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Full Paper

Functionalized Melissa Plant Extract-Mediated Al_2O_3/Fe_2O_3 Nanocomposite Potentiometric Sensor for Determination of Diphenhydramine

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Abstract- A sensitive, simple, cost-effective, and eco-friendly method has been suggested for the determination of the drug diphenhydramine (DPH) in pure and pharmaceutical formulations. The method depended on the preparation of the nano-aluminum oxide (Al_2O_3 NPs) and nano-iron oxide (Fe_2O_3 NPs) using the Melissa plant extract. The main purpose of this study is to determine the extent of change in electrical potential by using copper wire and aluminum wire, four electrodes were prepared. All electrodes showed Nernstian response, the best response was equal to 57.75 mv/decade for the electrode made from (sodium tetraphenylborate STPB- diphenhydramine) as an ion pair with TBP as a plasticizer and (Al_2O_3 /Fe_2O_3) NPS with the aluminum wire membrane electrode, also the concentration range was 1.0×10^{-2} to 1.0×10^{-8} mole.L^{-1} with detection limit near to 2.07×10^{-7} mole.L^{-1}. The value of the correlation coefficient (R^2) was 0.9998. In this study, we succeeded in producing nanomaterials from green sources, with applied them in the potentiometric determination of the drug (DPH) to increase the sensitive of the preparation electrodes. These methods have become more desirable because they are characterized by ease of preparation, low cost, and do not use materials harmful to the environment.

Keywords- Green Synthesis; Diphenhydramine; Potentiometric determination; Al_2O_3/Fe_2O_3-NPs; Dried Melissa Plant

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1. INTRODUCTION

Ion-selective membrane electrodes are considered an automated classification and are defined as electro-analytical sensors that respond selectively to the substances to be analyzed through chemical interactions between them [1]. Ion-selective membrane electrodes were discovered in 1890 by the scientist Qstwald [2]. The technology is known as Nano, which has emerged in the twenty-first century, is the study of matter and control of its dimensions, which range from (1-100) nm, where the unique properties allow for new applications [3,4]. The creation of nanomaterials and products that do not negatively impact the environment or human health, as well as the creation of nanoproducts that address environmental issues, are the two main objectives of green nanotechnology. Additionally, this technology creates nanomaterials using the most recent developments in green chemistry and green engineering [5,6]. The creation of goods that directly or indirectly benefit the environment is the second objective of green nanotechnology. Desalinating water, treating pollutants, cleaning up hazardous waste sites, and detecting and tracking environmental pollutants are all possible with nanomaterials or direct products [7]. In order to create new nanoparticles with the desired qualities needed for the development of biosensors, biomedical, cosmetics, electrochemical nanobiotechnology, antibacterial, electronics, sensing, and applications, green nanotechnology offers new techniques utilizing plant extract [8]. Nanopharmocology is the use of nanotechnology to discover and develop new methods for liberating medicinal substances and drugs and reducing their sizes to nanoscale size. This will improve the properties of pharmaceutical substances, especially when used in treating diseases [9]. This technology has many benefits in the pharmaceutical field, the most important of which are [10,11]: delivering drugs to the target location in the body, improving the poor solubility of drugs, maintaining therapeutic efficiency and effectiveness, preserving drugs from degrading, reducing treatment expenses, and nanopharmaceutical products are much cheaper than traditional products. Nanoparticles are of great importance for many applications such as sensors, building materials, electronics, drug delivery systems, and cancer diagnosis [12]. Diphenhydramine hydrochloride is a white crystalline powder that has no odor and is optically inactive and melts at temperatures ranging between 167-172^{0}C. Its scientific name is 2-(diphenylmethoxy)-N,N-dimethylethanamine and compositional formula shown in Figure 1.

