CHAPTER 1

Introduction and Scope of the Thesis

Contents

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1.1 Introduction

Diabetes mellitus, or in short diabetes, is a metabolic disorder resulting in elevated blood sugar levels over a long period of time. If not given proper medical attention, it can raise many complications like diabetic ketoacidosis, hyperglycemic state, cardiovascular diseases, stroke, kidney diseases, foot alsur, nerves damage, damage to eyes, cognitive impairment, and even death [1]. Diabetic results from either failure to produce enough insulin owing to loss of beta cells (type 1 diabetic) or due to insulin resistance (type 2 diabetics).

Diabetes is mainly lifestyle disorder affecting around 9% of the world's adult population [1]. Trends suggest that these numbers will continue to raise, leading to multiplications' of a person's risks of early death. According to the international Diabetes foundations (IDF) report, the number of affected people by diabetes was 246 million in 2006 and kept increasing to 285 million in 2009, 366 million in 2011,450 million in 2015, and 463 million in 2019. If this trend follows, the projected number of diabetic patients will be 700 million by 2045 [2]. This trend is graphically shown in figure 1.1.

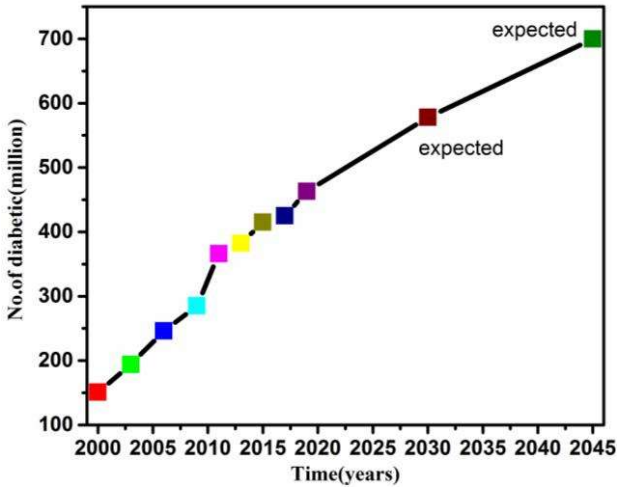


Figure. 1.1 Number of diabetic patients (in millions) worldwide with time (years) (International Diabetes Federation., 2017)

There is no preventive measure for type 1 diabetes. However, type 2 diabetes, responsible for around 90% of the total diabetic cases, can be prevented by maintaining a healthy lifestyle. Management of type 2 diabetics' patients focuses on controlling the blood sugar level close to the normal levels without causing low blood sugar. This can be accomplished with dietary changes, exercise, weight loss, and medications. Regular monitoring of blood sugar levels of these patients is must. This is usually accomplished by a blood sugar test, which measures glucose per unit volume of blood. Most testing procedures include taking a drop of blood by pricking with a needle and dropping on a sensitive and reliable sensors strike attached with appropriate electronic modules. This electronics module shows the accurate blood sugar levels by measuring it against standard calibrations [3].

According to IDF reports, expenditure on treatment and monitoring of diabetes was 376 billion USD in 2009 and 673 billion USD in 2015. If this trend follows, the projected cost will be around 800 billion USD. This trend is shown in figure 1.2. It is

easily understandable how diabetes has become an economic burden to society [4]-[5]. Therefore, governments' policies and current research focus on developing cheaper and more efficient management with sound monitoring systems [6]-[7]. My research goal is to create more efficient, robust, and more inexpensive blood glucose monitoring sensors.

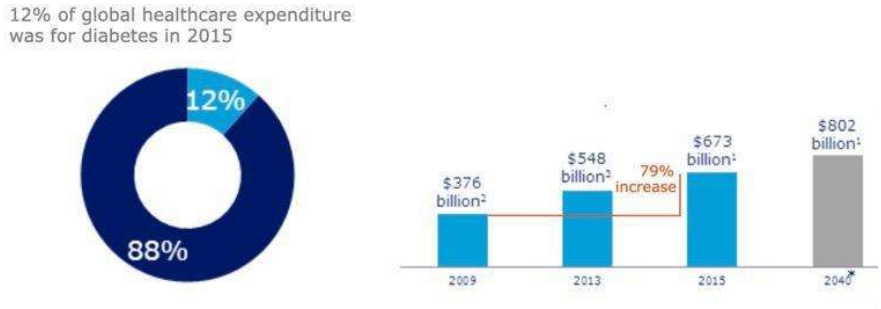


Figure. 1.2 Health care cost for a diabetic patient (da Rocha Fernandes et al., 2016)[5].

Most of the glucose monitoring sensors are electrochemical amperometric bio-sensors where glucose is oxidized and converted to gluconolactone under an applied bias in the presence of a catalyst. Measurements of the oxidative current corresponding to this glucose to gluconolactone oxidation process give the blood sugar content when compared with an oxidative current versus glucose concentrations calibration process. Instead of a three-electrode electrochemical cell, an extended gate FET(field-effect transistors) can also be employed for glucose concentration detection where the sensing electrode is connected to the gate of commercially available FET. Based on the nature of the catalyst, these sensors are broadly categorized into two groups, namely

(i) GO_X enzyme based sensors and

(ii) Non-enzymatic sensors.

In enzymatic sensors, glucose oxidase (GOX) works as a catalyst for the oxidation process [8], whereas in non-enzymatic sensors, an oxide based hybrid inorganic nanomaterial serves the purpose of the catalyst.

1.2 Enzyme Based Glucose Sensors

In enzyme-based glucose sensing Gox reacts with glucose and directly oxidizes glucose to gluconic acid and H_2O_2 [9]. The reaction is given below.

$$Glucose + H2O + O2 \xrightarrow{Gox} Gluconic\ acid + H2\ O2$$

1.2.1 The First Generation of Glucose Sensing

The structure of the second-generation enzymatic glucose sensors is shown in figure1.3(a). Gox enzyme is used in the Ist generation of glucose sensing. In first-generation glucose-sensing, a positive potential higher than 1 volt versus Ag/AgCl is applied to detect the analytes directly. But the side effect of this higher potential cause oxidation of ascorbic acid, uric acid, lactic acid, etc.[10]. Oxidation of other interference like ascorbic acid, uric acid, and lactic acid, along with glucose, creates selectivity problems towards the target analyte. Additional mediators have been used to decrease the overpotential and minimize the oxidation of interfering species. Pt nano-particle helps the oxidation of glucose and increases the sensitivity of the glucose detection by increasing the oxidation of H_2O_2, as shown in figure 1.3 (b) [11]. However, the strong reactive nature of Pt towards H_2O_2 gives a higher reaction potential of the electrode, which is a drawback. To solve the overpotential issue, prussian blue (PB) has been used in place of Pt for lowering the reaction potential near 0 volts versus Ag/AgCl, as shown in figure 1.3 (b) [12]. PB based glucose sensors utilize the reduction of H_2O_2.

