

Liquid-Phase Electrochemical Determination of Methyl Ethyl Ketone Using CuO/HAp-like Modified PGE

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Abstract: Monitoring of Methyl Ethyl Ketone (MEK) is essential for industrial safety and biomedical diagnostics, serving as a reliable biomarker for metabolic disorders. Conventional detection techniques require bulky, expensive instrumentation, limiting portable use. In this study, a low-cost and disposable electrochemical sensor was fabricated using a Pencil Graphite Electrode (PGE) modified with a porous Hydroxyapatite-like (HAp-like) interlayer and Copper Oxide (CuO). The HAp-like scaffold minimized the copper agglomeration and increased the electroactive surface area, with SEM and EDX confirming homogeneous CuO distribution. Toward MEK, the sensor exhibited a “signal-off” response, systematically suppressing the anodic peak current. This is consistent with a steric-hindrance mechanism where analyte adsorption blocks interfacial electron transfer. Evaluated via square-wave voltammetry (SWV) in phosphate buffer (PBS, pH 10.0), the sensor demonstrated dual linear ranges (0.1-5.0 mM and 5.0-50 mM) with a 1.04 mM limit of detection. The sensor demonstrated consistent reproducibility with an overall relative standard deviation (RSD) of 2.83% (n=15) and an inter-day RSD of 1.94%, while retaining 107.2% of its initial response after a 14-day storage period. Validated in PBS pH 10.0, this CuO/HAp-like/PGE platform is presented as a proof-of-concept for liquid-phase MEK detection, establishing a foundation for future monitoring under simulated physiological conditions.

Keywords: copper oxide nanoparticles; electrochemical sensor; hydroxyapatite-like; methyl ethyl ketone; pencil graphite electrode; “signal-off” mechanism.

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1. Introduction

Monitoring of volatile organic compounds (VOCs) is a priority across industrial safety, environmental protection, and non-invasive healthcare monitoring [1,2]. Among VOCs, Methyl Ethyl Ketone (MEK) is of particular interest due to its dual nature as both a hazardous industrial solvent and a metabolic by-product. Industrial settings require exposure limits, as MEK vapor exposure can cause severe respiratory and neurological issues [3]. In the biomedical domain, low concentrations of MEK in exhaled breath have been investigated as

candidate biomarkers for specific metabolic deviations and malignancies [4]. Recent work continues to develop MEK/2-butanone detection platforms, primarily gas-phase chemiresistive and optical devices [5,6]. There is therefore a need for reliable MEK sensors that support workplace safety while also advancing point-of-care diagnostic technologies.

Current detection methods, based mainly on Gas Chromatography-Mass Spectrometry (GC-MS), involve high cost, bulky instrumentation, and complex operational requirements, which limit their use for rapid, on-site screening. Electrochemical sensors provide an alternative, offering portability, sensitivity, and rapid analysis [7] and have been reviewed recently for breath-based and chronic-disease monitoring [8]. Non-enzymatic sensors based on transition metal oxides are of particular interest. Copper oxide (CuO), owing to its low toxicity and electrocatalytic activity towards organic oxidation in alkaline media, is a widely studied candidate for such applications [9–11]. However, the practical utility of metal oxide-based sensors is often limited by particle agglomeration and reduced effective surface area, which lower sensitivity and signal stability [12]. Engineering the electrode interface to use the catalytic surface of CuO efficiently is therefore an important step in sensor design.

Direct gas-phase detection of MEK is also challenging. Chemiresistive gas sensors often require high operating temperatures and are subject to interference caused by the high humidity (>90% RH) of breath [12,13]. Moreover, collecting breath samples in gas bags or canisters is prone to analyte loss from surface adsorption and leakage over time, particularly for polar ketones like MEK [14,15]. Capturing volatile biomarkers in an aqueous medium (e.g., via exhaled breath condensate) addresses these issues: given the high water solubility of MEK, this 'gas-to-liquid' extraction not only eliminates humidity interference but also minimizes volatilization losses by stabilizing the analyte in the liquid phase [16,17]. VOCs partitioned into aqueous breath condensate are generally present at low (sub-millimolar to millimolar) aqueous concentrations [18,19], a range compatible with room-temperature electrochemical platforms.

Despite this potential, a disposable, liquid-phase electrochemical interface for MEK detection has not been reported. Specifically, the use of a biocompatible Hydroxyapatite-like (HAp-like) scaffold to disperse catalytic copper sites on a disposable pencil graphite surface has not been investigated for this analyte. Consequently, a low-cost and disposable sensing platform based on Pencil Graphite Electrodes (PGEs) modified with a Hydroxyapatite-like interlayer and Copper Oxide Nanoparticles (CuONPs) is proposed in this study. While PGEs provide an economical and accessible substrate, and the HAp-like interlayer adds a dispersing function to the sensor architecture, the porous HAp-like scaffold limits CuONP agglomeration and increases the electroactive surface area [20,21]. By optimizing electrodeposition parameters, the sensor's ability to detect MEK in a standard supporting electrolyte is demonstrated, establishing a proof of concept for liquid-phase MEK detection and potential extension to industrial and biomedical applications.

2. Materials and Methods

The methodology followed a five-stage protocol: (i) preparation of reagents and supporting electrolytes; (ii) electrodeposition of the sensing interface, with an optimization study of the modification parameters (potential and time) based on electrochemical profiling, morphological analysis, and calculation of surface coverage; (iii) structural characterization of the optimized CuO/HAp-like/PGE interface by SEM and EDX; (iv) analytical evaluation of MEK detection, sensor reproducibility, and stability; and (v) mechanistic validation via *ex-situ*

Gas Chromatography-Mass Spectrometry (GC-MS). The specific instrumentation, fabrication steps, and data analysis procedures utilized throughout these stages are detailed in the subsequent sections.

2.1. Reagents and solutions.

Copper (II) sulfate pentahydrate ($\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$, Merck, Darmstadt, Germany, $\geq 99\%$), potassium sulfate (K_2SO_4 , Tekkim, Bursa, Türkiye), sulfuric acid (H_2SO_4 , Sigma-Aldrich, St. Louis, MO, USA, $\geq 98\%$), sodium hydroxide (NaOH , Sigma-Aldrich, St. Louis, MO, USA, $\geq 98\%$), calcium chloride (CaCl_2 , Sigma-Aldrich, St. Louis, MO, USA, $\geq 97\%$), ammonium dihydrogen phosphate ($\text{NH}_4\text{H}_2\text{PO}_4$, Merck, Darmstadt, Germany, $\geq 98\%$), ethanol absolute ($\text{C}_2\text{H}_5\text{OH}$, Merck, Darmstadt, Germany, $\geq 99\%$) and methyl ethyl ketone (MEK, $\text{C}_4\text{H}_8\text{O}$, Merck, Darmstadt, Germany, analytical grade) were used as received without further purification. All aqueous solutions were prepared using distilled water. All prepared stock solutions were stored at 4°C under light-protected conditions to maintain chemical stability until analysis.

2.2. Instrumentation.

Electrochemical experiments were performed using a potentiostat/galvanostat (PalmSens4, PalmSens, The Netherlands) controlled with PSTrace 5.6 software. A three-electrode configuration was employed with a pencil graphite electrode (PGE, Tombow 0.5 mm, Japan) as the working electrode, a platinum wire as the counter electrode, and Ag/AgCl (3 M KCl) as the reference electrode. Morphological and elemental characterization was carried out by scanning electron microscopy (SEM, Tescan GAIA3, Czech Republic) coupled with energy-dispersive X-ray spectroscopy (EDX, Oxford X-Max 150 EDS, UK). Reference analyses for validation were performed using gas chromatography–mass spectrometry (GC-MS, Agilent Technologies 6890N GC/5973 MS, USA).

2.3. Preparation of the modified electrode.

Commercial 0.5 mm 2B pencil graphite leads (Tombow, Japan) were used as disposable working electrodes. To ensure consistent exposure, approximately 20 mm of the electrode tip was immersed into the corresponding solutions during both modification and measurement steps. The fabrication process involved several sequential stages [22]. Initially, surface impurities were removed from the bare PGEs by electrochemical pretreatment in 0.1 M acetate buffer (pH 5.0) at +1.4 V for 30 s [23].

A calcium phosphate (HAp-like) interlayer was formed by a dip-coating process. This involved sequential immersion in 0.12 M CaCl_2 for 5 min, followed by 0.06 M $\text{NH}_4\text{H}_2\text{PO}_4$ for 5 min. The electrodes were air-dried at room temperature between steps. This wet-chemistry treatment created a porous calcium phosphate scaffold, serving as a HAp-like interlayer to provide nucleation sites for copper growth [24]. The synthesized surface modifier is deliberately referred to as "HAp-like" rather than stoichiometric hydroxyapatite (HAp). Energy-dispersive X-ray spectroscopy (EDX) analysis revealed that the calcium-to-phosphorus (Ca/P) molar ratio deviates significantly from the ideal stoichiometric value of 1.67 expected for pure crystalline HAp. Specifically, the elemental composition indicated a higher proportion of phosphorus relative to calcium ($\text{P} > \text{Ca}$), suggesting the formation of a calcium-deficient apatite phase or an amorphous calcium phosphate precursor. Due to these compositional variations and inherent characterization limitations, the term "HAp-like" is adopted to

accurately represent the synthesized material's structural characteristics without overstating its phase purity.

