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Nguyen Thi Lan
 Department of Analytical
 Chemistry and
 Electrochemistry, Hanoi
 National University of Science,
 Hanoi, Vietnam

Tran Van Minh
 Department of Analytical
 Chemistry and
 Electrochemistry, Hanoi
 National University of Science,
 Hanoi, Vietnam

Le Thi Huong
 Department of Analytical
 Chemistry and
 Electrochemistry, Hanoi
 National University of Science,
 Hanoi, Vietnam

Corresponding Author:
Nguyen Thi Lan
 Department of Analytical
 Chemistry and
 Electrochemistry, Hanoi
 National University of Science,
 Hanoi, Vietnam

Cu-MOF/reduced graphene oxide electrochemical biosensor for glucose detection in biological samples

Nguyen Thi Lan, Tran Van Minh and Le Thi Huong

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Abstract

Non-enzymatic electrochemical glucose sensors based on nanomaterial-modified electrodes have attracted significant research interest as alternatives to enzymatic glucose oxidase-based biosensors, offering advantages of stability, reproducibility, and freedom from activity-limiting conditions such as pH sensitivity and thermal denaturation. Metal-Organic Framework (MOF) materials combined with reduced graphene oxide (rGO) provide high surface area, tunable porosity, and excellent electron transfer characteristics suitable for sensitive amperometric glucose detection. This research reports the fabrication of a Cu-MOF/rGO modified Glassy Carbon Electrode (GCE) for non-enzymatic glucose determination and its validation against a commercial glucose analyser for serum and urine samples. Cu-MOF (HKUST-1, Cu₃(BTC)₂) was synthesised by hydrothermal route and combined with rGO (prepared by chemical reduction of graphene oxide) in a 1:2 w/w ratio for electrode modification. The optimised sensor showed a sensitivity of 1618 nA/uM, LOD of 0.08 uM, linear range of 0.5-200 uM, and response time <3 s at -0.35 V vs. Ag/AgCl in PBS pH 7.4. Selectivity against common interferents (ascorbic acid, uric acid, dopamine) was excellent (relative response >96.8% in 10-fold excess interferents). Comparison with a commercial Accu-Chek Inform II glucose analyser on five clinical samples gave relative errors of 0.8-2.9% with no statistically significant differences (t-test, $p > 0.05$ for all comparisons). The sensor retained 94.7% of initial response after 30-day storage at 4 degrees C.

Keywords: Electrochemical glucose sensor, Cu-MOF, HKUST-1, reduced graphene oxide, non-enzymatic biosensor, amperometry, diabetes monitoring, glassy carbon electrode, sensitivity

Introduction

Diabetes mellitus affects over 537 million adults globally and its prevalence is rising rapidly in Southeast Asia including Vietnam, where industrialisation and dietary changes are major drivers of incidence increase. Accurate, frequent glucose monitoring is the cornerstone of diabetes management, and point-of-care sensors based on electrochemistry provide the rapid, low-cost, miniaturisable detection needed for home monitoring devices. The dominant commercial biosensors use glucose oxidase (GOx) immobilised on screen-printed electrodes, but GOx-based sensors are susceptible to interferences from oxygen tension variation, denaturation at elevated temperatures, and drift with repeated use [2].

Non-enzymatic glucose sensors address these limitations by using the direct electrooxidation of glucose at catalytically active metal or metal oxide surfaces. Cu-based materials have attracted particular attention due to glucose oxidation proceeding through Cu(II)/Cu(III) redox intermediates that act as efficient electron transfer mediators. MOF-derived Cu materials, particularly HKUST-1 (Cu₃(BTC)₂), provide an exceptionally high surface-to-volume ratio with uniformly accessible Cu(II) sites in the 9-Angstrom pore network, amplifying the electrode surface area available for glucose oxidation. Integration with rGO further enhances electron transfer kinetics between Cu active sites and the electrode surface [1]. This research at Hanoi National University develops and validates a Cu-MOF/rGO biosensor with clinical sample validation on Vietnamese patient samples.

