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Coated Wire, Coated Graphite and Modified Carbon Paste Electrodes for Potentiometric Determination of Azithromycin

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Abstract

For the assessment of the drug azithromycin (AZ) in biological and pharmaceutical samples, three different types of ion selective electrodes were created: the modified carbon paste electrode (MCPE), coated graphite electrode (CGE), and coated wire electrode (CWE). The electrodes followed the Nernst equation in the range (1.0×10^{-7} - 1.0×10^{-1} , 1.0×10^{-6} - 1.0×10^{-1} and 1.0×10^{-5} - 1.0×10^{-1})M range, with a slope of (58.355, 57.937, and 56,127) mV/decade and a low detection limit of (5.0339×10^{-8} , 5.111×10^{-7} and 4.8486×10^{-6}) M for (MCPE, CGE and CWE)electrodes respectively. The suggested sensors additionally demonstrated long-term stability and worked following preparation without significant changes in the potential or slope values, the analysis method is very sensitive and selective, and the t-test and F-test at a 95% confidence level were used to perform the statistics precisely and accurately.

Keywords : Azithromycin, Coated wire electrode, Coated graphite electrode, multiwall carbon nanotubes**.**

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أقطاب السلك المطلي،الجرافيت المطلي وعجينة الكربون المحورة لتقدير الأزيثروميسين بطريقة جهدية

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الخلاصة

لتقدير عقار الأزيثروميسين في العينات البيولوجية والصيدلانية، تم تحضير ثلاثة أنواع مختلفة من الأقطاب الانتقائية الأيونية: قطب عجينة الكربون المحورة , قطب الجرافيت المطلي وقطب السلك المطلي. اتبعت الأقطاب معادلة نيرنست في المدى (1×10^{-1} - 1.0×10^{-7}، 1×10^{-1} - 1×10^{-6} و1×10^{-1} - 1×10^{-5}) مولاري , مع ميل قدره (58,355، 57,937، 56,127) mV/decade وذات حد كشف منخفض قدره ($5,339\times10^{-8}$، $5,111\times10^{-7}$، $4,8486\times10^{-6}$) مولاري للقطب عجينة الكربون المطور , قطب الجرافيت المطلي وقطب السلك المطلي على التوالي . بالإضافة إلى ذلك، أظهرت الاقطاب المقترحة ثباتًا على المدى الطويل دون تغييرات في قيم الجهد أو الميل. بالإضافة إلى ذلك، فإن طريقة ,التحليل حساسة للغاية وانتقائية و لإثبات ان الإحصائيات ذات دقة وتوافق تم استخدام اختبار F-test وt-test عند مستوى ثقة 95% .

الكلمات المفتاحية: ألازيثرومايسين، قطب السلك المطلي، قطب الجرافيت المطلي، أنابيب الكربون النانوية متعددة الجدران.

Introduction

Azithromycin (AZ) chemically it is (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)13-((2,6-Dideoxy-3-C-methyl-3-O-methyl-alpha-L-ribo-hexopyranosyl)oxy)-2-ethyl-3,4,10-trihydroxy3,5,6,8,10,12,14 heptamethyl-11-((3,4,6-trideoxy-3-(dimethylamino)-beta-D-xylo-hexopyranosyl)oxy)-1-oxa-6-azacyclopentadecan-15-one. has chemical structure showed in figure(1) [1]. Is an antibiotic is used to treat a wide range of bacterial infections caused by gram-positive and gram-negative bacteria [2,3].The presence of the nitrogen atom in the ring changed the pharmacokinetics, chemistry, and microbiological properties of AZ. By inhibiting the synthesis of proteins, it is able to stop the growth of bacteria. [4] Many adults and children use it for respiratory tract infections, skin and soft tissue infections, moderate otitis media, sinusitis, pharyngitis, cystic fibrosis, severe bronchitis, GIT infections, tonsil infections, and as an anti-

inflammatory in patients with chronic obstructive pulmonary disease[5,6]. And is among the antibiotics with the top sales worldwide [7].There were different published articles for the analysis of AZ in different pharmaceutical and biological forms various analysis techniques are used in these published articles such as spectrophotometry [8-10] ,HPLC [11,12], RP-HPLC [13-15], glassy carbon [16], cyclic voltammetry [17] flow injection-Amperometric [18] and UV Radiation [19].

The current work aims to develop a precise, sensitive, and selective method for an assessment of AZ in pure, pharmaceutical and biological forms using modified electrode with MWCNTs (MCPE) and unmodified electrodes (CGE and CWE). For all sensors, the basic analytical parameters were calculated and compared.

