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Therapeutic monitoring of Proguanil in urine using a CuS/CuO@MWCNT-Based Electrochemical Sensor

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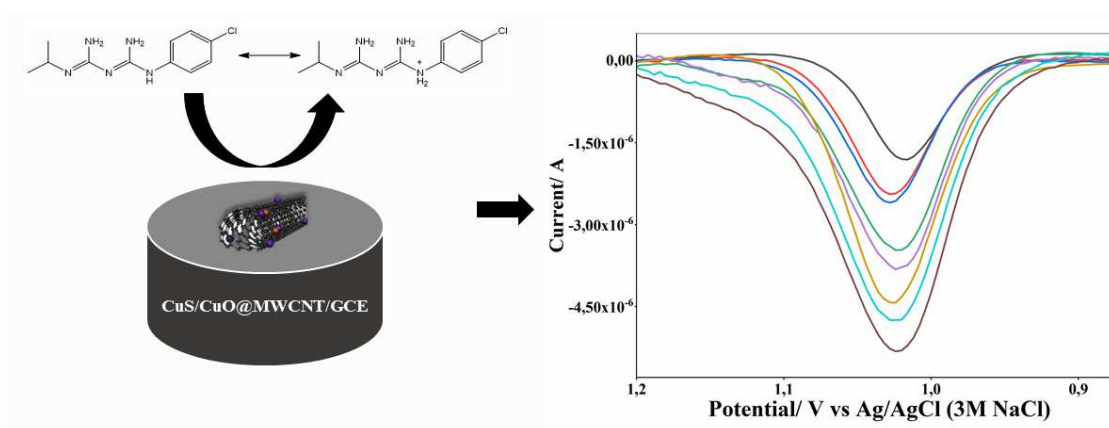
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Graphical abstract



Abstract

This study presents a ternary nanocomposite comprising copper sulphide (CuS) and copper oxide (CuO) nanoparticles coated multi-walled carbon nanotubes (MWCNT) for the determination of Proguanil in urine. The composite was synthesised via a simple one-step, environmentally friendly hydrothermal method. A modified working electrode was fabricated by drop-casting the composite on the surface of the bare electrode. The resulting electrochemical sensor (CuS/CuO@MWCNT/GCE) demonstrated a low limit of detection (LOD) of 3.4×10^{-7} M and a broad linear detection range from 1×10^{-5} to 8×10^{-5} M for Proguanil. The fabricated electrode successfully detected Proguanil in urine samples prepared in phosphate buffer (pH 3.5), achieving an LOD of 4.5×10^{-7} M, thereby confirming its applicability for real sample analysis. Furthermore, the fabricated sensor exhibited excellent

selectivity in the presence of various interfering agents, with an average accuracy of 96.71%, and showed high reproducibility, with a relative standard deviation (RSD) of 0.45% across three identically fabricated electrodes tested in triplicate. These results demonstrate the potential of the CuS/CuO@MWCNT/GCE sensor as a reliable tool for proguanil monitoring in urine.

Keywords: Proguanil, Antimalarial drug monitoring, Nanomaterials, Electrochemical sensor

1. Introduction

To date, malaria is still a major public health issue worldwide. According to the World Health Organisation (WHO), a person dies every single minute from the disease, and a high percentage of deaths are in sub-Saharan Africa (1,2). Proguanil, an antimalarial agent of the biguanide class, was first introduced as Paludrine in the 1940s to treat and prevent malaria in travellers to endemic areas. It is a prodrug of the cytochrome P450 enzyme CYP2C19. Cycloguanil, the active metabolite of proguanil, inhibits the Plasmodium dihydrofolate reductase (DHFR) enzyme, thereby disrupting folic acid synthesis and halting DNA synthesis in the parasite, which prevents schizont replication during the erythrocytic stage of the parasite's life cycle (3–6). Due to increasing Plasmodium resistance, proguanil is no longer used as monotherapy. It is now recommended to be combined with atovaquone, marketed as Malarone, for the treatment of uncomplicated malaria and as prophylaxis for travellers (7,8). Minor genetic variations, known as polymorphisms, can significantly impact the effectiveness of antimalarial treatment and prevention (9–11). People are classified as poor metabolizers when they have reduced CYP2C19 activity. They are commonly found in 1–7.5% of African and African American populations, 3–10% in Caucasians, and around 19% in Asian populations. Extensive metabolizers exhibit normal oxidative CYP2C19 activity (12). CYP2C19 activity is reduced in poor metabolizers, resulting in lower cycloguanil levels and increased risk of treatment failure (13). To minimise the risk to patients, it is essential to monitor proguanil concentrations.

Therapeutic drug monitoring (TDM) has become crucial for personalised patient management to optimise therapy (14). TDM assists clinicians by quantifying the serum concentration of a drug, enabling them to adjust the dose accordingly to achieve an optimal level in the serum. This concentration is essential for ensuring the treatment's efficacy and safety (15,16). While blood and plasma are commonly used for TDM, urine samples, due to their practical advantages, such as non-invasive collection, improved patient compliance, and suitability for routine analysis in resource-limited endemic regions, are gaining ground in TDM (17). Given the complexity of the biological matrix, detecting an analyte under such conditions requires a robust analytical method capable of overcoming potential interference from co-existing agents. For Proguanil monitoring, chromatographic methods, particularly High-Performance Liquid Chromatography (HPLC) and Liquid Chromatography-Mass Spectrometry (LC-MS), have been employed (10,18–20). However, these techniques require organic solvents, which can harm the environment, involve expensive and sophisticated instrumentation, demand highly trained personnel, and may involve time-consuming procedures. Recently, electrochemical

methods have proven effective at addressing the drawbacks associated with chromatographic techniques. These methods are generally faster, more cost-effective, and readily miniaturised, while offering very low detection limits and excellent selectivity, particularly when applied to complex biological matrices (21–24).

Very few electrochemical sensors have been investigated to monitor proguanil, despite this approach being the simplest and most cost-effective (25–28). Moreover, the sensors developed were primarily intended for quality control applications. Hence, there is a significant need to develop additional electrochemical sensors to monitor proguanil.