Following the HAp-like modification, copper nanoparticles (CuNPs) were electrodeposited from an electrolyte containing 10 mM CuSO₄ and 0.1 M K₂SO₄ (adjusted to pH 1.0 with H₂SO₄). To determine the optimum fabrication conditions, deposition potentials (E_{dep}) ranging from −0.16 V to −0.9 V were evaluated, and deposition times (t_{dep}) were varied between 100 s and 250 s. Finally, the metallic CuNPs were converted into electrocatalytically active copper oxide species by cycling the electrode in 0.1 M NaOH (−0.34 V to −0.6 V, 100 mV s^{−1}, 20 cycles) to yield the CuO/HAp-like/PGE sensor.

The electroactive surface coverage of the deposited copper species was determined by integrating the anodic stripping peak current. The surface concentration was calculated using Equation 1 [25]:

$$\Gamma = \frac{Q}{nFA} \quad (1)$$

where Γ is the surface coverage (mol cm^{−2}), Q is the background-subtracted charge of the anodic stripping process (C), n is the number of electrons transferred ($n=2$), F is the Faraday constant (96485 C mol^{−1}), and A is the geometric surface area of the working electrode (0.316 cm², calculated for 0.5 mm diameter and 20 mm immersion depth).

2.4. Electrochemical measurements.

MEK was determined by Square Wave Voltammetry (SWV) [26] in 0.1 M Phosphate Buffered Saline (PBS) adjusted to pH 10.0. The alkaline medium is required for copper-mediated electrocatalysis, which proceeds through high-valence Cu-O/OH surface species that are stable only at high pH [27]; pH 10.0 was therefore selected on mechanistic grounds rather than as a physiological condition. To eliminate potential memory effects and surface fouling from repetitive scanning, we conducted independent measurements at each concentration point. A series of separate sample solutions were prepared containing MEK concentrations ranging from 0.1 mM to 50 mM. For each measurement, a new CuO/HAp-like/PGE sensor was employed. The electrode was immersed in the prepared solution, and the potential was scanned from 0.1 V to −0.6 V with a frequency of 25 Hz, a pulse amplitude of 25 mV, and a step potential of 5 mV. All measurements were conducted at room temperature.

3. Results and Discussion

3.1. Electrodeposition mechanism and morphological characterization.

To understand the sensor architecture, the deposition process was investigated using Cyclic Voltammetry (CV) in an acidic copper bath. As shown in Figure 1, the voltammogram exhibits a clear anodic peak at 0.1 V, corresponding to the oxidation of Cu to Cu²⁺. In the reverse scan, a cathodic peak at −0.15 V indicates the reduction of Cu²⁺ back to metallic copper. Detailed analysis shows that the cathodic current begins to rise at −0.08 V, marking the initiation of copper deposition. This deposition process follows a consecutive two-step electron transfer mechanism accepted in the literature [28]. The first step involves the reduction of cupric ions to the cuprous intermediate, which is kinetically identified as the slow step (Cu²⁺ + e[−] → Cu⁺). This is immediately followed by the rapid reduction of the intermediate to metallic copper, resulting in the observed current increase (Cu⁺ + e[−] → Cu).

The broad signal at more negative potentials further suggests diffusion-controlled kinetics. Furthermore, a characteristic nucleation loop (crossover) is observed between the anodic and cathodic branches. This hysteresis is a known sign of the electrocrystallization process and confirms that copper deposition on the PGE scaffold follows a nucleation-growth mechanism [29].

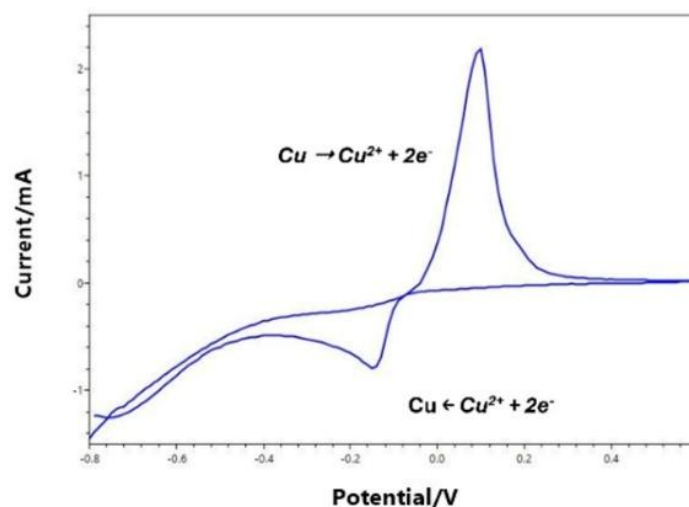


Figure 1. Characteristic cyclic voltammogram of copper electrodeposition recorded in 10 mM CuSO₄ + 0.1 M K₂SO₄ (pH 5.0).

The electrochemical properties of the modified electrode were further characterized in a 0.1 M NaOH solution to verify the presence and stability of the copper species (Figure 2a). Upon initiating the anodic scan, two distinct oxidation signals were recorded at -0.35 V (Peak I) and -0.10 V (Peak II). These features are characteristic of the multi-step oxidation process of copper in alkaline environments. Specifically, Peak I represents the initial transformation of metallic Cu into Cu(I) species, leading to the formation of a CuOH/Cu₂O layer (Eqs. 2 and 3). As the potential moves in the positive direction, Peak II emerges, signifying the further oxidation of this Cu(I) sub-layer into more stable Cu(II) species (CuO and Cu(OH)₂) (Eq. 4). Furthermore, the broad oxidation wave observed in the 0.0 V to 0.5 V region is associated with the transition toward high-valence Cu(III) species (Cu₂O₃), which are known to be highly active in alkaline electrolytes. On the reverse cathodic scan, two prominent reduction peaks at -0.50 V (Peak III) and -0.85 V (Peak IV) were observed. These signals correspond to the sequential reduction of the CuO surface back to Cu₂O and, eventually, to metallic Cu [21,22]. The absence of these redox couples on the bare PGE confirms that the observed electrochemical activity is exclusively due to the successfully deposited CuONPs.

The cycling stability of the sensor was evaluated through repetitive voltammetric scans (Figure 2b). A notable decrease in current was observed during scans over the full potential range, attributed to irreversible stripping of copper species at highly negative potentials and surface reorganization. To mitigate this and ensure a robust sensing interface, a dedicated stabilization protocol was implemented by applying 20 cycles within a restricted potential window of -0.34 V to -0.6 V. This specific range was strategically selected to maintain surface integrity; by limiting the cathodic scan to -0.6 V, deep reduction of CuO back to metallic copper (typically observed around -0.85 V) was effectively prevented, while the anodic limit of -0.34 V allowed for the selective stabilization of the Cu(I)/Cu₂O sub-layer around the first oxidation wave. This approach avoids the structural strain associated with higher-valence oxides, ensuring a highly reproducible surface state for subsequent analytical measurements.

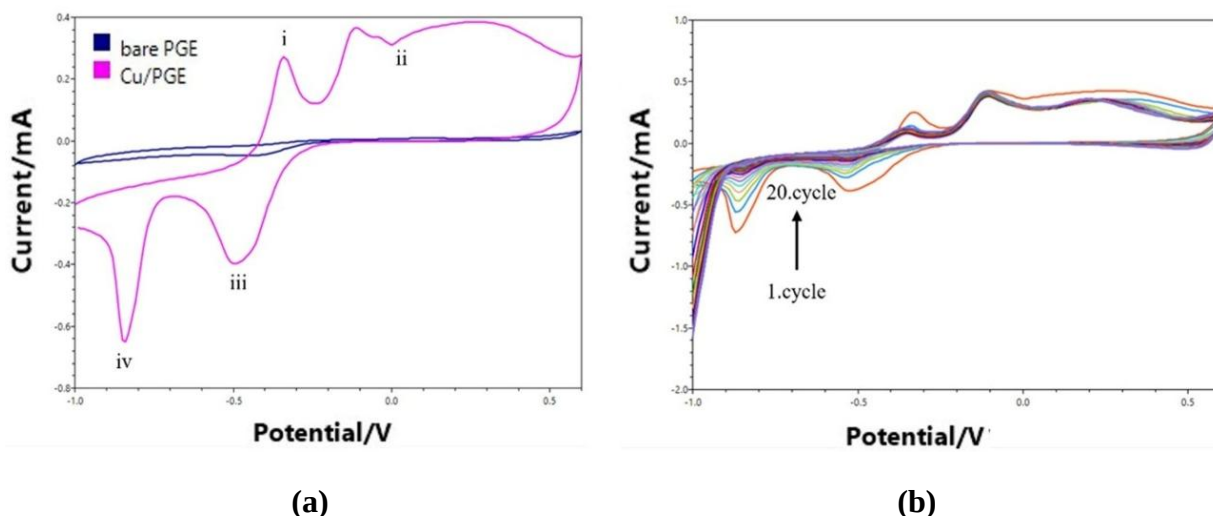
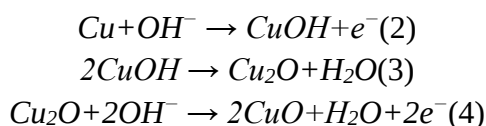


Figure 2. (a) CVs of bare and Cu modified PGE at -0.6 V for 200s in 0.1 M NaOH at a scan rate of 100 mV s $^{-1}$. (b) Twenty successive CV scans of CuNP/PGE in NaOH at a scan rate of 100 mV s $^{-1}$.