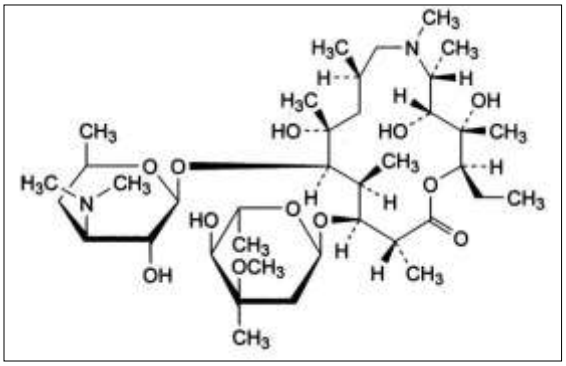

Figure 1: chemical Structure of Azithromycin

Material and Methods

1. Apparatus

HANNA instruments 213 pH meter, Jenway 3310 pH meter, and calomel electrodes from a Swiss supplier were used for laboratory potentiometric measurements. For the elemental analysis CHN, Perkin Elmer USA 2400 series II was utilized.

2. materials

Deionized distilled water was used to prepare the stock solutions. The following chemical martials were used in the work: Azithromycin (AZ) (SDI ,Samara-Iraq) Polyvinyl chloride (PVC) (Fluka) , Di butyl phthalate (Fluka), Graphite rod (Sony corporation), Tetra hydro

furan.(THF) (BDH) , phosphmolybdic acid (PMA) (BDH) multiwall carbon nanotubes (MWCNTs) (Fluka) . Pharmaceutical Sample such as (Azax 500 mg) tablets NOBEK ILAC-Turkiya, (CITROMYCIN 500 mg) tablets, Citropharma lnc- Canada and (ZAHA 200 mg/5 ml) syrup Ajanta pharma limited India were obtained from local pharmacies.

3. Pharmaceutical Sample preparation

3.1 (CITROMYCIN 500 mg/tablet) and (Azax 500 mg/tablet)

For each sample (CITROMYCIN and Azax) three tablets were crushed using pestle and mortar and then dissolved appropriate amount in (100) ml of deionized distilled water to obtain (1.0×10^{-2}) M. more dilute solutions for each sample were prepared by appropriate dilution with deionized distilled water.

3.2 (ZAHA 200mg/5 ml syrup)

Solution of (1.0×10^{-2}) M of ZAHA syrup was prepared using 100-mL volumetric flask where 19.6 ml accurately was transferred, deionized distilled water was used to dissolve and completed the volume. More dilute solutions for each sample were prepared using appropriate dilution with deionized distilled water.

3.4 stock solution of AZ drug

stock solution of AZ drug 1.0×10^{-1} M was prepared using 100-mL volumetric flask where 0.785 g accurately weighed was transferred, deionized distilled water was used to dissolve it and completed the volume Drug was diluted appropriately with deionized distilled water to obtain diluted solutions (1.0×10^{-8} -1.0×10^{-2}) M.

3.5 Stock Solutions of Interfering Ions

By dissolving appropriate amount of these compounds NaCl , KCl , NaBr , $CaCl_2$, $NaNO_3$, Na_2SO_4 , Na_2CO_3 , Glucose, Fructose and Starch in 100 ml deionized distilled water in volumetric flasks, solutions of 1.0×10^{-3} M were prepared.

3.6 Preparation of ion-pair

Yellow precipitate formed when 50 mL (1.0×10^{-2}) M of PMA was mixed with 25 mL (1.0×10^{-2}) M of AZ in order to prepare he ion-pair AZ-PMA. The precipitate was filtered, washed several times with deionized distilled water and allowed to dry for few days at room temperature. Elemental analysis was used to prove the expected composition of the ion-pair complex, which has a molar ratio of 1:1 for AZ-PMA , the obtained results as indicated in table 1.The calculated and found elemental analysis data for the ion-pair complex are in good agreement with its structure.

Table 1: Elemental analysis of the (AZ-PMA) ion pair

AZ-PMA			
Element	%C	%H	%N
Found	15.02	0.39	0.93
Calculated	15.00	0.4	0.92
Formula	$[C_{38}H_{72}N_2O_{12}][H_3PO_{40}Mo_{12}].26H_2O$		

3.7 Preparation of membrane

All of the components utilized to prepare the membrane mixture were precisely weighed: [60% plasticizer di butyl phthalate (DBP), 30% poly vinyl chloride (PVC), and 10% ion-pair (AZ-PMA)]. and then dissolved in 10 mL of an organic solvent (THF) and stirred for 10 minutes to get a homogeneous mixture.