H_2O_2 reduces the negative potential, and current increases as the concentration of H_2O_2 increases. Therefore glucose concentration can be measured by measuring the concentration of H_2O_2, which is related as shown in equation 1.

$$Glucose + H2O + O2 \xrightarrow{Gox} Gluconic\ Acid + H2O2 \qquad |(1)$$

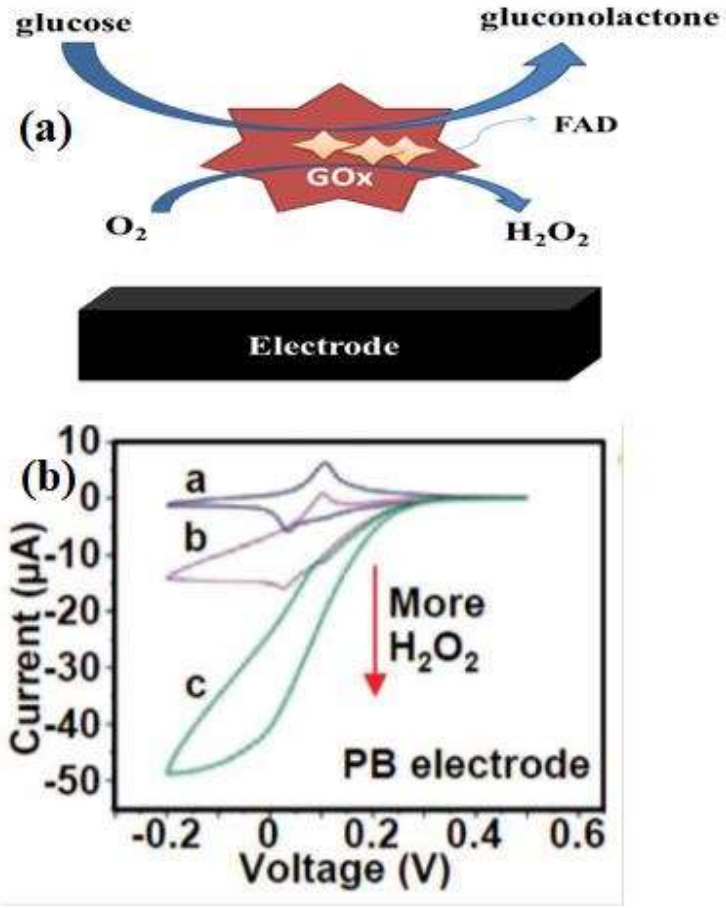


Figure. 1.3: (a) Schematic diagram of 1st generation enzymatic based glucose sensing (b) Cyclic voltammograms (CVs) of Prussian blue (PB) modified electrode absence (curve a) and presence (curves b and c) of 0.3mM and 1.2 mM H_2O_2, respectively. (https://pubs.rsc.org/en/content/articlehtml/2015/ay/c5ay01329a).

1.2.2 Second Generation Enzyme Based Glucose Sensor

The structure of the second generation enzyme-based glucose sensors is shown in figure 1.4. Second generation glucose sensors can be achieved by replacing O_2 in first-

generation glucose sensors with artificial mediators to resolve the issue of oxygen deficit in the measured sample [13], [14]. Small redox-active molecules like ferrocene derivates, conductive organic salt, ferrocyanide, etc., are used as electron mediators. With the help of electron mediator, electron transfer rate has been improved in between flavin adenine dinucleotide (FAD) (redox center of active sites of enzyme) and electrode surface by reversible and a fast redox reaction [15], [16], [17].

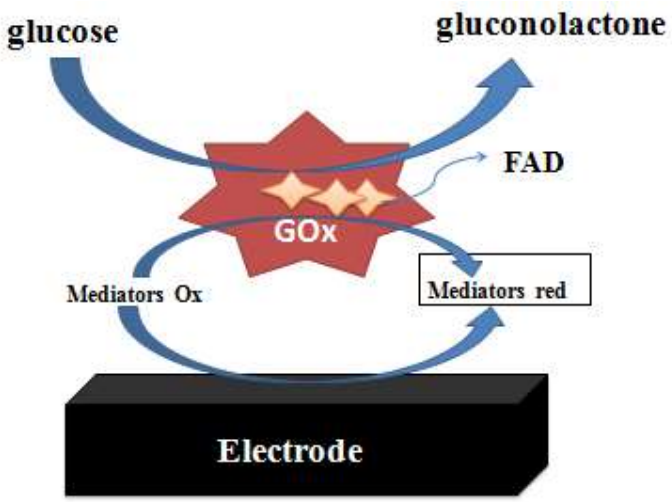


Figure. 1.4: Schematic diagram of 2nd generation enzymatic based glucose sensing

However, there are still some problems that exist in second-generation sensors. The first problem is to maintain the closed distance between the enzyme and electrode surface so that less molecule diffusion takes place. This diffusion process is dreadful for prolonged use, and it needs a more complicated and elaborated way to tether the mediators between enzyme and electrode [18]. Although the rate of reaction between enzyme and mediator is faster than that of O2, yet dissolved oxygen competes with the mediator and reduces the accuracy of the system [19]. Mediators also oxidize the other interfering species, which further decrease the accuracy and efficiency of the

sensors[20].

1.2.3 Third-Generation Enzyme-Based Glucose Sensor

The structure of the third-generation enzymatic glucose sensor is shown in figure1.5. In this type of enzymatic sensor, there are no requirements of any mediators between the electrode and the enzyme's active site. In this type of glucose sensor, direct electron transfer takes place between the electrode and the active site of the enzyme [21]. The development of these types of mediator-free glucose sensors is facilitated by the development of nano-size and porous materials [22]. Initially, the biggest problem for direct electron transfer between the electrode and enzyme was the existence of thick protein in which the redox sites are embedded [23]- [26]. The use of advanced porous materials for the working electrodes and sophisticated electrical wiring techniques help to properly entrap and encompass the protein, which makes the direct electron transfer between the enzyme and the electrode feasible [27]-[29]. The most crucial point of this system is the successful removal of possible interferences. Therefore the conversion of the enzymatic identification events of glucose to amperometric signals becomes direct, irrespective of the concentration of oxygen or redox mediators [30]-[32]. In summary, this new system would avoid the complications of tailored mediators and improve selectivity and sensitivity.