Electrochemical sensors typically employ a three-electrode system, including a reference electrode, a working electrode, and a counter electrode. Modifying the working electrode surface with nanomaterials significantly enhances the sensor's performance (29,30). Among these nanomaterials, transition metal oxides, such as copper oxide (CuO), are widely used to develop highly conductive sensors. CuO is a p-type semiconductor with low cost and good stability, making it a nanomaterial of great interest in catalysis, gas sensing, semiconductors, and biosensors (31,32). Transition metal sulphides (TMS) have recently garnered considerable attention due to their high electrical conductivity and excellent redox capabilities. Owing to the relatively weak metal–sulphur (M–S) bonding, they offer greater potential for developing electrochemical sensors than metal oxides (33). Among these TMS, copper sulphide (CuS) has gained significant interest due to its high stability, non-toxicity, low cost, and electrocatalytic properties. CuS has been widely applied in various fields, including solar cells, rechargeable lithium batteries, and biosensors (34,35). Multi-walled carbon nanotubes (MWCNTs) have been widely utilised in research for many years to develop electrochemical sensors due to their exceptional properties, including a large surface area, excellent electrical conductivity, thermal stability, and high chemical stability (36,37). Their high specific surface area enhances the number of active sites available for interaction with target analytes, facilitating the uniform dispersion of nanoparticles, such as CuO or CuS. This has enabled the development of sensors based on MWCNT combined with CuS or CuO. CuS-MWCNT and CuO-MWCNT nanocomposite-based sensors have been reported to detect analytes such as nitrite, glucose, dopamine, Doxepin, and hepatitis B surface antigen (38–42). To the best of our knowledge, no study has investigated the combination of these three nanomaterials.

In this work, we aimed to integrate CuO and CuS with MWCNTs to leverage the large surface area and electrical conductivity of MWCNT, the ability of CuS/CuO to provide active catalytic sites, and to facilitate electron transfer to enable the electrochemical determination of Proguanil within urine (43,44). The hydrothermal method was employed to synthesise

CuS/CuO@MWCNT due to its simplicity and environmentally friendly nature (45).

2. Experimental

2.1. Apparatus

The nanocomposite morphology was examined using transmission electron microscopy (TEM, JEOL 101, USA) and field emission scanning electron microscopy (FE-SEM, ZEISS Ultra Plus, Germany). Elemental composition was determined by energy-dispersive X-ray spectroscopy (EDX). A MiniFlex600-PXRD (Rigaku Analytical Devices, USA) was used at 40 kV and 15 mA to record the X-ray diffraction patterns. The patterns were recorded at a 2θ range of 5° – 90° at a scan speed of $0.01^\circ 2\theta \text{ s}^{-1}$ using secondary graphite monochromator Cu K alpha radiation ($\lambda = 1.54 \text{ \AA}$). Electrochemical measurements were carried out using a CHI660E electrochemical workstation (CH Instruments, USA) in a three-electrode configuration comprising a glassy carbon electrode (GCE, 3.00 mm diameter) as the working electrode, a platinum wire as the counter electrode, and an Ag/AgCl (3.00 M NaCl) electrode as the reference. A 2.5 mM ferri/ferrocyanide solution in 0.1 M KCl was used as the redox probe.

2.2. Chemicals and Reagents

MWCNTs, $\text{Cu}(\text{CH}_3\text{COO})_2 \cdot \text{H}_2\text{O}$, $[(\text{NH}_2)_2\text{CS}]$, Proguanil, and other reagents were purchased from Sigma-Aldrich South Africa. All chemicals were of analytical grade and were used as received, without further purification.

2.3 Synthesis of CuS/CuO@MWCNT composite

The method described by Pan et al. was adapted and modified to synthesise CuS/CuO@MWCNT (46). Copper (II) acetate monohydrate $[\text{Cu}(\text{CH}_3\text{COO})_2 \cdot \text{H}_2\text{O}]$ was used as the copper source, and thiourea $[(\text{NH}_2)_2\text{CS}]$ served as the sulphur source. 50 mg of MWCNT was dispersed in 50 mL of deionised water under vigorous magnetic stirring. To this well-dispersed suspension, 1 mmol of $\text{Cu}(\text{CH}_3\text{COO})_2 \cdot \text{H}_2\text{O}$ and 2 mmol of thiourea were added, and the mixture was stirred intensely for 10 minutes. The resulting solution was transferred into a 100 mL Teflon-lined stainless-steel autoclave, sealed tightly, and heated at 200°C in an electric oven for 48 hours. The autoclave was allowed to cool naturally to room temperature after the reaction was complete. The resulting suspension containing the composite was centrifuged and washed several times with deionised water and ethanol. The final black product was dried at 60°C to yield the CuS/CuO@MWCNT nanocomposite.

2.4 Fabrication of Modified Electrode

The surface of the glassy carbon electrode (GCE) was polished using 0.05 μm alumina slurry and subsequently rinsed with deionised water. A 5 μL drop of a 1 mg/mL suspension of CuS/CuO@MWCNT and MWCNT was cast onto the GCE surface and dried under an infrared lamp for 15 minutes. The resulting electrodes were designated as CuS/CuO@MWCNT/GCE and MWCNT/GCE and used for electrochemical measurements.

2.5 Detection of Proguanil in Urine

Urine samples from healthy individuals were diluted 100-fold with 0.1 M phosphate buffer (pH 3.5) to minimise matrix effects. The diluted samples were then spiked with various concentrations of Proguanil. The CuS/CuO@MWCNT/GCE electrode enabled efficient detection of Proguanil in these samples.

2.6 Electrochemical Behaviour of Modified Electrode toward Proguanil

The optimal pH for the interaction between CuS/CuO@MWCNT/GCE and Proguanil was 3.5. Therefore, all measurements were performed at this pH in 0.1 M phosphate buffer. The effect of concentration was investigated over a range of 10 to 80 μM Proguanil. The selectivity of the electrode was assessed using mixtures containing Primaquine, ascorbic acid, uric acid, glucose, and inorganic ions (K^+ , Cl^- , Mg^{2+} , SO_4^{2-} , Na^+ , HCO_3^-). Finally, the reproducibility was evaluated using three identical electrodes.

