Article

Utility of a green synthesized NiO nanoparticles sensor for the determination of triprolidine hydrochloride in pure form and commercial products.

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Abstract

In this study, an environmentally friendly biomethod was developed for the green synthesis of nickel oxide nanoparticles (NiONPs) by lemon balm extract due to its bioreductive ability , this process is completely green, and free of toxic and hazardous solvents ,the optical, catalytic and structural properties of NiONPs were studied, through the use of XRD and SEM measurement, the results showed the formation of pure and crystalline NiONPs, we also manufactured electrodes for the determination of the drug triprolidine hydrochloride (TRI), the first electrode is the traditional coated graphite electrode (I) (TRI-PTA-TBP), as for the second electrode, the nano-coated graphite electrode (II) (TRI-PTA-TBPNiONPs), the results showed that the linear range for the conventional selectivity of electrode (I) is between (10^{-2} – 10^{-6}) mol/L, while the linear range for the nanoelectrode (II) is between (10^{-2} – 10^{-8}) mol/L, and the inclination of electrode (I) was calculated at (54.5) millivolts/knot, while the inclination of electrode (II) was estimated at (58.25) millivolts/knot, the results also showed that the estimation factor for electrode (I (is (0.9991), while the estimation factor for the electrode (II) is (0.9999), through these results, we have concluded that the graphite electrode coated with nickel nanoparticles (II) is more sensitive and selective than the traditional coated graphite electrode (I),these poles succeeded in identifying (TRI) In its various pharmaceutical formulations, the validation of the method was evaluated according to IUPAC recommendations as this method is an environmentally friendly technology and does not require sample pretreatment or derivatization.

Keywords: Tripyridine hydrochloride; coated graphite sensors ; nickel oxide nanoparticles; selective electrodes Ionic.

1-Introduction

Tripyridine hydrochloride: It is fromH1-receptor inhibitors are antihistamines [1], a chemical compound used as an over-the-counter drug that has anticholinergic properties, It is used to treat symptoms associated with allergies and is sometimes combined with other cold medications manufactured to combat flu-like symptoms, as is the case with many antihistamine medications [2] ,triprolidine inhibits H1 receptors and thus prevents histamine from binding to its receptors, as the binding of histamine leads to the appearance of symptoms such as (sneezing, itching, runny nose, watery eyes), Its molecular weight is (314.85) g/mol, and its structural formula is:

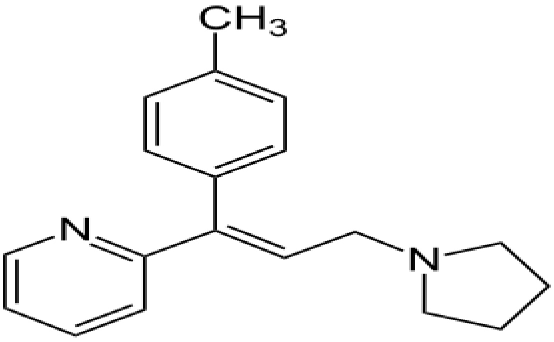

figure (1) Structural formula of Tri proledine hydrochloride

Tripyridine hydrochloride is used to treat symptoms of allergies and seasonal allergies, such as coughing, sneezing, nasal congestion, itching, and eye inflammation[3] , the drug works by inhibiting the effect of histamine, a chemical that the body secretes during an allergic reaction, and thus helps relieve the symptoms associated with allergies.

Several analytical techniques have been reported for the quantitative determination of TRI including various HPLC methods for the analysis of TRI either alone or in combination with other drugs in their pharmaceutical dosage forms [4-7] , the compound was identified using capillary electrophoresis in the presence of paracetamol [8] , and TRI was also analyzed using spectrophotometry [9-11] , where we created ion-selective electrodes for [12,13] (TRI) and development of selective electrodes as a sensor for measuring concentration (TRI) whether separately or in pharmaceutical preparations , these electrodes rely on the transfer of ions in the electrolyte solution , and when the selective electrode is placed in a solution containing ions interacting with the selective membrane, a transfer of ions occurs across the membrane, leading to a difference in potential between the membrane and the electrolyte solution [14] , selective electrodes can be used to measure the concentration of ions in solutions by measuring the voltage between the selective electrode and a reference electrode [15-16] , Since their discovery in 1890, selective electrodes have been greatly developed, one of the most important developments was the discovery of the glass electrode to measure the function of acidity (pH) in 1900, other selective electrodes were developed to measure the concentration of other types of ions such as (Ca, K, Na) [17,18], and their ability to respond quickly to changes in concentrations, the simple change in acid function (PH) is also considered easy to prepare, develop, and cost, electrochemical techniques are currently considered one of the most environmentally friendly methods used in the field of pharmaceutical research, as they do not require the use of dangerous solutions or organic solvents, these techniques rely on the use of electrodes, Ion-selective electrodes (ISEs) are based on the movement of substances across a special membrane and are widely used to determine drugs in their pure and pharmaceutical forms, ion-selective electrodes (ISEs) are characterized by their high selectivity in accurately determining analytes in complex, turbid, colored and viscous solutions without separation [19], the process of measuring concentration depends on measuring the change in electrical potential across the selective membrane that interacts with the target ion, pre-calibration is used to create a calibration curve that links the change in electrical potential to the concentration of the target compound, the measurement process usually includes sample preparation, preparing the selective electrodes, and measuring output voltage, selective electrode technology is a fast and accurate method for analyzing the concentration of chemical compounds such as (TRI) however the selective electrodes must be optimized and calibrated to ensure accurate measurements it may be additional analyzes are also necessary to ensure that the concentrations measured by the selective electrodes are consistent with other approved methods of analysis[20].

