uric acid, methyldopa, and all chemicals were bought from Sigma-Aldrich and Merck Company. 0.1 M Phosphate buffer (PB) was applied as the electrolyte solution. 0.1 M KCl including 5 mM [Fe(CN)₆]³⁻/⁴⁻ was used as the electro-active probe. All utilized chemical materials were of analytical grade.

2.2. Apparatus

The morphology of nanoparticles and nanocomposite was explored using scanning electron microscopy (SEM). An x-ray Diffraction (XRD) with a source of the Cu Kα radiation was applied for the crystal structure investigation. The electrochemical tests were performed by the palm sense EM State series equipped with a three-electrode system (an Ag/AgCl electrode, a platinum wire, and a GCE as the reference, counter, and working electrodes, respectively).
2.3. Preparation of the CeVO₄-CuWO₄
First, the cerium nitrate (1 mmol) was dissolved in bi-distilled water (30 ml) at ambient temperature. Besides, ammonium vanadate (1 mmol) was dissolved in distilled water (30 ml) for 30 min at 25 °C on a magnetic stirrer at a constant rate. Subsequently, the two above-mentioned solutions were mixed under the ultrasonic waves at ambient temperature. Two separate aqueous solutions of copper nitrate (1 mmol) and sodium tungstate (1 mmol) were prepared utilizing bi-distilled water (pH = 5) at ambient temperature. After that, the cerium vanadate and sodium tungstate solutions were mixed, and copper tungstate solution was then added dropwise to this prepared mixture solution under the ultrasonic wave at room temperature. The formation of the CeVO₄-CuWO₄ heterostructures was confirmed by yellowish-brown sediment. The resulting sediment was calcination for 1 h at 25 °C.

2.4. Fabrication of the CeVO₄-CuWO₄/GCE
A well-dispersed suspension of the synthesized CeVO₄-CuWO₄ nano powder (1 mg mL⁻¹) was prepared in deionized water. Afterward, 7 μl (the optimal amount) of the CeVO₄-CuWO₄ suspension was placed on the GCE surface and left to dry in an oven at 50 °C, which was then stored at ambient conditions before being used.

2.5. Preparation of the blood serum samples
The performance of the CeVO₄-CuWO₄-based modified electrode was examined on the human blood serum collected from a man (middle-aged) in the Blood Transfusion Organization of Iran (Tehran). 1 ml of that blood serum was diluted 10 times with buffer (with optimum pH). The methyldopa content of that sample was determined by the standard addition procedure.

3. Results and discussion

3.1. Characterization of the CeVO₄-CuWO₄/GCE
The synthesized CeVO₄, CuWO₄, and CeVO₄-CuWO₄ nanostructures were evaluated by FT-IR spectroscopy, which acquired spectra were shown in figure 1. FTIR spectrum of the CeVO₄ (figure 1(a)) revealed an intensive
absorption band at 824.23 cm$^{-1}$ and a small band at 528 cm$^{-1}$ that may be related to the bands of V–O and Ce–O, respectively. The broad peak at 3429.38 cm$^{-1}$ can be assigned to the O–H stretching vibrations of H$_2$O molecules. In the case of CuWO$_4$, the deformation of W–O bonds in the octahedral structure of WO$_4$ appears below 600 cm$^{-1}$. Also, the absorption peak at 845 cm$^{-1}$ was due to the stretching of Cu–O. The absorption bands of the OH-stretching and bending vibration of water are observed at 3417 cm$^{-1}$ and 1624 cm$^{-1}$, respectively. The FTIR spectrum of the CeVO$_4$-CuWO$_4$ nanocomposite exhibits the absorption peaks of the CeVO$_4$ as well as the CuWO$_4$. The bonds around 800 cm$^{-1}$ correspond to V–O and Cu–O, also the peaks at 400–600 cm$^{-1}$ are related to Ce–O and W–O. The absorption peaks located at 3430 cm$^{-1}$ and 1629 cm$^{-1}$ are attributed to the stretching and bending vibration of the hydroxyl groups of water.

