



Electrocatalytic oxidation and amperometric determination of sulfasalazine using bimetal oxide nanoparticles–decorated graphene oxide composite modified glassy carbon electrode at neutral pH

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Abstract

Cube-shaped samarium orthovanadate (SmVO_4) nanoparticles were interconnected with a graphene oxide sheet (GOS) using a simple and eco-friendly method to generate a SmVO_4 @GOS nanocomposite. SmVO_4 was characterized using various spectroscopic and microscopic techniques, which confirmed the wrapping of GOS around the SmVO_4 nanoparticles. SmVO_4 @GOS was then used to modify a glassy carbon electrode (GCE), which was evaluated for its electrochemical performance toward the assay of sulfasalazine (SSZ), an antibiotic drug. Cyclic voltammetry and amperometry were both used for the assay of SSZ using the SmVO_4 @GOS-modified GCE at pH 7. The modified amperometric sensor is more sensitive, with a low detection limit (2.16 nM) and wide linear range of 20 nM–667 μM (Ag/AgCl). The electrochemical oxidation of SSZ was tested with blood serum and urine samples at physiological pH with recoveries in the range 96.1–98.6%. It indicates that the modified electrochemical sensor has good sensitivity and practical applicability toward SSZ detection. In the field of non-enzymatic sensors, SmVO_4 @GOS/GCE provides a highly promising performance. Therefore, the electrochemical sensors have capacity for extensive analytical applications in biomedical devices.

Keywords Electrochemical detection · Cyclic voltammetry · Amperometry · Graphene oxide sheets · Transition metal oxides · Drug determination · Biological analysis

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Introduction

Sulfasalazine (SSZ) is a sulfonamide-type drug and is sold under the trade names Azulfidine, Salazopyrin, and Sulfazine. SSZ is an antibiotic class of drug used extensively for the treatment of various inflammatory bowel diseases such as ulcerative colitis and Crohn's disease [1–4]. In addition, SSZ is used to treat rheumatoid arthritis, which is associated with psoriatic and reactive arthritis [5]. SSZ consists of an azo bond, which connects the sulfonamide of pyridyl benzene with salicylic acid. Adverse effects from the continuous intake of SSZ occur in 3–20% of patients, which can lead to cancer and hemopoietic disorders. Physicians therefore need to be aware of the dosage given and the amount of SSZ present in the serum. According to medical researchers, the acceptable SSZ content in serum during treatment is 6–32 $\mu\text{g}\cdot\text{mL}^{-1}$ [1]. In addition to the dose, oral consumption of SSZ may lead to health risks such as obstruction in the urinary tract and intestines and the severe accumulation of kidney stones. To avoid risks associated with overdosing, easy and fast detection of SSZ in serum can minimize adverse effects on patients. Recently, sulfasalazine residue has been found in the ecosystem owing to improper disposal, and 25% of sulfa drugs can cause folate deficiency, kidney stones, megaloblastic anemia, and hemolytic anemia [5, 6]. There are several reports in the literature regarding the assay of SSZ using UV–visible spectrophotometry, high-performance liquid chromatography (HPLC), solid-phase extraction coupled with capillary electrophoresis, and gas chromatographic–tandem mass spectroscopic techniques (GC–MS) [6–10]. However, these methods have issues related to sensitivity, selectivity, range of detection, and interference in real-world samples; they are also tedious and require expertise. The electrochemical sensors are an alternative to overcome the above limitations, providing sensitive, precise, and accurate results with a low limit of detection (LOD) toward the SSZ assay. Tremendous effort has been made by researchers across the globe to fabricate materials for the surface modification of electrochemical sensor electrodes; these materials include carbon-based nanomaterials (i.e., carbon nanotubes, graphene, and graphene oxide), nanoparticles and nanocomposites, polymeric materials, and ionic liquids [11, 12]. Materials used for electrochemical sensors should possess good conductivity, speed up electron transfer kinetics, and have the capacity to oxidize a given drug molecule. At present, rare-earth metals/metal vanadates are generating much interest among researchers in terms of their electrochemical performance in supercapacitors, solar cells, batteries, sensors, and so on. Rare-earth metals exhibit a 4f structure, which enhances electrochemical behavior and provides several paths for electron transition.

Recently, rare-earth metal vanadates have been receiving increased attention from material scientists as they possess high stability, low toxicity, multiple valence states, rich oxygen vacancies, good energy density and conductivity, and tunable band gaps [9, 13–15]. Transition metal–based vanadates have been used in various fields such as energy storage, gas sensors, solar cells, electrochemical sensors, and supercapacitors because they possess admirable energy gaps and stable structures. CeVO_4 , PrVO_4 , LuVO_4 , and SmVO_4 nanoparticles have been exploited as electrode materials for the detection of drug molecules [16–18]. Among these, Sm-based vanadates are important because of their mixed oxidation states (+2 and +3), higher ionic conductivity, elevated ionic radius (1.08 Å), great surface basicity, and low critical voltage. Usually, SmVO_4 exhibits two crystalline phases, namely, monoclinic (monazite m-type) and tetragonal (t-type) [19]. Lanthanides in general show better coordination with the m-type crystalline phase than with the t-type phase owing to their high coordination number [20–23]. Hence, SmVO_4 in a monoclinic phase is thermally more stable than that in a metastable tetragonal phase. Synthesis of tetragonal-phase SmVO_4 using conventional methods is very complicated, and it is challenging to synthesize SmVO_4 without using toxic solvents and surfactants. The few reports on the synthesis of SmVO_4 in the literature mainly focus on photocatalytic studies of SmVO_4 [24, 25]. Reports on the electrochemical detection of SSZ mention the use of a glassy carbon electrode (GCE), poly(3-methylthiophene) coated on GCE, $\text{GO}/\text{Fe}_3\text{O}_4/\text{SiO}_2/\text{CPE}$, NiO NPs-CPE, NiO/CNT CPE, and $\text{MWCNTCOOH}/\text{BA-SPCE}$ as electrode modifiers and electrodes. However, these materials lack sensitivity and selectivity in the electrochemical detection of SSZ. To date, there has been no report on the electrocatalytic performance of SmVO_4 for the detection of anti-rheumatic drugs. Still, SmVO_4 in its pure tetragonal phase is not beneficial for electrochemical sensors because such a structure reduces the conductivity, which in turn increases the resistivity owing to the blockage of electron–hole pairs [26, 27].

These limitations of SmVO_4 could be overcome by doping with metal oxides, metallic and non-metallic ions, organic semiconductors, additives, carbon-based materials, and so on [28]. Among these, carbon-based materials such as carbon nanotubes (CNTs), graphene oxide sheets (GOSs), carbon spheres, and $\text{g-C}_3\text{N}_4$ are better supporting materials for metal orthovanadates. GOSs are beneficial owing to their enhanced surface area, increased mechanical strength, flexibility, and good conductivity [29–32]. Because of the superior performance of graphene in biochemical sensors as a result of its large specific surface area, ease of modification, wide potential window, high electron transfer rate, high charge-carrier mobility, and low electrical noise levels [33, 34], it can be used for highly sensitive detection, efficient receptor immobilization, easy

interaction with biomolecules, and promotion of electron transfer between reagents and graphene [35–39]. Graphene oxide is easily dispersed in organic solvents, water, and other matrices because of the presence of oxygen functions. This is a significant advantage when graphene oxide is combined with polymers or ceramic matrixes to improve its mechanical and electrical characteristics. Graphene-based biochemical sensors outperform traditional carbon electrode-based sensors in terms of sensitivity, LOD, and reaction time. As a result, a variety of graphene-based biochemical sensors for health monitoring have been presented (Scheme 1). The abovementioned properties of two-dimensional (2D) graphene sheets are additional advantages in the electrochemical detection of drugs in pharmaceutical research. For any electrochemical application, the sheet-like structure of the material facilitates electron mobility and electrolyte diffusion.