3.8 Construction of Coated Graphite Electrode (CGE)

It was fabricated using pure graphite rod a (5.5 cm length and 8.0 mm diameter) and surrounded with polyethylene tube. The electrode surface was coated with the membrane by repeatedly immersing one end of the graphite rod in the coating mixture (prepared as previously described in above paragraph 2-6) and allowing dry in the air. The other end of the rod was connected to a pH-meter using insulated copper wire [20].

3.9 Construction of Coated Wire Electrode (CWE)

Copper wire was used to prepare CWE, and it was washed with HNO_3, rinsed with deionized distilled water, dried with an organic solvent (acetone), and then allowed to dry. The copper wire should have tight insulation and be (8 cm length and 2 mm in diameter). The wire was left 1 cm from both ends exposed and un insulated. one end of the wire was coated with coating mixture (prepared as previously described in paragraph 2-6 above) and allowed to dry in the air. The electrode was then dunking in an AZ solution of 1×10^{-2} M and the other end of the copper wire was connected to a pH meter[21].

3.9 Construction of Modified Carbon Paste Electrode (MCPE)

In an agate mortar, accurate weights of (0.1) g of suitable ion pairs, (0.59) g of extremely pure graphite powder, plasticizer (0.3) g DBP, and (0.01) g multiwall carbon nanotubes were mixed to prepare the sensing electrodes. This mixture paste was packaged carefully in a plastic tube with a 3 mm i.d and a 4 mm length. The new carbon paste surface was gently polished with filter paper to produce a smooth and shiny surface[22].

Results and Discussion

1. Potentiometric response

Calomel reference electrode immersed with fabricated electrodes MCPE , CGE and CWE in AZ drug solutions (1.0×10^{-8} - 1.0×10^{-1})M were used for potentiometric measurements. For each solution the E (mV) was recorded and calibration curve was plotted E(mV) versus –log [AZ] as shown in figure (2). Table (2) shows the parameters of the electrodes, including the detection limit, the slope, and the range of linearity of the characteristics. where it can be observed that the electrode prepared with MWCNTs has more advantages than the electrode that wasn't modified. showed an almost constant slope of the electrode, a lower detection limit, a wider liner range, and high stability over time.

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Table 2 : Analytical parameters for the fabricated electrodes

ELECTRODE TYPE	LINER RANGE M	SLOPES (MV DECADE^{-1})	UPPER DETECTION LIMIT M (UDL)	LOWER DETECTION LIMIT M (LDL)
MCPE	1.0×10^{-7} - 1.0×10^{-1}	58.355	0.2073	5.0339×10^{-8}
CGE	1.0×10^{-6} - 1.0×10^{-1}	57.937	0.2080	5.1110×10^{-7}
CWE	1.0×10^{-5} - 1.0×10^{-1}	56.127	0.2080	4.8486×10^{-6}

The present work is considered more sensitive and wider rang than other methods according to Table 3, and this method is easy to use and safe.

Table 3: Comparison between MCPE and other methods for determination AZ drug

LOWER DETECTION LIMIT M	LINER RANGE M	REFERENCE
5.034×10^{-8}	1×10^{-1} - 1×10^{-7}	MCPE*
1.37×10^{-6}	(0.53×10^{-5} - 2.56×10^{-5})	[9]
1.8×10^{-6}	(1.28×10^{-5} - 6.4×10^{-5})	[11]
2.56×10^{-5}	(6.41×10^{-5} - 19.23×10^{-5})	[14]
3.03×10^{-9}	1×10^{-5} - 1×10^{-8}	[16]