The XRD patterns of the synthesized CuWO$_4$, CeVO$_4$, and CeVO$_4$-CuWO$_4$ compounds were demonstrated in figure 2. The XRD profile of the CeVO$_4$ in figure 2(a) exhibits a series of diffraction peaks with crystal planes of CeVO$_4$ (JCPDS No. 12-0757) at 18.19° (101), 24.10° (200), 32.41° (112), 34.23° (220), 47.81° (312), and 49.28° (400). The sharp XRD peaks revealed that the synthesized CeVO$_4$ nanoparticles have an excellent crystalline nature. Figure 2(b) shows the XRD pattern for CuWO$_4$ nanoparticles and the characteristic peaks at 19.1°, 24.8°, 29.7°, 31.6°, 36.8°, and 42.9° corresponding to (001), (011), (111), (002), and (121) crystal planes of CuWO$_4$ nanostructures (JCPDS No. 12-0757). The CuWO$_4$ diffraction peaks with extreme intensity and narrow width indicate the high crystallization quality of the crystals. The CeVO$_4$-CuWO$_4$ nanocomposite presented a combination of two phases of CeVO$_4$ (JCPDS No. 12-0757) and CuWO$_4$ (JCPDS No 88-0269). The diffraction peaks were observed at 2θ of 24.10° (200), 32.41° (112), and 47.82° (312), consistent with the reported values for
CeVO₄ nanostructure and the peaks at 19.0°, 24.6°, 29.8°, 31.5°, and 42.09° confirm the CuWO₄ presence in the final nanocomposite structure (figure 3(c)).

To analyze the morphological features of the prepared CeVO₄, CuWO₄, and CeVO₄-CuWO₄ samples, scanning electron microscopy (SEM) was performed. Figure 3(a) shows an SEM image of the synthesized CeVO₄ nanocrystals. The resulting products consist of hexagonal and plate-like crystals. Besides, small rod-shaped particles with inhomogeneous size distributions can also be observed. The SEM image of the CuWO₄ powder was shown in figure 3(b). The CuWO₄ particles are mostly spherical in shape and agglomerated, and their size is about 25–32 nm. In the SEM image of the CeVO₄-CuWO₄ nanocomposite, agglomerated spherical and hexagonal morphologies are observed (figure 3(c)).

Figure 4 demonstrates the EDS analysis of the CeVO₄-CuWO₄ by displaying the existence of the Ce, V, O, Cu, and W elements with different weight percentages in its structure.

3.2. Electrochemical evaluations

Employing the cyclic voltammetry (CV), the sensing capability of the prepared electrodes was tested in the Fe(CN)₆³⁻/⁴⁻ solution as an active probe regarding its well-known reversible redox reaction (figure 5). As shown in figure 5, compared to the unmodified GCE, the redox response of the utilized probe was effectively improved by modified electrodes. The appearance of weak anodic and cathodic peaks with 230 mV potential separation

![Figure 5](image_url)

**Figure 5.** CVs of the GCE, CeVO₄/GCE, CuWO₄/GCE and CeVO₄-CuWO₄/GCE in the Fe(CN)₆³⁻/⁴⁻; the sweep rate of 50 mV s⁻¹.

![Figure 6](image_url)

**Figure 6.** CVs of the GCE, CeVO₄/GCE, CuWO₄/GCE and CeVO₄-CuWO₄/GCE in 0.1 M PBS (pH = 2.0) containing 50 μM methyldopa; scan rate = 50 mV s⁻¹.
(ΔE) at the bare GCE indicates the slow electron transfer with a limited kinetic process. Meantime, the ΔE decreased to 203 and 200 mV at the CuWO4/GCE and CeVO4/GCE, respectively, and obvious increment in the peak current (Ip). An observable enhancement in the Ip was achieved for the CeVO4-CuWO4/GCE, for which the ΔE value was decreased to 100 mV. The improved electrochemical response can be ascribed to the good
conductivity, and fast electron transfer ability of the CeVO$_4$–CuWO$_4$ nanocomposite covered the electrode surface.

For further proof, the CVs of the unmodified GCE, CeVO$_4$/GCE, CuWO$_4$/GCE and CeVO$_4$–CuWO$_4$/GCE were recorded in the Fe(CN)$_6^{3-/4-}$ solution at various scan rates. According to $I$–$v^{1/2}$ curves and the Randles–Sevcik equation, the electrochemical surface area of the CeVO$_4$–CuWO$_4$/GCE was obtained equal to 0.063 cm$^2$ that compared to the unmodified GCE (0.028 cm$^2$), CeVO$_4$/GCE (0.041 cm$^2$) and CuWO$_4$/GCE (0.047 cm$^2$), provided more efficient sensing interface with higher electroactive surface area. Besides, the efficiency of the GCE, CeVO$_4$/GCE, CuWO$_4$/GCE, and CeVO$_4$–CuWO$_4$/GCE was evaluated in the detection of the methyldopa, by recording corresponding CVs in 0.1 M PBS of pH = 2.0, containing 50 μM methyldopa at 50 mV s$^{-1}$ (figure 6). As evidence in figure 6, the CeVO$_4$–CuWO$_4$/GCE provides a better platform for the methyldopa sensing with two well-separated sharp peaks with less $\Delta E_p$ value and higher peak currents than the GCE, CeVO$_4$/GCE, and CuWO$_4$/GCE. Notably, the methyldopa response at the bare GCE and CeVO$_4$/GCE was irreversible and weak, but a quasi-reversible redox behavior was resulted in the case of CuWO$_4$/GCE, while a well-defined totally reversible response obtained for the CeVO$_4$–CuWO$_4$/GCE. Again, the electrocatalytic performance with the higher effective surface area is concluded for the CeVO$_4$–CuWO$_4$ nanocomposite toward methyldopa reaction.

