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Electrochemical Detection Of N-Nitrosodimethylamine Using Poly-Catechol Modified Glassy Carbon Electrodes With Silver Nanoparticle Enhancement

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NDMA which is N-Nitrosodimethylamine is a genotoxic compound that is easily found as an impurity in drugs at very low concentrations with their carcinogenic effect it alters the gene and forms toxicity into it. This NDMA is present in many anti-diabetic, cardiovascular, and gastroprotective drugs hence several drugs were investigated for the presence of NDMA, and the compound was banned in 2019. In this research, an electrochemical method was developed for the investigation of NDMA by utilizing glassy carbon electrode (GCE) sensing platforms. The nanomaterial that was used to superimpose into it was silver nanoparticles embedded with poly cyst-amine (poly CA) due to this the electrochemical and analytical performance of the modified probe showed high sensitivity. Analytical instruments such as Cyclic Voltammetry, Square Wave Voltammetry, and Differential Pulse Voltammetry were utilized to characterize the electrochemical behavior of NDMA at modified and non-modified electrodes. The effective surface topography of the electrodes was evaluated utilizing electrochemical techniques which resulted in a substantial increase upon modification with poly CA films. Moreover, an interference study was conducted to assess the selectivity and specificity of electrodes in NDMA detection in the presence of the interfering phases. The research results into the promising performance of the electrochemical sensor which shows highly selective and sensitive NDMA detection. The contribution and findings resulted in the development of advanced sensors for investigating carcinogenic material from pharmaceuticals and industrial process control.

Keywords: NDMA, Poly CA, AgNP, Cyclic Voltammetry, Square Wave Voltammetry, Electrochemical Sensor.

1.0 Introduction

N-nitrosodimethylamine (NDMA) is a potent carcinogenic compound that results in the genotoxicity found in various pharmaceuticals, environmental and industrial sources including drugs such as anti-diabetic, cardiovascular and gastroprotective, agricultural runoff, various wastewater effluents, and Industrial process. [1-4] NDMA due to its potential carcinogenicity acts as an impurity in pharmaceuticals which results in gene alteration in humans which leads to rare diseases and officially banned certain drugs under the EU in 2019. [5] According to the reports drugs with NDMA contamination such as Ranitidine banned worldwide in 2019 which was prescribed for heartburn, and batches of Valsartan were banned in 2018 due to this carcinogenic contamination, similarly Metformin an anti-diabetic drug was also found with NDMA impurity and was banned in 2020. [6-8] Therefore, Investigation of this impurity because of the carcinogenic properties and potential health hazards a vital need for sensitive and specific analytical methods for NDMA detection qualitatively and quantitatively is a need of hour. Hence electrochemical sensor was developed and synthesized due to its high sensitivity, rapid response, and cost-effectiveness. [9] Glassy carbon electrodes (GCE) modified with functional materials have resulted in great potential for electrochemical execution i.e. highly selective for NDMA detection. [10] In this research, modification such as electrochemical deposition of the poly-cystamine (poly-CA) is layered onto a glassy carbon electrode which results in a large increase in surface topography for the analyte interaction. [11] Furthermore, nanomaterial such as silver nanoparticles plays a vital role in modifying probes resulting in high sensitivity and selectivity when they are attached to the poly CA film to enhance the response of the sensor. [12] In this research paper, we have evaluated the electrochemical properties and analytical performance of the modified probe utilizing poly CA, AgNPs, and GCE for the detection of NDMA with techniques such as cyclic voltammetry, square wave voltammetry, and differential pulse voltammetry. Additionally, interference studies were conducted to assess the selectivity of the modified probe in complex sample matrices. This developed probe was utilized to investigate NDMA within drug samples. By enhancing our understanding of the electrochemical behavior of NDMA at modified electrode surfaces, we aim to facilitate the development of sensitive and reliable analytical methods for NDMA detection in diverse sample matrices.