2 - Materials and Methods

2-1- Chemicals

Samarra Pharmaceutical Industries (SDI) produces triprolidine hydrochloride , The Fluka firm supplied 99.9% pure triperoleine powder (100 mg) and chloride aqueous nickel $NiCl2.6H2O$ to Sigma-Aldrich (Hamburg, Germany), The analytical chemistry laboratory at Tikrit University's College of Science produced a variety of materials, including tetrahydrofuran (99.9% THF), polyvinyl chloride (PVC), 99.0% tributyl phthalate (99.0% TBP), and hydrochloric acid and sodium hydroxide solutions, both of which were supplied by BDH with a purity of 99.9%. Deionized water was also produced there. supplied methylcellulose, glucose maltose, magnesium citrate, croscarmellose sodium, and phosphotanexacetic acid (99.9% PTA).

2 - 2 - Tools and devices

All experimental studies were carried out using a 211-HANNA pH meter (HANNA instruments, Smithfield, VA, USA) , Another pH meter (Metrohm-744) was used to adjust the pH of the analytical samples , sartorius BL210 S AG GottIngen, Jenway-pH Meter 3310, electric mill , centrifuge , scanning electron microscope (SEM ,JSM-7610FTokyo , Japan), diffractometer (Shimadzu XRD-6000 kyoto , Japan) , calomel electrode Co.(Germany) No13-639-52 fisher sientific as a reference electrode , electric drying oven (Germany) , Jenway hot plate with magnetic stirrer(Germany),Sci Finetech-Muffle furnace-FTMF-705(Germany).

2-3-The Cyperus Seeds Extract

Cyperus seeds were cleaned, washed with distilled water, and dried in the sun for two days. They were then dried in an oven for twenty-four hours at 100 degrees celsius. Next, the seeds were ground using a home electric grinder to produce a particle size smaller than 0.42 mm. Next, the powder was sifted through a hole-sized clip (0.42 mm). finally, the powder was weighed (10 mg) using a scale with four decimal places. finally, the powder was soaked in (100 ml) of distilled water and heated to a temperature of (80°C) using an electric heater , this was done for approximately an hour, after which it was left to cool at room temperature and filtered with filter paper, then transferred the cyperus plant extract solution into a 250 ml vitreous glass beaker and kept it somewhere secure until needed.

2 - 4 - Green Preparation of Nanoparticles (NiONPs)

(NiONPs) were created via a previously revealed green synthesis technique , in order to prepare (NiONPs), 10 milliliters of the cyperus plant extract and 10 milliliters of Nikel Sulfate concentration (0.1M) are combined and continuously stirred for thirty minutes using a magnetic stirrer. During this time, slowly add drops of NaOH with a concentration of 2 M while stirring the mixture; the mixture's yellowish brown color indicates the formation of calcium nanoparticles. The sediment is then filtered through filter paper and repeatedly washed with distilled water to remove excess sodium hydroxide , then dry it in a convection oven for an hour. After that, the precipitate is calcined for three hours at 500°C in an incineration oven. The calcium particles are then retained, and the resulting nanoparticles are stored in a secure location until needed.

2-5- Preparation of the standard solution of Tri proledine HCL (0.01M)

It was made by melting 0.3148 gm of TRI powder in a glass beaker with a capacity of 25 ml of deionized water , It was then placed in a large glass bottle and diluted and supplemented with deionized water to the appropriate level , a series of standard solutions (10^{-3} – 10^{-8} M) were then prepared from it using the law of dilution

2-6- Preparation of the ion pair (TRI-PTA)

The ionic double is made by combining (50 ml) of TRI with a focus of (0.01 M) and (50 ml) of flocculating agent (PTA) with a focus of (0.01 M) in a (250 ml) glass beaker , the mixture is then continuously stirred for 20 minutes using a magnetic stirrer, and the mixture is left in a dark place for 24 hours until a brown precipitate forms , the precipitate is then filtered and repeatedly washed with distilled water, dried in an electric oven set to 70 degrees celsius, weighed, and stored in a secure location until needed.