In the present study, we synthesized single-crystalline SmVO_4 nanoparticles wrapped with GOSs (SmVO_4 @GOS) using a deep eutectic solvent via the hydrothermal method. The as-prepared SmVO_4 @GOS electrocatalyst was used to modify a GCE, and we evaluated the electrochemical performance of the modified GCE using cyclic voltammetry (CV), electrochemical impedance spectroscopy (EIS), and amperometric analysis (AMP). The modified GCE exhibited better electrochemical characteristics for SSZ detection compared to a bare GCE. The selectivity of the SmVO_4 @GOS/GCE was further evaluated by detecting SSZ in blood serum and human urine samples. The obtained electrochemical and actual sample results, recovery percentage, concentration range, and LOD values indicated that SmVO_4 @GOS/GCE

could serve as an alternate material for the simple, swift, and sensitive detection of SSZ in active pharmaceutical ingredients and formulations and in real-world samples.

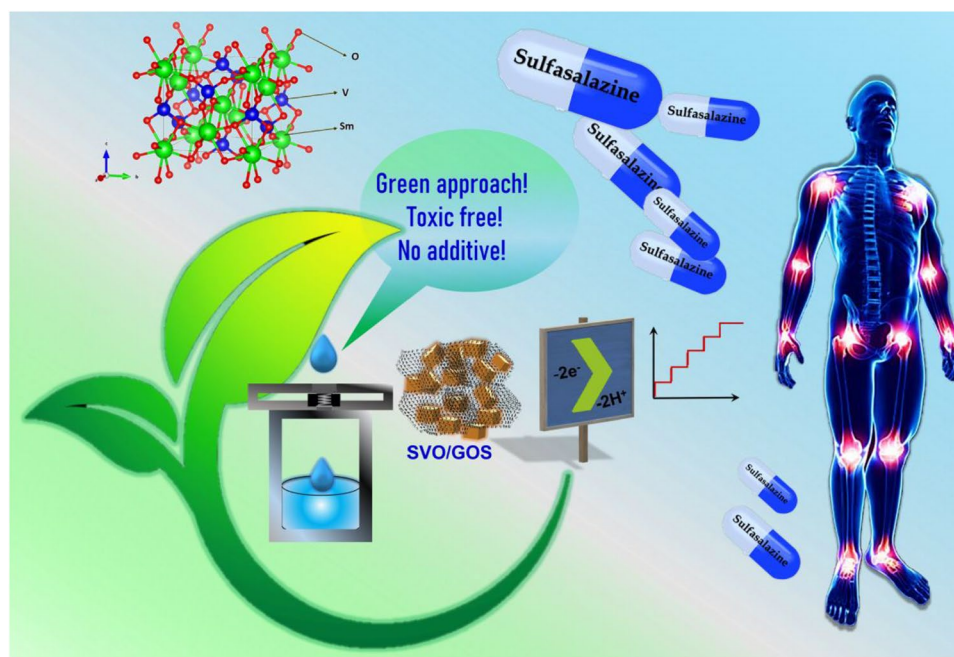
Experimental section

Materials and methods

Samarium(III) nitrate hexahydrate ($\text{Sm}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$; 99.9%), ammonium metavanadate (NH_4VO_3 ; ACS reagent, $\geq 99.0\%$), urea (ACS reagent, 99.0–100.5%), polyethylene glycol (PEG; average molecular weight—6000), sulfasalazine (analytical grade, 98.0–101.5%), and all other chemicals were procured from Sigma-Aldrich (<https://www.sigmaaldrich.com/TW/en>) and used without further purification. Phosphate buffer (PB, 0.05 M) was prepared using NaH_2PO_4 ($\geq 99.0\%$) and Na_2HPO_4 ($\geq 99.0\%$), and diluted HCl/NaOH was used to prepare buffers with different pH values. Graphene oxide was synthesized using the modified Hummers method. The methods and experimental details for these materials are given in the Supporting information. Human blood serum and urine samples were collected from the Chang Gung Memorial Hospital, Taiwan.

TEM images were obtained using a JEOL JEM-2100F instrument operating at 200 kV. SEM was obtained using HAADF-SEM, and the energy-dispersive X-ray analysis (EDS) device fitted with an electron microscope was used to examine the elemental composition of a sample. Elemental analysis was ascertained using an elemental

Scheme 1 Synthesis of metal vanadate-related bimetal oxide nanoparticles with a graphene oxide composite for electrochemical applications



analyzer (Perkin Elmer, Series II 2400). XPS measurements were conducted on a PHI 5000 Versa probe II scanning XPS microprobe (ULVAC-PHI) spectrometer equipped with Al-K α X-ray radiation ($h\nu = 1486.6$ eV). Wide-angle X-ray diffraction patterns were recorded on a PANalytical X'Pert PRO diffractometer using graphite-monochromatic Cu-K α radiation ($\lambda = 0.1541$ nm), and samples were scanned from 5 to 75° at a rate of 5° min⁻¹. High-performance liquid chromatography (HPLC) was used on a Waters Alliance e2695 (250 × 4.6 mm) with an ALPHA 10 isocratic pump; fractions were detected with a TOPAZ dual UV detector, and data was analyzed using the Peak-ABC software. Methanol and acetic acid (mobile phase) were used (flow rate = 0.6 mL/min, $\lambda = 300$ nm). CV experiments were carried out on a CHI 1205A analyzer electrochemical workstation (USA working station). A conventional three-electrode system consists of an Ag/AgCl (saturated KCl) electrode as the reference electrode, a platinum wire as the auxiliary electrode, and SmVO₄/GOS modified GCE (glassy carbon electrode) as the working electrode.

Green synthesis of SmVO₄ NPs and SmVO₄@GOS

Samarium orthovanadate nanocubes were synthesized by the hydrothermal method. NH₄VO₃ (10 mmol) and 5 mmol Sm(NO₃)₃·6H₂O were dissolved in a 2:1 (PEG–urea) deep eutectic solvent. The nanocubes were transferred to a Teflon-coated hydrothermal autoclave and placed in an oven at 180 °C for 12 h. The obtained precipitate was washed with distilled water and ethanol several times and dried in an oven overnight. The resultant powder comprised SmVO₄ nanoparticles. The

GOS (5 mg) [40] and 5 mg of SmVO₄ were dissolved in deionized (DI) water and ultrasonicated for 30 min. The resulting compound was denoted as SmVO₄@GOS. A schematic representation of the synthesis procedure is given in Scheme 2. Details on the materials and methods used for the synthesis of GOS are given in the Supporting information file.