2.0 Experimental Conditions

2.1 Fabrication of AgNp/MWCNT/ Nafion Modified GCE

Various steps were incorporated during the fabrication process of silver nanoparticles and multiwalled carbon nanotubes (AgNp/MWCNT/Nafion) with the binding agent Nafion priorly modified with a glassy carbon electrode (GCE). In the first step, the surface modification of GCE was processed by mechanically polishing with alumina slurry and rinsed with double distilled water to remove the residual particles. Following the above-mentioned procedure a sequential sonication in solution of methanol and nitric acid (HNO3) in the ratio of 1:1, later on, acetone and double distilled water were utilized to ensure thorough cleaning. In the second step, separate MWCNTs were functionalized with the reflux of 6M nitric acid solution. This procedure was retained for 10 hours to introduce oxygenated functional groups. These functionalized MWCNTs were then filtered, washed, and dried. Similarly in the third step, AgNPs were subsequently synthesized with the chemical reduction method. The functionalism MWCNT was dispersed in 0.5% Nafion solution through sonication and uniform suspension was created. The synthesized AgNps were subsequently mixed with MWCNTs/Nafion suspension. In the Final step, the AgNP/MWCNT/Nafion composite was cast dropwise onto the glassy carbon electrode surface and dried at room temperature. The morphological structure of the modified electrode was characterized by various analytical and electrochemical techniques such as Scanning Electron Microscope (SEM), Cyclic Voltammetry, and Square wave Voltammetry.

2.2 Preparation of NDMA solution

Standardized NDMA was prepared to take NDMA solution by Sigma Aldrich which consists of 5000 microgram/ml NDMA into it. For the preparation, a 5mM solution of NDMA was taken and dissolved in 10 ml of methanol as solvent. The solution was filtered through the Whatman 41 filter paper into a 10 ml volumetric flask to remove the particulate matter. Finally, quantitative dilutions were prepared such as 1mM to 5mM solutions for experimental studies.

2.3 Biosynthesis of silver nanoparticles using Hyphaene thebaica

Silver nanoparticles were synthesized utilizing green and eco-friendly techniques, and Hyphaene thebaica plant extract was used for the preparation of AgNPs. Addition of 20 ml of the extract into a solution containing 60 ml of 2mM $AgNO_3$, a distinct color shift from an initial brown hue to deeper darkish brown which indicates AgNP formation, attributed to the reduction capabilities of the compounds in the hyphaene thebaica. After, synthesis the heterogeneous solution was centrifuged at 8000 rpm for the duration of 20 min, and this procedure was repeated twice to ensure enhanced isolation and purity of the nanoparticles. The solution obtained is dried under a lyophilizer and the powder yield obtained through it was characterized.

2.4 Formation of poly-CA Film

A Polycystamine film was formed using an electropolymerization process on the surface of the modified electrode. In the first step, an electrochemical cell was functionalized with an MWCNT/ Nafion/AgNP modified electrode as a working electrode, a platinum wire as the counter electrode, and an appropriate reference electrode (Ag/AgCl). These electrodes were absorbed in an electrolyte solution which consist of a specified amount of the carbazole monomer and a supporting electrolyte. By the application of suitable anodic potential within the predetermined range, the carbazole monomer undergoes oxidative polymerization on the electrode surface, resulting in the formation of a polymer film. The conditions, such as applied potential, the concentration of monomer, and electrolyte composition were optimized precisely to obtain uniform electroactive poly CA film on the modified electrode. This film is a sensing interface for the desired electrochemical detection and analysis.

2.5 Electrodeposition of poly-CA on GCE

The electrodeposition of the poly CA film was carried out on a clean glassy carbon electrode (GCE) surface. The GCE was first immersed in a 1mM cystamine hydrochloride solution prepared in phosphate-buffered saline (PBS) 0.1 M. Cyclic Voltammetry was performed on the glassy carbon electrode, scanning potential between -1.2V and + 2.5V for a total 20 cycles. Within this process, the cystamine undergoes electro-oxidative polymerization, resulting in the formation of poly CA film on the GCE surface. In the second step, the modified electrode was rinsed thoroughly with distilled water to remove residual solvent and allowed to dry at room temperature. A thin blue colored poly CA film as a result immobilized on the GCE surface. Here blue color confirms the electrodeposition of Poly CA film. Subsequent electrochemical characterization and sensing applications have been observed.