2-7 - Membrane composition and electrode fabrication

In order to create a typical sensor film, (0.01 mg) of the ionic double and (0.19 mg) of PVC were combined in a (10 ml) large capacity glass container , the mixture was then dissolved in (5 ml) of solvent (THF) , after thoroughly mixing with a glass stirrer, add (0.35 ml) of plasticizer (TBP) , after giving it a good hour to allow the membrane to fully form, we remove the graphite sensor and thoroughly clean it with distilled water, after allowing acetone to dry, we pierced one end of the sensor deeply with a drill (0.5 cm) and offered (2 mm) , we then placed the sensor inside a polyethylene tube, leaving one end pole length (1 cm) for plating , next, we added a length of copper wire (8 cm) and knocked the perforated sensor several times, each at a 10 second interval, so that we could connect it to a potential difference device , finally, we scanned the graphite in the membrane solution multiple times, every minute, and let it dry for thirty minutes, In order to create a nano sensor membrane (NiONPs), we combine (0.01 mg) of the ionic double with (0.19 mg) of PVC and (5 mg) of the particle (NiONPs) in a (10 ml) glass beaker , we then dissolve the particles in (5 ml) of solvent (THF) , using a glass motor, thoroughly mix; add (0.35 ml) of plasticizer (TBP) , after giving it a good hour to allow the membrane to fully form, we take a graphite sensor and thoroughly clean it with distilled water and acetone, then allowed it to dry before offering to hole it at one end with a deep electric drill (0.5 cm) (2mm) Insert the sensor into the polyethylene tube, leaving one end of the pole lengthwise (1 cm) for plating , next , insert an 8-cm piece of copper wire through the perforation in the sensor and securely fasten it to the potential difference device , the graphite sensor is then repeatedly applied to the membrane solution at a rate of ten seconds per minute, and it is allowed to dry for thirty minutes.

2 -8- Calibration curve

Each of the (25 ml) of (10^{-2} – 10^{-8} M) TRI standard solution was assessed and evaluated independently using the proposed sensors and reference electrode. figure (2) shows the potential values as a function of -logarithm TRI concentrations as displayed on the calibration graphs of each sensor

2-9- The effect of (PH)

We use a (25 ml) glass beaker to hold (20 ml) of drug TRI at concentrations of (10^{-2} – 10^{-4} M) , the calomel sensor is then submerged in each of the constructed sensors (I, II), in that order, and we measure the potential difference after adjusting the acid function ratio from (1.8 – 5) , Following each measurement , the manufactured sensors and the standard calomel sensor were cleaned and soaked in distilled water before being dried , we then plotted the relationship between the potential difference and the acid function in the excel program, and the results are displayed in figure (3) .

2-10- The effect of temperature

We measure the potential difference after varying the temperature of the two concentrations solution (10^{-2} , 10^{-4} M) from (10 – 50) degrees Celsius , we then draw the relationship between potential difference and temperature in the excel program, and the results are shown in figure (4) , we take (20 ml) for concentrations (10^{-2} – 10^{-4} M) from a drug TRI in a (25 ml) glass beaker , the calomel electrode is then immersed with each of the manufactured sensors (I,II) respectively.

2-11- Analytical Applications

The suggested sensors TRI-PTA-NiONPs were used separately to determine each concentration of the tested medication , Ten Samafed® tablets (150 mg/tablet) were finely crushed, and 0.53 gm was dissolved in distilled water to make a standard solution of (10^{-2}) mol / L. Working solutions were created to achieve varied concentrations of TRI in the range of (10^{-3} – 10^{-6}) mol / L .

3- Results and discussion

3.1. Characterization of the Synthesized Nanoparticles

The scanning electron microscope (SEM) technique uses a concentrated, high-energy electron beam to interact with the surface of the sample it is exposed to , this interaction produces a distinct set of signals on the surface of the solid sample being examined and allows for the creation of topographical images , the SEM technique can reveal a great deal of information about the surface of the sample , this method mostly depends on how much of the spot is exposed to the electron beam and how much of an impact it has, since the electron beam is often scanned using raster scanning, and the signal's position is then merged to provide a precise image of the sample's surface under test, figure (5) illustrates the compound (NiONPs) imaged by scanning electron microscopy, which revealed rods with diameters ranging from (129 – 208) nanometers as well as (208 nm) and some microns whose dimensions ranged from (45-81 nm) .