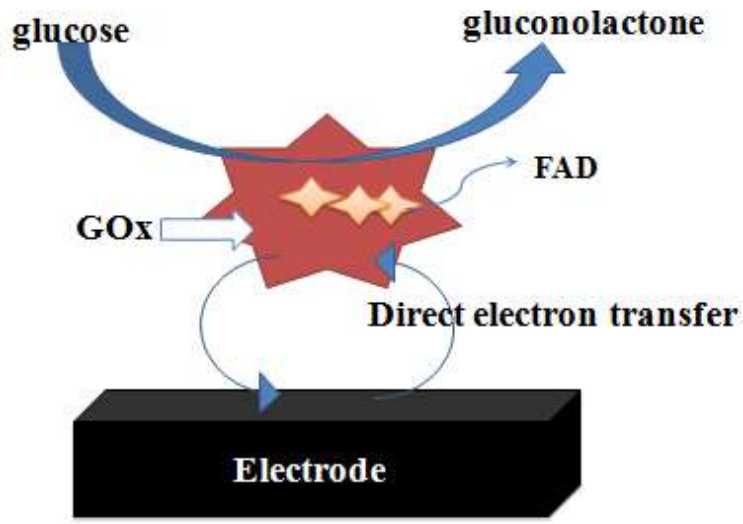


Figure. 1.5: Schematic diagram of 3rd generation enzymatic based glucose sensing.

1.3 Non Enzymatic Glucose sensors (Metal Oxide Based Sensors)

Stability is the most severe problem of all enzyme-based sensors [33]-[34]. This stability problem occurs due to chemical and thermal deformations of the enzyme-based glucose sensors. Enzymatic sensors also deteriorate during the fabrication, packaging, storing, and use. The performances of the sensors are greatly reduced in temperatures higher than 40 °C, and when the pH value is less than two or greater than 8, these sensors can be severely damaged. It is challenging to eliminate deformations, including thermal or chemical deformation, during fabrication, packing, storing, and use. In detail, when the temperature is higher than 40 °C or pH< 2 and pH>8 could cause severe damage to the sensor [35],[36].

For the welfare of humanity, it is essential to reduce the upcoming harms by knowing the problems in real-time. The scientific community and researchers have to develop a sensor that can sense the possible harms and send the alert signal to the human. Metal

oxide semiconductor materials have been used as a sensor to sense in many applications. For good sensing performance, nanometer-scale and smaller crystalline size metal oxide-based materials are preferred due to their higher active surface area. These metal oxide-based sensors are of more demand if it is a non-toxic, low cost and present abundantly in nature. These metal oxide-based semiconductors have been used in many applications like humidity sensors, gas sensors, bio-sensors, and ultraviolet sensors [37]. The important metal oxide-based based electrode which is used as a sensor in many applications are zinc oxide (ZnO), Copper oxide (CuO and Cu2O), Titanium oxide (TiO2), tin oxide (SnO and SnO2), tungsten oxide (WO3). The performance of these metal oxide-based nanostructures can be improved by optimizing the size, shape, doping, and presence of defects [38]. Among the various applications, this thesis is mainly focused on glucose-sensing applications.

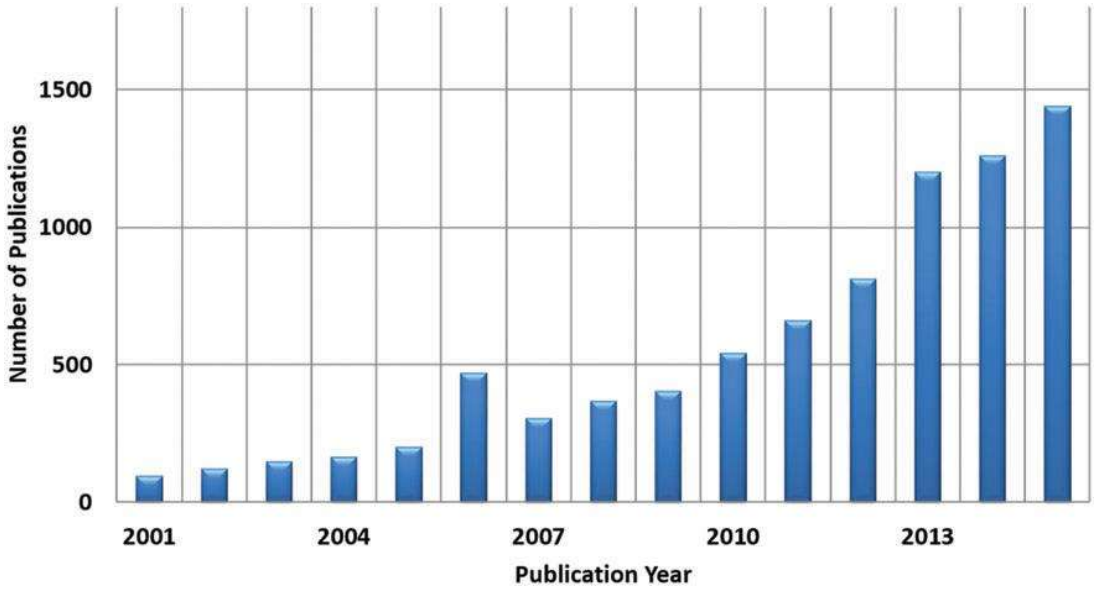


Figure1.6: Graph between total numbers of publication for non- enzymatic glucose sensors with respect to time (years) Zhu et al., 2016, Advances in non-enzymatic glucose sensors based on metal oxides. J. Mater. Chem. B (https://doi.org/10.1039/ C6TB02037B)9uj).[39]

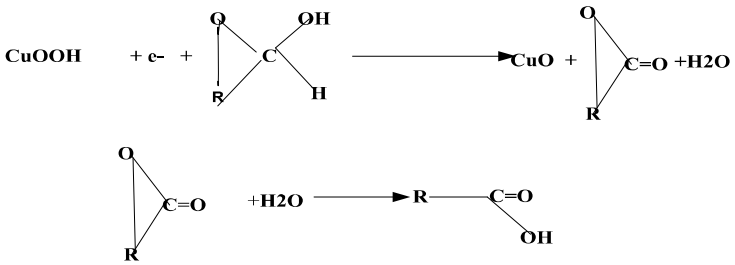
Figure1.6 explains the total number of publications in the field of non-enzymatic glucose sensors increased from 97 to 1447 in the interval of 15 years (2001 to 2015). This is a radical increment in non-enzymatic based glucose sensors suggesting tremendous interest among researchers in the development of non-enzymatic glucose sensors. .

1.3.1 Working of Non-Enzymatic Based Glucose Sensing

Working principle of non-enzymatic based glucose sensors is explained here**.** Here multivalent cation of the oxide materials mimics the role of the Gox enzyme and convert the glucose to glucotone[39].

$$CuO + H_2O + 2OH^- \rightarrow Cu(OH)_4^- + e^-$$

Or, $$CuO + H_2O \rightarrow CuOOH + e^- + H^+$$



$$Glucose \rightarrow Gluconolactone + e^-$$

$$Cu(III) + e^- \rightarrow Cu(II)$$

Cu(III)+Glucose→Glucoconolactone+Cu(II)

$$Gluconolactone \rightarrow Glucononic\ Acid\ (Hydrolysis)$$

1.4 Characterization Technique for Evaluation of Hybrid Oxide Nano Structures based Glucose Sensors

1.4.1 Scanning Electron microscopy

Scanning electron microscopy(SEM) is generally used for microstructure, morphological and compositional analysis [38]. In a SEM, a focused electron beam (up to 30keV) is scanned over the surface of the specimen in raster scanning mode, Thereby generating a map or SEM image. An electron beam interacts with the specimen and generates secondary electron, backscattered electron, and characteristics of X-ray photons, which in turn are detected by respective detectors to give morphological contrast, compositional contrast, and elemental information.

