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Development of CuO nanoparticles modified electrochemical sensor for detection of salbutamol

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Keywords: CuO nanoparticles, electrochemical biosensor, metal oxide, salbutamol

Abstract

Metal oxide structures are being utilized in an increasing variety of applications. This study used cyclic and differential pulse voltammetry techniques to investigate the possible utilization of copper oxide (CuO) nanoparticles modified carbon paste electrode (CPE) for the redox reactions of salbutamol (SAL). The electrochemical performance of the SAL analyte in a complex matrix environment in Ventolin was evaluated in order to assess the appropriateness of the proposed sensor in a real sample environment. CuO nanoparticles were produced via a straightforward, cost-effective and efficient sol–gel method, and characterization studies of synthesized CuO nanoparticles were performed by scanning electron microscopy, x-ray Diffraction (XRD), and x-ray photoelectron spectroscopy. The synthesized CuO nanoparticles had a spherical shape and particle size was found to be 74 nm. The crystal size of the CuO particles was calculated to be 21.79 nm using the Debye–Scherrer equation. Under optimal conditions, differential pulse voltammetry demonstrated a linear response in the 50 nM to 100 μM range, with a salbutamol detection limit of 50 nM (S/N = 3). The SAL concentration ($R^2 = 0.9971$) was found to have a good correlation coefficient. The reproducibility of the biosensor was investigated and evaluated with a relative standard deviation of 3% (n = 8). The storage stability of CuO modified CPE for two weeks was evaluated based on the response of DP current measured at intervals every two days. According to the measurement results, the modified electrode exhibited good stability and reproducibility while maintaining 80% of its stability. It is also a rapid and dependable sensor candidate with a measurement time of approximately 20 s. The developed electrode has been utilized successfully to determine doping material with improved performance.

1. Introduction

$\beta-2$ agonists are effective bronchodilators for the treatment of diseases such as chronic bronchitis and asthma. Salbutamol sulfate (SBS) [1- (4-hydroxy-) 3-hydroxyphenyl) −2-tetra-butyl amino ethanol sulfate] is a well-known $\beta-2$ agonist, which works by loosening the muscles and airways in the lungs, thereby providing airflow and facilitating breathing. SBS is widely used in oral or inhaled forms to treat asthma, bronchitis, emphysema, and in general, breathing diseases with bronchoconstriction in children and adults [1–3]. It is also used to prevent premature travail in pregnancy [4]. In some cases, the drug may be overdosed, because of the widespread prescription and easy accessibility of drugs, especially containing salbutamol. Nonetheless, unethical sportsmen have abused $\beta-2$ agonists for their doping effects. While these drugs do not provide any advantage to asthmatics compared to non-asthmatic athletes, some non-asthmatic athletes receive a β-2 agonist drug to enhance their

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performance (increase in exercise strength or exercise duration) with strong adrenergic stimulation and a potential anabolic-like effect [5]. The use of high doses of salbutamol in sports is prohibited due to its abuse as a stimulant and anabolic agent. The World Anti Doping Agency (WADA) and the International Olympic Committee (IOC) require each athlete to prove medical necessity and obtain permission to use this class of medicines for medical purposes and are only permitted for asthmatic or exercise-induced asthmatic athletes by inhalers [6, 7]. The WADA and IOC concluded that a salbutamol concentration in the urine of more than 1000 ng ml^{-1} qualified as a positive doping test. Concerns remain with salbutamol abuse, and it is allowed to be used up to the recommended dose of athletes as it is necessary for the treatment and control of asthma, but it has been decided that the process should be followed [6, 8, 9]. Because of salbutamol's role in doping, its determination has become a widely discussed topic. Until now, many analytical methods for the determination of salbutamol have been reported, such as high-performance liquid chromatography [10, 11], immunoassay [12, 13], spectrophotometry [14, 15], capillary electrophoresis, colorimetry [16, 17], electrochemiluminescence [18, 19] and electrochemical determination [20, 21]. However, most of these methods require various derivatization steps as well as more sophisticated procedures such as efficient extraction purification or a combination of different detection methods before the final analysis. These approaches need complicated instrumentation and are time-consuming and quite costly. Additionally, some of these methods might not have adequate detection limits or satisfactory selectivity. Electroanalytical techniques have been demonstrated to be a beneficial alternative to other methods owing to their low cost, simplicity, low background current, broad potential range, high sensitivity and selectivity, accuracy and speed, precision, and fast surface renewal [22–26]. In addition to all these advantages, there is still a need to develop a more efficient method of identifying SAL with high sensitivity and selectivity. The voltammetric technique, which is one of the electrochemical analysis methods, has been considered to be the most widely used approach in many studies due to its high sensitivity, good signal ratio, simplicity, and applicability. Voltammetric sensors, which function as working electrodes, collect data on the redox processes in solution when a potential is applied and are used to create voltammograms that display the redox reactions relevant to the chosen electroactive chemical [27, 28]. Carbon electrodes are widely used because of their high aspect ratio and specific surface area, chemical stability, chemical inertia, low background current, low production cost, simplicity of modification based on the target analyte, and suitability for a variety of sensing and detection applications [29, 30]. Carbon paste electrodes (CPEs) have drawn attention among the carbon electrodes, because of their distinctive chemical stability, simplicity and speed of preparation, low cost, versatility to combine various materials during paste preparation and porous surface CPEs, extremely low background current (compared to graphite electrode), great specific surface area and high aspect ratio. The fact that they can be used in both positive and negative potentials depending on the supporting electrolyte has significantly increased the importance of CPE [31–33]. Additionally, it is simple to modify an electrode to develop a qualitatively new sensor with the desired properties [34]. Despite all these favorable properties, bare CPEs may be susceptible to electrode challenges, electrode contamination, and difficulties with interrupted electron transfer reactions. For these reasons, modification of the electrodes with the usage of chemical substances is of great interest to achieve the desired properties. In recent years, many studies on the modification of electrodes have been published in the literature to enhance the speed, selectivity, and sensitivity of electrochemical determinations [35–37]. Nowadays, nanoparticles, fullerenes, and carbon nanotubes are being utilized in biomedical and sensor applications as a result of notable characteristics of nanomaterials, such as smaller size, and superior optical, magnetic, and mechanical properties. It has been found that using electrodes modified with nanoparticles could catalyze the electrochemical reactions, which lead to higher peak current and less positive oxidation potential [38]. Metal oxide nanoparticles have recently attracted considerable interest among the nanoparticles [32, 39–41]. A p-type semiconductor known as copper oxide (CuO), has remarkable properties such as high conductivity, good stability, efficient electrode in photovoltaics and high catalytic activity. It also has a narrow band gap of 1.2 eV. CuO has found wide-ranging applications in semiconductors, catalysts, gas sensors, field-effect transistors, and biosensors owing to its distinctive characteristics [42–45]. The rapid movement of analytes through electrodes or sensors designed from nanomaterials with a high surface area/volume ratio improves sensing and catalytic response [46]. CuO nanoparticles have been shown to be versatile and efficient in the detection of a variety of analytes, in addition to salbutamol in previous studies on electrochemical sensing. For instance, research has looked at CuO modified electrodes for the detection of organic contaminants, medicinal substances, and heavy metal ions, and the results have been positive. Moreover, studies on several nanomaterials, including metal, carbon nanotube, and graphene oxide, have demonstrated the potential to enhance the sensitivity and selectivity of electrochemical sensors for the detection of salbutamol [44, 47–52]. Alahmadi *et al* synthesized a CuO nanosheet-containing nanocomposite-based electrode material (CuO NSs/CAB) for the detection of hydrazine (HZ) in environmental samples. In the investigation where CuO layers function as active electrocatalysts, a highly sensitive sensor with a low detection limit (0.15 μM) and a broad linear range of 0.5–100 mM was successfully achieved. With a high recovery range of 96.34%–99.64%, great stability, and strong reproducibility, the CuO NSs/CAB electrode that was created

