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Using Screen-Printed Electrodes Modified with Carbon Based Nanomaterials for Sensitive Detection of Biologically Relevant Molecules

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by
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- Where I have consulted the published work of others, this is always clearly attributed.
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Using Screen-Printed Electrodes Modified with Carbon Based Nanomaterials for Sensitive Detection of Biologically Relevant Molecules

Abstract

Biologically relevant molecules such as glucose, hydrogen peroxide, and dopamine are important for human body and directly affect some bodily functions. Sensitive measurement of these molecules enables humans to prevent some serious problems arising from abnormal levels of these molecules. In this thesis, glucose and dopamine were measured using screen-printed electrodes (SPE) modified with various types of carbon-based nanomaterials. The SPEs used here are commercially available electrodes in which all the necessary components (working, counter and reference electrodes) for the measurement of these molecules are integrated. Nanomaterials can greatly affect the sensitivity of the electrodes by providing a larger surface area for molecules and also significantly increase electron transfer rate from molecules to the electrode. Basically, the impact of various nanomaterials on sensitive detection of dopamine were compared and the best performing one was used for enzyme-free glucose detection. The sensor had a very low detection limit and therefore has great potential for non-invasive detection of glucose in other bodily fluids such as saliva, sweat and tear where the concentration of glucose is low as compared to blood.

Keywords: Screen-printed electrodes, carbon nanotubes, graphene, gold nanoparticels, glucose, dopamine

Biyolojik Olarak Önemli Moleküllerin Duyarlı Tespiti İçin Karbon Bazlı Nanomalzemeler ile Modifiye Edilmiş Ekran Baskılı Elektrotların Kullanılması

Öz

Glikoz, hidrojen peroksit ve dopamin gibi biyolojik olarak ilgili moleküller insan vücudu için önemlidir ve bazı vücut fonksiyonlarını doğrudan etkiler. Bu moleküllerin hassas ölçümü, insanların bu moleküllerin anormal seviyelerinden kaynaklanan bazı ciddi sorunlarla karşılaşmasının önlemesinde etkin olarak kullanılabilir. Bu çalışmada, glikoz ve dopamin, çeşitli karbon bazlı nanomalzemelerle modifiye edilmiş ekran baskılı elektrotlar (SPE) kullanılarak ölçülmüştür. Burada kullanılan SPE'ler, elektroaktif moleküllerin ölçümü için gerekli tüm bileşenlerin (çalışma, sayaç ve referans elektrotları) entegre halde içeren ve ticari olarak temin edilebilen elektrotlardır. Nanomalzemeler, moleküller için daha geniş bir yüzey alanı sağlayarak elektrotların hassasiyetini büyük ölçüde etkileyebilir ve ayrıca moleküllerden elektrota elektron transfer hızını önemli ölçüde artırabilir. Temel olarak, bu çalışmada çeşitli nanomalzemelerin dopaminin hassas tespiti üzerindeki etkisi karşılaştırılmış ve enzimsiz glikoz tespiti için en iyi performans gösteren modifiye SPE kullanılmıştır. Geliştirilen sensörün hem dopamine hem de glikoz için çok düşük bir tespit limitine sahip olduğu gözlemlenmiştir. Dolayısıyla, tükürük, ter ve gözyaşı gibi glikoz konsantrasyonunun kana kıyasla düşük olduğu diğer vücut sıvılarında invazif olmayan glikoz tespiti için geliştirilen elektrokimyasal sensörün büyük bir potansiyele sahip olduğu düşünülmektedir.

Anahtar Kelimeler: Ekran baskılı elektrotlar, karbon nanotüpler, grafen, Altın nanoparçacıklar, glikoz, dopamin

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Table of Contents

Declaration of Authorship ii

Abstract iii

Öz iv

Acknowledgment v

List of Figures viii

List of Tables ix

List of Abbreviations x

List of Symbols xi

1 Introduction 1

1.1 Screen-Printed Electrodes [SPEs] 1

1.1.1 Applications of SPEs in Electrochemical Analysis 2

1.2 Carbon Nanotubes [CNTs] 4

1.3 Gold Nanoparticles [AuNPs] 6

1.4 Graphene Foam [GF] 7

1.5 Dopamine [DA] 8

1.5.1 Dopamine's Functions, Deficiency, and Effects on Human Body 8

1.5.2 DA Measurement Methods 11

1.5.3 Using Nanomaterials for Electrochemical Detection of DA 12

1.6 Glucose 13

1.6.1 Glucose's Functions, Deficiency and Effects on Human Body 13

1.6.2 Glucose Measurement Methods 13

1.6.3 Using Nanomaterials for Electrochemical Detection of Glucose 16

1.7 Aim of the Study 20

2 Materials and Methods 21

2.1 Materials 21

2.2 Modification of SPCEs with MWCNT-Spng, GF and MWCNT-Spng-AuNPs 21

2.2.1 MWCNT-Spng/SPCE 21

2.2.2 GF/SPCE 22

2.2.3 MWCNT-Spng-AuNPs/SPCE 22

2.3 SEM Imaging 23

2.4 Electrochemical Impedance Spectroscopy [EIS] Analysis 23

2.5 Electrochemical Detection of DA and Selectivity Test 23

2.6 Electrochemical Enzyme-Free Glucose Detection and Selectivity Test 24

3 Results and Discussion 25

4 Conclusion 37

References 38

Appendices 53

Appendix A Publications from the Thesis 53

Curriculum Vitae 54

List of Figures

Figure 1 (a) EIS curves bare SPCE and SPCE modified with different volumes of MWCNT, (b) EIS curves of GF/SPE, MWCNT-Spng/SPE and MWCNT-Spng-AuNPs/SPE 26

Figure 2 SEM image of bare SPCE 27

Figure 3 SEM image of MWCNT-Spng/SPCE 27

Figure 4 SEM image of GF/SPCE 28

Figure 5 SEM image of MWCNT-Spng-AuNPs/SPCE 28

Figure 6 EDS analysis of bare and modified SPCEs 29

Figure 7 Chronoamperometric and calibration curves for (0, 5, 10, 25, 50, 100 and 200 μM) concentrations of DA at +0.2 V (vs. Ag/AgCl) for 120s. (a_{i-ii}) Bare SPCE, (b_{i-ii}) GF/SPCE, (c_{i-ii}) MWCNT-Spng/SPCE, (d_{i-ii}) MWCNT-Spng-AuNPs/SPCE 30

Figure 8 (a) CV curves of 200 μM DA measured by bare and MWCNT-Spng-AuNP/SPE, selectivity of MWCNT-Spng-AuNP/SPE for DA in the presence of (b) UA, (c) AA, (d) glucose, NaCl, KCL 33

Figure 9 Figure 9: (a) CV curves of MWCNT-Spng-AuNP/SPCE for 0,2, and 5 mM glucose in alkaline solution, (b) chronoamperometric curves of different glucose concentrations in alkaline solution, (c) calibration curve, (d) glucose selectivity test in the existence of several interference. 35

List of Tables

Table 1 Comparison of electrochemical detection of DA using different modified electrodes 31

Table 2 Analytical performance comparison of various enzyme-free glucose sensors.....36

List of Abbreviations

3D	3 Dimensional
Ag	Silver
Au	Gold
CNTs	Carbon Nanotubes
Cu	Copper
CV	Cyclic Voltammetry
CVD	Chemical Vapor Deposition
DA	Dopamine
DPV	Differential Pulse Voltammetry
EDS	Energy Dispersive Spectroscopy
EIS	Electrochemical Impedance Spectroscopy
GF	Graphene Foam
LOD	Limit of Detection
MWCNT-Spng	Multi-Wall Carbon Nanotube Sponge
R_{ct}	Charge Transfer Resistance
SEM	Scanning Electron Microscopy
SWCNTs	Single Wall Carbon Nanotubes
SPEs	Screen-Printed Electrodes
SPCEs	Screen-Printed Carbon Electrodes
WE	Working Electrode

List of Symbols

μA	Micro Ampere
μg	Micro Gram
μM	Micro Molar
μL	Micro Liter
nM	Nano Molar
Ω	Ohm
V	Volt

Chapter 1

Introduction

1.1 Screen-printed electrodes (SPEs)

The emergence of screen-printing technology has brought a whole new world of possibilities for using electrochemical methods for environmental analysis without the need for a centralized laboratory [1]. The use of screen printed electrodes (SPEs), was originally made available in the 1990s, and its stability, mass manufacturing, repeatability, and low cost led to their success. These SPEs were ductile when drawn in various forms, constructed on different materials, and properly changed with several modifiers [2]. There are several commercial sources for SPEs in various configurations, and making handmade ones in small quantities with screen-printing equipment is fairly easy. SPEs formats can be changed depending on the needs for a certain analyte. Furthermore, the surface of SPEs may be simply adjusted to suit a range of objectives involving various pollutants and to accomplish a variety of benefits. DNA sequences, enzymes, inorganic nanostructured materials, noble metals are all examples of SPEs modifiers for environmental study. Simple, low-cost analytical procedures are combined with simplicity of use and transportability in SPEs. As a result, as has been demonstrated over the last several years, SPEs may be effectively implemented to in situ environmental studies and obtain improved detection [1]. The use of metallic nanoparticles to modify SPEs results in increased surface area and increased electrical conductivity. These modifications result in increased surface activity, which leads to enhanced reaction speeds and detection sensitivity. Nanoparticles electrodeposition may be done directly on screen printed carbon electrodes (SPCEs) strips, according to studies.

Electrochemical analysis allows for reliable, rapid, and perhaps on-site investigation of a growing number of biological types, environmental pollutants, heavy metals, and

pharmaceutical formulations. SPCE strips have increased selectivity and sensitivity while having no effect on interferent electrochemical processes [2].

1.1.1 Applications of SPEs in Electrochemical Analysis

Screen printed advances in sensors and biosensors have made great development in recent years, with a large number of scholarly publications published on the subject. SPEs provide a number of benefits over traditional electrodes, including the ability to be utilized in small volumes and the ability to build repeatable, accurate, and sensitive sensors [2].

Detection and measurement of biological species and pharmaceutical compounds such as antioxidants, amino acids, catecholamines is among SPEs' applications [2].
Lee et al. reported the proof of concept for the determination of homocysteine and glutathione by using multi-walled carbon nanotube SPE, it was performed by using catechol electrochemically oxidized by the 1,4-Michael addition process with or without cysteine. The results of employing re-usable and/or disposable sensors for medical and biological objectives, as well as the prospective benefits, are presented in their study [3].
In another study Lee et al. used square wave voltammetry and a SPE using carbon nanotubes to develop an electroanalytical technique to assess decreasing and total glutathione levels. The sensitivity was measured to be (0.64 ± 0.008) μM and limit of detection (LOD) to be(3.0±0.07) μM using cyclic voltammetry, according to this study. The glutathione levels and errors obtained using this approach on human saliva were compatible with commercially accessible enzyme assay experiments [4].

Multiple investigations have used direct electrochemical techniques to detect amino acids on treated and untreated electrodes. For this purpose, detecting amino acids inside pharmaceutical drugs at the surface of adjusted SPEs is recommended as a simple, quick, and sensitive method.
Su and Cheng studied how cysteine is oxidized electrocatalytically using SPE customized with electrogenerated poly(3,4-ethylenedioxythiophene) film. As per cyclic voltammetric analyses, the modified electrode minimizes overpotential and enhances cysteine oxidation activity when compared to standard SPEs. Employing

flow injection amerpometry in an ideal condition, excellent analytical features such as high sensitivity, appropriate dynamic range, and low LOD were attained [5].