3. Results and Discussion

3.1. Characterisation of Materials

EDS and XRD were employed to verify the successful synthesis of CuS/CuO@MWCNT by confirming its chemical composition. As shown in **Figure 1a**, the EDS spectrum revealed characteristic peaks corresponding to carbon (C), oxygen (O), copper (Cu), and sulphur (S). The elemental composition of the CuS/CuO@MWCNT composite was found to be 58.02% carbon, 27.75% copper, 11.84% sulphur, and 2.39% oxygen. As expected, these results suggest the presence of copper sulphide (CuS), copper oxide (CuO), and multi-walled carbon nanotubes. XRD analysis (**Figure 1b**) further confirms the presence of these materials. The XRD pattern exhibits characteristic peaks at 2θ values of 27.2° , 27.8° , 29.3° , 31.8° , 32.8° , 48.0° , and 59.4° , corresponding to the indexed peaks of CuS (covellite, COD 9008388). Peaks observed at 32.3° , 35.2° , 38.9° , 46.2° , and 52.7° were indexed to CuO (tenorite, COD 9015821). MWCNT exhibited diffraction peaks at 26.3° and 46.2° . These XRD results confirm

the elemental composition revealed by EDS and strongly indicate the successful synthesis of the CuS/CuO@MWCNT nanocomposite.

The morphological characterisation of the nanocomposites was evaluated using TEM and SEM. The tubular morphology with smooth surfaces observed in the SEM image (**Figure 1c**) confirms the presence of MWCNT. Spherical CuS nanoparticles, appearing as aggregates with a relatively uniform shape, and uniformly sized CuO nanoparticles were both heterogeneously distributed across the surface of the MWCNTs. The TEM micrographs further confirmed these observations. As shown in **Figure 1d**, larger, aggregated CuS nanoparticles and smaller CuO nanoparticles were spread across the surface of the MWCNT.

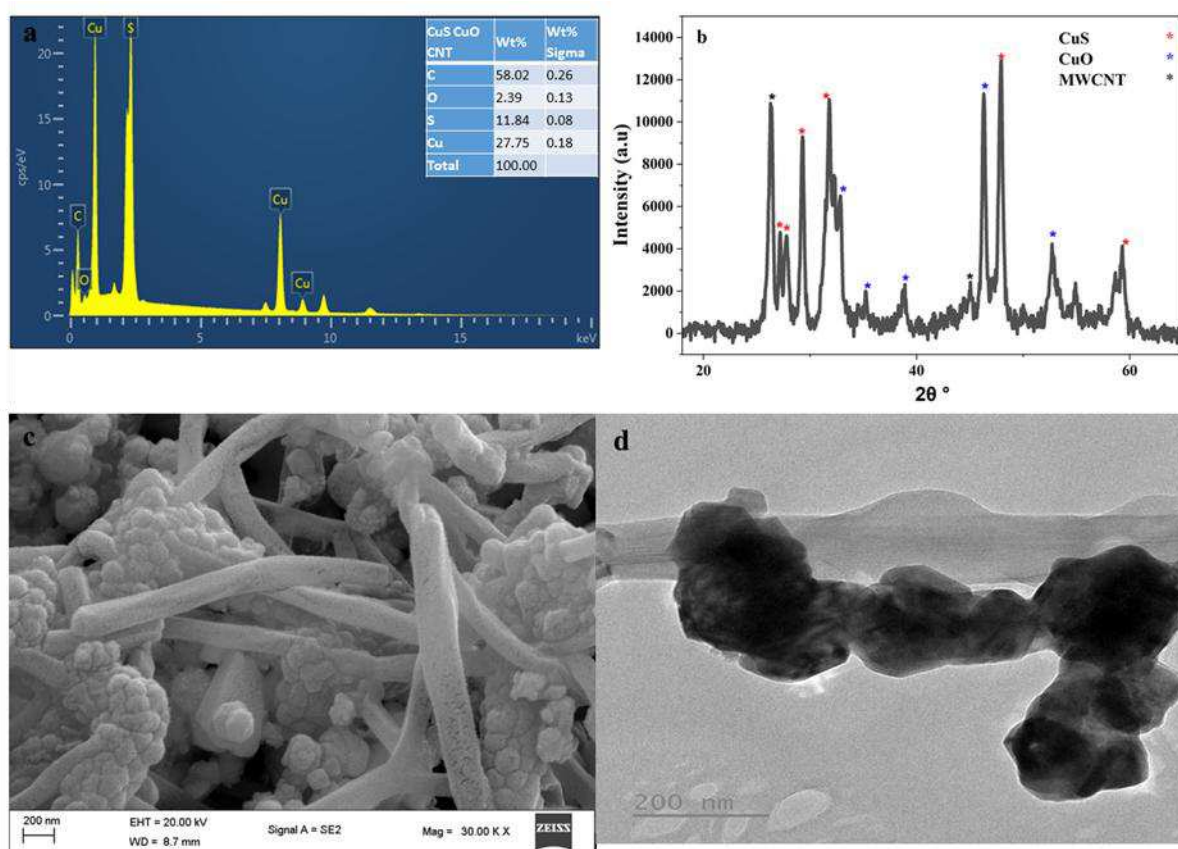


Figure 1. (a) SEM–EDX spectrum, (b) XRD pattern, (c) SEM image, and (d) TEM image of CuS/CuO@MWCNT.

3.2 Electrochemical Characterisation

The electrochemical properties of the fabricated electrode, namely, MWCNT/GCE, CuS/CuO@MWCNT/GCE and the bare GCE, were evaluated and compared using cyclic voltammetry (CV) and electrochemical impedance spectroscopy (EIS) in 2.5 mM

ferrocyanide/ferricyanide solution ($\text{Fe}(\text{CN})_6^{3-}/\text{Fe}(\text{CN})_6^{4-}$) as electrochemical probe with 0.1 M KCl as the electrolyte. CV was performed in the potential window of 0.4-0.6 V at a scan rate of 100 mV/s with a sampling interval of 0.001 V.