The electrolyte pH affects the catalytic reaction efficiency of the CeVO$_4$–CuWO$_4$/GCE toward methyldopa redox reaction. Figure 7(a) shows CV responses of the 50 μM methyldopa in a PBS (2.0 ≤ pH ≤ 7.0). The peak current value of the methyldopa redox reaction was decreased as the solution pH was increased, and the position of the peaks was shifted to less positive potentials, indicating the contribution of protons in the electron transfer steps. Since the maximum peak current was observed at pH with a more favorable peaks shape, the pH = 2.0 was considered as the optimum condition in the following experiments.

Scheme 2. The electrochemical redox mechanism of methyldopa.

Figure 9. (a) DPVs of the CeVO$_4$–CuWO$_4$/GCE in different concentrations of methyldopa from 0.02–400 μM and (b) the plot of the $I_{pa}$ as a function of methyldopa concentration in the range of 0.02–400.
Furthermore, the peak potential-pH plot (figure 7(b)) obeyed a linear behavior whose slope was equal to $-0.061$ V/pH. This value is equal to the Nernstian amount (0.059) at 25 °C, suggesting that the electro-catalytic process of the methyldopa on the CeVO$_4$-CuWO$_4$/GCE surface follows a two electrons/two protons process.

The mechanism of the methyldopa electrochemical process was studied by recording the CVs of 50 μM methyldopa (10 $\leq$ scan rates $\leq$200 mV s$^{-1}$) using the CeVO$_4$-CuWO$_4$/GCE (figure 8(a)). Figure 8(b) depicts the linear dependence of Log $I_{pa}$ on the Log $v$ with $R^2 = 0.999$ and slope of 0.774 indicating that the oxidation of methyldopa at CeVO$_4$-CuWO$_4$/GCE is under control of a mixed adsorption-diffusion process. Regarding previous works [53, 54], it can be mentioned that methyldopa species adsorb on the electrode surface and penetrate the GCE surface through the porous nanostructure of the CeVO$_4$-CuWO$_4$. The Laviron equation [29] for the surface-adsorbed electroactive compounds was utilized to estimate values of charge transfer coefficient ($\alpha$) and apparent charge transfer rate constant ($k_\alpha$) for the oxidation of methyldopa at CeVO$_4$-CuWO$_4$/GCE. Figure 8(c) demonstrates the plot of $E_p$ as a function of Log $I_p$ for the CeVO$_4$-CuWO$_4$/GCE at the potential sweep rates of 10–200 mV s$^{-1}$ in the PBS (pH 2). The magnitude of $\alpha$ and $k_\alpha$ for methyldopa oxidation was resulted in 0.45 and 2.32 s$^{-1}$, respectively.

The pK$_a$ values of 2.2 and 9.7 for the methyldopa showed that while the carbocyclic moiety is almost deprotonated at pH = 2.0, the amine group is in protonated from. Moreover, the observation of the almost reversible behavior for the electro-oxidation of methyldopa in optimized pH value (2.0) reveals a simple one-step oxidation pathway in the absence of further Michael addition process, if it happened, it would change the reaction mechanism to the Electrochemical-Chemical-Electrochemical (ECE). As a result, the redox mechanism according to scheme 2 is proposed for methyldopa oxidation at pH = 2 using CeVO$_4$-CuWO$_4$/GCE.

To examine the applicability of the prepared sensor in detecting methyldopa, various concentrations of the methyldopa in a range of 0.02 to 400 μM were synchronously injected into the electrochemical cell, and the analysis was performed by the differential pulse voltammetry (DPV) technique (figure 9(a)). The equation of the linear relationship between the peak current and the methyldopa concentrations was as $I_{pa}$ ($\mu A$) = 29.13 C (μM) + 3.19 for 0.02 to 1 μM and $I_{pa}$ (μA) = 0.16 C (μM) + 31.72 for 1 to 400 μM. The estimated limit of detection (LOD) according to the (signal/noise) = 3 was equal to 6 nM. Table 1 lists the reported modified electrodes in the literature used for development of methyldopa electrochemical sensors. As observed, the
A sensitive sensor based on the CeVO₄ and CuWO₄ nanomaterials was developed for the detection of methyldopa. This prepared nanocomposite was used for modification of the GCE surface by a simple drop-casting method. The cost-effective sensing interface exhibited excellent conductivity, high surface area, catalytic activity, good selectivity that resulted in sensitive responses with a well-separated oxidation peak of methyldopa. The reproducibility of the CeVO₄-CuWO₄/GCE effectively preserved its electro-activity and indicated good repeatability, durability, and reproducibility for the methyldopa measurement in real samples.

