UNIVERSITI PUTRA MALAYSIA

PREPARATION OF MODIFIED CdSe/ZnS QUANTUM DOTS AND GOLD NANOPARTICLES FOR GLUCOSE AND DENGUE DETECTION

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By

SAMSULIDA BINTI ABD. RAHMAN

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

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January 2018

Chairman : Professor Nor Azah binti Yusof, PhD
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Development of sensors combined with nanomaterials becoming an interesting area due to their unique optical properties. In this research, two different biosensor utilizing CdSe/ZnS quantum dots (QDs) and gold nanoparticles (AuNPs) have been developed and successfully applied to detect glucose and dengue virus DNA, respectively. CdSe/ZnS QDs is utilized in our first prepared biosensor for glucose monitoring. The CdSe/ZnS QDs was successfully prepared via hot injection method while the ZnS layer was made using the successive ionic layer adsorption and reaction (SILAR) method. The prepared QDs was spherical monodisperse with uniform sizes of 3 to 3.2 nm and 10 to 12 nm for CdSe core QDs and CdSe/ZnS core-shells QDs, respectively. The prepared CdSe/ZnS QDs has been modified with organic ligand for glucose analysis. Detection was performed using glucose concentrations ranging from 0 to 40 mM with linear relationship was observed from 0 to 10 mM (with R^2 = 0.9964) and limit of detection was obtained at 0.3 mM. Comparison between our developed biosensor with commercialized assay kit result in 99% similarity thus indicated that the developed biosensor utilizing CdSe/ZnS QDs was reliable for the detection of glucose.

AuNPs is utilized in our second prepared biosensor for dengue virus detection. Positively charged AuNPs was interacting with negatively charged PNA/DNA hybridised biochip via electrostatic interaction and successfully used to detect dengue virus using both naked eye and optical scanner. Detection of dengue virus was study using concentration ranging from 10 pM to 1 µM with a detection limit was obtained at 10 pM. Repeatability and reproducibility study gave relative standard deviations (RSD) less than 5% in all measurements, which indicate that the chips produced in this study are suitable for mass fabrication of devices with similar

responses. Comparison study between our developed PNA/DNA biochip with real time RT-PCR was investigated and obtaining 88% agreement.

Both scopes covered in this study give new possibilities for healthcare monitoring, where these studies improved the specificity and selectivity of the developed biosensor.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

PENYEDIAAN CdSe/ZnS TITIK KUANTUM DIUBAH SUAI DAN NANOPARTIKEL EMAS UNTUK PENGESANAN GLUKOSA DAN DENGGI

Oleh

SAMSULIDA BINTI ABD. RAHMAN

Januari 2018

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Pembangunan pengesan yang digabungkan dengan bahan-bahan bersazi nano menjadi satu bidang yang sangat menarik di sebabkan oleh keunikan ciri-ciri optikal bahan-bahan tersebut. Dalam kajian ini, dua biosensor berbeza yang menggunakan titik kuantum (QDs) CdSe/ZnS dan nanopartikel emas (AuNPs) telah di bangunkan dan telah berjaya diaplikasi untuk mengesan glukosa dan DNA virus denggi, masing-masing. Titik kuantum (QDs) CdSe/ZnS telah digunakan dalam penyediaan biosensor pertama kami untuk pengesanan glukosa. Teras titik kuantum (QDs) iaitu, CdSe telah berjaya dihasilkan melalui kaedah suntikan panas dengan lapisan ZnS itu dibuat menggunakan kaedah penjerapan dan tindak balas lapisan ion berturut-turut (SILAR). Titik kuantum (QDs) CdSe/ZnS yang telah disediakan adalah *monodisperse* sfera dengan saiz seragam 3 hingga 3.2 nm dan 10 hingga 12 nm, untuk teras QDs, CdSe dan teras-lapisan QDs, CdSe/ZnS, masing-masing. QDs CdSe/ZnS yang telah disediakan telah diubahsuai menggunakan ligan organik untuk digunakan untuk analisa glukosa. Pengesanan glukosa dijalankan dengan menggunakan kepekatan glukosa di antara julat 0 hingga 40 mM dengan perkadaran terus diperhatikan dari kepekatan 0 hingga 10 mM (dengan R^2 = 0.9964) dan had pengesanan 0.3 mM. Kajian perbandingan di antara biosensor yang dibangunkan dengan kit komersil sedia ada menghasilkan keputusan persamaan sebanyak 99% sekaligus menunjukkan bahawa biosensor yang dibuat menggunakan QDs CdSe/ZnS adalah sesuai untuk pengesanan glukosa.