2.6 Modification of Poly-CA GCE with AgNPs

After the electrodeposition process, the electrode was further modified with silver nanoparticles. The previously synthesized AgNP solution was added onto poly-CA coated GCE using the drop-casting technique and a desired loading was achieved. Other deposition techniques such as spin coating are also employed to deposit AgNP onto poly CA film. After the deposition of AgNP, the modified electrode is dried at room temperature or under mild heating conditions. During the drying process, the silver nanoparticles become immobilized and affixed onto the poly CA film, forming a nanocomposite structure. This modification step aimed to take advantage of the unique properties of AgNPs, such as their high electrical conductivity, catalytic activity, and plasmonic effects, to enhance the overall performance of the electrochemical sensor. The resulting poly-CA/AgNP nanocomposite film on the GCE served as the sensing interface for various electroanalytical applications, benefiting from the synergistic effects of the conducting polymer and metallic nanoparticles.
Here is an expanded draft for the experimental section on the electrochemical detection of NDMA using the AgNP/poly-CA/GCE:

2.7 Electrochemical Setup:

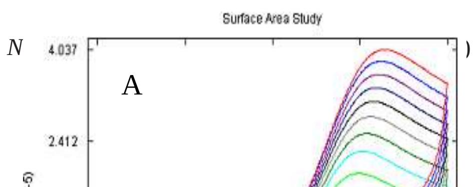
2.7.1 Cyclic Voltammetry (CV):

A single, irreversible reduction peak was observed for NDMA at both electrodes, indicating an irreversible electrode process involving the reduction of NDMA Initial cyclic voltammetry (CV) conditions were kept for both a bare glassy carbon electrode (GCE) the scanning conditions were kept at -0.2 V to -0.8 V at a scan rate of 0.1 V/s..

2.7.2 Square Wave Voltammetry (SWV):

Subsequently, square wave voltammetry (SWV) conditions were conducted using the bare GCE, poly-CA/GCE, and AgNP/poly-CA/GCE in the potential range of -0.2 V to -0.8 V. At the bare GCE, a broad reduction peak was observed at -0.64 V with a peak current of 8.9837 µA, suggesting slow electron transfer kinetics potentially due to electrode fouling by the reduction product adsorbed on the electrode surface.

3.0 Result Poly-CA/GCE



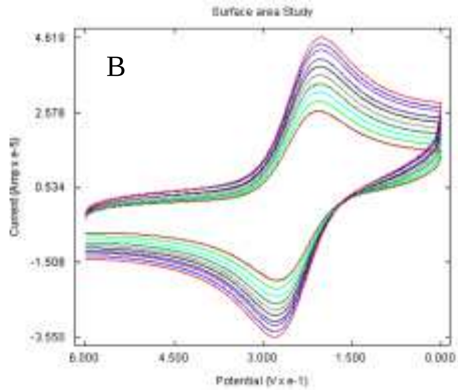


Figure 1: Surface area study at a) bare GCE and b) poly- CA/GCE

Here, cyclic voltammetry is the electrochemical technique utilized to measure effective surface areas of the electrodes in a solution containing a redox probe. As shown in figure 1, a notable surface area of 0.0911 cm^2 was exhibited on the glassy carbon electrode. At the same time, the surface area was effectively increased on the modified glassy carbon electrode electro-deposited with poly CA film to 0.1476 cm^2. The significant change in the electroactive surface results in the successful modification of GCE with poly CA film, which concludes higher porosity and roughness on the polymer film leading to a large accessible surface area for the electrochemical reactions compared to bare GCE. Hence, enhanced surface area to improve sensitivity and overall performance of the modified electrode for electro analytical applications for effective electrode- electrolyte interface.