MCPE* was the constructed electrode in present work

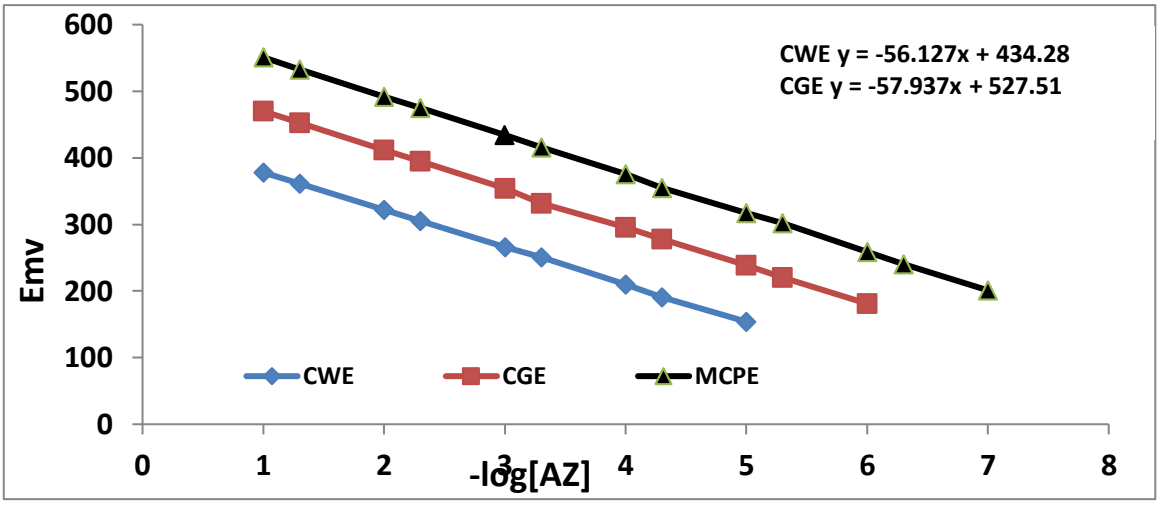

Figure 2 : Calibration curve of the fabricated electrodes.

2. Effect of pH

The optimal pH range in which the electrode potential is steady and independent on the pH of the sample was determined. For this, the electrode potential was measured in a AZ solution (1.0×10^{-4}) M with a pH range of (1–10). NaOH and/or HCl solutions were used to adjust the pH . Figure 3 indicates the relationship between the electrode potential and the pH value of the solutions for each electrode. It is obvious that the MCPE electrode had a wider pH range (2-7) than the unmodified electrode CWE and CGE (3-5) for both and was more resistant to the interfering effects of H^+ ions.

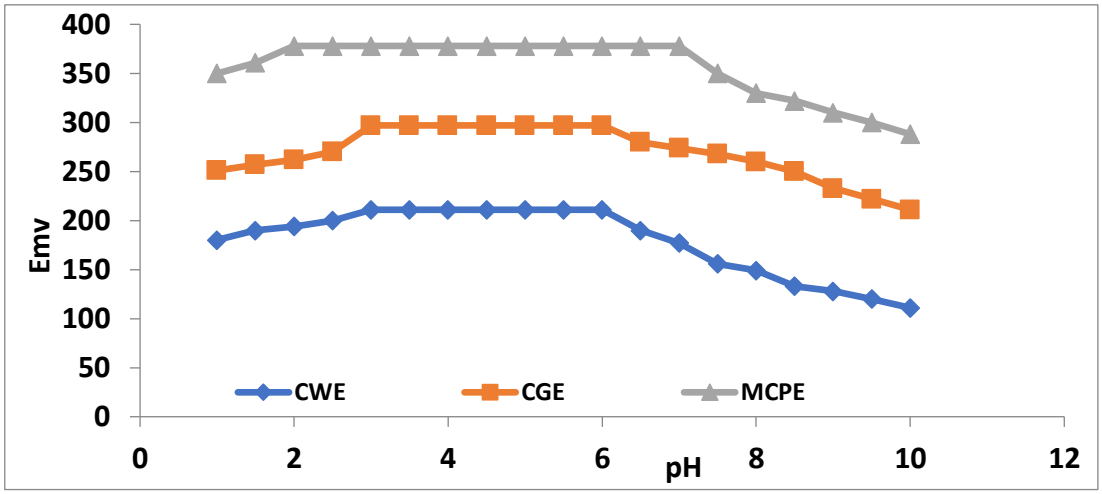

Figure 3 : Effect of pH for CWE,CGE and MCPE electrodes

3. Effect of temperature

A series of various temperature values (5 - 85)°C were used to investigate the effect of temperature, by changing the temperature of the pure drug solution for a concentration of (1.0×10^{-4}) M AZ solution, the change in potential was measured. The temperature and the measured potential were plotted. The results in (figure 4) showed that for both CWE and CGE electrodes, the optimal temperature for use is (10 – 50) °C, whereas the modified electrode with MWCNTs had a wider temperature range (10 – 70) °C. The results indicate all of the construction electrodes are highly thermally stable without obviously changing their Nernstian slope.