Catecholamines have recently been the focus of interest due to their critical function in the central nervous system. Catecholamines influence practically each tissue in humans, causing many cardiovascular, endocrine, neural and metabolic consequences, as well as impacting the intestinal barrier and the immune system. The brain, neural tissues, and adrenal glands all produce catecholamines. In reaction to mental or physical stress, the body produces catecholamines. Examples of catecholamine are dopamine, adrenaline, and noradrenaline.

Zhang et al. designed an electrochemical dopamine sensor using magnetic multi-walled carbon nanotubes (MWCNTs) with magnetism-assisted tuning. This electrode showed outstanding selectivity for the detection of dopamine, with ascorbic acid interfering virtually insignificantly, which coexists with dopamine in various biological substances and causes interference. The recovery was satisfactory with less than 2.27% percent rejection sensitivity dysphoria within a range of 97.43-102.94% percent when utilized to detect dopamine in spiked blood human blood [6].

Electrodes of this sort have also been utilized to create portable electrochemical sensors. Such sensors have the capacity to do environmental investigations, such as water quality tests for organic contaminants, heavy metals, , and other species, which are common.

Pesticides have been extensively used to eliminate or fend off pests in various sectors as a large and diverse category of agricultural agents. Pesticides' widespread use has inevitably had negative consequences for human health in the places in which they are used. Pesticides have a negative effect on organs among which respiratory, cardiovascular, immunological, renal, and endocrine systems are included. Damage is induced by the permanent inhibition of acetylcholine esterase, which leads to disorders in humans such as Alzheimer's, diabetes, renal failure, Parkinson's, and others. As a result, the development of accurate, quick, and economical analytical methods for identifying minuscule amounts of pesticides in the environment is critical [2]. Hassani et al. developed a label-free electrochemical aptasensor for the detection of diazinon, a common organophosphorous molecule. The SPE employed in this investigation was modified using thiolated aptamers after immobilizing the aptamers on gold nanoparticles (AuNPs). Diazinon concentrations ranging from 0.1 to 1000 nM

were used to analyze current variation. The sensor had a LOD of 0.0169 nM, according to this research [7].

Another work by Khairy et al. proposes that SPE modified with nickel oxide nanoplatelets might be used to determine organophosphate pesticides. After applying differential pulse voltammetry (DPV) to the modified electrode with the presence of organophosphate pesticide, a distinctive peak current was spotted at 1.0 V (vs. Ag/AgCl). Organophosphate pesticide determination was obtained with a LOD of 0.024 μM and concentration range of 0.1-30 μM [8].

Environmental pollutants have resulted from urbanization and rapid industrial progress. Heavy metals seem to be the most common of these pollutants. Several of these heavy metals, which are essential for use in industries, if released into open areas, may make its way into the human body via the food chain and pose negative health impacts on people. Heavy metal contamination is the focus of attention for researchers when it comes to the dangers of heavy metal deposits in food and the natural environment [2].

In their investigation, single-walled carbon nanohorns (SWCNH) were employed by Yao et al. to modify an SPE. The sensor was tested to detect lead and cadmium, and it showed distinct peaks for each of these elements. At is best, for both lead and cadmium, the linearity of SPE modified with SWCNH ranged between 1.0 and 60.0 μg/L. The LOD for lead was 0.4 μg/L and for cadmium it was 0.2 μg/L. The concentrations of lead and cadmium ions in milk and honey samples were determined using this modified electrode [9].

1.2 Carbon Nanotubes [CNTs]

For identifying infectious illnesses, metabolic problems, quickly progressing malignancies, and determining the presence of environmental contaminants, there is an growing demand for rapid, cost-effective, reusable, efficient, and sensitive detection devices. The majority of traditional treatments are intrusive, sluggish, costly, and time-consuming, and they necessitate highly specialized tools. The use of nano-scaled materials in biosensors as signal transducers has helped to overcome the limitations of conventional sensors. CNTs are an attractive choice for biosensing purposes because of their great mechanical strength, higher electrical conductivity,

and capacity to function as effective signal transducers. CNTs are also becoming more important in the creation of biosensors due to their large surface areas and readily functionalizability of their surfaces for the immobilization of receptor. Chemical approaches are being used to develop new tools and systems in order to comprehend biological systems, as well as disease detection and therapy, in the rapidly growing area of CNTs, this way CNTs bridge biology with physical sciences. CNTs come in two different varieties: single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs). Rolling a sheet of graphene into a cylinder forms SWCNT. MWCNT on the other hand, is created by stacking successive graphene cylinders with a 0.34 nm interlayer gap. Structure of CNTs identify their functionality and properties [10]. SWCNTs have exceptional chemical stability, electrical conductivity qualities and good mechanical properties. MWCNTs have metallic electrical characteristics that are comparable to metallic SWCNTs, making them more appropriate for electrochemical purposes in several ways [11].

MWCNTs are employed as a delivery mechanism for big macromolecules such as DNA since their optical features are less remarkable than SWCNTs. Both forms of CNTs have a one-dimensional geometry and have great electrical conductivity property, robust adsorbing activity, and bioconsistency. These qualities allow CNTs to conduct large currents with less heat generation [12]. Immunosensors, amperometric enzyme electrodes, and nucleic acid detecting devices are all being investigated using electrochemical biosensors utilizing electrochemical biosensors.

In medical services, food safety, and environmental monitoring, electrochemical biosensors based on enzymes have been widely employed. Healthcare is the primary use for biosensors. The measurement of levels blood glucose , particularly for diabetics by utilizing glucose biosensors is one of its uses in this field [13,14]. The hunt for biomarkers, like proteins, metabolites or peptides or, that are distinctive and typical of a specific disease condition or cell type, has been one of the motivating elements in fundamental and applied science. The most prevalent form of biomarker utilized in clinical purposes is protein biomarkers [15].

Because of their unique nanotube structure with extremely substantial ratios of length to diameter (as high as 132,000,000:1), CNTs are frequently chosen for biosensor manufacturing among a range of nanomaterials [16].

Furthermore, CNTs' ends and sidewalls may be readily adjusted by adding nearly any

chemical species. Because of their high sensitivity, CNTs can indeed be great nanoscaled sensor transducers. CNTs can increase the electrochemical activity of key biomolecules and accelerate the kinetics of fast electron transport for a vast scope of electroactive types, according to the literature [17]. CNTs are a preferred nanomaterial for building electrochemical biosensors due to their ease of detection of biomolecules and also improved electrochemical reactivity of NADH and hydrogen peroxide. These features, together with the employment of the appropriate crosslinking reagents for antibodies and receptor enzymes on the electrodes, result in sensitive, fast, dependable, cost-effective and reusable biosensing devices for analytes.

The essential features of a functional biosensor are predictability and sensitivity and specificity so it can be trusted regardless of the alterations in the biological environment. The benefits of nanomaterials have been combined in a new category of biosensors known as nanobiosensors, which incorporates nanomaterials. CNTs are highly adapted to transduce electric signals produced by identification of a target because of their tiny size and good electrochemical and electrical characteristics. They therefore play a crucial role in the latest advancements of enzyme-based biosensors [10]. Electrochemical biosensors are widely used because of their inexpensive cost, quick reaction times, simplicity of use, and tiny size. CNTs have been shown to be equivalent to or better than most alternative electrodes in detecting ions, protein biomarkers and metabolites due to their tiny size and good electrochemical characteristics [18].

1.3 Gold Nanoparticles [AuNPs]

Because of their unique electrical, magnetic, optical, mechanical, physical, and chemical capabilities, gold nanoparticles (AuNPs) with sizes ranging from units to hundreds of nanometers have recently attracted widespread interest in several sectors of medicine, biology, physics, and chemistry. In recent years, they've gotten a lot of interest for their prospective uses in industries and nanomedicine.

AuNPs exhibit significant optical fading out at near visible and infrared wavelengths, which can be adjusted by adjusting the size of the particle. AuNPs are becoming a more widely used nanomaterial due to recent breakthroughs in their high-yield production, synthesis method, stability, and bioconjugation. Bulk gold is chemically

inert; nevertheless, gold nanoparticles have an extraordinarily high chemical reactivity [19].

AuNPs are not the same as gold particles in that the bigger size is a yellow neutral solid, while AuNPs are an antioxidant-capable wine-red complex. AuNPs come in a different diameters, ranging typically from 1 nm to 8 μm, and they often come in a variety of shapes. AuNPs can engage with the epidermal barrier to improve delivery and penetration of high molecular weight active drugs. They are being looked at as potential options for transdermal delivery system and skin immunization and optimization [20].

AuNPs have also been investigated as a possible medication and gene delivery mechanism in cancer treatment. Yet, intensive study is needed to uncover the actual potential of AuNPs [20]

In biosensors based on enzymes, AuNPs are commonly used. The development of significant thiol connections between organic molecules and nanoparticles distinguishes AuNPs as extremely biocompatible and conductive [21]. As a result, AuNPs provide an ideal habitat for enzyme immobilization. Enzyme immobilization onto AuNPs can significantly boost their activity [22].

1.4 Graphene Foam [GF]

Graphene made up of sp^2 hybridization that has an atomic dimension of 0.34 nm organized in a 2D honeycomb structure. Its outstanding mechanical, thermal, electrical, physical, optical, and structural features, as well as its cost-effective production, band gap tailoring, biofunctionalization, and dimension customization, unique biocompatibility, and biodegradability, have piqued attention in recent years [23,24].

Due to its unique characteristics, it has a wide range of applications, including transistors, electrodes, chemical sensors, nanoelectronics, and energy storage and conversion devices.

In biomedical areas graphene and its various compound have attracted huge interest, in their applications in biomedical areas they have been utilized in drug delivery,

inhibitions (viral, parasitical, and bacterial), tissue engineering, photothermal therapy, medical imaging, biosensors, and stem cell differentiation [23].

3D graphene designs have a macroporous form that is inter - connected and exhibits super low density activity. The use of 3D graphene structures, particularly 3D graphene foams, is a viable solution to the problems that 2D graphene presents. One of several 3D graphene designs, graphene foam (GF), is a linked uninterrupted structure of graphene sheets that is rising in popularity due to its better electrical, mechanical, and thermal characteristics. Aside from its multipurpose features, 3D graphene foam may be used as an excellent reinforcement material in composites, with uses in biomedical and electronics [25].

GF can be synthesized using different methods, but, when compared to other technologies, chemical vapor deposition (CVD) may synthesize few layers and huge areas of graphene through process optimization. Because to robust van der Waals interactions, the resulting graphene may stack, reducing its particular surface area and physical properties [26].

1.5 Dopamine [DA]

1.5.1 Dopamine’s Functions, Deficiency and Effects on Human Body

Dopamine is a neuromodulatory chemical with multiple functions in cells. It is an organic compound that is a member of the phenethylamine and catecholamine families. Approximately 80% of the brain's catecholamine content is made up of dopamine. It is an amine created by deleting a carboxyl group from an L-DOPA molecule, which is produced in the kidneys and brain. Dopamine is a neurotransmitter in the brain, which is a chemical released by neurons to carry messages to other nerve cellsAlthough neurotransmitters are made in certain parts of the brain, their effects are sensed all over the body [27,28]. There are several distinct dopamine pathways in the brain, one of which is crucial for the driving force behind reward-motivated behavior. Most sorts of incentives raise dopamine levels in the brain when they are anticipated [29]. Many addictive medicines either boost or prevent dopamine reuptake into

neurons after it is released. Other dopamine passageways in the brain are engaged in motor control and hormone release control. These routes and cell types make up a neuromodulatory dopamine system [30].

Dopamine is frequently depicted as the primary molecule of pleasure in popular culture and the media, although current pharmacological view is that it confers motivational salience instead [31,32]. Dopamine, in other words, indicates an outcome's perceived motivational eminence which directs the organism's behavior to go in the direction of or away from that result [33].