In the CV measurements (**Figure 2a**), the bare GCE exhibited anodic and cathodic peak currents of -5.682×10^{-5} A and 5.522×10^{-5} A, respectively, with a peak-to-peak separation potential (ΔE_p) of 122 mV. Upon modification with MWCNT, the anodic peak current increased to 9.77×10^{-5} A, and the ΔE_p decreased to 100 mV. This enhancement is attributed to the excellent electrocatalytic properties of MWCNT (47). The highest peak current (9.944×10^{-5} A) was observed after further modification with the CuS/CuO@MWCNT composite, with a ΔE_p of 112 mV. This suggests that the composite increased GCE's conductivity, enabling faster electron transfer. The decrease in ΔE_p further indicates enhanced electron transfer kinetics at the surface of the modified electrodes. The reversibility of the redox reaction was assessed through the anodic-to-cathodic peak current ratio, which was close to 1, as expected for a reversible system, confirming good electrochemical performance (15).

EIS is commonly employed to assess the electron transport properties of electrodes. In EIS, the resistance to electron transfer at the electrode-electrolyte interface is represented by the charge transfer resistance (R_{ct}), which is typically observed as the semicircular portion of the Nyquist plot (**Figure 2b**). A low R_{ct} value indicates a faster electron transfer process, whereas a high R_{ct} suggests a slower process (48). The R_{ct} value for the bare electrode, MWCNT/GCE, and CuS/CuO@MWCNT/GCE were 228.8 Ω , 0.001 Ω , and 19.98 Ω , respectively. As expected, the immobilisation of MWCNT and the nanocomposite CuS/CuO@MWCNT on the working electrode surface contributed to a reduction in R_{ct} , given the good conductivity of MWCNT, CuO, and CuS.

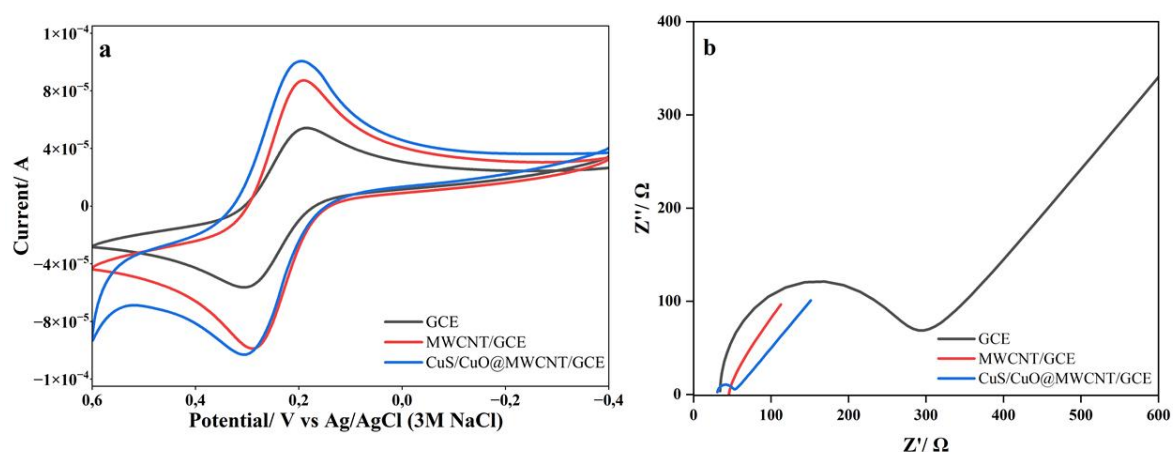


Figure 2. (a) Cyclic voltammograms of the unmodified GCE, MWCNT/GCE, and

CuS/CuO@MWCNT/GCE and (b) Nyquist diagrams of the unmodified GCE, MWCNT/GCE, and CuS/CuO@MWCNT/GCE recorded using a 2.5 mM $[\text{Fe}(\text{CN})_6]^{3-/4-}$ solution dissolved in 0.1 M KCl.

These results corroborate the CV findings and confirm the successful immobilisation of the composite onto the GCE surface. MWCNT showed rapid electron transfer and better conductivity compared to the composite. However, the initial detection of Proguanil with MWCNT and the composite revealed that the composite was almost three times more sensitive to Proguanil than MWCNT alone. So, the composite was selected for further analysis.

Table 1. CV and EIS data of the bare electrode and the modified electrodes (MWCNT/GCE and CuS/CuO@MWCNT/GCE)

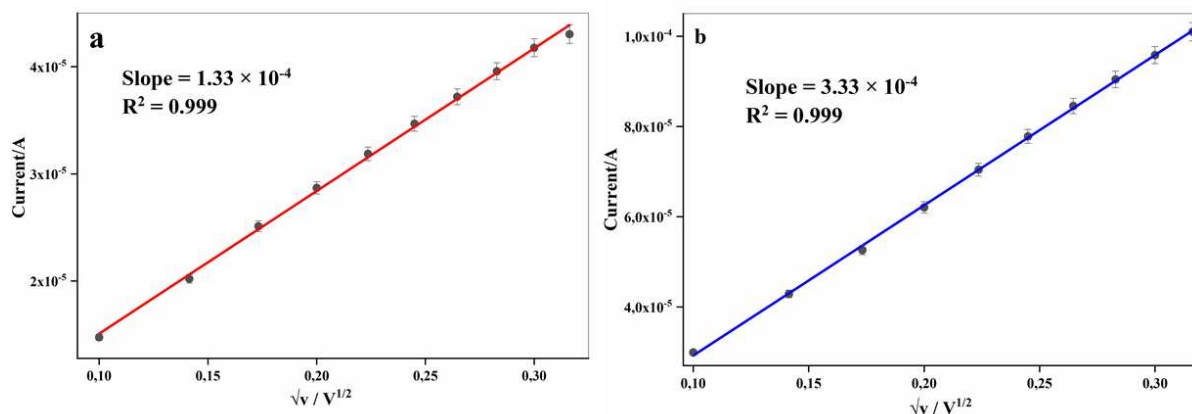
Material	Cyclic voltammetry		EIS			
	I _{pa} /I _{pc}	ΔE _p (mV)	R _s (Ω)	R _{ct} (Ω)	Z _w (Ω)	C _{dl} (Farad)
GCE	1.03	122	34.25	228.8	0.0006258	5.469×10^{-7}
MWCNT	1.01	100	45.77	0.001	0.002737	3.416×10^{-4}
CuS/CuO@MWCNT	1.00	112	30.48	19.98	0.002794	8.096×10^{-7}