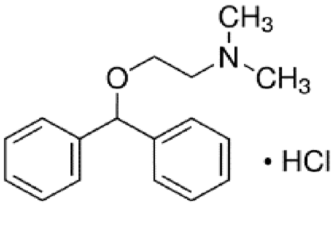

Figure 1. The chemical structure of diphenhydramine hydrochloride

Its molecular formula is $C_{17}H_{21}NO$ and its molecular weight is 291.85 g/mol diphenhydramine hydrochloride, an H1-receptor antagonist, is widely used as an antitussive, antiemetic and anti-allergic drug may be present in a variety of pharmaceutical formulations. In severe allergic conditions, it is typically injected intramuscularly or intravenously and taken orally as tablets, capsules, or syrup [12]. Many methods have been proposed to determine diphenhydramine hydrochloride including high liquid perform chromatography HPLC [13]. Continuous Flow Injection Analysis Method [14] spectrometry [15] and conductometric titration[16]. This study was used metal oxide nanoparticles such as Al_2O_3 and Fe_2O_3 NPs which prepared with green methods to increase the sensitive values in detection limit and wide concentration ranges with high Nernstian response for diphenhydramine hydrochloride (DPH) electrodes and compared the results with the values of diphenhydramine hydrochloride electrodes that prepared with conventional methods.

2. EXPERIMENTAL SECTION

2.1. Chemicals

Sodium hydroxide (NaOH), hydrochloric acid (HCl), potassium aluminum sulphate ($AlK(SO_4)_2.18H_2O$), hydrated iron chloride ($FeCl_3.6H_2O$), sodium tetraphenylborate (STPB), tetrahydrofuran (THF), Tri-butyl phosphate (TBP), Poly(vinyl chloride) (PVC), glucose, maltose, magnesium stearate, methylcellulose.

2.2. Tools and Devices

It is used EUTECH INSTRUMENTS pH 700, Jenway-pH Meter 3310, Calomel Electrode Co. (Germany). Fisher Scientific, Beschıckung/Loadıng-Modell 100-800, Jenway Hot Plate with magnetic stirrer (Germany), Sartorius BL210 S AG GOTTINGEN.

2.3. Preparation of *Melissa* extract

10 g was taken from the dried *Melissa* plant and put it in a beaker with 250 ml and add 150 ml of distilled water with heated at 80°C for 30 min, after that filtrated the yellow solution then kept it at room temperature to be used for preparation of the metal oxide nanoparticles.

2.4. Green Preparation of Nanoparticles (Al_2O_3 NPS)

At a concentration of 0.05 mol.L^{-1}, 100 milliliters of aqueous potassium aluminum sulphate were made using extremely pure distilled water, followed by the addition of 20 ml of Melissa extract, 0.5 g of sodium hydroxide, and 60 ml of the solution, which was then stirred for an hour. After adjusting the pH to 12, we dry the mixture for forty-five minutes at eighty degrees Celsius. As a result, we will get yellowish-colored aluminum nanoparticles.

2.5. Green Preparation of Nanoparticles (Fe_2O_3NPS)

Using extremely pure distilled water, 100 milliliters of aqueous iron chloride with a concentration of 0.01 mol.L^{-1} was made. After that, the mixture was put in a beaker and heated to 70°C for 30 minutes while being constantly stirred. The pH was then adjusted to 11 after we used a burette to add 40 ml of the Melissa extract drop by drop. After 50 minutes of stirring, we thoroughly wash the filtrate with distilled water to get rid of the salts, and then we dry it for 22 hours at 80°C. As a result, we will get dark red iron nanoparticles [17].

2.6. Preparation of a standard solution of diphenhydramine hydrochloride (0.01 mol.L^{-1})

It is made by dissolving 0.2918 g of the drug DPH powder in 100 ml of volumetric flask water, then adding more distilled water until the desired level is reached. A range of solutions, from (1.0×10^{-2} to 1.0×10^{-8}) mol.L^{-1}, are then made by dilution.

2.7. Preparation of the ion pair (DPH-STPB)

In a 50 ml beaker, 10 ml of the precipitating agent STPB is added to 10 ml of the drug DPH at the same concentrations (1.0×10^{-2}) mol.L^{-1} to create the ionic double (DPH-STPB). We filter the solution after 24 hours after observing the formation of a white precipitate, and we let the filtrate dry for 72 hours at laboratory temperature.