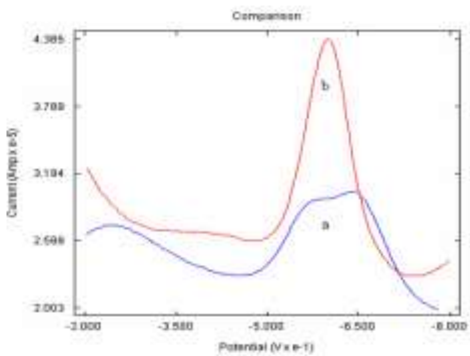


Figure 2: Overlay of (a) IA at bare GCE (b) poly- CA/

GCE/NDMA

To investigate the electrochemical behavior of NDMA at bare GCE and poly-CA as shown in figure 2 modified electrode was measured using the Square wave voltammetry (SWV) technique. The voltammograms were recorded in the potential range from -0.2 V to -0.8 V in 10 ppb NDMA solution. At bare GCE, a reduction peak is observed at -0.64V with a peak current of 8.9837 µA. These reverse reduction peak exhibits a broad shape, suggesting sluggish electron transfer kinetics at the bare electrode surface. This broadening could be attributed to the fouling of the electrode by the adsorption of reduction products, hindering the electron transfer process.
In contrast, the poly-CA modified GCE is expected to exhibit improved electron transfer characteristics due to the conductive nature of the polymer film and its ability to facilitate charge transport. Additionally, the increased effective surface area of the modified electrode could enhance the sensitivity toward NDMA detection by providing more active sites for the electrochemical reaction. The SWV results highlight the potential benefits of electrode modification with conductive polymers like poly-CA in improving the electroanalytical performance of NDMA sensing.

AgNP/poly –CA/GCE

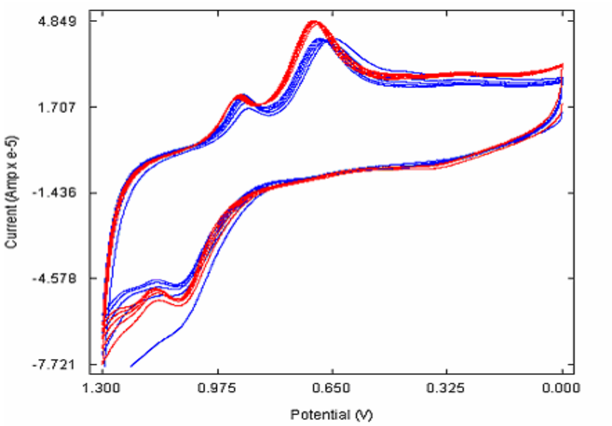


Figure 3: CV graph of AgNP/poly_CA/GCE

As shown in Figure 3, a plot of current versus applied potential in cyclic voltammograms is utilized for an electrochemical analysis involving an irreversible reduction process. The blue curve obtained in Figure 3 represents a CV of poly-CA/GCE whereas, the red curve represents a CV of AgNP/poly- CA/GCE. In both the voltammograms, a single reduction peak is been observed during the forward scan which indicates the reduction of the NDMA at the modified electrodes. The absence of a corresponding oxidative peak during the reverse scan confirms the irreversible nature of the electrode process. AgNP/poly-CA/GCE (red curve) shows slightly more negative reduction peak potential in comparison with the poly-CA/GCE (blue curve) which results in a potential shift due to the presence of silver nanoparticles in the composite film. Similarly, the peak currents for the reduction process are higher with the silver nanocomposite which indicates an enhanced electrochemical response and improved sensitivity for the NDMA detection with the nanocomposite modified electrode. The irreversible reduction process confirms NDMA exhibits an irreversible electrode process at the modified electrodes.

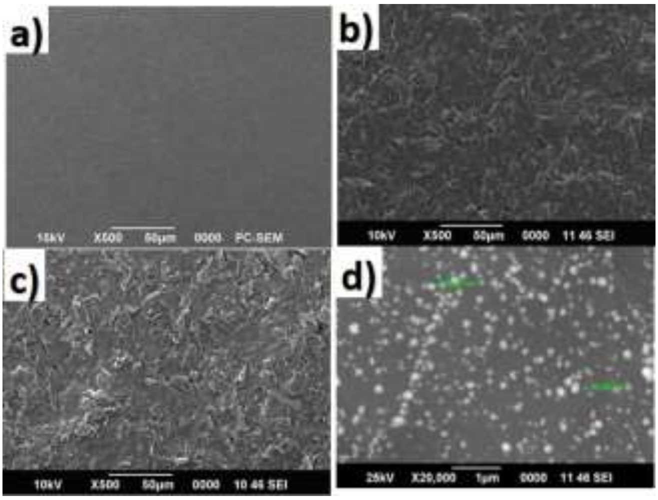


Figure 4: SEM images of a) bare GCE and b) poly -CA/GCE c) SEM image of AgNP/poly – CA/GCE d) AgNP/poly– CA/GCE showing the size of AgNPs

