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The Impact of Varying Plasticizers on Coated Graphite Electrodes Performance for Doxycycline Hyclate Estimation

Aveen Kh. Mohammed[1], Muthana S. Ali[2]

[1]Kirkuk General Education Directorate, Ministry of Education, Iraq.

[2]Department of Science, College of Basic Education, Diyala University, Iraq.

Corresponding Author: Aveen@tu..edu.iq,basicsci18@uodiyala.edu.iq

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Keywords: Coated graphite electrode, Doxycycline hyclate, Di butyl phthalate, Graphite rode, Monodoks capsules.

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Abstract:

Coated graphite electrodes (CGE) are used in this study. Doxycycline hyclate (DOX) has been successfully detected using the manufactured electrodes DOX-DBP, DOX-TBP, and DOX-NB in pure, pharmaceutical (monodoks 100 mg/capsules), and biological formulations. With a low percentage of RSD (1.18-2.16) %, the percentage of recoveries was found to be within the range of (96.99-103.68) %, indicating the accuracy of the drug estimation method at optimum conditions pH (2-6) and temperature (10-45). Additionally, it was discovered to have a long life, low detection limit, broad linearity and a good slope as compared to the construction electrodes. Also this method is rapid, economical and has excellent potential stability. Employing the t-test and F-test to assess the validity and efficacy of using the manufactured electrodes, the results demonstrate that the electrodes were successful and that there was no discernible difference between the technique suggested and the standard method.

Keywords*:* Coated graphite electrode, Di butyl phthalate, Doxycycline hyclate, Graphite rode, Monodoks capsules.

تأثير تغيير الملدنات على أداء أقطاب الجرافيت المطلية لتقدير هيكلات الدوكسيسيكلين

أفين خيرالله محمد [١]، مثنى سعيد علي [٢]

المديرية العامة لتربية كركوك، وزارة التربية، العراق ١

قسم العلوم، كلية التربية الاساسية، جامعة ديالى، العراق٢

الايميل الرسمي: Aveen@tu..edu.iq,basicsci18@uodiyala.edu.iq

الخلاصة:

تستعمل في هذه الدراسة أقطاب الجرافيت المطلية (CGE). حيث تم تقدير هيكلات الدوكسيسيكلين (DOX) بنجاح في شكله النقي والمستحضر الصيدلاني (مونودوكس ١٠٠ ملغ/كبسولات) والسوائل البيولوجية باستخدام الأقطاب المصنعة DOX-DBP و DOX-TBP و DOX-NB , حيث كانت (RSD)% نسبته منخفضة %(1.18-2.16)، ونسبة الاسترجاعية كانت تتراوح بين (٩٦,٩٩-١٠٣,٦٨)%، وتدل هذه النتائج على دقة الطريقة لتقدير الدواء في الظروف المثلى من درجة الحامضية (٢-٦) ودرجة الحرارة (١٠-٤٥) °م. فضلا عن ذلك، وُجد أن هذه الطريقة تتميز بعمر طويل للاقطاب، وحد كشف منخفض، وخطية واسعة، وميل جيد عندما قرن مع اقطاب محضرة بطرق اخرى. كما تتميز هذه الطريقة بالسرعة والاقتصادية وبثباتية عالية للجهد. وباستمال اختبار t واختبار F لتقييم صحة وفعالية استخدام الأقطاب الكهربائية المصنعة، أظهرت النتائج أن الأقطاب الكهربائية كانت ناجحة وأنه لا يوجد فرق واضح بين التقنية المقترحة والطريقة القياسية.

الكلمات المفتاحية: قطب الجرافيت المطلي، ثنائي بيوتيل الفثالات، هيكلات الدوكسيسيكلين، قضيب الجرافيت، كبسولات المونودوكس.