Nanopartikel emas (AuNPs) telah digunakan dalam penyediaan biosensor kedua kami untuk pengesanan virus denggi. Caj positif AuNPs bertindakbalas dengan caj negatif biochip PNA/DNA melalui tindakbalas elektrostatik dan telah berjaya digunakan untuk pengesanan virus denggi menggunakan dua kaedah iaitu mata kasar

dan pengimbas optik. Pengesanan virus denggi telah dijalankan menggunakan kepekatan virus denggi di antara julat 10 pM hingga 1 μM dengan had pengesanan kaedah pengesanan ini adalah pada 10 pM. Kajian kebolehulangan dan kebolehasilan ini memberikan sisihan piawai relatif (RSD) kurang daripada 5% dalam semua pengesanan, di mana ia menunjukkan bahawa peranti biocip yang dihasilkan dalam kajian ini adalah sesuai untuk dihasilkan secara besar-besaran dengan tindak balas yang sama. Kajian perbandingan di antara biochip PNA/DNA yang dibangunkan dan RT-PCR telah dijalankan dan memperoleh 88% kesesuaian.

Kedua-dua skop dalam kajian ini telah memberikan kemungkinan baru untuk pemantauan kesihatan, di mana keputusan yang diperoleh dalam kajian ini dapat meningkatkan pengkhususan dan pemilihan oleh biosensor yang telah di bangunkan.

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I certify that a Thesis Examination Committee has met on 3 January 2018 to conduct the final examination of Samsulida binti Abd. Rahman on her thesis entitled "Preparation of Modified CdSe/ZnS Quantum Dots and Gold Nanoparticles for Glucose and Dengue Detection" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

AFP	α-Fetoprotein
Anti-AFP	α-Fetoprotein Antibody
APS	Aminopropyl Silanes
APTMS	3-Aminopropyltrimethoxysilane
AuNPs	Gold Nanoparticles
AuNR	Gold Nanorods
BSA	Bovine Serum Albumin
CTAB	Hexadecyltrimethylammonium Bromide
DMF	N,N-Dimethylformamide
DNA	Deoxyribonucleic acid
cDNA	Complementary DNA
ssDNA	Single Stranded DNA
DTCs	Dithiocarbamates
EDC	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide Hydrochloride
EDTA	Ethylenediaminetetraacetic Acid
FCS	Fetal Calf Serum
GSH	Glutathione
GOX	Glucose Oxidase
H_5N_1	A Subtype of the Influenza A Virus
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HepG2	Human Liver Cancer Cell Line

HER2	Human Epidermal Growth Factor Receptor-2
HRP	Horseradish Peroxidase
HUSM	Hospital Universiti Sains Malaysia
LOD	Limit of Detection
MAA	Mercaptoacetic Acid
MOI	Multiplicity of Infection
MPA	Mercaptopropionic Acid
MPs	Magnetic Nanoparticles
MPS	Mercaptopropyltris(methyloxy) Silane
MSA	Mercaptosuccinic Acid
MUA	Mercaptoundecanoic Acid
NIH-3T3	Mouse Fibroblast Cells
NHS	N-Hydroxysulfosuccinimide
ODE	1-octadecene
OP	Organophosphorus
PBS	Phosphate Buffer Saline Solution
PBST	Phosphate Buffer Saline-Tween Solution
PEG	Polyethylene Glycol
PNA	Peptide Nucleic Acid
QDs	Quantum Dots
qRT-PCR	Quantitative Reverse Transcription Polymerase Chain Reaction
RNA	Ribonucleic acid
miRNA	Micro RNA
SDS	Sodium Dodecyl Sulphate

SILAR	Successive Ionic Layer Adsorption and Reaction
SSC	Saline Sodium Citrate (Buffer)
TBE	Tris Borate EDTA
TEM	Transmission Electron Microscope
TGA	Thioglycolic Acid
TOP	Trioctylphosphine
TOPO	Trioctylphosphine Oxide
Tris-HCl	Tris-Hydrochloric Acid Buffer Solution
UV-Visible	Ultraviolet–visible
W/O	Water-in-Oil

CHAPTER 1

INTRODUCTION

1.1 Biosensor

A biosensor is a chemical sensor that utilizes biological elements such as enzymes, proteins, DNA or antibodies which have been immobilised on a transducer to detect its biological event. Currently, biosensors are immobilised with sensitive biological molecules on its solid surface by utilizing specific recognition among biological molecules to capture target analytes onto the sensor surface. A reaction will occur between the biological elements and target analyte, thus giving the reaction signal. The solid surface acts as a signal indicator to convert the generated signals into detectable electrical signals such as voltage, current, and impedance or optical signals such as UV-visible, photoluminescence, and chemiluminescence. This method enables the qualitative and quantitative analysis of target molecules (Basudam & Sarmishtha, 2004).