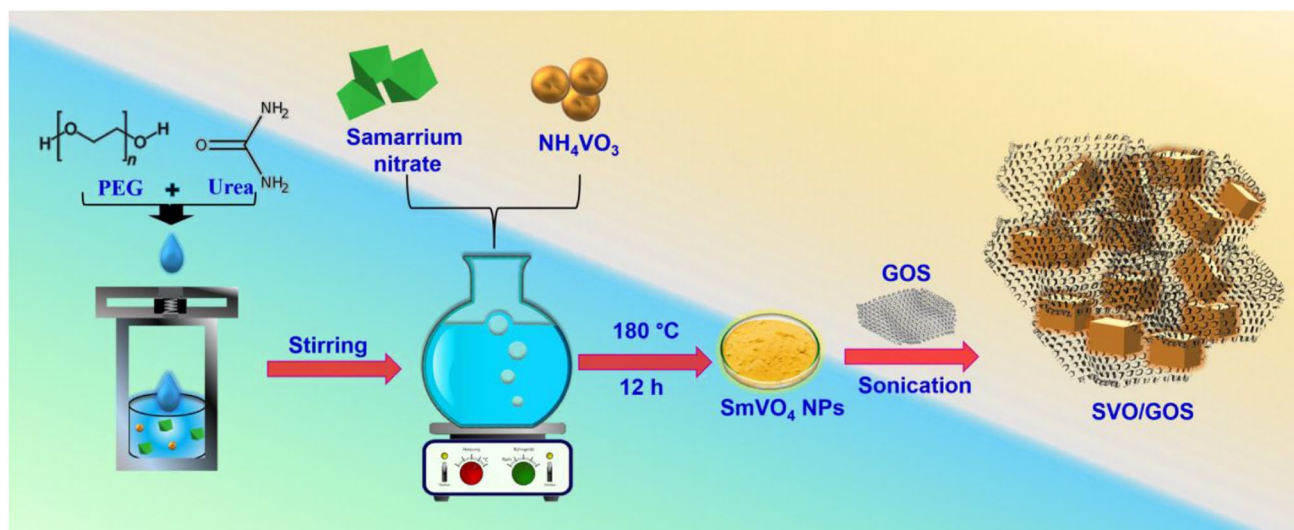
Fabrication of SmVO₄@GOS modified GCE

A GCE working electrode was modified using SmVO₄@GOS. First, the GCE was polished using 0.05- μ m alumina powder and sonicated in water. The suspension (2 mg mL⁻¹) was dispersed in DI water through sonication, and 7 μ L of the suspension was drop casted on GCE and used after drying at 65 °C.

Results and discussion

Choice of materials

Various bimetal oxides and vanadate materials such as MnCo₂O₄, CoVO₄, ZnO–Co₃O₄, GO/Fe₃O₄, and SmVO₄ nanoparticles have been used to develop selective and sensitive drug detection sensors. Among them, SmVO₄ particles have gained wide acceptance for the trace determination of SSZ when used with a composite modified GCE owing to their high electrical conductivity, the ability to form composites with many carbon materials, simple preparation, wide potential window, and insensitivity to dissolved oxygen. More importantly, SmVO₄ showed good electrochemical response to SSZ in previous experiments.



Scheme 2 Schematic of the synthesis of the SmVO₄@GOS composite and electrocatalytic application

Nanomaterials have been widely used to construct electrochemical sensors because of their various shapes, sizes, and compositions, which can increase the analytical selectivity and sensitivity. In particular, GOS-related materials have been a hot research topic in the past few years because of their unique construction. The many functional groups on the surface of GOSs can interact with samarium vanadates, which facilitates the formation of the composite. The excellent absorption property and large surface area of the unique GOS structure combined with the abilities of SmVO_4 provided a potential electrode material for the detection of SSZ.

Chemical composition of the SmVO_4 @GOS composite

The crystalline structure and phase of nanocomposites are important features in determining their electrochemical characteristics. The X-ray diffraction (XRD) patterns of the synthesized GOSs and SmVO_4 @GOS are given in Fig. 1A. The characteristic peaks of SmVO_4 at (101), (200), (211), (112), (220), (301), (103), (321), (312), (400), (411), (420), (332), (204), (431), and (224) are well correlated with standard JCPDS no. 87–1526 and indicate the metastable tetragonal phase [41]. A slight broad hump observed at $2\theta = 10.7^\circ$ with (001) indicates (JCPDS card no. 41–1487) the effective wrapping of GOS around the SmVO_4 nanoparticles [42]. The crystalline size of SmVO_4 @GOS was calculated using Eq. (1).

$$D_p = (k\lambda / \beta \cos\theta) \quad (1)$$

where D_p is the grain size of the particle (nm), k is the Scherrer constant ($k = 0.94$), λ is the X-ray wavelength (1.54178 Å), β is the full width at half maximum (FWHM) of the diffraction peak, and θ is the angle of diffraction. The calculated average size of SmVO_4 @GOS was found to be 124.7 nm for the major peaks.

To better understand the elemental interactions of SmVO_4 @GOS, XPS analyses were conducted and the obtained survey spectra of GOS and SmVO_4 @GOS are given in Fig. 1B. Figure 2A represents the high-resolution X-ray photoelectron spectroscopy (XPS) spectrum of Sm, which exhibits two characteristic peaks at 1085 and 1112 eV, attributed to $\text{Sm}^{3+} 3d_{3/2}$ and $3d_{5/2}$, respectively. The XPS spectrum of V is depicted in Fig. 2B. It consists of $\text{V}2p_{1/2}$ and $2p_{3/2}$ peaks at 528.35 eV and 521.44 eV, respectively, indicating the +5 oxidation state of V [43, 44]. Peaks between 535 and 529 eV are observed in Fig. 2C indicating the presence of O 1s [45, 46]. Peaks at 280 to 298 eV (Fig. 2D) belong to C 1s and disclose the presence of C–C, C–O, and C=O of GOS [45]. These XPS results clearly indicate the formation of a SmVO_4 @GOS composite.

Morphological analysis of the SmVO_4 @GOS composite

The morphology and shape of the as-prepared SmVO_4 @GOS composite were evaluated by using field emission scanning electron microscopy (FESEM) and transmission electron microscopy (TEM). Figure 3 A1–A3 show the FESEM images of the composites. The SmVO_4 particles clearly have a cube-shaped structure less than 100 nm across and approximately 30–70 nm thick. There are also some small

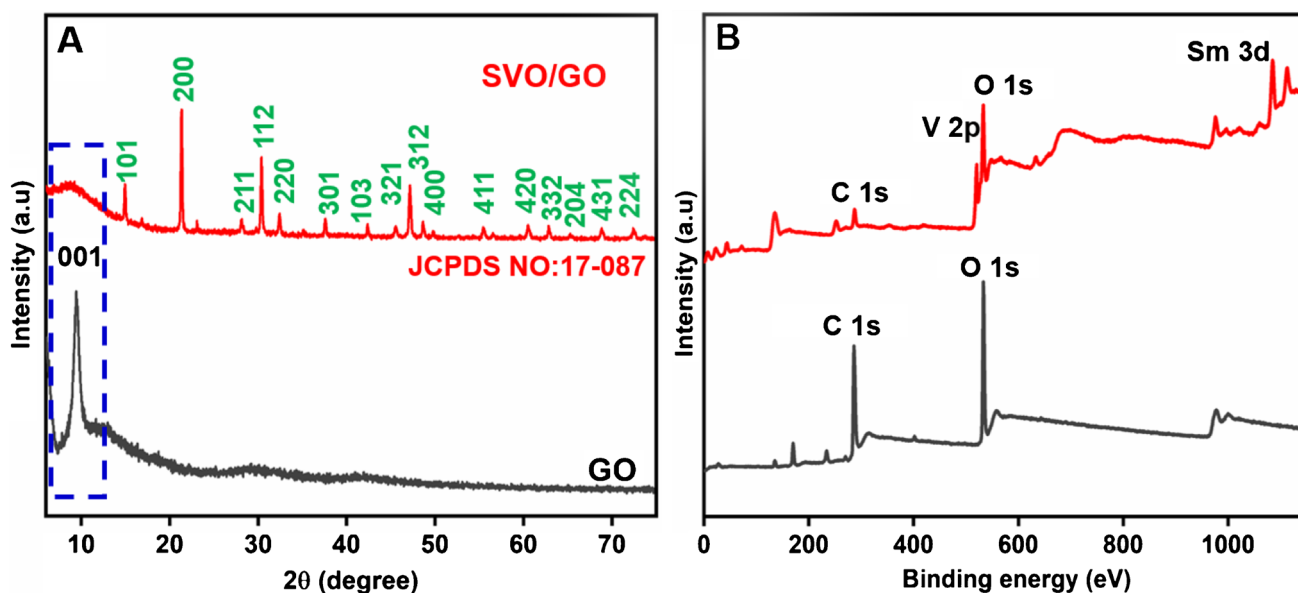


Fig. 1 A XRD patterns of GOS and SmVO_4 @GOS. B XPS analyses of GOS and SmVO_4 @GOS