3.3. Effect of Scan Rate

The modified electrode's effective electroactive area was estimated by running the CV measurements of both the bare GCE and the CuS/CuO@MWCNT/GCE in a 2.5 mM $[\text{Fe}(\text{CN})_6]^{3-}/[\text{Fe}(\text{CN})_6]^{4-}$ solution as an electrochemical probe containing 0.1 M KCl as the electrolyte at scan rates between 1 mV/s and 100 mV/s. The slope of the linear plot of peak current (I_p) versus the square root of the scan rate ($v^{1/2}$) was applied in the Randles–Ševčík equation (**Eq. 1**) to calculate the surface area (A) (15).

$$I_p = 2.69 \times 10^5 n^{3/2} A D^{1/2} v^{1/2} C_0 \quad \text{Eq. 1}$$

In this equation, I_p represents the anodic peak current (A), A is the electroactive surface area (cm^2), D is the diffusion coefficient of the redox probe ($7.60 \times 10^{-6} \text{ cm}^2/\text{s}$ for $\text{K}_4[\text{Fe}(\text{CN})_6]$), n is the number of electrons transferred (1 for the ferrocyanide/ferricyanide redox couple), v is the scan rate (V/s), and C_0 is the concentration of the analyte (mol/cm^3). The calculated electroactive surface areas for the unmodified GCE and the $\text{CuS}/\text{CuO}@/\text{MWCNT}/\text{GCE}$ were



0.0719 cm^2 and 0.1797 cm^2 , respectively. As expected, the modification with $\text{CuS}/\text{CuO}@/\text{MWCNT}$ significantly enhanced the electroactive surface area.

Figure 3. Linear relationship between anodic peak current and the square root of the scan rate for (a) bare GCE and (b) $\text{CuS}/\text{CuO}@/\text{MWCNT}/\text{GCE}$.

3.4. Electrochemical Behaviour of Modified Electrode toward Proguanil

The electrochemical oxidation of 0.1 mM Proguanil was evaluated using the bare GCE, MWCNT/GCE, and $\text{CuS}/\text{CuO}@/\text{MWCNT}/\text{GCE}$ electrodes by DPV in phosphate buffer (pH 3.5). Within the potential window of 0.5 to 1.4 V, a blank phosphate buffer using the bare GCE showed no peak current. Similarly, 0.1 mM Proguanil in phosphate buffer (pH 3.5) on the bare GCE also exhibited no peak, indicating poor electrocatalytic properties and slow electron transfer kinetics of the bare GCE for Proguanil detection. Upon modification with MWCNT, the detection of 0.1 mM Proguanil produced a peak current of $2.364 \times 10^{-6} \text{ A}$ ($E_p = 1.028 \text{ V}$). Further modification with the $\text{CuS}/\text{CuO}@/\text{MWCNT}$ composite resulted in the highest peak current of $6.473 \times 10^{-6} \text{ A}$ ($E_p = 1.032 \text{ V}$) as shown in **Figure 4**. The $\text{CuS}/\text{CuO}@/\text{MWCNT}/\text{GCE}$ exhibited a peak current approximately three times higher than that of the MWCNT/GCE, demonstrating the synergistic effect of its components. While the MWCNT exhibited faster electron transfer and better conductivity during electrochemical characterisation, the $\text{CuS}/\text{CuO}@/\text{MWCNT}$ displayed a superior ability to detect proguanil, as evidenced by an exceptionally higher peak current. This means that the presence of CuS and CuO improved the

material's sensitivity to proguanil. While MWCNTs contribute a high surface area, CuS and CuO provide abundant catalytic sites, collectively promoting more efficient electron transfer on the modified electrode surface.

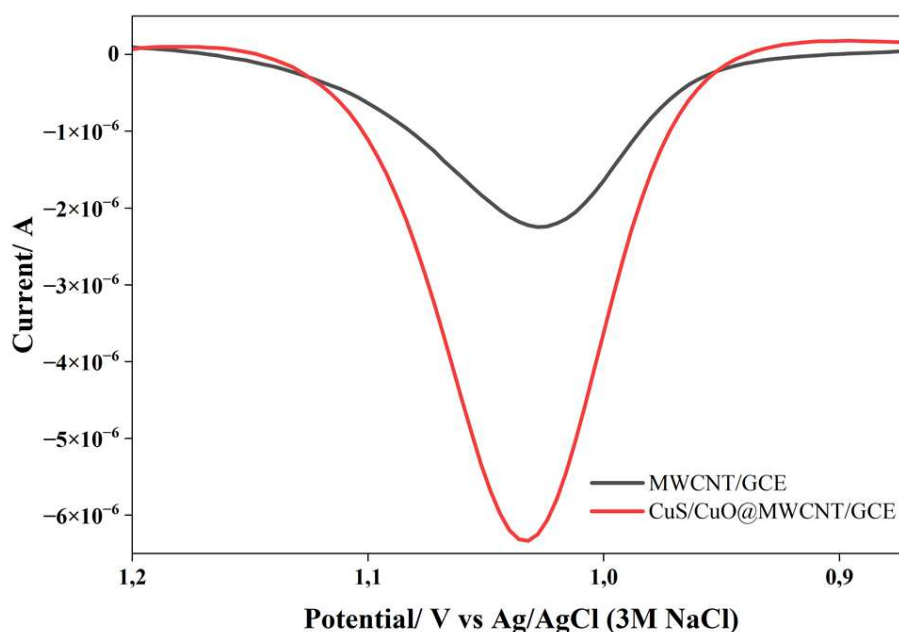


Figure 4. Differential pulse voltammograms of 0.1 mM Proguanil in phosphate buffer (0.1 M, pH 3.5) using MWCNT/GCE and CuS/CuO@MWCNT/GCE.