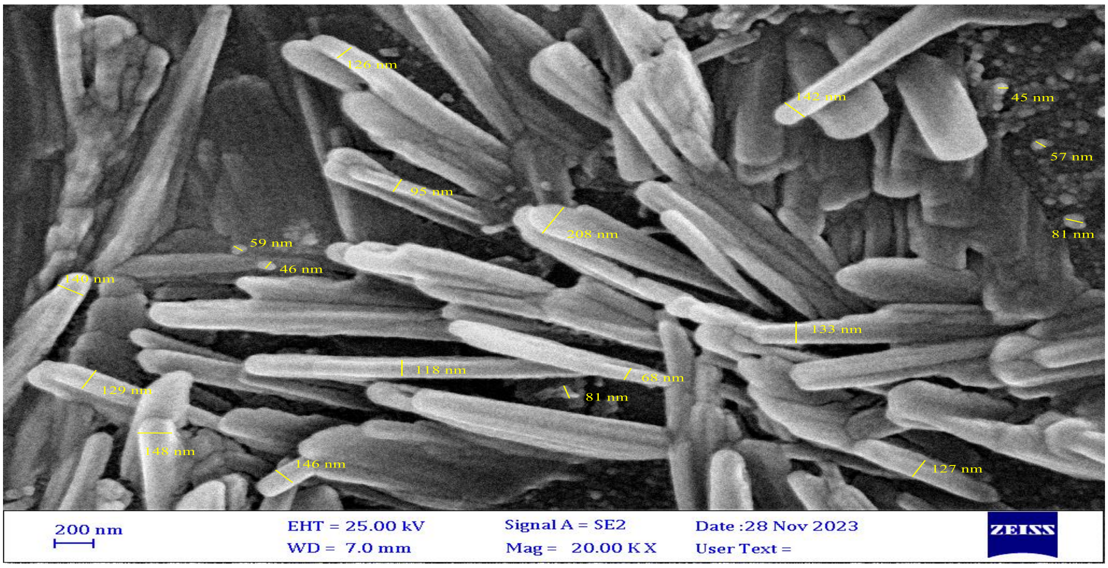

Figure (5) The imaging Scanning electron microscope SEM for (NiONPs)

The crystal structures of the NiONPs prepared using cyperus plant extract were confirmed by XRD analysis as shown in Figure (6), where X-ray diffraction analysis revealed characteristic bands of peaks at 2θ starting from (31.7-76) , table (1) also shows the XRD results of the nanoprecipitate (NiONPs) using cyperus plant extract, which showed many parameters and structural characteristics of the materials such as the size of the particles, the width of the beams at the average height, the location of the peaks and the distances between the crystal layers, and that D represents the particle size, where the average crystal size (32.4 nm) according to the scherrer equation to calculate the size of the crystals.

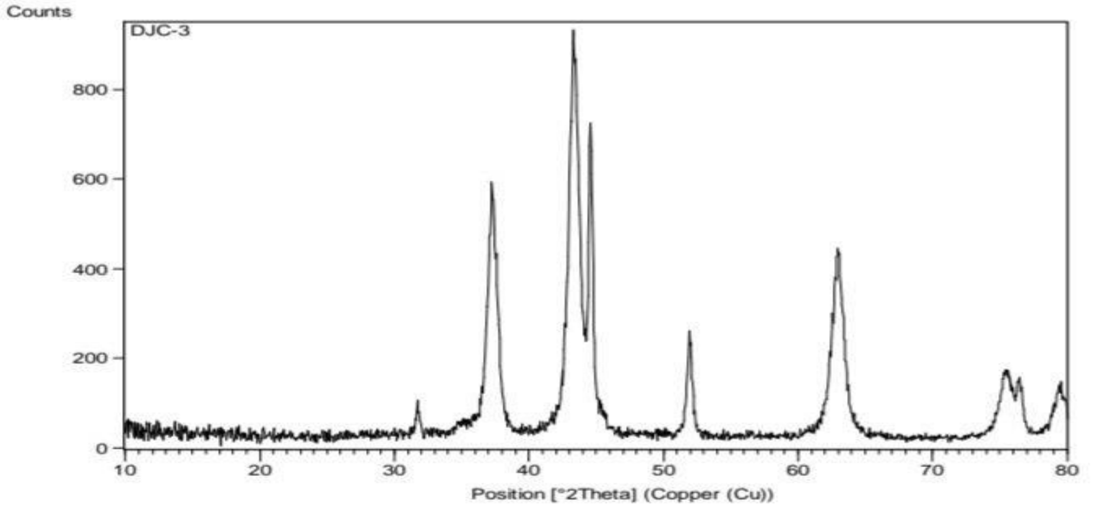

Figure (6) XRD patterns of green synthesized (NiONPs) using syperus extract

Table (1) X-ray diffraction (XRD) results for particles (NiONPs) prepared using syperus extract