proved to be a selective sensor for detecting HZ in ambient samples [53]. Buledi *et al* used a modified glassy carbon electrode with CuO nanostructures to create an electrochemical sensor for the simultaneous detection of hydroquinone (HQ) and ascorbic acid (AA). In this work, differential pulse voltammetry using CuO/GCE was used to determine HQ and AA simultaneously. They found that the linear response ranges for HQ and AA were 0.0003–0.355 mM and 0.0001–0.30 mM, respectively, for simultaneous determination with variation of analyte concentrations. The simultaneous measurement of HQ and AA in cosmetic samples as well as the independent measurement of AA in fruit juices were both accomplished using CuO/GCE [54]. Toghan *et al* developed a biosensor to detect SAL in PBS. The cyclic voltammetry technique was used to examine the electrochemical behavior of SAL at glassy carbon electrodes. Repetitive cyclic voltammograms of SAL (89.55 μM) in PBS at the established biosensor were used to examine the repeatability of the data; the relative standard deviation (RSD) was 6.2%. According to their research, Developed GO/poly(O-NBA)/GCE exhibits a significant level of selectivity and sensitivity against SAL [55]. Shanbhag *et al* synthesized hafnium-doped tungsten oxide ($Hf.WO_3$) nanorods by hydrothermal route. They detect medication salbutamol (SBM) and paracetamol (PAR) by using a promoted the carbon paste electrode (CPE). Their results show that square wave voltammetry was also employed to estimate 1.28×10^{-9} and 2.42×10^{-9} M detection limits for PAR and SBM, respectively [48]. Nonetheless, to the best of our knowledge, there are only a limited number of studies on synthesis, characterization and electrochemical performance approach used for CuO nanoparticles in comparison to other metal oxides in the transition series such as ZnO [56], TiO_2 [57], SnO_2 [58], and Fe_2O_3 [59], Mn_2O_3 [38]. Some physical and chemical techniques have recently been described for synthesizing CuO nanoparticles, including sonochemical method [60], one-step solid-state reaction method at ambient temperature [61], electrochemical method [62], and sol–gel technique. The sol–gel process enables control over important structural factors like as morphology, particle size, crystallinity, and composition. Modifying these parameters during synthesis provides a substantial benefit in manipulating the chemical and physical properties of the produced nanostructures, providing effective performance [63, 64].

Salbutamol is commonly manufactured and distributed as salbutamol sulfate in pharmaceutical marketing. Salbutamol sulfate is the active pharmaceutical ingredient (API) in several commercially available quick-relief medication formulations. It is available under several brand names, including Ventolin^{TM} [65]. The reason for using ventolin syrup as a source of Salbutamol is its easy availability. A detailed literature review revealed that various publications have been reported on the implementation of nanoparticle-based materials for the electrochemical determination of salbutamol. Luo *et al* improved a modified glassy carbon electrode with $NiFe_2O_4$ nanoparticles to detect salbutamol in pork samples. Their results showed that the sensor modified using $NiFe_2O_4$ nanoparticles had higher sensitivity in detecting salbutamol with a low detection limit, satisfactory linear concentration range, excellent stability and high sensitivity [66]. Goyal *et al* used an indium tin oxide (NGITO) electrode that has been enhanced with nanogold particles to detect salbutamol and they ascertained that the detection limit was 75 ng ml^{-1} [9]. Liu *et al* established an ultrasensitive electrochemical immunosensor for the detection of salbutamol (SAL) using horseradish peroxidase-multiwalled carbon nanotube-antibody (HRP-MWCNTs-Ab) bioconjugates and chitosan-iron oxide-poly(amino-amine) dendrimers-gold nanoparticles (CS-Fe_3O_4-PAMAM-GNPs) based nanocomposites. Their results showed that the SAL detection limit of the study was determined to be 0.06 ng ml^{-1}, and a calibration plot with a linear range of 0.11 ng ml^{-1} to 1061 ng ml^{-1} ($r = 0.9984$) was obtained [67]. As far as we know from the study results in the literature, the use of carbon paste electrodes modified with CuO nanoparticles for the detection of salbutamol in Ventolin syrup has not been reported to date. In addition to the easy availability of Ventolin syrup, other sensor applications have used chemically pure Salbutamol/salbutamol sulfate as the SAL source. In the present study, SAL can be determined in a complex matrix medium (2.4 mg salbutamol sulfate, equivalent to 2 mg salbutamol per 5 ml, plus auxiliary substances: Sodium citrate BP, citric acid monohydrate, hydroxypropyl methylcellulose, 2910 USP Type 4000, sodium benzoate BP, sodium saccharin BP, orange flavor IFF, sodium chloride BP, deionized water). Therefore, it is possible to acquire results that are more similar to the sample that simulates realistic circumstances.

CuO nanoparticles modified CPE for the detection of salbutamol sulfate in Ventolin syrup is the goal of our work. The sol–gel process was employed to produce CuO nanoparticles for use in the CPE modification designed to facilitate SAL detection, and structural characterization investigations were performed on the achieved CuO nanoparticles. Additionally, electrochemical performance studies were evaluated for SAL detection using an electrochemical sensor obtained using CPE modified with CuO nanoparticles.