Extensive use of biosensors in healthcare monitoring eventually rely on the techniques of biosensor development, where this technique allows for rapid detection with high selectivity and sensitivity (Sarathi Vasan et al., 2013). There are many options for biosensor detection such as amperometric, potentiometric, and optical and field effect transistors. However, in this study, the focus is given only on biosensors that use optic as its detection method. Most of the optical based biosensors did not require extensive instrumentation, and some researchers have reported that their optical based biosensors incorporated with nanomaterials can be viewed via naked eye, making them relatively inexpensive. Nowadays, optical based biosensors are commonly used in many healthcare monitoring and clinical applications for a broad range of analytes (Kim et al., 2016).

1.2 Glucose Detection

Glucose is one of the earliest healthcare analyte that being used in biosensor development. First glucose sensor was developed in 1841 where it was focusing in urine samples (John T. Hayford et al., 1843). Nevertheless, the relationship between glucose level in urine samples and plasma samples was inconsistent. Starting from there, many research have been performed to fabricate sensor (biosensor, chemical sensor or physical sensor) for determination of glucose levels with high sensitivity, high reliability, high repeatability, high reproducibility and low cost.

Recognize practices for monitoring of glucose levels nowadays is rely on blood samples and it is widely used method for the diagnosis of glucose level in human body. For diabetic patients, they shall always monitor their glucose level via

obtaining their blood sample. This invasive method usually was done via finger pricking. The blood was introduced onto a sensor test strip, consequently read by a handheld electronic reader, which shows the glucose concentration in the patient's blood. This finger pricking resulting in the pain and inconvenience to the human. The invasive approached method serves several limitations including painful sampling, fewer glucose tests could be performed for each time finger pricking, inadequate blood glucose control, produce more complications and large fluctuations between different sampling time (Burge et al., 2008 and Pickup et al., 2008).

Many research and methods in sensing area have been conducted to overcome all the problems. Among these methods, the electrochemical biosensors were the most eminent and remains the widely used to date (Lee et al., 2007 and Chakraborty et al., 2008) due to their significant advantages. Despite that, optical sensors becoming very vital considering that they are invulnerable to electromagnetic distraction, easy to miniaturize and only require low power supply (Kevin and Heather, 2010). Among the various optical detections, fluorescence based is considerably sensitive, but the deficiency during sensor establishment is a frequent congestion that always reported in many studies (Muscatello et al., 2009).

Significant research has been reported to overcome the deficiency during development of glucose sensor. Nanotechnology has influence these research via offering large surface area of established sensors, enhancing the catalytic properties as well as providing nanoscale sensors.

Due to the limitation that occurs when using invasive sampling procedure and deficiency during sensor establishment as reported previously, herein we propose to develop a biosensor incorporated with nanomaterial to measure glucose via fluorescence-based detection since many advantages offered by nanotechnology. Thus, in this study, a biosensor that comprised with semiconductor nanomaterials namely CdSe/ZnS Quantum dots (QDs) for determination of glucose level in human urine samples will be established. Performance of the established biosensor namely sensitivity and limit of detection of glucose detection in non-invasive urine samples is hoped can be enhanced via our proposed method.

1.3 Dengue Detection

Beside glucose monitoring, many biosensor approaches are focusing on dengue detection since there is no specific treatment available for this disease nowadays. Thus, accurate laboratory diagnosis is very helpful in controlling this disease (Om and Rafidah, 2015). Dengue virus is one of the contagious tropical diseases that raise a serious problem in the world (Monath, 1994). Ordinarily, symptoms for dengue fever and dengue hemorrhagic fever can be seen after more than 5 to 6 days of fever (Halstead and O'Rourke, 1977, Gubler, 1998).

To date, no effective vaccine or medicines are available to deter or heal dengue fever (Chang et al., 2001). Besides, there is no specific therapeutic treatment for dengue virus infection. Nowadays, focus only given on mosquito eradication strategies to prevent the dengue disease. This strategy only being conducted after several dengue fever cases were reported in certain case areas but success of this method is limited (Baeumner et al., 2002).

It is crucial for a physician to diagnose dengue fever rapidly, properly, and accurately to achieve shorter operation time and to avoid excessive labor. Diagnosis based on existing symptoms is very problematic since the initial dengue virus infection symptoms are similar to those of influenza, measles, malaria, typhus, yellow fever, and other virus infections (Baeumner et al., 2002).

There are many conventional methods have been used for the detection of dengue virus. One of the most common methods is ELISA assays based on the detection of IgG and IgM antibodies to dengue virus (Chakravarti et al., 2000). However, the results are affected by cross-reactivity with other flaviviruses. Furthermore, conventional methods require at minimum five (5) days after patient getting high fever to be detected due to the lack of sufficient immune to produce detectable antibodies in patient's blood. Tissue culture and immune-fluorescence are other conventional approaches for the detection of dengue virus (Young et al., 2000; Vene et al., 1995; Porter et al., 1999). Unfortunately, these two methods are limited in terms of specificity, sensitivity, ease of use, and speed.