Pos. [°2Th.]	FWHM	d-spacing	Height	Rel. Int.	D nm	Average

	[°2Th.]	[A°]	[cts]	[%]		D nm
31.7385	**0.1968**	**2.81937**	**73.62**	**8.54**	**43.84332**	**32.43305**
37.2755	**0.2952**	**2.41232**	**530.94**	**61.58**	**29.67092**	
43.3409	**0.2460**	**2.08775**	**862.13**	**100.00**	**36.30373**	
44.5822	**0.2952**	**2.03246**	**694.16**	**80.52**	**30.38568**	
51.9522	**0.2460**	**1.76015**	**213.37**	**24.75**	**37.52922**	
62.9813	**0.3444**	**1.47587**	**418.27**	**48.52**	**28.26056**	
75.4655	**0.6888**	**1.25974**	**141.78**	**16.45**	**15.23536**	
76.4453	**0.3936**	**1.24602**	**121.60**	**14.10**	**26.84045**	
31.7385	**0.1968**	**2.81937**	**73.62**	**8.54**	**43.84332**	
37.2755	**0.2952**	**2.41232**	**530.94**	**61.58**	**29.67092**	
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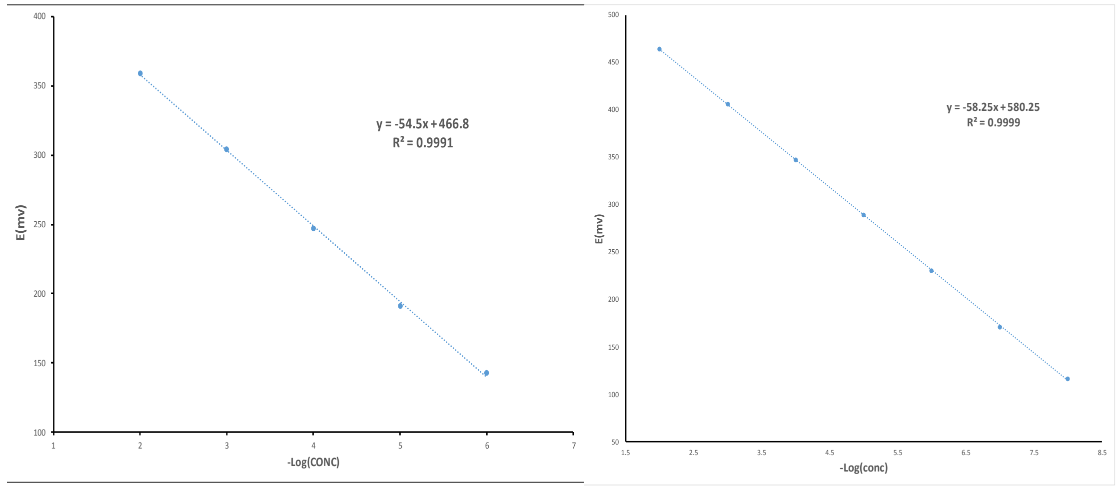
Table(2) electrochemical response characteristics of traditional (TRI-PTA-TBP) sensor , and modified (TRI-PTA-TBP-NiONPs) sensor.

Parameters	traditional TRI-PTA-TBP Sensor	Modified (TRI-PTA-TBP-NiONPs) Sensor
Slope (mv/decade)	54.5	58.25
Regression equation	-54.5×+466.8	-58.25×+580.25
Iinear range (M)	$10^{-2} – 10^{-6}$	$10^{-2} – 10^{-8}$
Correlation Coefficient(r)	0.9991	0.9999
Response Time/s	8 - 36	4 - 29
Wrking PH range	3.2 – 3.8	2.8 – 3.8
Lifetime/day	24	34
Temperature C	20 - 30	20 - 30
LOD	2.18×10^{-7}	4.6×10^{-9}

The interaction of the medication (TRI) and the precipitate (PTA) results in the formation of the ionic anionic pair (TRI-PTA) , when PVC and the plasticizer tributyl phthalate (TBP) are present, the stable ion pair (TRI-PTA) can dissolve in organic solvents such (THF) , the ion pair melts uniformly thanks to this fluidized substance, and it then diffuses uniformly into the electrode membrane , the linear range of the modified sensors (I,II) and the conventional ion pair is between (10^{-2} - 10^{-6}) mol/L and (10^{-2} - 10^{-8}) mol/L, respectively, according to the results displayed in table (2) , additionally, it was discovered that the slopes of the modified and traditional sensors (I , II) were, respectively,(54.5,58.25) MV/nodes , the sensors' estimation coefficients (0.9991, 0.9999) show that they are both quite near to unity for a concentration of (10^{-2}) mol/L, the response times of modified and conventional sensors (I,II) are (8 ,4), respectively , and (36,29) seconds for concentrations of (10^{-6},10^{-8}) mol/L , additionally, the conventional and modified sensors (I,II) have respective lifespans of 21 and 35 days. The ideal temperature for both sensors to function at is 25 degrees celsius , the PH function was examined in the estimate process (TRI) , for both modified and conventional sensors (10^{-4},10^{-2}) mol/L, the optimal range of the acidity function is (3.2 - 3.8) and (2.8 – 3.8), respectively , variations in acid levels can impact the response and performance of conventional and nanoelectrodes (I,II) specifically, when operating in the (2.8-3.8) and (3.2-3.8) linear pH ranges .