Dopamine is primarily a local paracrine that is a central nervous system-external messenger. It blocks norepinephrine release at normal concentrations (An organic compound that serves the body and brain as a neurotransmitter and hormone) and serves as a vasodilator (Vasodilation is the widening of blood vessels) in blood vessels; it raises sodium excretion and kidneys' production of urine; it lowers the pancreas' ability to produce insulin; it preserves intestinal mucosa and lowers gastrointestinal motility in the digestive system; and it reduces lymphocyte activity in the immune system. With the exception of blood vessels, each of these peripheral systems produces dopamine locally, which allows it to act nearby the cells that release it.

Dopamine system dysfunctions are associated to several serious neurological conditions, and some of the primary medications used to treat them that work by altering dopamine's effects. The loss of dopamine-secreting neurons in the substantia nigra causes Parkinson's disease, which is a degenerative disorder characterized by motor and tremor dysfunction. There is evidence that schizophrenia is linked to changes in dopamine activity, and the majority of antipsychotic medicines are dopamine antagonists, which suppress dopamine activity [34]. Anti-nausea medicines with similar dopamine antagonist properties are also available. Attention deficit hyperactivity disorder (ADHD) and restless legs syndrome are both associated with decreased dopamine activity [35].

In addition to higher-order processes like motivation, arousal, reinforcement, and reward, dopamine also plays a role in lower-order processes including breastfeeding, sexual fulfillment, and nausea inside the brain. The neuromodulatory dopamine system is composed of dopaminergic cell types and pathways [36].

One of functions of dopamine in the body is rewarding. The attractive and motivating feature of a stimulus that generates appetitive behavior and consummatory behavior is referred to as reward in the reward system . Dopamine serves as a reward signal for the brain in part. A reward's value, salience, and context are encoded in the initial dopamine response . In the context of reward-related cognition, dopamine also functions as an error signal for reward prediction, explaining the extent to which the value of a reward is unexpected [37].

Both the inside and outside of dopamine's systemhave been shown to have pleasure regions, consequently, certain, but not all, aspects of pleasure-related cognition are mediated by dopamine neurotransmission[38,39]. For instance, direct electrical stimulation of dopamine pathways utilizing brain-implanted electrodes, is seen as gratifying, and numerous animals are prepared to put in the effort to acquire it [40].

Dopamine operates on immune cells, particularly lymphocytes, through receptors on their surface. Furthermore, immune cells can produce and release dopamine [41]. The bone marrow, spleen, and circulatory system's immunological cells are affected by dopamine. The main impact of dopamine on lymphocytes is a decrease in their level of activity. The system's functional relevance is unknown, but it provides a plausible pathway for interactions between the neurological and immune systems, which might be important to various autoimmune illnesses [42].

All dopamine receptor subtypes are present in the nephron cells of the kidneys, which house the renal dopaminergic system [43]. It increases the rate of glomerular filtration, excretion of sodium in urine, and blood supply to the kidneys. A reduction in sodium excretion as a result of impaired renal dopamine function may lead to blood pressure increase. Numerous illnesses, including edema, oxidative stress, and hereditary or essential hypertension, have been linked to abnormalities in dopamine production or receptors. Hypertension can be caused by oxidative stress [44].

Dopamine plays a complicated role in the pancreas. The pancreas is divided into two sections: exocrine and endocrine. Dopamine and other substances, including digestive enzymes, are produced and secreted by the exocrine component into the small intestine.

The endocrine component of the pancreas, the pancreatic islets, manufacture and release hormones into the circulation, including insulin. There's evidence that dopamine receptors are present in the beta cells that generate insulin in the islets, and that dopamine inhibits insulin secretion [45].

Age-related declines in dopamine synthesis and receptor density in the brain have been seen in several studies [46]. Several neurological problems that worsen with aging, such as reduced arm swing and increasing stiffness, are considered to be caused by dopamine depletion.

Another disease related to the depletion of dopamine is Parkinson's disease, A mobility disorder associated with aging, it is characterized by overall stiffness, sluggishness, and limb shaking while not being used. In extreme stages, it progresses to dementia and ultimately death. Most of the symptoms are caused by the substantia nigra's loss of dopamine-secreting cells [47].

Changes in dopamine neurotransmission are associated with attention deficit hyperactivity disorder (ADHD), This, among other things, creates problems with working memory, forgetting or losing data, and controlling focus (attentional control), inhibition control, and activity management [48].

1.5.2 DA Measurement Methods

Due to the significance of DA and its functions in the body, Platforms for the sensitive and selective measurement of dopamine concentrations are urgently needed [49]. To present, traditional colorimetric/column-based approaches for detecting dopamine are found to be successful and they have received much interest. Recently coupling this approach with gold (Au) and silver (Ag) nanoparticles has been widely used for DA and other biomolecules' analysis [50-52]. The Au and Ag nanoparticles may be used as an excellent color indicator due to their extraordinarily high absorption spectra and considerable sensitivity of optical characteristics on size of particles, shape, and distance. When Au NPs approach each other and begin to aggregate, The surface plasmon band's red shift causes the hue of the Au solution to change from red to blue. As a result, even at nanomolar concentrations, Au NPs may be employed for extremely sensitive detection with minimum material consumption [53].

However, these procedures are often time-consuming and labor intensive, which makes early identification of a number of dopamine-related neurological illnesses difficult, and they need the use of various expensive diagnostic substances [54-58].

To far, several methodologies are being used to investigate DA and its metabolites. Electrochemical, chemiluminescent, spectrometric, fluorometric, and chromatographic procedures are among the most extensively utilized [59]. Among these, electrochemical detection is a straightforward and convenient technology for measuring numerous neurotransmitters such as dopamine, gamma-aminobutyric acid, and serotonin, and it is gaining interest [60-64].

1.5.3 Using Nanomaterials for Electrochemical Detection of DA

Despite electrochemical technique being one of the most convenient techniques for DA detection, the low concentration level of dopamine in blood is a major problem for its identification [65,66], signal interference from other biological substances such glucose, uric acid and, ascorbic acid amplifies the problem even further. To this purpose, a number of researches have documented a range of platforms based on the integration of conductive micro/nanomaterials or polymers on the electrode surface [67]. Owing to their high conductivity and outstanding electrocatalytic characteristics, metals like gold, silver, and platinum have been used on the electrode surface to take advantage of their high surface-to-volume ratios. The techniques used to modify such metallic nanostructures on conducting surfaces fall into two categories: (a) metal nanoparticle production and subsequent chemical linker attachment to the electrode surface and (b) electrochemical/chemical deposition of metal nanostructures directly on the substrates. Nanostructured electrodes incorporated into sensor applications have been shown to improve both selectivity and sensitivity not only for neurotransmitter detection such as DA, but also for other biological elements such as glucose, proteins, pathogens, DNA, RNA. When comparing these nanostructured electrodes to conventional electrodes, however, serious concerns such as electrical signal instability and increase in signal variations have been raised, this is caused due to the difficulty in controlling the size, shape and number of nanomaterials used for electrode modification [68].

1.6 Glucose

1.6.1 Glucose's Functions, Deficiency and Effects on Human Body

In the living organism, glucose is a primary energy source for cellular function. Maintaining a correct glucose concentration in the blood is critical, and in human physiology, the homeostatic mechanism tightly regulates the glucose level [69]. Diabetes mellitus is the most common condition associated with the metabolic disorder involved in glucose processing and it is among the most prevalent chronic illnesses brought on by a defect in insulin secretion. [70]. It's usually linked to a pancreatic defect that prevents it from producing enough insulin [Type I] or aberrant cells that not even respond to or resist insulin [Type II] [71,72].

Hyperglycemia is caused by an excess of glucose in the blood plasma, which can lead to blindness [73], cardiovascular diseases [74-76], and renal failure [77,78]. Chronic hyperglycemia can occur in both type I and type II diabetes, resulting in a variety of metabolic problems. Hyperglycemia can induce damage to tissues and organ failure, which can lead to a variety of problems and even an increase in death rate. Because of the serious medical consequences of diabetes-related problems, personal measurement and control of blood glucose levels is essential [79-81]. As a result, glucose sensors have been created to accurately assess blood glucose concentrations and to aid in the exact administration of appropriate medications for homeostatic management.

1.6.2 Glucose Measurement Methods

Various methods exist for the measurement of glucose, but among them optical and electrochemical techniques have been extensively studied. Optical approaches rely on a change in color in an indication that represents glucose content. During an enzymatic process in which glucose is converted to its metabolites , the color of the dyes changes [82-88]. Although individuals have a simple way to monitor their glucose levels by a shift in color, it is insufficient for quantifying glucose levels and ineffective for

assessing low levels of glucose. Even when it is possible to take quantitative measures, they sometimes necessitate the use of a large spectrophotometer, rendering the colorimetric approach impractical for commercial application. Thus, spectroscopic glucose detection technologies are appropriate for application in specialist settings like hospitals [89].

The most extensively used approach in glucose sensors is electrochemical analysis, which provides a straightforward and quantitative mode of operation [90]. A variety of glucose concentrations can be detected by electrochemical glucose sensors. Monitoring electrochemical signals results in immediate conversion to glucose concentrations. The continuous monitoring of glucose levels with portable glucometers has benefited greatly from amperometric detection based on enzyme reactions. Numerous studies have been carried out to enhance eletrode structure, functionalization of surface methods, and electrochemical analysis methodologies with the purpose of developing more accurate measurements and a selectable mode of operation.
A variety of glucose measurement techniques, including noninvasive glucose monitoring and direct blood glucose monitoring devices, have been created, allowing for patient-friendly diabetic care [91].

For glucose monitoring, a variety of enzymatic electrochemical glucose sensors have been designed. Invasive glucose monitoring is the method that can detect blood glucose most precisely, and detection kits for blood glucose have been extensively developed, particularly in portable or implanted versions [90,92].
For portable glucometers, blood drawn with a needle is taken on a disposable strip that is connected to the glucometer and used to measure the level of blood glucose. This approach is popular because the equipment is simple and straightforward to use, and blood glucose levels may be measured promptly. This point-of-care monitoring, on the other hand, does not offer a totally constant of glucose concentration profile and has a tendency to overlooking rapid jumps in blood glucose levels between tests. Clinics also make use of an implanted glucose sensor. The implanted sensor is more intrusive and sensitive to biofouling, but it provides continuous glucose readings [93]. Additionally, because the glucose measured in this method is the intravenous blood glucose and not peripheral blood glucose, the results are more accurate and clinically

helpful thanks to an implanted sensor. Despite the existence of these blood-based monitoring technologies, because the invasive detection process causes discomfort and difficulties, diabetes individuals don't always adhere to the routine [81]. Pediatric patients with Type I diabetes make up a sizeable portion of those who are particularly uncomfortable with the needle-pricking procedure necessary for blood-based glucometers. It is vitally necessary to develop a painless and non-invasive method for measuring glucose levels.

Sweat, tears, interstitial fluid, and saliva may all be retrieved noninvasively or with low invasiveness, and they contain glucose in quantities that can be correlated to that can be seen in blood. Due to this link, as an alternative, these biofluids have become novel analytes of interest for non-invasive blood glucose monitoring. However, several factors are required to ensure the quality and accuracy of glucose levels determinations from these biofluids. These biofluids have lower levels of glucose than blood does, which is one of the most important considerations. Although contaminants in tears cause little interference, there are issues with the power supply of the glucose sensor on the contact lens to work independently and wireless transmission of data. Regarding saliva, the analyte can be simply collected by spitting, but the huge number of contaminants in the fluid makes isolating the actual concentration of glucose from the fluid problematic. In the instance of interstitial fluid, a novel device for continuous glucose monitoring has been presented, although it involves the subcutaneous insertion of a needle, which may be painful for potential users. Wearable devices that use iontophoresis or reverse iontophoresis on the skin for noninvasive glucose measurement in interstitial fluid have been created to alleviate these disadvantages, but further research is needed. A monitoring device for sweat is broadly applicable and conveniently accessible, but for each measurement it has the drawback of requiring the patient to sweat. All of these innovative glucose monitoring systems have challenges that have yet to be overcome. For instance, a substantial association between each biofluid-based measurement and blood plasma glucose levels has yet to be demonstrated, and the correlation may vary by individual. However, these painless noninvasive techniques are very promising since people with diabetes may monitor their levels of glucose more comfortably and simply. With more effective and patient-friendly diabetes care procedures, the concern with their quality of life, notably possible trauma from needles used in glucose testing, should be eliminated [91].