2.8. Membrane composition and electrode fabrication

In a 10-milliliter beaker, 0.19 grams of PVC and 0.01 grams of DPH-TPB were combined, dissolved in 5 milliliters of THF, and thoroughly mixed with a glass stirrer. 0.35 milliliters of the plasticizer TBP was then added to create the traditional DPH-STPB-TBP coated copper wire film electrode (I) and the traditional DPH-STPB-TBP coated aluminum wire electrode (II). Subsequently, two 5-cm-long wires-one made of copper and the other of aluminum-were taken. After thoroughly cleaning them with distilled water and acetone, they were allowed to dry. A polyethylene tube was used to hold them. The potential difference device was connected to one end of the wire. After repeatedly submerging the other end in the aforementioned mixture to create a thick layer, it was allowed to dry for a short while. The procedure should then be repeated multiple times until a thick membrane layer is formed. To create the copper wire membrane electrode modified electrode (III) and the aluminum wire membrane electrode modified electrode (IV) coated with nanoparticles (DPH-STPB-TBP-Fe_2O_3 NPs-Al_2O_3 NPs). 0.01 g of Dual Ionic (DPH-STPB) and 0.005 g of each of the green-methods-prepared Al_2O_3 NPs and Fe_2O_3 NPs were combined with 0.19 g of PVC in 10 ml. They were then dissolved in 5 ml of THF and thoroughly mixed with a glass stirrer. Subsequently, two 5-cm-long wires-one made of copper and the other of aluminum-were taken. After thoroughly cleaning them with distilled water and acetone, they were allowed to air dry. A polyethylene tube was used to hold them. The potential difference device was connected to one end of the wire. To create a thick layer of film, the other end was repeatedly submerged in the aforementioned mixture and allowed to dry for a short while. minutes and carry out the procedure multiple times until a thick membrane layer is formed.

2.9. Calibration curve

Using electrodes made of (I, II, III, IV) the two conventional selective electrodes and the two nano-selective electrodes, (25 ml) were measured for a range of concentrations from (1.0×10^{-2}-1.0×10^{-8}) mol.L^{-1} of DPH solution at a rate of six readings per concentration in series with a Calomel reference electrode.

2.10. pH effect

Two solutions of sodium hydroxide (NaOH) and hydrochloric acid (HCl) with concentrations (0.1, 1, 0.01) mol.L^{-1} are used to adjust the pH in order to determine the effect of the pH function on the drug DPH. The voltage is then measured (mV) using manufactured electrodes (I,II,III,IV) with the reference electrode.

3. RESULTS AND DISCUSSION

3.1. Scanning Electron Microscope (SEM) of Al_2O_3NPs and Fe_2O_3 NPs

Scanning electron microscope imaging of aluminum particles showed fairly regular nanograins as shown in Figure 2 whose dimensions ranged between 18-43 nm Also, many dark areas that indicate the gaps in the compound indicate the high porosity of the sample.