2. Experimental

2.1. Reagents and equipment

Graphite powder (99.5%), mineral oil, copper acetate dihydrate ($Cu(CH_3COO)_2.H_2O$), and sodium hydroxide (NaOH) (99% are procured from Sigma Aldrich, USA. Monoethanolamine (C_2H_7NO) (MEA) (99.5%) and 2-propanol ($CH_3CH(OH)CH_3$) are from Merck. All chemicals are of the reagent grade and utilized without further purification. Ultrapure water from the Purelab Option-Q system was used in the experiments.

2.2. Preparation of sol–gel derived CuO nanoparticles, bare CPE and CuO nanoparticles modified CPE

CuO nanoparticles were synthesized by using copper acetate dihydrate, isopropyl alcohol, and monoethanolamine chemicals supplied from Merck. First, copper acetate was dissolved in isopropyl alcohol. Following that, the copper acetate solution was mixed with a MEA stabilizer. The final product is CuO nanoparticles produced by drying (overnight at 80 °C) and calcining the resulting gel (at 500 °C for 1 h), respectively. In our previous study, the procedure for the preparation of CuO nanoparticles with different particle sizes has been described in more detail [68]. Synthesized CuO nanoparticles composed of the monoclinic phase structure of CuO (JCPDS PDF, no. 45–0937) with high crystalline degree [69]. In our study, CuO modified carbon paste electrodes were prepared by CuO nanoparticles with an average size of 74 nm.

The standard approach to making bare carbon paste (CP) electrodes involves combining graphite powder (85 wt%) and mineral oil (15 wt%) in an agate mortar for 20 min. Next, the paste is placed inside a glass rod which measures 10 cm in length and 1 centimeter in diameter. A blend of varied weights of graphite powder and CuO nanoparticles, depending on the proportion of CuO nanoparticles (2, 5, 10, 15, and 20 wt%), is mixed with 0.15 g of mineral oil to develop the modified electrodes. The mixture is then mixed in a mortar for 20 min to achieve a homogenous mixture. The stacking procedure into the glass rod is the same for bare CPE and CuO modified CPE electrodes. The ground copper wire is used to create electrical connections. Both electrode surfaces are carefully polished and smoothed before each measurement.

2.3. Characterization of CuO nanoparticles and electrochemical measurements

The Rigaku, D/Max-2200/PC diffractometer was utilized to examine the phase structure of the synthesized CuO nanoparticles. CuKα radiation was applied in the 2 theta angular range of 20°–90°, with a scanning rate of 4°/min. X-ray Photoelectron Spectroscopy (XPS) is an effective method for determining phase purity, chemical composition and electron valence states in a sample. XPS surface analysis was performed using a Thermo-Scientific XPS instrument with a beam size of 400 nm diameter (x-ray source: monochromatic Al Kα (λ_n = 1486.69 eV). The size distribution of CuO nanoparticles produced from sol–gel was ascertained via the dynamic light scattering (DLS) method with a Malvern ZetaSizer Nano ZS90. The LEO EVO-40xVP scanning electron microscope was used to perform morphological analysis of the produced CuO nanoparticles.

Electrochemical measurements were obtained with Metroohm Autolab Type 3 potentiostat/galvanostat device with a three-electrode system (working electrode: self-designed carbon paste electrode 'CPE', reference electrode: Ag / AgCl and counter electrode: Pt). For measuring pH, a pH meter (WTW, Germany) was utilized. All of the experiments were performed at ambient conditions (25 ± 1 °C). Anodic stripping voltammetry (ASV) measurement experiments were conducted by the following step: analytical species are reduced (electrodeposition) at the working electrode for 240 sec at −300 mV and then oxidized. The potential range was determined as ± 1 V at a scan rate of 40 mV s^{-1}. The cyclic voltammetry (CV) study was carried out in a 0.1 M pH 7.5 PO_4^{2-} buffer solution including 0.1 M (KNO_3) and 8.5 × 10^{-5} M Ventolin syrup. Differential pulse anodic stripping voltammetry (DPASV) measurements were made by using different accumulation times and potential values in a buffer solution containing 0.1 M pH 7.5 PO_4^{2-} 0.1 M (KNO_3).

3. Result and discussion

3.1. Characterization of sol–gel derived CuO nanoparticles

The XRD pattern of the synthesized CuO nanoparticles is displayed in figure 1. The XRD patterns clearly show that the synthesized CuO nanoparticles are composed of a high degree of crystallinity in a monoclinic phase structure of CuO (JCPDS PDF, no. 45–0937). The crystallite size value of the synthesized CuO nanoparticles was estimated using the Debye–Scherrer equation, and the result was found to be 21.79 nm [69].

SEM images and particle size histogram of CuO nanoparticles are displayed in figures 2(a) and (b), respectively. As seen in figure 2(a), the produced CuO nanoparticles are seen to be round and spherical. Figure 2(b) depicts that the average particle size of CuO nanoparticles is around 74 nm. The homogeneous particle distribution observed in the SEM image is further supported by the particle size histogram, which shows that the synthesized particles have a very narrow size dispersion.

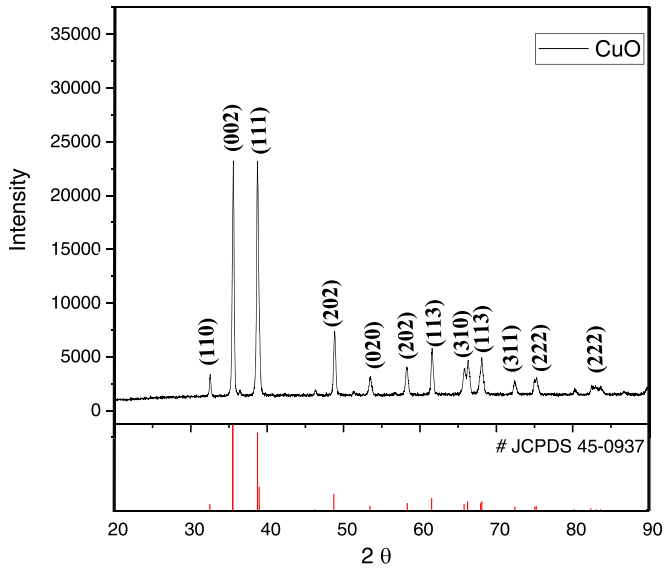


Figure 1. XRD pattern of synthesized sol–gel derived CuO nanoparticles.