1.6.3 Using Nanomaterials for Electrochemical Detection of Glucose

Researchers are spurred on by breakthroughs in nanotechnology, microfluidics, and downsizing, as well as developments in point-of-care sensor technologies, to build user-friendly, sensitive, and cost-effective glucose monitoring instruments. Using a variety of glucose sensing technologies in conjunction with POC biosensors, precise on-site and on-time measurement has been achieved using several glucose sensor systems. When improvement using 3D technology or smartphone-integrated electronic readers integration is used in these sensors, they hold a lot of potential for patients with glucose metabolism problems [94]. Individuals can use POC biosensors to reliably and conveniently measure their blood glucose concentration without the need for expert staff or a medical checkup.

The enormous need for low-cost, quick, and precise means of measuring blood glucose levels has piqued the industry's interest in developing novel glucose sensors. Glucose sensors can make use of a variety of transducers, including optical, magnetic, electrochemical, acoustic, and thermal ones.

The most well researched of these are electrochemical systems, which may be divided into two categories depending on whether or not an enzyme is utilized as a sensing material. The oxidation of glucose can be catalyzed by an enzyme or a suitable element such as noble metals, metal-oxides, transition metals, and so on, resulting in an electron flow that can be monitored to determine the quantity of glucose [95].

Specific enzymes act as receptors in enzyme-based glucose meters, which measure glucose. Glucose-oxidase is more affordable, bioactive, and stable than other glucose oxidizing enzymes [96].

Since the introduction of the first generation of glucose sensors, glucose sensors based on enzymes have been especially well-liked due to the high sensitivity and selectivity of enzymes. Recently, nanomaterials have been introduced to glucose sensors that use enzymes to increase the rate of electron transfer. Noble and transition metal nanoparticles, nanostructured metal-oxides or metalsulfides, carbon nanotubes,

graphene, conductive polymers are examples of these nanomaterials. For example, using a gold nanoparticles (AuNPs), functionalized ZnO nanostructure on a glassy carbon electrode as a glucose oxidase entrapment matrix is a simple way to make a glucose sensor [97].

Cu-trimesic acid metal organic systems were also used on the 3D macroporous carbon integrated electrode in addition to AuNPs. Glucose oxidase was immobilized on AuNPs after AuNPs were electrodeposited onto metal organic frameworks. The AuNPs increased the electrocatalytic activity of metal organic frameworks by supporting glucose oxidase catalyzed O2 reduction to water. To give a reference signal, Cu-trimesic acie metal organic frameworks catalyzed glucose oxidation. Cu-trimesic acid reduction current rose as glucose was added, whereas oxygen reduction current dropped as oxygen was used by the glucose oxidase catalyzed glucose oxidation process. As a result, the sensor's response was determined by the ratio of current densities for these reduction processes [98,99].

The temperatures, pH ranges, and humidity conditions of enzyme-based glucose sensors are limited [100]. This feature has prompted researchers to look for enzyme-free electrochemical glucose sensors as a possible replacement. Several research have been conducted utilizing various approaches to produce such detecting systems, with nanoscale sensing materials being the most frequent. This feature has prompted researchers to look for non-enzymatic electrochemical glucose sensors as a possible replacement. Several research have been conducted utilizing various ways to construct such detection systems, with nano-structured metallic types often paired with conductive elements to boost sensing functioning.

Noble metals such as gold, platinum, palladium and transition metals such as nickel, copper and cobalt are utilized in metal-based glucose sensors because they can electrocatalytically accelerate glucose oxidation [101]. Because of its availability, low toxicity, inexpensive cost, and high electrocatalytic activity for oxidation of glucose, Ni is frequently used in glucose measurement researches. Ni nanoparticles on porous silica flour, for example, are employed for enzyme-free glucose measurement. Chemically reducing Ni2+ ions oxidation of the surface of Si atoms, nickel nanoparticles are bonded to porous silica, this process is done in an ammonium

fluoride solution [102]. The porous support may simply be loaded with nanoparticles using this in situ redox reaction approach.

Because of its remarkable catalytic activity and durability, platinum is one of the most extensively utilized electrode materials. By expanding the nanosized surface area of Pt, these excellent features may be further enhanced. For example, in blood samples an electrochemically roughened platinum electrode was used to achieve a better sensitivity and selectivity for glucose detection [103].

Given that it is biocompatible and has a significant electrocatalytic activity for glucose oxidation, gold is frequently used in glucose detectors. Furthermore, using gold as a nanoparticle results in a vast surface area with several reactive sites. For example, pine-like gold nanoparticles on the surface of a polycrystalline gold were employed to detect glucose, and electrodeposition was used to deposit gold nanoparticles on the gold electrode modified with histidine [104].

Palladium, with its anti-poisoning properties, is another appropriate metal for making a glucose detector. For example, Palladium nanostructures on a porous gallium nitride electrode have been used to detect glucose [105].

Because of their synergistic action for glucose oxidation, multi-metallic electrodes can give greater electrocatalytic functioning than single element electrodes [106]. Because of the huge surface area, using multi-metallic electrodes with nanoscale structures enhances sensitivity. Cu-Ag nanostructured composite superstructures, for example, can be used as enzyme-free glucose detector [107].
In a study, After glucose was introduced to the electrode, Cu-Ag superstructures demonstrated a fourfold increase in anodic current compared to Cu superstructure electrodes. With a LOD of 0.08 M and ultrahigh sensitivity (7745.7 μ A mM^{-1} cm^{-2}), The amperometric signal of the Cu-Ag superstructure and the glucose concentration were found to be linearly correlated between 0.005-3.5 mM. In studies using diluted human serum in 0.5 M NaOH, the sensor was also put to the test. The measured levels matched the results of commercial glucose meters [107].

Although valuable metals and transitional metals are promising materials for enzyme-free glucose detectors, their use is limited due to their expensive cost. A more cost-effective option is their metal. To boost their electrical conductivity and generate

ordered nanoscaled structures with vast surface area and surplus active site, they are typically combined with conductive backing materials such as nickel foam or Cu foam. For instance, combining cobalt III oxide (Co_3O_4) nanoclusters with 3D kenaf stem-derived carbon to create a glucose detector is a promising strategy.

Owing to their redox behavior, electrical conductivity, and strong electron affinity, conducting polymers are useful materials for biosensors fabrication. Furthermore, they are simple to produce, stable, and economical, all of which are important characteristics for biosensor development. As a consequence of the synergistic interaction of these distinct components, their electrocatalytic performance is often increased by integrating metal-oxide or metal nanomaterials, graphene, and CNTs [108]. In a study, polyaniline, in combination with CuNPs and graphene was used to make enzyme-free glucose detectors, resulting in very sensitive diagnostic systems [109]. Functionalized conductive polymer and CuNPs have also been used to make multicomponent nanobead-based detectors [108].

Carbon nanotubes (CNTs) are another class of nanomaterials utilized for the making of glucose sensors, owing to their high aspect ratio, wide surface area, excellent chemical and thermal durability, and outstanding optical and electrical characteristics, CNTs are ideal materials for biosensors [110]. They are particularly appealing nanomaterials for electrochemical detection of glucose because of their strong electrical conductivity and huge surface area. Multi-wall carbon nanotubes (MWCNTs) can be used as a support for catalytic silver nanoparticles in the detection of glucose [111].

Another type of nanoscaled material used for glucose sensors is graphene, because of its adjustable electrical characteristics, huge potential range, high electrical conductivity, and high electrochemical, mechanical, and thermal durability, graphene is employed in electrochemical detecting techniques [112]. Graphene may be utilized as a component of composite electrode layouts to improve detector performance. An enzyme-free glucose sensor built from porous $CoNi_2Se_4$ on nickel foam substrate with reduced graphene oxide is a good demonstration of composite electrodes. In this case, because of their improved charge transport properties and greater redox tenability, transition metal chalcogenides are used instead of their oxide equivalents [113].

Unique nanostructures and methodologies have been presented to provide revolutionary advances to existing glucose detectors as a result of the recent rise in nanotechnology research. For the oxidation of glucose metal oxides and metals in the form of nanomaterials have a larger surface area. CNTs and graphene have also gotten a lot of interest because of their high conductivity, which enhances electron transfer rate and hence raises sensitivity. The majority of nanotechnology research has been on the manufacturing and integration of nanostructured materials in order to improve the quality of electrochemical glucose sensors [95].

1.7 Aim of the Study

The aim of this study was to modify SPEs with various carbon and gold based nanoparticles to achieve a sensitive electrode capable of detecting and measuring biological molecules at relatively low concentrations. For this purpose, nanostructured GF, MWCNT-Spng, and MWCNT-Spng-AuNPs were used to modify SPCEs and For the determination of dopamine, their electrocatalytic activity was compared. Unlike conventional electrodes modified with MWCNT, to form a thick and physically separable layer of MWCNT-Spng on the surface of SPCE, very concentrated MWCNT was drop-cased multiple times on the surface. For the characterization and scanning of the surface of the modified electrodes, scanning electron microscopy (SEM), electrochemical impedance spectroscopy (EIS), and energy dispersive X-ray spectroscopy (EDS) were used. According to the findings, charge transfer resistance (R_{ct}) and electrocatalytic performance of SPCE that were used for the detection of DA were significantly enhanced after each surface modification. MWCNT-Spng-AuNPs/SPCE, on the other hand demonstrated the highest electrochemical performance, and to highlight its potential for further uses it was investigated for very sensitive enzyme-free detection of glucose. Using 3D carbon-based nanomaterials of such types for the modification of SPEs is thought to hold a lot of promise for the selective and sensitive detection of physiologically relevant chemicals.

Chapter 2

Materials and Methods

2.1 Materials

MWCNTs - length: 8-18 μm (Nanografi, Turkey), SPCE (Metrohm DropSens, Spain), DA hydrochloride (Sigma-Aldrich, USA), HCl-Fuming 37% (Sigma-Aldrich, USA), lactic acid (Sigma-Aldrich, USA), phosphate buffered saline (PBS - 0.01 M phosphate buffer, 0.0027 M KCl and 0.137 M NaCl, pH 7.4 at 25°) (Sigma-Aldrich, USA), D-(+)-glucose (Sigma-Aldrich, USA), sucrose (Sigma-Aldrich, USA), urea (Sigma-Aldrich, USA), uric acid (UA) (Sigma-Aldrich, USA), ascorbic acid (AA)(Sigma-Aldrich, USA), KCl (Sigma-Aldrich, USA), NaCl (Sigma-Aldrich, USA), NaOH (Sigma-Aldrich, USA), auric acid ($HAuCl_4$) (Sigma-Aldrich, USA), potassium ferricyanide ($K_3Fe(CN)_6$) (Sigma-Aldrich, USA) potassium ferrocyanide ($K_4Fe(CN)_6$) (Sigma-Aldrich, USA), poly (methylmethacrylate) (PMMA) (Sigma-Aldrich, USA), chlorobenzene (Sigma-Aldrich), USA. Nickel foam (Ni-F) (99.9%, thickness: 1.6 mm, density: 420 g/m2) was purchased from Alantum Advanced Technology Materials, China.