1. Introduction:

Doxycycline hyclate (DOX) chemically it is Hydrochloride hemiethanol hemihydrate of (4S,4aR,5S,5aR,6R,12aS)-4-(dimethylamino)-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11, 12a-octahydrotetracene-2-carboxamide. has chemical structure showed in **Figure 1** in pharmaceutical samples, doxycycline hyclate is utilized more frequently. because it is significantly more soluble in water than another form of doxycycline. [1,2]. A broad-spectrum antibiotic that is classified as part of the tetracycline class, doxycycline can find use in medicine for both humans and animals [3]. In order to treat pulmonary illnesses DOX has been used extensively during the COVID surge [4]. Additionally, DOX has been shown to be effective against microorganisms, inflammation, urinary tract infections, and some bacterial sexually transmitted diseases [5]. has antitumor effects as well [6]. The examination of DOX in different biological and pharmacological formulations has been studied in many of published articles using a variety of analysis techniques, including spectrophotometry [7-13], RP-HPLC [14] HPLC [15-17], HPLC-mass [18], HPTLC [19], ratiometric probe [20], flow injection [21], Fluorometric [22-24], glassy carbon [25], potentiometric sensor [26,27] and voltammetry [28].

The purpose of this work is to use coated graphite electrodes (CGE) with three types of plasticizers (DOX-DBP, DOX-TBP and DOX-NB) to develop a simple, inexpensive, and widely linear range analytical method for determining DOX in pharmaceutical and pure formulations. The basic analytical measures were calculated and compared and attracted a lot of attention due to their exceptional properties, which include good chemical stability, accurate and sensitivity.

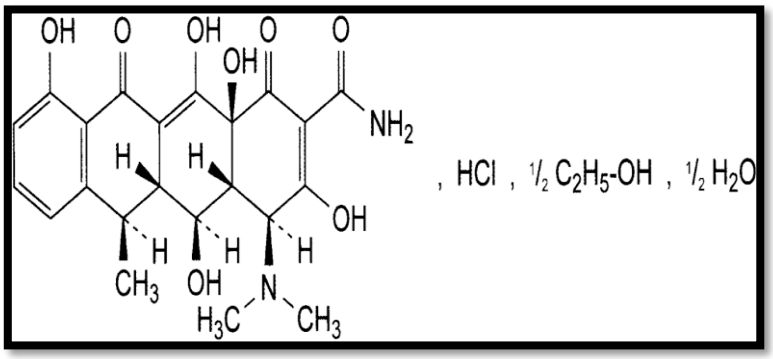


Figure 1: Chemical Structure of Doxycycline Hyclate

2. Material and methods:

2-1- Instrumentation

Potentiometric measurements were performed using a HANNA instruments pH301 and a Jenway 3310 pH-meter, equipped with calomel reference electrodes (Swiss supplier). Elemental analysis (CHN) was carried out using a PerkinElmer USA 2400 Series II analyzer.

2-2-Materials

Deionized distilled water (DDW) was used throughout all experiments. Doxycycline (DOX) was kindly provided as a gift from SDI (Samara, Iraq). Poly (vinyl chloride) (PVC), dibutyl phthalate (DBP), nitrobenzene (NB), tetrahydrofuran (THF), graphite rods, phosphomolybdic acid (PMA), and tributyl phosphate (TBP) were purchased from Sigma-Aldrich. Pharmaceutical-grade doxycycline monohydrate capsules (Monodoks, 100 mg) were purchased from a local pharmacy.

2-3- Preparation of stock solutions

A precisely weighed quantity of DOX (5.129 g) was transferred to a 100 mL volumetric flask and dissolved in deionized distilled water to prepare a 0.1 M (1.0×10^{-1} M) stock solution. The volume was then made up to the mark with DDW. Subsequent working solutions in the concentration range of 10 nM to 10 mM (1.0×10^{-8} M to 1.0×10^{-2} M) were prepared by appropriate serial dilution of the stock solution with deionized distilled water.

2-4- Pharmaceutical sample preparation (monodoks100 mg/ capsules)

A suitable quantity of powdered capsules of (monodoks) was dissolved in 50 mL of deionized distilled water to create (1.0×10^{-1}) M in order to prepare this sample. Deionized distilled water was used to properly dilute the other diluted solutions.