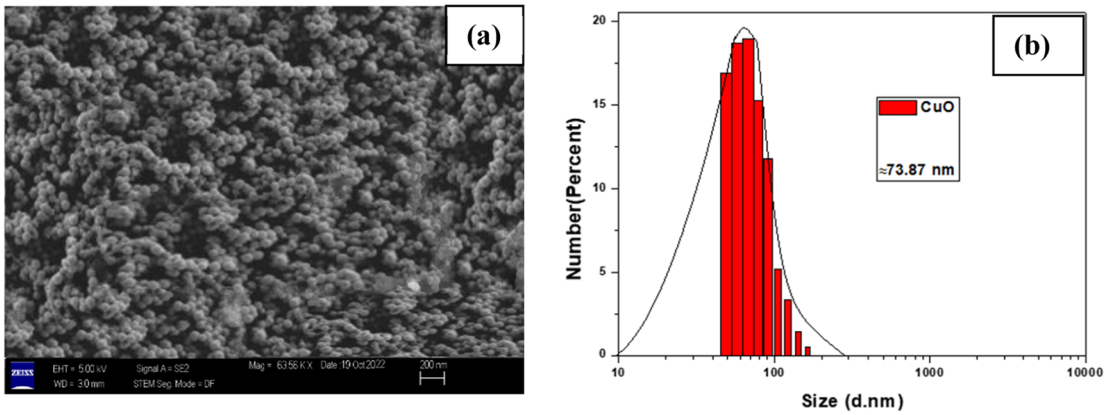


Figure 2. (a) SEM images and (b) particle size distribution of the synthesized CuO nanoparticles.

XPS analysis is used to determine the different oxidative states of elements as well as to investigate the chemical constituents present on the nanostructural surface and their binding energies. Figure 3 shows the chemical states of CuO nanoparticles by XPS analysis. Figure 3(a) shows the full spectrum of CuO nanoparticles including Cu2p and O1s spectra. As a result of broad spectrum analysis, it was determined that only Cu, O and C elements were present in the sample. The presence of element C was attributed to incidental carbon formed by exposure of the sample to air. A characteristic spin–orbit splitting peak attributed to the Cu^{2+} ion is found at around 20 eV. The Cu $2p_{3/2}$ and Cu $2p_{1/2}$ peaks are located at about 934 eV and 954 eV, respectively, indicating the presence of Cu ions in the synthesized nanoparticles. Furthermore, the presence of Cu^{2+} and the $3d^9$ electronic configuration of the partially filled d-block is indicated by two short peaks observed at approximately 945 eV and 960 eV (figure 3(b)).The O(1 s) core level spectrum of CuO is presented in figure 3(c). Both peaks are located around 530.6 and 532.24 eV and represent the O(1 s) core level of CuO. Furthermore, the peak at 532.15 eV points to hydroxyl groups or chemically absorbed water molecules on the surface of CuO, while the other peak at 530.6 eV is due to the O^{2-} ion. The binding energy values of Cu and O are in agreement with the studies in the literature [70–74].

3.2. Electrochemical characterization of bare and modified electrodes

To improve the performance of the designed sensor and increase its sensitivity and selectivity, optimization tests should be carried out utilizing the modified electrochemical sensor. In this study, different influencing factors such as the amount of nanoparticles, accumulation potential and time, support electrolyte effect and pH value, which affect the performance of the sensor material to be designed, were examined in detail. Firstly, an

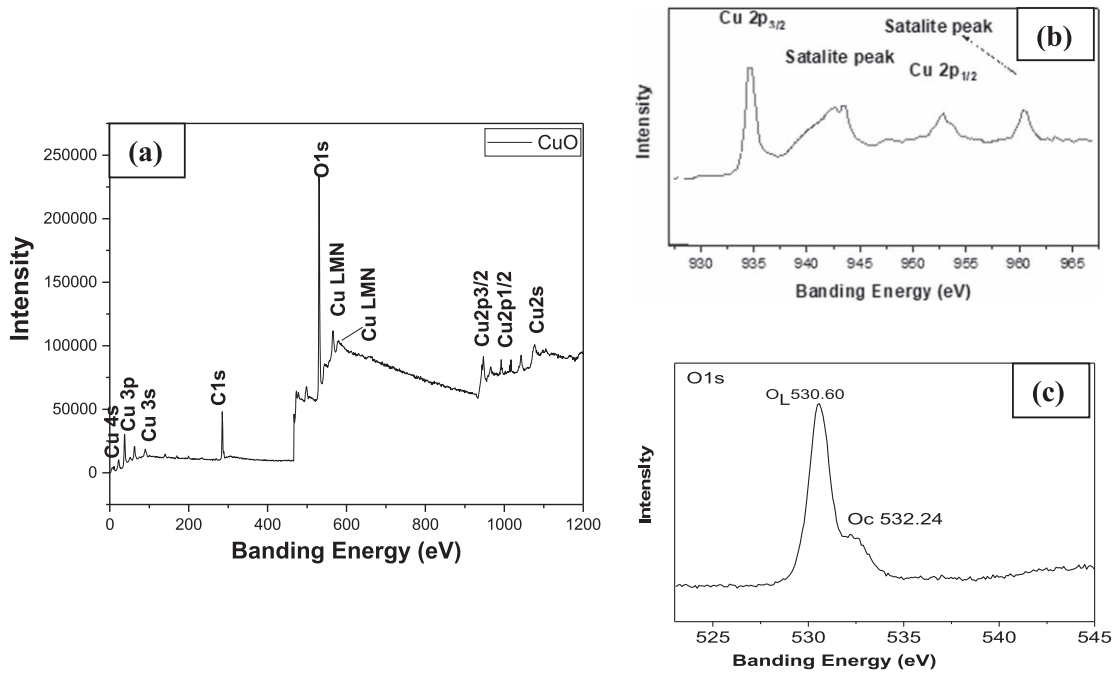


Figure 3. (a) X-ray photoelectron spectroscopy of the CuO nanoparticles (b) Core level spectra of copper, (c) Core level spectra of oxygen.

appropriate deposition was carried out using a bare and CuO nanoparticle modified CPE electrode, followed by the oxidation behavior of the SAL was initially investigated using cyclic voltammograms (CV). When it comes to conducting electrochemical experiments, cyclic voltammetry is one of the most beneficial techniques because it is straightforward to use and yields rich information about the electrochemical reactions that are defined by the relationship between the potential and the current. The cyclic voltammogram of a reversible process is characterized by the following parameter values:

$$\Delta E_P = (E_{pc} - E_{pa})$$

where ΔE_p is the difference in peak potentials, and E_{pa} is the anodic peak potential, E_{pc} is the cathodic peak potential [75].