As shown in Figure 4 the morphological characteristics have resulted using Scanning electron microscopy for different electrode modifications. Figure A shows a bare glassy carbon electrode which is observed smooth and featureless during magnification. Figure B comprises of poly CA- modified GCE surface. The successful deposition of poly CA film is observed by rough and Porus texture compared to the bare GCE electrode. Figure C results in AgNP/poly-CA/GCE composite, here silver nanoparticles are incorporated with poly CA film on GCE which concludes a more textured surface on the probe with the polymer matrix. Figure d is the result of higher magnification of the silver nanoparticle which reveals the presence of discrete AGNP with the polymer composite. The size of the nanocomposite from the scale bar it was estimated with the range of 20-30nm. SEM images provide visual evidence of the successful modification of the GCE surface with the poly-CA film and the subsequent incorporation of AgNPs into the polymer matrix, resulting in the AgNP/ poly-CA/GCE nanocomposite electrode for enhanced electrochemical performance.

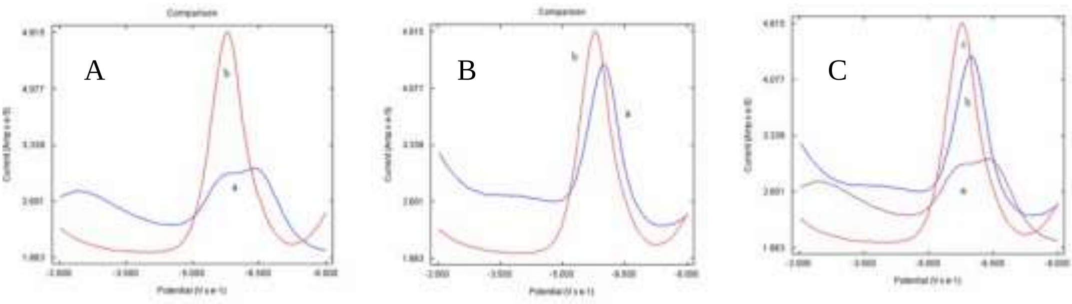


Figure 5: SWV graph of different electrode

A) blue curve shows bare GCE and Red curve shows AgNP/ poly-CA/GCE

B) blue curve shows poly CA/GCE and Red curve shows AgNP/ poly-CA/GCE

Pink curve shows bare GCE, blue curve shows poly CA/GCE and Red curve shows AgNP/ poly-CA/GCE

As shown in Figure 5 well-defined reduction peak for NDMA was obtained utilizing square wave voltammetry Figures a b and c show the reduction peak of bare GCE, Poly CA/GCE, and AgNP/ poly CA/ GCE respectively. The conditions for the measurement were conducted in the potential range of -0.2 V to -0.8 V at a scan rate of 0.06 V/s. The peak current at AgNP/poly-CA/GCE, NDMA exhibited a well-defined reduction peak at a potential of -0.576 V and current 28.2567 µA respectively compared to the bare GCE. The silver nanoparticle nanocomposite shows significant improvement in the electrochemical response towards NDMA with a reduction in cathodic peak potential. The reduction peak potential shifted positively by approximately 0.07 V (70 mV) at the AgNP/poly-CA/GCE compared to the bare GCE. The positive shift in terms of thermodynamics and kinetics is favorable at the modified electrode surface. Enhancement observed in the peak was three times higher than that of bare GCE. Hence, a significant increase in peak current shows a remarkable improvement in electrochemical sensitivity towards NDMA detection with the synergistic effects of poly CA film and AgNPs. Thus a superior analytical performance of the modified electrode can be qualitatively and quantitatively detect NDMA.