Typical resolution in SEM is around 1nm in secondary electron imaging mode. In energy dispersed spectroscopy (EDS) and elemental mapping mode, the energy resolution is around 1 to 10eV, and the special resolution is around 10nm. A field emission gun SEM (Model: Carl Zeiss Microscopy Ltd, EVO MA 15/18) was used for scanning electron microscopic investigations of our nanohybrid materials. The Schematic diagram of the SEM is shown in figure 1.7. The SEM images of CuO nanowires (NWs), CuO nanowires with gold nanoparticles (GNP), and ZnO nanorods have been used for materials characterization.

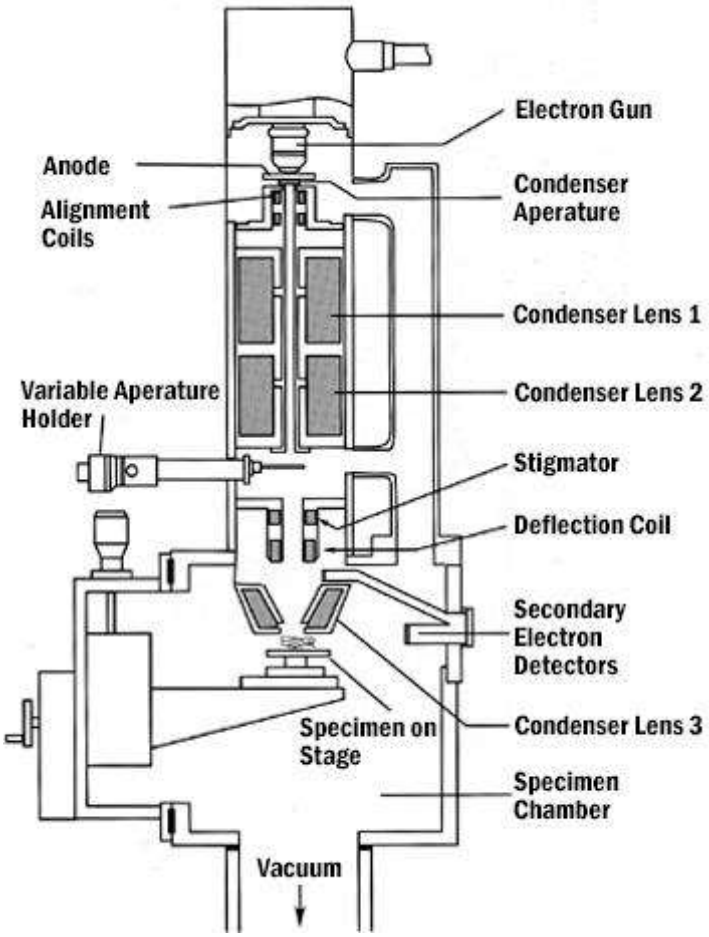


Figure. 1.7: Layout of optical component of basic Scanning of Electron Microscopy (SEM). https://cmrf.research.uiowa.edu/scanning-electron-microscopy.

1.4.2 Transmission electron Microscopy (TEM)

Scanning electron microscopy(SEM) is generally used for microstructure, morphological and compositional analysis [38]. In a SEM, a focused electron beam (up to 30keV) is scanned over the surface of the specimen in raster scanning mode, Thereby generating a map or SEM image. An electron beam interacts with the specimen and generates secondary electron, backscattered electron, and characteristics of X-ray photons, which in turn are detected by respective detector TEM is used to obtain the micro-structural, crystallographic and elemental information from nanostructure [38]. A

focused electron beam of around 200kVenergy is irradiated on the sample, and the sample generates an image with mass- thickness or diffraction contrast or both after the electron beam is transmitted through the sample. Mass thickness contrast arises due to localized variation in thickness as well as average atomic weight. Diffraction contrast is only shown by crystalline materials and arises due to localized variation in orientation or crystalline phases. Electron diffraction patterns from small selected regions can also be collected to analyze and deduce the single crystalline, polycrystalline, polyphasic, or hetero-structural nature of the specimen. This technique is known as the selected area diffraction pattern (SAED). Characteristic X- rays emitted from the specimen after interaction of the electron beam can also be collected by EDS detectors to give localized elemental information and composition of the specimen. At high magnification (>150000 x), lattice fringes may also be noticed and used to confirm the crystalline phases. This technique is called high-resolution transmission of electron microscopy (HRTEM). TEM imaging source resolutions up to around 0.1nm depending on magnification. For the current research work, we used a field emission gun transmission electron microscope (Tecnai G2 20 TWIN from FEI, USA). The spatial distribution of the nanohybrids (Au nanoparticles coated CuO NWs, copper oxide nanoparticles coated Zinc oxide nanorod) was ascertained by bright-field TEM, HRTEM, SAED, and EDS. A Schematic of the TEM image is shown in figure 1.8.