3.2. Optimization of sensor architecture.

The optimization involved (i) evaluating the impact of the HAp-like interlayer, and (ii) screening the electrodeposition conditions (potential and time) using a full factorial design. A total of 16 combinations were evaluated by varying the deposition potential (-0.16 , -0.30 , -0.60 , and -0.90 V) and time (100, 150, 200, and 250 s) simultaneously. Before proceeding to the optimization steps, the fundamental role of the Hydroxyapatite-like (HAp-like) interlayer was established. A comparative Cyclic Voltammetry (CV) analysis was performed to evaluate the electrochemical performance of the copper oxide-coated bare PGE (CuO/PGE) versus the HAp-like modified PGE (CuO/HAp-like/PGE) under identical deposition conditions.

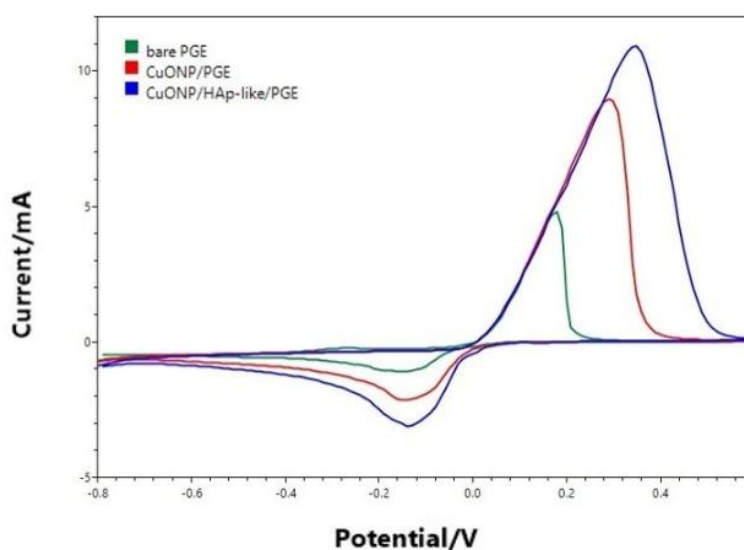


Figure 3. Comparative cyclic voltammograms of CuO/PGE and CuO/HAp-like/PGE in 10 mM CuSO $_4$ solution (pH 5.0).

As presented in Figure 3, the HAp-like modified interface demonstrated an enhanced electrochemical response. The CuO/HAp-like/PGE exhibited a 1.3-fold increase in peak

current compared to the CuO/PGE. This signal enhancement is attributed to the increased effective electroactive surface area provided by the porous and hydrophilic HAP-like layer, which offers a high density of nucleation sites. By preventing the random agglomeration of copper nanoparticles, the HAP-like scaffold improves ionic accessibility and stability.

Using the HAP-like modified interface, the effects of deposition potential (-0.16 to -0.90 V) and time (100 to 250 s) were examined. First, the deposition potential was varied from -0.16 V to -0.90 V (Figure 4a). The anodic peak current generally increased as the potential shifted towards more negative values, reaching a maximum at -0.90 V. However, significant deformations and instability were observed in the voltammograms at this negative limit. To validate these observations at the target deposition duration, all potential values were re-evaluated at a fixed time of 200 s (Figure 4b). While -0.60 V yielded a high current response (8.23 mA) with a well-defined and stable peak shape, the response at -0.90 V was marked by significant peak distortion.

To further confirm that the instability at -0.90 V was an inherent characteristic of the potential rather than a time-specific issue, an evaluation was performed across all tested time parameters at this specific potential (Figure 4c). The persistent lack of peak symmetry and reproducible signals in these results confirmed the unsuitability of -0.90 V for reliable sensor development [31]. Consequently, -0.60 V was selected as the optimum deposition potential.

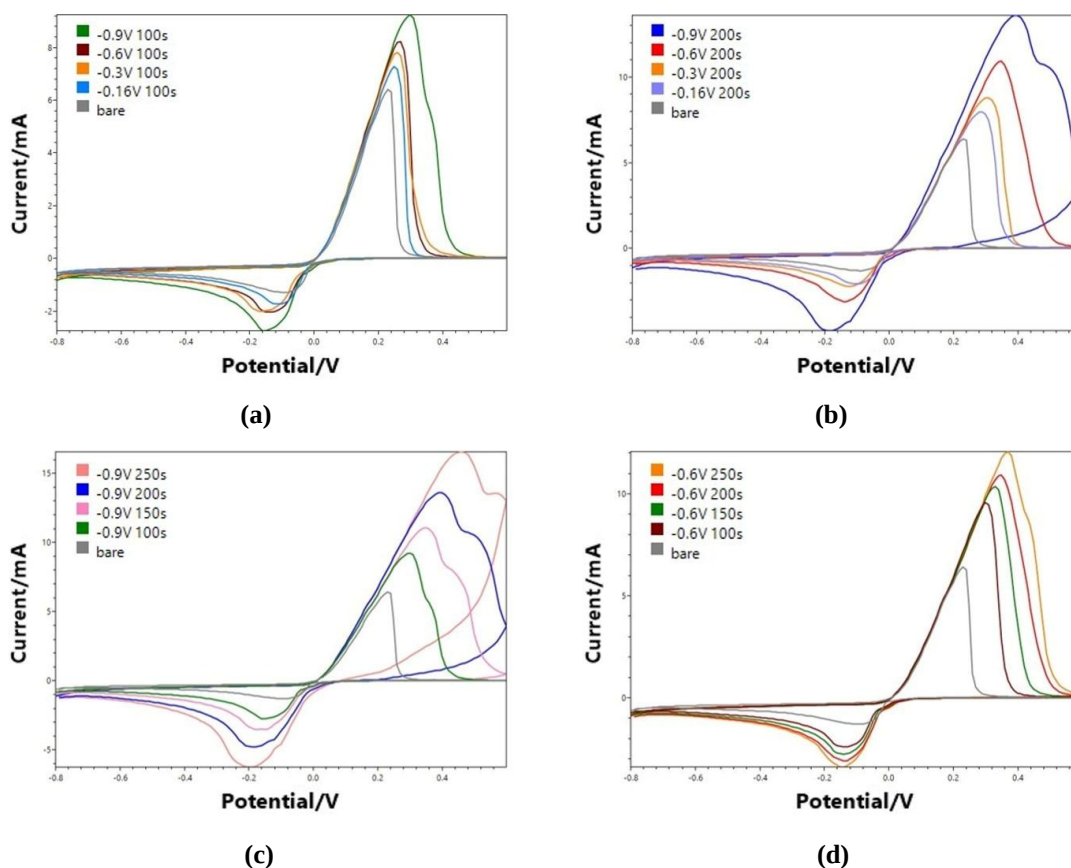


Figure 4. Optimization of electrodeposition parameters for the CuO/HAP-like/PGE: **(a)** Evaluation of deposition potential from -0.16 V to -0.9 V, **(b)** Comparative voltammetric responses at -0.6 V and -0.9 V at a fixed deposition time of 200 s, **(c)** Analysis of peak instability at -0.9 V across various deposition times 100–250 s, and **(d)** Optimization of deposition time at -0.6 V (100–250 s). All measurements were performed in 10 mM CuSO_4 solution (pH 5.0).

Regarding the deposition time (Figure 4d), the sensor response was evaluated between 100 s and 250 s at the optimized potential of -0.60 V. As expected for an adsorptive

accumulation process, the peak current increased with time, reaching its maximum at 250 s (12.075 mA). Although the signal magnitude was highest at 250 s, distortions in the peak morphology (i.e., peak broadening) were observed, indicating excessive surface saturation. On the other hand, at 200 s, a sharp and high-intensity signal (10.917 mA) was recorded without any morphological deformation. Therefore, 200 s was chosen as the final optimum deposition time for subsequent experiments.

The effect of deposition potential (Edep) on the surface coverage (Γ) was also analyzed by integrating the anodic stripping peaks, with the background charge measured at the bare PGE ($Q_{\text{bare}} = 1.70 \times 10^4 \mu\text{C}$) subtracted from the values obtained at modified electrodes. The surface coverage increased with the applied driving force, reaching a maximum value at the most negative potential of -0.9 V . Although the highest surface coverage was calculated at -0.9 V , this excessive charge accumulation suggests the possibility of uncontrolled bulk deposition or aggregation rather than a uniform catalytic layer. Such bulky structures often suffer from mechanical instability and lower active surface area availability. Under the optimized experimental conditions (-0.6 V , 200 s), the electroactive surface coverage (Γ) corresponds to a stable and catalytically active layer, distinct from the excessive accumulation observed at -0.9 V . The charge and coverage values are summarized in Table 1 in a single unit system (Coulombs):

Table 1. Background-subtracted anodic stripping charge and calculated surface coverage (Eq. 1; $n = 2$, $F = 96485 \text{ C mol}^{-1}$, $A = 0.316 \text{ cm}^2$).