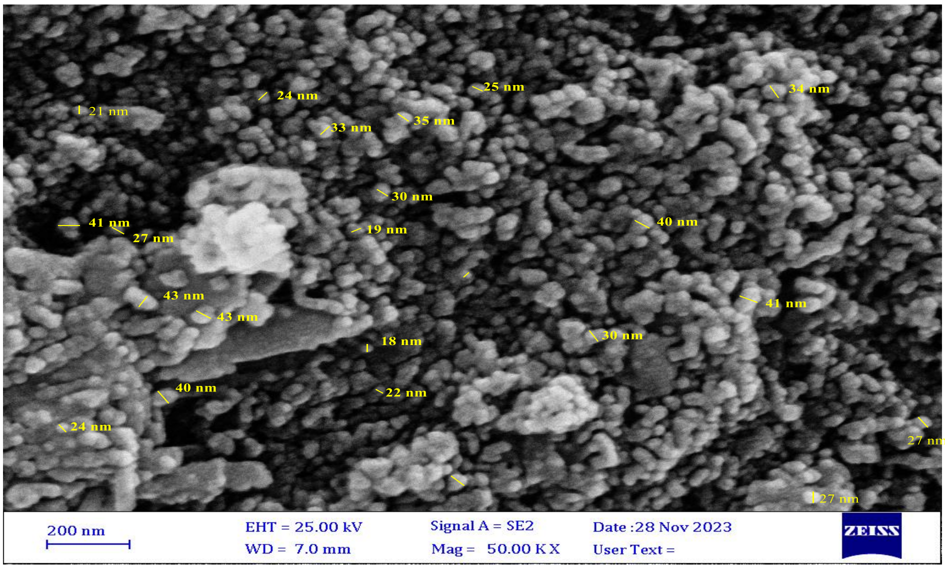

Figure 2. The image of scanning electron microscope (SEM) of Al_2O_3 NPs

Also, the scanning electron microscope imaging of iron nanoparticles showed folds and clusters, clustered with some nanograins whose dimensions ranged between 36-81 nm The dark areas also indicate the high porosity of the sample, as shown in Figure 3. The high porosity of the sample means an increase in the area of the Al_2O_3 NPs and Fe_2O_3 NPs. The importance of nanomaterials is mainly evident in their high surface-to-volume ratio due to their extreme smallness, and this feature increases contact. Its surface with other bodies [18,19].

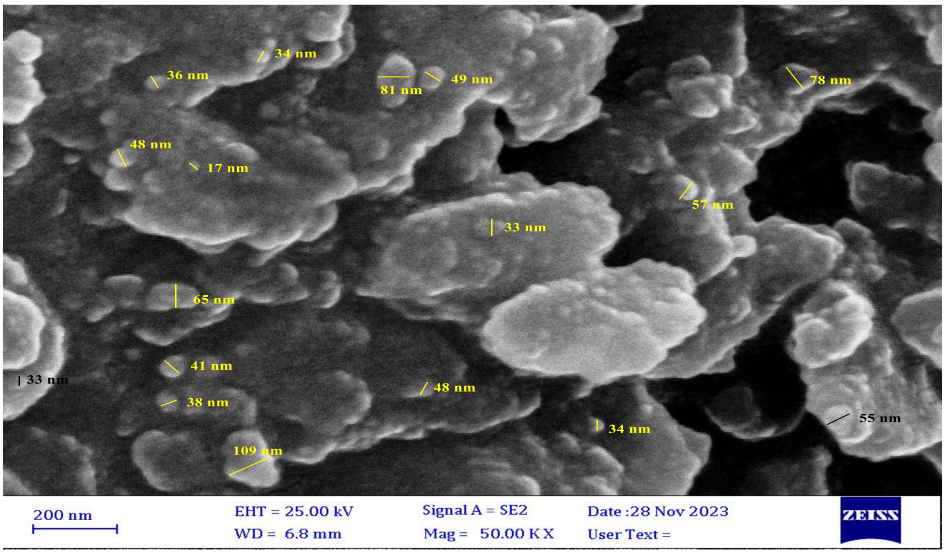

Figure 3. The image of scanning electron microscope (SEM) of Fe_2O_3 NPs

3.2. pH Effect

From Figures 4-7 the effect of pH on the electrode's response was studied and the best electrode reading was found to be in the range of 4.5-5.5. Increasing or decreasing the pH beyond this range will affect the electrode's response. And the parameters of diphenhydramine HCl electrodes were illustrated in Table 1.

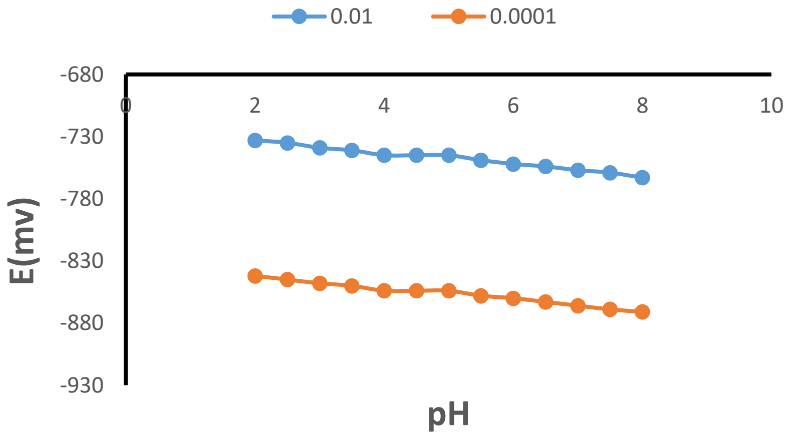

Figure 4. The effect of PH for DPH-STPB-TBP coated copper wire electrode (I)