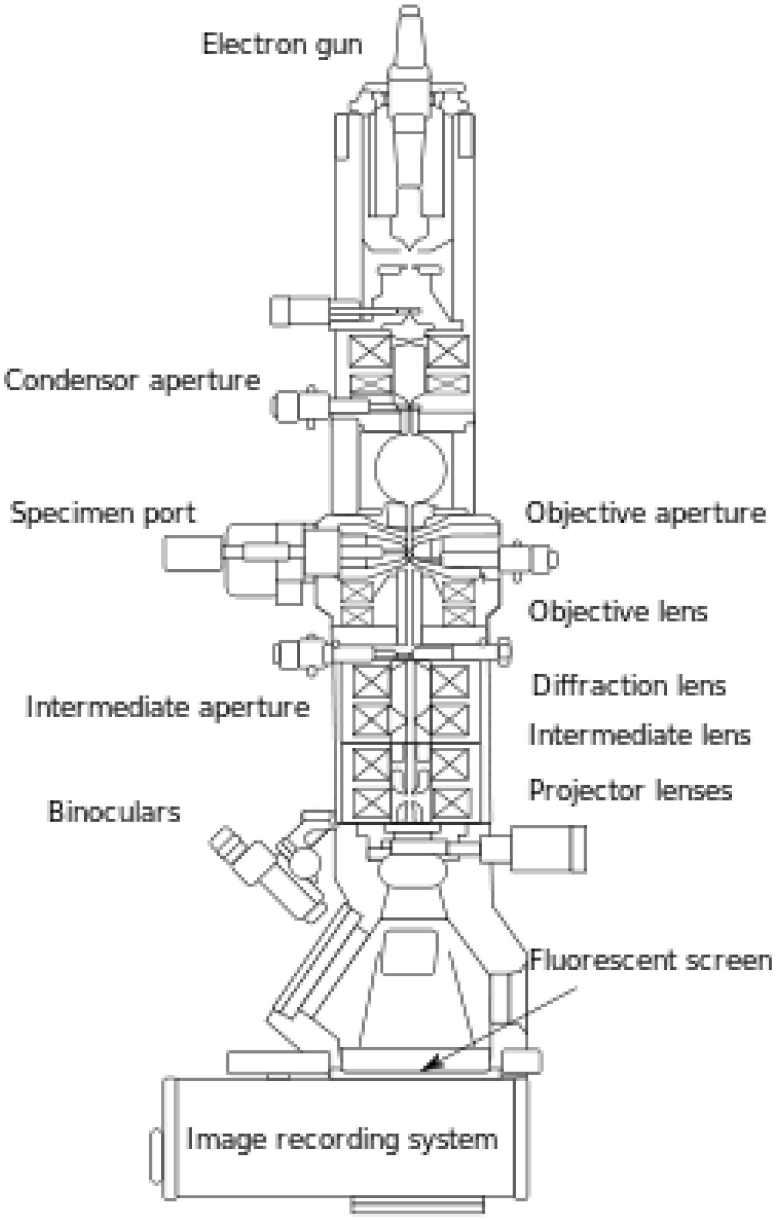


Figure.1.8 Layout of optical component of basic Transmission of Electron Miscroscopy (TEM) https://en.wikipedia.org/wiki/Transmission_electron_microscopy#/ media/ File:Scheme_TEM_en.svg

1.4.3 A Powder X-Ray Diffraction:

Powder diffraction technique is routine structural characterization technique through which we can identified the phases / constituent of a powder polycrystalline sample containing mixture of phases or constituents [38]. The technique is based on X-ray

diffraction where a known characteristic and monochromatic X-ray radiation is diffracted by different

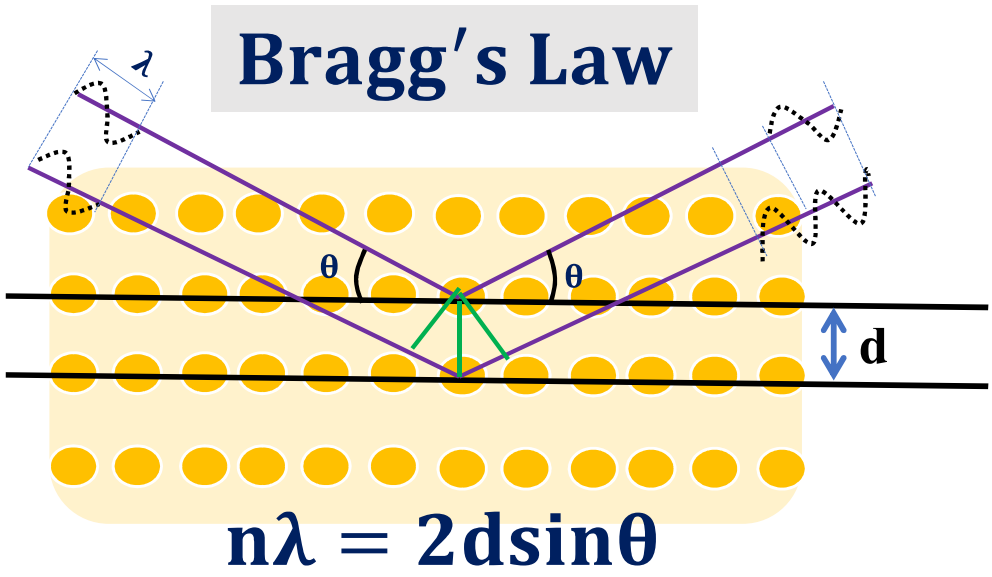


Figure 1.9: XRD measurement using Bragg's law

crystal planes at different angles, as shown in figure1.9. This diffraction follows the Bragg,s law given by $n\lambda = 2d \sin\theta$.

Where n denotes the diffraction order, λ is the wavelength of the rays, d is the inter-planar spacing of the diffracting planes, and θ is the half diffraction angle. Intensity versus 2θ plot is generated where peaks corresponding to different diffracting planes appear at different 2θ values.D spacing corresponding to different 2θ values is matched with a standard ICDD database, and crystal phases are identified. This thesis uses a Smart Lab X-Ray Diffractometer from Rigaku, Japan, for the XRD measurement with Cu Kα radiation (.λ=1.5418Å).

1.4.4 Cyclic Voltammetry:

The complete measurement set-up of Cyclic Voltammetry is shown in figure 1.10(a).Cyclic voltammetry is an important electro analytical technique where of the working electrode is measured against a biasing potential which is cyclied between the set range of potential .range is decided based on occurrence of the redox potential peaks of the analyte. These experiment are performed in a three electrode electrochemical sensors and potential of the working electrode is measured against a referenced electrode like (Ag/AgCl:3 M KCl).The corresponding current response is measured against a counter electrode (egg. platinum electrode). Potential is linearly ramped against time from one end of the set potential range to another and then reversed to the first end. This potentials cycling range repeated multiple times. Whenever there is a oxidation or reduction process current increase abruptly and reaches a peak at a potentials corresponding to complete conversion to oxidize/reduces product. Consider the following reversible reaction.

$$M^{+} + e^{-} \leftrightarrow M$$

Anodic oxidation peak will occur at a potential where all M converts to M^{+}. Similarly a reduction peak will appear corresponding to complete conversion to M^{+} to M. This is shown in figure 1.10 (b).

Peak oxidation current or peak reduction current depends on both scan rate and concentration of the analyte therefore measuring the peak oxidation /reduction current at affixed scan rate and comparing it with a known peak current versus concentration calibration plot, unknown concentration of the analyte can be determined.