Condition	$Q_{\text{net}} (\text{C})$	$\Gamma (\text{mol cm}^{-2})$
-0.6 V , 200 s (optimum)	2.56×10^{-4}	4.20×10^{-9}
-0.9 V	2.43×10^{-2}	3.98×10^{-7}

SEM analysis further verified these findings (Figure 5). The surface modified at -0.90 V exhibited a deformed and irregular structure characterized by large agglomerates and prominent physical discontinuities (Figure 5(J–O)). These structural defects indicate a lack of film stability and poor surface uniformity. In contrast, the electrode prepared at the optimum potential of -0.60 V displayed a more homogeneous and well-ordered surface topology (Figure 5(D–I)). Particularly at a deposition time of 200 s, a uniform distribution of nanoparticles within a porous network was observed, providing a favorable structure for electrocatalytic activity. Additionally, EDX elemental mapping confirmed the successful and uniform distribution of copper (Cu) across the electrode surface (Figure 6a). To quantify the particle distribution, size analysis was performed using ImageJ software ($n=100$). As presented in the histogram (Figure 6b), the CuO/HAp-like nanoparticles exhibited a narrow size distribution with an average diameter of $207.4 \pm 37.7 \text{ nm}$. These findings confirm that -0.60 V yields the optimal surface morphology, ensuring both high surface area and structural integrity for the sensor.

3.3. Electrochemical detection of MEK and sensing mechanism.

The determination of Methyl Ethyl Ketone (MEK) was performed using Square Wave Voltammetry (SWV). The sensor showed a concentration-dependent suppression of the anodic peak current (a “signal-off” response), governed by the steric hindrance of the analyte on the electrode surface [32].

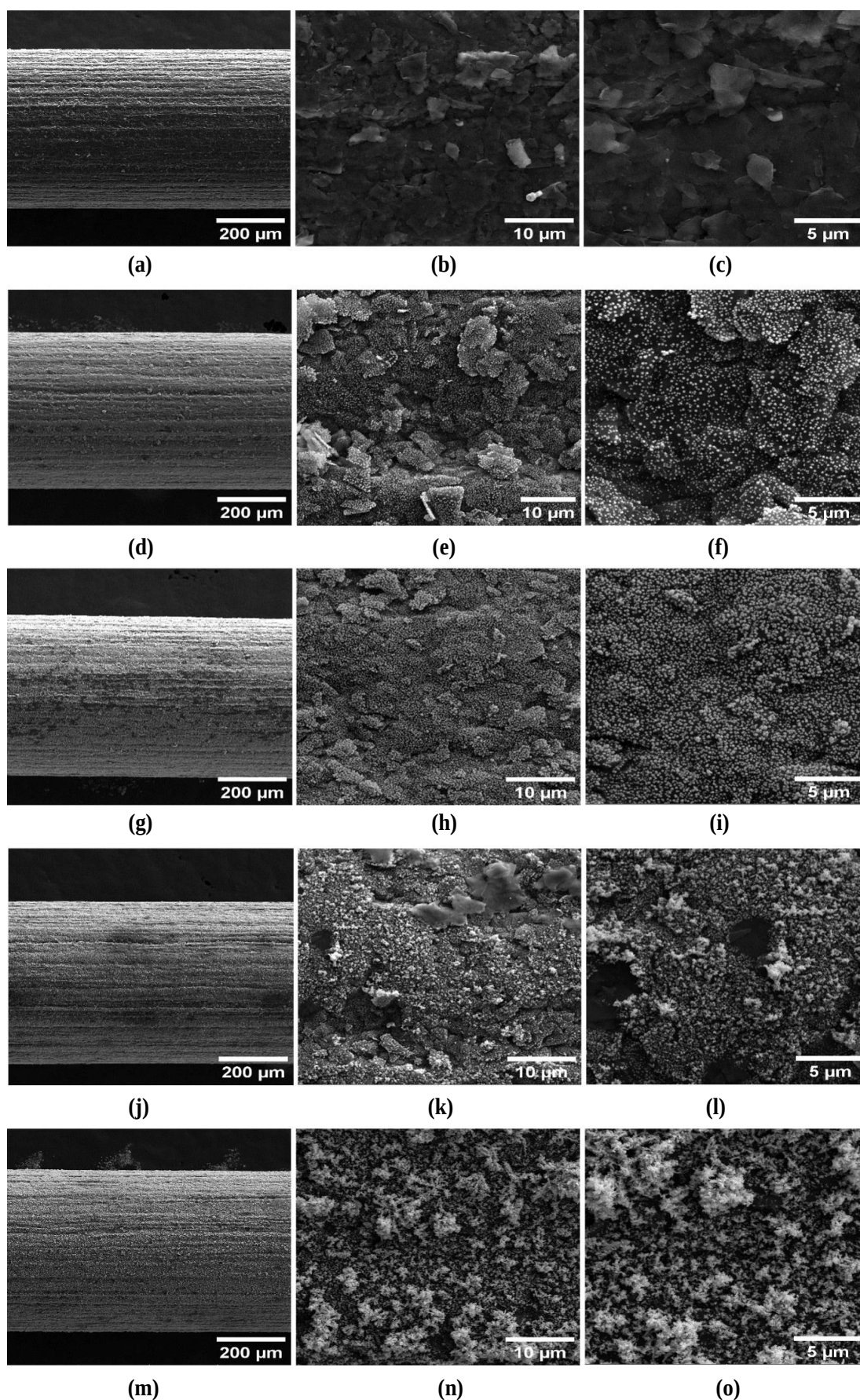


Figure 5. SEM micrographs of the electrode surfaces at different modification stages and parameters: (a–c) bare PGE, (d–f) CuO/HAp-like/PGE prepared at -0.6 V for 100 s, (g–i) CuO/HAp-like/PGE at -0.6 V for 200 s (showing a homogeneous and porous network), (j–l) CuO/HAp-like/PGE at -0.9 V for 100 s, and (m–o) CuO/HAp-like/PGE at -0.9 V for 200 s (exhibiting significant surface agglomeration and clusters).

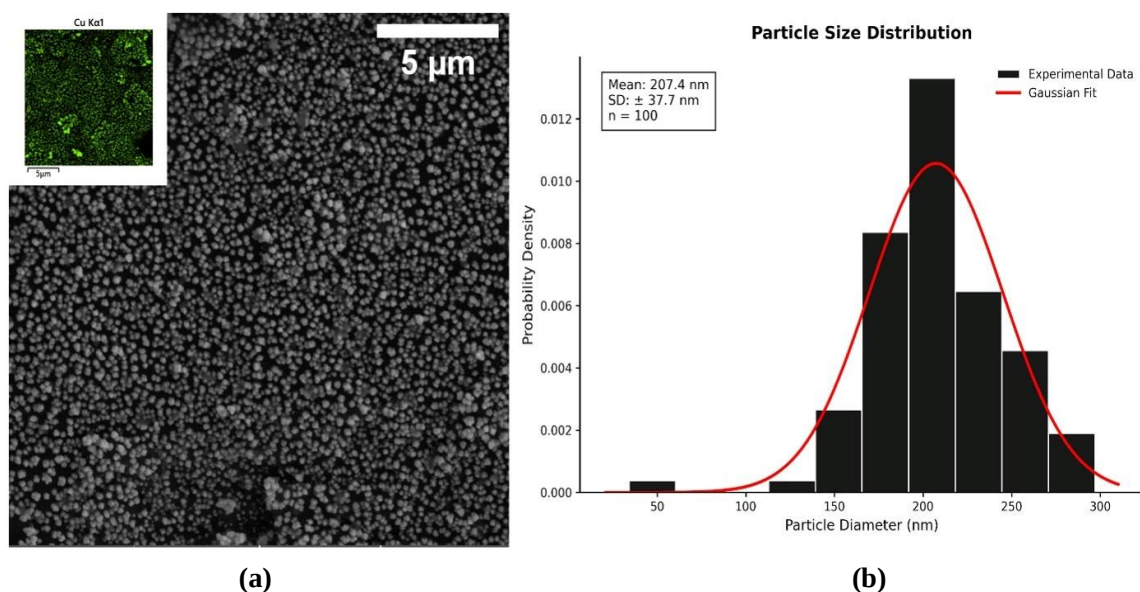


Figure 6. Detailed surface and particle characterization of the optimized CuO/HAp-like/PGE (−0.6 V, 200 s): (a) Representative SEM micrograph showing the catalyst distribution with the corresponding EDX elemental analysis (inset), and (b) Particle size distribution histogram derived from ImageJ analysis.

The calibration plot exhibited two distinct linear dynamic ranges (Figure 7a). To demonstrate the reproducibility of the analytical response, each calibration point was evaluated through independent replicate measurements ($n=10$). The corresponding standard deviations were plotted as error bars, and an unweighted linear regression model was applied to extract the calibration parameters without altering the statistical significance of the individual measurements.

This dual-linear phenomenon is consistent with the theoretical principles of adsorption isotherms on heterogeneous surfaces [33]. The first linear region, observed from 0.1 mM to 5.0 mM, gave:

$$I_{pa} (\mu A) = -4.284 \times C_{MEK} + 389.47 \quad (R^2=0.994)$$

This high-sensitivity regime is attributed to the availability of abundant active sites on the porous CuO/HAp-like scaffold. Under these low-concentration conditions, the adsorption kinetics follow a linear approximation ($\beta C \ll 1$) where the attainment of equilibrium coverage is diffusion-controlled, allowing for rapid analyte-surface interaction as described in classical electrochemical theory [33]. At higher concentrations (5.0 mM to 50 mM), a second linear range was established with a lower sensitivity:

$$I_{pa} (\mu A) = -0.997 \times C_{MEK} + 372.88 \quad (R^2=0.980)$$

The exact breakpoint between these two dynamic ranges (5.0 mM) was mathematically determined using segmented piecewise linear regression (Figure 7b), an iterative algorithm that identified the global optimum minimizing the residual sum of squares. Furthermore, the statistical validity of the dual-linear model was supported by residual analysis (Figure 7c), which showed a random scatter indicative of homoscedasticity. Additionally, error distribution plots showed a pattern consistent with normal analytical measurements (Figure 7d).