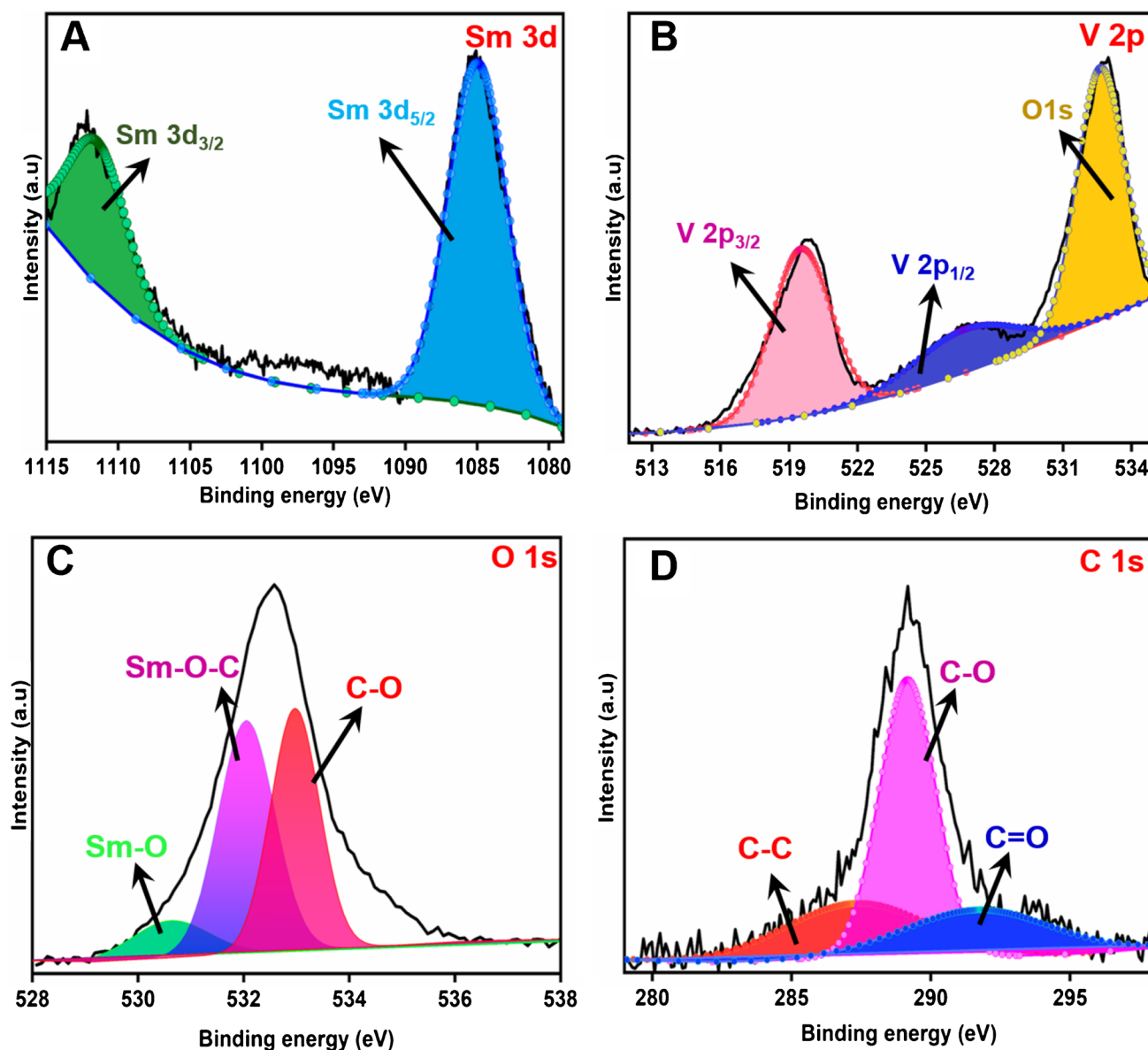
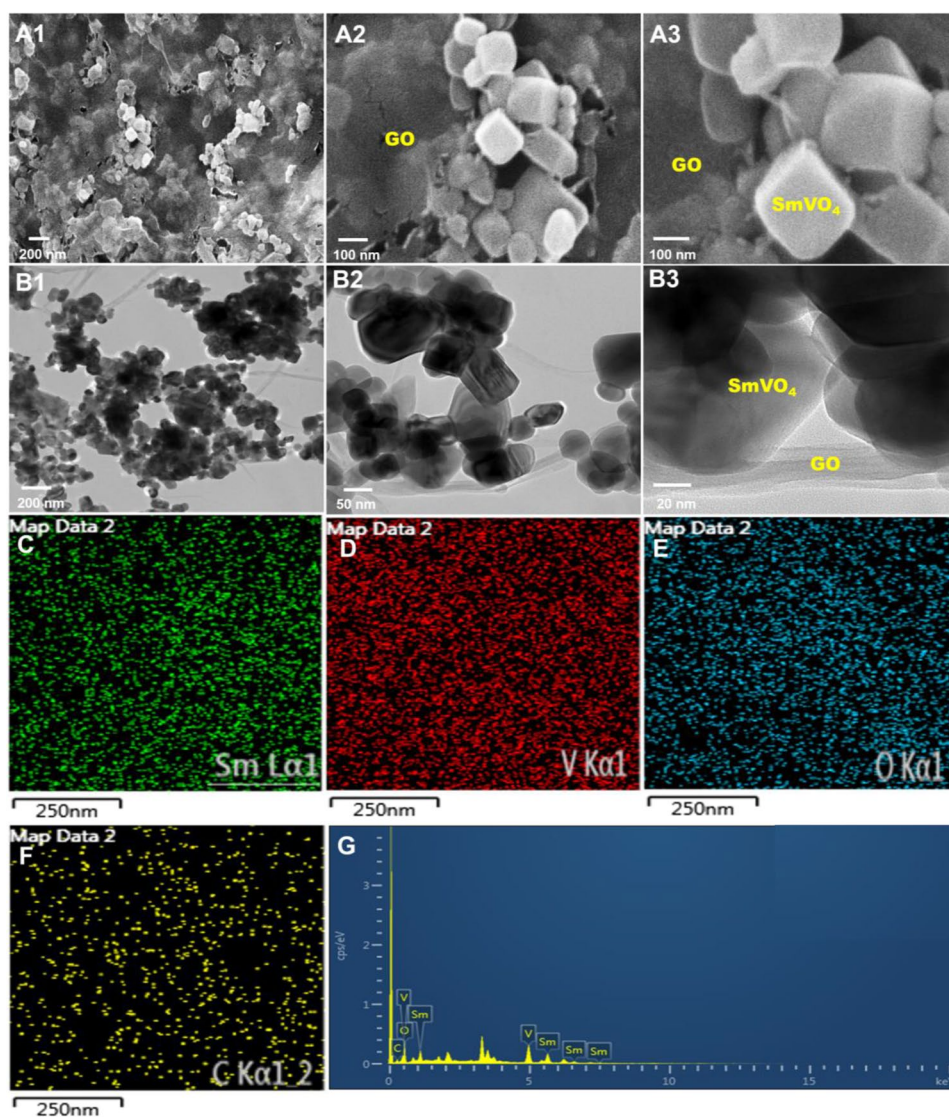