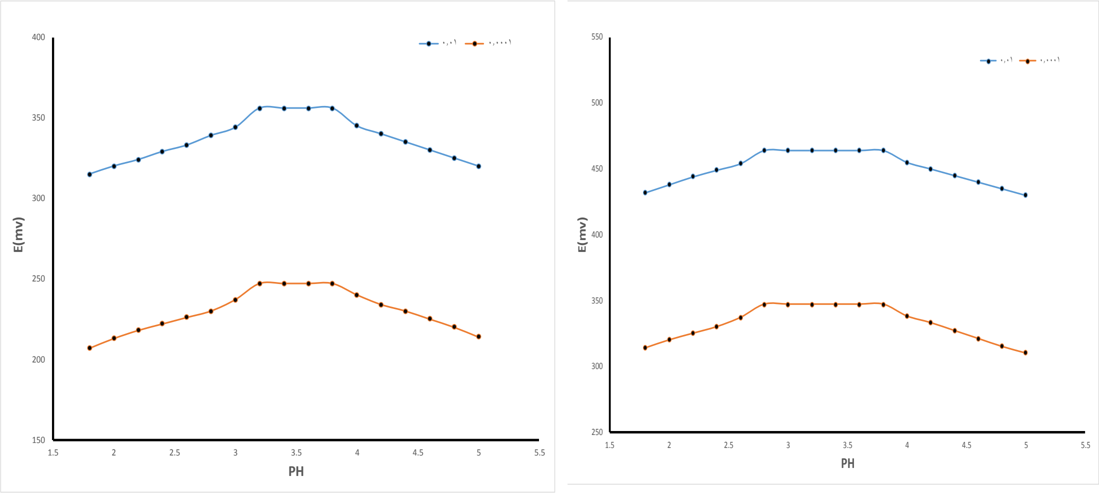
Phagocaustic alterations can impact the response and performance of both conventional and nanoelectrodes (I,II) , more specifically , two distinct amounts (10^{-4}, 10^{-2}) mol/L can influence drug detection while operating within the linear pH range (3.2 - 3.8, 2.8 - 3.8) , respectively , when working in very acidic circumstances, electrodes (I,II) exhibit low voltage values , this reduction can be linked to the pharmaceutical ingredient's creation of a white precipitate as a result of its interaction or blockage of the medication substance.

Additionally, the solution being measured turns turbid, and an increase in the concentration of the hydroxyl ion may cause flocculation on the electrode membrane. As a result, there is intense competition between the hydroxyl and drug ions for the position of double ions, which reduces the interaction between the ions and results in a decrease in the linearity gradient , a decrease in potential difference values is also seen when hydrochloric acid solution drops are added to create low pH conditions , this drop indicates a higher concentration of hydrogen ions, which can be explained by the interference of hydronium ions , this leads to the formation of hydrogen ion pairs, which are very sensitive to hydronium ions present in the solution under measurement but less sensitive to drug ions.



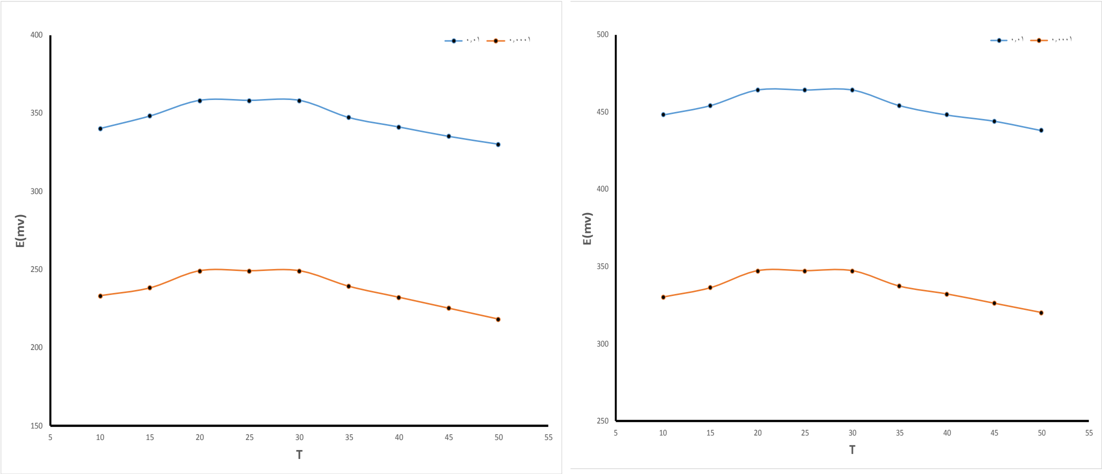
(a) **(b)**

Figure (2) Calibration graphs of the fabricated (a) traditional (TRI-PTA-TBP) Sensor , and (b) Modified (TRI-PTA-TBP-NiONPs) Sensor



(a) **(b)**

Figure (3) The effect of acid function , (a) traditional (TRI-PTA-TBP) Sensor , and (b) Modified (TRI-PTA-TBP-NiONPs) Sensor



(a) **(b)**

Figure (4) effect of temperature , (a) traditional (TRI-PTA-TBP) Sensor , (b) Modified (TRI-PTA-TBP-NiONPs) Sensor

Table (3) statistical treatment of the Samafed® results of the calibration curve for traditional TRI-PTA-TBP and Modified (TRI-PTA-TBP-NiONPs) sensors .