2.2 Modification of SPCEs with MWCNT-Spng, GF and MWCNT-Spng-AuNPs

2.2.1 MWCNT-Spng/SPCE

Unlike conventional MWCNT modified electrodes, a highly concentrated MWCNT solution was drop-casted on the SPCE surface numerous times to enhance the thickness of the MWCNT-Spng film and establish a physically separate layer.Drop-

casting MWCNTs (4% wt) solution on the working electrode (WE) of an SPCE to generate a thick layer of sponge. MWCNTs were added to the surface of an SPCE in amounts of 4, 8, 12, and 16 µl. 2 µl of MWCNT was poured onto the electrode to limit the alteration to the WE surface, and let to dry at room temperature for 10 minutes after each drop. To get the appropriate volumes (4, 8, 12, and 16 µL), this technique was repeated for each electrode.

2.2.2 GF/SPCE

GF was used to modify the surface of SPCE (GF/SPCE). More information on the characterization and synthesis of GF can be accessed elsewhere [114]. Under atmospheric pressure, GF was synthesized on a commercial Ni-F substrate using the CVD technique (AP-CVD). To decrease surface oxides of Ni-F, a Ni-F was inserted in the core of a quartz tube in a CVD furnace (PROTECH- PT-O1200-60IIIC-4C CVD Furnace) and annealed at 1000°C with a flow of Ar (1000 sccm) and H_2 (10 sccm). After the annealing process, 99.999 percent pure CH_4 (20 sccm) flowed for five minutes with Ar (1000 sccm) and H_2 (10 sccm) gases. Following the synthesis, the CVD chamber was cooled to room temperature at a rate of 100°C per minute. After that, 4 percent PMMA in chlorobenzene was applied to the Ni-GF, and it was allowed to dry for 30 minutes. To appropriately transfer the PMMA coated Ni-GF to the SPCE surface prior to the nickel etching procedure, a metal tube with a diameter of 5 mm was used. After that, Ni-F was etched in a suitable volume of hydrochloric acid (HCl) at 50°C for an overnight period. Following Ni dissipation, the left spherical GF was soaked in hot acetone for 30 minutes to remove PMMA.

2.2.3 MWCNT-Spng-AuNPs/SPCE

For chronoamperometric deposition of AuNPs, 2 mM $HAuCl_4$ (0.1 M NaCl, 1.5 wt % HCl) solution was used and a MWCNT-Spng/SPCE was submerged into it [115]. Using a potentiostat (Autolab PGSTAT204, Metrohm, Switzerland), a continuous potential of -0.2V (vs Ag/AgCl) was applied for 30 minutes for electrochemical deposition of AuNPs on MWCNT-Spng/SPCE.

2.3 SEM Imaging

On a Carl Zeiss 300VP SEM and EDS equipment, a computer-assisted SEM/EDS analysis was done to scan the surface changed SPCEs and validate 3D carbon-based nanomaterial alteration using EDAX TEAM (Texture and Elemental Analytic Measurement) software. . Prior to SEM photography, a 5-nm thick gold layer was used to coat all surface modified SPCEs. EDS was used to examine the elemental compositions across a 4 μm^2 region at a magnification of $25x10^3$.

2.4 Electrochemical Impedance Spectroscopy [EIS] Analysis

EIS analyses of SPCE, MWCNT-Spng/SPCE, GF/SPCE, and MWCNT-Spng-AuNPs/SPCE were carried out in a 5 mM $[Fe(CN)_6]^{3-/4-}$ in 0.1 M KCl solution. With a signal of 10 mV amplitude and a frequency of 10 Hz to 10 kHz, the impedance spectra were recorded at open circuit potential. The Randles circuit model was used to calculate the R_{ct} values, which were generated using the fit and simulation option in the AUTOLAB 302 Nova 2.1.5 program.

2.5 Electrochemical Detection of DA and Selectivity Test

Chronoamperometry was used to evaluate the electrocatalytic activity of bare SPCE, MWCNT-Spng/SPCE, GF/SPCE, and MWCNT-Spng-AuNPs/SPCE for DA measurement and detection. For the electrochemical oxidation of DA, the potential for every SPCE's WE was maintained at +0.2 V (vs. Ag/AgCl) for 120 seconds at different concentrations (0, 5, 10, 25, 50, 100, and 200 μM) of DA in PBS containing DA solution [114]. The calibration curves were obtained using 120 s oxidation currents. The following equation was used to determine the limit of detection (LOD) based on three replicates: LOD = 3.3 (calibration curve slope / standard deviation). At a scan rate of 50 mV/s the voltage was swept from 0 to 0.4 V (vs. Ag/AgCl) in 200 M DA to obtain the CV curves of plain SPCE and MWCNT-Spng-AuNPs/SPCE. Using DPV, the selectivity test of theses electrodes was performed for DA in the presence of uric

acid (UA). To generate DPV curves in 100 M DA with different concentrations of UA (0, 150, and 250 M), AA (0, 1 and 10 mM), glucose (5 mM), KCl (5 mM), and NaCl, the voltage was swept from 0/-0.1 to +0.5 V (vs. Ag/AgCl) at 50 mV amplitude (5mM).

2.6 Electrochemical Enzyme-free Glucose Detection and Selectivity Test

Among the modified electrodes only MWCNT-Spng-AuNPs/SPCE was used to electrochemically detect glucose without the use of enzyme. In alkaline solutions (0.1 M NaOH in PBS) which contained glucose at different concentrations (0, 2, and 5 mM), the CV curves were plotted. For this purpose WE's potential was swept from − 0.6 V to + 0.8 V (vs. Ag/AgCl) at a scan rate of 50 mV/s. In alkaline solution, glucose was detected by choronoamperometry at concentrations of 0, 0.05, 0.1, 0.2, 0.5, 1, 2, and 5 mM. The potential was set at +0.8 V (vs. Ag/AgCl) for 5 sec, and then it was reduced to -0.075 V (vs. Ag/AgCl). For the calibration curve, the most recent glucose oxidation currents were used. The LOD was derived using the following calculation based on three replicates: LOD = 3.3 × (standard deviation of the calibration curve / the slope of the calibration curve). Finally, chronoamperometry was used to perform the selectivity test. The change in current was seen for glucose, urea, sucrose, lactate, and glucose again after establishing a steady current at -0.075 V (vs. Ag/AgCl) [116,117].

In the detection solution, the final concentration of each interferent was set at 10 mM.

Chapter 3

Results and Discussion

Drop-casting and drying of MWCNTs (4% wt) at different volumes on SPCEs' WE resulted in a thick layer of MWCNT-Spng. The WE of SPCE was modified with different concentrations of MWCNTs (4, 8, 12, and 16 µL). When compared to bare SPCE, modification of the WE of SPCE with 4 µL of MWCNT solution resulted in a considerable drop in R_{ct} from 2.38 ± 0.38 Ωk to 141.8 ± 51.2 Ω, as it is demonstrated in the Nyquist plot in Figure 1a. The results reveal that growing a thick layer of MWCNT dramatically enhances electron transfer rate and lowers impedance at the electrode surface, which is critical for very sensitive measurements. In certain cases, rising the amount of MWCNT solution improved the R_{ct} value. The R_{ct} values of 8 µL and 12 µL of MWCNT were (70.9 ± 13.5 Ω) and (57.5 ± 7.5 Ω) respectively which were almost identical, indicating that R_{ct} value was not improved considerably when the volume of MWCNT solution was increased. Furthermore, after increasing the volume of MWCNT to 16 µL, the thick layer came off the surface of SPCE as a whole and it was immersed in the test solution, resulting in a higher R_{ct} value. To put it in other words, by increasing the volume of MWCNT a more unstable layer was rendered. As a result, 8 µl of MWCNT was used to form a steady MWCNT-Spng layer with a low R_{ct} value.

For making a MWCNT-Spng-AuNPs/SPCE, AuNPs were deposited electrochemically on SPCE that was previously modified with 8 µL MWCNT-Spng. After the electrochemical deposition of AuNPs the R_{ct} value dropped from 70.9 ± 13.5 Ω (R_{ct} value SPCE modified with 8 µL MWCNT-Spng) to 34.6 ± 17.7 Ω according to the EIS results shown in Figure 1b, this indicates the improvement in the electron transfer rate and hence the electrode's conductivity.

When the WE was modified with GF the R_{ct} value obtained was 97 ± 29.4 Ω which is lower when compared to bare SPCE's R_{ct} value (2.38 ± 0.38 kΩ). Although using GF

to modify the surface lowered the R_{ct} value, the value was still much greater than MWCNT-Spng/SPCEs. It's probable that the structure of GF resulted in a looser contact with the surface of SPCE than MWCNTs, resulting in a substantially larger electrode surface impedance. The comparison of R_{ct} values for each modification is demonstrated in Figure 1b.

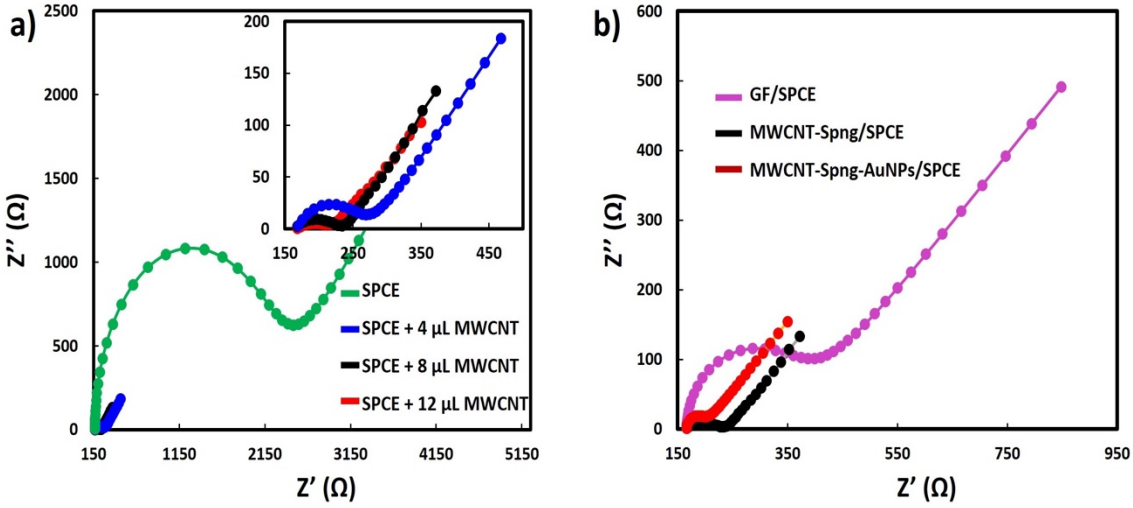

Figure 1: (a) EIS curves bare SPCE and SPCE modified with different volumes of MWCNT, (b) EIS curves of GF/SPE, MWCNT-Spng/SPE and MWCNT-Spng-AuNPs/SPE

The surfaces of all modified SPCEs, as well as a bare SPCE, were then imaged using SEM. The bare electrode, as shown in Figure 2, displayed considerable surface roughness, cracks, and uneven microstructures that looked like flake. The MWCNT-Spng/SPCE surface was more regular than the bare electrode due to the MWCNTs' porous structure and significant surface coverage as it is visible in Figure 3. The layer was removed from the surface of SPCE after multiple washes with dH_2O, demonstrating the creation of a thick (8 µL) MWCNT-Spng film. The adopted technique for GF synthesis and transfer to the surface of WE of an SPCE was obviously successful, as shown in Figure 4.

AuNPs were evenly distributed throughout the surface of whole MWCNT-Spng/SPCE. MWCNTs may be seen beneath where electrochemically produced AuNPs were developed vertically over the MWCNT-Spng layer, this can be seen in Figure 5. AuNP clusters were found to have an average size distribution of 544.5 ± 77 nm.