3.5. Effect of pH

The influence of pH on the oxidation of 0.1 mM Proguanil was investigated using the CuS/CuO@MWCNT/GCE electrode in phosphate buffer solutions ranging from pH 3.5 to 7.5. **Figure 5a** shows that the peak current initially increased (pH 3.5). However, the peak current gradually decreased as the pH increased, reaching its lowest value at pH 7.5. The highest peak current was observed at pH 3.5, which was chosen as the optimal pH for further experiments. Moreover, a negative shift in the oxidation peak potential of Proguanil was observed with increasing pH, suggesting the participation of both protons and electrons in the electrochemical reaction. A linear relationship (**Figure 5b**) represented by **Eq. 2** was found between the oxidation peak potential and pH, with a slope of -55.6 mV/pH, close to the theoretical Nernstian value (59 mV)(49). This result suggests that the oxidation of Proguanil at the CuS/CuO@MWCNT/GCE electrode has a balanced number of electrons and protons, which agrees with previous studies (50). Moreover, Nate et al. investigated the oxidation mechanism of Proguanil. Their similar results revealed an irreversible oxidation mechanism for Proguanil, as illustrated in **Figure 6**. We therefore hypothesise that the detection of proguanil at CuS/CuO@MWCNT/GCE follows a similar mechanism (26,51).

$$E_p \text{ (mV)} = 1228.2 - 55.6 \text{ pH} \text{ (} R^2 = 0.992 \text{)}$$

Eq 2

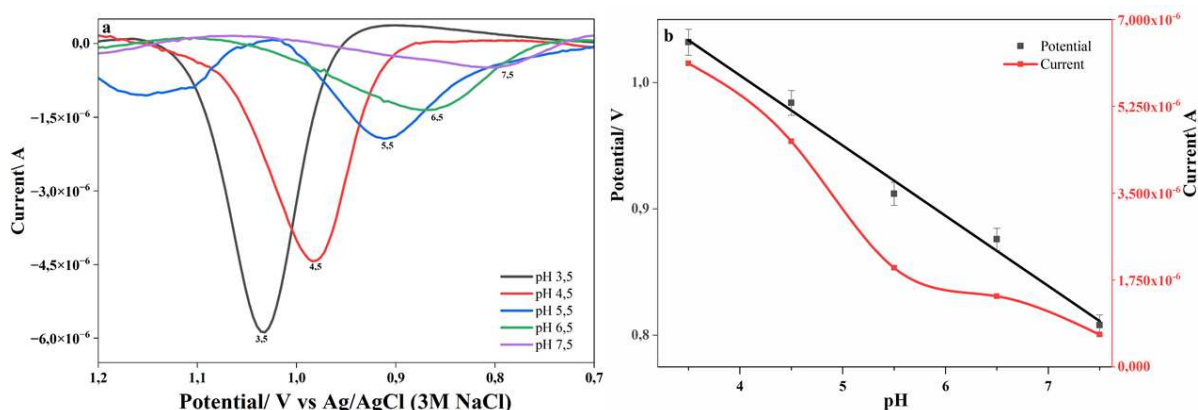


Figure 5. (a) DP voltammograms of 0.1 mM Proguanil in phosphate buffer solutions of varying pH (3.5–7.5) and (b) corresponding plots showing the linear correlation between pH and the oxidation peak potential, as well as pH versus peak current.

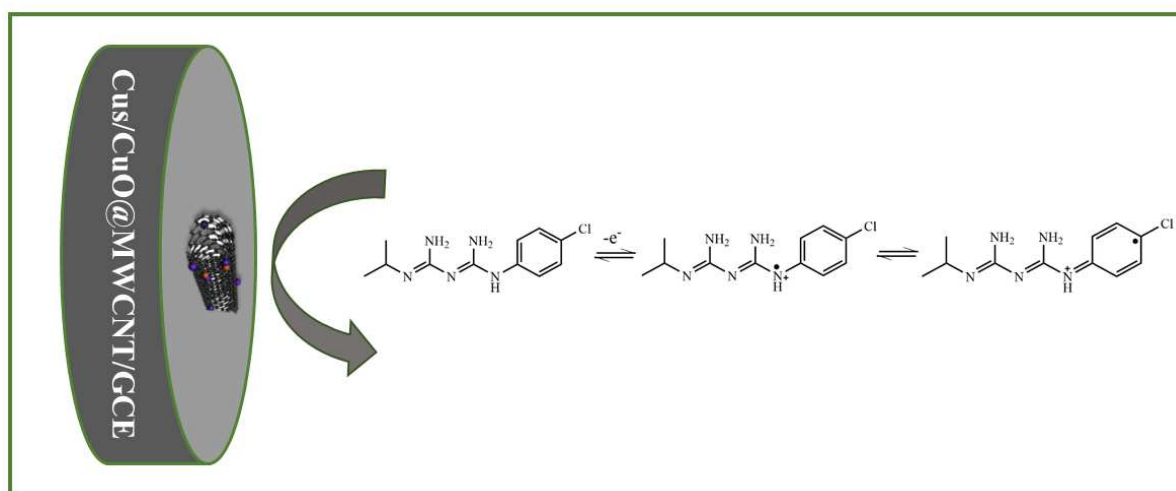


Figure 6. Proposed oxidation mechanism of 0.1 mM Proguanil at the CuS/CuO@MWCNT/GCE electrode

3.6. Analytical Performance

The CuS/CuO@MWCNT/GCE electrode was evaluated for its analytical performance in phosphate buffer at pH 3.5 by varying the Proguanil concentration from 10 μ M to 80 μ M using DPV. **Figure 7a** illustrates the increase in peak current observed with increasing Proguanil concentration. A linear relationship between Proguanil concentration and peak current was established (**Figure 7b**), as described by **Eq. 3**. The limit of detection (LOD) of the sensor was calculated using **Eq. 4**:

$$I_p \text{ (}\mu\text{A)} = 0.05 [\text{Prog}] + 1.382 \text{ (} R^2 = 0.986 \text{)}$$

Eq. 3

$$\text{LOD} = 3S/m$$

Eq. 4

where S represents the background noise, determined as the standard deviation of ten measurements performed with the unmodified electrode in blank phosphate buffer ($S = 5.687 \times 10^{-9}$ A), and m is the slope of the linear relationship between peak current and concentration. The CuS/CuO@MWCNT/GCE sensor demonstrated a LOD of 3.4×10^{-7} M and offered the advantage of a broader linear range (1×10^{-5} to 8×10^{-5} M). The fabricated sensor exhibits excellent sensitivity, with a lower LOD than GCE-based Proguanil detection. Although this sensor does not have the lowest LOD compared to those presented in **Table 2**, it offers the distinct advantage of a broader linear range, which is beneficial for applications in therapeutic monitoring of proguanil. Furthermore, the sensor is synthesised via a one-step, environmentally friendly method and is the first to report the synergistic use of CuS, CuO, and MWCNT in electrochemical sensing.