Fig. 2 XPS analyses of **A** Sm 3d, **B** V 2p, **C** O 1s, and **D** C 1s

irregular particles attached to the surface. Closer observation of the SmVO_4 @GOS nanocomposite clearly indicates the layer-by-layer stacking of GOS wrapped around the SmVO_4 nanoparticles. It was not possible to distinguish between the SmVO_4 and GOS phases in the FESEM images, possibly because of the poor phase contrast. Therefore, the materials were further subjected to TEM studies (Fig. 3B1–B3), which confirmed the wrapping of the GOS layer around the nanoparticle surface. It was clearly indicated that thin layers of GOS and cube-shaped SmVO_4 particles were interconnected with each other in Fig. 3B3. The figure also shows the clear contact between the SmVO_4 nanoparticles and the

GOSs, which is essential for improving the electron transfer reaction. The TEM images also revealed that this wrapped material was evenly dispersed, which may facilitate the quick access of ions and electrons to the active surfaces, thereby allowing a quick transfer reaction. This would result in better output and thus better power performance. Energy-dispersive X-ray spectroscopy (EDS) analysis and mapping were carried out for the as-synthesized materials. Figure 3C–F display the mapping images of SmVO_4 @GOS, in which Sm, V, O, and C are uniformly distributed. Figure 3G shows the EDS profile of SmVO_4 @GOS, which confirms the elements of Sm, V, O, and C.

Fig. 3 A1–A3 SEM and B1–B3 TEM images of SmVO_4 @GOS. C–F Elemental mapping images and G elemental analysis of SmVO_4 @GOS



Electrochemical characterization of the SmVO_4 @GOS electrode

The electrical resistance and interface between the electrolyte and the surface of an electrode are key features of an electrochemical sensor, which was investigated using EIS. The obtained Nyquist plots of bare GCE, GOS/GCE, SmVO_4 /GCE, and SmVO_4 @GOS/GCE in 0.1 M KCl in the presence of 5 mM $[\text{Fe}(\text{CN})_6]^{-3/4}$ are given in Fig. 4A. The semicircular portion of SmVO_4 @GOS/GCE is relatively small compared to those of GCE and GOS/GCE. The R_{ct} values (Fig. 4A, inset) for the three different electrodes were computed and found to be 52.63 Ω , 61.02 Ω , 118.26 Ω , and 234.12 Ω for SmVO_4 @GOS/GCE, SmVO_4 /GCE, GOS/GCE, and bare GCE, respectively. The lowered resistance of the SmVO_4 @GOS nanocomposite was owing to the increased conductance and larger surface area, which facilitated the diffusion and mobility of electrons in the

electrolyte medium [47, 48]. The electrochemical active surface area was calculated by the CV method, and the surface area of SmVO_4 @GOS/GCE was found 0.141 cm^2 using the Randles–Sevcik equation.

Optimization of the electrochemical conditions and electrodes

The quantity of the composite used on the surface of an electrode plays a vital role in the electrochemical performance of the electrode. The concentration of SmVO_4 @GOS was varied from 0.5 to 2.5 mg mL^{-1} in 0.05 M phosphate buffer (PB; pH 7.0) at a 0.05 V s^{-1} scan rate. The obtained plot is given in Fig. S1A. The figure indicates that the anodic current response increased continuously toward the oxidation of SSZ as the concentration of SmVO_4 @GOS increased from 0.5 to 2.5 mg mL^{-1} . With a further increase in the

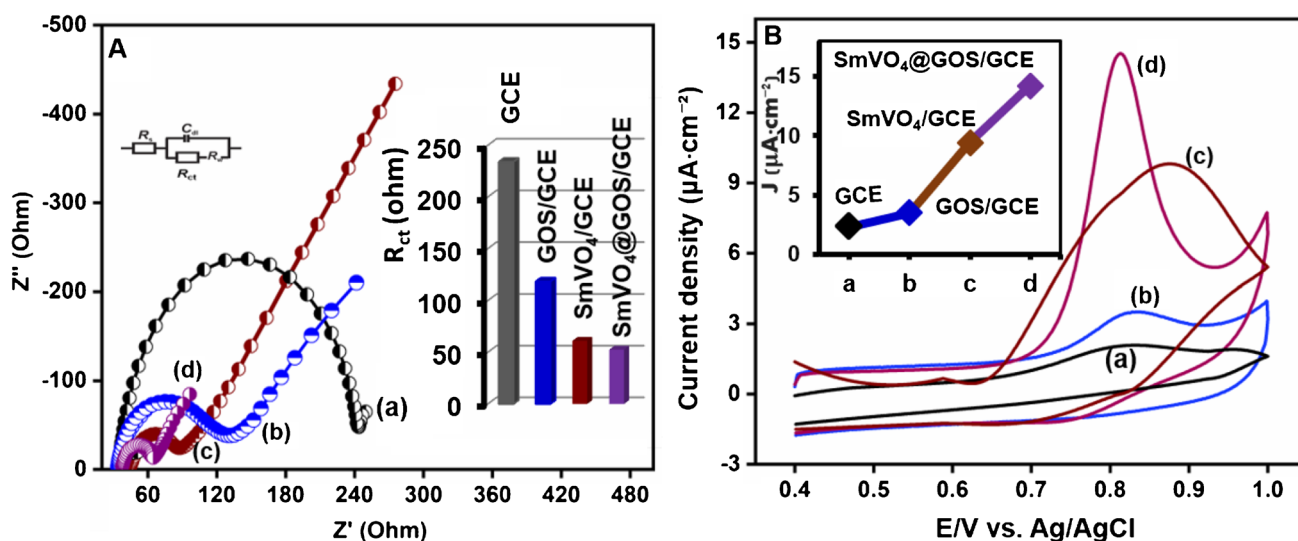


Fig. 4 A EIS patterns of (a) bare GCE, (b) GOS/GCE, (c) SmVO₄/GCE, and (d) SmVO₄@GOS/GCE in 5 mM [Fe(CN)₆]^{3-/4-} containing 0.1 M KCl as the electrolyte (inset: Randles circuit). B CV

responses for 100 μM SSZ at (a) bare GCE, (b) GOS/GCE, (c) SmVO₄/GCE, and (d) SmVO₄@GOS/GCE in 0.05 M PB (pH=7) at a 50 mV s^{-1} scan rate

concentration (1.0 mg mL^{-1}), the current response toward the oxidation of SSZ decreased because of the blocking of active sites at high concentrations of the nanocomposite. The highest oxidation peak current was achieved for 1.0 mg mL^{-1} , which was thus the optimal concentration of SmVO₄@GOS for the detection of SSZ. Furthermore, coating of SmVO₄@GOS volume was optimized. Seven microliters of the composite modified electrode has achieved high peak current. The data are given in Fig. S1B of the Supporting information.