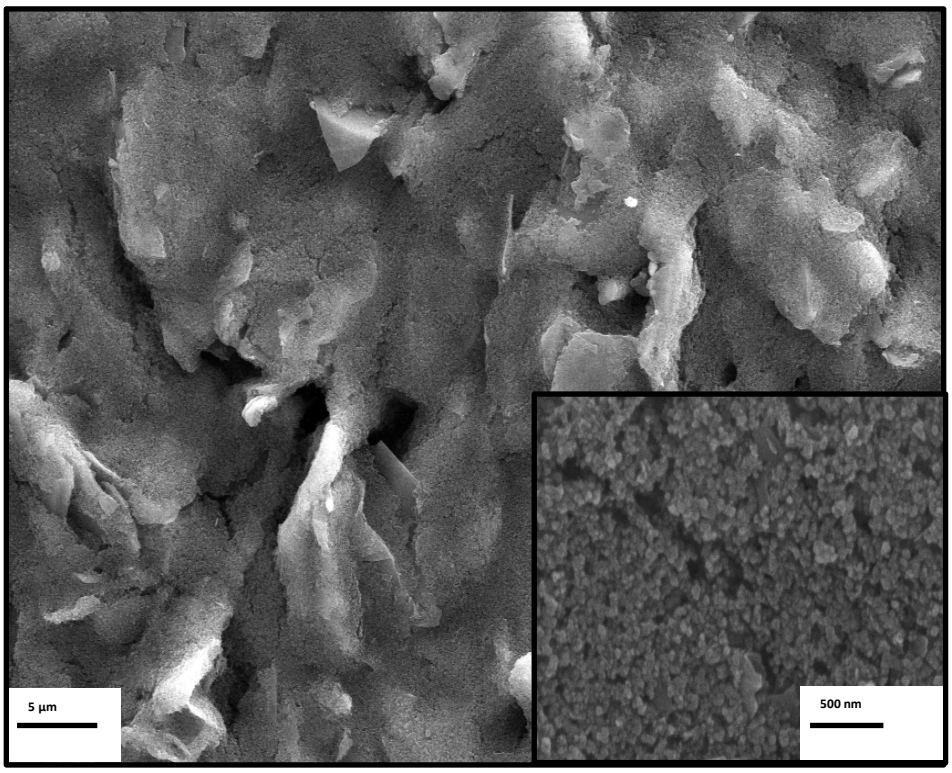

Figure 2: SEM image of bare SPCE

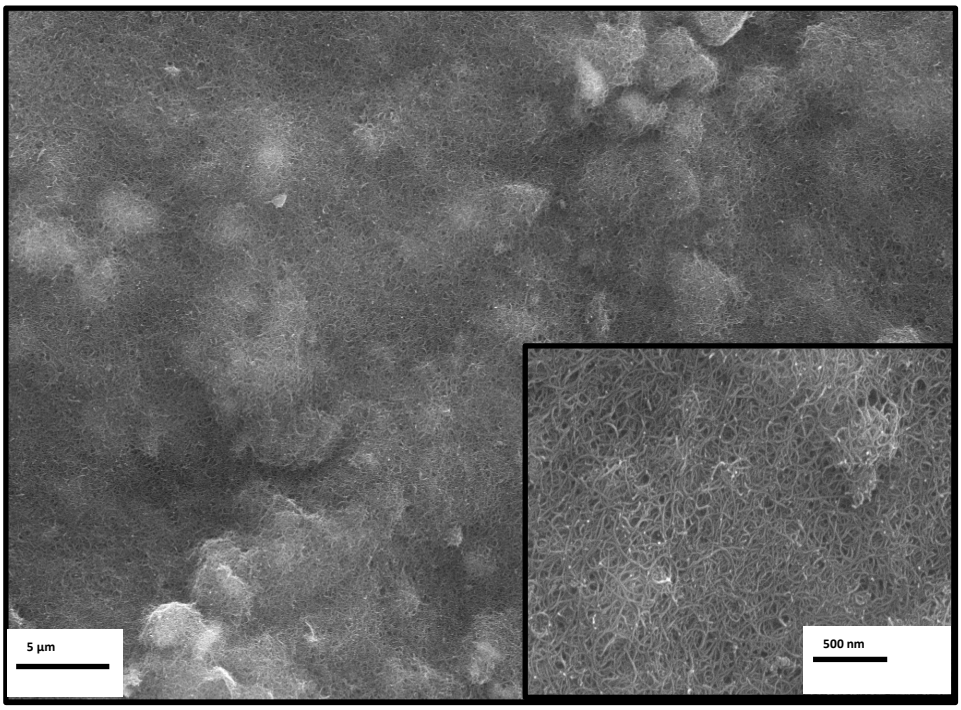

Figure 3: SEM image of MWCNT-Spng/SPCE

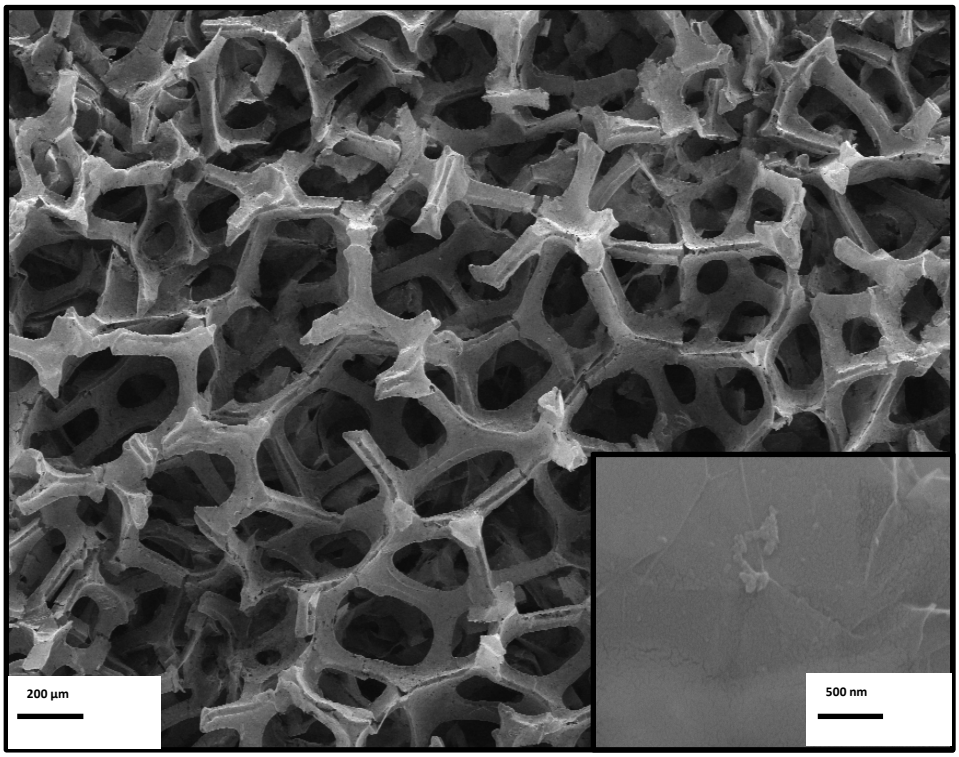

Figure 4: SEM image of GF/SPCE

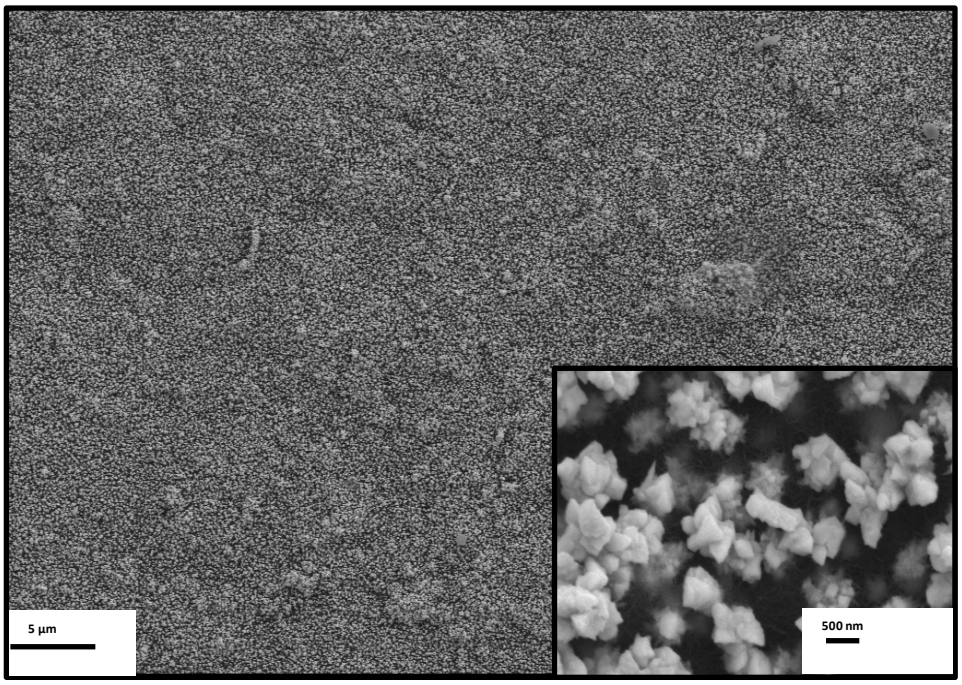

Figure 5: SEM image of MWCNT-Spng-AuNPs/SPCE

In addition, the elemental makeup of the surface was determined via EDS analysis for all modified SPCEs in a limited region, and the findings are shown in Figure 6. According to the findings of the energy spectrum analysis (SEM-EDS), bare SPCE was made of 94.56 % (Atomic %) C, MWCNT-Spng/SPCE was made of 88.73 % (Atomic %) C, and GF/SPCE was made of 100 % (Atomic %) C. The surface composition of the MWCNT-Spng-AuNPs/SPCE was 82.09 % (Atomic %) C and 16.16 % (Atomic %) Au, this indicated that the nanomaterial deposited electrochemically is Au.

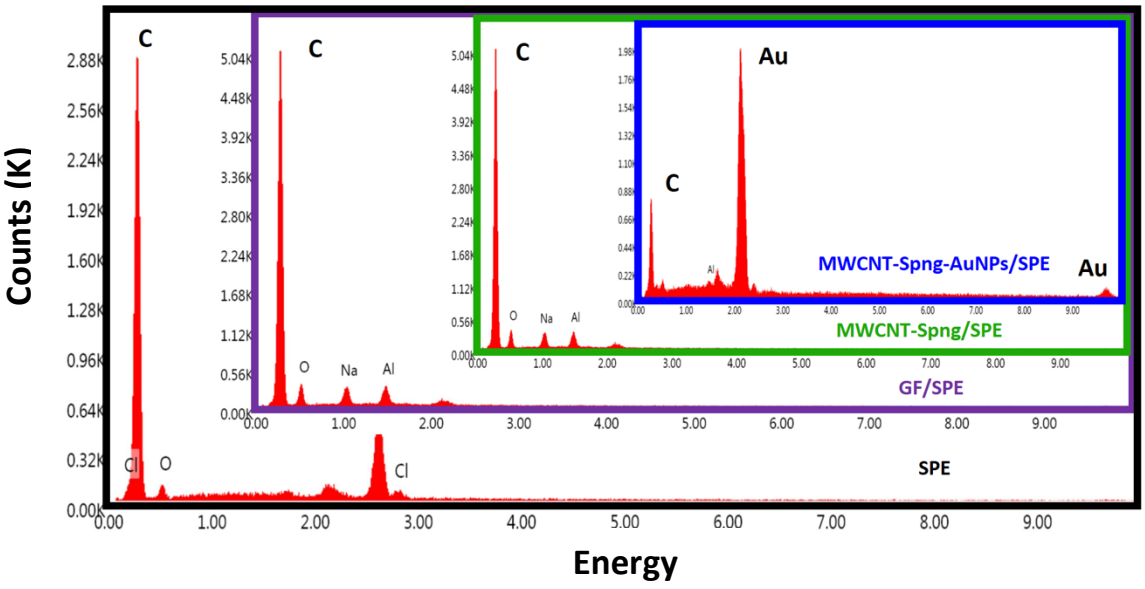

Figure 6: EDS analysis of bare and modified SPCEs

DA was used to assess the influence of surface modification on bioanalysis performance. In the range of 0 to 200 µM for DA's concentration, all electrodes provided a linear response with an R^2 value higher than 0.99 and effectively identified 5 µM of DA (S/N > 3) (demonstrated in Figure 7). Furthermore, as compared to bare SPCE, MWCNT-Spng/SPCE showed 2.15 fold, GF/SPCE showed 2.17 fold, and MWCNT-Spng-AuNPs/SPCE showed 3.14 fold increases in DA oxidation current amplitude. The bare SPCE, as predicted, had the lowest sensitivity (62.6 µA/mM·cm^2) and a LOD of 4.14 µM. (Figure 7ai-ii). The addition of a GF layer to the surface resulted in a significant rise in the surface area-to-volume ratio, in a result of which the electrocatalytic activity of the detecting electrode was increased, resulting in a sensitivity increase of more than two folds (127.4 µA/mM·cm2) and a LOD value of 1.12 µM. (Figure 7bi-ii). MWCNT-Spng, like GF, significantly increased catalytic performance when compared to bare SPCE which had a sensitivity of 125