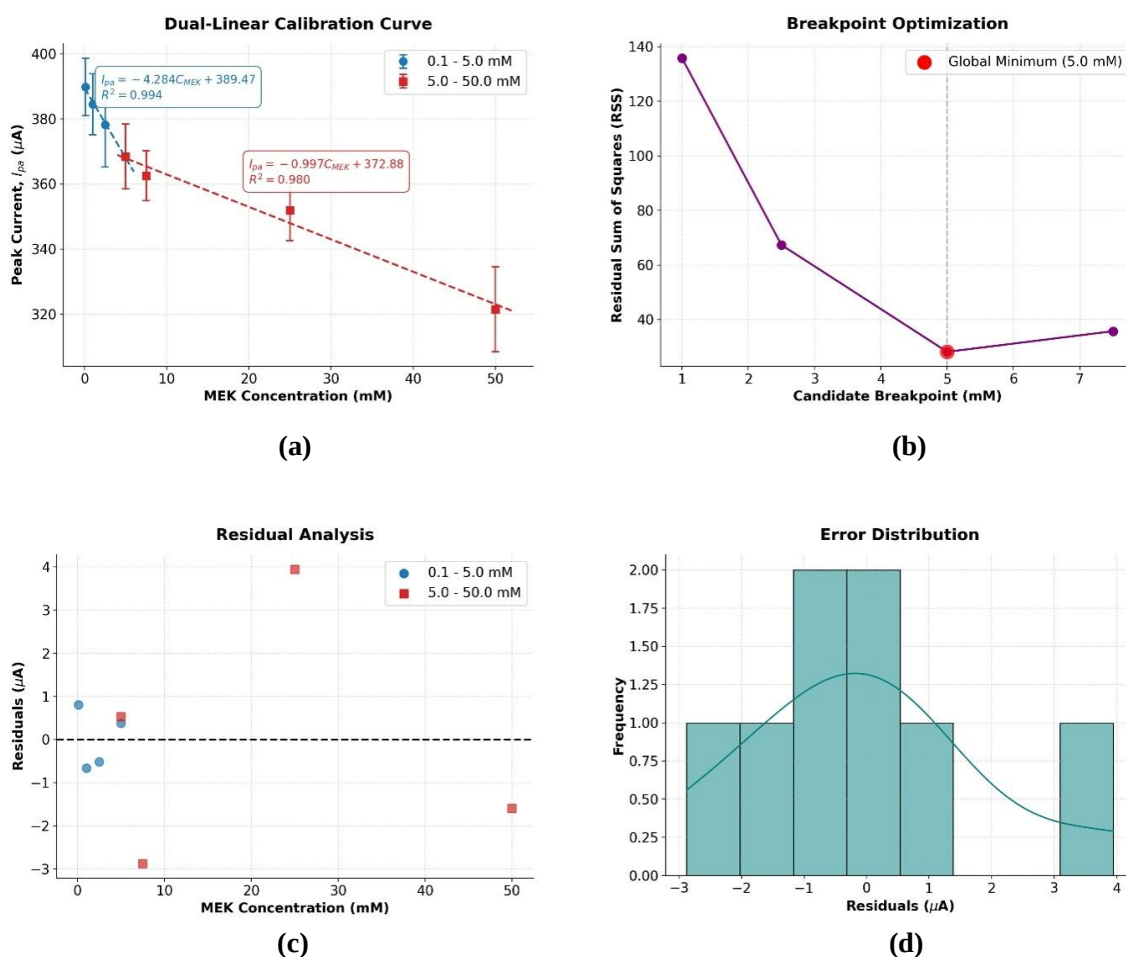


Figure 6. Analytical performance and statistical validation of the CuO/HAP-like/PGE sensor. (a) Dual-linear range calibration curve for MEK detection with error bars representing the standard deviation of replicate measurements (n=10); (b) Segmented piecewise linear regression confirming the mathematical optimum of the 5.0 mM breakpoint; (c) Residual analysis plot indicating homoscedasticity and the absence of systematic bias; (d) Error distribution confirming the normality of the analytical response.

This transition in slope is ascribed to the progressive saturation of the electrode surface. As the surface coverage (Γ) approaches the saturation limit, the steric barrier effect becomes dominant, and the signal response shifts from a diffusion-limited to a surface-saturation-limited kinetic model. Similar dual-linear behavior has been extensively reported for nanostructured metal-oxide and nanocomposite-based sensors, confirming that surface saturation at high analyte concentrations necessitates a multi-stage calibration model rather than a single linear fit. Specifically, Wanjari *et al.* [34] recently demonstrated that such dual-range sensitivity is a characteristic feature of adsorption-limited kinetics in porous nanostructures. This consistency with current literature highlights the versatility of the CuO/HAP-like/PGE platform, demonstrating its capability to balance high sensitivity for trace analysis with reliable detection at elevated concentrations.

The electrochemical sensing mechanism of Methyl Ethyl Ketone (MEK) on the CuO/HAP-like modified interface was identified as a distinct “Signal-Off” process, standing in contrast to the conventional electrocatalytic oxidation (“Signal-On”) typically reported for transition metal oxides. While standard amperometric sensors generally rely on the analyte reducing high-valence oxide species to enhance the anodic current, the systematic attenuation of the peak current observed in this study points to a dominant steric hindrance effect. As described in analogous metal-oxide systems [29,30], the strong adsorption of MEK molecules

onto the electroactive copper oxide centers effectively blocks the access of hydroxide ions (OH^-) required for the redox regeneration of the catalyst. Consequently, the adsorbed analyte forms a diffusion barrier that increases the interfacial charge transfer resistance. To investigate the adsorption-based sensing mechanism and the effects of the electrode modifications, representative control experiments were evaluated using Square Wave Voltammetry (SWV). As shown in Figure 8a, the bare PGE and HAp-like modified PGE exhibited negligible currents in the presence of 1 mM MEK. In contrast, an evident electrochemical signal was observed following the CuO modification. The CuO/HAp-like/PGE interface demonstrated a higher peak current compared to CuO/PGE, suggesting that the HAp-like scaffold may contribute to an increased active surface area and facilitate the distribution of the CuO nanoparticles.

Furthermore, to evaluate the current attenuation associated with the "Signal-Off" behavior, SWV responses were compared for both the CuO/PGE and the CuO/HAp-like/PGE interfaces (Figure 8b and 8c). When the MEK concentration increased from 1 mM to 10 mM, a decrease in the peak currents was observed for both electrodes. This current drop was more pronounced for the CuO/HAp-like/PGE platform (decreasing from 446.3 μA to 408.6 μA) compared to the CuO/PGE control (which decreased from 415.9 μA to 394.9 μA). These observations are consistent with a "Signal-Off" mechanism, suggesting that MEK molecules likely adsorb onto and block the available active sites on the modified electrode surface. Additionally, the reproducibility of this characteristic signal-off behavior across multiple independent electrodes is comprehensively evaluated in Section 3.5.