2-5- Ion pair preparation (DOX-PMA)

50 mL of PMA and 50 mL of DOX at (1.0×10^{-2}) M were combined to create the ion-pair DOX-PMA precipitate. After filtering, the precipitate was repeatedly washed with deionized water and left to dry at room temp for some days. The supposed ion-pair complex composition, with a molar ratio of 1:1 for DOX-PMA, was determined by elemental analysis; the results are shown in **Table 1 below.**

Table (1): C.H.N. for the (DOX-PMA) ion pair

DOX-PMA			
Element	***%C***	***%H***	***%N***
Found	9.99	2.90	1.00
Calculated	9.97	2.91	1.01
Formula	$[C_{23}H_{29}N_2O_9Cl][H_3PO_{40}Mo_{12}].24H_2O$		

2-7- Construction of electrodes (DOX-DBP, DOX-TBP and DOX-NB)

The process described previously [29] is used to prepare PVC membranes and assemble them into the sensor. These membranes employed three different kinds of plasticizers [DBP, TBP, and NB] to prepare coated graphite electrodes (CGE).

3. Results and Discussion:

3-1- Linearity, slope and detection limit

Potentiometric measurements were performed using a Calomel reference electrode immersed in DOX drug solutions (1.0×10^{-8} - 1.0×10^{-1}) M. E (mV) was measured for every solution, and a calibration curve was plotted, as seen in **Figure 2** , E(mV) versus –log [DOX]. DBP plasticizer is renowned for its superior plasticizing effectiveness and PVC compatibility the electrodes' parameters can be seen in **Table 2** where it is obvious that the electrode made with DBP plasticizer has wider liner range than the electrode made with TBP and NB and All prepared electrodes demonstrated a near-Nernstian slope and a low detection limit. Furthermore, when compared to other reported electrodes for doxycycline detection, the proposed electrodes were found to possess a superior combination of a wide linear range and a low detection limit. A

comparative summary of the performance characteristics between the suggested electrodes and previously published ones is provided in Table 2.

Table (2): Analytical parameters for the DOX-DBP, DOX-TBP and DOX-NB electrodes and comparison with those previously published in the literature

Electrode type	*Liner range M*	*Slopes (mV decade-1*	*Upper detection limit M*	*Lower detection limit M*
present study				
DOX -DBP	1.0×10^{-6} - 1.0×10^{-1}	58.64	0.2019	4.76×10^{-7}
DOX-TBP	5.0×10^{-6} - 1.0×10^{-2}	58.13	0.0207	2.37×10^{-6}
DOX -NB	1.0×10^{-5} - 1.0×10^{-2}	57.93	0.0203	5.00×10^{-6}
previously published electrodes				
[26]	1.0×10^{-5} - 1.0×10^{-2}	54.4	Not cited	4.0×10^{-6}
[27]	1.99×10^{-5} - 3.19×10^{-3}	62.30	Not cited	1.33×10^{-5}

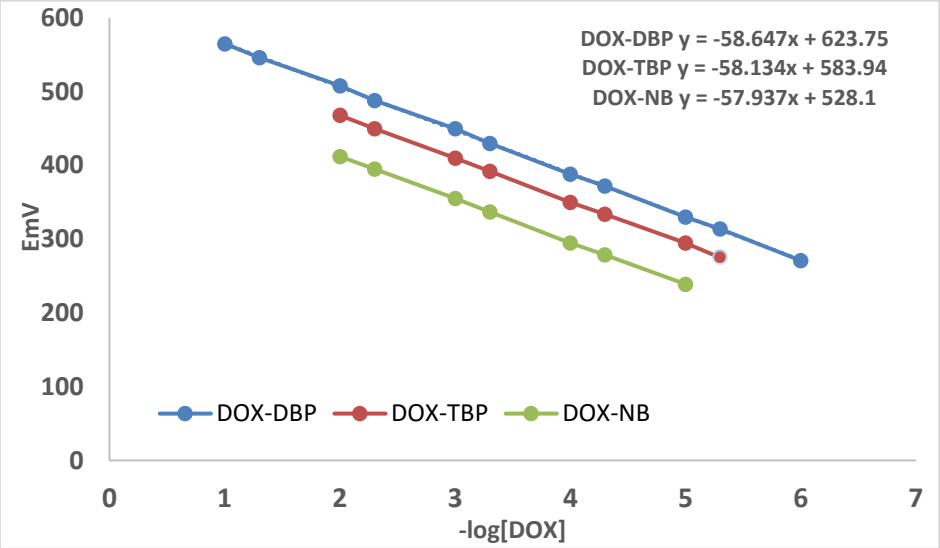


Figure 2 : calibration curve of DOX for the manufactured electrodes

3-2- Effect of pH

The ideal pH range was determined, within which the electrode potential is constant independent of the pH of the sample. The electrode potential was measured in a DOX solution (1.0×10^{-4}) M with a pH range of 1–8 for this purpose. Using KOH and/or HCl solutions, the pH