μA/mM·cm^2 and LOD of 1.72 μM (Figure 7ci-ii). GF/SPCE somewhat had better performance than MWCNT-Spng/SPCE, despite the fact that MWCNT-Spng/SPCE had a substantially lower surface impedance. It might be because GF/SPCE has a significantly higher surface area-to-volume ratio than MWCNT-Spng/SPCE.

AuNPs are commonly utilized to increase electron transfer and sensitivity by modifying electrode surfaces. They are acknowledged to have a variety of essential electrochemical sensor features, such as a high surface activity and a large surface area-to-volume ratio. Thus, an additional layer of AuNPs was added to the surface of a MWCNT-Spng/SPCE. As previously stated, this modification significantly lowered surface impedance. As a consequence, the sensitivity (183 μA/mM·cm^2) and LOD (0.83 μM) values achieved were higher than those of GF/SPCE (Figure 7di-ii). AuNPs were grown vertically atop MWCNTs, as shown in Figure 5, with MWCNT bundles visible beneath. In other words, the composite had a large surface area to volume ratio and exhibited a structure resembling nanopores. The confinement effect and increased surface area-to-volume ratio may explain MWCNT-Spng-AuNPs/SPCE's improved electrocatalytic activity.

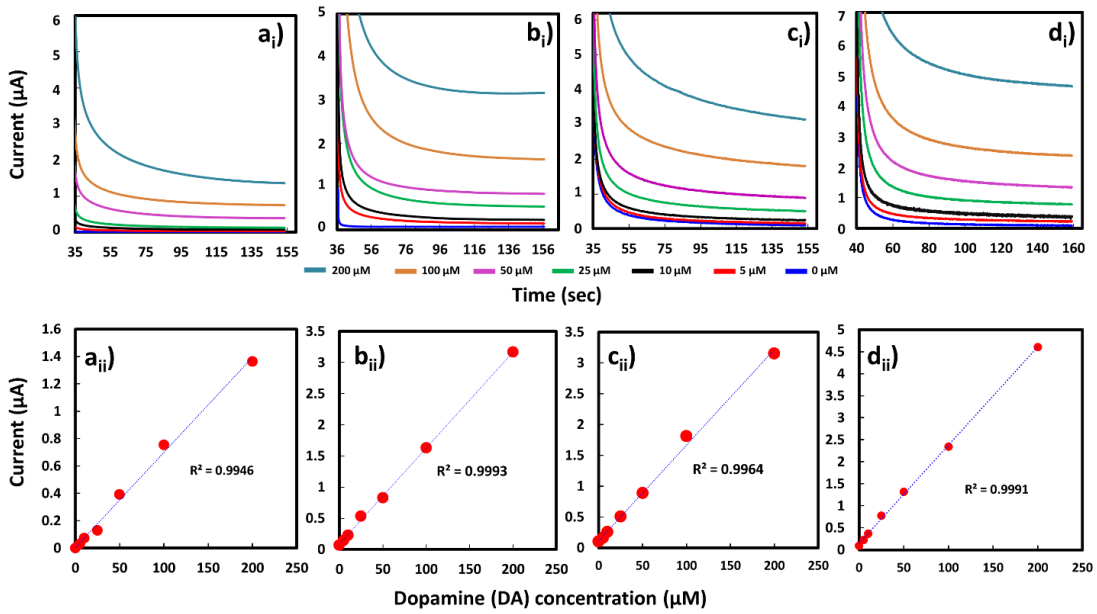

Figure 7: Chronoamperometric and calibration curves for (0, 5, 10, 25, 50, 100 and 200 μM) concentrations of DA at +0.2 V (vs. Ag/AgCl) for 120s. (a$_{i-ii}$) Bare SPCE, (b$_{i-ii}$) GF/SPCE, (c$_{i-ii}$) MWCNT-Spng/SPCE, (d$_{i-ii}$) MWCNT-Spng-AuNPs/SPCE

According to several recent researches, reactants are encouraged to linger near the electrode surface for a longer period of time than usual due to the nanoporous structures' significantly confined area (confinement effect), hence improving the material's catalytic efficiency.

SPCE, GF/SPCE, MWCNT-Spng/SPCE, and MWCNT-Spng-AuNPs/SPCE were compared to recent findings that electrochemically detected DA using various modified electrodes. Regarding sensitivity and LOD, it appears that all modified SPCEs outperformed the majority of these electrodes. Table below demonstrates the comparison between various modified electrodes for the electrochemical detection of DA.

Table 1: Comparison of electrochemical detection of DA using different modified electrodes

(Table continues in next page)

Electrode type	LOD (µM)	Sensitivity (µA/mM·cm^2)	Linear range (mM)	Reference
SPE	4.14	62.588	0.005 – 0.2	**This work**
GF/SPE	1.12	127.38	0.005 – 0.2	**This work**
MWCNT-Spng/SPE	1.72	125	0.005 – 0.2	**This work**
MWCNT-Spng-AuNPs/SPE	0.83	183	0.005 – 0.2	**This work**
PPy/ferrocyanide/carbon paste electrode	15.1	–	0.2 – 0.95	[118]
Au/PPy/Ag/GCE	50	–	0.1 – 5	[119]
PPy/-cyclodextrin/GCE	6	–	2 – 10	[120]
CAuNE	5.83	10	1 – 100	[121]
pGO-GNP-pGO-modified ITO electrode	1.28	10	0.0001 – 0.03	[122]

PPy-MCM-48/Au	2.5	–	0.002 – 0.12	[123]
MWCNT/Fe_3O_4 /2,3-Nc	1.77	1350	0.00327 – 0.0243	[124]
MWCNT/β-CD/GCE	6.70	116.63	0.01 – 0.08	[125]
PPy/S-β-CD/GCE	3.20	886	–	[126]
Pdop@GR/MWCNTs	1.0	–	0.007 – 0.297	[127]
Pyrolytic carbon	2.3	200	18 – 270	[128]
Pt–Ag/Gr	0.012	-	0.0001 – 0.06	[129]
Au-Cu_2O/rGO	3.9	-	0.01 – 0.09	[130]
GR-AuNP/GCE	1.44	-	0.003 – 0.140	[131]
β-CD/rGO/SPE	0.017	-	0.00005 – 0.05	[132]

Furthermore, CV curves obtained at a scan rate of 50 mV/sec in 200 μM DA revealed that after the modification of the surface of SPCE with MWCNT-Spng-AuNPs, the peak-to-peak voltage separation (ΔEp) value of SPCE decreased from 137 mV to 42mV, demonstrating the good impact of modification as shown in Figure 8a. In terms of selectivity, the results confirm that DA can be selectively and accurately be detected by using MWCNT-Spng-AuNP/SPCE. Figure 8b demonstrates selectivity of this electrode towards DA when different concentrations (0, 150, 250 μM) of uric acid (UA) were added to the solution. When ascorbic acid (AA) was added to the solution in varying concentrations (0, 1, 10 mM), the modified electrode again demonstrated a good performance for DA selectivity (Figure 8c). Figure 8d shows the selectivity performance of this electrode when merely 100 μM of DA was measured and then 5 mM of glucose, NaCl, and KCL were added separately to 100 μM DA solution.

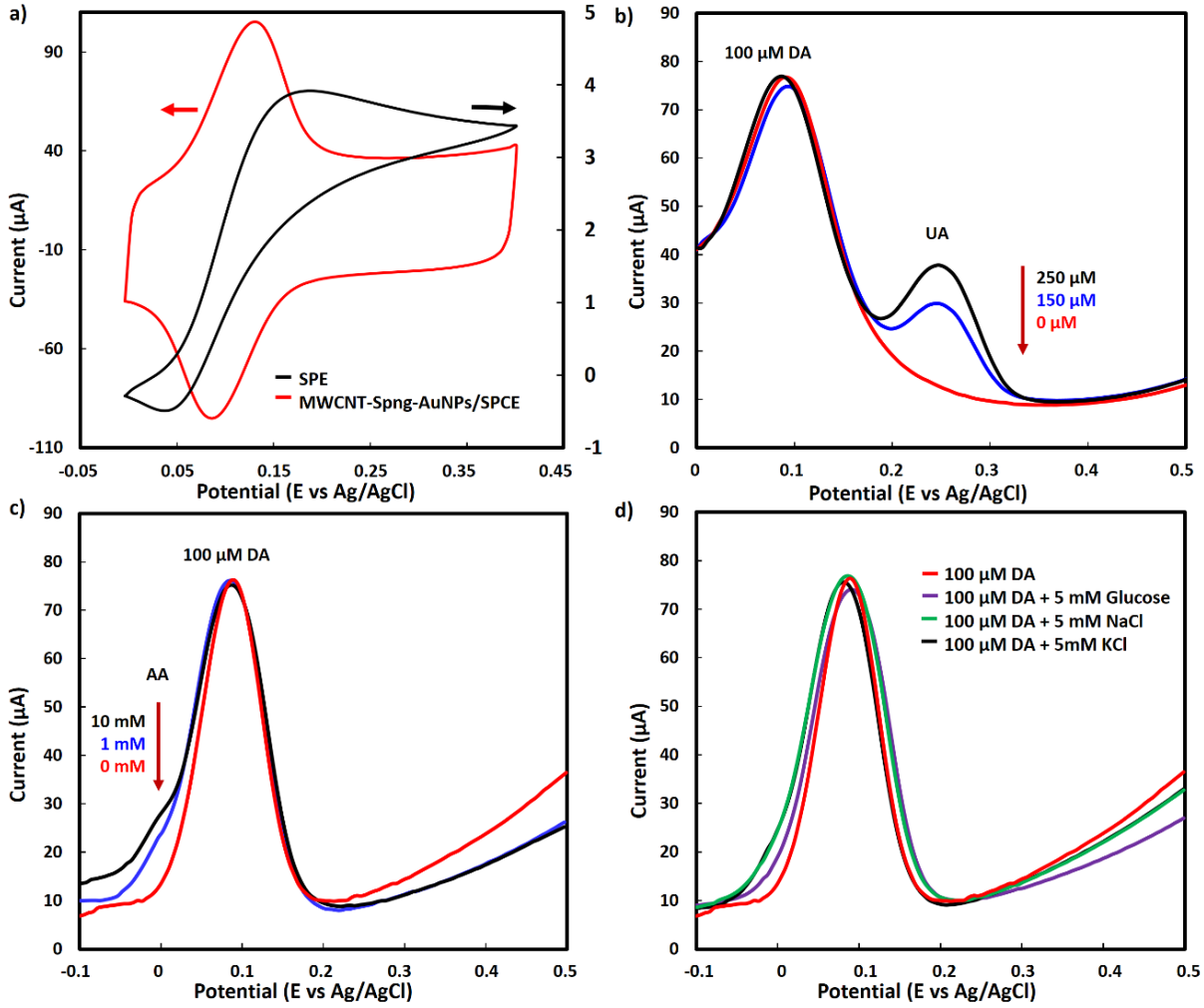

Figure 8: (a) CV curves of 200 µM DA measured by bare and MWCNT-Spng-AuNP/SPCE, selectivity of MWCNT-Spng-AuNP/SPE for DA in the presence of (b) UA, (c) AA, (d) glucose, NaCl, KCL.