Figure 4 presents the CV curves of 8.5×10^{-5} M SAL in 0.1 M pH 7.5 PO_4^{2-} buffer solution including 0.1 M (KNO_3) acquired in the potential range of −1.0 to 1.0 V at a scan rate of 40 mVs^{-1}. At the CuO nanoparticle modified CPE, one anodic peak is observed at about 0.64 V versus Ag/AgCl observed in the presence of SAL. In comparison with bare CPE, the oxidative peak current at the modified CPE was larger.

It can be suggested that the modified CPE offers an appropriate environment for SAL to transfer electrons and has a significant electrocatalytic contribution to SAL oxidation. The outstanding electrocatalytic activity of the CuO nanoparticle modified CPE may be attributed to the characteristic properties of CuO nanoparticles, such as significant specific surface area, remarkable electronic properties, excellent conductivity and stability [38–40, 47, 48]. The modified electrode showed no electrochemical response in the absence of SAL, indicating that the peak at 0.64 V was due to the SAL oxidation. All of the findings demonstrated that modifying CuO nanoparticles can significantly promote the surface activity of existing electrodes.

3.3. Optimization of parameters for salbutamol determination

3.3.1. Effect of composition of CuO modified CPE

The increased CuO nanoparticle content in the modified electrodes has a considerable impact sensitivity of electrochemical sensors. Therefore, the composition of the CuO-modified CPE must be modified to improve sensor sensitivity by altering the quantity of incorporated CuO nanoparticles. Differential pulse (DP) measurements were used to examine the performance of modified electrodes produced with different concentrations (2 to 20 wt%) of CuO nanoparticles. DP measurements were performed in 0.1 M pH 7.5 PO_4^{2-} buffer solution including 0.1 M (KNO_3) in the presence of 5×10^{-5} M Ventolin by modified CPE. Accumulation was performed at − 0.3 V for 240 s under continuous stirring and then kept for 15 s. Data was obtained at a scan rate of 40 mVs^{-1} in the potential range between 0.0 V and 0.9 V^{-1}. As shown in figure 5, the available responses increased until the 10% wt amount. It can be seen that the current response decreases with

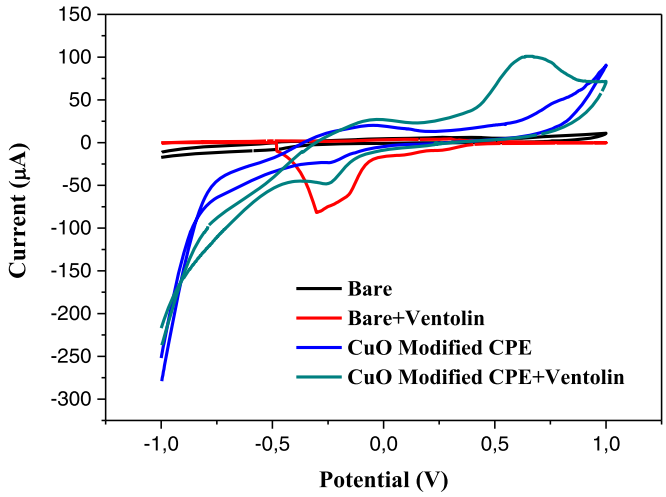


Figure 4. CV curves at a bare CPE and 10 wt% CuO nanoparticles modified CPE in the absence and presence of 8.5×10^{-5} M SAL 0.1 M pH 7.5 PO_4^{2-} buffer solution including 0.1 M (KNO_3).

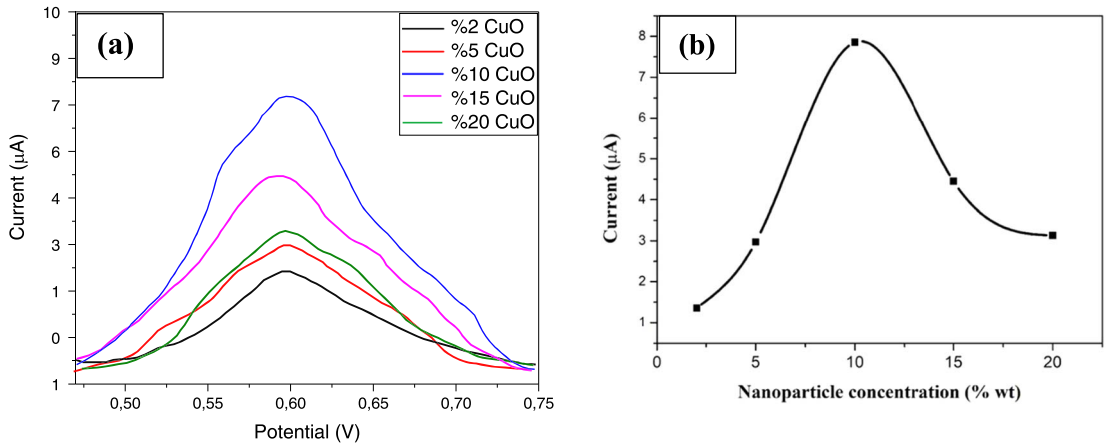


Figure 5. (a) DP response, (b) Current values; obtained from differential pulse measurement using different amounts (2 to 20 wt%) of CuO modified CPE in 0.1 M pH 7.5 PO_4^{2-} buffer solution including 0.1 M (KNO_3) in the presence of 5×10^{-5} M Ventolin.

the CuO nanoparticle incorporation in the modified CPE electrode being more than 10%. For this reason, a higher particle content in the modified CPE electrode results in a reduced signal acquisition. The amount of nanoparticles per unit volume increases with an increase in particle additive content, which results in a decrease in the contact surface area with the electrolyte and lower accessible detection zones. Furthermore, by preventing easy electron transfer in the presence of a greater amount of catalyst, the loss in catalytic characteristics and consequently conductivity causes the peak current to decrease. Also, by preventing facile electron transfer in the presence of a greater number of nanoparticles, the decreased catalytic characteristics and consequently conductivity are the cause of the peak current decrease [76, 77]. Based on the findings, the amount of CuO nanoparticles used to modify the CPE electrode in the research was determined as 10% by weight.

3.3.2. Accumulation time and potential effect

The impact of accumulation potential on the value of peak current was studied by differential pulse method at an accumulation time of 240 s in 0.1 M KNO_3 solution containing 5×10^{-5} M Ventolin. The measurement was performed at a scanning range from 0.00 V to 0.9 V and a scan rate of 40 mV s^{-1}.