was adjusted. **Figure 3** illustrates how the electrode potential and solution pH relate to one another. It is clear that the DOX-DBP, DOX-TBP, and DOX-NB sensors have a pH range of (2–6). Potential measurements decrease at pH values below 2 and above 6 because the efficacy of doxycycline hyclate is diminished in solutions with a pH below 2, and it is quickly destroyed in alkali hydroxide solutions [2].

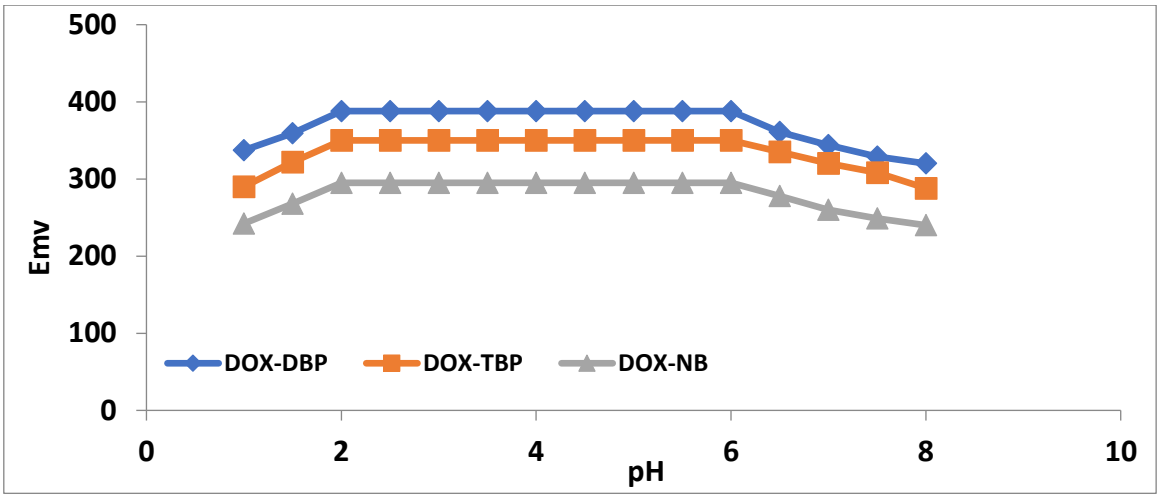


Figure 3: Effect of pH for (DOX-DBP, DOX-TBP, and DOX-NB) electrodes

3-3- Temperature's impact

Using a range of temperature values (5–70) °C, the impact of temperature was investigated. The electrode potential was measured in a DOX solution (1.0×10^{-3}) M with a temperature range (5-70) °C. The results displayed in **Figure 4** showed that the DOX-DBP, DOX-TBP, and DOX-NB electrodes work best at temperatures between 10 and 45 °C. Without appreciably changing its Nernstian slope, the results indicate that each fabrication electrode has a high degree of thermal stability.