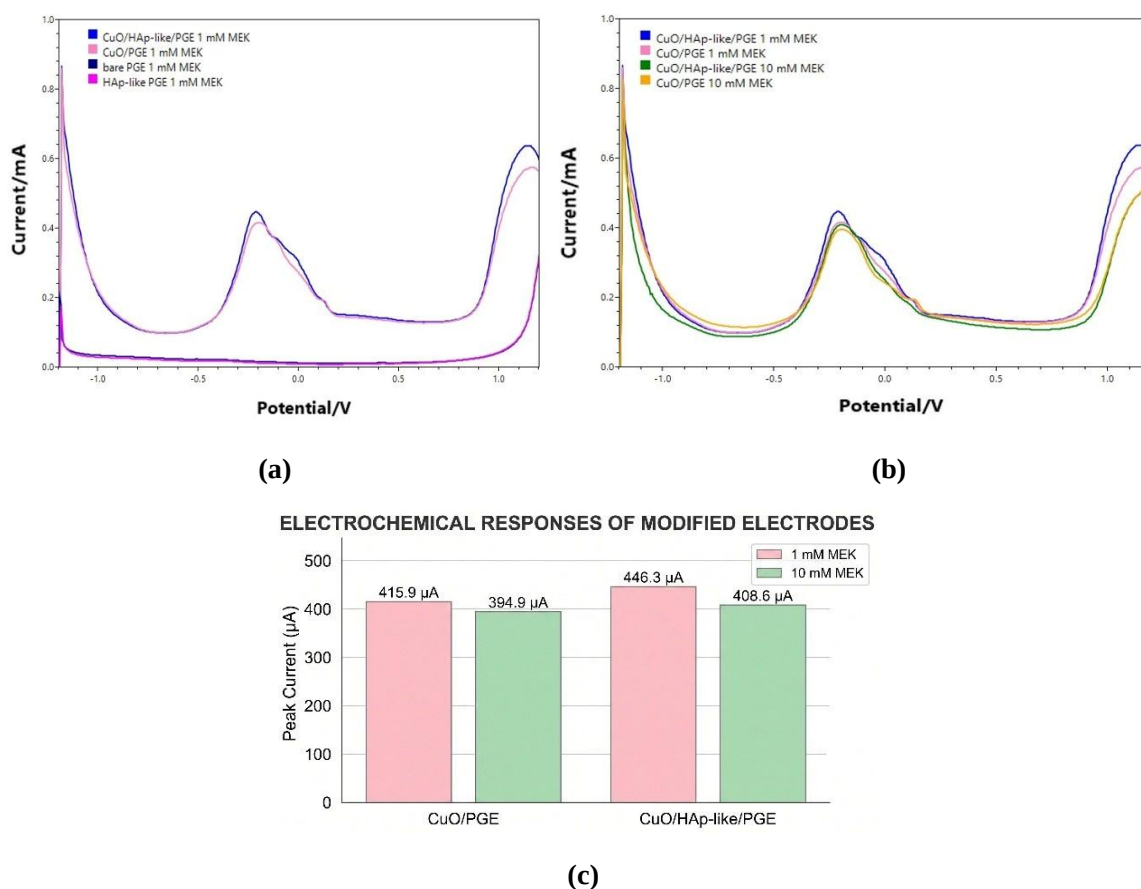


Figure 7. Validation of the sensing mechanism using Square Wave Voltammetry (SWV). (a) SWV responses of bare PGE, HAp-like/PGE, CuO/PGE, and CuO/HAp-like/PGE in 1 mM MEK; (b) SWV profiles of CuO/PGE and CuO/HAp-like/PGE at 1 mM and 10 mM MEK; (c) Bar chart showing the "Signal-Off" current attenuation upon concentration increase.

Based on the high-sensitivity range, the LOD (calculated as $3.3\sigma_{\text{blank}}/m$, with σ the standard deviation of the blank response and m the slope of the 0.1–5.0 mM segment) was 1.04 mM. The corresponding limit of quantification ($\text{LOQ} = 10\sigma/m$) was 3.15 mM. Oxidation peaks were still visually resolved at 0.1 mM; however, validated quantitation below the LOQ (signal-to-noise, precision, and accuracy at sub-millimolar levels) was not established, and these values are not claimed here. The linear response up to 50 mM covers the higher concentrations relevant to industrial leakage scenarios.

To validate the analytical accuracy of the dual-linear calibration model, we evaluated the sensor's performance across a concentration range (0.1 mM to 50.0 mM). The recovery rates were determined by back-calculating the measured peak currents using the corresponding linear regression equations (Table 2).

Table 2. Analytical recovery of MEK detection using the proposed CuO/HAp-like/PGE sensor.

Concentration Target(mM)	Measured Peak Current (μA)	Calculated MEK Concentration (mM)	Recovery (%)
0.5	386.48	0.57	113.2
2.5	380.02	2.21	88.2
20.0	351.30	21.64	108.2
40.0	338.48	34.50	86.3

The sensor yielded recovery values ranging from 86.3% to 113.2% across the tested concentrations. These results fall within the internationally accepted analytical range of 80%–120%. The observed trend across the dynamic range—featuring an overestimation at the sub-millimolar level (0.5 mM, 113.2%) and a negative deviation at higher concentrations (40.0 mM, 86.3%)—is consistent with the adsorption-limited kinetic model proposed for the signal-off mechanism at the CuO/HAp-like interface. Specifically, the high-end deviation reflects the gradual saturation of active binding sites, while low-concentration background variations account for the overestimation near the sub-LOD boundary.

The proposed signal-off mechanism was further corroborated by *ex-situ* GC-MS analysis. Standard solutions with initial concentrations of 0.1, 1.0, 5.0, and 10.0 mM were analyzed before and after the voltammetric measurements under sealed conditions to minimize evaporation losses. The initial calibration exhibited high linearity ($R^2 = 0.9946$), confirming the precision of the analytical method. Chromatographic measurements of the bulk electrolyte before and after voltammetric scans revealed a significant depletion of MEK concentration (up to ~52% removal at 10 mM), without the detection of volatile oxidation byproducts (Table 3).

Table 3. GC-MS analysis of MEK concentrations in the bulk electrolyte before and after electrochemical measurements.

Initial Concentration (mM)	Calculated Final Concentration (mM)*	Removal (%)	Mechanism Insight
0.1	0.08	16.2%	Initial Surface Interaction
1.0	0.73	26.9%	Progressive Adsorption
5.0	4.18	16.5%	Equilibrium Approach
10.0	4.81	51.9%	Dense Interfacial Accumulation

These findings are consistent with the site-specific chemisorption of MEK at the CuO/HAp-like interface rather than electrochemical degradation. To minimize background interference and accurately differentiate site-specific adsorption from natural evaporation or non-specific physical sorption, the Extracted Ion Chromatogram (EIC) for m/z 43 was utilized for quantification. Mechanistic controls, including a stored blank solution, bare PGE, HAp-like/PGE, and the complete CuO/HAp-like/PGE interface, were systematically evaluated.

At 10.0 mM, natural evaporation accounted for a 9.3% loss, while non-specific sorption on bare PGE and HAp-like/PGE resulted in 25.4% and 39.4% depletion, respectively (Table 4). The complete CuO/HAp-like/PGE interface exhibited a 55.4% depletion again. A consistent trend was observed at 1.0 mM, with a 35.1% removal for the fully modified electrode (Table 4). These observations are consistent with the hypothesis that the current suppression is associated with the site-specific chemisorption of MEK molecules at the CuO/HAp-like interface, rather than solely non-specific accumulation.

Table 4. Targeted GC-MS (m/z 43) analysis of MEK depletion across different interfaces at 1.0 mM and 10.0 mM initial concentrations to isolate the signal-off mechanism.

Initial conc. (mM)	Test condition/ Interface	Removal (%)
1 mM	Blank (Reference)	0
	Stored Solution	9.3
	Bare PGE	23.9
	HAp-like/PGE	30.7
	CuO/HAp-like/PGE	35.1
10 mM	Blank (Reference)	0
	Stored Solution	9.3
	Bare PGE	25.4
	HAp-like/PGE	39.4
	CuO/HAp-like/PGE	55.4

Following the GC-MS analysis of MEK dissolution in the liquid phase, Electrochemical Impedance Spectroscopy (EIS) was employed to investigate the interfacial properties and the binding behavior of MEK onto the sensor surface. As depicted in Figure 9a, the bare PGE and HAp-like/PGE exhibited capacitive behaviors with impedance values in the $M\Omega$ range, which is consistent with the deposition of the resistive HAp-like matrix. Conversely, the incorporation of CuO (Figure 9b) led to a decrease in the charge transfer resistance (R_{ct}), reflecting the conductive nature of the CuO structures.

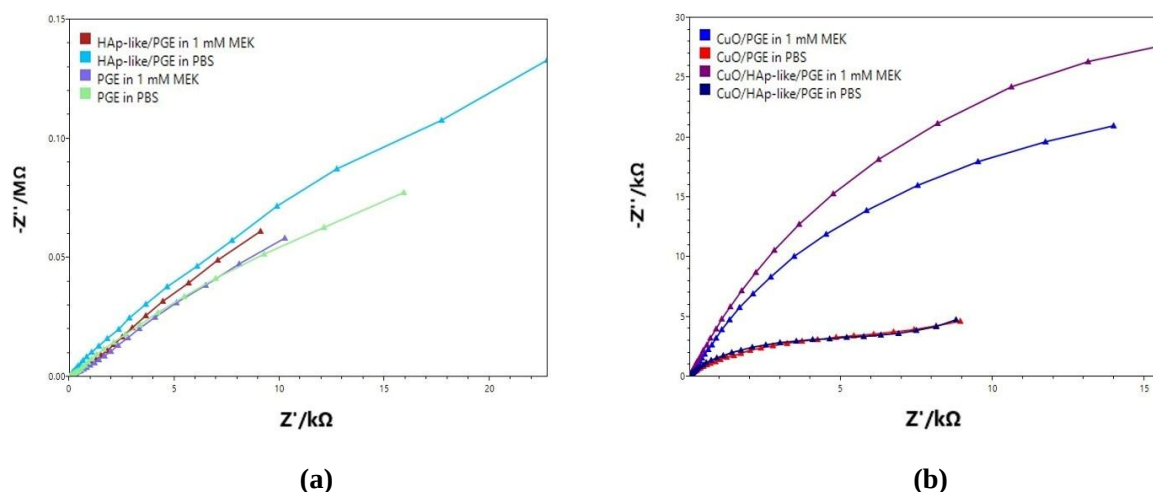


Figure 8. Electrochemical impedance spectra (Nyquist plots) of the electrodes: (a) bare PGE and HAp-like/PGE; (b) CuO/PGE (control) and CuO/HAp-like/PGE (sensor) before and after MEK adsorption. (Note: "After MEK" indicates that the electrode was incubated in 1 mM MEK solution prior to the measurement in PBS).

The Nyquist plots of the CuO/HAp-like/PGE sensor in PBS and 1 mM MEK were further evaluated to understand the sensing mechanism, upon the addition of 1 mM MEK, the R_{ct} value of the CuO/HAp-like/PGE increased compared to the blank PBS (Figure 9b). This increase in impedance indicates that MEK molecules adsorb onto the modified electrode surface.