Electrocatalytic activity of SmVO₄@GOS/GCE in phosphate buffer

SSZ oxidation using different materials on the electrode was carried out. The CV responses of 100 μM of SSZ in 0.05 M PB (pH 7) at a scan rate of 0.05 V s^{-1} in the presence of bare GCE, GOS/GCE, SmVO₄/GCE, and SmVO₄@GOS/GCE are shown in Fig. 4B. The low conductivity between GCE and the electrolyte resulted in poor electrochemical performance. The GOS/GCE exhibits a small hump, indicating a slight anodic current response of $3.4 \mu\text{A}$ compared to the bare GCE at the same potential. The maximum anodic peak current is observed for the SmVO₄@GOS/GCE at a similar potential, with a high current response of $14.2 \mu\text{A}$. This confirms the excellent capacity of SmVO₄@GOS/GCE toward the detection of SSZ in 0.05 M PB owing to the enhanced conductivity of the modified GCE.

Figure 5A shows the impact of SSZ concentration in the range of 25 to 275 μM at a 0.05 V s^{-1} scan rate in 0.05 M PB (pH 7). The results indicate that the anodic peak current

response increased with increasing SSZ concentration owing to its effective oxidation. The linearity plot of SSZ concentration against current is given in the inset in Fig. 5A, which shows good linearity with the regression equation $y = 0.431 [\mu\text{M}] + 0.21$ and $R^2 = 0.9897$. This regression equation indicates that the oxidation of SSZ at SmVO₄@GOS/GCE follows that of antifouling reactions. To study the effect of the scan rate on the oxidation of SSZ, the scan rate was varied from 0.02 to 0.2 V s^{-1} , and the obtained response is shown in Fig. 5B. The figure shows an increase in anodic peak current with an increasing scan rate, with a slight shift in the anodic peak toward higher potentials. The inset in Fig. 5B shows the calibration plot of anodic current against the square root of the scan rate, where the regression equation $y = 5.313x + 0.4201$ and $R^2 = 0.985$ clearly indicate the diffusion control process involved in the electrochemical oxidation of SSZ in 0.05 M PB in the presence of SmVO₄@GOS/GCE (Scheme 3).

The medium in which the electrochemical reaction occurs is also important in electrochemical sensors. Hence, the CV response was recorded for the oxidation of SSZ using SmVO₄@GOS/GCE at different pH values. The evaluation was performed for 50 μM SSZ at a 50 mV s^{-1} scan rate, and the pH was varied from 6 to 10 (Fig. S2). Figure 6 indicates the drastic change in the CV response with respect to its shape, with irreversible peaks for the oxidation of SSZ. At lower pH values, a lower peak current is observed, and the maximum peak occurs at pH 7. Upon increasing the pH to alkaline (8–10), a gradual decrease in the anodic peak current is observed. This indicates that 0.05 M PB at pH 7 is the optimal pH value for the effective oxidation of SSZ using SmVO₄@GOS/GCE.

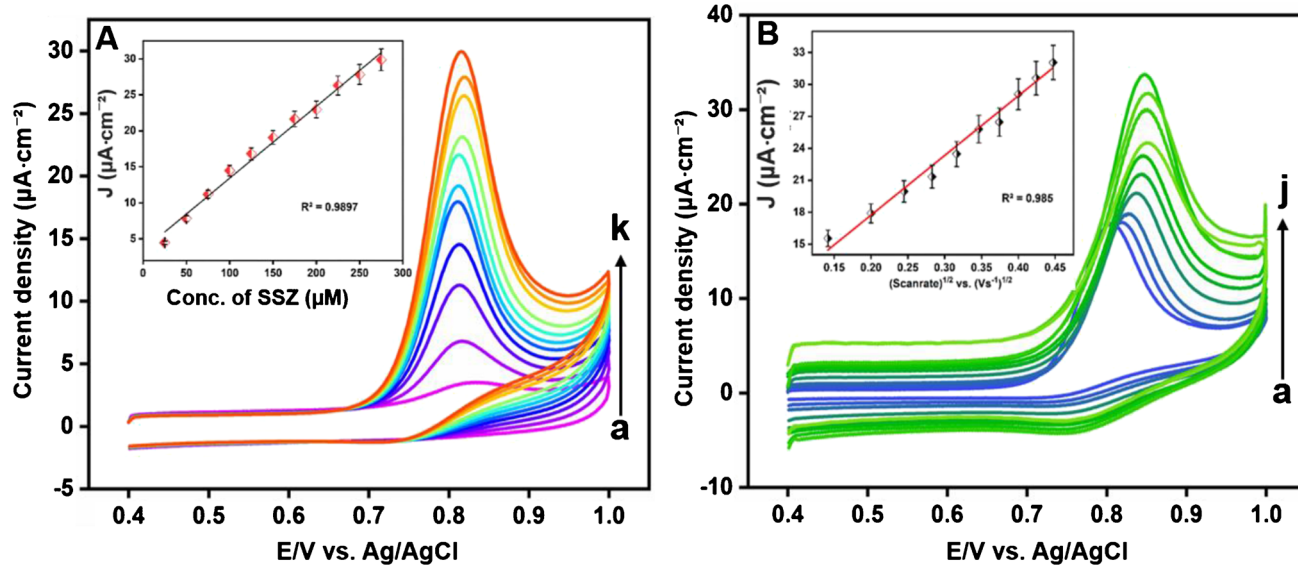


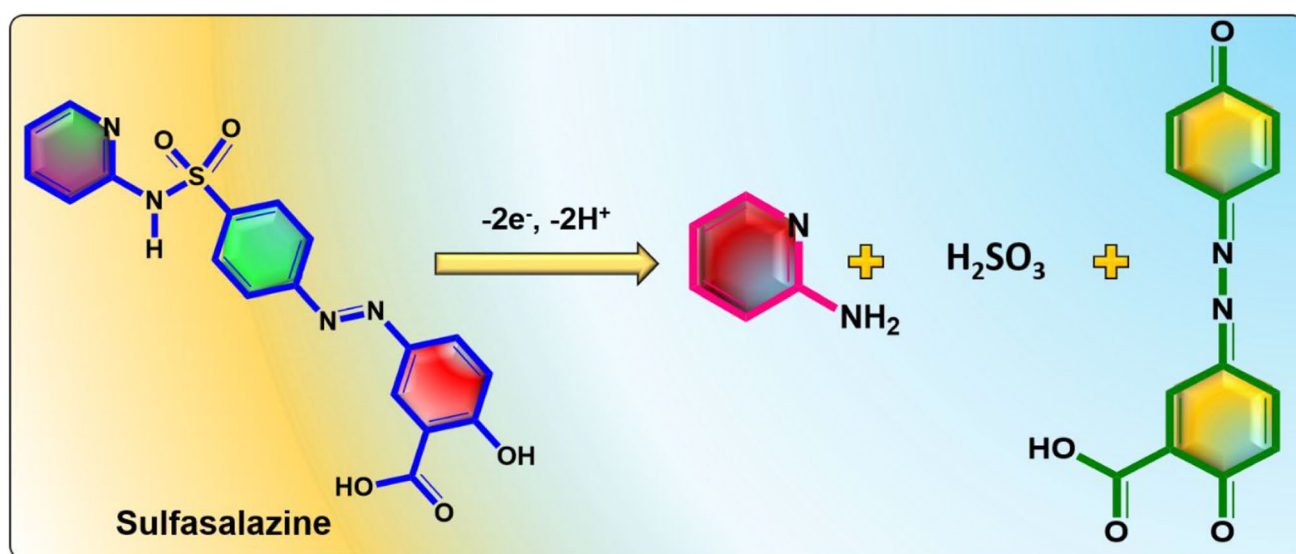
Fig. 5 **A** CV of $\text{SmVO}_4@\text{GOS}/\text{GCE}$ for different quantities of SSZ (25 to 275 μM) in 0.05 M PB (pH=7). Inset: corresponding linear dependence plot between the concentration of SSZ (μM) and current density ($\mu\text{A}\cdot\text{cm}^{-2}$). **B** CV curves of $\text{SmVO}_4@\text{GOS}/\text{GCE}$ containing