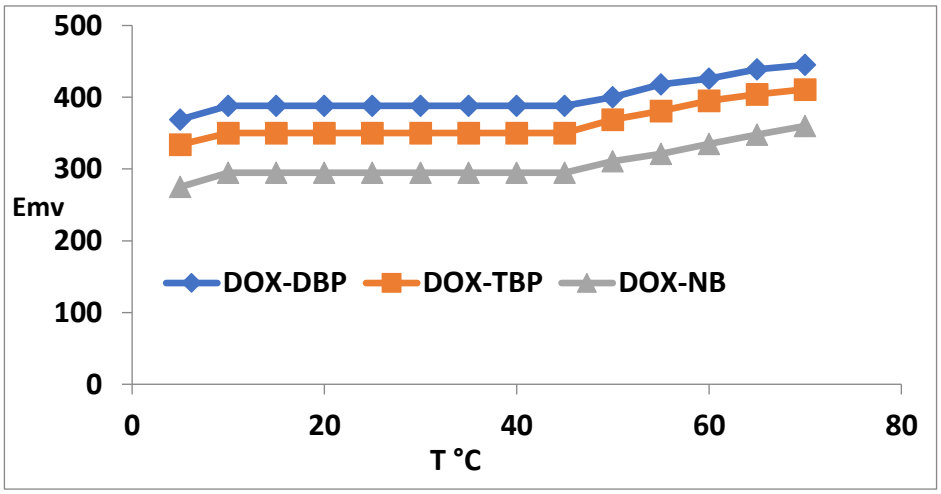


Figure (4): Temperature's impact on manufactured electrode response

3-4- Life time

The stability of the construction electrodes was assessed by by performing potentiometric analyses three times a week in the various DOX drug solutions. The results showed that the potential value and Nernstian slope could be maintained without significantly altering the use of the (DOX-DBP, DOX-TBP, and DOX-NB) electrodes for (27, 32, and 40) days, respectively. The electrodes' potential was gradually observed to be decreasing, and the Nernstian slope was gradually drifting. This may be due to the formation of a water layer between the solid contact (graphite rod) and membrane phase [30].

3-5- Interference studied

The selectivity coefficients for the manufactured electrodes (DOX-DBP, DOX-TBP, and DOX-NB) were determined using the separate solution method (SSM) [31]. The coefficients were calculated using the following equation:

$$\text{Log } K = (E_j - E_i) / S$$

as described previously [32]. The results, presented in Table 3, reveal high selectivity of the sensors towards doxycycline (DOX). The very low values of the selectivity coefficient (K) for each electrode indicate that the electrode potential was unaffected by interfering ions, demonstrating excellent selectivity for the target analyte.

Table 3: K values of the constructed sensors

Interfering ion	***Selectivity coefficient values*** $K_{i,j}^{pot}$		
	DOX-DBP	***DOX-TBP***	***DOX-NB***
Na^{1+}	5.84×10^{-2}	6.55×10^{-2}	7.09×10^{-2}
K^{1+}	5.10×10^{-1}	5.92×10^{-1}	6.67×10^{-1}
Ca^{2+}	9.53×10^{-2}	9.96×10^{-2}	4.71×10^{-1}
Cl^{1-}	3.43×10^{-1}	6.06×10^{-1}	6.59×10^{-1}
Br^{1-}	2.98×10^{-1}	3.71×10^{-1}	6.92×10^{-2}
CO_3^{1-}	2.17×10^{-1}	2.88×10^{-1}	4.81×10^{-1}
NO_3^{1-}	3.44×10^{-1}	6.01×10^{-1}	6.50×10^{-1}
SO_4^{2-}	4.00×10^{-2}	7.60×10^{-2}	1.25×10^{-1}
Glucose	8.33×10^{-3}	9.78×10^{-3}	2.00×10^{-2}
Fructose	1.30×10^{-2}	3.69×10^{-2}	8.99×10^{-2}

Starch	3.48×10^{-2}	3.77×10^{-2}	5.51×10^{-2}

3-6- Accuracy and precision

The accuracy and precision of the procedure were assessed by examining the pure drug and repeating each solution multiple times. Precision and accuracy were evaluated utilizing recovery% and relative standard deviation% (RSD%). The RSD% ranged from 1.1873% to 2.1691%, while recovery percentages ranged from 96.99% to 102.86%. These techniques have respectable accuracy and precision, as shown by the results **Table 4**.

Table 4: Statistics for measuring pure DOX with manufactured sensors.

Electrodes	***Taken [DOX] M***	***Found [DOX] M***	***%Recovery***	***%RE***
DOX-DBP	1×10^{-1}	1.0064×10^{-1}	100.64	0.64
	1×10^{-2}	9.8537×10^{-3}	98.54	1.46
	1×10^{-3}	1.0035×10^{-3}	100.35	0.35
	1×10^{-4}	9.8251×10^{-5}	98.25	1.75
	1×10^{-5}	1.0006×10^{-5}	100.06	0.06
	1×10^{-6}	9.7965×10^{-7}	97.96	2.04
%Mean ± SD	99.30 ± 1.17			
n	6			
Variance	1.39			
%RE	-0.69			
%RSD	1.18			
DOX -TBP	1×10^{-2}	1.0130×10^{-2}	101.30	1.30
	1×10^{-3}	1.0184×10^{-3}	101.84	1.84
	1×10^{-4}	9.8413×10^{-5}	98.41	−1.59
	1×10^{-5}	9.8936×10^{-6}	98.93	−1.07
	5×10^{-6}	4.8498×10^{-6}	96.99	−3.01
%Mean ± SD	99.499±2.03			
N	5			
Variance	4.13			
%RE	-0.50			
%RSD	2.04			