As the accumulated potential rises from − 0.5 V to − 0.3 V, the peak current value is observed to increase first, and then abruptly decrease when the accumulated potential shifts more positively in the direction of the peak (figure 6(a)). Thus, the optimum value of the accumulating potential was found to be 0.3 V. Investigations were conducted on the effect of accumulation time on the SAL oxidation peak current at −0.3 V, which was measured under similar conditions. It was found that there was a gradual increment in SAL peak current with increasing accumulation time. As can be demonstrated in figure 6(b), peak currents showed a significant

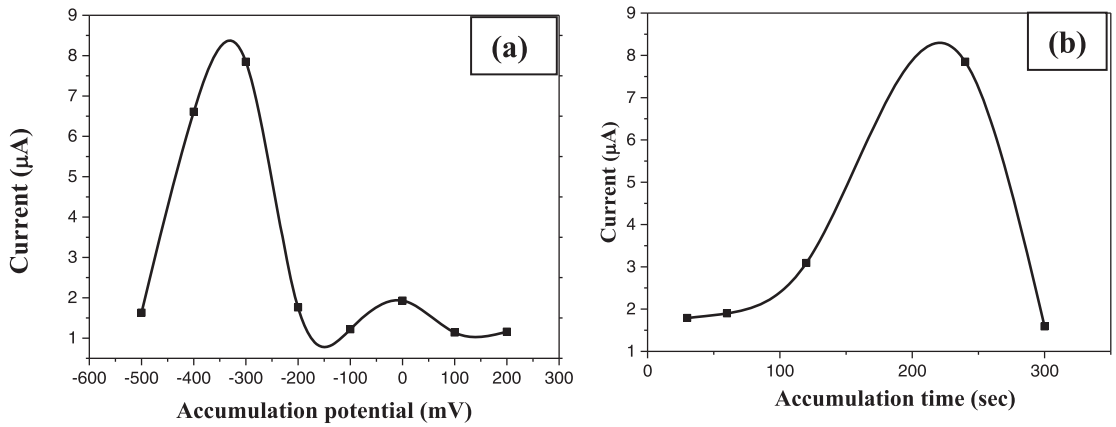


Figure 6. (a). The impact of accumulation potential and (b) Accumulating time on the peak current of 5×10^{-5} M SAL in 0.1 M pH 7.5 PO_4^{2-} buffer solution including 0.1 M (KNO_3) on the 10 wt% CuO nanoparticles modified CPE at a scan rate of 40 mV s^{-1}.

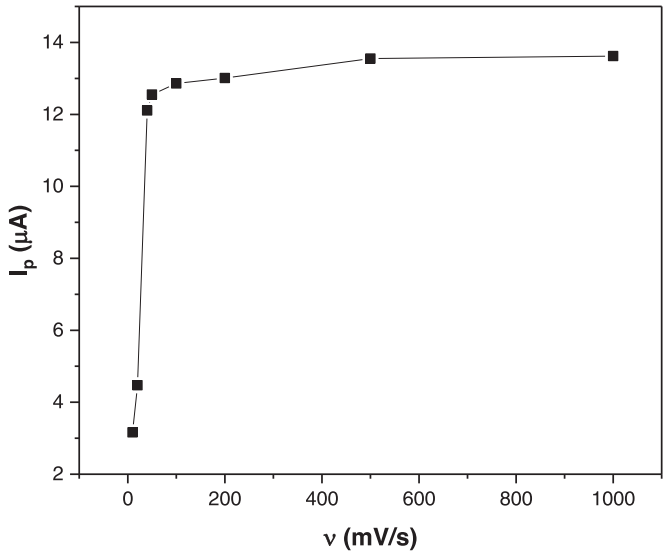


Figure 7. Current variations at different scan speeds for CPE modified with 10 wt% CuO nanoparticles.

decrease beyond 240 s. In this regard, 240 s was selected as the optimum accumulation time taking into account the sensitivity as well as the analyzing speed.

3.3.3. Scan rate effect

The impact of varying scanning speeds on the peak current for the created sensors was ascertained by evaluating the efficacy of 1.0×10^{-5} M salbutamol through voltammetric measurement. A substantial relationship between scan rate and peak current was found in experiments utilizing a broad range of scan rates, from 10 to 1000 mV s^{-1} (figure 7).

The increase in peak current at higher scanning speeds is attributed to the acceleration of the electrochemical behavior of salbutamol and an improvement in the sensitivity of the sensor. On the other hand, a decrease in peak increases in current was noted at very high scan rates, which may be connected to diffusion control at the electrode surface. Finally, the findings demonstrated that the best sensitivity was achieved at a scan rate of 40 mV s^{-1}.

3.3.4. Effect of support electrolite and pH

The performance of electrochemical cells depends on factors such as ion conductivity and stability of the electrolyte. Low oxygen ion mobility at the electrode/electrolyte interface and the rate of interfacial redox reactions limit the performance of electrochemical sensors. Therefore, it is important to use electrolytes with

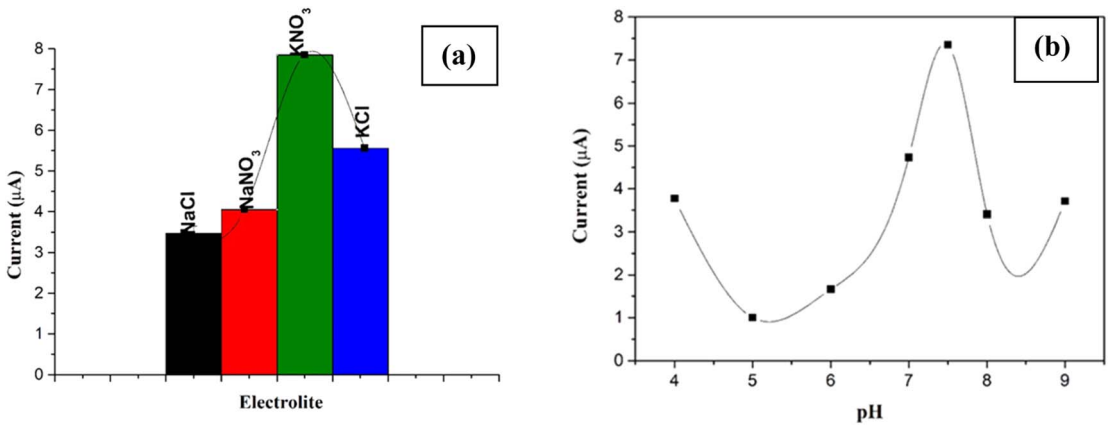


Figure 8. Effects of (a) supporting electrolyte solution type, and (b) solution pH on the values of the DP peak current (The concentration of SAL solution is 5×10^{-5} M).