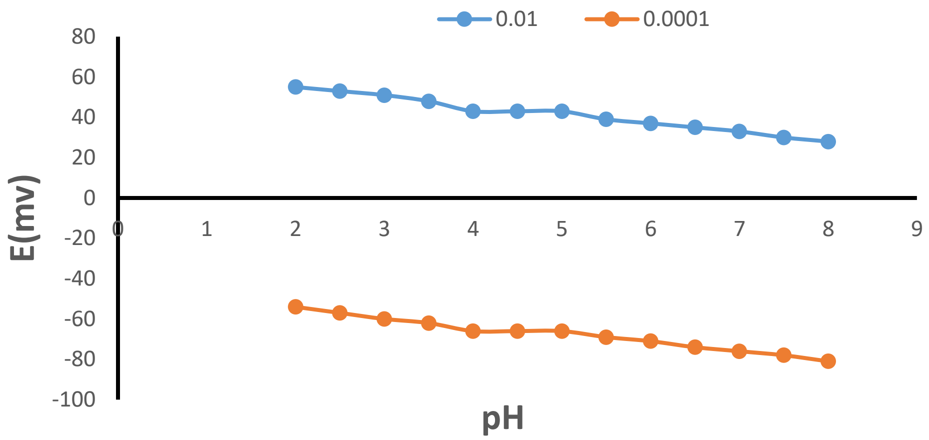

Figure 5. The effect of PH for DPH-STPB-TBP coated aluminum wire electrode (II)

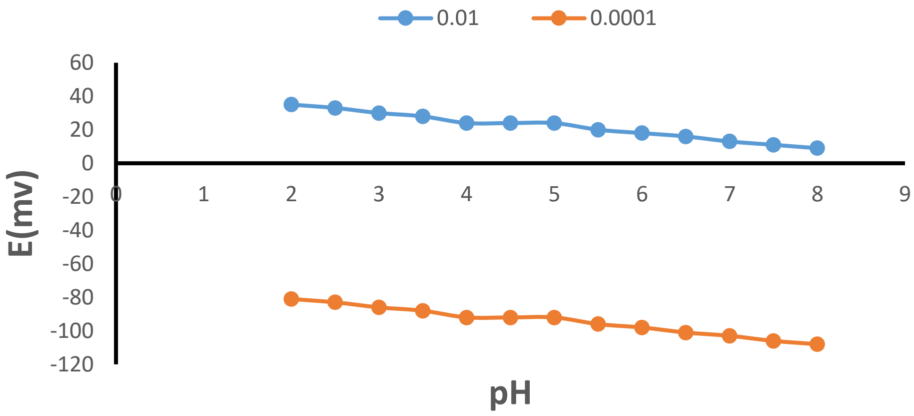

Figure 6. The effect of PH for DPH-STPB-TBP-Al_2O_3 NPS-Fe_2O_3 NPs modified electrode (III)