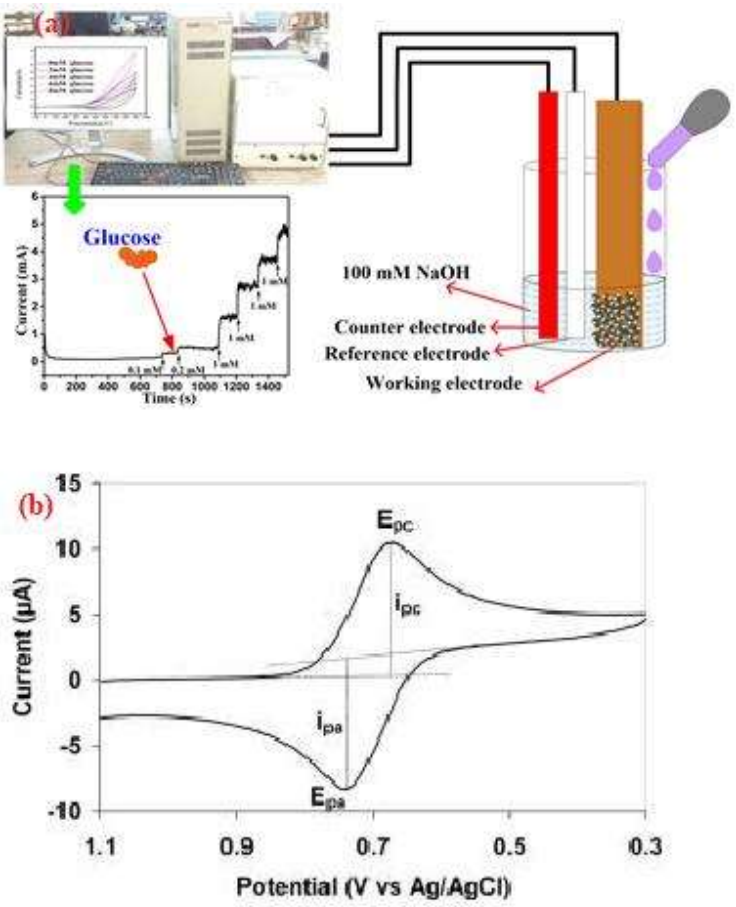


Figure.1.10: (a) Set-up and working of cyclic voltammetry measurement (b) Typical cyclic voltammogram where and show the peak cathodic and anodic current respectively for A reversible reaction (https://en.wikipedia.org/wiki/Cyclic_ voltammetry #/media/File:Cyclovoltammogram.jpg)

This method is used to measure the concentration of glucose by measuring the peak oxidation current of glucose to gluconic acid conversion. CV measurements have been performed with an electrochemical workstation (Model CS: 350, S/N: 1609178, Corr test Instrument, China).An electrochemical workstation (number and name) was used for all the electrochemical measurement performed in the thesis. The schematic of the experimental setup is shown in figure [40].

1.4.5 Electrical Characterization

In this section, the discussion has been focused on electrical parameters of the field-effect transistor which is commercially available (CD-4007UB.) .The working electrode acts as extended gate of the FET. Electrical characterization can be used to find out various properties such as Id-Vg, Id-Vd, Current time graph, and Voltage time graph. The current-voltage and current time graph of the device are studied by using Keysight B1500A as shown in figure1. 11.

Figure 1.11: Semiconductor parameter analyzer for the measurement of various electrical parameter

1.5 Literature Review

This thesis aims to fabricate and characterize metal oxide-based nanostructure for the sensing of glucose. The sensing mechanism of the non-enzymatic based glucose sensing is entirely different from enzymatic based glucose sensors where electrodes are required to satisfy some important requirements such as large specific surface, outstanding conductivity, and high electrocatalytic activity, effective electron transfer

from electrocatalysts to the conductive substrate, good selectivity, high stability and good reproducibility [41].

1.5.1 Review of the Enzyme Less based Glucose Sensors

Metals (Pt, Au, and Ni) were initially used more intensively as catalysts for non-enzymatic glucose sensors. Among these metal, Pt and Au electrode has been limited by chloride poisoning and high cost [42]-[44]. Though the Ni electrode is less costly than Pt and Au electrodes, it is unstable in low or neutral pH solutions. NiOOH catalysis depends on the hydroxyl anion of the electrolyte [44]. Hence metal oxide has been found as an electro-catalyst for electro-oxidization. Moreover, these metal oxides have been extensively investigated recently due to their high stability, low cost, good sensitivity, and rapid response [45]-[47].

F.Xiao et al. [48] had been fabricated on flexible sensors on graphene paper decorated with PtAu-MnO2 nano-composite. Sensors performance is very good in terms of linearity(0.1mM to30 mM) high sensitivity (58.54 μA mM^{-1} cm^{-2}) low detection limit (0.02mM, S/N=3).

J.Chen et al. have been fabricated MnO2/MWCNT based electrode worked in an alkaline medium with linearity up to 28mM and sensitivity of 33.19 μA mM-1 cm-2 [49]. Bare MWCNT based glucose sensor had problems with the interferences caused by the oxidation of common interfering species such as ascorbic acid, dopamine, and uric acid. This problem can be suppressed by using the electrode MnO_2/MWCNT [49]. Rare research has been done on MnO2 based materials due to their low ion diffusion, low electronic conductivity (10^{-5}-$10^{-6}$$Scm^{-1}$), and Mn dissolution into solutions

[50].ZnO is an essential material for different types of sensing. Till 2011, ZnO has not been used as a glucose sensing. G.N.Dar et al. [51] first published a ZnO nanorod decorated on a glassy carbon electrode for sensing of non-enzymatic glucose sensors. The electrode's sensitivity is 5.601μA mM^{-1} cm^{-2}, the detection limit of the electrode is 0.5 μM, and linearity has been achieved in the range of 0.001-0.01mM.

The performance of the ZnO nanorod can be improved by combining another metal oxide (CuO, and NiO) with ZnO. S. SoYoon et al. [52] reported Cu substrate /CuO leaf/ZnO nanorod gives a good sensitivity of 408 μA mM^{-1} cm^{-2} and improved linearity with a comparison of bare ZnO NR(ZnO nanorod). ZnO nanomaterial's based electrode has a promising electrocatalyst for glucose sensing. Still, the operating voltage is very high that caused by unexpected output signal encouraged by the oxidation of other interferences like ascorbic acid, uric acid, dopamine, etc.

For enzyme-free glucose sensing, Co_3O_4 had been verified as a capable material by several research investigations [53]–[58] because of its environmentally benign nature, low cost, electrocatalytic properties, and good conductivity. Y. Ding et al. [53] were the first to report the application of Co_3O_4 in enzyme-free glucose sensing. In their paper, Co_3O_4 nanofibers (NFs) were synthesized via a facile two steps process (i) electrospinning (ii) subsequent calculations. The sensitivity obtained by these electrodes was 5.601 μA mM^{-1} cm^{-2}, while linearity was obtained up to 2.04mM with a detection limit (0.97 μM) in 0.1M NaOH solution.Dong et al. [59] fabricated electrodes with 3D grapheme foam/Co3O4nano wire composite. The sensitivity obtained by the electrode was as high as 3390 μA mM^{-1} cm^{-2}.with a detection limit of 25nM(S/N=8.5). But the linearity range was so poor up to 0.08mM.