100 μM SSZ at scan rates of 0.02–0.2 V s^{-1} in 0.05 M PB (pH=7). Inset: corresponding linear calibration plot for the square root of the scan rate (V s^{-1}) vs. current density ($\mu\text{A}\cdot\text{cm}^{-2}$)

The corresponding calibration plot of E_{pa} versus pH is represented in Fig. S3. Moreover, the regression equation is noted as $E_{\text{pa}} = -0.053 \text{ pH} + 1.13$ ($R^2 = 0.991$). A slope value of 53 mV pH^{-1} is close to the theoretical Nernstian value, specifying an equivalent number of electrons and proton movement in the electrochemical reaction. This maximum response at neutral pH is advantageous as most studies in the biological and medical fields take place at this pH. At neutral pH, the drug under study, SSZ, underwent an irreversible electro-oxidation process according

to the $2e^-$ and 2H^+ transfer mechanism given in Scheme 3 [1, 2].

The electrochemical performance of $\text{SmVO}_4@\text{GOS}/\text{GCE}$ toward the oxidation of SSZ was also investigated through AMP studies at 0.82 V (Ag/AgCl). The AMP response was evaluated to understand the range, LOD, and sensitivity. Figure 6A, B depict the amperometric profile of SSZ detection using $\text{SmVO}_4@\text{GOS}/\text{GCE}$ in 0.05 M PB (pH=7) at a 0.05 V s^{-1} scan rate. The oxidation peak current increases steadily with the



Scheme 3 Electro-oxidation of SSZ at $\text{SmVO}_4@\text{GOS}/\text{GCE}$ in 0.05 M PB (pH 7)

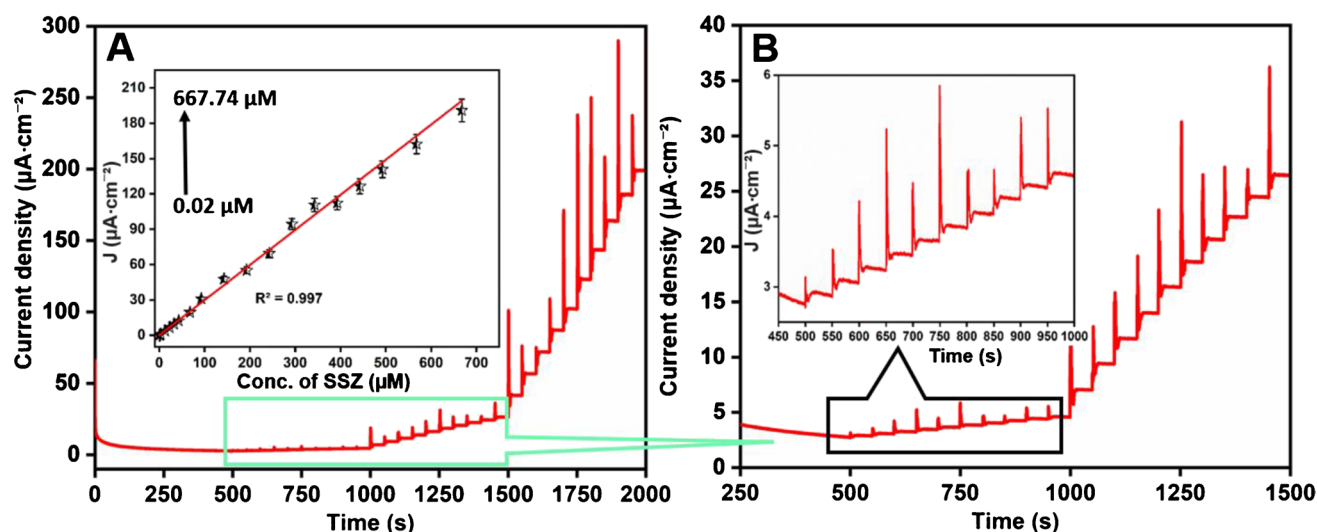


Fig. 6 A, B Amperometric responses of $\text{SmVO}_4\text{/GOS/GCE}$ for different quantities of SSZ (0.02–667 μM) in 0.05 M PB with pH = 7 at 0.82 V (rotation speed, 1200 rpm). Inset: corresponding linear dependence plot for the concentration of SSZ (μM) vs. current density ($\mu\text{A}\cdot\text{cm}^{-2}$)

sequential addition of SSZ. The calibration plot of current against concentration of SSZ (Fig. 6A, inset) shows a linear relationship, having a linear regression equation of $I_{pa} (\mu\text{A}) = 1.246 [\mu\text{M}] + 0.813$ and a coefficient of $R^2 = 0.997$. The amperometric response toward the oxidation of SSZ covered a wide range of detection, from 0.02 to 667 μM , with $6.23 \mu\text{A} \mu\text{M}^{-1} \text{cm}^{-2}$ sensitivity and a 2.16 nM LOD value. The achieved sensitivity and LOD value for the detection of SSZ using $\text{SmVO}_4\text{/GOS/GCE}$

are superior to those of many earlier reported methods, as given in Table 1, and thus should be of great interest.

Because many pharmaceutical formulations consist of one or more combinations of active drugs, selectivity toward the detection of individual components is a significant characteristic of an $\text{SmVO}_4\text{/GOS/GCE}$ electrochemical sensor. The selectivity analysis was performed with a 20-fold higher concentration of SSZ, along with the following possible interfering analytes: uric acid

Table 1 Analytical parameters for determining sulfasalazine at $\text{SmVO}_4\text{/GOS/GCE}$

Modified electrode	Linear range (μM)	Sensitivity ($\mu\text{A} \mu\text{M}^{-1} \text{cm}^{-2}$)	LOD (μM)	Method	Ref
Antimony film–modified GCE	3–250	–	0.78	SWV	[49]
GCE	10–50	–	3.43	DPV	[50]
Poly (3-methylthiophene)-coated GCE	0.75–320	0.257	0.25	SWV	[51]
GO/ $\text{Fe}_3\text{O}_4\text{/SiO}_2\text{/CPE}$	1–300	–	0.4	LSV	[2]
NiO NP-CPE	0.009–1.6	1.32	0.0017	SWV	[52]
SSZ MIP-modified CPE	0.01–1.0	–	0.0046	DPV	[53]
Bismuth-film electrode	5–31	–	1.4	SWV	[54]
NiO/CNT CPE	0.5–800	0.238	0.09	SWV	[3]
Mercury electrode	0.1–1.0	–	4.1	AdSV	[1]
Pt/SWNT/GCE	0.5–20	–	0.086	SWV	[55]
MWCNTCOOH/BA-SPCE	1.0–70	–	0.3	DPV	[6]
$\text{SmVO}_4\text{/CNF/GCE}$	0.009–445	4.03	0.0013	AMP	[9]
$\text{MnCo}_2\text{O}_4\text{/C}_3\text{N}_4$	0.01–95.4	9.28	0.003	DPV	[56]
$\text{ZnO-CO}_3\text{O}_4$	0.005–18.5	0.142	0.012	PCA	[57]
$\text{SmVO}_4\text{/GOS/GCE}$	0.02–667.74	6.231	0.00216	AMP	This work

SWV square wave voltammetry, DPV differential pulse voltammetry, LSV linear sweep voltammetry, AdSV adsorptive stripping voltammetry, GCE glassy carbon electrode, CPE carbon paste electrode, SPCE screen-printed carbon electrode, MWCNTCOOH/BA multiwalled carbon nanotubes/benzyl acetate, PCA photoelectrochemical analysis.