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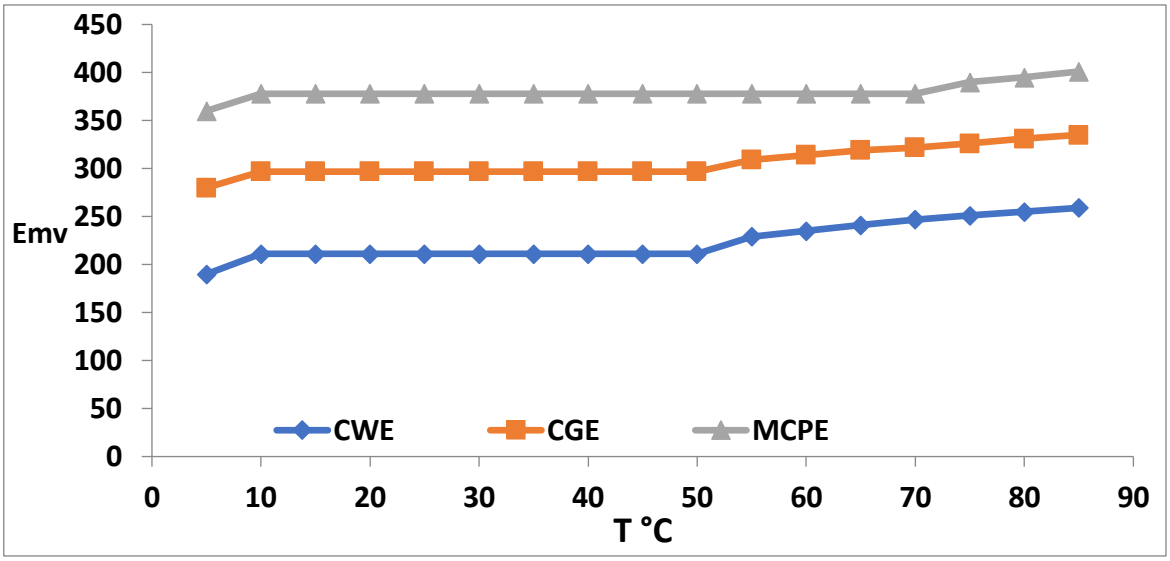

Figure 4 : Effect of temperature on the response of (MCPE, CGE, and CWE) electrodes

4. Selectivity of the studied sensors

To determine the selectivity coefficient for manufactured electrodes (MCPE,CGE and CWE), SSM was used [23]. In this method, the potential of newly fabricated electrodes was measured, AZ drug solution and foreign substances (organic and inorganic compounds) solution are presented in same concentrations in two separate solutions, the selectivity coefficient was calculated using the equation shown below: Log K = (Ej- Ei)/S, where Ei is the electrode potential in AZ solution (1.0×10^{-3}) M, Ej is the electrode potential of the interfering ion in (1.0×10^{-3})M, and S is the calibration curve's slope. The results in table 4 indicates the K values and reveals a high selectivity of the electrodes (MCPE, CGE and CWE) towards the AZ. It also reveals that both positive and negative ions had no effect on the stability of the electrodes, and the K value of interference was very low for each electrode, indicating that the associated ions in the dosage form would not cause interferences.

Table 4: foreign substance and its effect on the constructed electrodes

FOREIGN (1×10^{-3})M	SELECTIVITY COEFFICIENT VALUES $K_{I,J}^{POT}$		
	AZ-PMA-DBP		
	CWE	CGE	MCPE
Na^{1+}	6.19×10^{-1}	4.09×10^{-1}	3.80×10^{-1}
K^{1+}	4.44×10^{-1}	3.91×10^{-1}	3.60×10^{-1}
Ca^{2+}	5.29×10^{-2}	4.79×10^{-2}	4.11×10^{-2}
Cl^{1-}	8.40×10^{-2}	7.52×10^{-2}	6.99×10^{-2}
Br^{1-}	9.84×10^{-2}	9.00×10^{-2}	8.27×10^{-2}
CO_3^{2-}	7.00×10^{-2}	6.67×10^{-2}	6.09×10^{-2}
SO_4^{2-}	3.29×10^{-2}	2.72×10^{-2}	1.81×10^{-2}
Glucose	9.88×10^{-3}	8.00×10^{-3}	5.71×10^{-3}
Fructose	1.98×10^{-2}	1.44×10^{-2}	1.11×10^{-2}
Starch	3.81×10^{-2}	3.11×10^{-2}	2.70×10^{-2}

5. Life time

Potentiometric measurements in the various AZ drug solutions were taken three times every week in order to determine the stability of (MCPE, CGE, and CWE) electrodes. The findings demonstrated that (CWE, CGE, and MCPE) electrodes could be used for (25, 31, and 39) days, respectively, without significantly changing the potential value or Nernstian slope. After a while, it was noticed that the potential of the electrodes was decreasing and that the Nernstian slope was drifting. This may be because a water layer had formed between the solid contact and membrane phase.[24].