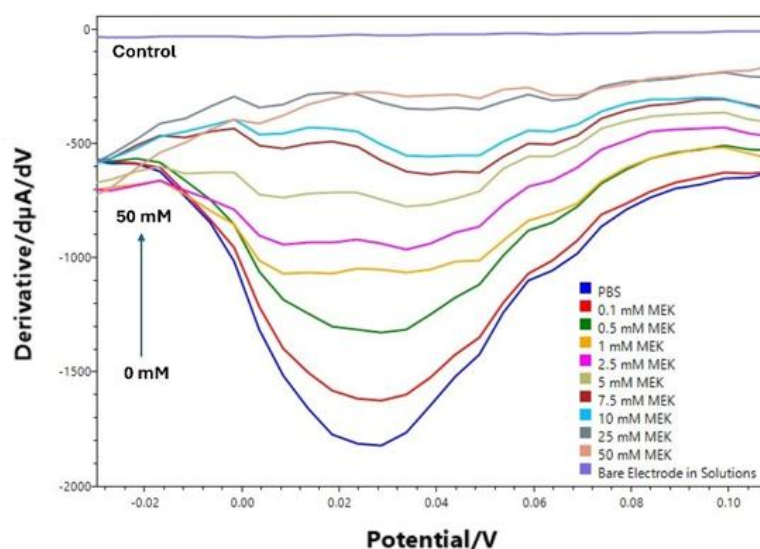


Figure 9. First derivative Square Wave Voltammograms (dI/dE) showing the systematic signal evolution and high peak resolution with increasing MEK concentrations (0.1 – 50 mM).

The adsorbed MEK molecules act as an insulating barrier at the electrode-electrolyte interface, hindering electron transfer. This behavior is consistent with the observed decrease in voltammetric currents, supporting the "Signal-Off" adsorption-based mechanism of the proposed sensor.

To scrutinize the morphological stability of the sensor response, the first derivative of the voltammetric data (dI/dE) was analyzed (Figure 10). This mathematical treatment revealed a highly ordered progression in peak envelopes, confirming that a consistent structural interaction drives signal suppression rather than random current fluctuations. The derivative plots' preserved peak resolution further validates the specific interaction between MEK and the CuO/HAp-like interface.

3.4. Selectivity and interference.

In the biomedical domain, breath analysis involves a complex matrix of volatile organic compounds. Acetone is an abundant ketone in exhaled breath and shares a similar chemical structure with MEK, making it a relevant candidate for evaluating sensor specificity. Other water-soluble volatile compounds, such as acetonitrile and ethyl acetate, are also detected in varying concentrations in breath samples.

To evaluate the sensor's selectivity, the study was conducted in two steps: a 1:1 equimolar evaluation and a simulated breath "interference pool". In the equimolar evaluation, the baseline voltammogram recorded in pure PBS (pH 10) exhibited a primary oxidation peak and a native secondary anodic shoulder. Introducing individual interferents (such as acetone) often overlapped with the native baseline, occasionally producing an additive effect that slightly increased the anodic current.

To verify whether the suppression of the native shoulder was specifically induced by MEK or simply a result of increased total organic concentration, control measurements were conducted by sequentially adding higher concentrations of the interferents. Increasing the concentration of these individual species did not suppress the native PBS shoulder or replicate the signal drop. However, the subsequent addition of MEK to these solutions suppressed the secondary shoulder and caused a consistent signal drop at the primary peak region (Figure 11).

To simulate physiological conditions, an "interference pool" was prepared. The selection of the water-soluble interferents and their concentration ratios were based on human breath profiling literature [36]. The concentrations within this pool were proportioned by maintaining MEK at its detection threshold while scaling the selected interferents according to their relative physiological abundances reported in exhaled breath. The voltammetric responses for the interference pool were consistent with the equimolar findings. The native shoulder structure, which remained present with the pooled interferents, was suppressed upon the introduction of MEK (Figure 11e-f).

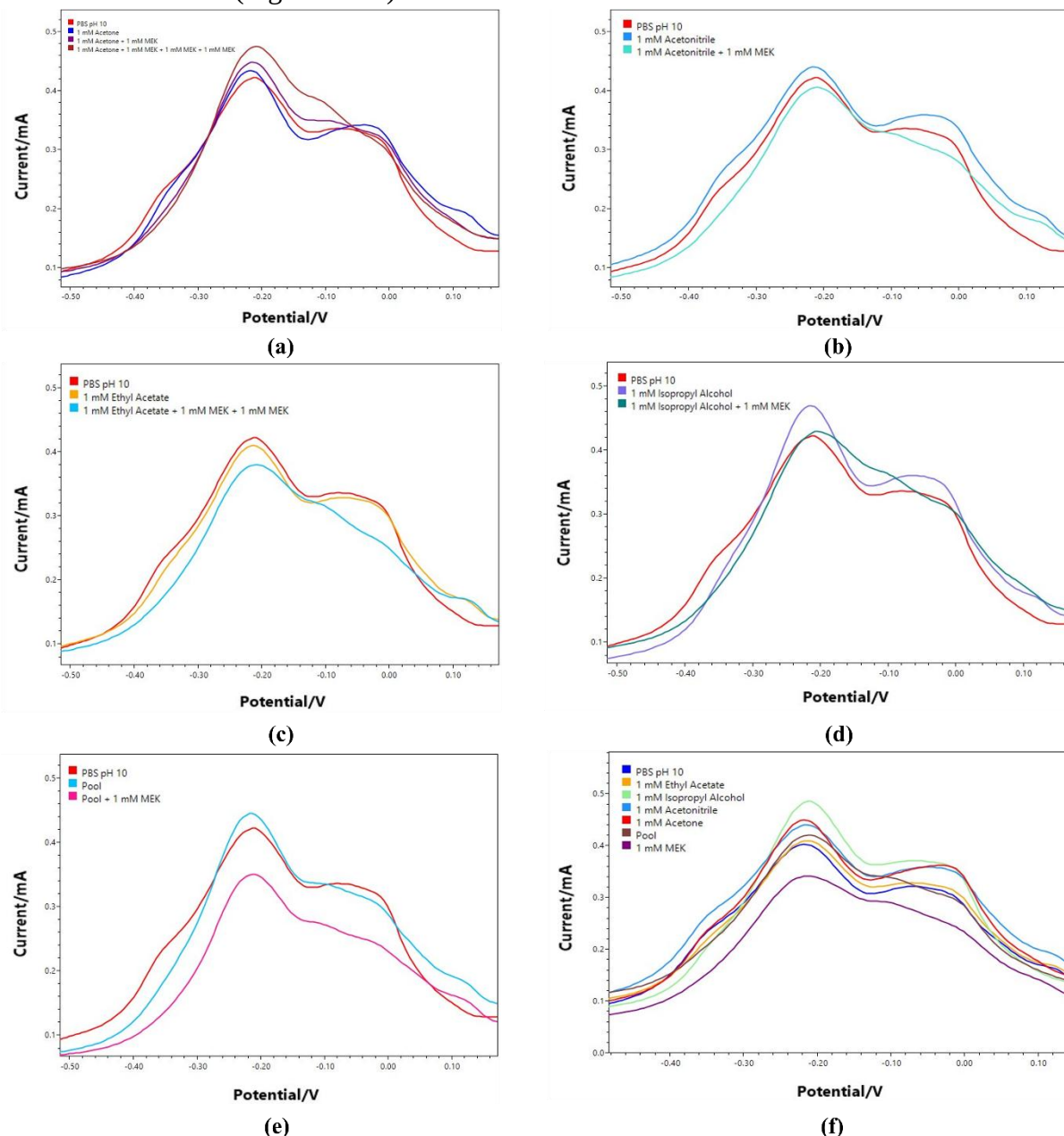


Figure 10. Voltammetric selectivity of the CuO/HAP-like/PGE sensor. **(a–d)** Individual interference tests showing the native anodic shoulder preservation. **(e)** Interference pool simulation, illustrating signal suppression upon 1 mM MEK addition. **(f)** Comparative response demonstrating MEK-specific signal-off behavior despite co-solvent interference.

This reversal of the signal trend confirms that the suppression is not a result of bulk solvent concentration, but rather an electrochemical response to MEK. The morphological changes suggest that MEK undergoes preferential adsorption onto the CuO/HAP-like/PGE surface, driven by a higher binding affinity than the interferents. By occupying these active

sites, MEK effectively displaces background electrolytes and sterically blocks species like acetone from interacting with the electrode surface. This competitive surface-blocking dynamic disrupts the native electrochemical pathways responsible for the secondary anodic shoulder, isolates the MEK signal, and confirms the non-enzymatic, adsorption-based detection mechanism proposed in this study.

For the industrial application, the sensor's matrix tolerance was evaluated using actual wastewater samples from commercial printing facilities (Companies A, B, and C). This approach also served as a practical real-matrix demonstration because collecting standardized human breath condensate is constrained. The analysis used the standard addition method adapted for signal-off sensing, plotting the signal drop against the added MEK concentration.

3.5. Reproducibility and stability.

The reproducibility of the CuO/HAp-like/PGE sensor was evaluated on both an intra-day and inter-day basis by measuring the electrochemical response of fifteen independently prepared electrodes to 1.0 mM MEK under identical conditions. To determine intra-day reproducibility, five separate electrodes ($n=5$) were fabricated and tested on the same day, and this procedure was repeated over three different days. The evaluations yielded intra-day Relative Standard Deviations (RSDs) of 2.05%, 3.27%, and 1.85%, respectively. Furthermore, the inter-day reproducibility, assessed by comparing the mean peak current responses across the three distinct days, demonstrated an RSD of 1.94% (with an overall combined RSD of 2.83% for all 15 electrodes). These findings indicate an acceptable level of reproducibility and stability for the proposed sensor fabrication process.