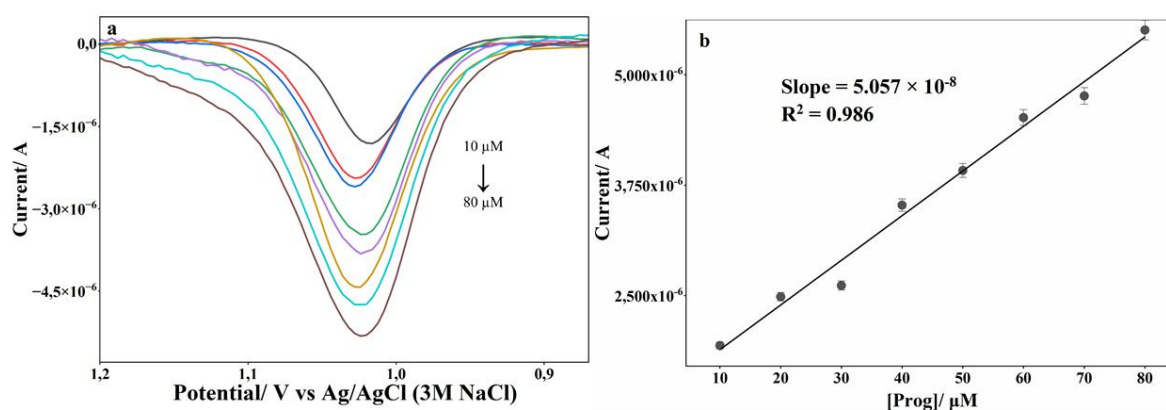


Figure 7. (a) DP voltammograms for increasing concentrations of Proguanil (10 μM to 80 μM); (b) Linear plot of peak current versus Proguanil concentration.

Table 2. Comparison of different Proguanil electrochemical sensors

Electrode	Technique	LOD (M)	Linear Range (M)	References
Renewable silver amalgam film electrode	SWV	2.9×10^{-8}	$1 \times 10^{-7} - 6 \times 10^{-6}$	(52)
CWE/phosphotungstic acid	Potentiometry	1×10^{-6}	$1 \times 10^{-5} - 1 \times 10^{-2}$	(53)
MWCNTs-iron oxide/GCE	DPV	1.96×10^{-8}	$0.7 \times 10^{-6} - 1.9 \times 10^{-5}$	(50)
PANI- Co_3O_4 /GCE	DPV	1.42×10^{-9}	$1.6 \times 10^{-5} - 2.8 \times 10^{-5}$	(51)

CuS/CuO@MWCNT/GC E	DPV	3.4×10^{-7}	$1 \times 10^{-5} - 8 \times 10^{-5}$	Present work
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3.7. Real Sample Analysis and Interference Studies

Real sample analysis was conducted to confirm the practical applicability of the CuS/CuO@MWCNT/GCE sensor for therapeutic monitoring. Given that approximately 40-60% of proguanil is excreted unchanged in the urine, urine samples were selected for therapeutic monitoring of Proguanil (54). A 0.1 M phosphate buffer solution (pH 3.5) was prepared using urine samples diluted 100-fold to minimise matrix effects. This diluted solution was spiked with known concentrations of Proguanil (10 μ M to 80 μ M). The sensor detected Proguanil in urine samples as depicted in **Figure 8a**, showing a linear relationship (**Figure 8b**) described in **Eq. 5**:

$$I_p (\mu A) = 0.038 [\text{Prog}] + 2.311 (R^2 = 0.984) \quad \text{Eq. 5}$$

The selectivity of the CuS/CuO@MWCNT-modified electrode towards Proguanil was assessed using DPV. A 0.1 mM Proguanil solution was detected in situations involving interfering substances, including ascorbic acid, glucose, uric acid, various inorganic salts such as KCl (K^+ , Cl^-), $MgSO_4$ (Mg^{2+} , SO_4^{2-}), $NaHCO_3$ (Na^+ , and HCO_3^-), as well as the antimalarial drug primaquine. The DP voltammograms were recorded using the CuS/CuO@MWCNT/GCE sensor as illustrated in **Figure 9a**. An average accuracy of 96.71% was achieved, indicating that Proguanil can be reliably detected when these interfering substances are present, thus demonstrating the sensor's high selectivity.

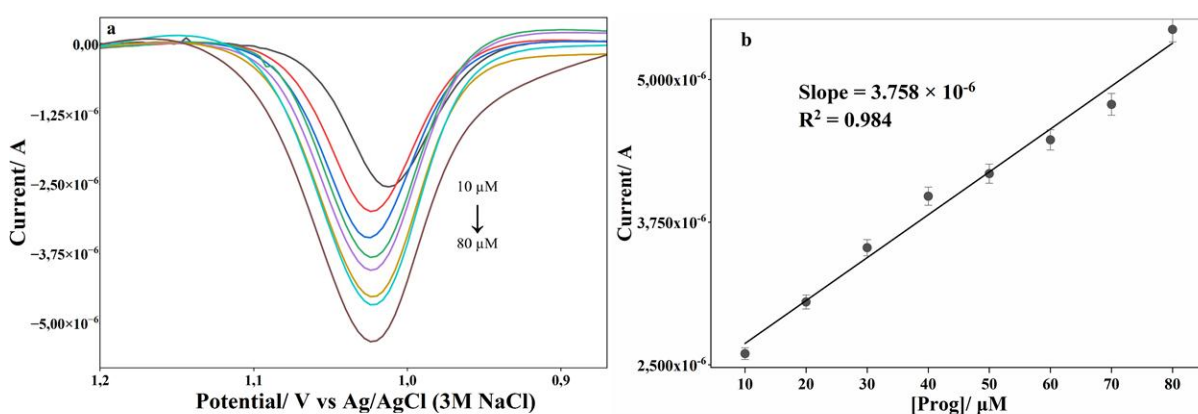


Figure 8. (a) DP voltammograms of 10 μ M to 80 μ M of Proguanil in diluted urine samples in phosphate buffer at pH 3.5; (b) Linear calibration plot of peak current versus Proguanil concentration in urine.