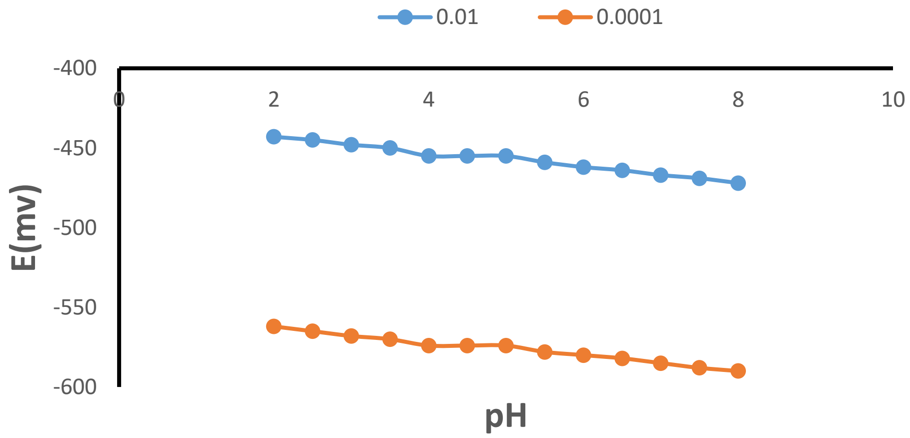

Figure 7. The effect of PH for DPH-STPB- TBP-Al_2O_3NPS- Fe_2O_3NPS modified electrode (IV)

Table 1. The parameter of the electrochemical reaction of conventional (Al_2O_3 NPS) electrode, modified (Al_2O_3 NPs) electrode, conventional (Fe_2O_3 NPs) electrode, and modified (Fe_2O_3 NPs) electrode

Parameter	**DPH-STPB-TBP (I)**	**DPH-STPB-TBP (II)**	**DPH-STPB-TBP-Al_2O_3 NPS-Fe_2O_3 NPS (III)**	**DPH_STPB-TBP-Al_2O_3 NPS-Fe_2O_3 NPS (IV)**
Slope ($mV.decade^{-1}$)	54.4	54.1	57.75	57.64
Linear range ($mol.L^{-1}$)	1.0×10^{-2}-1.0×10^{-6}	1.0×10^{-2}-1.0×10^{-6}	1.0×10^{-2}-1.0×10^{-8}	1.0×10^{-2}-1.0×10^{-8}
Correlation Coefficient (R^2)	0.9999	0.9999	0.9998	0.9998
Response time (s)	10-35	14-38	4-32	6-36
Working pH range	4.5-5.5	4.5-5.5	4.5-5.5	4.5-5.5
Lifetime (day)	24	19	36	30
Temperature (ºC)	25_30	25_30	25_30	25_30
LOD ($mol.L^{-1}$)	1.92×10^{-5}	1.72×10^{-5}	2.07×10^{-7}	3.70×10^{-7}

The combination of the drug (DPH), the precipitating agent (STPB), and a plasticizer like tri-butyl phosphate (TBP) produced the ion pair (DPH-STPB). The dissociation of the ion pair is homogeneous. The concentration ranges for the conventional selective electrodes are (1.0×10^{-2}-1.0×10^{-6}) $mol.L^{-1}$, and for the nano-selective electrodes, they are (1.0×10^{-2}-1.0×10^{-8}) $mol.L^{-1}$, according to the results in Table 1. For the electrodes (I,II,III,IV), the corresponding slope values were 54.4,54.1,57.75,57.64) ($mV.decade^{-1}$). Response times were 10–35 s for electrode I, 14–35 s for electrode II, 4–32 s for electrode III, and 6–36 s for electrode IV. For the electrodes (I, II, III, IV), the correlation coefficients (R^2) were determined to be (0.9999, 0.9999, 0.9998, 0.9998), respectively. As Table 1 illustrates, the nanoelectrode has a longer lifespan than the conventional electrode. Additionally, Figures 8 to 11 display the diphenhydramine HCl electrode calibration curves.

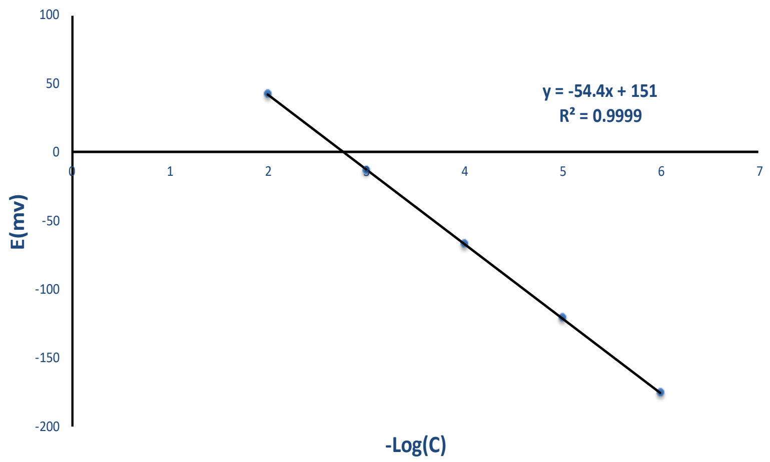

Figure 8. Calibration chart for Conventional copper electrode(I)