Stability was investigated by storing the electrodes at room temperature for 14 days. Following this period, 107.2% of the initial current response was retained, with a shift in average peak currents from 436.0 μA to 467.3 μA . This 7.2% signal increase is analytically interpreted as a minor baseline drift resulting from the dynamic evolution of the electroactive surface. According to the Randles-Sevcik equation ($I_p \propto A$) [37], this points to an increase in the effective electroactive surface area. Given the highly porous nature of the HAp-like scaffold and the reactive copper species, this positive drift is attributed to gradual surface aging driven by two main factors. First, trace hydration of the hygroscopic HAp-like scaffold occurs even under desiccated storage conditions. As demonstrated by Khtaoui *et al.* (2021), hydroxyapatite structures readily adsorb ambient moisture to form a hydrated layer, which enhances surface ionic conductivity and reduces interfacial resistance [38]. Second, spontaneous mild oxidation of the copper surface acts as a contributing factor. Prolonged oxidation promotes in situ growth of CuO nanostructures, which roughen the surface and increase the surface-to-volume ratio, creating additional active sites for the redox reaction [39]. Together, this time-dependent hydration and oxidation improve electrolyte accessibility to the porous microstructure, resulting in the observed slight increase in peak current rather than signal degradation. Although the electroactive surface dynamically ages over time, the observed drift remains well within the acceptable $\pm 10\%$ analytical tolerance. Therefore, the sensor remains functional for at least two weeks, though periodic recalibration may be advised for highly precise measurements.

3.6. Real matrix application.

The CuO/HAp-like/PGE platform was developed as a proof-of-concept for the liquid-phase detection of MEK. To assess its applicability across different environments, a two-step validation approach was used. The biomedical application was simulated using a breath "interference pool" (described in detail in Section 3.4) due to the logistical and ethical constraints of collecting standardized human breath condensate. For an evaluation in a genuine complex matrix, industrial wastewater was utilized.

Wastewater samples from three commercial printing facilities (Samples A, B, and C) were analyzed. The standard addition method was adapted for the signal-off mechanism by plotting the signal drop ($\Delta I = I_{\text{blank}} - I_{\text{measured}}$) against the added MEK concentration. A spike-recovery test was also performed to evaluate analytical accuracy.

Sample A served as a model for standard, filtered industrial effluent. The standard addition curve was linear ($R^2 = 0.995$) across sequential MEK additions of 1.0, 3.0, and 5.0 mM. Based on the regression equation ($\Delta I = 13.76x + 1.97$), the absolute x-intercept was 0.14 mM. Accounting for the 1:9 dilution applied during sample preparation, the initial MEK concentration in the original wastewater was 1.4 mM (Table 5). The recovery rates for the spikes ranged from 71.6% to 113.2%, with an average recovery of 93.7%. These results indicate that the sensor can quantify MEK in matrices with moderate interference.

Table 5. Determination of MEK and spike-recovery analysis in industrial wastewater (Sample A).

Added MEK (mM)	Measured ΔI (μA)	Calculated Added Concentration (mM)	Recovery (%)
0.0	2.88	0.14 (Initial)	-
1.0	11.83	0.716	71.6
3.0	48.74	3.398	113.2
5.0	68.28	4.819	96.4

*Average Recovery: 93.7%

To determine the sensor's operational limitations, Samples B and C were analyzed. In Sample B, which contained a higher initial MEK concentration (estimated at ~ 15.8 mM), the signal drop plateaued after the initial additions. This indicates rapid saturation of the HAp-like adsorption sites, which prevents linear regression at higher concentrations.

Sample C exhibited strong matrix interference, typical of untreated effluents. Adding 1.0 mM MEK resulted in a signal increase (443.36 μA) instead of a drop, accompanied by current fluctuations during further additions. This response suggests the presence of competing electroactive species or surface-active compounds in the untreated effluent, which likely interfered with MEK adsorption through competitive binding or non-specific blocking of active sites.

Overall, while the sensor functions effectively in filtered samples (Sample A), complex industrial effluents (Samples B and C) require specific pre-treatment steps, such as filtration or further dilution, before electrochemical measurement.

3.7. Comparison with reported literature.

The analytical performance of the fabricated CuO/HAp-like/PGE sensor was benchmarked against a wide spectrum of sensing technologies, ranging from advanced gas sensors to liquid-phase systems (Table 6). It is observed that the field is currently dominated by gas-phase chemiresistive sensors. Ultralow detection limits (down to the ppb level) have been reported for SnO_2/NiO -modified ZnO nanosheets [39] and $\text{Co}_3\text{O}_4/\text{SnO}_2$ hollow spheres [40]. However, effective operation is typically restricted to elevated temperatures (>200 $^\circ\text{C}$),

which limits the direct applicability of these devices in temperature-sensitive biological fluids [41].

Table 6. Comparison of the analytical performance of the proposed CuO/HAp-like/PGE sensor with other reported MEK sensors.

Electrode / Sensing Material	Method / Phase	Analyte	Linear Range	LOD	Ref.
Co-ZnO (ZIF-67 Derived)	Chemiresistive (Gas)	MEK	1 – 100 ppm	0.045 ppm	[39]
Co ₃ O ₄ /SnO ₂ Hollow Spheres	Chemiresistive (Gas)	MEK	1 – 100 ppm	1 ppb	[40]
V ₂ O ₅ Nanostructures	Cataluminescence (Gas)	MEK	1.4 – 555 mM	0.97 µM	[41]
Ag-Cu Alloy NPs	EIS (Liquid)	MEK	0.1 µM – 1.0 mM	0.10 µM	[42]
Au-Ag / Chloroplasts	CV (Liquid)	MEK	1.3 – 10.4 mM*	Not reported	[43]
CuO/HAp-like/PGE	SWV (Liquid)	MEK	0.1 – 5.0 mM	1.04 mM	This Work

*Calculated from the reported data.

In the domain of liquid-phase detection—which is essential for physiological monitoring—noble metal-based approaches like Ag-Cu alloys [42] and biosynthesized Au-Ag interfaces [43] have been shown to offer effective sensitivity but are often associated with complex and costly synthesis protocols.

To address these limitations, a single-use and affordable pencil graphite substrate was utilized in this study. Although the obtained LOD (1.04 mM) is higher than that of gas-phase counterparts, the proposed sensor indicated promising potential for monitoring the clinically relevant range of ketone bodies in biofluids. Furthermore, in contrast to the complex heterojunctions required for gas sensing, a straightforward "Signal-Off" mechanism operating at room temperature was validated, offering a robust alternative for routine screening.

4. Conclusions

In this work, a cost-effective and disposable electrochemical sensing platform based on a copper oxide-decorated hydroxyapatite-like modified Pencil Graphite Electrode (CuO/HAp-like/PGE) was successfully developed for the reliable determination of Methyl Ethyl Ketone (MEK). A pivotal finding of this study is the elucidation of a distinct adsorption-induced “Signal-Off” sensing mechanism, which was independently validated via *ex-situ* GC-MS analysis. The sensor provided two linear dynamic ranges, covering both low-concentration screening and high-concentration quantification.

Beyond its analytical sensitivity, the platform showed selectivity against structural analogs and a stable response over 14 days (within ±10%), attributed to surface hydration of the HAp-like scaffold. These features address the critical limitations of conventional, bulky GC-MS techniques by providing a rapid, room-temperature, and easily deployable alternative.

While the current system is optimized and validated in controlled laboratory environments using standard supporting electrolytes, it provides a stable, selective foundation for complex-matrix analysis.

Given the disposable nature of the PGE substrate and the interface's validated performance, this study provides proof of concept for portable liquid-phase MEK monitoring. Future investigations will focus on translating this architecture into a point-of-care (POC) prototype and validating its diagnostic efficacy using large-scale clinical breath-condensate cohorts, alongside real-time industrial safety monitoring.

Author Contributions

Conceptualization, S.V.I., F.K., S.G., and E.B.D.; methodology, S.V.I.; formal analysis, S.V.I.; investigation, S.V.I.; data curation, S.V.I.; writing—original draft preparation, S.V.I.; writing—review and editing, S.V.I., F.K., S.G., and E.B.D. All authors have read and agreed to the published version of the manuscript.

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Data supporting the findings of this study are available upon reasonable request from the corresponding author.

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Conflicts of Interest

The authors declare no conflict of interest.

Artificial Intelligence Disclosure

Artificial intelligence-based tools were used solely for language editing and stylistic refinement of the manuscript. The authors remain fully responsible for the content of this work.

Abbreviations

Abbreviation	Definition
PGE	Pencil Graphite Electrode
HAp	Hydroxyapatite
HAp-like	Hydroxyapatite-like interlayer (calcium-deficient or amorphous calcium phosphate)
MEK	Methyl Ethyl Ketone
PBS	Phosphate Buffered Saline
CuO	Copper Oxide
CuNPs	Copper Nanoparticles
CuONPs	Copper Oxide Nanoparticles
CV	Cyclic Voltammetry

Abbreviation	Definition
SWV	Square Wave Voltammetry
VOCs	Volatile Organic Compounds
SEM	Scanning Electron Microscopy
EDX	Energy-dispersive X-ray Spectroscopy
GC-MS	Gas Chromatography-Mass Spectrometry
LOD	Limit of Detection
RSD	Relative Standard Deviation
POC	Point-of-care

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