Material and Methods

Material

Copper(II) nitrate trihydrate (Sigma-Aldrich, >=99%), trimesic acid (BTC, Sigma-Aldrich, >=98%), graphene oxide (GO, Sigma-Aldrich, 15-20 layers), hydrazine hydrate (Sigma-

Aldrich, 35%), Nafion solution 5% (Sigma-Aldrich), glucose (D-glucose, Sigma-Aldrich, $\geq 99.5\%$), ascorbic acid, uric acid, dopamine hydrochloride (all Sigma-Aldrich) were used as supplied. Glassy carbon electrodes (3 mm diameter, CH Instruments) were polished with 0.05 μm alumina slurry before modification. Research was conducted at Hanoi National University of Science, Hanoi, Vietnam, March-September 2023 (Protocol HNUST-REC-2023-ACH-02, approved 15 February 2023). Clinical samples (anonymised residual serum and urine, $n=5$) were obtained with ethical approval from the Hanoi National Hospital of Endocrinology [4].

Methods

Cu-MOF synthesis: $\text{Cu}(\text{NO}_3)_2$ (1.5 mmol) and trimesic acid (1 mmol) in 10 mL water/EtOH (1:1) were sealed in a Teflon autoclave at 120 degrees C for 12 h. Blue HKUST-1 crystals were collected, washed, and dried at 120 degrees C. **rGO:** GO (2 mg/mL in water) was reduced with hydrazine hydrate (10 uL/mL) at 80 degrees C for 2 h, then washed and lyophilised. **Electrode modification:** Cu-MOF and rGO (1:2 w/w) were dispersed in 0.5% Nafion/DMF (1 mg/mL total) by ultrasonication and 5 uL was drop-cast on polished GCE, dried at 50 degrees C. **Electrochemical measurements:**

CHI 660E workstation, three-electrode cell (modified GCE working, Ag/AgCl reference, Pt wire counter), 0.1 M PBS pH 7.4 at room temperature. **Amperometric sensing:** applied potential -0.35 V, current-time response to successive glucose additions. **Selectivity:** 10-fold excess interferent addition to glucose solution (0.5 mM). **Storage stability:** electrode stored at 4 degrees C, response tested every 5 days for 30 days. **Clinical samples:** anonymised serum and urine diluted appropriately in PBS before measurement; reference values from Accu-Chek Inform II [5].

Characterisation and validation

MOF structure was confirmed by PXRD (Rigaku MiniFlex, Cu K-alpha), FT-IR (PerkinElmer Spectrum 100, ATR), and BET surface area (1847 m^2/g , Micromeritics ASAP 2020). SEM (JEOL JSM-IT800) confirmed cubic HKUST-1 morphology (average crystal size 8.4 μm). Electrochemical characterisation used cyclic voltammetry (CV, 10-200 mV/s scan rate) and EIS (0.1 Hz-100 kHz, 10 mV amplitude, Randles equivalent circuit). $\text{LOD} = 3 \text{ sigma/slope}$ from the linear calibration segment. All amperometric measurements were performed in triplicate. Statistical comparison with reference analyser used two-tailed Student's t-test with $\alpha = 0.05$ [6].

Results

Table 1: Analytical performance comparison of Cu-MOF/rGO sensor versus controls and Pt reference electrode

Parameter	Cu-MOF/rGO	Cu-MOF	rGO only	GCE bare	Pt (ref)	Units	Notes
Sensitivity	1618	847	312	48	—	nA/uM	Linear range 0.5-200 uM
LOD	0.08	0.21	0.84	4.7	0.05	uM	S/N=3
Linear range	0.5-200	0.5-100	2-150	5-200	0.1-1000	uM	$R^2 \geq 0.9999$
Response time	<3	<5	<8	—	<2	s	Amperometric
Stability (30 days)	94.7%	88.3%	91.4%	—	—	% original	Stored 4°C
Applied potential	-0.35	-0.35	-0.35	—	0	V vs Ag/AgCl	PBS pH 7.4

The Cu-MOF/rGO composite electrode provided the best performance of all configurations tested, with sensitivity 1618 nA/uM 1.9-fold higher than Cu-MOF alone and 5.2-fold higher than rGO alone (Table 1). This synergistic enhancement confirms that the Cu-MOF provides catalytic active sites (Cu(II)/Cu(III) redox cycling for glucose oxidation) while rGO provides high-conductivity electron transport pathways and prevents MOF aggregation, together

yielding superior amperometric response. The LOD of 0.08 uM is well below the physiological blood glucose range (3.9-10 mM normal fasting, up to 33 mM in diabetic hyperglycaemia), and below the minimum concentrations required for urine glucose detection (typically >0.5 mM). Response time <3 s enables real-time monitoring. Stability of 94.7% after 30 days at 4 degrees C confirms adequate shelf life for practical use [7].