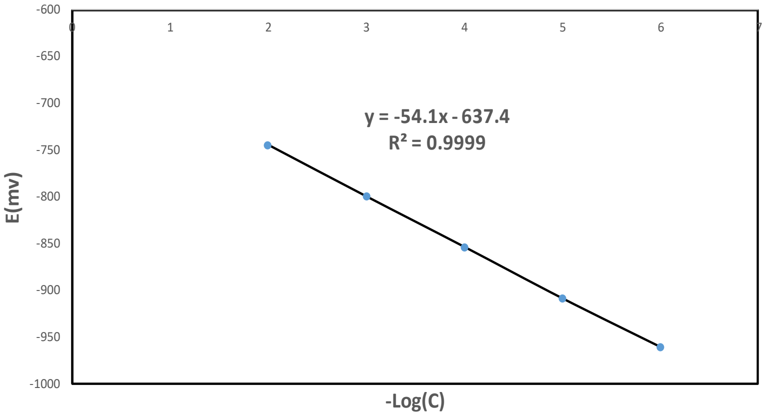

Figure 9. Calibration chart for conventional aluminum electrode (II)

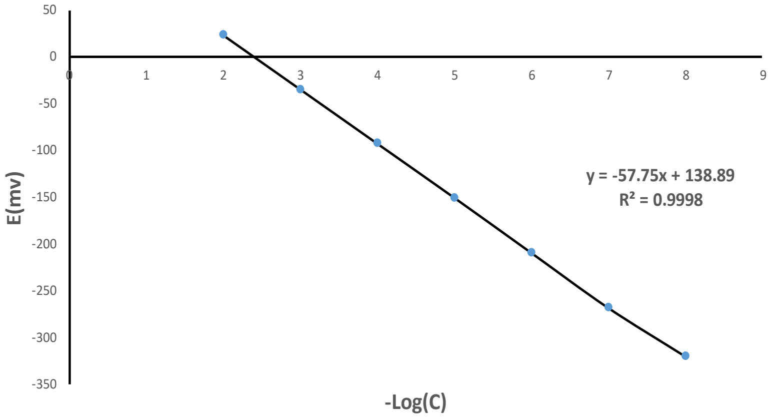

Figure 10. Calibration chart for copper nanoelectrode (III)

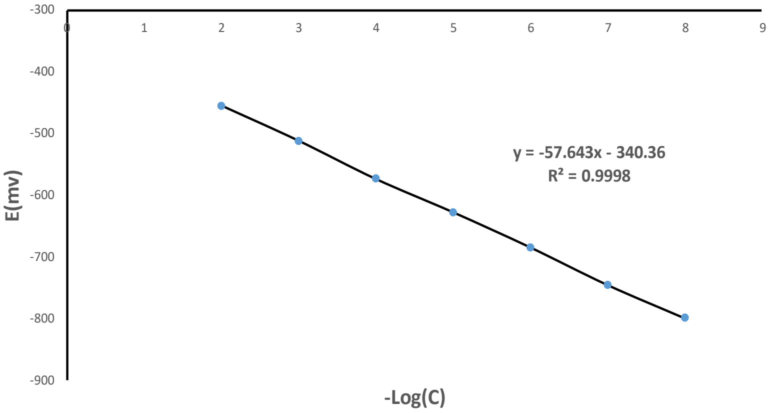

Figure 11. Calibration chart for aluminum nanoelectrode(IV)

3.3. The Selectivity

The selectivity coefficient for diphenhydramine HCl electrodes were calculated at concentration 1.0×10^{-3} mol.L^{-1} by applying the following equation [20,21]:

$$\text{Log}_{.\ \text{Kpot A,B}} = [\ (E_B - E_A)\ z\ A\ F / 2.303\ RT\ ] + (1\ _{z\ A} / _{z\ B}\ )\ \log a\ A.$$

In Table 2, it can be seen that the nano electrodes (III, IV) are more selective than the traditional electrodes (I, II). The values of the selectivity coefficient for all electrodes (I, II, III, IV) were less than the correct one, and this it indicates that the additives do not cause interference towards the material studied.