To check whether some common existing substances in urine or blood serum might affect the analysis of the methyldopa, the DPVs of the CeVO₄-CuWO₄/GCE were recorded in 0.1 M PBS (pH = 7) containing 25 μM of methyldopa in the presence of Mg²⁺, Na⁺, K⁺, Cl⁻, and SO₄²⁻ (1 mM), uric acid, L-Cysteine, H₂O₂, glucose, and caffeine. The results showed all of the tested substances have no sensible interference on the current and position of the methyldopa oxidation peaks, and the change of signals in the presence of the interferences was less than ±5% (Table 3). There is hydroquinone functional group in the structure of both methyldopa and DA which is responsible of the appeared oxidation peak in the evaluated potential range. Therefore, their oxidation peaks overlap with each other. The uric acid and ascorbic acid oxidation response was investigated using CeVO₄-CuWO₄/GCE. No oxidation peak was observed for AA at the evaluated potential window and the UA response did not interfere with methyldopa signal. These findings confirm the sensor applicability for the selective detection of methyldopa.

| Species          | Concentration (mM) | Current change % |
|------------------|--------------------|------------------|
| Mg²⁺             | 1                  | −0.21            |
| Na⁺              | 1                  | −0.52            |
| K⁺               | 1                  | −0.67            |
| Cl⁻              | 1                  | −0.89            |
| SO₄²⁻            | 1                  | −1.12            |
| Uric acid        | 0.01               | 1.03             |
| L-Cysteine       | 1                  | −1.33            |
| H₂O₂             | 1                  | −1.53            |
| Glucose          | 1                  | −1.58            |
| Caffeine         | 1                  | −1.61            |

Table 3. The effect of the interference species in the analysis of the 25 μM methyldopa at CeVO₄-CuWO₄/GCE.

reported LODs were in the range of 0.12–1000 nM. As listed in Table 1, the proposed sensor’s performance based on the linear working range and LOD value in the measurement of the methyldopa in comparison to other reported modified electrodes indicate a similar or even better response. But it seems utilizing the CeVO₄-CuWO₄/GCE as a simple and cost-effective platform is better comparing to other applied nanomaterials or electrodes. This observation shows the excellent capability of the CeVO₄-CuWO₄ nanocomposite in the catalysis reaction owning to the electron transfer facilitation and surface area increase, which may be promising as an efficient platform in the other electrochemical fields.

The practical application of the CeVO₄-CuWO₄/GCE was examined in measurements of methyldopa in a serum sample. According to Table 2, the applicable recovery values were resulted for methyldopa contents in tested samples using CeVO₄-CuWO₄/GCE. The obtained recoveries were in the range of 96%–98.2%. These results confirm the suitable capability of the CeVO₄-CuWO₄/GCE for the measurements of methyldopa in real samples.

The reproducibility of the CeVO₄-CuWO₄/GCE was examined by DPV measurements of ten sensors. The relative standard deviation (RSD) calculated for the DPVs responses (Iₚₚₐ) was 3.1%, which indicated the good reproducibility of the CeVO₄-CuWO₄/GCE. Also, the analytical repeatability of the sensor was confirmed by a low RSD value (2.2%) resulted from three performed analyses utilizing one CeVO₄-CuWO₄/GCE. The durability of the CeVO₄-CuWO₄ modifier on the GCE surface was examined for four weeks. The responses of DPVs during different days showed negligible variation Iₚₚ after four weeks, which reduced less than 3% relative to the first day, and the Eₚ was remained unchanged. These findings illustrated that the CeVO₄-CuWO₄/GCE effectively preserved its electro-activity and indicated good repeatability, durability, and reproducibility for the CeVO₄-CuWO₄/GCE.

4. Conclusion

A sensitive sensor based on the CeVO₄ and CuWO₄ nanomaterials was developed for the detection of methyldopa. This prepared nanocomposite was used for modification of the GCE surface by a simple drop-casting method. The cost-effective sensing interface exhibited excellent conductivity, high surface area, catalytic activity, good selectivity that resulted in sensitive responses with a well-separated oxidation peak of methyldopa from the potential interferences. The CeVO₄-CuWO₄/GCE showed a wide linear quantification range of 0.02–400 μM, and the limit of detection of 0.006 μM (S/N = 3) for methyldopa. The satisfactory findings of the sensor’s applicability in analysis of the urine and blood serum samples may be an appropriate paradigm in the methyldopa measurement in clinical samples.
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Data availability statement

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

Conflict of interest

The authors declare that they have no conflict of interest.

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