Because of their resistance to surface poisoning, chemical stability, and biocompatibility, AuNPs are well-known for their electrocatalytic activity oxidize glucose in alkaline solutions. Therefore, the enzyme-free glucose detection by MWCNT-Spng-AuNPs/SPCE was also tested. For 0 and 5 mM glucose in alkaline solutions, CV curves of the MWCNT-Spng-AuNPs/SPCE were generated (Figure 9a). The formation of AuOH sites on the surface of the Au electrode by the adsorption of -OH groups by catalytically oxidizing glucose to gluconolactone is a crucial determining factor. In 5 mM glucose, two peaks formed in the anodic (forward) and one peak in the cathodic (backward) scans, as shown in Figure 9a. After rising the potential, the surface of Au electrode is covered with -OH groups as a result AuOH

sites are formed, which are then transformed into Au_2O_3 after oxidation. The oxidation of gluconolactone and glucose, respectively, are responsible for peaks (i.) and (iii.). Peak (i.) did not grow linearly with the increase in the concentration of glucose because gluconolactone inhibited the oxidation of AuOH sites to Au_2O_3 and -OH adsorption, therefore caused a sudden drop in the amount of AuOH sites that were accessible. Upon reversal of the potential (cathodic scan), AuOH is produced after the reduction of Au_2O_3, this raises the number of AuOH sites accessible for glucose oxidation (5 mM glucose - peak iv. at -0.075). With 2 mM glucose, a similar response was obtained (Figure 9a). Unlike MWCNT-Spng-AuNPs/ SPCE, from the CV curves no detectable peak was obtained when 5 mM glucose in alkaline solution was tested using SPCE and MWCNT-Spng/SPCE. For glucose detection at various concentrations by MWCNT-Spng-AuNPs/SPCE using chronoamperometry, for 5sec the potential was raised to + 0.8 V (vs. Ag/AgCl) and Au_2O_3 was obtained from the oxidation of AuOH sites, then for the reduction of Au_2O_3 back to AuOH -0.075 V (vs. Ag/AgCl) (obtained from Figure 9a) was applied for 10 sec, rising the accessible AuOH sites for glucose oxidation.

Using the chosen chronoamperometric measurement method, glucose concentration-dependent behavior was obtained when the modified electrode was used for different concentrations of glucose (0, 0.05, 0.1, , as shown in Figure 9b, in which the last measured current was proportionate to the glucose concentration. The method presumably prevented gluconolactone oxidation and AuOH site oxidation to Au_2O_3. Using the last oxidation current for every level of glucose concentration, a calibration curve was produced (Figure 9c, Figure 10). A LOD of 4.96 μM and a sensitivity of 526.4 $\mu A/mM \cdot cm^2$ was calculated for MWCNT-Spng-AuNPs/SPCE. For two different ranges of 0-0.2 mM (R2 = 0.9963) and 0.2-5 mM (R2 = 0.9962) glucose concentrations the electrode displayed a linear response, indicating that the sensor was capable of detecting both quite low and high glucose concentrations [114].

Table 2 compares certain analytical properties of MWCNT-Spng-AuNPs/ SPCE to literature findings published. According to the findings as shown in table 2, the MWCNT-Spng-AuNPs/SPCE had a low LOD and a high sensitivity. Finally, chronoamperometry was used to assess the sensor's selectivity against various physiologically relevant chemicals such as sucrose, lactate and urea. The outcomes amply demonstrated that, the sensor's response was not greatly impacted by these chemicals, however the addition of glucose caused a large rise in the oxidation current.

(Figure 9d). As a result, it can be safely said that MWCNT-Spng-AuNPs/SPCE was quite high glucose-selective even when other molecules were present.

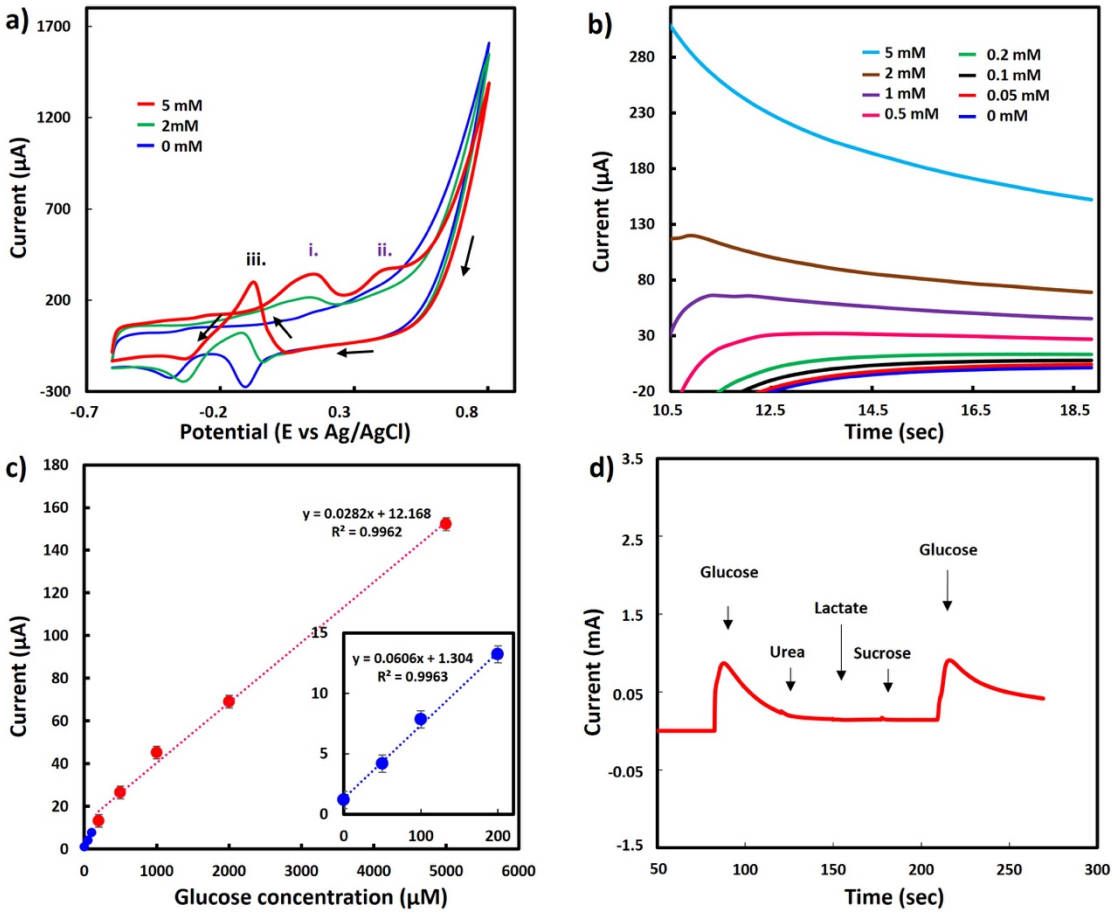

Figure 9: (a) CV curves of MWCNT-Spng-AuNP/SPCE for 0,2, and 5 mM glucose in alkaline solution, (b) chronoamperometric curves of different glucose concentrations in alkaline solution, (c) calibration curve, (d) glucose selectivity test in the existence of several interference.

Table 2: Analytical performance comparison of various enzyme-free glucose sensors

Electrode type	LOD (µM)	Sensitivity (µA/mM·cm^2)	Linear range (mM)	Reference
MWCNT-Spng-AuNPs/SPE	**7.63**	**408**	**0 – 50**	**This work**
IrO_2/ PbO_2-carbon microelectrodes	50	–	0.1 – 20	[134]
CuxO flowers	49	1620	0 – 6	[135]
Self-assembled Co_3O_4-MWCNT /GCE	10.42	5089.1	0.05 – 12	[136]
MoS_2-Au/Pt	390	142.68	0.01 – 19.07	[137]
Au-Pd/MoS_2	400	184.9	0.5 – 20	[138]
MWCNT-CuBTC	10	14.949	0.2 – 1	[139]

Chapter 4

Conclusion

In this work, MWCNT-Spng, MWCNT-Spng-AuNPs, and GF were used to modify the surface of SPCEs, for the detection of DA they were then assessed for electrocatalytic performance, R_{ct} values, and elemental composition. The foam structure of GF was preserved after being transferred to an SPCE's surface as it was revealed from SEM images, but MWCNT-Spng exhibited a spongy structure and MWCNT-Spng-AuNPs exhibited a nanoporous structure. Surface modifications with these nanoparticles were effective, according to EDS data. In comparison to bare SPCEs, all modified SPCEs showed significantly lower impedance and higher DA detection sensitivity. GF decreased the Rct value as compared to unmodified SPCE, but it was still much greater than MWCNT-Spng/SPCE, though, which may be linked to GF's rigid structure. MWCNTs totally concealed and straightened SPCE's surface, in contrast to GF. For DA detection, though, GF/SPCE showed a lower LOD and improved sensitivity than MWCNT-Spng; this might be owing to GF's larger surface area-to-volume ratio. Compared to GF/SPCE, electrochemically depositing AuNP on MWCNT-Spng/SPCE increased electrochemical properties. The the confinement effect and huge surface area-to-volume ratio are thought to have led to this result. MWCNT-Spng-AuNPs/SPCE was also tested for high sensitivity non-enzymatic detection of glucose to see whether it may be employed in other applications. The electrode exhibited a decent sensitivity and a significantly improved LOD when compared to some of the electrochemical sensors recently reported, according to the findings. It also showed remarkable glucose selectivity in the presence of several biologically relevant chemicals. The findings of this work are likely to aid analytical researchers in comparing the effect of different 3D nanomaterials based on carbon on the electrocatalytic behavior of SPCEs and developing very sensitive and selective sensors for use in biological applications.

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Appendix A

Publications from the Thesis

Journal Articles

1. ŞEN M, Azizi E, Avcı İ, Aykaç A, Ensarioğlu K, Ok İ, et al. Screen Printed Carbon Electrodes Modified with 3D Nanostructured Materials for Bioanalysis: A Comparison Study. SSRN Electronic Journal. 2021;

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Publications:

1. ŞEN M, Azizi E, Avcı İ, Aykaç A, Ensarioğlu K, Ok İ, et al. Screen Printed Carbon Electrodes Modified with 3D Nanostructured Materials for Bioanalysis: A Comparison Study. SSRN Electronic Journal. 2021;

Presentations at conferences:

1. Serkan, Ç., Şenay, M., Samet, Ç., Ehsan, A., Aydın, A. (2018, September 19-22), A novel methodology on evaluation of upper extremity motor functions, 9th International Biomechanics Conference, Eskisehir, Turkey.
2. Ehsan, A., Nermin, T,A. (2021, January 28-29), Design of a temperature measurement system for photothermal laser applications, International Icontech Symposium-3 on Innovative Surveys in Positive Sciences, Oujda, Morocco