Table 2. The values of $K_{i,j}^{pot}$ for the diphenhydramine HCl-manufactured electrodes

Ion Overlapping	**Selectivity coefficient $K_{i,j}^{pot}$**			
	Coated wire electrodes			
	I	**II**	**III**	**IV**
Glucose	0.227	0.087	0.119	0.052
Maltose	0.184	0.091	0.182	0.068
Cross Carmellose	0.148	0.099	0.147	0.084
Methyl Cellulose	0.169	0.107	0.279	0.074
Magnesium Setrate	0.125	0.081	0.174	0.084

Table 3. The statistical treatment of the direct method for diphenhydramine HCl electrodes

Samples	**Electrode I**			**Electrode II**		
Pure Drug	**Taken -log[DPH] M**	**Found -log[DPH] M**	**%Rec**	**Taken -log[DPH] M**	**Found -log[DPH] M**	**%Rec**
	6.0	5.988	99.80	8.0	7.946	99.32
	5.0	4.984	99.68	7.0	7.045	100.64
	4.0	3.997	99.92	6.0	6.024	100.4
	3.0	3.011	100.36	5.0	5.002	100.04
	2.0	2.007	100.35	4.0	3.998	99.95
				3.0	2.993	99.76
				2.0	1.989	99.45
%SE **%RSD**	0.128 0.341			0.152 0.404		
Samples	**Electrode III**			**Electrode IV**		
Pure Drug	**Taken -log[DPH] M**	**Found -log[DPH] M**	**%Rec**	**Taken -log[DPH] M**	**Found -log[DPH] M**	**%Re**
	6.0	5.937	98.95	8.0	7.973	99.66
	5.0	4.994	99.88	7.0	7.037	100.52
	4.0	4.015	100.37	6.0	5.978	99.63
	3.0	3.017	100.56	5.0	4.990	99.80
	2.0	2.000	100.00	4.0	4.052	101.3
				3.0	2.977	99.23
				2.0	1.988	99.40
%SE **%RSD**	0.211 0.559			0.274 0.727		

3.4. Analytical Application

Using the prepared diphenhydramine HCl electrodes, the direct method was used to determine the pure drug. For the diphenhydramine HCl electrodes, the computed results for %RSD were approximately %0.341%, 0.404, %0.559, and %0.727. The suggested method's high accuracy and precision were demonstrated by the good recoveries and low relative standard deviations that were obtained.

Additionally, the diphenhydramine HCl coated wire electrodes with nanoparticles demonstrated high sensitivity, quick static response dynamic time, long-term stability for drug solution, and applicability across a broad concentration range with little sample pretreatment. These results are demonstrated in Table 3 and can be regarded as an excellent tool for routine DPH determination.

4. CONCLUSION

This study demonstrated that the two electrodes coated with nano-oxides and the two conventional electrodes for the drug (DPH) produced different results in terms of selectivity and sensitivity. In addition to stable results, it was demonstrated that the two electrodes (III, IV) have higher selectivity and sensitivity, as well as a faster response time, than (I, II). This is because of the characteristics of nanoparticles in the electrical improvement process. Their smaller size and larger surface area make them more sensitive and selective, and these characteristics allowed us to study the drug (DPH) with low limits and wide concentration ranges. Because of the nanoparticles' favorable physical and chemical characteristics, the drug ions move quickly toward the coating, which accounts for the high sensitivity of the electrodes coated with them. Electrodes coated with nanoparticles have proven to be a reliable method for detecting DPH in research facilities and pharmaceutical compounds.

Declarations of interest

The authors declare no conflict of interest in this reported work.

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