DOX-NB	1×10^{-2}	9.9105×10^{-3}	99.10	−0.90
	1×10^{-3}	1.0286×10^{-3}	102.86	2.86
	1×10^{-4}	9.8611×10^{-5}	98.61	−1.39
	1×10^{-5}	1.0235×10^{-5}	102.35	2.35
%Mean ± SD	100.73±2.18			
n	4			
Variance	4.77			
%RE	0.73			
%RSD	2.16			

3-8- Application of the method

Under optimal conditions for working, the proposed technique could be used to determine DOX in biological formulations and pharmaceutical formulations (Monodoks 100 mg/capsules) using the direct method and the standard addition method. **Table 5** provides a summary of the results that were obtained. The findings presented in Table 5 suggest that the method has good efficiency and estimation accuracy because the recovery percentages for the pharmaceutical form analysis ranged from 98.55 % to 103.6808 %, while the recovery percentages for biological formulations ranged from 98.19 % to 101.08 %.

Table 5: Manufactured electrodes for determinations of DOX in pharmaceutical and biological samples

Electrode	***Sample***	***Taken [DOX] M***	***Found [DOX] M***	***%Recovery***	***%RE***
Direct method					
DOX-DBP	Monodoks	7×10^{-3}	6.8986×10^{-3}	98.55	-1.45
DOX-TBP		7×10^{-3}	7.0930×10^{-3}	101.32	1.32
DOX-NB		7×10^{-3}	6.9304×10^{-3}	99.00	-0.99
Standard addition method					
DOX-DBP	Monodoks	2×10^{-4}	2.0225×10^{-4}	101.12	1.12
DOX-TBP		2×10^{-4}	2.0325×10^{-4}	101.62	1.62
DOX-NB		2×10^{-4}	2.0736×10^{-4}	103.68	3.68
biological forms					

DOX-DBP	Urine	2×10^{-3}	1.9639×10^{-3}	98.19	-1.81
DOX-TBP		2×10^{-3}	1.997×10^{-3}	99.85	-0.15
DOX-NB		2×10^{-3}	2.0216×10^{-3}	101.08	1.08
DOX-DBP	Plasma	2×10^{-3}	2.0028×10^{-3}	100.14	0.14
DOX-TBP		2×10^{-3}	2.0128×10^{-3}	100.14	0.64
DOX-NB		2×10^{-3}	1.9818×10^{-3}	99.09	-0.91

3-9- Robustness and ruggedness

The process of evaluating a method's robustness involved changing the aqueous solution to ethanol and seeing how it held up against small changes in standard operating parameters Results are displayed in the **Figure 5**. Ruggedness was assessed in this study using a different pH meter and was derived from the analysis of the same drug under various conditions (pH meter Jenway 3310). Results are displayed in the **Figure 6.** [32,33]