6. Response time

The dynamic response time, which is the time required to reach the steady state with a potential change of ±1 mV from the point at which constructed electrodes and the reference electrode of the AZ solutions make contact, Response time is an essential aspect for analytical applications of ion selective electrodes [25]. According to this study, the shortest time required to reach stable potential is 18 seconds, while the longest time required to reach stable potential is 66 seconds which shown in (Figure 5).

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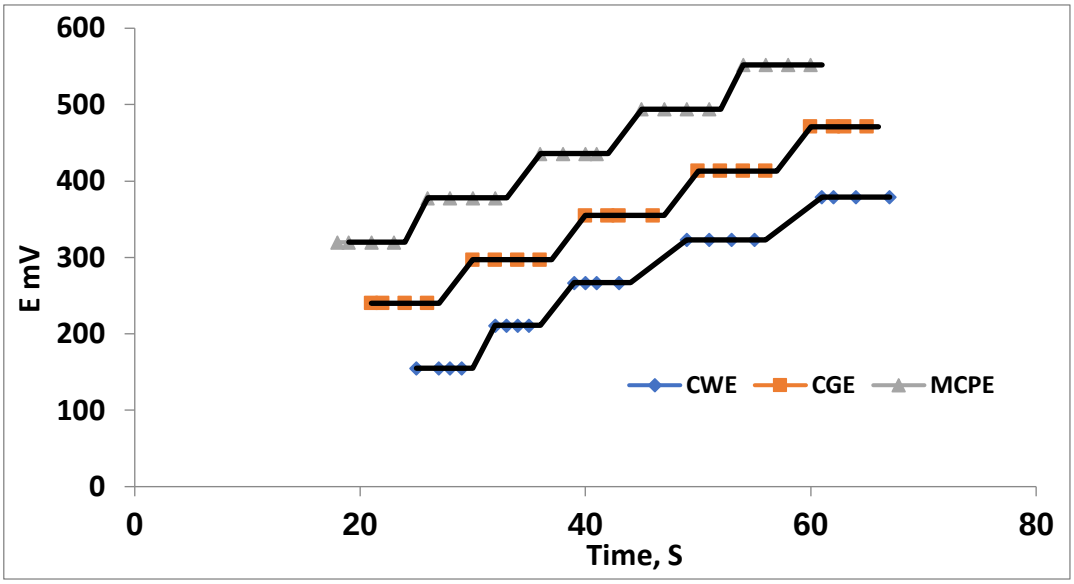

Figure 5 : (MCPE, CGE, and CWE) electrode response time

7. Precision and Accuracy

Pure drug was analyzed, and each solution was repeated five, six, or seven times in order to measure the method's accuracy and precision. The percentages of relative standard deviation (RSD%) and relative error (RE%) were used to evaluate precision and accuracy. Both RE% and RSD% have values that are no greater than (2.4369) and (1.6932), respectively. The results obtained (Table 5) demonstrate that these methods have acceptable precision and accuracy.

Table 5: Statistics for the measurement of AZ in pure form using fabricated electrodes.

SAMPLE	TAKEN [AZ] M	FOUND [AZ] M	%RECOVERY	%RE
CWE	1×10^{-1}	9.9374×10^{-2}	99.37	-0.62
	1×10^{-2}	9.9893×10^{-3}	99.89	-0.10
	1×10^{-3}	1.0041×10^{-3}	100.41	0.41
	1×10^{-4}	1.0094×10^{-4}	100.93	0.93
	1×10^{-5}	1.0146×10^{-5}	101.46	1.46
%Mean ± SD	100.41 ± 0.8272			

n	5			
Variance	0.6843			
%RE	0.4179			
%RSD	0.8237			
CGE	1×10^{-1}	1.0171×10^{-1}	101.71	1.71
	1×10^{-2}	1.0145×10^{-2}	101.45	1.45
	1×10^{-3}	1.0120×10^{-3}	101.20	1.20
	1×10^{-4}	1.0095×10^{-4}	100.95	0.95
	1×10^{-5}	1.0478×10^{-5}	104.78	4.78
	1×10^{-6}	1.0451×10^{-6}	104.51	4.51
%Mean ± SD	102.43 ± 1.7345			
n	6			
Variance	3.0086			
%RE	2.4369			
%RSD	1.6932			
MCPE	1×10^{-1}	1.0189×10^{-1}	101.89	1.89
	1×10^{-2}	9.9331×10^{-3}	99.33	-0.66
	1×10^{-3}	1.0073×10^{-3}	100.73	0.73
	1×10^{-4}	1.0215×10^{-4}	102.15	2.15
	1×10^{-5}	9.9586×10^{-6}	99.58	-0.41
	1×10^{-6}	1.0099×10^{-6}	100.99	0.99
	1×10^{-7}	9.6497×10^{-7}	96.49	-3.50
%Mean ± SD	100.781 ± 1.0561			
n	7			
Variance	1.1154			
%RE	0.7812			
%RSD	1.0479			