Table 1. Detailed data of DP values of supporting electrolyte solution.

Supporting electrolyte solution	Peak current i_p (μA)	Peak potential E_p (mV)
NaCl	3.47	0.61
$NaNO_3$	4.05	0.60
KCl	5.55	0.59
KNO_3	7.85	0.55

high oxygen ion conductivity. When working with transition metal oxides, buffer solutions are often preferred over standard electrolytes. Buffer solutions provide for reliable outcomes at varying pH levels by maintaining a steady pH. Furthermore, buffer solutions prevent undesirable reactions by reducing the influence of factors such as acidity or alkalinity in the environment and preserving the properties of transition metal oxides. Therefore, the use of buffer solutions is important to obtain more reliable and reproducible results when working with transition metal oxides [78, 79].

The effect of supporting electrolytes was evaluated by performing the experiments at different supporting electrolytes such as NaCl, $NaNO_3$, KCl, and KNO_3 solution (concentration 0.1 M) (table 1). Measurements were tested by the DP method by using 10% wt CuO nanoparticle modified CPE. The oxidation peak current of SAL reached a maximum in the KNO_3 solution, shown in table 1. The SAL's oxidation peak was examined in 0.1 M KNO_3 supporting electrolyte with a pH range of 4 to 9 (figure 8(b)). It is seen that the current responses decrease with increasing pH at the beginning. The lowest current response was recorded at pH 5.0 and increased towards the neutral environment. The highest current value was obtained at pH 7.5 [80, 81].

Therefore, pH 7.5 0.1 M KNO_3 solution was used in the present work. The oxidative potential shifts negatively as the pH increases, indicating that it is accompanied by proton transfer to the reaction. A reason for the decrease in peak height from pH 4 to pH 5; at pH 4, is the presence of hydrous Cu (II) oxide and hydroxide, at which point the SAL current response reads as about 0.8 V. Additionally, the peak response of about 0.6 V in the case of a pH increase from pH 5 to pH 7.5 can be explained by the existence in the Cu (II) O form. The decrease after pH 7.5 was due to the formation of CuOH, and the SAL response was taken at 0.4 V (figure 8(b)) [82, 83].

3.3.5. Calibration curve and limit of detection

Under the optimized conditions, SAL was quantitatively analyzed by differential pulse measurement (DP). Figure 9 depicts the relation between SAL concentration and anodic peak current across the range of 0.05 to 500 μM. SAL concentration has been demonstrated to increase the oxidation peak current. The calibration graph was obtained for CPE modified with 10 wt% CuO nanoparticles under measurement conditions with a scan rate of 40 mV s^{-1} at different SAL concentrations in 0.1 M pH 7.5 PBS containing 0.1 M KNO_3. Additionally. a comparable calibration plot for the quantification of SAL is shown in the inset.

A correlation coefficient (R^2) of 0.9971 was reported for the calibration range of SAL concentration, which was 50 nM to 100 μM. To calculate the detection limit (LOD), the formula 3 S m^{-1} was employed, where S is the standard deviation of the peak current of the lowest concentration over the relevant linearity range (3 runs), and m value is the slope of the calibration plot. LOD was found to be 50 nmol.L^{-1}.When compared to the research in

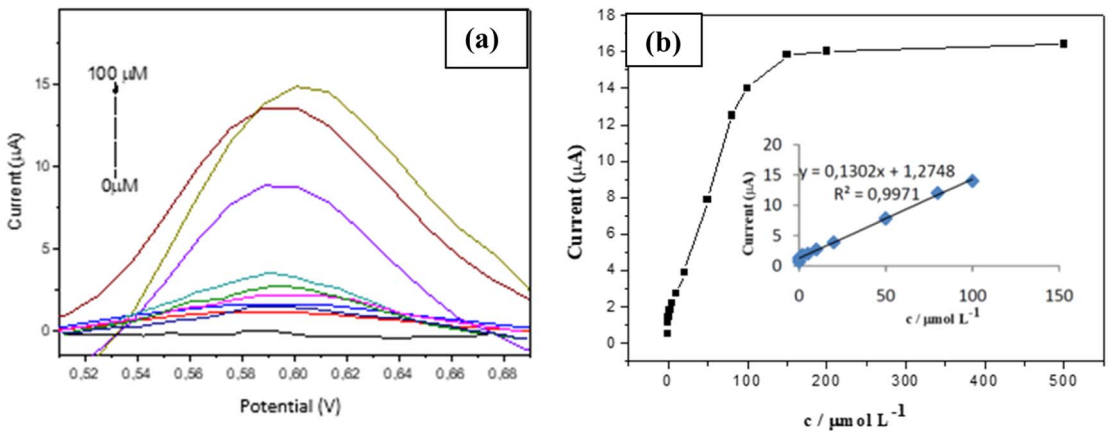


Figure 9. (a). DP responses of CuO nanoparticles modified CPE to different, (b) calibration plot used to quantify SAL.

the literature, the developed sensor was determined to have better qualities than the electrodes that were described, based on the findings that were obtained. [9, 84–86]. It was established that our results agreed with the findings of the study conducted by Li *et al* [87] (table 2). The detection limit of CuO NP-modified CPE is substantially lower than that of other studies when compared with the references listed in the given table. A wider linear measurement range indicates that the electrode is performing better and transferring energy more efficiently according to studies in the literature [9, 76, 84, 85]. The high surface area and excellent conductivity of nanoparticle-modified carbon paste electrodes make them a viable option for reproducible measurements during electrochemical reactions. This electrode has superior properties such as high reproducibility and fast measurement time, while providing a wider linear measurement range. This study shows that there is a strong linear correlation between SAL concentration and the modified carbon paste electrode, and CPE modified with CuO nanoparticles is a fast, sensitive and reliable sensor. These findings are also consistent with previous SAL studies with different particles, indicating that this study is an important contribution to the literature. Moreover, the CPE that has been modified with CuO nanoparticles is an extremely fast and reliable sensor, with a measurement time of approximately 20 s. These data indicate a good linear correlation between the modified carbon paste electrode and SAL concentration.