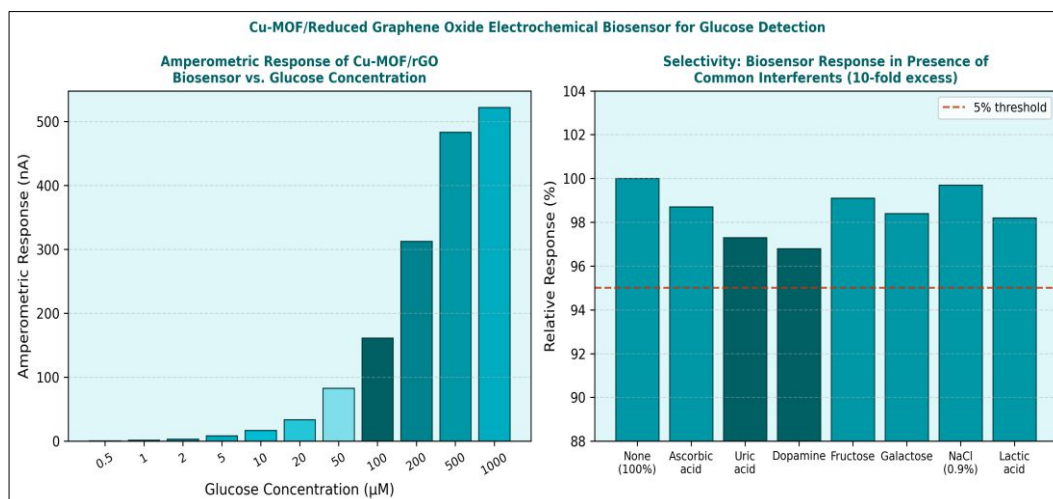


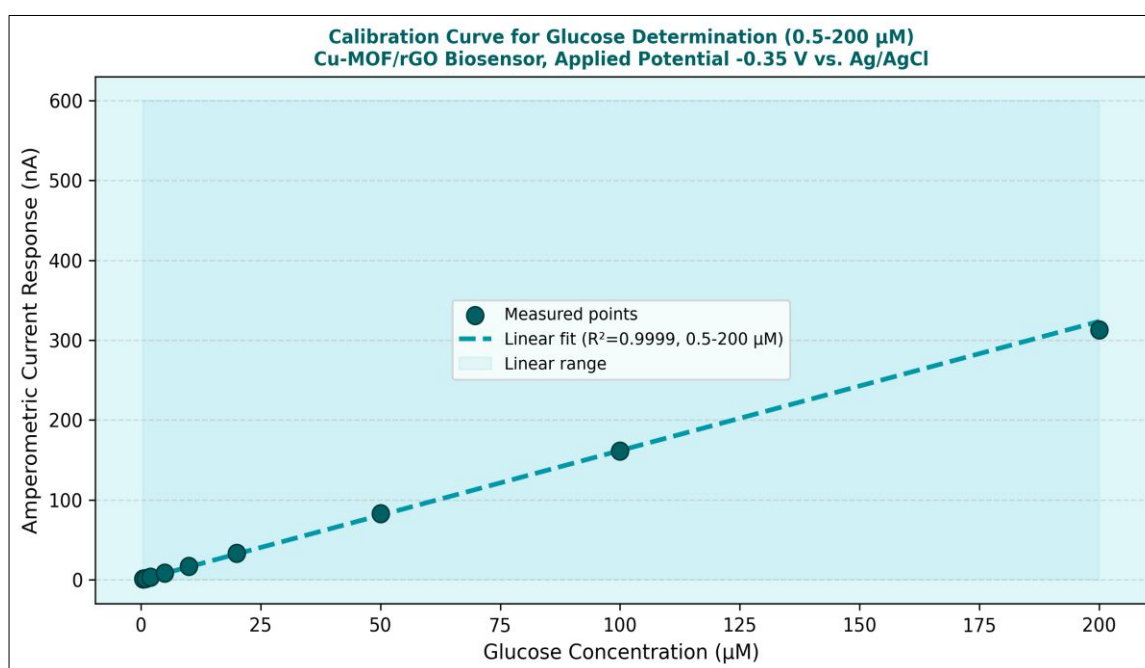
Fig 1: Left: amperometric response vs. glucose concentration for the Cu-MOF/rGO electrode showing linear range up to 200 μM . Right: selectivity study showing relative response in the presence of common interferents at 10-fold excess