8. Analytical Applications

Direct and standard addition methods using (MCPE, CGE, and CWE) electrodes were used to analyze AZ in pharmaceutical formulations (CITROMYCIN 500 mg/tablet, Azax 500

mg/tablet, and ZAHA 200mg/5 ml syrup). According to the obtained% recoveries, the prepared electrodes have shown they are able to determine the AZ drug. Additionally, the constructed electrodes (MCPE, CGE, and CWE) were successfully used to determine the AZ in biological fluids such plasma and urine. the results were indicated in Table 6.

Table 6: Direct and standard addition methods for determinations of AZ in pharmaceutical and biological forms using MCPE , CGE and CWE electrodes.

ELECTRODE	SAMPLE	TAKEN [AZ] M	FOUND [AZ] M	%RECOVERY	%RE
Direct method					
MCPE	Citromycin	7×10^{-3}	6.9640×10^{-3}	99.48	-0.51
	Azax	5×10^{-3}	5.0789×10^{-3}	101.5772	1.57
	Zaha	3×10^{-3}	3.0408×10^{-3}	101.36	1.36
CGE	Citromycin	7×10^{-3}	6.8184×10^{-3}	97.40	-2.60
	Azax	5×10^{-3}	5.1625×10^{-3}	103.25	3.25
	Zaha	3×10^{-3}	2.9595×10^{-3}	98.65	-1.35
CWE	Citromycin	7×10^{-3}	6.9053×10^{-3}	98.64	-1.36
	Azax	5×10^{-3}	4.9733×10^{-3}	99.46	-0.53
	Zaha	3×10^{-3}	3.0398×10^{-3}	101.32	1.32
Standard addition method					
MCPE	Azax	2×10^{-4}	2.0044×10^{-4}	100.2212	0.22
CGE	Azax	2×10^{-4}	2.0199×10^{-4}	100.9988	0.99
CWE	Azax	2×10^{-4}	2.0430×10^{-4}	102.1523	2.15
biological forms					
MCPE	Urine	2×10^{-3}	1.9701×10^{-3}	98.50	-1.49
CGE	Urine	2×10^{-3}	1.9889×10^{-3}	99.45	-0.55
CWE	Urine	2×10^{-3}	2.0169×10^{-3}	100.8449	0.84
MCPE	Plasma	2×10^{-3}	2.0494×10^{-3}	102.47	2.47
CGE	Plasma	2×10^{-3}	2.0695×10^{-3}	103.47	3.47
CWE	Plasma	2×10^{-3}	1.9358×10^{-3}	96.79	-3.21

9. Robustness and Ruggedness

Robustness was determined by observing how a method stands up to slight variations in normal operating parameters , it was performed by switching the aqueous solution to ethanol . Ruggedness obtained by the analysis of the same samples under a variety of conditions, in this study it was evaluated using a different pH-meter model (HANNA instruments 213). Findings are indicate in figure (6 and 7) [20].