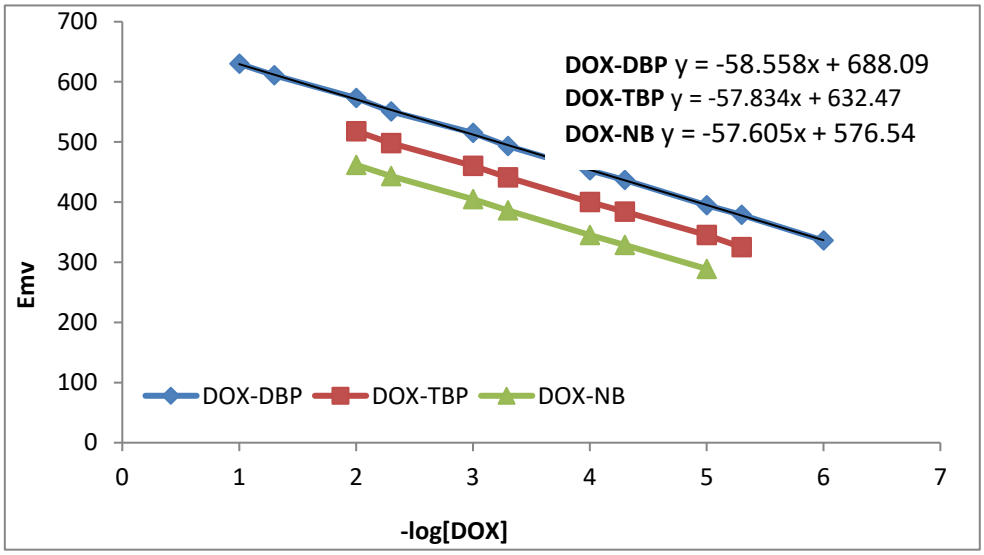


Figure 5: The robustness of the manufactured electrodes

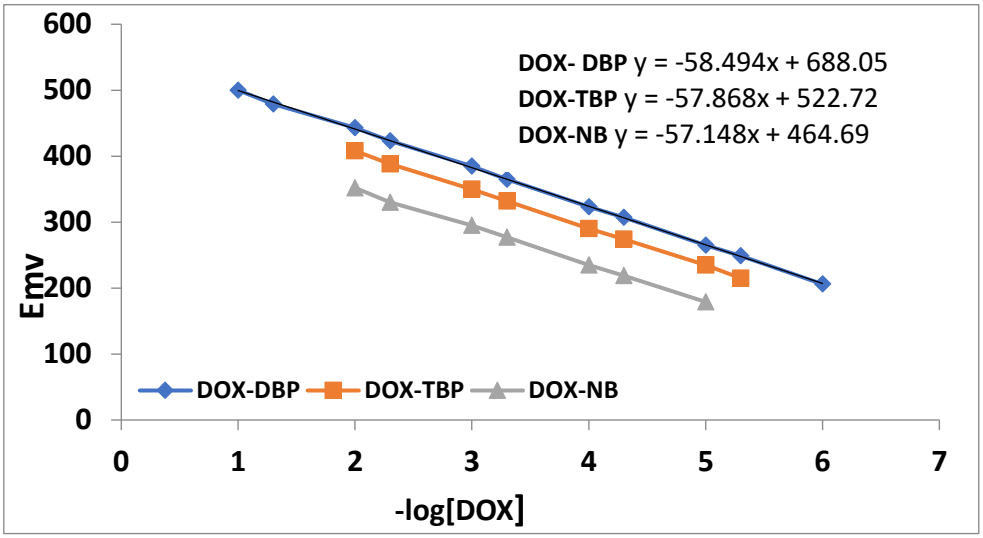


Figure 6: Ruggedness of the manufactured electrodes

3-10- Assessment of results

Employing the t-test and F-test to assess the validity and efficacy of using the manufactured electrodes for determining (Monodoks 100 mg/capsules), the results in Table 6 demonstrate that the electrodes were successful and that there was no discernible difference between the technique suggested and the standard method.

Table 6: The t-test and F-test are used to assess the results.

Electrode	*%Mean ±SD*	*n*	*Calculated t-test*	*Tabulated t-test for %95*	*Calculated F-test*	*Tabulated F-test for %95*
DOX-DBP	99.30 ± 1.17	6	0.78	2.57	0.80	5.19
DOX-TBP	99.49 ± 2.03	5	-1.92	2.78	0.26	6.39
DOX-NB	100.73±2.18	4	1.80	3.18	0.23	9.12
Standard method* (HPLC)	100.28± 1.05	5	0.00	0.00	0.00	0.00

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

4. Conclusions

The present method uses construction electrodes (DOX-DBP, DOX-TBP, and DOX-NB) to measure DOX in biological formulation (urine and plasma) and pharmaceutical forms. The manufactured electrodes had a long life time, a low detection limit, broad linearity, a good slope, and very good potential stability. Statistical analyses indicate that the accuracy and precision of all electrodes are respectable. The constructed sensors were unaffected by to foreign ions and highly sensitive to DOX drugs.

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