Parameters	(TRI-PTA-TBP)			(TRI-PTA-TBP-NiONPs)		
	Taken –Log conc mol.L^{1-}	Found Mol.L^{1-}	Recovery %	Taken –Log conc mol.L^{1-}	Found Mol.L^{1}	Recovery %
Pure Drug	6.0	5.94	99.00	8.0	7.97	99.62
	5.0	4.95	99.00	7.0	7.02	100.28
	4.0	3.95	98.75	6.0	6.01	100.16
	3.0	2.96	98.66	5.0	5.00	100.00
	2.0	1.95	97.5	4.0	4.004	100.1
				3.0	2.99	99.66

				2.0	1.99	99.5
%Mean∓SD	98.58 ∓ 0.6			99.9 ∓ 0.3		
n	5			7		
Variance	0.38			0.09		
%SE	0.27			0.11		
%RSD	0.63			0.3		

TRI-PTA-TBP and TRI-PTA-TBP-NiO sensors were used to test the TRI in its commercial product, which is Samafed® film coated tablets (150 mg/tablet) , the expected values for the two sensors were 99.9±0.3 and 98.58±0.6, respectively (Table 3) , the results showed that compared to the TRI-PTA-TBP sensor, the TRI-PTA-TBP-NiO sensor was more sensitive to detect TRI analyte , Because of the metal oxide nanocomposite's special physical and chemical characteristics, its large surface area, which enhances interfacial contact between the detected analytes and the sensor membrane's active sites, high conductivity, and high dynamic stability, the TRI-PTA-TBP-NiO sensor was able to detect the target analyte. The projected values were compared to those of a previously established method based on silicon tungstic acid preparation of a PVC sensor [21] , the results were statistically analyzed [22] , there were no appreciable variations in the positive and consistent results.

Table (4) Values of the selectivity coefficient (K) obtained from both traditional and modified sensors (I, II)

Foreign Compound	$K_{i,j}^{pot}$	
	traditional and Modified Sensors	
	TRI-PTA-TBP (I)	TRI-PTA-TBP-NiONPs(II)
Glucose	0.280	0.092
Maltose	0.226	0.082
Methyl Cellulose	0.19	0.079
Cross carmellose	0.318	0.117
Magnesium stearate	0.346	0.070

Based on Table (4) results, it can be observed that modified TRI-PTA-TBP-NiONPs sensor (II) is more selective than its traditional TRI-PTA-TBP sensor (I) , additionally, the selectivity coefficient values for both the modified and traditional sensors (I, II) are less than one, suggesting that the additives (glucose, maltose, methyl cellulose, cross-carmellose, and magnesium stearate) don't seem to interfere with the ion that needs to be detected .

4 – Conclusions

After standard and customized sensors were manufactured, researchers evaluated electrochemistry and potentiometry , We designate one of these sensors as the "second sensor" since it has been coated with calcium nanoparticles, or kaunps , The properties of TRI in both its pure and medical preparation forms are estimated using these sensors , this investigation revealed a discernible difference between the modified sensor (II) and the traditional sensor (I) in terms of their capacity to identify histamine and antimicrobial TRI , in comparison to the standard sensor (I), the modified sensor (II) demonstrated a higher response and a faster reaction time , this can be explained by the way calcium oxide molecules work to improve electrical performance , they also have a large surface area and small particle size, which make them more sensitive and selective , these features enable the modified (second) sensor to search for the drug TRI rapidly, with low limits and a wide range of concentrations , their excellent physical and chemical characteristics enable them to transmit the drug's ions swiftly , the redesigned (second) sensor is hence more sensitive to the medication TRI , the free energy of transportation of the drug ion between the selective electrode membrane and the drug solution, which is measured inversely, is proportional to its selective ability, these features enable the improved (second) sensor to swiftly identify TRI medicines in hospitals and research facilities.

REFERENCES

[1] - Goldsmith P, Dowd PM (January 1993). "The new H1 antihistamines.Treatment of urticaria and other clinical problems". *Dermatologic* Clinics. 2, United States Pharmacopoeia Convention, Rockville (2011).

[2] - Williams, B. O., Liao, S. H., Lai, A. A., Arnold, J. D., Perkins, J. G., Blum, M. R., & Findlay, J. W. (1984). Bioavailability of pseudoephedrine and triprolidine from combination and single-ingredient products. *Clinical Pharmacy*, *3*(6), 638-643.

[3] - Goldsmith, P., & Dowd, P. M. (1993). The new H1 antihistamines: Treatment of urticaria and other clinical problems. *Dermatologic clinics*, *11*(1), 87-95

[4] - Farouk Bassuoni, Y., Essam, H., Saad Elzanfaly, E., Zaazaa, H. E. S., & Mohamed Kelani, K. (2020). Green potentiometric method for determination of triprolidine hydrochloride and pseudoephedrine hydrochloride in their different pharmaceutical matrices using liquid and solid contact gold electrodes. *Analytical and Bioanalytical Electrochemistry*, *12*(6), 793-809.