Due to the limitation via using the method described previously, many researchers have used molecular assays based on nucleic acid amplification for dengue virus detections. In this method, firstly, dengue genomic RNA needs to be converted into DNA (Kow et al., 2001; Laue et al., 1999; Killen et al., 1993; Lanciotte et al., 1992; Henchal et al., 1991) using polymerase chain reaction (PCR). Double stranded DNA, which the product yields from PCR reaction, must be denatured before being used as probe hybridization based detection method. Although, this method offers sensitive detection, however it is time consuming, expensive as it involves high cost instrumentation, hard for miniaturization and not labor-free since it requires a molecular biologist to handle this assay.

Similarly, real-time polymerase chain reaction (RT-PCR) (Kaltenboeck and Wang, 2005), DNA microarrays (gene chip) (Brown and Botstein, 1999), surface plasmon resonance biacore instrument (Marks et al., 1999) and GeneXpert system (Petersen et al., 1999) offer fast and sensitive tools to detect the dengue virus disease. However, these instruments involve high cost and require well-trained employees for running. Conventional bioassay is one of the methods that have been developed to detect DNA sequences of dengue virus (Drummond et al., 2003; Koehne et al., 2004). However, these conventional methods fail to provide enough specific information and require labeling with external reagents such as enzymes and/or fluorescent dyes. Besides, the labeling procedure may cause suppression in the

specific recognition of DNA-DNA hybridizations. Furthermore, the labeling procedure is time consuming and causes a high background signal.

Recently, diagnosis of dengue virus using nucleic acid based on biosensor technology is becoming more important. It has generated new techniques for detection of DNA dengue virus. Most of them are rapid, easy to operate, reusable, cheap, sensitive and serotype-specific. Thus, more efforts have been made to seek an ideal tool for fast, sensitive, low-cost, and easy-to-use dengue virus detection based on nucleic acids (Piunno and Krull, 2005; Hahn et al., 2005). In addition, the sensitivity of the detection was further enhanced by the use of nanomaterials.

Common nanomaterials that used in the establishment of optical biosensor are QDs, gold nanoparticles (AuNPs), silver nanoparticles (AgNPs) and many others. These nanomaterials will be used as color indicator in developed biosensor. Incorporation of QDs in development of biosensor involving labeling process which will contribute to several disadvantageous such as non-specific binding of DNA sequence, time consuming and increasing in noise background as discussed previously. Other nanomaterials that widely used in sensing area are AgNPs. Even so, usage of AgNPs as color indicator in sensing development shows several limitations. One of the limitations is functionalization or modification of AgNPs can cause chemical degradation of nanoparticles to silver ions (Ag^{+}) as well as the surface of AgNPs can be easily oxidized if there are no additional steps taken to prevent it from oxidized.

Due to the disadvantageous of QDs and AgNPs, AuNPs will be used as color indicator where it will be incorporated with developed biosensor for the detection of DNA dengue virus. Performance of the proposed biochip namely accuracy, fast, specificity and selectivity of DNA dengue virus detection in blood samples is hoped can be enhanced via our proposed method where hybridized PNA/DNA biochip incorporated with AuNPs as color indicator. Due to the advantageous offered, this study will be focusing on the development of a label-free biochip incorporated with nanomaterials for naked eye detection of DNA dengue virus. Label-free detection systems have become increasingly popular nowadays where it offers high possibility of realizing more convenient detection systems compared to conventional methods. In addition, it can be used to overcome the problem facing by using previous detection method. The accuracy and specificity also will be confirmed with validation and comparison study.

1.4 Scope of Research

Due to the limitation and problem that discussed earlier in sub-chapter 1.2 and 1.3 for glucose and dengue detection, respectively, herein we propose to develop a biosensor incorporated with nanomaterial for healthcare monitoring since many advantages offered by nanotechnology.

This study will focus on the development of two different sensors based on two different nanomaterials for healthcare monitoring as stated below:

1. Preparation of modified CdSe/ZnS core-shell QDs for glucose monitoring
2. Preparation of biochips based on modified AuNPs for DNA dengue virus (serotype I) detection.

These nanomaterials were chosen due to their special characteristics that makes them suitable for optical biosensor applications.

1.5 Objectives of This Research

The objectives of this research are:

i. To prepare, modify and characterize the CdSe/ZnS core-shell QDs for glucose detection in non-invasive human urine samples.
ii. To prepare and modify the AuNPs for dengue detection in patient's blood samples.

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