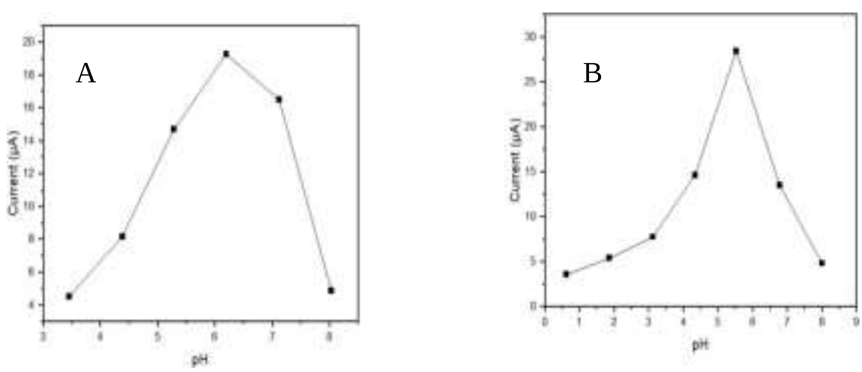


Figure 6: Effect of pH on Bare and modified electrode A) NDMA at polyCA/GCE B) NDMA at AgNP/PolyCA/GCE

As shown in Figure 6, the effect of pH was investigated on the electrochemical behavior of N-Nitrosodimethylamine (NDMA) using various buffer media solutions which, mainly consist of 0.1M solution of phosphate buffer, acetate buffer, citrate buffer, H2SO4, NaOH, NaCl, and KNO3, utilizing square wave voltammetry (SWV) at developed sensors. Amongst all the media, a distinctly defined reduction peak of NDMA was observed at 0.1M phosphate buffer solutions. The characterization of NDMA encompassed parameters such as peak potential, peak current, peak separation, and peak shape offering thermodynamics and kinetics of NDMA reduction at the electrode surface. The sensitivity and selectivity of the sensor were observed by the sharp and defined reduction peak of NDMA enhanced on the surface of the electrode. Further investigation of the detection of limit, and limit of quantification was crucial for assessing its practical monitoring of the NDMA into drug and water samples. Overall, the systematic study of the electrochemical behavior of NDMA in different media provides high performance for NDMA detection and analysis.

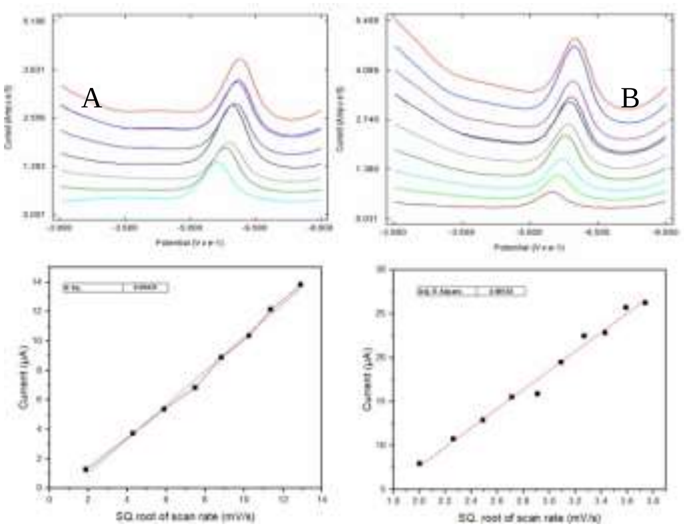


Figure 7: Effect of Scan rate on Bare and modified electrode A) poly Ca/GCE B) AgNP/ polyCA/GCE

As shown in Figure 7, the cathodic peak of 10 ppb of NDMA was measured between the scanning rates of 20 to 180 mV/s utilizing square wave voltammetry. The trend line indicates increased cathodic peak current with higher scan rates. This is generally known as the electrochemical behavior, where the faster scan rate promotes rapid transport of the analyte molecules on the surface of the electrodes which, results in enhanced current responses on the electrode surface. The proportional increase in the peak current in 10 ppb NDMA with poly/CA/GCE is attributed to the improved kinetics of the electrochemical reaction at the electrode surface, facilitated by faster