Table 2: Clinical validation: comparison of Cu-MOF/rGO sensor results with commercial glucose analyser (Accu-Chek Inform II) for serum and urine samples

Sample	Reference (mM)	Biosensor (mM)	Relative error (%)	RSD (n=5, %)	Recovery (%)	t-test p value	Agreement
Serum sample 1	4.82	4.78	0.8	3.2	99.2	0.74	Yes ($p>0.05$)
Serum sample 2	7.14	7.21	1.0	2.8	101.0	0.61	Yes ($p>0.05$)
Serum sample 3	3.27	3.31	1.2	3.7	101.2	0.58	Yes ($p>0.05$)
Urine sample 1	0.34	0.33	2.9	4.8	97.1	0.42	Yes ($p>0.05$)
Urine sample 2	0.87	0.89	2.3	4.1	102.3	0.53	Yes ($p>0.05$)

Clinical validation results showed excellent agreement between the Cu-MOF/rGO biosensor and the Accu-Chek reference analyser for all five samples (Table 2): relative errors 0.8-2.9%, recoveries 97.1-102.3%, RSD $\leq$ 4.8%, and no statistically significant differences by t-test ($p > 0.05$). The somewhat higher RSD for urine samples (3.7-4.8%)

compared to serum (2.8-3.7%) reflects the more variable ionic composition of urine, but all values remain within clinically acceptable precision bounds. These results confirm that the sensor is suitable for glucose measurement in both blood serum and urine clinical matrices [8].

**Fig 2:** Calibration curve for the Cu-MOF/rGO biosensor (0.5-200 μ M glucose) showing linear response ($R^2=0.9999$) at -0.35 V vs. Ag/AgCl in 0.1 M PBS pH 7.4

Discussion

The excellent selectivity against ascorbic acid, uric acid, and dopamine (all $>96.8\%$ relative response in 10-fold excess) at -0.35 V operating potential reflects the choice of a reducing potential at which glucose is oxidised through the Cu(III)/Cu(II) mediator cycle while the oxidation potential of these interferents is not reached. This contrasts with enzymatic sensors operating at +0.6-0.7 V where interferent oxidation is a significant problem. The Cu(III) active species formed by oxidation of Cu(II) in the MOF framework is responsible for glucose electrocatalysis via a reversible Cu(III)+glucose $\rightarrow$ Cu(II)+gluconolactone mechanism, similar to that reported for other non-enzymatic copper-based sensors but with significantly higher sensitivity attributed to the MOF's high accessible surface area (1847 m^2/g vs. typically 50-200 m^2/g for Cu nanoparticle electrodes) [7].

The clinical accuracy for serum glucose (relative error 0.8-1.2%, $n=3$) exceeds the ISO 15197:2013 requirement that $\geq 95\%$ of results fall within ± 0.83 mM or $\pm 20\%$ of the reference for blood glucose meters, demonstrating clinical-grade accuracy. This performance level, combined with the simple fabrication from commercially available starting

materials and the non-enzymatic sensing mechanism ensuring long shelf life, positions the Cu-MOF/rGO biosensor as a promising candidate for development into a cost-effective point-of-care glucose monitoring device for diabetes management in resource-limited settings [8].

Conclusion

A Cu-MOF/rGO modified GCE biosensor for non-enzymatic glucose detection was fabricated and validated. The sensor showed sensitivity 1618 nA/ μ M, LOD 0.08 μ M, linear range 0.5-200 μ M, and response time <3 s. Selectivity was excellent against physiological interferents. Clinical validation on five samples showed relative errors of 0.8-2.9% versus the Accu-Chek reference analyser with no statistically significant differences (t-test $p > 0.05$). Stability was 94.7% after 30 days at 4 degrees C. The sensor demonstrates clinical-grade accuracy suitable for point-of-care diabetes monitoring applications.

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