[5] - Shakya, A. K., Arafat, T. A., Abuawwad, A. N., Melhim, M., Al-Ghani, J., & Yacoub, M. J. (2009). Simultaneous determination of triprolidine and pseudoephedrine in human plasma by liquid chromatography–ion trap mass spectrometry. *Journal of Chromatography B*, *877*(32), 4071-4078.

[6] - El-Gindy, A., Attia, K. A. S., Nassar, M. W., Abu Seada, H. H., & Shoeib, M. A. S. (2013). HPLC method for determination of paracetamol, psedoephedrine, triprolidine, methylparaben, propylparaben, sodium benzoate, and their related substances in pharmaceutical syrup. *Journal of Liquid Chromatography & Related Technologies*, *36*(9), 1251-1263.

[7] - Akhtar, M. J., Khan, S., & Hafiz, M. (1994). High-performance liquid chromatographic assay for the determination of paracetamol, pseudoephedrine hydrochloride and triprolidine hydrochloride. *Journal of pharmaceutical and biomedical analysis*, *12*(3), 379-382..

[8] - Monocytogenes, L., Kurkure, N. V., & Tembhurne, P. A. THE INDIAN JOURNAL OF VETERINARY SCIENCES & BIOTECHNOLOGY.

[9] - Rao, P. M., Santosh, T., & Babu, K. R. (2016). Development, validation & stress degradation studies of triprolidine by reverse phase-high performance liquid chromatographgy (rp-hplc). *International Journal of Pharmaceutics and Drug Analysis*, 72-78.

[10] - Abdulrahman, S. A., & Qazzan, J. A. M. (2023). SENSITIVE SPECTROPHOTOMETRIC DETERMINATION OF TRIPROLIDINE HYDROCHLORIDE DRUG IN THE CAPSULES VIA ION PAIR COMPLEX FORMATION. *Química Nova*, *46*, 860-866.

[11] - Martindale "The Extra Pharmacopeia -The Complete Drug Reference" edited by Sean. C, Sweetman, Pharmaceutical press, London, UK, 36th ed., 2009: 565, 592.

[12] - Zayed, S. I. M. (2004). New plastic membrane and carbon paste ion selective electrodes for the determination of triprolidine. *Analytical sciences*, *20*(7), 1043-1048.

[13] - Issa, Y. M., Attia, F. M. A., & Ismail, N. S. (2010). Mixed ion-exchanger chemically modified carbon paste ion-selective electrodes for determination of triprolidine hydrochloride. *Journal of Advanced Research*, *1*(1), 79-85.

[14] - Hussien, E.; Abdel-Gawad, F.; Issa, Y.; "Ion- selective electrodes for determination of fluoxetine in capsules and in biological fluids", Biochem. Eng. J. 53(2), 210–215, 2011.

[15] - K. Othmer, Encyclopedia of Chemical Technology, 1981, 13, 233.J. Korgto, Ion Selective Electrodes, Cambridge University Press, 1975, p2, 48.

[16] - D. Skooge & D. West, Fundumentals of Analytical Chemistry, 4th edition, Saunders College Poblishing, Japan.1982, p.398-400.

[17] - E. Pungor, Analytical Sciences, 1998, 14, 249. Qi, L., Liang, R., Jiang, T. and Qin, W., 2022. Anti-fouling polymeric membrane ion-selective electrodes. TrAC Trends in Analytical Chemistry, p.116572.

[18] - Ahmed Ali Abdel Sahib; University of Babylon College of Science “Preparation of a new selective electrode for palladium ion based on coronal ether” 2008, 206-214.

[19] - Hassan, S. S., Mahmoud, W. H., & Othman, A. H. M. (1996). Determination of ranitidine in pharmaceutical preparations using manual and flow injection potentiometry and spectrophotometry. *Analytica chimica acta*, *332*(1), 39-48..

[20] - Vázquez, M. E., López, J. R., Medina-Rodelo, D., Jiménez-Edeza, M., Castaneda-Ruelas, G. M., López, A. M., ... & Méndez, P. F. (2019). Electrochemical study, structural characterization and antimicrobial activity of Silver and Copper Oxide (CuO) nanoparticles synthesized by a Green Method Using L-ascorbic Acid and Chitosan. *International journal of electrochemical science*, *14*(7), 6366-6375.

[21] - Makarov, V. V., Love, A. J., Sinitsyna, O. V., Makarova, S. S., Yaminsky, I. V., Taliansky, M. E., & Kalinina, N. O. (2014). “Green” nanotechnologies: synthesis of metal nanoparticles using plants. *Acta Naturae (англоязычная версия)*, *6*(1 (20)), 35-44.

[22] - Lisak, G. (2021). Reliable environmental trace heavy metal analysis with potentiometric ion sensors-reality or a distant dream. Environmental Pollution, 289, 117882.