Copper oxide is one of the best materials for optical, electrical, photovoltaic devices, gas sensors, magnetic storage media, field emission emitters, and lithium-ion electrodes applications because of its natural abundance in nature, and low production costs, good catalytic and electrochemical properties [60]. Particularly copper oxide electrode as glucose sensors is also well recognized. Copper oxide as a nanostructure is more stable for electro-analysis than copper as an element [61]. With the rapid advancement in enzyme less glucose detection, a chain of CuO nanostructure have also been widely planned and fabricated to increase their intrinsic characteristics and performances in glucose sensors, including nanospheres[62], nanoparticle [63], nanowires [64]–[66], nanofiber [67], nanorod [68], and flower-like structures[69]–[71]. Ni et al. [72] used CuO NWs on Copper foil at 0.1M NaOH solution, while Li et al. [41] used CuO NWs on Copper foam at 1M of NaOH solution gives high sensitivity with good linearity, as mention in table1. Bao et al. [74] used an Au electrode modified by NF/AuNPs/CuO-MoS2, which gives the high sensitivity of 872.71 μA cm−2 mM−1 and linearity up to 5.67mM. Recently Zhang et al. [75] observed that glucose sensing performance was improved by synergistic effect between CuO NWs and NiCo2O4. Gao et al. [76] have been used three-dimensional Cu@Cu2O aerogels for glucose sensing performance, sensitivity obtained from this electrode is 195 mA mM-1cm-2with 0.6 μM detection limit, and linearity is up to 17.1 mM. Xu et al. [77] used Ag-CuO nanocomposite on rGO (reduced graphene oxide) substrate and achieved the sensitivity of 214.37 $\mu AmM^{-1}cm^{-2}$ with high linearity range of 0.01-28mM. Chakraborty et al. [78] synthesized CuO NRs hydrothermally with the coating of Au nanoparticles. With the help of this nanocomposite, an excellent sensitivity of 2009 $\mu AmM^{-1}cm^{-2}$ and detection limit of 0.17 μM. A detailed comparison between different metal oxide nanostructured based

glucose sensors is mention in table 1.1. On the basis of the discussions presented above and observations listed in table 1.1, it is observed that metal oxides nanostructures can be effectively explored for the electrodes of glucose sensors. Among various metal oxides, CuO nanostructures are the most widely explored material for non-enzymetic glucose sensors. It is also observed that the performance of the glucose sensors can be drastically improved by using Au nanoparticles coating on the metal oxide nanostructured electrodes. Moreover, the performance of the glucose sensors is can be varied by changing the concentration of the medium.

Table 1.1: Comparison of Metal Oxide Nano Structure Based Glucose Sensors

Type of Electrodes	Detection Limit (μM)	Sensitivity ($\mu AmM^{-1}cm^{-2}$)	Linear range(mM)	Ref.	Medium
Au NPs decorated on CuO NRs	0.17	2009	0.005-1.325	78	0.1M NaOH
Ag-CuO/rGO	0.76	214.37	0.01-28mM	77	0.1M NaOH
Cu@Cu_2O aerogels	0.6	195000	up to 17.1	76	0.1M NaOH
CuO NWs and $NiCo_2O_4$	0.6	1423.91	5.664	75	0.05M NaOH
AuNPs/CuO-MoS2	0.5	872.71	up to 5.67	74	0.05M NaOH
CuO NWs	0.05	1886.3	0.002-3.56	72	0.1M NaOH
CuO NWs/Cu foam	0.3	2217.4	0.001-18.8	41	1M NaOH
CuO nanosphere	1	404.53	0-2.55	63	0.1M NaOH
Co_3O_4 Nanofiber	0.97	36.25	Up to 2.04	54	0.1 M NaOH
Co_3O_4 /graphene	0.025	3390	Up to 0.08	60	0.1 M NaOH
NiO/MWCNTs	2	1770	Up to 7	73	0.1M NaOH
ZnO nanorods	0.5	5.601	0.001-0.01	52	0.1M PBS, pH=7.4
CuO nanoleaf/ZnO NRs	18	408	0.1-1	53	0.1M NaOH

MnO_2/MWCNT	-	33.19	Up to 28	49	0.1M NaOH
Coral like PtAu-MnO_2	20	58.54	0.1-30	50	0.1M PBS, pH=7.4

1.5.2 FET Based Enzyme-Less Glucose Sensing:

FET provides a practical, low-cost, robust platform to various nanostructures to achieve higher current amplification with an improved signal-to-noise ratio with respect to other sensing methods. FET also gives real-time measurement capability with outstanding sensitivity for bio and chemical molecules. Due to the aforementioned reasons, non-enzymatic-based FET has been used for glucose sensing applications [79]. Rafiq Ahemad et al. [79] used NiO quantum dot decorated on ZnO NRs as a sensitive material that gets the broad linearity up to 50mM and sensitivity of 13.14 $\mu AmM^{-1}cm^{-2}$ with the help of FET. Rafiq Ahmad et al.[80] have used ZnO NRs decorated with Fe_2O_3 nanoparticles as a sensing material achieved the wide linearity up to 18 mM and very low detection limit of 12µM with good selectivity. Zong et al. [81] took the ZnO nanorods as glucose sensing materials with a high sensitivity of 1600 µAmM-1cm-2 and a low detection limit of up to 1 µM with good quality selectivity. This sensor had been used for continuous monitoring of diabetes.

1.5.3 EGFET Based Enzyme-Less Glucose Sensing:

First ion sensing-FET (IS-FET) was developed in 1970 [82]; after many different methods and sensing, the membrane has been developed for various sensing applications like glucose sensing in human blood, ion sensing, and pH sensing [83], [84]. However, the major disadvantage of the IS-FET is poor stability because of the fragile nature of the membrane deprivation in extreme conditions and higher noise level due to its inherent internal gain. To overcome these limitations, an extended-gate (EG)

field-effect transistor (FET) device is used as an alternative to IS-FET. An externally developed sensing electrode is connected to the gate of a commercially available FET. In 2011, passivated ZnO nanorod connected to the gate of commercial MOSFET for glucose sensing applications [85]. In 2014 with the help of EGFET, glucose had been sensed with a sensitivity of 5.62mV/M with a linearity range of 2-7mM [86]. In 2015 Qi et al.[87] used ZnO nanoarray as an active material connected to the gate of commercial MOSFET sensed the glucose with a sensitivity of 0.39 μV/mM with a linearity range of 0.02mM-0.1mM. In 2016 Al-doped ZnO nanorod based active materials were used as an extended gate of commercial MOSFET [88]. In 2019, Singh et al. [89] had sensed both glucose and pH with the help of EGFET. In 2019 Khalifa et al. [90] have sensed the glucose with the help of EGFET; Ni film on ITO substrate has been taken as an active material and got the sensitivity of 22.44 μA/mM with a linearity range of 2-7 mM. Comparison between different EGFET based glucose sensors are mentioned in table 1.2.