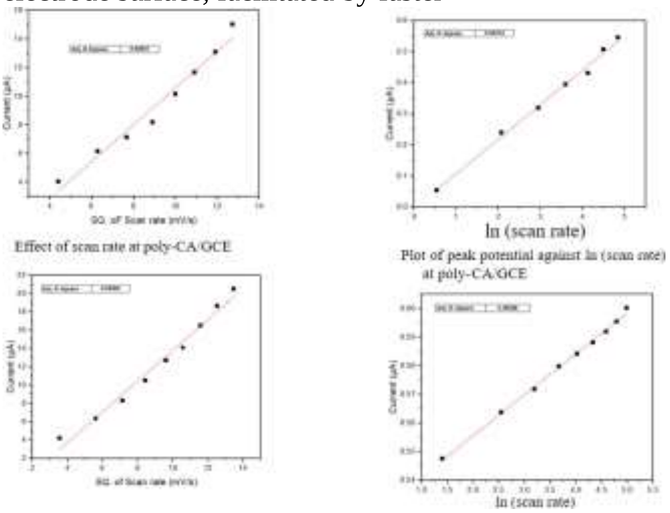


Figure 8: Effect of Scan rate on Bare and modified electrode

electron transfer processes and enhanced mass transport. Similarly, in silver nanoparticles with nanocomposite, the scan rates of 10 ppb NDMA were investigated. Due to the presence of silver nanocomposite, the electrocatalytic activity is enhanced leading to the amplified cathodic peak currents compared to poly CA/GCE alone as shown in Figure 8. Hence utilization of the silver nanocomposite gives a synergistic effect on the electrode with reduction kinetics. Thus the importance of scan rates in the electrochemical response of NDMA is sensitive towards the sample monitoring and analytical applications.

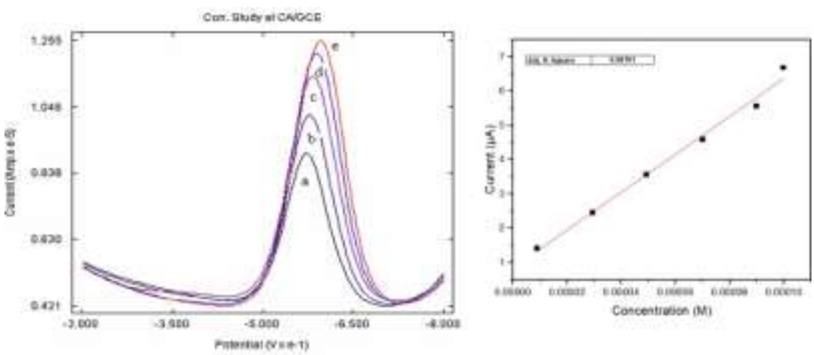


Figure 9: DPV of NDMA a)10ppb b) 30 ppb c) 50 ppb d) 70 ppb e) 1 ppm at poly CA/GCE at 25 °C

As shown in Figure 9, Differential Pulse Voltammetry (DPV) was performed to generate voltammograms of N-Nitrosodimethylamine (NDMA) at various concentrations (a) 10 ppb (b) 30 ppb (c) 50 ppb (d) 70 ppb and (e) 1ppm respectively utilizing poly CA/GCE probe at

25°C. DPV
technique is highly sensitive and selective for the detection of analytes with the application series of potential pulses and measuring the resulting current response through the technique. Additionally calibration of NDMA with poly CA/GCE was plotted and regression coefficient obtained 0.98761 served as a qualitative tool for determination of the concentration of unknown samples based on measured peak currents. The calibration curve results a linear relationship between peak current and NDMA with different concentrations at subsequent measurements for the analysis at 25°C.