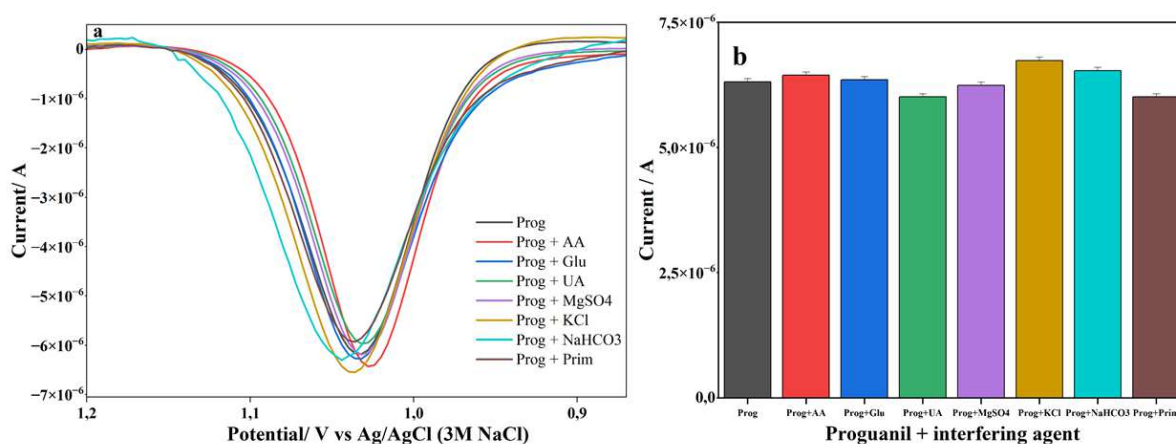


Figure 9. (a) DP voltammograms of 0.1 mM Proguanil (Prog) alone and in the presence of common interfering agents: ascorbic acid (AA), glucose (Glu), uric acid (UA), magnesium sulfate (MgSO₄), potassium chloride (KCl), sodium bicarbonate (NaHCO₃), and primaquine (Prim); (b) Corresponding column showing peak current variations.

3.8. Reproducibility

The reproducibility of the sensor was evaluated by detecting 0.1 mM Proguanil using three similarly fabricated CuS/CuO@MWCNT/GCE electrodes, each tested in triplicate. A low relative standard deviation (RSD) of 0.45% confirmed the sensor's high precision and minimal variation in repeated measurements, highlighting its excellent reproducibility.

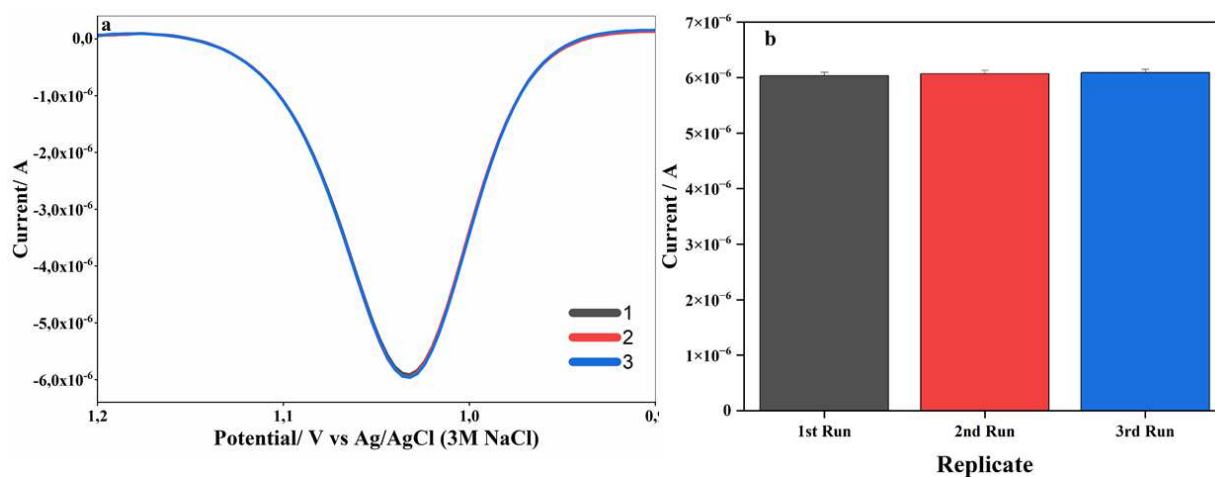


Figure 10. (a) DP voltammograms recorded using three different fabricated CuS/CuO@MWCNT/GCE sensors, each measured in triplicate; (b) Corresponding bar graph showing reproducibility of the measurements.

4. Conclusion

This study employed a cost-effective, straightforward hydrothermal method to synthesise a CuS/CuO@MWCNT nanocomposite for the detection of proguanil. The successful synthesis

of the composite was confirmed through EDS, XRD, SEM, and TEM analyses. The electrochemical behaviour of CuS/CuO@MWCNT was evaluated using CV and EIS, both of which confirmed enhanced conductivity and electrocatalytic properties of the newly fabricated CuS/CuO@MWCNT/GCE sensor. The CuS/CuO@MWCNT-based electrochemical sensor enabled the detection of Proguanil with a LOD as low as 3.4×10^{-7} M. The CuS/CuO@MWCNT/GCE sensor effectively detected Proguanil in urine samples and maintained good selectivity under conditions with interfering substances, achieving an average accuracy of 96.71% and excellent reproducibility (RSD = 0.45%). The proposed sensor is therefore a promising tool for monitoring Proguanil therapy in urine, contributing to effective malaria treatment.

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Conflict of interest

The authors declare that no known competing financial interests or personal relationships exist that could have influenced the work reported in this paper.

Author contributions

Malachie Monyele Tembo: Conceptualisation; Methodology; Investigation; drafting of the manuscript. John Alake: Conceptualisation, Supervision, Validation and review of the manuscript. Darko Kwabena Adu: Supervision, Validation and review of the manuscript. Blessing Wisdom Ike: Validation. Lungelo Miya: Validation. Priyanka Govender: Validation. Karpoormath: Supervision; funding and resources acquisition; review of the manuscript.

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