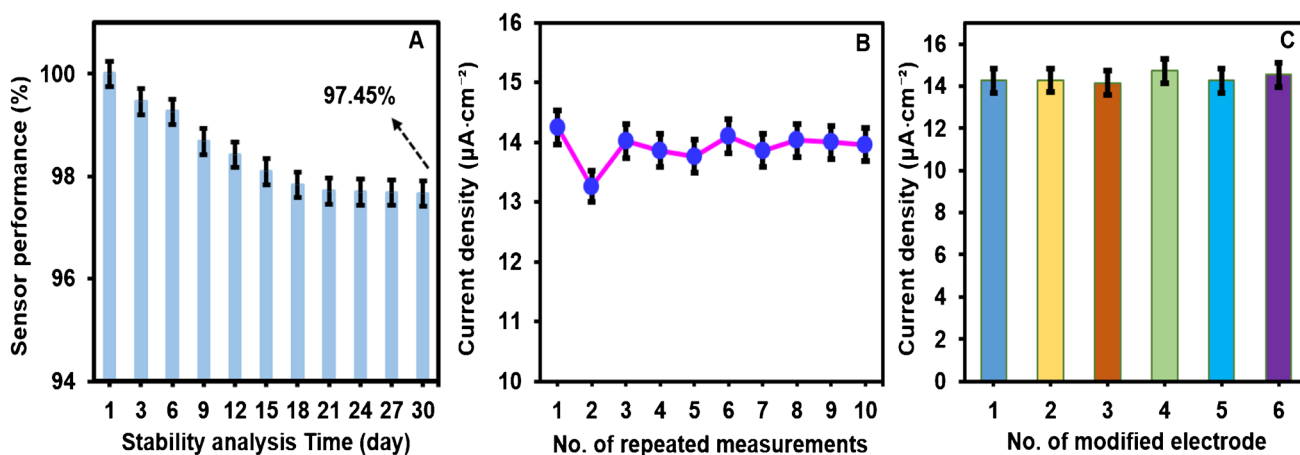


Fig. 7 **A** Calibration plot for stability analysis up to 30 days. **B** Repeatability analysis of the $\text{SmVO}_4\text{/GOS}$ modified electrode. **C** Reproducibility analysis of the modified sensor using six electrodes

(UA), dopamine (DA), paracetamol (PA), flutamide (Flu), nitrofurazone (NF), nitrofurantoin (NFT), hydrogen peroxide (H_2O_2), epinephrine (EPN), ciprofloxacin (CFX), norfloxacin (NFX), metronidazole (MTZ), chloramphenicol (CAP), paraoxon (PXN), fenitrothion (FTN), chlorpyrifos (CPF), dichlorvos (DCR), hydroquinone (HQ), catechol (CC), nitrate ions (NO_3^-), chlorine ions (Cl^-), and fenhexamid (FXD). Figure S3A shows no high changes in the oxidation peak current response, even with the addition of the abovementioned common interfering pharmaceuticals (drugs, herbicides, pesticides, fungicides, hydroquinone, catechol, flavonoids, pollutants, biogenic amines, ion species). Based on the literature and our experiments, dopamine, epinephrine, and uric acid are oxidized at 0.2, 0.31, and 0.38 V (Ag/AgCl) peak potentials, respectively. Mainly, those analytes are oxidized at below 0.6 V (Ag/AgCl). In this work, our modified $\text{SmVO}_4\text{/GOS/GCE}$ electrode shows SSZ peak at above 0.8 V (Ag/AgCl). Therefore, those analytes have

not affected our modified sensors toward SSZ detection. Moreover, interference aspect of ascorbic acid and sulfamethoxazole is checked in the presence of SSZ. There is no major difference in the SSZ peak response due to effective oxidation of SSZ.

Using 100 μM of SSZ, the amperometric response was recorded continuously for 30 days (once every 3 days). After every use of the electrode, it was placed at 4 $^\circ\text{C}$ (Fig. 7A). Even after 30 days, the $\text{SmVO}_4\text{/GOS/GCE}$ electrode exhibited good stability and managed to retain 97.4% of its initial value. In addition, the repeatability of the bimetal oxide-based graphene oxide modified electrode was analyzed, and the RSD value of 3.26% is obtained (Fig. 7B). To better understand the precision of the electrode, the amperometric response toward the oxidation of 100 μM of SSZ was investigated by using six different electrodes ($\text{SmVO}_4\text{/GOS/GCE-1-6}$). The obtained RSD value of 3.26% indicates the excellent precision of the electrode (Fig. 7C).

Table 2 Determination of SSZ in spiked biological samples at the $\text{SmVO}_4\text{/GOS}$ modified electrode

Real samples	Added (nM)	Found (nM)		Recovery (%)		RSD/ $\pm\%$ ($n=3$)	
		AMP	HPLC	AMP	HPLC	AMP	HPLC
Blood serum	0	0	0	0	0	0	0
	50.0	48.9	49.0	97.8	98.0	2.13	1.89
	100	99.7	99.8	99.7	99.8	1.06	1.03
	200	197	198	98.5	99.0	2.14	1.49
Urine sample	0	0	0	0	0	–	0
	50.0	49.2	49.3	98.4	98.6	1.86	1.29
	100	98.7	99.1	98.7	99.1	1.98	1.34
	200	196	198	98	99.0	1.02	1.13

Practical applicability of SmVO₄@GOS/GCE toward SSZ

Any fabricated electrode for the detection of pharmaceutical compounds needs to demonstrate its practical applicability using real-world samples, pharmaceutical formulations, etc. Human blood serum and urine samples were selected to study the oxidation of SSZ using SmVO₄@GOS/GCE. Details regarding the purchase of materials and the sample preparation method are given in the Supporting information. The recovery studies were performed by following a standard addition procedure. The original urine and blood serum failed to show any response toward the oxidation of SSZ. The amperometric response was monitored after spiking SSZ to the biological samples under optimum conditions, and the results are given in Table 2. The recovery ranges were 96.7–98.6% and 96.1–97.1% for the human serum and urine samples, respectively. These recovery results indicate that the fabricated electrode exhibited good amperometric response toward SSZ oxidation, even in the presence of unknown interferences. Thus, the fabricated SmVO₄@GOS/GCE proved to be an excellent amperometric probe for the effective oxidation of SSZ for day-to-day real-time applications.

Conclusion

A deep eutectic solvent in association with the hydrothermal method was developed for the synthesis of samarium orthovanadate particles wrapped in graphene oxide sheets. The SmVO₄@GOS nanocomposite was used to modify a GCE for use as a working electrode for sensing an anti-rheumatic drug (SSZ). The amperometric technique was found to be more sensitive than CV, with a wide linear range of detection toward the detection of SSZ. The enhanced electrochemical behavior of SmVO₄@GOS/GCE was owing to the enhanced conductivity and increased surface area. The fabricated electrode demonstrated excellent selectivity in detecting SSZ in the presence of known drugs and unknown interferences. The most required parameter of an electrochemical sensor is its real-time application, which was perfectly met by SmVO₄@GOS/GCE. The additional advantage of the electrode is its stability and reproducibility. The electrochemical performance of SmVO₄@GOS/GCE toward the detection of SSZ indicated its high sensitivity, selectivity, stability, accuracy, and precision, and as a result, it is suitable for use in the medical and pharmaceutical industries.

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Declarations

Conflict of interest The authors declare no competing interests.

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