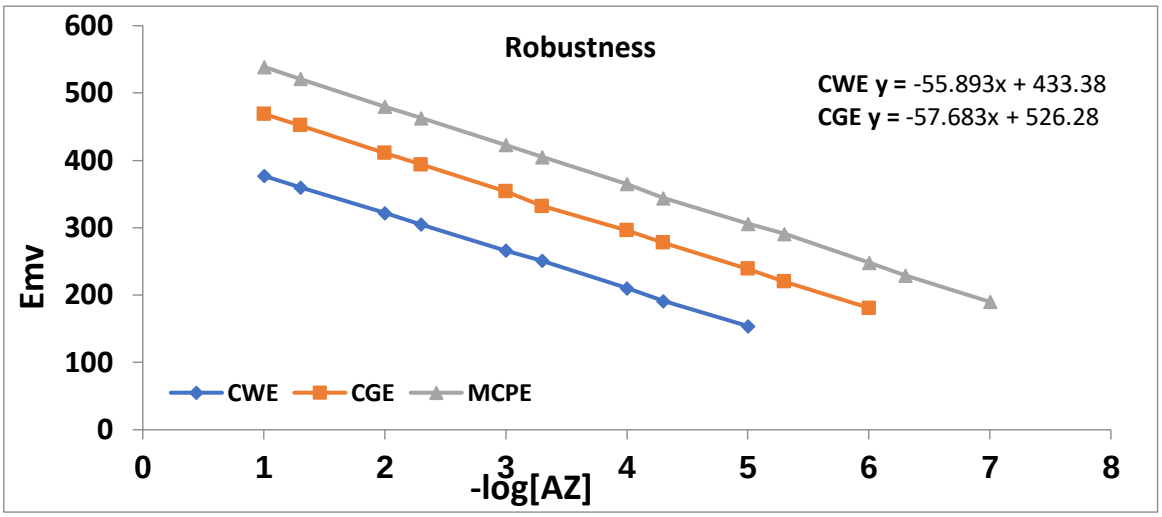

Figure 6 : Robustness of (CWE,CGE and MCPE) electrodes

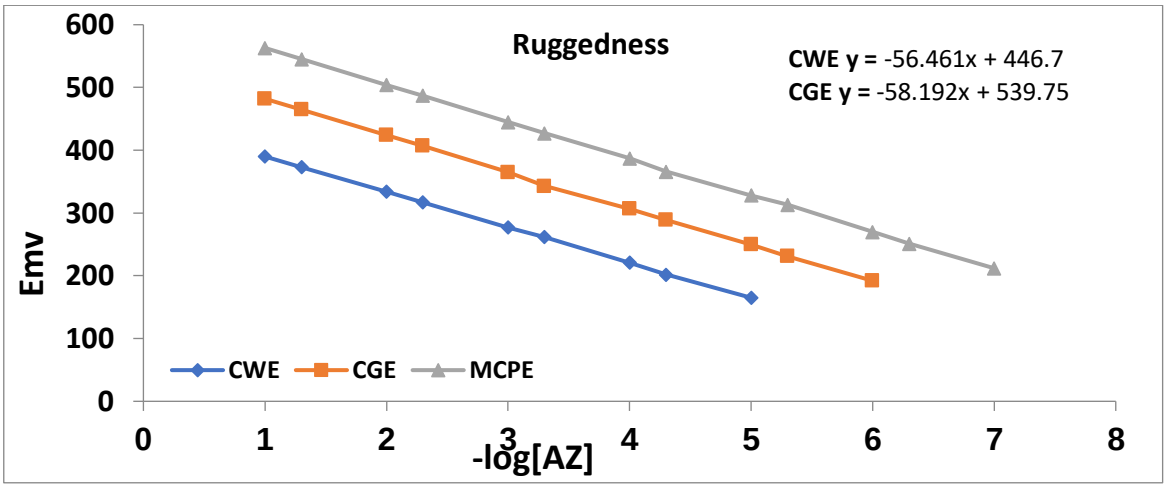

Figure 7 : Ruggedness of (CWE,CGE and MCPE) electrodes

10. Evaluation of the Results

The results in (table 7) show that the constructed electrodes were successful and that there was no significant difference between the suggested method and the standard method when using the t-test and F-test to determine the validity and success of applying the constructed electrodes for determining pharmaceutical preparations (Azax 500 mg/tablet).

Table 7 : Evaluation of the results utilize t-test and F-test

ELECTRODE	%MEAN ±SD	N	CALCULATED T-TEST	TABULATED T-TEST FOR %95	CALCULATED F-TEST	TABULATED F-TEST FOR %95
MCPE	100.781 ± 1.0561	7	-0.4983	2.45	0.5811	4.53
CGE	102.43 ± 1.7345	6	2.0055	2.57	0.2154	5.19
CWE	100.41 ± 0.8272	5	1.7050	2.78	0.9472	6.39
Standard method* (HPLC)	100.69± 0.8051	5	0.00	0.00	0.00	0.00

*The constitutional method (USP41) for Wadi Al-Rafidain Pharmaceutical Industries using HPLC

Conclusion

- ✓ The present method for measuring AZ in pharmaceutical formulations and biological fluids used a constructed electrodes (MCPE, CGE, and CWE).
- ✓ The constructed sensors had a good slope, very good potential stability, a low detection limit, high sensitivity, and an acceptable recovery.
- ✓ According to statistical analyses, all electrodes are appropriate to use in the field of medicine.
- ✓ Comparing modified electrodes with MWCNTs to unmodified electrodes, the modified electrodes' parameters were better.

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