Table1. 2: EGFET based glucose sensors

Sensing Membrane	**Fabrication mode**	**Sensitivity**	**Range**	**Linearity**
Ni flim on ITO substrate[90]	DC magnetron sputtering	22.44μA/mM	2-7mM	0.98
RuOx[89]	Sol-gel	6.89mV/mM	1-8 m	99.3
Al-doped ZnO nano structure[88]	Hydrothermal	60.5μA/mM	1-13.9mM	99.96
ZnO Nano array[87]	Sol-gel	0.39μV/mM	0.02-.1mM	0.967
Nb_2O_5[86]	LPCVD	5.62mV/M	2-7 mM	0.880
Passivated ZnO[85]	Photo electrochemical	20.3 μA/mM	--	--

1.5.4 Major Observation From The Literature Survey:

Various metal -oxide based working electrodes have been used for non-enzymatic glucose sensing applications. Among them, Copper oxide nanostructured has been frequently used for the sensing of the electrode due to its low fabrication cost, facile fabrication, abundant availability in nature, good catalytic properties [63], [71]-[72], [91]-[97]. Sensitivity of CuO nanostructure based working electrode can be increased by use of nobel metal as co -catalyst. Coating of nobel metals like (Ag and Au) on CuO nanao structure make the device more attractive for glucose sensing applications [93], [97]. With the help of EGFET, only the sensing electrode part is required to fabricate different sensing electrodes is worked for various sensing applications[39],[95]-[97]. In the case of EGFET base sensors, there is no need to fabricate transistors. Different sensing materials are required for different sensing electrodes, which are worked for different sensing applications [65],[92]. From the Table 1.2, it is observed that the sensitivity of the EGFET based sensors is in the order of μA/mM or μV/mM, and linearity is less than 10 mM. Thus, there is an ample opportunity to enhance the performance of the EGFET based glucose sensors by exploring various materials for glucose sensing applications. In this thesis, attempt has been made to examine the performances of the two EGFET based glucose sensors by exploring Au nanoparticles coated CuO NWs and CuO nanoparticles coated ZnO nanorods for electrodes in the proposed EGFET sensors.

1.6 Motivation and Problem Definition

The use of copper oxide nanowires and gold nanoparticles for glucose sensing applications requires widespread study of materials engineering, chemistry, and device engineering. Sensitivity and linearity are the main parameters for devices and the overall performance of glucose sensors. To achieve widespread linearity and better sensitivity, researches use different approaches [74], [95]-[98].

CuO is regarded as one of the best metal oxide semiconductors for its glucose sensing application because of its abundance in nature, low fabrication cost and good catalytic and electrochemical properties [63], [68], [74]-[75], [92]-[97].The nano composite of metal oxide semiconductors and nobel metals are estimated to be very good glucose sensing materials because of good electro-catalytic catalytic performance of metal oxide and high conducting properties of the nobel metals [97]. In view of the above, Li et al. [97] have tried with the use of Au/CuO nano cauliflower nano-composite for sensing of glucose for the first time. With the help of Noble metal (Au) and metal oxide semiconductor (CuO), Li et al. [97] have observed an improvement in the conductivity and accelerated electron transfer, and good selectivity and sensitivity toward the glucose detection. Li et al. [97] have reported a non-enzymatic based glucose sensing approach using Au/CuO nano-cauliflower nano-composite. In cauliflower structure, gold has been distributed only on the top of the CuO nanowire. An optimum result can be obtained if gold is uniformly distributed throughout the CuO nanowire. These arrangements take the maximum advantages of the catalytic property CuO nanowire and conducting property of gold nano-particles (NPs). The enhanced catalytic properties and high direct electron transfer via CuO NWs in the presence of Au NPs give a large surface-to-

volume ratio to result in the drastic improvement in sensitivity and linear range of the glucose sensor under study.

In the view of the above, we have used uniformaly distributed gold nanoparticles on CuO NWs as co catalyst and CuO NWs has been used as catalyst for improving the sensitivity of the glucose sensors. Improved catalytic property due to CuO NWs and direct electron transfer due to gold nano particle (GNP) caused high surface to volume ratio results drastic enhancement in the sensitivity and linear range of the glucose sensor under study.

1.7 Scope of the Thesis:

We have already discussed glucose-sensing with the help of enzymes and without the use of enzymes. Enzyme-based glucose sensors have high selectivity, sensitivity, and low detection limit [23]. However, the stability of the enzyme-based glucose sensors is significantly affected by the relative humidity, working temperature, and pH value [72]. Further, the fabrication cost of enzyme based glucose sensors is relatively higher than the non-enzyme-based glucose sensors [98]-[100]. For low fabrication cost and better stability, metaloxide based electrodes (Enzyme free) have been used as glucose sensors. A Nobel material (Au, Ag, and Pt) with metal oxide (CuO, and ZnO) nanostructure has been used as glucose sensors.

Additionally, in this thesis, metal oxide-based nanostructure has been used as an extended Gate with FET. This thesis includes five chapters, including the present chapter. The outline of the other chapters is given below.

Chapter 2: Copper oxide NWs with gold nanoparticles used as a working electrode in non-enzymatic based glucose sensing. CuO NWs had been formed with the help of chemical etching and then heating. Because of the above discussion, we have used Gold nanoparticles as co-catalyst, and CuO NWs have been used as a catalyst for improving the sensitivity of the glucose sensors. Improved catalytic property due to CuO NWs and direct electron transfer due to gold nanoparticles (GNP) caused the high surface to volume ratio results drastic enhancement in the sensitivity and linear range of the glucose sensor under study. A complete reaction has been performed in a solution of 0.1M NaOH. This study is further extended with 0.5M NaOH and 1M NaOH solvent. More concentrated solvent gives a wide linear range of glucose sensing, which is more beneficial for moderate and severe diabetic patients.

Chapter 3: In this chapter, a CuO nanowire-based electrode has been used for glucose sensing. CuO NWs electrode has been used as an extended gate (EG) field-effect transistors (FET). CuO NWs electrode-based EGFET has also been investigated for glucose-sensing for the first time without taking the help of neither any enzyme nor any organic receptor. This sensor is also capable of detecting the glucose concentration in human blood and human serum. The performance of these glucose sensors can be determined with the help of linearity and sensitivity.

Chapter 4: In this work, a CuO nanoparticle (NPs) decorated zinc oxide nanorods (ZnO NRs) on fluorine-doped tin oxide (FTO) substrate has been used as a working electrode. This working electrode has been used as an extended gate for field-effect transistors. The extended-gate field-effect transistor (EGFET) is to works as a glucose sensor. This novel concept of CuO NPs decorated ZnO nanorods based EGFET glucose

sensing is believed to be extended for sensing other saccharides such as fructose, sucrose, and mannose. Moreover, this sensor is well performed in terms of selectivity, repeatability, and stability.

Chapter 5: This chapter includes the summary and conclusion of the work of the present thesis. This chapter also contains future work related to the current area of research.