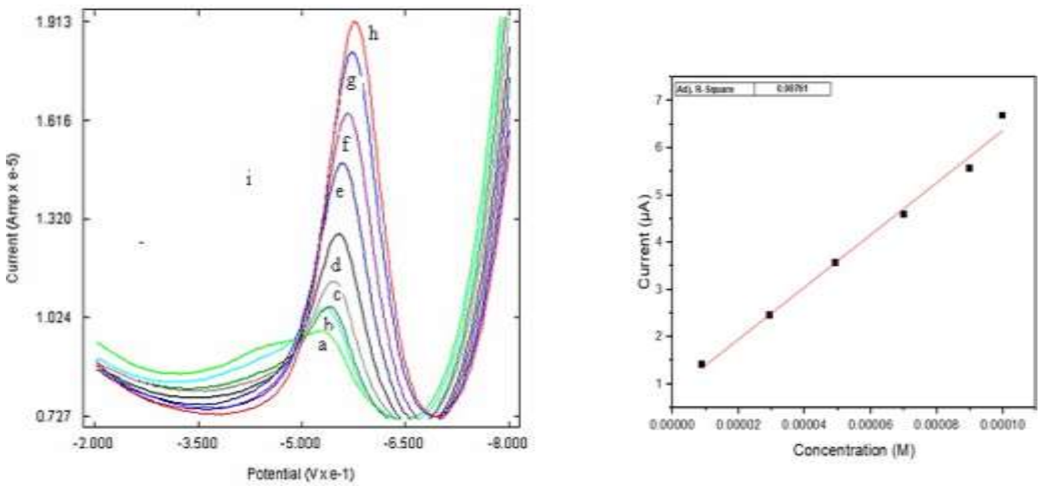


Figure 10: Differential Pulse Voltammograms of NDMA of different concentrations a) 10 ppb

b) 50 ppb c) 70 ppb d) 90 ppb e) 2ppm f) 6ppm g) 8ppm h) 10 ppm at AgNP/poly-CA/GCE at 25^{0}C

As shown in Figure 10, Differential Pulse Voltammetry (DPV) was conducted to generate voltammograms of N-Nitrosodimethylamine (NDMA) at various concentrations a) 10 ppb b) 50 ppb c) 70 ppb d) 90 ppb e) 2ppm f) 6ppm g) 8ppm h) 10 ppm with silver nanocomposite at 250C. The calibration curve obtained was linear between peak current and NDMA concentration comparing the current for the unknown samples and concluded that with silver nanoparticles the values obtained were more sensitive and selective for the unknown samples to curve. DPV enhances the applicability of the samples for qualitative and quantitative detection.

4.0 Interference Study

Table 1: Interference study of NDMA

Substance	Concentration (ppm)	Current (μA)	Signal Change (%)
NDMA	10	19.2691	-
Urea	100	18.4167	4.42
Sodium	100	19.9546	3.55
Potassium	100	18.4584	4.20
Glucose	100	19.6587	2.02
Chlorine	100	19.9546	3.55
Ascorbic Acid	100	18.8578	2.13
Sulfate	100	18.4584	4.20
Lactose	100	20.0864	4.24

The selection of poly-CA/GCE was investigated with the effect of various foreign species for the determination of NDMA in the concentration of 10 ppm. The major interfering species utilized in the study were urea, sodium, potassium, glucose, chlorine, ascorbic acid, sulfate, and lactose in the concentration of 100 ppm which was 100 fold more compared to the concentration of NDMA. The results obtained were in the range of 5% which concludes that no interfering species gets interrupted during the electrochemical reaction and a precise highly selective cathodic peak is obtained on the modified electrode which determines NDMA with the accurate results as shown in Table 1. Hence, the selective electrochemical method is been design for reliable detection of the pharmaceuticals matrices.

5.0 Conclusion

Our study concludes the determination of NDMA form pharmaceuticals with the electrochemical reaction of the polymer composite on the glassy carbon electrode bind with the silver nano particles. In this research, the polymer was deposited on the GCE which gave rise to the effective surface area of the electrode which leads to high porosity and roughness to the polymer film which are key areas for the electrochemical reactions. The poly-CA/GCE results improved electron transfer kinetics compared to the bare GCE, reduction peak observed in square wave voltammograms (SWV) of NDMA. Additionally, silver nanoparticles are incorporated with the poly CA film on the GCE resulting in the formation of AgNP/poly-CA/GCE electrodes. The presence of the silver nanoparticles gives a positive shift which significantly increases the peak current inducing the electrochemical performance and sensitivity for NDMA detection. The selectivity of the polymer electrode was also evaluated using an interference study with 100 folds of the foreign species for the qualitative and quantitative analysis of NDMA from the pharmaceutical sample matrices. The results obtained throughout the research were a platform for the identification of NDMA from the pharmaceutical and water samples with probes having high electrochemical performance for the analysis. The research also optimizes the effects in electrode design and material composition for the development of a more advanced electrochemical sensor for the detection of NDMA.

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