It is clear from the results of this investigation that the developed approach produces relatively higher sensitivity or a wider linear range than previous SAL electrochemical sensors that have been published in the literature. A summary of the performance of the developed approach in comparison to published research on the electrochemical detection of salbutamol sulfate is shown in table 2. The chart makes it abundantly evident that the current method, which is very simple and inexpensive, does not require a laborious preparation process, and performs better in terms of both the detection limit and linear range than the majority of previously described methods

3.3.6. Reproducibility, stability and selectivity of the CuO nanoparticle modified CPE

The reproducibility, stability and selectivity of the CPE electrode were evaluated by DP under the optimum conditions. The reproducibility of the sensors was carried out with 8 parallel sensors by comparing the oxidation peak current of 5×10^{-5} M SAL under identical conditions. The repeatability of the biosensor was examined and the relative standard deviation values were calculated as 3%. ($n = 8$). The storage stability of the CuO-modified CPE is monitored by evaluating the response of the DP current during the course of two weeks, every other day. When the electrode was not in use, it was stored in a dry environment. It can retain 80% of the initial signal after 2 weeks. The experimental results indicate that the modified electrode has good stability and reproducibility.

As a final step in confirming the selectivity of the CuO modified CPE sensor, various possible interferents were examined to define their impact on the determination of SAL. To evaluate the interferences of these foreign species dopamine, starch, ascorbic acid, epinefrine, glucose, Na^{+}, and Fe^{3+} studies were performed. Figure 10 shows the test results suggest that 8.5×10^{-5} M concentration of this interference, except for dopamine, have no observable impact on SAL signals with deflections below 10 wt%. The obtained data showed that this method has good selectivity for SAL determination.

Table 3 provides a brief description of the parametric values used in the present research and the optimum results obtained. This table provides a quick overview of how the analysis was performed, providing critical information on the methodology and experimental design of the study. Accordingly, table 3 summarizes the

Table 2. Comparison of various SAL determination techniques.

Method/electrode	Method	Linear range ($\times 10^{-6}$ molL^{-1})	Detection limit ($\times 10^{-6}$ molL^{-1})	Reproductibility (RSD%)	References
Nano/Au modified ITO	square wave voltammetry	0.2–8.36	0.31	2.02	[9]
GP-PEDOT:PSS/SPCE	inkjet-printing technique	5–550	1.25	7.5	[84]
G-Au/GCE	differential pulse voltammetry	0.05–200	5.91	3.1	[85]
SMWCNTa -NF	differential pulse voltammetry	0.10–0.30	0.10	5.3	[86]
Nano-Au-L/cys-MWNTs NF/GCE	differential pulse voltammetry	0.09–7.00	0.05	4.3	[87]
CuO nanoparticles modified CPE	Anodic stripping voltammetry	0.05–100	0.05	3	Present work

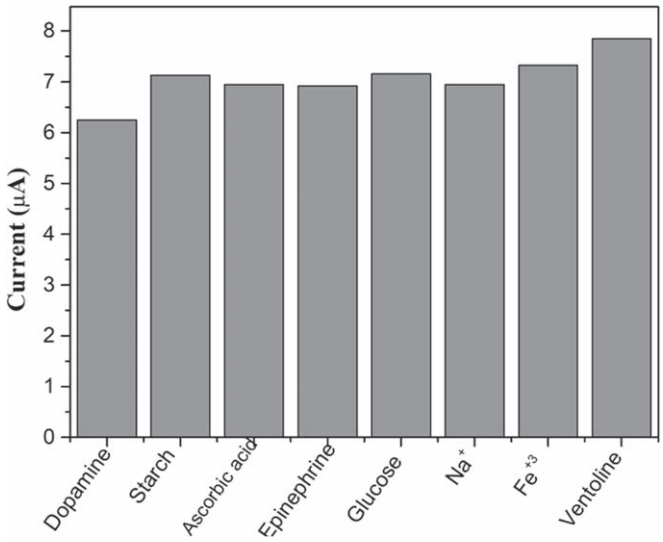


Figure 10. DP responses of CPE modified with CuO nanoparticles toward 8.5×10^{-5} M SAL 0.1 M pH 7.5 PO_4^{2-} buffer solution including 0.1 M KNO_3 and other interference compounds.

Table 3. Experimental parameters and brief summary of our study.

Related parameter	Investigated values
CuO nanoparticles (wt%)	2, 5, 10, 15, 20
Accumulation time (sec)	30, 60, 120, 240, 300
Accumulation potential (mV)	−500–200 (with 100 mV interval)
Scan rate (mV/s)	10, 20 ,50, 100, 200, 500, 1000
Support electrolite type	NaCl, $NaNO_3$, KCl and KNO_3
pH	4, 5, 6, 7, 7.5, 8, 9

Optimum conditions: %10 wt% CuO, −300 mV, 240 sec, 40 mV s^{-1}, 0.1 M KNO_3 and pH 7.5

Annotation: Differential pulse voltammetry demonsrated a linear response in the 50 nM to 100 μM range, with a salbutamol detection limit of 50 nM (S/N = 3). The SAL concentration (R^2= 0.9971) was found to have a good correlation coefficient. The reproducibility of the biosensor was investigated and evaluated with a relative standard deviation of 3% (n = 8), and the storage stability of CuO-modified CPE for two weeks was evaluated by the response of DP current every other day, the results show that the modified electrode retains 80% and exhibited strong stability and reproducibility.

findings of the study and gives a brief evaluation of the main results of our study and its contribution to the literature.

4. Conclusion

CuO modified CPEs were designed by a simple mixing method as a novel sensing platform for the electrochemical determination of SAL. The effect of various CuO nanoparticle incorporation in a modified CPE electrode was investigated using the effective current response, and a CPE design was developed using a 10% by weight nanoparticle addition. According to the CuO nanoparticle modified CPE indicated good selectivity and reproducibility. Furthermore, the modified electrode exhibited excellent stability for at least 14 days. Modified CPE was shown to exhibit better electrocatalytic activity in detecting SAL than bare CPE. Under the optimized experimental conditions, the linear range was 0.05–100 μM for SAL, which could be applicable for real sample determination. In terms of repeatability and reproducibility values, nanoparticle enhanced carbon paste electrodes are a better option than other electrode types due to their high surface area and superior conductivity. The developed sensor functions better and transmits energy more efficiently, as seen by the linear measurement range results, and the detection limit of CuO NP-modified CPE in the present research is lower than in earlier

investigations. Furthermore, with a measurement duration of roughly 20 s, the CuO nanoparticle-modified CPE sensor is incredibly rapid and reliable. As a result of our study, it is demonstrated that the CuO nanoparticle modified CPE may be used as an electroanalytical sensor for detecting SAL even under ambient conditions containing starch, ascorbic acid, adrenaline, and glucose.

Data availability statement

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

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